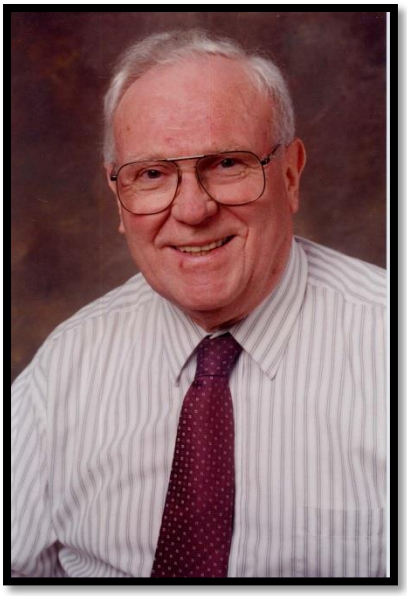
Dr. David J.W. Grant Symposium

Solid-State Pharmaceutics



June 14-16, 2023

University of Minnesota
Twin Cities Campus
Moos Tower 2-690

COLLEGE OF PHARMACY

UNIVERSITY OF MINNESOTA
Driven to Discover℠

6th David J.W. Grant Symposium
on
SOLID-STATE PHARMACEUTICS

June 14-16, 2023

Program Chair

Prof. *Changquan Calvin Sun*

Department of Pharmaceutics, University of Minnesota

Program Committee Members

Prof. *Lian Yu*, University of Wisconsin-Madison

Dr. *Geoff G.Z. Zhang*, Abbvie Inc.

Event Coordinator

Amanda Hokanson

College of Pharmacy

June 14, 2023

4:30 – 6:30pm **Evening reception (Campus Club)**
6:30 – 7:30pm **Dinner**
7:30 – 7:45pm **Welcome**
7:45 – 8:30pm **Keynote:** "Developing Quality Tablets through Materials Science and Engineering"
Changquan Calvin Sun (University of Minnesota)
2022 recipient of "David J. W. Grant NIPTE Distinguished Scholar Award in Basic Pharmaceutics"

June 15, 2023 (Day 1)

7:00 – 8:00am **Breakfast (Moos Tower 2-690)**

8:00 – 8:10am **Welcome**
Dr. Changquan Calvin Sun (program host)

Session I Crystalline Pharmaceuticals and Crystallization

8:10 – 8:50am **Effect of Free Surface on Crystal Nucleation and Polymorph Selection in Molecular Liquids and Glasses**
Lian Yu (University of Wisconsin-Madison)

8:50 – 9:30am **Mechanism of Stabilization of Amorphous Dispersion above its Overlap Concentration (*c**): Delay of the First Nucleation Event**
Sichen Song (University of Minnesota)

9:30 – 9:45am **GROUP PHOTO (3rd Floor Weaver-Densford Hall) & BREAK**

9:45 – 10:25am **Intelligent Cloud-Based Algorithms for Reducing Risk in Crystallization Process Development**
Mike Bellucci (XtalPi)

10:25 – 11:05am **Computational Studies on the Crystallization Development and Characterization of Pharmaceutical Crystals**
Yuriy A. Abramov (J-Star)

11:05am – 12:00pm **Flash presentations by poster presenting authors**

12:00pm – 1:30pm **Lunch and Poster session**

1:35 – 2:15pm **Solid Form Complexity and Chameleonic Behavior of Conformationally Flexible Paritaprevir**
Ahmad Y. Sheikh (Abbvie)

2:15 – 2:55pm **Solid Form Risk Assessment During Development: Examples of Early Form Screening and the Impact of Crystal Structure Prediction**
Jon Selbo (Eli Lilly)

2:55 – 3:10pm **BREAK**

Session II Amorphous Pharmaceuticals

3:10 – 3:50pm **Assessing the Crystallization Propensity of Amorphous Solid Dispersions Using the Time-Temperature-Transformation Diagram**
Raj Suryanarayanan (University of Minnesota)

