The Ramanbhai Foundation 8th International Symposium on
Current Trends in Healthcare

"Advances in New Drug Discovery & Development"

Feb 2-4, 2017, Ahmedabad, India

Scientific Abstracts

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Advancing Drug Discovery & Development

Zydus dedicated to life

INNOVATION IN LIFE SCIENCE

Zydus Research Centre

ZRC Misslon

ZRC aims to be

the most admired

pharmaceutical research center

for innovation in life science

dedicated to alleviate

human sufferings.

Contents

Message from the Chief Patron

Dear Delegates,

It's a pleasure to welcome you all to the Ramanbhai Foundation 8th International Symposium.

Over the last 14 years, our overarching aim through the RBF Symposium has been to create a platform for knowledge-sharing where researchers, scientists, academicians and the industry can converge, discuss and share new trends in Drug Discovery and Development. The process of drug discovery requires the best scientific minds to come together, highly sophisticated technologies, and complex project management skills to bring efforts to fruition.

This year's theme of the Ramanbhai Patel International Symposium is to understand these linkages as we explore advances in Drug Discovery and Development.

As a global healthcare provider our mission at Zydus is to create healthier communities and we continue to look at innovative solutions to bridge unmet healthcare needs. Our aim has been to leverage the India advantage in terms of developmental capabilities right from lab to market. Driven by this commitment, the pharma innovation and bioinnovation in our journey of discovery has been quite heartening.

It is the relentless effort of over 1200 researchers across 19 sites who look at differentiated medicines for the future and a focussed approach that led to the discovery of two innovative breakthroughs from our fold - Lipaglyn, the novel drug to be approved for the treatment of diabetic dyslipidemia in India which is our own patented NCE and Exemptia, the world's first biosimilar for Adalimumab, the largest selling therapy worldwide for inflammatory arthritis. But this is just the beginning and we have a long way to go on this exciting journey of innovation ahead.

I strongly believe that innovation in life sciences is going to unlock the keys to solving many of the diseases that we are burdened with. There are abundant opportunities for innovation waiting to be explored in every sphere of healthcare and pharmaceuticals and there are ideas that can make a significant improvement or a difference.

With 25 speakers and experts, this knowledge sharing forum on the 'Advances in Drug Discovery and Development' promises to be very insightful and interesting. We are confident that you will find the Ramanbhai Foundation 8th International Symposium, an enriching experience.

Warm regards,

Pankaj R. Patel
Chief Patron

About Ramanbhai Foundation

A first-generation entrepreneur, Mr. Ramanbhai Patel was one of the stalwarts of the Indian Pharmaceutical Industry. At a time when the newly independent nation was heavily dependent on imports of drugs and pharmaceuticals, he had set out to prove that an indigenous company could provide innovative, research-based quality medicines.

Born at Kathor in South Gujarat on the 19th of August 1925, he began his career as an academician at the L.M. College of Pharmacy, a premier institute in Ahmedabad. This short stint in academics formed a lasting imprint on his mind and the resolve to contribute to the cause of research and education grew stronger over the years.

In 1952, Mr. Ramanbhai Patel turned a pharma entrepreneur. Armed with a sound business acumen, he laid a strong foundation for Cadila and contributed to the growth of the Indian Pharmaceutical Industry. Zydus Cadila today enjoys the coveted distinction of being one of the leading pharma groups in the country and a global healthcare provider.

Mr. Ramanbhai Patel had published several outstanding research papers and used to taken keen interest in research activities of the group. Today, Zydus Cadila is amongst the top investors in research. Mr. Ramanbhai Patel's contributions in the field of pharmaceutical education were equally noteworthy. Gujarat which earlier had only one pharmacy college now has several reputed pharmacy colleges. More importantly, Ramanbhai was instrumental in taking pharmaceutical education to the rural heartland of Gujarat, making professional courses more accessible to students in smaller townships.

In recognition of his services, Mr. Ramanbhai Patel had been bestowed with several prestigious awards: President of India's Import Substitution Award in 1973. Prof. M.L. Shroff Memorial National Award in 1987, The Glory of India Award in 1991 at Washington, Grahak Suraksha Award in 1992, Acharya Prafulla Chandra Ray Memorial Gold Medal in 1993 and the Eminent Pharmacist Award in 1994.

In a fitting tribute to his outstanding contributions to the growth of the pharma industry in India, he was conferred the Gujarat Businessman of Year Award in the year 2000. He was also honoured by Express Pharma Pulse with the 'Lifetime Contribution Award' for his contributions to the Indian pharma industry.

On the occasion of Gujarat's Pharma Centenary Celebrations in January 2008, Mr. Ramanbhai B. Patel was posthumously awarded a special plaque in recognition for his efforts in laying a firm foundation for Gujarat's pharmaceutical industry in the Post Independence era.

With a firm belief that new avenues would surely emerge, if one has the will to discover it, he dedicated his life to the quest for knowledge, as an academician, entrepreneur and a researcher.

The Zydus Research Centre, a state-of-the-art facility which was set up during his lifetime, spearheads the research initiatives of the Zydus group and supports the quest for innovations and excellence in the field of research.

The Ramanbhai Foundation today continues to spearhead programmes in the field of pharmaceutical research, education and healthcare – areas close to the Late Founder Chairman's heart.

The Ramanbhai Foundation is committed to a number of special initiatives in the field of education. The Zydus School for Excellence which was a dream nurtured by Mr. Ramanbhai B. Patel has been set up to provide a rich academic environment where children can seek creative expressions for their endeavours.

The Ramanbhai Patel - AMA Centre for Excellence in Education has also been set up to raise the bars of excellence in the field of education through progressive learning programmes for academicians, knowledge sharing forums and by studying successful models of education and creating a platform for sharing these experiences.

The Ramanbhai Foundation alongwith the Indian Pharmaceutical Association has set up the IPA-Shri Ramanbhai B. Patel Foundation (IRF) to recognise and honour lifetime achievements of senior pharmacists who have contributed to the growth of the profession of pharmacy in India. The IRF also awards merit scholarships to deserving students in the field of Pharmaceutical Sciences.

The Ramanbhai Patel International Symposium held every two years is devoted to the discussion on the current trends and developments in Pharmaceutical Sciences. Through the symposia, the Foundation aims to bridge the research endeavors taking place across the world and create a platform for knowledge sharing, tracing the development of new molecules from the laboratory to the market.

About Zydus

Zydus Cadila is a fully integrated, global healthcare provider, with strengths all along the pharmaceutical value chain. With a core competence in the field of healthcare, Zydus Cadila provides total healthcare solutions ranging from formulations, active pharmaceutical ingredients and animal healthcare products to wellness products.

In 2014, the group launched Exemptia, the world's first biosimilar of Adalimumab, the largest selling therapy worldwide for inflammatory arthritis. Zydus is also the only Indian pharma company to launch its own patented NCE – Lipaglyn, the novel drug approved for the treatment of diabetic dyslipidemia.

As a leading healthcare provider, it aims to become a global research based pharmaceutical company by 2020. The Zydus group bagged the India Pharma Overall Excellence Award and India Pharma Innovation of the Year Award from the Govt. of India. The group also won the CII Industrial Innovation Grand Jury Award of being the Most Innovative Company of the Year and declared the most Innovative Pharmaceutical Company by Thomson Reuters.

In its mission to create healthier communities globally, Zydus Cadila delivers wide ranging healthcare solutions and value to its customers. With over 19500 employees worldwide, a world-class research and development centre dedicated to discovery research and state-of-the-art manufacturing plants, the group is dedicated to improving people's lives.

The group has a team of around 1200 research professionals spearheading its research and development programme of which nearly 400 scientists alone are involved in the NME research programme at Zydus Research Centre, the group's state-of-the-art R&D centre. Within a short span of time, the group has made remarkable progress on the New Molecular Entity (NME) research and has several candidates in various stages of clinical development.

- **NCE research**
  - Cardio-Metabolic diseases
  - Inflammation & pain
  - Oncology
- **Biologics**
  - Biosimilar Therapeutic proteins
  - Biosimilar Monoclonal antibodies
  - Biobetters and Novel biologics
- Vaccines
  - Infectious diseases

About Zydus Research Centre

The Zydus Research Centre is the dedicated research arm of the Zydus Group. With its team of over 400 research professionals, ZRC spearheads the group's quest of creating healthier and happier communities globally. Spread over an area of over 4,75,000 sq ft, ZRC is working on cutting edge technologies in 14 different scientific disciplines to discover novel therapeutic agents. The center has capabilities to conduct drug discovery & development from concept to IND enabling preclinical and clinical studies.

About Vaccine Technology Centre

Vaccine Technology Centre (VTC) is the Vaccine division of the Zydus Group. VTC has two state-of-the-art R & D Centers, one located in Catania, Italy; and the other in Ahmedabad, in the western part of India.

Zydus Vaccine division has indigenously developed, manufactured and launched India's first vaccine against H1N1 (Vaxiflu-S). The Vaccine Division's Rabies Vaccine Manufacturing facility has received WHO pre-qualification, and is one of the largest Rabies manufacturing facility in India.

The current programs under development include vaccine candidates designed to address infectious diseases like next-generation Influenza, Measles-Mumps-Rubella-Varicella, Typhoid, DPT-HiB, Hepatitis-B, Hepatitis-A, Hepatitis-E, Japanese Encephalitis, HPV and combination vaccines. Research is also focused on developing a Malaria vaccine.

About Zydus Biologics

Zydus Biologics is the biologics divisions of the Zydus group. The Zydus Biologics division has capabilities to discover and develop therapeutic proteins and monoclonal antibodies.

The division has a cGMP facility for manufacturing therapeutic protein based drugs and has developed and launched several therapeutic protein based drugs. The division also has an 11,000 litre cGMP facility for manufacturing monoclonal antibodies.

Program Schedule

Ramanbhai Foundation 8th International Symposium on Current Trends in Healthcare "Advances in New Drug Discovery And Development"

February 2-4, 2017

09.30 hrs	**Welcome address** **Shri. Pankaj R. Patel** Chief Patron The Ramanbhai Foundation, 8th International Symposium
09.40 hrs	**Lighting of the lamp**
09.45 hrs	**Opening remarks by Guest of Honour**  **Dr. Richard DiMarchi** Standiford H. Cox Distinguished Professor of Chemistry, Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University
09.55 hrs	**Introduction to the keynote speaker** **Dr. Sharvil P. Patel** Deputy Managing Director Zydus Cadila
10.00	**Keynote address:** *" The Problem of Reproducibility in Biomedical Research"*  **Jeff Flier, M.D.** HMS Dean (2007-16) **Harvard Medical School**, Harvard University
10.45	**Q & A** session
11.00 hrs	**Vote of Thanks** **Mr. Ganesh Nayak** COO & Executive Director Zydus Cadila
11.30	***Poster and Exhibition Session Inauguration*** ***Dr. Sharvil P. Patel*** *Deputy Managing Director* *Zydus Cadila*
12:30 hrs	**Lunch**

Session I : Gastrointestinal and Liver Diseases

Chairpersons:

- Charles F. Burant, MD, Ph.D., Professor of Metabolism, The Burant Lab, University of Michigan Medical School
- Dr. S.K.Sarin, MD, DM, Senior Professor and Head, Hepatology, Director, Institute of Liver and Biliary Sciences (ILBS), &vWHO CC on Viral Hepatitis and Liver Diseases, New Delhi
- Dr Ajay Duseja, Department of Hepatology, PGIMER, Chandigarh

14:00 hrs

"Molecular Mediators of NAFLD"

Jay Horton, MD

Distinguished Chair in Human Nutrition,
The University of Texas Southwestern Medical Center

14:30 hrs

"Specificity Matters –Musings on (somewhat unconventional) development of a targeted immunomodulatory biologic"

Asit Parikh, MD, Ph.D
Head of GI Therapeutic Area Unit, Takeda Pharmaceuticals

15.00 hrs

"NASH in India: Perspectives and Prospects for management"

S.K.Sarin, MD, DM

Senior Professor and Head, Hepatology, Director, Institute of Liver and Biliary Sciences (ILBS), & WHO CC on Viral Hepatitis and Liver Diseases, New Delhi

15.30 hrs Tea Break

16:00 hrs

"Non-alcoholic steatohepatitis modulation by novel FXR & PPAR agonists"

Bart Staels, Ph.D.

Director UMR INSERM 1011, Professor at the Faculty of Pharmacy,
Université Lille 2, France

16:30 hrs

"Hepatocyte PPARα is protective against NAFLD in neonate and adult mice"

Walter Wahli, Ph.D

Professor of Metabolic Disease, Lee Kong Chian School of Medicine,
Nanyang Technological University, Singapore

17:00 hrs

"Translating scientific discovery into a cure for NASH"

Arun Sanyal, MD

Professor of Medicine, Physiology and Molecular Pathology,
Virginia Commonwealth University

17:30 hrs **Wrap-up**

Session II : Cancer Therapeutics

09:15 hrs **Introduction**

Chairpersons:

- Kapil Dhingra, MD; Retired Vice President, Roche, Director, KAPital Consulting LLC
- Phil Dawson, Ph.D., Associate Dean of Graduate Studies, Department of Chemistry California, Campus, The Scripps Research Institute

09.30 hrs

"Enabling personalized medicine in oncology: Current status and perspectives on the future"

Kapil Dhingra, MD

Retired Vice President, Roche, Director, KAPital Consulting LLC

10:00 hrs

"T-cell engineering for Cancer Application"

Martin Pule, M.D.

Founder & Chief Scientific Officer, Autolus Limited

10:30 hrs

"ZYTP1 - a novel PARP inhibitor for management of solid tumors"

Mukul Jain, Ph. D.

Senior Vice President, Pharmacology & Toxicology
Zydus Research Center

11:00 hrs **Tea-Break**

11:30 hrs

"Discovery of New Protein Drug Targets by Comprehensively Screening the Extracellular Proteome"

Lewis T. "Rusty" Williams, M.D., Ph.D.

Founder, President and CEO, Five Prime Therapeutics, Inc.

12:00 hrs

"Mouse Models for Pharmacogenomic Discovery"

Karen Reue, Ph.D.

Professor, Human Genetics, Department of Human
Genetics, David Geffen School of Medicine, University of California, Los Angeles

12:30 hrs **Lunch & Poster Sessions**

Session III : Anti-infectives & Public Health

Chairpersons:

- Bikash Medhi, MBBS,MD(AIIMS),MAMS,FIMSA, Professor, Dept. of Pharmacology, PGIMER, Chandigarh
- Reinhard Glueck, Ph.D; Chief Scientific Officer Zydus – VTC

14:00 hrs

"Public-Private Partnerships to Accelerate Innovation in Product Development"

Rajeev Venkayya, MD

President of Global Vaccine Business Unit, Takeda Pharmaceuticals

14:30 hrs

"Developing next-generation malaria medicines to address drug resistance and increase the operational feasibility of malaria elimination efforts"

Jörg Möhrle, Ph.D.

Vice President, Head of Translational Medicine, Research & Development, Medicines for Malaria Venture

15:00 hrs Tea Break

15.30 hrs

"The Discovery and Development of New Antivirals"

Manoj Desai, Ph.D.

Vice President, Medicinal Chemistry, Gilead Sciences

16.00 hrs

"Opportunities and Challenges in the Vaccine Industry"

Rahul Singhvi, Sc.D.

Chief Operating Officer, Takeda Vaccines

16:30 hrs **Panel Discussion**

"Is there more integration between cancer, viral disease and the microbiome?"

- Jeff Flier, M.D., HMS Dean (2007-16), Harvard Medical School,
- Richard DiMarchi, Ph.D., Standiford H. Cox Distinguished Professor of Chemistry, Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University
- Rajeev Venkayya, MD, President of Global Vaccine Business Unit, Takeda Pharmaceuticals
- Kapil Dhingra, MD, Retired Vice President, Roche, Director, KAPital Consulting LLC
- Manoj Desai, Ph.D., Vice President, Medicinal Chemistry, Gilead Sciences
- Arun Sanyal, MD, Professor of Medicine, Physiology and Molecular Pathology, Virginia Commonwealth University

17:30 hrs **Wrap-up**

Session IV : Cardio-metabolic Diseases

09.15 hrs **Introduction**

Chairpersons:

- Jeff Flier, M.D; Harvard Medical School, Harvard University
- Jay Horton, MD Distinguished Chair in Human Nutrition, The University of Texas Southwestern Medical Center

09:30 hrs

"FGF21:physiology and therapeutic potential"

Terry Flier, MD

Professor of Medicine, Harvard Medical School
Division of Endocrinology, Beth Israel Deaconess Medical Center

10:00 hrs

"Evolving mechanisms and continued challenges of the FGF-21 pathway as a therapeutic target"

Saswata Talukdar, Ph.D.

Director and Leader of Cardio-Metabolic Disease,
Early Discovery group, Merck Research Laboratories

10:30 hrs

"Metabolism and metabolic aging"

Charles F. Burant, MD, Ph.D.

Professor of Metabolism, The Burant Lab, University of Michigan Medical School

11:00 hrs

"Melanocortins: From Pharmacology to Pharmacotherapy"

Roger Cone, Ph.D.

Mary Sue Coleman Director, Life Sciences Institute
Professor of Molecular and Integrative Physiology, University of Michigan

11:30 hrs **Lunch & Posters**

Session V : Chemical Biotechnology

Chairpersons:

- Lewis T. "Rusty" Williams, M.D., Ph.D., Founder, President and CEO, Five Prime Therapeutics, Inc.
- Manoj Desai, Ph.D., Vice President, Medicinal Chemistry, Gilead Sciences

14:00 hrs

"Plants as bio-factories for producing peptide-based pharmaceuticals"

David Craik, Ph.D.

Group Leader, Chemistry and Structural
Biology Division, The University of Queensland

14:30 hrs

"Making connections in peptide chemistry"

Phil Dawson, Ph.D.

Associate Dean of Graduate Studies, Department of Chemistry California
Campus, The Scripps Research Institute

15:00 hrs

"High productive cell-lines, ADC process development and challenges"

Palani Palaniappan, Ph.D.

Vice President & Head,
Biologics & New Modalities Development, Takeda Pharmaceuticals

15:30 hrs

"Chemical Biotechnology Applied to Metabolic Diseases"

Richard DiMarchi, Ph.D.

Standiford H. Cox Distinguished Professor of Chemistry,
Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University

16:00 hrs **Best Poster Awards**

- Oral Poster Presentation 1 (10 min)
- Oral Poster Presentation 2 (10 min)
- Oral Poster Presentation 3 (10 min)

16:30 hrs **Closing Remarks**

Dr. Sharvil P. Patel

Deputy Managing Director, Zydus Cadila

Speaker Profiles & Abstracts

Keynote address

Jeff Flier, M.D.

Dean of the Faculty of Medicine,
Harvard Medical School, Harvard University

Dr. Jeffrey S. Flier became the 21st Dean of the Faculty of Medicine at Harvard University on September 1, 2007. Flier, an endocrinologist and an authority on the molecular causes of obesity and diabetes, is also the Caroline Shields Walker Professor of Medicine at Harvard Medical School.

Topic

The Problem of Reproducibility in Biomedical Research

Jay Horton, MD

Distinguished Chair in Human Nutrition, The University of Texas Southwestern, Medical Center

Dr. Jay D. Horton, Professor of Internal Medicine and of Molecular Genetics at UT Southwestern Medical Center. His research focuses on key aspects of lipid synthesis, insulin action, and cholesterol metabolism. Among many accomplishments, his characterization of secreted PCSK9 and this protein's interactions with low density lipoprotein receptors provided the foundation for a new class of agents just approved by the FDA for lowering serum cholesterol levels.

Topic

Molecular Mediators of NAFLD

Obesity and insulin resistance are strongly associated with the development of nonalcoholic fatty liver disease (NAFLD). The excess triglyceride that accumulates in hepatocytes is derived from multiple sources, one of which is de novo lipogenesis. Fatty acid synthesis in liver is regulated by SREBP-1c, a transcription factor that activates genes involved in fatty acid synthesis. The first committed enzyme in fatty acid synthesis, acetyl-CoA carboxylase (ACC), is also regulated by phosphorylation/dephosphorylation, and protein polymerization. Previously, we showed that MIG12, a 22 kDa cytosolic protein, binds to ACC and lowers the threshold for citrate-induced ACC activation. All of these factors contribute to the development of hepatic steatosis. Here, we further explore the interrelated molecular and physiological functions of these lipogenic regulators in the development of NAFLD and investigate the feasibility of each as therapeutic targets for the treatment of NAFLD.

Asit Parikh, MD, Ph.D

Head of GI Therapeutic Area Unit, Takeda Pharmaceuticals

Asit Parikh, M.D. Ph.D., is currently the Sr. VP and Head of GI Therapeutic Area at Takeda Pharmaceuticals. Dr. Parikh earned his Ph.D in Biochemistry and MD degrees from Vanderbilt University, completed internal medicine residency at the University of Pennsylvania, and subspecialty training in gastroenterology at the Massachusetts General Hospital, with postdoctoral work in Cancer Biology at MIT. He also remains actively engaged in the practice of gastroenterology and internal medicine as a part-time coverage staff physician at Newton-Wellesley Hospital.

Topic

Specificity Matters –Musings on (somewhat unconventional) development of a targeted immunomodulatory biologic

S.K.Sarin, MD, DM

Senior Professor and Head, Hepatology, Director, Institute of Liver and Biliary Sciences (ILBS), & WHO CC on Viral Hepatitis and Liver Diseases, New Delhi

Prof Shiv Kumar Sarin is the Senior Professor and Head, Hepatology and Director, Institute of Liver and Biliary Sciences, New Delhi. He was instrumental in setting up the Institute of Liver and Biliary Sciences (ILBS), under the auspices of the Govt of Delhi. He has more than 480 publications to his credit, edited 13 books on liver diseases and contributed 83 chapters in various medical text books. He has helped develop 18 major guidelines; including six major Asian Pacific Treatment Guidelines in Liver diseases. He is credited with several new treatment protocols for liver diseases, specially variceal bleeding, liver regeneration, hepatitis B and acute-on-chronic liver failure. He is the founding Co-Chief Editor of Hepatology International. Has been a recipient of the highest Award in Science in India, The World Academy of Medical Sciences International Prize, EASL International Recognition Award and 'Most Distinguished Physician from India" from the American Association of Physicians of India.

Topic

NASH in India: Perspectives and Prospects for management

Bart Staels, Ph.D.

Director UMR INSERM 1011,
Professor at the Faculty of Pharmacy, Université Lille 2, France

Prof. Bart Staels's research has focused on the molecular pharmacology of cardiovascular and metabolic diseases, including dyslipidemia and type 2 diabetes in particular examines the role of nuclear receptors (such as PPARs, FXR, and Rev-erbα RORα) in the control of inflammation, lipid metabolism and glucose homeostasis, as well as transcription mechanisms involved. Bart Staels was among the first to identify the crucial role of nuclear receptor PPARa in controlling the metabolism of lipids and glucose, as well as its cardiovascular function in humans.

Topic

Non-alcoholic steatohepatitis modulation by PPAR agonists

Non-alcoholic fatty liver disease (NAFLD) is a liver pathology with increasing prevalence due to the obesity epidemic. Hence, NAFLD represents a rising threat to public health due to hepatic and cardiovascular complication. Currently, no effective treatments are available to treat NAFLD and its complications such as cirrhosis and liver cancer. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors which regulate lipid and glucose metabolism as well as inflammation. In this presentation, we will review recent findings on the pathophysiological role of PPARs in the different stages of NAFLD, from steatosis development to steatohepatitis and fibrosis, as well as the preclinical and clinical evidences for potential therapeutical use of PPAR agonists in the treatment of NAFLD. PPARs play a role in modulating hepatic triglyceride accumulation, a hallmark of the development of NAFLD. Moreover, PPARs may also influence the evolution of reversible steatosis towards more advanced active NASH and fibrosis. Large controlled trials of long duration to assess the long-term clinical benefits of PPAR agonists in humans are ongoing.

Walter Wahli, Ph.D

Professor of Metabolic Disease, Lee Kong Chian School of Medicine,
Imperial College London & Nanyang Technological University

Prof Wahli is internationally recognised for his contributions to the area of energy metabolism. He has provided fundamental insights into the functions of transcription factors (PPARs) activated by fatty acids and eicosanoids. His discoveries contributed in advancing our understanding of the molecular mode of action of these natural compounds, which signaling impacts most key biological processes in vertebrates.

Topic

Hepatocyte PPARα is protective against NAFLD in neonate and adult mice

Arun Sanyal, MD

Professor of Medicine, Physiology and Molecular Pathology, Virginia Commonwealth University

Dr. Arun Sanyal is a Professor of Medicine, Physiology and Molecular Pathology at Virginia Commonwealth University School of Medicine in Richmond, Virginia. He has over 25 years of experience as a hepatologist and has served as the secretary and president of the American Association for Study of Liver Diseases, founding member of the Hepatology board of the American Board of Internal Medicine, chair of the NIH hepatobiliary pathophysiology study section and member of the council of the NIH. He has been continuously funded by the NIH for over 25 years.

Topic

Translating scientific discovery into a cure for NASH

Kapil Dhingra, MD

Retired Vice President, Roche,

Director, KAPital Consulting LLC, USA

Dr. Dhingra founded KAPital Consulting, LLC, a healthcare consulting firm. From 1999 to 2008, Dr. Dhingra served at Hoffmann-La Roche as Vice President, Head, Oncology Disease Biology Leadership Team, and Head, Oncology Clinical Development. Prior to Roche, Dr. Dhingra worked as a Senior Clinical Research Physician with Eli Lilly and Company. Dr. Dhingra is currently an advisor to several biotechnology and pharmaceutical companies and serves on the board of directors of Micromet, Algeta ASA, Biovex, Inc., and Coferon.

Topic

Enabling personalized medicine in oncology: Current status and perspectives on the future

Martin Pule, M.D.

Founder & Chief Scientific Officer

Autolus Limited, London

Dr. Martin Pule is the Founder of Autolus Limited and serves as its Chief Scientific Officer. Dr. Pule is Clinical Senior Lecturer in the Dept. of Haematology at UCL Cancer Institute and Honorary Consultant in Haematology at University College London Hospital. His research is focused on many aspects of genetic engineering of T-cells for cancer treatment, with a particular focus on CARs. He entered the T-cell engineering field in 2001 as a traveling Fulbright Scholar at the Center for Cell and Gene Therapy at Baylor College of Medicine, Houston. Dr. Pule was the first to describe third generation forms of CARs and described one of the first clinical studies of CARS, which showed efficacy in a solid cancer. He serves as Director of the UCL Chimeric Antigen Receptor (CAR) programme. Dr. Pule holds a Bachelor of Medicine and Bachelor of Surgery from University College Dublin and is a Fellow of the Royal College of Pathologists.

Topic

T-cell engineering for Cancer Application

Dr. Mukul R. Jain, Ph.D

Sr. Vice President,
Zydus Research Centre, Ahmedabad

Dr. Mukul Jain is a Senior Vice President and leading the nonclinical research & development group at Zydus Research Centre (ZRC) at Ahmedabad. Since July, 2000 he has been associated with Zydus Cadila group and is involved in discovery & development of New Chemical Entities in different therapeutic areas. He was the key person involved in discovery & development of Saroglitazar / LipaglynTM, the first new drug from Indian Pharmaceutical Industry in recent time and also the first 'Glitazar' class drug approved anywhere in the world for human use. Besides Saroglitazar, his group has contributed to development of 14 other NCEs that received IND approvals in India or abroad. He has also contributed to nonclinical development of 13 recombinant biologics and 12 vaccines of Zydus Cadila.

Dr. Jain obtained his B.Pharm, M.Pharm & PhD degrees as well as a diploma in business management from Nagpur University and has also done a course in Executive Management at IIM, Ahmedabad. He has acquired more than 25 years' total research experience, starting with Nagpur University, Nagpur, Wockhardt Research Centre, Aurangabad; Ranbaxy Research Lab, Delhi; University of Florida at Gainesville, USA; NIPER, Mohali and then at Zydus Research Centre, Ahmedabad.

Although he is associated with an Industry, but has maintained academic interest and guided 13 PhD students and several masters' students. He has more than 260 research publications to his credit, which include 126 full length research papers in peer-reviewed International journals. He has also contributed to more than 40 patents as co-inventor.

Dr. Jain is a Fellow of Academy of Sciences for Animal Welfare and a member of various International Scientific Societies including AAAS, AACR, AASLD, ACS, ADA, ASPET, EASD, IBRO and IPS.

Topic

ZYTP1 - a novel PARP inhibitor for management of solid tumors

Poly (ADP-ribose) polymerase (PARP) are nuclear enzymes activated by DNA strand breaks and are involved in recruitment of DNA repair proteins at the sites of damage, whereas tankyrases are key regulators of cellular processes such as telomere pathway and Wnt signaling. Studies have shown that PARP and TNK inhibition have significant anti-tumor effect in several types of cancers including BRCA -ve breast cancers.

Zydus has discovered a novel PARP-TNKS inhibitor named ZYTP1 using a series of in vitro and in vivo assays. ZYTP1 was found to be a potent PARP and TNKS inhibitor in cell free assay. In vitro cell killing potency of ZYTP1 was tested in a panel of cell lines including BRCA -ve cells. In a BRCA -ve cell line, MDA-MB436, ZYTP1 alone showed good cell kill potency. ZYTP1 was found to potentiate methyl methane sulfone (MMS)-mediated cell killing activity in various cell lines. The pharmacokinetic profile of ZYTP1 was determined in preclinical species including rodents and non-rodents. ZYTP1 demonstrated good Caco2 permeability and oral bioavailability. ZYTP1 was also tested in different xenograft models in combination with temozolomide (TMZ) and cisplatin. ZYTP1 showed efficacy in colon, prostate, ovarian and lung cancer xenograft models in combination with temozolomide (TMZ) or cisplatin. In comparative efficacy studies in lung cancer xenograft model, ZYTP1 showed superior efficacy than olaparib an approved PARP inhibitor drug. In colon tumor xenograft model, ZYTP1 inhibited PARylation. ZYTP1 showed efficacy as a single agent in a BRCA -ve breast cancer xenograft model. In a repeat dose once-daily oral toxicity study in rats and dogs, it was found to have good safety margins.

In conclusion, ZYTP1 is a novel molecule that shows potential for development as a treatment for various types of solid tumors.

Lewis T. "Rusty" Williams, M.D., Ph.D.

Founder, President and CEO,
Five Prime Therapeutics, Inc.

Dr. Lewis T. Williams, also known as Rusty, M.D, Ph.D, founded Five Prime Therapeutics, Inc. in December 2001 and has been its Chief Executive Officer and President since August 2011 and its Chairman since March 15, 2016. He is a member of the National Academy of Sciences and a fellow of the American Academy of Arts & Sciences. Dr. Williams received his M.D. and Ph.D. degrees from Duke University. He trained in Internal Medicine and Cardiology at the Massachusetts General Hospital.

Topic

Discovery of New Protein Drug Targets by Comprehensively Screening the Extracellular Proteome

Five Prime built a comprehensive protein library with the goal of being able to systematically test essentially all human cell surface and secreted proteins for their potential to be protein drugs or antibody targets. We screen our proprietary collection of 5700 proteins in: 1) functional cell-based assays that are automated and often have high content "readouts", 2) in vivo screens in which we test hundreds of proteins for effects in mouse models of a disease, and 3) functional or biophysical ligand/receptor matching screens to identify binding partners for "orphan" receptors or ligands. Using these approaches, we have identified numerous new targets for a variety of diseases, including muscle disease, cancer, respiratory disease and fibrosis. Our current internal focus is immuno-oncology. Five Prime is testing three protein drug candidates in clinical trials, developing multiple pre-clinical candidates, including three in IND-enabling studies, and researching numerous new targets identified through our discovery platform.

Karen Reue, Ph.D.

Professor, Human Genetics, Department of Human
Genetics, David Geffen School of Medicine, University of California, Los Angeles

Dr. Karen Reue is Professor of Human Genetics at UCLA. Her research interest is on Genes underlying disorders in lipid and glucose metabolism. Her recent work has focused on the fatty liver dystrophy (fld) mutation, which results in lipodystrophy (lack of fat tissue), insulin resistance, and increased susceptibility to atherosclerosis. Using a positional cloning approach, her team identified the fld mutation in a novel gene that we named Lipin. They are studying the role of lipin in fat tissue development and metabolic disorders in several models, including engineered mouse strains, cultured cells, human adipose tissue, and invertebrate organisms.

Topic

Mouse Models for Pharmacogenomic Discovery: Statins and Diabetes

Statins are among the most widely prescribed drugs in the world, used to treat elevated cholesterol levels and reduce the risk of cardiovascular disease. Despite their irrefutable effectiveness in reducing risk of cardiovascular disease, large randomized clinical trials have documented adverse effects. Depending on criteria, 5-15% of statin drug users develop myopathy, and recently statins have been associated with a 9-12% increase in risk for new-onset diabetes in men, with up to 30% increased risk in women. To identify genes and pathways that influence susceptibility to adverse statin effects we are using a panel of 100 inbred mouse strains known as the Hybrid Mouse Diversity Panel. We are also utilizing mouse models with altered sex hormones and sex chromosomes to investigate the basis for enhanced statin-induced diabetes specifically in females. Our studies will contribute to our knowledge of metabolic pathways that influence diabetes and muscle health.

Rajeev Venkayya, MD

President of Global Vaccine Business Unit, Takeda Pharmaceuticals

Dr. Rajeev Venkayya serves as President of the Vaccine Business Unit. He joined Takeda in 2012 to launch the global vaccine business, building upon a longstanding business in Japan. Since then, he has formed a global organization and established a high-impact vaccine pipeline that includes promising late-stage candidates for dengue and norovirus, gained through the acquisitions of LigoCyte and Inviragen Inc. Prior to Takeda, Dr. Venkayya served as Director of Vaccine Delivery in the Global Health Program at the Bill & Melinda Gates Foundation, where he was responsible for the Foundation's efforts in polio eradication and new vaccine introduction, and a grant portfolio of $500M/year. While at the foundation, he served on the Board of the Global Alliance for Vaccines and Immunization (GAVI).

Topic

Public-Private Partnerships to Accelerate Innovation in Product Development

Jörg Möhrle, Ph.D.

Vice President, Head of Translational Medicine,
Research & Development,
Medicines for Malaria Venture

Dr. Jörg leads MMV's translational medicine team, which manages antimalarial drug development projects from candidate selection to proof-of-concept. He has experience of working in clinical development in the pharmaceutical and biotech industry across a range of indications. He studied biochemistry in Tübingen University, Germany, and did master's research in electron transport in cyanobacteria in Cambridge, UK receiving an MPhil and obtained my PhD from Basel University for work on protein kinases of Plasmodium falciparum.

Topic

Developing next-generation malaria medicines to address drug resistance and increase the operational feasibility of malaria elimination efforts

Aims: In 2015 the World Health Assembly endorsed the WHO Global Technical Strategy for Malaria 2016-2030[1], which aims to reduce global malaria incidence and mortality rates by 90%. While progress towards malaria reduction and elimination can be made using existing tools, there is general consensus the operational feasibility and impact of malaria elimination efforts will be enhanced by the availability of improved interventions, including drugs. Furthermore, new drugs are needed to address the increasing prevalence of drug resistant parasites. The Malaria Eradication Research Agenda (malERA) published a target profile for the 'ideal' malaria elimination/eradication drug[2] - a Single Encounter Radical Cure and Prophylaxis (SERCaP) intervention capable of achieving rapid reduction in parasitemia, sterilizing the human host of all forms of the parasite, reducing/preventing onwards transmission and providing some degree of post-treatment protection against reinfection. The aim of this talk is to provide an update on the strategy and progress of the Medicines for Malaria Venture (MMV) and its partners in developing novel anti-malarial medicines that meet these requirements.

Methods: MMV's current efforts focus on delivering improved interventions for children and pregnant women, including chemo-prevention, drugs to address resistance and improved drugs for relapsing malaria, all ideally as single dose medicines. MMV works with a consortium of partners to screen chemical libraries, initially via high throughput screening (HTS) against whole parasites. Compounds that are confirmed as active in the HTS are then 'finger-printed' using a selection of assays covering the various lifecycle stages of the parasite[3]. PK/PD data obtained in a humanized SCID mouse model for *P. falciparum* are used within lead optimization to support the first human dose prediction required at preclinical candidate selection[4]. Clinical development of novel malaria agents now utilizes a controlled human infection model[5] for blood stage *Pf* infection, allowing early assessment of PK/PD in humans, facilitating early portfolio de-risking and dose selection.

Results: To date more than 7 million compounds have been screened against whole parasites. Over 25,000 compounds with EC_{50}<1 uM have been identified. Importantly, many of these compounds are active against targets different from the currently approved anti-malaria medicines. Drug candidates covering six novel targets have been selected for development. Twenty-five compounds have been identified where no drug-resistance phenotypes could be generated. Novel study concepts in translational medicine enable us to progress new molecules quickly and to test their antiparasitic activity in the human hosts. This enables MMV to prioritze early promising candidates and progress these into late stage clinical development.

Conclusion: MMV and its partners have bought forward a portfolio of novel antimalarial drugs focused on addressing key unmet medical needs, including compounds to address drug resistance and support malaria elimination efforts. Through these efforts, pathways to kill the parasite have more than doubled over the last 10 years, providing the potential to address drug resistant parasites. Early PK/PD assessment in the HuSCID mouse model, coupled with the use of the controlled human model for *Pf* blood-stage infection has identified potent compounds with rapid parasite clearance kinetics and long half lives, supporting their potential inclusion into future SERCaP regimens for malaria elimination.

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Manoj Desai, Ph.D.

Vice President, Medicinal Chemistry
Gilead Sciences

Dr. Manoj C. Desai is Vice President, Medicinal Chemistry at Gilead Sciences since 2003. He served as Divisional VP of Research at Chiron from 1994 to 2003, where he was functional head of chemistry. Prior to Chiron he was a medicinal chemist for seven years at Pfizer Central Research. Dr. Desai was a Post-Doctoral Fellow in the laboratories of Professor Herbert C. Brown and Professor E. J. Corey.

Topic

The Discovery and Development of New Antivirals

In the last thirty five years, HIV-I, the retrovirus responsible for the acquired immunodeficiency syndrome (AIDS) has gone from being a lethal disease to one treated by approved therapies. The development of single tablet regimens (STRs) has brought a substantial decrease in death rate due to HIV infection. Although the highly active anti-retroviral therapy (HAART) provides durable control of virus replication in many patients, it is not devoid of unwanted secondary effect, some of which are now surfacing in aging populations under long-term treatment. Further simplification of treatment and identification of more safer and effective drug combinations (Stribild® and Genvoya®) have been developed to improve patient adherence. At Week 96, switching to Genvoya® maintained viral suppression, and was associated with stable eGFR, reductions in proteinuria, and improvements in proximal renal tubular function, and hip and spine BMD. The talk will cover the evolution of HIV treatment since the introduction of viread in 2001.

Rahul Singhvi, Sc.D.

Chief Operating Officer, Takeda Vaccines

Rahul Singhvi, ScD, MBA, is Chief Operating Officer of Takeda's Global Vaccine Business Unit and is responsible for global supply of vaccines at the Takeda Pharmaceutical Company. Dr. Singhvi is a recognized business leader in the pharmaceutical industry and has deep experience in vaccine development and manufacturing. Before joining Takeda, Dr. Singhvi was President and CEO of Novavax, a Nasdaq-listed biotechnology company. In 2010, Novavax was named one of the ten most innovative companies in the biotechnology industry by Fast Company magazine. During his tenure at Novavax, Dr. Singhvi transformed the company from a specialty pharmaceutical business to a premier vaccine development company. Singhvi's professional career began at Merck & Co in 1994, where he held several key positions in R&D and manufacturing. At Merck, he co-lead the varicella-zoster virus vaccine project team that oversaw the development of Varivax®III (chickenpox vaccine), ProQuad® (MMRV pediatric combination vaccine) and Zostavax® (Shingles vaccine). Dr. Singhvi graduated as the top ranked chemical engineer from IIT, Kanpur, India and obtained both his MS and ScD chemical engineering degrees from MIT. He received an MBA degree from the Wharton School of the University of Pennsylvania, where he graduated as a Palmer Scholar.

Topic

Opportunities and Challenges in the Vaccine Industry

The epidemic of obesity and its associated comorbidities represents a medicinal challenge that warrants broad molecular diversity. In concert with multiple collaborators, most notably Matthias Tschoep and his associates we have pioneered the recruitment of endogenous hormones and physiological mechanisms optimized for pharmacological purposes as a means to address the broad heterogeneity constituted by the multiple diseases associated with the metabolic syndrome. From the earliest demonstration with lispro-insulin to the most recent discovery of single molecule, mixed incretin agonists we have pursued the discovery of chemically optimized macromolecules directed at the successful management of diabetes, obesity and related diseases. We have coined the term "chemical biotechnology" to reflect the integration of classical small and large molecule-based pharmacology, while advancing the chemical methodology in synthesis of complex macromolecules. The integrated biology of these peptides, proteins and nuclear hormones has provided a library of drug candidates replicated across multiple academic and commercial laboratories that have advanced to human clinical studies in metabolic diseases.

Terry Flier, MD

Professor of Medicine, Harvard Medical School
Division of Endocrinology, Beth Israel Deaconess Medical Center

Dr. Eleftheria Maratos-Flier is Professor of Medicine at Beth Israel Deaconess Medical Center, Harvard University. Her major interest is the role of the CNS in regulating feeding behavior and energy homeostasis. Her lab is focused on particular hypothalamic-striatal pathways and in particular on the role of the hormone leptin and the neuropeptide MCH in modulating motivated behavior. We integrate changes in observed behavior with changes in gene expression and signaling pathways and neuronal electrophysiology.

Topic

FGF21: physiology and therapeutic potential

Saswata Talukdar, Ph.D.

Director and Leader of CardioMetabolic Disease,
Early Discovery group, Merck

Dr. Talukdar received his B.Sc. in Chemistry and M.Sc. in Biochemistry from the University of Calcutta, India. He then moved to the U.S. and completed his Ph.D. in Biochemistry and Molecular Biology at the West Virginia University School of Medicine. He had a productive postdoctoral research period in the laboratory of Jerry Olefsky at UCSD where he published a series of high-impact papers on insulin resistance and different approaches to improving insulin sensitivity, e.g., various GPCR's including 21, 105, 120 as well as FGF21. Before joining Merck, he was Biology leader on FGF21, and led a matrixed team representing many disciplines to guide a preclinical asset through to Phase 1. He was the Biology point of contact and team member for the Ertugliflozin-Sitagliptin Phase 3 development joint project between Pfizer and Merck, and is serving the role at Merck. He has authored several publications and maintains a strong external network with KOLs through invited talks in National and International meetings. Saswata is passionate about science and committed to a career in research in an attempt to bring the next generation therapeutic to improve patients' lives.

Topic

Evolving mechanisms and continued challenges of the FGF-21 pathway as a therapeutic target

Charles F. Burant, MD, Ph.D.

Dr. Robert C. and Veronica Atkins
Professor of Metabolism, The Burant Lab,
University of Michigan Medical School

Dr. Burant's clinical interests are in the area of metabolic syndromes and management of Type II Diabetes. His research laboratory investigates the mechanisms of insulin resistance and utilizes animal models of diabetes to identify pathways important in understanding diabetes progression. Additionally, his lab also studies adult pancreatic progenitor cells and how they might be used to generate new insulin secreting β-cells.

Topic

Metabolism and metabolic aging

Roger Cone, Ph.D.

Mary Sue Coleman Director, Life Sciences Institute
Professor of Molecular and Integrative Physiology
University of Michigan

Dr. Cone's research is at the forefront of work directed toward understanding how the brain controls body weight. His research is focused not only on the normal process, but also on the pathophysiological mechanisms that lead to common obesity, severe monogenic obesity, metabolic syndrome, cachexia or disease wasting, anorexia nervosa, and other eating disorders.

Topic

Melanocortins: From Pharmacology to Pharmacotherapy

The melanocortin-4 receptor (MC4R) is an unusual G-protein coupled receptor that plays a critical role in energy homeostasis, and is a well-validated drug target for both obesity and cachexia. Attempts to develop small molecule agonists of the MC4R for obesity have been thwarted by a target-mediated pressor activity. Recently, a peptide analogue of the native a-MSH ligand was demonstrated in clinical trials in POMC null patients to produce profound weight loss with no pressor side effects (Kuhnen et al, NEJM 375, 240-246, 2016). The molecular basis for this remains unknown, and we describe here a number of aspects of melanocortin pharmacology that may allow for more systematic approaches to drug discovery. One approach involves the development and characterization of small molecule allosteric modulators of the MC4R. We show an example here, GSK3397744, of such a compound we developed, that inhibits food intake with no pressor activity. Surprisingly, a-MSH appears to couple the MC4R to both G protein signaling, and a G protein-independent pathway involving regulation of an inwardly rectifying K channel, Kir 7.1. We are currently investigating the role of biased signaling through either GaS or Kir7.1 as a second approach to differentiating the pressor and anorexic effects of MC4R signaling. Lastly, we describe an autoinhibitory pathway regulating the activity of MC4R neurons involving the presynaptic role of the melanocortin-3 receptor regulating GABA release onto MC4R neurons, suggesting MC3R antagonists may also be interesting compounds for obesity treatment. Supported by RO1 DK070332 and GlaxoSmithKline (RDC).

David J Craik, Ph.D.

Group Leader, Chemistry and Structural Biology Division,
Institute for Molecular Bioscience,
The University of Queensland

Dr. David's work focuses on Protein structure in drug and insecticide design. His research discovers and determines structural information on peptides and proteins to design drugs to more effectively treat human disease and develop natural protein-based insecticides.

Topic

Plants as biofactories for producing peptide-based pharmaceuticals

Naturally occurring cyclic peptides offer great potential as leads for drug design. This talk will focus on a class of cyclic peptides known as cyclotides, which are topologically unique in that they have a head-to-tail cyclised peptide backbone and a cystine knotted arrangement of disulfide bonds. This makes them exceptionally stable to chemical, thermal or enzymatic treatments and, indeed, they are amongst nature's most stable proteins. Because of their exceptional stability and well-defined structures cyclotides make excellent templates for drug design applications. This presentation will describe the discovery of cyclotides in plants, their structural characterization, and applications in drug design for the treatment of cancer, obesity, autoimmune disease (multiple sclerosis) and pain, as well as our efforts towards the expression of pharmaceutical cyclotides and other cyclic peptides in plant 'biofactories', particularly in Arabidopsis, tobacco and petunia.

Phil Dawson, Ph.D.

Associate Dean of Graduate Studies
Professor, Departments of Chemistry and Cell & Molecular Biology
The Scripps Research Institute, La Jolla

Dr. Dawson's research focuses on the development of synthetic tools for the chemical synthesis proteins and bioconjugation. These tools are applied to the study of protein structure and function, nanoparticles and the development of peptides and proteins designed to act as immunogens or therapeutics against pathogenic viruses.

Topic

Making connections in peptide chemistry

Chemical ligation approaches have become essential tools for the engineering of complex molecules including proteins, nucleic acids and nanoparticles. What makes these reactions so useful is their compatibility with the biological "solvent" water, and a high level of chemoselectivity that enables their application in complex molecular environments. We have worked to develop several ligation chemistries that are highly chemoselective and have sufficient ligation rates to be useful at low concentrations. The optimization of the native chemical ligation methodology, improved routes to the required peptide intermediates, and application of these methods to complex targets will be presented. We have addressed the challenge of covalent assembly of macromolecules and nanoparticles. In these systems, a "native" linkage is irrelevant and the main criteria for a successful ligation methodology are fast reaction rates and high chemoselectivity. We have found that the specific catalysis of imine type reactions enable the controlled assembly and disassembly of macromolecular complexes in aqueous solution at micromolar concentrations. The utility of these methods in projects spanning immunogen design, nanoparticles, mirror image protein and peptide therapeutics will be discussed.

Palani Palaniappan, Ph.D.

Vice President & Head,
Biologics & New Modalities Development, Takeda Pharmaceuticals

Dr. Palani is currently head of global biologics CMC at Takeda. Throughout his tenure at Takeda and previously at BiogenIdec, Gilead Sciences and Par Pharmaceuticals, he has been interested in integral approaches of drug development. He has participated in CMC development and manufacturing of a number of marketed products to help patients with debilitating diseases. Dr. Palani obtained his BS/MA from Annamalai University and PhD from IIT-Kanpur. He had also spent several years as a post-doc at Virginia Commonwealth University, Richmond, VA and University of California, Riverside, CA.

Topic

High productive cell-lines, ADC process development and challenges

In biologics development one of the key decisions to be made relates to cell line and expression system. Often, one uses a less optimized initial cell line to get the program underway into the clinic to gain speed. When POC/POM is achieved using the initial materials, there is opportunity to optimize the cell line for late stage development and commercialization. This approach -while still applicable- is somewhat outdated given the extent of development in oncology and rare diseases where quick pivotal development is necessary and possible. This discussion will examine the complex interplay of parameters that drive cell line decisions in today's development arena with some examples from speaker's own experience in this area.

Richard DiMarchi, Ph.D.

Standiford H. Cox Distinguished Professor of Chemistry, Linda & Jack Gill Chair in Biomolecular Sciences, Indiana University

Dr. DiMarchi's contributions in peptide & protein sciences consists of three decades of work in academia, the pharmaceutical industry and biotechnology companies. He is a co-founder of Ambrx, Inc., Marcadia Biotech, Assembly and Calibrium Biotech. He has served as a scientific advisor to multiple pharmaceutical companies and three venture funds; 5AM, TMP, and Twilight.

Topic

Chemical Biotechnology Applied to Metabolic Diseases

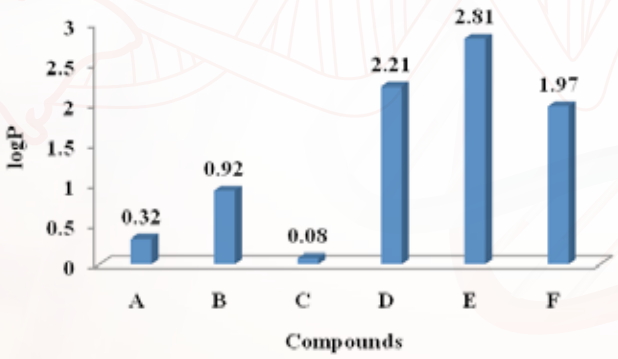
The epidemic of obesity and its associated comorbidities represents a medicinal challenge that warrants broad molecular diversity. In concert with multiple collaborators, most notably Matthias Tschoep and his associates we have pioneered the recruitment of endogenous hormones and physiological mechanisms optimized for pharmacological purposes as a means to address the broad heterogeneity constituted by the multiple diseases associated with the metabolic syndrome. From the earliest demonstration with lispro-insulin to the most recent discovery of single molecule, mixed incretin agonists we have pursued the discovery of chemically optimized macromolecules directed at the successful management of diabetes, obesity and related diseases. We have coined the term "chemical biotechnology" to reflect the integration of classical small and large molecule-based pharmacology, while advancing the chemical methodology in synthesis of complex macromolecules. The integrated biology of these peptides, proteins and nuclear hormones has provided a library of drug candidates replicated across multiple academic and commercial laboratories that have advanced to human clinical studies in metabolic diseases.

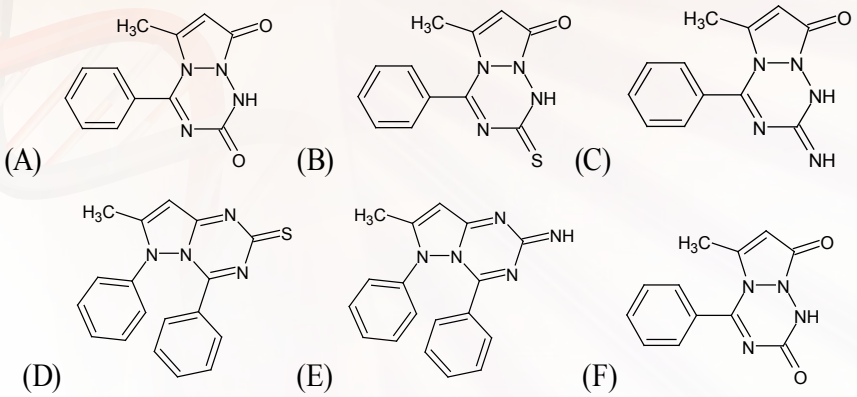
Poster Abstracts

P001. Bioisosteric synthesis and U.V. spectral behaviour of tetra-azo fused ring pyrazolo-tetrazine and pyrazolo-triazine moieties having variable hetero atoms oxygen/sulfur/ nitrogen potential for partition coefficient

Md. Abdullah Hil B. Rupak, Astha P. Sanyal, Yash B. Patel, Charmi P. Patel and Dhrubo Jyoti Sen
Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

Solubility of any organic compounds in water or organic solvent depend on the presence of functional groups having electronegative atoms like oxygen, nitrogen and sulfur either in single entity or as a functional groups. The electronegativity of these atoms is as follows O: 3.44, N: 3.04, S: 2.58 which can act as heteroatoms in heterocyclic ring also either in fused ring or single ring. Solubility profile is determined by logarithmic partition coefficient values (logP) which is the ratio of solubility of compound in organic phase and water phase. The synthesized compounds are of two series: pyrazolo-tetrazine & pyrazolo-triazine moieties having variable hetero atoms: Oxygen/Sulfur/Nitrogen which produce compounds. In pyrazolo-tetrazine ring system all four nitrogen atoms are in ring and three nitrogen atoms and subsequently placed serially whereas in pyrazolo-triazine three nitrogen atoms are in ring but in alternate positions separated by carbon atom so logP profile of pyrazolo-triazines are higher than pyrazolo-tetrazines [pyrazolo-triazines>pyrazolo-tetrazines]. The three electronegative elements are O: 3.44, N: 3.04, S: 2.58 as hetero atoms are in active part to make fused ring heterocyclic moiety of five membered with six membered due to urea (X=O), thiourea (X=S) and guanidine (X=NH). Oxygen and sulfur both have two lone pair of electrons but electronegativity of O>S and due to less electronegativity of sulfur the logP profile of sulfur derivative becomes higher than oxygen derivatives whereas in nitrogen there is one lone pair of electrons so the logP profile of nitrogen becomes more less. Logarithmic value of partition coefficient is represented as logP which is logP=log[Corganic÷Caquous]. Ratio of concentration of sample in organic phase and aqueous phase is partition coefficient and logarithm of that is logP. Molecular tailoring of tetrazine and triazine series has been divided into pyrazole+tetrazine for pyrazolo-tetrazine (logP: –1.20) and pyrazole+triazine for pyrazolo-triazine (logP: –0.77). In pyrazolo-tetrazine both nitrogen hetero atoms (1st & 2nd) of the tetrazine ring is fused with both nitrogen hetero atoms (1st & 2nd) of pyrazole [pyrazolo[1,2-a][1,2,3,5]tetrazine] and in pyrazolo-triazine one nitrogen hetero atom of triazine (5th) is fused with one nitrogen hetero atom (1st) of pyrazole [pyrazolo[1,5-a][1,3,5]triazine]. In both heterocyclic ring cases face a is common so pyrazolo[1,2-a]tetrazine and pyrazolo[1,5-a]triazine rings are generated which on tailoring produced the following fragmentation parts. Both of series of 6-methyl-4-phenyl-8H-pyrazolo[1,2-a][1,2,3,5]tetrazine and 7-methyl-4,6-diphenylpyrazolo[1,5-a][1,3,5]triazin having same hetero atoms oxgen/sulfur/nitrogen shows different logP schedule due to the presence of one phenyl ring in tetrazine and two phenyl rings in triazine nucleus: pyrazolo-triazines (logP: –0.77)>pyrazolo-tetrazines (logP: –1.20) and the lipid solubility of pyrazolo-triazines is greater than pyrazolo-tetrazines series because pyrazolo-tetrazines undergo keto-enol tautomerism due to the presence of lactam ring [cyclic amide (imide): -C(=X)-NH-; X=O/S/NH] which is not possible in pyrazolo-triazines because there is no replaceable hydrogen atom to possess keto-enol tautomerism:





(A) 6-methyl-4-phenyl-8H-pyrazolo[1,2-a][1,2,3,5]tetrazine-2,8(1H)-dione for urea (logP=0.32), (B) 6-methyl-4-phenyl-2-thioxo-1,2-dihydro-8H-pyrazolo[1,2-a][1,2,3,5]tetrazin-8-one for thiourea (logP=0.92), (C) 6-methyl-2-imino-4-phenyl-1,2-dihydro-8H-pyrazolo[1,2-a][1,2,3,5]tetrazin-8-one for guanidine (logP=0.08), (D) 7-methyl-4,6-diphenylpyrazolo[1,5-a][1,3,5]triazin-2(6H)-one for urea (logP=2.21), (E) 7-methyl-4,6-diphenylpyrazolo[1,5-a][1,3,5]triazine-2(6H)-thione for thiourea (logP=2.81) (F) 7-methyl-4,6-diphenylpyrazolo[1,5-a][1,3,5]triazin-2(6H)-imine for guanidine (logP=1.97)

logP of urea derivative of pyrazolo-triazine is greater than urea derivative of pyrazolo-tetrazine ring (2.21>0.32), logP of thiourea derivative of pyrazolo-triazine is greater than thiourea derivative of pyrazolo-tetrazine (2.81>0.92) and logP of guanidine derivative of pyrazolo-triazine is greater than guanidine derivative of pyrazolo-tetrazine (1.97>0.08). Pyrazolo-triazine series show higher values than pyrazolo-tetrazine series for all three cases of urea/thiourea/guanidine derivatives due to variable electronegativity by following the order: thiourea (S: 0.92 & 2.81)>urea (O: 0.32 & 2.21)>guanidine (NH: 0.08 & 1.97). U.V. spectrum of all six compounds showed the same parameters: thiourea moiety of pyrazolo-tetrazine and pyrazolo-triazine (612nm & 624nm)>urea moiety of pyrazolo-tetrazine and pyrazolo-triazine (522nm & 553nm)>guanidine moiety of pyrazolo-tetrazine and pyrazolo-triazine (424nm & 482nm) and each time tetrazines value is found lesser than triazines (tetrazine<triazine). Here absorbance becomes constant for all six compounds because in both series the fused ring heterocyclic rings have four nitrogen atoms so the absorbance gives 1.00 value but the wave lengths change due to logP.

P002. Simultaneous determination of metformin, saxagliptin and its active metabolite 5-hydroxy saxagliptin in human plasma by LC–MS/MS and its pharmacokinetic study in healthy Indian subjects

Priyanka A. Shah and Pranav S. Shrivastav,
School of Sciences, Gujarat Unversity, Navarangpura, Ahmedabad-380009

A reliable, specific and rapid liquid chromatography-tandem mass spectrometry method is proposed for the simultaneous determination of metformin (MET), saxagliptin (SAXA) and its active metabolite, 5-hydroxy saxagliptin (5-OH SAXA) in human plasma. Sample preparation was accomplished from 50 µL plasma sample by solid phase extraction on Phenomenex Strata-X (30 mg/1.0 mL) cartridges using sodium dodecyl sulfate as an ion-pair reagent. Reversed-phase chromatographic resolution of analytes was possible within 3.5 min on ACE 5CN (150 mm Ð 4.6 mm, 5 µm) column using acetonitrile and10.0 mM ammonium formate buffer, pH 5.0 (80:20, v/v) as the mobile phase. Triple quadrupole mass spectrometric detection was performed using electrospray ionization in the positive ionization mode to monitor the transitions at m/z 130.1 ® 60.1, m/z 316.4 ® 180.5 and m/z 332.4 ® 196.2 for MET, SAXA and 5-OH SAXA respectively. The calibration curves showed good linearity (r2 ≥ 0.9992) over the established concentration range with a limit of quantification of 1.50, 0.10 and 0.20 ng/mL for MET, SAXA and 5-OH SAXA respectively. The extraction recoveries obtained from spiked plasma samples were highly consistent for MET (75.12-77.84 %), SAXA (85.90-87.84 %) and 5-OH SAXA (80.32-82.69 %) across quality controls. The intra-batch and inter-batch imprecision did not exceed 5.4 % for all the analytes. The validated method was successfully applied to a bioequivalence study with a fixed-dose formulation consisting of 5 mg SAXA and 500 mg MET in 18 healthy subjects. The reproducibility of the assay was demonstrated by reanalysis of 87 incurred samples.

P003. Determination of Average polymer length of Polyoxyl 20 Cetostearyl Ether by FT-NMR

Jigar Gajjar, Amit Patel, R.Murugan

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Polyoxyl 20 Cetostearyl Ether is a mixture of mono-cetostearyl (mixed hexadecyl and octadecyl) ethers of mixed polyoxyethylene diols, the average polymer length being equivalent to not less than 17.2 and not more than 25.0 oxyethylene units. We have developed method on FTNMR 400 MHz. 1H spectra were recorded using Zg30 Pulprog, 30º flip angle with Relaxation delay 1 second and number of scan. The 1H chemical shift values were reported in ppm with respect to TMS Signal as Reference std.

P004. Differential scanning calorimeter: A new tool in assessment of mixing uniformity in pharmaceutical powder blend

Suchandra Bagchi, Manju Misra
National Institute Of Pharmaceutical Education and Research (NIPER)-Ahmedabad, Palaj, Opposite Air Force station, Gandhinagar-382355, Gujarat, India

The mixing of powders and granular material is of central importance for the quality and performance of a pharmaceutical product. Assessing mixing uniformity of a powder blend in pharmaceutical formulation of a low dose potent drug is a very critical step . Conventional methods like UV, HPLC which are used for content uniformity assessment are tedious in terms of process. In recent years modern experimental techniques like FT-RAMAN, FT-NIR are being widely used for online monitoring of mixing uniformity, however these are expensive techniques. Thermal analytical methods like differential scanning calorimetry [DSC] are rapid method requiring very lesser sample for quantification. In this project we have made use of enthalpy values obtained from DSC for estimation of mixing uniformity in powder blend mixed using high shear mixture granulator. Influence of various parameters like melting behavior of drug and excipients, bulk density of excipients and mixing time on the results of enthalpy values was also evaluated. The results from DSC analysis were further confirmed using HPLC analysis and a correlation was proposed between the two analytical methods. It was observed that at lower levels of drug i.e. 0.5%, 1% and 2%, the relative standard deviation values obtained using DSC were higher than that using HPLC but at concentration above 5% of drug, the results of DSC and HPLC were quite similar. It was concluded that DSC could reliably predict the uniformity of mixing in powder blend where drug loading was above 5%, however results accuracy was somewhat less below this level.

P005. Estimation of UV inactive MPEG content in Benzonatate API by LCMS

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Benzonatate is a non-narcotic oral cough suppressant, or antitussive, with effects that last from 6 to 8 hours. Since it is not an opioid, benzonatate is not as prone to abuse like some other cough medications such as codeine. MPEG (Methoxy poly ethylene glycol) chain is a structural part of benzonatate API and also a degradation product. MPEG is generally non-toxic substance. But recently cutaneous toxicity has been proved of MPEG in higher and repetitive dosage. Since MPEG is obviously present in benzonatate in some amount, it is necessary to quantify its amount. A novel method has been developed for estimation of MPEG (Monomethoxy poly ethylene glycol) in benzonatate API. PEGs are UV inactive. Hence for quantification of such impurities LCMS is a novel approach. This method is having 7 ng/mL LOD and 24 ng/mL LOQ concentrations. At LOQ level %RSD of six replicate injections was achieved 1.2% with 49 S/N ratio. The precision expressed as relative standard deviation was 1.2% for this method. Linearity expressed as Co-efficient of determination (R2) was achieved 0.9981. Also accuracy of 99.0%-103.8% was gained. This how very sensitive method to estimate trace amount of MPEG precisely and accurately in Benzonatate API was validated and successfully applied for analysis.

