CANADIAN SOCIETY FOR PHARMACEUTICAL SCIENCES

CSPS 9th ANNUAL SYMPOSIUM:

Current Scientific Regulatory Challenges in Drug Development & Safety

May 24-27, 2006
Crowne Plaza Hotel, Ottawa, Canada

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Reviews & Commentaries

Original Articles

9th International Symposium on Pharmaceutical Sciences – Current Scientific Regulatory Challenges in Drug Development and Safety.

Exhibits, Wednesday, May 24, 6:00 p.m.-8:00 p.m.; Thursday & Friday, May 25 & 26, 8:00 a.m.-4:00 p.m., International Ballroom A, Victoria and Foyer, Lower Level, Crowne Plaza

Symposia, Thursday & Friday, May 25 & 26, 8:00 a.m.-5:00 p.m.; International Ballroom B/C, Lower Level, Crowne Plaza; Saturday, May 27, 8:00 a.m.-noon, International Ballroom B/C, Lower Level, Crowne Plaza

CSPS Annual Meeting, Thursday, May 25, 5:00 p.m.-6:00 p.m., International Ballroom B/C, Lower Level, Crowne Plaza

Graduate Student Mixer, Thursday, May 25, International Ballroom A, Victoria and Foyer, Lower Level, Crowne Plaza

CSPS Dinner & Awards, Friday, May 26, 6:00 p.m.-9:00 p.m., Pinnacle, Penthouse Level; Cash Bar in Pinnacle Foyer, Penthouse Level, Crowne Plaza

CSPS Programme

Wednesday, May 24, 2006

6:00 p.m.-7:00 p.m. **Registration,** Foyer, Lower Level. Registration desk will be open Thursday, 8am-4pm; Friday, 8am-4pm; and Saturday 8:30-10am.

6:00 p.m.-8:00 p.m. **Wine & Cheese Reception**, Ballroom B/C, Lower Level

Thursday, May 25, 2006

8:00am-4:00pm Registration desk open

8:00 a.m.-5:00 p.m. **CSPS Poster Presentations**, Ballroom A, Victoria and Foyer.

8:30 a.m.-5:00 p.m. **Symposium**, Ballroom B/C, Lower Level

8:30 a.m. **Welcoming remarks,** Leanne Embree, President, CSPS

Session 1: ***Drug Disposition.*** Ballroom B/C, Chair: Gordon McKay, University of Saskatchewan, Saskatoon, SK, Canada

9:00 a.m. **Plenary lecture**.

Prediction of Drug Absorption and Disposition Based on the BCS.

Leslie Z. Benet, University of California, San Francisco, California, USA

10:00 a.m. **Coffee/Tea Break.** Meet the poster presenters.

10:30 a.m. **Non-P450 Drug Metabolism.** Edward M. Hawes**,** University of Saskatchewan, Saskatoon, Saskatchewan, Canada

11:00 a.m. **Cellular Localization and Function of ABC Membrane - Associated Drug Efflux Transporters in the Brain.** Reina Bendayan, University of Toronto, Toronto, Ontario, Canada

11:30 a.m. **Medical Cannabis and a New Aerosol Product**. Ethan Russo, GW Pharmaceuticals, Missoula, Montana, USA

Noon **Lunch Break.** Meet the poster presenters.

Noon-1:30 p.m. **Journal of Pharmacy & Pharmaceutical Sciences Editorial Meeting**, York Room, Convention Level, Crowne Plaza.

Session 2: ***Safety Issues .*** Ballroom B/C , Chairs: Jim Gallivan, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada; Christine Nestruck, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

1:30 p.m. **Issues In Hepatotoxicity**. Jack Utrecht, University of Toronto, Toronto, Ontario, Canada

2:15 p.m. **Drug-Natural Health Product, Food, Nutraceutical, Parenteral Inter-actions.** Brian Foster, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

3:00 p.m. **Coffee/Tea Break.** Meet the poster presenters.

3:30 p.m. **Safety Assessment in Clinical Trials.** Jim Gallivan, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada

4:15 p.m. **Pharmacogenomics and Pharmaco-genetics: State of the Regulatory Art.** Agnes Klein, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada

5:00 p.m. **CSPS Annual General Meeting**, Ballroom B/C

6:00 p.m. **Graduate Student Mixer**, Ballroom A, Victoria and Foyer. Elizabeth Vadas, InSciTech, Kirkland, Quebec, Canada; John Clements, University of Alberta, Edmonton, Alberta, Canada; Amyn Sayani, Glaxo Smith Kline, Mississauga, Ontario, Canada

Friday, May 26, 2006

8:00am-4:00pm Registration desk open

8:00 a.m.-5:00 p.m. **Poster Presentations**, Ballroom A, Victoria and Foyer.

8:30 a.m.- 5:00 p.m. **Symposium**, Ballroom B/C

Session 3: ***Pharmacokinetics: Focus on Dose Proportionality and Other Applications of Population Pharmacokinetics (POP PK) .*** Ballroom B/C, Chairs: Iain McGilveray, McGilveray Pharmacon Inc. & University of Ottawa, Ottawa, Ontario, Canada; Murray Ducharme, MDS Pharma Services & Université de Montréal, Montréal, Quebec, Canada

8:30 a.m. **Welcome,** Iain McGilveray, McGilveray Pharmacon Inc. & University of Ottawa, Ottawa, Ontario, Canada, and, Murray Ducharme, MDS Pharma Services & Université de Montréal, Montréal, Quebec, Canada

8:35 a.m. **Development of Therapeutic Products Directorate, Health Canada Guidance on Non-Linear Kinetics (Dose Proportionality).** Jake Thiessen, University of Toronto, Toronto, Canada.

9:05 a.m. **Introduction and Background on the Use of POP PK, Differences With Conventional Methods, Strengths and Limitations of this Approach.** Tom Ludden, GloboMax, Hanover, Maryland, USA

9:30 a.m. **A Case Example of Using POP PK Approaches to Determine the Dose Proportionality and PK Linearity and DDI of a Compound.** Diane Mould, Projections Research, Inc., Phoenixville, Pennsylvania, USA

9:55 a.m. **Coffee/Tea Break.** Meet the poster presenters.

10:20 a.m. **The Strengths and Advantages of Doing POP PK and PKPD Studies Throughout Drug Development with Case Examples.** Murray Ducharme, MDS Pharma Services & Université de Montréal, Montréal, Quebec, Canada

10:45 a.m. **Using POP PK and POP PKPD for Drug Development: Regulatory Perspectives.** Panel Discussion with Eric Ormsby, Health Canada, Ottawa, Ontario, Canada; and above speakers

Noon **Lunch Break.** Meet the poster presenters.

Session 4: ***Ideas for Revising the Bioequivalence Guideline A.*** Ballroom B/C, Convenor: Laszlo Endrenyi, University of Toronto, Toronto, Ontario, Canada. Chairs: Corey B. Toal, Bayer Inc., Toronto, Ontario, Canada; Yu-Chung Tsang, Apotex Inc., Toronto, Ontario, Canada

1:30 p.m. **Welcome,** Laszlo Endrenyi, University of Toronto, Toronto, Ontario, Canada

1:35 p.m. **Planned Revisions of the Canadian Bioequivalence Guideline A.** Eric Ormsby, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

2:10 p.m. **Comments from FDA, the Pharmaceutical Industry, CRO's and Academia.** Barbara M. Davit, FDA, Office of Generic Drugs, Rockville, Maryland, USA; Corey B. Toal, Bayer Inc., Toronto, Ontario, Canada; *Yu*-Chung Tsang, Apotex Inc., Toronto, Ontario, Canada; Murray P. Ducharme, MDS Pharma Services & Université de Montréal, Montréal, Quebec, Canada; Mario Tanguay, SFBC Anapharm, Montreal, Quebec, Canada

3:00 p.m. **Coffee/Tea Break.** Meet the poster presenters.

3:30 p.m. **Comments from FDA, the Pharmaceutical Industry, CRO's, and Academia.** Kamal K. Midha**,** University of Saskatchewan, Saskatoon, Saskatchewan, Canada; Laszlo Endrenyi, University of Toronto, Toronto, Ontario, Canada

3:50 p.m. **Comments and questions from the floor.**

5:00 p.m. **Presentation of Poster Awards:** Gattefosse Canada/CSPS Research Award, Antoine A. Noujaim Award of Excellence, Biovail Contract Research Award of Excellence, Cedarlane Award of Excellence, *Presented by Leanne Embree*; and Merck Company Foundation Undergraduate Summer Studentship Programme Research Award, *Presented by* Kishor Wasan, University of British Columbia, Vancouver, British Columbia, Canada

6:00 p.m. **CSPS Dinner & Awards**, Pinnacle, Penthouse Level; Cash Bar in Pinnacle Foyer, Penthouse Level

Saturday, May 27, 2006

8:30am-10am Registration desk open

8:30 a.m.-Noon **Symposium**, Ballroom B/C

Session 5: ***Regulatory Issues.*** Ballroom B/C , Chairs: Eric Ormsby, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario; Brian Foster, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

8:30 a.m. **Emerging Regulatory Issues in Pharmaceuticals.** Omer Boudreau, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

9:15 a.m. **Emerging Biotechnology Regulatory Issues in Biologics and Genetic Therapies Directorate.** Pierre Charest, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Ontario, Canada

10:00 a.m. **Coffee/Tea Break.**

10:30 a.m. **To be announced.**

11:00 a.m. **Nanotechnology.** Hans Yu, Office of Biotechnology and Science, Health Canada, Ottawa, Ontario, Canada

11:30 a.m. **Therapeutic Product Classification.** Micheline Ho, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

Noon **Closing:** Leanne Embree, Canadian Society for Pharmaceutical Sciences

Scientific Programme Committee

Brian Foster, PhD, Therapeutic Products Directorate, Health Canada (Chair)

Eric Ormsby, Therapeutic Products Directorate, Health Canada (Co-Chair)

Gordon McKay, PhD, University of Saskatchewan, Saskatoon, Saskatchewan (Co-Chair)

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Carlos Leon[1], Guosong Qiu[2], Hana Kolac[2], John S. Hill[2] and Kishor M. Wasan[1]; [1]Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada; [2]iCAPTURE Centre, St. Paul's Hospital, University of British Columbia

59 Influence of Lipid Excipients, Capryol PGMC and Gelucire 44/14 on P-glycoprotein (P-gp) activity in Human Colon Adenocarcinoma (Caco-2) Cells.

Andrea Thamboo, Kristina Sachs-Barrable, Stephen D. Lee, and Kishor M. Wasan, Faculty of Pharmaceutical Sciences, University of British Columbia

60 COMPARISON OF PHYSICOCHEMICAL DATA VS DISSOLUTION DATA TO ESTABLISH IN VITRO/IN VIVO CORRELATIONS

Hai Weil, Izzy Kanfer[2], Marie Di Maso[3], and Raimar Loebenberg[1]; [1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada; [2]Faculty of Pharmacy, Rhodes University, South Africa; [3]Pharmaceutical Research & Development group, Merck Frosst, Canada

61 Structural Similarity between Human Bitter Taste Receptors and Histamine H1-Receptor

Jian Yang and Jim Fang; College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada

62 Hemodynamic effects of diltiazem in different rat models following repeated subcutaneous injections in vivo

Pollen K.F. Yeung[1], Angelita Alcos[1], Jinglan Tang[1], William L. Casley[2]; [1]Pharmacokinetics & Metabolism Laboratory, College of Pharmacy, Dalhousie University, Halifax, Canada; [2]Centre for Biologics Research, Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada, Banting Research Centre, Ottawa, Canada

63 A sensitive and specific HPLC assay of cladribine for pharmacokinetic studies in rats
Pollen K.F. Yeung, Ameer Jaraar, Carrie Ferguson, Soulatchana Narayanan; Pharmacokinetics and Metabolism Laboratory, College of Pharmacy, Faculty of Health Professions, Dalhousie University, Halifax, Canada

64 Design, Synthesis and Anticonvulsant Activity of New 1,3,4-Oxadiazole Derivatives as Benzodiazepine Receptor Agonists
Afshin Zarghi *, Avideh Ahadian, and Hamid R. Khojastehpoor; Department of Medicinal Chemistry, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran

65 A Validated New UV Spectrophotometric Method for Determination of Ascorbic Acid in Its Effervescent Dosage Forms
Wenming Zeng, Frank Martinuzzi, and Alexander MacGregor; Department of Research and Development, Toronto Institute of Pharmaceutical Technology, Toronto, Canada

66 Tablet Formulation Development for a Poorly Water Soluble New Chemical Entity
Kai Zhang, Andrea Toth, Kay Koch-Gaynor, Wlodek Karolak, Myrna Dela-Cruz, David Valentini, Phyllis Dawson, Mehran Maleki; GlaxoSmithKline, Pharmaceutical Development, Mississauga, Canada

67 Dendritic cell targeting of MUC-1 breast cancer peptide expressed on bacterial surface
Jany H. Zhang, Pravin K. Bhatnagar, Welson W. Wang, John F. Nomellini*, John Smit*, and Mavanur R. Suresh; Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada and *Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada

68 Non-invasive Assessment of the In Vivo Pharmacokinetics of Liposomes Using CT and MR Imaging
Jinzi Zheng[1], Mike Dunne[2], David A. Jaffray[1, 3-4], Christine Allen[2]*; [1]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; [2]Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; [3]Department of Radiation Physics, Princess Margaret Hospital, University Health Network, Toronto, Ontario, Canada; [4]Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada; *Dr. Christine Allen, Ph.D, Faculty of Pharmacy, University of Toronto, Toronto, Canada

69 Pharmaceutical Care Services in Hospitals of Kuwait
Awad AI, Al-Ebrahim S, Abahussain E, Department of Pharmacy Practice, Faculty of Pharmacy, Kuwait University

70 Normal Pharmacodynamic Response and Pharmacokinetics of Verapamil in Rheumatoid Arthritis Patients Treated with Infliximab
Spencer Ling, Richard Z. Lewanczuk, Anthony S. Russell, Brendan Ihejirika, and Fakhreddin Jamali. Faculties of Pharmacy and Medicine, University of Alberta, Edmonton, Canada

71 Validation of a liquid chromatography tandem mass spectrometry assay method for the determination of sertraline in human plasma
Adrien Musuku, Gina deBoer, Grace van der Gugten, CANTEST BioPharma Services, Burnaby, BC

72 Validation of a liquid chromatography mass spectrometry assay method for the determination of trimethoprim and sulfamethoxazole in human plasma
Adrien Musuku, Luis Sojo, Sarah Bonorand, Grace van der Gugten, CANTEST BioPharma Services, Burnaby, BC

73 Validation of a liquid chromatography tandem mass spectrometry assay method for the determination of verapamil and norverapamil in human plasma
Adrien Musuku, Gina de Boer, Meng Yu, CANTEST BioPharma Services, Burnaby, BC

Symposium 2006 Awards

CSPS Award of Leadership in Canadian Pharmaceutical Sciences
Not awarded for 2006

GlaxoSmithKline/CSPS Early Career Award
Recipient: Dr. Christine Allen, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Poster Awards

- **Gattefosse Canada/CSPS Research Award -**
  - Christine Allen, Leslie Dan, Faculty of Pharmacy, University of Toronto
- **Antoine A. Noujaim Award of Excellence**
  - Negar Gharavi, University of Alberta
- **Biovail Contract Research Award of Excellence**
  - Jubo Liu, University of Toronto
- **Cedarlane Award of Excellence**
  - Justin Grant, University of Toronto

Merck Company Foundation Undergraduate Summer Student Award Recipients and Poster Competition, National Directors: Dr. Kishor M. Wasan, Faculty of Pharmaceutical Sciences, University of British Columbia and Dr. Dale Meisner, Merck-Frosst Canada Ltd.

These awards were established with the aim of encouraging pharmacy students to go into research. Funding in the form of research fellowships gives students an opportunity to work over the summer in research laboratories in all AFPC accredited Pharmacy Schools across Canada. The criteria of selection was based on academic excellence (i.e. grades), letters of reference and evidence of service to the faculty. Selection of the winners was determined by March 1st and all the winners and supervisors' names and a summary of their research project were sent to Merck Company Foundation.

Name of Recipient	Supervisor(s)	Title of Project	University/ Administrator
Mr. Framin Mark 2nd Year Pharmacy	Dr. Urs Hafeli	Toxicity Measurement of Magnetic Nanoparticles	University of British Columbia
Mr. Jeremy Reid 2nd Year Pharmacy	Dr. Husam Younes	Mechanistic release study of water soluble drugs from hydrophobic/ amphiphilic elastomeric matrices	Memorial University
Aneri Gupta 2nd Year Pharmacy	Dr. Mike Namaka	The Role of Superantigen-Producing Staphylococcus aureus in the Etiology of Multiple Sclerosis	University of Manitoba
Ms. Jany Zhang 2nd Year Pharmacy	Dr. Mavanur R.Suresh	Dendritic Cell Targeting of MUC-1 Breast Cancer Peptide Expressed on Bacterial Surface	University of Alberta
Mrs. Taryn Reid 3rd Year Pharmacy	Dr. David Jakeman	Growth, Extraction and Isolation of Novel Jadomycins	Dalhousie University
Ms. Jaklin Iskander 3rd Year Pharmacy	Dr. Heather Boon	Natural Health Products: Is there evidence for safety and efficacy?	University of Toronto
Mr. Jason Jobse 2nd Year Pharmacy	Dr. Jane Alcorn	The effect of the flaxseed lignan, secoisolariciresinol diglucoside, on triglyceride levels in a hypertriglyceridemic rat model.	University of Saskatchewan
Miss Marilou Grenier 2nd Year Pharmacy	Dr Roxane Pouliot	Effet de l'acide rétinoïque sur l'hyperprolifération et la différenciation cellulaire des kératinocytes psoriasiques	Laval University

Speaker Abstracts

Session 1: Drug Disposition

Prediction of Drug Absorption and Disposition Based on the BCS
Leslie Z. Benet, Department of Biopharmaceutical Sciences, University of California, San Francisco, CA

The Biopharmaceutics Classification System (BCS) was developed to allow prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability and solubility Although the BCS is useful for characterizing drugs in Class 1 (high permeability; high solubility) for which drug dosage form dissolution alone may be amenable for waiver of *in vivo* bioequivalence studies, there is little predictability concerning drugs in Classes 2 (high permeability; low solubility), 3 (low permeability; high solubility) and 4 (low permeability; low solubility). Last year (Pharm Res 22:13-22, 2005), we suggested that a modification of such a classification system, designated the Biopharmaceutics Drug Disposition Classification System (BDDCS), may be useful in predicting overall drug disposition including: routes of drug elimination; the effects of efflux and absorptive transporters on oral drug absorption; when transporter-enzyme interplay will yield clinically significant effects (e.g., low bioavailability and drug-drug interactions); the direction, mechanism and importance of food effects; and transporter effects on post-absorptive systemic drug concentrations following oral and i.v. dosing. In BDDCS, Classes 1 and 2 drugs are predominantly eliminated by metabolism, while Classes 3 and 4 drugs are predominantly eliminated unchanged via urinary or biliary excretion. Transporter effects will be negligible for Class 1 compounds. Efflux transporter effects will predominate in predicting the oral exposure of Class 2 compounds, while absorptive transporters will have a major influence on the oral exposure of Class 3 compounds. We suggest that the BDDCS, using elimination and solubility criteria, may provide predictability of disposition profiles for all classes of drugs.

Non-P450 Drug Metabolism
Edward (Ted) M. Hawes, Professor Emeritus, College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada

The vast array of metabolic reactions of xenobiotics can be conveniently classified as either oxidations, reductions, conjugations, or nucleophilic trapping processes. Most conjugations involve S_N2 reactions of electrophilic adenosine-containing cofactors with nucleophilic sites in xenobiotics, while formation of amino acid conjugates requires prior activation of the carboxylic acid substrate. Nucleophilic trapping processes involve reactions of water, glutathione, or other cellular nucleophiles (including protein and nucleic acid) with electrophilic xenobiotics. Categorization of each general route of drug metabolism as resulting in either increase or decrease in toxicity and pharmacological activity is problematic. For example, although glucuronidation is traditionally regarded as a route of detoxification, acyl glucuronides and narcotic analgesic ether glucuronides have been associated with toxicity and pharmacological activity, respectively. The gene families of many non-P450 enzymes are well categorized (e.g., UGTs and GSTs), and in some cases genetic variations are a potential major factor in affecting interindividual variations (FMO3, NAT2, TPMT, UGT1A1). Virtually any type of metabolic reaction may play a role in drug activation; widely quoted examples include O-acetylation of aromatic amines, glutathione S-conjugation of haloalkanes, and O-sulphation of various N-hydroxy functional groups. Although drug toxicity cannot be accurately predicted, approaches can be used in drug discovery and development to minimize potential problems. These approaches include use of structure-metabolism relationships in drug design, small molecule trapping agents, and radiolabelled substrate. Selected routes of non-P450 drug metabolism will be discussed, including involvement in contributing to interindividual variation and bioactivation.

Cellular localization and function of ABC membrane-associated drug efflux transporters in the brain

Reina Bendayan, University of Toronto, Toronto, Canada

Several families of membrane transport proteins can regulate drug distribution in the central nervous system. In particular, members of the ATP-binding Cassette (ABC) superfamily of transporters, such as P-glycoprotein (ABCCB1/MDR1), multidrug resistance-associated proteins (MRPs/ABCC) and breast cancer resistance protein (BCRP/ABCG2), localized at the brain barriers and brain parenchyma can play a major role in the overall disposition of drugs in the brain. The goals of this presentation are: i) to provide an overview on the molecular expression, cellular/subcellular location and functional activity of ABC membrane-associated transporters, primarily P-glycoprotein and MRPs in several brain cellular compartments (i.e., brain microvessel endothelial cells, astrocytes and microglia) and ii) to discuss their clinical implications in the pharmacotherapy of neurological disorders (i.e., HIV infection).

Medicinal Cannabis and a New Oro-mucosal aerosol

Ethan Russo, Senior Medical Advisor, GW Pharmaceuticals, Missoula, Montana, USA

THC inhibits cAMP through G-protein receptor coupling. It is a partial agonist on CB_1 receptors, especially in pain pathways. THC actions include analgesia, muscle relaxant and anti-inflammatory effects. Cannabidiol (CBD) has anti-anxiety, anti-psychotic, anti-oxidant, anti-inflammatory, immunomodulatory effects, and prevents glutamate excitotoxicity.

Sativex® is a well-characterised botanical drug product derived from two clonal cannabis chemovars, one THC-predominant (Tetranabinex®) and another CBD-predominant (Nabidiolex®), yielding a botanical drug substance (BDS) of defined composition with controlled reproducibility. THC and CBD comprise some 70% (w/w) of the BDS, with minor cannabinoids (5 – 6%), terpenoids (6 – 7%, most GRAS), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS). Sativex is administered oromucosally with each 100 µL pump-action spray providing 2.7 mg of THC and 2.5 mg of CBD, in an ethanol: propylene glycol vehicle with 0.05% peppermint flavouring. To date, RCTs show Sativex to have statistically significant benefits in several medically intractable conditions: pain associated with peripheral neuropathy, rheumatoid arthritis, cancer pain unresponsive to opiates and neuropathic pain in multiple sclerosis (indication for the NOC/C of Sativex in Canada in 2005), as well as spasticity, and lower urinary tract symptoms associated with MS, and sleep quality in these various disorders. In all studies, Sativex has been used as add-on therapy in patients who have not responded adequately to their existing medication. These trials and their safety-extension studies (up to four years) have demonstrated no abuse or diversion of Sativex, no tolerance to symptomatic benefits, or significant withdrawal effects upon sudden discontinuation.

Session 2: Safety Issues

Issues in Hepatotoxicity
Jack Uetrecht, Leslie Dan Faculty of Pharmacy, University of Toronto

Adverse drug reactions have become a major cause of drug candidate failure. Idiosyncratic reactions are especially difficult to deal with, and hepatotoxicity is the most common type of idiosyncratic reaction leading to drug withdrawal. It would be a major advantage if risk could be determined early. Current animal testing does not predict the risk of idiosyncratic reactions. It appears that most idiosyncratic reactions are mediated by reactive metabolites; therefore, screens for reactive metabolites may make drug candidates safer. Several companies have invested heavily in this concept, but it is not clear whether it really decreases risk. In clinical trials, the best predictor of idiosyncratic hepatotoxicity is an elevation of ALT; however, several drugs are associated with a significant incidence of elevated ALTs without posing a significant risk for liver failure. After the drug reaches the market, databases of spontaneous reports can provide an important early warning; however, causality assessment is very important. This is especially important because there are many other causes of liver failure. In order to improve on our ability to predict the risk of hepatotoxicity, we need a much better understanding of the basic mechanisms involved. Idiosyncratic hepatotoxicity has been divided into immune-mediated reactions and metabolic idiosyncrasy; however, metabolic idiosyncrasy in particular is undefined. An important tool for mechanistic studies is valid animal models and two animal models of idiosyncratic reactions will be presented; however, developing animal models is difficult because such reactions are also idiosyncratic in animals. Funded by CIHR.

