American Association of Pharmaceutical Scientists

Northeast Regional Discussion Group

23rd Annual Meeting

1st Virtual Meeting

April 16, 2021

aaps-nerdg.org

Zoom meeting Technology and Support provided by

Albany College of Pharmacy and Health Sciences

Message from the Chair

Dear Conference Attendees:

Thank you for participating in this year's American Association of Pharmaceutical Scientists Northeast Regional Discussion Group (AAPS-NERDG) annual meeting. NERDG is one of the largest and most active regional discussion groups within AAPS, and that is due in large part to your participation in this meeting. For the first time, we have changed our annual meeting to a virtual format because of the COVID-19 pandemic. Although this has led to some changes to the usual schedule, this year's planning committee has worked hard to again include opportunities for learning and interacting with others in the industry.

This year, our keynote speaker is Dr. Justin Hanes from the Center for Nanomedicine at the Johns Hopkins University. Many thanks to Dr. Hanes for sharing his insights on the pharmaceutical industry.

In the morning, we have Short Topic Presentation sessions on Pharmacokinetics and Biomarkers, Industrial Pharmacy, and Process Modeling. This year, in place of a poster session, we have a Rapid Fire Presentation session covering research from a broad selection of topics. Please consult the program for the presentation schedule. Additionally, students will be competing for the Academic Research Award with presentations on their research topics. The winners will be announced in the afternoon. Feel free to attend any sessions that interest you.

In the afternoon, we have four round table discussions covering Inhalation/Respiratory Drug Development; Bioanalytical Development for *in vivo* Biomarkers and DMPK; Computational Modeling to Aid Pharmaceutical Development – Solid State Chemistry; and Physicochemical & Biophysical Stability Assessments Across Therapeutic Modalities.

In lieu of vendor tables, we have included presentations from sponsors in the main room who have generously supported this meeting. FreeThink Technologies will be presenting in the morning. We will also have sponsor presentations in the afternoon from Ashland, Bruker, and Shin-Etsu. We are also grateful to JRS Pharma, who supported the 1st and 2nd place prizes for the Academic Research Awards, and Simulations Plus, who sponsored the 3rd place prize. Additionally, Gattefossé generously sponsored many student registrations this year. Pfizer has been a consistent corporate sponsor throughout the years and continued to provide support this year. The sponsors are listed in the program; please take some time to click on the logos and visit their websites to learn more about them.

A special thanks to the Albany College of Pharmacy and Health Sciences for providing and supporting the Zoom technology for this year's virtual meeting.

This has obviously been an unusual year, and I would like to thank and acknowledge this year's planning committee. This is an all-volunteer organization and they have put in many hours assembling a meeting that is adapted to the circumstances. This day would not be possible without their dedication and hard work.

Welcome and enjoy the meeting!

Sincerely,

Jennifer Chu
AAPS-NERDG Chair (2020-2021)
FreeThink Technologies

Time	Sessions				
8:15-8:45	Join Meeting/Networking				
8:45-9:00	Opening Address (Main Room)				
9:00-10:00	Keynote Speaker – Translation of Advanced Drug Delivery Technologies by Dr. Justin Hanes (Main Room)				
10:00-10:30	FreeThink Technologies Presentation (Main Room)				
10:30-11:30	Rapid Fire Presentations (Room 1)	Short Topic Presentations – Pharmacokinetics and Biomarkers (Room 2)	Short Topic Presentations – Industrial Pharmacy (Room 3)	Short Topic Presentations – Process Modeling (Room 4)	Academic Research Award Session (Room 5)
11:30-12:30			Networking (Rooms 3, 6, and 7)		
12:30-1:00	Lunch Break and Networking (All Rooms)				
1:00-2:15	Round Table – Inhalation/Respiratory Drug Development (Room 1)	Round Table – Bioanalytical Development for *in vivo* Biomarkers and DMPK (Room 2)	Networking (Rooms 5, 6, 7)	Round Table – Computational Modeling to Aid Pharmaceutical Development – Solid State Chemistry (Room 3)	Round Table – Physicochemical & Biophysical Stability Assessments Across Therapeutic Modalities (Room 4)
2:15-2:30	Ashland Presentation (Main Room)				
2:30-2:45	Bruker Presentation (Main Room)				
2:45-3:00	Shin-Etsu Presentation (Main Room)				
3:00-3:15	Business Meeting				
3:15-3:30	Award Ceremony Sponsored by JRS Pharma and Simulations Plus (Main Room)				
3:30-3:45	Social Hour/Networking (Rooms 1-6)			Break	
3:45-4:30				2022 NERDG Planning Meeting (Room 7)	

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Keynote Speaker

Justin Hanes, Ph.D.
Lewis J. Ort Professor
Director, The Center for Nanomedicine at the Wilmer Eye Institute
John Hopkins University School of Medicine

Translation of Advanced Drug Delivery Technologies

Justin Hanes is the Lewis J. Ort Professor and Director of the Center for Nanomedicine at the Johns Hopkins University. He holds faculty appointments in the departments of Ophthalmology, Biomedical Engineering, Chemical & Biomolecular Engineering, Neurosurgery, Oncology, and Pharmacology & Molecular Sciences.

He was the 2019-2020 President of the Controlled Release Society.

He is an inventor on more than 125 patents and patent applications focused in the area of advanced drug and gene delivery systems. Multiple products based on these patents have been approved by the US FDA and are helping millions of patients. Dr. Hanes has co-founded 10 pharmaceutical companies, and they have more than 10 different drugs in ongoing or planned Phase 2 or 3 clinical trials.

Dr. Hanes is also a Venture Partner with Camden Partners where he serves as the Chief Scientist of the Camden Partners Nexus Fund.

Dr. Hanes was inducted into the National Academy of Inventors in 2014 and is a fellow of the American Association of Pharmaceutical Scientists (AAPS). Awards he has received from the AAPS include the Ebert Prize and the Innovation in Biotechnology Award (which he has won twice). He has been named among “The World’s Top 100 Young Innovators and Leaders in Technology and Business” by the *MIT Technology Review*, “The World’s Most Influential Scientific Minds” by Thompson Reuters (multiple times), and an Edward C. Nagy Investigator by the National Institute of Biomedical Imaging and Bioengineering of the NIH. His degrees are in Chemical Engineering from UCLA (B.S. 1991) and MIT (Ph.D. 1996), and he completed a postdoctoral fellowship in Oncology and Neurosurgery at Johns Hopkins prior to joining the faculty of the Johns Hopkins University in 1998.

Rapid Fire Presentations (RFP), Part 1

Session	Time	Title	Presenter	Affiliation
RFP Part 1 Moderator: Iman Zaghloul (Room 1)	10:30 – 10:38	Development and Evaluation of Thermo-responsive *In-situ* Hydrogels for Extended Release via Subcutaneous Administration	Wenzhan Yang	Astra Zeneca
	10:38 – 10:46	Activ-Blister™ solutions provide superior protection of a model drug product over cold-form foil	Maria Krisch	FreeThink Technologies
	10:47 – 10:55	Preclinical development of thermosensitive hydrogel drug delivery systems for sustained release	Prashant Agarwal	Amgen
	10:55 – 11:03	Evaluating the Impact of Sparse Dissolution Datasets on the Quality of IVIVC Model Validation: Case Study Using Tofacitinib Osmotic Modified Release Formulation	Hao-Jui Hsu	Pfizer
	11:04 – 11:12	Preformulatin Considerations for Making Glimepiride into Orodispersible Film	Yadnya Gharat	Massachusetts College of Pharmacy and Health Sciences
	11:12 – 11:20	Application of Translational Pharmaceutics In Accelerating The Development Of Modified Release Dosage Forms	Aruna Railkar	Quotient Sciences
	11:21 – 11:29	Loss in weight feeder (LWF) performance of Benecel™ PH DC HPMC	Brian Phillips	Ashland

Rapid Fire Presentations (RFP), Part 2

Session	Time	Title	Presenter	Affiliation
RFP Part 2 Moderator: Sameera Sansare (Room 1)	11:30 – 11:38	Comprehensive Monitoring of Testosterone by Microextraction and Ultrafiltration	Zeyad Barakat	Albany College of Pharmacy and Health Sciences
	11:38 – 11:46	In-Vitro Dissolution Study of a Low Strength Reservoir Transdermal Patch Using Testosterone as Model Drug	Ria Vashishth	Massachusetts College of Pharmacy and Health Sciences
	11:47 – 11:55	Endocannabinoids may modify and regulate the Blood Brain Barrier (BBB) permeability	Kofi Hagan	Albany College of Pharmacy and Health Sciences
	11:55 – 12:03	Digital drug formulation and design: critical insights from microstructure imaging	Joshua Lomeo	DigiM Solution
	12:04 – 12:12	Process Understanding using the Consigma Continuous Film Coating in line with Direct Compression Continuous Manufacturing	Antonio Smith	Pfizer
	12:12 – 12:20	Modeling of drying of pharmaceutical wet granules in a fluidized bed dryer using an Eulerian-Langrangian approach	Hossain Aziz	University of Connecticut
	12:21 – 12:29	Risk Mitigation of Excipient-Related Special Cause Variation	Brian Carlin	DFE Pharma

Short Topic Presentations (STP)

Session	Time	Title	Presenter	Affiliation
Pharmacokinetics and Biomarkers Moderator: Marcel Musteata (Room 2)	10:30 – 11:00	Impact of Intraperitoneal Catheter Dimensions on Cellular Response	Jia He	University of Connecticut
	11:00 – 11:30	Minimally invasive nasal depot (MIND) technique for direct CNS delivery of blood-brain barrier impermeant oligonucleotides	Smrithi Padmakumar	Northeastern University
	11:30 – 12:00	A PBPK Approach to Evaluate Pharmacokinetics of Simvastatin in a Developed Non-Celiac Gluten Sensitivity Population	Andrella King	Massachusetts College of Pharmacy and Health Sciences
	12:00 – 12:30	A Novel Blood-Based Biomarker Distinguishes Estrogen-Negative Solid Tumors in Patient Samples	Srinidi Mohan	University of New England
Industrial Pharmacy Moderator: Zhao Li (Room 3)	10:30 – 11:00	Development of PLGA Based Implants Using Hot Melt Extrusion for Sustained Release of Drugs	Amol Batra	Ashland
	11:00 – 11:30	Effect of Hypromellose particle size on interfacial bonding and mechanical strength of bilayer tablets	Shao-Yu Chang	Ashland
Process Modeling Moderators: Xuechun (Lucy) Wang (Room 4)	10:30 – 11:00	Development of a coupled CFD-DEM model for the drying process in a fluidized bed dryer	Sameera Sansare	University of Connecticut
	11:00 – 11:30	CFD modeling of drop dynamics during inkjet based 3D printing process	Tanu Mehta	University of Connecticut
	11:30 – 12:00	CGMD and CFD Simulation of Continuous Manufacturing of Polymeric Micelles	Tibo Duran	University of Connecticut