P006. Estimation of trace level of PGI-5 impurity in Candesartan Cilexetil API by LCMS

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Candesartan Cilexetil is Angiotensin II receptor type 1 antagonists that have been widely used in treatment of various disorders like hypertension, heart failure, myocardial infarction and diabetic nephropathy. PGI-5 is one of the impurities of Candesartan Cilexetil API. PGI-5 is N-Ethylanthranylic acid analogue impurity of Candesartan Cilexetil. PGI-5 impurity is potential genotoxic impurity. So the regulation of PGI-5 in Candesartan Cilexetil is mandatory. A sensitive and selective LCMS method has been developed for estimation of PGI-5 impurity in Candesartan Cilexetil API. The proposed method is having LOD 0.5 ng/mL and LOQ 1.6 ng/mL. At LOQ level the %RSD of six replicate injections was achieved 2.3% with 18.8 S/N ratio. This much lower LOD and LOQ levels of both method itself show the sensitivity of LCMS method in impurity quantification at trace level. The precision expressed as relative standard deviation was 6.2% for this method. Linearity expressed as Co-efficient of determination (R2) was achieved 0.9992. Also accuracy of 102.0%-105.2% was gained. This how very sensitive method to estimate trace amount of PGI-5 precisely and accurately in Candesartan Cilexetil API was validated and successfully applied for analysis.

P007. Bio-analytical method development and validation for simultaneous estimation of Aceclofenac and Drotaverine Hydrochloride in human plasma by RP-HPLC

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A simple, accurate, precise and robust RP-HPLC method has been developed for the simultaneous estimation of Aceclofenac and Drotaverine Hydrochloride in human plasma by DoE approach. The conditions were optimized by taking trials at different pH and mobile phase ratio. Kromasil C8 column (150 x 4.6 mm, 5µm) was used as the stationary phase. For the estimation of both the drugs, UV detection was done at 230 nm wavelength using mobile phase of ACN: Ammonium acetate buffer pH 3.5 (53:47 v/v) with 1ml/min of flow rate. Out of the three types of extraction procedures viz. Protein precipitation, Liquid-liquid extraction and Solid-phase extraction applied; good recovery was obtained using Solid-phase extraction and hence was selected for extraction of Aceclofenac and Drotaverine Hydrochloride from the plasma. Average recovery of the extracted sample from the plasma was found to be 71 % and 98 % for Aceclofenac and Drotaverine Hydrochloride respectively. Linearity over the concentration ranges of 30 – 9000 ng/ml and 50 – 180 ng/ml with correlation coefficient values 0.9952 and 0.9926 was obtained for Aceclofenac and Drotaverine Hydrochloride respectively. The % CV for Aceclofenac and Drotaverine Hydrochloride was found to be less than 10% and less than 5% respectively. Bio-analytical samples were found to be stable over three freeze-thaw cycles showing good stability of drugs in plasma. The bio-analytical method was validated for selectivity, linearity, accuracy, precision, stability according to USFDA guidelines and can be applicable for the pharmacokinetic profiling of these drugs in human plasma.

P008. A Critical review of an Impurity profile of major bronchodilators used in asthma

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Asthma is defined as heterogeneous disease which is usually characterized by chronic airway inflammation (GINA 2016) and it affects 334 million people worldwide (Global asthma report 2014). Bronchodilators are central in the treatment of airway disorders, especially with asthma. Impurities will mostly be present in all drug substances and products. Force degradation is used

for better understanding of active pharmaceutical ingredients and drug product stability and to provide information about degradation pathways and degradation products. The review describes the impurity profile and force degradation studies for three major classes of bronchodilators namely β2-adrenoceptor agonists, muscarinic receptor antagonists and xanthine. The impurity

profiling and forced degradation studies were discussed with name and number of impurities and

degradants present in different matrices (API or formulation). It focuses on various analytical methods including 1) Chromatographic techniques like TLC; HPTLC; HPLC; GC 2) Spectroscopic techniques like UV; IR; NMR; MS and 3) hyphenated techniques like GC-MS; LC-MS; CE-MS; SFC-MS; LC-NMR; CE-NMR; LC-FTIR for the identification and quantification of impurities and degradants. The general scheme is set up for the estimation of the impurity profile of pharmaceuticals including active pharmaceutical ingredient as well as drug products.

P009. Impurity profiling of Vardenafil by LC-MS/MS by applying QbD approach

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Quality by design approach is a systematic concept for separation of all degradation peaks in impurity profiling. QbD approach for impurity profiling reduce time, cost and chance of rejection. Boxbehnken design to optimize % degradation shows that 1.4 N HCl, 45 ºC for 10 hr and 1 N NaOH, 60 ºC for 11 hr get 20-25 % degradation of drug but no specific degradation peak was observed. Screening was done using Plackett-Burman design and CCD (central composite design) was applied for optimization of the final condition. Optimized condition was A: ACN: Water (100: 400, v/v), pH adjusted to 4.7; B: ACN: Water (300: 200, v/v) with gradient method, flow rate 0.6 mL/min, 239 nm at 20 ºC. Stress studies and the kinetic study shows that VR is liable to degradation which follows first order kinetic. The degradation behavior of VR in different stress conditions was evaluated by LC-MS/MS, it shows five degradation products during sunlight degradation. Different degradation product structures were confirmed by fragmentation pattern studies of VR by MS/MS. The probable mechanism of degradation of VR was derived for different stress degradation conditions. From stability study can conclude that Vardenafil is more liable to sunlight and peroxide with compare to hydrolysis so special precaution is require during handling and packaging. The developed stability indicating method was applied for marketed formulation and validated as per ICH guideline.

P010. Impurity profiling of Avanafil by LC-MS/MS by applying QbD approach

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Quality by design approach is a systematic concept for separation of all degradation peaks in impurity profiling. QbD approach for impurity profiling reduce time, cost and chance of rejection. Boxbehnken design to optimize % degradation shows that 1.2 N HCl, 70 ºC for 9 hr and 1 N NaOH, 60 ºC for 11 hr get 20-25 % degradation. Screening was done using Plackett-Burman design and CCD (central composite design) was applied for optimization of the final condition. Optimized condition was 10 mM ammonium acetate: ACN (60:40, v/v), pH 4.5, flowrate 0.9 mL/min, 239 nm and 20 ºC. Stress studies and the kinetic study shows that AV is liable to degradation which follows first order kinetic. The degradation behavior of AV in different stress conditions was evaluated by LC-MS/MS, it shows 14 degradation products from which, DP 3 was major degradant. Different degradation product structures were confirmed by fragmentation pattern studies of AV by MS/MS. The probable mechanism of degradation of AV was derived for different stress degradation conditions. From stability study can conclude that Avanafil is liable to light, hydrolysis and temperature so special precaution is require during handling and packaging. The developed stability indicating method was applied for marketed formulation and validated as per ICH guideline.

P011. Development and validation of HPTLC method for Simultaneous estimation of Andrographolide, Gallic acid and Kutkin in HEPASAVE syrup: A Polyherbal formulation

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A new, simple, accurate, sensitive, precise, reproducible and robust High-performance thin layer chromatography (HPTLC) method was developed using a Poly-herbal formulation, HEPASAVE Syrup (Cadila Pharmaceutical Ltd.). Hepasave syrup, an Ayurvedic Proprietary

Medicine which is used particularly as a Powerful Hepato-protective, an Antioxidant, and a Bitter tonic. The herbal constituents of the formulation include Amalaki, Haritaki, Bibhitaki, Vasa, Bhunimba, Katuka, Nimba, Amruta, Galo, Sarpankha and also a flavored syrup base. Present investigation includes simultaneous estimation of three biomarkers namely Andrographolide (AG), Gallic acid (GA) and Kutkin (KT) using HPTLC method. Different extracts has been prepared to check for presence of active phytoconstituents. The quantification of the three biomarkers was performed on a TLC aluminium plates pre-coated with silica gel 60F254 as stationary phase and using mobile phase saturated with Toluene: Ethyl acetate: Formic acid: Methanol (3:3:0.8:0.4, v/v/v/v) at room temperature (25 ± 2 º C). Camag TLC scanner III was used for simultaneous spectro-densitometric scanning and analysis in absorbance mode at 254nm. The system was found to give compact spots for Andrographolide, Gallic acid and Kutkin with the respective Rf value of 0.72, 0.61 and 0.17. The amount of AG, GA and KT in the formulation were quantified and were found to be 1.27 %w/v, 1.15 %w/v and 0.014 %w/v, respectively. The amount of Andrographolide, Gallic acid and Kutkin in the prepared extract were found to be 7.6 %w/v, 6.92 %w/v and 0.22 %w/v, respectively. The present method was validated by linearity, accuracy, precision according to ICH guidelines.

P012. Effect of Acute renal failure on the pharmacokinetics of ciprofloxacin, a renally excreted drug and fasiglifam, a hepatobiliary transported drug of the Paper

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The aim of this study was to investigate the effects of cisplatin induced acute renal failure (ARF) in rats on the pharmacokinetics of ciprofloxacin and fasiglifam, whose disposition is governed by renal and hepato-biliary routes, respectively. Twenty four male Sprague-Dawley rats (normal and ARF rats, n=3/ route) were dosed with ciprofloxacin at 5 mg/kg via oral and 1 mg/kg via intravenous bolus route of administration and fasiglifam was dosed at 3 mg/kg via oral and 1 mg/kg via intravenous bolus route of administration, separately. Plasma sample ware collected and analyzed using LC-MS/MS methods and pharmacokinetic analysis was performed by Phoenix (Pharsight) software using non-compartmental model. Following oral administration of ciprofloxacin in ARF rats, bioavailability was 3.3 fold higher than that in normal rats (79% versus 24%). Total plasma clearance (Cl/F) was drastically decreased in ARF rats to 3.48 fold of the normal rats (55.8 versus 194.3 mL/min/kg) and oral half-life (t1/2po) was 1.85 fold longer in ARF rats than that in normal rats (3.6 versus 1.9 h). Following oral administration of fasiglifam in ARF rats, bioavailability was slightly decreased to 0.75 fold than that in normal rats (57% versus 76%). Plasma clearance (Cl/F) was increased in ARF rats to 1.55 fold of the normal rats (1.4 versus 0.9 mL/min/kg) and oral half-life (t1/2po) was 1.51 fold longer in ARF rats than that in normal rats (8.6 versus 5.7 h). Cisplatin-induced ARF significantly enhanced the bioavailability and decreased the plasma clearance of renally cleared ciprofloxacin. However, the decreased oral bioavailability of fasiglifam in ARF rats suggested that hepato-biliary disposition may be altered .and therefore, warrants further investigation to probe underlying mechanism.

P013. Stability indicating RP-HPLC method development and validation for simultaneous estimation of omeprazole and cinitapride in capsules

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A simple Stability indicating RP-HPLC method was developed for the simultaneous estimation of Omeprazole and Cinitapride from their Pharmaceutical dosage form in presence of degradation products. Stationary phase used was Hypersil BDS C18 column (150 mm x 4.6 mm, 5µm). The separation was achieved using mobile phase containing Methanol: 0.02M Potassium Dihydrogen Phosphate buffer (pH 6.8) (60:40 v/v). The flow rate was 1.0 ml/min. The retention times of Omeprazole and Cinitapride were found to be 6.56 and 2.83 min, respectively. The total run time was 10 min within which two active compound and their degradation products were separated. Acid, Base, Peroxide, Thermal and Photolytic degradation was carried out and significant degradation was achieved. The method was found to be specific enough to separate degradation products from main analyte. The method was linear in the range of 20-140 µg/ml (r=0.9997) and 3-21 µg/ml (r=0.9992) for Omeprazole and Cinitapride, respectively. The described method was validated with respect to specificity, linearity, accuracy, precision, LOD and LOQ. Result of each parameter was

met with its acceptance criteria. So it was concluded that the method is found suitable for analysis of two drugs in presence of their degradation products.

P014. Analytical Method Development and Validation for Estimation of Vitamin E Acetate from Multi - Vitamin Dosage Form Using Quality by Design (QbD) Approach

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A simple RP-HPLC method for determination of vitamin E acetate from multivitamin tablet dosage form has been developed and validated using Quality by Design approach. Vitamin E acetate extraction from multi-vitamin dosage form was carried out using n-hexane and dimethyl sulfoxide. The chromatographic separation was achieved using Partisil ODS-3 (100 mm Ð 4.6 mm, 5µ) column using the mobile phase consisting of methanol: acetonitrile:1% OPA in water (75:20:5). The flow rate was 1.0 mL/min and effluent was detected at 254 nm. The retention time of vitamin E acetate was 6.96 min. Quality by Design approach was applied to reduce the development trials for optimization of analytical method. Miscellaneous response surface methodology was applied using Design Expert software. Column temperature and acetonitrile composition in mobile phase were two critical parameters considered for QbD. The response was measured in terms of number of plates and retention time of vitamin E acetate. Contour plot and 3D surface graphs were obtained from software. Peak purity spectra indicated the absence of co-eluting peaks with the main peak of vitamin E acetate. The method was validated using ICH guideline. Linearity of the method was found to be in the range of 0.03 – 0.09 IU. Correlation coefficient (r2) obtained was 0.9993. Values of all the other parameters were within the prescribed limits.

P015. PAT (Process Analytical Technology) in pharmaceutical development

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Pharma industry goal is to improve formulations so as to provide patients innovative and more efficient solutions, and thus achieve commercial break through. For this, improvements in existing technologies are required. The emerging Process Analytical Technologies (PAT) strategy is to guide the drug industry in achieving various goals. PAT are used to provide and inform timely analysis of significant quality parameters with the end goal of improving final product quality as well as reducing manufacturing costs, thereby significantly benefiting the Pharmaceutical Industry in manufacturing area. The potential for improved operational control and compliance resulting from continuous real-time quality assurance was highlighted as a likely benefit that would result from PAT implementation. Materials made within the design space will produce an acceptable product, and the changes within the design space are (regulatory) acceptable. These same principles and concepts have been applied to the development of analytical methods, and termed Analytical QbD (AQbD). The first steps in an Analytical Quality-by-Design (AQbD) method development include understanding the analysis needs (e.g., purpose, specificity, sensitivity, cycle time, on-line/off-line, qualitative/quantitative, accuracy, precision) and selection of the technique that will meet these criteria. One set of analytical tools applied during the development and scale-up of drug substances and dosage forms include in-situ analytics, chemometrics and modeling i.e., Process Analytical Technology (PAT) tools. PAT provides better knowledge of raw materials, manufacturing parameters and their impact on finished product quality. This will result in a more robust process, better products, and a huge cost savings for the manufacturer.

P016. Stability indicating method development and validation for related substance of atazanavir sulphate capsule by RP-HPLC by using QbD approach

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The concept of quality by design (QbD) is not new to the pharmaceutical industries; it has been widely accepted and applied in Pharmaceutical manufacturing industry. But when we deal in terms of analytical chemistry it has proven its worth in developing a robust and accurate method. Various Analytical target profile (ATP) were identified and design of experiment was generated using Design Expert 10. The Stability indicating method was developed for Atazanavir Sulphate, a protease inhibitor, using RP-HPLC by QbD approach. Forced degradation study was performed on capsule dosage form under acid, alkaline, oxidative, UV radiation, thermal and degradation of Atazanavir sulphate was observed under acidic, alkaline and oxidative conditions. Further, validation of the method was performed. And it was concluded that this method can be applied for routine quality control of Atazanavir sulphate in capsule dosage forms as well as in bulk drug.

P017. A simple method for isolation and estimation of marmelosin from Aegle marmelos

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Aegle marmelos, commonly known as Bael belonging to the family Rutaceae, is amoderate-sized, slender, aromatic and indigenous tree of India. The ancient systems of medicine, including Roman, Ayurveda, Greek, Siddha and Unani have mentioned its therapeutic applications in cardiovascular disorders, diabetes, diarrhoea and dysentery. Phytochemical screening of Aegle marmelos fruit revealed the presence of Alkaloids, Tannins, Carbohydrates, Coumarin and Steroids. Marmelosin, a coumarin, was isolated from the fruit of Aegle marmelos, which was characterized by various spectroscopic methods (i.e UV, IR, Mass Spectroscopy). HPTLC method was developed for the quantification of marmelosin. The mobile phase optimized was Toluene: Ethyl acetate (80:20 v/v) which gave good resolution for marmelosin at Rf 0.66±0.03. The separation was followed by detection of marmelosin at 310nm using Camag TLC scanner 3 with CATS4 software. The linearity was found to be within range 100-300 ng/spot. The correlation coefficient was 0.9994.The LOD and LOQ were found to be 8.70 ng/spot and 26.4 ng/spot respectively. The method was validated according to the ICH guidelines. The proposed method was further applied for estimation of marmelosin in fruit extract of Aegle marmelos and Ayurvedic formulations containing Aegle marmelos.

P018. Development and validation of stability indicating assay method for anti-Parkinson drugs in tablet dosage form by RP-HPLC

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An approach for the forced degradation study has been applied for the development of assay method for determination of Levodopa, Carbidopa and Entacapone in the formulation in presence of its degradation products. The separation was achieved on a Inertsil ODS-3 column (100 mm x 4.6 mm, 5 µm), at 40°C by using a mobile phase consisting of Buffer of pH 2.0: Acetonitrile: Isopropyl alcohol (78:12:10, v/v/v) at a flow rate of 1.5 ml/min, and UV detection at 225 nm. In the present study, comprehensive stress testing of Levodopa, Carbidopa and Entacapone was carried out according to ICH guideline Q1A (R2). Drugs were subjected to acid hydrolysis, alkali hydrolysis, oxidation and dry heat to apply stress conditions. There were no other co eluting, interfering peaks from excipients, impurities or degradation products due to variable stress conditions, and the method is specific for determination of Levodopa, Carbidopa and Entacapone in the presence of degradation products. Degradation products produced as a result of stress studies did not interfere in the estimation of Levodopa, Carbidopa and Entacapone. The method was linear in the range of 80-240 µg/ml (r = 0.9993), 20-60 µg/ml (r = 0.9987), 80-240 µg/ml (r = 0.9988) for Levodopa, Carbidopa and Entacapone respectively. The method was validated in terms of system suitability, linearity, precision, accuracy, specificity and robustness. It was concluded that the method is fast and is suitable for the high-throughput analysis of these three drugs in presence of degradation products.

P019. Development and validation of stability indicating RP-HPLC method for estimation of Paliperidone in tablets

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Stability of the pharmaceutical product is most important, so that work was carried out to develop a new, simple, precise, accurate, validated stability indicating RP-HPLC method for estimation of Paliperdone. A gradient RP-HPLC method was developed for related substances of Paliperdone. Stability indicating RP-HPLC method for estimation of Paliperdone was carried out by using Buffer (pH6.7): Acetonitrile: Methanol in the ratio of (600:250:150) %v/v/v as the mobile phase and Zorbax Extend C18, 150x4.6mm, 5µ Agilent) column as the stationary phase with detection wavelength of 279 nm. Flow rate was 1.5 ml/min. A gradient RP-HPLC method for related substances of Paliperdone was developed by using mobile phase A: Buffer (pH6.7) and mobile phase B: Methanol as mobile phase and X BridgeTM C18, 150x4.6mm, 5µ column used as the stationary phase with detection wavelength of 279 nm. Flow rate was 1.0 ml/min. Retention time for Paliperidone was 4.9 min. Linearity was obtained in the concentration range of 15-75 µg/ml. Recovery study was performed to confirm the accuracy of methods. The assay method was validated as per ICH guidelines. All the impurities were well resolved from the Paliperidone. Among the four known impurities of Paliperidone, IMP.C and IMP.D was may found to be degradent in acid degradation peroxide degradation and thermal degradation. Good resolution between the peaks corresponding to degradation and process related impurities from the analyte were achieved.

P020. Stability indicating method development and validation for simultaneous estimation of nicotinamide and salicylic acid

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Nicotinamide is anti-inflammatory agent. Salicylic acid is anti-fungal agent, anti-infective agent and keratolytic agent. Nicotinamide and Salicylic acid combination is used for treatment of pimples, oily skin and also for acne and blemish prone skin. Stability indicating reverse phase high performance liquid chromatography method was developed and validated for Nicotinamide and Salicylic acid because not a single method was reported for the same combination. The wavelength selected for quantitation was 226nm. The separation was achieved using Chromatopak C-18 (250mm x 4.6 mm, 5 µm) column, mobile phase containing Methanol and Water (0.1% TEA and 0.15 gm Hexane sulphonic acid and pH 3.0 adjusted with Glacial acetic acid) in the ratio of (40:60 v/v), at a flow rate of 1.0 ml/min. The retention time for Nicotinamide and Salicylic acid was 4.343 min and 17.673 min respectively. During force degradation, drug products were subjected to hydrolysis (acid and base hydrolysis), oxidative degradation, thermal degradation and Photo degradation. The % degradation was found to be 10 to 20% for both Nicotinamide and Salicylic acid in the given condition using developed RP- HPLC method. The method specifically estimates both the drugs in the presence of all the degradants generated during forced degradation study. The method was validated as per ICH guidelines. The linearity was observed in the concentration range of 225-315 µg/ml for Nicotinamide and 75-105 µg/ml for Salicylic acid. The correlation coefficient was found to be 0.9971 and 0.9985 for Nicotinamide and Salicylic acid respectively. The developed method was specific and precise and can be used for simultaneous estimation of Nicotinamide and Salicylic acid.

P021. Method development and validation for isomeric separation of xylidine and its estimation in pharmaceutical dosage form

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A sensitive high performance liquid chromatographic method was developed and validated for separation and estimation of xylidine toxic impurities in Lidocaine hydrochloride. Xylidine isomers have very toxic effects like genotoxicity, hepatotoxicity and nephrotoxicity hence the impurities of xylidine isomers in Lidocaine above the genotoxic limit can be life threatening. Applying the concept of threshold of toxicological concern, a limit of 5 ppm for each xylidine isomeric impurities were calculated based on maximum daily dose of drug. Efficient chromatographic separation was achieved on Fortis Biphenyl column (150mm x 4.6mm id, 5µm particle size) using mobile phase composed of Formic acid 0.1% (pH adjusted to 4 with Triethylamine) : Acetonitrile (70:30 v/v), at 1ml/min flow rate & eluent was monitored at 210nm. The retention time of 2,4xylidine, 2,5xylidine and 2,6xylidine were found to be 6.172, 8.104 and 9.808min respectively. The developed method was validated as per ICH guideline. Linearity was

established for xylidine isomers in range of 0.125 to 1µg/ml. The limit of detection for 2,4xylidine, 2,5xylidine and 2,6xylidine were 0.016, 0.013 and 0.015 respectively. The limit of quantitation for 2,4xylidine, 2,5xylidineand and 2,6xylidine were 0.048, 0.041 and 0.047 respectively. The %recovery of 2,4xylidine, 2,5xylidine and 2,6xylidine were found in range of 97.4-103.8%, 94.6-100.4% and 97.9-100.4% respectively. The validated method is suitable for routine quantification of impurities in Lidocaine hydrochloride in pharmaceutical dosage form.

P022. Development and Validation of Stability Indicating HPLC Method for Simultaneous Estimation of Acetaminophen, Chlorpheniramine Maleate and Phenylephrine in Tablet Dosage Formulation

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A new stability indicating high performance liquid chromatographic (HPLC) method was developed for the determination of acetaminophen, phenylephrine hydrochloride, and chlorpheniramine maleate in combined pharmaceutical tablet dosage forms. Different pure solvents with different proportions are tried as mobile phase for the development of method. The separation of all individual peaks was achieved on Synergy 4 µ Hydro-RP 80A (250mm x 4.6µ m), C18 column, using gradient elution of buffer(1ml T.F.A in 1000 ml water) : (mobile phase A) and acetonitrile (mobile phase B) at flow rate of 0.8 ml/min and quantification was achieved by PDA detector at wavelength 275nm with the total run time of 22 min. Retention time of phenylephrine hydrochloride was found at 3.2min, acetaminophen at 4.7 min and chlorpheniramine maleate found at 10.6 min. As results optimum retention time and good resolution obtained with appropriate tailing factor. The method was validated with respect to linearity, precision, accuracy and recovery. Further, degradation studies of the method was performed. Forced degradation of analytes was carried out under acidic, basic, oxidative, thermal and humidity conditions. This simple, fast, economical and precise high performance liquid chromatographic method can be adopted for routine quality control analysis. The method was found to be specific enough to separate degradation products from main analytes.

P023. Skin Permeation Estimation Using Fluorescein Sodium as a Marker and its Enhancement Using Fulvic Acid

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In cosmetic industry majority of the products have site of application on the skin, therefore skin penetration enhancers are important class of ingredients for the industry. Skin penetration enhancers have been used to improve bioavailability and increase the range of actives to be administered by topical and transdermal route. Considering the same the attempt has been carried out to enhance the permeation of Fluorescein sodium using Fulvic acid (FA). An O/W cream base was formulated incorporating Fluorescein sodium as an active. Other batches were prepared which contained Fulvic acid in different concentrations (2mg, 4mg,6mg,8mg) while Fluorescein sodium was constant in all the batches. Permeation study was performed using osmosis membrane of prepared batched. The blank batch which did not contain FA showed 19% penetration of Fluorescein sodium. Whereas batches which contains 2mg, 4mg, 6mg, and 8mg of FA shows penetration of 33%, 38%, 20% and 22% respectively. Batch of cream containing 4mg of FA showed maximum permeation and it was selected as optimized batch. Furthermore, the permeation study was carried out on Goat skin using optimized batch along with blank batch. The result of permeation study on Goat skin showed similar results, 39% penetration in blank cream whereas cream containing 4mg FA showed highest amount of permeation i.e. 77%. Hence we can conclude that Fulvic acid can be used as a permeation enhancer.

P024. Smart piezoelectric nanofibrous scaffold for cartilage regeneration

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Piezoelectricmaterials are considered as smart materials owing to transduce the applied mechanical

pressure into electrical signals and vice-versa. The cartilage regeneration and repair is a major challenge till date due to its complex structure. Present study has been carried out to give augmented tissue regeneration at rapid manner. Piezoelectric mechanism is utilized to stimulate the cartilage regeneration without addition of stimulating factors. Optimum piezoelectric coefficient is achieved by blending of polymer PHBV (poly-(3-hydroxybutyrate-co-3-hydroxyvalerate). Scaffolds are prepared by electrospinning technique to mimic the natural cartilage like structure. The scaffold has shown suitable mechanical and physical properties (degradation and hydrophilic) to withstand when scaffold is subjected to functional loads and cellular interactions, respectively. Furthermore, scaffolds are subjected to corona poling to develop surface charge density by strong electric field. In-vitro cell culture studies are performed to evaluate the biological activity of the scaffolds. The poled scaffolds have been demonstrated enhanced chondrocyte cell adhesion, proliferation and viability compare to un-poled samples. Therefore, the novel concept based on piezoelectric effect is definitely a breakthrough for cartilage regeneration therapy.

P025. Use of differential scanning calorimetry in predicting interaction in a four drug antiretroviral drug combination for paediatric application

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World Health Organization consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in the pediatric population recommends a 4-in-1 dosage regimen of zidovudine, lamivudine, lopinavir and Ritonavir as one of the urgently needed formulations. However currently there are no 4 drug child-friendly combinations like sprinkles or granules commercially available to reduce the pill burden on children. An important parameter in developing the four drug combination will be drug -drug compatibility. Differential Scanning Calorimetry (DSC) is a useful tool to estimate the drug- drug compatibility which has been used persistently for many years. In this study, DSC was performed for physical mixture of dual, triple and quadruple combinations of the mentioned drugs and thermal behaviour of the mixture was used to predict the likely probability of drug interacting with each other, which in long run may lead to incompatibility. The DSC curves for zidovudine-lamivudine combinations showed a shift in the melting point of lamivudine towards a lower side and broadening of the endothermic event. There was also an overlapping of peaks for zidovudine-ritonavir combination. Among the triple drug combinations, events corresponding to Ritonavir+lopinavir+lamivudine could be only observed clearly. While in all triple drug combinations containing zidovudine with lamivudine in addition to a third drug, there was shift in the melting point of lamivudine towards lower side and broadening of the endothermic event. In combinations of zidovudine and ritonavir a single peak corresponding to both these drugs was seen in the triple drug combinations as well. The four drug combination of all these drugs showed these above mentioned features like shifting of lamivudine peak to a lower side along with its broadening, a combined single peak corresponding to zidovudine and ritonavir. It would be worth investigating that whether these observations would end up into incompatibilities in the formulation.

P026. Development and validation of stability indicating assay method development for Betulinic acid using High performance liquid chromatographic technique

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A simple, selective, precise stability indicating high performance thin layer chromatography and high performance liquid chromatography of isolated Betulinic acid was developed and Validated. The stability indicating HPLC method was developed and validated for quantification of Betulinic acid in different forced degradation conditions. Optimized mobile phase was used Acetonitrile: Water (93:7). The method is based on high performance liquid chromatography using Purosphere® STAR, Reversed Phase (C-18, 250mm Ð 4.6mm, 5µm) column. Detection was carried out at 207nm wavelength. The Rt value of isolated Betulinic acid was 7.55 ± 0.1. The linear regression analysis data for the calibration plots showed good linear relationship with r= 0.999 with respect to peak area in the concentration range 20-90 µg per ml. The method was validated for precision. The limit of detection and

quantification were 0.3631 µg per ml and 1.101 µg per ml, respectively. Isolated Betulinic acid was subjected to acid and base hydrolysis, oxidation, photo degradation, and thermal degradation. The drug undergoes degradation under oxidation, acidic and basic conditions. This indicates that the drug is susceptible to acid hydrolysis, base hydrolysis and oxidation. As the methods could effectively quantify the isolated Betulinic acid in different forced degradation conditions, it can be employed as stability indicating method.

P027. Analytical Development and Validation of Stability Indicating HPLC Method for Estimation of Dolutegravir in Tablet Dosage Form

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A Simple, accurate, specific and rugged reverse phase liquid chromatographic method was developed and validated for the estimation of Dolutegravir in tablet dosage form. In the HPLC method, analysis of the drug was carried out on the X bridge C18,150 mm x 4.6 mm, 5 µm column using a mixture of acetonitrile: phosphate buffer (pH 6.5) in the ratio of 70:30 v/v as the mobile phase at the flow rate 1.2 mL/min. Column oven temperature was 35°C and the column eluent was detected by using UV detector at detection wavelength 258 nm. The retention time of Dolutegravir was found to be 8.3 and linearity of the method was found to be between 5-15 µg/mL. The method was validated as per ICH guideline and applied successfully for the estimation of Dolutegravir from tablet formulation.

P028. Get slim to fulfill the dream

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Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. People are generally considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight by the square of the person's height, is over 30kg/m^2, with the range 25–30kg/m^2 defined as overweight. Overweight is having extra body weight from muscle, bone, fat and/or water. Obesity is having a high amount of extra body fat. Body mass index (BMI) is a useful measure of overweight and obesity. Talk to your health care provider if you are concerned about your BMI. Many factors can contribute to a person's weight. These factors include environment, family history and genetics, metabolism (the way your body changes food and oxygen into energy), and behavior or habits. Energy balance is important for maintaining a healthy weight. The amount of energy or calories you get from food and drinks (energy IN) is balanced with the energy your body uses for things like breathing, digesting, and being physically active (energy OUT):

The same amount of energy IN and energy OUT over time=weight stays the same (energy balance) More energy IN than OUT over time=weight gain; More energy OUT than IN over time=weight loss

To maintain a healthy weight, your energy IN and OUT don't have to balance exactly every day. It's the balance over time that helps you maintain a healthy weight. You can reach and maintain a healthy weight if you: Follow a healthy diet, and if you are overweight or obese, reduce your daily intake by 500 calories for weight loss. Limit the time you spend being physically inactive.

BMI(kg/m^2)		**Classification**
From	**Upto**	
0	18.5	Underweight
18.5	25.0	Normal or Healthy Weight
25.0	30	Overweight
30.0	35.0	Class I Obesity (Severe Obesity)
35.0	40.0	Class II Obesity (Morbid Obesity)
40.0	More	Class III Obesity (Super Obesity)

BMI (body mass index) is a common measurement used to determine whether you are at an appropriate

weight. It is calculated using your height and weight. The Centers for Disease Control and Prevention reports that a BMI of 18.5-24.9 is healthy. A BMI between 25 and 29.9 is considered overweight and over 30 is obese. Reducing BMI requires losing weight through a healthy diet and exercise. While quick weight loss is possible, it's not recommended: It can slow your metabolism and compromise your health. Health experts recommend a weight loss of 1-2lbs/week.

Diet to Lower BMI:

Step 1: Reduce your calories. Eating more food than your body needs leads to weight gain and a higher BMI. The more calories you cut, the faster you'll lose weight; however, don't go on a strict diet. Too few calories can slow your metabolism and prevent weight loss. Women should have at least 1,200 calories and men 1,500 calories a day.

Step 2: Cut sugar and processed foods from your diet. These foods have little to no nutritional value and can add weight even if you keep your calories low, according to the National Institute of Health.

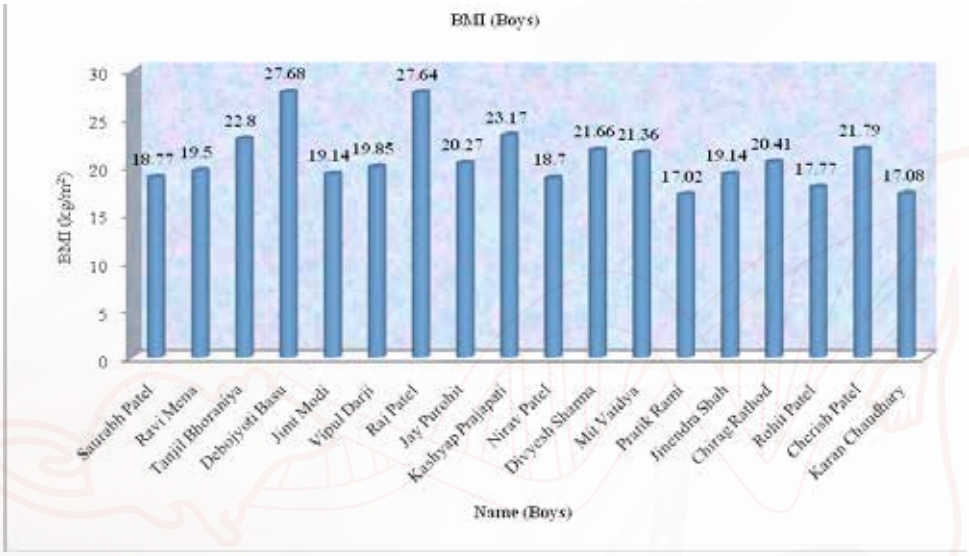
Step 3: Eat fresh, whole foods, recommends a diet of lean proteins, low-fat dairy, fresh vegetables and fruit and whole grains.

Exercise to Lower BMI:

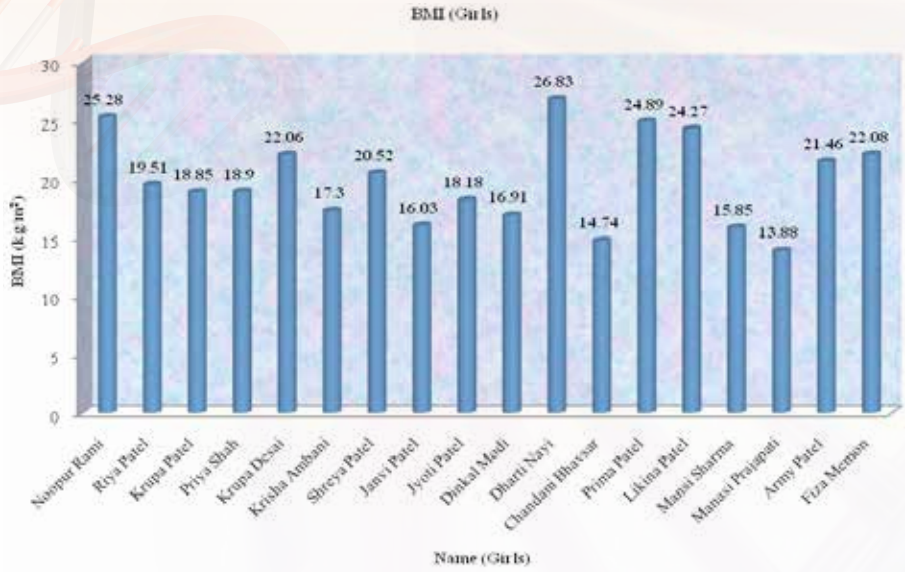
Step 1: Exercise 60 minutes five days a week. The Centers for Disease Control reports that 30 minutes of aerobic exercise is acceptable for health, but 60 minutes is best for weight loss and lowering BMI. Choose activities you enjoy that increase your heart rate such as bicycling, tennis or aerobic dance.

Step 2: Perform resistance training twice a week. Resistance training builds muscle, which helps you burn more calories and speeds up your metabolism. Perform exercises that target the major muscle groups including the legs, glutes, abs, back and arms.

Step 3: Increase your activity throughout your day. Taking the stairs instead of the elevator and parking away from your destination to walk farther will burn calories to help you lose weight and lower your BMI. Other ways to fit activity in your day include standing instead of sitting and going for a walk instead of watching television.



BMI Histogram (Boys)



BMI Histogram (Girls)

Tips: Get at least six but no more than eight hours of sleep every night. The National Institute of Health reports that people who got less than six hours or more than eight hours of sleep were more likely to gain weight. Body mass is developed by bones, muscles and fat. Entire body is structured on the framework on bones (skeleton), muscles (various organs) and fat (adipose tissues) and body weight and height depends on all three factors. BMI∞mass and BMI∞1÷height2; so BMI is directly proportional to body mass and inversely proportional to height2. OBESITY & SLIMFIT both have seven letters in each which gives indication to enjoy another word VIBGYOR of seven letters to enjoy colorful life.

P029. Design, synthesis and evaluation of antidiabetic activity of new substituted alkyl carboxylic acid derivatives

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Diabetes is one of the largest global health emergencies of 21st century. According to the IDF Diabetes Atlas 2015, India is home to the second largest number of adults living with diabetes. Current treatments such as metformin, sulfonylureas etc. are deployed primarily to either improve insulin secretion, peripheral insulin sensitivity, or both. In the development of novel insulinotropic agent, GPR40/FFA1 is attractive target because, GPR40 agonists can directly increase Ca^{2+} concentrations in pancreatic β-cells enabling a robust insulinotropic effect, mediate insulin release which is glucose-dependent, hence low risk of hypoglycemia and restore or preserve islet cell function. In the current study, a novel series of substituted alkyl carboxylic acid derivatives (101-109 & 201-209) were synthesized and their anti-diabetic activity was evaluated using in-vitro assays. The synthetic compounds consist of three different substructures. Every sub structural part was optimized keeping other parts static. The structures of the compounds were confirmed by 1H-NMR, 13C-NMR, FT-IR, and LC-MS. Among all the synthesized derivatives some compounds showed moderate alpha amylase and alpha glucosidase inhibition. ADME profiling of the synthesized derivatives was also done using Schrodinger software. Results of this study suggests that these synthetic compounds can serve as novel molecular templates for construction of potentially anti-diabetic drugs.

P030. Novel cyclic sulfite Containing GPR119 agonists as anti-diabetic agents

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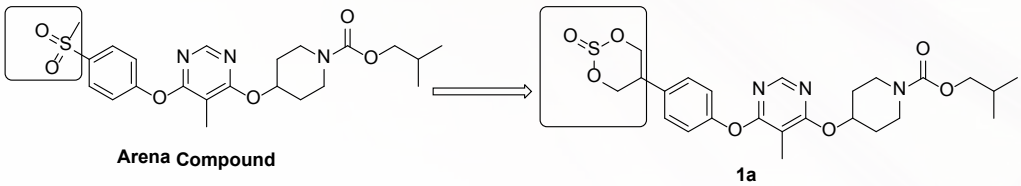

GPR119 is increasingly seen as an attractive target for the treatment of type II diabetes and other elements of the metabolic syndrome. During a programme aimed at developing agonists of the GPR119 Receptor, we identified a series of novel compounds containing cyclic sulfite as a replacement for methane sulfonyl group in a known chemo type. The lead compound 1a exhibited both in-vitro potency in a cell based assay and in-vivo efficacy in relevant animal models. Further exploration of this novel class of compounds is in progress.

P031. High salt diet evokes Cardiovascular and Renal dysfunction in Uninephrectomized rats: Involvement of Renin-Angiotensin System and microRNAs

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In live kidney donors, no major adverse cardiovascular and renal events were reported. High salt intake leads to cardiovascular and renal complications in binephric (normal) scenario in both pressure-dependent and independent manner. Data depicting the effect of high salt diet on the quality of life of live kidney donated people is miniscule. Hence, the present study was planned to determine the effect of high salt diet on the cardiovascular and renal functions of uninephrectomized rats. Male Sprague Dawley rats (200-250g) were uninephrectomized, initially fed normal pellet diet (NPD) for 12 weeks to exactly mimic the clinical setting and then for 20 weeks with high salt diet (10% w/w NaCl). Biochemical, functional and histological measurements, western blotting and RT-qPCR were carried out. High salt diet impaired cardiac and renal architecture & functions, increased in-vivo cardiovascular reactivity to angiotensin II owing to enormously increased angiotensin II type 1 receptors and L-type calcium channels, in uninephrectomized rats. SERCA, p-AMPK decreased and p-AKT increased and the microRNAs-25, -155, -99b, -451 regulating these proteins also altered significantly in the heart of these rats. Cardiovascular and renal functions, which were unchanged in uninephrectomized rats, were worsened with the high salt dietary intervention. Cardiac dysfunction and remodeling involved activation of cardiac renin-angiotensin system and AKT; altered SERCA, p-AMPK and miR-25, -155, -99b, -451. This study highlights the harmful effects of high salt and suggests the restriction of salt intake in live kidney donors besides normal (binephric) people and showcases miRNAs as novel diagnostic and therapeutic targets.

P032. Novel Sulfonamide Derivatives as Potent TGR5 Receptor Agonists

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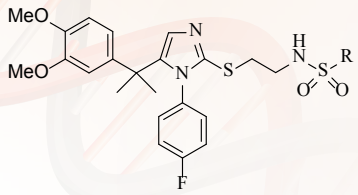

Takeda G-protein receptor 5 (TGR5), also known as G protein bile acid receptor 1 (GPBAR1), activation of which has been shown to play a key role in pathways associated with diabetes, metabolic syndrome, and autoimmune disease. TGR5 receptor belongs to the family of G-protein coupled receptor (GPCR). A novel series of sulfonamide derivatives were synthesized as potent agents of TGR5 based on the Modeling studies. Several compounds exhibited excellent potency. These novel TGR5 receptor agonists are potentially useful therapeutics for metabolic disorders such as type II diabetes and its associated complications.

under conventional heating and microwave irradiation. A series of new 2-aminopyrrole-3-carbonitriles were synthesized from the reaction of benzoin, primary aromatic amines and malononitrile, from which a number of pyrrolo[2,3-d]pyrimidines were synthesized. The structures of the newly synthesized compounds were established on the basis of elemental and spectral (IR, 1H NMR and Mass) studies. Some of the prepared compounds 7-(4-methoxyphenyl)-5,6-diphenyl-7H-pyrrolo [2,3-d]pyrimidin-4(3H)-ones, 7-(3-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-thione and N-(7-(2-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d] pyrimidine)N-aryl amines showed potent antitubercular activity.

P033. Anti-diabetic and Anti-hyperlipidemic Potential of *Ocimum basilicum Linn* seed extract and its isolated compound

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Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The present study was designed to investigate the anti-diabetic and anti-hyperlipidemic potential of *O. basilicum* Linn seeds, which are widely used as traditional treatment for diabetes mellitus. The methanolic extract of seeds of *O. basilicum* (40 mg/kg) and isolated compound apigenin (1mg/kg) were administered orally to streptozotocin (STZ) induced diabetic rat for 15 days. Anti-diabetic effect, change in body weight and lipid profile of diabetic rat treated with methanolic extracts and apigenin were assessed and compared with normal, diabetic control and standard drug treated rat. Methanolic extract (40 mg/kg) and apigenin (1 mg/ kg) produced a significant reduction in fasting blood glucose level ($p<0.01$) & ($p<0.001$), respectively in streptozotocin-induced diabetic rat. Significant differences were also observed in serum lipid profile and body weight of methanolic extract and apigenin treated diabetic rat, when compared with diabetic, normal and standard drug treated rat. The results of the histological examinations of the pancreas and liver showed that *O.basilicum* seeds extract and apigenin protected the islet architecture and prevented disordered structure of the liver. The study displayed that *O.basilicum* seed extract and apigenin can alleviate hyperglycaemia and hyperlipemia in STZ-induced diabetic rats might by improving insulin secretion and sensitivity. Methanolic extract of *O.basilicum* seeds and apigenin exhibited significant anti-hyperglycemic and antihyperlipidemic activities in streptozotocin-induced diabetes in rat.

P034. GLP-1 analogue (ZYD1) and estrogen in combination therapy to treat diabetic nephropathy

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Diabetic nephropathy (DN), a common complication of diabetes mellitus is known to develop in 30-40% of all the patients suffering from diabetes mellitus. DN is reported to be major cause of renal failure when compared to any other disease causing kidney failure. Currently available therapies provides only symptomatic relief and unable to treat the underlying pathophysiology of diabetic

nephropathy. Glucagon like peptide (GLP-1) agonists work as insulin secretagogues and their combination with insulin sensitizing agents is known to provide better glucose control. Estradiol on the other hand, is known for its renoprotective effects by inhibiting apoptosis, transforming growth factor-ß (TGF-ß) and extracellular matrix (ECM). Thus, present study is designed to study the protective effect of combination therapy of GLP-1 agonist (ZYD1) and estradiol on rodent model of diabetic nephropathy. Diabetic nephropathy was induced in male rodents (Sprague Dawley rats and db/db mice) by using combination of streptozotocin and unilateral nephrectomy (NPx). Renoprotective effect was evaluated by measuring several metabolic parameters such as serum creatinine, serum and urine urea, urine albumin, serum transforming growth factor-ß1, serum tumor necrosis factor-α, triglycerides and glomerulus filtration rate (GFR). Histopathology of kidney tissues was also done to assess the morphological changes. Combination of estradiol (0.1 mg/kg, s.c., BID) with ZYD1 (5mg/kg, s.c, BID) resulted in a significant decrease in serum creatinine, TGF-ß1 and TNF-α levels as compared to vehicle treated nephropathic rats. Although, we did not observed any effect on serum and urine urea and urine albumin levels in any of the treated groups. In db/db mouse model as well we found significant decrease in serum creatinine, serum urea, serum TGF-ß1 and urine TNF-α levels in combination therapy group. At the same time, combination therapy in db/db mice results in significant increase in urine creatinine and urea and increased GFR levels as compared to vehicle control group. Histopathological findings demonstrates minimum collagen deposition in combination group and space of the renal corpuscle was found to return to the normal. Thus, findings from the present study suggests that combination therapy of ZYD1 and estradiol may be beneficial for the treatment of diabetic nephropathy.

P035. Comparison Study of Major Adverse Cardiac Events in Patients Underwent Coronary Angioplasty Either With or Without Drug Eluting Stent

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To compare MACE in coronary angioplasty treated patients with DES or BMS. This retrospective study enrolled 211 patients at a tertiary care hospital with DES or BMS. The primary end point was death and the composite end point of death or MI, CSA, UA at 1, 6 and 12 months. All patients had angiographically documented CAD and underwent PTCA and were divided into two groups based on type of stent- 129 in the BMS and 82 in the DES. Statistically it was found that the mean age, height, weight were similar in both groups. Patients who received DES had higher prevalence of family history of IHD and Previous CABG. There was a significant difference (P=0.009) in case of vessel treated- LAD and LMCA received DES more frequently, while BMS was implanted in RCA and LCX. Results suggest overall MACE at 1, 6 and 12 months did not depend on type of stent used. The Overall MACE incidence:

•At the end of 1, 6 and 12 months: in BMS - 5 (3.87%) & 4 (4.87%), 13 (10.07%) & DES: 7 (8.53%) and 20 (15.50%) & 10 (12.19%) respectively.

P036. The Na^+-D-glucose co-transporters SGLT1 and SGLT2 as new targets for the treatment of diabetes

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Diabetes is a metabolic disease characterized by hyperglycemia. According to WHO, the number of diabetic patients would be approximately 366 million by 2030. The symptoms are polyphagia, polyuria, polydipsia. The risk factors includes heredity, environmental factors, unhealthy eating habits, sedentary lifestyle, stress etc. The hyperglycemic effect of diabetes leads to cardiovascular disorders, retinopathy, neuropathy, and nephropathy. In this review we will discuss about SGLT1 & SGLT2 (Sodium glucose co-transport 2) inhibitors for the treatment of diabetes. The SGLT1 inhibitors reduce glucose absorption and decrease blood glucose excursions after taking meal. SGLT2 inhibitors inhibit the Na+-D-glucose co-transporters & there by increase the renal excretion of glucose, they also decrease the risk of cardiovascular disorders, polyphagia, & nephropathy.
The antidiabetic drugs includes empagliflozin, dapagliflozin, canagliflozin & ipragliflozin are in the pipeline for SGLT2 target. Canagliflozin is the only antidiabetic drug approved by FDA. So SGLT2 would be the promising target for the treatment of diabetes.

P037. Coagonist of glucagon and GLP-1 improves symptoms of non-alcoholic steatohepatitis in mice model

Vishal Patel[1,2], Amit Joharapurkar[1], Samadhan Kshirsagar[1], Brijesh Sutariya[1], Maulik Patel[1] Hiren M. Patel[1], Dhreendrakumar Pandey[1], Ramchandra Ranvir[1], Shekhar Kadam[1], Viren Kothule[1], Dinesh Patel[1], Dipam Patel[1], Rajesh Bahekar[1] and Mukul R. Jain[1]

[1]Zydus Research Centre, Sarkhej-Bavla National Highway-8A, Moraiya, Ahmedabad – 382 213, Gujarat, [2]K.B. Institute of Pharmaceutical Education and Research, Gandhinagar.

Non-alcoholic fatty live disease (NAFLD) is considered to be the manifestation of the metabolic syndrome in the liver. Non-alcoholic steatohepatitis (NASH) is a severe form of NAFLD, characterized by steatosis in concert with inflammation, which can progress to liver fibrosis and cirrhosis. Novel therapy that effectively treats hepatic fat accumulation and inflammation is needed. We investigated the effect of a coagonist of GLP-1 receptor and glucagon receptor in mice model. C57BL/6J mice fed with choline-deficient, L-amino acid defined, high-fat diet (CDAHFD) develop a condition similar to human NASH. After 8 weeks of CDAHFD feeding, animals were treated with exendin-4 (50 µg/kg), glucagon (150 µg/kg) or coagonist (150µg/kg) for next 8 weeks. Coagonist and exendin-4 showed reduction in serum aspartate aminotransferase(AST), alanine aminotransferase (ALT), and liver lipids. Exendin-4 and coagonist showed reduction in hydroxyproline content, however, glucagon treatment did not alter it. The expression of pro-inflammatory genes namely MMP-9, TNF-α, MCP-1 and TIMP-1 were also suppressed in exendin-4, glucagon and coagonist treatment. Histological investigation of liver revealed significant reduction in steatosis, ballooning, inflammation, and fibrosis in animals treated with exendin-4, glucagon and coagonist, which can be correlated with histological score of fat accumulation, NASH and fibrosis. These results also indicate that coagonist is being more potent in alleviating NASH than exendin-4 or alone glucagon.

P038. Free Fatty Acid Receptors (FFARs): a new emerging target for type 2 diabetes mellitus

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Diabetes mellitus is a metabolic disorder in which blood glucose level raises high in the bloodstream, because of deficiency of insulin (Type 1) and development of insulin resistance (T2DM) in diabetic patients. Diabetic patients suffer serious complication with the development of disease as like obesity, heart failure and risk of stroke. The worldwide prevalence of diabetes is likely to increase from 422 million people in 2014 to 592 million by 2035. In current scenario of anti-hyperglycemic targets, various novel targets have been identified and various therapeutics are GLP-1 agonists, DPP-4 inhibitors, SGLT2 inhibitors, and GPCR agonist. New approach for free fatty acids FFAs), FFA1 (GPR40) and GPR120, broaden our views towards nutrients as signaling molecules. GPR40 receptors activated by medium or long chain fatty acids, which stimulates the release of calcium into the cytosol and increase in [Ca2+]I is responsible for the exocytosis in pancreatic β cells, and release of insulin. GPR120 is a protein member of rhodhopsin family G protein receptors, which is expressed in the intestinal tract and in adipose tissue cell activated by medium to long chain fatty acids which stimulates GLP-1 secretion and subsequently increases secretion of insulin GPR119 receptor agonist causes an increase in intracellular cAMP levels via GĐs coupling to adenylatecyclase. Thus, GPR119 modulate insulin release from beta cell and GLP-1 from enteroendocrine cells. In current phase there are no marketed drugs for GPCR target. Novel GPR40 agonist TAK875 from Takeda reached up to phase III and then discontinued due to liver toxicity. In this review, we focus on GPCR involved in type 2 diabetes, which offer emerging anti-diabetic agonists to produce newer generation of anti-diabetic drugs against type 2 diabetes.

P039. Coagonist of GLP-1 and glucagon protects against diet-induced non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Maulik Patel[1], Vishal Patel[1,2], Amit Joharapurkar[1], Samadhan Kshirsagar[1], Brijesh Sutariya[1], Hiren M. Patel[1], Dhreendrakumar Pandey[1], Ramchandra Ranvir[1], Shekhar Kadam[1], Viren Kothule[1], Dinesh Patel[1], Dipam Patel[1], Rajesh Bahekar[1], and Mukul R. Jain[1]

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NAFLD (Non-alcoholic fatty liver disease), a disorder involving insulin resistance, obesity, dyslipidemia and improper functioning of liver, leads to nonalcoholic steatohepatitis (NASH) and cirrhosis and subsequently death. There are very limited therapeutic options approved for the management of NAFLD/NASH. Coagonist of GLP-1 receptor and glucagon receptor have been demonstrated to reduce obesity and hyperglycemia in preclinical models. In this study, we investigated role of coagonist in preventing NAFLD and NASH after chronic treatment in diet induced obese (DIO) mice. Chronic treatment of coagonist (150 µg/kg) decreased body weight gain, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) triglycerides, total cholesterol, LDL, and hepatic triglycerides and cholesterol content. This treatment also increased basal and epinephrine- and insulin-stimulated lipolysis. Additionally, coagonist increased energy expenditure and reduced respiratory quotient. Coagonist-treated animals demonstrated lesser hepatic inflammation and fat accumulation when compared to vehicle-treated controls. Hydroxyproline in liver, a marker of collagen content and relative liver weight were reduced with coagonist treatment. The results indicate that coagonist treatment increases fat utilization, insulin sensitivity and prevents development of diet induced NASH or NAFLD.

P040. Anti-diabetic, anti-oxidant and PPARĐ agonist activity of a polyherbal formulation

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Diabetes mellitus is a metabolic disorder characterized by insufficiency of insulin secretion or action. Glucose oxidation is believed to be the main source of free radicals so diabetes is accompanied by increased production of reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide. Increased oxidative stress is an important factor in the development of diabetes and its complications. In the past few years there is increased interest in the therapeutic potential of medicinal plants as antioxidant and hypoglycemic supplements, because of their effectiveness and minimal side effects. In this context, present study was undertaken to evaluate the anti-diabetic activity and anti-oxidant of a polyherbal formulation containing hydro-alcoholic extracts of five different herbs, that is, Myristica fragrans, Andrographis paniculata, Gymnema sylvestre, Eugenia jambolana and Momordica charantia in streptozotocin induced Type II diabetic rats. Treatment with the polyherbal formulation at an oral dose of 400mg/kg for six weeks produced a significant decrease in streptozotocin induced serum glucose in diabetic rats compared to control group. The antioxidant potential of polyherbal formulation was measured by DPPH (1, 1-Diphenyl, 2- picryl-hydrazyl) free radical scavenging assay at 515 nm. IC50 value of methanolic extract of the polyherbal formulation was found to be 5.02 µg/ml. The polyherbal formulation was also evaluated for PPARĐ agonist activity to determine the mechanism of action which indicated the upregulation of PPARĐ gene expression comparable to the standard drug Rosiglitazone.

P041. Combination of glucagon-GLP-1 coagonist with inhibitor of microsomal triglyceride transfer protein improves obesity and liver steatosis in Zucker fatty rats

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Dyslipidemia is the disorder of lipoprotein metabolism associated with obesity and diabetes. Microsomal triglyceride transfer protein (MTP), the enzyme involved in the secretion and assembly of ApoB containing lipoprotein from liver and intestine, is upregulated in dyslipidemia. MTP inhibitors show significant hypolipidemic activity, but hepatic steatosis limits their therapeutic use. Dual agonist of GLP-1 receptor and glucagon receptor reduces body weight, improves insulin sensitivity and improves lipid profile independent of food consumption in diabetic models. Dual agonist also reduces hepatic lipid accumulation. We have investigated effects of combination of MTP inhibitor with a dual agonist on metabolic syndrome in Zucker fatty rats. Zucker fatty rats were treated either with MTP inhibitor Lomitapide (BMS201038, 0.3 mg/kg, once a day), a glucagon-GLP-1 coagonist (150 µg/kg, twice a day) or their combination for two weeks. All the treatment caused reduction in body weight, the effect of the combination was more pronounced than any single treatment. These changes were accompanied by a significant improvement of insulin sensitivity and improvement in lipid profile in all treatment groups. MTP inhibitor increased in liver lipids, which was attenuated when the coagonist treatment was combined with it. These data indicate that coagonism of GLP-1 and glucagon receptors and blockade of MTP provides an effective means of counteracting obesity and related abnormalities in a genetic model of obesity and dyslipidemia.

P042. Antihyperglycemic and antihyperlipidemic effect of Pimpinella anisum oil in high fat diet induced type II diabetes mellitus

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Pimpinella anisum (P.anisum) seeds (Anise) are commonly consumed in India as a spice. P.anisum oil contains rich content of trans-anethole reported to possess potent anti-oxidant activity. Diabetes is a metabolic disorder characterized by elevated levels of blood glucose, leading to serious complications attributed to generation of reactive oxygen species. The present study was designed to evaluate the anti-hyperglycemic and anti-hyperlipidemic effects of the P.anisum oil in diabetic animals. Healthy Sprague-Dawley rats were randomly divided into 5 groups named Normal control, Control treated with P.anisum oil, Diabetic control, Diabetic treated with P.anisum oil, Diabetic treated with standard quercetin. Diabetes was induced by high fat diet for the initial period of two weeks. Following this, animals were injected with streptozotocin (35mg/kg, i.p.). After two weeks, diabetes was confirmed by measuring serum glucose levels and animals showing serum glucose levels higher than 150 mg/dl were considered diabetic. The treatment of P.anisum oil (250 mg/kg) and quercetin (1 mg/kg) were given for a period of 10 weeks after induction of diabetes. After 10 weeks, animals showed characteristic signs of diabetes like weight gain, polydipsia and polyuria. These effects were controlled in the animals treated with trans-anethole and quercetin. Serum glucose, glycated hemoglobin, total cholesterol, triglycerides, LDL-cholesterol, VLDL were altered in the diabetic animals which were improved by the treatment. Our data suggests that P.anisum oil was able to control the hyperglycemic status along with beneficial effect on the altered lipid profile of diabetic animals. This effect may be attributed to the presence of trans-anethole.

P043. Activation of double-stranded RNA-dependent protein kinase pathway impairs insulin signaling in L6 muscle cells

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Double stranded RNA (dsRNA) activated protein kinase R (PKR), a ubiquitously expressed serine/threonine kinase is a key inducer of inflammation, insulin resistance and glucose homeostasis in obesity. Recent studies have demonstrated that PKR can respond to metabolic stress in mice as well as in humans. However the underlying molecular mechanism is not fully understood. The aim of the present study was to examine the effect of high glucose (HG) on cultured rat L6 muscle cells and to investigate whether inhibition of PKR could prevent any deleterious effects of HG in these cells. PKR expression was determined by immunofluorescence and immunoblotting. The expression of different insulin signaling gene markers were measured by RT-PCR. Oxidative stress and apoptosis were determined by flow cytometry. HG treated L6 muscle cells developed a significant increase in PKR expression. Impaired insulin signaling as well as reduced insulin stimulated glucose uptake was observed in HG treated L6 muscle cells. A significant increase in reactive oxygen species generation and apoptosis formation was also observed in HG treated cultured L6 muscle cells. All these effects of HG were attenuated by a selective PKR inhibitor imoxin. Our study demonstrates PKR may have an additive role against the deleterious effects of HG in diabetes. Prevention of PKR activation, by safer and specific inhibitors is a therapeutic option in metabolic disorders that needs to be explored further.

P044. Diabetes Associated with Atherosclerosis

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Complications of Atherosclerosis cause most morbidity and mortality in patients with Diabetes Mellitus. Atherosclerosis is more frequent in patients with diabetes compared with patients having no diabetes. Conversely, recent data suggest that diabetic patients are more predisposed to the development of

diabetes than the normal persons, leads to recommendation of more aggressive treatment in patients with diabetes association. Important risk factors for atherosclerosis in diabetic patients include, insulin resistance, endothelial dysfunction, platelet hyperaggregability, coagulation abnormalities, hyperlipidemia, altered secretion and function of local-regulatory substances, impaired response to injury, obesity and angiogenesis. Therefore, strict glucose control alone is insufficient, a multifaceted approach targeting all mechanisms is required. Blood pressure control, lipid-lowering treatment, anti-platelet drugs, anti-oxidants, cholesterol absorption inhibitors, PPAR agonists, nicotinic acid derivatives and bile acid sequestrants significantly reduce the risk of cardiovascular events. This update reviews the current knowledge regarding risk factors and treatment of patients having "Diabetes Associated with Atherosclerosis".

P045. Role of ghrelin and GLP-1 in diabetes remission in patients undergoing bariatric surgery

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The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030.Patients with uncontrolled diabetes often option for surgical interventions like bariatric surgery. Bariatric surgery is carried out on stomach and/or intestine to facilitate the weight loss. There are mainly 3 types of surgeries: 1) Restrictive Eg: Vertical banded gastroplasty (VBG) and adjustable gastric banding. 2) Malabsorptive Eg: Biliopancreatic diversion and sleeve. 3) Combination of both (Restrictive and Malabsorptive) Eg: RYGB. Remission of diabetes after bariatric surgery where systemic review and Meta analysis was done which showed that complete resolution was achieved in 78.1% of the patients. The mechanism by which the bariatric surgery is remitting diabetes is related to two important parameters i.e. Ghrelin and GLP-1.The level of ghrelin after bariatric surgery a study showed that initially level of ghrelin decreased in the fasting condition and then it returned to normal level and some of the study also showed that increased the level of ghrelin after bariatric surgery and sometime no change was observed in ghrelin level after surgery and GLP-1 is associated with bariatric surgery the level of GLP-1 is increased after bariatric surgery is reported. The current review focuses on role of ghrelin and GLP-1 in diabetes remission after bariatric surgery.

P046. Opioid receptors in cardiovascular diseases

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According to WHO, cardiovascular diseases are responsible for two-thirds of the deaths globally. Moreover cardiovascular diseases are the number one cause of death throughout the world killing nearly 17 million people annually, which is 3 in every 10 deaths. In the past decade, considerable improvements have been made in the diagnosis and treatment of heart diseases. New therapeutic targets are being identified resulting from emerging insights into disease mechanisms and new strategies are also being tested, possibly leading to new treatment options. Opioid compounds and G-protein coupled opioid receptor (OR)s have been studied widely in terms of central nervous system (CNS) actions relating to pain management and drug abuse. It is not surprising that OR agonism or antagonism induces acute or delayed cytoprotective states in myocardium, rendering ORs an attractive target for protection of cardiac tissue from the potentially fatal consequences of heart diseases. Also opioids can confer an extended window of cardio protection. While the mechanisms may not be fully understood, they appear to play an important role in in various cardiovascular diseases such as myocardial ischemia, congestive heart failure, hyperlipidaemia and hypertension. As opioids are currently used both postoperatively and for both acute and chronic pain, it would not take a long period of drug development before opioids will be approved for use as cardio protective agents. This review focuses on the new knowledge acquired about the role of the opioid receptors in various cardiovascular diseases.

P047. Comparison of CABG &PCI with recent advancement in treatment of myocardial infraction

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Myocardial infarction is the condition of irreversible cell death of heart muscle that results to form prolonged ischemia, the coronary arteries that supplies blood to heart get obstruction. Comparative effects of Coronary artery bypass surgery & percutaneous coronary artery interventions on long-term mortality and morbidity by performing a meta-analysis of all randomized clinical trials of the current era that compared the 2 treatment techniques in patients with multi vessel disease. Both the techniques are safe and established treatment modalities of invasive revascularization for patients with coronary artery disease. Multi vessel disease is mostly treated either with coronary artery bypass grafting & drug eluting stunts. With the advent of Drug eluting stunts conventional bare metal stents are seldom used now in multi vessel disease. In diabetic patients with multi vessel disease, concern of repeat revascularization was notably higher with DES-PCI at long term. In diabetic MVD patient, CABG having better clinical outcomes and being more cost effective approach when compared to DES-PCI at long term.