Drug, Food, Natural Health Product Interactions
Dr. Brian C. Foster, Senior Science Advisor, Therapeutic Products Directorate, Health Canada, and Adjunct Professor, Faculty of Medicine, University of Ottawa, Ottawa, Canada

Natural health products (NHPs) and functional foods are widely used as complementary alternative medicines (CAMs). Traditional uses of CAMs have generally proven safe, but their current pattern of consumption and uses in the global context has changed. Many NHPs are being used concurrently by every patient population and serious adverse events have been identified. Health Canada on February 9 and 10, 2006 hosted an international symposium on Drug, Food, NHP Interactions. Highlights from this symposium on grapefruit, traditional medicine formulations, mechanistic and pharmacovigilance issues, as well as pitfalls normally found in these studies will be presented. Recent reports have demonstrated that NHPs are substrates for more than one metabolism enzyme and transport protein. The presentation will also relate our recent findings with more than 195 NHPs and biomarkers that have been screened in our laboratories to determine their effect on cytochrome P450-mediated metabolism. The public health issues of clinically relevant drug, food, and NHP interactions, particularly in populations on polypharmacy or with polymorphisms affecting drug disposition, will also be discussed.

Safety Assessment in Clinical Trials

Jim Gallivan, Clinical Trials Division, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada, Ottawa, Canada

Safety assessment is a continuous process that begins prior to the first exposure of humans and continues throughout drug development. Clinical trials are essential to the drug development process because they provide quantitative information needed for the assessment of efficacy and safety for the market authorization of new drugs and for continued marketing. This presentation will review the regulatory framework and procedures to evaluate safety and to minimize the risks to subjects prior to, and during, clinical trials. Future directions in safety assessment in clinical trials will also be considered.

Pharmacogenomics: The state and art of the Regulatory Science

Agnes V. Klein MD, DPH, Director, Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutic Products, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Canada

Pharmacogenomics as a part of drug development and the search for rational targets for therapeutics is based on scientific activities that apply the knowledge acquired during the Genome Project. The fact that the era of blockbuster drugs appears to have drawn to a close, has lent additional impetus to this and other related "omics" areas. Genetics as a science has provided insights into the predisposition of individuals to diseases and has opened up areas where Biomarkers have come to the forefront. Thus, opportunities have been opened to the conversion of these Biomarkers as targets for therapy creating a promise for better tailored and more individualized therapy. The era of Pharmacogenomics has spawned such products as Herceptin and Erbitux that are targeted at specific mutations of tumour cells which then can be suppressed by the appropriately targeted product. It has also become clear that many of the metabolic variants for pharmaceuticals result in different levels of efficacy for different subpopulations and that the safety of therapeutics may be linked to genetic factors. However, PGx has not been incorporated as yet into daily drug development. In order to facilitate this reality both regulatory and policy bodies have been preoccupied with the development of enabling policies and nomenclature. Hence a documents produced by CIOMS, another by the EMEA, and yet another guidance document generated by the FDA. Canada is not far behind and has just posted a guidance document for PGx, to gather comments and input from stakeholders. Finally, in October 2005, the ICH has taken up the banner of Pharmacogenomics and a guidance document on nomenclature will be worked on starting June 2006. This talk will provide a few details on the Canadian perspective of what HC's position has been and compare and contrast existing guidelines, placing them in appropriate context.

Session 3: Pharmacokinetics: focus on dose proportionality and other applications of population pharmacokinetics (POP PK)

Development of therapeutic products directorate, Health Canada guidance on non-linear kinetics (Dose proportionality).
Jake J. Thiessen, Leslie Dan Faculty of Pharmacy University of Toronto, Toronto, Ontario, Canada.

During the 1990-92 period, the Canadian Expert Advisory Committee (EAC) on bioavailability, chaired by Dr. John Ruedy, produced Reports A, B, C offering bioavailability and bioequivalence guidelines encompassing a spectrum of drugs and products. Report A was made official by Health Canada in 1992, and provided a guidance for conventional formulations of oral drugs that had uncomplicated characteristics. Various exceptions were identified in this guidance including modified release formulations (a 1996 official guidance dealt with this (Part B: Oral Modified Release Formulations)) and drugs with so-called complicated or variable pharmacokinetics, including non-linear kinetics. More recently, Health Canada provided a document regarding bioequivalence requirements for drugs exhibiting non-linear pharmacokinetics. In essence, this guidance specifies that, with some exceptions, studies are required in the fasted and fed states. For drugs where the non-linear concentration range is reached only after multiple doses within the approved dosing regimen, studies utilizing multiple units of the highest formulation strength or steady-state studies in the non-linear range may be required. For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths resulting in less than proportional increases in AUC with increasing dose, the comparative bioavailability studies shall be conducted on at least the lowest strength (single dose unit). For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability studies shall be conducted on at least the highest strength.

Introduction and Background on the Use of Population Pharmacokinetics: Differences with Conventional Methods, Strengths and Limitations of This Approach.
Thomas M. Ludden, GloboMax, a Division of ICON plc, Ellicott City, MD, USA

Since the introduction of the concept of using mixed effect modeling (MEM) to study pharmacokinetics (population pharmacokinetics) in 1972, the application of this methodology has grown until today it is used throughout the drug development process and in post-approval monitoring of drug safety and efficacy. MEM involves the development of a mathematical description of the influences of fixed effects (time, dose, demographics, concurrent drug therapy, etc.) and random effects (variability between individuals, between different dosing occasions, residual variability) on an outcome variable (drug concentration or effect). Such an analysis differs from conventional two-stage analysis in that it estimates both fixed and random effects simultaneously. The two-stage approach fails to correctly partition variability among its various sources. This is particularly true if the data per individual are sparse but less so with dense and informative data. The primary advantage of MEM is primarily its ability to extract information from data sets with moderate information per individual. The primary disadvantage of MEM is that it may require substantial time devoted to model building efforts, a process that makes it difficult to have a rigorous statistical interpretation of the results. A dual-phased approach to a MEM analysis can sometimes be used to balance the advantages and disadvantages of MEM. The initial phase can address previously stated hypotheses, while the second phase can be devoted to exploratory analyses.

Using Mixed Effects Modeling (MEM) to Evaluate Dose Proportionality (DP) and the Effect of Concomitantly Administered Medications (CM) in Patients

Diane R Mould, PhD, Projections Research Inc., Phoenixville, PA

The development of new therapeutic agents has become more complex over time. Because patients are seldom treated with only one agent, and may require dose adjustments, evaluations of DP and CM are critical. Furthermore, the effects of age and disease can alter the pharmacokinetics in patients. Determining appropriate dose regimens requires understanding patient specific changes in disposition and drug sensitivity, as well as evaluation of the likely drug combinations that may be used. The development of therapeutic agents should investigate these issues, however, evaluating dose proportionality and drug interactions in patients may be difficult due to ethical constraints or for other practical reasons. The use of population pharmacokinetic (PPK) analysis has become an important tool in drug development. Using MEM, sparse sampling schedules can provide information about PPK in patients. Although model based evaluations inherently include assumptions and the model can not always be completely specified prior to analysis, several methodologies have been proposed for inferential evaluation. For such work, the study design is important, the analysis plan should be pre-specified to the extent possible, and the anticipated power and type I error should be evaluated for the design and the model. The PPK model performance must be evaluated rigorously and the assumptions used in the model should be verified. Two cases are presented as examples of using MEM for the evaluation of DP and CM for anti-viral agents. The results show that with an adequate study design, DP and the effect of CM can be evaluated with good precision.

Strengths and advantages of doing Population PK and PK/PD studies throughout the Drug Development Process

Murray P. Ducharme, PharmD, FCCP, FCP, Vice President, PK and PD, MDS Pharma Services, and Professeur Associé, Faculté de Pharmacie, University of Montreal, Montreal, Canada.

This presentation will be broken up into three parts. First, we will review the differences between individual and population approaches in PK/PD and explain the key elements supporting the increasing use of the population approach. Secondly, we will present the current state of the art of using population PK/PD studies within the drug development process and contrast this with what has been done in the past. Finally, case examples will be presented to highlight the advantages and strengths of this approach within the drug development process.

Session 5: Regulatory issues

Emerging regulatory issues in pharmaceuticals

Omer Boudreau, Director General, Therapeutic Products Directorate, Health Canada, Ottawa, Canada

This talk will provide an update on the Therapeutic Products Directorate (TPD) activities and accomplishments. TPD is currently outlining its plan for the upcoming year. Planning is the key for the success of any organizations but it can be derailed by unexpected situations. New developing scientific issues are always a challenge that TPD must be ready to face. Performance Sustainability and Modernizing the Regulatory Framework are two major objectives in our strategic plan that could strongly impact the emerging regulatory issues in pharmaceuticals. Modernizing of the regulatory framework through a new framework (Progressive Licensing) will enable us to monitor and assess the entire product cycle. As there are many regulatory gaps in the current framework, the new framework would allow sound risk management and access to new drug therapies while continuously monitoring and reassessing for safety, quality and efficacy. The presentation will also cover some notable activities in 2005, how the elimination of backlog and performance sustainability have been achieved, and point out some emerging regulatory issues/trends.

Emerging biotechnology regulatory issues in biologics and genetic therapies directorate

Pierre Charest, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Canada

Not available at time of publication.

Nanotechnology and the management of health risks: Regulatory oversight and challenges
Hans Yu, Chief, Departmental Biotechnology Office, Health Canada

Nanotechnology is a complex and rapidly evolving field of science and discovery that involves creating and/or manipulating materials at a very small scale (in the billionths of a metre). It is considered a transformative technology widely perceived to have significant socio-economic impacts in Canada and worldwide. Regulating products to ensure the health and safety of Canadians and the environment is a priority of federal regulatory departments and agencies. While the scope of nanotechnology applications is broad, some of the greatest potential benefits may be in the health field. Anticipating issues that arises from scientific advances is important to Health Canada in its role of helping Canadians to maintain and improve their health. Key to the protection of human health and the environment is the need to understand the science that underpins 1) risk assessment, 2) approaches to risk management and 3) regulatory decision-making. This talk will discuss the properties of nanomaterials, and describe various examples of medical applications of nanotechnology, how they might be regulated at Health Canada, and the challenges facing the department as the technology evolves.

Challenges in Product Classification
Micheline Ho, Senior Advisor, Office of Risk Management, Therapeutic Products Directorate, Health Canada

Health Canada has the responsibility to ensure that products [e.g. pharmaceuticals, medical devices, food, cosmetics or pest control products] regulated under the various legislative instruments within its mandate are in compliance with the relevant statutes [including the Food and Drugs Act, Pest Control Products Act]. In order to fulfill this responsibility, it is necessary to be clear as to which product types are covered by each statute. Although this may seem to be a simple issue at first glance, it is in fact becoming a significant challenge. This challenge is the result of, not only the introduction of new product types, but more likely the result of new types of representations for existing product types, such as: health foods, new product combinations (e.g. medicated stents), co-packaged products or "convenience packages", while we attempt to increase clarity and transparency in the regulatory process. The presentation will provide specific examples to illustrate the challenges faced by the regulator, as well as potential pitfalls in classification decisions and an international perspective on the issue of product classification.

Speaker Biographies

Reina Bendayan
Associate Professor and Chair, Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Reina Bendayan is an Associate Professor and Chair, Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto. After obtaining a Bachelors of Sciences in Pharmacy and a Hospital Pharmacy Residency Program at the University of Montreal, Reina Bendayan completed a Doctor of Pharmacy at the University of Florida and a three year Medical Research Council Post-Doctoral Fellowship Program in Clinical Pharmacology and Membrane Cell Biology at the University of Toronto. Dr. Bendayan's research program at the University of Toronto is primarily focused on Membrane Transport and Therapeutics with an emphasis in the field of HIV/AIDS Antiviral Drug Transport and Metabolism in the Brain. Her research is primarily funded by the Canadian Institutes of Health Research, Canadian Foundation for AIDS Research and the Ontario HIV Treatment Network, Ministry of Health of Ontario. Reina Bendayan received a five year career scientist award from the Ministry of Health of Ontario.

Leslie Z. Benet, Ph.D.
Professor of Biopharmaceutical Sciences and Pharmaceutical Chemistry, Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, USA

Dr. Benet received his AB, BS and MS from the University of Michigan, and Ph.D. from UCSF. He has received six honorary doctorates: Uppsala University, Sweden (PharmD, 1987), Leiden University, The Netherlands (Ph.D., 1995), University of Illinois at Chicago (DSc, 1997), Philadelphia College of Pharmacy and Science (DSc, 1997), Long Island University (D.Sc. 1999) and University of Athens (Ph.D., 2005). Dr. Benet is a Fellow of AAPS, AAAS and APRS. In 1985 he served as President of the Academy of Pharmaceutical Sciences. During 1986, Dr. Benet was a founder and first President of the AAPS. In 1987 he was elected to membership in the Institute of Medicine of the US National Academy of Sciences. In 1993-4 he served as President of the American Association of Colleges of Pharmacy (AACP) and from 1996-2000 as Chair of the FIP Board of Pharmaceutical Sciences. In 1989 he received the first AAPS Distinguished Pharmaceutical Scientist Award; in 1991, the AACP Volwiler Research Achievement Award; in 1995, the Rawls-Palmer Award of the American Society for Clinical Pharmacology and Therapeutics; in 2000, the APhA Higuchi Research Prize and the AAPS Wurster Award in Pharmaceutics; in 2001 the FIP Høst-Madsen Medal; and in 2004, the Pharmaceutical Sciences World Congress Research Achievement Award and the Controlled Release Society's Career Achievement in Oral Drug Delivery Award. Dr. Benet has over 470 scientific publications and holds 11 patents. His most recent studies have addressed the interplay of metabolic enzymes and transporter proteins. He is listed among the 250 most highly cited pharmacologists world-wide.

Omer Boudreau
Associated Director General, Therapeutic Products Directorate, Health Canada, Ottawa, Canada

Omer Boudreau has extensive management experience in the Public Service, both as a program manager and as a director of human resource. Since joining Health Canada, Omer has occupied the position of Associated Director General in the Therapeutic Products Directorate and, for a brief period, that of Director General, Policy and Strategic Planning. Prior to joining Health Canada, he has held increasingly senior positions in Transport Canada, Veterans Affairs Canada, and the National Archives of Canada. Omer holds a degree in Political Science from Carleton University and is a graduate of the Public Service Accelerated Executive Development Program.

Dr. Pierre J. Charest, Ph.D.
Director General, Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Santé Canada - Health Canada, Ottawa, Canada

In September 2005, Dr. Pierre Charest was appointed Director General, Biologics and Genetic Therapies Directorate in the Health Products and Food Branch at Health Canada. Prior to this appointment, Dr. Pierre Charest was Director General of the Office of Biotechnology and Science in the Health Products and Food Branch at Health Canada for a period of approx. 3 years. Dr. Charest has over 17 years of experience in biotechnology in the areas of management, policy development and research in agriculture, forestry and health. Previous to joining Health Canada, Dr. Charest was Director of the Science Program for the Canadian Forest Service during which he participated in the federal government task force that renewed the Canadian Biotechnology Strategy in 1998. He held a number of other positions with the Canadian Forest Service including Project Leader in Biotechnology. Dr. Charest had a productive research career as he authored or co-authored 77 scientific publications, presented 80 scientific communications and 28 invited lectures. He has been solicited frequently as a member of granting agencies review boards such as NSERC, the Canada Foundation for Innovation, and the Canadian Institutes of Health Research. He has received numerous awards, including three Federal Public Service Awards. Dr. Charest has obtained his Ph.D. in Molecular Biology at Carleton University in 1989, and previously, his MSc And BScA from Laval University in agronomy.

Barbara Davit, PhD
FDA, CDER, Office of Generic Drugs, Davison of Bioequivalence, Rockville, Maryland, USA

Barbara Davit is presently the Deputy Director of the Division of Bioequivalence in the Office of Generic Drugs, Center for Drug Evaluation and Research (CDER), US-Food and Drug Administration (FDA). Her professional areas of expertise are pharmaco-kinetics and drug metabolism. Dr. Davit holds a Ph.D. in Nutrition Biochemistry from the University of California, Davis, and a B.S. in Chemistry from Georgian Court College. Dr. Davit began her career in pharmacokinetics as a postdoctoral fellow at the California Primate Research Center, where she investigated bilirubin metabolism and kinetics. Following her postdoctoral work, Dr. Davit worked at the CRO Hazelton Washington (now Covance), first as a toxicologist, and later as a pharmacokineticist. Dr. Davit joined CDER/FDA in 1991. She is active in regulatory guidance development, and contributed to the CDER guidances on renal impairment, *in vivo* drug interaction studies, bioavailability/bioequivalence, electronic submissions, and developing generics for the drug products clozapine and potassium chloride. She also contributed to the ICH guide-lines on toxicokinetics and preclinical tissue distribution studies. Dr. Davit is currently the pharmacokinetics and bioequivalence expert on the Office of Generic Drugs team to implement the President's Emergency Plan for Aids Relief (PEPFAR). She was a member of the international expert panel that published the HHS, UNAIDS, WHO, and SADC co-sponsored document, "Scientific and Technical Principles for Fixed Dose Combination Drug Products." She participated in writing the draft CDER guidance on developing fixed-dose and co-packaged combination products to treat HIV disease. Dr. Davit has co-authored several book chapters on bioequivalence testing of generic drug products.

Murray P. Ducharme, PharmD, FCCP, FCP
Vice President, PK and PD, MDS Pharma Services, and Professeur Associé, Faculté de Pharmacie, University of Montreal, Montreal, Canada.

Murray P. Ducharme, PharmD, FCCP, FCP is Vice President of PK/PD at MDS Pharma Services. In this capacity, he is responsible for the work of approximately 150 pharmacokineticists and statisticians dedicated at providing to both generic and innovator pharmaceutical companies all types of pharmacokinetic and statistical analyses necessary to do during the drug development process. These include bioequivalence, drug interactions, and population pharmacokinetic/pharmacodynamic studies. He also serves as a Professeur Associé at the Faculté de Pharmacie, University of Montreal, where he directs the research work of doctoral and post-doctoral students in clinical pharmacology. Dr. Ducharme has authored or co-authored more than 100 articles, abstracts, book chapters and manuals. He has also presented more than 200 posters and seminars at conferences, symposiums, meetings and workshops.

Laszlo Endrenyi, Ph.D.
University of Toronto, Toronto, Canada

Dr. Endrenyi is Professor Emeritus of pharmacology and biostatistics in the University of Toronto. He has served the university in various positions including on its Governing Council and as Associate Dean of Graduate Studies. Externally, he has served on grant review committees and editorial boards of research journals including the Amer. J. Physiol, J. Pharmacokin. Pharmacodyn., J. Pharm. Pharm. Sci., and J. Pharm. Sci. He edited a book on Kinetic Data Analysis, and has published over 140 research papers including over 30 on the principles and evaluation of bioavailability and bioequivalence. He has consulted with the Food and Drug Administration and the Health Protection Branch and served on their advisory committees. He has also consulted with industry in the areas of pharmacokinetics, biostatistics, the design and evaluation of experiments, clinical trials, and the analysis of bioavailability and bioequivalence studies.

Brian C. Foster
Therapeutic Products Directorate, Health Canada, Ottawa, Canada

Dr. Foster is a Senior Science Advisor in the Office of Science, Therapeutic Products Directorate, Health Canada. He received his Ph.D. in Medicinal Chemistry at the University of Alberta through research on alternative models for drug interactions and metabolism. Since joining Health Canada, his research has been in the areas of toxicology and drug disposition. His current research interest is in the area of drug disposition, pharmacogenetics, and how natural health products affect the safety and efficacy of conventional therapeutic products. Dr. Foster is an Adjunct Professor, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa where he has a joint Health Canada - University of Ottawa Centre for Research in Biopharmaceuticals and Biotechnology laboratory. He teaches graduate level courses on drug disposition and pharmacogenetics.

Jim Gallivan, Ph.D.
Assessment Officer, Clinical Trials Division, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada, Ottawa, Canada

Dr. Gallivan is a senior reviewer in the Clinical Trials Division in the Biologics and Genetic Therapies Directorate of Health Canada. He received his B.Sc. and M.Sc. in Zoology at the University of Guelph and his Ph.D. in Medical Sciences (Cardiorespiratory Physiology) at McMaster University. He completed post-doctoral studies in comparative respiratory physiology and pathology/epidemiology at McMaster University and in the Ontario Veterinary College at the University of Guelph. Following two years of teaching and research at the University of Swaziland in Africa, he returned to Canada where he taught university and worked on research project design, data quality control and data analysis prior to joining Health Canada. His research background is in physiology, pathology, and epidemiology.

Edward (Ted) M. Hawes
Professor Emeritus, College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada

Ted Hawes was a member of the pharmacy faculty of the University of Saskatchewan from 1967 to 2000. He taught in the areas of medicinal chemistry and drug interactions, and conducted research projects in drug metabolism. More recent projects are undertaken in Pharmalytics Inc., Saskatoon. Research interests have focused on the metabolism of nitrogen containing heterocyclic xenobiotics including certain psychotropic drugs, H_1 receptor antagonists, and nicotine and pyrrolizidine alkaloids. The *in vivo* studies of such xenobiotics include delineation of the importance of phenotype, exploration of the use of stable isotope labelled compounds, and the formation of quaternary ammonium-linked glucuronide metabolites. The *in vitro* studies include delineation of the cyto-chrome P450, flavin-containing monooxygenase, and UDP glucuronosyltransferase enzymes involved in various routes of metabolism, and structure-metabolism relationship studies on N-glucuronidation. More than 110 refereed publications resulted, and he supervised 11 Ph.D. students. The Medical Research Council/ Canadian Institutes of Health Research awarded the vast majority of research funding that included funding over 26 years and the first Program Grant awarded to a pharmacy faculty; and he served on various committees thereof. Recognition of his research included award of a Fellowship of the Royal Society of Chemistry in 1988, a D.Sc. degree of the University of London in 1989, and the McNeil Award of the Association of Faculties of Pharmacy of Canada in 1992.

Micheline Ho
Senior Advisor, Office of Risk Management, Therapeutic Products Directorate, Health Canada, Ottawa, Canada

Micheline Ho obtained her Bachelor's degree in Chemistry from the University of Montreal and subsequently pursued studies at the University of Ottawa in Pharmacology and Business Administration. She has been with the Department of Health, in various capacities, since the 1970s. Her responsibilities have included the pre- and post-market evaluation of prescription and non-prescription drugs, as well as the establishment of national policies and standards in consumer labelling, advertising and drug information. She was also responsible for the development of Monographs and Labelling Standards, as well as for the assessment of patient and professional drug product information. Micheline Ho is currently a Senior Advisor in the Office of Risk Management and the Chair of the Steering Committee for the Product Monograph Project for the Therapeutic Products Directorate.

Agnes V. Klein MD, DPH
Director, Centre for the Evaluation of Radiopahrmacetuicals and Biotherapeutic Products, Biologics and Genetic Therapies Directorate, Health Canada, Ottawa, Canada

Dr. Klein received her medical degree from the University of Toronto. She trained in Endocrinology, Medical Biochemistry and Public and Community Health. She joined Health Canada and the Drugs Directorate in late 1974 and has occupied many and varied scientific and management positions within Health Canada and its regulatory arms, including having acted as the Director of the Bureau of Human Prescription Drugs and as Director for the Biologics and Genetic Therapies Evaluation Centre. Dr. Klein has been with the Biologics and Genetic Therapies Directorate since April 2000. From September 2001, she occupied first the position of Manager, Clinical Evaluation Division, of a newly created Division responsible for Clinical Trial Application as well as the pre-market review and decisions in respect of post-market events relating to biological/ biotechnology agents. Since September 2004, Dr. Klein has variously occupied the positions of Senior Medical Advisor and Acting Director for a newly created evaluation centre within BGTD. Dr. Klein was an active participant in the CIOMS document on Pharmacogenetics and Pharmacoeconomics. In addition, Dr Klein is the Canadian representative to the OECD Steering Committee on Pharmacogenomics: Canada and Australia are co-chairing this working group which is preparing a Pharmacogenomics Workshop to be held in Rome, toward the end of October, 2005. Most recently, Dr. Klein has been actively involved in the ICH process. Dr. Klein's special interests include the appropriate design of clinical trials and the various and complex ethical issues attendant to the design and conduct of clinical trials and other studies in human subjects. Dr. Klein is a member of Health Canada's Research Ethics Board. Dr. Klein is an active member of several medical and scientific organizations nationally and internationally.

Thomas M. Ludden
Vice-President, Pharmcometric Research and Development, GloboMax, a Division of ICON plc, Ellicott City, Maryland, USA

Dr. Ludden is Vice-President, Pharmacometric Research and Development, GloboMax, the Strategic Development Division of ICON plc, Hanover, MD. He received a B.S in Pharmacy and Ph.D. in Pharmacology from the University of Missouri at Kansas City. Prior to joining GloboMax in July, 1999, he was Parke-Davis Professor and Chair, Department of Pharmaceutical Sciences, at UNMC. During the period 1991 to 1995 Dr. Ludden served consecutively as an Expert Consultant, Senior Staff Scientist and Director, Division of Biopharmaceutics, Office of Research Resources, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD. From 1975 to 1991, he was a faculty member of the College of Pharmacy, University of Texas at Austin and the University of Texas Health Science Center at San Antonio. He is a Fellow of the American College of Clinical Pharmacy and of the American Association of Pharmaceutical Scientists. In 1996, he received the Russell R. Miller Award from the American College of Clinical Pharmacy. He served as the U.S. Editor for the *Journal of Pharmacokinetics and Pharmacodynamics* from 1998 to 2005 and currently serves on the editorial board for *Pharmaceutical Research*. Research interests are pharmacokinetics, pharmacodynamics and pharmacometrics.

