Society for Pharmaceutical Dissolution Science

DISSO INDIA 2013

First International Annual Symposium

Conference days: May 3rd & 4th, 2013

Venue: The Lalit, Mumbai

Scientific Abstract Book

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Solutions for Pharmaceutical Testing

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Message from Chief Guest

Dr. B. Suresh

Vice-Chancellor, JSS University, Mysore & President of Pharmacy Council of India, New Delhi

I am delighted to know SPDS has organised their first International Pharmaceutical Dissolution Conference - Disso India 2013 at Mumbai for Industries and Academia professionals to get enriched with the technological advancement related to dissolution sciences. These kinds of events will add value to the participants and will enable them to perform better in their respective functions.

SPDS is being a super speciality society and the first of its kind and I am optimistic that their initiative will reach across the globe and help the Pharmaceutical professionals in order to improve the quality of drug produced at their site.

Wishing all the success for the organizers and to succeed in future endeavours.

Dr. B Suresh
Vice-Chancellor, JSS University, Mysore
President of Pharmacy Council of India, New Delhi

Message from Scientific Committee Chairman

Dr. Mrs. Mangal Nagarsenker
Professor & HOD, Dept. of Pharmaceutics, Bombay College of Pharmacy. , Mumbai, India

In vitro dissolution testing plays a key role during several stages of drug product development process. Its role covers a broad spectrum, ranging from quality control tool to monitor batch-to-batch consistency of drug release from a dosage form, to an in vitro surrogate for predicting in vivo performance of the formulation.

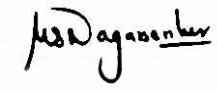
Society for Pharmaceutical Dissolution Science (SPDS) has been formed with the objective of promoting the science and technological development in the important field of dissolution among pharmaceutical professionals, academia, students and regulatory bodies.

The "Disso India 2013" scheduled on 3rd and 4th May 2013 is the first major event organised by SPDS. The scientific program team has put in place an impressive program which will discuss latest developments in major areas of dissolution studies.

The two day symposium will address topics related to dissolution techniques with reference to different delivery systems, regulations relevant to dissolution, automation, validation studies and role of dissolution in prediction of in vivo performance. Participants will have a great opportunity to get updates on current development in dissolution science from a galaxy of national and international experts.

The program will also have a pre-symposium training work shop and poster sessions for young scientists.

I wish this symposium a great success and that it provides the participants excellent opportunity for knowledge sharing and networking.



Dr. Mrs. Mangal Nagarsenker
Professor & HOD, Dept. of Pharmaceutics,
Bombay College of Pharmacy, Mumbai, India

Message from Chairman - Disso India 2013

Dr. Vinay G Nayak
President-Technical operations, Alembic Pharmaceuticals Ltd. Vadodara, India

The pharmaceutical fraternity have well developed learning groups such as ISPE, DIA, Chromatographic Society, PDA PAC and many others.

The important in-vitro testing for dosage form Quality mapping, done by Dissolution test, has been missing a group input - as a scientific discussion group - to discuss the finer aspects of the correct method to be chosen, its validation and harmonized testing. This SPDS group was set up with the objective of providing opportunity to share knowledge on this subject of dissolution testing.

With this conference, the best of scientists and experts in this field will set the tone for similar scientific meetings and exploration of the nuances of this technique going forward.

SPDS has set the tone by opening Chapters all over India to create awareness and integrating scientists with Dissolution testing technology as their area of expertise to share information under one umbrella

I thank the team who has set up this event and worked hard to fructify the very first international meet in Mumbai

I also convey my sincere thanks to the experts who have come from various parts of the world to share and educate our scientists on these interesting topics

Wishing All Success to Disso India 2013

Regards

Dr. Vinay G Nayak
President-Technical operations, Alembic Pharmaceuticals Ltd. Vadodara, India

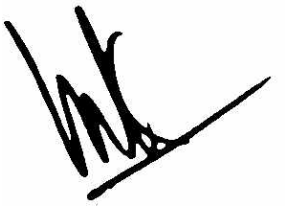
Message from President - SPDS

Mr. Vijay Kshirsagar
Executive Vice President-Corporate QA & Regulatory Affairs, Unichem Laboratories Ltd, Mumbai, India

On the eve of this unique event of Disso India, I would like to extend my greetings to all of you. SPDS is probably the first society in the world dedicated to a specialized topic like Dissolution. In a short span of just about an year sapling has taken the shape of tree which is now ready to branch all over. Support received from all of you and particularly from Dr Vinod Shah of ex-US FDA, revered as the encyclopedia of dissolution, has been phenomenal.

We are all grateful to our esteemed international and national speakers for having accepted our invitation and the overwhelming support received from the pharmaceutical fraternity and the event sponsors. I am sure SPDS will be the new benchmark for India's initiative in the field of pharmaceutical science.

All my colleagues at SPDS deserve a special applause for carving out this beautiful event and working hard for it's success. For Dr Ramswamy, the General Secretary of SPDS, who in real sense is driving the Society, it is like a dream come true. I am sure the event will help our pharmaceutical professionals to design the dissolution strategy for their new products in a manner to have desired in vitro-in vivo correlation.



Mr. Vijay Kshirsagar
Executive Vice President-Corporate QA & Regulatory Affairs,
Unichem Laboratories Ltd, Mumbai, India

Message from General Secretary - SPDS

Dr. L. Ramaswamy

Managing Director, Sotax India Pvt Ltd, Mumbai

I extend my warm welcome to one and all who have accepted our invitation and marked your presence here today or registered as a delegates/ partners with Disso India 2013. For me at SPDS , Disso India 2013 is crossing another mile stone towards it journey to accomplish the Vision and Mission.

I wish to express my profound thanks and gratitude to our Founder President of SPDS, Mr. Vijay Khsirsagar and the Chairman of Disso India 2013, Dr. Vinay G Nayak, who have guided us always and the Scientific Committee Chairman, Dr. Mrs. Mangal Nagarsenkar, HOD and Professor of Pharmaceutics, Bombay College of Pharmacy and all the other committee members who have carved a high quality , industry oriented two days scientific sessions where in a plethora of eminent global and national speakers of high repute are delivering key note address and lectures. I am optimistic that it is going to be a great value addition to the Pharma Scientists, Analysts , Pharmacy faculties, students, Ph.D Scholars and all others participating in this special event. In addition to the International symposium Sotax India Pvt. Ltd. and Institute of Chemical Technology, Mumbai have come together to host one day pre-conference workshop on 2nd May 2013.

I must mention here Dr. Vinod P Shah from USA, Dr. Umesh Banakar, USA, Dr. B. Suresh, India, Dr. S. K. Kukarni, India and Sotax Management Team ,Switzerland who have extended unconditional support to me and SPDS right from the start till what it is today.

At all times, our endeavour in SPDS is to update the Science and Technological Advancement in Pharmaceutical Dissolution Sciences to our Industry Scientists, Pharmacy faculties & Students , and Regulatory professionals through seminars, workshops, symposia, one to one presentations and demonstrations.

To achieve the above in the quickest and best possible way, we are taking SPDS to the Global Platform in this year.

I look forward a whole hearted supports from our Chief Guest of today's function, all Invitees, delegates, Disso India 2013 Industry partners, all the organizing committee members of this event, Office Bearers and Executive Council Members of SPDS, Pharma Faculties and students from across the globe, regulatory Professionals, Media & press reporters, Pharmaceutical Companies, Instruments and Pharma testing equipments manufacturers and marketers, CRO's CMO's and all others.

Let us all join hands together to make SPDS a great professional organization whose ultimate aim is to improve the quality of the drug produced across the Globe.

Best Regards

Dr. L. Ramaswamy

Managing Director, Sotax India Pvt Ltd, Mumbai

Introduction

Society for Pharmaceutical Dissolution Science

Society for Pharmaceutical Dissolution Science was formed on 16th July 2012 at Mumbai with the objective of promoting the science and technological development in the field of dissolution among pharmaceutical professionals , academia, students, regulatory bodies, etc.

SPDS was formally launched at 64th IPC congress at Chennai by Dr. B. Suresh and the Convention Chairman Mr. S. V. Veeramani on 9th December 2012.

Vision : To be as one of the most prominent professionals body focusing on Dissolution Science among the Pharmaceutical Industry and Academia

Mission : To dissipate the science & advancement taking place in the field of dissolution related to clinical application and methods.

Management Executive Committee

Office Bearers

Vijay Kshirsagar - President
Executive Vice President-Corporate QA & Regulatory Affairs, Unichem Lab Ltd, Mumbai.

Dr. L. Ramaswamy - General Secretary
Managing Director, Sotax India Pvt Ltd, Mumbai

Ramsingar Pal - Treasurer
General Manager - Technical, Sotax India Pvt Ltd. , Mumbai

Executive Members

Dr. Mrs. M. Nagarsenkar
Professor & HOD, Dept. of Pharmaceutics, Bombay College of Pharmacy. , Mumbai.

Dr. (Mrs.) Abha Doshi
Principal, MET Institute of Pharmacy. Bandra(w), Mumbai

Dr. B. M. Rao
Director, Analytical Development & Engg. Services, Janssen-Pharma Compnies of J&J. , Mumbai.

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Vice President - Analytical Development, Famycare Limited. , Mumbai.

Vijayanand Chakrapani
Assistant General Manager - Corporate QA, Mylan Laboratories Ltd. , Hydrabad.

Dr. (Mrs.) Mala Menon
Professor-Dept of Pharmaceutics, Bombay College of Pharmacy. , Mumbai.

Umesh Bhosale
Sr.Manager - Analytical Development, Bharat serums & Vaccines Ltd R&D. , Mumbai.

Dr. Shripad Naik
Sr.Manager, R&D, Janssen-Pharma Companies of J&J. , Mumbai.

Sanjay Chaudhari
Sr. Principal Scientist - Analytical R & D, Centaur Pharmaceuticals Ltd.

Mahesh Fukey
Manager - Analytical Development, Tevapharm India Pvt Ltd. , Goa.

Candeth Castello
Director, Stability Control, Tevapharm India Pvt. Ltd.

Mr. Rajesh Sirwani
General Manager-F&D, Zydus Cadila, Ahmedabad

B. Ramamohan
Manager-QC, Dr.Reddy's Laboratories Ltd. , Hydrabad.

Dr. N. D. Satyanarayan
Asst. Professor - Pharmaceutical Chemistry, Kuvempu University PG Centre. , Karnataka.

Scientific Committee

National Scientific Committee

Dr. Mrs. M. Nagarsenkar - Chairman
Professor & HOD, Dept. of Pharmaceutics, Bombay College of Pharmacy. , Mumbai.

Dr.(Mrs.) Padma V. Devarajan
Professor & HOD, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology. , Mumbai

Dr. (Mrs.) Abha Doshi
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Dr. (Mrs.) Mala Menon
Professor-Dept of Pharmaceutics, Bombay College of Pharmacy. , Mumbai.

Dr. (Mrs.)Krishnapriya Mohanraj
Prof. & Head - Pharmaceutical Analysis Bombay College of Pharmacy. , Mumbai.

Dr. S. S. Poddar
Prof. & HOD Pharmaceutics, KMKundnani College of Pharmacy. , Mumbai.

Dr. (Mrs.) Vandana B. Patravale
Professor of Pharmaceutics Department of Pharmaceutical Sciences and Technology Institute of Chemical Technology. , Mumbai.

Dr.N.D.Satyanarayan
Asst. Professor - Pharmaceutical Chemistry, Kuvempu University PG Centre. , Karnataka.

Dr. (Mrs.) K. K. Singh
Principal & Professor of Pharmaceutics C. U. Shah College of Pharmacy SNDT Woman's Univercity. , Mumbai.

Dr. B. M. Rao
Director, Analytical Development & Engg. Services, Janssen-Pharma Compnies of J&J. , Mumbai.

International Scientific Committee

Dr. Vinod Shah
Ex.US FDA, Pharmaceutical Consultant, USA

Dr. Umesh Banakar
Proff. & President, Banakar Consulting Services,USA.

Dr. Jean Michel Cardot
Professor & Head - Dept of Biopharmaceutics and Pharmaceutical Technology, Universite d'Auvergne, France

Mr. Samir Haddouchi
Managing Director, SPS Pharma services, France.

Dr. Vinod Shah

Ex.US FDA, Pharmaceutical Consultant, USA

Dr. Shah is a pharmaceutical consultant. He was Scientific Secretary (2003 – 2011) of International Pharmaceutical Federation (FIP), and is now Chair of Regulatory Sciences Special Interest Group of FIP. He is an Adjunct Faculty at JSS University, India.

Dr. Shah retired from US FDA (Food and Drug Administration) as a Senior Research Scientist after 30 years of service in July 2005. He has developed several Regulatory Guidances for Pharmaceutical Industry in the area of biopharmaceutics. He has received several FDA Awards including Award of Merit, Scientific Achievement Award and Distinguished Career Service Award.

Dr. Shah is a Fellow of American Association of Pharmaceutical Scientist (AAPS) and FIP. He is author/co-author of over 260 scientific papers and is a co-editor of three books. Dr. Shah was the President of AAPS in 2003 and is a recipient of AAPS Distinguished Service Award and Pharmaceutical Sciences World Congress (PSWC) Research Achievement Award. He is a recipient of FIP Lifetime Achievement Award in Pharmaceutical Sciences and Honorary Doctorate from Semmelweis University.

Role of Dissolution and In Vitro Release in Regulating Pharmaceuticals

Over last four decades, the dissolution test has evolved as a most powerful tool to characterize oral drug product performance. This is possible only because of our knowledge and understanding of science behind the test methodology. One of the most important applications of dissolution test is its use in providing biowaiver. Concept of biowaiver is appealing as it avoids unnecessary human studies. The dissolution test has brought about significant changes in regulatory perspectives. A clear trend is established where dissolution test has moved from traditional quality control (QC) test to an in vitro bioequivalence test. An appropriate dissolution test procedure is a simple and economical method that can be utilized effectively for drug product approval without sacrificing the drug product quality. The concept of dissolution is also applied to novel dosage forms, and is slowly gaining its way towards product performance test and possibly biowaivers.

SPDS Dissolution Conference: Disso India 2013. Mumbai, India, May 3-4, 2013

BCS & Biowaivers – Dissolution Test Methodologies.

Biopharmaceutics Classification System (BCS) is a scientific framework for classifying the active pharmaceutical ingredient (API, drug substance) based on its aqueous solubility and intestinal permeability into four classes: Class1: high solubility/high permeability; Class 2: low solubility/high permeability; Class 3: high solubility/low permeability and Class 4: low solubility/low permeability. When combined with the dissolution of the drug product, the BCS takes into account the three major factors, solubility, intestinal permeability and dissolution, that govern the rate and extent of drug absorption from immediate release (IR) solid oral dosage form. BCS guidance is applicable only for Class 1 immediate release, non-narrow therapeutic drug product. The dissolution test for the product is to be carried out under mild conditions in aqueous buffers. The concept of biowaiver is appealing as it avoids unnecessary human studies. However, it was concluded that the FDA's BCS guidance is too rigid and conservative. Considering the foundation of BCS and the scientific principles involved, WHO proposed extension of biowaivers for (1) Class 2 weak acids which dissolve rapidly in pH 6.8 and (2) Class 3 drugs with very rapid dissolution characteristics. In all instances, the dissolution profile of the test product is compared with the reference product under pH 1.2, 4.5 and 6.8 test conditions. This new paradigm in bioequivalence testing does not sacrifice the drug product quality.

Vatsala Naageshwaran

Associate Director, Scientific Operations, Absorption Systems, USA

Vatsala Naageshwaran has worked for several biotechnology / pharmaceutical companies as a research scientist with experience in drug discovery, assay validation, and product development.
Currently as Associate Director, Scientific Operations for Absorption Systems, Vatsala collaboratively drives research and expansion of CellPort, Absorption Systems' exclusive drug transporter technology. Vatsala has made presentations and performed workshops on drug transporters at various conferences most recently at the 2011 Fall Symposium organized by the Delaware Valley Drug Metabolism Group (DVDMG) and at IQPC's Clinically Relevant Drug Transporters Conference in 2011 and 2012 Prior to joining Absorption Systems, Vatsala made significant contributions at Supergen in the development of drug candidate Amuvatinib (MP-470). Her research has been featured at national conferences such as AACR and EORTC and she has authored publications submitted to peer-reviewed journals. Prior to this Vatsala worked at Myriad Genetics focusing on BRAC clinical data analysis for hereditary breast and ovarian cancer. Vatsala has a Masters degree in biochemistry and molecular biology.

Profile

- Associate Director Scientific and Business Operations at Absorption Systems, a leading preclinical CRO
- Significant experience in study design preparation and oversight of Customer studies including BCS classification, drug metabolism, permeability, drug transporters, pharmacokinetic and tox studies
- Project lead on internal research projects to facilitate development of new commercial assays and services
- Skilled in collaborating with interdepartmental teams to drive product development.
- Excellent presentation and verbal / written communication skills, preparing and presenting posters and workshops at national conferences / meetings and submitting manuscripts to peer-reviewed journals.
- Research Scientist with seven years of experience in the Biotechnology / Pharmaceutical industry, including significant experience in Oncology Research and Data Management.
- Extensive experience in assay development for the latest drug targets including kinase ,protein-protein interaction targets, transcription factor targets
- Demonstrated expertise in molecular biology, working extensively with assay development and specific molecular biology techniques.
- Extensive experience in data analysis/ management and in SOP preparation and maintenance

Permeability Classification of Highly Variable Drugs Using the In Vitro Caco-2 Assay

The biopharmaceutical classification system (BCS) provides the scientific basis that supports in vivo bioavailability and bioequivalence waivers for immediate-release solid dosage form drugs that have high solubility, high intestinal permeability and rapid dissolution. In vitro permeability assays provide direct assessment of absorption potential whereas in vivo BE studies assess drug absorption indirectly via evaluation of a pharmacokinetic profile. With the latter, post-absorption events such as metabolism and enterohepatic recycling can result in increased variability. Highly variable drugs (HVDs) often require a greater numbers of subjects to minimize the erroneous conclusion of inequivalence when in fact they are therapeutically equivalent. For HVDs that exhibit consistently inconsistent PK due to extensive first-pass metabolism, human mass balance and bioavailability studies may result in ambiguous or incorrect BCS classification because the variability inherent in human studies is compounded by the intrinsic properties of the drug substances. In such cases, in vitro testing provides consistent, and accurate classification as the variability associated with permeability and solubility measurements is less dependent on the factors that exaggerate the variability of human testing. The presentation will highlight the utility of a validated Caco-2 monolayer system in establishing the accurate permeability classification of such compounds.

Inherently conservative, Caco-2 cells demonstrate that compound classification and robustness of efflux transporter expression is consistent across an established assay widow (both passage number and days in culture), is not susceptible to operator differences, and can be used for successful classification at two physiologically relevant apical pH levels (6.5 and 7.4). Drawing from the decade long experience of performing in vitro permeability studies for both generic compounds and NCEs that belong to a variety of therapeutic classes, case studies will be presented to share feedback received from the regulatory agencies and highlight the benefit and value of the in vitro approach in successfully enabling the biowaiver of compounds including highly variable drugs.

Samir Haddouchi

Managing Director, SPS Pharma Services, Clermont Ferrand - France

Prior to joining SPS Pharma Services in 2005, Samir spent more than 10 years in the pharmaceutical industry.
As a chemist, he started working on the analytical development of agrochemical compounds at Sandoz Agro in the region of Basel (Switzerland).
During the Novartis merger, he moved to Orléans (France) in 1998 to join the analytical group in the technical development department where he became responsible for dissolution.
Since he joined SPS Pharma Services, Samir manages SPS facility in Clermont Ferrand (France) and is in charge of projects management.

Recent conferences and lectures:

2009: **Controlled Release Society meeting in Copenhagen (Denmark)** Dissolution methods for the characterization of bioceramic granules

2009: **US FDA Office of Generic Drugs in Rockville, MD (USA)**
Using flow through cell methods in ANDAs dossiers

2010: **Controlled Release Society meeting in Portland, OR (USA)**
Characterization techniques used in the Pharmaceutical industry
Release Technology Workshop: Dissolution applications using the flow through cell

2010 **Sotax Dissolution Congress in Basel (Switzerland)**
Injectable suspensions dissolution techniques

2011 **Bombay College of Pharmacy in Mumbai (India)**
Dissolution: An effective tool for NDDS development

2011 **SFDAIED Dissolution Congress in Beijing and ShangHai (China)**
Dissolution techniques used in the Pharmaceutical industry.

2012 **44th SFSTP Congress in Montpellier (France)**
Member of the Scientific Committee chairing the Congress.

2012 **Controlled Release Society meeting in Quebec City (Canada)**
Release rate testing of injectable formulations using USP Apparatus 4

Dissolution testing of modified release systems

The past decades have seen an increase in the number of innovative modified release platforms available with the goal of either providing the patient with a better treatment or protect the products from the generic competition.

Such complex formulations call for sophisticated dissolution methods able to provide with a good understanding of both API and formulations properties. This presentation will discus the topics to be considered when developing dissolution methods and will present some related case studies.

Automation in dissolution testing and validation

Automation is present since years in the pharmaceutical laboratories. It is also available to automate the various steps of dissolution methods. This purpose of this presentation is to discuss how automation can be implemented in the field of dissolution testing and how to validate automated methods.

Prof. Dr. Jean-Michel Cardot

Professor, Department of Biopharmaceutics and Pharmaceutical Technology, Auvergne University, France

J-M. Cardot is professor and head of the Department of Biopharmaceutics and Pharmaceutical Technology from the Universite d'Auvergne, France.

J-M. Cardot joined in 1987 Ciba-Geigy and Novartis in development departments in Basel and in Paris. He created in 1999 a company dedicated to the production of technical and clinical batches of high potent activity drugs that he left to enter in University in 2002.

From 1992 to 2002 J-M. Cardot was also associated professor in the University of Clermont-Ferrand in Biopharmaceuticals department. Since 2002 Jean-Michel Cardot is Professor Department of Biopharmaceutics and Pharmaceutical Technology, Universite d'Auvergne, France.

J-M. Cardot has a Pharm D. and a Ph. D. from Clermont-Ferrand University and Masters from Clermont-Ferrand (Biopharmaceutical) Paris (Statitics) and Marseilles (Pharmacokinetics) Universities.

Professor Cardot's main research fields include biopharmaceutical aspects of drug development, in vitro-in vivo correlations and in vitro dissolution tests.

Statistics and modeling in *in vitro* release studies

Dissolution results are often seen only as a QC results mandatory but of limited value. However the dissolution is a tool which reflect the API characteristics, the formulation and the process used during the production. Dissolution is of a great help during initial steps to optimize and secure the development and afterwards to insure the quality of the finished product during the commercial production. The present talk focusses in a first part on the evaluation and modelisation of the dissolution data comparing the more common techniques. In the second part the various options to compare dissolution curves are presented and commented associated with their acceptance by regulatory authorities in the various regions of the world

Dr. Umesh Banakar

Prof. & President, Banakar consulting Services, USA

Umesh V. Banakar, Ph.D. is Professor of Pharmaceutics and an Independent Consultant/Advisor to Pharmaceutical Industry and Academia worldwide with extensive contribution in drug product development and evaluation (in vitro **and clinical).**

He is on the International Scientific Advisory Board of several pharmaceutical corporations worldwide. Of date, he has successfully completed several Pharmaceutical Product Development Technology Transfer through education assignments sponsored by the UN/IESC and other pharmaceutical corporations worldwide. Additionally, he has served as **testifying/non-testifying expert in patent litigations** in the disciplines of pharmaceutical formulations/technology, clinical investigations and dissolution testing. Furthermore, he has planned and executed the development, both in vitro and clinical, of **several NDAs and ANDAs (both IR and MR products)**. He is the Founding **Chairperson of 2 International CROs**.

He has authored over 100 publications, over 100 published abstracts and presentations, numerous specialized workshop manuals, several chapters and monographs, over 45 expert book reviews and 5 guest editorials. The texts that he has authored include: **Pharmaceutical Dissolution Testing, Drug Development Process: Increasing efficiency and cost effectiveness**, among others. He is the co-author of an electronic text**: Basic Pharmacokinetics**. He is on the roster of experts with WHO, United Nations – TOKTEN program and International Executive Service Corps (IESC). He is listed in Who's Who in Biotechnology, Who's Who Among Asian Americans, and American Men and Women of Science.

IN VITRO - IN VIVO CORRELATIONS [IVIVC]: What makes them challenging ?

Dissolution testing, is a regular quality control procedure in good manufacturing practice. However, the dissolution test can be employed prospectively – while developing a formulation with appropriate drug release characteristics, and retrospectively – to assess whether a dosage form is releasing the drug consistently at prescribed/predetermined rate and extent. The principal assumption underlying these two applications of this test is that the dissolution test is able to adequately represent, if not predict, the biological performance, i.e., bioavailability, of the drug.

As of date, in vitro dissolution tests seem to be the most reliable predictors of in vivo availability. Although official test have great practical value, the fact that there is still a need for test more directly related to bioavailability has been recognized. While the bioavailability of drug substances and drug products in humans can provide a confirmatory evidence of a potential relationship between dissolution and physiological availability, it is often impractical to perform extensive and expensive human testing.

Numerous attempts have been made to understand, develop and potentially quantify the correlation between dissolution and bioavailability. Additionally, several compendial descriptions and regulatory guidelines are available that provide assistance and direction in establishing and demonstrating such correlations. However, accomplishing an IVIVC still appears to be elusive and potentially comprehensible only in a handful of circumstances. A brief, yet comprehensive conceptual understanding of the challenges associated with developing et demonstrating an of IVIVC is essential, thus being the central focus of this presentation.

Prof. Dr. Mukesh C. Gohel

Course Coordinator (postgraduate program, Pharmacy) Institute of Life Sciences, Ahmedabad University, India

Prof. Dr. Mukesh Gohel is a course coordinator in the postgraduate program in pharmacy at the Institute of Life Sciences, Ahmedabad University, Ahmedabad. Prior to joining Ahmedabad University in January 2012, he was principal and professor at L. M. College of Pharmacy, Ahmedabad. He has a total of 41 years of teaching experience and more than 25 years of research experience. He is an approved Ph. D. guide in more than five Universities. He has guided more than 100 M. Pharm. students and 15 Ph. D. Students. He has published more than 150 research papers in national and international refereed journals of repute. He has published more than 30 papers in the area of dissolution technologies/science. He has not only suggested the major improvements to f_2 calculation science, techniques for enhancing dissolution but has also suggested numerous new ways for mathematical modelling of the dissolution data. He holds 10 formulation patents on the dosage forms such as tablets and capsules. He has been an invited speaker at wide array of conferences and seminars, including the recently held conference on Quality by Design (QbD) in Pharma Development by CPHI conferences in Ahmedabad in the year 2012. He has been providing training to R&D personnel of leading pharmaceutical companies in India in the areas of Quality by Design, Design of Experiments (DOE) and Parenteral Dosage Form Development. His current areas of interest are sustained release formulations, dissolution improvement of Active Pharmaceutical ingredient (API), Design of Experiments, QBD, Process Analytical Technology (PAT), Lean Drug Manufacturing, Monte Carlo simulations and Six Sigma Principles. He is recipients of various research grants from All India Council of Technical Education (AICTE). He is reviewer in many national and international journals. He has won many awards including IDMA research award for publishing the best research work.