P048. Glucose-responsive drug delivery: A new approach for the treatment of Diabetes

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Diabetes is caused by lack of secretion of insulin or reduction in its sensitivity. Recent treatments for diabetes do not fulfill the requirements for maintaining normal glucose level in blood. In the field of smart drug delivery, there is a great challenge to develop formulations which can sense glucose and give response by delivering suitable amount of insulin. This approach is called as "fully synthetic pancreas" envisions closed-loop insulin therapy. The approaches for incorporating glucose sensing into formulations are mainly - enzymatic sensing, natural glucose-binding proteins and synthetic molecular recognition. Also by employing different types of polymers, Glucose-responsive release of insulin is achieved by using different polymers. The approaches are systems based on glucose oxidase, lectin and phenyl boronic acid (PBA). The challenges lead to the realization of closed-loop insulin therapy is highly significant, and include improved response time, more reliable fidelity in glycemic control, improved biocompatibility with delivery materials and assurance of both safety and efficacy. The major advantages of this system include reduced dosing frequency, ease of preparation, maintenance of desired therapeutic concentration with single dose, prolonged release of incorporated drug, reduced side effects and improved stability. This system is increasingly successful due to its release pattern mimicking that of the endogenous release of insulin. With advancement of novel drug delivery systems, glucose-responsive drug delivery system provides a link between therapeutic requirement and drug delivery. Thus this system has significant impact on improving therapeutic management of type-I and type-II diabetes. The present review will discuss challenges, opportunities and applications of Glucose responsive drug delivery system.

P049. Coagonist of GLP-1 and glucagon alleviate CCl4 -induced hepatic inflammation in diet-induced obese mice

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Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are common clinico-pathological conditions affecting millions of patients worldwide, mostly associated with insulin resistance and obesity. Although number of therapeutic options have been explored for management of NAFLD/NASH, no pharmacological treatment is yet optimum. Administration of carbon tetrachloride (CCl_4) in mice fed on high-fat diet (HFD) results into acute hepatic inflammation associated with metabolic alteration similar to clinical situation of NASH. We have evaluated effect of coagonist of GLP-1 and glucagon in this model. In acute study, diet induced obese (DIO) mice were treated with coagonist (150 µg/kg), exendin-4 (50 µg/kg) and glucagon (150 µg/kg) and administered CCl_4 (0.5 ml/kg). In chronic study, CCl_4 was administered twice a week for six week, along with twice a day treatment of coagonist, exendin-4 and glucagon. Coagonist and exendin-4 reduced serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), while glucagon did not affect serum AST and ALT after acute administration. After acute treatment, serum triglycerides were reduced after coagonist and exendin-4 treatment but not after glucagon administration. Repeated treatment of coagonist, exendin-4 and glucagon showed reduction in body weight, serum triglycerides,

ALT, AST and liver lipids. Histological investigation of liver revealed significant reduction in steatosis, ballooning, inflammation and fibrosis in animals treated with exendin-4, glucagon and coagonist, which correlated with histological score for fat accumulation, NASH and fibrosis. We observed that coagonist is more effective than exendin-4 or glucagon in reducing CCl_4 -induced hepatic inflammation in diet-induced obese mice.

P050. Beneficial role of DPP4 inhibitor in cerebrovascular complications associated with diabetes

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Cerebrovascular complication make diabetic patients 2-6 times more vulnerable to a stroke event. In addition, when patients with diabetes experience an acute ischemic stroke they are more likely to die or be severely disabled. Increased the risk of Cerebrovascular complication for type 2 diabetes patients and worsening glycemic control relate directly to stroke risk. The most common site of CV in patients with diabetes is occlusion of small blood vessels, which leads to increase in atherosclerosis. Epidemiology studies show that hyperglycemia is strongly associated with cerebrovascular event. Hyperglycemia contributes to vascular damage by several mechanisms such as endothelial dysfunction, oxidative stress, arthrosclerosis and hypercoagulability. Diabetes is injurious effects on vascular endothelial and leads to progress of cerebrovascular complication. Thus the strategy to reduce cerebrovascular stroke with diabetes is to reduce type 2 hyperglycemia. Various inhibitor reduce the glucose at plasma levels. Among all, Gliptins reduce sugar level by inhibit the degradation of the incretins, glucagon like peptide-1and glucose-dependent insulinotropic peptide. The mechanism of DPP4 inhibitor may prevent the hyperglycemia as well as risk of vascular damage by improving fine glycemic control. Therefore, Gliptins are useful in reducing the risk of cerebrovascular event in patients with diabetes.

P051. Prescribing pattern and risk factor evaluation for Cardio vascular conditions: A cross sectional and prospective study

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Cardiovascular diseases (CVD) account for high morbidity and mortality all over the world. A study of prescription pattern ensures rational pharmacotherapy and assures quality medical care to the patients. Prior permission from the Institutional Ethics Committee was obtained, and a cross sectional & prospective study of cardiovascular drugs was conducted on 120 patients of Department of Cardiology at JIVRAJMEHTA Smarak Health Foundation, Ahmedabad. The duration of the study will be of months from June 2016 to November 2016. The prescriptions of the patient who are treated during the course of the study will be audited prospectively using a specially designed form to record the required information. The data were statistically analyzed and presented as counts and percentages. Majority of the patients were male (59%), and most of the patients belonged to age group of 51-60 years. Hypertension, coronary artery disease, left ventricular failure reported as common cardiac conditions. Most common drug class was antiplatelets, dyslipidemic agents, beta blockers, and vitamin supplements. Aspirin and clopidogrel is being the mostly used combination drug. The present study concluded that the percentage of drugs prescribed with fixed dose combinations and injection form was low. Polypharmacy was observed. In addition major cardiovascular risk factors were the same in both sexes, This study shows the relationship between common lifestyle choices, cardio metabolic conditions (i.e., lifestyle related disease), and CVD. Risk increase further because of rapid and its accompanying lifestyle changes. Risk of the cardiovascular disease increases with the age.

P052. Synthesis and glucose uptake activation of 3-amino acid analogues of 1,4-naphthoquinone

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Globally, as of 2015, an estimated 415 million people had diabetes, with type 2 making up about 90% of the cases. Its incidence is increasing rapidly, and by 2040, this number is estimated to almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. Control of post prandial (after meal) blood sugar is critical in the treatment and therapeutic approach in the control of blood sugar. Naphthoquinones are class of secondary metabolites widespread in nature such as plants, fungi. The 1-4 naphthoquinone pharmacophore is known to impart pronounced biological effects like antifungal, antimalarial, enzyme inhibition, HIV inhibition, anti-tumor, anti-mycobacterial, anticancer and many more. The substitution at various position of naphthoquinones plays important role in biological activities. Hence synthesizing different analogues may lead to emergence of better drugs with potent anti-diabetic activity. In present study analogues were synthesized using amino acids as a reactant, purified and characterized by Spectral analysis. Analogues were found to be non-toxic to (3T3-L1) skeletal muscle cell lines ($p<0.0001$, $F=91.32$) and (C2C12) adipocyte cells lines ($p<0.0001$, $F=60.84$). All the analogues showed significant increase in % glucose uptake. At 50 µg/ml concentration total 7 analogues possess potent glucose uptake activity compared to pioglitazone ($p<0.05$).

P053. Production of Islet-like insulin producing cell clusters in-vitro from mesenchymal stem cells.

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Diabetes is a life-long disease characterized by hyperglycemia, polyphagia and increased fatigue. Type 1 diabetes Mellitus (T1D) is a chronic disease that involves the progressive destruction of pancreatic beta-cells, ultimately resulting in the loss of insulin production and secretion from the pancreas. The goal of clinical Intervention are to arrest the onset and delay the progression of autoimmunity, reverse beta-cell destruction and to restore glucose metabolism along with restoring of the immune homeostasis. The regenerative potential of stem cells can provide self-replenishing supply of glucose –responsive insulin –producing beta cells. In addition, the immune modulatory properties of the stem cells can be used to prevent autoimmunity. In present study, we used mesenchymal stem cells (MSC's) and further differentiated them to pancreatic beta cells. These differentiated cells were characterized by different stage specific markers. Further in-vivo studies need to be done before their use in clinical application. Thus these differentiated cells may be a promising source of cells based therapy for Type 1 diabetes, which will help us to overcome the drawbacks of the conventional diabetes therapy.

P054. ZYX1, a novel and potent GPR40 agonist shows good efficacy and safety profile in preclinical models

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GPR40, one of the G protein-coupled receptors predominantly expressed in pancreatic ß-cells, mediates enhancement of glucose-stimulated insulin secretion by free fatty acids. Takeda has developed TAK-875 (Fasiglifam) a potent and selective GPR40/FFAR1 agonist for the treatment of type 2 diabetes mellitus (T2DM) but recently discontinued due to hepatotoxicity. ZYX1 was identified as a potent and selective small molecule agonist for GPR40/FFAR1, which exhibits EC^{50} of 7 nM and 2.7 nM in cell based functional IP1 ELISA assay and Ca2+ mobilization assay done in HEK-293 cells with hGPR40 respectively. ZYX1 has shown potent and dose dependent AUC glucose lowering efficacy in OGTT in nSTZ Wistar rats and in Zucker fatty rats (ED^{50}-0.05 mg/kg and 0.2 mg/kg, p.o. with 6 fold and 2.5-fold rise in glucose dependent insulin secretion respectively) . Unlike TAK-875, ZYX1 has also shown anti-diabetic efficacy in DIO mice and db/db mice like models of type 2 diabetes. After repeat dose administration in Zucker fa/fa and db/db mice for 4 weeks it showed consistent efficacy and no tachyphylaxis. ZYX1 has shown significant (74%) increase in glucose infusion rate (GIR) measured using hyperglycemic clamp model in male SD rats confirming its glucose dependent insulin secretagogue activity. Its hepatotoxicity was evaluated in Non Alcoholic Steatohepatitis (NASH) model and it did not showed any worsening of disease condition. Moreover, ZYX1 is devoid of any hypoglycemic potential up to 600X of ED^{50} dose and maximum tolerable dose was found to be 1000 mg/kg in Wistar rats and NOAEL was found to be 300 mg/kg, p.o. dose in 10 days repeat dose toxicity

study in rats. Based on its efficacy and safety profile ZYX1 shows good potential for treatment of type 2 diabetes.

P055. In-silico molecular docking studies of naphthoquinone derivatives on PTP1B and PPAR-g for the development of potential antidiabetic agents

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Globally, diabetes mellitus is reported to be leading cause of morbidity and mortality. Molecules possessing naphthoquinone scaffold are found to be active as antidiabetic, anticancer, antialzheimer's agents by interfering in intracellular redox cycling as well as intercellular signaling. Through literature survey it was found that naphthoquinones act as inhibitors of PTP1B enzyme while thiazolidinedione moiety decreases glucose level in blood via PPAR-g activation. Thus combining these two active scaffolds may give rise to molecules with increased antidiabetic activity as well as reducing side effects. Targeting PTP1B inhibits dephosphorylation, while activation of PPAR-γ induces tissue sensitivity to insulin. A hypothetical library of molecules was prepared and molecular docking studies performed on PTP1B (PDB ID: 2QBQ), PPAR-γ (PDB ID: 4EMA) involved in type 2 diabetes pathways whereas selectivity studies were performed on TCPTP (PDB ID: 2CM2) using the GLIDE XP module in Schrodinger Suite. Docking studies revealed that the molecule SH040 is showing selectivity towards PTP1B by interaction with catalytic site amino acid residues such as ARG 221, SER 216 with docking score of -6.163, as compared to TCPTP with docking score of -5.04. The docking studies on PPAR-γ revealed that compound SH03 interacted with HIS 449 via π-π stacking, hydrogen bond interaction with SER 289 and HIS 323 and having a docking score of -10.799, which is more than that of rosiglitazone (-8.593) taken as standard drug. These studies reveal that naphthoquinone-thiazolidinedione hybrid molecules may give rise to molecules with desirable antidiabetic activity.

P056. SAROGLITAZAR: A Novel and Promising Drug for the Treatment of Lipid-induced Insulin Resistance

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Discovery of Preventing the obesity-induced PPARγ-pSer273 by partial and non-agonists of PPARγ improves the insulin sensitivity without adverse effects raised new hopes for PPARγ targeted drugs. However, none of these small molecules entered the market due their undesirable pharmaco-chemical properties. Hence, in the current study, we investigated whether Saroglitazar improves the insulin sensitivity by inhibiting lipid-induced PPARγ-pSer273. Glucose uptake was measured in palmitate-treated cells by NBDG-fluorescence assay kit. Gene expressions were studied by q-PCR. PPARγ phosphorylation was measured by western blot using suitable antibody. Treatment of 3T3-L1 cells with Saroglitazar abrogated palmitate-mediated down-regulation of glucose uptake in adipocytes. Further, Saroglitazar significantly reduced PA-induced PPARγ-pSer273 and restored the expression of genes dysregulated by obesity-induced PPAR-γ phosphorylation i.e., adiponectin, adipsin. Further, Saroglitazar treated db/db and HFD-fed mice showed reduced levels of PPAR-γ phosphorylation and increased expression of adiponectin and adipsin in adipose tissue followed by enhanced systemic insulin sensitivity. Moreover, Saroglitazar treatment ameliorated the lipid-induced inflammation in-vitro and in-vivo. Our results indicate that Saroglitazar prevents obesity-induced inflammation and PPARγ-pSer273 and improves insulin sensitivity. Saroglitazar therefore acts as a novel PPARα/γ dual agonist that acts like other small molecules which inhibit obesity associated PPARγ phosphorylation. Since the drug is devoid of major adverse events as published clinical results so far, it may be a better insulin sensitizer compared to other small molecule inhibitors of PPARγ phosphorylation.

P057. Synthesis and antihyperlipidemic activity of some novel acetal derivatives and their effect on autophagy

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality, with atherosclerosis as one of the major cause. Degradation processes are important for functioning of eukaryotic cells. Potential role of autophagy in modulation of lipid metabolism has been identified and autophagy plays crucial role in obesity and atherosclerosis. S, N- Acetal derivatives were synthesised, characterized by IR, Mass and 1H NMR spectroscopy and screened for their effect on autophagy. This type of compound were reported as potent Acyl Co-A Cholesterol Acyl Transferase (ACAT) inhibitor when screened by cell death assay in-vitro as well as by Poloxamer 407 induced hyperlipidaemia in rat model in-vivo activity.

P058. Glucose regulation by Kidneys: A new target for Diabetes Mellitus

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Diabetes is a complex metabolic disorder arising from the combination of genetic and environmental factors. Characterized by insufficient insulin production by the pancreas or insulin resistance or both, diabetes results in chronic hyperglycemia. It is majorly a lifestyle disorder but owing to the "Asian Phenotype", South Asians tend to be more susceptible to this disorder. One of the main mechanisms through which kidneys help to regulate glucose homeostasis is via glucose reabsorption. Found in the proximal renal tubule, sodium glucose co-transporters (SGLT) help kidneys to achieve this function. Renal threshold for glucose excretion has found to be increased in patients with Diabetes Mellitus, possibly due to upregulation of SGLT-2 expression. Thus the maintenance of hyperglycemia in Diabetes Mellitus patients could be contributed to glucose reabsorption via these cotransporters. SGLT-2 inhibitors decrease the glucose threshold of kidneys, thereby increasing glucosuria which helps in regulating the body glucose levels. When used independently of exogenous insulin, they have shown durable glucose lowering efficacy with a low risk of significant hypoglycemia. It has also not been associated with weight gain, which is a common side effect of most of the currently used drugs for Diabetes Mellitus therapy. Another advantage of this class includes regulation of blood pressure. It can be used as a monotherapy or add-on therapy. Thus, these drugs offer a new hope for people suffering from both obesity and diabetes not responding to conventional therapy.

P059. Inhibition studies of human insulin fibrillation by morin hydrate

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The extracellular amyloid deposits of distinct polypeptide that dominates its composition in the form of highly ordered cross Ð structure, is the pathological basis for protein misfolding diseases, such as Alzheimer's disease with high social and medical relevance and other localized diseases, i.e. insulin-derived amyloidosis which are rare and become a diagnostic challenge for the physicians. As amyloid fibrils and prefibrillar soluble oligomers are cytotoxic, plentiful efforts have been made to inhibit fibrillation process as a therapeutic strategy. Small molecules have been widely used as a fibrillation inhibitors. Here, we have studied the effects of morin hydrate on fibrillation of human insulin as a model protein. The effect of morin hydrate on insulin fibrillation was determined using Thioflavin T fluorescence, Congo red absorbance, circular dichroism (CD), transmission electron microscopy (TEM), computational docking and molecular dynamics (MD). These studies showed that morin hydrate significantly attenuates nucleation and therefore inhibits insulin fibrillation and fibril induced hemolysis in a dose dependent manner. Fluorescence quench-titration study revealed that morin hydrate has relatively strong binding affinity with insulin. Computational docking and MD studies suggested that hydrogen bonds and hydrophobic forces prominently contribute to stabilizing interaction. These findings provides anti-amyloid property and the binding stoichiometry between morin hydrate and insulin that would be helpful for pharmacokinetics.

P060. Signaling from endosome regulates GLP-1R mediated insulin secretion in pancreatic ß cells

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The glucagon like peptide GLP-1 receptor (GLP-1R) plays a major role in glucose stimulated insulin secretion. In my present study I used novel functional peptide GLP-TMR to monitor internalization of the receptor. We observed prolonged association between receptor ligand complex and soring to lysosomes for degradation. At endosomes this complex was found to co localize with adenylate cyclase and we also observed the association between internalized receptor ligand complex - Rab5 and generating sustained cAMP in Rab5 compartments. Both pharmacological inhibition of internalization and alteration of Rab5 stoichiometry have been shown to attenuate GLP-1R mediated cyclic AMP generation and GSIS. Our study underlines a paradigm shift in GLP-1R signaling and trafficking. The receptor ligand complex triggers cAMP generation both in plasma membrane and in Rab5 endosomal compartment, which has implications for receptor-mediated regulation of insulin secretion.

P061. Lipid accumulation in pancreatic beta cells: its impact on incretin modulated pancreatic beta cell energetics

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Accumulation of Fatty acid and Cholesterol in pancreatic ß-cells impedes GLP-1R function and blunt GSIS in pancreatic ß-cells. Here in our present study we explored the mechanism by which accumulation of fatty acid and cholesterol attenuate pancreatic beta cell function. We reported that prolonged association of beta arrestin-1 and GalphaS with GLP-1 receptor–ligand complex supports sustained cyclic AMP generation from endosomes to regulate GLP-1R mediated potentiation of insulin secretion. Our present data reveals that accumulation of palmitate limits the distribution of GalphaS to plasma membrane thereby blunting endosomal cyclic AMP generation causing attenuation of phosphorylation of PKA substrates and reduction in GSIS. Palmitate accumulation significantly blunts cellular respiration in pancreatic ß-cells. As real time respirometry reveals, palmitate treatment reduces oxygen consumption rate significantly in control and GLP-1 treated pancreatic ß-cells contributing to reduction in insulin exocytosis. Studies from our laboratory further shows that feeding of cholesterol enriched diet to Sprague Dawley rats resulted in accumulation of cholesterol in pancreatic islets. Our data reveals that cholesterol accumulation in BRIN-BD11 pancreatic ß disrupts mitochondria-ER contact which attenuates mitochondrial function as revealed by real time respirometry. To explore the phenomenon further we inhibited Mitochondrial Calcium Uniporter which regulates mitochondria-ER contact in pancreatic β-cells. Our data reveals that treatment of pancreatic ß-cells with small molecule inhibitor Ru360 reduces oxygen consumption rate and blunts GLP-1R mediated cyclic AMP generation and potentiation of GSIS. Similar results are obtained by dominant negative mutant of MCU which inhibits the function of the Calcium uniporter. The data taken together reveals that fatty acid and cholesterol may have different mechanisms by which they attenuate GLP-1R function in pancreatic ß-cells; efforts are presently underway to explore small molecule-mediated intervention to restore GLP-1R function in lipid enriched pancreatic ß-cells.

P062. Fenofibrate Reverses Palmitate Induced Impairment in Glucose Uptake in Skeletal Muscle Cells by Preventing Cytosolic Ceramide Accumulation

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The lipid induced insulin resistance is a major pathophysiologic mechanism underlying glucose intolerance of varying severity. PPARα-agonists are proven as effective hypolipidemic agents. The aim of this study was to see if impaired glucose uptake in palmitate treated myotubes is reversed by fenofibrate. Palmitate-treated myotubes were used as a model for insulin resistance, impaired glucose uptake, fatty acid oxidation and ceramide synthesis. mRNA levels of CPT1 and CPT2 were determined by PCR array and Q-PCR. The incubation of myotubes with 750 uM palmitate

not only reduced glucose uptake but also impaired fatty acid oxidation and cytosolic ceramide accumulation. Palmitate upregulated CPT1b expression in L6 myotubes, while CPT2 expression level remained unchanged. The altered stoichiometric ratio between the two CPT isoforms led to reduced fatty acid oxidation (FAO), ceramide accumulation and impaired glucose uptake, whereas administration of 200 μM fenofibrate significantly reversed the above abnormalities by increasing CPT2 mRNA levels and restoring CPT1b to CPT2 ratio. Palmitate-induced alteration in the stoichiometric ratio of mitochondrial CPT isoforms leads to incomplete FAO and enhanced cytosolic ceramide accumulation that lead to insulin resistance. Fenofibrate ameliorated insulin resistance by restoring the altered stoichiometry by upregulating CPT2 and preventing, cytoplasmic ceramide accumulation.

P063. Posological dose of therapeutics over prophylaxis in toxicological serendipity

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Drug, any chemical substance that affects the functioning of living things and the organisms (such as bacteria, fungi and viruses) that infect them. Pharmacology, the science of drugs, deals with all aspects of drugs in medicine, including their mode of action, physical and chemical properties, metabolism, therapeutics and toxicity. The therapeutic index of a drug is the ratio between the dosage that causes a toxic/lethal effect and the dosage that causes a therapeutic effect. The term pharmacotherapy refers to the use of drugs for treating diseases, whereas pharmacology is the study of drug action on living systems. It is the interaction of the drug molecules and drug receptors that brings about a therapeutic effect. However, it is extremely essential to administer the drug in the right dose to achieve such an effect. If taken in large doses, certain drugs could cause adverse effects. Thus, in order to reap the benefits, it is essential to assess the right dose. Therapeutic drug monitoring (TDM) becomes essential to determine the dose at which a drug will be safe and effective, especially with those with a narrow therapeutic index (NTI). Also, monitoring might be required when the patient is affected by a medical condition that has an adverse effect on the clearance of NTI drugs. There's no denying the fact that drug metabolism could vary from person to person. Thus, the key to avoid drug-related problems is to consider the drug's therapeutic index and other relevant factors for ensuring safety. Therapeutic index (TI) refers to any of the several indices that are used for measuring a drug's safety. The most common TI is the ratio of the median lethal dose to the median effective dose of a drug. The formula for TI is: LD^{50}/ED^{50}. LD^{50} stands for median lethal dose and ED^{50} stands for median effective dose (therapeutic dose). LD^{50} refers to the dose that would produce a lethal effect in 50% of the population, whereas ED^{50} refers to the dose that will produce the desired therapeutic effect in 50% of the population. This index is commonly used to measure a drug's safety. The therapeutic index formula is: TD^{50}/ED^{50}. TD^{50} stands for the median toxic dose, whereas ED^{50} stands for the median effective dose. TD^{50} refers to the minimum drug dose that would produce a toxic effect in 50% of the population, whereas ED^{50} refers to the minimum drug dose that will produce the desired therapeutic effect in 50% of the population. Another related concept is that of therapeutic range (TR). TR is the range of doses/concentrations at which a therapeutic agent or drug produces a therapeutic response without causing any significant adverse effect in patients. It can be measured by: MEC/MTC. MEC stands for minimum effective concentration, whereas MTC stands for minimum toxic concentration. MEC is the minimum concentration of the drug that is required for achieving the therapeutic effect, whereas MTC is the minimum concentration at which toxicity occurs. Basically, if at a particular dosage, a drug is above MTC, it would cause adverse effects. Similarly, a drug below MEC will not produce the desired therapeutic response. While prescribing drugs, healthcare providers rely on their clinical experience and the results of drug trials that determine the TI of a drug. The larger value of TI indicates that there is a wide margin between the toxic and effective dose, whereas a smaller value indicates that there is a narrow margin between the effective and toxic dose. In case of drugs that have a low TI, even a small increase in the dosage can produce toxic effects. Additional care must be taken while prescribing a drug with a narrow TI. Therefore, the pharmaceutical industry has been making efforts to replace NTI drugs (drugs that could be toxic at relatively low levels) with drugs with higher TIs. Healthcare providers mostly prescribe drugs that have a wide margin of safety. However, they might sometimes prescribe NTI drugs when the medical condition is of a serious nature and other safer options are not available. In such cases, monitoring the effects of the drug becomes essential. Initially, the ratio of the LD^{50} and ED^{50} was determined through animal studies. It must be noted that the ratio measured by animal studies might not be very accurate when it comes to humans. Also, human subjects cannot be used for determining a median lethal dose, for obvious reasons. To add to that, using animals for determining a lethal dose raises ethical issues. While this ratio might not give an accurate estimate of toxicity in

humans, even defining an effective dose might not be a simple task. Also, median values for animals or healthy individuals might not be right for individuals of different age groups or those affected by diseases. According to the Food and Drug Administration of the United States (FDA), narrow therapeutic range (NTR) drug products are those 'containing certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation'. According to the Therapeutic Products Directorate of Health, Canada, an NTR drug is that wherein the ratio of the lowest concentration at which clinical toxicity occurs to the median concentration providing a therapeutic effect is less than or equal to two. Some drugs that have a narrow therapeutic index are: Warfarin, Lithium, Digoxin, Phenytoin, Gentamicin, Amphotericin B, 5-fluorouracil, AZT (Zidovudine). Care must be taken to determine the right dose for the aforementioned drugs in individual cases, as administration of large doses could cause adverse effects. On a concluding note, the concept of therapeutic index has some limitations, but it is clinically significant, as it lays stress on the importance of the margin of safety of a drug. Drugs that have a narrow or relatively narrow TI are still used when safer alternatives are not available. Under such circumstances, therapeutic drug monitoring becomes extremely important. In such cases, the plasma levels of the drug should be monitored regularly.

P064. Formulation Development of Lipid Nanoparticulate System for the Treatment of Inflammatory bowel disease

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Inflammatory bowel disease (IBD) is a cascade of inflammatory conditions marked by aberrations in small intestine and colon. It is a long lasting disease and the treatment includes long term doses that causes severe adverse effects as a result of systemic absorption. Hence a local targeted treatment that aids delivering the drug at the site of inflammation serves as a safe therapy. Budesonide is a glucocorticoid that inhibits various inflammatory cells causing induction in remission of active disease. The present study deals with formulation of a targeted preparation of budesonide loaded nanostructured lipid carriers (NLCs) that helps local delivery of drug without getting degraded in body. NLCs were prepared by using hot homogenization technique. Various preliminary trials were performed for optimization of the NLCs in which process as well as formulation parameters were studied. Based on preliminary trials, 3 factors viz. concentration of drug, concentration of surfactant and concentration of co-surfactant were optimized using Box-Behnken Design. The ligand appended drug loaded NLCs were developed in order to achieve an active targeting and selective adhesion region. Transferrin (Tf) was covalently bound to the surface of NLCs, and were characterized for local drug release in colon. In-vitro studies of NLCs depict a premature release of drug in the stomach and small intestine. As enteric coating of NLCs is difficult to achieve, pellets were prepared. In-vivo benefit for drug loaded folate appended NLCs were studied in colitis rat models. Ligand appended NLCs showed an added improvement of the selectivity of bioadhesion towards inflamed cells which moderately results into better therapeutic efficiency. Ligand appended NLCs decreased neutrophil infiltration, MPO activity and the levels of inflammatory markers in the colon and also improved the histopathological scores of the colonic region. Taking into consideration the above mentioned facts, it can concluded that the developed system could be used as a promising tool for the treatment of IBD.

P065. Formulation and Optimization of Transdermal Drug Delivery System of Nimodipine

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Transdermal route of drug delivery offers a potential non-invasive way of drug administration with several advantages including avoidance of first-pass metabolism, sustained release of drug, self-administration, ease of elimination of therapy at any point of time and better patient compliance. Nimodipine, a dihydropyridine calcium-channel blocker, acts particularly on cerebral blood vessels and widely used in cerebrovascular disorders, particularly in the prevention and treatment of ischaemic neurological deficits after aneurysmal subarachnoid haemorrhage. But, major drawback associated with nimodipine is extensive hepatic first pass metabolism leading to reduced bioavailability (~13%) when given via oral route. The purpose of present investigation was to formulate a promising transdermal drug delivery system of nimodipine to bypass extensive first pass metabolism and improve

bioavailability. The transdermal patch was prepared by solvent casting technique and evaluated for tensile strength, folding endurance, drug content and content uniformity, In-vitro drug permeation, scanning electron microscopy and residual solvent content study. Various formulation parameters viz. amount of drug, drug to polymer ratio, amount of solvents and solvent ratio, amount of plasticizer and amount of permeation enhancer were optimized to get desired formulation. The results demonstrated that developed transdermal patch of nimodipine possess desired physical and mechanical properties and provides steady state flux with higher permeability coefficient. The developed patch was found stable $400^{C} \pm 20^{C}$/75% ± 5% RH for 6 months. Thus, it could be concluded that the optimized formulation can be served as a good alternative for effective delivery of drugs, like nimodipine, enduring extensive first pass metabolism.

P066. Exploring the potential of bovine oil enriched microemulsion of fluvoxamine maleate for brain targeting via intranasal route

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Purpose of the present investigation was to explore the potential of butter oil (BO) as novel permeation enhancer to enhance the drug concentration in the brain when given intranasally. Fluvoxamine maleate (FM) was selected as a model drug since it undergoes extensive first-pass metabolism (80 %) leading to poor oral bioavailability of 53%. FM:BO binary mixture was prepared by simple physical mixing in the ratio of 1:9 to 9:1. Diffusion study was performed to obtain optimized FM:BO ratio. FM loaded microemulsion (ME) system (FM ME) was developed by water titration method. Optimized ratio of FM:BO showing higher permeation for FM was added into ME to obtain FM:BO ME. Globule size, viscosity and pH of FM ME and FM:BO ME was found be 50.17 ± 2.17 and 66.21 ± 3.05 nm, 12.09 ± 0.08 and 13.03 ± 0.046 cP, and 5.8 ± 0.3 and 6.2 ± 0.2 respectively. Nasal diffusion data revealed that FM:BO ME showed higher permeation (70.37 ± 0.40%) for FM in comparison to FM ME (52.97 ± 0.45%) and FM solution (43.00 ± 0.78%). Nearly 1.6 folds higher nasal diffusion of FM:BO ME compared to DS suggested higher permeation of FM from FM:BO ME to receptor compartment.

Overall, it was concluded that BO enhances the bioavailability of poorly permeable drugs across the brain, thereby proving its potential in the area of brain drug delivery system.

P067. Cerium oxide nanoparticles protect human keratinocytes from BSO generated oxidative stress

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Owing to unique antioxidant property cerium oxide nanoparticles (CeNPs) have found several applications in biomedical field. This redox active nanomaterials exhibit catalase and superoxide dismutase (SOD) enzyme like activity, which are controlled by the oxidation state (+4 / +3) of surface atom present on the surface of nanoparticles. This study, explores the antioxidant effect of PEGylated CeNPs against oxidative stress generated by BSO in Human keratinocytes (HaCaT cells). BSO serves as glutathione depleting agent and alters the cellular redox potential by inhibiting the glutathione (GSH) synthesis enzyme i.e. γ-glutamylcysteine synthetase (γ-GCS). GSH naturally present in cells and acts as ROS scavenger via redox cycle, its depletion cause free radical generation and adverse effect on cells, which are associated with several diseases like asthma, acne vulgaris, cystic fibrosis, aging, AIDS/HIV. In this study, HaCaT cells were exposed with BSO to alter its redox potential followed by measurement of toxicity, micronucleus formation, nuclear fragmentation and ROS generation as well as expression of proteins and genes involve in antioxidant pathway of cells. Result depicts that CeNPs act as potent antioxidant and protects the cells from oxidative damage induce by depleting GSH, without acting on intracellular GSH content (Figure 1). PEGylated CeNPs pretreated cells followed by BSO exposure showed better survival and less ROS generation, LDH release and nuclear fragmentation in comparison to only BSO exposed cells. BSO treatment affects the expression of antioxidant genes and proteins in HaCaT cells, whereas, cells pre incubated with PEGylated CeNPs reduces their role by quenching free radical generated. Our finding substantiates the reinforcement of CeNPs as pharmacological agents towards oxidative stress mediated disorders.

DBLS communication no. is DBLS-73.

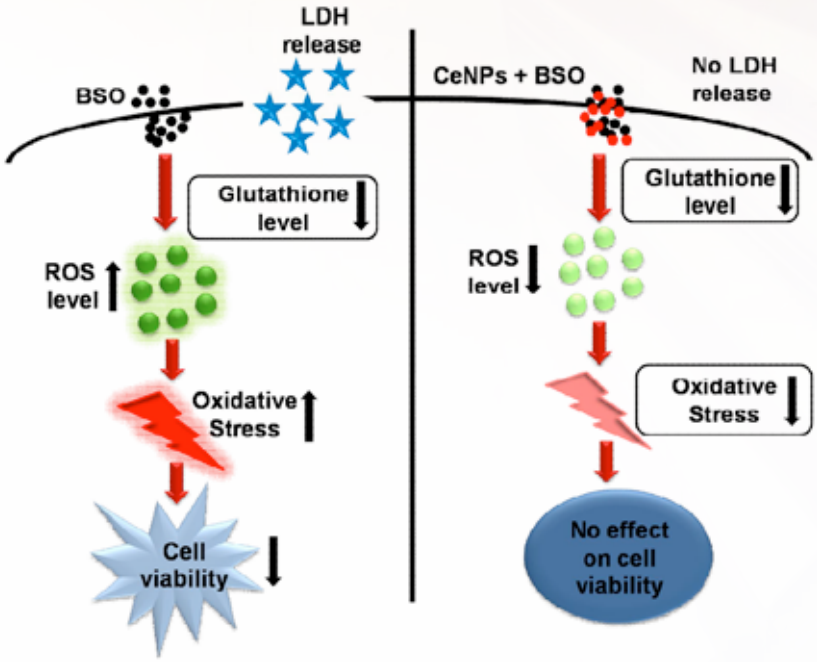

Figure 1: Schematic representation showing CeNPs protective effect towards BSO generated oxidative stress

P068. In-vitro release behavior of cucurmin-cyclodextrin complex loaded chitosan hydrogels

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Bioactive wound dressing material prepared using natural polymers are gaining momentum due to biocompatibility and biodegradability. Cucurmin is an effective anti- inflammatory and anti- oxidant molecule promoting wound healing process. Cucurmin is sparsely soluble in aqueous solutions thereby limiting its therapeutic potential. The present study explores fabrication of chitosan hydrogel with cucurmin and cyclodextrin, a solubility enhancer widely used in pharmaceutical formulations. Curcumin was loaded along with α-, β- and γ- cyclodextrin into the chitosan hydrogel by in situ method and their release efficiencies were compared. Mechanical properties, Entrapment efficiency and structural characterization of the chitosan hydrogel were investigated by thickness meter, UV -Visible spectrophotometer, Fourier transmission infrared spectroscopy (FTIR) and scanning electron microscope (SEM). Chitosan films loaded with β-cyclodextrin was found to be around 19±1.9mm in thickness, whereas that of plain chitosan film is 15±2mm. FTIR spectrum and SEM revealed that the curcumin is encapsulated within cyclodextrin. Swelling behavior and water retention capability of plain chitosan and loaded chitosan hydrogels were examined parallelly with plain chitosan showing 90% swelling ability in acetate buffer higher than the loaded films. To ensure any change in biological activity due to encapsulation, antioxidant potential of cucurmin present in chitosan films were determined by DPPH Assay and 75% DPPH scavenging activity was observed. The present study evaluates the in vitro release of cucurmin from chitosan hydrogels and ascertains the drug release mechanism. The prepared chitosan film with cucurmin and cyclodextrin showed promising cucurmin release mechanism fitting Higuchi and first order drug release models.

P069. Formulation and evaluation of polymeric microneedle arrays for transdermal delivery of therapeutic proteins

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Most of the therapeutic proteins/peptides are delivered parenterally. The problem associated with parenteral delivery leads to poor patient compliance. Oral delivery is not suitable for biologics as proteins degrade in the harsh GI environment. Other routes of delivery such as nasal and pulmonary are not suitable because of the presence of metabolic enzymes in nasal mucosal cavity and irreversible lung damage respectively. In case of transdermal delivery, stratum corneum acts as a barrier. The biodegradable polymeric microneedle array on application to skin temporarily ruptures the stratum corneum layer and delivers the proteins to dermal layer of the skin from which it diffuses and reaches the systemic circulation via blood vessels residing in dermal region of skin. Alpha chorionic gonadotropin is protein used in the treatment of infertility in women, is marketed as parenteral formulation. In the present studies alpha chorionic gonadotropin were delivered systemically through fabricated polymeric microneedle arrays. Immediate release polymeric microneedles of PVP were formulated and characterized for mechanical strength, insertion force, insertion ratio, penetration force, in vitro release study, ex-vivo permeation study. The influence of formulation and process variables on mechanical strength of the microneedles was also studied. It was concluded from the experimental observations that polymeric microneedle array is as efficient as injectables for systemic delivery of therapeutic biologics with an additional advantage of patient compliance.

P070. Studies on critical formulation parameters affecting the drug release employing the concept of design of experiments

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The objective of the present study was to identify critical formulation parameters affecting the drug release from controlled porosity osmotic tablet of milnacipran hydrochloride employing the concept of design of experiments. The optimized amount of Ethocel (X1) and mannitol (X2) in core and percentage of sorbitol (X3) in coat were determined employing a three-factor, three-level Box-Behnken design. Direct compression technique was employed for preparing the core tablets. The tablets were coated with cellulose acetate. The in vitro drug release study was carried out in an acidic medium (pH 1.2) for 2 h and thereafter the dissolution study was conducted in phosphate buffer (pH 6.8). The selected dependent variables were the cumulative percentage of milnacipran hydrochloride dissolved after 1 (Y1), 8 (Y2), 16 (Y3) and 24 h (Y4). Correlating the independent variables with dependent variables were evolved. Optimization was performed for the three independent variables using the decided target ranges; Y1£20%; Y2=45±5%; Y3=72±5%; Y4=100%. The optimized amounts of Ethocel (X1), mannitol (X2) and percentage of sorbitol (X3), were 30, 100 and 30 respectively. The optimized formulation showed a release prole that was close to the predicted values. The drug was released by anomalous diffusion from the optimized formulation.

P071. Nose to brain targeted delivery of donepezilliposome based in-situ gel in treatment of alzheimer's disease

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The purpose of present research work was to study potential of actively loaded Donepezil (DON) liposome based in-situ gel for treatment of Alzheimer's disease by intranasal route. Oral administration of DON shows poor bioavailability (only 40%) due to first pass metabolism, gastric irritation and hydrophilicity limits the effective concentration at brain. Thus to overcome these limitations, nano-liposome of DON was formulated by ethanol injection method. Various parameters like ammonium sulphate concentration, drug loading pH and duration were studied. The optimized composition was dispersed in gellan gum (0.5% w/w) and xanthan gum (0.15% w/w) to formulate in-situ gel and characterized. Toxicity on nasal

mucosa and In-vivo efficacy using scopolamine induced amnesia model were done. Ammonium sulphate concentration of 400 mM, drug loading pH 5.5 and drug loading duration of 1 h was found to be optimum conditions which showed higher entrapment efficiency. Optimized batch of liposome showed around 90% entrapment efficiency with particle size of 110 nm. FTIR, DSC and XRD studies showed formation of less ordered crystalline structure of lipid matrix favouring higher DON encapsulation. DON liposome based in-situ gel showed 6.5 times higher nasal permeation as compared to DON solution based in-situ gel and was comparable to marketed products for other parameters. DON liposome based gel did not show any toxicity on nasal mucosa during histopath studies. In-vivo efficacy tested in scopolamine induced amnesia model indicated significant improvement in cognitive function in rats treated with developed liposome based formulation as compared to the marketed tablet. Thus actively loaded liposome based in-situ gel is a promising approach for the intranasal delivery of DON for the therapeutic improvement.

P072. Self-emulsifying drug delivery system: Challenges and Opportunities

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Although oral route is preferred over other, lower aqueous drug solubility limits the bioavailability of many new chemical entities administered. The reported literature of positive effects of lipids on bioavailability of such compounds gave birth to newer approach of developing self-emulsifying drug delivery system (SEDDS). SEDDS is an isotropic mixture of oil, surfactant and co-surfactant/cosolvent which upon dispersion in lumen of gastrointestinal tract, forms fine oil in water emulsion. Drug remains in solubilized state and additionally it may adsorbed by lymphatic pathway and thus by passing first pass metabolism. The major challenges include characterization specially inability of in-vitro dissolution methods to reflect the in-vivo performance of formulation. Further the digestion of lipids may affect the solubilization of drug and hence lipid digestion studies should be performed. Liquid SMEDDS can easily be marketed in soft gelatin capsules or converted into solid SMEDDS using various techniques preferably adsorbents to increase shelf life and filled in to hard gelatin capsules. We can conclude that extensive in-vitro characterization in biorelevant conditions can be a key to success for SEDDS.

P073. Novel Polymeric Micelles: applications in target imaging and drug delivery in cancer

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Polymeric micelles, self-assembling nano-constructs of amphiphilic copolymers are widely considered as convenient nanocarriers for variety of applications, such as diagnostic imaging, drug/gene delivery. Drugs used in cancer treatments are rapidly evolving, moving beyond chemotherapy of signal transduction inhibitors. Polymeric micelles deliver poorly water-soluble anticancer agents, assured stability, and safety. In sequential drug delivery, polymeric micelles participate in pretreatment strategies that “prime” solid tumors and enhance penetration of secondarily administered anticancer agent or nanocarrier. The improved delivery of poorly water-soluble anticancer agents by polymeric micelles via concurrent or sequential regimens offers novel and interesting strategies for cancer treatment. Polymeric micelles are composed of two phases: inner core and outer shell. Outer part is answerable for interactions with biocomponents such as proteins and cells. These types of interactions define pharmacokinetic performance and bio-distribution of drugs; thus, in-vivo delivery of drugs may be controlled by outer shell fragment self-sufficiently of inner core, which is responsible for pharmacological action through drug loading and release. This complex structure is more encouraging the construction of highly functionalized carrier systems than the conventional polymeric carrier systems, as properties of both phases are freely and independently controlled through a selection of the polymer chains that are appropriate for each segment of block copolymers. Moreover, pH-, thermo-, ultrasound-, enzyme- and light-sensitive blockcopolymers allow for controlled micelle dissociation and triggered drug release in response to pathological specific stimuli and/or externally applied signals. Polymeric micelles are uniquely suited for multi-drug delivery in search for synergistic, selective, and safe anticancer drugs.

P074. Development of Chitosan-Nano Silver Oxide Wound Healing Film

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A break in the epithelial integrity of the skin with disruption of the structure and function of underlying normal tissue is referred as wound. Current healing therapy hinders the process of wound healing. Variety of wound dressings are available in market targeting different aspects of the healing process. Silver being the powerful antiseptic is available naturally and chitosan being biocompatible, biodegradable, hemostatic, anti-infectional wound healing accelerator provoke intensive research interest in this area. The current research is focused to augment the wound healing activity of chitosan and broad anti-bacterial activity of silver nanoparticles. In the present research, synthesis of Silver nano particle impregnated film (SNPF) was done in two steps. Firstly, silver oxide nanoparticles were prepared by chemical method using citrate reduction of silver nitrate. Nanoparticles were characterized using dynamic light scattering (DLS) method followed by incorporation of 2% chitosan solution into it. The developed Nano formulation was converted to film with chitosan as film forming agent. Antibacterial efficacy of these SNPF was assessed using Gram-negative (E.coli) bacterial studies. SNPF were evaluated for their mechanical properties like tensile strength, percentage elongation, swelling behaviour, water vapour transmission rate (WVTR). Developed SNPF will be further optimized for evaluating its antibacterial property. It can be concluded that SNPF is highly promising wound healing agent warranting further studies.

P075. Evaluation techniques for taste masking in oral dinsintegrating dosage forms

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Oral route of administration is considered to be most convenient route of administration. Orally disintegrating dosage forms disintegrate and disperse rapidly in mouth without administration of water. These dosage form include orally disintegrating tablets, films, oral lyophilisate. One of the critical parameter for evaluation of these dosage forms is taste. As some drugs possess bitter taste, taste masking becomes important parameter for evaluation. There are many techniques available for taste masking such as addition of sweetener and flavor, coating, complexation and use of ion exchange resins. The evaluation of taste perception can be done by selection of panelist trained previously for tasting different concentration of the drug. Alternative approach is evaluation of samples for taste masking using a panel of volunteers and filling of questionnaire related to taste masking, perception and palatability. However, safety and ethical issues are key concerns with such techniques. In the last decade, electronic taste assessment technique called Electronic tongue has emerged. It measures sensor signals with placebo, drug with bitter taste and formulation utilizing taste masking technique. It has application in food industry, environment monitoring besides in pharmaceutical industry. Electronic tongue utilizes the principle of potentiometry. The dosage form is converted to a solution in a suitable dissolution medium for assessment. Electronic tongue is marketed under the name Insent® and Astree™. Many dosage forms containing bitter drugs such as Diclofenac sodium, Sildenafil citrate, Cetirizine hydrochloride, Quinine sulphate are evaluated using electronic assessment technique. However, the major limitation of this technique is high cost.

P076. A combined approach of nanoparticles with iontophoresis using macrolide antibiotic for the treatment of eye diseases

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The aim of the work was to formulate Solid Lipid nanoparticles of macrolide antibiotic for the treatment of endophthalmitis and to enhance its permeation using a novel non-invasive technique 'Ionotophorosis'. Solid lipid nanoparticles were prepared by nano-precipitation technique followed by ultra-sonication method. For the selection of lipid, surfactant and co-surfactnat, initially solubility studies were performed. Preliminary trials and fraction factorial design were carried out for final screening of selected lipid, surfactant and co-surfactant using varying the concentration of lipid, Surfactant and co-surfactant ratio and Surfactant concentration. From the fraction factorial design, two significant factors were selected i.e Drug to lipid ratio and Sonication time. For further optimization 32 full factorial design was applied. The dependent variables selected were particle size, % entrapment efficiency and % drug loading. Based

on QbD approach, the final formulation was optimized. In-vitro diffusion studies were performed using multi diffusion cells in phosphate buffer 7.4. To enhance the permeation of drug, the optimized final formulation was undergone through iontophoretic technique. Ex-vivo study was performed on the goat eye and the permeation was checked. The iontophoresis technique was found to be very useful as systemic toxicity can be avoided due to enhanced permeation. So, with combination of the solid lipid nanoparticles and iontophoresis, controlled release formulation along with increased permeation can be formulated and intra-vitreal injections can be avoided.

P077. A Review on: Self emulsifying drug delivery system to improve bioavailability

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Oral route has always been the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms because it is very suitable for drug delivery and non-invasive. The oral drug delivery system of lipophilic drugs has a major challenge because of low and erratic bioavailability which results from poor solubility. This may lead to high intra-inter variability, lack of dose proportionality and therapeutic failure. More than 50% of potential drug products suffer from poor water solubility. The improvement of bioavailability of drugs with properties one of the greatest challenge in drug formulation. For the therapeutic delivery of lipophilic active molecules (BCS class II and IV drugs), lipid based formulations are inviting increasing attention. There are number of technologies are available to deal with improving bioavailability of insoluble drugs such as micronization, solid dispersion and different technologies and poor solubility. One of the techniques is Self-emulsifying drug delivery system. Self-emulsifying drug delivery system (SEDDS) has ability to improve bioavailability of poorly aqueous soluble drugs. SEDDS consists of oil, surfactant and co-surfactant. Combination of these used to measure solubility of poorly water soluble drugs and increased the absorption. SEDDS has gained attention due to enhance bioavailability enabling reducing in dose and most consistent profile of absorption, selective targeting of drug toward specific absorption window in GIT and protection of drug from the unreceptive environment in gut. This article provides you a complete overview of self-emulsifying drug delivery system to enhance bioavailability.

P078. Photosensitizer-loaded poly(ethylene glycol)-poly(d,l-lactic acid) polymeric micelles for effective photodynamic therapy

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Lack of effective treatment results in the low survival for patients with cancer. Photodynamic therapy (PDT) has emerged as an effective therapeutic option for the treatment of various tumors. In PDT, certain compounds, known as photosensitizers generate light-induced cytotoxic reactive oxygen species (ROS) to induce cell apoptosis or necrosis. Chlorines are promising compounds for PDT because of their high absorption in the infra-red wavelength region. However, the poor solubility, high rate of aggregation, rapid blood clearance, and weak internalization of the photosensitizers inhibit its anticancer efficacy. In our study, a poly(ethylene glycol)-poly(d,l-lactic acid) nanocarrier (mPEG-PLA) is employed as a carrier of the hydrophobic photosensitizer, chlorin e6 (Ce6). The Ce6-encapsulated micelles were stable with particle size of 189.6 ± 14.32 with zeta potential -20.2 ± 4.73 (Ce6-mPEG-PLA). The micelles significantly promoted the cellular internalization of Ce6, enhanced the generation of ROS in the tumor cells after irradiation compared to free Ce6. The cellular phototoxicity of Ce6-mPEG-PLA against A549 human lung adenocarcinoma cells was markedly enhanced compared to free Ce6 in-vitro. As a result of their efficient cellular delivery, small size, and lack of dark cytotoxicity in normal tissues, the Ce6-loaded mPEG-PLA micelles may provide an effective tool for photodynamic therapy of solid tumors.

P079. Studies in development and optimization of rifampicin loaded chitosan nanoparticles for the treatment of tuberculosis by pulmonary delivery.

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The present work was carried to develop, evaluate and optimize rifampicin loaded spray dried chitosan nanoparticles for pulmonary delivery of rifampicin. Rifampicin is the first line agent for the treatment of tuberculosis and pulmonary delivery of nanoparticle formulation of rifampicin would direct deliver the drug to lungs which could reduce drug associated side effects. Spray drying process variables studied for effect on mean particles size, entrapment efficiency and cumulative drug release, indicated that feed rate had a major effect on mean particle size of nanoparticles. Tripolyphosphate was found to be a superior cross linking agent as compared to glutaraldehyde. Based on preliminary studies a 32 full factorial design was applied to evaluate and quantify the effect of independent formulation variables namely concentration of chitosan (X1) and polymer: drug ratio on predetermined dependent variables namely mean particle size (Y1), cumulative drug release at 1 hr. (Y2) and at 24 hr. (Y3). The statistical analysis revealed that both independent variables had a significant effect ($p < 0.05$) on dependent variables. The optimized formulation prepared by applying desirability approach (Minitab 17 software), revealed a close agreement between theoretical and practical results. The optimized formulation (D = 0.8145) had mass median aerodynamic diameter (MMAD) of 4.83 µm, indicating that the nanoparticles would be able to reach to deep lungs and could successfully deliver the drug to alveolar macrophage.

P080. Quantum dots: a miracle tool in nano-formulations and its evaluation

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Nano-formulations with their unique properties have cemented a formidable place in the field of pharmaceutical technology and have been a revolution in specific and targeted drug delivery. Chemotherapy demands that nanoparticles should have target specificity and for this it is important to monitor the efficacy of nanoparticles and how nanoparticles act on cancer cells. Novel nanocarriers like Quantum dots (Q-dots) have carved a niche' for themselves in not only as a nanocarrier but also as an evaluation tool for tracking nanoparticles inside body after administration. Quantum Dots are tiny semi-conductor nano-crystals, composed of elements of periodic groups II-VI or III-V (for.eg. cadmium), that are used widely in bioconjugation. Unlike conventional carriers used, Quantum dots employ narrow particle size range (2nm- 10nm), they do not elicit immunogenic response, enhance PK properties and have minimal side effects. Quantum dots help in real-time monitoring of nanoparticle inside body thus enabling to acquire morphological characteristics of tumor which is a prerequisite in designing targeted nano-system. Recent trends in surface engineering and replacing toxic metals with organic compounds in Q-dots to reduce its toxicity inside body has led to its use directly as a novel drug delivery system. Quantum dots has emerged as a miracle tool in tracking of nanoparticles inside the body and has surely been a breakthrough in monitoring and evaluation of nano-formulations. Modified Q-dots on other hand has shown a promising and bright future as a novel drug delivery system, enough to keep researchers' mind tingling with quest for an innovation.

P081. Dissolution enhancement of an antifungal drugusing nanosuspension approach

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Oral administration is the most favorable route of drug delivery. Nevertheless, many hydrophilic drugs, administered orally exhibit low oral bioavailability due to low solubility. BCS class-II drugs are major challenge to modern drug delivery system, because of their poor water solubility and there by poor dissolution which leads to low bioavailability. Approaches like addition of solubilizers, co-solvency, micronization or nanonization may be used to enhance the dissolution of drugs. Nanosuspensions have revealed their potential to tackle problems associated with the delivery of poorly soluble drugs, and are unique because of their simplicity with respect to manufacturing and scalability. Itraconazole (ITN) shows only 45% bioavailability because of its low solubility. Various techniques like High speed homogenization, High Pressure Homogenization and reprecipitation + high pressure homogenization (NANOEDGETM) were screened with purpose of selection of best suitable technique to formulate nanosuspension. Out of which NANOEDGETM was found good. Suitable surface stabilizer and surfactant were selected on the basis of drug-excipient compatibility and particle size. The spray drying method was used and obtained powder was blended with HPMC E5 as surface stabilizer and filled into the capsule after blending with other diluents. Evaluation parameters

like Particle size, % Drug release, moisture content and % assay were performed. Optimized batch had 81% dissolution, which shows 1.52 times more solubility than marketed formulation. Amongst all the techniques NANOEDGETM was found most suitable for nanosuspensions formulation. Further optimized formulation of ITN Nanosuspension was proven stable in stability study (40 °C/75% RH). Formulating nanosuspension of ITN had increased the dissolution. In conclusion, the developed nanosuspension of ITN may improve bioavailability.

P082. Development and Characterization of Matrix Based Sustained Release Delivery System of Ropinirole Hydrochloride

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Ropinirole hydrochloride, a non-ergoline dopamine agonist, is recommended for use in Parkinsonism and Restless Leg Syndrome. Rapid absorption and elimination of the drug from the conventional tablet, as reflected from the AUC which shows a typical peak-valley curve; necessitates the uniform concentration in body to produce the therapeutic effects. Owing to rapid solubility of the drug, it is further difficult to maintain a steady state plasma level by sustaining the drug release and also seems challenging. The present study was aimed to develop sustained release matrix tablets of Ropinirole hydrochloride using different types of hydrophilic and hydrophobic polymers in combination, with wax materials such as Cutina and Compritol in varying concentrations. PVP K30 in Isopropyl Alcohol was used as a granulating fluid. It was found that combination of HPMC K100M and Benecel with wax material Cutina showed satisfactory results. Simplex lattice design was adopted to optimize amount of HPMC K100M (X1) and Benecel (X2) in different proportions and amount of Cutina (X3), while studying the effect of these variables on the responses i.e. dissolution profile of the matrix tablets after 2hours (Y1), 8hours (Y2) and 18hours (Y3). Optimization of the batch was done by statistical treatment of the data using surface response plot. Results revealed that all three variables were significantly affecting to all three responses. Design was further validated by formulation and evaluation of check point batch. Stability study for the optimized batch indicated good stability.

P083. Current update in oral osmotic drug delivery systems

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Conventional drug delivery systems show erratic drug release and difficulty in achieving required concentration at particular target. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. The osmotic-controlled release oral delivery system is an advanced drug delivery technology that involves osmogens which create osmotic pressure as the driving force to deliver usually once-daily, in several therapeutic areas and overcome above mentioned drawbacks. Oral route is widely used routes of drug administration because of its advantages of ease of administration, improved patient compliance and convenience. Oral ODDS release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT. It is mainly governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). ORAL Osmotic drug delivery devices are composed of an osmotically active drug core, which is surrounded by a rate controlling membrane. Oral ODDS is driven by an osmotic gradient rather than the concentration of drug in the device. In the market as Oral ODDS Anti-psychotic, Anti-hypertensive and Anti-diabetic drugs are available. The aim of present work is to discuss formulation, factors, advantages disadvantages, different types of oral osmotic system and current update in Oral ODDS.

P084. pH responsive drug delivery system: an overview

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The conventional drug delivery system has many limitations requires high drug dose, repetitive administrations, may not have controlled release, toxicity and many side effects. As controlled

drug delivery system is used to target drug to specific site to obtain desired effect as well as to improve the pharmacokinetics profile of drug, out of various stimulus, the tissue pH become more significant parameter. In certain type of drug administrations, it is required to deliver drug in accordance to the pH of the tissue's environmental and physiological conditions. Different organ systems exhibit different pH, which opens up pH as one of the most preferable stimulus in controlled delivery system. pH responsive drug delivery system (PRDDS) deliver the drug at specific time as per the pathological requirement of the disease leads to improved patient therapeutic efficacy and compliance. The PRDDS has been widely used in treatment of diseases like asthma, cardiovascular diseases, peptic ulcer, hypertension, cancer and many more. Some pH sensitive polymers like poly acrylic acid, poly (N, N- diethylaminoethyl methacrylate), poly (L-lysine), poly (vinyl pyridine), poly (vinyl pyrrolidine), poly (vinyl-immidazole) and chitosan are used extensively. These polymers show a sharp change in properties with small or modest changes in pH condition, makes PRDDS as one of the smart drug delivery system. Newer polymers are developed today which proven pH dependent. This explored opportunities of these polymers in biotechnology, nanotechnology and colloid based drug delivery system.

P085. Future perspectives of protein and peptide in parenteral drug delivery system

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Protein and peptide are structural and functional unit of life confrom amino acids. Discovery of insulin in the early 1900s initiated the research and development to improve the means of protein delivery in patients. Although, great emphasis has been placed on bringing oral protein and peptide therapeutics to market, parenteral delivery still remains the major mode of administration. Other routes such as oral, nasal, pulmonary and buccal are considered more suitable and convenient compared to parenteral administration. However, improving biological half-life, stability, bioavability and therapeutic efficacy is central to protein and peptide delivery. Several approaches have been tried in the past to improve protein and peptide in-vitro/in-vivo stability and performance. Approaches may be broadly categorized as chemical modification and colloidal delivery systems. Various chemical approaches such as PEGylation, hyperglycosylation, mannosylation, and colloidal carriers including microparticles, nanoparticles, liposomes, carbon nanotubes and micelles are used for improving protein and peptide delivery. The main advantages of protein and peptide through parenteral route is rapid absorption, bypassing of first pass metabolism, avoidance of proteolytic degradation. Some limitations are overdosing necrosis, local tissue reaction and hyper sensitivity. Recent advances in protein and peptide thermosensetive in-situ gel using Pluronic is developed which shown prolong drug release by parenteral route holds the bright future in various therapy. The present review is an attempt to discuss the novel approaches and applications of parenteral protein and peptide drug delivery.

P086. Design and optimization of Multiparticulate System of Gastro Protective Agent

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Multiparticulate drug delivery systems (MDS) has gained importance over conventional tablet dosage form as it offers several advantages like by-passing gastric transit time, reduced chances of dose dumping, improved dissolution due to larger surface area. MDS also provides variable release profile in unit dosage form. Gastro-protective agent (GPA), as name itself suggests, functions as agent protecting the mucous membrane from being damaged. Various GPAs available are classified based on their mechanism to protect gastric mucosa. One such category, Proton pump inhibitors, comprise of agents like Omeprazole, Rabeprazole, Esomeprazole, Lansoprazole. Current study involves development and optimization of immediate release pellets of Esomeprazole magnesium trihydrate. It has been available as delayed release pellets, tablets and suspension. The pellets were manufactured using extrusion-spheronization process. Water, being used as granulating fluid, an alkalinizer had to be added to the formulation, to stabilize the drug. Microcrystalline cellulose was used as spheronizing aid, hydroxypropyl cellulose as binder and Croscarmellose sodium as disintegrant. Central composite design was used for optimization of formulation and runs suggested were manufactured and evaluated. Evaluation parameters include pellet size distribution, circularity of the manufactured pellets, assay and dissolution. Scanning electron microscopy was performed to study the surface morphology of the final pellet batch. Pellets of good sphericity were achieved which showed nearly complete drug release within 30-45 min. Immediate release pellets were successfully designed and optimized.

P087. Transungual drug delivery system: a promising tool for treatment of nail cancer.

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Nails due to their uninterrupted exposure to warm and moist environment have been susceptible to various bacterial and fungal infections like onchomycosis and psoriasis. Demerits associated with conventional dosage forms like topical creams and oral formulations are irritation, lesser retention time and excessive adhesiveness leading to patient non-compliance. Transungual drug delivery has emerged as one of the most potential and a novel approach in combat of such diseases. Recent trends have been on using nail lacquers as a vehicle to improve permeation through nail. These formulations are essentially organic solutions of film-forming polymer and contain drug to be delivered. The major advantage of Nail lacquers are that they can produce reasonable drying time without developing bloom, thus improving patient compliance. The major hurdle in this field of transungual delivery for effective drug delivery includes, a wide array of options in improving penetration through nail using various mechanical, physical and chemical methods. However Evaluation of transungual drug delivery is currently under investigation and has not been reported in any guideline or official compendia. Sophisticated techniques such as iontophoresis and photodynamic therapy have been proven to improve transungual permeation. Bottlenecks to transungual drug delivery are the limited permeability of the nail as its chemical composition differs from the body membrane. So the recent focus is emphasizing on development of water based lacquers which may hydrate the nail plate and enhance the permeation into nail. There is need to explore newer avenues for making transungual dds effects.

P088. Gastro-retentive Drug Delivery System : An insight

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Sustained release formulation provides the merits of lower frequency of administration, absence of fluctuations in plasma concentration, reduction in side effects and patient compliance. However, few of the drugs fails to perform better due to natural physiological drawbacks like site-specific absorption, pH-dependent solubility and absorption, site specific degradation, etc. Novel approach as Gastro-retentive formulation is a type of sustained release formulation, which resolves the above issues by providing longer retention in stomach (upper region of GI tract) and allowing the sustained release of drug like infusion therapy to either site of absorption or site of action for getting desired therapeutic outcomes. Gastro-retention may be achieved by floating system (low density formulation), expandable system (swellable formulation), bioadhesive system or high-density systems. Variety of drugs has been explored for GRDDS and many of them have been clinically proven. Different research scientists have proposed several evaluation techniques to assess the formulation parameters by in-vitro techniques like floating time, floating lag time, swelling index, bioadhesion, modified dissolution techniques, etc. Moreover, various in-vivo techniques has been used to check the gastro-retention as formulation performance like roentegenography, gamma scintigraphy, ultrasonogrpahy, etc. The current review focuses on approaches for GRDDS, drugs seeking gastro-retention, in-vitro and in-vivo techniques for evaluation as well as review on current market status for GRDDS based platform technologies and products by multi-national companies. This review would provide an insight about current trends in GRDDS to formulation scientists.

P089. Niosomes drug delivery in cancer therapy

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Cancer is one of the major issues in health-care to deal with. Though various research have been done on cancer therapy, the challenge to achieve localized drug delivery system to the targeted cells without harming the healthy normal cells still remains as a major concern for the scientists. Non-ionic surfactant vesicles (NSVs or Niosomes) are getting a great attention as a cancer targeted drug delivery system due to their promising result in the field of cancer therapy. Niosomes are made up of non-ionic surfactant entrapped in cholesterol moiety. They may be uni-lamellar or multi-lamellar depending on the method used to prepare them. The stability of the niosomes depends on type of surfactant, nature of drug encapsulated in the vesicle and storage temperature. Niosomes can entrap

both hydrophilic and hydrophobic drug, prolong its circulation in the body and enhance the penetration of drug into targeted tissues and reduces the risk of toxicity. Many niosomal drug delivary via transdermal route shows improvement in its therapeutic efficacy. Since Niosomes are biodegradable, biocompatible and non-immunogenic, they can be utilized for drug delivery without any side effects. Niosomes have been successfully developed for targeted drug delivery in treatment of breast cancer and ovarian cancer. Anti-tumor agent like florouracil, tamoxifen, methotrexate, paclitaxel, doxorubicin have been delivered using niosomal drug delivery system.