Academic Research Award (ARA) Presentations

Session	Time	Title	Presenter	Affiliation
ARA Moderator: Dana Gates (Room 5)	10:30-10:40	Introduction		
	10:40-11:00	Impact of Lyoprotectants and Freezing Conditions on the Stability of Freeze-Dried Nanoparticles	Wei-Chung Luo	University of Connecticut
	11:00-11:20	Targeting Multiple OncomiRs using PLGA Nanoparticles for Lymphoma Therapy	Karishma Dhuri	University of Connecticut
	11:20-11:40	Green synthesis and evaluation of anti-oxidative potential of Superparamagnetic Iron Nanoparticles (SPIONs) for the targeted drug therapy	Neha Tyagi	Jamia Hamdard
	11:40-12:00	Physico-biochemical and *in vivo* evaluations of cell-permeable poly-L-histidine patched nanoparticles	Aniket Wahane	University of Connecticut
	12:00-12:20	Anti-inflammatory drug release kinetics and transport mechanism from a long-acting reservoir-based polymeric system	Jia He	University of Connecticut

Round Table Sessions

Session	Speaker (Affiliation)	Title
Inhalation/Respiratory Drug Development Moderators: Vivek Gupta and James Ormes (Room 1)	David Cipolla (Insmed)	Repositioning/Repurposing Drug as Inhalation Products
	Andrew Brunskill (Merck & Co)	Phase and Attribute Control for API for Dry Powder Inhaler Use
	Sandro RP da Rocha (Virginia Commonwealth University)	Nanomedicines for Pulmonary Drug Delivery
Bioanalytical Development for *in vivo* Biomarkers and DMPK Moderators: HaiAn Zheng and Scott Fountain (Room 2)	Jan Beumer (University of Pittsburgh School of Pharmacy)	Mass Balance Studies in oncology and beyond
	Marcel Musteata (Albany College of Pharmacy and Health Sciences)	Can We Tell the Full Story of Drug Concentrations in Biological Samples?
Computational Modeling to Aid Pharmaceutical Development – Solid State Chemistry Moderators: Hyunsoo Park and Heather Frericks Schmidt (Room 3)	Yuriy Abramov (XtalPi)	Guiding Cocrystallization and Solubility Improvement of Pharmaceutical Compounds with Physics-based Modeling
	Dongyue Xin (Boehringer Ingelheim)	A Machine Learning Approach for Pharmaceutical Solvate Prediction
	Mike Lovette (Amgen)	A Model for Solubility Prediction to Guide Solvent Selection within Process Development
Physicochemical and Biophysical Stability Assessments across Therapeutic Modalities Moderators: Sanjay Gayakwad and Kruti Soni (Room 4)	Pradyot Nandi (Bristol Myers Squibb)	A rational preformulation approach for biologics aiding candidate selection at the preclinical stage
	George Bou-Assaf (Biogen)	Biophysical Characterization of AAV products: Challenges and Opportunities

SAVE THE DATE!!

American Association of Pharmaceutical Scientists

Northeast Regional Discussion Group

24th Annual Meeting

April 22, 2022

Hartford Marriott Farmington

15 Farm Springs Road

Farmington, CT 06032

ABSTRACTS

Development and Evaluation of Thermo-responsive *In-situ* Hydrogels for Extended Release via Subcutaneous Administration

Wenzhan Yang[1*], Divya Sharma[1,2,#], Steve Cook[1], Stacey Marden[1], Jianyan Wang[1], Aixiang Xue[3], Dave Wagner[4], Guangnong Zhang[4], Faraj Atassi[1]

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Purpose:

Hydrogels are three-dimensional crosslinked hydrophilic polymeric networks that are tunable to undergo sol-gel transformation in response to temperature, pH, or enzymatic activities. The first of these is known as thermo-sensitive hydrogel or thermogel. Thermogels are important for drug delivery as they are in solution form prior to administration, but undergo gelation in-situ, to form a gel in the body. Two thermogels were investigated for sustained release using tri-polymer poly lactic-co-glycolic acid-PEG-poly lactic-co-glycolic acid and poly(lactide-co-caprolactone)-b-Poly(ethylene glycol)-b-Poly(lactide-co-caprolactone) (PLCL-PEG-PLCL) with model compounds having various physicochemical properties.

Methods:

Gelling temperatures of hydrogels were measured in a glass tube using the reported inversion method. The hydrogel design space was explored by constructing the sol-gel phase diagrams with model compounds. Design of experiments (DOE) was employed to assess the significance of formulation factors. Drug release experiments were conducted in glass tubes equilibrated in a water bath at 37°C. In vivo assessment of the formulation behavior and PK profiles of the chosen hydrogels with a model compound were conducted in rats.

Results:

Increasing the drug load up to 10% resulted in minor decrease in the gelling temperatures for all formulations. The sol-gel phase diagrams are dependent on the drug type. All hydrogels showed extended drug release in vitro except for a highly soluble model compound under the dissolution conditions tested. PK results of the two hydrogels tested did not show significant differences in vivo for a hydrophilic model compound tested.

Conclusions:

PK assessment is required to understand the in vivo performance of in situ hydrogels.

Keywords: hydrogel, gel phase transition, sol-gel phase diagram, in vitro drug release

Activ-Blister™ solutions provide superior protection of a model drug product over cold-form foil

Maria Krisch*[1], Craig Voellmicke[2], Steve Medford[3], Philip Waterman[1], Austin Ziska[1]

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Purpose:

FreeThink Technologies, Inc., Aptar CSP Technologies, and PCI Pharma Services compared the efficacy of Activ-Blister™ packaging configurations with cold-form foil in maintaining the stability of a model tableted drug product. The study also examined whether a predictive stability approach could be successfully used with these desiccant products.

Methods:

An Accelerated Stability Assessment Program (ASAP) study was carried out and growth of the main degradant of the active ingredient was quantified by HPLC analysis. The data were modeled using the ASAPprime® software and included four different packaging configurations: cold-form foil blisters, thermoform incorporating Activ-Blister™ technology with molecular sieve, thermoform incorporating Activ-Blister™ technology with silica gel, and thermoform blisters alone. Four typical ICH storage conditions were also evaluated: 25°C/60% RH, 30°C/65% RH, 30°C/75% RH and 40°C/75% RH. Two different initial relative humidities were modeled to assess the impact of starting water content on shelf-life. To confirm the modeling results, tablets were packaged and stored under these conditions for up to 6 months prior to analysis.

Results:

As predicted from the ASAP study, the packaging configurations can be ranked from most protective to least protective towards degradation in the following way: Activ-Blister™ technology with molecular sieve > Activ-Blister™ technology with silica gel > cold-form foil > thermoform blister alone. The advantage of Activ-Blister™ solutions over cold-form foil was particularly pronounced when the drug product had a high initial water content. ASAPprime® predictions of degradant growth within packaging agreed with the data generated from the stressed blistered tablets at all packaging, storage and initial water conditions.

Conclusions:

Activ-Blister™ packaging configurations incorporating thermoform blisters outperformed cold-form foil blisters in protecting a tablet drug product against chemical degradation over six months. ASAPprime® can effectively model packaging configurations incorporating molecular sieve and silica gel versions of Activ-Blister™ packaging and predict the shelf-life of a product using Activ-Blister™ technology.

Keywords: Stability, desiccant, Activ-Blister™, ASAP, ASAPprime®

Preclinical development of thermosensitive hydrogel drug delivery systems for sustained release

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Purpose:

Sustained release formulations are important tools for converting efficacious molecules into therapeutic products. For example, hydrogels enable the rapid assessment of sustained release strategies, which is especially important during preclinical development where drug substance quantities are limited and fast turnaround times are the norm. This work focuses on the development and characterization of two commercially available thermosensitive hydrogel systems that are made up of block copolymers of poly(lactic-co-glycolic acid)-b-poly(ethylene glycol)-b-poly(lactic-co-glycolic acid) (PLGA) and poly(lactide-co-caprolactone)-b-poly(ethylene glycol)-b-poly(lactide-co-caprolactone) (PLCL), leading to the development of a preclinical formulation platform to routinely and reliably dose molecules requiring sustained release.

Methods:

Mesh size, viscosity, storage modulus and $T_{sol\text{-}gel}$ are some critical attributes of a thermosensitive hydrogel drug delivery system. Understanding the relationship between these attributes is the key to deploy and develop a hydrogel formulation that can release drug at a tunable rate into systemic circulation. Understanding the structure of the gel network is critical to determine the factors controlling the release of therapeutics out of these gels. The structures were characterized via the gel mesh sizes, which were estimated using two orthogonal techniques: small angle X-ray scattering (SAXS) and oscillatory rheology. $T_{sol\text{-}gel}$ was measured using tube-inversion and rheology. In-vitro release was measured by layering PBS onto a drug loaded hydrogel and release was quantified by measuring concentration of drug using RP-HPLC.

Results:

The mesh sizes of these hydrogels (~ 20-60 nm) was larger than the hydrodynamic radius of lysozyme (~ 1.4 nm), indicating that release of lysozyme would be diffusion dominated. *In vitro* experiments showed 2x higher cumulative drug release from PLCL as compared to PLGA, which was correlated to the higher complex viscosity of the PLGA gel, increasing the frictional drag on lysozyme and reducing the diffusivity of lysozyme through PLGA gel network as compared to PLCL.

Conclusions:

In conclusion, two commercially available tri-block copolymers were thoroughly characterized, that can be easily formulated and dosed at room temperature, forming a physically crosslinked hydrogel upon injection. The key factors affecting drug release from these systems were studied and it was demonstrated that these systems can successfully delay the *in vitro* release of a small protein.

Keywords: Preformulation, Controlled delivery, Hydrogel(s), Drug delivery system(s), PLGA

Evaluating the Impact of Sparse Dissolution Datasets on the Quality of IVIVC Model Validation: Case Study Using Tofacitinib Osmotic Modified Release Formulation

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Purpose:

To evaluate the impact that the number and distribution of dissolution data points used to develop a Level A in-vitro in-vivo correlation (IVIVC) for tofacitinib modified-released (MR) tablet has on the percent prediction errors determined during model validation.

Methods:

Dissolution and PK data were used from a previously published level A IVIVC for tofacitinib MR tablets (Eur. J. Pharm. Sci 2020, 147: 105200). In the present study, the dissolution data set was used with four dissolution models (Hill, Weibull, double Weibull, and Makoid-Banakar), as well as raw data, for IVIVC model development. The number of dissolution time points was gradually reduced from the original 41 points to a minimum of 3 points. Fast- and slow-release formulations were used for internal validation and the medium-release formulation was used for external validation. Percent predictions error (%PE) values from each of the modeling scenario were determined.