Iain J. McGilveray

Dr. McGilveray obtained a Ph. D. in Pharmaceutical Science in Glasgow, Scotland, trained in pharmacokinetics at the U. of California, San Francisco and worked in drug research in Health Canada for over 30 years. His research interests have included, biopharmaceutics, bioanalytical methodology, dissolution, pharmacokinetics, metabolites, pharmacodynamics and chiral effects, but principally have been focused on bioavailability and bioequivalence and he has contributed to more than 160 research publications. Dr. McGilveray is a Fellow of the AAPS and Canadian Institute of Chemistry, and is past-chair (1999) of the Regulatory Sciences section of AAPS and served on the FIP Board of Pharmaceutical Sciences (1988-96). He has organized and participated in many scientific conferences internationally, including AAPS, CSPS, DIA as well as FIP and he received the DIA Distinguished Career Award in 1998. He is interested in new scientific approaches to drug regulation and harmonization of standards, having been advisor to WHO and FDA. He is a consultant and an adjunct professor (medicine) University of Ottawa.

Gordon McKay
Past President, CSPS; CEO, Pharmalytics

Dr. Gordon McKay received his BSc and PhD degrees in biochemistry from the University of Saskatchewan. After a brief postdoctoral training period in pharmaceutical science, he was appointed as a research associate and adjunct professor of pharmacy in the College of Pharmacy at the University of Saskatchewan and a principal investigator in the Drug Metabolism, Drug Disposition Research Group headed by Dr. Kamal K. Midha at this same institution. The research group received the first program grant awarded by the Medical Research Council to a College of Pharmacy and the first ever awarded to the University of Saskatchewan. This research was renewed for a total of 11 years after which the group began to focus on collaborative research with the pharmaceutical industry and has continued in this regard for 25 years. Dr. McKay was awarded fellowship in the American Association of Pharmaceutical Sciences in 1994 for his original contributions to pharmaceutical analysis and was one of the founding members of the Canadian Society for Pharmaceutical Sciences on whose executive he is currently Past President. He is a scientific organizer for numerous scientific meetings including the Bioanalytical Validation meetings, the Tandem Mass Spectrometry Workshops held annually for the last 16 years, and BioInternational. He has served on the editorial board for JPharmSci and has been a member of the Pharmaceutical Sciences review committee for MRC/CIHR and has served on numerous university boards and committees. Dr. McKay has published more than 170 original scientific publications and authored more then 210 scientific presentations. Currently, he is a full professor in the College of Pharmacy and Nutrition and the chief executive officer for a new not-for-profit research institute at the University of Saskatchewan which is focused on collaborative research with the pharmaceutical industry aimed at discovering, developing, and training in the areas of pharmaceutical science.

Kamal Midha
College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada

Dr. Midha is Adjunct Professor of the College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada. Midha's innovative approaches to drug studies have yielded over 300 research articles, and he has received numerous research awards from all over the world, which include the Kolthoff Gold Medal from the American Pharmaceutical Association, Washington D.C. USA; Research Achievement Award from The World Congress of Pharmaceutical Sciences Kyoto, Japan; Eminent International Scientist Award from the Indian Drug Manufacturers Association, Mumbai, India. In 1995, Dr. Midha was invested with Canada's highest award, The Order of Canada. Dr. Midha is Vice-President of the International Pharmaceutical Federation (FIP) and his leadership in pharmaceutical sciences has included chairmanship of the Board of Pharmaceutical Sciences of FIP, co-chairmanship of Bio-International Conferences sponsored by FIP and the American Association of Pharmaceutical Scientists, and membership on the editorial boards of several journals. He is a recognized authority on issues of bioavailability, bioequivalence, bioanalysis, pharmacokinetics, and pharmacodynamics. Dr. Midha works globally with pharmaceutical industry as an advisor.

Diane R Mould
President, Projections Research Inc.,
Phoenixville, PA, USA

Dr Mould obtained her PhD in Pharmaceutics and Pharmaceutical Chemistry at the Ohio State University in 1989. She spent 16 years as a pharmacokineticist in the pharmaceutical industry where she specialized in population pharmacokinetic and pharmacodynamic modeling. During this time, she has conducted population PK/PD analyses of hematopoietic agents, monoclonal antibodies, anti-cancer and anti-viral agents, antipsychotic and sedative/hypnotic agents. Dr Mould has also been involved in clinical trial simulation and study design in drug development for 16 years. She was a member of the Scientific Advisory Group for PharSight where she assisted in the development of their clinical trial simulation package. Currently, Dr Mould is the president of Projections Research Inc, a consulting company offering pharmacokinetic and pharmacometric services to the pharmaceutical industry. She has published 17 peer-reviewed articles, 8 book chapters, and has made numerous national and international presentations on advanced modeling approaches and simulation work. She currently holds a position as an adjunct professor at the University of Rhode Island at Providence and teaches a class on disease progress modeling at the National Institutes of Health.

A.C. Nestruck, M.Sc., Ph.D.
Therapeutic Products Directorate, Health Canada, Ottawa, Canada

Dr. Nestruck obtained her M.Sc. in Physiology from the University of Western Ontario and her Ph.D. in Veterinary Clinical Studies from the University of Saskatchewan. Her post-graduate experience includes a post-doctoral fellowship in Biochemistry at McGill University, as Chercheur boursier (Research Scholar) at the Institut de Recherches Cliniques de Montréal, as Research Scholar at the Max Planck Institute for Medical Research in Heidelberg and the University Hospital Goettingen, Germany, followed by several years as a Senior Scientist with the Atherosclerosis and Hyperlipidemia Research Group at the Institut de Recherches Cliniques de Montréal. Dr. Nestruck spent several years in the pharmaceutical industry as Director, Scientific Affairs with Boehringer Mannheim Canada and as Director, Clinical Research with BioChem Pharma and Biochem Vaccines. Dr. Nestruck joined the Office of Clinical Trials (formerly Clinical Trials and Special Access Programme) of the Therapeutic Products Directorate, Health Canada in 1997. She is a senior reviewer of Clinical Trial Applications in the areas of Oncology and Metabolic diseases; a member of several internal and external working groups and acted as Manager in 1999-2000; 2003-04 and 2006.

Eric Ormsby
Office of Science, Therapeutic Products Directorate, Health Canada, Ottawa, Canada

Eric has worked for Health Canada for 25 years, almost entirely in some form of what is now called the Therapeutic Products Directorate (TPD). The TPD is responsible for pre-market assessment of pharmaceuticals and medical devices. Eric has been involved in bioequivalence issues since 1986 when Canada first began to develop a regulatory framework for bioequivalence. Eric obtained a BSc. in Genetics and Statistics from the University of Guelph and a MSc. in Biostatistics also from Guelph. Currently he is acting manager of the Office of Science, Policy Bureau of TPD. This Office has the responsibility of managing TPD's access to external expert advice, managing the reconsideration process and the development of science based regulations, policies and guidelines.

Ethan Russo, MD
Senior Medical Advisor, GW Pharmaceuticals, Missoula, Montana, USA

Ethan Russo, MD, is a board-certified child and adult neurologist formerly with Montana Neurobehavioral Specialists in Missoula, MT. He is a researcher in migraine, ethnobotany, medicinal plants, and cannabis and cannabinoids in pain management. He serves in a consultancy position as Senior Medical Advisor to GW Pharmaceuticals, a British company devoted to the development of novel prescription preparations of cannabis and other medicinal plants. Dr. Russo holds faculty appointments as adjunct associate professor in the Department of Pharmaceutical Sciences of the University of Montana, and clinical associate professor in the Department of Medicine of the University of Washington. He is the author of *Handbook of Psychotropic Herbs: A Scientific Analysis of Herbal Preparations for Psychiatric Conditions*. He was co-editor with Franjo Grotenhermen of the book, *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential*, and author of the novel, *The Last Sorcerer: Echoes of the Rainforest*, all from Haworth Press. Dr. Russo was the founding editor of *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal and Synthetic Cannabinoids*, whose charter issue was released in January 2001. Three double-issues are also published as books: *Cannabis Therapeutics in HIV/AIDS*, *Women and Cannabis: Medicine, Science and Sociology*, and *Cannabis: From Pariah to Prescription*. He has published numerous book chapters, and over thirty peer-reviewed articles on topics of neurology, clinical cannabis, and medicinal plants. His most recent article is: Russo, E.B., and G.W. Guy. 2006. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Medical Hypotheses 66(2):234-246.

Mario Tanguay
Vice-president, Scientific and Regulatory Affairs, SFBC Anapharm, Québec, Canada

Dr. Tanguay holds a bachelor's degree in pharmacy and obtained an MSc and a PhD in pharmacology from the University of Montreal. He has been a co-investigator in hundreds of pharmacokinetic and Phase I studies (including bioavailability and bioequivalence, drug interactions, etc.). Dr. Tanguay has more than 5 years of experience in Contract Research Organizations. He previously worked for 5 years in clinical research at Wyeth-Ayerst and Pharmacia. He also worked as a community pharmacist for many years and has been a guest lecturer on numerous occasions at Laval University, Sherbrooke University, and University of Montreal. Dr. Tanguay is a member of many scientific associations including the American Association of Pharmaceutical Scientists (AAPS), the American Society for Clinical Pharmacology and Therapeutics (ASCPT), and the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Jake J. Thiessen
Professor, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada and Hallman Director, School of Pharmacy, University of Waterloo, Waterloo, Canada

Jake Thiessen earned his undergraduate Pharmacy degree from University of Manitoba and his doctoral degree from the University of California, San Francisco, California. Jake has been at the Faculty of Pharmacy, University of Toronto for about 33 years. He has taught pharmacokinetics at the undergraduate and graduate levels. His current research interests include the pharmacokinetics and pharmacodynamics of cancer chemo-therapeutic agents, identifying new cancer treatment strategies, and defining the kinetics and response to iron chelators. Following a period as associate dean in Toronto, he was invited in the fall of 2004 to become the founding director of the new University of Waterloo School of Pharmacy. Among his extra-university involvements, Jake has chaired the Ontario Ministry of Health Drug Quality and Therapeutics Committee and served on the Pharmaceutical Inquiry of Ontario. He continues to chair the Health Canada Scientific Advisory Committee on Bioavailability and Bioequivalence, and has served as President and Past-President of the Canadian Council for Accreditation of Pharmacy Programs.

Corey B. Toal
Director, Scientific Development, Bayer Inc., Toronto, Canada

Corey Toal is the Director of a multidisciplinary group of scientists that work out of the Medical department at Bayer with the top medical specialists around the country in each of the therapeutic areas in which they have drugs. His particular specialty is in the realm of cardiovascular drugs and clinical pharmacology. He obtained his PhD in pharmacology from the University of Toronto in 1985. He subsequently completed a post-doctoral fellowship in Clinical Sciences also at the University of Toronto. He is presently an Assistant Professor of Pharmacology at the University of Toronto where he has contributed to the teaching of Medical, Dentistry, and Pharmacology students. He continues to teach drug development and clinical trial design at the university. He is the Chair of the Corporate Relations committee for the Canadian Society of Clinical Pharmacology and presently sits on the Industry Practices Committee for Canada's Research-Based Pharmaceutical Companies (Rx&D).

Yu Chung Tsang
Chief Scientific Officer, Apotex Inc., Toronto, Canada

Dr. Yu Chung Tsang is currently working at Apotex Inc. as Chief Scientific Officer, Biopharmaceutics and Biostatistics. He obtained his Bachelor degree (1984) in Pharmacy and PhD degree in the area of Pharmacokinetics in 1990 from the University of Toronto. He has been with Apotex since then. His main responsibility is to provide scientific expertise and strategic direction in the design of bioequivalence studies and the analysis of data for the development of pharmaceutical products in the Apotex group of companies. To date, he has been involved with the design and data analysis of over a thousand bioequivalence studies for the registration of over 200 drugs in Canada, US, EU, and many other international marketplaces. He also provides statistical support in clinical trials of new chemical entities at Apotex. Dr. Tsang is a member of the Bioequivalence Committee of the Canadian Generic Pharmaceutical Association and the Highly Variable Drug working group of the US Generic Pharmaceutical Association. He also holds an academic appointment in the Faculty of Pharmacy, University of Toronto at the rank of Assistant Professor, Status Only.

Jack Uetrecht, MD, PhD
University of Toronto, Toronto, Canada

Dr. Uetrecht is Professor of Pharmacy and Medicine and the Canada Research Chair in Adverse Drug Reactions. He received his Ph.D. in organic chemistry at Cornell University in 1972, M.D. at Ohio State University in 1975 and did his medical residency at the University of Kansas Medical Center from 1975-1978. He completed a clinical pharmacology fellowship in 1981 at Vanderbilt University and then joined the faculty as an assistant professor. He moved to the University of Toronto in 1985 as an associate professor and was the associate dean of pharmacy from 1994 to 1998. He was awarded the Canada Research Chair in Adverse Drug Reactions in 2001 and is a Fellow of the Canadian Academy of Health Sciences. His research is focused on the mechanisms of idiosyncratic drug reactions.

Hans Yu
Chief, Biotechnology Science Unit, Departmental Biotechnology Office, Health Canada, Ottawa, Canada

Hans Yu is Chief of the Biotechnology Science Unit at Health Canada's Departmental Biotechnology Office. He studied biology as an undergraduate and graduated from Queen's University in 1990 with an MSc in molecular virology. Hans has 16 years of experience in the federal government dealing with biotechnology-related issues, with over 12 years of regulatory experience. Starting with Agriculture Canada, in a group which is now within the Canadian Food Inspection Agency, Hans conducted risk assessments of biological fertilizers and was involved in activities such as the development of biotech-related regulations, policies, and guidelines. He also was involved in international harmonization activities and worked with the United States Environmental Protection Agency and the Organization for Economic Cooperation and Development (OECD). In 1998, Hans moved to Health Canada where he conducted risks assessments of environmental and industrial biotechnology applications under the Canadian Environmental Protection Act, and later became Head of the Biotechnology Section responsible for these assessments. Hans presently manages a multi-disciplinary team responsible for coordinating a broad range of horizontal bio- and nano-technology policy issues impacting the department. He chairs the departmental working group on nanotechnology which was established in 2004, is an active member of the federal NanoNetwork, and has been involved in a number of international activities such as being part of the Canadian delegation to the 2005 OECD workshop on the safety of manufactured nanomaterials.

Poster Presentations

Current Scientific Regulatory Challenges in Drug Development & Safety

Posters numbered **1 to 37** will be on display from 8-5 on **Thursday, May 25**
Posters numbered **38 to 73** will be on display from 8-5 on **Friday, May 26**

Presenters will be available by their posters during the coffee and lunch breaks.

1 Calcium Silicate Based Floating Granular Delivery System for Ranitidine Hydrochloride: A Novel Approach to Control Oral Delivery Via Gastric Retention

Ashish Jain, *Prateek Jain,* R.K. Agrawal, Pharmaceutics Division, Department of Pharmaceutical Sciences, Dr. H. S. Gour University, Sagar

Purpose: We prepared an intragastric floating granules using porous calcium silicate (FLR) as a floating carrier, which has floating ability due to the air included in the pores when they are covered with a polymer. Method: Floating granules were prepared by dropping a10% (w/v) ethanol solution of hydroxylpropylmethylcellulose (HPMC) and ethyl cellulose (EC) in four different concentration ratios (5:95, 10:90,15:85 and 20:80) while the 4.5g ranitidine hydrochloride adsorb 15g FLR was being agitated in a beaker. After the mixture was dried in vacuum and sieved (No. 22), we regarded the granules obtained as ranitidine hydrochloride primary coated granules (RHPCG). After drying, the ethanol solution of polymer was dropped and dried in vacuum again, and sieving was carried out to obtain ranitidine hydrochloride secondary coated granules (RHSCG).Results: The floating property of RHSCG was better than that of RHPCG. A longer floating time was observed with a lower HPMC concentration in composition ratio Since HPMC begins to erode when the HPMC ratio of the HPMC/EC matrix system is over 15%. It was observed by a scanning electron microscope (SEM) that more pores of FLR in RHSCG were covered with a polymer than those in RHPCG. RHSCG showed a smaller release rate than RHPCG. It also has a sustained drug release properties. The serum concentration Cmax of ranitidine hydrochloride in rats, which received (5:95) HPMC: EC coated formulation RHSCG1 was found to be 1.56 µg/ml after (tmax) 5 hr and AUC0-7 was 7.58 µg.hr/ml. Conclusion: These results suggest that FLR is a useful carrier for the development of floating and sustained release preparations. Acknowledgements: The first name author is thankful to All India Council of Technical Education for financial assistance.

2 Development of EGF-Conjugated Block Copolymer Micelles for Actively Targeted Drug Delivery to EGFR-Overexpressed Cancers

Helen Lee 1, Faquan Zeng 1, Christine Allen 1,2,3*; 1. Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy; 2. Department of Chemical Engineering and Applied Chemistry, Faculty of Applied Science and Engineering; 3. Department of Chemistry, Faculty of Arts and Science

PURPOSE: Nano-sized polymeric micelles formed from amphiphilic copolymers are capable of encapsulating and delivering hydrophobic drugs to tumors by passive targeting. Recently, much effort has focused on developing actively targeted drug-loaded micelles via ligand-coupling in order to further increase drug selectivity towards cancer cells. We have conjugated epidermal growth factor (EGF) to poly(ethylene glycol)-block-poly(δ-valerolactone) (PEG-b-PVL) copolymers for the preparation of micelles that target drugs to EGF receptor (EGFR) overexpressed cancer cells. METHODS: Targeted micelles were prepared from EGF-PEG-b-PVL copolymers; while non-targeted micelles were formed from the PEG-b-PVL copolymers. A hydrophobic fluorescent probe was loaded into the micelles to serve as a tracer for cell uptake studies. The cell uptake profiles of the targeted and non-targeted micelles were evaluated in EGFR-overexpressed breast cancer cells (MDA-MB-468) by fluorescence-measurements and confocal microscopic analysis. RESULTS: The targeted and non-targeted micelles were found to have mean diameters of 32 nm and 45 nm, respectively. Minimal cell uptake was detected in cells incubated with non-targeted micelles; while incubation of cells with the targeted micelles resulted in significant intracellular accumulation. In addition, the presence of EGF reduced the intracellular accumulation of targeted micelles to a similar level as observed in cells incubated with non-targeted micelles. Confocal microscopic analysis also revealed that the targeted micelles mainly localized in the perinuclear region, with occasional nuclear localization. CONCLUSION: EGF-conjugated micelles were internalized by MDA-MB-468 breast cancer cells via receptor-mediated endocytosis, which may allow for more efficient delivery of anticancer agents to EGFR-overexpressed cancer cells.

3 Biological and Mechanical Evaluation of a Polymer-Lipid Blend for Drug Delivery

J. Grant[1], V. Vassileva[1], M. Piquette-Miller[1], C. Allen[1]*, 1. Leslie Dan Faculty of Pharmacy, Department of Pharmaceutical Sciences

PURPOSE: We developed a novel blend composed of the natural polysaccharide chitosan and the lipid egg phosphatidyl-choline (ePC). The biological and mechanical properties of the chitosan-ePC film were evaluated for use in localized drug delivery. **METHODS:** The *in vitro* cytotoxicity was determined in CHO-K1 fibroblast cells and SKOV-3 human ovarian adenocarcinoma cells. The degree of protein adsorption to the films was evaluated in fetal bovine serum; while the *in vivo* biocompatibility was assessed in healthy CD-1 mice by examining the chitosan-ePC film macroscopically and histopathologically following a one-month implantation. The mechanical properties were determined by dynamic mechanical analysis and Instron testing. Nanoparticles containing the hydrophobic anticancer agent paclitaxel were dispersed throughout the chitosan-ePC film and the drug release profile was analyzed in physiologically relevant media. **RESULTS:** A negligible reduction in cell viability and a minimal degree of protein adsorption to the chitosan-ePC films provided preliminary indications of the biocompatibility of the chitosan-ePC film. Furthermore, no observable signs of infection, inflammation, local irritation or fibrous encapsulation were observed in the CD-1 mice implanted with the chitosan-ePC film. In addition, the modulus of the chitosan-ePC films was found to decrease significantly as the amount of lipid increased, thus creating a softer biomaterial that is suitable for use as an implant. A sustained release of paclitaxel from the film was achieved over a four-month period. **CONCLUSION:** The chitosan-ePC film has shown excellent biocompatibility and mechanical properties, and may be a promising implant system for the sustained delivery of hydrophobic agents.

4 Evaluation of a Pharmaceutical Care Service for Asthmatic Patients in Sudan

Awad AI1, Abdelhamid K2, Gasmallah A3, 1. Department of Pharmacy Practice, Faculty of Pharmacy, Kuwait University; 2. Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, Sudan, 3. Department of Internal medicine, Faculty of Medicine, Al Neelain University, Sudan

Purpose: To evaluate the impact of a pharmaceutical care service for asthmatic patients. **Methods:** A prospective, randomized, controlled study was conducted in Shaab teaching hospital, Khartoum. Patients were allocated randomly either in the intervention group, 60 patients and control group, 40 patients. Data were collected via structured, developed and pre-tested questionnaire. Some of data were collected by face to face interview of patients, others via physical examination and laboratory investigations. The outcome measures were determined at baseline and during follow-up of every two weeks for 6 months. Data were analyzed using SPSS version 11, level of significance $P < 0.05$. **Results:** At the end of the study period the mean reduction in frequency of acute attacks (1.91± 0.18 Vs 1.0±0.14; P=0.03), nocturnal asthma symptoms (3.5±0.3 Vs 1.1±0.2; P=0.02) and frequency of using inhaled β_2 agonists (19.9 ± 2.1 Vs 3.3±0.3; P=0.01) per week were significantly greater in the intervention group compared to control. A significant mean reduction (P=0.002) in the days of sickness/week was in the intervention group (1.4 ± 0.4), while in control group there was an increase by (1.0 ± 0.1). The rate of hospitalization decreased significantly (P= 0.009) in intervention group, while non-significantly increased (P = 0.3) in control. The intervention group showed a significant greater improvement in the score for assessing the inhalation technique (P<0.001), patient's knowledge about asthma (P<0.001), patient's compliance to drug-therapy (P=0.01) and non-drug therapy general measures (P<0.05), and the ratio of inhaled steroids to bronchodilators use (P<0.05). **Conclusion:** Pharmacist led-interventions have improved final and intermediate patients' outcome measures. The present results support the value of collaboration between physicians, pharmacists and patients, which improved the quality of care for asthmatic patients.

5 Interest of Community Pharmacists in Health Promotion in Kuwait

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Purpose: To describe the current practice of community pharmacists with regard to their provision of health promotion activities, identify their willingness to participate in health promotion and identify the barriers that may limit their participation. **Methods**: The study included 70 community pharmacies that were selected using stratified and systematic random sampling. Data were colleted via face-to-face structured interview of the respondents using a pre-tested questionnaire. **Results:** The majority of study participants (65.2%) were strongly involved in counselling patients on health promotion related to medications, but less involved in counselling them on the other personal health behaviours. Most of the pharmacists perceived themselves as very prepared to counsel patients on taking drugs (70%) and less prepared to counsel them on other personal health behaviours. Half of the participants (50%) claimed a high level of success in helping patients to change their behaviour with regard to medications, but not with regard to other personal health behaviours. The majority of the study participants (74.3%) have the interest and willingness to participate in continuing education programs so as to learn more about health promotion. The barriers facing community pharmacists' participation in health promotion activities as perceived by respondents were as follow: lack of pharmacists' time (60%), lack of patients' time (50%), lack of information and/or training (32.9%), and lack of privacy or pharmacy physical design (32%). **Conclusions** Community pharmacists reported to achieve considerable success in helping patients to change their behaviour in relation to medications, but were less confident of their ability to change personal health behaviours. The majority of the respondents have the willingness to be a prime source of advice and support on health promotion.

6 Preparation and Characterization of Polysorbate 80 Coated PLGA Nanoparticles for Effective Brain Delivery of Anticancer Drug - Imatinib Mesylate

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Purpose: The objective of this study was to formulate and evaluate polysorbate-80 coated nanoparticles of Imatinib mesylate using biodegradable and biocompatible polymeric material - PLGA for effective brain delivery. Imatinib mesylate (IM) is a selective protein tyrosine kinase inhibitor which inhibits the Bcr-Abl and cKIT tyrosine kinases in chronic myeloid leukemia and gastrointestinal stromal tumor, respectively. Although, IM has promising penitential in the treatment of brain tumors, it shows poor brain penetration because of efflux transport. Nanoparticulate formulations have the potential to overcome efflux transport system and also to alter tissue distribution through enhanced permeation and retention (EPR) effect of several water soluble drugs. **Methods:** Emulsification followed by solvent evaporation technique was adopted for preparation of polysorbate-80 coated PLGA nanoparticles of IM. Encapsulation efficacy, total drug content and *in vitro* release profile were studied using stability indicating HPLC method. Morphological characters of the nanoparticles like shape, average size, and size distribution were studied using AFM, PCS, and TEM. Additionally, drug-excipient compatibility studies were performed using HPLC, FTIR, and DSC. Rat *in situ* absorption model was used to study intestinal absorption of pure drug and prepared nanoparticles. Moreover, *in vivo* brain uptake was investigated for pure drug and prepared nanoparticles in Rat model. **Results:** Nanoparticles have shown good entrapment efficiency (91.5%) with high drug content. Additionally, it has provided extended drug release for over 24 hours when studied in specially designed diffusion cell equipped with dialysis membrane. AFM studies revealed the spherical shape of particles, while TEM and PCS studies confirmed mean size of 200 nm with narrow size distribution (poly-dispersity index 0.05). HPLC, DSC, and FTIR studies confirmed that the drug did not have any physical or

chemical incompatibilities with polymer and other excipients. *In situ* rat intestinal absorption study showed significant absorption of prepared nanoparticles. *In vivo* brain uptake studies in rat model revealed enhanced permeation of nanoparticles compared to pure drug. **Conclusion**: Adopted method of preparation has provided polysorbate-80 coated PLGA nanoparticles with high drug content and good entrapment efficiency. Prepared nanoparticles not only controlled the release but also enhanced spatial delivery of drug to brain. These nanoparticle formulations can be used for effective brain delivery of water soluble drugs like IM.