3:50 – 4:30pm **Oral Delivery of BCS IV Compound: 50+% Drug Loaded Formulations of Redispersal Amorphous Nanoparticles**
Devalina Law (Abbvie)

4:30 – 5:10pm **Novel Total Diffraction Methods for Amorphous Material Characterization**
Simon Bates (Rigaku Americas)

5:10pm **ADJOURN DAY I (Posters are open through the evening)**

June 16, 2023 (Day 2)

7:00am – 8:00am **Breakfast (Moos Tower 2-690)**

Session III Novel Technologies

8:00 – 8:40am **Manifold Embedding of Molecular Quantum Information for Chemical Deep Learning**
Tonglei Li (Purdue University)

8:40 – 9:20am **What Atomic Force Microscopy Can See on Organic Crystals**
Igor Sokolov (Tufts University)

9:20 – 10:00am **Material Sparing Estimation of Bioavailability and Drug Precipitation Using An Artificial Gut Simulator**
Ron Siegel (University of Minnesota)
Helen Hou (Genentech)

10:00 – 10:15am **BREAK**

10:15 – 10:55am **The Membrane Permeability of Nonpermeable Drug Particles**
Na Li (University of Connecticut)

10:55 – 11:35am **Solid Form Landscape: Changes and Challenges in the Last Decade**
Z. Jian Li (Pharmaron)

11:35am – 1:30pm **Lunch and Poster Session** *(please remove posters at end of session)*

Session IV	**Solids Development**
1:30 – 2:10pm	**Development of ASD Formulation for Clinical Studies - From Amorphous Theoretical Solubility Calculation to ASD Tablet Development** Wei Zhang (Genentech)
2:10 – 2:50pm	**Drug Product Manufacturing Challenges for Amorphous Solid Dispersions and Hydrated APIs** Kapil Arora (Pfizer)
2:50 – 3:05pm	**BREAK**
3:05 - 5:00pm	**Panel discussion: Outstanding Problems and Emerging Research Trend in Pharmaceutical Solid State Research**
5:00pm	**Closing remarks**

Posters will be presented throughout the symposium in the 2nd floor hallway of Moos Tower.

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David J.W. Grant and Marilyn J. Grant Fellowship in Physical Pharmacy University of Minnesota

1. Yushi Feng	2004 - 2005
2. Amardeep S.B. Bhalla	2005 - 2006
3. Dabing Chen	2006 - 2007
4. Enxian Lu	2007 - 2008
5. Pengyun Zeng	2008 - 2009
6. Sunny P. Bhardwaj	2009 - 2011
7. Sayantan Chattoraj	2011 - 2012
8. Michael R. Burcusa	2012 - 2013
9. Frederick Osei-Yeboah	2013 – 2014
10. Wei-Jhe Sun	2014 – 2016
11. Shao-yu Chang	2016 – 2018
12. Kunlin Wang	2018 - 2019
13. Hongbo Chen	2019 – 2020
14. Yiwang Guo & Navpreet Kaur	2020 – 2021
15. Jayesh Sonje	2021 – 2022
16. Gerrit Vreeman	2022 – 2023

AAPS David J.W. Grant Research Award in Physical Pharmacy

1. Steve R. Byrn	2009
2. Lian Yu	2011
3. Raj Suryanarayanan	2013
4. Anthony Hickey	2015

David J. W. Grant NIPTE Distinguished Scholar Award in Basic Pharmaceutics

1. Dale E. Wurster	2018
2. Kenneth Morris	2020
3. Changquan Calvin Sun	2022

Invited Speaker Presentations

Keynote

Developing Quality Tablets through Materials Science and Engineering

Changquan Calvin Sun, Ph.D.