Gaining In-depth insights on QbD in Dissolution Testing

The concept of Quality by Design (QbD) has been fully endorsed by FDA and hence all the ANDA dossiers are prepared considering science in the development. Dissolution is an integral part of the dossier preparation since it is used in all the phases of drug development. The major shortcomings of the conventional approach (non-QbD) to dissolution testing will be outlined and the need for analytical QbD (A-QbD) in dissolution will be justified. The critical factors influencing the results of dissolution testing will also be summarized. The use of fishbone diagram and design of experiments (DOE) to list and identify critical factors will be taken up. An idea about design space in dissolution testing will be covered in the presentation. The effect of dose dumping in presence of alcohol intake will be linked with QbD since clinical needs and safety of patient is of prime importance in QbD. In-vitro in-vivo correlation (IVIVC) in dissolution testing will be covered keeping in mind QbD requirements. The factors influencing dissolution stability will be discussed. The use of multivariate data analysis (principal component analysis) will be discussed for reducing the sampling time to cut down the cost of analysis and saving of analysis time. To facilitate research at industry, possibility of using surrogates for dissolution will be taken up. A link will be established between QbD, process analytical technology (PAT), good manufacturing practices (GMP) and standard operating procedure (SOP).

Dr. Sandip B. Tiwari

Technical Director: South Asia, Colorcon Asia Private Limited, India

Dr. Sandip B. Tiwari is currently Technical Director-South Asia, Colorcon Asia Pvt. Ltd, Goa, India. In his current role, Dr. Tiwari is responsible for the technical activities of the company in South Asia region. He is also responsible for leading the Formulation Center of Excellence (FCE) Laboratory in Goa. Prior to his relocation to India in July 2011, Sandip was a Senior Manager, Product Development at Colorcon Inc., Harleysville, PA, USA for over 5 years, where he was responsible for the development of the extended release (ER) hydrophilic matrix system portfolioincluding design and development of osmotic drug delivery technology platform, implementation of Quality by Design (QbD) initiatives, and development and evaluation of alternative tools/ techniques for dissolution testing of ER formulations.

Dr. Tiwari was also a post-doctoral fellow at Northeastern University, Boston, MA, USA where he investigated the application of nanotechnology in drug delivery and diagnostics. While in India, Dr. Tiwari worked at the Zydus Research Center, Ahmedabad, India, as an Associate Research Scientist and then as a Senior Scientist and Head of the Department of Novel Drug Delivery Systems. He has over 15 years experience in the pharmaceutical field and has participated in various stages of drug development during his career. He earned his PhD in Pharmaceutical Sciences from College of Pharmaceutical Sciences, Manipal, Karnataka, India.

He has written six book chapters/ monographs and contributed more than 100 research publications and conference presentations in the areas of dissolution science, controlled release technology, non-invasive drug delivery, and nanotechnology. He has spoken at many national and international conferences as an invited speaker.

Effect of Excipients on Dissolution: Case Studies with Bio-relevant/ Hydro-alcoholic media

Matrix formulations based on hydrophilic polymeric excipients are highly popular extended release (ER) dosage forms. Obtaining a specific dissolution profile with these matrix formulations using USP apparatus I or II is well established within the pharmaceutical industry. However, there have been studies on the relevancy of these methods as tools for formulation development and optimization. Although these methods are excellent tools for quality control purposes, they may not have the necessary sophistication for analyzing impact of excipients on dissolution profiles and for prediction of the in-vivo performance of the product under development

USP Apparatus III (reciprocating cylinder) with bio-relevant media may provide conditions and information that correlate to in- vivo performance. USP apparatus III was designed for simulating varying physiological conditions as the dosage form traverses the human digestive tract. The dosage form is exposed to a series of dissolution media representing physiological fluids and GI transit in the human digestive tract. The reciprocation rate and screen size can be selected to approximate hydrodynamic conditions. Apparatus III with bio-relevant media offers a physiologically based dissolution testing method for studying dosage forms under fasted or fed conditions.

This presentation will discuss case studies with extended release matrix hydrophilic formulations evaluated using Apparatus I/ II and Apparatus III with bio-relevant dissolution media. Dissolution profiles were generated in- vitro and compared to Innovator reference listed drug (RLD). Results from this study clearly indicated that the use of Apparatus III with bio-relevant dissolution media can provide useful information during formulation development, mainly to assess the impact of formulation excipients and drug delivery technology on dissolution profiles.

In addition, the potential effect of alcoholic drinks in significantly accelerating drug release from ER oral formulations has been of some concern. Concomitant alcoholic beverage ingestion may modify the release characteristics of ER formulations, causing dose dumping, which may threaten patient safety. The FDA recommends that ER medicinal products should be tested during development to ensure dosage form robustness in hydro-alcoholic media. The second part of the presentation will discuss the influence of hydro-alcoholic media on hydration and drug release from hydrophilic polymeric matrices using model APIs with differing solubilities in water. Impact of excipients in matrix formulations on dissolution profile in hydro-alcoholic media will also be discussed.

Prof. Dr. Diane J. Burgess

Professor of Pharmaceutics, University of Connecticut, USA

Dr. Burgess is Board of Trustees Distinguished Professor of Pharmaceutics, at the University of Connecticut. She has over 160 publications, over 420 research presentations at major scientific meetings, over 210 invited lectures, and has presented 15 keynote addresses. Her research efforts focus on gene and drug delivery: microspheres, emulsions, liposomes, hydrogels, as well as interfacial chemistry and implantable biosensors for glucose monitoring. Dr. Burgess was the 2010 President of the Controlled Release Society (CRS), the 2002 President of the American Association of Pharmaceutical Scientists (AAPS) and is an AAPS, CRS and an American Institute for Medical and Biological Engineering (AIBE) fellow. She is also an international fellow of the Association of Pharmaceutical Science and Technology Japan (APSTJ). Dr. Burgess is editor of the International Journal of Pharmaceutics and serves on the editorial boards of nine international journals. Among other prestigious awards, she is the 2011 recipient of the Nagai APSTJ International Woman Scientist Award. Dr. Burgess is an outstanding teacher and has twice been voted Teacher of the Year by her students. She designed and coordinates a summer Study Abroad Program for University of Connecticut pharmacy, premed and other science majors to go to China to learn about Traditional Chinese Medicine and immerse themselves in a different culture. Dr. Burgess has recently been appointed to the University of Connecticut Academic Vision Committee (a committee that will draft the next University of Connecticut academic plan 2014-2020).

In Vitro Release Testing of Particulate Systems

There is no United States Pharmacopeia (USP) apparatus designed specifically to test particulate systems. However, apparatus 4 has been applied with success to micro- and nano-sized drug delivery systems. For example, USP apparatus 4 has been adapted for microspheres[1] as well as implants and drug eluting stents, and is under review for other complex drug delivery systems. In the case if microspheres, glass beads are interspersed between the microspheres to prevent aggregation during release studies and to more closely simulate the in vivo conditions where microspheres are interspersed among cells e.g. at the s.c. site.[1] There is an ongoing effort to develop a standardized method or methods for microparticulates, although specific formulations may require some adaptation of the method and/or conditions used. Furthest along is a method for microsphere dosage forms that is being considered for compendial adaptation. Validation testing of an accelerated method for in vitro release testing of microspheres will be presented. Our laboratory has also developed a USP 4 adapter for use with liposome and other nanosized materials. In vitro release testing of liposomes and nanoparticles using dialysis methods will be discussed. In vitro release methods that are being considered for particulates include: dialysis sac, sample-and-separate, ultrafiltration, continuous flow methods and microdialysis. Considerations for in vitro method development include product related factors, such as: formulation dispersibility, stability, injection volume, viscosity and biocompatibility, as well as factors related to the injection site and drug properties, such as partitioning into fatty tissue, absence of sink conditions and any barriers to dug partitioning. Irritancy at the in vivo site can affect drug release due to resulting edema as well as the presence of increased numbers of neutrophils and macrophages. In vivo factors affecting drug release will be discussed.

Acknowledgements :

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Dr. Kailas Thakker

Co-founder & President, Tergus Pharma, LLC, USA

Kailas Thakker graduated from Department of Technology Mumbai with a degree in Pharmacy and went to USA for graduate work. There she earned Master's degree from Columbia University in New York and Doctor of Philosophy from University of Kansas while being mentored by world renowned industry leader and father of pharmaceutics, Dr. Takeru Higuchi.

She worked at United States Pharmacopeia for over 12 years and then went on to head Analytical departments at small venture backed virtual pharmaceutical companies.

About 19 years ago, Kailas founded Analytical Solutions with a vision to provide quality analytical services to the pharmaceutical industry. Working with regulatory, compendia and industry leaders, she started working towards developing and improving in vitro release test using Franz diffusion cells. About 18 months ago, Analytical Solutions expanded the service base to offer product development services. With the change of the service platform, came the change of name, Tergus Pharma. Today, Tergus Pharma offers comprehensive product development service to pharmaceutical industry with emphasis on topical products from concept commercialization.

Drug Release Testing of Topical Dosage Forms using Diffusion Cells.

In Vitro Release Test (IVRT) as a performance test has been in development for many years. Vertical Diffusion cells are the most widely used apparatus for evaluating release of a topical dosage form. IVRT is described Chapter <1724> of the United States Pharmacopeia and will become official in early fall of 2013.

The purpose of a true performance test for a dosage form is to monitor the consistency in manufacturing and predict continued product quality of that dosage form. In addition, IVRT can be a very useful drug product development tool for topical dosage forms. When designed appropriately, it can monitor variations in API release that result from changes in physico-chemical properties of the product, such as viscosity, changes in excipient type or source, change in manufacturing process, or changes to the API (such as particle size distribution). It is a useful tool to understand the release characteristics of the dosage form thus allowing developmental scientists to select appropriate clinical candidate.

Scale-Up and Post Approval changes for non-sterile semisolid dosage forms (SUPAC- SS) guidance published in 1997, allows manufacturers of topical dosage forms to use validated IVRT to compare batches pre and post changes for certain levels of changes. Knowing the release profile of the product at the early stage and subsequently throughout the development cycle allows scientists to make appropriate changes to the drug product when necessary.

Mr. Vijay Kshirsagar

Executive Vice President-Corporate QA & Regulatory Affairs, Unichem Laboratories Ltd, Mumbai, India

Mr. Vijay Kshirsagar is a hard core Quality Assurance & Regulatory professional having worked for more than 38 years for reputed names in Indian Pharmaceutical Industry. He is currently the Executive Vice President-CQA & RA of Unichem Laboratories Limited based in Mumbai since last 6.5 years. Prior to Unichem he worked for Ranbaxy Laboratories Limited as Director-Quality (Pharma) & also for Sun Pharma, Lupin, German Remedies, IPCA & Tata Pharma. He has successfully represented his company in US and UK courts regarding IP related matters (Para IV filing).

Mr. Vijay has led from front for successful completion of several regulatory inspections by US FDA, MHRA, EDQM, ANVISA, WHO, TGA etc., both for Pharma & API. Mr. Kshirsagar has been a frequent trainer in India & abroad through several platforms like ISPE, IDMA, IPC, CPHI, USP, PPS etc. He has presented variety of topics related to cGMP, GLP, CV, AMV, Stability testing, Dissolution testing, Microbiological Validations, QbD, Aseptic Monitoring, Handling Regulatory Queries, Root Cause Analysis, CAPA, etc. He is currently working on the board of Directors of ISPE-India. He is also the President of 'Society for Pharmaceutical Dissolution Science'. He has been conferred upon with an 'Outstanding Analyst Award 2012' by IDMA for his contribution towards pharmaceutical analysis. Mr. Kshirsagar has a Post Graduate degree in Organo-analytical Chemistry by Research, from Mumbai University.

Mr Kshirsagar is now coming out of his regular employment with Unichem and will be working as a Consultant for his present company (Unichem) and other pharmaceutical firms. As a consultant he would offer his services for areas related to **T**raining, **R**egulatory, **A**uditing & **C**ompliance. Hence he has planned to name it as **TRAC** Consulting.

DEALING WITH OUT OF SPECIFICATION RESULTS OBTAINED IN DISSOLUTION TESTING

OOS is still a cause of great concern to regulatory bodies all across the globe. Different degree of understanding have led to many different approaches towards investigation of OOS results. Further the dissolution testing is particularly critical considering the impact of wrong results if any. Presentation is aimed at explaining possible common reasons for OOS results, explaining the decision tree step by step, doing impact analysis & arriving at proper corrective & preventive actions.

Available guidance's from US FDA and EU authorities shall form the basis of discussions. Number of case studies too shall be presented to sensitize on the issues involved.

Dr. Vinay G Nayak

President-Technical operations, Alembic Pharmaceuticals Ltd. Vadodara, India

Dr. Vinay Nayak is a highly motivated pharmaceutical professional with more than 28 years of experience working with 4 reputed Pharmaceutical organizations. Responsible for building and leading professional teams of various technical functions through which these organizations grew in strength in domestic and international markets. Strong interpersonal skills, connectivity with industries current trends and experienced in Technical operations involving Dosage forms and API's and Quality operations with leadership of Research and Development and Regulatory Affairs. Responsible for setting industry standards in manufacturing operations, Quality control, Quality Assurance, R&D / RA systems across big organizations.

Dr. Nayak has been a member of Indian Pharmacopeia commission, member of Advisory Board of USP, Chairman of IFPRESS which supplies IP references standards, Advisor to Govt. of India for framing national guidelines on GMP and GLP.

Dr. Nayak is expert in the area of Inhalation technology and eminent speaker at national and international conference.

Harmonisation of Pharmacopoeal Dissolution Testing

The pharmacopoeias of USP, EP JP and IP have their own chapters on General monographs for testing each type of dosage forms which are different from each other.

Added to the differences in testing methodology on individual product dissolution test there are differences in the form of calculation of results, some pharmacopoeia use a single point result, others allow repeat testing based on statistics, and some methods average out the results.

We all know that dissolution test serves two purposes.

1 To map the test product against the reference product in 3 to 5 different media at various time points and calculate the similarity factor before a decision is taken to go for Bio-equivalence studies.
2 To use the dissolution method to evaluate each manufactured batch in accordance with the bio-batch or the specified pharmacopoeia method as Quality Control specifications.

The presentation highlights the differences in the dissolution between USP, EP, JP and IP in terms of General monograph, setting limits and standards and new developments by each of these standard setting organization's at harmonization to one Global standard.

All aspects of differences and attempts at harmonization will be discussed.

The speaker is a member of Indian Pharmacopoeia since 1991and also worked closely with USP &EP in the area of development of monographs.

P001-Lyophilization Monophase Solution Technique for Improvement of the Solubility and Dissolution of Piroxicam

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Department of Pharmaceutics, J.S.S College of Pharmacy, J.S.S. University, S.S Nagar, Mysore, India.

Introduction:-

Piroxicam, an anti-inflammatory drug, exhibits poor water solubility, dissolution and flow properties [1]. The aim of the present study was to improve the solubility and dissolution rate of Piroxicam by preparing crystals using the freeze drying technique, and employing solvents DMF and chloroform. [2].

Key words: - Piroxicam, Lyophilization monophase solution, Direct compression tablets, freeze dried crystal

Experimental Methods:-

Preparation of freeze dried crystals of Piroxicam : Piroxicam (2.5g) was dissolved in 25 ml of is DMF heated at 45^0 until a clear solution was obtained. The drug solution was poured in to 68 ml solvent mixture consisting of water and chloroform (7ml) maintained at room temperature. The resulting solution was shifted to 100 ml glass bottle and then transferred to and maintained in an ultra low freezer at - 40 ^{0}C for 24 hr. The frozen drug solution was placed in a lyophilizer for 72 hr (IISHIN Lab. Co. Ltd. Korea), with a condenser temperature of - 40^0C and a pressure of 7×10^{-2} mbar followed by a secondary drying at 25 ^{0}C for 24 hr. The resulting crystals were stored in desiccators at room temperature until further experiment.

Recrystallized Piroxicam:-Recrystallized sample of Piroxicam was prepared by using Piroxicam and various solvent compositions with occasional shaking with glass rod to find out the impact of solvents and process on Piroxicam.

Determination of residual solvents in Freeze dried crystals by gas:- GC studies were carried out on SHIMADZU model 2014 gas chromatograph.

Characterization of freeze dried crystals:-Freeze dried crystals were characterized by Differential scanning calorimetry, Fourier transform infrared spectroscopy, X-Ray Diffraction, and Scanning electron microscope.

Solubility studies:-The solubility of freeze dried crystals in distilled water was determined by taking excess quantity of freeze dried crystals. The vials were shaken for 24 hours on mechanical shaker (Presto Testing Instruments, Mumbai) and the drug concentration was determined spectrophotometrically at 332 nm.

Dissolution studies of agglomerates:-The dissolution of Piroxicam pure sample, freeze dried crystals and recrystallized sample was determined by using USP dissolution apparatus Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml of Phosphate buffer (pH 7.4). The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 332 nm.

Determination of the physical stability:-To determine the physical stability of freeze dried crystals, they were packed in suitable packaging (sample were kept in 10 ml transparent glass bottle and covered by aluminum foil) and placed in a stability chamber maintained at 40^0C and 75% relative humidity (RH) for 90 days.

Preparation of tablets:-Piroxicam tablets containing different crystals were prepared by direct compression with directly compressible tablet excipients using Single Rotary Tablet Punching Machine (Riddhi Pharma Machinery Limited, Mumbai).

Results and Discussion:-

The solvent system involved in preparation of freeze dried crystals was DMF, chloroform and water in ratio of (25:7:25). The selection of these solvents was based on the miscibility of the each of the solvents and the solubility of Piroxicam in individual solvent.The resulting crystals were small in size, and were found to be free flowing compared to commercial Piroxicam. The % yield found to be in the range of 60-80% and drug content was in the range of 97-99%. Gas chromatography results confirmed that there were 3.8 and 2.4 ppm residual of DMF and chloroform present in the freeze dried crystals respectively, which was much lower than the permitted limits i.e. 880 & 60 ppm respectively.The DSC thermograms showed a sharp endothermic peak for all the Piroxicam crystals. This one step melt is due to only one crystal form (Triclinic) of the Piroxicam formed during the crystallization process.

Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor

distortion of bond angles, or even a result of the presence of a solvent of crystallization.

The characteristic peak of the Piroxicam appeared in the 2θ range of 0–60°. All the prepared crystals of Piroxicam showed similar peak positions (2θ) in X-ray diffraction.(Fig 1)

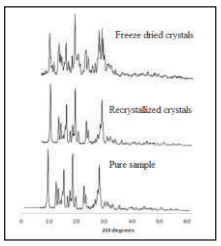

Fig.1:X-ray diffraction spectra of Piroxicam Samples

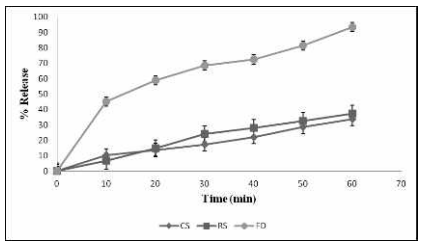

Fig. 2: Dissolution of different Piroxicam Crystals

In SEM study showed that crystals of pure sample are of the smallest size (5-10 µm) and they have irregular shapes. Recrystallization crystals were of intermediate size (7-18 µm) and appeared rod like. The freeze dried crystals were formed by microcrystalline precipitates, with a smooth surface and average (particle size of around 365 nm). Freeze dried crystals showed increased solubility compared to the **commercial piroxicam** in distilled water **which was more than ten folds (0.0924 mg/ml) than commercial piroxicam (0.0084 mg/ml), and dissolution rate was increased four fold; also, the dissolution rate of tablets prepared from freeze dried crystals showed marked improvement in dissolution rate.** Stability studies indicated that the freeze dried crystals of Piroxicam were stable for 90 days.

Conclusion:-

Freeze dried crystals of Piroxicam were found to possess decreased crystallinity and improved mechanical properties, enhanced solubility, were safe in terms of solvent residuals, and the dissolution of tablets containing freeze dried Piroxicam showed improved release compared to tablets containing pure sample. In conclusion, freeze drying technique can be used for Piroxicam to enhance the solubility and to achieve better dissolution from tablets prepared by direct compression.

Acknowledgements

The authors are thankful to **Principal, J.S.S.College of Pharmacy** for providing facilities to carry out this work.

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P002-Timolol Maleate loaded Chitosan Mucoadhesive Nanoparticles for Better Bioavailability in Ocular drug delivery system

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Introduction: Glaucoma is the 2nd major cause of blindness in the world after cataract. Management of glaucoma through eye drops that reduce IOP (Intra ocular pressure) has major deficiencies including low patient compliance and low bioavailability. Many effective anti-glaucoma drugs, available for the treatment of ocular hypertension and open angle glaucoma are associated with rapid and extensive precorneal loss caused by drainage and high tear fluid turnover. This study has focussed on the design of mucoadhesive nanoparticulate carrier system containing timolol maleate for ocular delivery to improve its corneal absorption.

Keywords: Timolol Maleate, Chitosan, Nanoparticle, Mucoadhesive, Glaucoma

Experimental:

Preformulation studies which encompass the purity of drug candidate, its calibration curve in artificial tear fluid and the compatibility between the drug and the selected polymers were evaluated **[1]**.

Formulation and optimisation of chitosan-polyacrylic acid (CS-PAA) nanoparticles (NP) Different batches of CS-PAA nanoparticles were prepared by template polymerisation method. In order to induce polymerisation of acrylic monomers, an initiator potassium persulfate was added to the solution of chitosan dissolved in 50ml of acrylic acid (AA). The pH value of the system was maintained at about 4. The mixure was maintained at 70°C, under magnetic stirring and nitrogen atmosphere. The reaction was stopped once the mixture became opalescent. The solution was dialyzed against distilled water in a 12-14 KD cut off membrane for three days, to remove the unreacted monomer and other reagents.

Evaluation of CS-PAA nanoparticles

Physiochemical Characterisation: Selected NP was evaluated to determine particle size, zeta potential, polydispersity index and encapsulation efficiency

Invitro **drug release study:** This was studied by using dialysis bag diffusion technique using simulated tear fluid of pH 7.4, as medium, and at 37±0.5°C. In order to elucidate mode and mechanism of drug release, the in vitro release data obtained for the formulation was fitted into various kinetic models **[2]**

In vitro **transcorneal permeation study** Goat corneas were used to study the permeation of Timolol Maleate across the corneal membrane. The study was carried out in Franz diffusion cell. The upper chamber served as a donor compartment in which one drop of drug formulation under study was placed. The lower chamber served as a receiver compartment that was filled with simulated tear fluid. The whole system was maintained at 37 ± 0.5°C. At predetermined time interval, , aliquots were withdrawn, for upto 6 hrs,and the amount of Timolol Maleate by UV-Visible spectrometer at wavelength of 294nm.

Results and Discussions

Formulation and optimisation of Chitosan Polyacrylic acid (CS-PAA) nanoparticles

Synthesis of CSS-PAA nanoparticles was done by template polymerisation method. As the polymerization time extended, the amount of PAA in the solution increased, and the system changed initially from a clear solution to an opalescent emulsion indicating the formation of CS-PAA nanoparticles. The electrostatic interaction between PAA (negative charge) and CS (positive charge) promoted the self-assembly of Nanoparticles.

Evaluation of CS-PAA nanoparticles: Since the optimised formulation F6 and F8 showed appreciable values for the below parameters, they were found ideal for ocular drug delivery. Among all the batches, F8 showed the maximum entrapment efficiency of 69.75 % (Tables 1 & 2).

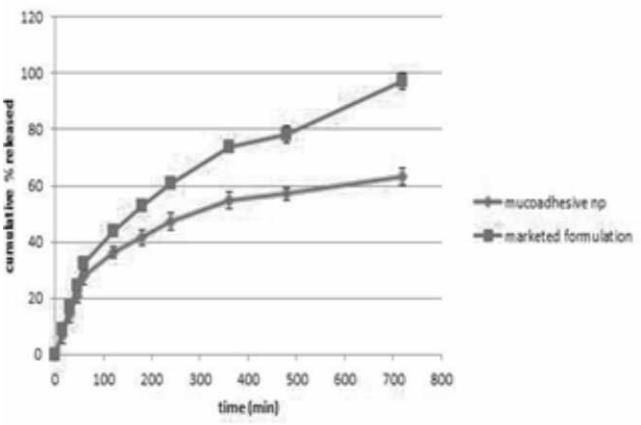
Table 1

BATCH	AA	CS	K2S2O8	Z-Average	Zeta potential	PDI
F6	12 mM	3 mM	0.1 mM	378.1nm	-7.42mV	0.432
F8	6 mM	6 mM	0.1 mM	141.29nm	23.30mV	0.339

Table 2

Release kinetics				
FORMULATION	R^2			
	Zero order	First order	Higuchi's	Peppa's plot
Ideal batch	0.7791	0.875	0.9502	N=0.534

In vitro drug release study: Only about 30% drug was released within 1 hour and then 63% of drug was released within 12 hours indicating the sustained release of drug from the nanoparticle core shell. This comparison between nanoparticles with marketed formulation demonstrated that the mucoadhesive nanoparticle was better in retention of Timolol Maleate. The transcorneal permeability study has also corroborated this observation. The in vitro release data obtained for mucoadhesive nanoparticle formulation, in simulated tear fluid pH 7.4, was fitted into various kinetic models. The results are shown in Fig 1. Korsmeyer-Peppa's plot showed that the developed formulation F8 exhibits the mechanism of anomalous diffusion which is ideal for drug absorption.



Conclusion: From all of the above studies, it is to be highlighted that the developed formulation is a viable alternative to the conventional eye drops, and due to its sustained effect in ocular milieu, it can be a promising, safe and convenient formulation for the management of glaucoma.

ACKNOWLEDGEMENTS

I thank the Principal, J.S.S College of Pharmacy, Ooty for providing all the facilities for carrying out this work.

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P003 - Formulation and in vitro release evaluation of Telmisartan melt dispersion

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Key words: Telmisartan, pH modifiers, Gelucire, solid dispersion

Introduction:

Telmisartan (TEL) is angiotensin II inhibitor used in treatment of hypertension.TEL is BCS class II drug showing poor and pH dependent solubility. It is a readily ionisable drug with high solubility in strong acidic and basic conditions [1] and extremely low solubility in pH range 3-9. Solid dispersion is one of the methods to improve dissolution of poorly soluble drugs and subsequently their oral bioavailability.

Methods

TEL melt dispersions were prepared by melt method using Gelucire 44/14 or 50/13 and alkalisers like sodium hydroxide, sodium bicarbonate, magnesium hydroxide. Briefly, molten Gelucire was added to TEL dispersion in alkaliser solution. Avicel PH 101 was added to the paste and kneaded well to form dough. Dough was passed through 25# sieve. The granules obtained were further evaluated.

Optimisation

TEL melt dispersions were prepared with varying concentrations of Gelucire and alkaliser as given in table 1.

Table 1: TEL melt dispersion granules composition

Formulation	T1	T2	T3	T4	T5	T6	T7	T8	T9
TEL	4	4	4	4	4	4	4	4	4
Gelucire44/14	16	80	-	16	16	16	-	16	-
Gelucire 50/13	-	-	16	-	-	-	-	-	16
NaOH	-	-	-	-	-	0.33	0.33	0.33	0.33
NaHCO3	-	-	-	1	-	-	~1	~1	~1
MgO	-	-	-	-	1	-	~.0.2	~0.2	~0.2
Avicel ph101	-	-	-	-	-	32	32	32	32

Evaluation: Drug content in formulation was analysed by UV method. In vitro dissolution studies were performed on formulation equivalent to 20 mg TEL using USP type II paddle apparatus in 900 mL of pH 7.5 phosphate buffer USP at 37^0 C, 75 rpm for 2h.Aliquots were analysed for TEL content by UV spectroscopy. Dissolution of optimized formulation (T8) was also performed in 0.1M HCl.