Results:

When raw data is used, reducing the dissolution points significantly increased %PE and, in some cases, caused validation failures. If time points were properly selected, a validated level A IVIVC model may still be achieved with only 3 data points (one individual internal %PE between 10%-15%). The two best fit dissolution models, Hill and double Weibull models, were selected for further studies as the other 2 models deviated from the raw data and increased PEs. The Hill model was found to be the most suitable model for the tofacitinib MR platform, as it substantially decreased the %PEs under most dissolution data conditions evaluated, while the double Weibull model failed to perform curve fitting when 12 or fewer data points were used. With only 3 dissolution points, the Hill model could adequately capture the dissolution profile of this delivery platform, resulting in a maximum average internal PE of 2.4% and a maximum external PE of 3.4%.

Conclusions:

This study demonstrates more sparser dissolution datasets increase the %PE. Extremely sparse datasets can lead to model validation failures. For this tofacitinib MR platform, fitting sparse dissolution datasets containing a minimum of 3 points to the Hill model was observed to reduces the %PE and likelihood of validation failure

Keywords: Tofacitinib, modified release, IVIVC, extrudable core system, osmotic delivery

Preformulatin Considerations for Making Glimepiride into Orodispersible Film

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Purpose:

Glimepiride is used in patients with non-insulin-dependent diabetes mellitus. FDA Orange Book listed one low strength dosage form. This project investigated the feasibility of making into Orodispersible film (ODF). It is a novel gel formulation with edible polymer in a postage stamp size to dissolve within 1min for rapid drug release. The water solubility found in literatures ranges from partly miscible to <0.004mg/mL. Since partly miscible and very poor solubility are not descriptive terms in the Solubility Table, we set forth to include solubility test.

Methods:

Differential scanning calorimetry examined the purity of active ingredients. HPLC method and standard solutions were prepared according to description in compendium monograph and LiChrosorb RP18 column. Glimepiride of 2.4 mg submerged in a beaker containing 4L water, while some powders of 3.6 and 4.4 mg remained unwetted. 10 mg of glimepiride were further subject to 10L water for 48h prior to UV spectrophotometry and HPLC assays.

Results:

DSC showed that the melt temperature of glimepiride is 213.52oC. The linearity of standard curve was 0.004-1.0mg/mL. System suitability was 0.06%-0.29%. HPLC recorded drug peak at the limit of quantification level from the samples taken from 10 mg in 10 L of water. We further diluted 1 mL of such samples with 4 and 9 mL of acetonitrile. Three small peaks appeared among all HPLC injections, which corresponded to glimepiride retention time in standard samples suggesting that glimepiride is practically insoluble in water.

Conclusions:

ODF as nonreclosables may be considered if patients have difficulties in swallowing glimepiride tablets for two reasons. ODF may be fabricated using solvent casting method. The melt temperature of glimepiride, 213.52°C, should endure the process. Second, glimepiride tablets are low lengths, which enables glimepiride to formulate into ODF, which upper limit is about 30 mg. Since glimepiride is practically insoluble in water, the absorption is expected in intestines, not oral cavity.

Keywords: Glimepiride, Orodispersible Film, Solubility, Differential Scanning Calorimetry, HPLC

Application Of Translational Pharmaceutics In Accelerating The Development Of Modified Release Dosage Forms

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Purpose:

To demonstrate an optimized approach to developing oral modified-release (MR) dosage forms using the Translational Pharmaceutics platform. This approach uses emerging human data to inform adjustment of formulation composition in an adaptive clinical study.

Development of MR formulations is complicated by the interplay between drug molecule, dosage form and gastro-intestinal physiology factors. Therefore, in vitro and preclinical studies often fail to predict formulation performance in humans and in guiding the development of an optimal MR product.

This presentation highlights the use of a formulation design space, real-time manufacturing and a flexible clinical design in overcoming the limitations described above to accelerate successful MR product development whilst maintaining regulatory and quality compliance.

Methods:

A 2-dimensional formulation design-space was defined, with drug release rate and drug dose as the two variables to support in vivo MR product optimization. The clinical protocol complemented the CMC submission, allowing formulation compositions within the approved design space to be selected and manufactured in real-time for testing in healthy subjects.

Results:

Direct-compression matrix tablets were developed for QSC-1, drug loading (x mg—y mg) with in vitro drug release (80%) between 7h—16h achieved using different levels of HPMC. Release profiles and short-term (7-14 day) stability data on the corner prototypes were submitted to the regulatory authority. A five-period cross-over PK study in healthy subjects (N=12) was conducted on MR prototypes (IR tablet as reference). The decision-making strategy involved the use of emerging PK data to guide the selection of the next MR prototype for dosing. Iterative formula composition adjustments within the trial yielded an optimal prototype after 4 dosing periods. Compared to the IR tablet, the lead formulation with higher dose/slower release achieved the target AUC while reducing C_{max} below the $C_{AE\text{-}threshold}$, and increased T_{max} by 5h.

Conclusions:

Translational Pharmaceutics enabled iterative real-time manufacturing and clinical testing of MR formulation prototypes within an approved formulation design space and contributed to the accelerated development (<7 months) of an optimized MR product with desired PK profile (reduced C_{max}, overcoming C_{max} related adverse events (AE), extending the efficacious levels to achieve QD dosing).

Keywords: Translational Pharmaceutics, Modified release, Real time manufacturing, Accelerating development

Loss in weight feeder (LWF) performance of Benecel™ PH DC HPMC

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Purpose:

Continuous manufacturing (CM) is growing more popular in the pharmaceutical industry because of its economic and technical superiority to batch manufacturing.[1] CM requires, however, precise and reliable powder feeding to attain the critical quality attributes (CQA's) expected of pharmaceutical products; loss-in-weight feeders (LWFs), which gravimetrically control powder feed rate, are typically employed for this purpose. LWF testing therefore can confirm CM process robustness. Thus, in this study, Benecel™ PH DC hydroxypropyl methyl cellulose (HPMC), an excipient designed for direct compression, was evaluated using a LWF to determine its potential performance in CM.

Methods:

Materials were evaluated for bulk density and powder flow via a Brookfield Powder Flow Tester (PFT); aeration energy was determined via an FT4 powder rheometer. Feed studies were conducted on a K-Tron, KSU-II LWF using auger twin screws at nominal feed rates of 2 and 12 kg/h. For each trial, material was filled to a height that would cover the hopper blade. During each trial, the values of drive command percentage [i.e. motor velocity] (CMD %), net weight (kg), and mass flowrate (kg/h) were recorded for further analysis.

Each trial was concluded after 5 or more repeat points of 110% CMD were displayed on the K-tron (this is indicative of a point in feeding where the hopper no longer contains enough material to reliably maintain mass flowrate setpoint.)

Results:

Material characterization, via the Brookfield PFT, revealed that Benecel™ K100M PH DC HPMC was more freely flowing than CR material. This was because the DC material possessed higher bulk density (0.35 versus 0.29 g/mL) and was less cohesive. FT4 studies revealed that air velocity reduced Basic Flowability Energy (BFE) more for DC than CR material and at higher air velocity DC material also possessed a lower BFE; both observations suggested less powder cohesion.

At a feed rate of 2 kg/h, Benecel™ K100M PH DC HPMC demonstrated lower average CMD% (10.4%) and CMD% standard deviation (0.82%) than Benecel™ K100M PH CR HPMC (13.5%/1.00%.) At a feed rate of 12 kg/h, Benecel™ K100M PH DC HPMC demonstrated lower average CMD% (60.6%) and CMD% standard deviation (5.5%) than Benecel™ K100M PH CR HPMC (76.8%/6.4%) Lower CMD% and CMD% standard deviation indicated improved feeding performance. Benecel™ K100M PH DC HPMC achieved a smaller RSD% for mass flow rate, especially at the higher setpoint of 12 kg/h. This suggested that the flow of DC HPMC was more tightly controlled and would lead to less complications in downstream processing. Thus, Benecel™ K100M PH DC HPMC exhibited improved feeding performance compared to Benecel™ K100M PH CR HPMC.

Conclusions:

Material characterization revealed that Benecel™ K100M PH DC HPMC had intrinsically superior powder properties such as less cohesion and higher bulk density, leading to a better flow profile when tested on a

Brookfield PFT. This result correlated well with testing conducted on a LWF feeder which more closely resembles a real world, continuous manufacturing scenario. Through LWF testing, Benecel™ K100M PH DC HPMC demonstrated improved feeding performance compared to Benecel™ K100M PH CR HPMC. LWF testing can practically study powder flowability and predict real-world powder processability.

Reference:

1. Leuenberger H. New trends in the production of pharmaceutical granules: batch versus continuous processing. Eur. J. Pharm. Biopharm. 2001: 52(3): 289-96

Keywords: continuous manufacturing, direct compression, feeder

Comprehensive Monitoring of Testosterone by Microextraction and Ultrafiltration

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Purpose:

Total testosterone (TT) concentration has historically been used to describe its effects on the body, but this does not provide the needed information about the unbound free testosterone (FT) available to carry out the various metabolic and cellular processes. Testosterone binds to two plasma proteins, sex hormone binding globulin (SHBG) and albumin. The concentrations of the plasma proteins vary according to a person's age, ethnicity, and disease state. The main objective of this research was to apply new pharmacokinetic analysis techniques to simultaneously measure free and total concentrations of testosterone as well as the plasma binding capacity for a sample.

Methods:

The free and total concentrations of testosterone in solutions of albumin and in plasma samples were determined experimentally using microextraction and ultrafiltration techniques. Each of these techniques was used with two quantification procedures: addition of an isotopically labeled testosterone standard and a method based on multiple sequential analysis of the same sample. All approaches were applied for both testosterone and phenytoin (reference compound). Hypersep SpinTips (ThermoScientific) were used for microextraction and Centrifree centrifugal filters (Millipore) were used for ultrafiltration. Corresponding equations were established to quantitatively determine both TT and FT as well as the plasma binding capacity (PBC). LCMS was used to analyze the biological samples.

Results:

For ultrafiltration, the FT concentration was determined first and was utilized to determine TT and PBC. For microextraction, the extraction constant and the amount extracted were used to determine all three types of concentrations. All results were compared to the standard analytical protocol based on protein precipitation. Methods based on addition of labeled compound were the simplest, fastest, and most reproducible. Methods based on ultrafiltration were more accurate for measuring FT while methods based on microextraction were more sensitive and more accurate for measuring TT. The overall accuracy of the new approaches for PBC, FT, and TT was between 94-109%, 87-113%, and 94-122% respectively.

Conclusions:

The above-mentioned techniques were successfully used to determine the PBC as well as the free and total concentrations of testosterone. These methods can be utilized to personalize drug dosage and therapy to individual patients.