Department of Pharmaceutics, University of Minnesota
308 Harvard St. SE, WDH 9-177, Minneapolis, MN 55455
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Abstract. Tablets are important for drug delivery due to their excellent stability, good patient compliance, low manufacturing cost, and ability to be produced in large quantities. However, designing a quality tablet product is challenging because several performance criteria must be met simultaneously. To meet these criteria, a formulator must choose excipients from several functional groups, each of which has tens or more possible options. Given the enormous number of possible combinations of excipients, it is difficult to obtain an optimal formulation for a given drug. Additionally, the optimal formulation also varies with the dose and physicochemical properties of each drug. Developing a high-quality tablet is, therefore, an extremely challenging task. Formulators need to overcome several challenges to ensure robust performance (e.g., dissolution, stability, content uniformity, low friability) and manufacturability (e.g., powder flow, tabletability, punch sticking). Historically, the pharmaceutical industry has relied on trial-and-error approaches to develop tablet products, guided by the design of experiments. This empirical approach is both time- and API-intensive, but there is still no guarantee of quality after all these efforts. As a result, pharmaceutical companies often face problems with tablets not meeting established quality criteria, and in the worst case, product recall becomes necessary. Guided by the concept of the Materials Science Tetrahedron, we have employed various particle and crystal engineering approaches to address tablet manufacturing problems and ensure superior performance. This approach has led to a significant reduction in API consumption and the time required for developing high-quality tablets. Our efforts are aimed at filling knowledge gaps to enable the ultimate digital design of tablets based on molecular structure.

Biography: Dr. Sun is a Professor of Pharmaceutics in the Department of Pharmaceutics at the University of Minnesota. He earned his Ph.D. in Pharmaceutics from the University of Minnesota in 2000. After spending 8 years in the pharmaceutical industry, he returned to the University of Minnesota as an Assistant Professor. Dr. Sun's research focuses on the formulation development of tablet products by appropriately applying principles of materials science and engineering principles. This includes 1) crystal and particle engineering for superior powder flow and compaction properties, and 2) understanding and controlling common pharmaceutical unit operations, such as blending, granulation, and tableting. He has published over 240 papers in these areas with more than 12,400 citations (Google Scholar). Dr. Sun is a fellow of the AAAS, AAPS, and RSC. He received the *2019 Ralph Shangraw Memorial Award from the International Pharmaceutical Excipient Council (IPEC)* and the *2022 David J. W. Grant NIPTE Distinguished Scholar Award in Basic Pharmaceutics*.

Effect of Free Surface on Crystal Nucleation and Polymorph Selection in Molecular Liquids and Glasses

Lian Yu, PhD

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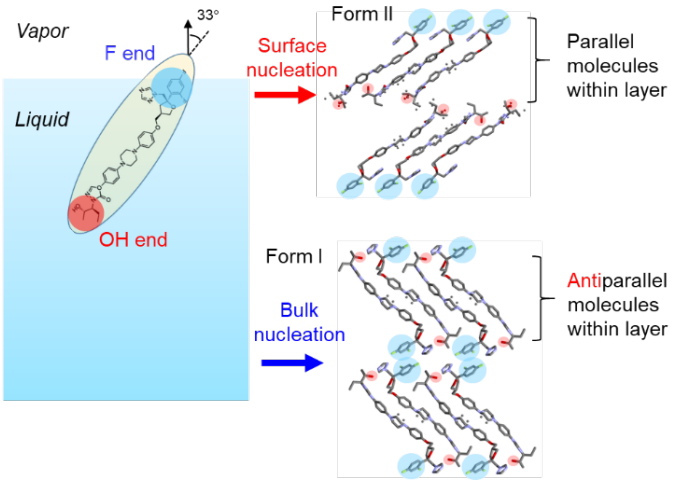
Abstract. Molecules at a liquid/vapor interface experience a different environment from those in the bulk, leading preferred orientation, layering, and enhanced mobility. How does this affect the crystal nucleation process? The answer to this question is important for any amorphous material with a free surface, but despite its fundamental importance, the understanding in this area remains limited. We have measured the rates of crystal nucleation at the surface and in the bulk of molecular liquids. We find that surface nucleation can be vastly faster than bulk nucleation, by up to 12 orders of magnitude, and select a different polymorph. For the systems that exhibit this phenomenon, D-arabitol [1] and posaconazole [2], the surface molecules have an anisotropic organization that promotes the nucleation of a polymorph that is slow to nucleate in the bulk. The surface-nucleating polymorph has a polar and layered structure, and resembles the structure of the liquid/vapor interface. In contrast, water and acetaminophen [3] show more modest surface enhancement of nucleation without polymorph switch. The diversity of behaviors reflects the different degrees of surface reconstruction relative to the bulk and whether a polymorph exists that can benefit from the surface environment to nucleate. Our results highlight the importance of a liquid/vapor interface on crystal nucleation and polymorph selection in amorphous drugs, atmospheric water, and nanodroplets of metals. References: [1] Yao, X. et al. *J. Am. Chem. Soc.* **2022**, *144*, 26, 11638–11645. [2] Yao, X. et al. *J. Chem. Phys.***2022**, *157*, 194502. [3] Wu, H.; Yao, X. et al. *Crystal Growth and Design* **2022**, *22*, 5598–5606.