Results and Discussion

Assay TEL content was found to be in accordance to theoretical calculated values. Pure TEL powder dissolved ~ 9.3 % in pH 7.5 phosphate buffer solution in 2h.

Effect of Gelucire: Formulations prepared with TEL: Gelucire 44/14, 50/13 in 1:4 ratios showed 19.5, 16.9 % release (T1, T3) respectively at the end of 2 h. Increase in Gelucire proportion in T2 did not increase the dissolution of TEL further.

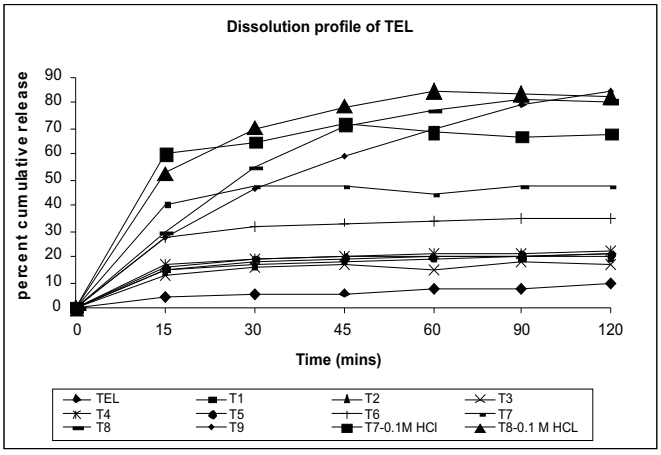
Effect of alkalisers: pH modifying agents were evaluated to modify the release rate of TEL melt dispersion prepared with sodium bicarbonate and magnesium hydroxide (Formulation T4, T5) showed nearly 20% TEL release in 2h as shown in fig.1. With addition of a stronger base, sodium hydroxide (T7), dissolution of TEL increased to nearly 45%. Sodium hydroxide increases the pH in the immediate vicinity of TEL in dissolution medium aiding in solubilisation. It is reported that TEL degrades in strong alkaline conditions [2]. Hence NaOH concentration was optimized in T6 to avoid degradation of TEL.

Effect of Gelucire with alkalisers: Formulation prepared with Gelucire 44/14 and all three alkalisers released 80% of TEL in 2 h (T8, T9). TEL melt dispersions prepared with Gelucire 50/13 showed dissolution profile similar to that of Gelucire 44/14.**TEL release from dispersion prepared with Gelucire and alkalisers (T8, T9) was significantly higher than the amount released from dispersion prepared without Gelucire (T7).** In acidic medium, TEL release from T7 and T8 was 70% and 85% respectively. It was evident that **Gelucire 44/14 and 50/13 significantly enhance dissolution of TEL from formulation.**

Gelucires which are polyethylene glycol glycerides, possess surfactant and self-emulsifying properties. It probably improves wettability of TEL and forms fine emulsion in dissolution medium solubilizing TEL. Gelucire effect on TEL dissolution is more pronounced in pH 7.5 buffer, dissolution medium for TEL tablets in USP monograph.

Locally available TEL tablets reportedly released <40% in 1h in pH 7.5 medium [3]. The optimized formulation T8, T9 showed 70-75% TEL release in 1h. Gelucire emerged as a potential dissolution enhancer for TEL.A combination of Gelucire and pH modifiers was effective in improving dissolution kinetics of TEL.

Fig. 1. Dissolution profile of TEL



Conclusion: We conclude that TEL dissolution can be improved with aid of surfactant like Gelucire and alkalisers. TEL solid dispersion will be promising approach to improve oral bioavailability.

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P004 - Pharmacokinetic Evaluation of Quinine in Tablet Formulation from Herbal Extract

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Keywords: Quinine, Cinchona officinalis, herbal tablets, herbal extracts.

Introduction:

Pharmacokinetics (PK) is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism. PK is divided into several areas which includes the extent and rate of Absorption, Distribution, Metabolism and Excretion. PK parameters are the only criteria to design the dosage regimen of specified herbal drug in order to avoid drug related side effects and toxicity in one hand and better therapeutic efficacy on the other hand. The pharmacokinetic determination of quinine through herbal extract has been undertaken to study the scientific data on pharmacokinetic profile of quinine in herbal extract. The rationale of this work was to formulate oral herbal tablets containing quinine and to determine the pharmacokinetic profile of this herbal extract tablets.

Methods:

Preparation of Cinchona Extract: This study involved collection of Cinchona officinalis. **Plant bark, from Homeopathic Medicinal Plant Cultivation Research Garden, Emerald, Ooty. Extraction was carried out with methanol and the semisolid extract obtained was** quantified for quinine content by HPTLC, followed by preformulation and compatibility studies. Tablets of the extract were formulated by direct compression technique. The best batch was subjected to in vitro dissolution studies and PK studies of the developed formulation using rabbit model, by oral route. The in vitro dissolution studies were carried out using USP apparatus type II (Electro lab, Mumbai, India) at 100 rpm. The dissolution medium consisted of 900 ml of 0.1N HCl acidic buffer pH 1.2 for upto one hour, maintained at 37°C ± 0.5°C. The drug release at different time intervals in withdrawn aliquots was measured by UV-visible spectrophotometer (Shimadzu) at a max of 250nm.

HPLC method was used to analyze Quinine content in plasma samples withdrawn in the PK studies on rabbits. A Shimadzu SPD-M20A HPLC [1,2] system was used for the analysis Stationary phase: Phenomenex GEMINI C_{18} (250 x 4.6 mm i.d., 5), Mobile Phase: Phosphate buffer (PH 3.5): Acetonitrile, Mobile phase ratio : 80:20 % v/v, Flow rate: 1.0 ml/min Sample volume : 20l using Hamilton injector, Detection : 254nm using SPD-M20A 230V PDA detector, Data station: LC solutions. The mobile phase was filtered through a 0.22m membrane and degassed using ultrasonicator. Extraction was performed using SPE catridge. All statistics were made by means of one way ANOVA followed by Tukeys test by using Graph pad Prism version 5 software. Non significant variation ($P<0.05$) was found when area under curve (AUC) of extract formulation was compared with pure and marketed formulation.

Results The study was focussed on formulation of oral herbal tablets containing quinine in herbal extract. The bark of Cinchona officinalis was used for extraction to get the quinine extract. The quantification of extract was done by HPTLC using pure quinine sulphate as the marker compound, and was found to be 5.16%w/w. The dissolution rate was found to be 98% after 1 hr for extract formulation (Fig 1); The human dosage was predicated by surface to area calculations, from the pharmacokinetic profile obtained for the quinine in herbal extract tablet after oral administration to rabbits (Table 1). The quinine content in extract tablet was found to be approximately 17.4mg/tablet, which is too small an amount to produce the reported therapeutic window against 300-600mg quinine dose. Therefore, for the predicted dosage, for the human adult, a very high amount of the extract containing quinine needs to be given to attain the required therapeutic range.

Fig 1: In vitro **drug release studies of Quinine, Extract and Marketed formulation**

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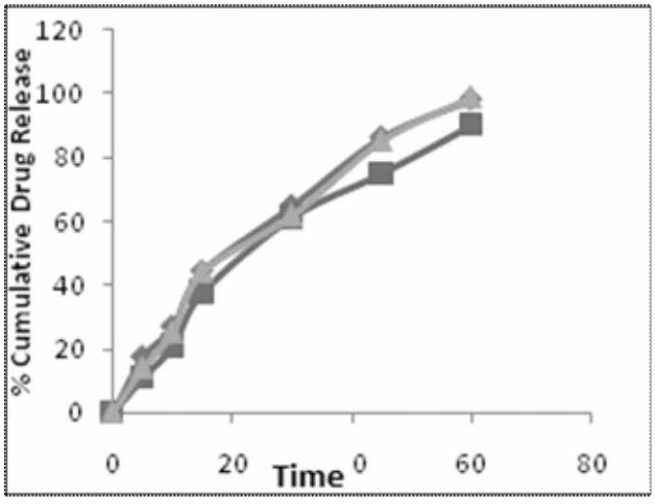

S.No	Parameters	Standard Formulation		Extract Formulation		Marketed Formulation	
		Dose 14 mg/kg	Dose 28mg/kg	Dose 271mg/kg	Dose 542mg/kg	Dose 14mg/kg	Dose 28mg/kg
1	C_{max} (µg/ml)	2.712	2.768	2.372	2.595	3.25	3.7
2	T_{max}(hr)	3	3	3	3	3	4
3	$K_{eli}(h^{-1})$	0.102009	0.081137	0.0462	0.112532	0.080521	0.063901
4	$t_{1/2(h)}$	6.794966	8.542876	15.00306	6.159557	8.608253	10.84718
5	AUC_{o-t} (µg.h/ml)	14.34761	18.72165	16.88695	12.60567	18.74689	25.93781
6	AUC_{0-inf} (µg.h/ml)	15.52232	20.68025	23.61455	13.5497	22.02407	32.6225
7	Lag time (hr^{-1})	No	No	No	No	No	No

Conclusions

The present study has provided comparative data on PK parameters of tablets prepared from Cinchona extract v/s pure quinine tablets and has also revealed that the herbal tablet is inadequate.

Acknowledgments

Authors wish to thank JSS University, Mysore and The Principal, JSS college of Pharmacy, Udhagamandalam for providing necessary facilities.

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P005 – Applying Biopharmaceutical Classification System (BCS) to Herbal Medicinal products

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Keywords: Solubility, Permeability, Biopharmaceutical Classification System

Introduction: In the regulatory process, efficacy, safety and appropriate pharmaceutical quality are mandatory for all medicinal products. In case of solid oral dosage forms for systemic action, the biopharmaceutical performance must also be characterized by suitable in - vitro and in- vivo investigations. These global requirements are not only relevant for synthetic chemical entities, but also for herbal remedies. However, due to their complex composition, such information is not available at the moment for most herbal medicinal products. **The present study attempts** to carry out meaningful dissolution tests for selected herbal products and to fit herbals into biopharmaceutical classification system.

Methods:

Selection of extracts and constituents to be fitted into BCS - curcumin, piperine, quercetine and rutin are the commonly used phytoconstituents which are used in several ayurvedic formulations alone or in a combined form.

Solubility estimation by shake flask method-The pH- solubility profile of the test drug substance was determined at 37 ± 1°C in aqueous media in buffers of pH in the range of 1- 7.5 (actual pH values : 1.2, 4.5, 6.8 and 7.4). A minimum of three replicate determinations of solubility at each pH condition was carried out. The herbal markers listed above and extract solutions were kept in the orbital shaker for 72 hours and at the end of 72 hours the samples were withdrawn and analysed by RP-UFLC.

Permeability studies-were carried out by everted intestinal sac method. The intestinal sacs were prepared from intestines of male white leghorn chicks. The excised intestines were suitably washed, cleaned and maintained in oxygenated Kreb's Ringer's solution. The proximal extremity of the intestine was turned back and ligated on a glass rod to form an everted bag. This bag was then mounted in the dissolution vessel as shown in Fig 1. Herbal drugs and the extracts were placed in the Krebs–Ringer solution media which is placed in the dissolution vessel (Fig 1). Dissolution vessel was supplied with aeration in order to maintain tissues. Samples were withdrawn from the specially designed sampling point and the drug permeability was calculated by injecting the sample into RP-UPLC.

Fig no 1: Everted tissue apparatus design model

Results and Discussion

Solubility Studies-A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of water over a pH range of 1–7.5 at 37 °C. The results of solubility studies at four different pH values (Table 1) indicated that all the samples had less solubility. Permeability study was carried out using Peff which is one major determinant of the fraction dose absorbed, and quantitatively represents the principal membrane transport coefficient of the intestinal mucosa of a substance. If the valve of Peff is higher or equal 1.78 then its highly permeable. Based on the Peff all the sample showed very low permeability ranging from 0.00014 – 0.082178 which are shown in table 2. Since all the markers and extract have low solubility with more dose number which is greater then 1 and low permeability value less than 90% hence all the compounds may be included as Class IV type.

Table 1: Solubility study for herbals

S.no	Name	Mo[mg]	Dose number (Do)				Solubility
			1.2	4.5	6.8	7.4	
1	Curcumin	500	15539.77	2305.545	24866.65	18521.95	Low
2	Quercetin	500	59345.42	26494.28	45007.54	186081.1	Low
3	Rutin	500	1026.246	1845.41	983.6464	1183.405	Low
4	Piperine	10	816.1933	517.5381	1382.457	1945.052	Low
5.	Orange peel extract	500	136.9118	186.8838	97.44229	118.242	Low
6	Thymus extract	500	296.2946	269.5933	287.7335	174.319	Low
7	Green tea extract	500	10.75468	25.61391	24.75089	18.72212	Low
8	*Glycyrrhiza glabra* extract	500	3.09553	3.563276	4.182946	3.98765	Low
9	*Piper nigrum* extract	10	768.5066	102.6051	1017.009	1055.632	Low

Note : If dose no is higher than 1 then it is a low soluble drug.

Conclusion

The current BCS classification of herbal extracts and their markers may improve the quality of herbal medicinal drugs. Once the herbals have been fitted in the classification system it is convenient to know the solubility and permeability of the compounds which helps in the formulation development and pharmacokinetic profiling of the drugs which are major limitations for herbal formulation.

Acknowledgments

Authors wish to thank JSS college of Pharmacy, Udhagamandalam and JSS University, Mysore for providing necessary facilities.

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P006 - In vitro permeation study of Cyclodextrin complex and Liposomes in topical delivery of Ketorolac and in vivo advantage

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Keywords:

Ketorolac, Cyclodextrins. Liposomes, In vitro Permeation, Topical.

Introduction:

Ketorolac (KTRA), a BCS class II drug used for treatment of moderate to severe pain, possesses half life of 4-6 hrs irrespective of administration route, thus compelling for frequent dosing to allay pain [1-4]. Though oral administration offers 90% bioavailability, KTR causes severe gastrointestinal (GI) side effects such as bleeding, perforation, GI ulcers and renal failure, thus limiting its oral application [4,5]. Parenteral administration is not patient friendly, more so when frequent dosing is inevitable. Aforesaid reasons coupled to its physicochemical properties (log P: ~2.3 and low M.W.: 255) renders KTRA an excellent candidate for topical/transdermal delivery. Experiments were undertaken to design cyclodextrin complex and liposomes of KTRA with objective to improve its effectiveness on topical application.

Methods:

Ketorolac – Hydroxy propyl β- CD (KTRA-HPBCD) complexes were prepared by kneading method. Liposomes were formulated by lipid film hydration method, containing either KTRA-HPBCD complex or Ketorolac tromethamine (KTRM). The KTRA-HPBCD complex was characterized by DSC, XRD, IR studies and showed excellent dissolution profile. Liposomal dispersions were also characterised for encapsulation efficiency and particle size analysis. Five formulations, namely, KTRM solution, KTRA saturated solution, KTRA-HPBCD complex as solution, KTRM containing liposomes (KTRM-L) and KTRA-HPBCD containing liposomes (KTRA-HPBCD-L) were evaluated for in vitro permeability studies employing guinea pig's abdominal skin on Franz diffusion cell. KTRA-HPBCD which showed best in vitro skin permeation was incorporated in to a gel formulation, and consequently evaluated for in vivo anti-inflammatory effect in rat paw edema model in mice, in comparison to orally delivered KTRM solution.

Results:

DSC, XRD and IR studies indicated of sufficient interaction between KTR and HPBCD and demonstrated amorphous nature of KTR after complexation which resulted in excellent dissolution. Encapsulation efficiency in liposomes was found to be 10.32±1.5% and 10.64±1.43% for KTRM and KTRA-HPBCD respectively. Size analysis revealed mean size of 3.82±0.19 μ and 4.91±0.05 μ for liposomes loaded with KTRM and KTRA-HPBCD respectively.

As shown in Fig. 1, in vitro permeability studies revealed that the complexation of the KTRA with the HPBCD significantly increased the permeation of KTRA from the skin as compared to all the other systems employed in the study ($P<0.05$). This corroborated well with in vivo results (Fig. 2) which revealed that KTRA-HPBCD gel was equally effective as orally delivered KTRM solution in demonstrating anti-inflammatory activity in mice at 6th hr.

Conclusion:

In vitro release evaluation of KTRA-HPBCD in transdermal penetration established its superior penetration ability. Topical KTRA-CD gel appeared to be an interesting and promising approach for KTRA delivery, circumventing the adverse effects associated with oral KTR therapy with no alteration of efficacy and is patient friendly unlike parenteral delivery.

Fig. 1: In vitro release profiles of various formulations evaluated:

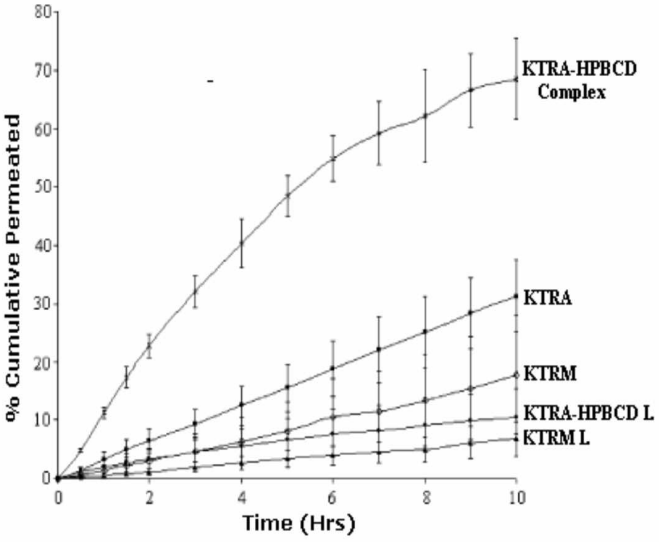
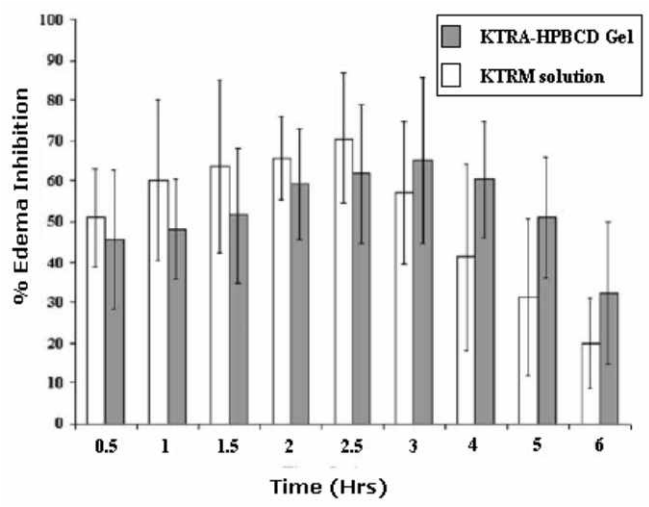


Fig. 2: In vivo anti-inflammatory study in mice



Acknowledgements: Authors are thankful to Phospholipid GmBH (Germany), Cerestar (USA) and Sun Pharma (India) for providing the gift samples of Phospholipon 90G and 90H, HPBCD and KTR, respectively.

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P007 - Investigation of In Vitro In Vivo Release Profiles of Buprenorphine Hydrochloride Loaded Nanoparticles For Colon Targeting

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Keywords:

Buprenorphine Hydrochloride, Eudragit S-100, Colonic pH, Nanoparticles, targeting.

Introduction:

Analgesic drugs with low oral bioavailability are generally given by parenteral, sublingual or transdermal routes. Design of oral modified release systems for poorly soluble drugs that are additionally CYP 3A substrates such as Buprenorphine HCl (BHCl) is challenging not only because of their low solubility and dissolution rate, but due to their high metabolic inactivation as well.

A modified release formulation of opioid analgesics has the potential to provide fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes and increased control over the management of pain. In addition, such a formulation may provide more constant plasma concentrations and clinical effects, less frequent peak to trough fluctuations and fewer side effects, compared with short acting opioids [(1)]. To overcome the limitations of presystemic metabolism, a targeting approach is proposed for site-specific drug delivery in those segments of the gut where expression of the CYP 3A enzymes is minimal [(2)].

Objective:

- To design and characterize modified release oral formulation of BHCl for Colon targeting.
- Development of suitable drug dissolution colonic media and in-vitro in-vivo evaluation of BHCl based on dissolution profile and pharmacokinetic data.

Experimental Methods:

Development of pH-sensitive nanoparticles: Eudragit® S100 nanoparticles were developed by solvent evaporation method. Drug loaded nanoparticles were prepared by adding aqueous phase containing drug and surfactant to polymeric organic phase. Nanoparticles were evaluated for parameters like: particle size by PCS (Beckman Coulter, USA), zeta potential (Malvern, USA), surface morphology and shape by transmission electron microscopy (TEM) (Philips), drug entrapment by HPLC (Perkin Elmer) and drug- polymer interactions by DSC.

In-vitro dissolution method development: Dissolution method with gradient pH was developed for assessment of low dose colon targeted formulation of BHCl. Factors like solubility of drug in different dissolution media, volume to maintain sink conditions and effect of presence of surfactants like SLS and Tween 80 in dissolution media were evaluated. Study was conducted in dialysis bags immersed in automated USP type 2 paddle apparatus (TDT-06T, ELECTROLAB, India) specially designed to study low dose formulations at 37^0C, 50 rpm and 100 ml dissolution medium. Aliquots were withdrawn at predetermined time intervals and were analyzed by validated HPLC method.

In-vivo studies:

Pharmacokinetic evaluation of the developed nanoparticles was attempted in healthy Wistar rats weighing 225-250g as per the Protocol no. CUSCP/IAEC/14/09-10 approved by Institutional Animal Ethics Committee.

Results & Discussion:

The particle size and PI of optimized nanoparticles were found to be 195.1 ±4.72 nm, PI 0.231±0.031. These values indicated narrow particle size distribution. Zeta potential value of -26±2 mV suggested good stability of the optimized formulation. BHCl was successfully loaded into Eudragit S 100 nanoparticulate matrix with entrapment efficiency of 71 % w/w.

The in-vitro drug release profiles of BHCl Solution (0.1% w/v) and BHCl loaded Eudragit nanoparticles were determined in pH 1.2 for 2 hrs followed by phosphate buffer pH 6.5 for 3 hrs and phosphate buffer pH 7.0 upto 24 hrs [(3)]. Significant controlled release of the drug was observed from BHCl loaded Eudragit nanoparticles compared to aqueous solution of BHCl (Fig 2). Drug released in the gastric pH (1.2) was found to be 5-10 %, whereas when formulation was subjected to colonic pH of 6.5 and above; the drug release increased significantly.

Approximately 85% of the drug was released from the nanoparticles in 24 hrs owing to solubility of Eudragit S 100 at simulated colonic pH. Hence, drug release from the optimized formulation was found to be sustained upto 24 hrs.

After oral administration of colon targeted formulation plasma concentrations were determined at time points corresponding to in vitro dissolution data. The C_{max}, T_{max} and AUC were calculated from the plasma concentration verses time plots. In-vivo data supported the hypothesis of improved oral bioavailability through distal colonic delivery of nanoparticles. The results indicated potential in-vitro in-vivo co-relation.

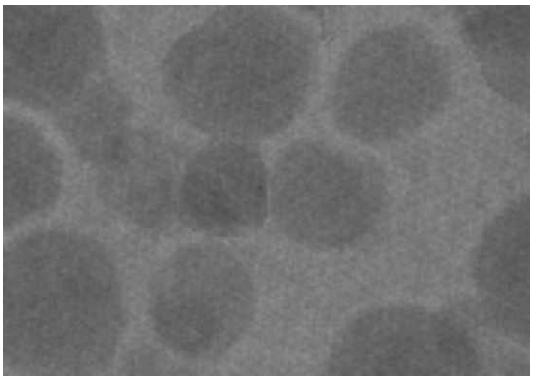

Figure 1: **TEM image of Eudragit NPs loaded with Buprenorphine HCl**

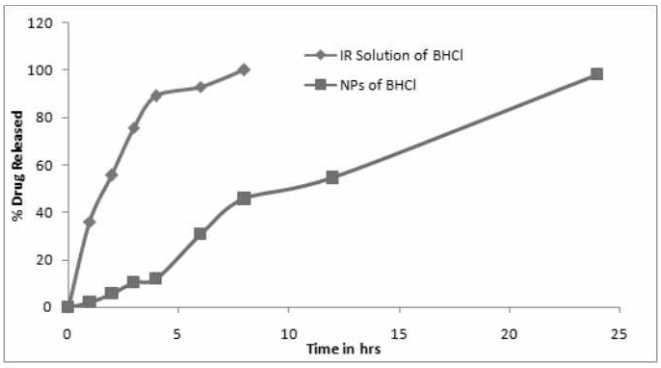

Figure 2: In vitro drug release profiles

Conclusions: For the colon targeting, it is an essential prerequisite that the drug release should be minimal until the dosage form reaches the colon. Dissolution media pH and surfactant concentrations showed profound influence on dissolution profile of Colonic nanoparticles. The developed formulation showed sustained in-vitro drug release profile for 24hrs. In-vivo studies confirmed the colonic delivery of Buprenorphine Hydrochloride. The in-vitro and in-vivo data depicted potential level A IVIVC.

Acknowledgments: Relmada Therapeutics, USA (Sponsors) and ELECTROLAB, India.

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P008 - ESTABLISHMENT OF PHARMACOKINETIC PARAMETERS FOR HERBAL DRUG CONTAINING FORSKOLIN

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Introduction:

Herbal medicines are being manufactured on a large scale in mechanical units, where manufacturers come across many problems such as availability of good quality raw materials and their authentication, proper standardization methodology and quality control evaluation of single drugs and formulations.

Aim and Objectives:

of this project work was to formulate oral herbal tablets containing forskolin in herbal extract (Coleus forskohlii) and to determine the pharmacokinetic profile of these tablets, and compare with that of pure drug. with a view to minimize cost, but also increasing the efficacy, safety, quality and better use of drugs.

Methods:

Solubility studies were done using various pH buffers. Extracts were prepared from the collected roots of Coleus forskohlii, by hot maceration method, and quantified by HPTLC. Tablets were prepared using direct compression method. The in vitro dissolution studies of the developed formulations were carried out using USP apparatus type II (Electro lab, Mumbai, India) at 100 rpm. The dissolution medium consisted of 900 ml of 0.1N HCl (pH 1.2 buffer) with 0.5%w/v SLS as the medium, for 90 mins at 37±0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu) at max 210 nm.[1] The pharmacokinetic studies have been performed and statistically interpretated. The study was carried out with a single dose administration in three healthy rabbits of either sex weighing 1.5 ± 0.2 kg for each dose of each formulation. [2]The dose for the study taken was 1.16mg/kg and 2.33 mg/kg of pure Forskolin and the dose for extract formulations were 17.90mg/kg and 15.58mg/kg respectively.