7 A specific and sensitive liquid chromatography-mass spectrometry (LC-MS) method for simultaneous determination of both amiodarone and desethylamiodarone in rat plasma

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Amiodarone (AM) is extensively used for its antiarrhythmic properties. In humans, the most prevalent circulating metabolite of AM is desethylamiodarone (DEA). In rat, a commonly used animal model, plasma concentrations of DEA are low, and near the lower limit of detection of most conventional assays using ultraviolet detection. Purpose: To develop a sensitive and specific high performance liquid chromatography-mass spectrometry (LC-MS) assay method for the determination of AM and DEA in rat plasma. Methods: To 0.1 mL of rat plasma samples containing 0.03 mL of internal standard (IS) solution (2.5 µg/mL ethopropazine), 0.3 mL of acetonitrile was added. Tubes were vortex mixed and centrifuged for 2 min and the supernatant was carefully transferred to new glass tubes. Then 0.3 mL of HPLC water and 3 mL of hexane were added. Tubes were vortex mixed for 30 s and centrifuged for 3 min. The top layer was transferred and evaporated to dryness in vacuo. Residues were reconstituted using 1 mL of mobile phase and 5-10 µL were injected into the LC-MS system consisting of a Waters Micromass ZQTM 4000 spectrometer coupled to a Waters autosampler and pump. A Waters XTerra® MS C18 3.5 µm (2.1×50 mm) column heated to 45°C was used for separation. The mobile phase consisted of methanol and 0.2% aqueous formic acid pumped as a linear gradient from 40:60 methanol:formic acid 0.2% to 90:10 over 15 min, at a constant flow rate of 0.2 mL/min. The concentrations of IS, DEA and AM were monitored for m/z values of 313.2 (IS), 617.90 (DEA) and 646.0 (AM). Results: In plasma, linearity was present between the peak height ratios and concentrations over the range of 10-1000 ng/mL for AM and 2.5-1000 ng/mL for DEA (r2>0.999). For HF and DHF intraday and interday CV were less than 20%, and mean error was <22%. After administration of AM to rats and assay of plasma, the eluted peaks representing AM, DEA and IS were all found to be free of interference. Conclusion: The LC-MS method was sensitive, specific and appropriate for the simultaneous assay of AM and DEA in rat plasma.

8 Role of Peroxisome Proliferators In Liver Fatty Acid-Binding Protein (L-FABP) Expression and Oxidative Function.

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INTRODUCTION: L-FABP has been shown to contain significant antioxidant activity. Pharmacological treatment directed at increasing or decreasing L-FABP levels was associated with either a decrease or increase in reactive oxygen species following H_2O_2 treatment. In this study we investigated the role of peroxisome proliferator-activated receptors (PPARs) in the expression and antioxidant activity of L-FABP. **METHODS:** L-FABP expressing 1548-hepatoma cells were treated with dexamethasone, clofibrate, PPAR alpha antagonist MK886, PPAR gamma antagonist GW9662 or combination treatment. Oxidative stress was induced by H_2O_2 incubation. The fluorescent marker, dichlorofluorescein (DCF), was employed to measure intracellular reactive oxygen species (ROS). **RESULTS:** L-FABP expressing 1548-hepatoma cells, treated with dexamethasone or clofibrate decreased and increased intracellular L-FABP levels, respectively. Expression of L-FABP was reduced after treatment with MK886 or GW9662. Clofibrate mediated L-FABP activation was inhibited by both PPAR antagonists. DCF data showed that ROS levels reflected L-FABP levels. **CONCLUSION**: Our study shows that PPAR agonists and antagonist treatment affects cellular antioxidant function. This study was supported by an operating grant from the Canadian Institute of Health Research.

9 LIPOSOMAL PRILOCAINE FORMULATION: STERILITY, STABILITY, AND LOCAL TOXICITY EVALUATION

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Purpose - Prilocaine (PLC) is an aminoamide local anesthetic widely used in dentistry. We have previously reported the preparation of a liposomal PLC (PLC_{LUV}) formulation with enhanced analgesic effects, in comparison to PLC in solution (Cereda et al., JPharmPharmacSci. 7:235, 2004). For PLC_{LUV} to be used in dentistry it is essential to evaluate its physicochemical stability before and after sterilization, as well as its toxic effects. **Methods** - PLC was encapsulated into extruded unilamellar liposomes composed by egg phosphatidylcholine:cholesterol:alfa-tocopherol (4:3:0.07, mol %). The formulation was steam sterilized at 121°C and 1 atm, for 15 min. Sterility was checked by pyrogen (Limulus amoebocyte lysate) and microbiologic (Brain-Heart Infusion) tests. The physical (size) stability of liposomes was evaluated by laser light-scattering (QLS) while the chemical stability of lipids (oxidation) and prilocaine was followed through the thiobarbituric acid reaction (TBARs) and H^1-Nuclear Magnetic Resonance (H^1-NMR), respectively. Finally, the paw edema test was used to assess the possible inflammatory effects of PLC_{LUV}. **Results** - PLC_{LUV} was found to be stable up to 30 days after preparation and analysis by QLS ($p = 0.9705$), TBARs ($p = 0.5207$) and H^1-NMR revealed no differences in the physicochemical stability of PLC or PLC_{LUV}, sterilized or not. PLC_{LUV} did not evoke rat paw edema, when compared to the control groups: saline, Hepes buffer, PLC in solution and $LUV_{PLC\text{-}free}$ ($p > 0.05$). **Conclusion** - Stability assays indicate autoclaving can be adopted to sterilize PLC_{LUV} in further scale-up experiments. Moreover, this formulation did not induce inflammatory effects on rats paw.

10 Determination of trigonelline in herbal extract and pharmaceutical dosage form by a validated HPTLC method

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PURPOSE: The objective of the present investigation was to develop a validated HPTLC method for the determination of Trigonelline in herbal extracts and in pharmaceutical dosage forms. **METHODS:** Analysis of trigonelline was performed on TLC aluminium plates pre-coated with silica gel 60F-254 as the stationary phase. The mobile phase consisted of n-propanol: methanol: water (4:1:4 v/v/v). Linear ascending development was carried out in twin trough glass chamber saturated with mobile phase at room temperature and the mobile phase was run up to 8 cm. Camag TLC scanner III was used for spectrodensitometric scanning and analysis in absorbance mode at 269 nm. **RESULTS**: The system was found to give compact spots for trigonelline (Rf value of 0.46 ± 0.01). The linear regression analysis data for the calibration plots showed good linear relationship with r^2 = 0.9991 ± 0.0002 in the concentration range 100-1200 ng per spot. The mean value (± S.D) of slope and intercept were 4.1312 ± 0.0491 and 208.2135 ± 4.5092 respectively. According to ICH guidelines the method was validated for precision, recovery, robustness and ruggedness. The mean % recoveries ranged from 98.29 – 102.19 %. The limits of detection and quantification were 2.27 ng and 7.58 ng, respectively. The trigonelline content of herbal extracts was quantified. Drug content estimated from the formulation was well within the limits (±5% of the labelled content of the formulations). **CONCLUSIONS:** Statistical analysis of the data showed that the method is reproducible and selective for the estimation of trigonelline. Since the proposed mobile phase effectively resolves trigonelline, the developed HPTLC method can be applied for identification and quantification of trigonelline in herbal extracts and pharmaceutical formulations.

11 Effects of inflammation and pravastatin on myocardial norepinephrine and matrix metalloproteinase-2 and -9 in rats.

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PURPOSE: Inflammatory conditions downregulate cardiac $beta_1$-receptors. Matrix metalloproteinases (MMPs) are involved in inflammatory processes and their inhibition can prevent the loss of contractile function. Activation of cardiac sympathetic nerves, something observed in rheumatoid arthritis patients, may contribute to reduced cardiovascular drug responsiveness in humans Pre-adjuvant arthritis (Pre-AA) is an inflammatory model that reduces cardiovascular response to propranolol. The diminished effect appears to be restored by, the hydroxymethylglutaryl-CoA reductase inhibitor pravastatin. **Hypothesis:** The anti-inflammatory effects of pravastatin will normalize elevated MMP-2, MMP-9, and norepinephrine (NE) in the myocardium **METHODS:** Rats were injected with *Mycobacterium butyricum*, and after four days oral pravastatin (6 mg/kg, BID) was given until day 8. In heart homogenates we detected MMP-2 and MMP-9 by gelatin-zymography, and using competitive ELISA we detected heart NE. **RESULTS:** After 8 days, Pre-AA caused a significant twenty-fold elevation in myocardial MMP-9 activity as compared with healthy rats (Average band density±SEM; 170±58 vs. 8.3±1.7 units/mg; n=12/group) that was not attenuated by pravastatin administration (Pre-AA/Placebo vs. Pre-AA/Pravastatin; 170±58 vs. 141±57 units/mg; n=12/group). Neither MMP-2 nor NE was influenced by Pre-AA induction or by pravastatin administration. **CONCLUSIONS:** The mechanism by which Pre-AA induces inflammation may involve MMP-9 activation, but how pravastatin assists in restoring cardiovascular drug non-responsiveness remains to be determined.

12 Design and Optimization of Multicomponent Pseudosolid Dispersions of Meloxicam

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Purpose: The purpose of present investigation was to study potential of water soluble dissolution enhancers polyvinylpyrrolidone K30, polyethylene glycol 400 and propylene glycol on in vitro dissolution of a poorly water soluble drug meloxicam to develop multi-component pseudosolid dispersion system. **Methods:** Preliminary studies were conducted using a physical mixture of meloxicam and the excipients lactose and microcrystalline cellulose while solid dispersions were prepared by solvent evaporation and cogrinding method using aqueous solution of these enhancers. Based on the data of preliminary studies, a 3^3 factorial design was adopted to optimize the concentration of solubilizing agents. The concentrations of enhancers polyvinylpyrrolidone K30, polyethylene glycol and propylene glycol were used as independent variables whereas angle of repose and in vitro dissolution were used as dependent variables. Full and reduced models were evolved for the dependent variables and the reduced models were further validated using two check points. Angle of re-pose < 35˚, percentage of drug dissolved in 30 min (Q_{30}) > 45%, 45 min (Q_{45}) > 55% and 120 min (Q_{120}) > 65% were used as constraints for the selection of optimized batch. Contour plots were presented for the selected dependent variables. **Results:** Polyvinylpyrrolidone was found to be more effective in increasing the drug dissolution, compared with liquid enhancers polyethylene glycol 400 and propylene glycol. The granule flow was adversely affected when high levels of liquid enhancers were incorporated in the formulations. Wet-ability studies were conducted to measure wetting time of selected batches and the improved dissolution was attributed to improved wetting and solubilizing effects of adjuvants from the pseudosolid dispersions of meloxicam. More than a five fold increase in drug dissolution was observed in some batches compared with pure drug powder. The similarity factor (f_2) for the selected batches were in the range 50-100 which were in accordance with the SUPAC FDA guidelines. **Conclusion:** Cogrinding of meloxicam with aqueous solution of dissolution enhancers offered potential advantages such as reduced cost, improved safety and environment friendliness as compared to solvent evaporation method which used dimethyl formamide. The studies revealed that optimum levels of solubility enhancers based on systematic statistical approach could be appropriately blended with pharmaceutical adjuvants to demonstrate significantly higher release rates of meloxicam in an economical and cost effective manner.

13 DEVELOPMENT OF CONTROLLED RELEASE PLATFORM FOR HIGH DOSE GASTRO RETENTIVE DRUG DELIVERY

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Purpose: This study was performed to prepare controlled release gastro retentive (GR) formulation for high dose drugs. Ciprofloxacin Hydrochloride had been selected as model drug. It is highly water-soluble drug with an absorption window at upper jejunum with dose of 598.47 mg. **Methods:** The matrix based controlled release formulation strategy for GR tablets were used. The drug is mixed with polymers and half of the amount of sodium bicarbonate and then the mix was granulated with isopropyl alcohol. Various polymer combinations have been tried viz: HPMC, Ethylcellulose, Sodium alginate, Xanthum gum, Kollidon SR and their combination thereof. An optimized platform for high dose GR formulation has been prepared. **Results:** Even with low compression forces tablets of astonishing hardness has been obtained with Kollidon SR and xanthum gum combination. Also these formulations have shown better floating behavior (18 Hr) as compared to HPMC based floating tablets, that sink after certain time. The formulation was achieved with lowest ratio of polymer to drug as low as 1:3. Similarly, amount of Sodium Bicarbonate to total tablet weight was achieved in ratio of 1:5. Dissolution profiles, 30% of the drug were released in first hr and 70% of the drug was released in next 8-10 Hrs. The total tablet weight was less than1g, the objective set for high dose formulation. **Conclusion:** Formulation of Ciprofloxacin Hydrochloride GR tablets in Kollidon SR and Xanthum gum combination were better than HPMC based formulations. A floating time of more than 18Hrs was easily achieved. Dissolution data proves 24 Hrs controlled release profile.

14 MODULATION OF CLASS III ANTIARRHYTHMIC PROPERTIES OF *d*-SOTALOL BY GLUCOSE CONCENTRATION

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Purpose: Prolongation of the QT interval on the electrocardiogram by blocking cardiac potassium channels is a well-known property of Class III antiarrhythmics, such as *d*-sotalol. Excessive QT prolongation is a trigger for ventricular arrhythmias (torsades de pointes). Interestingly, QT prolongation has also been associated with both hypo- and hyperglycemia seen in diabetes. We hypothesized that low and/or high glucose levels potentiate the effect of *d*-sotalol. **Methods**: Chinese hamster ovary cells were transfected with HERG, encoding I_{Kr}, a major repolarizing current of the human heart and the target of nearly all QT-prolonging drugs, including *d*-sotalol. Using the whole cell patch-clamp technique, the modulating effect of glucose on the I_{Kr}-blocking properties of *d*-sotalol was measured. **Results**: Both low (1 mM) and high (20 mM) glucose reduced I_{Kr} amplitude when compared to glucose 5 mM (normoglycemia), at baseline. Moreover, while *d*-sotalol 25 µM blocked I_{Kr} by 50±4% (n=5) at glucose 5 mM, block was 74±2% (n=5) at glucose 1 mM and 65±4% (n=5) at glucose 20 mM. **Conclusion**: This suggests that low and high blood glucose not only reduce baseline I_{Kr} amplitude, but potentiate the I_{Kr}-blocking properties of *d*-sotalol, further increasing its QT-prolonging effect and thereby increasing the risk for torsades de pointes. This is a Merck poster. Work also supported by FRSQ, Québec Heart Institute and HSFC.

15 Down-regulation of aryl hydrocarbon receptor-regulated genes by inflammation: the role of nitric oxide

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Purpose: We previously demonstrated that tumour necrosis factor-α (TNF-α) and lipopolysaccharide (LPS) down-regulate aryl hydrocarbon receptor (AHR)-regulated genes such as cytochrome P450 1a1 (Cyp1a1) and NADPH: quinone oxidoreductase (Nqo1) gene expression, yet the mechanisms involved remain unknown. The correlation between the inflammation-mediated suppression of AHR-regulated genes and the TNF-α or LPS-induced nitric oxide (NO) production especially in murine hepatoma Hepa1c1c7 cells has been questioned; therefore we investigated whether NO is involved in the modulation of Cyp1a1 and Nqo1 by TNF-α or LPS in Hepa 1c1c7 cells. **Methods:** For this purpose Hepa1c1c7 cells were incubated with TNF-α or LPS in the absence or presence of the selective inducible nitric oxide synthase (iNOS) inhibitor, L-N6-(1-iminoethyl) lysine (L-NIL) (1mM) and peroxynitrite decomposer, iron tetrakis (n-methyl-4'-pyridyl) porphyrinato (FeTMPyP) (5 μM). The amount of NO produced by various concentrations of TNF-α (1, 5, 10 ng/ml) and LPS (1, 5 μg/ml) in the absence or presence of L-NIL were measured by fluorometric HPLC assay. Cyp1a1 and Nqo1 mRNAs were assessed by Northern blot analysis. Cyp1a1 and Nqo1 activities were measured using 7-ethoxyresorufin and 2,6-dichlorophenolindo-phenol as substrates, respectively. **Results:** A significant dose-dependent increase in NO production was observed by various concentrations of TNF-α and LPS which was completely inhibited by L-NIL. Furthermore, TNF-α and LPS significantly induced iNOS expression in a dose-dependent manner. Both TNF-α and LPS strongly repressed the constitutive expression and the β-naphtho-flavone-mediated induction of Cyp1a1 and Nqo1 at mRNA and activity levels which were significantly prevented by L-NIL. However, FeTMPyP did not affect TNF-α and LPS-mediated down-regulation of Cyp1a1 and Nqo1 at both mRNA and activity levels. **Conclusion:** These results show that NO, but not peroxynitrite, may be involved in the down-regulation of AHR-regulated genes mediated by TNF-α or LPS. **Acknowledgement:** N.G. was supported by Rx & D HRF/CIHR Graduate Research Scholarship in Pharmacy.

16 Ciprofloxacin inhalable particles

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Purpose: The objective of this study was to develop a new type of effervescent inhalable carrier particles, which have an active release mechanism and contain ciprofloxacin, a potent and broad – spectrum antibiotic. **Methods**: Lactose, sodium carbonate, citric acid, polyethylene glycol 6000 and l-leucine were weighed and added to an aqueous ammonia solution. Ammonia was used to increase the pH of the solution to inhibit an effervescent reaction prior to spray drying. Ciprofloxacin was first dissolved in HCl 0.01N and then added to the ammonia-carbonate solution. Formulations were spray dried using Mini Buchi 190 spray dryer. The dispersibility and content of ciprofloxacin in the spray dried powders was determined using a Mark II Andersen impactor. Each impactor plate was washed with distilled water and assayed by UV spectrophotometry. The carrier particles sizes and shapes were investigated using a Hitachi S-2500 scanning electron microscope. The effervescent effect was investigated using a Zeiss LSM 51 confocal laser-scanning microscope. **Results**: The mass median aerodynamic diameter and geometric standard deviation of these formulations ranged from 2.8 to 3.6 μm and 1.95 to 2.07 respectively. The total amount of ciprofloxacin in the powders after spray drying was around 60-70%. Results from cascade impactor predicted that ciprofloxacin will be deposited in different regions of the respiratory tract but predominately in the alveolar region. **Conclusion**: This study shows that it is possible to produce carrier particles, which actively releases ciprofloxacin using effervescent inhalation technology.

17 IN VIVO SKIN PERMEATION OF SODIUM NAPROXEN FORMULATED IN PLURONIC F-127 GELS: EFFECT OF AZONE® AND TRANSCUTOL®

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PURPOSE: This work focuses on the effects of Azone® and Transcutol® formulated in PF-127 gels, on the human skin penetration of sodium naproxen *in vivo*. **METHODS:** PF-127 gel formulations were prepared (containing 3 % w/v of sodium naproxen). Formulation II (F-II) had ~24.8% Transcutol® and Formulation III (F-III) had a mixture of ~1.7 % Azone®/24.8% Transcutol®. The human subjects were dosed topically on the ventral forearm. The sodium naproxen distribution across the stratum corneum (SC) was determined by tape stripping and quantified by HPTLC. FTIR/ATR and TEWL were used to evaluate the effect of some of the components of the gel formulations on SC permeability properties. **RESULTS:** It was clearly confirmed that the presence of enhancers promoted sodium naproxen permeation. The combination of Azone® and Transcutol® (F-III) produced an approximately 2 to 3-fold increase in drug penetration with respect to F-II, suggesting a synergistic effect between Azone® and Transcutol®. Treatment of the skin with F-II increased the value of TEWL to 20.6 ± 1.7 g/h.m^2, and with F-III, TEWL reached 33.5 ± 2.6 g/h.m^2. A synergistic effect was proposed for the Azone®/Transcutol®mixture (F-III). A significant shift toward a higher wavenumber was observed for the methylene (CH_2) group vibration at 2850 cm^{-1}, only in the case of the Azone®/Transcutol® mixture (F-III). **CONCLUSIONS:** The experiments demonstrated that the inclusion of Transcutol® or Azone®/Transcutol® promotes sodium naproxen permeation across the skin. However, the Azone®/Transcutol combination appears to act synergistically.

18 Kinetic Studies of Pentachlorophenol (PCP) 4-Monooxygenase

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Purpose: Pentachlorophenol (PCP) is a major environmental pollutant of water, soil and air in North America. Although PCP was resistant to biodegradation when it was first introduced, a number of soil and aquatic bacteria have evolved a degradation pathway to mineralize PCP during the past half century. However, the degradation process is inefficient due to low activity and substrate specificity of the rate-limiting enzyme, PCP 4-monooxygenase. The current summer student project is to study the kinetic reactions of PCP 4-monooxygenase towards several environmental pollutants including PCP and polychlorinated biphenols (PCBs). **Methods:** PCP 4-monooxygenase was purified by a three step liquid chromatography method (Ni-NTA affinity column, phenyl-Sepharose hydrophobic column and Superdex 200 gel filtration column) on an ÄKTA Prime machine. The enzyme preparation was incubated with substrate at room temperature in the presence of NANPH and FAD. The kinetic reactions were quenched by 1M HCl at 10, 20, 30, 60, 90 and 120 minutes. The kinetic parameters were determined by measuring the yield of the products with a C8 column on a High Performance Liquid Chromatography (HPLC) system. **Results:** PCP 4-monooxygenase has higher than 90% purity as examined by SDS-PAGE. Its catalytic activity was shown to be similar to that reported in literature. It possesses none or very low if any activity towards PCBs. **Conclusion:** The enzyme preparation can be used to screen the ability of PCP 4-monooxygenase to metabolize other PCBs using HPLC analysis. **Acknowledgments:** *Merck Poster. Erin Fiege is a recipient of the 2005 Merck-Frosst Summer Studentship.

19 Are Steady-State Studies Necessary for Approval of Generic Modified Release Products?

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Purpose: To evaluate the importance of multiple-dose studies for bioequivalence evaluation of generic modified-release drug products at steady-state. Methods: Intra-subject variability for AUC and Cmax, as well as test to reference ratio of geometric means (GMR) for these parameters were compared in 10 pairs of single-dose and steady-state bioequivalence studies under fasting conditions. Results: Intra-subject variability at steady-state was lower than that after a single dose in 9 out of 10 cases for both AUC (mean 17.4% vs. 13.0%) and Cmax (mean 21.4% vs. 15.9%). These differences were statistically significant for both AUC ($p = 0.0068$) and Cmax ($p=0.0137$) (Wilcoxon Signed Ranks Test). The formulation differences in AUC at steady state were not different than those after a single dose, while average GMR values of Cmax appeared closer to 100% at steady state, compared to single dose. Conclusion: The intra-subject variability is smaller at steady-state than after a single-dose, suggesting that a single-dose design provides a more discriminatory condition for assessing the in-vivo performance of two products. This observation, in addition to the Cmax trend towards smaller formulation differences at steady-state in comparison to a single-dose, suggests that when a generic product passes all the bioequivalence criteria in a single-dose study with no notable formulation differences in pharmacokinetic parameters, a multiple-dose study at steady-state provides no additional value in bioequivalence assessment and therefore should not be required for regulatory approval.

20 In vitro inhibitory effect of African medicinal and food plants on human cytochrome P450 3A subfamily.

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Purpose: African Medicinal plants (AMPs) derived from roots, leaves or bark are an important component of traditional medicine (TM). These products, frequently administered by oral route could affect the bioavailability of drugs or other AMPs. Some of these products are also available as commercially available formulated products. Hence it is important to test these AMPs as they are prepared and used in their traditional and commercially available form. This study was undertaken to evaluate the extracts of AMPs on CYP3A4, CYP3A5 and CYP3A7 metabolic activity in vitro. **Methods:** The potential for these botanical species to affect human cytochrome P450 3A-mediated metabolism was determined using *in vitro* bioassays with the commercially available microsomes. **Results:** The results indicated that extracts of *Aframomum cuspidatum*, *Aframomum melegueta*, *Harrisonia abyssinica*, *Hypoxis rooperi* (traditional and commercial forms) and *Piper guineense* inhibited the ability of 3A4, 3A5 and 3A7-mediated metabolism. *Phyllanthus amarus* showed high inhibition on 3A5 and 3A7. The extracts of *Corchorus olitorius*, *Solanum macrocarpon*, *Talinum triangulare* and *Morinda lucida* inhibited CYP3A4 and CYP3A5 less than 20%. The activity of CYP3A7 was inhibited more than 30% by these same extracts. **Conclusion:** Frequently traditional medicines are polyherbal preparations, and it is thought that some of the plants present in a given preparation are used to increase the effectiveness or decrease the potential toxicity effect of others. Little scientific evaluation has been undertaken on these "co-administered medicinal plants". We conclude that oral administration of AMPs and particularly the co-administered plants may alter the disposition of other AMPs and conventional drugs.