Biography. Lian Yu is Professor of Pharmaceutical Sciences and Professor of Chemistry at the University of Wisconsin-Madison. He received a B.S. in chemistry from Peking University and a Ph.D. in physical chemistry from The Ohio State University. Before joining UW-Madison, he was a research scientist at Eli Lilly. His laboratory studies crystallization, polymorphism, glasses, and amorphous drug formulations.

Mechanism of Stabilization of Amorphous Dispersion above its Overlap Concentration (*c**): Delay of the First Nucleation Event

Sichen Song

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Abstract. Recently, we proposed a rheological approach for predicting physical stability of amorphous solid dispersions (ASDs) based on de Gennes's polymer overlap concentration (*c**) concept in polymer physics [Song, S,; et al. *J. Pharm. Sci.* 2023, 112, (1), 204-212]. We showed that the *c** value correlates strongly with both accelerated and long term stability (under ambient conditions for one year) against crystallization. When polymer concentration is below *c**, dilute ASDs exhibit similar crystallization tendencies to those of pure amorphous drug. For polymer concentrations exceeding *c**, ASDs exhibit greatly enhanced stability. The present study focuses on the mechanism of effective inhibition of crystallization, i.e., crystal nucleation and growth, using the *c** concept. Using D-sorbitol/polyvinylpyrrolidone (PVP) as a model system, our data show that when polymer concentration is below *c**, the time of the first nucleation event of D-sorbitol/PVP ASDs is almost identical to that of neat amorphous D-sorbitol. The first nucleation time dramatically increases when polymer concentration exceeds *c**. Our results suggest that the elevated physical stability of ASDs with polymer concentration above *c** is due to the effective inhibition of the first nucleation event.

Biography. Sichen Song is a third year Ph.D. candidate under the supervision of Prof. Ronald A. Siegel at Department of Pharmaceutics, University of Minnesota, where his thesis research focuses on development of high drug loaded amorphous solid dispersion formulations with higher quality, lower cost, and acceptable physical stability. He received a B.S. in Pharmaceutical Sciences from Shenyang Pharmaceutical University and a M.S. in Pharmaceutics from the University of Minnesota. He received a 2022 graduate student award from the International Pharmaceutical Excipients Council (IPEC) of the Americas Foundation.

Intelligent Cloud-Based Algorithms for Reducing Risk in Crystallization Process Development

Michael A. Bellucci*[,1], Anke Marx*[,2], Bing Wang[1], Liwen Fang[1], Yunfei Zhou[1], Chandler Greenwell[1], Zhuhong Li[1], Dirk Wandschneider[2], Jan Gerit Brandenburg[2], Guangxu Sun[1], Sivakumar Sekharan[1], Axel Becker[2]

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[2] Merck KGaA, Frankfurter Str. 250, A022/001, 64293 Darmstadt, Germany
bellucci@xtalpi.com