Keywords: Testosterone, protein binding, free concentrations, normalized concentrations

In-Vitro Dissolution Study of a Low Strength Reservoir Transdermal Patch Using Testosterone as Model Drug

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Purpose:

The aim is to prepare a sustained release once-daily transdermal patch containing 12.2 mg of testosterone using different rate-control polymers and release membranes respectively, and investigate the similarity factor f2 to compare the dissolution profiles of the patches. The FDA similarity factor is a measurement of the similarity profile in percent dissolution between the two curves. However, this measurement has not been applied to low strength dosage forms, such as testosterone replacement therapy, especially when such replacement therapy becomes a medical indication where patients may be taking several different dosage forms such as capsules, tablets, film or gel therapy anywhere from one to seven times a day.

Methods:

While the USP HPLC assay for testosterone uses a 21-min gradient method, our study utilized a modified an isocratic method developed by Samanidou VF, et al. (2007), with a Luna C18 column and validated using stability indication studies of acid, base, heat and hydrogen peroxide (presented in 2020 AAPS PharmSci 360, Poster# 894491). The transdermal patches were compounded using two different control polymers (Carbomer 941 and HPMC) and two release membranes 9702 and 9712 (gift of 3M, St Paul MN), keeping the same payload. The in-vitro dissolution study was adopted from the FDA In-vitro Dissolution Database using USP Apparatus V, with modification of the sampling schedule.

Results:

The release profiles were no different between Carbomer and HPMC whether the release membrane was 9702 or 9712 based on FDA similarity factor, f_2 values. However, the t-test showed that when 9712 was used as the release membrane the testosterone release was observed to be faster from Carbomer than from HPMC from 6h to 24h (17.68±2.93%, n = 3), while the f_2 value at 24h was 57.4 (not significant, but trending towards significant value, < 50).

Conclusions:

Based on the sample size and the use of testosterone as the model drug, we find that the t-test is more sensitive than f_2 similarity factor in determining the drug release differences between the two formulations in a low strength dosage form having low % of drug release.

Keywords: Testosterone, Carbomer 941, HPMC, FDA similarity factor, t-test.

Note: Plan to increase sample size when a chemical ordered for the second time arrived.

Endocannabinoids may modify and regulate the Blood Brain Barrier (BBB) permeability

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Purpose:

Endogenous Cannabinoid System (ECS) comprises the signaling network of endocannabinoids (eCB), such as N-arachidonoylethanolamine (AEA) and 2-Arachidonylglycerol (2AG), their receptors, and enzymes of biosynthesis or metabolism. Recently, Cannabinoid receptors were also found at the blood brain barrier (BBB), the interface between the central nervous system (CNS) and peripheral circulation. To systematically investigate the ECS of BBB at cellular and molecular level, we characterized CB1 and CB2 receptors in a human brain microvascular endothelia cell line (HBMEC). This study is to confirm our hypotheses that eCBs may modify and regulate the BBB physical integrity, especially under pathological stress such as ischemia.

Methods:

The impact of AEA and 2AG on endothelial membrane integrity was assessed by trans-endothelial electronic resistant (TEER) under normal and ischemic conditions. CB1 and CB2 in the HBMEC were quantified and monitored by RT-PCR and Western-blot protein analysis. The level of AEA and 2AG, either endogenous or added, were quantified and monitored by LCMS.

Results:

The CB1 expressions level were higher than CB2 in HBMEC under normal condition. Under ischemic stresses, the expression of CB1 decreased while CB2 increased, and both recovered within 24 hours. The barrier permeabilities decreased upon adding AEA and 2AG under bother normal and ischemic condition, which indicates the BBB proactive effects of eCB.

Conclusions:

Our study confirmed the presence of the ECS at the BBB. The endocannabinoids may maintain and regulate the BBB integrity through the ECS, especially under stress. Further studies to discover and understand the complete ECS of the BBB and their mechanism is essential to understanding the distribution and regulation of eCB of the BBB, as well as evaluate the impact of medical cannabis on the BBB, which is a critical drug delivery barrier and therapeutic target.

Keywords: Endogenous Cannabinoid System (ECS), endocannabinoids (eCBs), blood brain barrier (BBB), Cannabis, permeability, trans-endothelial electronical resistant (TEER)

Digital drug formulation and design: critical insights from microstructure imaging

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Purpose:

Microstructures are at the foundation of optimizing drug formulations and release performance. From the particle size of active ingredients to microporosity, these factors are critical towards understanding release mechanisms and engineering an effective drug product. To characterize these interconnected microstructures, an analytical technique must have high resolution, sensitivity, representative sampling, and 3D visualization. Conventional techniques are lacking in one or many of these areas. Digital drug formulation (DDF) is a novel platform that implements high resolution 3D imaging coupled with artificial intelligence (AI) analytics to quantify and understand the impact of microstructures on drug release.

Methods:

The DDF platform utilizes microstructure data obtained by 3D imaging modalities, including x-ray microscopy (XRM) and focused ion beam scanning electron microscopy (FIB-SEM). Through a cloud computing system DigiM I2S, image data is constructed into a digital sample of the drug product or intermediate. This digital twin of the real sample can be continually reused and reanalyzed. The microstructures are identified and labeled through AI-based analysis. A matrix of quantitative descriptors including volume fractions, particle size, particle dispersion, porosity, and transport properties are computed. These descriptors can be numerically adjusted to generate new drug microstructures. The behavior of real and generated microstructures on drug release is then studied with image-based release prediction.

Results:

The DDF workflow has been applied to study the sensitivity of drug release from a PLGA microsphere by changing the microstructure and evaluating image-based release profiles. Comparing the real microstructure with numerically generated microstructures, a significant impact on drug release was observed. By removing porosity, a release period of 3 weeks was extended to beyond 30 days. This evaluation provided guidance to formulation scientists on the longest drug release possible with this microsphere platform.

Conclusions:

The DDF model provides a framework to study the sensitivity of microstructures to formulation parameters (e.g. polymer choice, particle morphology) and process conditions (e.g. temperature, compaction force). The DDF platform can generate numerical drug formulations, evaluating the impacts of drug loading and micro-porosity. The numerical model allows a formulation scientist to rapidly traverse multi-variable parameter space, narrowing down an optimal formulation and best processing conditions.

Keywords: Microstructure, digital transformation, imaging, formulation

Process Understanding using the Consigma Continuous Film Coating in line with Direct Compression Continuous Manufacturing

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Purpose:

The purpose of this presentation is to share process knowledge and experience that the Portable Continuous Miniature and Modular (PCMM) team in Groton Connecticut has gained using the GEA Consigma Continuous Film Coater (CFC) for continuous film coating from a direct compression line.

Methods:

Using the knowledge gained from clinical and development batches the recipe and operation of the CFC was optimized for coating appearance and throughput across a variety of tablet sizes, shapes, and colors.

Results:

Improvements to in-process monitoring methods, process parameters and other operational updates allowed for the successful manufacture of 12 clinical batches. Knowledge management and improvements to the control strategy lead to increased yield and operational effeicienies on future manufactures. In 2020 the experience of the CFC was expanded to five different colors, three different active ingredients, three different tablet sizes, and two grades of coating solution.

Conclusions:

Knowledge gained by the PCMM team in Groton and the usage of the CFC allows for the production of high quality and reliable film coated tablets operating in line with a direct compression line.

Keywords: Continuous, CFC, PCMM, Coating, Manufacturing

Modeling of drying of pharmaceutical wet granules in a fluidized bed dryer using an Eulerian-Lagrangian approach

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Purpose:

Fluidized bed drying is a topic of interest for scientists and engineers because of its complicated physics and its presence in a wide range of industrial processes e.g. pharmaceutical product manufacturing, food processing, wood processing, reduction of iron ore, flue gas cleaning, the roasting of sulfide ores, drying of coal, catalyst industry and many more. Here, we propose a model based on coupled Computational Fluid Dynamics (CFD) and Discrete Element Method (DEM) approach to simulate the drying of granular particles in fluidized bed dryer associated to the drug manufacturing process. The drying process of wet granular particles in a fluidized bed dryer involves momentum, heat and mass transfer between the particles and the drying medium which is inherently a multiphase-multicomponent flow problem.

Methods:

The model was implemented using an opensource software CFDEM® coupling where the fluid phase was solved by OpenFOAM® codes and the motion of particles were calculated by LIGGGHTS® codes. The information between the fluid phase and particles were exchanged at certain time intervals. The software CFDEM® coupling was used because of its flexibility to include new models and its ability to handle large scale systems.

Results:

The model was validated with the results available in existing literatures. The CFDEM® coupling was capable of capturing the physical fluidization phenomena and predicting the fluidization velocity correctly for a packed particle bed. Our model was capable of capturing the heat and momentum transfer between the particles and the drying medium. Present work is going on the modification of the model to include moisture transfer between the particles and drying medium. It was observed that the fluidization of particles significantly improved the performance of the fluidized bed dryer.

Conclusions:

This validated coupled CFD-DEM model provides a better qualitative and quantitative understanding of the effects of different process parameters on the drying process which can be beneficial for the industry. This model can further help set up reliable scale up, troubleshooting or optimization schemes by greatly replacing the burden of the cost of design of experiments.

Keywords: Computational Fluid Dynamics, Discrete Element Method, Multiphase-Multicomponent Flow, Fluidized Bed Dryer

Risk Mitigation of Excipient-related Special Cause Variation

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Purpose:

The many degrees of freedom associated with excipients represents a significant but not exclusive source of Special Cause Variation (SCV) in pharmaceutical products. Although unpredictable and experimentally inaccessible several methods can be used to mitigate this risk.

Methods:

- Excipient Categorisation (Kano)
- Multivariate Monitoring
- Supplier Communication

Results:

- Kano categorisation of the impact from excipient variability into direct and immediate ("performance") vs indirect and delayed ("basic") avoids the binary categorisation into critical/non-critical, criticised in the 2011 FDA Validation Guidance.
- Multivariate monitoring techniques increase the detectability of product or process drift relative to traditional univariate monitoring and change control, where sudden product failure often occurs without warning.
- Supplier materials understanding may help identify Critical Material Attributes not included in pharmacopoeial or supplier specifications.

Conclusions:

SCV is less understood than Common Cause Variation. The latter is the inherent variability of the system and provides the statistical basis of traditional process control. Excipient variability is often associated with SCV but not necessarily causative. SCV is emergent and unpredictable and therefore cannot be factored into experiments during development. SCV is inevitable during a product lifecycle and must be factored into the Control Strategy using the methods discussed herein.