P090. Nanoparticles as smart drug delivery system for the management of cancer

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Cancer, a life threatening disease characterized by the uncontrolled growth and spread of abnormal cells, is still the top most common cause of death in the world. The mode of treatment used for management of various cancers includes surgery, radiation, hormone therapy, and chemotherapy. Although these conventional therapies have improved patient's survival, they have several limitations. For example, conventional cancer chemotherapy has the cancer therapeutic agents distributing non-specifically in the human body, thus these drugs affect both cancerous and normal cells. This non-specific distribution of drugs limits the therapeutic dose within cancer cells while providing excessive toxicities to normal cells, tissues, and organs; and thereby causing several adverse side effects. Nano formulations shows size in a range of 5-200 nm due to this it has been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy. They can not only be apart range from sizes (1-1000nm) but also be made using a variety of materials including polymers (e.g. biodegradable polymeric nanoparticles, dendrimers), lipids (e.g. solid-lipid nanoparticles, liposome), inorganic materials (e.g. metal nanoparticles, quantum dots), and biological materials (e.g. viral nanoparticles, albumin nanoparticles). In addition, they can be tailored to simultaneously carry both drugs and imaging probes and designed to specifically target molecules of diseased tissues. Nanoparticles for anti-cancer drug delivery had reached the first clinical trial in the mid-1980s, and many more products can explore and are under process. This review focuses on applications of nanoparticle and formulations of cancer drugs.

P091. Application of Ion Exchange Resin as a Carrier in Drug Delivery System

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Ion exchange resins are cross-linked polymers having high molecular weight, which are insoluble in water and manufactured from organic polymer having an ionizing functional group. Ion exchange resins (IER) are gaining popularity as pharmaceutical excipient due to their versatile property. IER works on the principle which involves a reversible process of interchanging the exchangeable ion of equal charge with the surrounding insoluble organic polymer having charged functional site. Resins contain appropriately substituted acidic groups, such as carboxylic and sulfonic for cation exchangers; or basic groups, such as quaternary ammonium group for anion exchangers. The characteristic of ion exchange resins mainly depends upon their physical properties such as degree of cross-linking, porosity, acid base strength, stability, purity and particle size. The use of IER plays an important role in the development of controlled or sustained release systems because of their better drug-retaining properties and prevention of dose dumping. These resins are also used in development of fast dissolving or site specific drug delivery system including nasal and transdermal drug delivery. Taste masking of bitter drug is one of the application of these resins. IER can be utilized to improve drug safety and efficacy, enhance patient compliance, reduce dosing intervals and increase drug stability. Major drawbacks include lower potential for dose variation, higher cost. Amberlite, Dowex are amongst the most widely used ion exchange resin in pharmaceutical industry. IER are now gaining more preference as an excipient in pharmaceutical drug delivery system due to their unique characteristics when compared with conventional excipients.

P092. Challenges in development of polymeric nano capsules in drug delivery.

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Conventional controlled drug delivery shows some of the problems of conventional therapy which can be overcome by nanocapsules having enhanced efficacy of given drug. Polymeric nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because of its unique properties i.e. sustained release properties, subcellular size, biocompatibility with tissue and cells. This review represent different preparation methods for nanocapsules like Emulsion-diffusion, Nano-precipitation, emulsion-coacervation, polymer coating and layer by layer, double emulsification from the view of the mechanistic and methodological aspects involved. Also, a comparative determination is given by the size, zeta potential, shell thickness, dispersion pH, release of the active substance, encapsulation efficiency in-vivo and in-vitro, stability using as the basis the data reported in the different research published. The main aim of this review is to delineate preparation technique available for production of polymeric nanocapsules. Due to advancement of technology, the drug loaded nanocapsules can be developed by simple, safe and reproducible techniques. Depending on the physicochemical characteristics of the drug, it is possible to choose best method for the preparation and the polymer to produce nanoparticles. The restrictions like one particular process or techniques is not suitable for all drugs, post preparative steps such as purification and preservation, inadequate stability of certain active compounds are to be solved. Despite of these technological challenges, nanoparticles have been shown great future prospectus for the development of drug delivery system.

P093. Preliminary Investigations In Development Of Fast Dissolving Film Of An Antipsychotic Drug

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In the current scenario oral drug delivery is a widely opted approach for drug administration; however, oral route confines some drawbacks in spite of its tremendous advantages. To overcome the disadvantages of swallowing or chocking problem, first pass metabolism and stability related issue; oral film formulations is one of the unique approach. The oral film technology is gaining popularity in geriatrics and pediatrics dosage forms as per its edge on over other formulations like patient compliance with minimal dose and frequency, as well as ability to form variety of films with varied therapeutic outcome. Fast dissolving film is the category of immediate release formulation which offers several advantages like rapid disintegration, quick dissolution and improved bioavailability. The present investigation focuses on formulation development of fast dissolving film of an anti-psychotic drug by solvent casting method. Developed films were evaluated for its organoleptic properties, casting ability, flexibility, tensile strength, mucoadhesion, disintegration and dissolution. Varieties of film forming polymers were explored in preliminary batches to identify suitable polymeric materials which provide desired formulation characteristics. Effect of casting surface, solvent media, temperature and duration for oven exposure were also studied. Concentration of film formers and plasticizers were varied and optimized. Tensile strength of films was found to be increased at higher concentration of polymer, whereas flexibility was increased at higher concentration of plasticizer. The study shown the possible solution for formulation of fast dissolving films with its desired characteristics.

P094. Exploring novel design and evaluation of implantable pressurize pump for delivery of sustained release formulation

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Implantable drug delivery systems are currently based on three basic mechanisms, swelling control, osmotic pumping and diffusion system. Based on these mechanisms five different types of pump systems like infusion pump, peristaltic pump, osmotic pump, positive displacement pump and controlled release micro-pumps have been marketed worldwide. Currently marketed osmotic implantable pumps have cost around 450-500$. This limits the applications of such type of devices for effective sustainable drug delivery at research level and development of novel mechanical pressurized pump having similar features like currently available implanted pumps would serve as a better and cost effective alternative. The proposed mechanical pressurize implantable pump (MPIP) will be made up of polyetheretherketone (PEEK) material outer side having high resistant towards any chemical and compatible with the internal body environment. The inner layer or drug reservoir of the device lined with PEEK material would serve as a movable chamber, with functionally controlled movement of diaphragm or piston at sustained pressure.

Drug chamber would be designed to have connection with connector to control the out flow of the fluid. The developed MPIP will be characterized for the delivery of all types of injectable conventional formulations like solutions, suspensions and emulsions. The characterization of formulation will be done on the basis of in-vivo compatibility of MPIP, in-vitro pumping efficiently, Start-Up time, Pumping duration/rate and reproducibility. The MPIP will be beneficial for cost effective way in research, and may be further useful clinically for powerless sustain release formulation delivery based drug development.

P095. Formulation and process challenges in solidification of Self Emulsifying Drug Delivery System (SEDDS)-Industrial Prospective

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Most of the recent discovery of new chemical entity are addressing the challenges of poor solubility and hence adversity in their formulation development. To counteract this crunch of formulation, as dispersion of drugs acts as a prerequisite for its absorption, lipids based systems play a viable role in acknowledging this criticality and improving the absorption of highly lipophilic drugs and further their bioavailability through its lymphatic pathway. Recent work on SEDDS lack industrial scalability, deficits patient compliance and becomes uneconomical on commercial scale. This article details about the development of a self-emulsifying drug delivery system of a BCS class II as model drug using QbD approach and the process challenges involved while its formulation and characterization. Conventional preparation of lipid formulations is typically in liquid form which possesses certain drawbacks. To step up over those drawbacks and improve the efficacy and stability of dosage form, solid lipid formulations are augmenting popularity in recent years- however it is less explored in public domain. Therefore this article also covers the challenges encountered in formulation of liquid SEDDS into its solid form. The selection of excipients is done on the basis of solubility study and the ratios are optimized with the help of ternary/ pseudo ternary diagrams. High shear granulation technique is used for solidifying liquid SEDDS and then its evaluation study is performed. The study focuses on the critical material attributes (CMA's) and critical process parameters (CPP's) involved in development of solid SEDDS of selected drug.

P096. Comparative *in-vitro* dissolution study of Pramipexole and Pramipexole pamoate by using USP paddle method and the flow through cell system

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Dissolution or in-vitro drug release study is helpful in preliminary stages of formulation development and also used as quality control tool to study any batch to batch variations of marketed products. Pramipexole pamoate salt have 30 times less solubility in 6.8 pH buffer solution as compared to pramipexole. In present work dissolution profile of pramipexole and pramipexole pamoate was evaluated by using the USP paddle method as well as with the flow through cell (USP-4 apparatus) system. In USP-2 apparatus, sample was kept inside dialysis bag and in USP-4 apparatus, 2 ml flow rate was used with open mode. The dissolution profile was compared and in case of USP paddle apparatus, the amount of drug released in pramipexole was 80 % in 1 hour, whereas in pramipexole pamoate, 80 % of drug was released within 24 hours. Similarly, in USP flow through cell system, 80-90 % of drug was released within 10 minutes in pramipexole and in pramipexole pamoate, 80 % of drug was released within 2-3 hours. The obtained dissolution data were analyzed using different kinetic models as well as difference (f1) and similarity (f2) factors, also dissolution comparison was done using both powdered sample and suspension. The dissolution results shows that dissolution was retarded in pramipexole pamoate salt as that of pramipexole and hence, pramipexole pamoate can be further developed as a long acting formulation.

P097. Effect of space radiations on the stability of selected drugs and their tablet formulations

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Safe and efficacious medicines are essential for well-being of humans, whether on earth or in space. Space medication has been challenged with problems related to efficacy possibly due to altered stability by unique environmental factors of space comprising microgravity, acceleration, vacuum and radiation. All other variables are controlled during space missions except space radiation, which can penetrated inside the spacecraft, hence, it can be most contributing factor causing instability of space medicines. Proton and neutron radiation might cause significant effects on the stability of pharmaceuticals, as proton radiation contributes highest dose in space radiation and neutrons are highly penetrative. Therefore, the aim of present work was to evaluate the effect of proton and neutron radiations on the stability of metoprolol tartrate, amlodipine besylate and ciprofloxacin hydrochloride API and their tablets at different dose. The colour of tablets got darkened after proton irradiation whereas there were no changes after neutron exposure. Chemical changes were evaluated by high performance liquid chromatographic method. Results indicated increased percentage of impurities after proton irradiation in all drugs except ciprofloxacin whereas the drugs were found to be stable following neutron exposure. Radiation degradation profile was compared with photodegradation profile to identify presence of any unknown impurity.

P098. New avenue in Colon Targeted Drug Delivery System

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Colon targeted drug delivery system (CTDDS) improves efficacy of drug and enable the localized treatment. It is mainly advantageous for treatment of inflammatory bowel disease, ulcerative colitis and Crohn's disease. Advances in oral drug delivery system have improved bioavailability of drugs to colon. Primary approaches for colon specific drug delivery (CDDS), which includes prodrug, pH and time dependent system and microbially triggered drug delivery system achieved limited success and having limitations. The main challenge of Oral targeted drug delivery is that it is not amenable to the administration of drug for lower gastro intestinal diseases due to their release at upper GI tract, which lead to limited availability at lower GI tract. Different dosage forms like tablets, capsules, pellets, multiparticulates, microspheres, liposome, nanoparticulates etc. are used for colon targeting. Challenges for this system is the wide range of pH values, metabolic degradation by colonic microflora, requires protection against variety of gastric enzymes, lower surface area and relative tightness of the tight junction in the colon restrict drug transport. It focused on different approaches, mainly on formulation, carrier system and/or coating system, bioactive stability, patient compliance and evaluation of colon specific drug delivery system. Newly developed CTDDS, which includes pressure controlled colonic delivery capsules (PCDCS) and osmotic controlled drug delivery are unique in terms of colon cancer in achieving in-vivo site specificity and feasibility of manufacturing

P099. Pellet Formulations by Extrusion – Spheronization: A Review

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Pellets are similar to granules which may either filled in capsules or compressed to form tablets. Pellets have achieved popularity due to its merits such as high level of sphericity, better flow properties, ease of capsule filling; uniform packing, ease of coating, even distribution in the GI tract, etc. as well as based on excipients used, it may be modified for enhancement of drug dissolution; sustained or controlled or site-specific delivery of the drug. Pellets can be prepared by various techniques like Extrusion spheronization, Drug layering, Cryopelletization, Freeze-pelletization, Globulation, Compression, Balling, etc. Extrusion spheronization is a versatile process capable of producing pellets having unique physical properties. The dump mass of drug with polymers or excipients are extruded out as cylindrical rod shapes; and spherical pellets are obtained by cutting and rotating extrudes at high speed in cylindrical spheronizer having metal disk with protrusions for cutting. The major advantage

of extrusion spheronization method over other methods of producing drug loaded pellets, is its ability to incorporate high levels of active components and provide a high degree of flexibility during the design and development of oral dosage forms. A variety of extruders are currently in the market, differing in design features and operational principles. Various extruders used are Gear, Radial, Die roller, Cone, Dome, Mixer, Basket, etc. by various market leaders like Caleva, NICA, etc. By way of presenting this review, formulation scientists would be enlightened with in-depth knowledge on pelletization by extrusion-spheronization technique.

P100. Development and optimization of solid lipid nanoparticle for the management of fungal diseases using the concept of design of experiments

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The occurrence of fungal diseases is on increasing edge due to change in the environmental conditions and lifestyle. Superficial fungal infections have a greater share among various skin infections, hence its management becomes priority. The major problem faced with the conventional drug regime are increases frequency of dosing thereby increasing risk of adverse effects and this reduces patient compliance. Apart from these, due to short residence time of drug the relapse rates are high. This paves a way for development of novel drug delivery systems that have added advantages of overcoming the shortcomings of conventional therapy. Solid lipid nanoparticles being composed of physiologically compatible material, have a potential for sustain drug delivery owing to their narrow particle size distribution and self retaining property. They aid in increasing the permeation and hence may prove to be effective in increasing the bioavailability. The concept of design of experiments was applied for the purpose of screening and optimizing various parameters including pre-homogenization time, speed of high speed homogenizer, concentration of surfactant, drug to lipid ratio, pressure and number of cycles. Suitable designs were applied based on preliminary trials to further continue with the formulation development which reduced the number of experiments. The particle size was in the range of 150-250nm. The optimized batch was further characterized for DSC, XRD, TEM and AFM, latter it was subjected to in-vitro and in-vivo testing. The stability study was performed as per ICH guidelines.

P101. Advancement in dry powder inhaler (DPI) – A review

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The dry powder inhaler (DPI) is emerging system for pulmonary drug delivery. Many patients have traditionally used DPIs to treat asthma and chronic obstructive pulmonary disease. Recently, the development of new DPIs for delivering therapeutic proteins such as insulin has been accelerated by patient demands, and innovative research. The effectiveness of a powdered drug inhalation depends on the inspiratory flow rate generated by the patient. Dry powder inhaler is chiefly composed of micronized drug admixed with the carrier particles of larger size which serve as a flow avail. The desired aerodynamic particle size for the drug to get settled in alveoli(which is the main target site) is 1-5 µm. Micronization is achieved by milling and sieving method. In other cases, new medications have completely bypassed conventional inhalers and been formulated for use with unique inhalers such as the Staccato® device. Among these different devices, integration of software and electronic assistance has become a shared trend. Dry powder inhalers are categorized as either passive or active devices depending on the source of airflow for powder aerosolization. These devices are further subdivided as single –dose reusable, multidose, and single-use devices. Whereas, the major issue with passive devices is flow-dependent de-agglomeration driven by inspiration for patients with compromised lung functions, active devices are more suitable to deliver pharmaceutical aerosol to the lungs. Dose counters and breath-actuated MDIs are anticipated to improve asthma control. Technological update of the current state-of-the-art designs proposed to overcome current challenges of existing devices is also provided.

P102. A review of silver nanoparticles as an emerging agent for wound healing

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Silver nanoparticles have been focused by researchers because of their significant antibacterial properties. Silver is known to be an effective germ fighter and hence are widely recognized recently. In this context silver nanotechnology plays an important role since silver (either metallic Ag+ or that existing in ion form of Ag+) is known to be a broad spectrum antibiotic with antiseptic, antimicrobial, anti-inflammatory and prohealing properties. Thus, silver nanoparticles play a critical role as an important class of materials that have found application mainly in health industry as antibacterial agents (wound dressing, medical equipment), also in cosmetic and food industry and textile coatings etc. A variety of preparation techniques have been reported for the synthesis of silver nanoparticles such as laser ablation, gamma irradiation, electron irradiation, chemical reduction, photochemical methods, microwave processing and biological synthetic methods. Though silver nanoparticles are rampantly used in medical procedures and devices as well as in various biological fields, they too have their drawback of toxicity. Most common toxicity is Agyria which is caused when silver ions release from the dressing in large open wounds and results in grey- bluish colouration of the skin. The present work on silver nanoparticles for wound healing provides helpful insight into the development of new antimicrobial agents with the synergistic enhancement of the antibacterial mechanism against pathogenic micro-organisms. In this regard, it is essential to study the processes occurring with silver nanoparticles in biological environments, and the factors affecting their toxicity.

P103. Encapsulation of Rifampicin in a solid based lipid matrix to improve its stability on oral administration

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Rifampicin (RIF), an essential drug of antitubercular therapy shows stability issues at acidic pH of the stomach. RIF was encapsulated into solid lipid nanoparticles (SLNs) to increase its stability and enhance the poor and unpredictable oral bioavailability. Solubility studies indicate Compritol 888 ATO as lipid of choice having the highest solubility for RIF amongst various long chain solid lipids. Tween 80 and Poloxamer 188 were selected as surfactants based on sphericity, particle size and polydispersity index. SLNs were fabricated by micro-emulsification method followed by Cold High Pressure Homogenizer technique with considerable amount of drug loading and entrapment efficiency. The RIF-SLNs were spherical in shape and were further characterized using TEM, FTIR, DSC and Powder-XRD techniques. These SLNs were formulated with mean Particle diameter about 200 nm having mono-dispersed nature. In-vitro drug release profiles indicate 94% drug release in Phosphate Buffer pH 7.4 in 168 hours. Single Oral dose was administered to Sprague-Dawley Rats (SD) and Pharmacokinetic (PK) parameters were statistically evaluated in comparison with free RIF molecule to assess the bioavailability profile for 168 hours. In-vitro drug release profiles of RIF-SLNs as compared to free drug can be translated as a potential to a reduction in dose and dosing frequency of RIF. Hence, SLNs serves as a potential for excellent nanocarrier to improve the stability of the drug by encapsulating it.

P104. Development of site specific drug delivery systems for the treatment of colorectal cancer

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The aim of the present work was to develop a delayed release multiparticulate drug delivery system of sodium valproate, and to achieve a colon targeting for the treatment of colorectal cancer. The formulation consisted of a core pellets containing hydroxypropyl methylcellulose used for achieving a controlled release of drug. The in-vitro dissolution studies revealed that the optimized formulation consisted of core pellets containing drug to HPMC K4M ratio of 1:1 is capable of providing controlled release characteristics. The core pellets were further coated with Eudragit® S100:Ethyl cellulose (EC) coating capable of delaying the drug release. In-vitro drug release studies revealed that the core pellets coated with 7.5% w/w (coating level) and Eudragit S100/ EC 30:70 ratio was able to retard the drug release for period of 5 h (lag time) and provide a controlled release characteristics for a period of 24 h. Thus, it was concluded that the developed drug loaded gastro-resistant multiparticulate drug delivery system exhibited promising colon targeting and hence, may be used for the treatment of colorectal cancer.

P105. Functionality Investigation of Chitosan-PVA Composite for Drug Delivery

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Chitosan is a biopolymer, which is an amino polysaccharide got from the N-deacetylation of chitin. Rather than every single other polysaccharide having a monograph in a pharmacopeia, chitosan has a cationic character in view of its essential amino gatherings. These essential amino gatherings are in charge of properties, for example, controlled medication discharge, mucoadhesion, in-situ gelation, transfection, pervasion improvement, and efflux pump inhibitory properties. Because of synthetic alterations, the vast majority of these properties can even be further moved forward. On the benefits of chitosan for different sorts of medication conveyance frameworks is given. It is a characteristic polymer in light of the nearness of degradable compound Chitosan. Chitosan is circuit with PVA different arrangements of Chitosan-PVA mixes have been concentrated on. In the present study polyvinyl liquor (PVA), a manufactured, long-chain polymer, has been assessed concerning its appropriateness as an ophthalmic vehicle and with specific accentuation on its surface contact time and its impact on rate of recovery of corneal epithelium. A white granular powder, polyvinyl liquor is accessible in various evaluations, each contrasting in level of polymerization, percent hydrolysis and remaining acetic acid derivation content. These influence a definitive physical and compound conduct with the outcome that one has a greatly adaptable arrangement of pitches with which to work. The phase morphology and mechanical property studied by scanning electron microscopy (SEM) and universal testing machine (UTM) at room temperature.

P106. Natural Polymers for colon targeted drug delivery system

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For many year colon targeted drug delivery system (CTDDS) have been studied extensively for sustained drug delivery to reduce dosing frequency, to delay delivery to the colon to achieve high local concentrations in the treatment of diseases of the distal gut, to delay delivery to a time appropriate to treat acute phases of disease (chronotherapy or chronopharmaceutics) and historically, to deliver to a region that is less hostile metabolically. CTDDS has been used for many diseases like ulcerative colitis, Crohn's disease, Colonic Polyps, Colorectal Cancer, Diverticulosis, etc. Mainly four approaches were introduce for achieving colon targeting which includes pH dependent approaches, Time-dependent approaches, Enzymatically triggered drug release approach and prodrug approach. The selection of polymer plays an important role for achieving colon targeting of drugs. Using different polymer in different ratio and combination with various technology one can obtain various types of drug release profile. Selected polymer must protect drug in stomach pH, prevent premature of drug release in small intestine, compatible with drugs or peptides and it must be biocompatible and biodegradable in nature. Among various types of polymer hydrogels, polymer blends of natural and/or synthetic polymers are used in the pharmaceutical formulations. In this review we mainly focus on natural polymer and its application for achieving colon targeting drug delivery.

P107. Fluidized Hot Melt Granulation as a Platform Technology for Preparation of Modified Release Tablets

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Fluidized hot melt granulation (FHMG) is an emerging technique which encompasses the benefits of both dry and wet granulation methods. It embodies an innovative granulation technique capable of mixing and agglomerating pharmaceutical powders to produce uniform granules suitable for manufacturing of pharmaceutically elegant solid dosage forms. FHMG offers several advantages like absence of solvent, suitable process for granulation of moisture sensitive drugs, ability to granulate powders with poor flow, to name a few. This study was aimed at investigating the impact of formulation and process variables on in-situ FHMG. In this work, hydrogenated castor oil was used as solid meltable binder (selected after screening study). Hydrogenated castor oil acted as dual function excipient: as a meltable binder and as a release retardant. In order to determine the granulation and nucleation mechanism several parameters were

scrutinized like granulation time, fluidization air velocity and fluidization air temperature. These parameters were correlated to granules particle size distribution, granules flow properties and compressibility. The obtained granules presented a narrow particle size distribution having good flow properties. The crystalline structure of modal drug was retained in the final granules. It was observed that binder hydrophobicity has an impact on release controlling power of the binder. The amount of binder added in the formulation was observed to be the key factor influencing the release profiles. It could be concluded that, FHMG is a simple and rapid granulating method which enables a formulator to manipulate drug release depending on the nature and concentration of the meltable binder.

P108. Pharmaceutical Mini-tablets: A Brief Review

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The controlled drug delivery systems reduce the frequency of the dosing and to increase the effectiveness of the drug by localization. In oral controlled drug delivery systems, multiunit dosage form (MUDFs), like pellets and minitablets are most popular. The objective with brief review on formulation of minitablets which is formulated and designed individually and incorporated into capsule to release the drug at different sites and at different rates. Different combinations of mini-tablets include immediate release, delayed release, and/or controlled release formulations. Formulation and development of minitablets is one of the most recent and challenging technologies that combine the advantages of both tablets and pellet-filled capsules in one dosage form. Among all MUDFs, mini-tablets offer several advantages like they can be manufactured relatively easily, they do not require any solvent for their production, can be coated reproducibly, and also requires less coating material as well as it offers great flexibility, target drug delivery, uniform bioavailability, diameter equal to or smaller than 2–3 mm and stability problems are less. Many types of mini tablets has been reported such as bio-adhesive mini tablets, pH responsive mini tablets, gastro retentive mini tablets, pediatric mini tablets, oral disintegrating mini tablets, etc. This review emphasizes on advantages of mini tablets, types of mini tablets, its methods of manufacturing and modes of administration, and evaluation of mini tablets.

P109. Lipid nanosystems for improved in-vivo efficacy of carbamazepine

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Epilepsy is a disease existent for ages and still continues to affect approximately 50 million individuals worldwide with around 10 million epilepsy cases in India.(1) Carbamazepine, a widely used antiepileptic drug since 1950's is limited by its higher dose and related incompliance as well as the associated side effects. Such issues are attributed to its low and variable bioavailability owing to its poor aqueous solubility. (2) These issues could be resolved by loading carbamazepine into solid lipid nanoparticles. The objective of this research work is to study the enhancement of bioavailability of carbamazepine by incorporating it in Compritol® based SLNs. The SLNs were prepared by micro-emulsification based technique utilizing Tween-80 and soy lecithin as the surfactant and co-surfactant respectively. SLNs were characterized for particle size and distribution, morphology, entrapment efficiency, compatibility, solid state characteristics, in-vitro drug release studies and residual solvent content. Effect of various formulation parameters was evaluated on the SLN properties. In-vivo pharmacodynamic studies were carried out in mice which reflected an increase in efficacy of carbamazepine when loaded into SLNs. In-vivo pharmacokinetic studies are also being carried out.

P110. Dry powder inhaler formulation of rifampicin nanoparticles intended for tuberculosis therapy: freeze dried preparation

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Tuberculosis is a dreadful disease serving as a threat to the life of millions of people worldwide. Inhaled therapy is emerging as a promising tuberculosis treatment attributed to more localized exposure of anti-TB drugs to the site of action. The current therapy involves

the administration of oral dosage forms for a long period of time thus leading to severe side effects. In the current research work, rifampicin nanoparticles were prepared to achieve local targeting into the lungs. The method of preparation used was ionic gelation followed by probe sonication. The prepared nanoparticles were characterized for particle size, entrapment efficiency and drug loading. Herein we developed dry powder of the nanoparticles by freeze drying. Lactose was used as drying adjuvant. The dry powder formulation was evaluated for aerosolization efficiency, rifampicin release, antimicrobial activity against Bacillus subtilis, pharmacokinetic studies and in-vivo toxicity studies using histopathology. The nanoparticles showed particle size ranging between 124.1±0.2 nm and entrapment efficiency of 72.00±0.1%. The dry powder showed MMAD of 3.3±0.18 µm and FPF value of 33.27±0.87. The formulation showed sustained release upto 24 h. The in-vivo studies showed maximum residence of the drug in the lungs of 24 h providing slow clearance of drug. No sign of toxicity was seen in the histopathological studies of the lungs. Thus freeze dried nanoparticles of rifampicin can prove to be efficient system for direct targeting of the lungs for the successful treatment of tuberculosis.

P111. Enhancement of Nebivolol Solubility using Nanocrystallization Formulation and Development

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In recent years, Nanocrystals have emerged as potential drug delivery system for the enhancement of water solubility of drug candidates. Nebivolol (BCS class II) is lipophillic drug used in hypertension having log P value of 3.8 and low water solubility of 4.43mg/L. High first pass metabolism accounts for low oral bioavailability (15-25%) of drug. The purpose of work was to develop Nebivolol nanocrystals for the enhancement of solubility and oral bioavailability. Further, Oral Disintegration Tablets (ODT) of Nebivolol nanocrystals was formulated for reduction of first pass metabolism. Nanocrystals were prepared using High Pressure Homogenization (HPH) technique. Various parameters including homogenization cycles, pressure, concentration of stabilizer, concentration of drug were optimized. Formulation was characterized by DSC, XRD and SEM analysis. Drying of nanosuspension was done by lyophilization with use of mannitol as cryoprotectant. Oral disintegration tablets (ODT) were formulated and % in-vitro drug release was performed as well as compared with marketed formulation. Prepared nanosuspension (0.5% drug, 0.1% pluronic F-68) was found to be having size, PDI and zeta potential of 270 ±20.6, 0.19 ±0.02, 18.2 ±1.7respectively. Process parameters optimized for final nanocrystal formulation were; homogenization pressure of 1000bar for 15 cycles. Cumulative % release from ODT was found to be 3 fold higher as compared to marketed formulation. Nanocrystalline formulation of Nebivolol was successfully developed and incorporated in ODT for desired effects.

P112. Development of copolymer to improve bioadhesion on soft tissue

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Balloon angioplasty has shown elastic recoil and negative remodeling of the arterial wall. Later, introduction of stents proved to be a significant advance in reducing the problems. But stimulated proliferation, migration of smooth muscle cells, and neointimal hyperplasia, is major constrain with the therapy. Brachytherapy and drug-eluting stents (DES) are considered the two breakthroughs against neointimal hyperplasia. However, concerns about stent thrombosis and incomplete elimination of in-stent restenosis with DES in complex lesions and patients justify the pursuit of research in this field. Therefore, drug eluting balloon came into the market that releases drug at the local site but the drug eluting balloon has less adhesion to the soft tissue which prevents uniform delivery of drug. The present study emphasizes on improving the bioadhesion on soft tissues and addressing the problem of uniform drug delivery. The bioadhesion on soft tissues can be improved by modifying the polymer by forming copolymers or functionalizing the polymer. In the present study sodium carboxymethylcellulose (NaCMC) has been chosen for the application. Copolymerization is done for further improving the bioadhesion. The enhancement in the bioadhesion is evaluated by hydrophilic behaviour study, platelet adhesion assay and texture analyser. Later, a thin film for coating onto the balloon is formed by electrospinning using the copolymerized and pure polymer. The nanofibers are characterized for surface morphology, mechanical properties, swelling and degradation behavior.

P113. Formulation and Evaluation of Solid Lipid Nanoparticels of Ritnovir for lymphatic targeting

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Advances in current understanding of the role of lymphatics in physiological changes and immunity, have driven the recognition that lymphatic targeted drug delivery systems have the potential to transform disease treatment strategies. In current research study, solid lipid nanoparticles formulation is investigated as targeting carriers for lymphatic system. Essential requirements for lymphatic targeting of solid lipid nanoparticles formulations includes, a logP value of the system between 3-5 and a particulate size range of 70-130nm. Solid lipid nanoparticles carriers were formulated with medium or long chain triglycerides, maintaining the size range within 70-130nm to ensure the lymphatic availability of antireteroviral drugs used in HIV therapy. Ritonavir is highly lipophilic (log p 3.9) protease inhibitors antiretroviral drug and less bioavailability. Ritonavir-SLNs were prepared with Precirol 5 ATO, Tween 80 and Poloxamer 188 as a lipid, surfactant and co-surfactant respectively using high pressure homogeniser. A (33) factorial design was employed; three factors such as lipid, surfactant and co-surfactant concentration were used. Parameters investigated includes particle size, polydispersity index (PDI), zeta potential, drug entrapment efficiency (EE %), drug loading efficiency (LE %) and in-vitro drug release of the SLNs. Optimized SLNs had particle size of 100±21 nm, zeta potential of–20±(–4.8) mV, EE o80±9.72% and cumulative drug release of 75±2.54% in 10 h.

P114. Novel Approaches in Colon Targeted Drug Deliveries

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Colon targeted drug deliveries are gaining importance for the treatment of colon diseases and for the local and systemic delivery of proteins, peptides, oligonucleotides, vaccines and other therapeutic drugs due to less enzymatic activity and longer transit time. Sustained colonic release of drugs is useful in nocturnal asthma, angina and arthritis. The aim of this poster is to focus on the recent novel approaches for colonic drug deliveries like-Nano-delivery for colon, pH sensitive colon- targeting polysaccharide hydrogel, Enterion capsule, Swallowable camera capsule, Robotic beetle, COLOL technology, CODESTM, MMXTM, PHLORALTM etc.

Keywords: Colon targeted drug deliveries, CODESTM, MMXTM, Enterion capsule.

P115. Formulation, Characterization and Optimization of Buccal Film of Local Anesthetic

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Local anesthetic is widely used for reversible loss of sensation and temporary relive from the local pain for mouth ulcer, and currently number of formulation like gels, cream, ointment, suspension, lozenges, tablet and spray are available for variety of drugs. Among all, semisolid formulations are widely used; however, longer stay of such formulation cause patient incompliance. The aim of the present study was to formulate and characterize the novel sustained release buccal film containing local anesthetic that could be hold for longer period into oral cavity which provides constant release of the drug for the longer period. In preliminary studies, variety of film forming polymers (HPMC 15cps, HPMC K4M, Pectin, Carbopol 934, HPC, PVP, PVA and Chitosan) were explored alone and in different combinations to obtain the buccal film formulation by solvent casting method; with desired characteristics like tensile strength, % elongation, folding endurance, drug diffusion (franz cell) and drug release study in dissolution apparatus. Experiments were also performed to optimize casting surface and amount of plasticizer to obtain the better film properties. The 32 factorial design was applied for further optimization of combination of selected polymers (PVA and Chitosan). The optimized batches were identified and formulated by generating the overlay contour plots to obtain the desired region. The optimized formulation were compared with the market formulations (semi-solid) for drug release study. In conclusion, the buccal film formulation of local anesthetic is promising formulation with improved retention time and desired drug release.

P116. Novel pH-independent delivery system of a poorly soluble weak base.

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pH-dependent solubility of BCS class-II drugs mainly affects their oral bioavailability. Majority of them are weak bases showing very significant solubility drop at increasing pH levels. Present study deals with formulation and optimization of pH-independent delivery system of a similar drug Quetiapine fumarate. Upper GI tract specific delivery of drug by microenvironment pH (pHM) modulation as dissolution enhancement was fabricated as multiunit filled capsule with once daily dosing frequency. The formulation was developed in the form of modified release capsule, comprising two components (i) bilayer capsule plug (CP) and mucoadhesive alginate beads (AB). The components were arranged in a manner that the extended drug release at upper GI tract was attained up to 18h. Each component was systematically optimized using 32 full factorial designs. Variables selected for optimization of CP were HPMC K100LV (X1CP) and Polyox® 303 WSR (X2CP) while those selected for AB were Noveon® AA-1 (X2AB) and fumaric acid (X2AB). In-vitro dissolution was carried out using modified multicompartment dissolution apparatus for more bio-relevant conditions. Responses measured during optimization were buoyancy parameters, drug released at specific time intervals, erosion study and mucoadhesion potential. The optimized formulation was characterized by relevant tests and stability study. In-vitro drug release kinetics of the optimized batch was best fitted in Weibull equation. In-vitro characterization of the delivery system revealed pH-independent release.

P117. QbD enabled formulation development of Orally Disintegrating Sustained Release Tablets (ODT-SR) of Poorly Water Soluble drug

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The aim of this study was to formulate and develop ODT-SR of a highly soluble drug Clozapine using QbD principles. The rationale behind formulation of ODT-SR was to prevent the drug from hepatic first pass metabolism. Initially the mucoadhesive microspheres were prepared and they were compressed in to the form of an Orally Disintegrating Tablet. For Microspheres, Initially risk assessment was performed to obtain critical material and process parameters. A Plackett- Burman design was than employed to find out most significant parameters. A 32 full factorial design was then used to find out main, interaction and quadratic effects of independent variables on response. Optimized batch was than compressed as an Orally Disintegrating Tablet. By Risk assessment, eight parameters were selected for further study. %Entrapment (Y1) and %Drug release (Y2) were selected as Critical Quality Attributes. Pareto ranking analysis suggested Drug: Polymer ratio(X1) and Stirring Speed(X2) were the most significant affecting parameters out of eight high risk variables. Optimization using Response Surface Methodology further clarified the relationship between the variables and CQAs and a design Space was established. The robustness of the process was also confirmed based on predicted and observed values. The optimized batch was than compressed and it releases the drug as per zero order kinetics. It can be concluded that ODT-SR can be successfully formulated using QbD principles.

P118. Cyclodextrin inclusion complexes of zolpidem tartrate for bioavailability enhancement

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β-CD complexes of Zolpidem tartrate were prepared in the molar ratio of 1:1 by kneading method and spray drying method. The FTIR, DSC and NMR studies depict the formation of complexes. In morphology studies the spray dried complexes were found to amorphous, uniform and homologous spherical particles whereas the pure drug was smooth, irregular surface and are needle like. The Percent drug content was found to be 98.4% for spray dried complexes and 97.8% for kneaded complexes. The in-vitro release of unprocessed drug, physical mixture, kneaded complex and spray dried complex was carried out in 0.01N HCl and about 66.32%, 71.7%, 76.81% and 95.46% drug release respectively was observed over a period 2h which shows improved dissolution rate of the drug. The prepared complexes were then subjected to stability studies for three months at 40ºC ± 2ºC/75% ± 5% RH. The drug content after 30, 60

and 90 days were found to be 98.21%, 97.01% and 96.79% respectively for spray dried complexes and 97.8%, 96.34% and 95.42% respectively for kneading complex. These observations suggest that the inclusion complexes were found to be stable under accelerated stability study conditions. In-vivo efficacy studies were performed to compare the inclusion complexes and pure unprocessed drug. The rats exhibited significant reduction ($P \leq 0.05$) in locomotor activity of pure drug, spray dried and kneading complexes on day 7 was 46.48%, 75.84% and 49.95% respectively and on day 14 was 55.04%, 65.79% and 66.62% respectively in comparison to control group. Thus, the drug complexes displayed better pharmacodynamic activity when compared with the pure drug.

P119. Development and characterization of polycaprolactone microspheres for rasagiline

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Parkinson's disease requires chronic treatment throughout life of patients which becomes less patient compliant as the patients suffer from rigidity of muscles and difficulty in swallowing which makes self-administration, oral intake and daily intake of drug inconvenient. Objective of the present study is to formulate and characterize long acting parenteral microspheres of rasagiline mesylate. Rasagiline mesylate was characterized by UV, NMR, FT-IR spectroscopy and DSC. Analytical method was developed and validated for ultraviolet spectroscopy and Ultra Performance Liquid Chromatography. Polycaprolactone microspheres were prepared using different methods. Different formulation variables such as drug-polymer ratio, outer phase PVA concentration, type of solvents used, outer phase volume and process variables such as homogenization speed, homogenization time were varied in order to obtain microspheres with optimum particle size, drug loading and entrapment efficiency. Microspheres obtained showed drug loading of 1.49-2.97 mg/ 100 mg of microspheres. Particle size and % yield varied from 4.79 to 35.64 µm and 42.13 to 85.93 % respectively. Drug release studies of microspheres showed release of drug for 45 days.

P120. Development of nanocrystals for solubility enhancement of carotenoid

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For more than two decades, naturally occurring carotenoids have gained importance among the researchers looking at their diverse applications. Amongst various carotenoids, lutein has an edge over the others due to its versatile use. However, it has been observed that the oral bioavailability of lutein is hampered due to its poor bioavailability which might be due to its lipophilic nature. The solubility enhancement techniques which have already been explored for lutein includes- nanocapsules, SNEDDS, micelles, liposomes, microemulsion, NLC, inclusion complexes, emulsion, SLN, SEPS etc.. Ball milling technique for size reduction is a cost effective, can be used at both lab scale and having ease in industrial scalability compared to High pressure homogenization. In present study, Plackett Burman Design was used for optimization of various process parameters of ball milling process.. The objective of the nanocrystal production of lutein was to develop formulations with increased solubility and dissolution using DoE approach. Optimized formulation was characterize using particle size analysis, solubility study, fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and in-vitro dissolution study. The D90 of optimized batch shows particle size 217nm(D90) which results in faster dissolution compared to pure lutien . The results of DSC and XRD study confirmed decrease in crystallinity of drug in nanocrystals as reason for improvement in solubility. The MTT assay shown antiproliferative activity of developed formulation. Thus, the results obtained in the study are in support for application of nanocrystal method in increasing the solubility and dissolution of Lutein.

P121. Design, Development and Optimization of Novel Trilayered Tablet Formulation For Controlled Delivery of Metoprolol Succinate

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Controlled release dosage forms maintain constant therapeutic levels of drug in the patient's

blood stream, ensuring chemical balance in blood chemistry, thus increasing the effectiveness of drug substance and reducing factors which might be detrimental to patients' health. Objective of the present study was to design, develop and optimize a controlled release formulation for BCS class I drug having no rate limiting factor towards its release from the formulation. In the present investigation, the release rate of metoprolol succinate taken as a model drug was controlled by formulating trilayered tablets composed of middle waxy matrix core and surface swellable hydrophilic barrier layers. Trilayered tablets were designed and optimized by 33 full factorial design taking drug release rates at 30mins, 6 and 12 hours as the response variable. Independent factors as critical quality attributes (CQAs) were screened from risk assessment studies. The design space constructed by applying DOE and multivariate analysis ensured formulation with the desired drug release. Data analysis revealed formulation containing drug: compitrol in 1:2 ratio, 200mg of HPMC K4M and 50mg of lactose as optimized based on desirability indices. Optimized formulation was evaluated for post compression parameters along with studies for swelling and erosion rate determination, morphology, release rate determination and release mechanism determination. Results revealed that all the excipients used in the formulation were compatible and the optimized formulation showed a release profile which was significantly similar to theoretically design release profile as per SUPAC guidelines. The release component "n" and regression coefficient values indicated Fickian based zero order drug release from the formulation.

P122. In-situ hydrogel of amine functionalised chitosan for the treatment of Rheumatoid arthritis

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Rheumatoid arthritis is an autoimmune disease. It is characterized by morning stiffness, fatigue, and fever. Treatment options of disease are non- steroidal anti-inflammatory (NSAIDs), Disease modifying anti-inflammatory drug and biological drug. They are symptomatic agents but produce unavoidable side effect like gastrointestinal toxicity, cardiovascular risk and anaphylaxis. Therefore, it is hypothesized that a polymer can be modified to achieve anti-inflammatory property and later the property can be utilized for the treatment of the disease. The modified polymer will be used for the formation of in-situ gel which can be used for site specific delivery of drug as well. Chitosan has been chosen for the functionalization with amine group which may improve its anti-inflammatory property. The rheological property and effect on molecular weight of amine functionalised chitosan was studied. The hydrogel of pure and functionalised chitosan has shown non -Newtonian flow behavior. The molecular weight has changed by functionalization and confirmation was done by FTIR.

P123. Development and evaluation of asiatic acid transdermal matrix patches for wound healing purpose

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The aim of this investigation is to develop and evaluate the novel transdermal drug delivery system (TDDS) for delivery of asiatic acid, isolated from S. robusta (SR) powder for wound healing purpose. The transdermal patches were prepared with hydroxyl propyl methyl cellulose (HPMC) polymer in methanolic solvent system and polyethylene glycol 400 (PEG400) or Propylene Glycol (PG) were used as plasticizers. The various physicochemical characterization studies of patches like tensile strength, thickness, folding endurance, percentage of elongation, moisture content and moisture uptake were carried out and In-vitro drug permeation studies of the patches were done for 8 hours in Franz diffusion cell using cellophane membrane as a skin membrane containing simulated wound fluid at 37°C. All prepared formulations indicated good physical stability. In-vitro permeation studies followed Higuchi kinetics, and the mechanism of release was diffusion-mediated. Transdermal films with HPMC and PG were showed the best result and it will be further subjected to the pharmacokinetic studies.

P124. Formulation development and optimization of Berberin loaded liposomes by Box-Behnken design: Stability and entrapment enhancement using stearic acid evidence from in-vitro ex-vivo stability study

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Berberine is a quaternary protoberberine alkaloid. It has multiple therapeutic actions that include the treatment of Cancer, bacterial infections, diarrhoea, intestinal parasitic infections etc. Previous reports suggest poor bioavailability of berberin due to low permeability through membrane due to its hydrophilic nature and metabolism. Liposomes are microscopic vesicles that are widely investigated for their use as drug delivery systems. Liposomes, like other nanoformulations, have several advantages viz., enhanced bioavailability, reduced toxicity, prevents metabolism and drug targeting using surface functionalization. But in-vivo stability and lower entrapment efficiency are the main hurdles for Liposomal drug delivery. The present study is designed for the formulation optimization of Berberin loaded liposomes prepared by thin film hydration method for better entrapment and in-vivo stability using stearic acid and cholesterol in optimum ratio as stabilizer. Critical process parameters (CPP) were selected by initial screening. Later, box-behnken design (BBD) was used for analyzing the effect of the selected CPP on critical quality attributes (CQA) and to generate a design space. The optimized formulation was further characterized by Transmission Electron Microscopy (TEM) and in-vitro drug release. Moreover, colloidal stability of the Liposomes in the biological milieu was assessed. Amounts of Phosphotidylcholine, cholesterol, stearic acid and sonication time were the selected independent factors for BBD. The delivery system showed sustained release over a period of 12 h. Berberin liposomes were found to be stable in the biological fluids indicating their in-vivo suitability.

P125. Design of 2,4-disubstituted Pyrimidine Derivatives as ALK Inhibitors using 3D QSAR, Pharmacophore and Molecular Docking Studies

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Cancer, also known malignancy is the most widespread and feared disease in the modern time. The Anaplastic Lymphoma Kinase (ALK) plays a major role in developing tumor processes and therefore has emerged as a promising target for therapy of certain cancers including the most prevalent non-small cell lung cancer (NSCLC). In the present work, 3D QSAR modeling, Pharmacophore generation and Molecular Docking studies were performed to identify important structural features responsible for ALK inhibition. A diverse set of 50 ALK inhibitors consisted of 2,4-disubstituted pyrimidine derivatives were used for CoMFA and CoMSIA (3D QSAR) and PLS analysis was used for validation of models. The alignment strategy was used for these compounds by means of Distill function defined in Sybyl X. The study produced models with satisfactory q2 of 0.908 and 0.832 for CoMFA and CoMSIA models, respectively. The Pharmacophore model was generated using GALAHAD module of Sybyl X. The Best model, having 6 features viz. 3 hydrophobic, 1 H-bond donor, 1 H-bond acceptor and 1-positively charged N, was taken as a query and virtual screening was performed using NCI database. Base on the information obtained through both approaches in form of features of pharmacophore model, hits of virtual screening and 3D-QSAR contour maps, 30 disubstituted pyrimidine analogues were designed. The designed molecules were subjected to the docking studies among which KP-7, 18, 26 & 27 showed good docking scores compared to the reference compound Ceritinib. This study may aid in development and optimization of novel more potent ALK inhibitors as anticancer agents.

P126. Role of NMDA Receptors in Chronic Constriction Injury Model of Neuropathic Pain: An Updated Meta-analysis

Kuhu Sharma, Dilip Sharma, Valencia Fernandes, Akash Deep Rawat, Shivangi Patel,

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Chronic Constriction Injury (CCI)-induced neuropathic pain is one of the most clinically relevant models that mimics the clinical symptoms observed in neuropathic pain patients, such as mechanical and thermal hyperalgesia. CCI-induced nerve injury involves release of pro-inflammatory cytokines and nociceptive mediators which increases the sensitivity of peripheral and central pain pathways by activating N-methyl-D-aspartate (NMDA) receptors. Here, we propose to study the neuroprotective effect of astaxanthin, a marine natural drug, having potent anti-oxidant and anti-inflammatory activities, in animal model of CCI-induced neuropathic pain. To explore further, a meta-analysis has been conducted to investigate the role of NMDA receptors in induction and maintenance of thermal and mechanical hypersensitivity in CCI model of neuropathic pain. Meta-analysis confirms the involvement of NMDA receptor up-regulation in spinal cord after chronic constriction injury. Based on the results of meta-analysis we proceeded to evaluate the antagonistic effect of the astaxanthin on NMDA receptor by using in-silico tools. The results obtained were encouraging enough to proceed further for in-vitro and in-vivo studies. Findings from the present study may open new therapeutic avenues for the prevention and treatment of neuropathic pain.

P127. Amelioration of Neuropathic Pain using Milk Thistle Seed Extracts

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Neuropathic pain is a debilitating condition that affects millions of individuals worldwide. Contemporary studies have found that tissue injury activates glial cells in the peripheral and central nervous system. Current pharmacotherapy for neuropathic pain such as opioids and non steroidal anti-inflammatory drugs (NSAIDs) predominantly act on symptomatic relief lacking satisfactory efficacy owing to tolerance development and undesirable side effects. Polyphenolic phytochemicals are ubiquitous in plants and are known to be protective in several neurodegenerative disorders due to their free radicals scavenging activity. Previous studies have reported milk thistle (Silybum marianum, Asteraceae) seed extracts to possess potent hepatoprotective, anti-alzheimer and anti-parkinsonism activities. In the present study we plan to investigate the neuroprotective effect of milk thistle seed extracts in model of neuropathic pain and its involvement in neuroinflammatory signaling cascade. Activation of p38 mitogen activated protein kinase (MAPK) is one of the hallmarks in nerve injury induced neuropathic pain. Our preliminary in-silico study suggests inhibition of p38 MAPK by active constituent from milk thistle seed extracts and forms basis for future in-vitro and in-vivo studies. We hypothesize that treatment with milk thistle seed extracts may provide a better therapeutic alternative for patients suffering from chronic neuropathic pain.

P128. Antitubulin Anticancer Agents

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Cancer is one of the leading cause of Death. According to ICMR there will be over 17 lakh new cancer cases in India by 2020.Therefore there is an urgent need to discover and develop novel and more effective drug. Microtubules are dynamic polymers of two closely related 55kDa proteins in cells called α and ß tubulin. During cell mitosis, microtubules the key cytoskeletal filaments extend from the cell centrosome to form mitotic spindle and fasten to the kinetochore of chromosomes .Then the kinetochores are gathered around the equatorial plate .Microtubules are in dynamic equilibrium with tubulin dimers. Disruption of dynamic equilibrium will lead to cell cycle arrest or cell apoptosis. Indole containing molecules can be a good candidate for antimitotic anticancer agents as vincristine and vinblastine that are current therapy as tubulin polymerization inhibitors contain indole ring. Current poster represents the hybrid of cinnamic acid derivatives and tryptamine containing indole moiety as antitubulin anticancer agents.

P129. miRNA profiling of triple negative breast cancer cells and its use in targeted delivery for cancer therapeutics

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Therapeutic clinical usage of miRNA mimics/inhibitors in various cancers is delimited because of various drawbacks. The most viable and easy option to overcome these is to modify the delivery system of miRNAs. Gold nanoparticles have unique physicochemical properties, enhanced permeability and retention in tumor tissue, their ability to be conjugated with drugs, and also anti-cancer activity. We thereby hypothesize that identification of novel miRNAs and delivery of novel miRNA mimics/ miRNA inhibitors by gold nanoparticles might be highly beneficial for targeted delivery in triple negative breast cancer. MiRNA microarray profiling was carried out by Affymetrix 4.0 microarray platform. MTT assay, western blotting, Quantitative real-time PCR and Scratch wound assay were performed to check cell viability, expression of proteins, and validation of miRNAs and migration of cancerous cells. Gold nanoparticles were synthesized by citrate reduction method. Affymetrix miRNA 4.0 microarray analysis revealed differential expression of several miRNAs, snoRNAs and stem loop miRNAs in MDA-MB-231 cells. MiR-941 inhibitor decreased migration and cell viability of triple negative breast cancer cells. Gold nanoparticles significantly decreased cell proliferation and protein expressions of SIRT1, ß-catenin, GSK-3ß, GATA-3, Cyclin D1, p53 and DNMT1, along with the increased acetyl-p53 and p-p38 in a dose dependent manner. MiR-941 inhibitor decreased the migration and cell viability of MDA-MB-231 cells. Gold nanoparticles alter Wnt/ GSK-3ß/ ß-catenin/ GATA-3/ Cyclin D1 axis and inhibits the proliferation of MDA-MB-231 cells. Further studies are in progress for miR-941 targets identification and miR-941 inhibitor-gold nanoparticles conjugation efficacy in MDA-MB-231 cells.

P130. Metabolic abnormalities in Cancer Cachexia

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It is estimated that about half of all patients with cancer go through an advanced stage which may be called as cancer cachexia (CC), being responsible for over 20% deaths in cancer patients. Cancer cachexia is a multifactorial systemic syndrome leading to clinical deterioration observed in cancer patients, characterized by weight loss, skeletal muscle wasting and which cannot be fully reversed by conventional nutritional support. Number of mechanisms involved in progression of cancer cachexia as anorexia, adipose tissue breakdown, changes in hormonal levels, role of inflammatory mediators, oxidative stress, muscle metabolism, and protein metabolism. Cancer cachexia is observed with some of the metabolic abnormalities as alterations in carbohydrate or glucose metabolism progressing via decreased hepatic glycogen stores, increase in glucose production, impairment of lipid handling between tissues, WAT (white adipose tissue) browning, energy balanced disorder linked to cytokine related inflammation, fatigue and weakness i.e. muscle wasting, insulin resistance, increased ZAG expression causing increased lipolytic response of adipose tissue. Most promising way to treat cancer cachexia is to cure the cancer, but this still remains a desired achievement in cancer. The options available are increasing nutritional intake, use of drugs or specific nutrients among others. The current review focuses on different mechanisms and metabolic abnormalities involved in cancer cachexia.

P131. Nanoparticle Assisted Combination Cancer Chemotherapy

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Emergence of chemoresistance , tumor metasatsis, high tumor burden and diagnosis at later stage of cancer necessitates the use of combination chemotherapy. Combination chemotherapy has become a part of chemotherapy regime for the drugs exhibiting therapeutically significant synergism. The alliance of field of Nanotechnology and oncology has helped to solve major therapeutic issues owing to differences in the drug properties, their pharmacokinetic and biodistribution. Recent advances in nanoparticulate technology have emerged as a redeemer in solving issues related to deliver a combination of two or more drugs. Unique colloidal behavior and targeting strategies have conferred an unprecedented ability to deliver combination of drugs in an optimized therapeutic manner. Co-loading of two or more drugs has been a challenging task for designing nanoparticles. Combination therapy using multi-drug nanoparticles have additional advantages as compared to combination therapies based on co-delivery of single drug nanoparticles. Multi-drug containing nanoparticles exhibit distinct features such as ratiometric drug loading ability, uniformity of vehicle and temporal drug release that in turn have major therapeutic implications. Multi-drug containing nanoparticulate systems for cancer chemotherapy have been discussed in the present review. Various nanoparticulate systems ranging from liposomes, polymeric

nanoparticles, dendrimers, and inorganic silica based nanoparticles have been extensively explored for the formulation of multidrug loaded nanoparticles. Delivery of different payloads such as cancer chemotherapy drugs and other oncologic therapeutics such as Si RNA, antiangiogenic agents, radiosensitizers and chemosensitizers have also been addressed in the review. Various challenges and future development strategies of multidrug nanoparticles have been discussed as a part of this review.

P132. Whole transcriptome analysis of Oral squamous cell carcinoma Subjects

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According to Indian Council of Medical Research (ICMR) report in 2016, the total number of new cancer cases is expected to be around 14.5 lakh and is likely to reach nearly 17.3 lakh new cases in 2020. Oral cancer is eight most common cancer worldwide and more than 90% of oral cancers are Squamous cell carcinoma (OSCC). In India, 60-80% of patients are present with advanced disease as compared to 40% in developed countries. Here in this research project, the main objective was to identify differentially expressed gene, novel gene and different mutations associated with human oral cancer using whole transcriptome sequencing using next generation sequencing using ion torrent platform. The final aim of this project was to study of genetic variation in OSCC population using NGS which could reveal modulated gene involved in KEGG pathway. The analysis of whole transcriptome of OSCC tumor was done and top 10 up-regulated and down-regulated genes were found for OSCC in KEGG pathway database which are involved in MAPK, Apoptosis and NOTCH signaling pathway. This study have identified somatic mutation in patient 1 (4330 up-regulated and 4039 down-regulated genes) and patient 2 (6346 up-regulated and 5751 down-regulated genes). It could verify the potential involvement of these genes in the development of oral cancer. The study will provide an extensive analysis of oral cancer in Gujarat population with identification of therapeutically important target for the treatment of oral cancer.

P133. Inhibition of Bruton's tyrosine kinase (BTK) attenuates experimental autoimmune encephalitis in mice

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Bruton's tyrosine kinase (BTK) inhibitors are demonstrated to be effective against several autoimmune diseases in preclinical and clinical studies. We aimed to investigate the effect of BTK inhibitor ibrutinib on experimental autoimmune encephalitis (EAE), an animal model of multiple sclerosis (MS). EAE was induced in C57BL/6 mice with immunization of myelin oligodendrocyte glycoprotein (MOG_{35-55}) in complete Freund's adjuvant followed by two doses of pertussis toxin (on day 0 & 2). Effect of BTK inhibitor, ibrutinib, was studied in-vitro in splenocytes isolated from MOG immunized mice and in-vivo on EAE disease progression. Pre-treatment of ibrutinib inhibited MOG-induced IL-17, IFN-γ, IL-6 & IL-1ß in isolated splenocytes in-vitro. Moreover, treatment with ibrutinib showed marked inhibition in incidences and severity of EAE in a dose-dependent manner. The results demonstrate that, inhibition of BTK, suppresses the in-vitro production of myelin antigen reactive Th1 & Th17 cell related cytokines such as IFN-γ & IL-17, which is associated with the amelioration of EAE disease.

P134. Efficacy and Safety Pharmacological Evaluation of mefenamic acid derivatives as Anti-inflammatory Agent

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The development of new COX-2 inhibitors with high efficacy and enhanced safety profile would be a great achievement in the development of anti-inflammatory drugs. The objective of our study was to perform the in-vitro and in-vivo pharmacological evaluation of mefenamic acid derivatives for anti-inflammatory activity. The derivatives were subjected to whole blood assay to confirm COX selectivity.

The in-vivo pharmacological evaluation for anti-inflammatory activity was carried out using Complete Freund's adjuvant. Safety profile of all compounds was evaluated by administration of dose three times higher than therapeutic dose. In whole blood assay derivatives produced reduction in thromboxane level and increase in PGE2 levels as compared to standard indicates COX-1 selectivity. Treatment of heterocyclic derivative to CFA induced RA animal showed significant improvement in physical parameters like body weight, arthritic index, paw volume and paw thickness as well as biochemical parameters like rheumatoid factor, interleukin-6, interleukin-10, prostaglandin E2, prostacyclin I2, thromboxane B2, SGPT, SGOT, potassium levels, urea, creatinine levels Treatment also showed protection in hemodynamic parameters like blood pressure and ECG as compared to disease control group. Derivative also showed improvement in splenomegaly and thymus to body weight ratio. Also a significant improvement in synovial joint and heart histopathology was observed by treatment. The ameliorative effect of heterocyclic derivative was observed in hyperplasia of synovium, pannus formation and destruction of the joint space and cardiomyopathy. Furthermore, in the toxicity studies, all compounds showed no ulcerogenic effect and produced minimal effects on liver and renal functions. From present study we can suggest that all compounds appeared to be a promising and safe option for the management of acute and chronic inflammatory conditions without GI and cardiovascular toxicity.

P135. 3D-QSAR Analysis of Pyrimidone Derivatives as PARP5 Inhibitors for the treatment of Cancer

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Cancer is a major public health problem and one of the leading cause of death worldwide. Since last decade, the treatment transition have occurred from cytotoxic chemotherapy to molecularly targeted cancer drug therapy which improved the lives of many cancer patients. PARP5 (TNKS) enzyme in its two isoforms, PARP5a and PARP5b is one of such novel and emerging target of cancer. It is a member of the subset of 17-membered PARP (poly(ADP-ribose) polymerase) family of proteins, which constitute many potential drug targets for cancer. PARP5 can be inhibited to target solid tumors with increased WNT signaling that are telomerase-dependent. Increased expression of PARP5a and PARP5b has been observed in many different cancers, including fibrosarcoma, ovarian cancer, glioblastoma, pancreatic adenocarcinoma, transitional cell carcinoma of the bladder, gastric cancer, colon cancer and breast cancers. Being a novel target for cancer, many molecules targeting it are in discovery pipeline. As a part of continuous research of designing novel PARP5 inhibitors, 3D-QSAR study was carried out using 41 reported pyrimidone derivatives and was validated using SybylX. Distill based alignment provided good results with q2 value of 0.651 and 0.650 and predictive r2 value of 0.989 and 0.983 for CoMFA and CoMSIA models, respectively. Contour maps of CoMFA (steric and electrostatic) and CoMSIA (steric, electrostatic, hydrogen bond donor and acceptor, hydrophobic) were generated and analyzed for favored and disfavored ligand features for the activity. The obtained information can be further utilized for the designing of novel molecules as PARP5 inhibitors.

P136. Novel drug targets for colon cancer associated with diabetes mellitus

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Colon cancer is now one of the significant health issues; it is said to be most common malignancy of the gastrointestinal tract. Diabetes Mellitus is also seriously growing health problem worldwide with chronic as well acute complication that negatively influences quality and survival of the individual. Scientific studies show strong potential association between diabetes mellitus and colon cancer. The excess risk of colon cancer has reached to 30% in Type 2 diabetes mellitus patients.. The underlying studies carried out suggest of insulin playing an important role in the carcinogenesis and the mechanism unifying between two diseases is hyperinsulimemia. ß cells decline over the course of the diseases as a result oral agents becomes less effective. Several anti-diabetic agents such as sulphonyl ureas, biguanides, dpp4 inhibitors, thiozolidinediones and α-glucosidase inhibitors are beneficial in controlling diabetes, their effects with respect to anti- cancer activity is controversial none being able to produce beneficial role in colon cancer associated with diabetes. Additionally given the side- effects with profile, there is a dire need for identification of novel targets which are effective in both colon cancer associated with type 2 diabetes. Novel targets such as Wingless pathway, Liver X receptors, Free fatty acids, estrogen receptors,

mTOR pathway, glucagon like peptide-1, sodium glucose co-transporters, IGF receptors, CDK 4 inhibitors, HDAC inhibitors are under evaluation. This presentation summarizes all the novel targets and explains their future scopes. More attention to the newer targets may lead us to attain our goal of effective treatment for colon cancer associated with diabetes mellitus.

P137. Lymphoma: Newer targets for Treatment.

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Lymphomas are heterogeneous group of cancers that play a prominent role in the history of oncology, being among the first cancers to respond to radiotherapy or systemic chemotherapy. Because of the heterogeneity present among the lymphomas, accurate diagnosis and staging are essential prerequisites to their effective management. This has led to the development of prognostic models in lymphoma, which use patient and disease characteristics to stratify patients by risk. Modern approaches to lymphomas include chemotherapy, combined-modality therapy and risk-adapted approaches that modify treatment based on initial response. Though effective therapy is available for types of lymphoma, relapse remains common in a number of subtypes, and management of relapsed and refractory disease remain research priorities. This review will discuss recent advances and targets which can be used for treatment of lymphoma

P138. Design, Synthesis and Biological Activity of Histone Deacetylase (HDAC) Inhibitors as Anticancer Agents

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Histone Deacetylases (HDACs) are found to regulate expression and activity of numerous proteins involved in cancer initiation and progression. Deacetylation of histone proteins by HDACs prevents expression of suppression genes and helps tumorigenesis. Thus, inhibition of HDAC activity is an alternative important approach for anticancer effect. Various small molecule HDAC inhibitors found to be effective anticancer agents. Vorinostat (SAHA) and Romidepsin (FK228) are approved by US-FDA for the treatment of cutaneous T-cell lymphoma, while Panabinostat and Belinostat are approved for multiple myeloma and peripheral T-cell lymphoma respectively. Other hydroxamic acid derivatives are in clinical trials but shows toxicity might be because of less selectivity towards HDAC isoforms. Small molecule HDAC inhibitors having aminobenzamide moiety e.g., entinostat (MS275) and mocetinostat (MGCD103) are selective towards HDACs 1, 2 and 3 undergoing clinical trials. Chidamide, a benzamide derivative is approved in China for peripheral T-cell lymphoma and has orphan drug status in Japan. BG45, a selective HDAC3 inhibitor showed significant inhibition of multiple myeloma cells in-vitro as well as in-vivo tumor growth inhibition in a murine xenograft model of multiple myeloma. We have designed and synthesized benzamide derivatives along with BG45 and evaluated in-vitro anticancer activity. From the cytotoxicity assay, some of the compounds showed effective cell growth inhibition. The promising synthesized compounds will be further characterized for their anticancer activity.