Abstract. Crystallization is the most widely used separation and purification process in the pharmaceutical industry. The resulting crystal structure and corresponding crystal morphology isolated from this process can have a profound influence on the physical properties and manufacturability of drug product APIs. Consequently, the ability to characterize the crystal polymorph landscape and control the crystal morphology are two fundamental aspects of pharmaceutical manufacturing. At XtalPi, we have developed a cloud-based computational platform that combines advanced physics-based algorithms with A.I/machine learning algorithms in order to mitigate polymorph risk and support rational design of crystallization experiments for improved morphological control. We highlight various applications from our Crystal Structure Prediction and Morphology platforms and discuss our recent investigation of the effect of polymer additives on the crystal growth of metformin HCl. This study was performed both with experiments and computational methods with the aim of developing a combined screening approach for crystal shape engineering. Additionally, we have developed analysis methods to characterize the morphology "landscape" and quantify the overall effect of solvent and additives on the predicted crystal habits. Further analysis of our molecular dynamics simulations was used to rationalize the effect of additives on the growth rate of specific crystal faces.

Biography. Dr. Michael Bellucci is a Senior Director at XtalPi, Inc. where he leads a research team that develops algorithm technologies for solid form development and risk assessment as well as drug discovery. Prior to his current role, he was research scientist at MIT in the Novartis-MIT Center for Continuous Manufacturing where he led many research projects in collaboration with pharmaceutical companies. His solid-state research has focused on combining computational chemistry and A.I./machine learning methods to study processes and properties associated with molecular crystals, such as solubility, morphology, surface adsorption, polymorphic transitions, and nucleation and crystallization. Michael is a theoretical and computational chemist by education and holds a Ph.D. in chemistry from Boston University.

Computational Support of Crystallization Development of Pharmaceutical Crystals

Yuriy A. Abramov, PhD

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Abstract. Crystallization development of active pharmaceutical ingredients (APIs) is a multiparameter optimization process which is time and cost consuming. These challenges may be mitigated by a combination of computational (virtual) and experimental approaches.[1] This presentation is focused on virtual screening approaches to guide multicomponent crystal (MCC) crystallization as well as impurities rejection by crystallization.

The screening of MCCs along salt-cocrystal continuum is a starting point for improving physicochemical properties of APIs. Performance of the virtual counterions screening methods for salt crystallization is evaluated and novel approaches to virtual solvent screening for MCCs (salts, cocrystals of salts, or cocrystals) crystallization development are proposed. The MCC virtual solvent screening models were successfully validated based on aripiprazole salt crystallization study.[2]
Application of novel comprehensive impurity uptake model, which considers solvent, lattice substitution, and doping level contributions to impurity incorporation into crystal structure as a solid solution during crystallization is discussed.[3]

Biography. Dr. Yuriy Abramov is an industrial computational scientist with over 18 years experience at Pfizer Inc. Currently he holds a position of an Executive Director of Computational Chemistry and Data Science at Porton Pharma Solutions. Prior to joining Porton Pharma, Yuriy Abramov worked for 3 years as a VP of scientific affairs at XtalPi Inc. Dr. Abramov also holds the position of an Adjunct Professor at Eshelman School of Pharmacy, University of North Carolina, Chapel Hill. He is also a Professor of Practice at School of Pharmacy at University of Connecticut, Storrs, CT. Dr. Abramov is an editor of the book “Computational Pharmaceutical Solid State Chemistry ", an author of over 80 publications in peer-reviewed journals and book chapters.

References.

1. Abramov, Y.A.; Sun, G.; Zeng, Q. Emerging Landscape of Computational Modeling in Pharmaceutical Development. **J. Chem. Inf. Model. 2022**, 62, 5, 1160–1171.
2. Shah, H.S.; Michelle, C.; Xie, T.; Chaturvedi, K.; Kuang. S.; Abramov, Y.A. Computational Approach to Virtual Salt Screening: A Case Study of Aripiprazole Salts Crystallization. Pharm Res. **2023**, ASAP.
3. Abramov, Y.A.; Zelellow, A.; Chen, C.-y.; Wang, J.; Sekharan, S. Novel Computational Approach to Guide Impurities Rejection by Crystallization: A Case Study of MRTX849 Impurities. Cryst. Growth Des. **2022**, 22, 12, 6844–6848.