21 Sustained Release Drug Delivery System for Peptides and Proteins Using Thermo-Responsive polymers

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Purposes: recently developing of peptide and protein drugs in sustained release forms widely have been studied. In this work, studying of sustained release delivery system of calcitonin as a protein with biodegradable thermo-responsive copolymers based on PL(G)A-PEG-PL(G)A has been investigated. Copolymers were synthesized by ring opening method. **Materials and Method**: The triblock copolymers with different ratio of Glycolide to D,L-Lactide according to Zenter method with little change were synthesized. Polymers structure and molecular weight were evaluated by 400 MHz H NMR and GPC. Purified copolymers were dissolved in acetate buffer (pH=4) and calcitonin as a model protein was loaded into vial containing polymer solution. Loaded vial incubate at 37^{o}C for 2 min and then release media was added to vial. The released of calcitonin was determined by HPLC method. **Results**: Copolymers were characterized by H NMR and GPC. Molecular weight of copolymers obtained by GPC and calculated from H NMR spectrums were found 5100-7200. Calcitonin release was evaluated for 7-10 days. Although 20±3% of calcitonin was released in 24 hours but, the release profile was linear up to 80 hours. Calculation shows the mechanism of release is based on diffusion. **Conclusion***:* thermo-response copolymer may be useful for short time sustained release of peptides and proteins.

22 Determination of fluconazole in human plasma using high performance liquid chromatographic method.

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Purpose: To describe a validated High performance liquid chromatographic (HPLC) method for the determination of Fluconazole in human plasma. **Methods:** Fluconazole in human plasma was extracted using dichloromethane as solvent by liquid extraction technique. Mobile phase consisting of 10 milli mole phosphate buffer, methanol and acetonitrile mixture (70:10:20) was used at the flow rate of 1 ml/min on a C18 column. The eluate was monitored using an UV detector set at 210 nm. Peak area ratio of the analyte to internal standard (Metoprolol) was used for the quantification of plasma samples. The method was validated for its accuracy, precision, linearity, sensitivity and specificity. **Results and conclusion:** The retention time of the analyte and internal standard were 5.7 and 8.1 min. respectively. The validation of the proposed method was carried out. The method was specific and sensitive with a quantification limit of 0.05µg/ml and detection limit of 0.02 µg/ml in plasma. The mean absolute recovery for Fluconazole using the present plasma extraction procedure was 75.8%. The intra and inter-day coefficient of variation and percent error values of the assay method were all in the acceptable range. Calibration curves were linear (r^2 > 0.999) from 0.05 to 8 µg/ml. The method was found to be simple, sensitive reproducible and specific. The suitability of the method was confirmed in the bioequivalence study of Fluconazole in human volunteers.

23 The Role of Superantigen Producing *Staphylococcus aureus* and *Streptococcus* in Multiple Sclerosis

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Background: Epidemiologic studies suggest that environmental factors, such as infectious diseases, may be associated with the underlying pathogenesis of Multiple Sclerosis (MS). This theory has evolved from the association between geographical location and prevalence of MS. Henceforth, patients residing in specific geographical locations may be predisposed to certain organisms such as *S. aureus* and/or *Streptococcus pyogene* that trigger MS. **Purpose:** The primary objective of this study is to determine if nasal carriage rates for *S. aureus* and/or *Streptococcus pyogene* correlate with acute exacerbations of MS. **Methods:** Study participants (n=240) recruited into the study will be divided into 3 main groups that include: *naïve control* (n=80), *active control* (n=80) and an *acute exacerbation group* (n=80). Participants from each main group will be further subdivided into four subgroups of 20 that correspond to each of the four seasons. Polymerase chain reactions (PCR) will be used to determine the toxin genotype for all *S. aureus* and/or *Streptococcus* isolates. Pulsed-field gel electrophoresis (PFGE) will be conducted on all isolates to determine the molecular relatedness of strains. **Results:** Nasal carriage rates for *S. aureus* and/or *Streptococcus pyogene* are increased in MS patients compared to controls. Nasal carriage rates of these organisms further increase during an MS attack. Seasonal variability appears to influence nasal colonization. **Conclusion:** The research identifies a novel mechanism by which antimicrobial treatments may be used as adjunctive therapy with conventional treatments to reduce MS exacerbations.

24 Concomitant blockade of leukotriene B_4 and platelet-activating factor receptors underline important roles of lipid mediators in acute inflammation

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Purpose. A number of studies reported the involvement of either leukotriene B_4 (LTB_4) or platelet-activating factor (PAF) in reperfusion injury. The aim of the present study was to determine the potentially co-operative effect of these mediators in regulating polymorphonuclear neutrophils (PMN) trafficking and plasma extravasation in remote tissues following 2 hours of bilateral hind limb ischemia and 4 hours of reperfusion. **Methods.** Rabbits were pre-treated orally with selective BLT1 (BIIL 284, 0.1 mg/kg) and/or PAF (WEB 2086, 10 mg/kg) receptor antagonists. Whole blood chemiluminescence, a measure of ROS generation, tissue oedema and myeloperoxidase activity, a marker of PMN accumulation, were assessed. **Results.** In the lung, PMN accumulation was reduced by 47 and 36% by BIIL 284 and WEB 2086 compared to vehicle-treated rabbits, respectively, whereas the inhibitory effect of combined drug administration was 96 ± 2% ($P<0.01$). Additive inhibitory effects of combined PAF and LTB_4 antagonists administration were observed for lung tissue oedema (53 ± 5%, $P<0.001$) and whole blood ROS generation (65 ± 2%, $P<0.01$). Similar inhibition of PMN accumulation and tissue oedema were observed for the liver and the intestine. **Conclusion.** Our results support that LTB_4 and PAF play a critical role in the regulation of PMN accumulation at remote sites following hind limb ischemia and reperfusion. The inhibitory effect on PMN trafficking is accompanied by a reduced systemic production of ROS by leukocytes. Supported by the Canadian Institutes of Health Research.

25 Evidence-Based Review of the Natural Health Product Hops (Humulus lupulus)

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Purpose: The Canadian public's interest in complementary and alternative medicine (CAM) has led to the need for a reliable source of CAM information. The CAMline website (www.camline.ca) was developed to meet this need. The CAMline website provides in-depth evidence-based reviews of natural health products. The purpose of this project was to assess the safety and efficacy of the natural health product hops and to write an evidence-based review. **Methods:** A MEDLINE search was conducted and textbooks were reviewed to gather information. The indications, adverse effects and drug interactions were categorized according to levels of evidence defined by CAMline. **Results:** The indication with the most evidence to date was found to be insomnia/sedation where at least six trials have found that valerian and hops used in combination may have some CNS effects, including possible positive influences on sleep. However, quality randomized controlled trials are required in order to determine the effect of hops alone for this indication. As well, although preliminary data have shown that the most common adverse effect associated with external exposure to hops is contact dermatitis, the relevance of this for those ingesting hops is not clear and further research is required to assess the safety of hops as an herbal preparation. **Conclusion:** In conclusion, an evidence-based review of the literature available for the natural health product hops indicates that further research is required before hops can be routinely recommended for any specific indication.

26 No Effect of the Flaxseed Lignan, Secoisolariciresinol Diglucoside, on Triglyceride Levels in a Hypertriglyceridemic Rat Model

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Background: Human clinical studies indicate possible flaxseed effects on triglyceride homeostasis. The flax component mediating possible changes in triglyceride levels is unknown. **Purpose:** Our study's purpose was to investigate the effects of the flaxseed lignan, secoisolariciresinol diglucoside (SDG), on triglyceride homeostasis in a hypertriglyceridemic rat model. **Methods:** Male Sprague-Dawley rats (n = 10) fed 10% fructose in water were dosed daily with SDG at 0 (vehicle), 4.4 or 8.8 μmol/kg body weight by oral gavage for two weeks. An additional rat group (control) was provided tap water and underwent daily sham (vehicle) oral gavage. Baseline (saphenous venepuncture) and 2 week (cardiac puncture) blood samples were taken (isoflurane) and analyzed for triglycerides, phospholipids and non-esterified fatty acids using standard diagnostic kits. After the 2 week blood sample, rats were killed humanely and livers and retroperitoneal fat were removed, weighed and stored for analysis. Real time RT-PCR assays assessed hepatic mRNA levels of two key transcription factors regulating triglyceride homeostasis, SREBP-1c and PPAR-α. **Results and Conclusions**: 10% fructose in water significantly increased serum triglyceride values. In the SDG 0 μmol/kg group, fructose decreased hepatic PPAR-α mRNA levels to 66% of control and increased SREBP-1c mRNA levels ~16-fold relative to control. SDG caused no significant changes in serum and hepatic triglycerides, serum non-esterified fatty acids and phospholipids, rate of weight gain, hepatic and retroperitoneal fat tissue weights, and hepatic mRNA levels of SREBP-1c or PPAR-α. In conclusion, SDG had no effect on triglyceride homeostasis in our rat model of hypertriglyceridemia.

27 Determination of Hypoxoside and Quality Control of Commercial Formulations of African Potato (Hypoxis hemerocallidea) using Capillary Zone Electrophoresis

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Purpose: Hypoxoside is a norlignan di-glucoside present in the corms of African Potato (AP), *Hypoxis hemerocallidea*, a popular African traditional medicine used for its nutritional and immune boosting properties. A highly specific analytical method involving Capillary Zone Electrophoresis (CZE) was developed for the quantitative analysis of hypoxoside, a major constituent in AP and this method was subsequently applied for the quality control of commercially available AP products. This technique has specific advantages over commonly used techniques such as HPLC, particularly with respect to the use of relatively non-toxic aqueous buffers thereby obviating the need for more expensive and relatively toxic HPLC grade organic solvents. **Methods:** A CZE method was developed and validated for the determination of the marker compound, hypoxoside, using a 25 mM sodium tetraborate buffer (pH 9.2). A detection wavelength of 260 nm was used and samples were loaded hydrodynamically onto an uncoated fused silica capillary (71cm x 50 µm i.d). Sulfafurazole (SF) was used as an internal standard. **Results:** The electrophoretic separation of hypoxoside and SF were achieved within 12 min. Linearity of the method was established throughout the range of 5-60 µg/ml and the assay provided a high degree of accuracy (100 ± 3%). The recovery of the method was found to be 100 ± 5% and the % RSD of the intraday and interday precision was better than 5.2 and 2.5% respectively. The limits of detection (LOD) and quantification (LOQ) were calculated to be 0.5 and 2 µg/ml respectively. **Conclusion:** This method was used for the assay and quality control of commercially available products containing AP. In addition, the method was shown to be stability-indicating, confirmed from stress testing of hypoxoside.

28 ANTI-INFLAMMATORY ACTIVITY OF VARIOUS EXTRACTS OF *GARCINIA MANGOSTANA* BY INHIBITION OF NITRIC OXIDE PRODUCTION FROM MOUSE MACROPHAGE RAW 264.7 CELL LINE.

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Purpose: Inflammation is a body's response to the damage caused to its cells by infectious, chemical and physical stimuli. Biological stimuli of inflammation include endotoxin (Lipo-polysaccride) released by gram-negative bacteria. The inflammatory cascade initiated by LPS results in release of various potent inflammatory mediators such as TNF-α, IL-1, IL-12 and nitric oxide by macrophage cells. In our present study we demonstrated the ethyl extract and acetone extract prepared from pericarp of *Garcinia mangostana* showing down regulation of nitric oxide production by murine macrophage RAW 264.7 cell line on stimulation with purified LPS. Methodology: The murine macrophage 264.7 cell lines was procured from ATTC and cultured by standard protocol. The nitric oxide estimation was performed by Griess assay. Results: Our experiment shows concentration ranging from 0.906µg/ml to 15.625µg/ml of ethyl acetate extract and 3.906µg/ml to 31.125µg/ml of acetone extract prepared from pericarp of *Garcinia mangostana* significantly inhibited nitric oxide production by murine macrophage 264.7 cell line when stimulated by 5µg/ml of purified LPS. Conclusion: We conclude from our results that ethyl extract and acetone extract prepared from the pericarp of *Garcinia mangostana* showing potent anti-inflammatory activity by inhibiting the nitric oxide production which is giving us a lead towards new drug development for treatment of inflammatory condition. The knowledge of exact mechanism of action needs further investigation.

29 Novel use of an *in vitro* method to predict the stability of block copolymer based nano-containers

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Purpose: To design an *in vitro* experiment that can assess the stability of polymeric micellar formulations of hydrophobic drugs such as cyclosporine A (CyA). **Methods:** Poly(ethylene oxide)-*b*-poly(ε-caprolactone) (PEO-*b*-PCL) *block* copolymers with respective PEO and PCL molecular weights of 5000 and 13000 g/mol were assembled to polymeric nano-containers and used for the encapsulation of CyA by a co-solvent evaporation method. Particles were characterized for their average diameter and CyA loading efficiency using light scattering and HPLC, respectively. Measurement of the unbound drug fraction was used to compare the stability of PEO-*b*-PCL formulations of CyA with 0.082 (low content, LC) and 0.229 mg/mg (high-content, HC) drug to polymer loading, to that of commercially available intravenous CyA (Sandimmune®). Blood was collected from Sprague-Dawley rats by cardiac puncture. Red blood cells (RBC) separated from rat blood samples were re-suspended in either Sørenson's phosphate buffer (pH 7.4) or rat plasma and incubated in quadruplicate with the polymeric or commercial CyA formulations (at a final concentration of 5 µg CyA/mL in blood) at 37°C for one hour. Samples of whole blood and centrifuged plasma or buffer were analyzed for CyA by HPLC. The unbound fraction of CyA (fu) was calculated by equations published by Schuhmacher *et al*. (J Pharm Sci, 2000, 89: 1008-21). The level of significance was set at p=0.05. **Results:** The CyA fu as part of Sandimmune® formulation was 45.6%. The fu of CyA from LC nanocarriers was significantly lower (36.1%) than that fu observed for Sandimmune®. The HC nanocarriers had fu of only 10.6%, which was significantly lower than the unbound fraction for both Sandimmune® and LC nanocarrier groups. **Conclusion:** Nanocarriers based on PEO-*b*-PCL copolymers are capable of changing the protein binding pattern of CyA. Higher drug contents can stabilize the encapsulation of CyA in the polymeric nanocarrier further. The plasma protein binding method has potential utility as a predictor of *in vivo* micellar stability.

30 A Comparison of the Quality of Published Articles Sponsored by Pharmaceutical Companies to Those Prepared by Independent Research Institutions.

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Purpose: To determine whether scientific quality of pharmaceutical company-sponsored (PCS) articles/scientific meeting abstracts differs from those sponsored by independent research institutions (non-pharmaceutical company; NPC). **Methods:** The quality scores of PCS vs NPC articles was compared in 27 therapeutic areas (TAs). Scores were obtained through the Thomson Message Mapping System (TMMS), using independently validated processes for evaluators to assess strengths/weaknesses of methodology, statistics, results, discussion, and analysis. The algorithm calculates a quality score for each article. Comparisons of mean quality scores were made using an unpaired t-test. **Results:** 11,534 articles/scientific abstracts were analyzed: 4,176 PCS; 460 NPC; and 6,898 no specific sponsorship. There were no differences (N.S.) between mean quality scores for PCS vs NPC in 20 TAs. A difference ($p<0.05$) in favor of PCS articles was observed in 5 TAs (climacteric/menopause, hepatitis B, osteoarthritis, pertussis, smoking cessation) and in favor of NPC articles in 2 TAs (ADHD, ulcerative colitis). Across all 27 TAs a difference ($P= 0.0064$) was found in favor of PCS vs NPC. A difference ($p= <0.0001$) was also found in favor of PCS vs all other articles. **Conclusion:** For 74% of TAs, there was no difference between the PCS and NPC articles with respect to mean quality scores; PCS published information was of quality similar to that of independent research. Overall, across a broad range of TAs, PCS sources were generally of superior quality than NPS; these findings provide a new insight into recent controversies regarding the potentially incomplete publication of research by pharmaceutical companies.

31 The Effect of Infliximab on Hepatic CYP Enzymes and Pharmacokinetics of Verapamil in Adjuvant Arthritis Rats

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Purpose. Clearance of verapamil is reduced under inflammatory conditions due to increased protein binding and inhibition of hepatic metabolism. Infliximab reduces pro-inflammatory mediators and has been shown to reverse the effects of inflammation on sotalol response in the rat. Since inflammation is also implicated in reduced drug clearance we hypothesized that infliximab treatment would reverse the effects of inflammation on drug metabolism and clearance. We examined hepatic cytochrome P450 content and pharmacokinetics of verapamil in rats treated with infliximab during the pre-arthritic (pre-AA) phase of adjuvant arthritic (AA) disease. **Methods**. Pre-AA was induced in male Sprague-Dawley rats with a tail base injection of *M. butyricum*. Animals were monitored for symptoms of arthritis, and levels of the pro-inflammatory mediators serum nitrite and C-reactive protein (CRP). On day 6, rats were administered single sc dose of infliximab (10 mg/kg). On day 14, a single iv dose of racemic verapamil (2 mg/kg) was administered, and S- and R-verapamil concentrations were determined by stereospecific HPLC. Hepatic CYP content and verapamil protein binding were also measured. **Results**. Serum nitrite levels were significantly elevated in pre-AA and AA phases of disease. Infliximab treatment did not suppress nitrite levels or reverse the effects of AA on pharmacokinetic indices. Total CYP and CYP3A contents, however, were significantly restored in AA rats treated with infliximab. **Conclusion**. Infliximab partially restores hepatic CYP enzyme levels, but not sufficiently to reverse the inflammation-induced reductions in verapamil clearance and free fraction.

32 **Pharmacokinetics and Biodistribution Profiles of the Micelle Forming Block Copolymer Poly (ethylene glycol)-block-Poly(caprolactone) Following Systemic Administration**

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PURPOSE: At present drugs relying on block copolymer micelles for formulation are under clinical trial evaluation for the treatment of various cancers. However, only a few studies have examined the in vivo fate of the copolymer micelles and unimers. In addition, the effect of the copolymer dose administered on the in vivo behavior of these systems remains relatively unexplored. Further in vivo evaluation of copolymer unimers and micelles will aid in advancing micelles as a more viable drug formulation strategy. METHODS: Poly (ethylene glycol)-b-poly (caprolactone) (MePEG-b-PCL) copolymers were synthesized and characterized. The physico-chemical properties of micelles formed from this series of copolymers were also evaluated. 3H-labeled MePEG5000-b-PCL5000 micelles were i.v. administered to Balb/C mice at copolymer doses of 250mg/kg, 2.5mg/kg and 0.2mg /kg in order to examine the distribution kinetics of 1) copolymer assembled as thermo-dynamically stable micelles 2) copolymer assembled as thermodynamically unstable micelles and 3) copolymer single chains, respectively. The biodistribution of the copolymer in the major organs was investigated and the main pharmacokinetic parameters were determined. RESULTS: The copolymer assembled as micelles is found to be effectively trapped within the plasma. The formation of micelles has also been found to inhibit the cellular uptake of this copolymer in the main elimination organs. CONCLUSION: The micelle system formed from MePEG5000-b-PCL5000 copolymer was found to be a kinetically stable drug delivery system with a long circulation lifetime. Therefore, if a drug is well-retained within the micelle core, this micelle system could serve as a true delivery carrier leading to a prolonged circulation lifetime for the encapsulated drug.

33 DISSOLUTION STUDY OF KANAMYCIN FORMULATED IN A TRANSDERMAL PATCH

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Purpose The present work focuses on the development of a transdermal patch containing kanamycin, as a complementary treatment for mycetoma due to Actinomadura madurae. **Methods** The drug was included in an Eudragit-E-100 matrix, forming a patch by pouring a solution in a mold and evaporating the solvent. Patches were then covered with an occlusive layer of ethyl cellulose. Triacetin was used as plasticizer. Two types of patches were prepared: i) Free kanamycin, ii) Kanamycin adsorbed onto silica gel. Patches were evaluated by their thickness, rupture force, rupture distance, bioadhesivity, bioadhesivity when dampened, water uptake, gaseous interchange and release rate studies. **Results** The composition of the optimal patch was as follows: Ethyl cellulose 24.4%, Eudragit-E-100 48.8%, triacetin 14.6%, erythromycin 2.4%, kanamycin adsorbed onto silica gel 9.8%. It was shown to have the following properties: Thickness 0.574$\pm$0.08 mm, rupture force 9314$\pm$350 $\vec{g}$, rupture distance 9.09+1.5 mm, bioadhesivity 86.67+31 $\vec{g}$, bioadhesivity when dampened 32.8+7.82 $\vec{g}$, water absorption after 2h: 0.029+0.014 g, gaseous interchange 3.73+2.87g/hm^2. The dissolution studies indicated that, when kanamycin was in its free form, 7.2% was released after 24h, and 3.2% when it was adsorbed (in both cases, the amount was quite enough to produce a 2.3 cm inhibition diameter in an antibiogram assay). **Conclusion** The patch described in the results showed good technological properties to be used as a release system. Permeation studies will be performed with this patch in healthy skin and in skin affected by *Actinomadura madurae*.

34 Cytotoxicity of magnetite nanoparticles surface-modified with polyethylene glycol triblock copolymers

Framin Mark, Dr. Urs O. Häfeli

Purpose The objective of this study was to investigate the toxicity of magnetite nanoparticles surface-modified with polyethylene glycol (PEG) triblock copolymers and of the polymer itself on prostate cancer cells (PC3) and human umbilical vein endothelial cells (HUVEC). We hypothesized that magnetite coated with longer tail block lengths would be less toxic. The overall goal is to use biocompatible and non-toxic magnetic particles as a potential magnetic drug delivery vehicle for in vivo applications. **Methods** Magnetite dispersions were prepared by coating the surfaces of magnetite nanoparticles with a diameter of 8.8±2.7 nm with a hydrophilic triblock copolymer having two PEG endblocks and containing controlled concentrations of carboxylic acid functional groups (PEG-COOH-PEG) in the central segment. An in vitro 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to assess the cell viability. Confocal microscopy was applied to follow the intracellular fate of magnetic particles at different time points. **Results** All pure triblock copolymers as well as the coated magnetite nanoparticles exhibited concentration dependent toxic effects. The pure polymers, however, were several folds more toxic than the magnetic nanoparticles. Within each group, the shorter the PEG tail lengths, the significantly more toxic they were (15K < 5K < 2K < 0.75K). Confocal microscopy confirmed that the polymer was more toxic than the magnetite nanoparticles. **Conclusion** Magnetic nanospheres coated with PEG triblock copolymers of 5K and 15K containing 20-50% of iron oxide seem relatively biocompatible and thus might be useful for magnetic drug delivery. NB. This project was funded by Merck Frosst to the Summer Student Research Program, Faculty of Pharmaceutical Sciences, UBC.

35 A Sensitive and Specific Liquid Chromatography/Mass Spectrometry Method for Quantitative Analysis of Cucurbitacin I in Non-Biological Samples and Rat Plasma.

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Purpose: to develop a liquid chromatography/mass spectrometry (LC/MS) method for quantitative analysis of cucurbitacin I, anti-cancer agent that inhibit JAK2/STAT3 signaling pathway, in non-biological solvents and rat plasma samples. **Methods:** Standard samples of cucurbtiacin I were prepared from stock solution of the compound (1mg/mL) in methanol. 4-hydroxybenzophenone was used as an internal standard (I.S.). Extraction of cucurbitacin I and I.S. from rat plasma was performed using acetonitrile/dichloromethane. LC-MS analyses were performed using Waters Micromass ZQ™ 4000 spectrometer coupled to Waters separations module. Chromatographic separation was achieved using C18 3.5 µm (2.1×50 mm) as the stationary phase and a mixture of acetonitrile: 1% formic acid in water with the ratio of 20:80 and linear gradient to 40:60 for 13 minutes at constant flow rate of 0.2 mL/min as mobile phase. Mass spectrometer was operated in negative ionization mode and analytes were quantified with single ion recording (SIR) at *m/z* 559 for cucurbitacin I and *m/z* 196 for I.S. **Results:** The standard curves over the concentration range of 5-10000 ng/mL for non-biological samples and 10-1000ng/mL for rat plasma samples were validated, yielding calibration curves with $R^2 > 0.99$. Intra- and inter-day coefficient of variation and mean intraday error were less than 20% at plasma concentration extending from 10-1000 ng/mL. **Conclusion**: The developed assay is sensitive and highly specific for quantitative analysis of cucurbitain I and it can be used for pharmacokinetics studies.