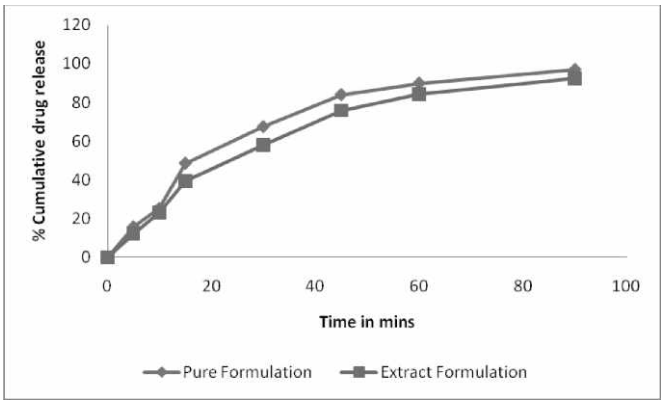

Table 1: Pharmacokinetic Parameters

S.No.	Parameters	Standard formulation		Extract Formulation	
		Dose: 1.16mg /kg	Dose: 2.33mg/ kg	Dose: 7.90mg/ kg	Dose: 15.58mg/kg
1	C_{max} (ng/ml)	673.09	795.14	677.74	848.88
2	t_{max} (h)	2	2	2	2
3	k_{el} (h^{-1})	0.0849	0.0780	0.0764	0.0740
4	$t_{1/2}$ (h)	8.16	8.87	9.06	9.36
5	$AUC_{(0-8)}$ (ng. h/ml)	3447.82	3749.11	3309.41	3984.74
6	$AUC_{(0-8)}$ (ng. h/ml)	5227.60	5882.60	5303.24	6384.21
7	Lag time (hr^{-1})	No	No	No	No

Results: Solubility studies have shown that the drug was highly soluble in pH 1.2 buffer. The quantification of forskolin content in the extract was determined by HPTLC by using pure forskolin as a marker compound and was found to be 14.68%w/w. The percentage cumulative release for pure drug and extract at 90 min were found to be 97.05 and 92.36 respectively. The pharmacokinetic data obtained for pure drug

and extract of forskolin shows no significant difference in C_{max} at t_{max} of 2hr. Even the rate of absorption was almost same with the reported therapeutic value of 0.003 to 300mg/kg/day and the obtained half life ranging from 8-10 hrs.

Conclusion: In conclusion it can be inferred that studies are needed to acess any advantages of the extract of forskolin compared to the pure form.

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P009 In Vivo Characterization and IVIVC of SNEDDS Containing Poorly Soluble Drug Olanzapine

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Key Words: SNEDDS, IVIVC, Olanzapine

Introduction:

This work deals with the investigation of in vivo bioavailability of Self Nanoemulsifying drug delivery system (SNEDDS) of Olanzapine, and development of in vitro- in vivo correlation for this formulation. In vitro dissolution testing is a powerful and useful method for determining product quality. The normal compendial approach for the dissolution medium cannot predict the actual in vivo conditions and to overcome this, biorelevent media are developed to mimic the in vivo physiological conditions[1]. Most lipid-based formulations are designed to deliver the entire dose in solution thereby bypassing the dissolution process in the gastro-intestinal (GI) tract, which has been recognized as one of the main prerequisites for the efficiency of these formulations[2]. Further, in vivo studies are necessary for the evaluation of bioavailability of drug from the lipid based formulations. The ultimate goal of in vitro - in vivo correlation (IVIVC) should be to establish a meaningful relationship between in vivo behavior of a dosage form and in vitro performance, which would allow in vitro data to be used as a surrogate for in vivo behavior.

Methodology:

In vitro dissolution studies: were performed in 0.1N HCl and also in the biorelevant medium (to mimic the in vivo conditions) to determine any changes in the dissolution of the formulation[3].

In vivo bioavailability studies: The bioavailability studies were conducted using New Zealand white rabbits and the pharmacokinetic parameters like Maximum plasma concentration (Cmax), time of maximum plasma concentration (tmax), Area under the curve 0 to 24 h ($AUC_{0\rightarrow t}$), Area under curve 0 to ∞($AUC_{0\rightarrow\infty}$), elimination half-life (t1/2), elimination rate constant (ke) [4]

Statistical analysis: Statistical analysis were conducted by one way ANOVA followed by Tukeys test to know whether there is significant increase in the bioavailability.

Further, the in vitro and in vivo results were analyzed and attempts were made to establish IVIVC[5].

Results and Discussion: Olanzapine was found to be highly soluble in 0.1 N HCl (90.3±2.3 mg/ml) and biorelevant medium (93.1±3.1 mg/ml).). In vitro dissolution studies showed that Olanzapine rapidly released (≥98%) from the optimized SNEDDS into the biorelevant medium. Peak concentration (C max) and time of peak concentration (T max) were obtained directly from the individual plasma-concentration time profiles. The area under the concentration- time curve from time zero to time t ($AUC_{0\rightarrow t}$) was calculated using the trapezoidal method. Based on in vivo bioavailability studies it was concluded that there is a 1.3 fold increase in the bioavailability when compared to marketed tablet formulation (OleanzTM 2.5 mg) and 1.6 fold increase when compared to that of drug suspension when Olanzapine was given as SNEDDS. Level A correlation was developed with the correlation factor 0.97.

Conclusion:

The level A correlation with correlation factor 0.97 was achieved and from this it was concluded that there is a good correlation between in vitro dissolution, and in vivo bioavailability data for the developed SNEDDS formulation of Olanzepine, and the dissolution studies could be used as a surrogate for the in vivo studies.

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P010 FORMULATION AND IN VITRO EVALUATION OF ORALLY DISINTEGRATING TABLETS OF RIZATRIPTAN BENZOATE

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Key Words:

Orally disintegrating tablets, Rizatriptan Benzoate, Direct Compression, Maxalt, Crospovidone

Introduction:

Oral drug delivery has been known for decades as the most widely utilized route of administration for the systemic delivery of drugs. Orally disintegrating tablets are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue [1]. Rizatriptan benzoate is used to treat migraine.

Aim and Objective:

The aim of the study was to design and formulate orally disintegrating tablets of Rizatriptan Benzoate comparable to the innovator's formulation. Orally disintegrating tablets were designed for the faster relief of migraine with faster onset of action, better disintegration time with better drug release and stability.

Method:

Formulation of oral disintegrating tablets containing Rizatriptan (5 mg) were prepared by direct compression technique[2]. Several batches (F1-F10) using different diluents (Spray dried lactose, Avicel, Pearlitol),super disintegrants (Crosscarmellose, Crospovidone, Sodium Starch glycolate) and lubricants (Magnesium stearate, Talc) . The API and excipients were checked for physical compatibility . The various tablets were evaluated for physicochemical properties and dissolution profiles. The dissolution test was carried out in USP apparatus Type II (paddle) with water as the dissolution medium. The samples were drawn at 5, 10, 15 minutes. The temperature was set at 37±0.5^{0}C and the rpm was set at 50. Samples withdrawn were analyzed for the percentage of drug released.

Results:

The final optimized formulation F4 was checked for various tablet parameters like Thickness **(2.8-3.2)mm**; Hardness (**1.5-1.80)kp**; Percentage Friability **(<1%)** and Disintegration time **(<30 seconds),** which were within the specified limits. The Dissolution (99±0.5%) and Assay results of F4 were found good when compared with the reference product (Maxalt). The reproducibility batch F4 was loaded for accelerated stability studies at **40±2°C/75±5% RH**. The results of stability data for 1st, 2nd and 3rdmonths (**40±2°C/75±5% RH**) were found to be good.The percentage release for the stability testing sample (F4) was found to be 100.2,99.8,99.5 respectively for 1st,2nd and 3rd months.

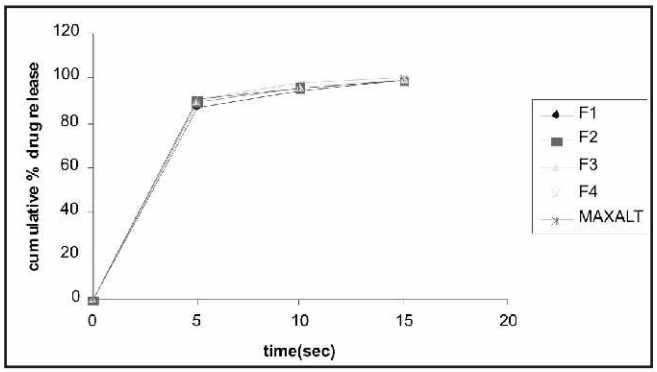

Fig 1: In vitro **release profile**

Conclusion:- Direct compression was used for the preparation of orally disintegrating tablets of Rizatriptan.Based on the preliminary studies various formulation trials (F1-F10) were carried out with different concentrations of superdisintegrants, diluents and lubricant. From the various formulations it was concluded that the Formulation F4 was finalized as the optimized formula. Formulation F4 showed satisfactory results with various physicochemical evaluation parameters like Hardness, Percentage weight loss, Disintegration time, Dissolution profile, Assay and Moisture content when compared with the marketed product. When subjected to accelerated stability studies the tablets were found to be stable. Rizatriptan ODT were successfully prepared by taking Avicel P^H 102 and Pearlitol 200 SD in the ratio of 30:70 respectively, crosspovidone (5%) as the superdisintegrant and Magnesium stearate (1.25) as the lubricant and the tablets were

compressed which gave good release profile when compared to the reference product-MAXALT(97.26%).There is no need to calculate the similarity factor(f2) as if the percentage release is more than 80% in 15 minutes or less than 15 minutes, there is no need to compare two profiles for immediate release tablets.

Acknowledgements:

I would like to extend my gratitude and regards to Dr. R.Amarnath, senior manager in Formulation Development (R & D) NATCO Pharma Ltd, Kothur, Hyderabad, for giving me this opportunity of doing project.

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P011 - In-vitro drug release studies of once a day dosing tablet formulated by judicious combination of salt and base form

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Key Words :- Bilayer tablet, fluoroquinolone, ethyl cellulose, HPMC, Kinetic models

Introduction: Oral products represent about 70% of the value of pharmaceutical sales and among drug delivery systems 60% of the market[1] .Within the oral drug delivery market, modified release formulations create the largest demand.

The drug for the present investigation falls under second generation class of fluoroquinolone antibiotics. The aim of this work was to design and characterize a bilayer tablet that involves two forms of the same drug. The highly soluble salt form is a component of the IR Layer and the less soluble base form is a component of the SR layer of the tablet. Attempts were made to retard the release of the base. Such system was expected to be helpful in reducing dosing frequency to once a day and thus increasing patient compliance.

Methods: Numerous trials with different formulation approaches like single layered tablets, bilayered tablets with matrix approach and release controlling functional coating with single polymer and combination of polymers were carried out. Different strategies like direct compression, dry granulation and wet granulation was carried out. Different polymers like ethyl cellulose and HPMC were studied as the release retarding polymers.

Dissolution studies were performed to measure the rate of drug release as a function of time. 0.1N HCl was selected as the release media and dissolution studies were carried out. The release of the drug was profiled for a maximum period of two hours using USP Apparatus type – II (Paddle) at 50 rpm. Spectrophotometric (UV-Vis) method of analysis was used to quantify drug release in dissolution tests.

Data analysis: Model dependant methods were used to investigate the kinetics of drug release from the formulation. For model dependant drug release, the drug release parameters were fitted into mathematical equations like Higuchi's model, Hixon crowell cube root model, zero order and first order models. Plots of cumulative % drug release vs time (zero order), log cumulative of % drug remaining vs time (first order kinetic model), % drug release vs square root of time (Higuchi model), cube root of % drug remaining in matrix vs time (Hixon –crowell cube root law) were made [2].

Results: Ethyl cellulose and hypromellose were used for retarding the release. From Fig.1 it can be seen that ethylcellulose 7cps was not able to retard the release and within 60 min gave 100% drug release. Wet granulation method with hypromellose as the release retardant in SR layer was found to be more feasible giving reproducible results.(Fig 2). Tablets compressed were smooth and shiny. Weight variation was within the limit of ±5%. Physical and chemical parameters of blend and formulation were evaluated.

In-vitro **dissolution studies**
The HPMC based formulation gave an initial burst effect to provide the loading dose of the drug followed by further release from the sustaining layer. The drug shows 90% release in 2 hours. The RSD showed less than 3% deviation when tested on 6 tablets.

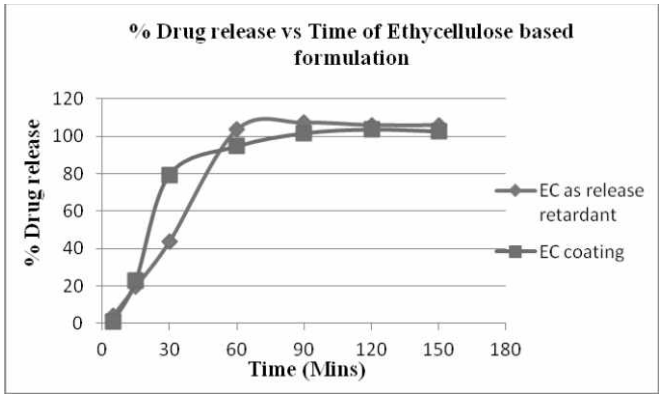

Fig 1 - % Drug release of ethylcellulose based formulation

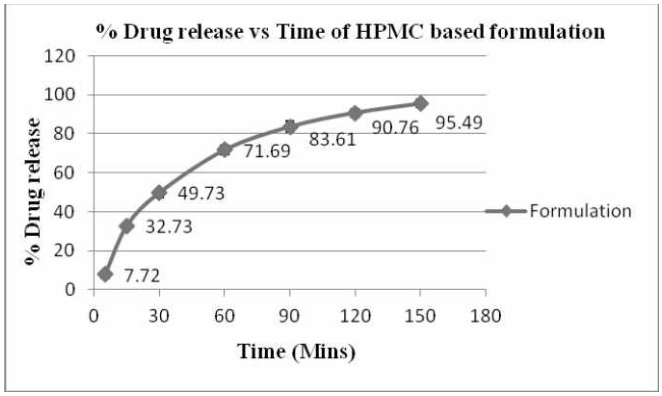

Fig 2- % Drug release of HPMC based formulation

Drug release kinetics

Best linearity was found in Higuchi's equation plot (r^2=0.9624) and Hixon-Crowell's cube root law (r^2=0.9796).

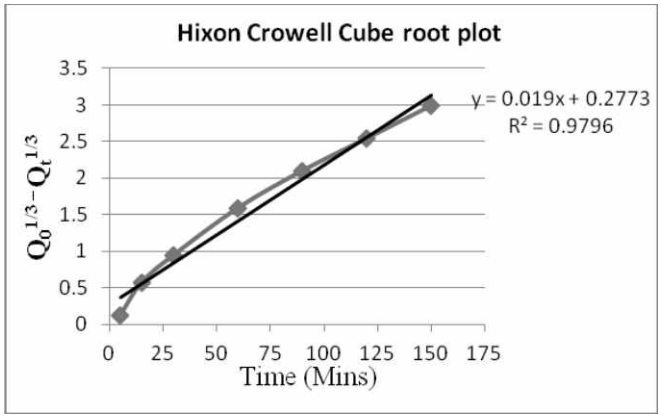

Fig 3 – Hixon-Crowell's cube root plot

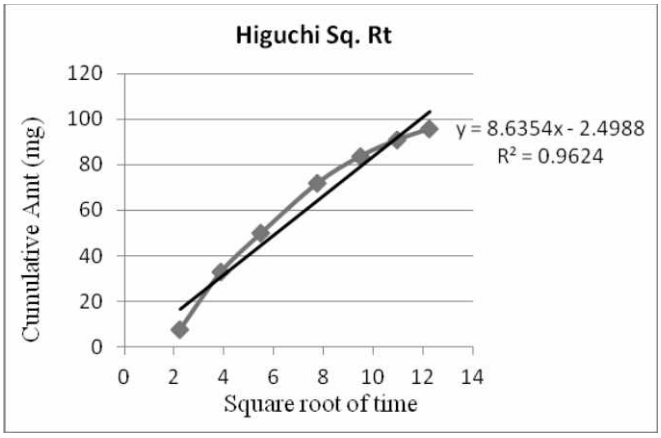

Fig 4 – Higuchi's square root plot

Conclusion

Extended release bilayer tablets of fluoroquinolone class of antibiotics was prepared successfully using HPMC as release retarding polymer to achieve desired dissolution profile. Drug release kinetics of this formulation relates best to Hixon-Crowell's cube law indicating a change in surface area and diameter of tablets with progressive dissolution of matrix as function of time.

Thus with the judicious combination of base and salt form of the drug in a single tablet, the frequency of drug administration can be made to once daily facilitating patient compliance.

Acknowledgements

We wish to express gratitude to Micro Labs Limited for this collaborative work.

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P012 Effect of Binder and Solublity Enhancer on Dissolution Behaviour of a vasodilator drug

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Key words:- Cilostazol, binder, solubiliser, synergistic effect.

Introduction:

Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. In recent trends, emerging and popularity gaining approach is the development of orally disintegrating tablet (ODT) formulation. ODT are solid unit dosage form which dissolve or disintegrate rapidly in the mouth without water or chewing [1]. Novel ODT address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for paediatric, geriatric and patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsule.

Cilostazol is BCS class II drug. It is a vasodilator used in the treatment of intermittent claudication. Intermittent claudication is generally observed in geriatric patients [2]. It needs immediate release and hence Cilostazol was formulated as orally disintegrating tablets. In the present work effect of variation in binder and solubiliser concentration on dissolution pattern was studied.

Method:

The ODT's were prepared by direct compression method using a superdisintegrant. Tablets were formulated by varying concentrations of binder and solubiliser and their dissolution pattern were studied using USP apparatus II with 0.3% w/v aqueous solution of SLS as dissolution medium.[3]

Result:

Increasing the concentration of PVPK-30 from 2%w/w to 2.5%w/w and 3%w/w decreased the amount of drug dissolved. Use of Poloxamer F-68 in the concentration range 8-15% w/w was around 86% denoting variation in its concentration did not significantly affect the extent of dissolution. Use of Poloxamer F-68 along with PVPK-30 increased the amount of drug dissolved.

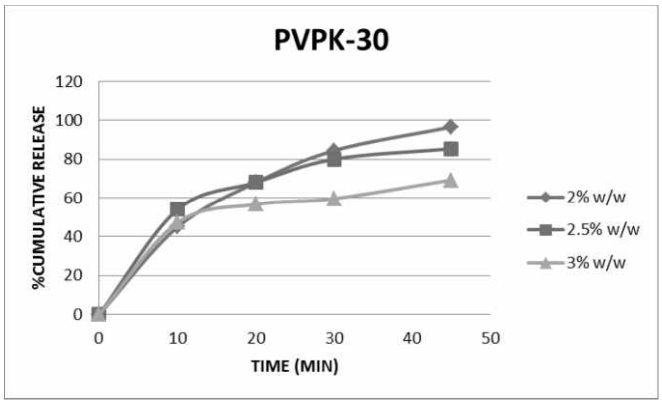

Fig.1: Effect of PVPK-30

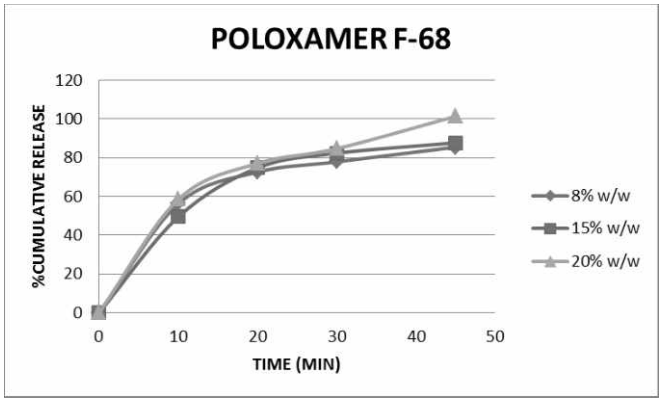

Fig.2: Effect of Poloxamer F-68

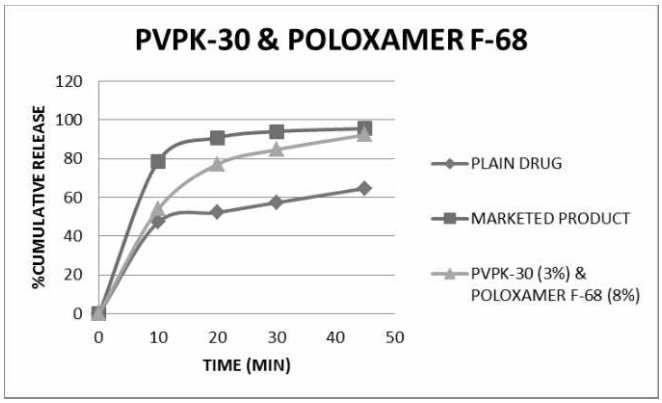

Fig 3: Effect of combination PVPK-30 & Poloxamer

Conclusion:

Increased concentration of PVPK-30 decreased the extent of dissolution indicating predominance of binder behaviour over solubilisation behaviour of PVPK-30. Combination of PVPK-30 and Poloxamer F-68 showed synergistic effect on the dissolution.

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P-013 The Comparison of In-Vitro Release Profiles for Metronidazole Topical Semisolid Dosage Forms

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Keywords

vertical diffusion cells, metronidazole, in-vitro release,

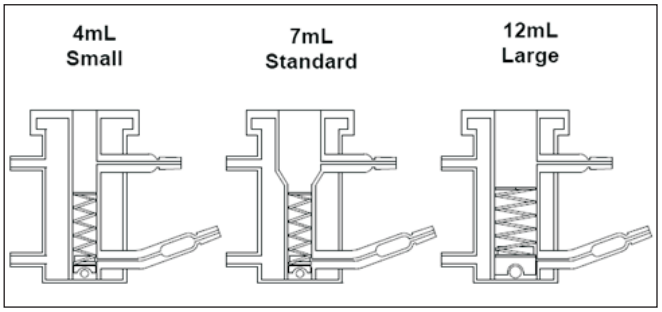
Introduction

In vitro release (IVR) methodology for topical semisolid dosage forms was developed in analogy with USP dissolution methodologies as quality control procedures and performance tests, for accurately guiding of development phase (reverse engineering) and for assessing the impact for various composition / process changes (Scale-UP and Post Approval Changes; SUPAC). Currently, several experimental devices (vertical diffusion cells, immersion cells, adaptions to flow-through cells) are included in United States Pharmacopoeia chapter <1724> (1).The aim of the study was to evaluate the inter-comparability of IVR data generated on three vertical diffusion cell systems, using various topical semisolid dosage forms containing metronidazole.

Materials and methods

The IVR tests were performed on five topical semisolid dosage forms containing 0,75% metronidazole (three creams, one emulsion and one gel). Three types of VDC were used (Hanson Microette, Hanson Research; figure 1), differing in the surface of the membrane available for diffusion (0,636 and 1,767 cm^2) and in the volume of the receptor chamber (4, 7 and 12 ml).

Figure 1. Comparative presentation of the design of vertical diffusion cells (Hanson Microette, Hanson Research Inc.)

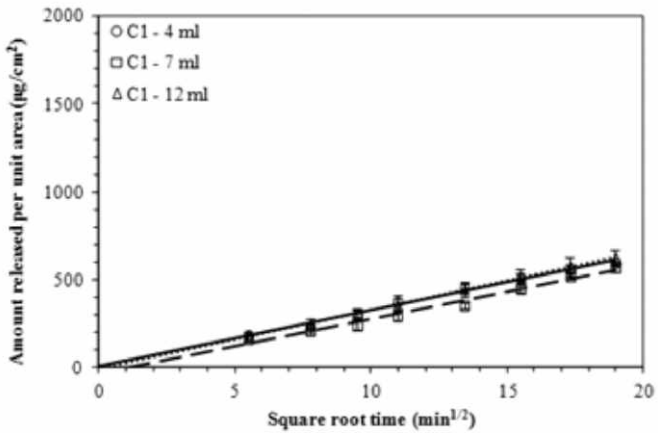


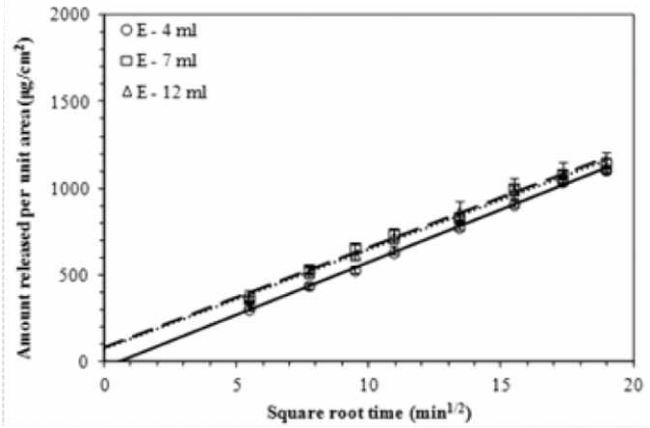
The IVR tests were conducted using polysulfone membranes (Tuffryn®, PALL Life Sciences, 25 mm, 0,45µm mean pore diameter), equilibrated for 30 minutes in the receptor media. The stirring rate was set to 400 rpm and the temperature of the systems was kept at 32±0,5°C. The comparison of the IVR profiles (n=6) was based on the recommended nonparametric statistical method for log slopes (2).

Results and discussions

The cumulative amount of metronidazole released per unit area was plotted versus square root of time. The slope of the regression line (correlation coefficients higher than 0.999) was calculated as the release rate, for each of the six testing units (2). The rank order of release rate depended on the hydro-lipophilic character of the dosage form. The results indicated that the variations of testing parameters induced by the differences in the VDC design generated similar IVR profiles, for a specific product (figure 2).

Figure 2. In vitro release profiles of metronidazole from cream (a) and emulsion (b) product obtained on 4 ml () 7 ml () and 12 ml () vertical diffusion cells. Error=±1 SD; n=6.





Using the standard, 7ml VDC as reference, the 90% confidence interval for the test to reference slope ratios 8th to 29th ratio interval was within the recommended 0.75 to 1.33. This demonstrates that, despite the differences in the design of the diffusion cells, e.g. the applied dose, determined by the thickness of the dosage wafers, stirring efficiency and surface to volume ratio, the IVR procedure generated similar data. Moreover, the procedure seems to be sensitive to the differences in the qualitative / quantitative composition of the semisolid formulations. A previous report indicated that in-vitro evaluations for metronidazole creams using the same methodology were correlated with in vivo dermatopharmacokinetic and dermal microdialysis data (3).Therefore, the IVR procedure is a robust, valuable tool for quality control and performance tests.

Conclusions

Similar IVR profiles were obtained for various semisolid topical formulations of metronidazole on three vertical diffusion cell systems. The release rate was significantly influenced by the hydro-lipophilic nature and composition of the dosage form and was independent on the variations in the design of the testing apparatus.

Acknowledgements

The authors kindly acknowledge the help and support of Dr.Lakshmanan Ramaswamy.

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P014 In-vitro Release Characterization of Sustained Release Chitosan based in- situ gelling Systems for Treatment of Bovine Mastitis

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Keywords: - Chitosan, in-situ gelling system, Bovine Mastitis

Introduction:
Bovine mastitis is the inflammation of mammary glands due to infection by bacterial or mycotic pathogens, and is responsible for severe economic losses in the dairy industry. There are two phases in the mammary glands of bovine animals - lactation phase (period of milking) and drying off (no production of milk) (Fig 1).

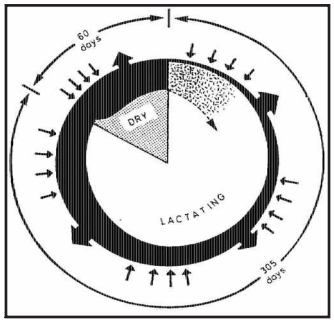

Fig 1: - Phases of Bovine mammary glands

At the end of lactation existing infections remain in the udder and, after the subsequent calving; the subclinical level of mastitis may be significantly higher than during the previous lactation[1]. Antibiotic therapy at drying-off is an important means of controlling bovine mastitis compared to lactation phase, as more uniform level of antibiotics can be maintained inside the gland for longer periods as there is no milk produced during this period. To ensure prolonged antibiotic activity, most intramammary formulations are oil-based suspensions. The active ingredient should be strongly bound to dry udder secretions and to udder tissue proteins, thus minimising its loss by diffusion into the blood stream. The dry period lasts for 60 days. Most antibiotic formulations persist during the early to mid dry period but do not cover the entire dry period[2]. The aim of the present research work was to evaluate the release characteristics of a novel antibiotic-based in-situ gelling system for intramammary administration, using neomycin sulphate as a model drug. The formed gel was intended to serve as a depot in the mammary tissue as a teat seal or physical barrier to environmental pathogens and provide a sustained release of Neomycin sulphate, for a entire dry period to protect new intramammary infections during dry cow period.