Keywords: Excipient Variability Impact Mitigation Multivariate

Impact of Intraperitoneal Catheter Dimensions on Cellular Response

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Purpose:

Intraperitoneal catheters have been applied in continuous intraperitoneal insulin infusion (CIPII) to directly deliver insulin into the intraperitoneal space for decades[1]. However, catheter obstruction is one of the factors limiting the transition of this technology into the wider diabetic population. The intraperitoneal implantation of the catheters elicits a series of inflammatory events that can ultimately result in catheter blockage and failure to deliver insulin. It has been reported that the dimensions of the implant can influence the recruitment of inflammatory cells to the implantation site[2-3]. Hence, understanding the effect of dimensions of intraperitoneal catheters (including the outer diameter of catheters and the length of implanted catheters in the IP space) on the host response at the cellular level can provide important insight to modulate the inflammatory response, improve the longevity of the catheters, and thus increase patient acceptance of CIPII.

Methods:

Catheters with either different outer diameters (0.1-inch vs 0.048-inch) or different length of IP portion were implanted intraperitoneally into rats and then explanted at different times. A gross macroscopic analysis was performed, followed by cytological evaluation of the blocked/encapsulated tissue surrounding the catheter tip end using various staining and imaging methods.

Results:

Macrophages, fibroblasts and foreign body giant cells were the major components of tip blockages for all groups. Compared to the catheters with an OD of 0.1 inch, the catheters with a smaller OD of 0.048 inch triggered less inflammation as evident from a reduction in the thickness of the fibrous capsule for all time points. In addition, catheters with longer IP portions shows a lower degree of catheter encapsulation than the catheters with shorter IP portions.

Conclusions:

The dimensions of intraperitoneal catheters influence the host response to catheters in both short and long durations of implantation. These results provide new insights to improve catheter design and thus decrease the incidence of catheter obstruction. In addition to reducing the inflammatory response to catheters at the implantation site, a good catheter design must maintain functionality (e.g. successful passage of insulin through the catheter lumen area) to achieve long-term performance.

References:

1. Renard, E., et al., *Catheter complications associated with implantable systems for peritoneal insulin delivery*. Diabetes Care. 1995. 18(3):300-6

2. Niikura, K., et al., *Gold nanoparticles as a vaccine platform: influence of size and shape on immunological responses in vitro and in vivo*. ACS nano, 2013. 7(5): p. 3926-3938.

3.Wang, Y., et al., *Foreign body reaction to implantable biosensors: effects of tissue trauma and implant size*. Journal of diabetes science and technology, 2015. 9(5): p. 966-977.

Keywords: Insulin delivery, device, foreign body reaction

Minimally invasive nasal depot (MIND) technique for direct CNS delivery of blood-brain barrier impermeant oligonucleotides

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Purpose:

The minimally invasive nasal depot (MIND) technique is a novel method of direct trans-nasal delivery to the central nervous system (CNS), derived from an endoscopic endonasal procedure routinely performed in outpatient ear, nose and throat (ENT) clinics. The goal of this study was to evaluate delivery and transfection of brain-derived neurotrophic factor (BDNF) expressing antagoNAT (AT) to the brain of naïve rats using MIND.

Methods:

Sprague Dawley rats were subjected to the MIND procedure for administering (BDNF AT as two formulations: AT in Pluronic F-127 Gel (AT-G) and AT in Liposome-in Pluronic F-127 Gel (AT-LiG) to investigate both pharmacokinetic and pharmacodynamic responses. The experimental animals were sacrificed at 2, 6, 12, 24, 48, 72 and 96 hours post-administration and AT levels and BDNF protein concentrations were measured from different sub-regions of rat brain. BDNF AT delivery using MIND was compared with the standard intracerebroventricular (ICV) approach.

Results:

The rat model of MIND established the minimal invasiveness and safety of the overall procedure relative to the traditionally followed invasive ICV or Intrathecal (IT) routes for CNS delivery. Both AT-G and AT-LiG formulations could provide sustained AT distribution in all brain sub-regions until 96 hours. Pharmacokinetic analyses revealed a more uniform profile with increased mean residence time (MRT) for AT-LiG relative to AT-G with a t_{max} of 12 hours and C_{max} ranging from 21.7- 46.7 pg*mL-1. The lack of measurable AT levels in plasma samples suggests the direct CNS-uptake offered by MIND through olfactory epithelium without any dependance on secondary- peripheral distribution. BDNF protein levels were significantly upregulated in the brain sub-regions of all animals administered with both formulations in comparison to the naïve BDNF levels. Compared to ICV administration of AT in solution, AT-Gel delivery via MIND showed relative bioavailability of > 40% particularly in those brain sub-regions such as hippocampus and substantia nigra.

Conclusions:

MIND approach provides efficient CNS delivery for BBB-impermeant drugs such as BDNF expressing AT with high direct brain uptake and distribution. The technique holds significant translational potential as a reliable and safer therapeutic strategy for CNS delivery of disease-modifying biological therapeutics.

Keywords: CNS delivery, Brain delivery, antagoNAT, BDNF, neurodegenerative diseases

A PBPK Approach to Evaluate Pharmacokinetics of Simvastatin in a Developed Non-Celiac Gluten Sensitivity Population

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Purpose:

The objective of this study was to assess the ability of a PBPK Non-Celiac Gluten Sensitivity (NCGS) model to predict plasma exposure of drugs in adult patients. A NCGS virtual population was developed, based on changes observed in an *in vivo* rat model that exhibits gliadin-induced enteropathy and pathological changes in jejunal mucosa, altered GI permeability, and altered gene expression of hepatic and intestinal transporters and metabolic enzymes.

Methods:

We used the SimCyp® compound file for simvastatin, a substrate of Pgp, OATP1B1 and Cyp3A4 to test our developed NCGS population model. Starting from Simcyp® Virtual Healthy Population, various parameters were changed in the developed NCGS population based on in vivo study in the rat model and literature values. Following a multiple daily oral dose of 20 mg of simvastatin, C_{max} and AUC in plasma and liver tissue were predicted in both Healthy and NCGS virtual human populations.

To validate the population model, we compared our results to the only published simvastatin clinical pharmacokinetics in enteropathy patients. The predicted simvastatin C_{max} ratio of the developed Population/ Simcyp® Virtual Healthy Population was thus compared to the observed published C_{max} ratio of simvastatin in celiac patients/ healthy volunteers. The model was also used to predict the simvastatin liver tissue concentrations for both healthy and NCGS patients

Results:

The calculated folds of predicted/ observed values of simvastatin in healthy and NCGS populations fall between (0.5-2). Thus the developed model appropriately predicted the plasma concentrations of simvastatin in these patients.

Our model confirms that the simvastatin C_{max} in NCGS patients increases by a factor greater than 2 compared to healthy volunteers. The model has also predicted a 2.8 fold increase in AUC. Moreover, it predicted an increase in simvastatin liver concentration and AUC of NCGS patients by a factor of 1.9 and 3.4 respectively.

Conclusions:

The Simcyp® NCGS population was successfully developed and correlated well with published clinical data. This population model can potentially be used in predicting the pharmacokinetics of multiple drugs in NCGS patients which represents 6 % of the US population.

Keywords: Simvastatin, NCGS, celiac, PBPK

A Novel Blood-Based Biomarker Distinguishes Estrogen-Negative Solid Tumors in Patient Samples

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Purpose:

We had previously identified Nw-hydroxy L-Arginine (NOHA) as a blood-based biomarker to distinguish estrogen receptor negative (ER–) from estrogen receptor positive (ER+) cancers, in breast (Issued U.S. Utility Patent 10,073,099), and in ovarian tumor patients (U.S. Utility patent, pending application 16/570,747). In this study we assess the utility of a competitive ELISA assay for NOHA measurement.

Methods:

Plasma samples from ER–/ER+ ovarian and breast cancer patients, categorized as low-grade tumor, were assessed for NOHA by a competitive ELISA method, that utilized a proprietary monoclonal antibody (U.S. Utility patent, pending application 16/570,747) specific for NOHA. The ELISA assay was evaluated on sensitivity, selectivity, precision, dilution linearity and percent recovery parameters. Statistical difference was set at $p<0.01$, from 4 repetitive samples ($n = 4$), for each tested criteria/condition.

Results:

Plasma NOHA measurement in ER– versus ER+ cancer patients, using the competitive ELISA assay, showed a reduction of ≥ 33.9 % in only ER– cancer patient plasma samples. This ER– tumor selective plasma NOHA reduction maintained its distinction between ER– ovarian cancer versus ER– breast cancer subtypes, with a ≥ 48.8% greater NOHA reduction in ER– Ovarian tumor than seen with ER– breast cancer. The reliability of the ELISA protocol was confirmed with the low percent-covariance, for all tested parameters of sensitivity (≤ 8.2%), selectivity (≤ 8.6%), precision (≤ 12.6%), dilution linearity (≤ 11.2%) and recovery (≤ 6.7%). Additionally, the sensitivity and selectivity in NOHA quantification by this ELISA assay was similar to those achievable with LC-MS assay.

Conclusions:

This study provides the first evidence suggesting the utility of a competitive ELISA assay for NOHA measurement. The methodology is simple yet sensitive for ER– cancer prognosis, and disease progression monitoring without the need for expensive analytical equipment (such as LC-MS), large lab space, or specialized technical training. It also displays its effectiveness in distinguishing between ER– tumor subtypes (i.e. ER– breast versus ER– ovarian tumors), and the ability for its development as a point-of-care kit.

Keywords: Estrogen-negative tumor, NOHA, biomarker, NOS2, nitric-oxide, serous ovarian carcinoma, breast cancer

Development of PLGA-Based Implants Using Hot Melt Extrusion for Sustained Release of Drugs

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Purpose:

Poly(lactic-co-glycolic acid), or PLGA, is one of the most extensively used polymers for medical and drug delivery applications. Matrix implants are PLGA based drug delivery systems which have solid, cylindrical rod shape and rigid structures. These implants allow for the controlled release of a drug for a period of months or even years. The release of the drug from these implants depends on the site of administration, drug solubility, polymer, and matrix properties such as erosion or diffusion of drug. The objective of this study was to investigate the impact of drug solubility, PLGA composition and extrusion processing conditions on drug release behavior from implants.

Methods:

Ester-terminated and acid-terminated Viatel™ PLGA with a 50:50 and 75:25 (LA:GA) co-polymer ratio were obtained from Ashland Specialties Ireland. Carbamazepine, a poorly water-soluble drug with a solubility of 18 mg/L was selected as a model compound.

Implants obtained from extrusion containing a specified amount of drug were weighed and incubated in 1 mL of PBS in a thermomixer set to 37 °C and 300 rpm. At predetermined time points, 1 mL (supernatant) of sample was drawn and filtered through a 0.45 µm filter. The volume was substituted with fresh buffer. Drug amount in the sample was quantified using reverse phase high-performance liquid chromatography (HPLC).