Solid Form Complexity and Chameleonic Behavior of Conformationally Flexible Paritaprevir

Ahmad Y Sheikh, PhD

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ahmad.sheikh@abbvie

Abstract. Direct acting anti-viral regimens have transformed therapeutic management of Hepatitis C across all prevalent genotypes. Most of the chemical matter in these regimens comprise of molecules well outside the traditional drug development chemical space and present significant challenges. Herein implications of high conformational flexibility and the presence of a 15-membered macrocyclic ring in Paritaprevir are reported through a combination of advanced computational and experimental methods with focus on molecular chameleonicity and crystal form complexity. The studies help explain how an evolving balance of inter and intra molecular interactions emanating from conformational flexibility drives properties and performance from crystallization to dissolution, permeation, and docking into the protein pocket.

Biography. Ahmad Sheikh is Global Head of Molecular Profiling and Drug Delivery and a Senior Research Fellow at AbbVie. His team is accountable for a broad range of deliverables across various stages of drug discovery and development. Ahmad has been pivotal in the development and commercialization of AbbVie's recently launched transformative medicine including, Viekira, Venclexta, Mavyret, and Rinvoq. He has authored over 35 scientific papers, 4 book chapters and is an inventor on 20 patents. Ahmad earned his B. Eng. and Ph.D. in chemical engineering from the University College London in the UK.

Solid Form Risk Assessment During Development: Examples of Early Form Screening And the Impact of Crystal Structure Prediction

Jon Selbo, PhD

Eli Lilly and Company
1223 W Morris Street, Indianapolis, IN 46221
Jon.selbo@lilly.com

Abstract. The risks associated with discovering a new and more stable polymorph are dependent on when the form is discovered during the development process and increase in severity from Discovery to post launch commercial changes. Effective early form screens have been developed that take into account the dual challenges of material availability and purity and have been coupled with crystal structure prediction (CSP) tools useful for pre-pivotal solid form selection. Data from 25 CSPs conducted over the last 5 years coupled with the results of experimental form screening showing correlation of CSP time to physiochemical properties, extent of screening, agreement of the experimental and CSP results, and correlation to significant/prolific solvation in the form landscape is presented. Solvation directed metastable form selection for Selpercatinib as a late-stage, drop-in program is also discussed.

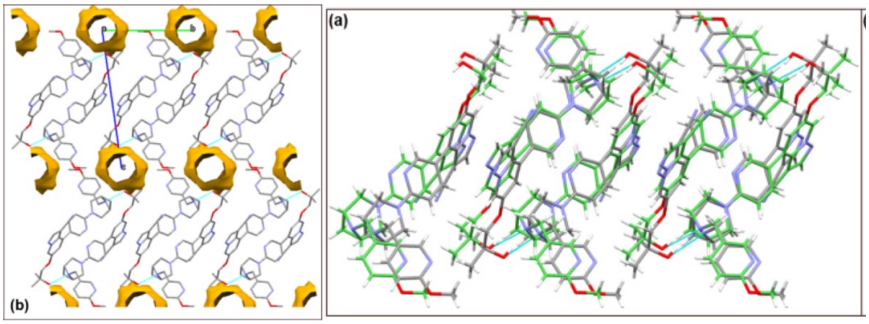

Figure 1. Crystal packing similarity between Selpercatinib Form A and labile isostructural solvates