EXPERIMENTAL:

Development of in situ **gelling systems:** In situ gelling systems based on temperature-dependent phase transition were developed using chitosan and glycerophosphate. The optimum concentrations of chitosan and glycerophosphate were selected based on the gelation temperature of the polymer solutions. Various crosslinkers such as PVA, Glucose, Glyoxal, Tripolyphosphate (TPP) were screened as release retardants.

In-vitro **release estimation of** in-situ **gelling systems**
By static method - for screening of cross linkers - The in situ gelling system (5ml) in dialysis bags were immersed in Phosphate buffer pH 7.2, in stoppered tubes and maintained at 37±1 ^{0}C. At periodic intervals, aliquots were withdrawn and drug content assessed by colorimetry and turbidimetry to check whether antibiotic concentration released was above MIC.

To mimic in vivo **condition**, selected in situ gelling system was gelled by immersing the sols in a water bath at 37±1 ^{0}C and then transferred to a dialysis bag. This bag was placed carefully in a rectangular ditch bored in a petri plate containing nutrient agar seeded with S.aureus, incubated at 37^{0}C, and the observed for presence of zones of inhibition. At intervals of 2 days, the dialysis bag was transferred to fresh seeded agar medium, for upto 45 days, and the zones of inhibition were observed.

RESULTS AND DISCUSSIONS:

Development of in situ **gelling systems:** The optimized in situ gelling systems were obtained as clear, odorless liquids, which were liquid at room temperature and formed gel at 37°C.

Screening of Crosslinkers:

The in vitro release profile from crosslinked (TPP) in situ gelling systems showed sustained release of antibiotic for up to 30 days compared to formulation without crosslinker (3 days) (Fig 2).

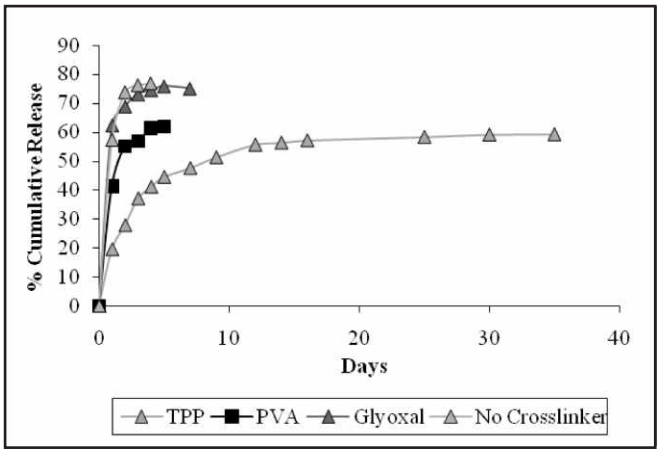

Fig 2: Comparative in-vitro **release profile**

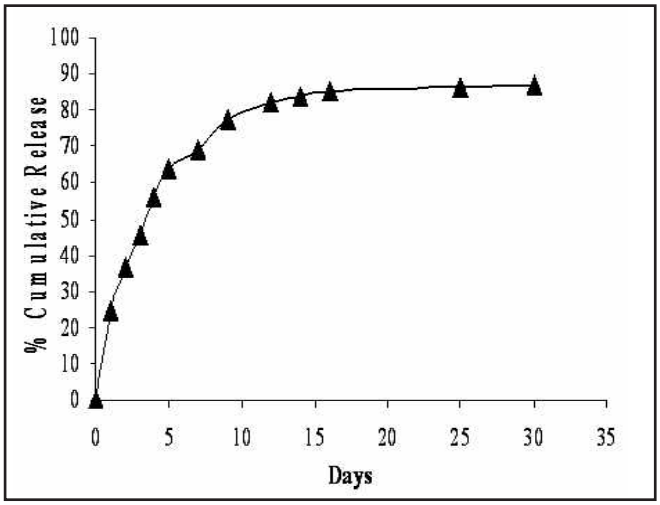

Fig 3: In-vitro release profile

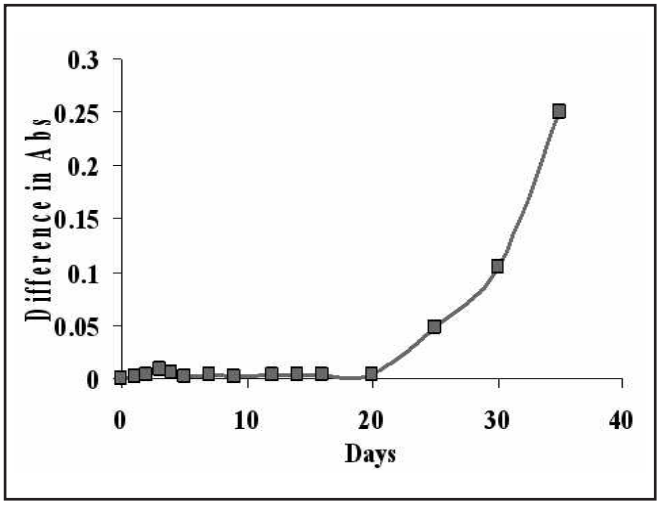

Fig 4: Microbiological estimation

Correlation was observed between colorimetric estimation and microbiological estimation, wherein upto 30 days, drug released was above MIC (0.6 - 2.0 µg/ml), after which drug levels released were below MIC (Fig 3 & 4).

In-vitro **release by Agar Diffusion Method:**
Zone of inhibition was observed, for every time point till 45 days indicating sustained release of the neomycin sulphate from the gelled delivery system. (Fig 5)

Fig 5: (a) Positive Control

(b) Day 1

© Day 25

(d) Day 45

CONCLUSION: This study reveals the feasibility of developing intramammary sustained release systems of antibiotic in the form of in situ gelling formulation, in which the release profile has been successfully correlated to antimicrobial activity for prolonged release systems.

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P015 Comparison of two formulation strategies for improvement in in vitro release profile of a class IV drug.

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Introduction:

MXE, a BCS Class IV molecule is a promising anticancer agent for treatment of breast cancer with major limitation of low oral bioavailability (approx. 5% in rats) [1, 2]. Studies were initiated to design cyclodextrin inclusion complexes of MXE to improve solubilisation potential and therefore oral bioavailability. Another formulation approach of design of self nanoemulsifying drug delivery systems (SNEDDS) was employed to improve solubilisation as well as permeation (another major limitation) of MXE. The two strategies were comparatively evaluated for improvement in in vitro release profile of drug.

Method:

MXE and BCD binary systems (MXE-BCD) were prepared by kneading [3], employing different MXE to BCD ratios viz. 1:1, 1:2, 1:3 kneaded complexes and 1:1 MXE – BCD physical mixture. IR and ^{1}H NMR studies were conducted to confirm mode of complexation. Dissolution profiles of the drug powder and binary systems were studied using pH 7.4 phosphate buffer saline (PBS) medium. SNEDDS were prepared by mixing the drug solubilised in Capryol 90 with different surfactants, in predetermined ratios. SNEDDS on dilution with filtered distilled water yielded nanoemulsion which was characterized for mean particle size and polydispersity index.

In vitro release profile of MXE – SNEDDS in 0.5 % SLS medium was studied using USP type II apparatus, modified with dialysis bag technique and was compared with MXE solution, MXE suspension and 1:1 MXE –BCD kneaded complex.

Results: The dissolution profiles of the binary mixtures (as seen in fig 1) clearly show improved dissolution in the order 1:2 MXE – BCD **>** 1:1 MXE – BCD, though difference was not remarkable. Pure MXE powder dissolved up to 30% at the end of 3 hours. This could be attributed to the inclusion of the drug molecule within the cavity of BCD as confirmed by IR and ^{1}H NMR studies. MXE – BCD complex in 1:1 ratio, which contained less quantity of BCD, was evaluated for in vitro release profile in comparison to SNEDDS.

When the in vitro release profiles were compared (as seen in fig 2), the SNEDDS showed faster release than MXE – BCD complex. This could be attributed to the presence of surfactant Solutol HS 15 (at 0.85%w/v concentration) in the SNEDDS formulation that retained the globule size below 100 nm providing for larger surface area for dissolution and hence faster release.

Fig 1: Dissolution profiles of MXE –BCD binary systems

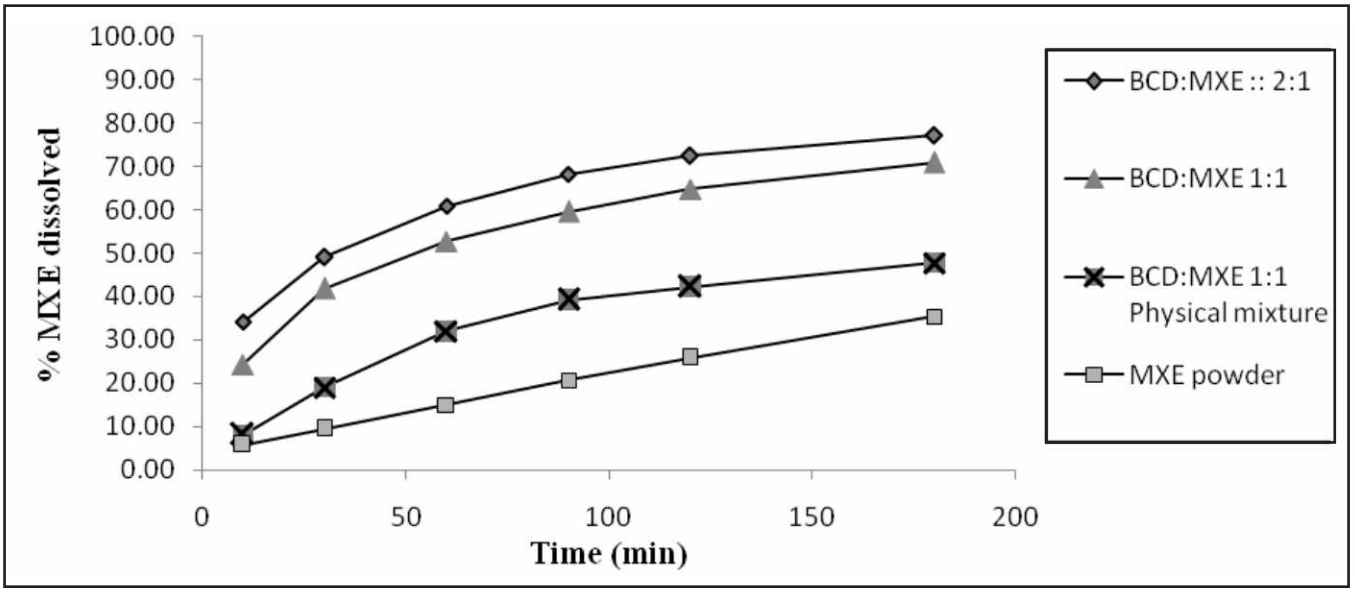
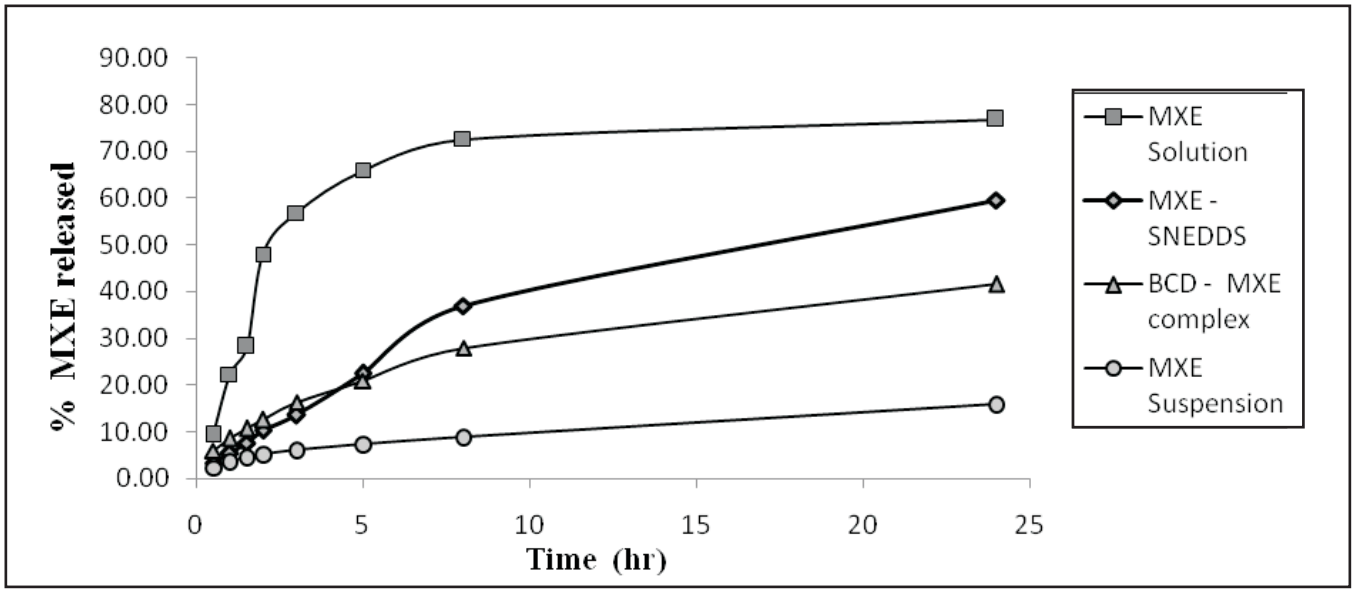


Fig 2: In vitro **release profile for different formulations**



Conclusion: Both the formulation strategies which are amenable to easy scale up show enhanced solubilization and improved release profiles of MXE in comparison to pure MXE powder.

Acknowledgements:

Authors are thankful to Naprod life sciences for providing gift sample of MXE. Authors also wish to acknowledge Mr. D. Jadhav and Dr. Sudha Srivastava, TIFR for conducting ^{1}H NMR studies. Authors are thankful to Gattefosse Pvt. Ltd., India and BASF India for providing gift samples of excipients.

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P016 Design and Fabrication of Continuous Dissolution-Absorption Apparatus

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Introduction:

Dissolution is a quality tool for determining the release behavior of the dosage form. Existing dissolution apparatus gives us the meaningful dissolution profile but not the strategy of permeability. If dissolution is the rate limiting step it leads to poor permeability of the drug. To find out the permeability of a drug one has to go for an everted gut sac technique, or for Franz diffusion cell, which was difficult and tedious to perform. The permeability/bioavailability for oral solid dosage forms are determined by performing animal trials, which is tedious and costly. Therefore, reliable and predictive in-vitro methods to quantify the dissolution of the drug and its transport across the membrane are required at an early stage in the drug development process for the oral solid dosage forms.

Aim

The major objective of this study was to design and construct a new version of dissolution permeability apparatus to estimate both dissolution and permeability to understand IVIVC

Methods and results

The continuous dissolution absorption apparatus (Fig.1) was fabricated using borosilicate glass by blow out technique. The experiment was carried out by using diclofenac sodium SR in pH 6.8 phosphate buffer. The membranes used were dialysis membrane and goat intestine. The alpha is the ratio between the permeation rate constant and dissolution rate constant. If the alpha is greater than 1 indicates dissolution rate limited absorption. An alpha value much less than 1 indicate permeation rate limited absorption. An alpha value of 1 indicates perfectly mixed dissolution and permeation absorption. The Kd (rate of dissolution) , Kp (rate of permeation), r2 value and alpha values were calculated as shown in table no:1 The α values of diclofenac sodium SR in pH 6.8 phosphate buffer, by using membranes were found to be 11.8,and 15.5.

Table.1. Kd and Kp values

	Dialysis membrane	Goat intestine
Kd (rate of dissolution)	0.328	0.231
Kp (rate of permeation)	3.94	3.6
r^2	0.994	0.993
α value	11.8	15.5

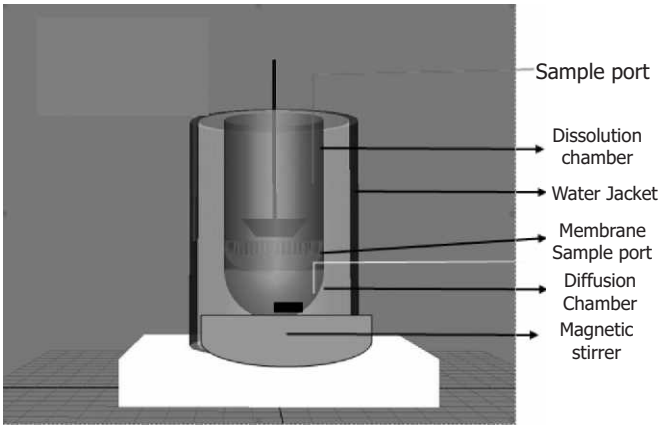

Fig1: Continuous Dissolution-Absorption Apparatus.

CONCLUSION:

The continuous dissolution-absorption system is used to predict dissolution-absorption relationship and is a potential tool for in vivo pre-assessment to understand IVIVC and characterizing prototype formulations and setting dissolution specifications. The results indicates a continuous dissolution-absorption system may have utility in the biopharmaceutical characterization of drug, determine the effect of excipients on the drug release and absorption and to tentatively asses the suitable medium for assessment of IVIVC. Further evaluation

should include the examination of more drugs of diverse biopharmaceutical properties by using different membranes.

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P017 - Evaluation of Dissolution Efficiency of Erlotinib Solid Dispersions

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Key words: Erlotinib, Solid dispersions, Gelucire50/13, Aeroperl 300, Dissolution efficiency.

Introduction : Variability in dissolution of poorly soluble drugs often manifests itself in a host of in vivo consequences, including decreased bioavailability, increased chances of food effects, more frequently incomplete release from dosage form and higher inter patient variability.The present study deals with the formulation of solid dispersion granules of erlotinib hydrochloride (ETB), a poorly soluble drug to overcome poor solubility and hence dissolution variation. ETB inhibits EGFRtyrosine kinase, and is used clinically for lung and pancreatic cancers.

Objective : The objective of the present researchwas to improve the aqueous solubility and to increase the dissolution efficiency of ETB thus improving the drugs in-vivo bioavailability.

Experimental Methods:

Preliminary studies: Solubility of drug in aqueous solutions of carriers like PEG 6000, PVP K-30 and Gelucire 50/13 were carried out in order to screen the components to be used for formulation of solid dispersion. The drug concentration was estimated by UV spectrophotometer at 336nm.To determine the appropriate medium for dissolution of poorly soluble ETB, in vitro dissolution studies were performed invarious dissolution media[1].

Preparation of physical mixtures and solid dispersions: Physical mixtures and solid dispersionsof ETB with carriers were prepared in the ratio of 1:5 (drug: carrier). Co-evaporation technique was used for PVP K-30 solid dispersion,whereas the fusion technique was used for PEG 6000 and Gelucire 50/13,followed by adsorption on Aeroperl 300

Evaluation of mixtures and solid dispersions:

a. **In vitro dissolution studies :** Dissolution studies of samples were performed according to USP XXIII type II apparatus in 0.25% SLS at 37±0.5°C and the rotation speed was 75 rpm.

b. **Physical characterization:** The physical mixtures and solid dispersions were characterized for FTIR spectrometry, DSC, XRD and SEM analysis.

c. **Data analysis:** The resultant data was analysed kinetically and dissolution efficiency was computed and compared [2].

Results and Discussion:

Selection of solid dispersion carrier was based on its apparent solubilising capacity towards drug and dissolution enhancement. Solubility of ETB was found to be linearly increased with increase in carrier concentration with the value of linear regression coefficient in the range of 0.9. Solubility improvement with PEG 6000, PVP K 30 and Gelucire 50/13 were found to be 11, 15 and 20 fold respectively. Such increase in solubility with increase in weight fraction of carriers was accompanied with further decrease in the values of ΔG°. The highest improvement in solubility of ETB was observed in Gelucire 50/13,which could be attributed to the high HLB value of Gelucire 50/13.

Based on the results for dissolution of ETB in various media, 0.25%SLS was selected as medium for dissolution studies.In-vitro dissolution profiles of physical mixtures did not show any significant improvement over plain ETB, whereas, in-vitro dissolution profiles of solid dispersions demonstrated marked improvement in dissolution over plain ETB. It was evident from the in vitro dissolution data, that thesolid dispersion with Gelucire 50/13 exhibited faster dissolution rate as compared to the drug alone with complete drug release in 20 minutes. This could be attributed to amorphonization of ETB in solid dispersion and increase in surface area for dissolution by use of surface adsorbent in the preparation of solid dispersions. The marked improvement in dissolution of ETB could also be attributed to formation of micro-emulsion when Gelucire 50/13 comes in contact with the dissolution medium [3]. Also as expected dissolution efficiency of Gelucire 50/13 was found to be highest amongst all the carriers studied. XRD and DSC analysis of solid dispersions revealed partial amorphonization of ETB, whereas photomicrographs showed complete adsorption of solid dispersions on surface adsorbent.

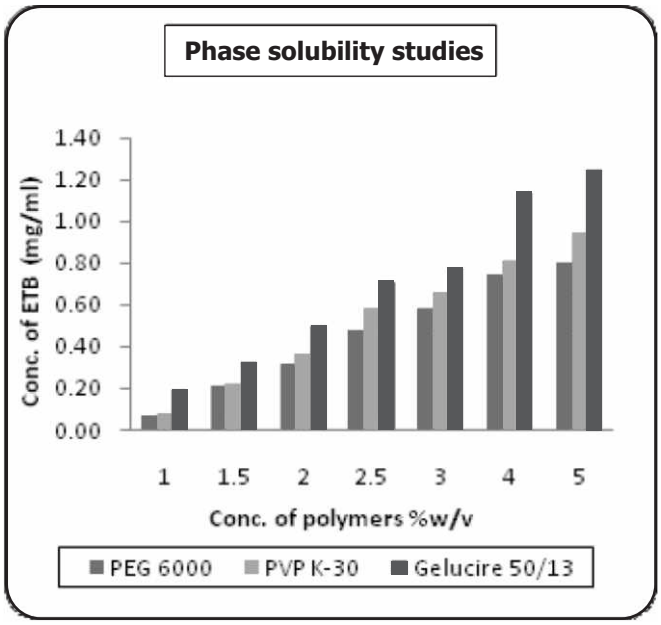

Fig.1- Phase solubility studies of ETB

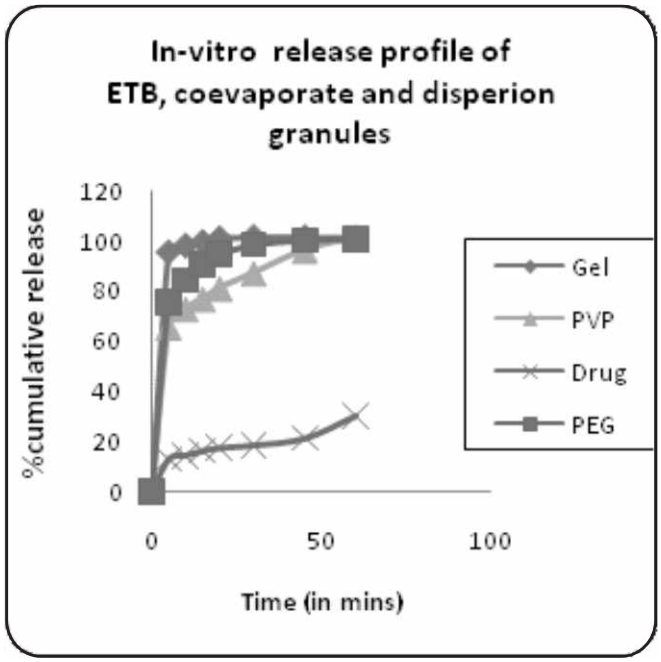

Fig. 2- *In-vitro* release profile of solid dispersions

Conclusion:

Solid dispersion technique was found to be promising for increasing solubility and hence dissolution rate of the poorly soluble drug,ETB.Various water-soluble carriers investigated in the current study enhanced the solubility and dissolution characteristics of the ETB to varying degrees. Gelucire 50/13 was found to be the most suitable carrier for solid dispersion of ETB.

Acknowledgements:

Authors wish to thank Cipla, Mumbai for the gift sample of drug and **Gattefossé India Pvt Ltd** for Gelucire 50/13.

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P018 IN VITRO RELEASE STUDIES OF FLUTICASONE PROPIONATE MICROSPHERES FOR INHALATION USING USP TYPE IV APPARATUS

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KEY WORDS: Fluticasone Propionate, microspheres, **USP Type IV apparatus**

INTRODUCTION:

Fluticasone Propionate (FP) is a medium potency corticosteroid, available as an intranasal and inhalation product for treatment of seasonal and perennial allergic rhinitis, asthma and chronic obstructive disease. The oral bioavailability of FP is the lowest of the marketed inhalational corticosteroids (ICS). FP is extensively metabolised in liver and undergoes almost complete first pass metabolism. The Dry powder Inhalation (DPI) microsphere-based formulation would prove to be advantageous in localizing the drug effect and achieving improved efficacy, reduction of dose and frequency, as well as sustained action. . In the present study FP microspheres for Dry powder Inhalation (DPI) were prepared using Bovine serum albumin (BSA) by two different techniques: spray drying and freeze drying. The release profiles of these microspheres were assessed using **USP Type IV apparatus.**

OBJECTIVE:

To evaluate the influence of various excipients and preparation techniques on the release behaviour of Fluticasone Propionate from polymeric microspheres for inhalation delivery.

EXPERIMENTAL:

A) Preparation of Bovine Serum Albumin (BSA) microspheres: HPβCD inclusion complexes of FP were prepared by spray drying and freeze drying techniques in different molar ratios. These complexes were dissolved in BSA solution and subjected to spray drying and freeze drying. The freeze dried complexes of HPβCD and microspheres were micronized by manual grinding and sieving through 20µm sieve.

B) In Vitro **release studies:** In vitro drug release studies of the developed microspheres were carried out using **USP type IV apparatus (**Sotax Dissotest CE1**) in simulated lung buffer (SLF pH 7.4) as dissolution medium maintained at 37°C ± 0.5°C.** The influence of different concentrations of Pluronic F 68 (PL), flow rate, albumin microspheres containing different ratios of HPβCD drug complexes and preparation method on the dissolution profile of FP and the microspheres was studied.

RESULT: The spray-dried microspheres were obtained as spherical, homogeneous and small sized (1–5 µm), free flowing powder, while with freeze drying irregularly shaped microparticles were obtained.

1) **Influence of different concentrations of Pluronic F 68 (PL)**: The presence of PL (0.5 - 1.0%) in the dissolution medium significantly increased the dissolution rate of FP (pure drug). The dissolution rate of FP in SLF containing 1.0% PL increased in a linear manner with increasing flow rate of the dissolution media as shown in Fig. 1.

2) **Influence of different flow rates:** The dissolution rate of FP (pure drug) in SLF containing 1.0% PL increased in a linear manner with increasing flow rates (0.5 – 1.5ml/min) of the dissolution media as shown in Fig. 2.

3) **Influence of preparation method:** Due to the amorphous nature and an increase in water solubility following complexation, the FP-HP**β**CD complexes prepared by spray drying (FP-HP**β**CD-SD), and freeze drying (FP-HP**β**CD-FD) showed significantly higher dissolution rates compared to pure FP and its physical mixture (FP-HP**β**CD-PM) as shown in Fig. 3.