Results:

The study determined the suitability of an HME process to obtain a dispersion of drug inside a polymeric matrix providing sustained drug release. The applicability of a hot-melt extrusion process to produce a homogeneous dispersion of drug inside the polymer matrix was confirmed. It was demonstrated that processing PLGA polymer via HME was suitable to enable sustained drug release. Differences in drug release between drug loaded implants indicated that the sustained release of drug depends on API characteristics, polymer properties and the interaction of PLGA mono- or oligomers with the API. The present study showed that extrusion process parameters may affect the distribution of drug into the PLGA matrix and therefore, the release of drug.

Conclusions:

API characteristics, polymer properties and process conditions are all important factors that impact the stability and release profile of a PLGA-based implant. Viatel™ bioresorbable polymers can be custom produced with defined chemical structures and open the door for the formulation of unique and innovative drug delivery systems.

Effect of Hypromellose particle size on interfacial bonding and mechanical strength of bilayer tablets

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Purpose:

Benecel™ HPMC is a widely used hydrophilic polymer in drug controlled-release solid dosage formulations, in which bilayer tablets have attracted lots of attention. In bilayer tablets, interfacial bonding strength and tablet mechanical strength are two key attributes. The goal of this study is to evaluate the impact of Benecel™ K100M XR or XRF HPMC particle size on interfacial bonding and mechanical strength of bilayer tablets from the viewpoint of material properties and compression parameters.

Methods:

Bilayer tablets are composed of one immediate and controlled-release layer. The controlled-release layers were formulated with either Benecel™ K100M XR or XRF HPMC grades. The Dv 90 for these grades is <250 and <190 respectively. Tablet mechanical strength was measured under compression forces of 10, 15, 20, and 25 kN. Interfacial bonding strength were measured by the tensile test under various compaction forces on bilayer tablets. After splitting bilayer tablets, the interfacial surface of each layer was analyzed using a Nanovea profilometer.

Results:

Bilayer tablets formulated with Benecel™ K100M XRF exhibited consistently stronger mechanical strength and thinner thickness than Benecel™ K100M XR tablets. In addition, Bilayer tablets containing microcrystalline cellulose were stronger and thinner than those with lactose. As for Interfacial bonding strength, Benecel™ K100M XRF tablets were higher than Benecel™ K100M XR, which can demonstrate the benefit of smaller particle size and higher compressibility of Benecel™ K100M XRF. Both of material properties contributed to larger particle contact area in the bulk and at the interface.

Conclusions:

Particle size affects mechanical properties of bilayer tablets, tablet mechanical strength and interfacial bonding strength, due to different compactability and interfacial surface area. The smaller particle size, Benecel™ K100M XRF HPMC, can contribute to higher tablet mechanical strength and greater interfacial bonding strength between layers, as compared to Benecel™ K100M XR HPMC. The incorporation of Benecel™ K100M XRF HPMC can be beneficial to the robustness of bi-layer tablets.

Keywords: Benecel™ HPMC, Bilayer tablets, particle size, drug release, mechanical strength

Development of a coupled CFD-DEM model for the drying process in fluidized bed dryer

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Purpose:

Drying is an essential unit operation in pharmaceutical dosage development process and is extensively used in wet granulation. Of all the drying processes, fluidized bed drying with a multiphase flow is the most popular technique because of the advantages that it provides, such as excellent solid-gas mixing, enhanced heat-mass transfer, which leads to efficient drying. However, a lack of fundamental understanding of the drying process of wet granules can potentially impede a manufacturing process. Thus, it is critical to understand the effect of process parameters on the quality attributes of the granules. Understanding these parameters using experiments can be expensive and time-consuming. Thus, an experimentally validated numerical model has been proposed to study the effect of process parameters on the flow and quality attributes of pharmaceutical granules.

Methods:

Drying process of wet granules is a multiphase flow process that contains a continuous phase (air), modeled by Computational Fluid Dynamics (CFD) and a discrete phase (solid), modeled by Discrete Element Method (DEM). Two commercial software, ANSYS FLUENT for CFD and EDEM for DEM were coupled to implement the CFD-DEM approach. A user-defined function was used to incorporate heat transfer and mass transfer between particles and air. Different heat transfer correlations and initial moisture content were explored. Ranz-Marshall correlation was used for mass transfer and Li-Mason correlation was used for the heat transfer. Different inlet air velocities and initial moisture contents were explored.

Results:

Experiments for validation were conducted in Glatt GPCG-2 fluid bed dryer at different process parameters. Preliminary study was conducted using dimensions from a reference paper. Once the coupling was confirmed, dimensions of the actual Glatt equipment to be used was created. Different inlet air velocities were used in the new dimension. The effect of heat transfer was studied through the velocity and pressure contours and product temperature. The mass transfer was evaluated by the loss of water fraction at each time step.

Conclusions:

Such a coupled CFD-DEM approach can provide a good model for studying the multiphase fluidization process. It contributes towards faster optimization of manufacturing process with lesser batch failures.

Keywords: CFD-DEM, fluidization, drying, heat transfer, mass transfer

CFD modeling of drop dynamics during Inkjet based 3D printing process

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Purpose:

3D printing is a rapidly expanding technology in various fields including pharmaceutical industry as it offers multiple advantages such as personalization of medicine, fabrication of complex dosage form and high drug loading. Binder jet 3D printing involves jetting of binder solution on top of the powder layer in layer-by-layer fashion. The properties of tablets are highly dependent upon jetting of the ink/binder solution from the printhead nozzle. In this study a preliminary finite volume based computational fluid dynamics (CFD) model has been developed to simulate liquid drop formation in a piezoelectric inkjet printhead.

Methods:

Finite volume method coupled with Volume of fluid (VOF)-Continuum Surface Force (CSF) model was used to solve the Navier-Stokes equations along with continuity equation and VOF advection equations. VOF model is used to track the advection of the interface and the surface tension effects were accounted using CSF model. This model was implemented using ANSYS Fluent software. The piezoelectric nozzle simulated here works by squeeze mode and creating pressure inside the nozzle when voltage is applied which consequently leads to drop jetting. The system geometry was created in ANSYS Space Claim with a nozzle diameter of 40µm and a stand-off distance of 4mm. Meshing was performed using ANSYS meshing. The pressure generation inside the nozzle was implemented by corresponding inlet velocity boundary condition.

Results:

Mesh independent study was performed by analyzing different mesh element sizes to find the optimum mesh element size in order to avoid the effect of different mesh sizes on the simulation results. The effect of different inlet velocity values was also studied. At present we are studying different ink solutions using the developed CFD model and validating the simulation data with experimental data.

Conclusions:

The drop formation is known to be influenced by the surface tension, viscosity, and density of the ink solution which will be studied using this model for different ink solutions used during the experimentation. This CFD model will help in evaluating the jettability of different ink solutions thereby helping to improve the printing process.

Keywords: Piezoelectric, ANSYS-Fluent, Volume of Fluid, Jettability

CGMD and CFD Simulation of Continuous Manufacturing of Polymeric Micelles

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Purpose:

Amphiphilic block copolymers are frequently used to generate polymeric micelles. The hydrophobic core of the micelles is used to encapsulate lipophilic drug molecules, while a good stability can be maintained by the outer hydrophilic shell in aqueous system. An innovative turbulent co-flow platform was previously developed to continuously produce drug loaded polymeric micelles. Intermolecular forces, such as dipole-dipole forces, was found to lead to polymer aggregation. The jet flow characteristics were also found to impact to the formation of the micelles. However, the underlying mechanism as well as details of material attributes are yet fully understood. In order to investigate the underlying mechanism and to predict the effect of material attributes and process parameters on the quality of the polymeric micelle formulation, we implemented a multiscale computational approach to simulate the formation of micelles under the coaxial turbulent jet flow conditions.

Methods:

All-atom (AA), coarse-grained molecular dynamics (CG-MD), as well as computational fluid dynamics (CFD) simulations have been conducted to not only reveal the effects to material attributes and processing parameters during the micelle formation, but also as parametric case studies for this process. The CFD simulation was implemented using Large Eddy Simulation (LES) model in COMSOL Multiphysics incorporating energy equation and high-resolution mesh in mixing area. The initial conditions introduced into the simulations were based on the experimental results of PEG-PLA (2kD-1.7kD). We applied both CHARMM and MARTINI force-fields for all-atom as well as coarse-grained simulations, respectively. The initial coordinates of models and their force field parameters were generated by CHARMM software and MARTINI forward mapping approach. The steepest decent algorithm was used in energy minimization with a 20 fs time step followed by 10 ns equilibration step in isothermal−isochoric ensemble at temperature of 300 K. The production runs were performed in isothermal-isobaric ensemble using the Nosé−Hoover thermostat and the Parrinello−Rahman barostat at pressure of 1 atm every 20 fs time steps. Periodic boundary conditions were adopted to study self-assembling process of empty and drug loaded polymeric micelles. For all simulations, block copolymer was randomly packed in the simulation box with explicit water and ethanol. Computations were performed in High Performance Center Supercomputer Cluster at the University of Connecticut.

Results:

With newly developed all-atom structure and CHARMM force field, we optimized CG-MD forward mapping strategy and force field parameters incorporating MARTINI standard beads and recent developed S-beads. We observed that polymeric micelles were formed successfully, and the predicted physical dimension matched those obtained in the actual experiment. The simulation of micelles formation and the size distribution the

micelles indicate that CHARMM, MARTINI force fields (FFs) can adequately capture the experiment behavior and results. By adjusting Smagorinsky coefficient (Cs) of LES model companied with energy and mass transfer equations, CFD simulations also successfully reproduced the unique flow patterns of ethanol/water and predicted accurately the temperature variations within the co-axial turbulent jet.

Conclusions:

To obtain a formation temperature comparable with the experiment, it is inevitable to incorporate the heat of mixing term into energy equation in CFD simulations. In MD simulations, optimized MARTINI forward mapping approach and copolymer building blocks allow us to track the self-assembly process of micelle formation. The multiscale approach used in this work can be effectively utilized as a powerful tool in the process of discovery, development, and optimization of new drug delivery systems in the co-flow continuous processing.

Keywords: Continuous processing, Polymeric micelles, Molecular dynamics simulations, Multiscale, Anticancer drug delivery

Impact of Lyoprotectants and Freezing Conditions on the Stability of Freeze-Dried Nanoparticles

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Purpose:

Freeze-drying can improve the long-term storage stability of nanoparticles (NPs) and maintain their effectiveness for disease prophylaxis and treatment, but either a poor formulation design or inappropriate freezing conditions can lead to irreversible particle aggregation or structure damage. The effects of various lyoprotectants and ice nucleation temperature on the stability of different types of NPs have not been studied comprehensively, hence this research can provide us with a better understanding on their impact and facilitate the advancement of freeze-dried NP products.