P139. Development of a Novel Anti-Neutropenic Factor – ANF-Rho™ for treatment of Chemotherapy Induced Neutropenia in Oncology

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ANF-Rho™ has been developed as a novel polyethylene glycol-modified granulocyte colony stimulating factor that has biophysical and biological properties that produce a distinct pharmacokinetic and pharmacodynamic profile as compared to pegfilgrastim (Neulasta®). It was evaluated in 5 and 13 weekly single and multiple doses studies to assess the pharmacokinetics, pharmacodynamics, genotoxicity, Juvenile toxicity and toxicity in the rat and primate as compared to Neulasta®. Rat and NHP study design included 5 ascending dosage groups, 100 to 1000 µg/Kg. Doses were administered by weekly subcutaneous injections on Day 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85 and 92 at a dose volume of 5 mL/kg for rats and

2mL/kg for primates. Genotoxicity assessments were evaluated using Salmonella typhimurium and Escherichia coli reverse mutation assay, rodent blood micronucleus assay and chromosomal aberration assay. Toxicology assessment included clinical observations, body weight change, food consumption, ophthalmic examination, function observational battery (motor activity, behavioral changes, coordination and sensory/motor reflex response), organ weight, bioanalytical and toxicokinetic analysis, immunogenicity, gross necropsy and histopathology. There were no related effects in body weight changes or food consumption. No biologically meaningful findings were noted during the function observational battery assessment. Genotoxicity studies found no signs of mutagenicity, clastogenicity or cytotoxicity. Five weeks toxicology results were unremarkable and sufficient to support advancement of ANF-Rho into Phase I clinical study and found to be safe, tolerable in ascending dose study and exhibited remarkable pharmacodynamics effects when compare to Neulasta®. Results from the 91-days rat neutropenia dosage model found that the blood pharmacodynamics parameters of ANF-Rho were significantly superior to Neulasta. Both PK and PD data demonstrate relatively predictable systemic exposures and activity following SC or IV dose levels in both rat and primate. These results advanced ANF-Rho into Phase II clinical studies in chemotherapy-induced neutropenia in solid tumor patients.

P140. A3 adenosine receptor agonist: a novel treatment option for xenograft mice model in lung cancer

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Lung cancer is the leading cause of cancer mortality in India and most other parts of world. The incidence and mortality of lung cancer have been continuously increased worldwide. The survival rate of lung cancer has been improved only 14% in contrast to the 5 years survival of 52% in other cancers. Adenosine receptor (AR) have been emerged as novel cancer specific target. A3AR levels in various tumor cells are up regulated, which may suggest that the specific AR may serve as a biological marker and as a target for specific ligands leading to cell growth inhibition. The aim was to study anticancer activity of A3 Adenosine receptor agonist in xenograft mice model. Anti-cancer activity for lung cancer were evaluated through in-vitro and in-vivo activity. In the present study the animals of various groups were injected with a single dose of A549 lung cancer cell line to potentiate tumor growth. TNF-α has been found to be elevated in lung cancer patients. VEGF is a known stimulus of angiogenesis in tumor development. The treatment with doxorubicin and/or A3AR agonist decreased TNF-alpha levels and VEGF levels. A significant decrease in lung to body weight ratio in Combination treated group compared to Disease control group as the tumor size decreases. A significant increase in WBC count in Combination treated group compared to Doxorubicin treated group as the result of myeloprotective effect of A3AR Agonist. In conclusion A3AR inhibited the tumor development in lung cancer and represented as a novel treatment option.

P141: Gold nanoparticles for cancer treatment: myths and reality

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Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's specific cells. Current treatments for various cancers include surgery, radiation, hormone therapy, and chemotherapy which exhibit survival However the therapeutic agents distributes non-specifically in the human body, thus affect both cancerous and normal cells.Goldnanoparticles(GNs)due to its small size offer great benefits over conventional chemotherapy in cancer treatment These include high surface area which provide dense drug loading, biocompatible, controlled dispersity, non-cytotoxicity to the normal cells.GN are generally synthesized by Chemical Methods i.e. turkevich method, brust-Schiffrin Method and some eco-friendly methods. It has been well recognised that the passage or unloading of antitumor drugs onto targeted tumour sites depend on several permeating mechanisms including passive targeting, active targeting, or a combination. Active targeting uses GNs that are pre-conjugated with various probes or targeting agents including antibodies, small molecules or peptides to locate and attack tumors. Passive targeting is simply taking advantage of the EPR (enhanced permeability and retention) effect to deposit antitumor drugs to tumors, which is a common characteristic of nanoparticle-based drug delivery to cancer. Heat generating gold nanoparticles and antibody attach gold nanoparticles

are the most recent progress in nanoparticles. The present review discussed the gold nanoparticles preparation, applications and future in cancer therapy.

P142: Design, synthesis and pharmacological evaluation of benzimidazole derivatives as hDHODH inhibitors

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Cancer is the second leading cause of death in the western world. Despite advances in diagnosis and treatment, overall survival of patients remains poor. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy. Human Dihydroorotate dehydrogenase (hDHODH) is an enzyme essential to the fourth and rate-limiting step in de novo pyrimidine biosynthesis and it catalyzes the conversion of dihydroorotate (DHO) to orotate concurrent (ORO) with the reduction of ubiquinone. The significance of pyrimidine bases for metabolism, cell and proliferation determines hDHODH as an attractive chemotherapeutic target for the development of new drug candidate in different biological and clinical applications for cancer, arthritis and malaria. Various molecules have been reported in literature for the inhibition of hDHODH enzyme which were taken into consideration to design a series of molecules which were evaluated by molecular docking studies in order to achieve, better anticancer agents. These molecules were subjected to the docking studies using the co-crystal structure of hDHODH retrieved from the protein data bank to predict both ligand orientation and binding affinity. Compounds were docked into the binding site of the protein using Surflex-Dock interface implemented into SYBYL X1.2. The compounds having best score in the target protein along with similar amino acid interactions as compared with the reference ligands (Brequinar) were selected for the synthesis. The synthesis of 1,2,5-trisubstituted benzimidazole derivatives was carried out by liquid phase combinatorial approach using soluble polymer assisted support (PEG5000). Synthesized compounds were characterized by IR, Mass, 1-H NMR and 13-C NMR. The purity of compounds was confirmed with HPLC analysis. The synthesized compounds were tested against hDHODH enzyme inhibition assay using Brequinar as standard. The synthesized compound the synthesized compounds demonstrate comparative biological activity the best compound being NDS-107 and NDS-108 which shows 86.04% and 83.39% inhibition respectively. Furthermore, the active molecules can be undertaken for pharmacokinetic study and in-vivo biological activity testing.

P143. To analyze safety and efficacy of everolimus in metastatic breast cancer

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Approximately 75% of the breast cancer are hormone receptor-positive and are typically managed with endocrine therapies, including aromatase inhibitors and selective estrogen receptor modulators. However, primary or acquired resistance to endocrine therapy results in disease progression in a large proportion of breast cancers. PI3K/AKT/mTOR pathway abnormalities are present in both primary and metastatic tumors. Increased PI3K/AKT/m TOR signaling is associated with resistance to endocrine and human epidermal growth factor receptor-2(HER-2) targeted therapies and relapse. Everolimus is an oral inhibitor of mTOR which enhance the treatment options for post-menopausal woman with hormone receptor positive, human epidermal growth factor receptor-2(HER2) negative metastatic breast cancer. Everolimus, in combination with exemestane has been approved for patients with advanced hormone receptor-positive/HER-2 negative in addition to HER-2 negative breast cancer who progress on prior endocrine therapy with either letrozole or anastrozole. Therefore, present study was designed to analyze the efficacy of Everolimus and exemestane in patients with metastatic breast cancer. Primary endpoint is proportion of progression-free patients and secondary endpoint is median progression-free survival and overall survival from the time of enrolment. Response rate, according to RECIST 1.1 and safety of Everolimus will be measured.

P144. Structural requirements for development of novel anti-cancer agents bearing ß-carboline ring

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In arena of new drug discovery and development,Ð-carboline ring played important role.This ring system has shown to be effective as anti-cancer, anti-inflammatory, anti-microbial, anti-viral, anti-thrombin,anti-HIV, anti-depressantand possess a range of other biological activities. ß-carbolines mainly exhibit their antitumor activity through multiple mechanisms such as intercalating into DNA, inhibiting Topol and II, CDK, MK-2, PLK1, IKKand kinesin Eg5. Structural alteration of these bioactive scaffolds may result in the development of new drugs with improved therapeutic properties. Structure–activity relationships (SAR) for in vitro and in vivo antitumor activities showed that the antitumor potential of ß-carbolines correlated to both the planarity of the molecule and the presence of substituents in position-1, 3 and 9 of ß-carboline nucleus.Interestingly, the compounds bearing a carboxylate, carboxyl, and acylamide substituents in position-3 of ß-carboline ring system displayed selectively cytotoxic activities and in addition compounds with a hydroxymethyl and carboxyaldehyde substituents in position-3 were almost inactive to all tumor cell lines.Incorporation of short alkyl substituent intoposition-9 of ß-carboline nucleus enhanced their cytotoxic activities ; the N2 -benzyl substituent on the ß-carboline core played a very important role in the modulation of the cytotoxic potencies.Substituted phenyl groupand heterocyclics at the C1 and C3-positions the ß-carboline core enhanced antitumor as well as DNA-binding ability.The antitumor potencies of ß-carboline derivatives were enhanced by the introduction of benzyl substituent into the position-2. It was also observed that ß-carboline hybrids have displayed potential antitumor properties.The development of newer ß-carboline derivatives is useful in isolation of a best possible new compounds having potential anticancer activity with minimum toxicity.

P145. Chemoresistance in cancer

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Chemoresistance is outlined as the resistance of a tumour to chemotherapy. Chemotherapy is usually capable of causing death in tumours and reducing the tumor bulk, several cancer patients experience recurrence and ultimately death attributable to treatment failure. In recent years, Cancer Stem Cells (CSCS) have gained intense interest as key tumor-initiating cells that may also play an integral role in recurrence following therapy. As such, variety of mechanisms of chemoresistance are known in CSCs. in this review, we will describe a number of these mechanisms of chemoresistance ,which are: P-glycoprotein induced chemoresistance, Chemoresistance owing to Aldehyde Dehydrogenase (ALDH) activity, B-cell lymphoma-2 (BCL2) related chemoresistance, hypoxia induced chemoresistance, activation of key signal pathway 'Notch' in inflicting chemoresistance . Further, we assess studies that demonstrate various strategies to overcome chemoresistance and treating chemoresistant cancers that are driven by CSCs. By understanding how CSCs escape chemotherapy, additional informed approaches to treating cancer may develop and that might improve clinical outcomes for cancer patients.

P147. Effects of Ibrutinib on a cecal ligation and puncture model in Balb/c mice

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Sepsis is the principal cause of fatality in the intensive care units worldwide. It involves uncontrolled inflammatory response resulting in multi-organ failure and even death. There are contradictory reports regarding B cell targeting and has shown to either protect or exacerbate inflammatory response and mortality in animal models of sepsis. Bruton's tyrosine kinase (BTK) inhibitors are demonstrated to be effective against several autoimmune diseases in preclinical animal models. In order to investigate the effect of ibrutinib, a Bruton's tyrosine kinase inhibitor, on sepsis, cecal ligation and puncture (CLP) surgery were performed on male Balb/c mice and were randomized into 4 groups to receive either ibrutinib (5 & 10 mg/kg, p.o) or vehicle. Sham-operated animals underwent identical laparotomy but did not undergo cecal ligation and puncture served as Sham control group. In order to examine inflammatory changes, mice (n = 10 per group) were euthanized at 6 h after CLP. Cell counts and cytokines were measured in the peritoneal lavage fluid. The survival rates were also observed. Total cell counts were measured and cytokine levels were measured by ELISA. In CLP model, ibrutinib reduced the secretion of TNF alpha, IL-1 beta, IL-6, IFN g and IL-17, associated with total cell counts. Histological findings also demonstrated that ibrutinib ameliorated liver damage. Ibrutinib treatment resulted in a dose dependent improvement in

survivability in CLP treated mice. The findings suggest that the effects of ibrutinib on an acute sepsis models in Balb/c mice may be due to decrease in inflammation as evident by the suppression of Th1 and Th17 cytokine.

P148. Design, synthesis and pharmacological screening of novel pteridine derivatives as aurora-b kinase inhibitors for cancer treatment.

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World-wide report of cancer risk and its mortality suggested that cancer has 2ndhighest death rate after metabolic disorders. Anti-mitotic drugs are well known from the 1980s as chemotherapeuticagents. A related kinase family members, Aurora Kinase (AurK) andCyclinDependent Kinase (CDK) have recently emerged asinterestingdualtargets for potential kinase inhibitorsofdrug development approach. Inhibition of those kinases lead to cell cycle delay or G2/M arrest followed by cell death.Variety of molecules were designed using molecular docking approach and best series of molecules bearing pteridine scaffold were synthesized as novel small molecules. All synthesized molecules were characterised by FT-IR, MASS, 1H, 13C NMR. All synthesized molecules were screened In-vitro over 7 different cancer cell lines like A549, HCT-115 etc. Results of the pre-screenign on cancer cell lines showed IC50 in range of 0.2 µM to 100 µM. Toxicity of all molecule was also checked using normal cell lines and majority of compounds were found non-toxic (>100 µM). In-vitro enzymatic inhibition was also checked on AurK and CDK-2 with % inhibiton and IC50 of all compounds. Further screening of important inhibitors were evaluate by Colony forming assay and cell signaling inhibition using cell cycle analysis (PI staininig) and found G2/M arrest in cancer cells. Appoptosis assay was also performed using Annexin-V FITC staining and 2 molecules were produce early appoptosis in low µM range. Both studies were perfoemed on sophisticated MUSE® analyser. These molecules were screened in-vivo in p388/D1 murine luekaemia model for increment of life span study and found increment in lifespan. These active molecules will be further explored in development of novel lead process.

P149. Chronic obstructive pulmonary disease (copd): updates on different targets for treatment

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The American thoracic society (ATS) defined COPD as an “anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, non-respiratory bronchiole , accompanied by destructive changes of the alveolar walls”. According to WHO estimates, 65 million people have moderate to severe COPD. Various treatment approaches for COPD are life style changes, medicines (broncho dilators, combination bronchodilators + inhaled glucocorticosteroids), vaccines(flu shots, pneumococcal vaccines), pulmonary rehabilitation, oxygen therapy, surgery, bullectomy, lung volume reduction surgery, lung transplant. The existing treatment includes improved acting ß2 adrenoceptor agonists, anticholinergics, corticosteroids, theophyllines, selective phosphodiesterase inhibitors and leukotriene modifiers. Promising class of medications, for example, the specific phosphodiesterase 4 inhibitors, which target principal pathophysiologic components. As COPD is radically expanding , more up to date medications are must to stop this ailment. For example, triple medication treatment with long acting beta-agonist, breathed in corticosteroid and anticholinergic (spiriva) ; new drugs for dilate blood vessels of calcium channel inhibitor class (epoprostenol) , supplanting oxygen treatment with mixed oxygen and helium treatment for enhancing exercise capacity; airway bypass or bronchoscopic surgery ; newer anti inflammatory drug (roflumilast) and lung volume reduction surgery are the more current methodologies for COPD treatment. However, numerous publication have looked at things like endobronchial valve, that piece the air from going into a part of the lung and, rather, let it turn out. Animal experiments have shows retinoic acid causes alveolar regeneration, the same action can be get in human with COPD.

P150. Wnt beta catenin pathway in cancer

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In UK, approximately over 3, 65,000 new cases were reported and mortality in 2006 was in excess that was of 1, 54,000. Around 1,684,211 cancer cases, these are the expectations for the diagnosis of cancer in 2016. Various pathways responsible for tumor formation are:-MAPK/ERK pathway, CAMP dependent pathway, IP3/DAG pathway and ß-catenin pathway.The Wnt signaling pathways are a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors. Wnt catenin pathway again is characterized into three different pathways naming: the canonical Wnt pathway, the noncanonical planar cell polarity pathway, and the noncanonical Wnt/calcium pathway. Basically the Wnt is the main factor responsible for the gene expression or gene suppression. In absence of Wnt there is complex formation called as destruction complex destructing B-catenin and hence suppressing the gene expression similarly when B catenin binds to the frizzled receptor there is phosphorylation of the terminal LRP causing the adhering of the destruction complex, and hence the B catenin now freely roams in cytoplasm resulting in the interference in gene expression. Wnt-5a is an antagonist which also antagonize canonical Wnt activity both in Xenopus embryos and mammalian cells. ß-catenin degradation may be the promotional factor for the WNT5a for its action of antagonism. Wnt-5a antagonizes the canonical Wnt signaling pathway by promoting GSK-3–independent degradation of ß-catenin. The review focuses on the WNT catenin pathway.

P151. Diabetes and cancer: the connection

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Diabetes mellitus is a long term metabolic disorder that is characterized by high blood sugar, insulin resistance, hyperinsulinemia and relative lack of insulin in cells. While cancer can be termed as the abnormal cell growth and proliferation. Epidemiological studies have demonstrated an association between type 2 diabetes and many types of cancers like breast, bladder , colorectal, liver and pancreatic .This association is mediated by hyperinsulinemia via insulin-like growth factor (IGF), they binds and activates both insulin and IGF receptors that are expressed on a number of cells including cancer cells. IGF-1-mediated receptor activation leads to cell growth, proliferation, and inhibition of apoptosis. Antidiabetic medication from biguanide class metformin have anticancer activity. While other antidiabetic like Sulfonylureas has been reported to have an increased risk for liver and pancreatic cancers with the use of its first- and second-generation agents, but with third-generation like glimepiride no such effects are been noted . Thiazolidinediones use for longer duration are associated with an increased risk of bladder cancer, whereas no risk was observed with rosiglitazone . Glucagon-like peptide (GLP)-1 is an incretin hormone, its agonists like Exenatide promotes stimulation of glucose-dependent insulin secretion . Long-term use of a GLP-1 agonist increases risk of pancreatic and thyroid cancer while decreases the risk of colorectal and breast cancer. So it would be correct enough to say that anti-diabetic medication have many connections with several types of cancers, which one of them are healthy or harmful for the patient will be discussed in this article.

P152. Advanced treatment in lung cancer

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Lung cancer is the top cancer killer worldwide with high mortality rate.2.2 million of total lung cancer cases and 1.9 million deaths are reported .Majority are belongs to non small cell lung cancer (NSCLC).The main targeted therapy in lung cancer is epidermal growth factor receptor (EGFR)which is tyrosine kinase inhibitors. In EGFR has been broadly explored as a drug therapy. However, the drug responses are not durable due to acquired resistance. So, the advanced treatment is needed. The advanced treatment in NSCLC is a microRNA ,shRNA, AND NrF2.miRNA functions as a guide by base pairing with target mRNA to negatively regulates its expression. shRNA system overcome the limitations of the genetic blockade of IGF-1R .one of the most important cancer therapy.NrF2 is a redox sensitive transcription factor. Inhibiting NrF2 significantlly inhibits tumour growth in lung cancer.

P153. A retrospective study for effectiveness of ayurvedic treatment in liver cirrhosis

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Cirrhosis is a chronic degenerative disease in which normal liver cells are damaged and are then replaced by scar tissue. Cirrhosis is defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. There are many complications of liver cirrhosis like ascites, hepatic encephalopathy, esophageal Varices, portal hypertension, renal failure, hepatocellular carcinoma. Many Allopathic treatment are available for liver cirrhosis but still there is no cure of liver cirrhosis. So, the rising number of patients with liver diseases directs the attention of the Ayurvedic medicine and other popular alternative medical therapies. Among these, the current study discusses a compilation of Ayurvedic medicines used for liver protection, such as Liv-52, Camellia sinensis (green tea), Glycyrrhizaglabra (licorice) and Emblica officinalis (Amla), Black Asphaltum(Shilajit), Picrorhiza Kurroa(Kutki). The increasing use of herbal medicines reflects their perceived effectiveness in the treatment and prevention of disease, and the belief that these treatments are safe because they are 'natural' and having a low side effects. The presented study evaluates the effects of ayurvedic medicines in the treatment of liver diseases.

P154. Ligand based and structure based stratergy for the designing of novel mtor inhibitors

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Cancer is a second major disease after metabolic disorders where number of cases of death is increasing gradually. mTOR is one of the most important target for treatment of cancer, specifically for breast and lung cancer. In the present research work, CoMFA and CoMSIA studies were performed on 50 compounds reported as mTOR inhibitors. Three different alignment methods were used and among them, Distill method was found to be best method. In CoMFA, leave one out cross validated coefficients (q^2), conventional coefficient (r^2) and predicted correlation coefficient (r^2 pred) values were found to be 0.664, 0.992 and 0.652, respectively. CoMSIA study was performed in 25 different combinations of features like steric, electrostatic, hydrogen bond donor, hydrogen bond acceptor and hydrophobic. From this, a combination of steric, electrostatic, hydrophobic (SEH) and combination of steric, electrostatic, hydrophobic, donor and acceptor (SEHDA) were found as best combinations. In CoMSIA (SEHDA), q^2, r^2 and r^2 pred were found to be 0.646, 0.977 and 0.682, respectively; while in the case of CoMSIA (SEH), the values were 0.739, 0.976 and 0.779, respectively. Contour maps were generated and validated by molecular dynamics simulations assisted molecular docking study. Based on the features obtained through this study, six novel mTOR inhibitors were designed and docked. In future, this study will be useful for designing of novel molecules with increased anticancer activity.

P155. Advances in the treatment of testicular cancer

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Testicular cancer is the most common solid tumour in young men and the treatment of testicular germ cell tumour (TGCT) has been called a success story of oncology, germ cell cancer being regarded as the "model of curable neoplasm. Despite being curable, germ cell tumours have become an important oncological disease as they occur in males from 15-35 years thus reducing a man's productive years greatly. GCT is a unique group of neoplasms where tumour markers are an integral part of diagnosis, staging, risk assessment and evaluation of response to therapy and detection of relapse. GCT includes teratomas, germinomas, choriocarcinomas and embryonal carcinoma. However this paper focuses on TGCT and the cause of changes in the genes of testicular cancerous cells so as to lead to even more effective treatment. Research has found that inherited variation in genes such as KITLG, SPRY4, DMRTI, BAKI, TERT, AFTIP increase the risk of testicular cancer thus help in preventing it. Certain mutations linked to chemotherapy are being to used to individualize treatments and find new drugs. Prediction of recurrence is done, so as to base therapy on it thus avoiding over treatment and under treatment. Chemo combinations are refined to see if eliminating, replacing drugs or lowering doses can reduce side effects. For tumour with poor prognosis, stem cell transplant is being studied. Identification of tumour associated protein, alpha-fetoprotein and human chorionic gonadotropin helps in facilitating treatment. These findings confirm the course of adjuvant chemotherapy reducing risks of relapse by 90-95%. This shows the applications of new treatment strategies are applied to achieve high cure rates.

P156. Immunotherapy in cancer

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Cancer Immunotherapy is branch if immunology that study interactions between immune system and cancer cell. Immunotherapy is becoming integral component of several cancer therapies. Cancer cell can be microbial protein, fusions Protein and mutated proteins. Immunotherapy can mark cancer cell by which they can be identified and hence Destroyed. Immunothery is more efficacious and less toxic. It use a range of manipulation of active antitumor immunity. These include monoclonal antibody, checkpoint, vaccination, other non specific immunotherapy. Monoclonal Antibody work by antibody dependent cell mediated cytotoxicity (ADCC). E.g. –almentuzumab used to treat Chronic lymphocytic leukemia. Immune checkpoint showing interaction between T-cell surface protein and Tumor cell surface protein generates inhibitory response to treat several cancers. E.g. nivolumab used in renal Cancer. As tumor prophylaxis, vaccination can be use for oncogenic microbial infection. E.g. spuleucel –T can Be used against prostate cancer. Other non specific drug related immunotherapies also help to prevent cancer. Like adjuvant introduction to tumor microenvironment and systemic delivery of cytokines. Other approach like Dendrite Cell, vector based vacation and many more are under research. This review encompasses several Immunotherapy techniques used currently in treatment of various types of cancers. Other novel therapy use for Treating this cancer is oncolytic virus therapy witch used genetically modified viruses against cancer cell.

P157. Primary human cancer cell-based platforms for screening new drugs and drug targets that inhibit cancer growth and metastasis

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Many cancers are detected late, many others relapse despite treatment. Hence, better diagnostic markers to identify cancer early, monitor its aggressiveness and metastatic potential, and its response to treatment are needed. Translational cell models that reflect the heterogeneity and complexity of human cancers are needed to improve the clinical success of drug candidates.

Epithelial-to-mesenchymal transition (EMT) is a normal developmental process that is reactivated in cancer. Epithelial cells transform into mesenchymal cells thereby acquiring the ability to detach, invade and migrate through the extra-cellular matrix to reach distal locations. They form metastatic loci leading to secondary tumors that cause death. The EMT process may also confer resistance to therapy leading to relapse of cancer. We have built an Indian cancers primary cell bank with appropriate ethical approvals and associated diagnostic and treatment data. Fresh sterile tumor samples are obtained direct from operation theatre and cultured for cells or 3Dspheres, as well as flash frozen for genomics/proteomics research. These disease cells are used to set up functional assays e.g., cell proliferation and apoptosis, generation of cancer stem cells, cytokine production, colony formation, wound healing, invasion etc. Matched serum/plasma from the same patient is used to correlate expression of markers in surgical tissue vs blood. Panels of gliomas (~25patient samples), breast (~50 patient samples), AML (~12) and prostate cancers have been cultured successfully. These co-cultures capture the diversity of cancer grades and stages, somatic & germline mutations, expression of different molecular markers and resistance to standard of care therapy. We have functional data to demonstrate differential effect of drugs on cell viability and cancer stem cells in 2D and 3D cellular formats.

An EMT model has been set up using normal epithelial cells obtained from breast reduction surgeries. The epithelial cells were immortalized and transformed by known inducers of EMT. Reporter genes that serve as assayable markers of EMT have been engineered in to enable high throughput screening including high content cellular imaging. We have data to show that the transformed cell line so obtained is a triple negative breast cancer. Several assays including sphere formation, migration etc. have been set-up to screen anti-metastatic activity of novel or repurposed compounds using our EMT platform. In conclusion, our biobank's access to human tumours has been used to develop disease-relevant cellular platforms, capturing many of the critical steps and pathways involved in human cancer growth, metastasis and chemo-resistance etc. These cell systems are very valuable in identifying markers of cancer progression, new drug candidates that can inhibit specific aspects of metastasis e.g., cell migration, invasion, generation of cancer stem cells in a phenotypic drug discovery mode. Molecular drivers of Indian cancers can be determined, as also Indian cell lines derived along the lines of ATCC, offering the promise of personalized medicine for Indian cancer patients.

P158. In-vitro cytotoxic evaluation of selected ethnomedicinal plants using brine shrimp lethality assay, mcf7 and vero cell lines

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The use of plants as a source of medicine has been an ancient practice and is an important component of the health care system providing a rich resource for natural drug research and development. Breast cancer has become the second largest cause of death amongst women worldwide because of the number of side effects of chemotherapy including toxicity to normal cells. Hence there is a need to find the better alternative drugs for the treatment of breast cancer with fewer side effects. In the present study, six ethnomedicinal plants namely Curculigo orchioides, Curcuma longa, Emblica officinalis, Teriminalia bellerica, Teriminalia chebula and Withania somnifera were studied for their use in breast cancer using two different models; brine shrimp lethality assay and MTT assay on MCF7 breast carcinoma cell line as well as Vero cell line , which is a normal cell line. The results suggested that Withania somnifera and Curcuma longa showed the most significant cytotoxicity in brine shrimp lethality assay as well as MTT assay. The cytottoxicity of Withania somnifera and Curcuma longa was 76.91% and 74.98% respectively on the breast carcinoma cell line at the concentration of 1000 µg/ml. No cytotoxicity was observed in any of the plants on the Vero cell line. Hence these plants can be further studied for their activity on breast cancer owing to their safety to normal cells. Further in-vitro and in-vivo studies along with the clinical studies are necessary to establish their use in the treatment of breast cancer.

P159. Formulation, optimization and evaluation of microspheres loaded capsules with budesonide and probiotics for the treatment of inflammatory bowel disease

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The given research aims at developing microspheres loaded capsules with Budesonide and probiotics for extended period of time in intestine for treatment of Inflammatory Bowel Disease. Microspheres were prepared by traditional extrusion method with ratios of mucoadhesive polymer Sodium alginate: HPMC [E5LV] (1:1) and 1% of acid resistance polymer Cellulose Acetate Phthalate (CAP). Screening batches were made for the selection of best mucoadhesive polymer from HPMC [E5LV], HPMC [E15LV] and HPMC [K15M]. Sodium alginate: HPMC [E5LV] (1:1) and 1% CAP were selected as the ideal carrier based on the evaluation. A 32 Full Factorial Design was used to optimize the different concentration of mucoadhesive and acid resistant polymers, by extrusion method. The optimized microspheres of Budesonide showed 25% mucoadhesion, 89.38% entrapment efficiency, 560 µm particle diameter, 10.71% swelling index and 90.10% In-vitro drug release in 12 hrs. The kinetic data were well fitted in zero order model and correlation value found to be 0.9944 which demonstrated extended release. Similarly, the optimized microspheres of probiotics showed 26% mucoadhesion, 88.31% entrapment efficiency, 534 µm particle diameter and 7.14% swelling index. The viable count of optimized formulation of probiotics microspheres was 109 CFU/g which is acceptable count for human administration. Short term stability study was carried out for the optimized batch at 5±3ºC (long term condition) and 25 ± 2ºC and 60 ±5% RH (accelerated condition) which emphasized a mucoadhesion and entrapment efficiency after 30 days.

P160. Role and functions of aurora kinase family in cancer: a complete review

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Since last few decades, number of death due to cancer is gradually increasing. More side effects are observed during treatment of cancer rather than to cure it. Till date, researchers have found more than 500 kinases as various targets to control cell-proliferation. Aurora kinase (AK) arises as one of the important targets since 1995. AK plays major role in the cell-division with spindle formation and spindle check point during mitosis. 3 members of Aurora kinase family - Aurora-A, B and C, have their own importance in mitosis. Structurally, Aurora-A and B are 67-76% similar and share work in mitosis by co-ordination with each other as well as with other co-factor's activation. Important functions of Aurora- A includes centrosome maturation and separation, bipolar spindle assembly formation, mitotic entry and cell cycle regulation.

Aurora-B has three important functions viz. phosphorylation of Histone H3 followed by chromatin proteins phosphorylation, a cytokinesis kinase and a spindle checkpoint kinase. Functional importance of Aurora-B includes but not limited to chromosome condensation, sister chromatid cohesin, mitotic spindle assembly, promoting chromosome bi-orientation, merotelic chromosome attachments and spindle assembly checkpoint. Aurora-C had a localized arrangement which is similar to Aurora-B during cell division. It interacts with INCENP and survivin same as of Aurora-B. Detailed knowledge of Aurora kinase family and their functions are very interesting and could be explored as an important target for cancer therapy.

P161. In-vitro cytotoxicity study of alcoholic extract of aerva javanica on cisplatin-induced toxicity in the vero cell line

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Cisplatin is a widely used anticancer drug that may induce serious toxicity in normal tissues including the kidneys. In recent times, there has been a surge in the popularity of herbal/traditional medicine. Vero cells, derived from kidney cells of green monkeys, have been used to study cell growth, differentiation, and cytotoxicity induced by different agents or conditions. Roots of Aerva javanica have been reported as pasanbheda. This study aimed at elucidating the protective effect of the alcoholic extract of Aerva javanica on cisplatin-induced toxicity in the Vero cell line. Cultured Vero cells were divided into four groups. In group I untreated Vero cells were taken as controls; in group II Vero cells were incubated with 25 µg /ml cisplatin; in group III the cells were incubated with an alcoholic extract of Aerva javanica and in group IV both cisplatin and Aerva javanica were added simultaneously to Vero cells. The cultured cells of all groups were incubated for 24 h and cytotoxic study was conducted using MTT assay. Aerva javanica alone did not show cytotoxicity on the vero cells and the combined therapy of cisplatin and Aerva javanica decreased the toxic effects of cisplatin on Vero cells. Hence, the findings support the use of Aerva javanica as a nephroprotective and can be used as an adjuvant therapy for the protection of tissues sensitive to cisplatin toxicity.

P162. Multi-targeted molecular docking studies of plant-based natural products on apoptosis and cell cycle pathways for anticancer activity

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Natural products are an attractive source of novel therapeutic compounds offering a tremendous chemical diversity. Plants have been the potential source of bioactive leads against cancer, with 60% of anticancer drugs having their origin from plants. Cancer is characterized by uncontrolled cell division by overcoming the signaling pathways involved in normal cell proliferation leading to apoptosis, extensive angiogenesis and metastasis. Proteins CDK6 (PDB Id: 1XO2) and CDK2 (PDB Id: 1DI8) are involved in G1 phase of cell cycle, whereas AKT1 (PDB Id: 3MV5) and mTOR (PDB Id: 4DRI) are involved in apoptosis and cell survival. Targeting these signaling pathways has been a promising strategy in combating cancer. With this rational 50 secondary metabolites reported from plants Plumeria rubra, Capparis decidua, Callistemon citrinus, Punica granatum and Magnolia champaka were selected for in silico molecular docking studies against these signaling pathways using the Glide XP module of Schrodinger Suite. It was discovered in this study that compounds plumaride-coumarate, r ubranonoside, 1-alpha-plumiride, rubradoid yielded excellent dock score with the proteins concluded with help of docking free energy along with forming, lipophilic interactions, hydrogen bond and electrostatic bond. Results of these studies can be useful to understand various protein-ligand interactions involved in signaling pathways to enhance cell growth inhibitory activity. These molecules may serve as leads for drug discovery as well as development of novel structural analogs which can be used as multi-targeted agents against cancer. Further experimental studies will be carried out for the validation of these findings.

P163. Molecular docking studies of naphthoquinone analogues as novel topoisomerase II inhibitors for potential anticancer agents

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Cancer which is characterized by the uncontrolled growth and spread of abnormal cells, is one of the major cause of death worldwide. Molecular docking studies have played a lead role in drug design and development. The quinone scaffold is versatile and is present in many of clinically used anticancer drugs. Our study focuses on molecular docking of a series of hypothetically developed napthoquinone derivatives, to identify their interactions on the DNA binding protein topoisomerase II (PDB ID:1ZXM). The results depict that the test molecules fit into the binding pocket of topoisomerase II in the desired fashion and interaction with the amino acids. Among the 54 derivatives, NIPERA-SPC2 was observed to have the highest docking score of -7.710 with significant hydrogen bond interactions with ASN120 and LYS168 residues, pi-pi stacking with ARG98 on the active site of 1ZXM. Doxorubicin taken as standard; when subjected to similar docking protocol had docking score of -6.240. In the upcoming future, the synthesized molecules would be evaluated for their in-vitro efficacy and activity.

P164. Exploring the anti-invasive and stemness-inhibiting potential of mTOR inhibitors: A novel strategy for anti-glioma therapy

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Glioblastoma (GBM) is the most lethal and common CNS tumor in adults. Despite the advancements in multimodality treatment, the prognosis of GBM patients remains dismal with poor survival period. The standard line of treatment involves surgical removal of tumor followed by chemotherapy with temozolomide(TMZ)-being the drug of choice. However, TMZ is inefficient with only 11% of the patients remaining progression free at 2 years post-treatment. The PI3K/AKT/mTOR is a major signaling for tumor survival, proliferation and progression making it an attractive target for therapeutic invention. Activation of mTOR promotes invasive phenotype and correlates with poor survival in GBM patients. Though preclinical and clinical studies have demonstrated antiproliferative and cytotoxic activity of mTOR inhibitors in GBM, their action on invasiveness and migration is not addressed. In this study, we demonstrate that mTOR inhibitors-Rapamycin(RAP), Temisirolimus(TEM), Torin-1(TOR) and PP242 suppressed invasion and migration induced by tumor activators through inhibition of PKC-Ð activity and NFÐB activity. Aggressive invasion and migration of tumors are associated with mesenchymal and stem-like cell properties. The findings also demonstrate that TEM and TOR reduced the expression of mesenchymal proteins- fibronectin, vimentin YKL-40 and neural stem cell markers and neurosphere- forming capacity of human GBM cell lines and primary cultures through inhibition of STAT-3 signaling. The findings support the hypothesis that targeting the mTOR pathway holds promise to offer a novel anticancer therapy through suppression of migration, invasion and stemness associated features and paves way for clinical trials of these drugs particularly TEM as it is FDA approved drug.

P165. Mediator of dna damage checkpoint protein 1 (MDC1) as a prognosticator for patients with oral squamous cell carcinoma

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The mediator of DNA damage checkpoint protein 1 (MDC1) is involved in the regulation of cell cycle check points and recruitment of several repair proteins to the site of DNA double stranded breaks (DSBs). The present study aims to correlate the expression of MDC1 protein with clinicopathological parameters and to evaluate its prognostic significance in patients with oral squamous cell carcinoma (OSCC). MDC1 protein expression was evaluated immunohistochemically from untreated 100 patients with OSCC using modified H-score method. The association of MDC1 immunostaining was evaluated with clinicopathological parameters. Univariate and multivariate survival analysis was carried out by Kaplan-Meier survival function and Cox regression forward stepwise method, respectively. Incidence of nuclear and cytoplasmic expression of MDC1 protein was 85% & 92%, respectively. Strong nuclear MDC1 protein expression was found to be significantly correlated with lymphnode metastasis (p=0.032) and reduced relapse free survival (p=0.005). Multivariate survival analysis revealed MDC1 as a significant independent prognosticator in predicting reduced relapse free survival (p=0.027). One of the noteworthy observation in relation to treatment was that the patients

exhibiting weak expression of nuclear MDC1 protein were benefited significantly when treated with surgery followed by radiation therapy (p=0.001) compared to surgery followed by chemo-radio therapy indicating that cells exhibiting low MDC1 were more sensitive to radiation therapy. Thus, present study showed that MDC1 protein expression could be used as a prognostic marker in predicting relapse free survival in patients with OSCC. OSCC patients expressing weak MDC1 protein could be benefited by adjuvant radiotherapy instead chemo-radiotherapy.

P166. Molecular docking studies, synthesis and biological evaluation of some novel mTOR/PI3K inhibitors

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Mammalian target of rapamycin (mTOR) and phosphoinositide-3-kinase (PI3K) are involved in the signaling pathway that regulates normal cellular functions which include cell division, growth and cell death (autophagy-type II cell death mechanism). The aberrant activation of these two key enzymes interplays in varied types of cancer. Thus mTOR/PI3K inhibition provide an eccentric target for therapeutic intervention in many cancers such as breast cancer, cervical cancer etc. With the help of molecular docking using Schrodinger, Maestro, v 10.2 software newer N-(substituted)-2-cyano-3-(substituted)-3-(methylthio)acrylamide derivatives were designed and synthesized. The synthesized molecules were characterized by IR, Mass, 1H NMR, 13C NMR spectroscopic techniques. The synthesized molecules were screened for their mTOR/PI3K dual kinase inhibition by western blot assay, GFP-mCherry assay and among all the compounds, LMBK1 has been found potent dual kinase inhibitor. The identified hits can be modified and optimized further for potency.

P167. Design and in-vitro evaluation of chronotherapeutic delivery system of a NSAID for rheumatoid arthritis

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The objective of the study was to design and evaluate chronotherapeutic delivery systems of Ketorolac Trometamol. Pulsatile systems are gaining a lot of interest as they deliver drug at the right site of action at the right time and in the right amount, thus increasing patient compliance. The basic design of pulsatile drug delivery system consists of formaldehyde treated hard gelatin capsule body, filled with Eudragit coated cellulose acetate (CA) microspheres of Ketorolac Trometamol and plugged with a hydrogel polymer. CA microspheres were prepared with different core: coat ratios by solvent evaporation technique. To achieve site specific delivery, the optimized CA microspheres were further coated with enteric polymers like Eudragit L-100 and Eudragit S-100 by solvent evaporation technique. Different plugging materials like Xanthan gum, Guar gum and HPMC K100M were used in the design of pulsatile capsule. The insoluble hard gelatin body was cap sealed by 5% ethyl cellulose solution and then the entire capsule was enteric coated with Hydroxypropyl Methylcellulose Phthalate (HPMCP) to render the system insoluble in gastric pH. Dissolution studies of the pulsatile devices revealed the absence of drug release in first three hours and negligible release in the fourth hour and thus a lag time of 3-4 hours was achieved. In conclusion, time and pH dependent pulsatile drug delivery system was successfully designed, evaluated and found satisfactory with respect to desired lag time which is needed in chronotherapeutic treatment of rheumatoid arthritis.

P168. A combined approach of nanoparticles with iontophoresis using macrolide antibiotic for the treatment of eye diseases

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The aim of the work was to formulate Solid Lipid nanoparticles of macrolide antibiotic for the treatment of endophthalmitis and to enhance its permeation using a novel non-invasive technique 'Ionotophorosis'. Solid lipid nanoparticles were prepared by nano-precipitation technique followed by ultra-sonication method. For the selection of lipid, surfactant and co-

surfactnat, initially solubility studies were performed. Preliminary trials and fraction factorial design were carried out for final screening of selected lipid, surfactant and co-surfactant using varying the concentration of lipid, Surfactant and co-surfactant ratio and Surfactant concentration. From the fraction factorial design, two significant factors were selected i.e Drug to lipid ratio and Sonication time. For further optimization 32 full factorial design was applied. The dependent variables selected were particle size, % entrapment efficiency and % drug loading. Based on QbD approach, the final formulation was optimized. In-vitro diffusion studies were performed using multi diffusion cells in phosphate buffer 7.4. To enhance the permeation of drug, the optimized final formulation was undergone through iontophoretic technique. Ex-vivo study was performed on the goat eye and the permeation was checked. The iontophoresis technique was found to be very useful as systemic toxicity can be avoided due to enhanced permeation. So, with combination of the solid lipid nanoparticles and iontophoresis, controlled release formulation along with increased permeation can be formulated and intra-vitreal injections can be avoided.

P169. Human DNA ligases: Emerging targets for cancer therapy

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Drug development is a continuous and progressive process. This becomes imperative in the case of cancer drug discovery where the world is facing the problem of drug-resistance and side effects of existing chemotherapeutics. Due to this, it is necessary to develop new and better drugs that can overcome the limitations of existing therapy. DNA repair proteins such as human DNA ligases are now being increasingly studied as new targets for the development of anticancer drugs. DNA ligases play important roles during the final steps of DNA replication and repair processes where they seal the nick between DNA strands. In humans, three types of DNA ligases are reported i.e. DNA ligase I (hLigI), DNA ligase III (hLigIII) and DNA ligase IV (hLigIV). hLigI and III seal the nick during single strand DNA breaks whereas hLigIV seals the nicks between double-strand breaks. Among the three, hLigI is the major replicative ligase and is also reported to be overexpressed in cancer cells. Therefore, it may be targeted for the development of novel targeted anticancer drugs, specially in combination with existing DNA damaging chemotherapeutic agents. In this direction, we report the synthesis of a novel series of Benzocoumarin-Stilbine hybrid molecules by a molecular hybridization approach. The most active compound in this series (C9M) shows specific targeting and inhibition of hLigI activity both in-vitro and ex-vivo, as well as encouraging in-vitro and in-vivo antitumor activities. Preclinical efficacy and toxicity studies show that the compound has moderately good pharmacokinetic properties and may be considered a good lead molecule for the development of novel ligase I inhibitors with anticancer activity.

P170. Therapeutic prospects of mitochondrial changes in cancer-cachexia

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Cancer cachexia, a complex metabolic syndrome associated with certain solid tumors results into negative energy balance and wasting of adipose and skeletal muscle mass leading to progressive weight loss irrespective of nutritional intake. Mitochondria, which is better known as the "powerhouse" of the cell is involved in regulating energy production. Mitochondrial dysfunction has been reported in cancer-cachexia – which might be responsible for altered cellular bioenergetics associated with the disorder. Such mitochondrial changes can be summarized majorly in two types viz. morphological and physiological changes. Morphology of the organelle in terms of its size and intra-organelle content is altered in cancer cachexia as a result of overexpression of mitofusin fusion proteins, mitochondrial permeability transition pores, inhibition of Na^+/K^+ exchange pump – all of which leads to increased solute influx inside the mitochondria which increases mitochondrial matrix volume, damages cristae and forms mega-mitochondria via fusion events. Additionally, overexpression of ryanodine receptors on sarcoplasmic reticulum in cachectic skeletal muscle is also reported which releases calcium from the stores leading to recruitment of mitochondrial fission proteins and formation of fragmented mitochondria. On the other hand, physiology of the organelle in cachexia is affected by overexpression of uncoupling proteins in cachectic skeletal muscle as well as adipose tissue which promotes uncoupled respiration and hence alters ATP production and mitochondrial

membrane potential. The present review aims to put forth the changes occurring in mitochondria and hence explore possible targets which can be exploited in cancer induced cachexia to study altered bioenergetics and metabolism.

P171. Cancer cachexia induced cardiovascular alterations : Mechanisms and therapeutic

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Cancer cachexia is a debilitating condition characterized by skeletal muscle wasting, lean body mass and significant weight loss. It is responsible for poor response to chemotherapy, reduced mobility and functionality, poor quality of life and high mortality rate. Mechanisms responsible for cancer cachexia are enhanced lipolysis, altered carbohydrate and protein metabolism along with increased inflammatory responses. All of these molecular mechanisms also contribute to development of cardiovascular complications. The major problem in cancer patients is that there is reduction in cardiac mass and cardiac contractility, cardiac fibrosis, remodelling and cardiac muscle atrophy. Apoptosis is the key mechanism for structural alterations of the heart. Also altered protein metabolism in cachexia leads to protein loss in heart contributing to cardiac atrophy. Ubiquitin Proteasome System, Calcium activated system and Autophagy-lysosomal cascades are key mechanisms for protein degradation. Several treatment strategies like ACE inhibitors, Angiotensin receptor blockers, aldosterone antagonists, Ð-blockers, estrogen modulators etc. have been studied for management of cardiovascular alteration in cancer cachexia. The current review focuses on the molecular mechanisms of cancer cachexia which lead to development of cardiovascular complications.

P172. Targeting prostate cancer with compounds possessing dual activity as androgen receptor antagonists and HDAC6 inhibitors

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Non-steroidal antiandrogen enzalutamide and steroidal antiandrogen abiraterone are approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). However, approximately 20–40% of patients have no response to these agents. The lack of response in these patients to these agents is postulated to the development of secondary resistance due to the presence of AR splice variants. HDAC6 has a role in regulating the androgen receptor (AR) by modulating heat shock protein 90 (Hsp90) acetylation, which controls the nuclear localization and activation of the AR in androgen-dependent and independent scenarios. The clinical evaluation of HDAC inhibitors as monotherapy for prostate cancer has not been promising. With dual-acting AR–HDAC6 inhibitors it should be possible to target patients who don't respond to enzalutamide. Herein, we describe our efforts to make dual-acting compounds which target AR and are also specific towards HDAC6, using enzalutamide as the AR binding element. Our efforts have identified compounds with potent dual activity (HDAC6 IC50 = 0.0356 μM and AR binding IC50 = <0.03 μM). Further cell-based activity, in vitro stability and pharmacokinetics of the potent compounds have been studied.

P173. Targeting oncogenic RAS: The quest for the holy grail in cancer drug discovery

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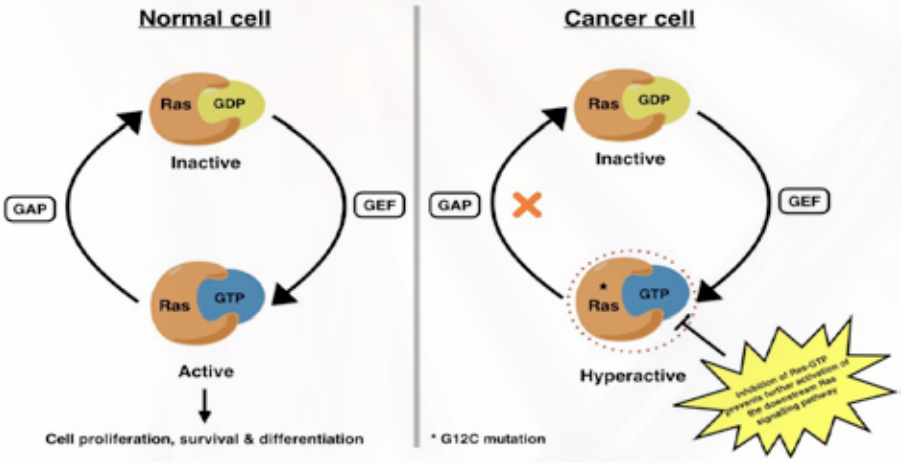
Cancer is considered to be a global health problem. Deregulation of the kinase activity has emerged as a major mechanism by which cancer cells evade normal physiological constraints on growth and survival. Such aberrant functions of the kinases in a cancer cell

have highlighted them as one of the most successful families of drug targets. Rat sarcoma (Ras) are small protein GTPases responsible for myriad of signalling cascades involved in highly diverse cellular processes in the normal cells. However, constitutively activating Ras mutations have been reported in many human cancers. Hence, Ras-signalling pathway has attracted considerable attention as a target for anticancer therapy. Targeting kinases via specific kinase inhibitors can result in highly specific and effective therapies which will enhance cancer therapy management. Nevertheless, the development of highly selective inhibitors still remains a major challenge for kinase chemical biology owing to the lack of successful design strategies. There is, therefore, an urgent need to devise new approaches to modulate kinase function. Innovative approaches in chemical biology have played a key role in developing the kinase target area.



In our present work, we propose to design and synthesize pyrophosphate-based inhibitors through a structure-guided drug design approach which will selectively inhibit Ras. Further, we aim to screen the chemically synthesized compounds from our in-house compound library for their inhibitory potential in-vitro and using cell-based assays. The successful completion of project may lead to the development of effective drug leads and provide opportunities for the development of new anticancer therapeutics.

P174. Karyotypic analysis of acute myeloid leukemia (AML) in 75 referral cases: one year report

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Cancer is one of the deadliest disease helping the human life around the world. In this study we have analyzed 75 referral cases of Acute Myeloid Leukemia (AML) registered in our Research Institute, Supratech Micropath Laboratory of Ahmedabad. Karyotype analysis of bone marrow and blood samples revealed 7 cases (9.3%) were AML positive. Out of these cases, 3 patients (4%) have recurrent chromosomal anomalies of t(8;21) and t(15;17) and other 4 (5.3%) had AML with Myelodysplastic syndrome s (MDS) related changes in which one karyotype had 4 chromosomal abnormalities viz, two each of trisomy and monosomy respectively . This group has poor prognosis. A new spectrum of groups of both herbal and synthetic origin will be awaited for future care.

P175. Endpoint evaluation in immunotherapy clinical trials: focus on irrecist

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Cliantha Research Ltd

Current methods for endpoint evaluations in Immunotherapy Trials

Historically, most solid tumor responses to cytotoxic agents have been radiologically assessed through use of the modified World Health Organization (mWHO) and the Response Evaluation Criteria in Solid

Tumors (RECIST) criteria. The recognition that tumor activity response patterns to Immuno-Oncology agents may be different compared to cytotoxic agents, led to the development of the immune-related response criteria (irRC). These criteria, released in 2009, were derived from the mWHO criteria and based on response patterns seen with ipilimumab.

Need for the more uniform and harmonized method of Evaluation

Unlike chemotherapy, which acts directly on the tumor, cancer immunotherapies exert their effects on the immune system and demonstrate new kinetics that involve building a cellular immune response, followed by changes in tumor burden or patient survival. Thus, adequate design and evaluation of immunotherapy clinical trials require a new development paradigm that includes reconsideration of evaluation of established endpoints. irRC has its own pitfall like erroneous consideration of pseudo progression and reset of baseline. Compared to RECIST, irRC is bidimensional and evaluates greater number of lesions. Studies have demonstrated that irRC unidimensional measurements, when compared to bidimensional measurements, are more reproducible, have less measurement variability and result in lower misclassification rates for response assessment.

irRECIST and its advantages

irRECIST is an innovative step which is expected to be simpler, more reproducible and less ambiguous to assess efficacy and effectiveness of immunotherapeutic agents, and provide response assessment that can be directly compared with the results from clinical trials in the past decade. It overcomes shortcomings of both the criteria including unidimensional measurements, inclusion and assessment of all detected lesions and avoiding early declaration of progressive disease. Few studies have been carried out to validate the criteria compared to irRC and RECIST 1.1. Currently 39 clinical trials are listed on ClinicalTrials.gov that uses irRECIST criteria for response evaluation.

Table 1: irRC vs irRECIST

Original irRC, Including WHO criteria References	irRECIST Modifications and clarifications
At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.	1. 0 Baseline: Measurable Lesion Definitions and Target Lesion Selection Follow the definitions from RECIST 1.1.
WHO 5.1.2 Unmeasurable Disease There are many forms of unmeasurable disease, and only a few are mentioned as examples: Lymphangitic pulmonary metastases. Skin involvement in breast cancer. Abdominal masses that can be palpated but not measured.	1.1. Baseline: Non-measurable Lesion Definitions Follow the definitions from RECIST 1.1
At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5Ð5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden: SPDindex lesions + SPDnew measured lesion	2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.
Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required).	2.2 Follow-up: Non-Target Lesion Assessment The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR.	2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new nonmeasurable lesions prevent irCR.
irRC Overall Tumor Assessments irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented irPR, decrease in tumor burden ≥50% relative to baseline • Confirmed by a consecutive assessment at least 4 weeks after first documentation irSD, not meeting criteria for irCR or irPR, in absence of irPD irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented	2.4 irRECIST Overall Tumor Assessments irCR, complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. irPR, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. irSD, failure to meet criteria for irCR or irPR in the absence of irPD. irNN, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD. irPD, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. irNE, used in exceptional cases where insufficient data exists. irND, in adjuvant setting when no disease is detected.

P176. Exploring marine flora as source of anti cancer drug leads by in-silico and in-vitro approach: a study on various solid tumor cell lines

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Oceans are a vast reservoir of bioactive natural products, some of which exhibit important and unique biological properties. Thus, many compounds isolated from marine sources are currently used in clinical trials or as prototypes for the design and synthesis of new therapeutic agents. In the present study, assessment of the anti cancer activity of marine plants collected from Marine National Park, Jamnagar Gujarat have been performed. Selected four marine plants extracts have been prepared and their effect on the proliferation and viability of specific cell types has been evaluated. Extracts (among hot/cold extracts of four marine plants) showing their significant cytotoxic effect as compared to other standard drugs were further analyzed to check if they have potential to induce apoptosis using flowcytometric assay. Cells were classified into four groups like live, early apoptotic, late apoptotic and dead or necrosis. All extracts significantly decreased number of viable cells, whereas late apoptotic cells as well as dead cells were shown to be increased. Moreover, among all the extracts Avicennia Marina (Hot extract) demonstrated the significant effect on early as well as late apoptosis, suggesting their potential to induce apoptosis in cell lines. A computational study have been carried out in which cell signaling target proteins have been screened against phytochemicals of selected Marine plants. Molecular docking and Molecular Dynamics studies have been performed to evaluate the selectivity of the phytochemicals against the target proteins based on their interaction profile. The computational view was validated by in-vitro studies which confirms the anti cancer potentiality of the selected medicinal plants.

P177. Effect of Mucuna pruriens (Linn) on acute dermal toxicity of Wister rat

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Mucuna pruriens (Linn) is Known as velvet bean or cow itch found in Africa, India and the Caribbean belonging to the family Fabaceae. Mucuna pruriens Linn is a herbaceous vine, generally tap rooted and reproducing by seeds, leaves have three leaflets up to 15 cm long, densely hairy beneath and rather silvery the lateral leaflets asymmetrical. Hair lining of mucuna seeds were tested for acute dermal toxicity. Hair lining were mixed with dusting powder and prepared three formulation according to concentration. This test was performed on rats based on OECD guideline number 404 (OECD, 1981a). In case of acute dermal toxicity study there was no treatment related mortality in any of the groups following topical application of formulations in either male and female rats for 14 days. Hematological Studies revealed that after application of tested formulation WBC like monocyte, neutrophil, eosinophil were increased. Serum biochemistry data did not produce significant differences between control and treated groups of both sexes in the majority of cases. In case of electrocardiography the animals showed normal value as compared to the control group. In whole body plethysmograph the treated animals showed similar value as compared to the normal group . After Sacrifice, the gross examination of the vital organs like liver, kidney and lungs, no noticeable hemorrhage and abnormal conditions were observed. The histopathological study did not showed any type of abnormality of skin in all treated group. It can be concluded from the finding of the present study that the finding of these studies support the safety use of the test substance Mucuna pruriens.

P178. PTP 1B Inhibitors: Effect of Heterocyclic Carboxylic acid Derivatives on Triaryl-sulfonamide Scaffold

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Diabetes is one of the major contributors to ill health in the current century. Currently available antihyperglycemic agents, including insulin promote weight gain, which further aggravates obesity associated cardiovascular risk and insulin resistance. In recent years, development of protein tyrosine phosphatase1B (PTP 1B) inhibitors has been considered as one of the best validated biological targets for the treatment of diabetes. In the present study we have synthesized mono-carboxylic derivatives of compound I and evaluated their use as selective PTP 1B inhibitors. The derivatives of tri-aryl sulfonamide were found to be selective PTP 1B inhibitors, which could be useful for the treatment of diabetes.

A novel series of heterocyclic carboxylic acid moiety containing triaryl-sulfonamide derivatives (6a-q, 13a-d & 15b) have been synthesized using appropriate synthetic scheme and evaluated their PTP 1B inhibitory activity using pNNP assay. The most potent compounds were further subjected for in vitro selectivity, over other PTPs (PTPß, LAR, CD45, VHR, SHP-1, SHP-2, and TCPTP). The lead compounds 13b & 15b showed potent in vitro PTP 1B inhibitory activity along with improved selectivity over TC-PTP. The most potent compounds 13b & 15b were subjected for in silico docking study and the docking study results were found to be in agreement with the observed in vitro PTP1B selectivity over other PTPs.

P179. Rational drug design studies: Semicarbazone based four binding site pharmacophoric model hypothesis for antiepileptic activity

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Epilepsy is a group of neurological disorder characterized by the periodic sudden loss or impairment of consciousness, often followed by convulsions. The epilepsy is the second leading neurological disorder with approximately 60 million patients. Although several novel anticonvulsants are available, still about one third of these medicines are ineffective to control the seizure, moreover characteristic side effects is also being observed. These facts necessitates the development of more effective and safer antiepileptic drug. A series of novel pyrimidine based semicarbazone were designed and synthesized on the basis of semicarbazone based pharmacophoric model to fulfill the structural requirements vital for anticonvulsant activity. The semicarbazones based pharmacophoric model comprises of

following four essential binding sites: (i) An aryl hydrophobic binding site with halo substituent; (ii) A hydrogen bonding domain; (iii) An electron donor group and (iv) Another hydrophobic-hydrophilic site controlling the pharmacokinetic features of the anticonvulsant. The chemical structures of the synthesized molecules were elucidated using elemental and spectral (IR, 1H NMR, 13C NMR and MS) analysis. The anticonvulsant activity of the test compounds were evaluated using maximal electroshock seizure (MES) and subcutaneous pentylenetrtrazole (scPTZ) models. The minimal motor impairment activity was determined in mice using the rotorod test. In the present study, all the test semicarbazones were subjected to molecular docking using Glide v5.8 (Schrodinger, LLC, New York). Some of the compounds were found to interact with ARG192, GLU270 and THR353 residues of 1OHV protein, present in GABA-AT receptor. The endeavours were accomplished to ascertain the structure-activity relationships among synthesized compounds.

P180. Mycobacterial protein tyrosine kinase a augments the secretion of PtpA by phosphorylation at tyrosine residues and the mechanism is stalled by inhibitors

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Phosphorylation and dephosphorylation are the key mechanisms for mycobacterial physiology and play critical roles in mycobacterial survival and in the pathogenesis. Mycobacteria evade host immune mechanism by inhibiting phagosome – lysosome fusion in which mycobacterial tyrosine phosphatase (PtpA) plays an indispensable role. Tyrosine kinase (PtkA) activated by autophosphorylation; phosphorylates PtpA, which subsequently leads to increase in its phosphatase activity. The activated PtpA after getting phosphorylated is secreted in phagosome of macrophage. In present study we have shown that the phosphorylation at two sites of PtpA; Y128 and Y129 are critical for PtkA mediated PtpA secretion and activity. The disruption of this interaction between PtkA and PtpA inhibits activation of later which further leads to the decrease in its secretion and in intracellular survival of mycobacteria. Further, the experiments have shown that inhibitors which inhibit the growth of mycobacteria, associate with the functional sites of PtpA and contend with the PtkA. This binding was further restated by looking at the anchorage of protein-protein and the protein-inhibitor complexes in the homology based structure models.

P181. Design and Synthesis of Benzofuran Based Pyrazolo[3,4-d]pyrimidinamine Derivatives as Potent and Selective PI3Kd Inhibitors

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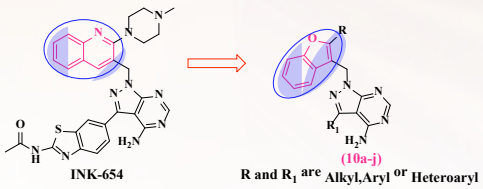
Phosphoinositide 3-kinases (PI3Ks) belong to a conserved family of lipid kinases and they are involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. Particularly, PI3Kδ is most discretely expressed and confined to leukocytes and has been implicated as a therapeutically useful target in the treatment of certain forms of blood cancer & inflammation. In the present study, we have synthesized a series of compounds 10a-j and evaluated their PI3Kδ inhibitory activity. The synthesis of titled compounds 10a-j was carried out by appropriate synthetic procedures. The derivatives of 1-(benzofuran-3-yl-methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (10a-j) has showed excellent PI3Kδ inhibitory activity and selectivity over other kinases. The in vitro testing of these compounds were carried out by PI3K ELISA assays of p110α/p85α, p110ß/p85α, p110δ/p85δ and p110γ: Among the compounds tested 10i & 10j showed good in vitro PI3Kδ inhibitory activity. Further these test compounds were subjected for selectivity in isoform specific in vitro assay & compound 10j exhibited better PI3Kδ selectivity.



P182. Comparative assessment of clinical- and histo-pathological changes of PEGG-CSF in Wistar rats

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Granulocyte colony-stimulating factor (G-CSF) is a haematopoietic growth factor required for the proliferation and differentiation of haematopoietic precursors of neutrophil. Pegstim® is a long-acting PEGylated form of recombinant human granulocyte colony-stimulating factor (GCSF) indicated in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The present experiment was designed with an objective of comparative assessment of clinical- and histo-pathological changes between Pegstim® and reference products (US & EU) in Wistar rats . Different groups of ten rats per sex each were administered with each product once weekly by subcutaneous injection at dose levels of 0.3, 1 and 3 mg/kg body weight for a period of 4-weeks. Hematological analysis revealed significant increase in total WBC count and in particular neutrophils counts were detected at all the dose levels of each product. In serum biochemical analysis, significant increase in alkaline phosphatase (ALP) was observed at all dose levels of each product. These anticipated pharmacodynamic effects were appeared to be comparable among all the three products. Histopathological evaluation revealed minimal to severe extramedullary hematopoiesis (granulopoiesis) and leukocytosis in red pulp of spleen and paler femoral bone marrow, which was associated with, minimal to severe myeloid hyperplasia (granulopoiesis) at epiphyseal region with increased osteoblastic and osteoclastic activity. Minimal to moderate extramedullary hematopoiesis (granulopoietic foci) and leukocytosis in hepatic vessels were observed in liver. These microscopic changes were found to be comparable and witnessed in all three products at all dose levels with varying degree of severity and were considered as test item-related reversible exaggerated pharmacological effects.