Influence of different ratios of FP-HPβCD complexes to albumin and preparation method: When ratio of FP-HPβCD complex to albumin was increased from 1:3 to 1:8, the release rate of FP significantly reduced in both freeze and spray dried microspheres as shown in Fig. 4. Spray-dried products (FPHPAL-SD) presented higher release profiles than freeze-dried (FPHPAL-FD) products. This could be attributed to the high surface present in the spray-dried products that are spherical, homogeneous and small sized (1–5 µm) powders. The presence of high amount of albumin decreased the release due to its low dissolution at alkaline pH (7.4) and by the slow diffusion of FP through the more hydrophilic albumin/cyclodextrin matrix layer around the lypophilic drug.

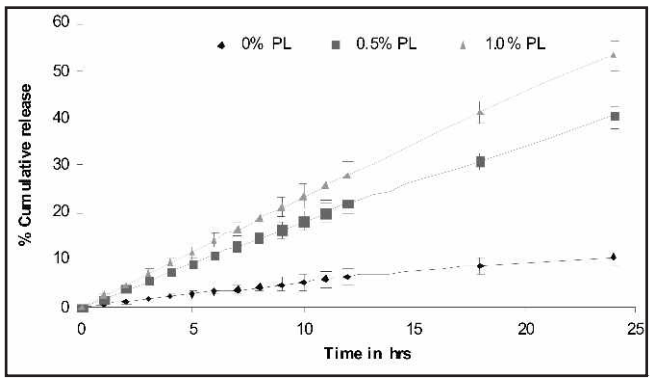

Fig. 1 Effect of different concentrations of Pluronic F-68 in SLF at 1 ml/min on FP dissolution.

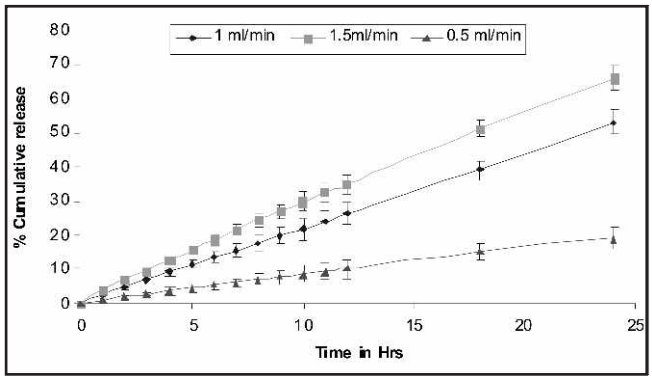

Fig. 2 FP dissolution in SLF containing 1.0% Pluronic F127 at different flow rates.

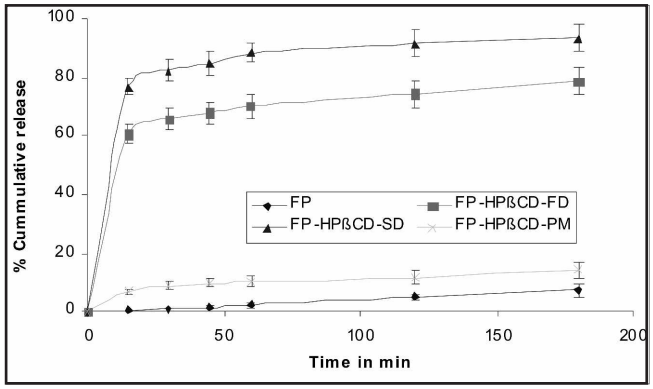

Fig. 3 In vitro release profiles of FP-HPβCD complexes prepared by freeze and spray drying

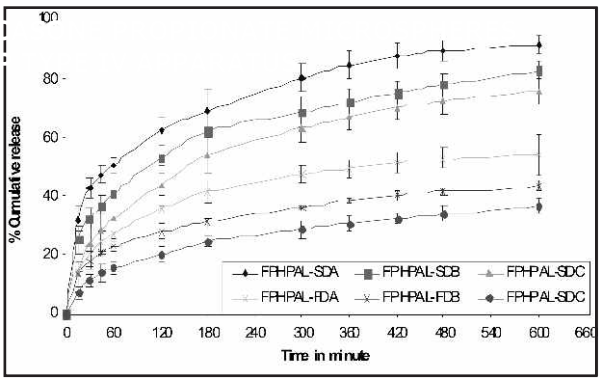

Fig. 4 In vitro release profiles of albumin microspheres of FP-HPβCD complexes prepared by freeze and spray drying.

CONCLUSION:

This study reveals the usefulness of USP **type IV apparatus** as an effective dissolution equipment for design and optimization of Novel Drug Delivery (NDD) systems for inhalation.

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P019 FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING BIOADHESIVE TABLET OF ZIDOVUDINE

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Introduction:

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. Several approaches are currently being used to prolong gastric retention time. Floating Drug Delivery Systems (FDDS) are designed to remain buoyant in the stomach for a prolonged period of time without reducing the gastric emptying rate; the drug is released slowly at the desired rate from the system during this increased gastric residence time.

Objectives

Zidovudine less residence in GI so, poor bioavailability, FDDS to Increase gastric residence time resulting in prolonged drug delivery and bioadhesive in gastrointestinal tract using HPMC and Polyethylene oxide, Xanthan gum, Carbopol as mucoadhesive and sustain release polymers.

Methods:

Floating tablets containing antiretroviral drug, zidovudine were prepared by wet granulation method using variable concentrations of HPMC K15M, Carbopol 974 PNF, Xanthan gum 180, and Polyethylene oxide N80 as polymers, lactose monohydrate as diluent, sodium bicarbonate, and citric acid as gas generating agents, magnesium stearate, and Aerosil 200 as lubricating agents, and water as binder. Prepared granules and compress the tablets using 8 station rotary tablet press.

Data Analysis:

Drug excipient compatibility study at 25ºC/60% RH and 40ºC/75% RH for one month was observed that there were no physical changes found in the drug-excipient mix. Drug was found to be compatible with all the excipients.

Swelling study was performed on all the batches it was found to be in range of 73% to 160% From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer.

Bioadhesive force of the tablets was measured on a modified physical balance; the xanthan gum showed pronounced (0.265 ±0.004) effect on bioadhesive strength .

Formulated floating tablets were subjected to in-vitro release studies these studies were carried out using USP Dissolution Apparatus 2, 0.1N Hcl.

The release data obtained for three formulations were shows only 67.11±1.45%, 81.12±0.12% and 98.11±1.01% cumulative drug release at 12 hrs.

Kinetic drug release data revealed that the floating bioadhesive tablets followed zero order release the R2 value ranged from 0.9617 to 0.9964; these values are higher than the first order release data R2 value ranges from 0.7580 to 0.9909.

The Higuchi diffusion equation showed R2 value ranges from 0.9186 to 0.9865.

To confirm the mechanism of drug release the in-vitro drug release data was fitted to Korsemeyer's Peppas model equation the slope values (n) were in range of 0.6814 to 0.8979 this shows the floating bioadhesive tablets follows non-fickian and zero order release.

Conclusion:

The study of floating bioadhesive tablets of Zidovudine, with sustained action upto 12 hours has been successfully designed, and it can be extrapolated for preparing gastroretentive therapeutic systems for the treatment of HIV infective disorders.

S.No.	Parameters	Results
1	Floating lag time	23 seconds
2	Total floating time	>12 hours
3	Percentage cumulative drug release at 12 hours(%)	101.14 ± 0.21
4	Bioadhesive strength(N)	0.248 ± 0.002
5	Zero order release (R2)	0.9877
6	korsemeyer's peppas model (n)	0.9809

P020 Dissolution Studies of Gastroretentive Drug Delivery System of Famotidine

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Keywords:
Famotidine, Gastro retentive drug delivery system, improved bioavailability, Gastric retention time

Introduction:
Famotidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and it is commonly used in the treatment of peptic ulcer disease and gastro esophageal reflux disease [1]. The prescribed dose of famotidine is 10 mg or 20 mg twice a day. Famotidine has biological half life of 2.5 to 4 hours. It has poor bioavailability in acidic medium. To improve bioavailability and efficacy in acidic pH of stomach suitable Gastro retentive Drug Delivery System (GRDDS) is a good option [2].

For effervescent Floating Drug Delivery System (FDDS), the matrices are prepared with swellable polymers such as Methocel or polysaccharides and effervescent component, sodium bicarbonate and citric acid. The matrices are so fabricated that on arrival in stomach, CO_2 is liberated by acidity of gastric contents and entrapped in the gellified hydrocolloid[3].

Materials: Famotidine, directly compressible Microcrystalline Cellulose were gift sample from Ankur Drugs and Pharmaceuticals Ltd., Mumbai, India; Kollidon-SR gift sample from BASF Hydroxypropyl methyl cellulose (HPMC) – 5 cps, 15 cps; Polyvinyl pyrollidone K-30; Isopropyl Alcohol (IPA), Sodium Bicarbonate, Talc, Magnesium Stearate. All other chemicals used were of analytical grade.

Experimental: HPMC, Kollidon SR with effervescent sodium bicarbonate formed the floating tablet. Tablets were prepared using dry granulation and wet granulation. The prepared tablets exhibited satisfactory physico-chemical characteristics. The powder blend and the compressed tablets were evaluated for pre compression, post compression parameters, floating time and dissolution profile.

Different batches of tablets were prepared as mentioned in table no.1

Result and Data Analysis: The dissolution profile for the different batches tried is as shown in Figs. 1 & 2. All the prepared batches remained buoyant for about 6 to 8 hours.

Table 1: Composition of different batches of Gastro Retentive Drug Delivery Systems

Ingredients (mg/tablet)	Formulation Code							
	A	B	C	D	E	F	G	H
Famotidine	120	120	120	120	120	120	120	120
HPMC (5 cps)	-	80	110	45	90	100	100	100
HPMC (15cps)	80	70	40	15	45	50	50	50
Kollidon SR	-	-	-	90	90	100	100	100
Sodium Bicarbonate	75	100	75	75	-	45	35	25
Directly compressible MCC	100	-	-	-	-	-	-	-
Cross Povidone	20	-	-	-	-	-	-	-
Talc	10	10	10	10	10	10	10	10
Magnesium Stearate	20	20	20	20	20	20	20	20
Total weight (mg)	425	400	375	375	375	445	435	425

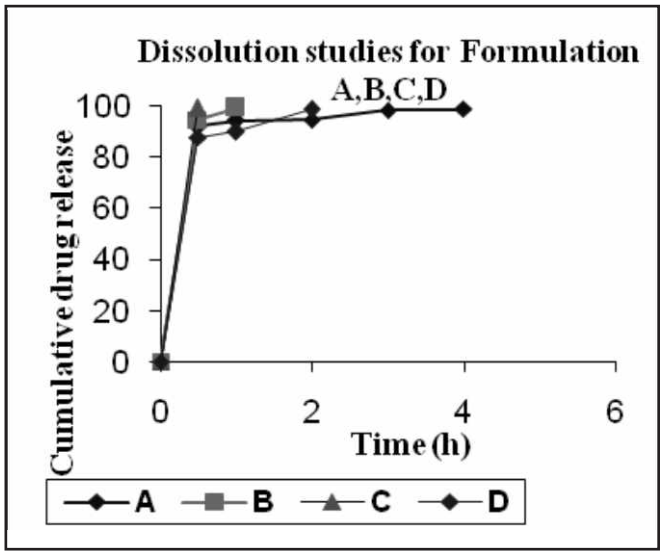

Fig.1 Dissolution studies for formula A,B,C,D

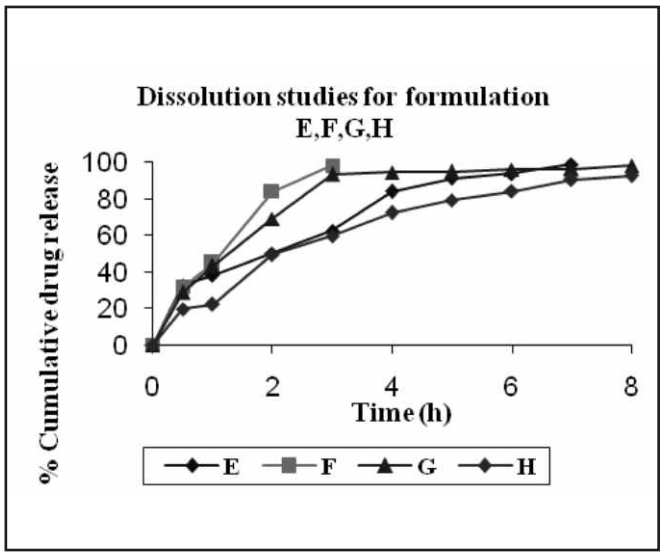

Fig.2 Dissolution studies for formula E,F,G,H

Conclusion:

This study discusses preparation and evaluation of Gastro retentive drug delivery system of Famotidine using effervescent and non-effervescent based system. The addition of gel forming polymers HPMC (5 and 15 cps) & Kollidon SR and effervescence producing agent sodium bicarbonate was essential to achieve buoyancy. Polymer swelling is crucial in determining drug release rate and also important for floatation. The dissolution studies of formulations prepared with sodium bicarbonate 25 mg/ tablet gives desired release in 8 hrs.

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P021 Assessment of Dissolution Behavior of Valsartan Dual Release Mini Matrix System Using Tablet in Capsule Technology

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Introduction: Multi unit dosage forms (MUDFs) show numerous advantages over single unit dosage form. MUDFs are less dependent on gastric emptying and on nutritional state as these are sufficiently small to be evacuated through the pylorus during the digestive phase. So,these factors less effect on dissolution of the active drug. Additionally owing to the reproducibility of transit times and high degree of dispersion in the digestive tract, multi particulate systems show less variation in dissolution (or) bioavailability of the drug.Mini tablets are small tablets with a diameter typically equal to (or) less than 3mm that are filled into a capsule or occasionally further compressed into larger tablets. It is possible to incorporate many different mini tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal tract, into one capsule. These combinations may include immediate release, delayed release and or controlled release minitablets. Valsartan belongs to a class of antihypertensive agents called angiotensin II receptor blockers (ARBs). Bioavailability is about 10% to 35%. Food decreases AUC about 40% and decreases Cmaxabout 50%.

Aim: The aim of present work is to produce a dual release delivery system of combining fast release minitablets together with the slow release minitablets of the drug Valsartan . This system can produce a rapid rise in the plasma concentrations and are required to promptly exercise the therapeutic effect followed by extended release phase in order to avoid repeated administration .

Methods and results: In current research work, dual release mini-matrix minitablets (F1, F2, F3) were prepared for Valsartan drug. Immediate release minitablets (F) were prepared using Avicel PH102 and superdisintegrant Croscarmellose. Sustained release minitablets (5 mg in weight) were prepared using hydrophilic polymer HPMC K100M at 20% (F1+F), 30% (F2+F), 40% (F3+F) w/w. The number of minitablets required for the dose of immediate release and sustained release were calculated and filled into a capsule size of 2. Evaluation of disintegration and dissolution of the minitabs were assessed . The dissolution studies were performed using phosphate buffer pH6.8. The results showed in fig.1 indiactes that the release profile of formulation (F1+F) was 98.43% for 4hr;formulation (F2+F) was 98.03% for 6hr and formulation (F3+F) was 98.54% for 9hr.Release data modeling studies were performed and found formulation (F1+F) follows first order release; formulation (F2+F) follows Higuchi model release and formulation (F3+F) follows zero order release. To conclude, the dual release behavior was attained by combining immediate release and sustained release minitablets of the drug which can be filled into one capsule so that the delivery system can deliver a first impulse of the dose in the shortest time possible (a few min) and a second fraction of the dose for a prolonged time at a constant rate. This type of formulation can be used in conditions like hypertension so as to get quick plasma concentration followed by prolonged action as it is required.

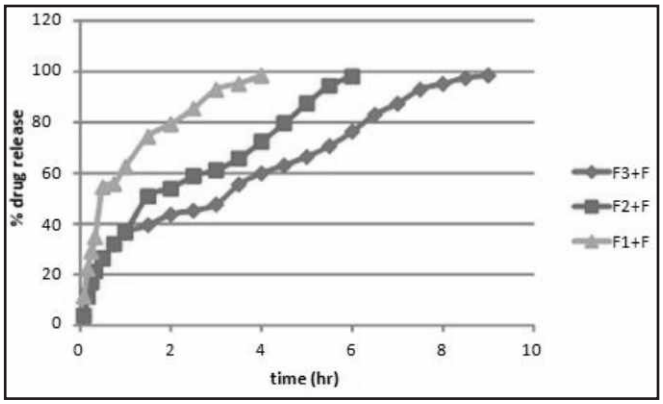

Fig.1. Graphical representation of dissolution study for formulations (F1+F, F2+F,F3+F)

Conclusion: To conclude, minitabs of Valsartan were successfully developed. These minitabs showed a dual release behavior, for upto 9 hours which was attained by combining immediate release and sustained release minitablets of the drug.

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P022 - Comparison of Gastroretentive Floating Tablets of losartan K with Conventional Marketed Tablets

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KEYWORDS: Losartan K, HPMC , Tamarind gum, Xanthan gum, marketed formulations.

INTRODUCTION: Losartan potassium is a potent antihypertensive drug which is a highly specific Angiotensin II AT1 receptor antagonist. It is readily absorbed from the gastro intestinal tract, having oral bioavailability of 33% and plasma elimination half life of 1.5 to 2.5 hours. The floating tablets of Losartan K were developed using Tamarind gum, Xanthan gum and known polymer HPMC

MATERIALS AND METHODS: Losartan potassium was received as a gift sample from Alkem Pharmaceuticals Ltd. Mg Stearate, Sodium bicarbonate, Xanthan gum and lactose Monohydrate were obtained from S.D Fine Chemicals Pvt. Ltd., HPMC and Tamarind gum were procured as gift samples from Colorcon Pvt ltd. and Bhavna Gum Udhyog, Gujarat respectively.

EXPERIMENTAL:

Table 1: Composition of Losartan potassium SR floating tablet

Name of Ingredients	F1	F2	F3	F4	F5	F6	F7
Losartan K	50	50	50	50	50	50	50
HPMCK 4 M	75	-	-	-	-	-	-
HPMC K 15M	-	50	-	25	50	25	50
HPMC K 100M	-	-	63	-	-	-	-
Tamarind gum	-	-	-	25	50	-	-
Xanthan gum	-	-	-			25	50
Lactose	104	129		129	79	129	79
Mg Stearate	1	1	1	1	1	1	1
Sodium bicarbonate	20	20	20	20	20	20	20

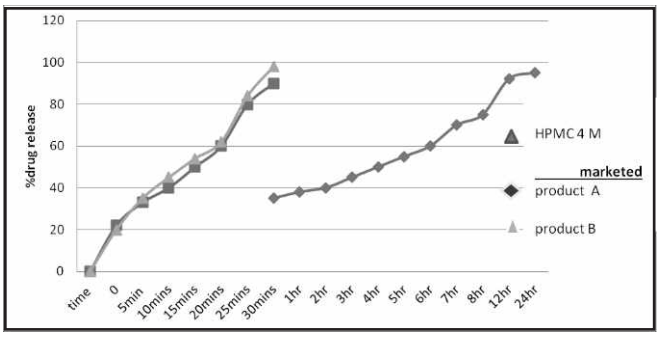
Individual weight of tablet = 250 mg

Preparation of sustained release tablets

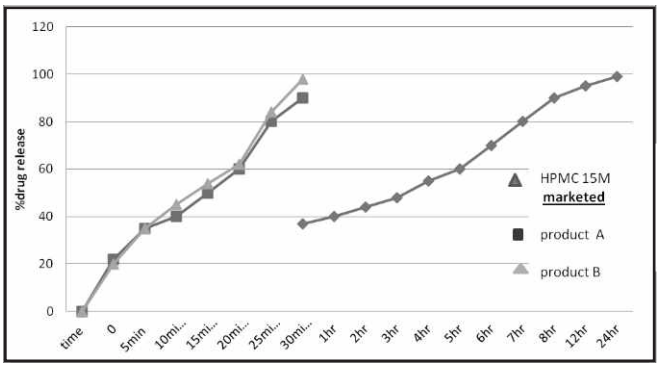
Losartan potassium Floating SR tablets (250 mg) were prepared by direct compression method using 8mm punch.

IN-VITRO **DRUG RELEASE STUDY:** Dissolution rate studies were carried out in USP apparatus II. 900 ml of 0.1N HCl was taken as dissolution medium. Dissolution was performed at 37 ± 0.5^0 at 75 rpm for 24 hours. The sample (5 ml) was withdrawn at specific intervals upto 24 hours and drug content in withdrawn aliquots were analysed by UV spectrometry at 205nm.

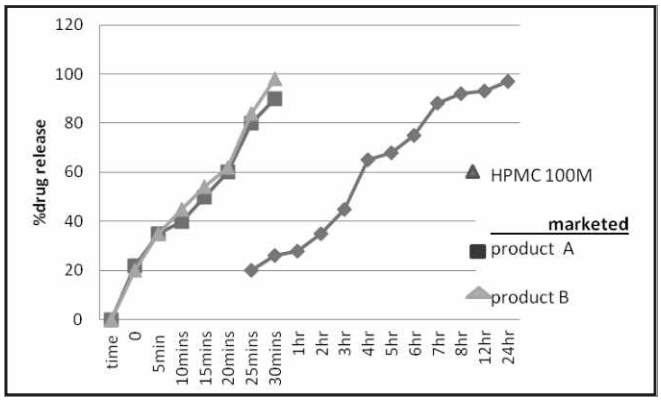
RESULTS AND DISCUSSION: Batches of Losartan potassium tablets were prepared according to table no. 1 using various grades of HPMC, tamarind gum & xanthan gum by direct compression method. The pre-compression & post-compression parameters were within prescribed limits of IP. All batches of tablets were found to exhibit short floating lag times in seconds and formulation F3 showed higher swelling as compared to others. The figures(1-5) depict the dissolution behavior of the tablets where all formulations showed



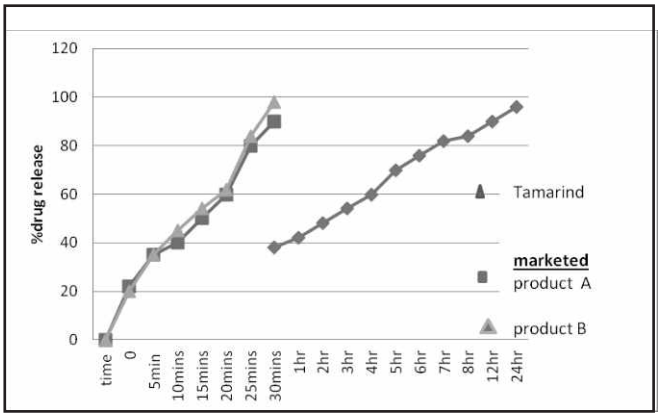
Figl: F1



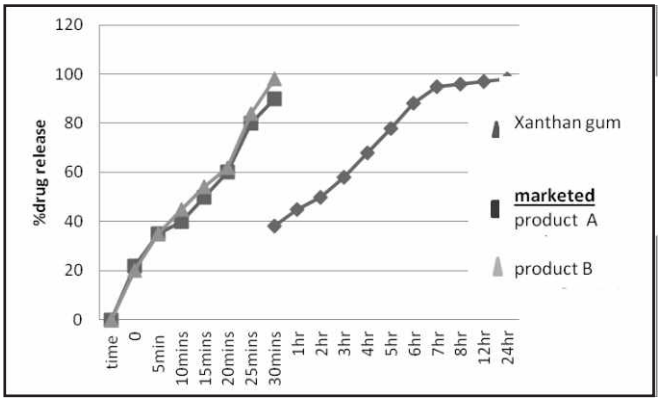
Figl: F2



Figl: F3



Figl: F4



Figl: F5

release for upto 24 hrs as compared to marketed formulation (A & B)which released drug within 40 minutes.

CONCLUSION: This study has resulted in successful development of gastroretentive floating tablets of the highly soluble drug, Losartan potassium using HPMC, tamarind gum and Xanthan gum as retardant polymers . It is evident from the results that formulation F7 prepared by using hydrophilic polymer HPMC K 15M and xanthan gum shows desired sustained release pattern as compared to other formulations studied.

ACKNOWLEDGEMENT: The authors are thankful to Colorcon Asia Pvt. Ltd, Bhavna Gum Udhyog. For gift samples of tamarind gum, Xanthan gum, HPMC. Authors are thankful to Alkem laborotaries ,Taloja for gift sample of Losartan K.

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Po23 Release mechanism of Doxorubicin from lipid polmer hybrid nanoparticles (Lipomer)

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Key words: Nanoformulation, Doxorubicin, lipomer, anticancer

Introduction: Doxorubicin (Dox) is an anthracycline antibiotic widely used for cancer chemotherapy but its usage is restricted due to its cardiotoxicity and nephrotoxicity. Nanocarriers hold good potential to deliver anticancer drugs to specific tissues by passive targeting or active targeting. Nanocarriers of Dox show reduced toxicity and hence an innovative carrier Dox lipomer which shows good potential for oral delivery has been developed in our laboratory. Lipomer comprises of a lipid polymer combination nanoparticle. In vitro dissolution studies help to establish mechanism of drug release, batch to batch consistency and to predict in vivo drug release profiles.

Objective: The present study discusses in vitro release mechanism of Dox from Dox lipomer.

Experimental Methods:
Drug release studies were carried out by dialysis bag method using dialysis membrane (HIMEDIA®, Molecular weight cut off 12000-14000 Dalton). The membrane was hydrated, tied at one end, Dox lipomer (equivalent to 5mg Dox) introduced , other end of bag tied and bag introduced into the basket of USP dissolution apparatus I (Electrolab, Mumbai, India) containing the release medium. The release media preheated to 37 ± 0.5 ºC consisted of 150 ml acetate buffer pH 4.5, 0.15M NaCl solution and 0.05M $CaCl_2$ solution and was stirred at 50rpm. Aliquots (5 ml) were withdrawn at specified time points and Dox concentration was determined by UV-Vis spectrophotometry at 478 nm. Percent cumulative drug release versus time profiles were plotted. The dissolution was carried out in triplicate.

Results and Discussion:
Dox Lipomer is a nanocarrier wherein Dox forms an ionic complex with the polymer Gantrez which is incorporated in a lipid matrix. Drug release profiles of Dox solution, Dox–Gantrez ionic complex and various Dox–LIPOMERs in acetate buffer pH 4.5 are shown in Figs. 1 & 2. To understand the mechanism of release, an ionic complex of Dox with Gantrez was evaluated as reference. While Dox solution revealed rapid release, Dox-LIPOMERs revealed slow and sustained release. Sustained Dox release from the LIPOMER is attributed to the lipid matrix imparting a barrier to drug release. To confirm the mechanism of drug release from Dox-LIPOMER, release was also carried out in demineralized water and media containing NaCl (0.15M) and $CaCl_2$ (0.05M). Data is shown in fig 1B. Fig 1B clearly shows slow release of Dox in demineralized water. In contrast, in presence of ions, enhancement in drug release is seen. This enhancement is independent of ion type but dependent on ion concentration. This confirms that the predominant mechanism of drug release from the LIPOMER is ion exchange.