Methods:

Three types of nanoparticles: solid lipid nanoparticles (SLNs), polymeric nanoparticles (PNs), and liposomes were freeze-dried with one of the selected lyoprotectants, including sucrose, trehalose, or mannitol using various freezing rate and ice nucleation temperature. At several time points after the freeze-drying process, the solid state of the formulations was evaluated by using differential scanning calorimetry and X-ray powder diffraction, and the particle size distribution was measured after reconstitution by using dynamic light scattering.

Results:

Lyoprotectants were requisite to maintain the particle size distribution of SLNs and liposomes throughout the freeze-drying process, whereas PNs remained in the original particle size even without lyoprotectants. Slow freezing rate increased both the mean particle size and polydispersity of SLNs and liposomes. While the control of ice nucleation did not induce significant differences in particle size distribution of NPs right after freeze-drying, it improved the long-term stability of SLNs.

Conclusions:

Different types of NPs have distinct vulnerabilities to particle aggregation during freeze-drying, and the choice of lyoprotectants is crucial for both protecting them from aggregation during the process and maintaining their stability during storage. Both the lyoprotectants and freezing conditions are important factors to consider in order to produce qualified freeze-dried NPs with good long-term stability.

Keywords: freeze-drying, nanoparticles, lyoprotectants, controlled nucleation, freezing rate

Targeting Multiple OncomiRs using PLGA Nanoparticles for Lymphoma Therapy

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Purpose:

Antisense therapeutics have garnered prominent attention due to their potential to target a myriad of disease conditions. The recent FDA approval of Vyondys 53 (Sarepta Therapeutics) is a ray of hope for Duchenne Muscular Dystrophy patients. MiRNAs (miRNAs) are small RNA molecules that control the translation of proteins and play key roles in regulating various cellular processes in the body. Targeting the overexpressed miRNAs in cancer (oncomiRs) using antisense strategy (antimiR) is one of the emerging cancer therapies. A major hurdle towards the clinical success of antisense therapy is the delivery. Here we formulated PLGA nanoparticles to encapsulate the antimiRs and evaluated their efficacy both *in vitro* and *in vivo* for lymphoma therapy. In this study we aim to target oncomiR-21 and oncomiR-155 simultaneously as a new strategy using two different synthetic nucleic acid analogs- Phosphorothioates (PS) and Peptide nucleic acid (PNA).

Methods:

We formulated antimiR-21 and antimiR-155 nanoparticles (NPs) using Poly(lactic-co-glycolic) acid (PLGA) polymer by double emulsion solvent evaporation technique and performed series of NP characterization to measure morphology (SEM), size (DLS), surface charge (zeta potential), and release profile (UV absorbance). We tested the cellular uptake properties of NPs via confocal microscopy and flow cytometry analysis. The oncomiR-21 and oncomiR-155 gene repression was determined using RT-PCR. Colony forming efficiency of these NPs were also evaluated. The efficacy of this strategy was evaluated by performing cell viability assay. We also evaluated the performance of these NPs in xenograft mice model.

Results:

We noticed ~90% oncomiR-155 knockdown and ~60% oncomiR-21 knockdown by simultaneous treatment of antimiR-21 and antimiR-155 NPs. We also observed ~70% and ~25% reduction in colony forming efficiency with PS NPs and PNA NPs respectively. We observed ~50% reduction in oncomiR-21 levels and ~80% reduction in oncomiR-155 levels in *in vivo* mice models.

Conclusions:

This project provides the frame work of targeting multiple oncomiRs for other cancer therapeutics too at the interface of nucleic acid chemistry and nanotechnology. The future goals include to study if this targeting strategy can help overcome chemoresistance, which is one of the major hurdles in cancer treatments.

Keywords: PLGA nanoparticles, antimiR, phosphorothioate, peptide nucleic acid

Green synthesis and evaluation of anti-oxidative potential of Superparamagnetic Iron Nanoparticles (SPIONs) for the targeted drug therapy

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Purpose:

The purpose of the study was to fabricate the iron oxide nanoparticles using green synthesis method and characterized for its anti-oxidant and anti-cancer potential.

Methods:

The iron oxide nanoparticles were synthesized using co-precipitation technique and characterized by Dynamic light scattering (DLS), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Radiation (FT-IR), X-ray diffraction (XRD) and Inductively coupled Plasma -Mass Spectrometry (ICP-MS). The magnetic property was assessed by Vibration Sample Magnetometer (VSM). The MTT assay and anti-oxidant activity was also carried out using ABTS scavenging assay. The uptake of the nanoparticles was studied by Confocal Laser Scanning Microscopy (CLSM).

Results:

The SPIONs were analyzed for particle size by Dynamic Light Scattering (DLS) and zeta potential which was found out to be -33.5 mV which showed that particles are stable. The nanoparticles showed anti-oxidant activity with an IC50 value of 50.92 µg/ml. The iron content was found out to be 520.85 mg/Kg in the colloidal suspension. The magnetization saturation was found to be 57.05 emu/g by VSM. The MTT assay was carried out using two cell lines MCF-7 and T47D cell lines and IC50 value was found out to be 50.86 µM and 45.98 µM respectively. The depth of permeation of fluorescent dye over the layers of intestinal lumen was evaluated by observing the intestinal tissues along with the 'z' axis. The fluorescence was detected up to 59.9 µm in case of plain dye solution, while the depth of permeation increased to 119.1 µm in case of SPIONs formulation containing ROD-B.

Conclusions:

The fabricated Iron oxide nanoparticles showed good anti-oxidant activity as evident by ABTS assay. They showed better permeation than plain rhodamine solution due to their nanoparticulate size as confirmed by Scanning electron microscopy. They are superparamagnetic in nature as manifested from vibration sample magnetometry.

Keywords: Green synthesis, superparamagnetic, MTT assay, Anti-oxidant activity, Confocal Laser Scanning Microscopy

Physico-biochemical and *in vivo* evaluations of cell-permeable poly-L-histidine patched nanoparticles

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Purpose:

Several cationic polymeric nanoformulations have been investigated for improving the transfection efficiency of small molecules and nucleic acid-based drugs. However, the excess of positive charge limits their clinical transition as it often leads to severe cell and tissue-based toxicity. Herein, we investigated a series of cationic poly-(lactic-co-glycolic acid) (PLGA)-histidine based nanoformulations for enhanced cytoplasmic delivery with minimal toxicity. We tested PLGA-histidine formulations for delivery of small molecule and nucleic acid based (peptide nucleic acid targeting microRNA-155) drugs.

Methods:

We formulated a series of PLGA-histidine formulations using double emulsion solvent evaporation technique. We have conducted comprehensive physico-biochemical characterizations of histidine-based formulations including loading analysis, release kinetics and cellular uptake studies using confocal and flow cytometry-based methods. Different solvent mixtures were explored for improved morphology, uniformity and size. Furthermore, the structural arrangement of histidine in these PLGA formulations was investigated using small-angle neutron scattering (SANS) experiments. For proof of principle, PLGA-poly-L-histidine formulations containing chemotherapeutic agent and peptide nucleic acids targeting microRNA-155 were tested *in vitro*. Extensive *in vivo* efficacy studies were performed in xenograft mice model including tumor growth inhibition and immunohistology. In addition, safety of PLGA-poly-L-histidine nanoformulations was established by histology, blood chemistry and complete blood count analysis.

Results:

We have successfully developed and optimized PLGA-histidine formulation with optimum solvent conditions that generated polymeric nanoparticles of small particle size (~170nm hydrodynamic diameter) with remarkable polydispersity index. PLGA-poly-L-histidine nanoformulations showcased highest cellular uptake by clathirin-mediated endocytosis than other PLGA formulations. SANS experiments confirmed the presence of small poly-L-histidine patches of 1 nm in size along the surface of the PLGA nanoparticles. Furthermore, PLGA-poly-L-histidine showed superior inhibition of tumor growth in comparison to PLGA *in vivo*. Immunohistochemistry analysis indicated lower proliferation and high apoptosis in PLGA-poly-L-histidine treated tumors with minimal toxicity.

Conclusions:

We have demonstrated an easy, scalable poly-L-histidine containing PLGA nanoformulations with superior cellular distribution and *in vivo* efficacy compared to other PLGA formulations. We established that aforementioned formulation can effectively deliver small molecules (chemotherapeutics) and nucleic acid analogs (PNA) for various therapeutic applications in a safe manner.

Keywords: Poly-L-Histidine, PLGA, nanoparticles, endosomal escape, microRNAs

Anti-inflammatory drug release kinetics and transport mechanism from a long-acting reservoir-based polymeric system

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Purpose:

The foreign body reaction (FBR) is one of the major challenges reducing implants' biocompatibility and longevity. Dexamethasone has shown promising compatibility to mitigate FBR. Polydimethylsiloxane (PDMS) provides a platform that enables a long-term (e.g. 3-5 years) dexamethasone release in a controlled manner. Various channeling agents can be added to modulate drug release rate. However, variations of drug solubility, the relaxation of polymer chain as well as the geometry of the reservoir lead to the differences in release patterns. Potential issues, such as dose dumping in the *in vivo* release, may results in toxicity. Accordingly, understanding the release kinetics and transport mechanism can provide an insight to design an efficient and safe dexamethasone eluting system to mitigate the foreign body reaction and achieve a long-term functionality of implants.

Methods:

A dexamethasone reservoir was prepared using a customized designed mold. A single type of channeling agent was incorporated in each reservoir. *In vitro* release testing (real-time and accelerated) coupled with imaging analysis was performed to correlate the release profiles with internal structure change. The swelling ratio of drug reservoirs as well as release profile was compared between different formulations using various mathematical functions.

Results:

PDMS polymeric system showed a controlled capability of drug release over a long duration. In the absence of channeling agent, less than 5% of drug released till 250 days. Highchi model showed the best fitting. The addition of channeling agent in the PDMS matrix increased drug release rate as well as swelling ratio and porosity in the following rank order: NaCl > sucrose > Na-CMC> PEG, with a tendency to switch from Highchi to zero-order model.

Conclusions:

PDMS reservoirs showed a channeling agent-dependent dexamethasone release profile. Influenced by the type and amount of channeling agents, kinetic modeling of dissolution profiles indicated that the mechanism of dexamethasone release ranges from diffusion governed or Fickian transport to anomalous type or non-Fickian transport. Despite a good ability to modulate release rate by some channeling agent, swelling to a large extent is likely to change the function of the implant and negatively influences its role of mitigating the foreign body reaction.