36 A validated high-performance thin-layer chromatographic method for determination of gatifloxacin from polymeric nanoparticles

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PURPOSE: Development and validation of an instrumental high-performance thin layer chromatographic (HPTLC) method for quantification of Gatifloxacin from biodegradable polymeric nanoparticles. **METHODS:** The method employed TLC aluminium plates pre-coated with silica gel 60F-254 (20 cm x 10 cm with 200 µm thickness, E Merck, Germany) as the stationary phase. The separation of gatifloxacin was achieved by employing a mobile phase consisting of n-propanol-methanol-strong ammonia (5:1:0.9 v/v/v). Linear ascending development was carried out in twin trough glass chamber saturated with mobile phase at room temperature and the mobile phase was run up to 8 cm. Spectrodensitometric scanning and analysis was performed on Camag TLC scanner III in absorbance mode at 292 nm. The source of radiation utilized was deuterium lamp. **RESULTS:** The system was found to give compact spots for the model drug (Rf value of 0.48 ± 0.004). The polynomial regression data for the calibration plots showed good linear relationship with $r^2 = 0.9953 \pm 0.0002$ in the concentration range of 400-1200 ng. The mean value (± S.D) of slope and intercept were found to be 9.6638 ± 0.0491and 956.331 ± 27.67137 respectively. The developed HPTLC method was validated as per the ICH Guidelines for precision, accuracy, robustness and ruggedness. The limits of detection (LOD) and quantification (LOQ) were found to be 2.73 ng and 8.27 ng respectively. Average % recovery (± % RSD) recorded was 100.24% ± 0.031. Mean concentration of Gatifloxacin detected from polymeric nanoparticles was well within the limits (± 5% of the labeled content of the formulations). **CONCLUSIONS:** The statistical analysis proves that the HPTLC method developed for quantification of gatifloxacin from polymeric nanoparticles is simple, sensitive, reproducible, selective and robust. The proposed method can be employed for routine estimation of gatifloxacin from colloidal carrier systems.

37 Preliminary assessment of interactions between selected alcoholamines and model skin sebum components

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PURPOSE. The aim was to evaluate the interactions between the components of model skin sebum and selected alcoholamines proposed for cleansing activity in the pilosebaceous unit area. **MATERIALS AND METHODS.** The rate and depth of penetration into the lipophilic bead imitating pilosebaceous unit lumen was measured using optical and multiple light scattering analysis devices for alcoholamines penetration activity assay. The activity differentiation of 0.5% aqueous alcoholamines solutions with a potential cleansing effect on the pilosebaceous unit was performed. **RESULTS.** The depth of aminomethylpropanol penetration increased from 0.080 mm after 15 min to 3.049 mm after 72 h. The depth of aminomethylpropendiol penetration increased with time from 0.148 to 4.064 respectively, of diisopropanolamine from 0.481 to 4.626, triethanolamine from 0.236 to 4.342, triisopropanolamine from 0.275 to 2.392 and trometamol from 0.338 to 4.580. The products of alcoholamines reaction with the model skin sebum components are easily dispersed in water. **CONCLUSIONS.** The rate of alcoholamines reaction with the model skin sebum depends on the alcoholamine, being the highest in the case of diisopropanolamine, decreasing to minimum for triisopropanolamine. Selected alcoholamines would be applied for in vivo research.

38 Validation of a liquid chromatography tandem mass spectrometry assay method for the determination of nateglinide in human plasma

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Purpose. Development and validation of an electrospray negative ion LC/MS/MS assay method for the quantitative determination of nateglinide in human plasma. **Methods.** Nateglinide and the internal standard (d_5-nateglinide) were extracted from 0.1 mL plasma by protein precipitation. Nateglinide was chromatographically separated on a ProntoSIL120-C_{18}-EPS (4.6 × 50 mm, 3 μm) column using isocratic elution with 20/80 (v/v) 0.1% formic acid/acetonitrile as mobile phase at a flow rate of 1.0 mL/min. Detection and quantitation were carried out by ESI-MS/MS monitoring the transitions m/z 316.2 to m/z 164.1 (nateglinide) and m/z 321.0 to m/z 169.0 (d_5-nateglinide). **Results.** The method was validated over a concentration range from 0.10 to 10.00 μg/mL using a linear calibration curve with a weighing factor of 1/x. Inter-batch precision (%CV) for standards ranged from 1.9 to 2.7. Inter-batch accuracy (%RE) ranged from -2.4 to 1.6, indicating an acceptable goodness-of-fit. Inter-batch assay precision (%CV) for quality control samples, based on individual batch means, ranged from 2.6 to 3.8 over four concentration levels, 0.10, 0.30, 4.00 and 9.00 μg/mL. Inter-batch assay accuracy (%RE) results for quality control samples ranged from -0.6 to 2.6 over four concentration levels. The mean correlation coefficient was 0.9997±0.0002. The mean assay recovery for nateglinide was 79.0±2.8%. Freeze/thaw stability was established at -40°C and -70°C for three cycles at each temperature. **Conclusions.** An accurate and rapid analytical assay was developed and successfully applied to the measurement of nateglinide in human plasma samples.

39 Qualification of a liquid chromatography tandem mass spectrometry assay method for the determination of scopolamine in human plasma

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Purpose. Qualification of an LC/MS/MS assay method for the quantitative determination of scopolamine in human plasma using atmospheric pressure electrospray ionization in positive ion mode. **Methods.** Scopolamine and the internal standard (atropine) were extracted from 0.20 mL human plasma by deproteination followed by liquid/liquid extraction using chlorobutane as extraction solvent. The analyte was chromatographically separated on a ACE 3 AQ (4.6 x 50mm, 3.0µm particle diameter) column using gradient elution with 60% acetonitrile to 40% 1 mM ammonium acetate as initial mobile phase followed by LC/MS/MS analysis. Detection and quantitation were carried out by ESI-MS/MS monitoring the transitions m/z 304.2 to m/z 138.1 (scopolamine) and m/z 290.2 to m/z 124.2 (atropine). **Results.** The method was validated over a concentration range from 0.05 to 10.00 ng/mL using a linear calibration curve with a weighting of 1/x. Inter-batch precision (%CV) for standards ranged from 2.3 to 11.0. Inter-batch accuracy (%RE) ranged from -5.9 to 4.7, indicating an acceptable goodness-of-fit. Inter-batch assay precision (%CV) for quality control samples, based on the individual batch means, ranged from 2.4 to 7.4 over four concentration levels. Inter-batch assay accuracy (%RE) results for quality control samples ranged from -2.6 to 3.7 over four concentration levels. The mean (n = 4) correlation coefficient was 0.9984 ± 0.0021. In-process stability was established for 10 hours. **Conclusions.** An accurate, sensitive and rapid analytical assay was developed and successfully applied to the measurement of scopolamine in human plasma samples.

40 Validation of a liquid chromatography tandem mass spectrometry assay method for the determination of levetiracetam in human plasma

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Purpose. Validation of an LC/MS/MS assay for the quantitative determination of levetiracetam in human plasma using atmospheric pressure electrospray ionization in positive ion mode. **Methods.** Levetiracetam and the internal standard (d_5-levetiracetam) were extracted from 50.00 µL plasma by protein precipitation. The analyte was chromatographically separated on a Zorbax Eclipse XDB-C8 (4.6 x 50mm, 3.5µm particle diameter) column using gradient elution with 95:5 0.1% formic acid in water and 100% methanol (v/v) as initial mobile phase followed by LC/MS/MS analysis. Detection and quantitation were carried out by ESI-MS/MS monitoring the transitions m/z 171.0 to 126.0 (levetiracetam) and m/z 176.0 to 131.0 (d_5-levetiracetam). **Results.** The method was validated over a concentration range from 0.10 to 25.00 µg/mL using a linear calibration curve with a weighing factor of $1/x^2$. Inter-batch precision (%CV) for standards ranged from 1.9 to 3.7. Inter-batch accuracy (%RE) ranged from -4.2 to 5.0, indicating an acceptable goodness-of-fit. Inter-batch assay precision (%CV) for quality control samples, based on individual batch means, ranged from 1.3 to 2.6 over four concentration levels, 0.10, 0.30, 10.00 and 20.00 µg/mL. Inter-batch assay accuracy (%RE) results for quality control samples ranged from -2.9 to 4.2 over four concentration levels. The mean (n=5) correlation coefficient was 0.9991 ± 0.0002. The mean assay recovery for levetiracetam was 88.8 ± 4.4. Freeze/thaw stability was established at -40°C and -70°C for three cycles at each temperature. **Conclusions.** An accurate and rapid analytical assay was developed and successfully applied to the measurement of levetiracetam in human plasma samples.

41 MICROENCAPSULATION OF THE SOLID DISPERSIONS OF GRISEOFULVIN— AN APPROACH TO OBTAIN A CONTROLLED AND COMPLETE RELEASE.

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Purpose: An attempt was made to improve the dissolution, of the poorly water soluble drug, Griseofulvin, by microencapsulation of solid dispersion using ethyl cellulose. **Methods**: The solid dispersions were prepared by a] fusion method, using PEG-4000 and PEG-6000, b] co precipitation method, using PVP (M.W. 50,000) and c] Physical mixtures. The solid dispersions (10% drug in PEG-4000) were microencapsulated with ethylcellulose, using coacervation phase separation technique by temperature change method. Microcapsules of plain drug and 10% griseofulvin in PEG-4000 solid dispersion were prepared in 1:1, 1:2 & 2:1 coat to core ratios. **Results:** Microcapsules consisting of 1:1 coat to core ratio, were found to have maximum drug content & showed controlled and uniform drug release pattern. Spectrophotometric evaluation showed absence of carrier-drug interaction. The microcapsules Griseofulvin in solid dispersion released 93.6% in 450 minutes as compared 17.2% in 480 minutes for microcapsules of drug alone. The percentage of unreleased drug plotted against time, illustrated first order kinetics. Stability studies conducted at various temperatures over a 5 week period found the microcapsules stable. The Microphotographs evidenced spherical and uniform microcapsules (average 39.77µ.) **Conclusion:** The complete and controlled release of poorly soluble drug was achieved. In-vivo studies are underway.

42 Colon targeted delivery of multiple coated 5-aminosalicylic acid tablets using Citric acid and Eudragit E 100.

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Purpose: To evaluate the role of Citric acid (CA) and Eudragit E 100 in delivering multiple coated 5-aminosalicylic acid (5-ASA) tablets intact to the colon. **Methods:** Tablets (diameter, 10.5 mm; weight, 300 mg) containing 66.67 % 5–ASA and 10 % CA prepared wet granularly. The aim achieved by imparting compression coat of HPMC 6 cps and Avicel® PH 112 (ratio, 1: 2) on them (diameter, 12.9 mm; weight, 440 mg) following sequential coat of Eudragit E 100 (diameter, 13.7 mm; weight, 466 mg), HPMC 6 cps (diameter, 14.3 mm; weight, 485 mg) and Eudragit S 100 (diameter, 15.2 mm; weight, 515 mg) respectively. To mimic gastric, duodenal, ileac and ascending colon transits of 5-ASA from final coated tablets, sequential in vitro dissolution (total time, 8 h; lag time, 5 h) studied using 0.1 N HCl (pH, 1.2) and phosphate buffers (pH, 6.0; 7.2, 6.4) respectively, colon targeted delivery in vivo by roentgenography. **Results:** Tablet's intactness observed in 0.1 N HCl, in phosphate buffer (pH; 6.0, except pH; 7.2). At pH 6.4 buffer, 5-ASA release attributed by external buffer's imbibitions through Eudragit E 100 coat dissolving CA. Its premature release from tablets prevented by insoluble Eudragit E 100 coat at terminal ileum pH, confirmed in vivo by roentgenography. **Conclusion:** CA and Eudragit E 100 played key role for colon targeted release of multiple coated 5-ASA tablets. Roentgenography helps to prove in vivo delivery.

43 Amphiphilic gels as a potential carrier for topical delivery in treatment of Psoriasis

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Purpose: In this study an attempt was made to develop Amphiphilic gels as novel carriers solely consisting of non-ionic surfactants bearing cyclosporine A, a drug used in the treatment of Postural psoriasis. Amphiphilic gels were characterized for microstructure, gelation temperature. In-vitro drug release was performed and suitable formulations were evaluated for antipsoriatic activity using mouse tail test. **Methods**: Gels consisting of cyclosporine were prepared by mixing the solid gelator (Spans) with the liquid phase (liquid Tweens) and heating them at 60°C to form a clear isotropic sol phase. The sol phase was cooled to form an opaque semisolid at room temperature. Gel microstructure was examined by microscopy while the gelation temperature was measured by differential scanning calorimetry (DSC). In vitro release of amphiphilic gels were evaluated using rat skin mounted in a Franz diffusion cell and it was further evaluated in vivo using a mouse tail test. This method uses topical treatment of a mouse tail with anti-psoriatic drugs to enhance orthokeratotic cell differentiation in the epidermal scales. This characteristic is used for direct measurement of drug efficacy in an animal model. **Results**: Gel microstructures consisted mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, formed a 3D network throughout the continuous phase. At temperatures near the skin surface temperature, the gels softened considerably. The release studies also supported drug release from the gel and accumulation in the dermis. This delivery vehicle of cyclosporine showed morphometric quantification of the conversion of parakeratotic into orthokeratotic regions in mouse tail scales. **Conclusion**: The use of Amphiphilic gels was demonstrated as an ideal vehicle for topical use of cyclosporine and was corroborated by histological studies in animals.

44 **Cyclodextrin as Enhancemer for Transdermal Delivery of Rofecoxib**

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Purpose: The purpose of the study was to determine the in vitro as well in vivo efficiencies of 1% carbopol hydrogel different preparations containing the rofecoxib (R), a COX–2 inhibitor anti-inflammatory drug with β-cyclodextrin (βCD). The release of plain drug was then compared with release of from trans dermal gel containing physical mixture of drug and βCD, inclusion complex of drug and βCD obtained by kneading method and in situ complex of drug and βCD obtained by reacting the drug and βCD within the gel. All solid inclusion complex abstained were then characterized by XRD, IR DSC and SEM, where as the in situ complex formation was evidenced only by release and permeation studies. Although many other derivative of CDs such as HP-βCD and R-βCD are better skin permeating enhancers but in this study βCD was employed because of ease of availability and low cost. **Method**: Solid inclusion complex was prepared by kneading method. Gel formulations were prepared by incorporating pure drug, physical mixture, inclusion complex and separately drug and βCD dispersed in propyleneglycol (to get in situ complex) to the gel base. Prepared gels were subjected to physical evaluation for its viscosity, pH and drug content. In vitro drug release and in vitro drug permeation experiments were carried out on Franz Diffusion Cell using cellophane membrane and human cadaver skin respectively. Selected formulations were evaluated for anti-inflammatory activity using the carrageenin –induced paw oedema in rats. **Results:** DSC and IR studies indicate the complexation where as X-RD studies indicate conversion of crystalline drug to porous, spherical and fluppy structures. The release rates when compared were found to be highest with gel containing inclusion complex than the gels containing pure drug, physical mixture and the in situ complex. A lag period was observed with all formulations. Physical stability was performed by freeze thaw cycling. The complex containing in situ complex was more stable. **Conclusion:** the overall data suggest that the prepared hydrogel of rofecoxib is highly efficient transdermal vehicle for the delivery of the drug at the site of action.

45 Versatile depo-carrier for controlled protein delivery

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Purpose: Therapeutic peptides and proteins demand an effective delivery system due to chemical and structural complexities. **Methods:** In the present study, IFN- α, model protein was stabilized by conjugation with methoxy - polyethylene glycol (mPEG, MW 5000D) and characterized. In process stability studies of pegylated IFN - α (IFN - α - mPEG- 5000) exhibited better stability when exposed to chloroform: diethyl ether (1: 1 ratio) mixture as well as variable vortexing time as compared to native IFN – α. Pegylated IFN- α were formulated as multivesicular liposomes (MVLs) for utilization as a delivery system for optimum use. MVLs were prepared by modified reverse phase evaporation method utilizing double emulsification technique followed by evaporation of organic solvents from chloroform-ether spherules suspended in water. Three sets of MVLs were prepared by varying lipid ratio. Formulated PEG-IFN- α MVLs was then characterized for shape, size, vesicle count, encapsulation efficiency and *in-vitro* release rate. **Results:** MVLs prepared were in the size range of 15-20 µm. Entrapment efficiencies of three formulations were in the range of 65-78%. *In vitro* release profile of IFN - α mPEG- 5000 containing MVLs in the PBS (PH-7.4) showed initial burst release with sustained and nearly complete release over a period of one week. In contrast plain IFN α -mPEG 5000 showed higher initial burst release i.e. 35% followed by almost complete loss of protein. **Conclusion**: Thus, it is evident from this study that MVLs could be a promising delivery system for controlled delivery of proteins together with protein modification approach i.e. pegylation.

46 **COMPARATIVE STRUCTURAL AND FUNGICIDAL STUDIES OF MONO-METHYL PHTHALATE AND ITS TIN(IV) DERIVATIVES.**

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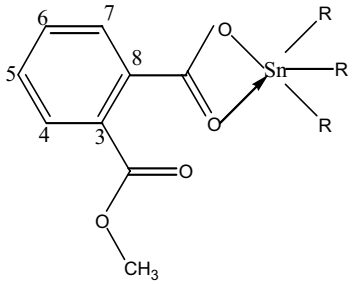
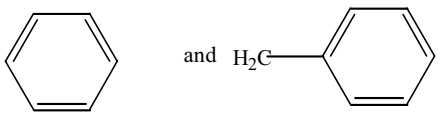
PURPOSE: The aim of the work is to synthesize, characterize and investigate the fungicidal properties of some organotin(IV) compounds with Mono-methyl phthalate. **METHODS**: The compounds were characterized by various spectroscopic techniques including ^{1}H- ^{13}C-^{119}Sn-NMR, FT-IR and ^{119}Sn Mössbauer studies. **DISSCUSSIONS**: On the basis of the spectroscopic techniques all the complexes show penta coordination with trigonal bipyramidal environment around the tin. The synthesized compounds were tested against a number of plant pathogenic fungi. The fungicidal data reveals that the tri-phenyltin(IV) compound proved to be powerful fungicide. Comparison between the fungicidal activity of the tri-alkyltin(IV) compounds show that the tri-phenyl tin(IV) complex is most active against all plant pathogens, rest of the complexes also exhibit significant antifungal activity but less than the former one.



Tri-organotin(IV) complexes

where R=CH_3, CH_2CH_3, $CH_2CH_2CH_2CH_3$,



47 Growth, Extraction and Isolation of Novel Jadomycins

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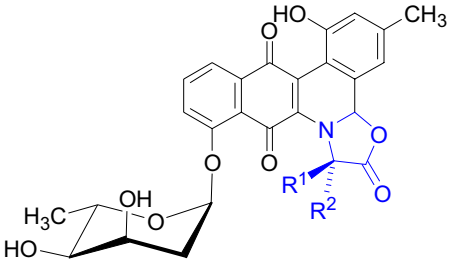
Purpose: The Jadomycins are modified angucycline antibiotics. Previous studies of angucycline anticancer antibiotics show activity against human carcinoma cells. These potential anticancer agents are prepared by fermentation and are isolated by a series of chemical isolation techniques. The objective of this research project was to feed two commercially available, non-natural amino acids (*R*- and *S*-phenylglycine) to *Streptomyces venezuelae* ISP5230, isolate and purify novel Jadomycins and characterize the compounds using mass spectrometry and N MR spectroscopy.



Analogues: *R*-phenylglycine: R^1 = Ph; R^2 = H, *S*-phenylglycine: R^1 = H; R^2 = Ph

Methods: *Streptomyces venezuelae* ISP5230 bacteria were fed *S*-phenylglycine or *R*-phenylglycine and shocked with ethanol to induce production of the Jadomycin B analogues; Jadomycin B analogues were isolated and purified by organic extraction and column chromatography; Isolated compounds were characterized by mass spectrometry and solution state Nuclear Magnetic Resonance (NMR) spectroscopy; **Results:** The jadomycins were identified through analysis of electrospray ionization mass spectrometry data of culture extracts, and subsequently by analysis of NMR spectra of purified products. The ESI-MS/MS data clearly showed a molecular ion corresponding to each jadomycin derivative. Characterization by NMR spectroscopy of the isolated *R* and *S* forms confirmed that both amino acids are incorporated into the oxazolone ring, and that stereochemistry is retained throughout the process. **Conclusions:** Incorporation of *S*- and *R*- phenylglycine by *Streptomyces venezuelae* ISP5230 results in production of novel Jadomycin B analogues modified in the oxazolone ring. Cytotoxic testing of these compounds is currently under way. **Acknowledgements:** Funding was provided by the Merck Foundation Summer student program and the Pharmacy Endowment Fund.

48 Pharmacological assessment of three concentration levels of a HA gel for the cicatrization of wounds

Withdrawn

49 Investigation on Niosomes with Zidovudine as a Carrier for Treating HIV Infection

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PURPOSE: Targeting the drugs to HIV infected cells is an important challenge today. Zidovudine an anti HIV drug has poor selectivity to macrophages and manifests dose dependent hematological toxicity. Developing a site specific formulation can minimize these unwanted effects and dose can also be reduced. Hence the present study is designed to investigate niosomes for the transport of antiviral drug Zidovudine. METHODS: Niosomes were prepared by hand shaking and rotary evaporator method using surfactant: cholesterol in the ratio 1:1, 1:3 and 1:5. Formulations were also prepared including Polyethylene glycol (PEG). Prepared niosomes were sonicated using Probe Sonicator. Vesicle size, size distribution was determined using optical microscopy and entrapment efficiency of drug was determined by solvent method. *In vitro* release studies were carried out by dialysis method. RESULTS: Niosomes prepared using rotary evaporator was reproducible when compared with the niosomes prepared by ether injection method. Sonicated vesicles are found to be stable when compared with unsonicated vesicles. The mean size of the vesicles was found to be in the range of 13- 20μ, which is the accepted diameter for niosomal injectable. Increase in the concentration of surfactants increases the drug entrapment by 10%. Similar observations were made with PEG. The drug release from PEG coated niosomes was slow during the initial hours in case of 1:1 and 1:3 ratio. Eighty percentage of drug was released over a period of 24 hours which confirms sustain release. Erratic release was observed from ratio 1:5. CONCLUSION: PEG coated niosomes containing Zidovudine can be an effective carrier for extending the life term of HIV infected patients by reducing the severity of infection at reservoir site.

50 Development and characterization of bi-layered multicomponent system of nimesulide and tizanidine

*Swarnlata Saraf** , Kamlesh Dashora and S. Saraf

Purpose: The rational fixed dose combination of nimesulide (NIM) and tizanidine (TIZ) are available in the market for the relief of inflammations, multiple sclerosis, myofascial pain, neuropathic pain and cerebral spasticity. The aim of this study was to develop a bi-layered system which is able to maintain plasma concentration without the need of frequent dosing and less side effects unlike in case of conventional dosage form and applicable for long term therapy. Till today, none of the sustained multicomponent formulation of NIM and TIZ is available in the market. **Methods**: Bi-layered system composed with matrix of core NIM and TIZ microparticles with additional immediate release layer of NIM complexed of beta-cyclodextrin. Various tablet formulation were prepared with varying concentration of TIZ microparticles and fixed dose of nimesulide. Physical characteristics and *in- vitro* release pattern were studied in alkaline phosphate buffer pH 6.8. Various kinetic models viz., Higuchi and Korsmeyer-Peppas were applied to know drug release pattern. **Results**: The prepared microparticles (ethyl cellulose: drug ratio i.e., 1:1,2:1 and 3:1) were free flowing (angle of repose< 30 degree) with the particle size varying from 215.38±11.52 to 227.36 ±12.89 respectively. The matrix tablet containing 2:1 polymer: drug ratio of TIZ microparticles and NIM showed parallel release kinetic pattern after 2 hr for more extended period (beyond 18 h) than conventional tablets. **Conclusion**: The corresponding rate constant (K_1), regression coefficient (r) and exponent coefficient (n) of NIM and TIZ were found to be 0.129,0.134,0.9923, 0.9917,0.789 and 0.784 respectively, which indicates anomalous transport and diffusion controlled mechanism.

51 Second Derivative Spectrophotometric Method for the Estimation of Atenolol and Hydrochlorthiazide in Combined Dosage forms

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Purpose: The combination of atenolol and hydrochlorthiazide has been emerged as one of the widely prescribed combination in single dosage forms as an anti-hypertensive agent. The literature revealed that no method of simultaneous estimation by uv-spectrophotometer of both the drugs in tablet dosage forms have been reported. Hence a simple, rapid, accurate, economical and sensitive second derivative Spectrophotometric simultaneous method for the determination of atenolol and hydrochlorthiazide in tablet formulation has been developed. **Method:** The Shimadzu Pharmaspec 1700 UV-visible spectrophotometer was used for the experimental purpose. The absorption maximum was found 274.5 nm and 323 nm respectively for atenolol and hydrochlorthiazide in 0.1N NaOH. Atenolol shows zero absorbance at 229.5 nm and hydrochlorthiazide at 234 nm respectively for second order derivative spectrophotometery. **Results:** Atenolol obeyed the Beer Lambert's law at 234 nm in the concentration range 4-28 µg/ml and hydrochlorthiazide 2-20 µg/ml at 229.5 nm. The method was employed for the estimation of drugs in marketed formulations the result showed the close proximity to the percentage of label claim (98.95-99.98%). The low value of standard deviation and relative standard deviation show the accuracy and precision of the method. The method was validated with the recovery study (99-101%) and the result show there is no interference with the excipients. **Conclusion:** From the above results it can be concluded that the proposed method is very sensitive and accurate. This method can be employed for the determination of atenolol and hydrochlorthiazide in combined dosages forms as well as in bulk drugs.