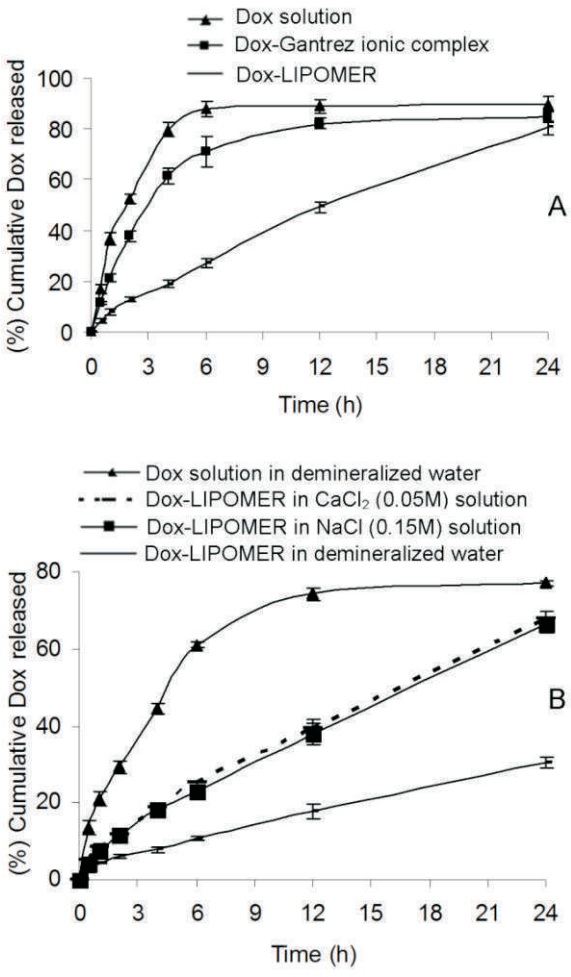

Fig. 1. In vitro **release profiles of Dox solution, Dox-Gantrez ionic complex and PGDS (Polyglyceryl -6 Distearate) based Dox-LIPOMER** in (A) acetate buffer pH 4.5 and (B) demineralized water, NaCl (0.15M) solution and $CaCl_2$ (0.05M) solution (mean ± S.D.; n = 3)

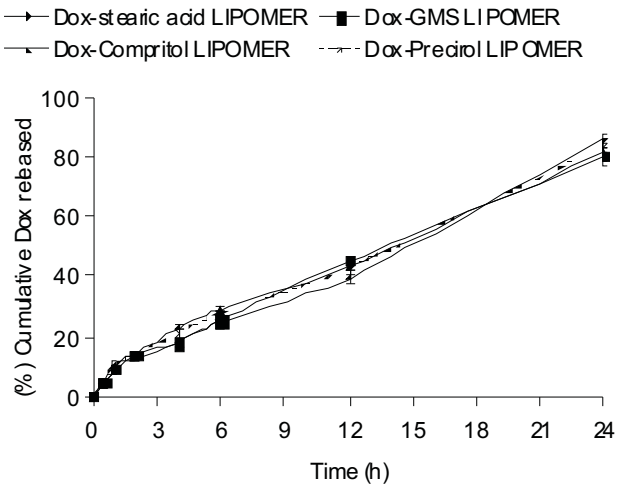

Fig.2. In vitro release profiles of various Dox-LIPOMERs in acetate buffer pH 4.5 (mean ± S.D.; n = 3).

The kinetics of Dox release from LIPOMER were fitted to various kinetic models such as zero-order, first-order, Higuchi equation, and Korsmeyer-Peppas equation and Dox release followed zero order kinetics (r^2 = 0.990) [2]. The release pattern of cytotoxic drug is critical as continuous exposure to low levels cytotoxic drugs may induce P-gp overexpression rendering the cancer cells more drug resistant. However rapid release of drug is also undesirable as it can lead to systemic toxicity[1].

Conclusion:
Although Dox-lipomer comprised of mixed polymer lipid, ion exchange contributed majorly towards drug release. Considering the sustained release nature of the Dox lipomer, these nanoparticles can be considered for in vivo studies to determine its potential for cancer treatment.

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Acknowledgements: UGC for SRF.

P024 Applications of In Vitro Diffusion Studies as Formulation Development Tool

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Key words: Franz diffusion cell, permeability, transmucosal, transdermal.

INTRODUCTION: Transdermal and transmucosal delivery systems include a host of delivery systems wherein drug is expected to traverse an intact biological barrier membrane such as skin / mucosal membrane and gain access to systemic circulation. Assessment of drug release rate and correlation with in vivo bioavailability for this class of formulations presents unique challenges. Commonly used in vitro methodologies include release studies such as those based on USP apparatus 5. However, diffusion experiments designed to evaluate drug permeation across various biological / artificial membranes can result in generation of more useful information. It can enable evaluation of permeability coefficients, permeation enhancement, and duration of permeation. Hence, while release studies can serve as quality control tests, permeability studies can serve as an indicator of in vivo performance.

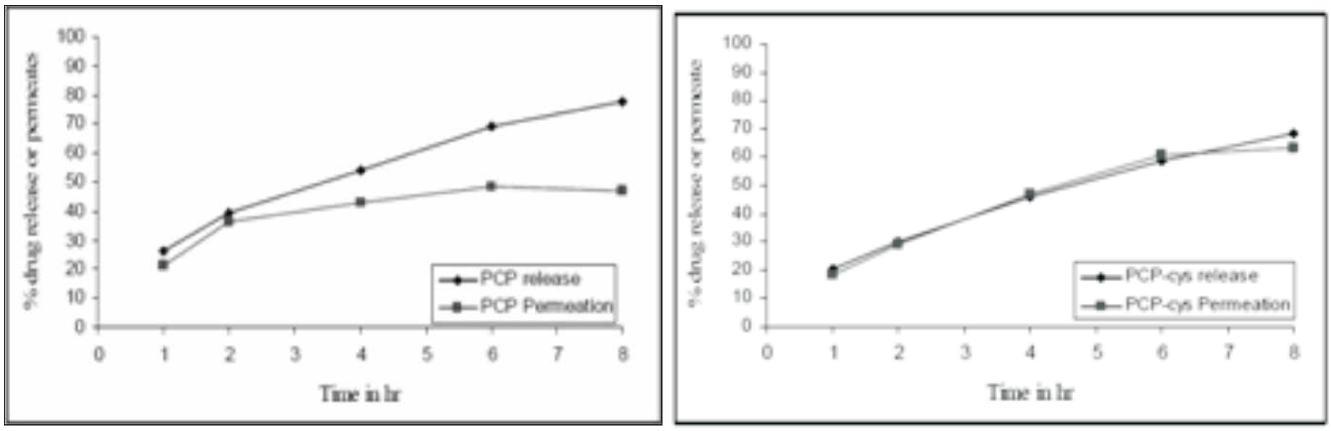
OBJECTIVE: The present paper discusses cases wherein in vitro permeability studies have proven to be useful in establishing important attributes of a formulation, such as permeation enhancement, in vivo performance, rank ordering of various formulations etc.

METHODOLOGY : All studies were carried out using vertical Franz diffusion cells (Lab Glass India). The donor compartment held the suitable dosage form as detailed in table 1. Receptor fluid in each case was designed to ensure sink conditions and was maintained at 37°C.

Case No	Drug	Intended Route of administration and dosage form	Release Methodology / Barrier for release studies	Permeability Barrier for permeation studies	Receptor fluid	*In vivo* Pharmaco-dynamic activity evaluated
I	Selegiline HCl	Buccal Mucoadhesive Tablet	USP type I apparatus, 40ml receptor fluid	Excised Porcine buccal mucosa	Phosphate buffer pH 6.8	-
II	Doxepin HCl	Intranasal Thermo reversible gel	Parchment Paper	Excised Sheep nasal mucosa	Phosphate buffer pH 6.4	Forced swim test
III	Bromo-criptine mesylate	Transdermal Microemulsion based gel	---	Excised Rat Skin		Locomotor activity

RESULTS AND DISCUSSION :

Case I : Buccoadhesive tablets containing selegiline HCl were prepared using polycarbophil (PC) as such and after derivatization through attachment of cysteine groups : a modification reported to confer permeation enhancing properties to the polymer[1]. This could be evidenced by the observation that drug in PC matrices permeated at a rate lower than that of in vitro release; whereas in case of tablets prepared using cysteine-PC, both release and permeation profiles are almost entirely overlapping. Thus while permeation is the rate determinant event in case of PC matrix, for cysteine–PC based matrix, drug flux was determined by drug release, since released drug was rapidly taken across buccal mucosa.



Case III is a study on microemulsion based[3] transdermal systems where *in vitro* permeation studies served to establish a rank order between formulations which show-ed close correlation with efficacy established through *in vivo* pharmaco-dynamic activity of bromocriptine mesylate.

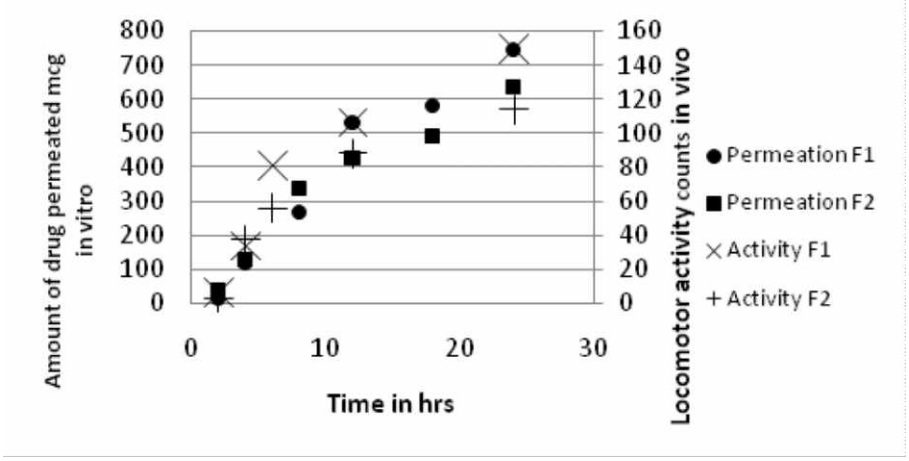


Fig. 2. In vitro **permeation and** in vivo **activity of bromocriptine from transdermal microemulsion** Spelling,what is F1 & F2 in the graphṢ **based gels.**

CONCLUSION : In vitro release and permeation studies can serve as important aids to guide formulation development of transdermal and transmucosal drug delivery systems and have potential as formulation assessment tools with good in vitro-in vivo correlation.

Acknowledgements : The authors are thankful to Themis, Torrent and Inga Labs for gift samples of selegiline HCl, Doxepin and Bromocriptine mesylate respectively.

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P025 - MODIFIED USP DISSOLUTION APPARATUS II FOR DISSOLUTION TESTING OF BUCCAL TABLETS OF RIVASTIGMINE HYDROGEN TARTRATE

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Introduction:

Over the last three decades bioadhesive systems become popular for localizing drug delivery systems, by retaining a dosage form in intimate contact with the absorption site for mucosal (local) or transmucosal (systemic) delivery.

Rivastigmine Hydrogen Tartrate (RHT) is used for treatment of mild to moderate dementia associated with Alzheimer's disease. RHT exhibits poor (40%) oral bioavailability due to extensive first pass metabolism. Delivery by buccal route results in direct entry of drug in to the systemic circulation which bypasses the hepatic metabolism and ultimately exhibits higher bioavailability. Our lab has a patented technology on compositions with enhanced bioadhesion (Devarajan et al., IP206334) which was utilized to design buccal tablets of RHT. Buccal tablets are intended to dissolve in small volume of saliva hence it is appropriate to evaluate in-vitro release in small volume of dissolution medium therefore we designed a modified USP apparatus II which could enable evaluation using less volume of medium.

Objective:

The objective of the present work was to design a, modified USP apparatus II for dissolution testing of buccal tablets.

Methodology:

Buccoadhesive tablets of RHT (7.2mg) comprising of bioadhesive polymer, bioadhesion enhancer and suitable excipients in different proportion were prepared by direct compression technique using single stroke tablet machine (Cadmach, India) with flat punches of 7 mm diameter. Tablets were evaluated for standard tablets parameters. Bioadhesion was carried out using inhouse modified bioadhesion tester.

In-vitro dissolution study was carried out in Modified USP apparatus type II (Fig.1) which contains glass vessel with internal diameter of 2.6 cm and height 7.1cm and stainless steel paddle with a lenght 1.3 cm. Medium was **pH 6.8 buffer (10ml) maintained at** 370.2C **at 75 RPM. Height of medium in the vessel was 2.7cm.** Aliquots (2 mL) were withdrawn at specific time intervals and were replaced with equal volume of the dissolution medium **and analyzed by UV-spectrophotometer at 264 nm.**

Results:

All tablet parameters were found to be within standard Pharmacopoeial limits. Inclusion of mannitol in tablets enhances bioadhesion. In an in-vitro dissolution apparatus to maintain equivalent agitation intensity two critical parameters are agitator and the volume of dissolution medium. In USP apparatus II having paddle length of 7.5 cm, the height of the medium when 1000mL used is approximately 14.3 cm, the ratio of height to paddle length is 1.91. In the modified apparatus we tried to maintain that ratio by creating paddle with 1.3 cm and dissolution medium height 2.7 cm (10mL) and the ratio was 2.07)

Drug release from the tablets was significantly influenced by the nature of polymer, with sodium carboxy methyl cellulose tablets exhibiting faster drug release than cabopol also carbopol exhibited incomplete release. This is attributed to highly cross linked structure of carbopol as compare to Na-CMC. Mannitol did not significantly affect drug release from the tablets (Fig.2). The drug release data when fitted to different kinetics models it exhibits Higuchi kinetic model with higher coefficient of correlation value 0.9960.

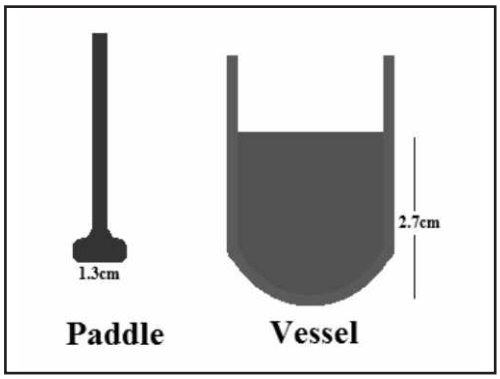

Fig.1- Modified USP apparatus type II

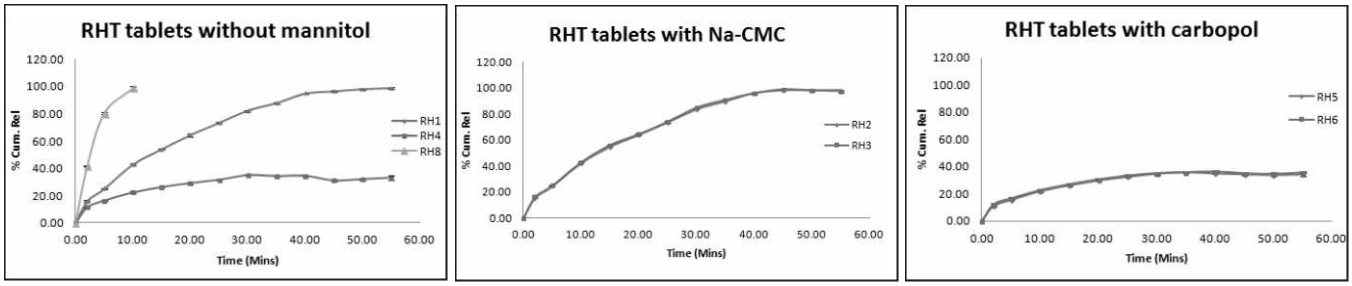

Fig.2- Dissolution profile

Conclusion:

Fast release buccal tablets of RHT were successfully developed. In vivo studies are however important to confirm the rationale of the modified dissolution apparatus developed in this study.

Reference:

Devarajan P. V., Gandhi A. S., Gore S. P., IP 206334

Acknowledgement:

Authors are thnkfull to Dr. Reddy's Laboratory Ltd. for gift sample of RHT.

Phoenix Pharmceuticals USA, for fellowship.

P026 Nanoprecipitating preconcentrate of a BCS Class II drug for improving its dissolution profile

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Keywords:

Nanosuspension; BCS; Ezetimibe; Amorphous, Nanoprecipitating preconcentrate

Introduction:

Poor aqueous solubility can be a major factor limiting GI absorption of the drug [1]. Nanosuspension, a colloidal dispersion of the the drug nanoparticles stabilized with either a single or a combination of stabilizers [2] possess potential to augment saturation solubility and therefore dissolution velocity, due to decrease in particle size of the drug [3] and in addition by manipulating drug in an amorphous state.

Ezetimibe (EZM), a BCS Class II drug with a high log P value of 4.5 was chosen for the study. It is anticipated that nanosizing of EZM will result in improvement in dissolution velocity of the drug leading to an increase in bioavailability.

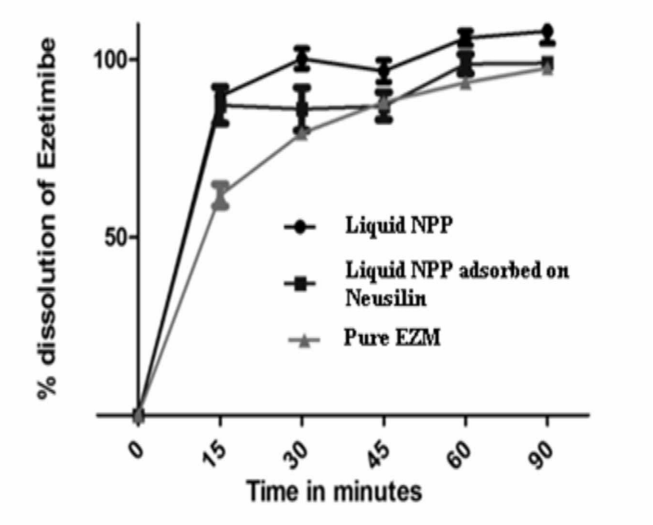
Experimental Work:

Initial experimentation involved analyzing the solubility profile of EZM in various hydrophilic surfactants like Tween 80, Cremophor EL and in lipophilic surfactants like Lecithin, Capryol 90. Nanoprecipitating preconcentrate (NPP) of EZM was prepared using a simple mix method wherein a combination of hydrophilic and lipophilic stabilizer was added to drug solution in biocompatible solvent to yield final preconcentrate. The liquid NPP system was transformed to granular mass form by adsorbing on Neusilin for ease of handling. The liquid as well as granular mass upon mixing with water was examined for particle size analysis, X-ray diffraction pattern, TEM for morphology evaluation and in vitro dissolution study. Dissolution testing was performed for pure EZM, liquid NPP and Neusilin based granular NPP. Sodium lauryl sulphate (SLS), 0.45% in acetate buffer pH 4.5 was used as the dissolution medium in a USP type II apparatus.

Results:

Particle size analysis of the EZM NPP on dilution with water revealed mean particle size in the range of 215-235 nm. The drug content was in accordance with the theoretical drug content. Powder X-ray diffraction studies revealed amorphization of the nano-drug particles. Transmission electron microscopy (TEM) of the drug particles confirmed the amorphous nature, with particles having uneven morphology. In vitro dissolution test of the NPP showed a considerable improvement in dissolution velocity of the drug, as compared to the pure drug. For liquid NPP, 100% dissolution of drug was observed in 30 mins, while for pure EZM powder, 100% dissolution was observed only after 90 mins. For adsorbed NPP, release profile was found to be similar to that obtained for liquid NPP, with more than 85% dissolution of drug observed after 15 mins, in comparison to pure EZM powder which dissolved upto 60% (fig.1).

Fig.1. Release profiles for EZM loaded NPPs and pure EZM powder:



Conclusion:

The EZM NPP system developed was amenable to easy scale up and on dilution with aqueous media, resulted in nanosuspension formation of EZM, exposing greater surface area to medium for dissolution. In vivo studies can be conducted to evaluate the ability of EZM NPP to improve efficacy of EZM.

Acknowledgements: Authors are thankful to Lupin Pvt Ltd., for providing gift sample of Ezetimibe, Gattefosse India for providing free samples of various oils and surfactants and Jaslok Hospital for TEM facility.

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P027 Dissolution Study Of Polymeric Combination Nanoparticles Of Doxycycline-rifampicin By Dialysis Bag Method

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KEY WORDS:

Combination Nanoparticles, dialysis bag method, simultaneous equation method

INTRODUCTION:

Recently the use of colloidal carriers as drug delivery systems is gaining more attention. Evaluation of the in vitro drug release is considered an important step during the development and quality control of such systems. Various methods available to assess the drug release from nanoparticulate systems can be broadly divided into 3 categories (i) membrane diffusion such as dialysis, reverse dialysis and diffusion cell; (ii) sample and separate using centrifugation, filtration and centrifugal ultrafiltration technique; (iii) in-situ measurement e.g., UV spectrometry, fluorescence spectrometry. Membrane diffusion techniques are considered the best for assessing the in vitro drug release from nanoparticles. In these techniques the colloidal carrier is separated from the sink release medium by a dialysis membrane which is permeable to the drug. The present study discusses in vitro release of Doxycycline (DOXY) and rifampicin (RFM) from combination nanoparticles (NP) .

OBJECTIVE:

The objective of present study was simultaneous analysis of doxycycline and rifampicin in combination nanoparticles and understanding release mechanism of both drugs from the nanoparticles.

EXPERIMENTAL METHOD:

Quantification of doxycycline and rifampicin
Doxycycline and rifampicin were quantified by UV spectroscopy using simultaneous equation method. λ_{max} of doxycycline and rifamipicin were found to be 275 nm and 475 nm, respectively. Based on λ_{max} standard curve of DOXY and RFM in combination was developed. Solutions were prepared at different concentrations - 5, 10 and 15 µg/ml. The absorbances of these solutions were recorded at the λ_{max} (275 nm and 475 nm) and plotted v/s. the concentrations to give the equation and calculate absorbtivity of both drugs by putting in the equations 1 and 2. The equations are as follows

Cx = (A2*ay1- A1*ay2)/(ax2*ay1-ax1*ay2)---------1
Cy = (A2*ay1- A1*ay2)/(ax2*ay1-ax1*ay2)---------2

Where, Cx =Concentration of Doxycycline, Cy =Concentration of Rifampicin, A1 = Absorbance of unknown sample at λmax 275 nm, A2 = Absorbance of unknown sample at λmax 475 nm
In vitro release study by dialysis bag method

The release of DOXY and RFM from the DOXY-RFM NP was determined by dialysis bag method. The dissolution medium was 100ml phosphate buffer pH 7.4. Dialysis membrane molecular weight cut off 70 Da was hydrated prior to use. Nanoparticulate dispersion (equivalent to 2 mg of DOXY and 4.5 mg of RFM) was introduced into the dialysis bag. The bag was introduced into the basket of USP Apparatus I and immersed in the dissolution medium. Aliquots of 5 ml were withdrawn at suitable time intervals and replaced with fresh buffer to maintain sink condition. A control experiment using a solution of DOXY-RFM to determine the release behaviour of the free drug was also performed.

RESULTS:

The nanoparticles were prepared containing doxycycline and rifampicin by using Gantrez AN 119 as a polymer and AOT as a surfactant. The simultaneous equation method developed enable accurate and reproducible quantification of both drugs. Both doxycycline (fig.1) and rifampicin (fig.2) exhibited sustained release from nanoparticles. However, doxycycline, a water soluble drug, revealed t_{50} value lower than rifampicin. Nanoparticles showed sustained release of RFM up to 12 h and doxycline up to 6 h.

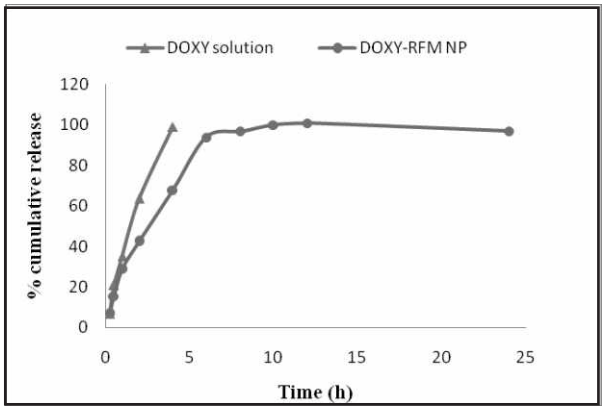

Fig 1 In vitro release profile of DOXY from DOXY-RFM solution and DOXY-

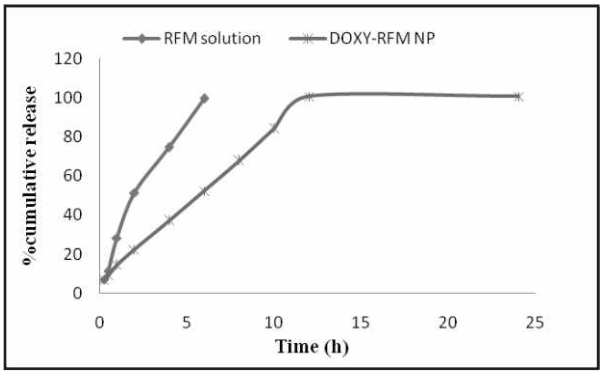

Fig 2 In vitro release profile of RFM from DOXY-RFM solution and DOXY-RFM NP

To investigate the drug-release kinetics, data were fitted to various kinetic models such as zero order, first order, Higuchi equation, and Korsmeyer–Peppas equation, and the coefficient of correlation (r^2) for DOXY and RFM from the NP is indicated in table 1.

Table 1. Models for release of DOXY and RFM

Sr. No.	Models	R^2 for DOXY	R^2 for RFM
1	Zero order kinetics	0.866	**0.999**
2	First order kinetics	**0.974**	0.754
3	Higuchi kinetic model	0.959	0.964
4	Koresmeyer-Peppas model	0.965	0.99

The R^2 values from the table suggest DOXY exhibits first order kinetics , while RFM follows zero order kinetics. The same could be related to the composition of the nanoparticles which comprise RFM complexed with AOT(docusate sodium)**.**

CONCLUSION:

Both drugs were quantified in combination and in vitro release study of DOXY-RFM nanoparticles reveals that RFM follows zero order kinetics due to ion exchange and doxycycline shows first order kinetics.

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ACKNOWLEDGEMENT:

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P028 Influence of concentration of ethyl cellulose on in vitro release of Metoclopramide HCl from floating sustained release microspheres

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KEYWORDS:

Floating SR microspheres, Metoclopramide HCl, Non-Aqueous Emulsion Solvent Evaporation Method, Ethyl cellulose

INTRODUCTION:

The present work focuses on formulation of floating SR drug delivery system. Metoclopramide HCl is a widely used anti-emetic drug. It is available as a conventional tablet in market and there is no sustained release formulation available in market. The daily dose of anti- emetic is 3-4 times a day. In chemotherapeutic treatment the dose is up to 6 times a day here patient compliance is very important and dosing is must. So as to reduce the dosing frequency and increase patient compliance a sustained release formulation is a must. A multi unit dosage form is prepared to avoid dose dumping and maximum availability of drug. As the drug has maximum absorption from upper GIT, floating drug delivery system is the perfect solution to solve the problem. Taking all this into consideration this research work aims on developing an effective floating sustained release multiple unit formulation. Gastrointestinal absorption of Metoclopramide HCl is uniform, rapid, and essentially complete and has a relatively short elimination half life (4-5hr). Thus, there is a strong clinical need and market potential for a dosage form that will deliver drug in sustained manner to give a prolonged action.

FORMULATION AND DEVLOPMENT OF MICROSPHERES:

Microspheres were prepared by Non-Aqueous Emulsion Solvent Evaporation Method. Drug and polymer were dissolved in DCM: ethanol (2:1) mixture. This was then dispersed into liquid paraffin containing SPAN80 and stirred at 900 rpm for 2h. Microspheres were filtered and dried.