P183. Non-clinical safety assessment of bevacizumab and trastuzumab biosimilars

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Bevacizumab and Trastuzumab are humanized recombinant monoclonal antibody and share the most expensive components of cancer therapy. Cadila Healthcare (CHL) is developing Biosimilar of Avastin® (bevacizumab) and Herceptin® (trastuzumab), to provide high quality biologics in a cost-effective manner. The comprehensive nonclinical studies were carried out to demonstrate equivalent in terms of quality and efficacy with reference products. The comprehensive nonclinical studies were carried out to demonstrate safety of biosimilars. Single intravenous injection revealed tolerability over a dose of 625 mg/kg & 400 mg/kg in mice and 500 mg/kg & 200 mg/kg in rats of biosimilar of Bevacizumab and Trastuzumab respectively. Biweekly repeated dose intravenous injection of biosimilar of Bevacizumab up to 310 mg/kg in rats and 155 mg/kg in rabbits revealed no adverse effects. Similarly, repeated intravenous injection (28 days) of biosimilar of Trastuzumab up to 125 mg/kg in rats and 62.5 mg/kg in rabbits at an interval of one week, revealed comparable safety profile. An approved reference innovator product, Avastin® at a dose of 62 mg/kg in rats and 31 mg/kg in rabbits and Herceptin® at a dose of 25 mg/kg in rats and 12.5 mg/kg in rabbits were used in these multiple dose studies of biosimilar of Bevacizumab and Trastuzumab, respectively. The immunogenic response was favorable to that of reference products. No adverse local tolerance effects were noticed at the site of injection. Therefore, it is concluded that the nonclinical safety assessment of biosimilar of Bevacizumab and Trastuzumab developed by Cadila Healthcare Ltd., seems to be comparable with the Avastin® and Herceptin®.

P184. Non-clinical safety assessment of Adalimumab

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Adalimumab (Exemptia), the fully human anti-TNF alpha monoclonal antibody to treat patients suffering from autoimmune disorders. Exemptia is a first biosimilar of adalimumab developed by Cadila Healthcar e Ltd., to treat autoimmune disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis. The objective of nonclinical single and multiple dose studies was to assess the comparison between Exemptia to a reference product (Humira®) in safety, purity and potency. Single dose studies revealed a good safety margin over a dose of 830 mg/kg in mice & 410 mg/kg in rats of Exemptia by both subcutaneous and intravenous administration. Multiple dose studies were conducted at a dose level of 4.1, 20.5 & 41 mg/kg of Exemptia and 4.1 mg/kg of reference product in rats, and 2.1, 10.5 & 21 mg/kg of Exemptia and 4.1 mg/kg of reference product in rabbits by weekly subcutaneous administration over a period of four weeks. No adverse effects were noticed during clinical examination, body weight and feed intake, clinical pathological and histopathological evaluation in these studies. No any differences were noticed from reference product in both rats and rabbits. The immunogenic response was favorable to that of reference product. No any adverse local tolerance effects were noticed at the site of injection. Thus, the overall nonclinical profile of Exemptia (Biosimilar of Adalimumab) seems to be comparable with the approved reference product, Humira®.

P185. Preclinical safety evaluation of a novel pegylated Erythropoietin

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Pegylated EPO is a novel, potent long-acting pegylated rHuEPO intended to treat anemia associated with chronic kidney disease. The in vivo pharmacodynamic and pharmacokinetic studies showed the promising erythropoiesis stimulatory activity and good exposure profile in various animal models studied and selected for development. Various toxicity studies were performed to assess its safety profile viz. acute toxicity, repeated dose toxicity, male fertility and local tolerance studies along with assessment of immunogenicity profile. Acute studies conducted in mice and rats by subcutaneous and intravenous routes revealed maximum tolerated dose as ≥2000 µg/kg. Repeated dose toxicity studies with toxicokinetics were performed in wistar rat and beagle dogs at different dose levels of up to 10 µg/kg body weight once weekly by subcutaneous injection for a period of four weeks. The resulted hematological changes indicative of exaggerated pharmacological effects characterized by higher RBC indices. The histopathological profiling was consistent with its pharmacological effects in both the species apart from secondary histomorphological changes in target organs. Histomorphological changes were observed in spleen, liver, femur and sternum with marrow, kidneys, adrenals, stomach and duodenum. Immunogenicity profile was studied in both species and very low titers of antibodies were developed against the pegylated EPO. Based on the repeated dose toxicity profile no observed-adverse-effect-level (NOAEL) was found to be 1 µg/kg in rats and 0.3 µg/kg in dogs. In addition, pegylated EPO did not affect any parameters related to male fertility, mucus membrane irritation and skin sensitization studies.

P186. In silico modeling studies of the phytoconstituents of Aegle marmelos extract

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Many herbs have been used in treatment of diabetes still very less reports about individual mechanism of action, are avialable. Aegle marmelos has been reported for its in vitro and in vivo activity against diabetes mellitus. The fruit extract of Aegle marmelos contains most of coumarins & it has been reported as potential therapeutic agents in treatment of diabetes. The present study reveals the relationship between structure and function of medicinally important constituents of this plant. To understand the binding mechanism of these active constituents, molecular modeling studies has been performed with various targets involved in diabetes dipeptidyl peptidase, protein tyrosine phosphate 1B, sodium potassium

ATPase, aldose reductase and glycogen synthase kinase-3ß using XP docking program of glide version 9.2, Schrodinger suit. These constituents showed favourable interaction with amino acid residue at the active site, there by substantiating their proven efficacy as antidiabetic agents.

P187. Development of cholesterol and hydrogen peroxide electrochemical biosensor

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Cholesterol and hydrogen peroxide is the important factors in determining the cardiac problems like atherosclerosis and oxidative stress, it is important to determine the levels of cholesterol and hydrogen peroxide (H_2O_2) in blood samples. There are a number of cholesterol and hydrogen peroxide sensors are available but the combination is not yet reported. In the current study, it is hypothesised to develop asensor having combination of both. The developed biosensor may be having high selectivity, sensitivity, linearity, and less detection time. Deposition of Graphene oxide(GO), polypyrrole(PPy) and multiwall carbon nanotubes(CNTs) has been done on indium tin oxide (ITO) electrode for comparing the data and surface morphology has been studied by optical and flouroscence miscroscopy. The electron transfer rate and average surface area has been found more with PPy/MWCNTs/ITO than GO/PPy/ITO electrode. So that by using poly pyrrole, multi wall carbon nanotubes as a matrix the immobilization of enzymes called cholesterol oxidase (ChOx) and horse radish peroxidase (HRP) have been done by covalent method and leaching behaviour and stability of immobilized enzymes has been studied. The surface characterization of developed biosensorhas been done by performing morphological studies by SEM, and the performance studies have been done using cyclic voltammetry and chrono amperometry.

P188. Design, synthesis and biological evaluation of new quinazolinone derivatives as potent antimicrobial agents

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Quinazolinone class of compounds is known to be an important chemical class with varied biological activities of pharmaceutical importance. They possess a variety of biological effects including antihypertensive, antimicrobial, anti-hyperlipidemic, antioxidant, anti-inflammatory, anticonvulsant, and anti-cancer activities1. Interest in quinazolinones has further increased since the report of compounds I and II as potent anti-bacterial agents. While compound I is found to be a potent Lpxc inhibitor2, compound II has been reported to be an inhibitor of penicillin binding protein PBP2a[3]. Inhibition of Lpxc leads to bactericidal activity against gram negative bacteria. Compound II and its related derivatives have been found to be inhibitors of methicillin-resistant S.aureus (MRSA). A new library of quinazolinone derivatives have been synthesized utilizing the structural features from the above two series of compounds and are evaluated against gram negative, gram positive bacteria and mycobacterium. The structure Activity Relationships will be discussed.

P189. Validation of fetal jugular blood collection technique in embryo-fetal developmental toxicity study

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Fetal blood collection is difficult technique during teratogenicity testing study in rodents when it is necessary to evaluate fetal exposure of test item e.g. Novel vaccines. Alternate to fetal blood collection is umbilical cord blood collection but due to contamination and less feasibility of umbilical cord blood collection we have standardized direct fetal blood collection from fetal jugular vein. In this validation the dams were hysterectomised at gestation day (GD) 20 and fetuses

were plucked carefully from gravid uterus. Pooled fetal blood collection from litter was carried out puncturing jugular vein using 26-gauze needle. Direct pipetting of fresh oozed out fetal blood has been done. This technique after technical training of individual personnel can serve as gold standard technique during Teratogenicity testing as and when required.

P190. 3D-QSAR molecular field based model of katp channel activation by 4, 6 di-substituted benzopyran derivatives

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We describe a 3D-QSAR molecular field based model which is capable of predicting the activity of novel openers or activators of K^{ATP} channels (KCO). Our model is the first 3D-QSAR model of KCOs that describes the molecular fields utilizing the electrostatic and volume fields as an empirical method to match different molecules in their bioactive confirmations with respect to the biological activity. The earlier developed model of 4, 6 disubstituted benzopyrans by Sharma et. al., 2008, provided a limited understanding of the required molecular field for developing newer analogues with K^{ATP} activity. The model is based on pED50 values required for myorelaxant activity by 4, 6 disubstituted benzopyrans based on molecular field of the structures and their alignment with the most potent compound of the series, i.e. Cromakalim. With an R2 of 0.99 for the training set of 25 compounds and a Leave-Many-Out (LMO) cross-validated value (Q2) of 0.496 with RMSETraining of 0.020, indicated that the model had optimum predictive ability on structurally diverse 4, 6 di-substituted benzopyrans. The developed model and the participating molecular field suggest that the replacement groups of 4, 6 di-substituted benzopyrans potential for structural optimization for the enhancement of biological activity. All our findings revealed critical features for the ligand activity, which could be useful in future development of K^{ATP} channel openers.

P191. Nephrotoxicity and drug discovery : A novel approach towards humanized prediction

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A large number of drugs are withdrawan at phase 3 & 4 level in drug discovery and development process due to inappropriate nephrotoxicity prediction. The reasons behind are unavailability of (1) preclinical models with close to human response (2) sensitive and specific biomarkers for early detect ion of nephrotoxicity. Animal models used in current scenario for the purpose are differentially responsive to xenobiotics and endogenous compounds when compared with humans. Therefore in the present study, an attempt has been made to establish an in vitro model for early and specific prediction of nephrotoxicity using human proximal tubular cell line, RPTEC/TERT1 with USFDA approved several new sensitive markers like kidney injury molecule 1(KIM 1), neutrophil gelatinase associated lipocalin (NGAL) and osteopontin (OPN). For eliciting nephrotoxic response, cell line was treated with known nephrotoxicants like cisplatin, cidofovir and zoledronate that have different mode of nephrotoxicity. After the treatment, conventional (alkaline phosphatase, gamma glutamyl transpeptidase, N-acetyl glucosaminidase) and newer (KIM-1, NGAL, OPN) biomarkers were measured. The results show significant changes in newer markers at mRNA and protein level while no significant change in the conventional markers. Our results suggests suitability of RPTEC/TERT1 as an in vitro nephrotoxicity prediction model at preclinical level, using the set of xenobiotics and biomarkers utilized in the study.

P192. Incidence of primary extraskeletal osteosarcoma in beagle dog- a case report

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Extraskeletal osteosarcoma is a rare neoplasm in older dogs (median age 11 years) with unknown etiology. Mutagenic effects of ionizing radiation, multiple minor trauma and genetic alterations are

possible risk factors. A 10 years old female beagle dog was presented with a clinical history of diarrhea, vomiting, in-appetence and pain at left abdominal region on palpation. Enlarged and misshapen left kidney was seen ultrasonographically and clinical pathology revealed high WBC count and biochemical parameters suggestive of kidney failure and muscle wasting. Dog did not respond to treatment and was found dead. Gross examination revealed emaciation, hide bound condition with pale mucous membrane, presence of yellow color fluid in the abdominal cavity and tumor mass of about 10 cm diameter adhered to the intestinal region, causing blockage of intestine. Kidneys were hard with yellowish discoloration at cortico-medullary junction. Left kidney was misshapen and enlarged. Liver revealed yellowish discoloration. Gall bladder was enlarged with thickened walls and bile stasis. Lungs presented diffuse small miliary nodules of about 0.5 cm diameter. Left ovary was enlarged with multiple hard nodules and reddish discoloration. Mammary gland revealed tumor mass of around 2.5 cm diameter. Uterus had small cyst. Histopathological examination of the tumor mass in the mesentery revealed primary osteosarcoma. Kidneys revealed nephroblastoma and metastatic osteosarcoma. Lungs revealed multiple diffuse metastatic osteosarcoma along with severe broncho-alveolar pneumonia. Enlarged ovary showed sex cord tumor. Mammary gland tumor mass exhibited fibroadenoma with squamous differentiation. Liver revealed bilirubin deposition (Halls stain), bile duct proliferation, thickening and hyalinization of ducts in the portal triad and capsular thickening. Gall bladder showed thickening of wall, hyalinization and distention with proteinaceous content.

P193. Discovery of dual kinase inhibitors of CK2 and GSK3ß: Combined qualitative and quantitative pharmacophore modeling approach

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PTEN (Phosphatase and Tensin homolog), a tumor suppressor protein, gets deactivated by CK2 (Casein Kinase 2) and GSK3ß (Glycogen Synthase Kinase 3ß), which is a major cause of PI3K/AKT-driven tumors. To surmount this problem the multi-target inhibitor strategy may be of great significance. The goal of this study was to design dual-target inhibitors of CK2 and GSK3ß using a combination of pharmacophore modeling and molecular docking studies. The common feature-based (qualitative) and 3DQSAR based (quantitative) pharmacophore models were generated and validated. The best pharmacophore models (Pharm18 and Hypo1) were comprised of two hydrogen-bond acceptors (HBA), one hydrophobic (HY), and one ring aromatic (RA) features. The models were exploited over the various chemical database and top mapped compounds from each database were selected. They were processed for Lipinski filter, ADMET analysis, and docking studies. We have obtained six hits with comparable dock score to the reported inhibitors. We have concluded Hit15 as a competent candidate based on its docking and DFT calculations. It showed 140.73 and 130.79 dock score in CK2 and GSK3ß respectively. The electronic property of Hit 15 showed the lowest energy gap (0.021) compared to other hits and active ligands which suggest its higher reactivity. In conclusion, this study may assist in the development of new potent dual kinase inhibitors of CK2 and GSK3ß. Also, the overture effort of combined qualitative and quantitative modeling for the development of multi-target inhibitors may support the future endeavors.

P194. Safety profile of TGR5; a novel G-protein coupled receptors during drug discovery toxicity studies

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TGR5 is a plasma membrane bound, G protein coupled receptor which maintains the homeostasis of bile acids thereby protecting liver from bile acid induced toxicity. We at Zydus Research Centre, department of pharmacology and toxicology have performed initial screening in discovery toxicity studies. The repeated dose toxicity study of ZY-A (50, 100 and 200 mg/kg) and ZY-B (25 and 50 mg/kg) compound was carried out in female mice for 10 days duration by intraperitoneal route. In ZYA, clinical signs seen in few mice were lethargy post dosing and recovered within 2h at 200 mg/kg. In ZYB compound, mortality was seen at 50 mg/kg. Convulsions were noticed at 50 mg/kg. Decline in grip strength at 200 (ZYA) and 50 (ZYB) mg/kg (neuromuscular impairment) was seen in both compounds. The surviving animals were sacrificed on day 11 and subjected for gross pathological examination.

Grossly, hemorrhage and white deposits at injection site and distended gall bladder was seen at 50 and 200 mg/kg in compound ZY-A and at 25 and 50 mg/kg body weight in compound ZY-B. Histologically, liver showed necrotic foci upto 100 mg/kg in ZY-A and 50 mg/kg in ZY-B. In gall bladder, hyperplastic epithelium and serosal inflammation was seen at 200 mg/kg in ZY-A and 50 mg/kg in ZY-B compound. Single incidence of necrosis of mucosa and crystals of bilirubin debris were seen in gall bladder at 50 mg/kg in both ZY-A and ZY-B compounds. The common lesions seen in both the compounds at injection site were hemorrhage and necrosis.

P195. Hepatoprotective activity of *Gymnosporia montana* leaf extracts using *ex- vivo* studies with liver slices and *in-vitro* using hep g2 cell lines

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The use of medicinal plants for the treatment of various diseases is as old as human civilization and has obtained a worldwide significance in the primary healthcare system. Inspite of their structural complexicity and many unknown chemical constituents, they have been frequently prescribed because of their use and efficacy, contributing to the disclosure of their therapeutic properties. Gymnosporia montana, commonly known as Vikalo, belongs to the family Celeastraceae. It is used ethnomedicinally as hepatoprotective. The fresh leaves of Vikalo are chewed in trible regions of Gujarat to cure jaundice. The different fractions were also tested for their MTT assay using Hep G2 cell line. Based on Ex- vivo studies with liver slices it can be concluded that from different concentration of leaf Gymnosporia montana, 70% of methanolic extract and petroleum ether fraction showed better protection at 1000µg/ml and 500µg/ml respectively. The hydro-alcoholic extract shows 16.12% cytotoxicity at 1000µg/ml and petroleum ether fraction shows 10.94% cytotoxicity. The present data suggests that the petroleum ether fraction and hydro-alcoholic extract of Gymnosporia montana does not have any significant cytotoxic effect on Hep G2 cell line.

P196. Design, synthesis and antidepressant activity of some Novel chromane derivatives

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Depression is a common and serious illness that affects millions of peoples each year. Many molecules are available for the treatment of depression but still it has become essential to design and explore novel series of antidepressant agents. The research present herein focused on the design and synthesis of novel series of selective serotonin reuptake inhibitors (SSRIs) by taking a Fluoxetine as a reference molecule. Novel chromane moiety with different substituents at 4th position is the structural scaffold of present study. Series of chromane derivatives have been synthesized having substituted amino side chain. All the compounds were synthesized as per the designed synthetic route. Compounds were characterized by physical data like melting point and TLC and spectral data by IR, 1H NMR, 13C NMR and Mass spectra. All the synthesized compounds were found to promising antidepressant activity. Among the series two compounds were found to more active than standard Fluoxetine in tail suspension test (TST). These two compounds were evaluated for serotonin reuptake inhibitor activity by 5-HTP potentiation test in mice and both the compounds were found to selective serotonin reuptake inhibitors and highly selective toward serotonin transporter. This new structural scaffold (Chromane) with amino side chain may open new era of antidepressant agents.

P197. Comparison of different QT correction formulae in beagle dogs for preclinical safety assessment

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A number of drugs belonging to different therapeutic classes cause increase in QT interval, and this change have been associated with ventricular arrhythmia. Investigation of changes in QT intervals in

pre-clinical toxicity and safety studies in dogs is therefore of potential value. There are numerous confounding factors leading to inaccurate QT measurement, making it difficult to evaluate the clinical and biological significance of minor QT changes, even when they are statistically significant. Differences in heart rate can be a consequence not only of autonomic conditioning but also of an external factor, like a drug. Regulatory guidances ICH S7B and E14 do not clearly state on which specific QTc (QT correction) method should be adopted for preclinical evaluation. Most commonly used QTc formulae are derived from human observations (Bazett's formula) and thus are not useful for other species like dogs, where the normal values of heart rate are higher compared to humans. The objective of this evaluation was to identify an appropriate correction formula by comparing five different formulae (Bazett's, Fridericia's, Framingham's, Van de Water's, and Hodge's) that could appropriately correct changes in QT interval in conscious beagle dogs in pre-clinical studies. In-house historical data from control animals were compiled for this analysis. QTc-RR interval scatter plot were generated for each formulae and the slope of each regression line was determined to compare different QTc formulae. Van de Water's formula gave slope closer to zero and a statistically non-significant p-value, indicating better consistency in calculating QTc values across the range of heart rates out of all the five formulae.

P198. Restless Legs Syndrome: Barely diagnosed & rarely treated disease

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Restless legs syndrome is a chronic progressive sleep associated sensory motor disorder which develops within the neurological disorders like Parkinsonism, Neuropathy pain and possible dementia. The global prevalence of restless legs syndrome is increasing day by day and research studies have been reported the essential need for research in specific diagnosis and treatment of restless legs syndrome. Prevalence of RLS is more in female and pregnant women than men in the almost whole world. In India and many other countries of Asia and throughout the world the term Restless legs syndrome (RLS) is still a questionnaire.. It is reported many a times by the physicians, neurologists and gynecologists mal-diagnosis of RLS in India and in others countries also. The exact pathophysiology of the RLS is still not clear, but some superficial assumptions regarding the progressions of disease and root of disease through the geneomolecular concepts. Few traditional chinese medicine and allopathic medicine have been reported a successful treatment of RLS, but it is either symptomatic or depends on time management. Dopamine agonist and opoids are possible symptomatic treatment for RLS, but no treatment is available if it entered in not in a severe stage of RLS. Relation to the lower cerebral ferric and dopamine levels are probably reported as the cause for Restlessness like, Although genetic biomarkers have been developed for the diagnosis of the disease. The core treatment of the disease is still under discovery. Early diagnosis of the disease can make difference in the first line treatment.

P199. Efficacy of pentacyclic triterpenoid molecule in animal model of cognitive dysfunction

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Cognitive dysfunction is one of the most common hallmarks of several disorders including Alzheimer's, schizophrenia, chronic fatigue syndrome, multiple sclerosis and depression. Most often it is associated with enhanced inflammation and neuronal cell death in brain regions associated with cognition. Intracerebroventricular streptozotocin (ICV-STZ)-induced animal model of cognitive dysfunction is widely used to study memory improvising effects of novel therapeutics. The present study was designed with an aim to investigate the neuroprotective effect of lupeol, a pharmacologically active triterpenoid, having potent anti-inflammatory and neuroprotective properties in an animal model of cognitive dysfunction. We performed in silico studies to evaluate the effect of lupeol on inhibition of acetylcholinesterase activity, one of the biomarkers of cognitive dysfunction. Our preliminary findings suggest the inhibition of acetylcholinesterase activity by lupeol. The results obtained are encouraging to move further to in-vitro and in-vivo studies to investigate the effect of lupeol on oxidative stress, mitochondrial dysfunction, neuroinflammation and cognitive function. Findings from the present study may suggest neuroprotective role of lupeol in amelioration of cognitive dysfunctions.

P200. Biochemical assessment of the amniotic fluid from hydroxyurea induced teratogenicity in pregnant female Wistar rats

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To determine biochemical markers used to assess renal function and maturation of the fetus in the amniotic fluid (AF) and maternal serum during pregnancy. AF contains nutrients and growth factors that facilitate fetal growth, provides mechanical cushioning and antimicrobial effectors that protect the fetus, and allows assessment of fetal maturity and disease. Concurrent control group treated with vehicle [Tween 80: 0.2% HEC in RO water (w/v)] and another group treated with positive teratogen of hydroxyurea at 150 mg/kg in this study. Each group contained 10 pregnant female rats. Each pregnant female rat was administered with vehicle and hydroxyurea from presumed gestation day 6 to 15 consecutively by oral route. One day prior to delivery i.e. Gestation day 20th , the pregnant females were undergo caesarian section to evaluate the fetuses for external and visceral anomalies. Embryo and fetal toxicity was assessed by estimation of clinical chemistry parameters such as glucose, creatinine, urea, AST, ALT, ALP, calcium in amniotic fluid of rat fetus, and maternal toxicity was assessed in serum biochemical analysis. The results of external examination showed that hydroxyurea gives the malformation in fetus. The results of glucose, AST, ALT, ALP, calcium of control vehicle and hydroxyurea group did not show any variation and/ or significance between the groups. However, creatinine and urea was markedly elevated in amniotic fluid of fetus and during maternal serum biochemical analysis. Based on the results obtained from this study, it is concluded that elevation of serum creatinine and urea in hydroxyrea treated group as compared to vehicle control was due to renal insufficiency in pregnant female rats, and higher levels of creatinine and urea in amniotic fluid indicating fetus kidney toxicity during pregnancy due to hydroxyurea.

P201. Chemistry of dark red coloured liquid tissue having deep metallic odour through oxygenated α, ß-unsaturated aldehyde

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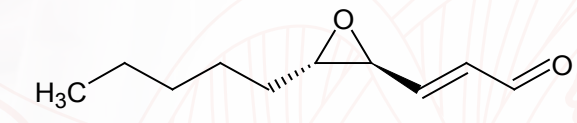
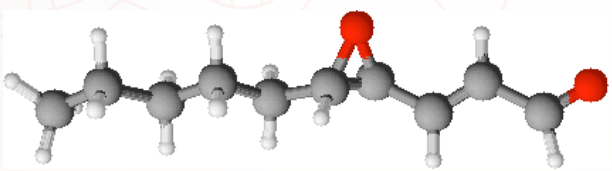
Blood is a liquid tissue having red in colour with characteristic metallic smell or odour. Smells are notoriously hard to pin down, describe and identify but most people agree that the smell of fresh blood has a distinct, metallic tang. You might assume this comes from the iron in our blood, but an organic compound—a type of aldehyde—is to blame. (2E)-3-(3-pentyl-2-oxiranyl) acryaldehyde or trans-4,5-Epoxy-(E)-2-decenal or (2E)-3-[(2S,3S)-3-pentyloxiran-2-yl]prop-2-enal all are same substances having aldehyde moiety (-CHO).

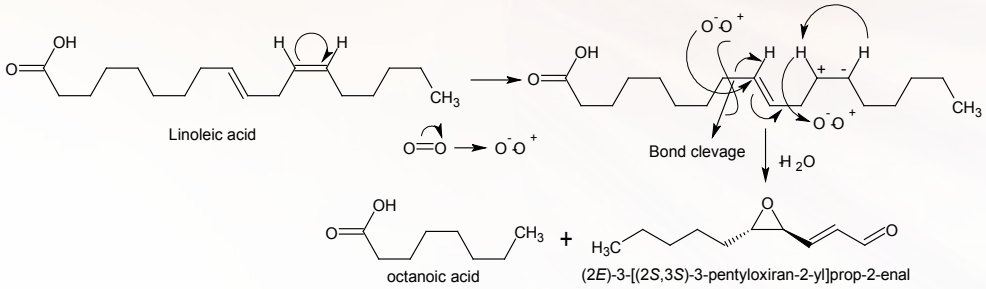


(2*E*)-3-[(2*S*,3*S*)-3-pentyloxiran-2-yl]prop-2-enal



(logP=1.73)

Unsaturated fatty acid has tendency to undergo rancidification due to the presence of double bond (δ: sigma bond and π: pi bond) in oxidative catabolism in-vivo by oxidase enzyme and in-vitro due to air oxidation. Unsaturated part undergoes reaction steps by initiation, propagation and termination steps followed by free radical formation in Initiation step, peroxide formation in Propagation step and hydro-peroxide step in termination step which produce obnoxious smell due to the formation of epoxide. Since blood is a biological fluid tissue so it produces metallic smell of characteristic odour.



Metallic odour of flesh or blood comes from the rancidification of linoleic acid is due to oxidation of unsaturated bonds by oxygen through initiation, propagation and termination steps of α,ß-unsaturation of acid into oxygenated aldehyde. The unpleasant foul smell is generated by biochemical oxidative reactions both in-vivo & in-vitro. LogP of this substance is 1.73 so it is semipolar in nature due to three membered oxirane ring and double bond and aldehyde linkage, so it is easily atomized into the atmospheric environment to disperse the odour.

Keywords: (2E)-3-(3-pentyl-2-oxiranyl)acryaldehyde, trans-4,5-Epoxy-(E)-2-decenal, (2E)-3-[(2S,3S)-3-pentyloxiran-2-yl]prop-2-enal, α, β-unsaturation, linoleic acid, initiation, propagation, termination, peroxide, hydroperoxide, epoxide, oxirane.

P202. A Review of QSAR Study on Various Anti-malarial Agents

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Malaria is most significant parasite disease caused by protozoal species Plasmodium. There are five species that infect humans (P. falciparum, P. vivex, P. malarie, P. ovale and P. knowlesi, in which P. falciparum is fatal. In this work we have reviewed 2D and 3D QSAR study on many anti-malarial agents which belongs to 4(1H) quinolones analogues, alkoxylated and hydroxylated chalcones by CoMFA and CoMSIA study, 2,5-diaminobenzophenone derivatives, urea derivatives, 7-substitued-4-amino quinolone derivatives, indolo[2,1-b] quinozoline 6,12-diones (tryptanthrins), aziridinyl-1,4-napthoquinone, 3-carboxyl-4(1 H) quinolones, synthetic prodiginines, peroxidic and tricyclic analogues of artemisinin. This review will be very helpful for the researchers and scientists who are working in the area of novel anti-malarial agents. This will, help in design and molecular modelling of novel anti-malarial agents based on QSAR study.

P203. Evaluation of the T-cell dependent antibody response (TDAR) to KLH in Wistar rats, in the presence of a known immunosuppressant with quasi-quantitative ELISA

Chetan Kajavadara, Satyam Patel, Darshan Valani, Ankur Bhatt, Kaushal Joshi, Siddharth Brahmbhatt, Rajesh Patel, Upendra Bhatnagar, Rajesh Sundar and Mukul Jain

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The primary antibody response to a T-cell dependent antigen such as Keyhole Limpet Hemocyanin (KLH) is widely used as follow up for immunotoxicity in non-clinical safety testing when drug candidate shows indication of immune suppression (e.g. change in hematological parameters such as neutropenia, monocytopenia or lymphocytopenia, decrease weight and/or pathological changes in immunological organs) in standard toxicity studies. KLH acts as an antigen and induces antiKLH antibody, when immunosuppressant is administered, the response to KLH in the form of antiKLH antibody decreases in comparison to vehicle control. In TDAR assay, 8 rats/sex/group received 0, 2, 4 and 6 mg/kg of Cyclophosphamide orally for 28 consecutive days. All the animals were immunized with single intravenous injection of KLH (300 µg/rat) without adjuvant. Pre-immunization serum was collected to determine cut point and post-immunization serum was collected to evaluate antibody response to KLH in comparison to pre-immunize serum as well as effect of cyclophosphamide on antibody generation in comparison of vehicle control. For primary screening purpose quasi-quantitative ELISA method was developed to screen antiKLH antibody titer. There is significant reduction in IgM ($P<0.001$) and IgG ($P<0.0$ 1) found at 6

mg/kg cyclophosphamide treated male animals. While there is significant reduction in IgM (P<0.01) and IgG (P<0.05) found at 4mg/kg cyclophosphamide treated female animals and there is significant reduction in IgM (P<0.0001) and IgG (P<0.0001) found at 6 mg/kg cyclophosphamide treated female animals.

P204. Pharmacophore mapping and molecular docking studies of heterocyclic compounds as ROCK-II inhibitors

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Multiple sclerosis is not an auto-immune disease, it is an immune mediated disease. Around 2.3 million people in the world are suffering from multiple sclerosis. The factors which are responsible for multiple sclerosis include immunology, environmental and genetic defects. Rho kinase enzyme particularly the ROCK-2 isoform plays vital role in the medical condition like multiple sclerosis. In the present study, various computational methods were used for the designing of molecules. Various approaches like pharmacophore modelling, virtual screening, molecular docking, in silico ADMET studies were utilized for designing of molecules. 8 different structures were taken for the pharmacophore generation. Pharmacophore model was developed using GALAHAD module of Sybyl X. The best model was selected which showed 2 hydrophobic, 1 donor atom, 2 acceptor site as essential features. It was further validated through GH and ROC method. Virtual screening which was performed on the generated model which retrieved 40 compounds showed Qfit value greater than 80%. Molecular docking studies were carried out on designed molecules using 2F2U as ROCK-2 protein. The designed compounds showed pi-pi stacking with TYR171 and all of them share hydrogen bonding and electrostatic interaction with MET172, ALA119, MET169, ALA231, LEU221, VAL106 amino acids.

P205. Review on Implications of Pharmacovigilance System in India

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Pharmacovigilance (PV) is very significant and inevitable part of drug discovery and development, which requires comprehensive documentation process and severe monitoring at every phase of drug development including risk management and pre & post-authorization safety studies. The number of adverse drug reaction (ADR) reported resulted in an increase in the volume of data handled, and to understand the pharmacovigilance, a high level of expertise is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal. Though India has its own Pharmacovigilance Program since 2010, there are certain deficiencies in the framework for ADR from the perspective of pharma industry, healthcare professional and general public due to which adverse events for marketed drugs are highly underreported. This necessitates an utmost requirement for effective regulations of the drug approval process and conscious pre and post approval vigilance of the undesired effects, especially in India. In response, strategies to improve the collection, integration and analysis of data related to post-marketing drug safety are being initiated or enhanced. There are certain provisions through which the PV in India can be strengthen by evaluating knowledge & perception of people related to healthcare towards ADR reporting and about PV, creating awareness about PV, developing a tool for easy reporting and a better regulatory system. Hence, PV helps to the patients get well and to manage optimally or ideally, avoid illness is a collective responsibility of industry, drug regulators, clinicians and healthcare professionals to enhance their contribution to public health.

P206. Tyrosine Kinase Inhibitors as Novel Target for New Drug Development: Opportunities and Challenges

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Tyrosine Kinase Inhibitors (TKI) are a newer class of drugs approved by FDA for various diseases. They are enzymes responsible for the activation of many proteins by signal transduction cascades and also the proteins are activated by adding a phosphate group to the protein, a step that TKI inhibits. These enzymes play an important role in cell proliferation and differentiation of cell. They are involved in

diverse biological processes like growth, differentiation, and apoptosis in response to external and internal stimuli. Their market value is expected to be around $45 billion in 2016 globally. Many are introduced into the market in the beginning of this decade like Afatinib, Axitinib, Bosutinib, Cobimetinib, Crizotinib and Erolotinib for various cancer and auto-immune diseases. Many multinational companies were benefitted by getting FDA approvals for their research molecules in this class. Many newer compounds are under investigation at different stages and areas for different types of leukemia, ovarian cancer, inflammatory disease, myelofibrosis, essential thrombocythemia, bone metastasis, hyperplasia's, restenosis, cardiac hypertrophy, immune disorders and Type-II diabetes which are awaited shortly. Any drug developments in this class also pose various opportunities and challenges against kinase targets and most importantly TKI resistance. Very interestingly new opportunities in TKI research are seen in the areas of Parkinson disease, diabetes and drug resistant malarial strain. In this presentation various opportunities and challenges will be discussed for developing new chemical compounds for TKI targets.

P207. Comparative analysis of mutation induction potential of 2-chloro propane (2-CP) by plate incorporation method and desiccator method

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2 Chloro Propane, also known as Isopropyl chloride is impurity found in drug substance and drug product. This is an alkyl halide class of impurity which is volatile in nature. Upon testing this impurity for bacterial reverse mutation (Ames) test using conventional plate incorporation and desiccator method – there was qualitative and quantitative difference in mutagenic response was observed. When tested using desiccator method, 2-CP has shown mutagenic response in Salmonella typhimurium TA1535, TA 100 and E.coli WP2 uvrA strains at concentration of 2.5 and 5 ml/desiccator in presence of metabolic activation system (10% S9 v/v). However, when tested the same strains at 5, 10 and 20 µl/plate using plate incorporation method in presence of S9 (10% v/v) there was no clear positive results observed. Similarly when 2 – CP was tested in absence of S9, Salmonella typhimurium TA100 strain demonstrated clear positive result at 2.5 and 5 ml/ desiccator using desiccator method while the same strain shown negative outcome up to 20 µl/plate using conventional plate incorporation method. Hence, while testing organic volatile solvents for mutagenicity in Ames test – desiccator method shall be preferred over conventional plate incorporation method.

P208. A review on medicinal chemistry of potassium channel modulator: update from decade of progress

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Ion channels are the specialized membrane protein that occur as a pore between cell membrane and organelles located inside the cell. Potassium channel are the most diverse subgroup of ion channels existing in excitable and non-excitable cells. When potassium channels open, potassium flows out from it, drives the membrane potential in the negative direction and quieting the cell activity. Medicinal chemistry attention to potassium channels as drug targets has grown with the realization that a variety of potassium channel openers and inhibitors offer significant therapeutic opportunities in neuronal, cardiac, smooth muscle, immune, and secretory systems. The present review mainly focuses on structure, pertaining biology and medicinal chemistry approaches towards potassium channel modulator as a potential target for the treatment of a variety of human diseases and will hopefully provide valuable insights for medicinal chemists interested in rational drug designing of potassium channel modulators.

P209. Anabolic effects of ZYPH0907, a novel orally bioavailable parathyroid hormone-1 receptor agonist

Hitesh Kadu, Shekhar Kadam, Viral Rajwadi, Praveen Jain, R.K. Ranvir, R. Bahekar, S. R. Sundar and Mukul R. Jain

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ZYPH0907 is a novel and orally bioavailable potent peptidomimetic based Parathyroid Hormone-1 receptor (PTH-1r) agonist developed by Cadila Healthcare Ltd. The PTH binds with PTH-1r and induces increase in serum calcium and cellular cyclic adenosine monophosphate (cAMP) which regulates the downstream cellular processes involved in bone remolding. Osteoporosis is a skeletal disorder characterized by diminished bone mass, decreased bone mineral density (BMD), decreased bone strength and increased risk of bone fracture. ZYPH0907 showed promising anti-osteoporotic activity with good exposure profile in various animal models studied and hence, was further studied to explore its exaggerated pharmacological effects in female Wistar rats. ZYPH0907 was administered at 0.3 and 3.0 mg/kg/day doses (15X and 150X of ED) via oral gavage daily for 42 days in female rats. Microscopic examination of bone at 3.0 mg/kg revealed treatment related exaggerated pharmacodynamic effects like mild to moderate increase in osteoblastic activity(6/6), minimal to moderate increase in trabecular thickening (5/6) and minimal to mild increase in fibrous bone matrix (3/6) as compared to control. At 0.3 mg/kg, minimal increase in osteoblastic activity (4/6) was noticed. These findings correlated with elevation in serum ALP at 0.3 mg/kg (32%) and 3.0 mg/kg (53%) indicative of increased osteoblastic activity. Suppression of calcium loss in urine and elevated excretion of urinary phosphate at ≥ 0.3 mg/kg could be attributed to the anabolic property of ZYPH0907. These preliminary results confirm discovery of potent and orally bioavailable PTH-1r agonist which acts as an effective anabolic agent for the treatment of osteoporosis.

P210. To investigate the prevalence, etiology and early diagnosis of polycystic ovarian syndrome in school going girls and also to determine the health related quality of life

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Polycystic ovarian syndrome is a gynecological disorder that usually occurs in women's having hormonal imbalances and is characterized by chronic anovulation, clinical and biochemical hyperandrogenesim. Aim of this cross-sectional study is to determine prevalence, etiology, early diagnosis, risk factors associated with polycystic ovarian syndrome such as obesity, socioeconomic status (SES) in school going girls in Ahmedabad in Gujarat. This study conducted on 881 adolescent's girls of age 13-18 years in five schools were selected by cluster sampling. PCOS was diagnosed by menstrual dysfunction and clinical hyperandrogenesim. Blood samples were collected for the estimation of Insulin, Testosterone and LH. SF12 questionnaire was used for determining of quality of life. Out of 881 girls, 119 girls were found to have PCOS, as defined by the Rotterdam criteria. Obesity, insulin resistance, are the risk factors associated with PCOS and remarkably with different socioeconomic development levels. Hirsutism, acne, dysmenorrhea and oligomenorrhea were most common phenotype observed in PCOS. The mean of LH and testosterone was not found statistically significant with PCOS.

P211. To study the effect of tocilizumab in ovariectomy induced post- menopausal osteoporosis in rat

Nimisha Kakadia, Neepa Shah

K.B. Institute of Pharmaceutical Education and Research, Gandhinagar, Gujarat, India

Osteoporosis is a skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue with increase in bone fragility which leads to fractures. In Post Menopausal Osteoporosis decrease in production of estrogen causes estrogen deficiency leads to cortical porosity and cause bone resorption. Many Drugs are available for treatment of postmenopausal osteoporosis, which increases Estrogen level, but alternatives are continuously being searched because of actual or possible side effects. Tocilizumab blocks IL-6, which has a major role in osteoporosis pathogenesis. So, Tocilizumab was selected to study anti-osteoporotic action. Female Sprague-Dawley rats were divided into five groups, each containing 8 animals. Group I (Normal control) received Normal Pellet Diet, Group II served as disease control (ovaroiectomized) and received vehicle only, group III (Standard control) treated with 2 mg/kg estrogen up to 75 days, group IV (Prophylaxis) treated with 0.4mg/kg Tocilizumab on day 15, 45 and 75, Group V (Treatment) treated with 0.4 mg/kg Tocilizumab on day 45 and 75. Blood was collected on Day 0, 45 & 90 days to evaluate biochemical and biomechanical parameters and bone mineral content. At the end of the study histopathology of the femur bone was done. Tocilizumab significantly increased ($p<0.05$) bone mineralization and calcium content of the bones, reduced serum alkaline phosphatase and urinary calcium excretion in ovariectomized rats. The ovariectomy-induced decline in the mechanical strength of the bones was also restored after treatment with tocilizumab. Similar results were also obtained after treatment of ovariectomized rats

with estrogen. In conclusion, Tocilizumab was effective in treating ovariectomy induced post-menopausal osteoporosis in Rat.

P212. Non-clinical safety assessment of recombinant based (rDNA) Hepatitis B vaccine

Chitrang Shah, Jitendra Patel, Viral Rajwadi, Shekhar Kadam, Viren Kothule, Gaurav Gupta, Ranvir RK, Upendra Bhatnagar, Rajesh Sundar, Mukul Jain

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Hepatitis B infection is an important public health concern all over the world. As no specific treatment is available, greatest emphasis is placed on prevention through immunization. A recently developed Hepatitis B (rDNA) vaccine, containing purified surface antigen of virus like particles derived from culturing genetically engineered Hansenula polymorpha yeast cells having the Hepatitis B surface antigen gene of Hepatitis B virus was evaluated to establish potential safety and tolerability of the Hepatitis B (rDNA) vaccine formulation. Non-clinical safety assessment was evaluated as single dose studies in mice and rats (i.m. and i.p.) and as repeat dose study in rats (i.m.). No signs of acute toxicity were noted in mice and rats through clinical signs and gross necropsy examination. The local reactions observed in both the species at the injection site were attributed to the property of an adjuvanted vaccine. Similarly, the absence of systemic toxicity was evaluated after repeated administrations in the rat. In repeated dose study, additionally histiocytosis and/or lymphoid hyperplasia at femoral lymph node were observed. The incidences of such local effects were considered as innate immune response generated against the vaccine antigens and enhanced by the adjuvants. The vaccine was shown to be well tolerated without any obvious signs of adverse systemic toxicity, with findings largely attributable to the adjuvant used. The immunogenicity profile showed measurable antibody titer. Therefore, in these non-clinical models, the single and repeated dose administrations of Hepatitis B (rDNA) vaccine were considered as well tolerated up to absolute human dose (l mL) .

P213. Assessment of the anti-tubercular activity of selected indian medicinal plants: a preliminary screening using the microplate alamar blue assay

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Tuberculosis (TB) is a global burden with one –third of the world's population infected with the pathogen Mycobacterium tuberculosis complex and annually 2 million deaths occur due to tuberculosis. This high incidence of infection and increased rate of MDR and XDR strains of the organism further complicated the problem of TB control and have called for an urgent need to develop new anti-TB drugs from plants. Plants are the important source of diverse range of bioactive principles. The revival of interests in plant derived drugs is mainly due to the current widespread belief that green medicine is safe and more dependable than expensive synthetic drugs, which have adverse side. Herbal remedies used in folk medicine provide an interesting and still largely unexplored source for the creation and development of new potential drugs effects. In the present study nine medicinal plants which are traditionally used to treat TB and related symptoms were selected for the study. Different crude extracts were prepared from the selected plants .Various concentrations of the extracts were screened for anti-TB activity against M. smegmatis strain using alamar blue assay. Various extracts from the plants that showed anti-TB activity were used to determine their respective MICs. Only three plants from all screened medicinal plants shows anti-TB activity. The MIC of *Oscimum sanctum*, *Alpinia galanga* and *Adhatoda vasica* extract was 250 µg/ml, 250 µg/ml and 125 µg/ml respectively. It can be concluded that the present study provided a scientific support for the traditional use of for treatment of tuberculosis.

P214. Neuroprotective potential of pentacyclic triterpeniods in animal model of schizophrenia

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Schizophrenia is a complex heterogenous mental disorder affecting aproximately 1% of the

world's population. It is characterized by positive (hallucinations, delusions, paranoia), negative (depression, anhedonia) symptoms and cognitive deficits. Dopaminergic overactivity in the mesolimbic region of the brain and abnormalities in the Akt/Gsk3ß pathway have been observed in schizophrenia. Phencyclidine induced animal model of schizophrenia efficiently mimics all the positive, negative and cognitive symptoms of schizophrenia. Currently available typical and atypical anti-psychotics have a number of adverse effects and tolerance develops over the course of time. Therefore, the present study is aimed to evaluate the effects of two pentacyclic triterpenoids, ursolic acid and betulinic acid having anti-oxidant, anti-inflammatory, anti-depressant and neuroprotective properties in the amelioration of the symptoms of schizophrenia. We performed in silico studies to evaluate the effect of these pentacyclic triterpenoids on Akt/Gsk3ß pathway which appears to be critical in this illness. The results obtained showed that ursolic acid significantly caused inhibition of Gsk3ß. The results obtained are encouraging and forms the basis of further in vitro and in vivo studies to evaluate their role in oxidative stress, neuroinflammation, mitochondrial function and behavioural alterations of schizophrenia. Therefore, we assume that these pentacyclic triterpenoids could prove to be a better therapeutic option to treat this chronic neurological psychiatric disorder.

P215. ZyCliniTree: A cohesive data platform to facilitate clinical research collaborations

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The principal investigator is the anchor and backbone of any clinical research operation. He collaborates and consults with the sponsor to ensure the ethical conduct and flawless execution of clinical trials. He is also responsible for regulatory compliance and patient safety. Thus, the selection of principal investigators (PIs) plays a pivotal role in determining the outcomes of clinical research. The quality and reliability of the data obtained is usually a direct consequence of the PI's involvement in and dedication towards the research operation. We at Zydus sensed the need for a comprehensive database that would simplify the challenging task of PI selection. We realized that reaching out to doctors across India regarding their specialization, availability and inclination to collaborate on clinical trials would give us an exhaustive data bank for future consultation. We built our Ahmedabad-based pivotal investigator database by reaching out to doctors online, and recording the information they provided. By creating a pan-India database, we will be able to substantially reduce costs, shorten timelines and avoid recruitment delays. This universal directory of investigators will ease our communication with current PIs and facilitate collaborations for new clinical trials in future. This initiative helps us in assessing the history and credentials of the investigators, their experience in clinical trials, patient recruitment techniques and availability of referral networks. It also helps us to understand the capability of sites and supporting staff on the standard of care and sponsor requirements for the research endeavors.

P216. Liquid phase polymer assisted combinatorial synthesis of various substituted 5h-benzimidazo[1,2-d][1,4]benzodiazepin-6(7h)-one derivatives as antitubercular agents

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Tuberculosis is one of the leading infectious diseases and carried by the bacteria Mycobacterium tuberculosis. The treatment of tuberculosis increasingly becoming problematic due to the development of resistance. The different types of Tb resistance are known till date which includes MDR TB (multi drug resistance TB) and XRD TB (extremely drug resistance TB). The treatments of all these resistant TB strains are becoming very difficult. Consequently, there is a pressing need for the development of novel TB drugs that are effective against both drug sensitive and resistant Mtb strains. From literature search for a novel target we observed FtsZ reported as a tubulin homologue, which is a highly conserved, ubiquitous and the most abundant bacterial cell division protein. In the presence of GTP, at a critical concentration of 1 - 0.5 µM, FtsZ subunits undergo cooperative assembly to form single-stranded proto filaments by stacking in a head-to-tail manner, wherein GTP is attached between two FtsZ subunits. Extensive lateral interactions between these overlapping proto filaments lead to the formation of a highly dynamic ring structure known as the Z-ring which takes part in the cell division process. Since FtsZ is a novel drug target, compounds targeting FtsZ are expected to be active against drug resistant Mtb strains. Furthermore, the validation of FtsZ as a novel antibacterial drug target has been confirmed by the work of various groups. On the basis of various previously reported active molecules we designed substituted 5H-Benzimidazo[1,2-d][1,4]benzodiazepin-6(7H)-

one derivatives which were subjected to molecular docking studies using SYBYL X1.2 and compounds with good score were synthesized by liquid phase combinatorial synthesis approach using soluble polymer assisted support (PEG5000). Synthesized compounds were characterised by Mass, 1H-NMR and 13C-NMR. Further synthesised molecules would be evaluated for their pharmacological activity by various *in-vitro* assay methods.

P217. Drug repurposing for progressive multifocal leukoencephalopathy: Can it be explored as new therapy?

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Progressive multifocal leukoencephalopathy (PML), an orphan disease, is a rare infection which damages the myelin sheath that covers and protects nerves in the white matter of the brain and is triggered by JC virus (John cunninghgum Virus). Although it is a rare disease but serious infection may lead to severe disability or death. Patients with very weak immune system are affected by this disease. Patients treated with Natalizumab as a treatment regimen for multiple sclerosis are at highest risk of PML. Many anti-viral therapies such as cidofovir and mefloquine have been tried for the management of PML but the results were not encouraging. To date, there is no convincing treatment found to treat PML. Further there are major challenges in new drug discovery or development for orphan disease such as limited information available on the disease, less preclinical studies, rare patient pool with similar background of medical history, unknown aetiology of diseases, operational and cost factors. Drug repurposing or Drug re-profiling offers to explore the existing knowledge on drugs, diseases and targets and helps us to find a novel use of an already available compound or drug lead for the development of new and better therapies. Repurposing/Repositioning of existing drugs with known pharmacology/toxicology for the treatment of orphan diseases is most appropriate, less time consuming and cost effective approach and can prove to be very valuable in bringing newer medication alternatives to rare disease patients. The complex treatment of PML should have therapeutic agent that can cross blood brain barrier. It is suggested in literature that use of 5HT2 antagonists results in improvement in progression of PML. Amongst all the drugs Mirtazapine shows promising results, also has evidences of some case reports and thus was investigated further. Hence, in the present study, considering Mirtazapine as a suitable drug regimen for PML, a clinical trial design has been developed for further research.

P218. Neuropharmacological action of Nardostachys Jatamansi

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Alzheimer's disease is a geriatric disorder characterised by amnesia and dementia. The pathology involves ß-amyloid plaque formation, Tau Hyperphosphorylation, Decrease in Acetylcholine availability, Free radical generation and oxidative Stress. The current available treatment includes Acetylcholinesterase inhibitors and NMDA receptor antagonists. Attention Deficit Hyperactivity Disorder (ADHD) is a paediatric disorder which is finding its prominence in adolescents and the adults. The pathology links ADHD to imbalance in the neurotransmitters, Genetic links to Dopamine Transporter Genes, Brain injury, Prenatal and Perinatal exposure to pollutants like Lead, mercury, polychlorinated biphenyls, etc The available treatments include Stimulant and Non-Stimulant medications. Ayurveda has classified *Nardostachys Jatamansi* as nootropic agent. This contains alkaloids, polyunsaturated fatty acids (PUFAs), carbohydrates, steroids and saponins which have properties may have neuroprotective effects. The possible mechanism for the AD and ADHD is a increase the acetylcholine level in the brain and decrease the free radicles in brain so protect the neuron cell. in a future may be a new molecule come out from this natural plants.

P219. A process for preparation of highly pure Micafungin Sodium API (antifungal)

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A process for the preparation of highly pure echinocandin semi synthetic antifungal drug Micafungin Sodium is described. It is administered intravenously and inhibits the production of beta-1,3-glucan, an essential component of fungal cell walls. Micafungin is indicated for the treatment of candidemia, acute disseminated candidiasis, Candida peritonitis, abscesses and esophageal candidiasis. Synthesis of Micafungin Sodium consists of mainly three steps: Chemical synthesis of side chain, Synthesis of API via coupling of side chain and main chain FR-179642 (in-house developed by Fermentation team) and Purification. Synthesis of side chain consists of six chemical steps, which includes alkylation of 4-Hydroxy acetophenone with 1-bromopentane in presence of base in THF at ambient temperature provides oily residue, which on aldol condensation with dimethyl terephthalate give the diaryl-ß-diketone having 85% yield. ß-diketone further reacted readily with ammonium formate to give a mixture of desired and undesired enamine in a ratio of 81:14. The regioselective purification by using mixture of ethyl acetate and n-heptane gives the desired product free from undesired isomer to not detected level by HPLC analysis. In the next step, cyclization of ß-keto enamine by using hydroxylamine hydrochloride converts to 3, 5-diarylisoxazole which on hydrolysis with base gives the highly pure 4-(5-(4-(pentyloxy) phenyl) isoxazol-3-yl) benzoic acid having 100% Purity by HPLC. This side chain via the active ester route on further reaction with main chain (FR-179642) in presence of sodium acetate and polar aprotic solvent at -5 to 0°C gives the crude Micafungin Sodium having purity of 95% with 92 to 94% yield. This specially designed coupling reaction directly gives the sodium salt although the research articles published earlier are making firstly Micafungin by chemical reaction and then converts into its sodium salt through column chromatography using resin. Further purification of the crude API by Preparative HPLC gives the ICH quality of API having purity more than 99.5% by HPLC. This efficient Zydus's process is highly cost effective and robust for scale up at commercial stage which fulfills the global regulatory requirements as well.

P220. Updates on potential targets for treatment of als (amyotrophic lateral sclerosis)

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Amyotrophic Lateral sclerosis (ALS) is a progressive neurodegenerative disease due to which motor neurons that control muscle movement are damaged. This disease is usually fatal as patient dies within 3–5 years of diagnosis in major cases from respiratory failure. Notwithstanding, contemplates propose that the association of different genes and environmental factors add to ALS in different cases. No cure has yet been found for ALS. The only available drug approved by FDA (Food and Drug Administration) for the treatment is Riluzole (Rilutek). Several newer potential targets for the treatment being developed are: 1) Mitochondrial Dysfunction and Oxidative Stress Pathways: Various functions of mitochondria like oxidative damage, calcium buffering, and motioning of apoptotic pathways puts the organelle in context for helpful methodologies; 2) Melatonin: Melatonin is a characteristic hormone delivered and emitted by the pineal gland. Study in disease models indicated constructive outcomes of melatonin in major neurodegenerative diseases; 3) Protein Aggregation, Altered Autophagy: Hereditary transformations lead to misfolded protein aggregation consequently developing neurodegenerative diseases. In ALS, a connection between the disease and changed autophagy was at first seen on morphological investigations of spinal cord tissues of ALS patients and models, indicating expanded number of autophagosomes; 4) Targeting the endocannabinoid system: The endocannabinoid plays many important roles in the body, some of which are antioxidant, anti-inflammatory and neuroprotective which benefited in treatment.

P221. Dose dependent Acetylcholinesterase and Butyrylcholinesterase activity of *B. ciliata* extracts and Bergenin

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Bergenia ciliata (Pashanbheda) belonging to Saxifragaceae family has prominent antioxidant and anti inflammatory activities. Extracts of the plant and bioactives possess potent anticancer, antiulcer, antidiabetic and antibacterial activity. Rhizomes are rich source of carbohydrates, flavonoids, phenolics, etc. Bergenin, a chief bioactive in the rhizomes, has been reported to exhibit many pharmacological activities including dose-dependent Ð-secretase inhibition. Further, norbergenin and its analogues exhibited stronger antioxidant activity and are also reported to prevent neuronal death. Thus, a preliminary in silico screening was performed, where bergenin was docked into acetylcholinesterase (AChE) (1B41) and

butyrylcholinesterase (BuChE) (1P0I) in order to determine their probable mechanism of action. Comparative gold scores of bergenin were found in good agreement to those of the standard reference drugs. Considering the broad range of activities and flavonoids rich profile of the plant, aqueous as well as methanolic extracts of B. ciliata were prepared and screened in vitro at five different doses (0.0125 ppm to 125 ppm) for inhibition of AChE and BuChE activity. Both the extracts showed significant dose dependent in vitro cholinesterase inhibition compared to donepezil. Methanolic extract (125 ppm) was able to inhibit the enzyme completely. Bergenin showed dose dependent cholinesterase inhibition at doses ranging from 10 mM to 31.45 µM. The results indicate potential of methanolic extracts and bergenin for Alzheimer's disease (AD) management by virtue of their action on these two important targets, and hence B. ciliata can further be explored for presence of other possible bioactives useful for AD management.

P222. Indigenous economic process for the preparation of Teneligliptin: a potent DPP-4 inhibitor

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The present research describes an economic and a commercially viable process for the preparation of a third generation oral anti-diabetic drug, Teneligliptin. The drug acts by inhibiting the DPP-4 enzyme resulting in increased incretin levels (Glucagon like peptide-1 and Gastric inhibitory Polypeptide) which inhibits glucagon release, that in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels. Synthesis of Teneligliptin involves the coupling of 5-amino-3 methyl-1-phenyl pyrazole with N,N-bis(2-chloroethyl)amine hydrochloride in a polar aprotic solvent and a strong base to obtain 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine which is isolated as acetate salt with a prominent 60-65% yield compared to 20-25% of other published processes, and has a remarkable impact on the overall production cost of the API. The acetate salt of piperazine compound thus obtained, undergoes reductive amination with (2S)-4-Oxo-2-(3-thiazolidinylcarbonyl)-1-pyrrolidinecarboxylic acid tert-butyl ester in a non-polar aprotic solvent and STAB followed by Boc-deprotection and hydrobromide salt formation using aqueous hydrobromic acid in alcohol to obtain the API having ICH quality with 80-85% yield. The final step of the process stands distinct to those published so far in an approach that it affords the pure API in a single step instead of a tedious process of isolating the free base, making a hydrobromide salt followed by purification. This economically viable process has been successfully transferred in plant for the production of Teneligliptin, commercially. The yield and quality parameters obtained on commercial scale replicate the data obtained in the laboratory showed the robustness of the process. This efficient process of Zydus, offers an advantage of achieving a cost effective API, which helps us to provide the cheapest formulation to the society in the name of Tenglyn.

P223. Targeting local receptors for surgical site infection

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Pathological condition known as surgical site infection (SSI); is the 3rd most common nosocomial infection. The condition is expected to have a morbidity rate of 3% and is majorly accounted to be due to micro-organisms and biofilm formation. Administration of antibiotics is majorly done for treatment in the condition. Centre for Disease Control and Prevention (CDC) commented upon benefits of using IV bolus pre-operative antibiotic therapy followed by oral antibiotics post-operatively. Polymeric microparticles containing antibiotic was developed focusing on switching over to local therapy regimen. The microparticles were prepared using re-emulsification-solvent removal technique. Formulated microparticles were screened for factors affecting the process by Placket Burman design containing 10 factors each considered at 2 levels. Further optimization was carried out using Box-Behnken design considering 3 factors each at 2 levels. The microparticles were characterized using UV-VIS spectrophotometry (encapsulation profile and drug loading), drug release from microparticles (in-vitro evaluation) and dynamic light scattering (DLS) technique. Further acceptability in terms of administration safety will be evaluated with the help of gas chromatography studies.

P224. Endoplasmic reticulum stress in alzheimer's disease

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Alzheimer's ailment is a neurodegenerative disorder which is distinguished by collection and accumulation of miss folded proteins and is related to the age. The pathological development of the Alzheimer's disease is due to the accumulation of ß amyloid proteins and the evolution of neurofibrillary tangles. Endoplasmic Reticulum is an organelle which is involved in protein bending and conservation of calcium equilibrium; any miss bending of protein in this organelle leads to the phenomenon of stress. There is a circumstance of calcium overload in the endoplasmic reticulum and mitochondria due to change in calcium management, which leads to the gathering of ß amyloid. The unfolded protein responses having inositol requiring enzyme-1(IRE1), double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK) and activating transcription factor-6 (ATF6) sensor transducers are produced as a result of the existence of the miss folded proteins in endoplasmic reticulum. There is a favorable impact seen in Alzheimer's disease because of cerebral dopamine neurotropic factor. This factor functions by eliminating the endoplasmic reticulum stress and declining the synaptotoxicity caused by ß amyloid. Presenilin-1 is associated to familial Alzheimer's disease. It prevents UPR which will drive to the advancement of Alzheimer's disease. The protein namely selenoprotein exists in the endoplasmic reticulum layer and is a novel objective for the treatment of Alzheimer's disease induced by endoplasmic reticulum stress. The decrease in endoplasmic reticulum stress and modification in phosphorylation of tau protein is seen as a result of selenoprotein.

P225. Role of serine protease inhibitors in prognosis of neurodegenerative disorders

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Serine protease inhibitors belong to a supergene family that include α-1 Anti chymotrypsin (ACT), Antitrypsin, antithrombin & angiotensin. Serine protease inhibitors are acute phase proteins synthesized in response to pro-inflammatory cytokines. It has been found that α-1 Anti chymotrypsin (ACT) plays an important role in Alzheimer's disease. ACT is over expressed in reactive astrocytes of patients with neurodegenerative disorders. Moreover ACT is tightly associated with virtually all amyloid plaques in AD brain. Under the influence of increased ACT levels astrocytosis occurs where change in astrocyte shape & function results from a new expression of gene & likely secondary reaction to ongoing neurodegeneration. This inflammatory response virtually leads to an increased proliferation of the neurodegenerative diseases. Recent studies show that astrocytic expression of ACT in APP transgenic mice leads to increased plaque deposition in the brain so these studies suggest that increased load of ACT promotes αß amyloid deposition. In this review we will summarize the probable mechanisms of neurodegenerative disease proliferation and moreover study the role of serine protease inhibitors for the same. This may shed light on how novel treatments for disorders like Alzheimer's disease can be developed in the future.

P226. Design and synthesis of Pyrimidine class of JAK inhibitors for the treatment of Rhumatoid arthritis

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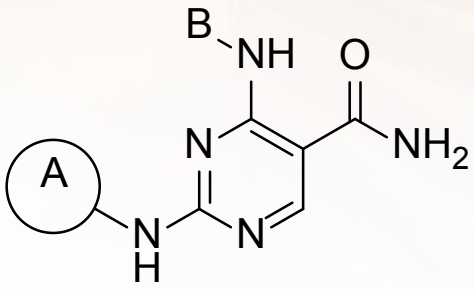
Janus kinase (JAK) is a family of intracellular, no receptor tyrosine kinase that transduces cytokine mediated signals via the JAK-STAT pathway. The association with relevant signaling pathways makes JAK an important target for therapeutic intervention in the treatment of auto immune disorders, various inflammatory diseases, and cancers. Presently only one pyrrolopyrimidine based JAK inhibitor, Tofacitinib is available in market for the treatment of rheumatoid arthritis [RA]. Tofacitinib is an expensive and are associated with various side effects. Hence there is still need for cheaper and safer JAK inhibitor for the treatment of RA. We choose to work on 2, 4-Disubstituted amino pyrimidine class of JAK inhibitors. Our synthesized compounds are equipotent to that of Tofacitinib. Invitro, pharmacokinetics and invivo data of selected compounds will be presented.



P227. A novel inhibitor of M. tuberculosis Adenosine Triphosphate (ATP) synthse against multi-drug resistant (MDR) –TB

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Multi-drug-resistant tuberculosis (MDR-TB) is a form of tuberculosis (TB) infection caused by bacteria that are resistant to first-line isoniazid and rifampin. Although newer targets, innovative drugs and effective combination regimen against TB bacilli are in obligatory need, no anti-TB drug has been approved by drug regulatory authorities for the past three decades except bedaquiline. Bedaquiline, a mycobacterial ATP synthase inhibitor, exhibited excellent efficacy in preclinical and clinical trials having bactericidal and sterilizing activity against MDR-TB.ATP synthase inhibitors (ASI) are a class of drug approved by FDA in 2012 for MDR-TB. They interfere with bacterial energy metabolism which specifically inhibits ATP synthase by binding to subunit C of the enzyme. In the case of bedaquiline, the target enzyme ATP synthase is require for survival in higher organisms, as it supplies cells with the bulk of their ATP via oxidative phosphorylation.ATP synthase is strongly conserved among prokaryotes and eukaryotes. Admittedly, ATP synthesis is coupled to the flow of protons from the intercristae region in mitochondria and the periplasmic space in bacteria to the mitochondrial matrix and the bacterial cytoplasm, respectively. Subunit c of ATP synthase, forming a membrane-spanning oligomer, is requiring for this proton transport. However an increased death rate, occurrence of serious side effects and trivial drug interactions with rifampicin and efavirenz warrants the caution for its usage. The present review will discuss the development of bedaquiline for the treatment of MDR-TB.