52 FORMULATION OF TARGETED TERBUTALINE SULPHATE MICROCAPSULES OF YEAST FOR ACUTE AND CHRONIC ASTHMA

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PURPOSE: The purpose of the work was to assess the ability of the yeast cell to act as a microcapsule and to formulate terbutaline sulphate microcapsule using yeast cells and preparation of dry powder inhalations of these microcapsules for acute and chronic asthma. Saccharomyces cerevisiae was the first micro organism chosen for micro encapsulation and its epithelial adherence is due to the property of being stripped down human cell. METHODS: A. PRETREATMENT OF YEAST CELLS: A suspension of fresh yeast was treated with over night with sodium azide(2 gram), a respiratory inhibitor which is used to prevent the cell from performing any energy dependent processes. The cells were autoclaved at 121^{o}c for 20 mins. By this process it was ensured that the yeast cells were made to lose its viability completely. hence possibility of fungal infection to occur; B. PREPARATION OF MICROCAPSULES: Drug, yeast and water were taken in the ratio of 1:2:4 and agitated with a magnetic stirrer for 4 hours at a temperature of 40^{0} c. the cells were then centrifuged for 10 mins. The supernatant solution was decanted and the cells were washed 5 times with distilled water and freeze dried for 48 hrs. The above procedure was repeated with 0.2 gm, 0.4 gm of the same drug with yeast and water in the same ratio of 1:2:4 at a temperature of 35^{0}c, 30^{0}c and 25^{0}c. a total of 12 samples were done using this process. RESULTS: The freeze dried samples of micro encapsulated drug with yeast cells were evaluated with parameters such as: yield, entrapment efficiency was analyzed using UV spectra at 295 nm; photographs of micro encapsulated drug using confocal microscope. Among the 12 samples the 6th sample constituted with 0.2 gm of drug, 0.4 gm of yeast and 6 ml of water maintained at 35^{0}c showed higher encapsulation yield of 14 micrograms. The release of the drug from the microcapsules showed first order kinetics sustained action. The dry powder mixture of the encapsulated yeast with spray dried lactose was prepared and powder characteristics studies are being undertaken. CONCLUSION: The present study envisages the epithelial adherence property of the yeast cells and its drug encapsulation capacity. So the formulated dry powder inhalation expected to be very effective, targeting the inflamed bronchial epithelial cells. The optimization of the microcapsules to diluent ratio in the dry powder inhalation is being carried out using invitro models.

53 Exploitation of Some Traditional Plant Drugs for Anti-fertility Activity

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Purpose: One approach pursued to identify new anti-fertility agents is the search of their presence in natural sources; for which we have made an attempt to scientifically authenticate the traditional use of some anti-fertility plant drugs namely, *Achyranthes aspera* Linn. (Amaranthaceae) roots, *Daucus carota* Linn. (Umbelliferae) seeds and *Hibiscus rosa-sinensis* Linn. (Malvaceae) roots were selected for their scientific authentication of their traditional use. **Methods**: The coarsely powdered drugs were extracted with ethanol (95%) by hot continuous extraction method and concentrated. The extracts were subjected to post-coital anti-fertility studies and estrogenic and anti-estrogenic studies. Post-coital anti-fertility studies: the extracts were administered at two different doses 200mg/kg and 400mg/kg to the female albino rats in the proesterous stage from day one to 7 of pregnancy. The number of implantation sites was counted on day 10. Estrogenic and anti-estrogenic activity: colony-bred immature female albino rats, 21-23 days old, weighing between 35 and 45 g, were selected for this activity. The extracts were administered at the dose of 400 mg/kg for 7 days. On day 8 the uteri were dissected out and weighed. Histological studies of the dissected were also performed.
R**esults:** The ethanol extracts of *Daucus carota* Linn. seeds and *Hibiscus rosa-sinensis* Linn. roots showed significant anti-implantation activity at the dose of 400 mg/kg body weight and ***Achyranthes aspera*** Linn. roots showed significant anti-implantation activity at the dose of 200 mg/kg body weight. All the three extracts acted as weak estrogens. The ethanol extract of *Daucus carota* Linn. seeds when given along with ethinyl estradiol acted as anti-estrogenic and the ethanol extracts of ***Achyranthes aspera*** Linn. and *Hibiscus rosa-sinensis* Linn. roots potentiated the effect of ethinyl estradiol. **Conclusion:** The three plant drugs have weak estrogenic activity thus authenticating traditional use.

54 A Study of the Antifungal and Antibacterial Activity of Some Essential Oils

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Purpose: Essential oils have been used since ancient times to alleviate various ailments like flatulence and colic discomfort, as appetizers, and as perfumery. Very recently their use has been exploited as an antiseptic, stimulant, expectorant, diuretic, etc. Today indiscriminate use of antibiotics has led to resistance of microbes, hence attention is being given to plant derived antimicrobials. The present study is aimed to evaluate the antifungal and antibacterial properties that inhibit or kill resistant organisms. **Methods**: The essential oils were obtained from the leaves of *Cymbopogan nardus* Linn./Rendle.(Gramineae), *Mentha arvensis* Linn.(Labiateae), *Mentha spicata* Linn.(Labiateae), Seeds of *Anethum sowa* Kurz.(Umbelliferae), fresh pericarp of *Citrus limon* Linn./Burn.f. (Rutaceae) by water steam distillation and dried over anhydrous sodium sulphate. The antimicrobial activity was tested by agar diffusion method by measuring zone of inhibition and minimum inhibitory concentration by turbidity method using Spectrophotometer at $_{max}$530 nm. **Results:** All the essential oils in pure form showed antibacterial activity against *Escherichia coli* NCIM 2065, *Staphyloccocus aureus* NCIM 2901, *S. aureus* NCIM 2079, *Bacillus cereus* NCIM 2322, *B. cereus* NCIM 2106, *B. coagulans* NCIM 2030 and *Proteus mirabilis* NCIM 2241 and antifungal activity against *Candida albicans* ATCC 10231, *Aspergillus niger* NCIM 590. In terms of their zone of inhibition *C. nardus* showed maximum inhibitory against *B. cereus. M. arvensis* oil against *E. coli,B. cereus* NICM 2106 and *P. mirabilis*. *M. spicata* against *B. cereus*, *S. aureus* NCIM 2901, *E. coli* and *P. mirabilis*. *A. sowa* oil against *E. coli, B. cereus* and *S. aureus.* **Conclusion**: On being compared with reference antibiotics, the results justify the role of essential oils in the discovery of new drugs from natural sources.

55 Synthesis and antimicrobial activity of a new series of N_1-substituted 1H-indazol-3-yl-acetic acid

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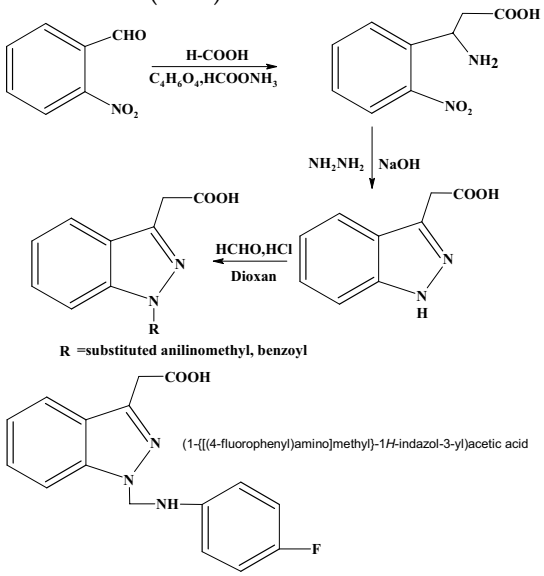
Purpose: Indazole derivatives possess a wide range of pharmacological activities like anti-inflammatory, antimicrobial, aldose reductase inhibitor, nitrous oxide inhibitor. In order to obtain new potent therapeutic agent we have synthesized a series of indazole derivatives containing substituted anilino methyl group at 1 position. **Method:** The titled compounds were synthesized by the reaction of malonic acid, formic acid, ammonium formate, and 2-nitro benzaldehyde to obtain the 3-amino-3- (2-nitrophenyl) propionic acid derivative (1). This was further reacted with hydrazine hydrate at 80°C using raney nickel as catalyst to yield indazole 3-acetic acid (2). Various substituted anilines were treated with indazole 3-acetic acid in presence of formaldehyde, dioxan, and hydrochloric acid to give N_1substituted indazole 3-acetic acid (3a-3l). **Scheme:**



All these compounds were recrystallized and obtained in satisfactory yield. Structures of synthesized compounds were confirmed by spectral analysis. Melting points were taken in open capillary tube and are uncorrected. Reaction was monitored by TLC. Results: All the compounds (3a-3l) were screened for antimicrobial activity against E.coli (EC), S.aureus (SA), B.substilis (BS), S.pyrogenes (SP)' K.pneumoia (KP) and P.vulgaris (PV) by cup plate method. After 24 hr of incubation at 37 °C the zone of inhibition were measured in mm. The activity was compared with the standard antibiotic. Results are expressed in tabular form. Figures indicate zone of inhibition in mm.

	R	Ec	Sa	Bs	Sp	Kp	Pv
3a	H	26	17	12	15	16	12
3b	-C_7H_5O	26	20	18	21	18	20
3c	-*p*-$C_8H_{10}N$	29	18	18	16	17	17
3d	-*p*-$C_8H_{10}NO$	29	18	14	23	25	15
3e	-*p*-C_8H_7NCl	26	19	18	21	22	20
3f	-*p*-$C_7H_7N_2O_2$	30	16	15	22	19	20
3g	-2,4di-$C_7H_6N_3O_4$	39	22	14	21	17	19
3h	-*o*-$C_7H_7N_2O_2$	30	17	20	20	18	18
3i	-*p*-$C_7H_8NSO_3$	30	18	20	18	13	20
3j	-*p*-C_8H_7NF	22	15	39	18	22	18
3k	-*m*-$C_7H_7N_2O_2$	26	20	18	20	18	20
3l	-*p*-$C_7H_9N_2SO_2$	17	14	18	15	17	15
Std.	Ofloxacin	40	27	38	35	22	30

Conclusion: The data expressed in tabular form indicates that the compounds (3c, 3f, 3g, 3h, 3i, 3j, 3k) have shown good antimicrobial activity against the microorganisms. These compounds are found to be more effective against *E.coli* and 3j was found to be effective against *B.substilis,* comparable to standard antibiotic. From these results, it can be concluded that the electron withdrawing substituents on benzene ring of aniline moiety at N_1 influences the antimicrobial activity. More number of compounds are necessary to be synthesized and their structure activity relationship is required to be studied.

56 Preparation and Characterization of Collagen based dual delivery system for effective wound healing

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Purpose: Wound is a pathological condition involving disruption of normal anatomical structures and function. We aimed to develop biocompatible collagen based delivery system to hasten and effectively facilitate the wound healing process. **Method:** Combined delivery system was prepared by loading alginate microspheres of proteolytic enzyme (serratiopeptidase) on gentamicin impregnated collagen (GIC) sheet. GIC sheet was prepared by soaking the collagen sheet in (10%)gentamicin solution. The serratiopeptidase loaded alginate microspheres were prepared by internal gelation method. Combined system was prepared by patting the serratiopeptidase microspheres on the application surface of GIC sheet. *In vivo* performance of combined delivery system was evaluated on albino rats in terms of physical, histological, cytological and biochemical assessment of wound healing. **Results:** Optimized serratiopeptidase alginate microspheres exhibited particle size in the range of 70-75µm with around 80 % loading. Microspheres showed initial burst release of 35% in first two hours followed by extended 83% release in 72 hours. GIC sheet retained substantial antimicrobial activity when tested for effectiveness on different strains of bacteria by agar diffusion method. Animal studies showed well-formed granulation tissue by day 7. Comparatively significant increase in percent wound reduction, protein content and Hydroxyproline content was observed (P<0.001). Histological studies further supported effective healing by increase in neutrophils along with proliferating fibroblasts and macrophages.

Conclusion: The prepared biocompatible dual delivery system can prove to be an effective system for rapid wound repair in terms of better tissue debridement, neovascularization, increased chemotaxis for fibroblasts and macrophages, removal of microbes from wound site and effective contraction.

57 Are the Current Bioequivalence (BE) Requirements Unnecessarily Stringent for the Approval of Generic Proton Pump Inhibitor (PPI) Products?

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Purpose. All PPIs are commercially available as enteric coated drug products in Canada. Many of them are known to exhibit highly variable drug absorption, especially under fed conditions. According to the TPD guidance (Part B), the ratio of geometric means (GMR) for C_{max} and its 90% confidence interval (CI) for AUC_T need to be within 80-125% in single-dose studies under fasting and fed conditions for the conclusion of BE. The appropriateness of these requirements for BE evaluation of PPI products was examined. **Methods.** Data from a multiple-dose, randomized, 2-way crossover, pharmacodynamic equivalence study of Apo-Omeprazole 20 mg Capsules and Losec 20 mg Tablets on 39 healthy subjects was used for the examination. The dosing regimen was 1x20 mg daily for 7 days with a washout of 14 days between periods. Intragastric pH monitoring for 24 hours following the last dose was performed for efficacy assessment of the two products. **Results.** The mean % of time with pH ≥3, the primary efficacy endpoint, was 50% for Apo-Omeprazole and 48% for Losec while the baseline value was 13%. The 90% CI of the difference between the two products was within ±20% of Losec mean. There was also no significant difference in mean 24-hour pH between them. Both products were well tolerated with no relevant differences in safety profiles. **Conclusion.** The two products provide equivalent clinical effects even though they are not bioequivalent. The current BE requirements for omeprazole products can be relaxed without any clinical implication. This is applicable to other PPIs.

58 Decreased expression of the low density lipoprotein receptor (LDLr) in human embryonic kidney cells using RNA interference

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Purpose: To develop an RNA interference approach to down regulate LDLr expression within a human embryonic kidney cell line (293T). **Materials and methods:** siRNA cloning: To generate the constructs, two pairs of complementary oligonucleotides, were annealed (LDLr-792 and LDLr-973). They were cloned into the pSHAG vector that directs the in vivo synthesis of siRNA. Positive clones acquired both kanamycin resistance and a new restriction site. An annexin V construct (AxV) was used as a siRNA control. siRNA transfection: 293T cells cultured in complete DMEM were seeded in pre-coated (Poly Lysine) plates to enhance adherence. Three days after transfection, the cells were washed and frozen. Western blot and RT-PCR: Cells were lysed in RIPA buffer, protein was quantified and the lysates were resolved by SDS-PAGE and transferred to nitrocellulose. Immunoblotting was carried out with commercial anti LDLr, SR-BI, annexin V and actin antibodies. RNA was isolated to prepare cDNA. Real time RT-PCR was performed to amplify the LDLr and GAPDH genes. **Results:** When compared with transfected control cells, the LDLr-792 and LDLr-973 constructs were associated with a reduction in LDLr protein expression of 70% and 50%, respectively. Interestingly, the cells transfected with AxV showed a higher LDLr protein expression, while annexin V expression was reduced by 70%. No differences were observed in SR-BI expression consistent with the specificity of the down-regulation effect. Quantitation of the LDLr mRNA by real time RT-PCR in LDLr-792 transfected cells indicated a reduction of 60% compared to control cells consistent with the immunoblot results. **Conclusions:** We have developed a tool to decrease LDLr expression in multiple cell lines. We will use this model to test the role of the LDLr in the internalization of drugs that interact with LDL. **Acknowledgements:** Funding was provided by a grant from CIHR to K.M.W and a grant from the St. Paul's Hospital Foun-dation to J.S.H. A portion of this work was presented at the 2005 AAPS Annual Meeting held in Nashville TN, USA.

59 Influence of Lipid Excipients, Capryol PGMC and Gelucire 44/14 on P-glycoprotein (P-gp) activity in Human Colon Adenocarcinoma (Caco-2) Cells.

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Purpose: The objective of this study was to determine the influence of lipid excipients, Capryol PGMC and Gelucire 44/14, on P-gp activity in Caco-2 cells. **Methods:** To determine non-toxic concentrations for Capryol PGMC and Gelucire 44/14 on Caco-2 cells, LDH, MTS and BCA assays were performed to determine cell plasma membrane integrity, mitochondrial respiration, and total protein concentration respectively. For P-gp efflux experiments, Caco-2 cells were seeded into 12-well plates. After cells reached 90% confluency, they were incubated overnight with previously determined non-toxic excipient concentrations and HBSS (control). The following day, a final concentration of 5□M RH-123 was added to each well and incubated for 3 hours. Plates were then washed with PBS and HBSS was added. RH-123 efflux was measured after certain time points. Cells were lysed with 1% Triton X-100 and RH-123 and BCA protein was determined. For Transwell studies, cells were incubated overnight with excipients on apical and basolateral sides. A final concentration of 5□M RH-123 was added only onto the basolateral side and RH-123 efflux (basolateral to apical transport) was measured after certain time points. At the end of the experiment, RH-123 content and BCA total protein in lysed cells were measured. The Dunnett test was used to measure statistical significance. **Results:** LDH, MTS and BCA (N=6) assays all correlated, showing that concentrations ≤ 0.1 v/v% Capryol PGMC and ≤ 0.02 w/v% Gelucire 44/14 are non-toxic to Caco-2 cells. Cells treated with 0.02 w/v% Gelucire 44/14 showed significant reduction ($p<0.001$) in the percent of RH-123 effluxed compared to the control, whereas lower concentrations for Gelucire 44/14 showed no significant reduction. Capryol PGMC showed no statistical difference between normalization of percentage RH-123 effluxed from Caco-2 cells treated with 0.1, 0.05 or 0.025 v/v% Capryol

PGMC to the control (HBSS). In the Transwell studies (basolateral to apical transport), 0.1, 0.05 and 0.025v/v% Capryol PGMC and 0.02 and 0.01w/v% Gelucire 44/14 showed significant increase ($P < 0.01$, 0.01, 0.05, 0.01 and 0.01 respectively) in the ratio of absorbance of RH-123 to milligrams of protein compared to the control. **Conclusion:** Our findings suggest that Caco-2 cells treated with lipid excipients, Capryol PGMC or Gelucire 44/14 at non-toxic concentrations may decrease the amount of RH-123 effluxed compared to untreated control cells, suggesting a reduction in P-gp activity. **Acknowledgments:** This project was funded by a Canadian Institute of Health Research Operating grant to KMW. A portion of this work was published at the 2005 AAPS Annual Meeting held in Nashville TN, USA.

60 COMPARISON OF PHYSICOCHEMICAL DATA VS DISSOLUTION DATA TO ESTABLISH IN VITRO/IN VIVO CORRELATIONS

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Purpose: To differentiate the physicochemical properties of different glyburide powders from different sources using material characterization methods. To predict the oral absorption of these powders using physicochemical data or dissolution data as input functions into the advanced compartmental absorption and transit model (ACAT). **Methods:** The material characterizations include SEM, X-Ray, Raman Spectrum, DSC, Particle Size Distribution Analysis, Surface Area and True Density. Solubility of glyburide was determined in different dissolution media at different pH values. The dissolution behaviors of two glyburide formulations (3.5 mg and 5 mg) were tested using apparatus 2, USP 28. The dissolution tests were performed using a multi-pH gradient method. The prediction of the fraction dose absorbed for each formulation was performed using GastroPlus™. The simulations were compared with clinical data. **Results:** The crystal forms of the different glyburide powders were similar; however, significant differences in morphology, surface area and particle size were determined. The solubility of the glyburide was pH-dependent. The particle size had significant influence on the simulations when only the solubility data were used. Both physicochemical and dissolution data could be used to successfully predict two 3.5 mg formulations. For a 5 mg formulation only the physicochemical data were able to predict the oral absorption. This was due to incomplete dissolution of this product of about 60%. **Conclusion:** Physicochemical data can be used to predict the oral absorption of glyburide. Dissolution data can only be used as input function if the in vitro dissolution reflects the in vivo dissolution.

61 Structural Similarity between Human Bitter Taste Receptors and Histamine H1-Receptor

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Purpose Bitter taste is the self-protection mechanism against poisonous substances evolved in mammals. In human, more than thirty bitter taste receptors (T2Rs) have been identified. Use of bitter substances to relieve inflammation-like symptoms has been used in traditional Chinese medicine. In the current study, we investigated the potential relationship between bitter taste and anti-inflammatory activity for H1-antihistamines. **Methods** The three-dimensional models of representative human bitter taste receptors (T2R5, T2R14, T2R16, T2R43 and T2R61) and histamine H1-receptor were built by homology modeling method using program MODELLER. H1-antihistamines were docked into the ligand binding sites of both the bitter taste receptors and the histamine H1-receptor by the docking software AUTODOCK. **Results** The bitter taste receptors exhibit very high structural similarities to the histamine H1-receptor. The root-mean-square deviations among the bitter taste receptors and between the bitter taste receptors and H1-receptor are less than 1.5 Å. A hydrophobic binding pocket similar to the H1-receptor ligand binding pocket is present in the bitter taste receptors. However, two basic residues Lys76 and Lys78, which can interact with polar functions groups of substrates, are adjacent to the hydrophobic binding pocket, implicating the bitter taste receptors may have a broader substrate spectrum than the histamine H1-receptor. **Conclusion** This study suggests that H1-antihistamines are likely to bind to the bitter taste receptors.

62 Hemodynamic effects of diltiazem in different rat models following repeated subcutaneous injections in vivo

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Purpose: To compare the hemodynamic effect of diltiazem in different rat models following repeated subcutaneous injection. **Methods:** Male SD, SHR, and WKY rats (Charles River Laboratories, n = 6 – 10 per group) weighing between 300 - 450 g were used. Each rat received either saline (control) or 5 mg/kg of diltiazem s.c. bid for 5 dose (Biovail Corp, Mississauga, Ont. Canada). Hemodynamic measurements were recorded continuously for each animal before and following treatment for up to 6 h. **Results:** The basal SBP in SD rats, WKY rats, and SHR in the control group were 126 ± 8, 132 ± 5, and 184 ± 6 mmHg,; and HR were 455 ± 23, 420 ± 8, and 464 ± 14 bpm, respectively. Diltiazem decreased SBP from 127 ± 5 to 98 ± 10 mmHg (23%), 140 ± 2 to 104 ± 3 mmHg (26%), and 150 ± 9 to 110 ± 7 mmHg (27%), and HR from 458 ± 11 to 404 ± 30 bpm (12%), 413 ± 11 to 391 ± 9 (5%), and 414 ± 43 to 348 ± 45 bpm (16%) following the last dose in SD rats, WKY rats, and SHR, respectively. The hemodynamic effects were more prolonged in the SHR. **Conclusion:** Hemodynamic effects after repeated administration of diltiazem were qualitatively and quantitatively similar in the SD rats, WKY rats, and SHR (Supported in part by a grant-in-aid from CIHR/NSHRF/PEF Regional Partnership Program, and a Collaborative Research Contract from Health Canada).

63 A sensitive and specific HPLC assay of cladribine for pharmacokinetic studies in rats

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Background and Purpose**: Claribine is a prototype of the nucleoside anticancer agents. To develop a sensitive and specific HPLC assay for cladribine in plasma for pharmacokinetic studies. Methods: Cladribine and the internal standard AZT were purchased from Sigma-Aldrich Chem. The HPLC system consisted of a Shimadzu LC-9A pump, a 3 µm, 250 x 2.0 I.D. high speed C_{18} column (Jupiter®), preceded by a 5 µm 4 x 4 mm i.d. C_{18} guard column (Licrocart®), an Agilent Model 1050 UV-VIS detector and a 3395 Integrator. The mobile phase was made up of 0.01M pH5 KH_2PO_4: methanol: acetonitrile (90:5:5). The system was operated at ambient temperature with a flow rate of 0.3 mL/min, and UV wavelength at 265 nm, and an operating pressure of ca. 1.56 kpsi. Extraction of cladribine and AZT from plasma was achieved by solid phase extraction using 100 mg/mL C18 SPE columns (Extra-sep®). The assay was validated for sensitivity, precision, specificity and application for pharmacokinetic study in rats.** Results**: Under these conditions, the average retention times of cladribine and AZT were 13.5 and 21 min, respectively, and recoveries were > 80%. Standard curves based on absolute on column injection of each compound were linear from 2.5 to 15 ng, with regression coefficient (r^2) 0.99 or greater. Sensitivities based on absolute injection were < 1 ng on column. Using a 50 uL plasma sample size, the intra-assay variations at 0.1 ug/mL were 7%, and inter-assay variations over a period of 3 months were 17%. The assay was used to study a single dose pharmacokinetic study of cladribine in rats after a 2 mg/kg dose.** Conclusions**: The described HPLC assay has adequate sensitivity and specificity to study pharmacokinetics of cladribine in rats** **(Supported in part by a Nova Scotia Health Research Foundation Innovation Grant and a Dalhousie Science Co-Op Program student scholarship to Ameer Jaraar).**

64 Design, Synthesis and Anticonvulsant Activity of New 1,3,4-Oxadiazole Derivatives as Benzodiazepine Receptor Agonists

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PURPOSE: A series of new 2-substituted-5-(2-benzylthio or benzyloxyphenyl)-1,3,4-oxadiazoles was designed and synthesized as anticonvulsant agents . **METHOD:** In order to synthesis of compounds 2-benzylthio or benzyloxyphenyl acid hydrazides were converted to 2-amino-5-(2-benzylthio or benzyloxyphenyl)-1,3,4-oxadiazoles using cyanogen bromide in methanol (75-84%).Conformational analysis of the 2-amino-5-[2-(p-fluoro)-benzylthio or benzyloxy phenyl)-1,3,4-oxadiazole and estazolam was preliminarily performed by MMX force field method implemented in PCMODEL 6.0 software. The conformers were optimized further by AM1 calculation using MOPAC 6.0 program. Global energy minima conformers of the designed compounds were superimposed on corresponding conformer of estazolam molecule, which was considered as a reference BZD agonist. The compounds were characterized by ^1H nuclear magnetic resonance, infrared, mass spectrometry and CHN analysis. The BZD activity of the synthesized compounds was determined through the evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of PTZ and electroshock as two routine models. **RESULT:** Most of the synthesized compounds showed anticonvulsant activity in both models. The benzyloxy phenyl -1,3,4-oxadiazoles had more anticonvulsant activity in compared with benzylthiophenyl derivatives. The fluoro substituent at para position of benzyloxy or benzylthio moiety gave the most active analogue in both series of compounds. **CONCLUSION:** Some 2-amino-5-aryl- 1,3,4-oxadiazoles with a simple non-rigid structure in which the flexible second out-of-plane aromatic ring, benzylthio or benzyloxy group, has a suitable substituent could show benzodiazepine activity.