Keywords: long-acting implant, release mechanisms, swelling, outside-in pore formation, foreign body reaction

Inhalation and Respiratory Drug Development

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Drug delivery via inhalation has been widely explored over last several decades. While the lungs offer a great avenue to deliver drugs for both local and system diseases, they present one of the most complicated physiological systems in the human body. Several novel approaches have been investigated to understand the complexity of new inhaled product development, and for repurposing/repositioning of currently available drugs as inhaled products. In this session, feasibility, and impact of few of these approaches will be discussed by our panelists.

Mr. Andrew Brunskill will discuss how changes in APIs phase behavior impact its manufacturing, and development of a robust dry powder inhaled product, and will present a development program aimed at addressing the phase behavior challenges of the APIs.

Dr David Cipolla will highlight the importance and logistical challenges associated with repositioning currently available oral/injectable products as inhaled regimens, a rational choice for local lung delivery. He will use examples of marketed and in-development repositioned products to establish complexities associated with such an approach.

Dr Sandro da Rocha will focus on emergence of orally inhaled nanomedicines for localized delivery to the lungs. He will use examples of dendrimer nanomedicines to navigate two of the most common issues with inhaled nanomedicines, (i) enhancing local aerosol accumulation; and (ii) modulating nanomedicine interaction with lung's physiological environment.

Repositioning/Repurposing Drugs as Inhalation Products

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It may come as a surprise that many of the early therapies developed to treat asthma and chronic obstructive pulmonary disease (COPD) were initially given orally or by injection and were later repositioned as inhaled products. This includes epinephrine, corticosteroids and the selective beta-2 agonists. In hindsight, the rationale for this change in delivery format appears obvious. Very little of the dose administered orally or by injection typically reaches the lung; thus, higher doses must be administered to be effective. Inhalation pharmaceutical development rarely follows the linear path that was originally outlined, and the target product profile often changes due to external factors or internal challenges. This presentation will describe the marketed inhaled products as well as examples of emerging inhaled products that represent repositioned or repurposed molecules.

Phase and Attribute Control for API for Dry Powder Inhaler Use

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A thorough understanding of the impact of API phase and particle attributes is critical for its use in dry powder inhalers (DPIs). Understanding the phase behavior throughout API manufacture, drug product manufacture and storage is a prerequisite in the development of a robust product. This work will detail a development program with a challenging phase landscape and will describe the variety tools and studies that were utilized during development.

Nanomedicines for Pulmonary Drug Delivery

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Formulation of orally inhaled nanomedicines can afford unique opportunities for the treatment of both local lung and systemic diseases. In order to realize those opportunities, however, we need to (i) understand how to modulate the interaction between the nanomedicines and the lung physiological environment and (ii) how to engineer efficient aerosol formulations of those nanomedicines. In this roundtable I will present some highlights of our efforts in designing dendrimer nanomedicines for local lung administration, with a focus on cancer.

Bioanalytical Development for Biomarkers & DMPK

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Pharmaceutical analysis plays a critical role in drug discovery and product development. At the core of this discipline are physicochemical and mathematical tools that help reveal the mechanisms of drug actions in physiological systems, as well as tracking the kinetics of absorption, metabolism, distribution and excretion (ADME) through the body. Qualitative and quantitative analysis of biomarkers, drugs and metabolites are becoming more and more sensitive and powerful. This roundtable forum will discuss the common and critical strategies of biomatrix sampling, method optimization, and data interpretation that are shared between biomarker and pharmacokinetics researchers, to stimulate more insightful approaches to further improve data-accuracy, throughput-efficiency, bio-relevance, and PK-PD-correlation.

Keywords:

pharmacokinetics, drug metabolism, biomarkers, LCMS, protein binding, mass balance, microdialysis, microextraction sampling

Mass Balance Studies in oncology and beyond

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A mass balance study investigates the plasma pharmacokinetics and excretion of both the unchanged drug and the total radioactivity (drug and metabolites), and allows elucidation of the metabolic fate of a drug. The main objective is the maximum recovery of the radioactive dose in urine and faeces, and sometimes expired air. Quantitation of drug related products is performed by conventional liquid scintillation or use of highly sensitive accelerator mass spectrometry.

Keywords:

Mass balance, metabolic fate, radioactivity, mass spectrometry

Can We Tell the Full Story of Drug Concentrations in Biological Samples?

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Many drugs have low therapeutic indices and large interindividual variability in plasma concentration, but also have great therapeutic potential. One of the main impediments to finding good correlations between drug concentration and effect at population levels is the high inter-individual variability in drug distribution between body components and target receptors.

Implementation of the precision medicine initiative as it relates to drug therapy requires analytical methods that provide pharmacogenomic, proteomic, and metabolomic data in addition to the usual drug concentration time course; furthermore, this often has to be done for a cocktail of drugs. To reduce cost and patient inconvenience, these data should be provided from a single small biological sample. Therefore, it is crucial to employ sample preparation methods that supply all the needed fractions while also providing information about distribution in the body and reversible binding among sample components.

In this regard, processing methods based on microdialysis, microextraction, and ultrafiltration are gaining popularity in clinical laboratories. Such sample preparation methods were successfully applied to investigate proteomics, metabolomics, free concentrations, and normalized concentrations.

Key Words:

microdialysis, microextraction

Computational Modeling in Pharmaceutical Development: Solid State Chemistry

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In this round table discussion experts will present their advances of computational modeling and discuss how solid state predictions aid the development of a drug. The solid form of an active pharmaceutical ingredient (API) can influence its solubility, manufacturability and stability. The pharmaceutical industry does a considerable amount of experimental work to identify a suitable solid form of an API and study its physical properties. Computational methods have been developed to support and now supplant experimental activities for pharmaceutical solids. These models have been used to guide solid state chemistry experiments through the selection of solvents, coformers and counterions. Computational methods using quantum chemistry and machine learning algorithms can even predict the crystal structure of an API from its two dimensional structure, without any experimental inputs or crystallographic knowledge. Crystal structure prediction and machine learning have been used to determine the propensity to crystallize more stable solid forms or solvates and hydrates of drug. Computational modeling can also predict the physical properties of an API, such as solubility, crystal shape, stability, etc., aiding its process and formulation development.

Keywords:

solid state chemistry, computational modeling, solubility, crystallization, solid form, polymorphism

Guiding Cocrystallization and Solubility Improvement of Pharmaceutical Compounds with Physics-based Modeling

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Solubility improvement of pharmaceutical compounds may be achieved by a chemical modification of the lead compound and/or by change of the solid form of the API (for example, by cocrystallization). A physics-based approach will be presented, which does not rely on any prior knowledge and explicitly describes the solid-state contribution, in order to guide the improvement of poor solubility during the lead optimization.[1] Since experimental cocrystal screening may be time and cost consuming, various computational approaches were recently proposed for a rational coformer selection to guide screening experiments.[2-6] However all those methods ignore the crystal packing contribution to cocrystallization. To address this limitation, an application of the crystal structure prediction (CSP) based approach to rational coformer screening will be presented.

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A Machine Learning Approach for Pharmaceutical Solvate Prediction

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The solid form of an active pharmaceutical ingredient (API) has significant impact on API material properties and drug product efficacy hence solid form control and engineering is a critical step in small molecule drug development. In this work, we have trained and tested machine learning models to predict solvate formation propensity for pharmaceutically relevant organic molecules.[1] Training and testing datasets can be readily extracted from the Cambridge Structural Database (CSD). The machine learning models, requiring only 2D structures as input, were able to predict solvate formation propensity for organic molecules with high success rate. Application of the machine learning models is demonstrated with a set of twenty drug-like molecules. Overall, the results show that machine learning models can be used as practical tools for fast and accurate prediction of solvate formation of pharmaceutical molecules.

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A model for solubility prediction to guide solvent selection within process development

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Solvent selection to obtain adequate yield and impurity rejection is a critical activity in the development of crystallization processes for compounds. This activity requires the determination of solubilities for a solute molecule (moreover a polymorph of a solute molecule) in a variety of different solvents and solvent combinations. Within a process development setting, the accurate determination of solubility for the entire set of possible process solvents and solvent blends is often impractical due to material and time concerns. A predictive model was developed to better facilitate the exploration of single solvent systems and blends.

This model was developed from a mechanistic perspective for crystal growth and dissolution, which is most applicable at temperatures far from (much colder than) the melting point of the crystal. The model can be implemented based on either the regression of a limited set of solubility data and the subsequent prediction of solute characteristics (magnitude of polar, dispersive and hydrogen bonding interactions, size) or using first principles-based approaches to approximate these characteristics directly. The regression approach has proven to be efficient (requiring minutes) and accurate for single solvent systems. This model has been extended to mixtures of two solvents and coupled with crystallization process design calculations to predict yield and provide a rough process outline. The intention being that once a “good” system has been determined using the model it can be verified experimentally.

Recently, this model was regressed and tested using a set of measured solubilities (617 single solvent measurements and 418 mixed solvent measurements) obtained by a working group within the Enabling Technologies Consortium. In this presentation the model formulation, regression steps and results are provided.

Physicochemical and Biophysical Stability Assessments across Therapeutic Modalities

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This roundtable focuses on biophysical characterization of complex molecules and their various applications. Identification of physical and chemical liabilities associated with new biologics molecules employing short-term and long-term forced degradation methods is a critical step which is followed by subsequent analysis using biophysical characterization techniques. The first part of this roundtable will discuss mitigation of molecule associated liabilities, that are identified by preformulation approach, with either formulation development scheme or by rational mutations in the protein sequence. The second part will discuss how traditional biophysical methods of protein characterization can be applied to AAV products. Challenges associated with biophysical tools as well as newer methods to overcome them will also be discussed.

Keywords:

Biophysical characterization, Adeno-associated viruses (AAV), Biologics, Mitigation strategies, Stability assessment, and Formulation development

A rational preformulation approach for biologics aiding candidate selection at the preclinical stage

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Rigorous characterization of biologics molecules at the preclinical stage is critical in the swift transition of candidates from the discovery phase to clinical phase. Within BMS, physical and chemical liabilities associated with new biologics molecules are identified employing short-term and long-term forced degradation methods with subsequent analysis using SEC, icIEF, MS peptide mapping and CE-SDS. In this presentation, 2 approaches will be discussed. First, a preformulation approach that is adopted for molecules exhibiting liabilities that can be mitigated by a formulation scheme. Second, a more thorough method of eliminating chemical liabilities is undertaken by rational mutations in the protein sequence. Overall, the choice of approach is based on the stability data generated in the pre-clinical stage allowing enough flexibility to select the strategy for clinical candidate selection.

Biophysical Characterization of AAV products: Challenges and Opportunities

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The structural complexity of AAV-based products presents several challenges for the biochemical and biophysical characterization of AAV products. We describe some of the traditional biophysical methods used for protein characterization and how they could or could not be applied for AAV products. We list some of the challenges associated with limited sample availability, and the high sample amounts required by some biophysical tools, and how we overcame them with new technology or methodology.