P228. Cardiac tissue engineering: Development of safe and efficient therapy

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According to causes of death by American heart association news the heart disease is the major cause of death in Americans than other disease. 23.4% of patients are died because of heart disease and according to world health organization (WHO) cardiovascular disease accounts for 24% of all death in India across age group and gender. Heart transplant is surgery to remove the diseased heart from a person and replaced it with healthy one from an organ donor. After an intense myocardial localized necrosis, noncontractile tissues i.e. fibrous tissues are gathered for tissue remodeling. Despite the fact that heart has a little regenerative potential through activation of stem cell functionality and cell multiplication, the rate of regeneration is inadequate to make up for myocyte scarcity. Subsequently, adjusted workload of a surviving myocardium may eventually prompt to crumbling in contractile capacity and congestive heart failure (CHF). Other than customary pharmacological treatments i.e. diuretics, Ð-blockers, angiotensin, and aldosterone inhibitors or heart transplant, examiners are assessing advanced approaches for treatment of CHF including mechanical gadgets, dynamic cardiomyoplasty, transmyocardial laser revascularization, and bioengineered heart. At the end, heart transplant remains the main choice with great long haul comes about.Lacking accessibility of sponsororgans, new approaches for management of expanding number of patients with heart failure is required. One promising methodology is upsurge quantity of live myocytes in the infracted heart utilizing various strategies for activation of cardiomyocyte cell cycle, supplement undifferentiated stem cellfor their differentiation and assembly, or cell transplantation. Hence transplantation of cardiac myocytes at the damagedarea of the heart can be proficient either by infusing cells or by embedding a bunch of engineered cardiovascular tissue in vitro. This review discusses the process of engineering the myocyte as therapeutic break through.

P229. Synthesis of carbohydrate based heterocyclic scaffold in new drug discovery and development

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In recent years, [1] considerable efforts have been employed in the discovery and development of new drugs. Currently there are a number of drug candidates in different phases of the discovery, pre-clinical and clinical development.There are also a number of ongoing trials using repurposed drugs, where different combinations and doses of drugs that are currently on the market, are being tested with a view of optimizing therapies. In modern synthetic organic chemistry, development of a novel and efficient method for the construction of several mono as well as poly heterocyclic scaffolds is one of the current areas of research interest.[2] Indeed, some of the carbohydrate derivatives like flavone C-glycosides,[3] from natural origins as well as the synthetic macrocyclic lactones having a C-linkage[4] were also reported to possess good therapeutic profiles viz., solubility, in vivo stability, target-binding affinity and cell permeability.[5] Thus the studies pertaining to heterocyclic carbohydrate derivatives with C-linkage have received increasing attention not only among synthetic organic chemists but also among medicinal chemists. Therefore, by considering the importance of N-heterocyclic based C-glycosides including other glycosides,[6] viz., N-glycosylamine, O-glycosides and their various biological and material applications, our present study focuses on the concise pathway to synthesize the novel class of sugar based pyrido (2,3-d)pyrimidine, pyrazole, quinoline, naphthyridine, xanthone and inden-1-ol derivatives.

P230. Quality risk management tools and its application in pharmaceutical manufacturing

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Quality risk management is a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process. That is based on current knowledge about assessing the probability, severity and detectability of the risk. QRM tools are used to overcome such critical parameters that directly affect the quality of the product and leads to financial loss to the pharmaceutical company. As per ICH Q9 guidelines, overview of QRM tools is described below. Formal risk approaches include four basic concepts: Risk assessment, Risk control, Risk review and Risk communication. Fundamentally in QRM tools, risk management is done by understanding what is important for control of equipment or design quality and then focusing resources on managing and controlling the risk aspects. Before risk can be managed, they need to be assessed by QRM tools. Criteria for risk assessment must be defined. Either a numerical scoring system or marker phrases such as “high,” “medium,” “low” can be used. Severity and likelihood of occurrence is detected. Team approach is recommended while using the QRM tools. The risk assessment process in the pharmaceutical industry is shown here using the example of a steam sterilizing autoclave replacement by using FMEA tool in consideration.

P231. Pharmacovigilance: Drug safety monitoring in U.S. and European Union

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The decision of accepting a medicinal product is based on its satisfying conditions between Benefits and Risks. When product is available in the market for the treatment of various diseases, it will create the new information about Benefits and Risk of that product. Every post market surveillance study is a phase IV study, which is an important phase of drug development process. Complete Safety of the product can be analysis after product marketing and in this stage pharmacovigilance activities become useful for getting the assurance of improvement in the national health. Pharmacovigilance is like a process for monitoring and evaluating adverse drug reactions and is an important phase in drug development. Adverse drug reactions can be reported directly to the United State via its MedWatch program and to the Europe via Eudravigilance program .The pharmacovigilance system in both U.S and Europe areas need the full available details about the obnoxious adverse events, medication fault and any other serious transmission by using medicinal product. In this review work, sincere efforts have been made for the comparison of both the systems of pharmacovigilance.

P232. Registration requirement and comparative studies of generic drug registration between Latam countries and U.S.

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LATAM region was introduced in the 16th century that contains Spanish and Portuguese colonist. LATAM region is emerging market for the pharmaceutical industry because of the region has more aged people above 65 years. While US is very stringent and tuff pharmaceutical developed market. Generic drug usage increased in LATAM region by 2 fold more in last 10 years and there will 10.53% pharmaceutical market growth rise by 2020. While regulated US market has 69% prescription of Generics. So, Comparison between Regulated (US) and Semi regulated (Chile and Brazil) market for registration requirements and post approval requirements. Brazil has country specific requirements as per Resolution 16/2007 and Chile has registration requirements as per Decree 30/2010. While US FDA has own specific CTD guidelines for submission of ANDA. There are country specific requirements for Regulated (US) and Semi regulated (Chile and Brazil) for the method validation, stability studies and packaging data. This mainly concentrate on the Quality, Technical and Post approval requirements for the Regulated market (US) and Semi regulated market (Chile and Brazil).

P233. PIC/S new draft guidance

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Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing Practice and Good Distribution Practices of medicinal products for human or veterinary use. The latest draft guidance published by PIC/S is "GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS- PI 041-1 (Draft 2)"on 10 August 2016. Data management is execution of policies and practices to manage the information throughout its lifecycle. Data integrity refers to how intact, complete and unaltered data remains along its life cycle. In recent years, suspensions of pharmaceutical imports to US and EU have been observed owing to data integrity breaches. Warning letters have been issued to leading pharmaceutical companies across the world. Hence, there was a need for more extensive and harmonized guidance for data integrity and management which is the main aim of the new draft guidance from PIC/S. The guidance promotes effective implementation of data integrity elements, proves as a handy tool for inspectors to make optimal use of time and also provides illustrative guidance on risk based control strategies. It explains the data governance system, its elements and organizational influences on it. The heart of the document lies in its detailed description of considerations for data integrity in both paper based and computerized systems. The aim of the present work is to throw light on critical aspects of this draft guidance.

P234. Data Integrity

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Data integrity refers to the complete, true and honest compilation of data. Data could be any textual, numerical, pictorial or graphical material which retains or conveys some information. Data integrity is the backbone to follow Good Manufacturing Practices. There are various guidelines, regarding data integrity, laid down by respective regulatory authorities of different countries. Data is said to be integrated when it is accurate, attributable, available, complete, consistent, contemporaneous, enduring, legible, original and trustworthy. Backdating, fabricating data, discarding data, presenting old data as new are various unethical practices which lead to data integrity breaching. The components of a data integrity report are: metadata, audit trail, static and dynamic records, backup etc. Document protection using passwords, creating an auditable trail, generating checksums are some of the methods undertaken to preserve data integrity. Validating computer systems, carrying out data integrity verification during internal

audits, explaining the importance of data integrity and training personnel to look into ways for detecting data integrity deficiencies and seeking external assistance to enhance data integrity investigation program are some of the steps taken to ensure data integrity. There have been multiple warning letters regarding data integrity issues filed by USFDA. The data integrity guidelines laid down by PIC/S is followed by its member countries which do not have a well-defined data integrity guideline yet. A positive data integrity report enhances the reputation and moral value of a pharmaceutical firm in the eyes of the regulators as well as its consumers. Present work describes different aspects of data integrity.

P235. Jacob Syndrome

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XYY syndrome (Jacob Syndrome) is a rare chromosomal disorder that affects males. It is caused by the presence of an extra Y chromosome. Males normally have one X and one Y chromosome however, individuals with this syndrome have one X and two Y chromosomes. Affected individuals are usually very tall and experience severe acne during adolescence. Symptoms include learning disabilities and behavioral problems such as impulsivity. In the past, there were many misconceptions about this disease. It was sometimes called the super-male disease because men with this syndrome were thought to be overly-aggressive and lacking in empathy. The individuals who were convicted by the court of Law under IPC 302 as murderers are subjected to cytogenetic study. Out of 140 individuals subjected to study 84 was found to have genetic defect of additional Y chromosome. By doing cytogenetic study of these criminals it was found that there is a definite association between the criminal behavior and XYY chromosome. The identifiable causes of death of XYY individuals are due to cancer, neurological disorders, pulmonary diseases, and trauma. Researchers are working to explore undiscovered facts about this syndrome to find out the exact cause behind the clinical problems inherent with this disease which are responsible for higher incidences of mortality.

P236. Preclinical Study in drug development process

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It is the stage of research that begins before clinical trials. It involves important feasibility, iterative testing and drug safety data. Study determines the safe dose for first in man study and assesses a product's safety profile. The main objective of this study is to develop adequate data to decide that it is reasonably safe proceed with human trials of the drug. It is also necessary to check a safety of drug on animals before starting to check on human being. It necessitates the appropriate choice of animal. The choice of species is based on which will give the best correlation to human trials. Differences in gut enzyme activity, circulatory system or other considerations make certain models more appropriate based on the dosage form, site of activity. The most commonly used species are murine, canine, primate and porcine. International and regional authorities and some regulatory guidelines usually require safety testing in at least two mammalian species, including one non rodent species prior to human trial authorization. During study drug may undergo pharmacokinetics, pharmacodynamics, ADME and toxicology testing. The data which are collected during study are acute pharmacology, metabolic stability, genomic biomarker analysis, pharmacogenomics, in vivo toxicity and in vitro toxicity of drug. There is no 'one size fits all' approach to the design of preclinical study. In this study drugs are established, according to the observed adverse effect which helps to determine the phase-1 clinical trial.

P237. Basic feature of Clinical Trials & Clinical Research

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Clinical trials also known as 'clinical Research studies' that follow a Pre- defined plan or Protocol. Clinical trials particularly those looking at new drugs, often start after successful animal studies the most promising treatments then move into clinical trials. Clinical trials for different Disease and Disorder are conducted for evaluating one or more interventions for treating a Disease, Syndrome or Condition and also finding ways to prevent the initial Development or recurrence of disease or condition. These can include

medicine, vaccine, or lifestyle change, among other approaches. The four Categories declared by FDA are Phase 1, Phase 2, Phase 3, and Phase 4. A clinical study involves research using human volunteers that is intended to add to medical knowledge. A Globalization of Clinical Study is relatively recent Phenomenon in which many of these studies are taking place on a global scale with significant increase of clinical trials in developing countries. Some of the Markets used for Globalization are united state, Western Europe, Germany, Japan, and India. The Clinical Research means Treatment of Patients and Systemic Investigation for getting the new conclusion. Research is important because Clinical trials test how well new approaches and interventions work in people. These approaches can be medical, behavioral, or management. Each study helps scientists to prevent, screen for, diagnose, manage, and treat a disease. People who take part in clinical trials contribute to the knowledge of how a disease progresses. Clinical research is conducted according to a plan (a protocol) or action plan. The plan describes what will be done in the study, how it will be conducted, and why each part of the study is necessary

P238. Transition-metal catalyzed direct C-H functionalization of Azoles

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Aromatic heterocycles, especially azoles, are important motifs in organic molecules because of their wide applications in pharmaceuticals and material science. The transition-metal catalyzed cross-coupling reaction of heteroaryl halide is a most practiced strategy with some limitation. However, metal-mediated direct C-H functionalization emerged recently as a powerful and complementary approach. In this context, we have synthesized a series of substituted azoles via insitu formation of hetroaryl-Cu(I) species. The transmetallation of this hetroaryl-Cu(I) species with organo-palladium intermediates resulted in direct C-H arylation of 1,3,4-thiadiazole with 49-84% of yield, although the cross coupling reaction is restricted to use sulfur compounds due to poisoning effect. This heteroaryl-Cu(I) species further coupled with phosphonium intermediate, generated insitu via reaction of tautomerizable heterocycle with PyBrop, to give biheterocyclic framework in good to excellent yields. Another approach to use this heteroaryl cuprate in multicomponent reaction (MCR), using aldehyde/ketone and amine, resulted in novel HA2 and HAK coupling giving direct access to secondary and even unprecedented tertiary alkylation of azoles. This alternate synthesis strategy will help us to generate several novel substituted azoles, which may be suitable for pharmaceutical application.

P239. Quality Metrics

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Quality is given prime importance in pharmaceutical industry. To produce products with highest quality, quality metrics are used throughout the pharmaceutical industry to monitor pharmaceutical quality systems, different processes of pharmaceutical industry for achieving improvements in industry. Quality metrics are improvised and they are systematic representation of Quality- Key Performance Indicators. They are indicators of whether quality management is good and meeting desired specifications or they are requiring amendments. Quality metrics are very useful for different regulatory agencies like USFDA. They help to develop compliance, inspection policies and practices. Quality metrics help to develop overall risk-based inspection scheduling of manufacturers, improve agency's ability to predict and thus overall prevention of future drug shortages by preventing mandatory recall of drug products. FDA published four essential metrics: Lot Acceptance Rate, Product Quality Complaint Rate, Confirmed out of Specifications Rate and Recall rate. Overall quality metrics increases visibility and transparency between industry and regulators.

P240. Study of Prescription Audit in Hospitalized Patients in Tertiary Care Hospital

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Prescription audit in department of surgery is important strategies in maintaining standards in pre-operative and post-operative care at the clinical level. The aim of present investigation

is to study the prescription pattern of drugs used in the department of surgery at tertiary care hospital. A prospective observational study of three months was conducted in the department of surgery at Jivraj Mehta Smarak Health Foundation. A prior permission was obtained from Institutional Ethics Committee (IEC). Total sixty six prescriptions of surgical patient were collected, scrutinized and statistically analyzed and reporting to department. Case record form of included patients were filled and examined. Finding are recorded for the gender differences, average age of the patients, diagnosis, a number of diseases, route of administration, drug category, frequency of administration and appropriateness of doses. Most of the cases are between the age group 15 to 90 years having 45 (68%) male and 21(32%) female. The demographic reports of our study showed age-wise distribution, 3(4%) of patients were found below 20 years of age, 18 (27%) of patients were found between 21 to 40 years of age group, 20 (930%) of patients were found between 41 to 60 years of age group, 18 (27%) of patients were found between 61-80 years of age group and 7(10%) of patients were found between 81-100 years of age. Out of 66 patients, nearby 22(33%) cases were found on gastrointestinal surgery, 21 (31%) orthopedic surgery, 4(4%) CVS surgery, 6(9%) Renal surgery and 4(6%) Dermatologic surgery. A total of 660 drugs were prescribed to the 66 cases, giving an average ten drugs per prescription. Most preferred route of drug administration was intravenous route (440 drugs, 66.6%) followed by oral (220 drugs, 33.3%). Anti-microbial and anti-inflammatory drugs are most prescribed drugs among the prescribed medicines.

P241. Generation of common pharmacophore hypothesis (CPH) for protein tyrosine phosphatase 1b (PTP1B) inhibitors using phase

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Protein tyrosine phosphatase 1B (PTP1B) has been involved in the regulation of the insulin and leptin signaling pathway and represents an novel target for the design of inhibitors in the treatment of type 2 diabetes and obesity. There is no small molecule available in market till now for PTP1B inhibitor. A five point pharmacophore was generated for protein tyrosine phosphatase 1B (PTP1B) inhibitors containing substituted thiophene scaffold as anti-diabetic and anti-obesity agents using PHASE. The generated pharmacophore yielded significant 3D-QSAR model with r2 of 0.97 for a training set of 42 molecules. The model also displayed excellent predictive power with correlation coefficient Q2 of 0.82 for a test set of 20 compounds. This validation study delivered assurance for the effectiveness of the common pharmacophore hypothesis to identify compounds with diverse structure with desired biological activity using virtual screening. The results presented in our study demonstrate various ways in which PHASE can be used to accelerate lead discovery and lead optimization, and to illuminate the details of ligand binding of protein tyrosine phosphatase 1B (PTP1B) inhibitors containing substituted thiophene scaffold as anti-diabetic and anti-obesity agents.

P242. Synthesis and Evaluation of Naphthoquinone Analogues as Antimycobacterial and Efflux pump inhibitors

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Naphthoquinones have been used as promising scaffolds for drug design studies against tuberculosis (TB), which is one of the top public health concerns worldwide. One third of world's population is latently affected by Mycobacterium tuberculosis (M.tb) with increasing incidence of multidrug resistant cases. The active multidrug efflux pump (EP) has been described as one of the mechanisms involved in the natural drug resistance of mycobacteria. Our research study focuses on utilizing naphthoquinone moiety as lead for developing antimycobacterial agents. In the present study, thirty derivatives of 1,4-naphthoquinone were synthesized via Multicomponent Oxidative Decarboxylation (long chain acid series) and Mannich reaction (amino-naphthoquinones). The compounds were purified by column chromatography and melting point recorded. These compounds were also characterized by various spectral analysis as IR, MS and NMR. The antimycobacterial activity was determined against fast replicating Mycobacterium smegmatis (M. smegmatis), which acts as a surrogate for MDR M.tb. Among thirty compounds, five compounds of amino-naphthoquinone series exhibited potent MIC in the range of 8-10 µg/ml. A checkerboard synergy assay was performed to identify naphthoquinone derivative that reduced the MIC and Efflux of Ethidium Bromide (EtBr), a known efflux pump substrate of M. smegmatis.

P243. Prescribing Quality for Neurological Conditions

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Neurological disorders are a significant cause of morbidity, mortality drug-drug interaction and adversely affect quality of life among the Patients. In India, more than 30% populations are suffering from neurological disorders. For that various types of drugs are prescribed. Before such policies can be implemented, detailed knowledge of prescribing practice is important. The objective of study was to prescribing practice in hospital. Prescriptions of patients attending neurology outpatient department were collected prospectively for 6 weeks. They were analyzed for prescribing pattern, WHO core prescribing indicators. Data of total 120 patients were collected, male female ratio 1:1. Migraine was the most common diagnosed (58%) and other followed by epilepsy, Parkinson's etc. Average no of drug prescribe per patient was 3.08. More than 80% of the drugs were prescribed from WHO essential drug list. Most commonly prescribe drug category was analgesic (30%). Average cost of medication per day was 28.58 Rs. Migraine is most common disorder among all patients. In drug categories vitamin supplements and analgesics were mostly prescribe.

P244. Study of drug-drug interactions in hospitalised geriatric patients at Tertiary care hospital

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Drug-drug interactions occur when a drug interacts, or interferes, with another drug. This can alter the way one or both of the drugs act in the body, or cause unexpected side effects. The present prospective, observational study was planned with the aim to find out occurence rate, classify severity of drug drug interactions, observe class / group of drugs having potential of DDI and Potentially Inappropriate Medication (PIM) prescribing in geriatric inpatients at Jivraj mehta Smarak Health Foundation, Ahmedabad for 5 months. Drug-drug interactions were identified by the Medscape® drug interaction checker software. Prior permission from the Institutional Ethics Committee was obtained. A total of 200 cases was collected & their follow up for 3 days was taken and analysed. The occurence rate of drug – drug interactions was 89.5 %, as 179 out of 200 prescriptions showed drug-drug interaction. Out of 200 patients, 1545 Possible drug – drug interactions were found in which 11 (0.71%) were contraindicated, 112 (7.24%) Serious drug interactions, 1016 (65.76%) Significant interactions and 406 (26.27%) minor interactions. Out of 1545 Possible drug – drug interactions, 972(62.91%) were pharmacodynamic interactions ,573(37.08%) were ph.cokinetic interactions. The most common DDI was found from the class Proton pump inhibitor + Antiplatelet drugs. Total 200 cases contained total 14 Potentially Inappropriate Medicines (PIM), according to Beers criteria. Total 1545 Possible drug – drug interactions were found from 200 patients, however none of them were clinically significant. Polypharmacy was frequent in the study. The number of potential DDIs increased with an increase in the number of drugs prescribed.

P245. Bamboo: Boon to mankind: A review for its Ethno medicinal uses, Phytochemistry, and Medicinal Potentials

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Medicinal plants, have fundamental and therapeutic importance, are the blessing to mankind to acquire healthy lifestyle. Bamboo (Family: Poaceae), the 'Green gold' has superior value in entirely indigenous traditional system of Asian medicine, for its immense medicinal and nutritional purposes and thus forms a core ingredient for research in many laboratories. Present review encases the numerous phytochemicals isolated from Bamboo species and its ethno medical and pharmacological potentials with molecular mechanisms and is briefly deliberated and recapitulated. The information documented in the present review was collected from more than 300 articles, published or accepted in the last five to six decades, and more than 20 e-books using various online databases. Additional information was obtained from various botanical books, patents, conference proceedings and dissertations. The extracts of various parts of bamboo especially leaves and shoot have numerous phytoconstituents viz. higher amount of polyphenols, phenolics, flavonoids, triterpenes, steroidal glycosides and

coumarins and other constituents like tannins, minerals, vitamins, amino acids and essential oils. The extract or plant is identified to be efficacious against diversified ailments like inflammation, ulcer, diabetes, bacteria, obesity, cancer, osteoporosis, cardiovascular diseases, and preventing other degenerative diseases. These actions are attributed to either regulation of various molecular pathway involved in several patho physiologies or antioxidant property which prevents the damage of cellular compartments from oxidative stress. Bamboo owing to its vivid phytochemical spectrum is an ideal plant with a great promise for the pharmaceutical, nutraceutical, cosmoceutical and the food industry.

P246. A Comprehensive Approach to Cleaning Validation

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Pharmaceutical manufacturers must validate their cleaning process to ensure compliance with standard regulatory authorities Pharmaceutical product and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, by cleaning agents, by microorganisms or by other materials e.g. air borne particle, dust, lubricants, raw materials, intermediates. Ineffective cleaning can lead to adulterated product, which may be from previous product batches, cleaning agent or other extraneous material introduced into generated by the process. Assembling and cleaning gear must be intended for powerful and reliable cleaning to maintain a strategic distance from cross-sullying and the cleaning forms must be confirmed as compelling. A compelling cleaning should be set up to give archived prove that the cleaning strategies utilized inside an office reliably controls potential remainder of item including intermediates and polluting influences), cleaning operators and superfluous material into consequent item to a level which is beneath foreordained levels. Cleaning validation is becoming more and more important as we deals with potent, complicated drug substances and complex biotechnology products. We have focused mainly presentation on cleaning approval and the related directions, level/level of cleaning, ways to deal with cleaning approval, components of cleaning approval, acknowledgment criteria, approval conventions, and approval reports.

P247. Importance of Quality Management System in Pharmaceuticals

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A quality management system (QMS) is a plan of action, processes and operation obligatory for designing and carrying out in the business region of an administration. Sometimes QMS is referred to as a set of documents but in practice it represents the entire system. It is a tool for optimum business management. America and Japan together introduced the concept of total quality management for improving the business statistics along with quality. In the 21st century the concept of sustainability and transparency was also included along with quality in QMS to seek better consumer gratification. Also it helps to meet with the regulatory aspects of quality business. The most widely used and accepted version of quality management system is ISO 9001:2015. It enables the organizations to implement their own processes. Few other ISO standards for quality are ISO 9000 series, ISO 14000 series for Environmental management systems, ISO 13485 series for quality management systems for medical devices, ISO 19011 for auditing management systems, and ISO/TS 16949 for QMS for automotive related products. A well planned strategy is the important factor that helps the organization to reach certain heights in terms of a quality product. The overall strategy of QMS implementation and execution depends on the Plan-Do-Check-Act (PDCA) cycle which enables recurring betterment in terms of output and QMS. The application of QMS is beneficial in many ways one of such ways it gain the customers confidence in the company leading to rise in sales and thereby business growth.

P248. Extended Bioisosterism led synthesis of Thiazole based derivatives to target Bcl-2 protein in cancer

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Cancer is a multifactorial, multigenicdisease involving multiple pathways. Simultaneously the discovery of novel molecules is multi-year, multidisciplinary and multimillion dollar affair. In this scenario drug repurposing or modification of existing ones with appropriate isosteres/bioisosteric replicas may thwart

progression of cancer in an effective way. In this paradigm, we are concerted to design novel anticancer molecules by taking well established anthelminthic drug Niclosamide, currently repurposed for various cancers by inducing apoptosis. Here the nitrophenyl ring of niclosamide is replaced with 5 membered heterocyclic rings like thiazole which is having metabolically robust nitrile group as a functional pendant and is in turn isosteric to nitro group. The drugscontaining thiazole nucleus is found to have possible implications in JNK, STAT3, Nf-κB, and Aktpathways. Moreover, thiazoles have been designated as master keys to open the lock of potential receptors.The low molecular weight compounds have been designed also taking into consideration Lipinski's rule of 5 and avoiding red flagging. Our designed ligands were docked with the protein responsible for apoptosis (Bcl-2). During computational study, we got surprising interaction between key amino acidof Bcl-2 proteins with designed molecules in comparison to niclosamide. Currently the synthesis of some molecules has been successfully done and biological studies are underway.

P249. Pharmaceutical quality system "ICH Q10 MODEL"

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Pharmaceutical industry is amongst most stringently regulated manufacturing units. Quality management system affects the ultimate quality of the finished product. Pharmaceutical Quality System specifies the modern quality system needed to establish and maintain a state of control that can ensure the realization of a quality drug product and facilitate continual improvement over the product's life cycle. ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts, includes applicable good manufacturing practice (GMP) regulations, and complements ICH "Q8 Pharmaceutical Development" and ICH "Q9 Quality Risk Management." ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Currently Pharmaceutical industry is way behind the other in Quality Management philosophies. The understanding and implementation of appropriate quality management system model enables a pharmaceutical organization to fulfill its ethical as well as regulatory responsibility of including management of identity, quality, safety, purity and efficacy of finished medicinal product. It makes good business sense.

P250. Clinical requirements for registration of Fixed Dose Combinations (FDCs) as per global perspective in South Africa, GCC, EU and US

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The Pharmaceutical market is growing leaps and bounds globally. Pharmaceutical companies are dealing in generic or branded medications and medical devices. However, they are subject to a variety of laws and regulations that govern the patenting, testing, safety, efficacy, quality and marketing of drugs. Till last decade the pharmaceutical sector was room around patent protection as majority of block buster molecules were patented by innovator Pharma Company. However, from 2018 to 2025 the era will be changed as many of the patent is getting expired and hence, two separate entities having complementary advantage to each other can be clubbed in single pharmaceutical dosage form to achieve better patient compliance. This leads to FDC development. Developing FDCs is one of the many reformulation strategies used in product lifecycle management. It has the potential to offer quicker commercial returns compared to developing a new chemical entity. They have shown success in treating cardiovascular diseases, diabetes, HIV/AIDS, tuberculosis, and malaria. The proposed combination should always be based on valid therapeutic principles. The clinical development of FDCs should correspond to each situation/intended claim. Also, particular attention should be drawn to the doses of each active substance in the fixed dose combination product. Each fixed dose combination should be carefully justified and clinically relevant in order to get registered. Hence, conclusively, clinical requirements play an important role in the FDC registration globally.

P251. PDUFA: A revolution in drug review process

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Prescription Drug User Fee Act abbreviate as PDUFA was introduced in 1993 by United States Congress under which pharmaceutical industries was bound to pay fees for drug review process for the drug they were willing to market which in turn facilitated the drug review process which was not that effective in past. The collected fees were bound to be for the use only in Centre for Drugs Evaluation and Research (CDER) or Centre for Biologics Evaluation and Research (CBER) drug approval purposes. The fees were to be collected in 3 ways: Application Fee, Establishment Fee, and Product Fee. Waivers are also offered under the act in which fees reduction or refunds are availed for small businesses and in order to encourage the new research to develop a new drug. Five amendments were done to improvise the act and to smoothen the drug review process. On the whole, PDUFA revolutionised the development of new drugs for threatened disease by having a fast drug approval process. In this work, concise and effective information about PDUFA is presented.

P252. Structure Activity Relationship (SAR) study of Benzimidazole scaffold for various biological activities

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Benzimidazoles are the heterocyclic ring systems which form an important part of vitamin B12 and have been attracting many (people who work to find information) all over the world to assess their potential medically helpful importance. They are known for their extremely important role in many sicknesses via different mechanisms. Substitution of benzimidazole center (of a cell or atom) is a crucial step in the drug discovery process. Therefore, it is necessary to gather the latest information along with the earlier information to understand the present status of benzimidazole center (of a cell or atom) in drug discovery. In the present review, benzimidazole derivatives with different pharmacological activities are described on the basis of SAR study using substitution pattern around the benzimidazole center (of a cell or atom) and aims to review the reported work related to the chemistry and (related to medical drugs) activities of benzimidazole derivatives during the last few years. This is the first compilation on (creation/combination) and medicinal aspects including structure-activity relationships of benzimidazole reported to date. A full understanding of the structure, medicine al and chemical properties of the benzimidazoles may help the (people who work to find information) to find out its use in treatment of some more (not stoppable/not able to be destroyed) sicknesses. In addition to it, some serious side effects connected with the benzimidazole can be animal desires entified and cure.

P253. Significance of Clinical Trials in Drug Development in India

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The importance of drug trials in promoting health services cannot be overemphasized. New drugs and therapies can improve the quality and lifespan of patients. While it is imperative that the number of clinical trials increase, the Government is also trying to ensure that the rights and safety of the subjects are protected and the quality of the trials performed in India improve to international standards. India has been a hub for conducting various multi centre trials. The Central Drugs Standard Control Organization (CDSCO), headed by the Drug Controller General of India (DCGI), lays down the regulations for the conduct of clinical trials in India. Clinical trials test potential treatments in human volunteers to see whether they should be approved for wider use in the general population. A treatment could be a drug, medical device, or biologic, such as a vaccine, blood product, or gene therapy. It is essential that now all clinical trials conducted in India should as per the International conference of Harmonization-Good Clinical Practices Guidelines (ICH-GCP) for clinical trials and follow the recently amended Schedule Y of the Drugs and Cosmetics Act. Thus understanding the regulations, guidelines and data gathered during clinical trials can make the way for better development of drug.

P254. Analytical lifecycle Management: Modern Approach in Process Validation

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The USP Validation and Verification Expert Panel recommend the adoption of an analytical lifecycle approach for the management of analytical procedures as a modern concept of process validation. It is described in ICH guidelines Q8, Q9, and Q10 which can be applied for analytical procedures. Adopting to this new approach it introduce new concepts in the USP that are: Analytical Target Profile with its predefined acceptance criteria, Analytical Control Strategy for the evaluation of the uncertainty in the analytical procedure, Risk Management as a risk analysis strategies, and Knowledge Management to know the potential effect of changes and how to implement it for an analytical procedure. In order with the process validation, there are three stages: Procedure Design (development and understanding), Procedure Performance Qualification, and Continued Procedure Performance Verification as a Lifecycle Stages of Analytical Procedure with an example of its changes with its appropriate actions. It concludes regarding the importance of lifecycle model with the comparison between traditional verses modern approaches in correlation with the analytical lifecycle management.

P255. Section 3(d) of Indian Patent Act

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The Patents Act, which was enforced in 1970 facilitated the growth of a domestic pharma industry in India. Now we can see the result as India has become a major exporter of generics. In 2005, IPA was modified in section 3(d) to prevent ever greening of patents. The Patent Act 2005 (amended) defines invention and makes clear that any knowledge or thing already existing cannot be patented. According to the amendment, to acquire patent protection in India, the substance has to pass the criterion to go beyond establishing the novelty, non-obviousness, inventive steps and industrial application test which are mentioned in TRIPS agreement and also fulfil the additional improved efficacy incorporated under section 3(d). However the innovators feel that this amendment is not providing adequate patent protection for multinational drug companies. But still cases like Novartis v/s Union of India & others (for Gleevec patent.) and a German MNC, Boehringer Ingelheim (for its respiratory drug, Spiriva) prove that Section 3(d) does not mean to violate the TRIPS directives rather prevents flippant patenting and at the same time does not hurdle valuable incremental innovations.

P256. Highly Artemisinin-Resistant Plasmodium Falciparum with Quinine Co-resistance Emerges under in vivo Artesunate Pressure

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Humanity is more reliant on artemisinin for the treatment and control of malaria, hence resistance is a major threat. Delayed parasite clearance time in Southeast Asia indicates that artemisinin resistance is evolving, but it is unclear if it will strengthen. We investigated the consequences of in vivo artesunate drug-pressure, applied as flash-dose or two-day regimens, on P. falciparum infecting human-erythrocytes in an immune-deficient mouse model. High-level artemisinin resistance evolved rapidly against both regimens up to near-lethal doses of artesunate (240mg/kg). In vitro drug sensitivity (IC50) remained unchanged as in vivo resistance rose up to 30mg/kg artesunate. Later, when in vivo resistance strengthened further, artesunate IC50 increased ten-fold. Despite exclusive exposure to artesunate, full-resistance to quinine - the only alternative treatment for severe-malaria - evolved in vivo, and was confirmed in vitro. The results show P. falciparum can evolve extreme artemisinin resistance, and challenging patterns of multi-drug resistance.

P257. An Over view of Quality by Design Approach

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Now-a-days quality by design (QbD) has become an essential part of the modern concept for quality of the pharmaceutical products. Since years, quality was achieved by trial and error basis for drug product development, which leads to high rate of post approval changes. As it is said by USFDA that quality cannot be achieved by checking it at the end but need to be inculcated throughout the development. Since January 2012, USFDA made it mandatory to use QbD in drug development. QbD increases flexibility, efficiencies and provides regulatory relief throughout the product life cycle in addition to build quality in product. QbD is a risk based scientific concept involving thorough understanding of product and process parameters which affects the quality of the product. Risk assessment, process analytical tools, mathematical and statistical parameters are important elements of the QbD. During the designing and development of product with QbD approach, quality target product profile (QTPP), critical quality attributes (CQA) are primary requirements and then needs to understand the impact of critical material attributes (CMA) and to control the sources of variability. When this is done, one need to generate the design space within which we can achieve the required quality of product. Finally controlled strategies are documented for all the attributes within which post approval changes can be justifies. However, many pharmaceutical industries are reluctant to use QbD tools due to time and cost factors. However they will realize long-term benefits with enhanced understanding of great potential of use of QbD during product development stages. QbD approach can also facilitate the use of innovative technologies and promote the use of new approaches to perform process validation, such as continuous quality verification and quality audit.

P258. Technical and Regulatory Considerations for Pharmaceutical Product lifecycle

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Currently, there is a lack of a harmonized approach to technical and regulatory considerations for the lifecycle management of pharmaceutical products. As per the ICH guideline, the main focus is on early stages of the product lifecycle, especially on Pharmaceutical development (ICH Q8). Furthermore, there is an inconsistent utilization of post-approval change management plans and comparability protocols. The pharmaceutical industry needs a more strategic manner to prospectively manage future changes. The key to attaining the desired state of ICH-Q12 and providing regulators assurance that most changes can be managed by the pharmaceutical industry, without extensive regulatory oversight, is to provide regulatory authorities assurance that all product quality aspects are managed within a robust Pharmaceutical Quality System over a product's lifecycle. There are some limitations that we need to overcome in order to achieve the desired quality product. Limitations such as 1) Regulatory Dossier, 2) Pharmaceutical Quality System aspects and 3) Post-Approval Change Management Plans and Protocols have been conquered under ICH Q12. ICH Q12 will indeed help manufacturers in adopting a good product quality manufacturing process. Major spotlight of this review is on how ICH Q12 will help manufacturer in achieving greater results in terms of quality of the pharmaceutical product and simultaneously smoothen the supply of products too.

P259. Pharmacophore mapping of sodium-dependent glucose co-transporter 2(SGLT2) inhibitors using phase

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Diabetes mellitus type 2 (T2DM) accounts for almost 90% of diabetes cases, with the property of insulin resistance and beta-cell dysfunction that induces hyperglycemia. Sodium-dependent glucose co-transporter 2 (SGLT2) plays a pivotal role in maintaining glucose equilibrium in the human body emerging as one of the most promising targets for the treatment of diabetes mellitus type 2. A series of c-aryl glucoside derivatives have been reported as SGLT2 inhibitors. Therefore, to determine the structural requisite of these SGLT2 inhibitors, five-point 3D pharmacophore model has been developed using the PHASE module of Schrodinger. The generated best pharmacophore hypothesis yielded a statistically significant with correlation coefficient of R2 = 0.81 for 70 training set molecules. The generated model showed

very good prediction power with Q2 = 0.72 for 37 test set molecules. Moreover the model generated could effectively distinguish selective inhibitors of SGLT2 from those of SGLT1. The geometry and features of pharmacophore are expected to be useful for the design of selective SGLT2 inhibitors.

P260. MRI contrasting layered double hydroxide nanoparticles for hyperthermia and photodynamic cancertherapy

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Conventional cancer treatments are facing long standing obstacleslead to lowest mortality rate. Present, research has been focused on alternativeapproaches to confrontation cancer by extent success rate. The study is carried out by synthesis of photodynamic molecules loaded gadolinium LDH nanoparticle for magnetic hyperthermia for cancer thernostics. LDH nanoparticles are synthesized by co-precipitation method, which have MRI contrasting activity. Hyperthermia effect is obtained by LDH nanoparticle, doped with Fe_2O_3 nanoparticles by non-covalent electrostatic interaction, while photodynamicmolecules(Photosensitizer) areloaded by ion exchange method. The doped LDH nanoparticles have demonstrated optimum temperature (42-44°C) for functional apoptosis. It is observed that synergetic effect is obtained in the LDH nanoparticles loaded with photodynamicmolecules as compare to the singular effect (either, hyperthermia or photodynamic effect) in in vitroculture studies. Hence, it is concluded that LDH nanoparticles loaded with photodynamicmolecule are demonstrated to enhancethetherapeuticeffect for cancer cell eradication with combined MRI diagnostic properties.

P261. Unraveling the mechanism of peroxidase - like activity of gold nanoparticles

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Recent investigations on inorganic nanomaterial exhibiting enzyme-like characters have offered several applications in biomedical field. Nanomaterials showing enzyme mimetic properties like catalase, peroxidase, oxidase and superoxide dismutase etc are investigated recently. Among them gold nanoparticles (AuNPs) have been reported as peroxidase mimics by us and several other groups worldwide. However, low substrate affinity and lack of clarity about mechanism of catalytic activity limits the catalytic performance of AuNPs. In our study, we have synthesized AuNPs carrying positive (CTAB coated), neutral (PEG coated) and negative (Citrate coated) charge and investigated their peroxidase - like activity, by TMB in presence of H_2O^2. The peroxidase - like activity results, revealed that AuNPs bearing no charge are better catalyst than negatively charged particles whereas positively charged AuNPs did not show any significant peroxidase activity. Additionally, the boosting effect of ATP on peroxidase - like activity of AuNPs was also explored, which showed ~ 3 fold and ~ 4 fold increase in activity of neutral AuNPs and negatively charged AuNPs, respectively. We further explored the role of hydroxyl (•OH) radicals in the peroxidase - like activity of AuNPs by using terephthalic acid (as a •OH radical detector). Surprisingly, we did not observe any increase in •OH radicals with the rise of AuNPs concentration. This suggests that •OH radical does not play any major role in peroxidase - like activity of AuNPs. We also investigated the role of ATP in imparting stability to oxidized TMB. Indeed, we observed that in presence of ATP, oxidized TMB remains stable for >48 hours, whereas in absence of ATP, oxidized TMB gets reduced in <24 hours.

P262. A facile synthesis of gold (core) - cerium oxide (shell) nanoparticles exhibiting biological peroxidase and superoxide dismutase enzyme like activity

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Nanomaterials exhibiting biological enzyme-like activity have become a growing area of interest and found several applications in the field of biomedicines such as biosensing, imaging and therapeutics. Gold nanoparticles (AuNPs) are known to possess intrinsic biological

peroxidase-like activity. The peroxidase-like activity of nanoparticles can be tuned to produce hydroxyl radical (· OH) radicals in mammalian cell cytoplasm for selective cytotoxicity in cancer/diseased cells. Cerium oxide nanoparticles (CeNPs) are known to exhibit superoxide dismutase (SOD) and catalase mimetic activity and shows protective effect against free radical in several cell lines and animal models. Although AuNPs and CeNPs individually show excellent enzyme-like properties, there is limited effort on synthesis of Au core- CeNPs shell nanoparticles exhibiting peroxidase and SOD, both activities. Such core-shell nanoparticles decipher cancer and healthy cells efficiently. Therefore, we have synthesized Au core- CeNPs shell type nanoparticles (Au@CeO_2 CSNPs), exhibiting both peroxidase and SOD-like activity. The Au@CeO_2 CSNPs are characterized by several techniques such as UV-Visible spectroscopy, Transmission electron microscopy, Fourier transform infrared spectroscopy, X-ray diffraction analysis, Photoluminescence spectroscopy, Energy dispersive X-ray spectroscopy. The results from these techniques show clear formation of Au@CeO_2 CSNPs of 70 nm diameter. The pH and temperature dependent peroxidase-like activity measurement revealed that, Au@CeO_2 CSNPs show maximum activity at pH 4 and 40°C temperature, respectively. Additionally, this Au@CeO_2 CSNPs also showed excellent SOD-like activity at neutral pH. The peroxidase-like activity of Au@CeO_2 CSNPs was exploited for glucose sensing with a linear detection range of 100µM to 1mM. Such dual enzyme character mimicking nanoparticles could facilitate further studies of the cooperation of peroxidase and SOD and generation of better therapeutics agent. DBLS communication number is DBLS-78

P263. Ganoderma (King of herbs): Health benefits as health supplements

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Ganoderma lucidum (G. lucidum), commonly referred to as Lingzhi in China, is a fungus which has been widely used through the centuries for the general promotion of health and longevity in Asian countries. The Latin word lucidus means “shiny” or “brilliant” and refers to the varnished appearance of the surface of the mushroom. In China, G. lucidum is called lingzhi, whereas in Japan the name for the Ganodermataceae family is reishi or mannentake. The anti-cancer effects of G. lucidum have been demonstrated in both in vitro and in vivo studies. In addition, the observed anti-cancer activities of Ganoderma have prompted its usage by cancer patients alongside chemotherapy. It has been known to have numerous pharmacological effects including immuno-modulating, anti-inflammatory, anti-cancer, anti-diabetic, anti-oxidative and radical-scavenging, and anti-aging effects. The main two bioactive components of G. lucidum can be broadly grouped into triterpenes and polysaccharides. Despite triterpenes and polysaccharides being widely known as the major active ingredients, the different biological pathways by which they exert their anti-cancer effect remain poorly defined. Several types of Ganoderma products are available on the market including ground fruiting bodies or mycelium processed into capsule or tablet form; extracts from fruiting body or mycelium dried and processed into capsule or tablet form, Ganoderma beer and Ganoderma hair tonics (Jong and Birmingham, 1992). Most mushrooms are 90% water by weight. For G. lucidum, the remaining 10% consists of 26–28% carbohydrate, 3–5% crude fat, 59% crude fibre, and 7–8% crude protein. In addition, G. lucidum contains a wide variety of bioactive constituents such as terpenoids, steroids, phenols, glycoproteins, and polysaccharides. In this review, we focused on the various health benefit of G. lucidum, in particular, the two main active ingredients: triterpenes and polysaccharides.

P264. Malaysia regulatory framework and registration requirements of generic drugs

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The Generic drugs Market of the ASEAN (Association of South East Asian Nations) countries are increasing in present scenario on day to day basis, so it is inevitable to regulate the drug product for its Safety, Efficacy and Quality. It includes ten member countries under the ASEAN declaration in which guidelines are particular regarding country like their labelling requirements and registration process whereas certain regulatory requirements are coordinated as the ASEAN guidelines. From ICH guidelines, these ASEAN guidelines are acquired. Under the ASEAN declaration ASEAN Consultative Committee for Standard & Quality – Pharmaceutical Product Working Group known as ACCSQ-PPWG was established for the synchronize for the pharmaceutical regulation. Generic drugs are cheaper than the new or innovator drugs and

the quality of the generics and innovator drug products are same, so the use of the Generic drug products is increased. The R&D for generics, which are expected to grow from 8.3% in 2010 to 12.8% of the total market by 2015, when they will be worth USD 12.3bn.

P265. Exploring the function of tetraspanin CD 151 via X-ray crystallography

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Tetraspanins are a family of small proteins that cross the membrane four times and form complexes by interacting between themselves and with a variety of transmembrane and cytosolic proteins and building a network of interactions referred as tetraspanin enriched micro domains (TEMs). These domains provide a signaling platform involved in many important cellular functions and malignant processes. CD151 is the one among the 33 types of tetraspanin which has direct interaction with integrin molecules on the cell surface. The primary function of the CD151 is to assemble integrins and other proteins present on the cell surface in cis- conformation, to build a TEM used as signaling platform. Tetraspanin CD151, in partnership with integrins α6ß1 and α6ß4, modulates tumor cell growth, invasion, migration, metastasis, and signaling and drug sensitivity. Targeting CD151 in cancer could be a promising therapy due to the importance of tetraspanins in several steps of tumor formation, communication with the environment, dissemination, and metastasis. Hence determination of the structure would pave way for understanding its role in the cellular signaling pathway and also help us to target CD151 with suitable inhibitor.

P266. Cheminformatics analysis of natural products –from chemical space to drug likeliness

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Natural products (NPs) are chemical compounds synthesized by any life form, and exhibit tremendous diversity. NPs have evolved to interact optimally with different biomolecules making them invaluable resource for rational drug design. We have analysed chemical properties of more than 4 Lac NPs, from Supernatural (SN2) and Universal Natural Products Database (UNPD) databases, and compared them with 1857 approved drugs. We show that the distribution of molecular weight, number of hydrogen bond donors and acceptors, and LogP for molecules in the three databases follows similar pattern. The proportion of compounds following Lipinski's 'rule of five' in UNPD, SN2, and approved drugs databases was observed to be 53.8%, 63.5%, and 77.3%, respectively. Failure to meet the LogP and molecular weight thresholds was the predominant reason for NPs being Lipinski's outliers. There results provide interesting insights into the drug-likeliness of NPs. Principle Component Analysis of NP chemical space using molecular descriptor was also performed. NPs were observed to occupy a larger and different chemical space as compared to the approved drugs. Overall, our results substantiate the value of NPs as potential lead molecules. The detailed cheminformatics analyses of NPs presented here would prove useful to intelligently perform virtual screening for drug discovery.

P267. Exaggerated pharmacological effect of ZYJK1, a novel janus kinases (JAKS) inhibitor, in wistar Rats

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Janus Kinases (JAKS) are non-receptor tyrosine kinases that are crucial components of diverse signal transduction pathways which govern cellular proliferation and apoptosis. JAK inhibitors act by inhibiting one or more of the JAKS family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby interfering with the JAK-STAT signaling pathway and have therapeutic application in the treatment of cancer and inflammatory diseases. ZYJK1 is a novel Janus Kinase inhibitor with selectivity for subtypes JAK1 and JAK2, developed by Cadila Healthcare Ltd. ZYJK1 exhibited promising

efficacy in preclinical models of inflammation and hence, it was further studied to explore its safety profile in Wistar rats. The ZYJK1 was administered at 0 (Vehicle control), 75 (low), 150 (mid) and 300 (high) mg/kg/day via oral gavage for 14 days in the both sexes (5/sex/dose). ZYJK1 treatment exhibited mortality in female rats (4/5) at 300 mg/kg during the second week of treatment. Transient salivation was observed post treatment at all dose levels. The clinical pathology investigation revealed lower total leucocytes, lymphocytes, eosinophils and basophils counts in males at all dose levels and lower eosinophils and basophils in females up to 150 mg/kg. Lower weights of spleen and thymus in both the sexes were correlated with lymphoid depletion noticed during histopathological examination. Similarly, lymphoid depletion in lymph nodes and hypocellularity of bone marrow was correlated with the lowered total and differentiated leucocyte counts. Based on the mechanism of action of this class of drug, the observed hematological and histopathological adverse effect are suggestive of exaggerated pharmacological effect of ZYJK1. However, further Tier-II immunotoxicity assay is warranted to assess risk-benefit ratio of ZYJK1 of humans.

P268. Cerium oxide nanoparticlesmediated protection of mammalian cells against organophosphate pesticide toxicity

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Acute poisoning with agricultural pesticideshas been a global health problem since several years. Among the pesticides, organophosphates, such as dichlorovos (DDVP), methyl parathion, chlorpyrifos are the most commonly used pesticidesthat cause serious health issues, particularly neurodegenerative diseases.The general mechanism of pesticide mediated toxicity is enhanced lipid peroxidation, reduced glutathione levels and concomitant increase in oxidative stress. Cerium oxide nanoparticles (CeNPs) are known to exhibit unique antioxidant properties which have been attributed to various biomedical applications. This redox active nanomaterial show excellent superoxide dismutaseand catalase mimetic activity due to its interconversion of Ce^{+3} to Ce^{+4} on its surface 'Ce' atoms. In the present study, we have explored the ability of CeNPs for scavenging free radicals from mammalian cell line (WRL-68)exposed to DDVP. By MTT assay, it was found that cells exposed to DDVP (100µM, 200µM) showed decrease in cell viability to 76% and 58%, whereas cells pre-exposed to CeNPs showed improved cell viability to 85% and 66%. Further, DCFDA assay results show that exposure of DDVP (100µM, 200µM) to cells lead to increase in free radicals (167%,211%), however, cells pre-exposed to CeNPs showed significant decrease in free radical level (151 %,166 %) with respect to control (100%). These observations suggest that the likely mechanism of protection of cells by CeNPs is by scavenging of free radicals. The physical interaction of DDVP and CeNPs experiments showed that CeNPs do not interact with DDVP suggestingthat in CeNPs treated cells, the protective effect is due to free radical scavengingby CeNPs and not by the physical interaction between DDVP and CeNPs.

P269. Synthesis of therapeutic homopolypeptides by novel deprotection combination

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Homo polypeptides find their applications in several fields of medicine, but their synthesis by solid phase peptide synthesis (SPPS) has been a continuing challenge. Homo polypeptide regions which are a resultant of uncontrolled genetic expansions have been shown to be responsible for the development of devastating human diseases. For example, expanded poly-Gln and poly-Ala tracts are linked with neurological disorders such as Huntington disease and Oculopharyngeal Muscular Dystrophy (OPMD), respectively. The self-assembly of these peptide repeats is a key determinant of corresponding protein aggregation and hence can be used to develop potent aggregation inhibitors. Despite their significance, these homo polypeptides as aggregation inhibitors are a relatively unexplored area as they are considered as a difficult sequence to be synthesized by conventional SPPS. This can be attributed to the fact that the yield of the final peptide is contaminated with the truncated sequences which co-elute with the final product. Considering the wide therapeutic value, we tested a novel combination of two deprotection agents and we found that 5 % Piperazine and 2% DBU in combination can be an effective reagent for a successful deprotection reaction. We used polyalanine, polyglutamine and polyarginine as a model sequences to demonstrate the efficiency of the piperazine/DBU solution. Our results show that piperazine /DBU combination drastically increased the yield and purity of polyalanine peptides by ~20% when compared to traditionally used piperidine. This indicated that piperazine /DBU can replace piperidine as a safer and more cost efficient deprotection reagent.

P270. Carbon nano-tubes (CNTs) supported metal catalyzed organic reactions

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The present research describes about Carbon nano-tube (CNTs) supported metal catalyzed organic reactions as novel heterogeneous catalyst system. Among the various allotropes of carbon, the choice of CNTs as support was motivated by their chemical, thermal and mechanical stability, chemical inertness (towards catalyzed organic transformation), high surface area. In addition, CNTs are electronically active and can contribute to the stabilization of transient higher oxidation states of metals. The gold-nanotube assembly (AuCNTs) is used for synthesis of a series of substituted N-formylated compounds at atmospheric conditions although reported classical research requires controlled O_2 environment and heating. Excellent chemselectivity was observed for formylation of primary amino group in the presence of phenolic OH and diaryl amino groups. Also, AuCNTs system is studied for oxidation of various substrates like phenols, hydroquinones, catechols, hydroxylamines and obtanied excellent yield from 81-95%. Similarly, PdCNTs were shown to be active for Suzuki coupling of aryl halides and RhCNTs in the dehydrogenation of N-heterocycles at room temperature without special environment and energy. Interestingly the RuCNTs system showed complete selectivity towards reduction of nitro group and converts into corresponding anilines or N-aryl hydroxylamines depending on the solvent system. On the basis several substituted anilines and N-aryl hydroxylamines derivatives were synthesized with good yield (95-99%). Low catalyst loading, high selectivity, mild conditions, stability and recyclability of the catalyst are some of the salient features of CNTs-metal catalyzed reactions. Although CNTs metal catalyzed reactions are not so popular but its exploration gives new dimensions to the science.

P271. Structural aspects of TSC1/2 complex, a molecular switch controlling various cell signaling pathways

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mTOR pathway is one of the most important and well-studied signaling cascades with respect to cancer. The major controllers of mTOR are the tumor suppressors Hamartin (TSC1) and Tuberin (TSC2), which lies in the heart of this cellular signaling pathway. Mutation in any of these genes will render them unsuccessful to have tuberin's GTPase activity towards Rheb, a small G-protein, which eventually keeps the mTOR activated. Such mutations lead to tuberous sclerosis complex, a multi-organ disease characterized by non-cancerous tumors in brain, skin, liver, kidney, lungs and heart. Also, it puts an individual at a higher risk for developing cancer in these organs. Several inhibitors have been designed for mTOR, while the actual source of the problem (TSC1 & TSC2) is left unchecked. The main reason for this is the lack of structure for both TSC1 and TSC2. Several studies have been made with Tsc mutated cohorts and the researchers have tried to analyze the etiology of the disease biochemically. Yet, deciphering the structure of this tumor suppressor complex would not only satiate the search for answers in mTOR pathway, but also throw limelight on plethora of protein-protein interactions in several other significant pathways.

P272. Neuroprotective effects of *Bergenia ciliata* extracts and bergenin against NMDA induced toxicity in SH-SY5Y cells: An in-vitro Analysis

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Bergenia ciliata (Haw.) Sternb. Also known as Pashanbheda is a plant belonging to family Saxifragaceae. The plant extracts find wide application in treatment of various urinary and kidney disorders as well as are claimed to possess potent antioxidant, antiinflammatory, immunomodulatory, antibacterial and anticancer activities. The plant is has also been used by Nepalese folk to alleviate symptoms related to Parkinson's disease. Bergenin, gallic acid, tannic acid etc. are out of the few major bioactives reported in the rhizomes to exhibit many pharmacological activities including neuroprotective action via BACE-1 inhibition, prevention of neuronal cell death, etc. Accordingly, the present study deals with investigation of neuroprotective effects of methanolic and aqueous plant extracts as well as bergenin isolated from them on SH-SY5Y human neuroblastoma cell line. MTT and Alamar blue assay using SH-SY5Y cell lines revealed that bergenin (upto 50 µM) as well as both the extracts (upto 50 µg/mL) did

not exhibit any toxicity on the SH-SY-5Y cell line and hence can be considered as safe. Bergenin as well as both the extracts were capable of significantly preventing SH-SY5Y cells from NMDA induced toxicity in a dose dependant manner and the results were comparable to those of donepezil and memantine as standards. Based on the results of in vitro analysis, it was found that extracts of B. ciliata as well as bergenin are promising candidates to be taken further for in vivo studies for evaluating their role in management of neurodegenerative disorders.

P273. Drug registration procedure in Kenya

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Drug registration in rest of the world is a challenging task as they are not harmonized in drug regulation. Drug registration in Kenya started in 1982; the process mainly involves an evaluation committee at the Kenya Pharmacy and Poisons Board (PPB). PPB is recognized as a department of the Ministry of Health (MoH). The PPB has adopted a new format for drug registration, called the 'Common Technical Document (CTD)', which is recognized internationally, by the WHO. This format for presentation of technical documentation will significantly reduce the time and resources needed for registration of pharmaceuticals and will ease the preparation of electronic dossier submissions. The committee reviews documents and product samples based on quality, safety and efficacy. The present work focuses on detailed requirements of drug registration process for gaining marketing authorization in Kenya in terms of technical data requirement for the dossier submission.

P274. Prenatal screening for rare co-inheritance of HbE and ß-Thalassemia traits in western India: A case report

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Co-inheritance of HbE with ß-thalassemia is rare in Western India. Case study: A family form Rajasthan had a proband having HbE / ß-thalassemia a co-inherited compound heterozygosity as revealed by DNA sequencing. It contained upper levels of HbE with altered haemoglobin (HbA) and red cell indices requiring blood transfusion periodically. The parents and CVS were HbE and thalassemia traits only. Massage: We suggest such families seek genetic screening before they adopt other reproductive choices for better management.

P275. A rare co-inheritance of Hb-D/ ß-thalassemia in two cases of a Rajasthani family: clinical relevance

Nidhi D Shah[1], Parth S Shah[1], Hari Shankar P Ray[1], Nikunj B Khatri[1], Ketan K Vaghasia[1], Sandip C Shah[1], Mandava V Rao[1,2]

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We report a rare case of compound heterozygous case of Hb-D-ß-thalassemia (Hb-D/ß+) in a Rajasthani family after analyzing blood, four samples (3 blood + CVS) using DNA sequencing and Hb electrophoresis including phenotypic indices. This condition is rare and identified in Rajasthan only with Hb-D/ß disease in two cases ie. father and CVS, though Hb-D Punjab traits are known. Hence, it is recommended that this condition may require blood transfusion on suggestion of clinician and phenotypic characters. Further six month old daughter suffered with ß0/ß0 mutations of homozygocity with blood transfusion too. There for it is rare and novel and is suggested to have prenatal screening for better management of families and to discourage marriages possessing such carriers in the society.

P276. Etiology of BOH patients in relation to genetic and biochemical indices in Gujarati population

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Pregnancy loss is an aggravating and devastating experience for the mother and clinicians. Anatomical defects of the reproductive system could be a cause of bad obstetric history (BOH). Approximately 12-15% of women with recurrent abortion have uterine malformation. The polycystic ovaries, septate uterus, Mullerian anomalies, etc are the anatomical abnormalities linked with recurrent early spontaneous abortions. In the present study, the blood samples from the women confirmed as BOH (28) were collected after duly filled consent forms. Age groups included in this study were 20-30 years (13), 31-40 years (11) and 41-50 years (4). Levels of various hormones viz., follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone and testosterone were evaluated by Chemiluminescence technique using Architect instrument and correlated with age. Molecular study of NR5A1 (nuclear receptor subfamily 5, group A, member 1), PON1 (paraoxonase 1) and ENPP1 (ectonucleotide pyrophosphatase 1) genes was done by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism method for their mutational and single nucleotide polymorphism (SNPs) analysis respectively. Other factors such as age, age at marriage, information of menstrual cycle, miscarriages, weight, height and medical history of family were also recorded. In this study, the patients belong to all the three age groups exhibited alterations in hormones analyzed. We also detected PON1 and ENPP1 polymorphisms in cases (2 and 3) respectively and an exon deletion in NR5A1 gene in one patient, which may be related to etiology of BOH condition. In conclusion, the study manifests numerous factors mentioned above are responsible to understand the etiology of this condition for proper management.

P277. Compound Heterozygosity of ß-Thalassemia Traits of HBB Gene in a Family: A Case Report

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We report in a Gujarati family in Western India consisting of rare co-inheritance of ß-Thalassemia (ß0/ß+) in a proband, son using trio samples parents and son of blood using gene sequence analysis, electrophoretic pattern of Hb levels and blood indices. The proband showed altered levels of Hb types with higher levels of HbF (90%) and low values of MCV and MCH supporting ß-thalassemia major. This case also possessed a compound heretozygotic condition c.92+5 G>C and c.47 G>A (ß0/ß+). Based on these, the proband was suggested blood transfusion by the clinician. Hence, it is suggested the family must undergo prenatal diagnosis for the next pregnancy to have better management.

P278. Karyotypic Analysis Of Chromosomal Polymorphism In Relation To Reproductive Failure

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This study was undertaken to elucidate the role of heteromorphism in causation of reproductive anomalies like infertility. In our study, cytogenetic analysis of 830 suspected referral cases of both sexes were assessed using standard karyotypic technique with Giemsa staining from their blood samples. We identified heteromorphism of D/G groups and non-acrocentric chromosomes following WHO nomenclature. Our data revealed that most of our heteromorphic cases (38;4.58%) were related to p arm satellites (ps^+) of the chromosomes and are related to infertility and abortion. No significant gender variation was noticed in this study. We hence, suggest that heteromorphism is associated with a loss of reproductive function, as heterochromatin may contain genes that regulate cellular roles in reproduction. Further, it becomes important that such cases are considered for molecular studies, genetic counseling and prenatal/pre-implantation screening.

P279. Screening of 30 families for β-thalassemia traits in our referral cases

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The ß thalassemia is one of the blood born-genetic disorders, affecting about 60,000 children in Indian families annually. We report a number of thirty referral families which were analyzed for their mutations of ß- thalassemia , as these traits are also to cause numerous combination of β- gene mutations in their probands. In our study, out of 8 common mutations, seven were detected in our referral cases, where maximum was the c.92+5 G>C (49%) and 619bp deletion (14%) followed by c.79 G>A (11%) and c.27_28insG (9%) and others in all cases. Family siblings contained an incidence of 46% against parents (60%) with homo- and heterozygosity condition which may need transfusions depending on variants and clinician reports. This study thus, helps finding out of the affected families having co-inherited mutations like HbE/β- thalassemia, HbD/β-thalassemia, β0/β+ thalassemia and such families are considered for prenatal screening before adoption of reproductive technologies.

P280. Mutation Analysis of ß-thalassemia in East-Westen Indian Population: A Recent Molecular Approach

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The β-thalassemia is the most prevalent genetic disorder in India. Its traits and co inheritance vary from mild to severe conditions resulting in thalassemia minor, intermediate and major depending upon many factors. The objective of this report was to identify the incidence of β-thalassemia traits, their coinheritance and mutations as well as to support the affected cases in East-Western Indian population for better management. Seventy five referral cases for β-thalassemia were analyzed for various β-thalassemia traits, heterozygosity and homozygosity conditions. Blood phenotypic parameters using cell counter and capillary electrophoresis were done. Analysis of common 8 mutations of thalassemia in India was assessed using ARMS PCR, end point PCR and DNA sequencing methods. Out of these referral cases from East-Western Indian region, 68 were detected positive of β-thalassemia (90.67%). Maximum cases were of β-thalassemia minor (49; 65.33%) followed by HbE traits (6; 8.0%) and β-thalassemia major including heterozygous and homozygous types and then others. Mutation analysis also revealed that the highest mutation was c.92+5G>C (41; 60.29%) followed by 619bp deletion (9; 13.23%) and c.79G>A (8; 11.76%) in our study group. Five cases exhibited co-inheritance with β-thalassemia minor affecting Rajasthan and Gujarati population in our study of western region of India. Hence, we strongly recommend these populations for genetic screening before adopting reproductive technologies and inter racial marital relations.