SCREENING OF POLYMER:

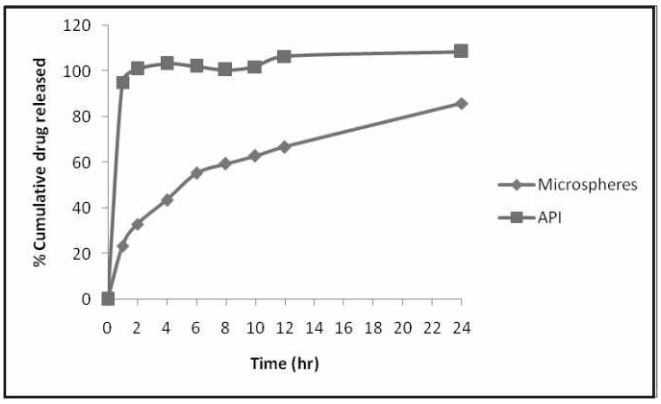
After formulation of trial batches of microspheres using different polymers and surfactants, ETHYL CELLULOSE and SPAN80 were selected for further studies. Screening was done on basis of evaluation of various parameters such as particle size, % entrapment efficiency, % buoyancy, % drug release. Further studies were carried out to check the effect of various concentrations of ethyl cellulose on drug release.

DISSOLUTION PROTOCOL:

The drug release rate from microspheres was determined using USP Type I apparatus (Basket dissolution apparatus). A weighed amount of microspheres equivalent to 30 mg of drug was filled into capsule and placed in the basket. 0.1 N HCl (pH 1.2, 900 ml) was used as a dissolution medium maintained at 37±0.5°C at a rotation speed of 100 rpm. 5 ml of sample was withdrawn at specific interval of time and the same amount of dissolution medium was replenished. Sample was passed through filter and analysed spectrophotometrically at 276 nm to determine the concentration of drug present in the dissolution medium. The dissolution study was continued for 24 h.

RESULT:

Optimized batch gave % recovery yield of 91.86% with % entrapment efficiency of 95.56% and % drug release of 85.95% at end of 24h, % Buoyancy of batch was 85 %. The external and internal morphology of the microspheres were studied by SEM. The X-RD studies of pure METO, EC and optimized microspheres were carried out. X-RD was carried out to investigate the effect of microencapsulation process on crystallinity of drug. The dissolution profile of microspheres was compared with plain API, which shows that drug is released in a sustained manner from formulation.



CONCLUSION:

The present study reports successful development of METO loaded floating microspheres with polymer Ethyl cellulose using Non-aqueous emulsion solvent evaporation method, with sustained action.

ACKNOWLEDGMENT:

Thankful to IPCA Laboratories and EVONIK Laboratories for gift samples of drug and polymers.

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P029 Comparison of Mucoadhesive Buccal Patches of Ondansetron HCl with Conventional Marketed Tablets

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KEYWORDS:

Ondansetron HCl (ODN HCl), Poly Vinyl Alcohol (PVA), Tamarind gum, Chitosan, Marketed tablet.

INTRODUCTION:

Ondansetron HCl is a potent antiemetic drug which is a highly selective Serotonin 5HT3 antagonist. It is effective in the treatment of nausea and vomiting associated with cancer chemotherapy. It is well absorbed and undergoes first-pass metabolism, having oral bioavailability 60% and has a relatively short plasma elimination half life of 3 to 5 hours. The promising pharmacokinetics and physicochemical properties of ODN HCl make it a suitable candidate for buccal drug delivery. The buccal patches were developed to increase bioavailability, bypass first-pass hepatic metabolism and prolong the release thereby increasing therapeutic efficacy of Ondansetron HCl by employing known mucoadhesive polymers PVA, tamarind gum and chitosan along with hydrophilic polymer polyvinyl pyrrolidone (PVP K-30). [1]

MATERIALS AND METHODS:

Ondansetron HCl was received as a gift sample from FDC Ltd.(Mumbai, India). Tamarind gum was procured as a gift sample from Bhavna Gum Udhyog (Gujarat, India) and chitosan from CIFD, (Cochin, India) PVP K-30, HPMC 15cps, Propylene glycol, DMSO, glacial acetic acid were obtained from SD Fine Chemicals Ltd. (Mumbai, India). PVA was supplied by CDH Ltd. (Mumbai, India).

PREPARATION OF MUCOADHESIVE BUCCAL PATCHES:

Ondansetron HCl buccal patches were prepared by solvent-casting method. The drug solution was added to the polymer solution and mixed thoroughly with the help of a magnetic stirrer. Propylene glycol and Dimethyl sulfoxide (DMSO) were then added as plasticizer and permeation enhancer respectively under stirring and this solution was poured into a glass Petri dish (9cm diameter) and allowed to dry at ambient temperature till a flexible film was formed. Dried films were carefully removed and cut into patches of 1.5cm in diameter, packed in aluminium foils and stored in airtight containers at room temperature for further study. The various batches prepared are as given in Table1.

Table 1: Composition of Buccal patches loaded with Ondansetron HCl

Name of Ingredients	F1	F2	F3
Ondansetron HCl (mg)	85	85	85
PVA (gm)	0.5	-	-
Tamarind gum (gm)	-	0.5	-
Chitosan (gm)	-	-	0.2
PVP K-30 (gm)	0.1	0.1	0.1
HPMC 15cps (gm)	-	-	0.2
Propylene glycol (ml)	0.5	0.5	0.5
DMSO (gm)	1	1	-
2% v/v Acetic acid (ml) q.s.	-	-	10
Water (ml) q.s.	10	10	-

Quantity of drug per 1.5cm diameter patch = 2.36mg

IN-VITRO DRUG RELEASE STUDY: Dissolution studies to assess the drug release from the buccal patches were carried out in USP apparatus II. 900 ml of phosphate buffer 6.8 was taken as dissolution medium and the release study was performed at 37 ± 0.5^0 at 50 rpm for 8 hours. Aliquots (5 ml) were withdrawn at specific time intervals for a period of upto 8 hours. Drug concentration in the withdrawn aliquots was assessed by UV spectrophotometry. Prepared formulations were compared with the marketed tablet.

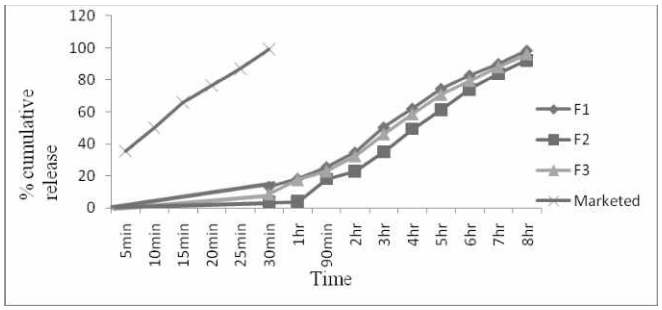

Fig. 1: Comparison of In Vitro **Release profiles of prepared formulations (F1-F3) with Marketed Tablet**

RESULTS AND DISCUSSION:

The Ondansetron HCl buccal patches were obtained as good flexible films with acceptable mucoadhesive strength, retention time, ex-vivo permeation and swelling properties. Drug content was found to be high (99.70%) and uniform in all formulations. The prepared formulations showed prolonged release of 8 hours in comparison to the marketed tablet which showed complete release within 30min.

CONCLUSION:

This study clearly demonstrated that Ondansetron HCl can be successfully delivered via the buccal route. The buccal patches prepared by using mucoadhesive polymer PVA along with PVP K-30 can be a promising drug delivery system for achieving controlled and prolonged release, and thereby achieving better therapeutic efficacy and improved patient compliance.

ACKNOWLEDGEMENT:

The authors are thankful to Bhavna Gum Udhyog, CIFD for gift samples of tamarind gum and chitosan respectively. Authors are also thankful to FDC Ltd., Jogeshwari for gift sample of Ondansetron Hcl.

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P030 Characterisation of Serratiopeptidase (SRP) Controlled Release Extrudates by In-Vitro Dissolution and Ex-vivo absorption studies

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Key Words: Serratiopeptidase (SRP), Solid dispersions, Bioadhesive extrudates

Introduction:

Serratiopeptidase (SRP) is a proteolytic enzyme obtained from the non pathogenic bacteria Serratia marcescences strain E-15 (ATCC 21074) and has found application as a very good anti-inflammatory and wound healing agent. Being an acid labile enzyme, it is available as enteric coated tablets or granules; also severe loss of activity is observed during compression of tablets. [1, 2]

Objective:

To develop novel mucoadhesive extrudates of SRP with a view to achieve better stabilization of the enzyme and controlled release, and characterise their in vitro release and ex vivo absorption behaviour.

Experimental:

1. Selection of Suitable Dissolution medium: The stability of SRP in various dissolution media, viz. Distilled water, Tris buffer (pH 7.0), and Phosphate buffer (pH 7.0) over a period of 12 hrs at 37°C and room temperature was assessed.

2. Selection of Stabilizers: In order to improve the stability of SRP, solid dispersions of SRP with β cyclodextrin, PEG 6000, and PVP K-30 were prepared by wet granulation, fusion and solvent evaporation techniques respectively. All prepared SRP solid dispersions were evaluated for stability at 5-8°C, ambient temperature and 65+5% RH, and accelerated temperature 40+2°C and 75+5% RH for 6 months.

3. Preparation of SRP Extrudates: The bioadhesive extrudates of SRP were prepared with various release retardants like HPMC, Sodium alginate and excipients like Lactose, MCC and PVP K-30 using die roller extruder equipment (UDRE 65E- Umang Pharmatech Pvt. Ltd., India). Optimization studies were carried out using 3^2 full factorial design, where independent variables were % of HPMC [Methocel K 100M CR] and Sodium alginate [Protanal 240D] and the dependent variables were percent cumulative drug release at 3 hrs and at 4 hrs.

   In-vitro release studies of the extrudates were carried out using USP Type I apparatus, [Medium: Tris Buffer (pH 7.0) - 900ml, 37+0.5°C and stirring speed-100 RPM]. The in vitro release profiles of all the batches were fitted to zero-order, first order, Hixson Crowell, Higuchi, Two third, Bamba and Baker Lonsdale to ascertain the kinetics of drug release. Selected optimized batch of SRP extrudates were filled into capsule size '0' and coated with Eudragit® L-100 D55 in fluid bed coater (FBC) (Minilab: Umang Pharmatech Pvt. Ltd., India)

4. Ex-vivo absorption studies: were carried out using guinea pig everted intestinal sac model in USP Apparatus Type II. The formulations were inserted into the intestinal sac with the help of applicator, followed by addition of 1.5ml of Tris buffer (pH 7.0).The intestinal segments were then tied and fixed to the paddle of dissolution apparatus. The % cumulative absorbed was compared with that of free enzyme and conventional marketed tablets.

Result:

SRP exhibited maximum enzyme activity in Tris buffer (pH 7.0), and hence this was selected as most suitable dissolution medium for evaluation of SRP products. Amongst all the SRP solid dispersions, SRP-PVP K -30 dispersion retained maximum amount of enzyme activity.

In optimization studies, both the factors viz. concentration of HPMC and sodium alginate significantly affected the in vitro enzyme release. Most of the experimental batches showed the best fit with zero order kinetics, which indicates that the drug release is controlled by a concentration independent diffusion mechanism; whereas some of the batches where concentration of retardants was higher showed the best fit for Krosmeyer Peppas model, indicating the mode of drug release to be Case II diffusion controlled.

Ex-vivo absorption studies showed that the release and absorption of the native enzyme and marketed preparation were more than 80% of enzyme in 3 hours, whereas optimized extrudate batches provided a slow release and sustained absorption over a 10 hour time period in Tris buffer (pH 7.0), which may be attributed to the presence of retarding polymers, HPMC and sodium alginate and the mucoadhesive nature of the polymers.

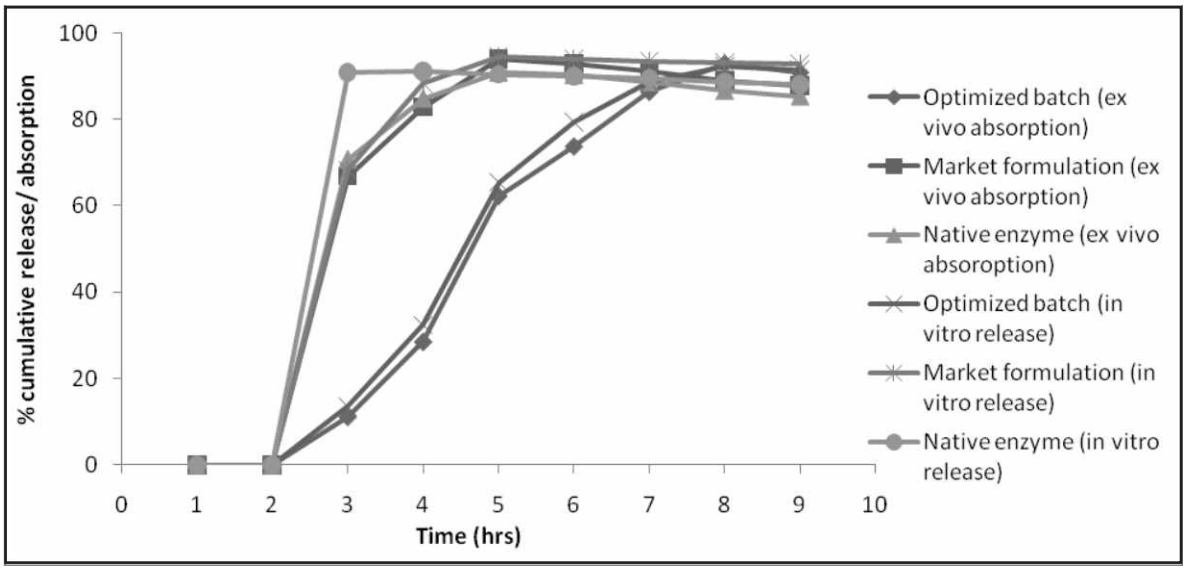

Fig:1 – Comparison between ex vivo absorption and in vitro release profiles of optimized batch of extrudates, marketed formulation and free enzyme.

Conclusion:

In conclusion, in vitro dissolution & ex- vivo absorption study helped in the design of the mucoadhesive controlled release SRP bioadhesive extrudates, which would provide an alternate to conventional tablets.

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Acknowledgements:

Advanced Enzyme Technologies Ltd, Umang Pharmatech Pvt Ltd.

P031- Development of Accelerated In-Vitro Dissolution Method to Evaluate Risperidone Release from PLGA Microspheres

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Keyword:

poly(dl-lactide-co-glycolide) (PLGA), real time in-vitro release (long term release), accelerated in-vitro release (short term release)

Introduction:

With the increased use of parentally administered PLGA microspheres having extended duration of action in vitro and in-vivo, drug release assessment becomes an important aspect.Evaluation of extended drug release upto 1-3 months under real-time conditionis both time consuming and expensive.[1]Temperature dependent accelerated in-vitro release to correlate and predict long term in-vitro release in short timehas been reported[1].The present research work reports an alternative approach whereby addition of solvent has been used for accelerating drug release from extended release microspheres.

Objective:

The objective of the present work was to develop a quick and reliable accelerated in-vitro release method to correlate and predict long term in-vitro release of Risperidone loaded PLGA microspheres.

Experimental Method:

Preparation of microspheres: PLGA microparticles were prepared by solvent extraction method.

Long- term in-vitro release:

10 mg Risperidone loaded PLGA microspheres were incubated with 10 ml of 50 mM Phosphate buffer (pH 7.4) containing 0.02 % Tween 80 and 0.05 % sodium azide at 37 º C in Bottle rotating apparatus at 50 rpm. Concentration of drug in dissolution medium was analysed by HPLC.

Short-term in-vitro **release:**

Dissolution conditions for accelerated in-vitro releasewere same as in long term release except that the dissolution media contained water miscible solvent. At different concentration level of solvent, temperatureoptimization was done for accelerated in-vitro release.

Result and Discussion:

Long- term in-vitro **release:**

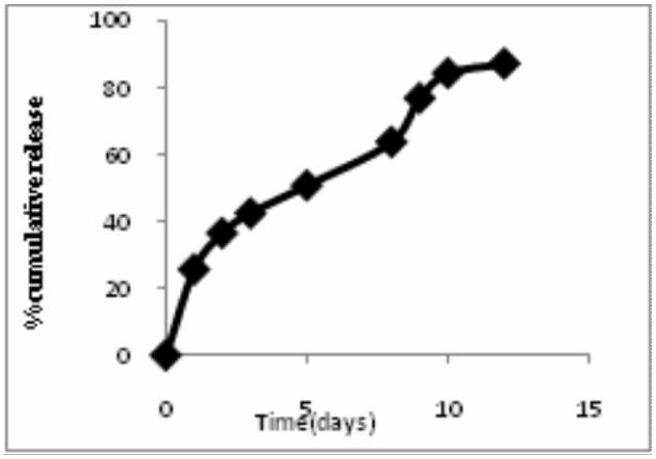
The in-vitro release profile of optimized formulation showed 87% release in 30 days in real time drug release condition.

Short-term in-vitro **release:**

Incorporation of solvent in dissolution media was found optimal for accelerating the in-vitrodrug release showing 87 % release within 12 days.

Short-Term Versus Long-Term (Real-Time) Correlation:

Correlation between short-term and long-term in-vitro release data was carried out after conversion by scaling factor. Regression coefficient of correlation plot was found to be 0.9973.



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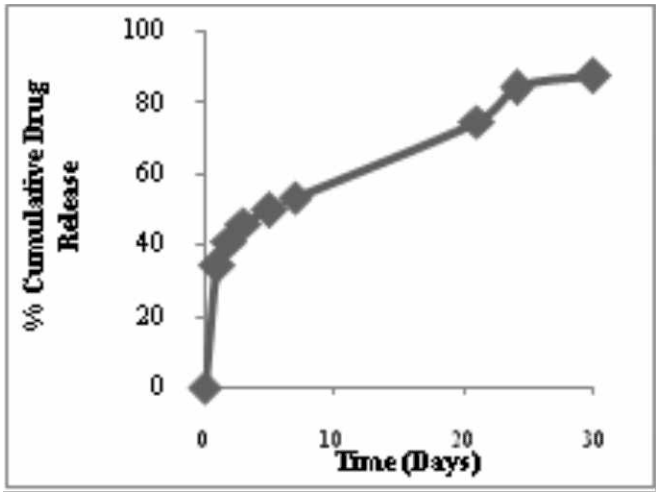

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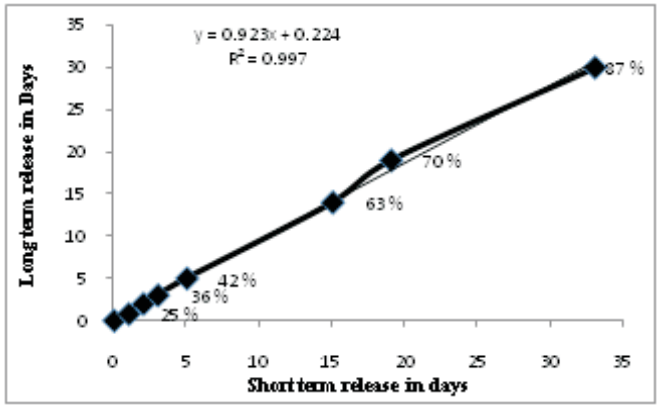

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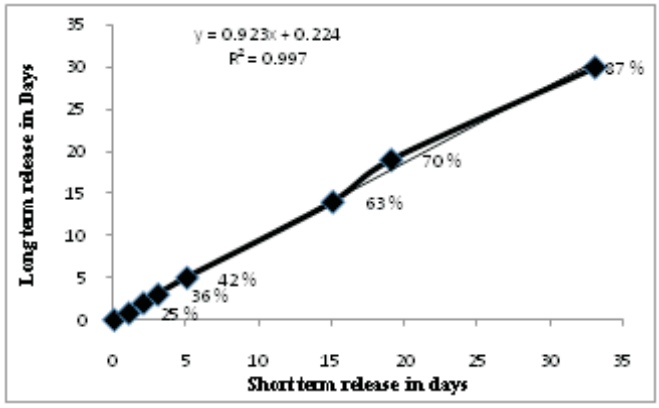

D

Fig.1:A) Real time release B) Accelerated release C) Correlation plot

Conclusion:

An accelerated method with high correlation with real time dissolution data has been successfully developed which would lead to quick and reliable in-vitro drug release testing from extended release formulation.

References:

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Acknowledgement:

Wochardt ltd for providing drug sample.

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James L. Waters[1], an industry pioneer and entrepreneur, founded Waters Corporation in 1958. After stints as a university math teacher, Naval officer and project engineer, Jim started his scientific instruments company in the basement of a Framingham, Massachusetts police station.

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Inauguration

Dr. B Suresh, Vice-Chancellor, JSS University, Mysore President of Pharmacy Council of India, New Delhi Together with the Chairman of the Congress Mr. Veeramani formally inaugurated the SPDS (Society for Pharmaceutical Dissolution Science) at 64th IPC congress at Chennai, on 8th Dec 2012

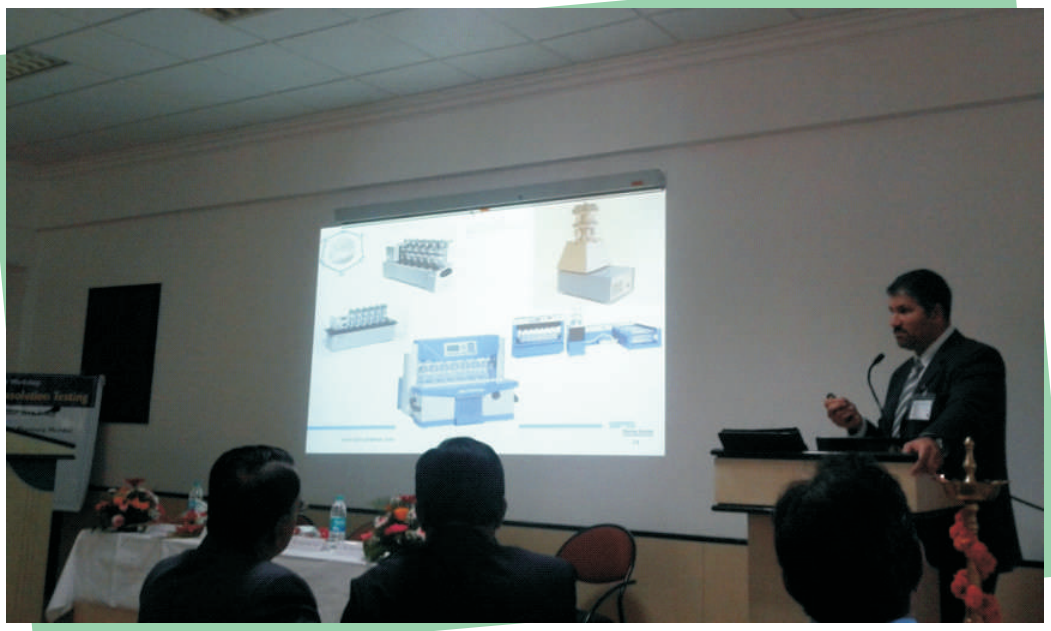
Dr. Ramaswamy introducing SPDS at 64th IPC

One Day Workshop - Dynamics of Dissolution Testing, 21st Dec 2012, Mumbai

Inauguration Ceremony : Lighting of the Lamp

(L-R: Dr.L Ramaswamy, Dr. S. K Kulkarni-Director, Bombay College of Pharmacy,
Mr. Vijay Kshirsagar-Executive Vice President-Corp. QA,Unichem Laboratories,
Mr. Samir Haddouchi-Managing Director-SPS Pharma Services,France)

One Day Workshop - Dynamics of Dissolution Testing, 21st Dec 2012, Mumbai



Mr. Samir Haddouchi-SPS Pharma Services, France during his presentation

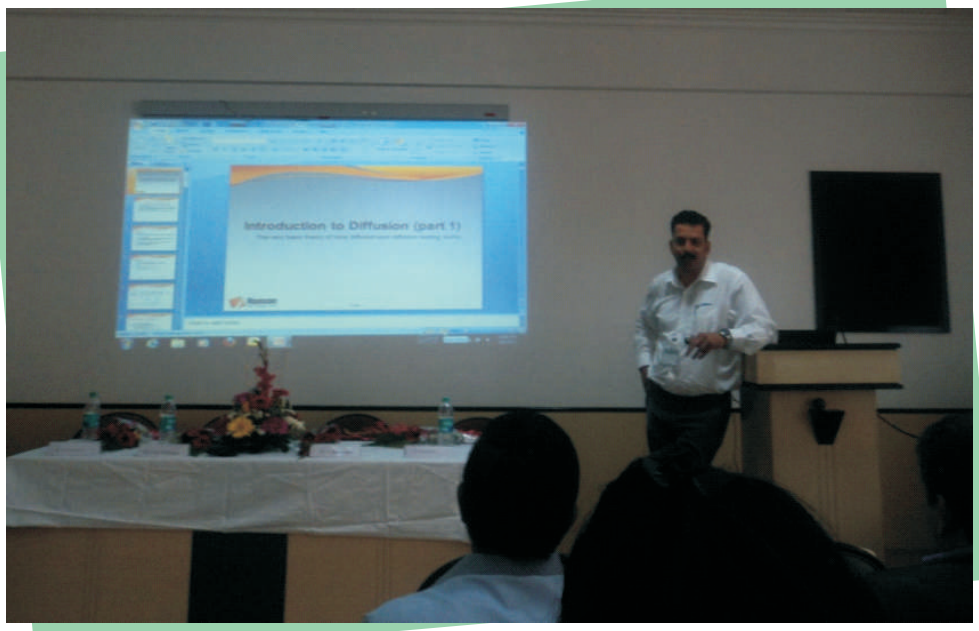
Dr.L Ramaswamy –General Secretary-SPDS

One Day Workshop - Dynamics of Dissolution Testing, 21st Dec 2012, Mumbai

Mr. R. S. Pal during the Live Demo of USP4 apparatus SOTAX CE7 Smart

Mr. Vijay Kshirsagar-Executive Vice President-Corp. QA,
Unichem Laboratories during his presentation

One Day Workshop - Updates on Dissolution Testing, 8th March 2013, Mumbai



Mr. Satish Kakodkar-Business Manager,Labindia on Transdermal Diffusion Cell Systems

Dr.Mrs. Mala Menon speaking on Dissolution approaches of Inhalation delivery systems

One Day Workshop - Updates on Dissolution Testing, 8th March 2013, Mumbai

Mr. Satish Kakodkar-Business Manager,Labindia during his presentation

Dr.Mrs. Mangal Nagarsenkar speaking on
"Drug Delivery Systems: Modulation of Dissolution Profile"

One Day Workshop - Updates on Dissolution Testing, 8th March 2013, Mumbai

Demonstration of Qualification –Mechanical as per USP and ASTM ON Labindia Dissolution bath

Audience during the Workshop

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Packaging Range

• Automatic Cartoning Machine • Automatic Vial Inspection Machine • Card Blister Machine

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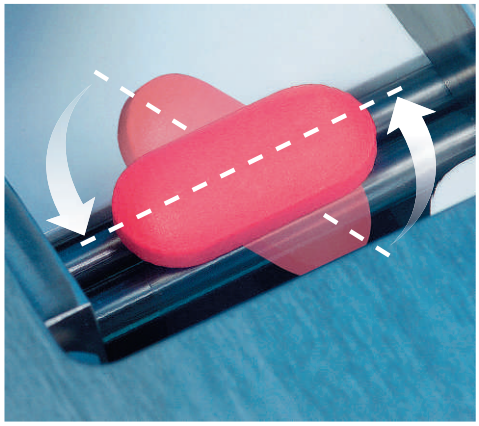

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