65 A Validated New UV Spectrophotometric Method for Determination of Ascorbic Acid in Its Effervescent Dosage Forms

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Purpose. The objective of this work was to develop and validate a new UV spectrophotometric method for determination of ascorbic acid (vitamin C) in its effervescent dosage forms. Methods. Ascorbic acid was first found to dissolve in methanol, and its solubility in it was measured to be 81.0 mg/ml at room temperature (22oC). The stability of ascorbic acid in mehanol at the room temperature was determined to be only 0.7% of oxidation within 1 hour compared with 46.0% of oxidation at the same period in de-ionized water. Ascorbic acid was found to have a maximum wavelength of 245 nm in methanol. Then, methanol was used to prepare analytical samples of effervescent vitamin C tablets for the UV determination of ascorbic acid, finding no interferences in the UV region from other substances because of their insolubility in methanol. Results. The analytical curve is linear (R2 = 0.9997) in range from 0.01 to 0.03 mg/ml. The recovery of ascorbic acid ranges from 98.3 to 101.4%. The method repeatability test results meet the relevant acceptance criteria (RSD < 2%). The analytical results from different operators in different days are in good agreement. This method is specific for ascorbic acid. The dilution factors and the small change in the sonication time have no any effects on the recovery of ascorbic acid. The analyte stablity in sample preparation is also validated. Conclusions. The validated method can be used for the routine determination of ascorbic acid for the dosage uniformity testing of effervescent vitamin C tablets with various strengths. This method is rapid, accurate and reliable, and methanol is not expensive and easily available, which can save much time and money for the manufacturers who produce the effevescent vitamin C products.

66 Tablet Formulation Development for a Poorly Water Soluble New Chemical Entity

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Purpose: To develop a tablet formulation using a conventional wet granulation method for new chemical entity X (NCE X), a BCS Class II compound (low aqueous solubility < 0.1 μg/ml and high permeability). Only micronized NCE X with D (v,50) of 1.7 μm was used. **Methods:** A HPLC method was used for solubilizer screen. A conventional wet granulation method was employed for tablet manufacturing. All excipients used were common materials available commercially. Dissolution profiles of tablets in simulated intestinal fluid (SIF) were assessed for formulation optimization. **Results:** Among all the investigated solubilizers, sodium dodecyl sulfate (SDS) emerged as the most efficient candidate for improving NCE X's aqueous solubility. Formulations incorporated with SDS confirmed this finding. In addition, tablet dissolution profiles also indicated povidone (PVP) acting as a possible solubility enhancer. Consequently, studies by Design of Experiments (DOE) were performed to investigate three possible factors (NCE X, SDS, and PVP) at multiple levels for formulation optimization. In all the formulations investigated, Formulation F14 was the best in terms of both dissolution rate and equilibrium concentration, whose dissolution profile was better than that from a gelucire capsule formulation with proven sufficient exposure in dog. A DMPK study in dog evaluating F14 tablet formulation against the gelucire capsule formulation indicated that the exposure for the F14 Tablet formulation was not significantly different from that obtained using the gelucire capsule formulation. **Conclusions:** A tablet formulation was developed successfully with sufficient exposure in dog. The tablets were developed with common excipients and manufactured by a conventional wet granulation method.

67 Dendritic cell targeting of MUC-1 breast cancer peptide expressed on bacterial surface

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Purpose: Whole bacterial cells can stimulate a T cell-mediated response; therefore, a bacterial formulation of Caulobacter crescentus displaying both MUC-1 breast cancer peptide and a Protein G binding domain was developed for targeting to dendritic cells (DCs). Since DCs are the most potent antigen processing cells, a specific antibody targeting system could enhance and/or stimulate an active specific immune response against cancer. **Methods**: Anti-DEC-205 antibody was produced by HB290 cells, purified on a Protein G column, and biotinylated. The C. crescentus bacteria constructs were grown in PYE media and characterized for MUC-1 and the Protein G domain by direct whole cell ELISA. **Results**: The ELISA results detected that the activity of both MUC-1 and the Protein G binding domain of the 4x MUC-1 construct was intense. In contrast, very little activity was detected for either domain of the 1x MUC-1 construct. Although the 2x MUC-1 construct had strong activity for the Protein G domain, there was weak reactivity for MUC-1. A difference in activity was detected when the concentrations of anti-MUC-1 and anti-DEC-205 were varied for the 4x MUC-1 construct. The preliminary simulated in vivo study demonstrated that anti-DEC-205 bound to the Protein G domain of the 4x MUC-1 construct was minimally displaced when other antibodies were added. **Conclusion**: The Protein G binding domain of the 4x MUC-1 C. crescentus construct could be used via an antibody-based targeting system, to present the MUC-1 breast cancer antigen or any other antigen integrated into the bacterial S-layer, to DCs.

68 Non-invasive Assessment of the In Vivo Pharmacokinetics of Liposomes Using CT and MR Imaging

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Purpose: Traditional evaluation of the pharmacokinetics of drugs and materials involves invasive tissue and plasma sampling. These methods require the use of large numbers of animals which introduces animal-to-animal variability and limits the number of time points that may be sampled. The present study is aimed to explore the use of non-invasive techniques such as computed tomography (CT) and magnetic resonance (MR) imaging to effectively track the in vivo circulation pathway of contrast agent modified lipid carriers in a rabbit model. Methods: A Female New Zealand White rabbit was administered liposomes encapsulating 200 mg/kg iodine and 16 mg/kg gadolinium. The rabbit was imaged in CT and MR at specific time points (up to 7 days) following liposome injection. The relative signal intensity increases measured in the two imaging modalities at the rabbit aorta were correlated with the iodine and gadolinium concentrations present in blood as measured by HPLC and ICP-AES analyses. Results: A linear concentration prediction range was found in both CT and MR with correlation coefficients of 0.9. Specifically, a clinical CT system operating at 120 kV and 200 mA was able to detect plasma iodine concentrations ranging from 100 µg/mL to 500 µg/mL, while a clinical 1.5 Tesla MR system was able to measure plasma gadolinium concentrations ranging from 20 µg/mL to 150 µg/mL. Conclusion: This pilot study showed the potential of employing CT and MR imaging to non-invasively map the distribution of liposome carriers in vivo. The successful refinement of this imaging-based pharmacokinetics assessment tool may facilitate delivery carrier design and optimization in both the preclinical and clinical settings. Acknowledgement: A portion of the following work will be presented (oral presentation) at the Nanotech 2006 Symposium that will take place on May 7-11, 2006 in Boston, MA, USA.

69 Pharmaceutical Care Services in Hospitals of Kuwait

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Purpose: To describe the current pharmacy practice in the general hospitals based on self-reported practice by pharmacists, explore the awareness of the pharmacists of the pharmaceutical care concept, identify their willingness to its implementation and the barriers that may limit the implementation. **Methods**: Eighty hospital pharmacists working in four general governmental hospitals were approached to be included in the study. Data were colleted via face-to-face structured interview of the respondents using a pre-tested questionnaire. **Results**: The response rate was 76.3%. Thirty five (57.4%) of the respondents had frequently performed interventions on the prescription through interacting with the medical doctors. Eighteen (29.5%) were frequently contacted by doctors requesting information about drugs. Thirty two (52.5%) had frequently provided patient counselling. Forty six (75.4%) of the respondents claimed that they were aware of the pharmaceutical care concept. Thirty five (76.1%) and 39.1% of those claiming to be aware of the pharmaceutical care concept indicated that its main focus is the patient and the appropriate objectives of the concept, respectively. Thirty (65.2%) of them claimed that they had already implemented the pharmaceutical care services in their practice. All respondents demonstrated willingness to implement the pharmaceutical care practice in their hospitals. The main barriers perceived by the participants were lack of time (78%), lack of staff (71.2%), and lack of educational programs and training (44.1%). **Conclusion:** The current practice of hospital pharmacists needs further improvement in relation to interaction with doctors and patient counselling. The lack of uniformity in the responses regarding the focus and objectives of pharmaceutical care indicates a lack of appropriate understanding in this matter. All respondents have shown high willingness towards the implementation of the pharmaceutical care services in their practice.

70 Normal Pharmacodynamic Response and Pharmacokinetics of Verapamil in Rheumatoid Arthritis Patients Treated with Infliximab

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Purpose. Potency of the cardiovascular drug verapamil is reduced in patients with rheumatoid arthritis (RA) despite elevated plasma drug concentrations. Excess pro-inflammatory mediators are associated with suppression of drug clearance and down-regulation of various cardiovascular receptors. Infliximab is an anti-TNFα monoclonal antibody that reduces the levels of a multitude of pro-inflammatory cytokines and has been shown to reverse the effects of inflammation on pharmacodynamic response to sotalol in the inflamed rat. We examined whether RA patients who are under treatment with infliximab still demonstrate reduced response to verapamil and decreased verapamil clearance. Methods. Twelve RA patients on infliximab therapy were matched with twelve healthy volunteers. Serum levels of interleukin-6 (IL-6), nitrite (NO_2^-), TNFα and C-reactive protein (CRP) were measured to assess degree of inflammation. Verapamil (80 mg) was administered orally, and then ECG, blood pressure and verapamil enantiomers concentrations were measured for 12 h. Results. Serum TNFα and CRP concentrations were significantly greater in infliximab treated patients compared with healthy controls (TNFα, $p<0.001$; CRP, $p=0.04$). Serum nitrite and IL-6 concentrations were not significantly different from controls. No significant differences in pharmacokinetics were observed between control and infliximab treated subjects. Pharmacodynamic response to verapamil was also not significantly different between the two groups in any of the measured parameters. Conclusion. Patients with RA who are treated with infliximab demonstrated similar plasma drug concentration and PR-interval response to verapamil when compared with healthy volunteers despite elevated TNFα and CRP concentrations. Pro-inflammatory mediators nitrite and IL-6, appear to be reduced by infliximab treatment.

71 Validation of a liquid chromatography tandem mass spectrometry assay method for the determination of sertraline in human plasma

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Purpose. Validation of an LC/MS/MS assay method using atmospheric pressure electrospray ionization in the positive ion mode for the measurement of sertraline in human plasma. **Methods.** Sertraline and the internal standard (d_3-sertraline) were extracted from 1.0 mL human plasma by liquid/liquid extraction using 1-chlorobutane as extraction solvent. The analyte was chromatographically separated on a Phenomenex LunaB C_{18} (2) (3 x 50 mm, 5 µm) column using a gradient elution with 0.05% aqueous TFA and 0.05% TFA in acetonitrile as the initial mobile phase, followed by LC/MS/MS analysis. Detection and quantitation were carried out by ESI-MS/MS monitoring the mass transitions from m/z 306 to 159 (sertraline) and m/z 309 to 159 (d_3-sertraline). **Results.** The method was validated over a concentration range from 0.25 to 100.00 ng/mL using a linear calibration curve with a weighting of $1/x^2$. Inter-batch precision (%CV) for standards ranged from 1.6 to 2.5. Inter-batch accuracy (%RE) ranged from -1.2 to 1.3, indicating an acceptable goodness-of-fit. Inter-batch assay precision (%CV) for quality control samples, ranged from 0.7 to 3.1 over five concentration levels. Inter-batch assay accuracy (%RE) results for quality control samples ranged from -2.9 to 14.3. The mean correlation coefficient was 0.9997 ± 0.0001. Assay recovery for sertraline was 77.4 % (%CV of 6.9), 65.4 % (%CV of 8.9) and 72.8 % (%CV of 8.4) at 0.75 ng/mL, 30.00 ng/mL and 80.00 ng/mL respectively. **Conclusions.** An accurate, sensitive and rapid LC/MS/MS analytical assay was validated and successfully applied to the measurement of sertraline in human plasma samples.

72 Validation of a liquid chromatography mass spectrometry assay method for the determination of trimethoprim and sulfamethoxazole in human plasma

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Purpose. To develop and validate an LC/MS method for the simultaneous determination of trimethoprim and sulfamethoxazole in human plasma. **Methods.** Trimethoprim, sulfamethoxazole and sulfisoxazole (internal standard), were extracted from 0.1 mL human plasma by liquid/liquid extraction using ethyl acetate as extraction solvent. The analytes were chromatographically separated on a Zorbax Extend C_{18} (4.6×50 mm, 3.5 µm) column using gradient elution with 95% 0.1% formic acid in water and 5% acetonitrile as initial mobile phase. Quantitation was carried out by monitoring selected ions at m/z 291 (trimethoprim), m/z 254 (sulfamethoxazole) and m/z 268 (sulfisoxazole). **Results.** The method was validated over a concentration range from 0.10 to 10.00 µg/mL (trimethoprim) and 1.00 to 100.00 µg/mL (sulfamethoxazole) using a quadratic calibration curve weighted $1/x^2$ for trimethoprim and 1/x for sulfamethoxazole. Inter-batch precision (%CV) for standards ranged from 1.6 to 4.1 (trimethoprim) and 1.2 to 3.0 (sulfamethoxazole). Inter-batch accuracy (%RE) ranged from -6.7 to 7.1 (trimethoprim) and -3.7 to 2.1 (sulfamethoxazole). Inter-batch assay precision (%CV) for quality control samples ranged from 1.5 to 5.3 (trimethoprim) and 1.1 to 3.8 (sulfamethoxazole). Inter-batch assay accuracy (%RE) for quality control samples ranged from -5.5 to 3.2 (trimethoprim) and -2.2 to 2.2 (sulfamethoxazole). The mean correlation coefficients were 0.9983±0.0010 (trimethoprim) and 0.9998±0.00001 (sulfamethoxazole). The mean assay recovery was 79.2±2.6% (trimethoprim) and 99.4±3.6% (sulfamethoxazole). Freeze/thaw stability was established at -40°C and -70°C for three cycles at each temperature. **Conclusions.** An accurate, sensitive and rapid analytical assay was applied to measure trimethoprim and sulfamethoxazole in clinical plasma samples.

73 Validation of a liquid chromatography tandem mass spectrometry assay method for the determination of verapamil and norverapamil in human plasma

Adrien Musuku, Gina de Boer, Meng Yu,
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Purpose. Validation of an LC/MS/MS method for the simultaneous determination of verapamil, and its metabolite, norverapamil, in human plasma. **Methods.** Verapamil, norverapamil and the internal standard, d_6-verapamil, were extracted from 0.1 mL human plasma by liquid/liquid extraction. The analytes were chromatographically separated on a reverse-phase Zorbax Extend-C_{18} (4.6×50 mm, 3.5 μm) column using gradient elution with initial mobile phase of 70% 10mM ammonium acetate in water and 30% acetonitrile. ESI mass spectra were acquired in positive ion mode with multiple reaction monitoring. Quantitation was carried out by monitoring mass transitions at m/z 455 to m/z 165 (verapamil), m/z 441 to m/z 165 (norverapamil) and m/z 461 to m/z 165 (d_6-verapamil). **Results.** The method was validated over a concentration range from 1.00 to 200.00 ng/mL for both analytes. Inter-batch precision (%CV) for standards ranged from 3.1 to 7.3 for verapamil and 4.4 to 8.3 for norverapamil. Inter-batch accuracy (%RE) ranged from -3.8 to 5.7 for verapamil and -3.9 to 4.3 for norverapamil. Inter-batch assay precision (%CV) for quality control samples ranged from 1.1 to 3.9 for verapamil and 3.2 to 6.1 for norverapamil. Inter-batch assay accuracy (%RE) results for quality control samples ranged from -5.6 to 1.2 for verapamil and -3.6 to 3.5 for norverapamil. The mean correlation coefficients were 0.9979 ± 0.0014 (verapamil) and 0.9977 ± 0.0014 (norverapamil). Freeze/thaw stability for three cycles was established at -40°C. **Conclusions.** An accurate, sensitive and rapid analytical assay was developed and applied to the measurement of verapamil and norverapamil in clinical samples.

Pre-registered Attendees as of 25 May

Last_Name	First_Name	Affiliation	Country
Abolfathi	Zohreh	SFBC Anapharm	Canada
Afshar Ghahremankhani	Ali	Tehran University of	Iran
Agarwal	Nitin	Ranbaxy	India
Aghamanoukian	Tamar	Biovail Contract Research	Canada
Allen	Christine	University of Toronto	Canada
Allen	Suzanne	Guest	
Awad Hussein	Abdelmoneim	Kuwait University	Kuwait
Bacanek	Dara	Biovail	Canada
Beacham	James	Astrolabe Analytica,	USA
Bendayan	Reina	University of Toronto	Canada
Bende	Girish	BITS	India
Benet	Carol	Guest	USA
Benet	Leslie	U of California, San Francisco	USA
Berger	Neil	Pharma Medica Research Inc.	Canada
Bharal	Nidhi	University College of	India
Blair	Simone	Innopharm Inc.	Canada
Boudjikanian	Lory	Gattefosse Canada Inc.	Canada
Boudreau	Omer	Therapeutic Products	Canada
Brocks	Dion	University of Alberta	Canada
Buchanan	Kathy	Novopharm Limited	Canada
Burdo	Pina	Biovail Contract Research	Canada
Camarco	Wayne	ISP (Canada) Inc.	Canada
Campanella	Corinne	Biovail	Canada
Cereda	Cintia	Universidade de Campinas	Brazil
Charest	Pierre	Health Canada	Canada
Chhipa	Pankaj		India
Chopra	Shruti	Jamia Hamdard University	India
Clements	John	University of Alberta	Canada
Cools-Lartigue	Neil	CCL Label	Canada
Dahiya	Sunita	Rajiv Academy for	India
Davit	Barbara	Div. of Bioequivalence,	USA
Demers	Daniel	Novartis Pharmaceuticals	Canada
Dhall	Vipan	NPS Pharmaceuticals	Canada
Diwan	Anupama	Jamia Hamdard University	India
Drolet	Benoit	Laval University	Canada

Dubins	David	Allied Research International	Canada
Ducharme	Murray	MDS Pharma Services	Canada
Dunlop	Heather	Health Canada - MHPD	Canada
Dussault	Catherine	Algorithme Pharma Inc.	Canada
Edwards	Edmond	Health Canada BGTD	Canada
Ely	Leticia	University of Alberta	Canada
Embree	Leanne	Angiotech Pharmaceuticals	Canada
Endrenyi	Laszlo	University of Toronto	Canada
Faan	Clara	BRI Biopharmaceutical	Canada
Fields	Anat	Apotex Inc.	Canada
Fontaine	Suzanne	CCL Label	Canada
Foster	Deborah	Guest	Canada
Foster	Brian	Health Canada	Canada
Gallivan	Jim	Health Canada	Canada
Garon	Julie	Algorithme Pharma Inc.	Canada
Ghani	Arshia	Pfizer Canada	Canada
Gharavi	Negar	University of Alberta	Canada
Girard	Denis	Science coord. & policy	Canada
Grant	Justin	University of Toronto	Canada
Hamdan	Leila	Canada	
Harbour	Karen	World Courier of Canada	Canada
Hassen	Abdullah	Health Canada	Canada
Hawes	Ted	University of Saskatchewan	Canada
He	Juan	Biovail	Canada
Ho	Micheline	Health Canada	Canada
Hunt	Melissa	Health Canada	Canada
Iskander	Jaklin	University of Toronto	Canada
Jain	Prateek	Dr. H.S. Gour University	India
Jamali	Fakhreddin	University of Alberta	Canada
Jamali-Keshavarz	Ella	Guest	Canada
Jobse	Jason	University of Saskatchewan	Canada
Kanfer	Izzy	Rhodes University	South Africa
Khan	Tanveer	International Islamic	Malaysia
Klein	Agnes	Health Canada	Canada
Kumar	Ravinder	GlaxoSmithKline	Canada
Kwok	David	BRI Biopharmaceutical	Canada
Laurin	Patricia	Health Canada	Canada
Lee	Helen	University of Toronto	Canada

Lefebvre	Marc	Algorithme Pharma Inc.	Canada
Lepage	Robert	Pharma Medica	Canada
Levitchi	Mihaela	Pharmascience Inc.	Canada
Liberti	Lawrence	Thomson Scientific	USA
Ling	Spencer	University of Alberta	Canada
Lisinski	Tracy	Astrolabe Analytica,	USA
Liu	Jubo	University of Toronto	Canada
Loebenberg	Raimar	University of Alberta	Canada
Lopez-Cervantes	Miriam	UNAM	Mexico
Ludden	Thomas	GloboMax, a division of	USA
Lutter	Lorelei	CANTEST BioPharma	Canada
Mark	Framin	University of British	Canada
Matienzo	Javier	Cobalt Pharmaceuticals Inc.	Canada
McGilveray	Ann	McGilveray Pharmacon Inc.	Canada
McGilveray	Iain	McGilveray Pharmacon Inc.	Canada
McKay	Gordon	Pharmalytics, Inc.	Canada
McKay	Lynn	guest	Canada
Midha	Kamal	University of Saskatchewan	Canada
Midha	Neelam	Guest	Canada
Mohamed Essa	Musthafa	Annamalai University	India
Moisan	Richard	Allied Research International	Canada
Montazeri Aliabadi	Hamidreza	University of Alberta	Canada
Mould	Diane	Projections Research Inc.	USA
Musial	Witold	Wroclaw Medical University	Poland
Musuku	Adrien	Cantest BioPharma Services	Canada
Najjemba	Hilda	Orient Pharmaceutical Ltd.	Uganda
Nestruck	Christine	Health Canada	Canada
Onyeukwu	Nnamdi Anny	ESCP	Nigeria
Orizaga-Brocks	Patricia	Guest	Canada
Ormsby	Rose	Guest	Canada
Ormsby	Eric	Health Canada	Canada
Oruna	Loida	State Center of Control and	Cuba
Patil	Scahinkumar	Shivaji University	India
Pesant	Madeleine	Pfizer Canada Inc.	Canada
Piquette-Miller	Micheline	University of Toronto	Canada
Poirier-Vachon	Karel	Gattefosse	Canada
Pop	Radu	Pharma Medica Research Inc.	Canada
Porszt	Erin	Cedarlane	Canada
Prajapati	Vipulkumar D.	Maliba Pharmacy College	India

Prokipcak	Becky	CanReg Inc.	Canada
Rajska-Neumann	Agnieszka	University of Medical	Poland
Rehman	Wajid	Gomal University	Pakistan
Reid	Taryn	Dalhousie University	Canada
Ricard	Guylaine	Laval University	Canada
Rocheleau	Marie-Josee	Bristol-Myers Squibb-PRI	Canada
Rose	Jhona	Health Canada	Canada
Russo	Ethan	GW Pharmaceuticals	USA
Samel	Amit	Mumbai University	India
Saratsiotis	Paul	World Courier	Canada
Sayani	Amyn	GlaxoSmithKline	Canada
Sebag	Oren	SFBC International	Canada
Seikaly	Hani	Janssen-Ortho Inc.	Canada
Simard	Chantale	Laval University	Canada
Skalski	Violetta	Health Canada	Canada
Smith	Garth	Cannasat Therapeutics Inc.	Canada
Smith	Beverly	ISP (Canada) Inc.	Canada
Spenard	Jean	Axcan Pharma	Canada
Sylvain	Michel	Health Canada	Canada
Tam	Julie	Canadian Generic	Canada
Tanguay	Mario	SFBC Anapharm	Canada
Thangam	Devi		India
Thiessen	Jake	University of Waterloo	Canada
Toal	Corey	Bayer Inc.	Canada
Tremblay	Patrice	Health Canada	Canada
Tsang	Yu Chung	Apotex Inc.	Canada
Tsolakos	George	Algorithme Pharma Inc.	Canada
Uetrecht	Jack	University of Toronto	Canada
Vadas	Elizabeth	InSciTech Inc.	Canada
Vonderhorst	Marc	International Specialty	USA
Wasan	Kishor	University of British	Canada
Williams	Ejalonibu	cancelled reg	Nigeria
Winocour	Peter	Aegera Therapeutics Inc.	Canada
Woolhouse	Michael	Guest	Canada
Yang	Jian	University of Saskatchewan	Canada
Yaraghi	Zari	Health Canada	Canada
Yeung	Pollen	Dalhousie University	Canada
Yu	Hans	Office of Biotechnology and	Canada
Yu	Yongmin	Health Canada	Canada

Zeng	Wenming	Toronto Institute of	Canada
Zhang	Jany	University of Alberta	Canada
Zhang	Kai	GlaxoSmithKline	Canada
Zheng	Jinzi	University of Toronto	Canada

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