P281. Outbreak of Chikungunya in Ahmedabad: A report from our centre, 2016

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Chikungunya (CHIK) fever is caused by C. virus and we analyzed 314 referral cases in post-monsoon of 2016 at our Supratech Micropath Laboratory and Research Institute. The temperature during this season ranges from 20 – 35°C and is favorable for mosquito breed. The patients were asked to fill consent forms after which blood samples were taken to detect seropositivity of the virus by Real Time – PCR. It was first confirmed by preliminary symptoms like sudden onset of fever, headache, severe muscle pain, nausea, fatigue and rashes as per clinician reports. The RT – PCR reports showed 68% (214) positivity of chikungunya virus. Additionally, these cases were correlated with low lymphocyte counts and altered Asparate Aminotransferase (AST) in the serum. This fever was more in all age groups being highest in 40 – 50 years during post-monsoon season viz October and November, of this academic year. Hence, it is

suggestive that this season is a period for such diseases and hygienic conditions like mosquito eradication, clean environment and other conditions are to be controlled. The significance of this data is discussed.

P282. Cytogenetic analysis of Down syndrome: A report from India

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Down Syndrome (DS) is the commonest autosomal disorder, trisomy 21 in children. It is identified by mental retardation and facial symptoms clinically. This study was conducted on 830 referral cases in our Institute of Ahmedabad Gujarat (India) and compared the epidemiology of this disease with World data available. Karyotype of blood culture of each case was analyzed using Carl Zeiss MetaSystems following WHO manual. A numbers of 82 cases were detected positive of Down syndrome (9.9%). Amongst, regular/classical free T21 (92.6%) was higher followed translocation (6.0%) and mosaics (1.2%). Maternal age and age independent factors are important for causing this disorder. Males are more affected due to male predominance. Further world survey of frequencies of it indicated regular free 21 are the highest amongst the other types. We hence concluded that identification of this genetic disorder helps an occurrence of mode of its type. Further, its identity assists genetic screening to suffered families for proper management.

P283. Syntheis and evaluation of pyrrolo[2,3-d]pyrimidines as anti tubercular agents

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A simple and efficient approach towards synthesis of new pyrrolo[2,3-d]pyrimidines has been developed under conventional heating and microwave irradiation. A series of new 2-aminopyrrole-3-carbonitriles were synthesized from the reaction of benzoin, primary aromatic amines and malononitrile, from which a number of pyrrolo[2,3-d]pyrimidines were synthesized. The structures of the newly synthesized compounds were established on the basis of elemental and spectral (IR, 1H NMR and Mass) studies. Some of the prepared compounds 7-(4-methoxyphenyl)-5,6-diphenyl-7H-pyrrolo [2,3-d]pyrimidin-4(3H)-ones, 7-(3-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-thione and N-(7-(2-methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d] pyrimidine)N-aryl amines showed potent antitubercular activity.

P284. Regulatory issues in medical device development

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Understanding of medical device regulation is now an important requirement for doctors and healthcare professionals alike. The current medical device regulation in Europe, outlining the current requirements for CE regulation. The EU is making major changes to the Medical Device Directive which is its regulatory scheme for devices. International Standards are being revised and updated, such as the IEC 60601 family, causing additional pressures on the industry. Outside of the European Union, the regulatory processes across different countries and the lack of harmonization with leads to wide variation in pre-market data requirements. Whilst in USA, new drugs require at least randomized controlled trials to gain regulatory approval, for medical devices even under the more stringent PMA approval process; only one controlled trial (not necessarily randomized trial) is required. The 510(k) pathway did not require clinical trials; the manufacturer was only required to demonstrate a device was 'substantially equivalent' to another device already on the market. However, an even more worrying issue with device regulation in both the EU and US is the use of 'substantially equivalent' in evidence submissions for regulatory purposes. Also in India, CDSCO regulates the medical device and its authorization. In general, the key thing is that small firm face lots of difficulty compared to larger firm in bringing medical device in market. Thus it requires to understand the regulatory issues in various countries for ease of innovation and marketing authorization of medical devices.

P285. Impact of quality assurance on product lifecycle

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Quality assurance (QA) is embedded throughout, interwoven within the framework of protocols, policies, procedures and audits. The role of QA in the current regulatory scenario is ever increasing and encompasses the activities performed by different departments in an organization. QA ensures that all changes impacting the product and the established systems at a manufacturing facility are documented and reviewed to analyze the impact. Quality and risk management continues to be a challenge creating significant business impact when deficiencies are identified during regulatory audits. An effective Quality Assurance is required to integrate and manage the quality beginning from product development to commercialization. Pharmaceutical products manufactured by licensed firms and reported to have quality defects of serious nature to affect the product safety and efficacy of the drug products. There is need to establish the linkage between GMP and GDP, thereby facilitating the devotion and personal attention to any given matter that ensures the pharmaceutical product with good quality standards. Each manufacturer should evaluate whether it has gained sufficient understanding about product life cycle to provide a high degree of assurance in its manufacturing process to justify distribution of the product. The product Lifecycle approach provides the capability to both manage and centralize product information, helping pharmaceutical companies by addressing some of the most essential needs, including fast-moving market, lowering overall operating and production costs and appreciating quality standards such as Quality by Design.

P286. Meta-analysis of liver transplantation in end stage liver disease patients

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Liver transplantation is now one of the significant health issue it is said to most common for causes like access alcohol consumption, hepatitis B and C, ascites, infection in liver. It is growing health problem worldwide with chronic as well as acute complication. That negatively influence quality and survival of the individual. Scientific studies show that strong potential liver transplantation for prevention of complication and reduce the risk of transplantation. The access risk of transplantation 50 to 60% for excessive alcoholism and hepatocellular carcinoma and liver cirrhosis several anti- rejection or immunosuppression therapy is used after liver transplantation and prevent the infection. This met analysis summarize all the complication treatment and management of liver transplantation and the ratio of survival rate and success rate. This met analysis perform by data extraction and search strategy including exclusion criteria and quality of studies, over all patient list, reoccurrence of disease and assessment of risk factor. The survival rate in liver transplantation in children is higher because of the biliary atresia than in adults. The patient will survive after liver transplantation procedure in one year or in five years. If patient is suffering from the liver problems dietary modification or the life style modification can lead to decrease the risk of the further problems related to liver diseases and that also increase the survival rate.

P287. Licarin B, a novel insulin sensitizer from *Myristica fragrans* acts via PPARγ and GLUT4 in the IRS-1/PI3K/AKT pathway in 3T3-L1 adipocytes

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There are high demands for safe and affordable insulin sensitizers from natural resources. The objective of the study is to characterize the cellular effect of Licarin B (LB), a neolignan from Myristica fragrans on the PPARγ and insulin signaling pathways in 3T3-L1 preadipocytes. The mechanism of action of LB on PPARγ and insulin signaling pathways were studied using in vitro and in silico methods. Functional activation of PPARγ in vitro was confirmed by 3T3-L1 preadipocyte differentiation, regulation of target genes and protein expression. LB caused triglyceride accumulation during adipogenesis but

significantly less compared to rosiglitazone (RG), a PPARγ full agonist. In in vitro time-resolved fluorescence resonance energy transfer-based competitive binding assay, LB showed an IC_{50} value of 2.4 μM whereas for RG and GW9662 it was 57.96 nM and 18.68 nM respectively. Virtual screening of LB with PPARγ showed hydrophobic interactions with a binding energy of –9.36 kcal mol^{-1}. Interestingly enough LB improved insulin sensitivity by up regulating the GLUT4 expression and translocation via IRS-1/PI3K/AKT pathway, enhanced adiponectin secretion and modulated mRNA expression profile of PPARγ target genes C/EBPα, IRS-2, and LPL significantly compared to RG. Overall results reveal LB is promising bioactive for insulin resistance and associated complications through its partial PPARγ activity and can be taken forward for development of insulin sensitizer.

P288. Review on rational molecular targets for cancer therapy

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Cancer chemotherapy has been one of the major medical advances in the last few decades. However, the drugs used for this therapy have a narrow therapeutic index, and often the responses produced are side effect and toxicity and long time treatment as well as suffer from drug resistance to specific genes. While, target specific therapy that has been introduced in recent years is directed selectively against cancer-specific protein molecule and their enzymes and signaling pathways and thus has more limited specific toxicities and that can also be filter off with some combination therapy. Tyrosine kinases are an especially important target because they play an important role in the modulation of growth factor signaling. This review focuses on different types of molecular target and their novelty with respect to existing chemotherapy and radiotherapy. The covered targets in the discussion are VEGFR, EGFR, MET, RAF, PIM kinase, Isomerase P1N1, MSP-RON. All above signaling pathways are involved in the growth and regulation of cells and blood vessels in the body and few are apoptosis inducer. Inhibition and modulation of these pathways promotes apoptosis and control proliferation of cancer cells and blood vessels. This review also focuses on Few Molecular targeted pathways acts on multiple site and they may produce several undesirable blockage of essential pathway of body like healing process, so understanding of all complex pathway which are interlinked somewhere is also essential before designing any molecules.

P289. Design and synthesis of N-Substituted-5H-[1,2,4]triazino[5,6-b]indol-3-amine derivatives as anti-alzheimer's agents

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Alzheimer's disease (AD) is an overwhelming neurodegenerative disorder characterized by a progressive and irreversible decline in cognitive functions. AD is fatal, and at present, there is no cure for it. Presently, majority of the therapeutic treatments for AD are aimed to inhibit acetylcholinesterase (AChE) to enhance acetylcholine (ACh) levels in brain. AChE inhibitors like tacrine, donepezil, rivastigmine and NMDA receptor antagonists like memantine are currently available for AD treatment. Tamboli et al. reported the novel triazine derivatives having good dual cholinesterase inhibitory activity and anti-oxidant activity. Another work from our laboratory, Kahned et al. also reported N-substituted triazinoindol-3-thiol derivatives with good dual cholinesterase activity. These two scaffolds were combined as N-substituted triazino indol-3-amine and evaluated for its dual cholinesterase inhibitory activity. All the synthesized compounds were screened for their inhibitory activity on the enzymes AChE and BuChE by Ellman's method (in vitro technique). Among the reported compounds, compound (6i) and compound (6j) have shown IC50 values of 6.16 μM and 6.61 μM for AChE respectively and IC50 values of 20.53 μM and 9.14 μM for BuChE respectively. These compounds contain tertiary amine groups like piperidine in compound (6i) and morpholine in compound (6j) linked to triazinoindole scaffold with aliphatic chain as linker. Interaction of compounds with the active site of enzyme was studied by docking. Thus, the N-substituted-5H-[1,2,4]triazino[5,6-b]indol-3-amine with tertiary amine like piperidine and morpholine, if suitably linked then there would chances that these compounds will show good dual cholinesterase activity and might be helpful for treatment of neurodegenerative disease.

P290. Insilco interaction prediction: An approach to define crosstalk between essential bimolecular interactions in CNS perspective

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Cells coordinate their biological function through secondary massager signals followed by several chemical, and electrical responses. These signals propagated on molecular level may not the result of single receptor activity but several receptor signals may associated with one single downstream spiking signal. These receptors associated collective interactions and the resulting response signal can be explained by prediction of cross –talk between such communicating receptor in direct or indirect manner. Here we report crosstalk, direct/ indirect interaction of CDK5 with other secondary massager pathway by several computational and online database associated interaction tools. By the use of String 10, Signalink 2.0, Pathway linker, KEGG pathway, EVEX database, Interologous interaction database, wiki pathway, ICR workspace, Ensamble and Expression atlas we have demonstrated a number of protein-protein interactions and identified possible cross talk between their signals. From RCSB Protein databank initially two proteins with PDB ID 1H4L and 4P91 for CDK5-P25 and Nogo1-R respectively were selected. By use of 3D molecular viewer/ Discovery studio 4.5. P-25 chains (C and D) were removed. Ligands and water molecules associated with 1H4L were removed. Similarly with 4P91; water molecules and ligands were isolated. From online available tool Cluspro (cluspro.bu.edu) by taking CDK5 as receptor and NogoR1 as its substrate; balanced, electrostatic favoured, hydrophobic-favoured, VdW+Elec interactions were detected. From all these interactions 10 balanced interactions are depicted here. Interactions between amino acid of two proteins were identified in Gold suit software.

P291. Synthesis and characterization of a series of pyrimidine derivatives with their antimicrobial potency

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In an effort to find a new pharmacologically active molecule we report here Synthesis and antimicrobial activity of a series of 4-(substitutedphenyl)-1,2,3,4-tetrahydro-2-imino-6-isopropyl-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4a-h) was achieved from different Aldehydes, N-(pyridin-3-yl)-3-oxo-butanamide and guanidine using catalytical amount of concentrated hydrochloric acid in ethanol/methanol & the product obtained was isolated and recrystallized from ethanol. The structures of the products were supported by FTIR, 1H NMR and mass spectral data.

P292. Stability indicating HPLC method for fix dose combination of tamsulosin and tolterodine tartrate

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Stability-indicating assay method (SIAM) with degradation mechanisms is necessary to study stability behavior of drug substances and drug products. Tamsulosin hydrochloride & Tolterodine tartrate combination is newly approved for the treatment of Benign Prostatic Hyperplasia (BPH). Chromatographic methods including HPTLC, LC-MS-MS, and HPLC methods including bio-analytical have been reported for estimation of Tolterodine and Tamsulosin either single or in combination have been reported. However, to our knowledge, stability indicating assay method (SIAM) for capsule formulation of Tamsulosin Hydrochloride & Tolterodine tartrate combination in commercial dosage forms, by HPLC has not been reported. So, the aim is to establish stability of Tamsulosin HCl & Tolterodine tatrate under stress conditions as per ICH like acid, alkali, thermal, oxidative & photolytic and to develop a validated stability-indicating HPLC assay method for fix dose combination of Tamsulosin HCl & Tolterodine tartrate.

P293. Innovation in mucoadhesive polymers for vaginal drug delivery

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Vagina has been explored as a possible route of drug administration for systemic drug delivery. It

has advantages such as large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs and self-insertion. The traditional commercial preparations such as creams, foams, gels, irrigations and tablets are known to reside in the vaginal cavity for relatively short period of time owing to the self-cleaning action of the vaginal tract and often requires multiple daily doses to ensure desired therapeutic effect. The vaginal route appears to be highly appropriate for mucoadhesive drug delivery systems in order to retain drugs for treating largely local conditions or for use in contraception. To prolong the residence time in the vaginal cavity, mucoadhesive polymers are explored. Mucoadhesive polymers adhere to the mucosa for longer period of time thus providing advantage in drug delivery. They are classified as natural, semi-synthetic and synthetic in nature. Most commonly used mucoadhesive polymers that are capable of forming hydrogels include natural polymers such as chitosan, pectin, tragacanth, carrageenan and sodium alginate, semi-synthetic such as cellulose derivatives and synthetic including polyacrylates, polycarbophil. Mucoadhesion is due to interpenetration of polymer chains into the mucus layer and subsequent polymer–mucin bonding. Polymers having high number of functional groups show promising mucoadhesion properties for example hydroxyl groups or unionized carboxylate groups. Molecular weight should be not be too high which restricts hydration and chain entanglement with mucin and not too low to give poor cohesion. Recently, modified polymers are synthesized to impart desired characteristics into the existing polymers.

P294. Adenoid cystic carcinoma of prostate : A rare case report

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Adenoid cystic carcinoma of the prostate is a rare variant of prostatic adenocarcinoma which is considered to have an indolent biological potential. However, outcome data are scant with only 1 Documented metastasis and death. We report a case of 49 year old male, who presented with urinary obstruction. Digital rectal examination and ultrasound revealed enlarged hard nodular prostate. His serum PSA level was 0.729 ng/ml. Histologically Adenoid cystic or cribriform pattern with prominent peri-neural invasion was seen on TURP chips and it was positive for c-KIT. After the diagnosis, Patient underwent radical prostatectomy. Patient was clinically stable during a limited follow up of one month.

P295. Diagnostic usefulness of ALK rearrangements in NSCLC patients by FISH Study: GCRI experience

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In non-small cell lung carcinoma (NSCLC),the most common ALK rearrangement is a fusion of ALK gene and echinoderm microtubule-associated protein-like 4 (EML4) genes, formed as a result of a small inversion within the short arm of chromosome 2, where the genes are located. EML4- ALK fusion protein serves as a therapeutic target for an ALK tyrosine kinase inhibitor, which has showed promising results when used in treating NSCLC patients carrying ALK rearrangement. In addition to EML4, other ALK fusion partners have also been reported in lung cancer. The identification of these rearrangements is important for guiding treatment decisions. so aim of study was to screen ALK gene fusions in NSCLCs and to compare the results detected by targeted resequencing with results detected by commonly used methods, including fluorescence in situ hybridization (FISH). FISH study was carried out using histopathologically proven NSCLC diagnosed patients Paraffin embedded tissue. Complete details on various clinicopathological variables, treatment and clinical status were collected at diagnosis. Total 72 patients were studied for FISH analysis using ALK break Apart probe. From these 72 patients 5 cases were observed as positive for ALK rearrangements and 67 cases observed as negative for ALK rearrangements. FISH signals with two yellow (red and green fusion) were considered as negative for ALK rearrangements and FISH signals with 1G1O1F considered as ALK rearrangements. ALK positive patients represent 7.1% of a population of selected NSCLC. ALK positive patients have different clinical features and a better outcome than EGFR WT and ALK negative patients.

P296. Evaluation of Her-2 neu gene by fluorescence in situ hybridization in breast cancer patients

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Over expression of human epidermal growth factor receptor-2 (HER-2/neu) oncogene in breast cancer patients is correlated with disease free survival (DFS) and overall survival (OS). The most commonly used methods for the detection of HER-2/neu status are immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). However, therse is a lot of controversy with regard to the best method. Aim present study was carried out to find out Her-2 neu expression in breast cancer patients. Comparison of fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) for the determination of HER2 status in breast cancer patients. Expression of Her-2 neu gene was carried out using Her-2 neu gene locus specific identifier probe using FISH technique. Histopathologically proven newly diagnosed breast cancer patients were included for FISH study by Her-2 neu gene. Paraffin embedded tissue will be used for FISH analysis. Total 156 patients were studied for Her-2 neu gene study expression. From these 156 patients, amplification of Her-2 neu gene was observed in 41 patients. Out of 41 patients 33 patients' IHC score was > greater than 2+ and 8 patients' IHC score was ≤ 2. The identification of HER-2/neu gene amplification status is important in making therapeutic decisions for patients with breast cancer. The current standard of practice is to test all patients with invasive breast cancer for HER-2/neu status at the time of initial diagnosis. Based on these results, we consider FISH to be the gold standardfor detecting HER-2/neu status in breast cancer.

P297. Molecular assessment of hypoxia and inflammatory markers in breast cancer

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Breast cancer is most frequently diagnosed cancer in women worldwide. Here, NFkB, HIF-1α, TGF- ß and TNF- α play an important role in cell growth and survival as well as apoptosis. The aim of the present study is to evaluate the NFkB, TGF-ß, HIF-1α and TNF α in the breast cancer patients. A total of 50 breast cancer patients were enrolled. Immunohistochemical on FFPE localization of NFkB, TGF-ß, HIF-1α and TNF-α were evaluated on FFPE tissue on ventana Benchmark. These markers were correlated with clinico-pathological parameter and DFS. Nuclear and nuclear +cytoplasmic expression of NFkB was noted in 78%, 66% of breast cancer patients respectively.Where ,Nuclear expression alone ,nuclear and cytoplasmic NFkB expression showed a higher incidence in patients with older age, post menopausal status and showed a decreasing with higher tumor size and disease stge. Further, higher nuclear expression of NFkB was noted in ER and PR positive tumors. Both expression reduced OS. Hence, cytoplasmic inform of NFkB also has a role in breast cancer 56% of breast cancer patients. Cytoplasmic expression of HIF-1α was noted in 94% breast cancer patients. which was seen higher in advance tumor which lead to reduce OS. Where TNF-α was noted in 50% of breast cancer patients. These markers were inter-correlated with each other. A significant positive correlation was noted between TGF-ß and TNF-α (r=0.332, p=0.22).While significant inverse correlation was noted between, and TNF-α (r= -0.291, p=0.040), NFkB cytoplasmic and TNF-α (r=-0.296, p=0.037). This study observed hypoxia, HIF-1α have a role in malignant transformation of breast cancer. Further, HIF-1α and TNF-α showed increasing aggressiveness with high grade tumor. NFkB and TGF-ß have a role in early stage breast cancer.

P298. Neuroendocrine carcinoma of urinary bladder : pathological aspect of a rare clinical entity

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Primary pure small cell carcinoma of urinary bladder is an extremely rare and highly aggressive tumor. It accounts for about 0.5-1% of all bladder tumors. A 57 years old male presented with complaints of intermittent hematuria. Computed tomography revealed a sessile mass of size 36´27 mm in urinary bladder. Transuretheral resection of tumor mass was performed and tissue fragments were sent to establish histologic type, degree of differentiation and invasion. The microscopic examination revealed poorly differentiated carcinoma with histomorphological features favoring small cell carcinoma (high grade neuroendocrine carcinoma) of bladder. The tumor infiltrated the full thickness of bladder wall. Immunohistochemistry was positive for markers synaptophysin, chromogranin and AE1 with MIB1 proliferative index of 80%-90% thus proving small cell carcinoma of bladder. Given the extremely aggressive nature and rarity of the disease a little is known about it so it becomes important to report such cases and define the best diagnostic and treatment approach.

P299. Drug resistance and metabolism of Ara-C in acute myeloid leukemia: *in-silico* & *in-vitro* approach

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Drug resistance and drug-related toxicities are the major obstacles in AML. Cytarabine (Ara-C) metabolizing enzymes Cytidine deaminase (CDA) and Deoxycytidine kinase (DCK) plays an important role in development of drug resistance in AML. Identification and use of novel chemical entity from natural source can be better target for cancer treatment with least toxicity. In-silico analysis was done against natural compounds library by YASARA. In-vitro analysis of shortlisted natural compounds was carried out by Combination index study. Validation study was carried out by COMET assay, CFU assay and Apoptosis assay. Gene expressions analysis of CDA and DCK were done by qRT-PCR. HPLC monitoring of cytidine and uridine was carried by HPLC. In-silico analysis of revealed Hesperidin and Silymarin as potent modulators of drug resistance related proteins. Synergism of natural compounds with cytarabine decreases its IC_{50} possibly due to modulation of drug efflux activity and hence, reduces toxicity. Relative quantification of CDA and DCK in different FLT3-ITD mutation and $CD34^{(+)}$ groups suggested response/resistance to treatment in AML. Circulating level of cytidine and uridine in patients undergoing chemotherapy reflect the cytarabine metabolism by leukemic cells which can ultimately predict the drug responsiveness during therapy. Study comes up with a unique combination of in-silico and in-vitro methods to validate the effect of phytochemical e.g. Hesperidin and Silymarin on leukemic stem cell. Therapeutic monitoring of cytidine and uridine in circulation can be used as treatment monitoring markers. Synergistic effect of natural compounds with chemotherapeutic drug may open up new avenues for multimodality approach to overcome resistance in AML.

P300. A novel bioactive from *Gracinia sp.* improves hepatic steatosis via up-regulation of PPAR α and AMPK activation

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The current obesity epidemics have resulted in a significant rise in its comorbidities prevalence. Liver is often significantly affected by obesity and hence, the non-alcoholic fatty liver disease (NAFLD) is regarded as the hepatic manifestation of metabolic syndrome, showing rising prevalence regardless of economic status or age worldwide. These disorders are tightly controlled by numerous regulatory systems involving specific transcription factors such as PPARα. The most important class of synthetic PPARα ligands/modulators is the fibrates. But due to the adverse effects of fibrates, recent research focuses on naturally occurring PPARα modulators. The present study was designed to investigate the effects of novel bioactive from Gracinia species in reducing lipid accumulation in oleic acid (OA) treated HepG2 cells. HepG2 cells were treated with OA or without CNC2 to observe lipid accumulation by estimating lipid content in medium. Also, we performed western blot analysis and real time PCR of fatty acid transporter (CD36), sterol regulatory element binding protein (SREBP)-1, fatty acid synthase (FAS), peroxisome proliferator activated receptor α (PPARα) and 5′ AMP-activated protein kinase (AMPK) protein. Our results shows that CNC2 reduce OA induced lipid accumulation. Furthermore, it regulates the expression levels of lipogenic enzymes, such as FAS and SREBPs, and the expression levels of PPARα, which are critical regulators of hepatic lipid metabolism through the AMPK signaling pathway. These results indicate that CNC2 has potential to acti¬vate PPARα & AMPK, thereby exert a regulatory effect on hepatic lipogenesis in hepatocytes. Therefore, CNC2 may be used as a therapeutic agent against fatty liver and lipid-related metabolic disorders.

P301. Optimization of stability indicating HPLC method for simultaneous estimation of Dexamethasone sodium phosphate and Gatiflixacin in ophthalmic formulation

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Parul institute of Pharmacy

Stability Indicating HPLC was developed and validated as per ICH guideline. In RP-HPLC, Chromatographic separation was achieved on Reversed-Phase ODS-BP Hyperchrome C18 column (250Ð4.6mm,5µm) in isocratic mode using 0.02M Phosphate buffer (pH-3.5 adjusted

using 1% Orthophosphoric acid) : Methanol (60:40) as the mobile phase at a flow rate 1.0 ml/min. In same chromatographic condition Force Degradation study was also done. Acid, Base, Oxidation, Thermal and Sunlight degradation study of both drugs were studied. Assay of marketed formulation was calculated using same method. In Stability RP-HPLC method, both drugs were separated by using given chromatographic condition. The DSP and GA were separated at 3.337 min and 5.707 min respectively. Linearity of DSP and GA was in the range of 5-15 µg/ml and 15-45 µg/ml, respectively. The % recoveries obtained for both drugs were 99.19 - 99.87 % (GA) and 98.78 -100.14 % (DSP), respectively. % RSD of result of all validation parameters was found < 2%.The detection limits for DSP and GA were 0.17 µg/ml and 0.66 µg/ml respectively, while Quantitation limits were 0.52 µg/ml and 1.99 µg/ml, respectively. Assay of marketed formulation was found 98-99%. In Force Degradation study revealed that Dexamethasone sodium phosphate was more degraded than Gatifloxacin. The amount of DSP and GA were separated from degradation peak without any interference. The proposed Stability Indicating HPLC method was sensitive, precise, accurate, stable and reproducible for analysis of DSP and GA in bulk and pharmaceutical formulation.

P302. Fabrication of self-assembled lipo-polymeric nanocarrier for enhanced delivery of chemotherapeutic molecules

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Cholesterol grafted copolymers can be used as an efficient nanocarrier to encapsulate hydrophobic drugs. The role of cholesterol is vital, as it is not only capable of influencing various cellular mechanisms but also facilitates self-assembly and impart micellar stability with improved encapsulation efficiency and solubility of hydrophobic molecules. Based on this objective; a novel methoxy Poly (ethylene glycol)-block-poly(carbonate-co-lactic acid)-graft-cholesterol conjugated copolymer was synthesized, characterized by 1H-NMR, GPC, FT-IR and DSC. The synthesized cholesterol grafted copolymer was efficient to encapsulate tamoxifen (TMX) to form self-assembled polymeric micelles. Primarily, a cyclic carbonate monomer, 2-methyl-2-benzyl oxy carbonyl-propylene carbonate (MBC) was synthesized and purified. Further, polymerization using mPEG along with MBC and DL-Lactide and Sn (Oct)2 as catalyst resulted in the formation of mPEG-P(MBC-co-LA). Catalytic hydrogenation using (Pd/Charcoal 10 %) yielded polymer containing carboxyl groups, with hydrophobic units of Lactic acid and PCC. Finally, cholesterol was coupled with synthesized polymeric block via ester coupling. Additionally, the formulation aspect involved a comparison between two techniques including film hydration and o/w emulsion solvent evaporation method. Optimization of the final formulation was based on selective parameters such as particle size, polydispersity index, hydration solvent and encapsulation efficiency. The {mPEG-b-(CB50-co-LA125)-cholesterol30} polymer was characterized by NMR Molecular weight 35,850 g/mol and Gel Permeation Chromatography. The particle size was found to be (>300nm) with an encapsulation efficiency (< 40%) by using film hydration method while a significant improvement in particle size (<160nm) and encapsulation efficiency (>77%) was achieved using solvent evaporation technique suggesting that cholesterol based polymers had successfully self-assembled to form micelles.In future, further studies are necessary to evaluate the potential and therapeutic efficiency of the optimized formulation.

P303. Synthesized cationic-polymeric nanocarrier mediated co-delivery of small molecule and oligonucleotides-based cancer therapeutics

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Aberrant gene expression can trigger various molecular events that not only result in carcinogenesis but also cause chemoresistance, metastasis and relapse. Gene-based therapies using siRNA/miRNA have been suggested as new treatment method to improve the current regimen ever they require used of novel carriers. The field of polymer design has evolved over the past decade and has resulted in the development of cationic amphiphilic copolymers with a wide variety of architectures and chemical properties. Cationic amphiphilic copolymers is an important class of carrier systems that are used as non-viral gene vectors. They are having various advantages as carriers like biodegradability, biocompatibility, amenable to chemical modifications and simplified formulation. Further, they could be suitably tailored to achieve

efficient miRNA/siRNA complexation as well as simultaneous delivery of small hydrophobic therapeutic molecules. In this work, we have synthesized amphiphilic cationic copolymer with mPEG as hydrophilic block while poly(carbonate-co-lactic acid) as hydrophobic block containing cationic chain that self-assembled with miRNA via electrostatic interactions to form micelleplexes. Further hydrophobic drugs such as docetaxel was loaded in hydrophobic core of micelleplexes. A cyclic carbonate monomer, 2-methyl-2-benzyl oxycarbonyl-propylene carbonate (MBC) was first synthesized and purified of the intermediate and its ring opening polymerization of MBC and lactide with mPEG as macroinitiator and Tin(II) 2-ethylhexanoate as catalyst gives mPEG-P(MBC-co-LA) copolymer with a favourable Lactic acid unit and MBC units. The protective benzyl groups from MBC were removed by catalytic hydrogenation (palladium on carbon) to obtain polymer containing carboxyl groups, mPEG-b-(CB-co-LA). Further, a cationic chain i.e. dimethyldipropylenetriamine was attached on carboxyl group by carbodimide-coupling chemistry and purified. The mPEG-b-(CB-{g-cation chain}-co-LA) polymer was characterized by Proton NMR and Gel Permeation Chromatography and Elemental analyser. Cationic polymer self-assembles to form micelles which showed a better particle size below 200 nm and a positive zeta potential indicating the ability of the polymer to complex with the negatively charged oligonucleotides with docetaxel at encapsulation efficiency of >75%. Agarose gel retardation assay showed that the synthesized cationic copolymer efficiently complexes with the miRNA at N/P ratio of 16:1. Together, these findings suggest that Cationic polymer based nanovector platform could be a potential candidate for systemic delivery of oligonucleotides to the tumor cells and can be a step forward in miRNA/siRNA-based cancer therapeutics.

P304. Development and validation of reverse-phase HPLC method for simultaneous determination of Lisofylline (LSF) and Pentoxifylline (PTX) in rat plasma and application to pharmacokinetics of LSF and PTX in rat

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Lisofylline (LSF) is an anti-inflammatory and immunomodulatory agent which proven activity in diabetes. It is active metabolite of another anti-inflammatory agent Pentoxifylline (PTX). Although a number of analytical method for quantification of LSF and PTX in plasma have been reported for pharmacokinetics and metabolic studies, each of these have significant disadvantages in terms of large sample volume, complex extraction procedure, use of highly sophisticated instruments like LC-MS. In this study, we developed and validated a method in rat plasma for simultaneous determination of LSF and PTX with the major objectives of ensuring minimum sample volume, ease of extraction, economic, sensitivity and avoiding use of any sophisticated instruments like LC-MS. LSF, PTX and 3-isobutyl 1-methyl xanthine (IBMX, internal standard) were separated on Intersil® ODS (C18) column (250 x 4.6 mm, 5µm) with mobile phase consisting of methanol: water (50:50 %v/v) run in isocratic mode at flow rate of 1 mL/min and detection wavelength selected as 273 nm. The retention time for LSF, PTX and IBMX were 6.50, 7.67 and 9.97 min respectively. A simple, single step extraction method using methylene chloride as extracting solvent was used for extracting the drugs from rat plasma (200 µL). The developed method was validated as per internationally accepted recommendations for bio-analytical method validation. The calibration curves were linear across the concentration range 50-5000 ng/mL with 10 ng/mL of LOD and 50 ng/mL of LLOQ for both analytes. Weighted linear regression was also performed on calibration data. The method was further used to analyze LSF and PTX after i.v. dose of 25 mg/kg in rat. A simple, sensitive, accurate and precise reverse-phase HPLC-PDA method was established for simultaneous determination of LSF and PTX in rat plasma.

P305. Microemulsion drug delivery system to address the bioavailability related issues of BCS CLASS–II drug

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Intranasal drug delivery is known to overcome the blood brain barrier for delivery of drugs to brain. The objective of this study was to prepare Microemulsion and Mucoadhesive microemulsion of the Antipsychotic drug and explore the possibility of brain targeting by nose-to-brain delivery. Microemulsion was prepared by water titration method and characterized

for drug content, particle size and size distribution, zeta potential, and in vitro drug-release study. To improve the solubility and enhance the brain uptake of the antipsychotic drug an o/w microemulsion was prepared and then converted in to gel form to increase the residence time of drug and to sustain the release of drug at targeted site of brain via nasal administration which give rapid absorption and higher bioavailability of drug, fast onset of therapeutic action, avoid of liver metabolism. The intrinsic solubility of drug is about 2.8µg/ml. The optimized microemulsion formulation consisted of Oleic acid, Tween 80:Isopropyl alcohol (3:1) and water. Characterization, with stability and nasal ciliotoxicity study of both the microemulsion and mucoadhesive microemulsion formulations were carried out. Microemulsion formulation which displayed optical transparency of 99.95%, globule size of 38.30 ± 1.09 nm, and polydispersity index of 0.129 ± 0.013 was selected for incorporation of mucoadhesive component. The drug-loaded mucoadhesive microemulsion that contains 0.5% wt/wt of polycarbophil displayed higher in vitro mucoadhesive potential (20.0 ± 3.0 min) and diffusion coefficient (0.3172 ± 0.03) than microemulsion. The residence time of drug in nasal cavity was increased and diffused in the nasal mucosal membrane in sustained manner.

P306. Synthesis and characterization of reducing agent stabilized gold nanoparticles for the delivery of methotrexate sodium

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Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells. Methotrexate sodium is Antineoplastic agent of Anti-metabolite class of chemotherapy drugs, which inhibits dihydrofolate reductase (DHFRase) and blocking the conversion of dihydro folic acid (DHFA) to tetrahydrofolic acid (THFA). Its dose is 3.3–30 mg/m2 daily based on type of cancer. About a third of an oral dose of methotrexate Sodium is metabolized by intestinal bacteria during absorption. Metal nanoparticles such as gold nanoparticles are having smaller size (~50 nm), more stable and relatively narrow size distribution which provide opportunities for effective active or passive targeted delivery. The gold nanoparticles were synthesized using chemical reduction method, involving the reduction of chloroauric acid by trisodium citrate and Methotrexate Sodium was loaded on to it. Physical observations and FTIR analysis showed that drug and excipients passes the drug-excipient compatibility study. The particle size, PDI, zeta potential, drug loading, drug content of optimized formulation were evaluated. The optimized formulation was found to be isotonic with blood. Stability study of the optimized formulation proved the integrity of the developed gold nanoparticles. The developed formulation was found to be stable. The present work reports a significant and a simple, process capable of synthesising size-controlled trisodium citrate stabilized gold nanoparticles rapidly under ambient conditions. The developed formulation holds promising future due to reduced particle size and has the potential for targeting the Methotrexate Sodium efficiently.

P307. Design, Synthesis and Biological Evaluation of Substituted Pyrimidine as Anti-Cancer Agents

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Cancer is one of the death causing disease all around the world. The anaplastic lymphoma kinase (ALK) is belonging to insulin receptor subfamily is one of the target for many type of cancers. The oncogenic activation of ALK was observed from very rare cancer to most prevalent non-small cell lung cancer (NSCLC) and ALK mutation were responsible for the disease state. More than two dozen of ALK fusion proteins were reported. This mutation had generated the failure in current therapy by the resistance mechanism. So, there is need for a potential candidate which can effectively acts on target as well as overcome the problem of resistance. In present study, CADD was done which includes 3D-QSAR, Pharmacophore and Virtual Screening. After using CADD tools leads were identified and further designing was done. Based on docking study top scoring molecules were synthesized and anti-cancer activity was performed on six molecules.

P308. Comparative Evaluation of Top-Down, Bottom-up and Combination Approaches on the Preparation of Olanzapine Nanosuspensionsion

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The emergence of various drug discovery technologies like combinatorial chemistry and high throughput screening techniques has led to a rapid increase in the number of poorly water soluble drugs. Nanonization can be universally applied as a solubility enhancement technique to counter the poor aqueous solubility issues of these drugs. The objective of this study is to prepare olanzapine (BCS Class II, solubility: 0.0942mg/ml, Log P:3.61) nanosuspension (NS) by using top-down, bottom-up, and combination approaches with different polymeric stabilizers for finding the technique that gives a most stable nanosuspensions with acceptable size and PDI. The nanosuspensions were characterized for size, PDI and zeta potential with different stabilizers and formulation techniques over a period of time for this purpose. Drug excipient interaction study was performed using DSC and hot stage microscopy before the selection of polymeric stabilizers. Nanosuspension prepared using the selected method and polymer was then optimized for various process parameters (rpm, solvent to antisolvent ratio etc.). The study also incorporates the effect of different stabilizer concentration on the stability of the NS under different stress condition.

P309. Production of islet-like insulin producing cell clusters in-vitrofrom mesenchymal stem cells

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Diabetes is a life-long disease characterized by hyperglycemia, polyphagia and increased fatigue. Type 1 diabetes Mellitus (T1D) is a chronic disease that involves the progressive destruction of pancreatic beta-cells, ultimately resulting in the loss of insulin production and secretion from the pancreas. The goal of clinical Intervention are to arrest the onset and delay the progression of autoimmunity, reverse beta-cell destruction and to restore glucose metabolism along with restoring of the immune homeostasis. The regenerative potential of stem cells can provide self-replenishing supply of glucose –responsive insulin –producing beta cells. In addition, the immune modulatory properties of the stem cells can be used to prevent autoimmunity. In present study, we used Mesenchymal stem cells (MSC's) and further differentiated them to pancreatic beta cells. These differentiated cells were characterized by different stage specific markers. Further in-vivo studies need to be done before their use in clinical application. Thus these differentiated cells may be a promising source of cells based therapy for Type1 diabetesWhich will help us to overcome the drawbacks of the conventional diabetes therapy.

P310. To decipher the serological immune profiles in dengue infection: an effort towards dengue vaccine candidate

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Dengue is an infection caused by Dengue virus (DENV) is a serious mosquito-borne pathogen causing significant global disease burden, either as classic dengue fever (DF) or in its most severe manifestation dengue hemorrhagic fever (DHF). Dengue virus (DENV) infects approximately 40 million people annuallyand in the absence of a vaccine or any specific drug for its treatment, an early diagnosis is considered indispensable to prevent any casualty. Humoral immune responses to DENV infection are observed to be complex andthe human antibodies that are potent and type specificneutralizing DENV represent a small fraction of the total DENV-specific antibodyresponse. Not much data is available on Gujarat Dengue isolates in a past decade. The current work is focused on elucidating the serological IgM and IgG profile of Dengue infections occurring in Gandhinagar and its neighboring areas.The study involves understanding how human antibodies neutralize or enhance DENV, by analyzing serologically using invitrotools ofimmunoassay so as to understand the adaptive immune response to the pathogens.Surface proteins of the virus are explored for their antigenic properties. The projects also intends to identify different antigenic epitopes using insilicobioinformatics tools in the form of antigenic peptides which if proven to be immunogenic can act as potential vaccine candidates. Moreover, it shall provide key information for formulation of efficient and safe novel vaccines.

P311. Stem cell derived retinal pigment epithelium cells: a new era for disease modeling and developing therapy of ocular degenerative diseases

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Retinal dystrophies (RD) are major causes of blindness affecting millions of people in the world. Retinitis pigmentosa (RP), age-related macular degeneration (AMD) and Stargardt disease (SD) are most common retinal degenerative diseases which are characterized by progressive dysfunction of photoreceptor (PR) and/or retinal pigment epithelium (RPE) cells. Gene and drug therapy are being explored as treatments for RP, GA, and SD, but they seem unlikely to be sight-restoring once PRs have perished. Cell-based therapies in the retina have been associated with the recovery of visual function in animal models of retinal degeneration. Replacement of photoreceptors and RPE is better option for restoring visual function in such a diseases. Stem cell derived RPE offers great promise to cell replacement therapy and several clinical trials are under way. The aim of this study is to differentiate mesenchymal stem cells into RPE using different chemical and biological factors for therapeutic applications. MSC derived RPE cells has been characterized by cell type specific marker expression in developing and terminally differentiated RPE by using Immunocytochemistry, RT-PCR and morphological changes. These findings may facilitate the development of stem cell based transplantation therapies for retinal diseases.

P312. In-vitro differentiation in to insulin producing cells: regenerative medicine for diabetes

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Diabetes is a chronic metabolic disorder that is associated with serious long term complications such as kidney diseases, neuropathy, cardiovascular diseases and blindness. Type I Diabetes Mellitus is caused due to the autoimmune destruction of pancreatic beta cells. Type II Diabetes Mellitus is caused by insulin resistance and later beta cells death by an apoptotic mechanism. The use of stem cells as regenerative medicine holds a great promise for the cure of this disease. The advantage of human induced pluoripotent stem cells has no ethical issues associated with it and has comparatively lesser immunogenicity. A non-integrative and non-viral alternative in the form of minicircle -DNA vector is discovered to obtain induced pluoripotentstem cells (ipsc). This minicircle -DNA vector induced pluoripotent stem cells can be differentiated into insulin producing cells. These differentiated insulin producing cells co-express PDX1 and C-peptide markers, suggesting that these cells possess the characteristics of mature pancreatic beta cells. This opens new avenues in cell based therapy for diabetes.

P313. Chitosan layered vesicular formulation for topical delivery in the eye

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Conjunctivitis (Pinkeye) refers to a complexity of eye characterized by an inflammation of conjunctiva following bacterial, viral, fungal as well as other agents. Ofloxacin (Fluoroquinolone anti-microbial agent) is a lipophilic drug with minimum water solubility (0.04 mg/ml). This investigation focus on development and optimization of chitosan coated niosomal formulation with reference to its entrapment efficiency, surface properties, in-vitro release kinetics, mucoadhesive properties, viscosity measurement, rheology and stability. In-vitro antimicrobial tasting was performed via zone of inhibition assay with the help of S. aureas as microbial strain indicator. In vivo irritation study and tear retention were also assessed in albino rabbits. Optimized formulation containing 0.4% w/v chitosan and span 60: cholesterol 2:1w/w showed the maximum entrapment efficiency (78.51±1.33%) with sustained release behavior (98.59±0.17% over 8 hr) and substantial mucoadhesive characteristic with no irritation, redness to conjunctiva, iris and cornea of albino rabbits. Antimicrobial activity of Ofloxacin niosome compared with its marketed formulation showed inhibition 34.34±0.52 mm and 22±1.0 mm, respectively against S.aureus. Chitosan encrusted niosomal formulation has potential application in retaining Ofloxacin in tear backed by its superior penetration for longer period of time in conjuctival segment of eye.

P314. Comparative study of post-approval changes registration in canada and europe

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The regulatory incompliance is one of the major issues of the Pharmaceutical industry, the product life cycle maintenance become critical to remain in the global market and generate revenue. The European medical agency (EMA) & Health Canada has clearly defined the regulatory framework for post approval changes which are known as variation filing in Europe and Post Notice of Compliance (NOC) Changes in Canada. The prior approvals are required to be taken for the implementation of any major changes, where in the minor changes are implemented and reported annually to the agency. The regulatory guidelines are ever-changing and hence interpreting those and implementing the same plays an important factor for getting on time approvals failing which can lead to the status of Non-Compliant and increased regulatory pressure, which will ultimately impact the business of the company. The present study focuses on identifying the current procedures and requirements in successful and compliant filing Post-approval changes in Europe and Canada and clearly classifying the changes and differences in filing of both the countries.

P315. Detoxification of poly (methyl methacrylate) vertebral bone cement by radical scavenging

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Poly (methyl methacrylate) polymer based bone cement is most commonly used augmentation material for joint arthroplasty, since its versatile properties. Despite, its strong applications, it has complex complications, particularly low fatigue resistance and toxicity. The present study is carried out to reduce the toxic effect without obstructing its polymerization thereby, mechanical properties. Selective natural antioxidant is identified through in silico studies, followed by the PMMA and antioxidant composite material is prepared. The identified antioxidants are active at body temperature. Scavenging of free radicals by natural anti-oxidant only at the body temperature whereas reaction temperature starts from 25°c and reaches up to 113°C. Therefore, the exothermic polymerization of the bone cement reaction is normal, which is confirmed through different assays such as DPPH assay, Superoxide assay, hydroxyl radical assay. Molecular weight determination and mechanical properties are quite similar to the pure bone cement. Hence, the bone cement toxicity (free radical) are significantly neutralized without obstructing of its physical and mechanical properties.

P316. Drug loaded gadolinium magnetic nanoparticles for hyperthermia and targeted chemotherapy

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Cancer is leading cause of the death these days since multifaceted diagnosis and therapy. Recent developments in on alternative methodologies give minimized side effects and improving treatment efficacy. Present study, super paramagnetic gadolinium nanoparticles has been utilized for diagnosis as well as therapy to treat cancer. Magnetic nanoparticle have been synthesized by co-precipitation method and loaded with anticancer drug for targeting delivery at tumor site. The nanoparticles have provided optimum hyperthermia effect for functional apoptosis with sustained drug delivery. Moreover, the nanoparticles are highly contrastive for MRI diagnosis. In vitro cell culture studies show the drug loaded nanoparticles have high synergetic impact on apoptosis as compare to the only hyperthermia and chemo. Therefore, the novel formulation with nanoparticles for cancer therapy may be better alternative to the conventional method for greater mortality.

P317. In silico screening of basellasaponins against various targets of diabetes mellitus

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Various extracts of Basella alba have been reported for its in vivo antidiabetic potential using animal models. The leaves and stem of the climber Basella alba contain a complex of saponin known as basellasaponins A, B, C, and D. In the present study an attempt has been made to use in silico techniques to understand and predict the drug likeliness of the identified phytoconstituents against the five different targets, dipeptidyl peptidase-4, protein tyrosine phosphatase 1B, sodium potassium ATPase, aldose reductase and glycogen synthase kinase-3Ð involved in diabetes using XP docking program of Glide, Schrödinger suit. Selected phytoconstituents showed favorable interactions with amino acid residues at the active sites which signify their potential as antidiabetic. This study will also help in identifying the plausible herd-drug interactions that may occur on simultaneous administration of this herb with synthetic antidiabetics like glimeperide, sitagliptin, repaglinide.

P318. Rational design, synthesis and computational validation of boronic acid derivatives in thwarting progression of cancer

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Fragment based drug design has led to successful synthesis of almost 30 marketed drugs till date. It is pertinent to mention that if each fragment of molecule is selected judiciously it may target the cancerous proteins effectively. In this context several molecules were studied and established pharmacophores chosen from well marketed anticancer drugs. Boronic acid derivatives in medicinal chemistry have marked impact reflected by many drugs that have hit the market like anticancer bortezomib, phenyl (2-(thiophen-2-yl)acetamido) methylboronicacid as ß-lactamase inhibitor, boronic acidketamide analogue as antiviral agent. Likewise, thiazoles as masterkeys, ester, amine, cinnamic acid have been judiciously assembled into molecule. Therationally designed ligands showed key interactions with several amino acids of M2-pyruvate kinase protein having definite role in cancer progression. In cancerous condition a dimeric form of M2PK over express and catalyzes conversion of phosphoenole pyruvate to pyruvate and terminate into lactate leadingto increasing up-take of glucose. The designed molecules provided excellent docking score in silico. Thereafter retro-synthetic strategies were designed and out of the three designed retro-routes, oneisgenerating leadmoleculesin ample yields. The designed molecules are currently being evaluated for their cytotoxicity.

P319. Effect of Herbal treatment in chronic disease induced Anemia

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There are many chronic diseases like, chronic liver disease, chronic kidney disease, cancer, etc., which are also characterized by anemia and decreases level of blood cells. In chronic liver disease like cirrhosis, there is an increase portal hypertension. This increase portal hypertension is responsible for various complications of cirrhosis including anemia. It leads to splenomegaly due to which there is an increase in blood cell sequestration. It causes decrease in blood cell count including platelets levels. Due to decrease in platelets, there will be increase in bleeding tendency. In cirrhosis, due to portal hypertension, gastropathy and increase bleeding tendency, chronic and severe blood loss from GIT can occur which is a major cause of anemia. In such patients, blood transfusion is the only solution for treatment of anemia when other oral supplements are ineffective at end stage liver disease. However, frequent blood transfusion can increase the chances for development of hepatic encephalopathy and other complications in the cirrhosis patients. Ayurveda, a tradition Indian system of medicine reports many plants as effective treatment for anemia. As an alternative, herbal treatment might be useful in such patients. We have performed retrospective study for evaluation of effect of herbal treatment in prevention and treatment of anemia in chronic liver disease patients. Total 60 cases were evaluation for the study. Patients were prescribed with the rasayana treatment. Laboratory reports were compiled and evaluated. We found improvement in the level of Hemoglobin content, RBC count, RBC indices, total and differential WBC, and platelet count in these patients in addition to improvement in other liver functions.

P320. Formulation Development and Evaluation of Floating Ring Capsule for Stomach Specific Drug Delivery

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Present investigation was aimed to develop a unique floating ring capsule dosage form of ciprofloxacin hydrochloride (CHL) which is well-known to have short elimination half-life and narrow absorption window. Formulated floating ring capsules were evaluated for its suitability for stomach specific drug delivery by employing different polymers such as Guar gum, Xanthan gum and Karaya gum. Formulations were assessed for interaction studies, in vitro buoyancy, weight uniformity, drug content, effect of polymer concentration on drug release and release kinetics. Experimental results demonstrated that natural polymers can be effectively exercised to formulate floating ring capsule dosage form for improved gastro retention and sustained drug release; which may be better and economic alternative for synthetic polymers due to their biocompatibility and degradability.

P321. Nose to brain targeting of nanostructure lipid carrier of quercetin for treatment of brain tumor

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Cancer is the most distressing and life threatening disease that enforces severe death worldwide. Brain tumour is the second leading cause of the cancer related deaths in children and young adults. Successful chemotherapy of cancer depends on the delivery of sufficient concentrations of an effective drug to tumour cells without causing intolerable toxicity to patient. Studies shows that direct delivery of the drug molecules from nose to brain is of vital impotence for the targeted delivery to CNS by bypassing BBB. Thus for the treatment of brain tumour the quercetin was targeted to CNS via nose to brain delivery. QUE-NLCs were formulated. Formulation was evaluated for various physicochemical properties such as particle size, zeta potential, drug loading, percent entrapment efficiency, Morphology study, in vitro drug release profile, histopathology analysis. In vitro cytotoxicity against astrocytoma–glioblastoma cell line (U373MG) and brain distribution study was evaluated. Formulated QUE –NLC also shows significant in vitro cytotoxicity against U373MG cell line. The results show that NLCs might be the promising approach for the intranasal delivery of the drug for the treatment of brain tumour.

P322. Diabetic neuropathy and memory loss

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Diabetes is a serious condition and may lead to neuropathy. The prevalence of painful diabetic neuropathy is increasing day by day and is progressively critical that needs the most ideal approach to diagnose and treat this condition. Ageing and diabetes are the major contributing factors, which will leads to memory loss. As memory loss progressively increase, it will lead to decrease in personal satisfaction and will put a pressure on both patients themselves and the families. Various factors play an important role in development of cognitive dysfunction like glucose metabolism abnormalities that are hyperglycemia and hypoglycemia, and Insulin action abnormalities which are insulin deficiency and insulin resistance.

P323. Tumor microenvironment on a chip: A newer smart approach mimicking cancer environment

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According to the American Cancer Society, cancer is the second most leading cause of death in the US. Cancer research has gained wide research interest throughout the world. Generally,

researchers rely on cell culture or animal models to study the different nano-bio interactions. However, the major drawbacks of these are that cell cultures lack the complexity of biological tissues surrounding the cancer while use of animal models give slower results, expensive and involves a lot of ethical issues. A newer smart approach has been reported which consists of a chip system mimicking the cancer environment. This smart technology is called Tumour microenvironment-on-a-chip (T-MOC). This chip system allows real-time analysis of nanoparticle accumulation by incorporation of tumor-like spheroids into the microfluidic channel at physiological flow conditions. The presence of three-dimensional tissue architecture and dynamic flow conditions in the system makes it accurate than in-vivo studies which lacks the above two properties. Thus, T-MOC chip is one of the most recent development that could bring about pivotal change in the field of cancer research, due to the increasing recognition for the limitations of animal experiments.

P324. Intranasal delivery of P- glycoprotein substrate using bovine lipid as permeation enhancer

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Brain targeting is difficult due to presence of Blood Brain Barrier (BBB) and efflux transporters like P-glycoprotein (P-gp). Intranasal microemulsion drug delivery system is one of the emerging approach for brain targeting. In this study we have formulated microemulsion of Amitriptyline hydrochloride, which is a P-glycoprotein Substrate. Cow Ghee has been widely used in ayurvedic formulations like ghritapaka and panchagavya. It consists of combination of fatty acids in different proportion and are known to increase the permeability of the drug through BBB. We have explored Cow Ghee for its Permeation enhancer activity in which drug was allowed to complex with it and this complex was incorporated in microemulsion. Interaction was studied using DSC, FTIR and Microscopy. A pseudo ternary phase diagram was plotted using triplot software to select suitable ratio of oil, surfactant, cosurfactant and water. The developed microemulsion system was evaluated for various physicochemical properties including Size, Zeta potential, pH, Dilution potential, Drug content, Viscosity, etc. In vitro and Ex vivo (using goat nasal mucosa) release studies of ME using franz diffusion cell was carried out where, Cow Ghee based ME showed increase in diffusion across the nasal mucosal membrane. In the in silico study, various fatty acids present in Cow Ghee were docked on P-glycoprotein for its inhibitory potential, hydrogen bonding and amino acids interaction. The study revealed that fatty acids like DHA, Linolenic acid, Linoleic acid, oleic acid, stearic acid, and palmitic acid showed good inhibition in comparison to the known inhibitor Verapamil.

P325. Simultaneous spectrophotometric determination of Celecoxib and Diacerein in bulk and capsule by Chemometric methods

Nisarg Patel, V.P.Nandubarker, A.J.Patel, S.G.Patel

Ramanbhai Patel College of Pharmacy-CHARUSAT and Zydus Research Center

Development and validation of chemometric methods for simultaneous estimation of DIA (Diacerein) and CEL (Celecoxib). Statistical comparison of developed methods using ANOVA.

Multivariate spectrophotometric methods were developed for simultaneous estimation of Celecoxib (CEL) and Diacerein (DIA) in combined dosage form. Chemometric methods including classical least square (CLS), inverse least square (ILS), principal component regression (PCR) and partial least square (PLS) were studied for simultaneous determination of CEL and DIA in capsule using spectrophotometry. A set of 25 standard mixtures containing both drugs were prepared in range of 5–25 µg mL−1 for CEL and 3–15 µg mL−1 for DIA. Analytical figure of merit (FOM), such as sensitivity, selectivity, analytical sensitivity, limit of detection and limit of quantitation were determined for chemometric methods. The proposed methods were applied for determination of two components from combined dosage form. Conclusion has been drawn based on the best multivariate analytical method for determination of assay value.

P326. An In silicostudy to evaluate the role of small heterocyclic moiety in the improvement of cognitive function

Shashikala R. Bhute, Rinkal Tanna, Deepaneeta Sarmah, Pallavi Rane, Tikendra Kumar, Vinod Tiwari, Kiran Kalia, Amit Shard and Pallab Bhattacharya

National Institute of Pharmaceutical Education and Research, Ahmedabad (NIPER-A), Gujarat, India

Mild cognitive impairment may eventually develop into Alzheimer's and other types of dementia. Alzheimer's disease (AD) is a chronic neurodegenerative disorder that manifests into disturbances of cognitive functionssuch as amnesia.The present study is designed to investigate the anti-amnesic effect ofa small heterocyclic lead compound on behavioural and neurochemical changes in animal model of cognitive impairment and AD. All compounds were designed taking into account Lipinski's rule of five.We firstly performed an in silicotesting of the lead compound. The parameters that were analyzed for determining in silicocompetence were docking score, protein-ligand binding free energy simulations, 3D pKa predictions, anti-oxidant and chelating properties. The test compound selected exhibitedan in vitroanticholinesterase activity in Ellman's assay. In futurewe plan to perform apreclinical acute toxicity testing of the drug substance in order to find out the optimal dose to be administered. Further, the improvement in cognitive functionwill be tested against scopolamine induced rodent model of amnesia and quinolinic acid induced rodent model of AD. We hypothesize that the lead heterocyclic moiety will show promising therapeutic effects in the animal model of cognitive impairment and AD.

P327. Preclinical assessment of Polyphenols in the treatment of Parkinson's disease: A meta-analysis

Pallavi Rane, Deepaneeta Sarmah, Shashikala R. Bhute,Tikendra Sonwan, Vinod Tiwari, Kiran Kalia, Pallab Bhattacharya

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Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world. It is associated with motor dysfunction and clinical symptoms like tremors, bradykinesia, muscle rigidity, postural instability and akinesia. The neuropathological hallmarks of PD are characterized by progressive and profound loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) and a depletion of postsynaptic dopamine levels within the striatum. There are also abnormal aggregates of protein alpha synuclein (αS) found in Lewy bodies (LBs) and Lewy neurites (LNs). Nordihydroguaiaretic acid (NDGA), a polyphenolic compound isolated from creosote bush (Larrea tridentata) has shown evidences of its neuroprotective effects against αS fibrillation in an in vitromodel of PD. To explore further, a meta-analysis has been conducted for those studies engaging the use of polyphenolic compound as an option for the treatment of PD. The study was conductedby an extensiveliterature search followed by identifying relevant studies using polyphenols as a therapeutic choice in animal models of PD. Our findings from the present meta-analysisstrongly supports a possible scope of polyphenolic compounds as a future promising therapy in PD.

P328. Use of mesenchymal stem cells (MSCs) in preclinical settings for ischemic stroke therapy: a meta-analysis

Deepaneeta Sarmah, Pallavi Rane, Shashikala R. Bhute, Tikendra Kumar, Vinod Tiwari, Kiran Kalia, Pallab Bhattacharya

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Stroke is a devastating condition and is a leading cause of death and disability worldwide. Intra-arterial (IA) delivery of mesenchymal stem cells (MSCs) for the treatment of ischemic strokehas a high potential for clinical translation.Studies from our lab have demonstrated that intra-arterial (IA) administration of MSCs improved ischemic outcome by reducing the infarct volume and functional deficits. To explore further, a meta-analysisof preclinical studies engaging the use of MSCs for ischemic stroke therapy was undertaken. Anextensiveliterature survey followed by identifying relevant studies using MSCs as therapy in animal models of ischemic stroke was pursued. Findings from the present meta analysissupports a promising scope and potential of MSCs therapy in ischemic stroke. As, mitochondrial dysfunction is also one of the majordeterminants of stroke pathogenesis, hence, our future work will explore the role of IA MSCs therapy in protecting mitochondria following stroke.

P329. Neuroprotective effects of alkaloid in preclinical model of stroke: a metanalysis

Tikendra Kumar, Shashikala Bhute, Pallavi Rane, Deepaneeta Sarmah, Vinod Tiwari, Kiran Kalia, Pallab Bhattacharya

National Institute of Pharmaceutical Education and Research, Ahmedabad (NIPER-A), Gujarat, India

Ischemic stroke is caused due to obstruction in blood flow to a part of brain leading to brain damage. Energy failure, excitotoxicity, acidosis, increase in intracellular calcium level, oxidative stress, mitochondrial dysfunction, inflammation, apoptosis and finally neurodegeneration are the outcome of such cerebrovascular event. Previous studies have reported the neuroprotective effects of alkaloid in improving stroke outcome. Studies from our lab have shown that Trigonelline (1-methyipyredinium-3-carboxylate hydrochloride), an alkaloid from Trigonella foenum graecum prevents the progression of neuronal infarction and also brings improvement in the stroke outcome in animal model. Hence, it was pertinent to explore its neuroprotective actions further. To pursue this, a meta-analysis has been conducted for those preclinical studies engaging the use of alkaloids for ischemic stroke therapy. The study was conducted by an extensive literature search followed by identifying studies using alkaloids as a neuroprotective agent in animal models of ischemic stroke. Findings from the present meta analysis strongly supports a scope of further investigations of alkaloid as a therapeutic choice for ischemic stroke.

P330. Oral cancer and its targets

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Oral cancer is at third position in leading cause of death. Annually 65, 00, 00 cases are reported and among them 35, 00,00 death of patient occur. Various risk factor which contribute in the development of the oral cancer are age, gender, ultraviolet light, smoking, tobacco, alcohol and virus like human papilloma. Oral cancer development occur due mutation of TP53 gene and infection cause by HPV. Different type of oral cancer include squamous cell cancer, lymphoma, veracious cancer, minor salivary gland cancer and adenoid cystic cancer. Some precancerous condition which are used in diagnosis are leukoplakia, erythroplakia and erythroleuloplalia. Most common medication which are mostly use in treatment are cisplatin and 5fluorouracil and other less commonly use medicine are carboplatin, bleomycin and methotrexate. Curcumin capsule, celecoxib and erlotinib are still in the clinical trial. Targeted therapy works by stopping of chemicals like hormone and some factor which are responsible for cell division or they kill cancerous cells by replacing the protein which are used in cell division in cancerous cell and some they developed angiogenesis process. Some targeted treatment include EGFR which inhibits growth of cell, TP53 gene use in suppression of proliferation and promote apoptosis, Sirtuin they promote cell survival, GSK3 improve cell promotion and regulation, FHL1 use in controlling abnormal apoptosis which cause cancerous condition and some other targets include CTGF, VEGFR, CTLA4, ADM, CD70gene, tyrosine protein kinase

P331. Brain cancer and its targets

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Brain cancer word itself is very much dangerous for the human being. Brain cancer is not much prevalent as compare to other cancers like oral cancer or others but it is very much prevalent all over the world. Once it occurs, it is difficult to remove brain cancer from the brain. Brain cancer is the subtype of different cancers occurs and it is the one of the leading cause of the death in cancer patient. According to the researches many medicines have been developed but no conquer therapeutic outcome is not seen in the patients. Here some targets are mentioned that by targeting the different targets therapeutic desired outcome can be achieve. And one of the leading malignant tumour is glioblastoma which arises from the astrocytes located in the different part of the brain and spinal cord and fluid. Targets like PTEN receptors, that is responsible for the different cell functioning like cell proliferation or cell division and by decreasing the cancerous proliferation of astrocytes cells that will leads to depletion of the AKT pathway and that leads to less astrocytes cancer formation and for that trastuzumab like drug can be also helpful for targeting the PTEN receptors. Like PTEN receptors there are many other targets like stem cells or the EGF receptors, targeting them in case of brain cancer can be helpful to remove the brain cancer and like that other technique is that microRNA for that normal functioning of the RNA gets alter and which deregulates the gene expression and in that mutation can also leads to generate the cancer in the brain and by targeting the different targets brain cancer like glioblastoma can be remove and one therapy like photodynamic therapy by using this therapy targeting the cancerous cells by the activating the photosensitive substances that will leads to kill the cancerous cells and healthy wellbeing can be achieved.

P332. Understanding of Albinism and its treatment

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Albinism is inherited conditions characterized by absent or decreased melanin in conjunction with characteristic ocular and visual pathway anomalies. Those which affected by this condition manifest varying degrees of hypo pigmentation and vision-related disability. These conditions mainly include oculocutaneous albinism and ocular albinism. These conditions generally are incurable but are static. Proper ophthalmic and dermatologic management may be crucial in maximizing visual potential and overall prognosis. Genetic counseling for the affected individuals and their families is recommended. Recent updates are available for the treatment is a novel approach to gene therapy of albino hair in histoculture with a retroviral streptomyces tyrosinase gene, nitisinone, L-dopa, lutein and zeaxanthin.

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