Biography. Jon Selbo is an Executive Director in Synthetic Molecule Design and Development at Eli Lilly and Company. As the group leader of the Solid State Group, he guides solid form research and selection from candidate selection to commercial launch and oversees preclinical process crystallization though first in human GMP production. Jon received his PhD in Physical Chemistry from the University of Nebraska Lincoln in 2000 under Professor Eckhardt and began his career at Pharmacia in Kalamazoo MI. After the acquisition of Pharmacia by Pfizer, he moved in 2003 to oversee Material Science for the St. Louis site and would go on to play a global role for Pfizer as one of the Material Science technical leaders. In 2008 Jon joined SSCI in West Lafayette where he led a contract research group solving solid form, preformulation, and intellectual property challenges for pharmaceutical and legal clients. He joined the SSCI site leadership team in 2013 and after acquisition of SSCI by AMRI in 2015, went on to lead analytical development at four global sites. He returned to SSCI as the General Manager and Site Head before being recruited to join Eli Lilly in 2018.

Assessing the Crystallization Propensity of Amorphous Solid Dispersions Using the Time-Temperature-Transformation Diagram

N. S. Krishna Kumar, Rahul Lalge, *Raj Suryanarayanan, Ph.D.*

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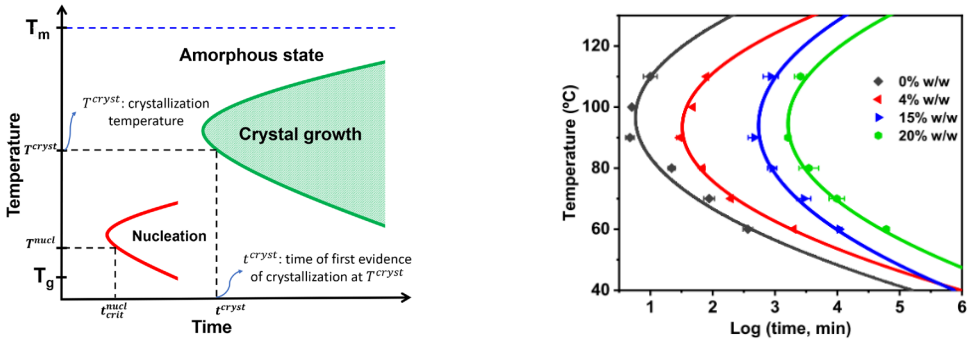
Abstract. Amorphization of crystalline drugs provides an avenue to enhance their solubility and possibly bioavailability. However, since this state is metastable, there is potential for reversion to the crystalline state. Hence, understanding the factors influencing the physical stability of amorphous pharmaceuticals is critical. The time-temperature-transformation (TTT) diagram provides the time and temperature dependence of the first evidence of crystallization. The TTT curves are the boundary between the completely amorphous and crystal growth regions (amorphous + crystalline; left panel, green curve). In amorphous solid dispersions (ASDs), which are drug-polymer molecular mixtures, the crystallization onset time increased significantly as a function of polymer concentration (right panel). The TTT diagram was then extended to identify the nucleation time as a function of both polymer concentration and temperature (left panel, red curve). Nucleated ASDs are "ticking time-bombs", with potential for crystallization during product storage. The time and temperature dependence of the nucleation propensity provides a strategy for preparing stable ASDs.



Time-temperature-transformation (TTT) diagrams. Left panel: Schematic of TTT diagram for crystallization (green curve) and nucleation (red curve). The t_{crit}^{nucl} is the critical nucleation timeat T^{nucl}, T_m is the melting point and T_g is the glass transition temperature. Right panel: TTT diagram of nifedipine ASDs with PVP concentration ranging from 0 to 20% w/w. (Ref: R. Lalge, N.S.K. Kumar and R. Suryanarayanan, Mol Pharm 2023, 20, 1806-1817)

Biography. Raj Suryanarayanan (Sury) is Professor and William and Mildred Peters Endowed Chair in the College of Pharmacy, University of Minnesota. He obtained his pharmacy degree from the Indian Institute of Technology in Varanasi, India and Ph.D. in Pharmaceutics from the University of British Columbia, Vancouver, Canada. The overall goal of his research is to apply principles of pharmaceutical materials science to the design of robust pharmaceutical dosage forms with reproducible and predictable properties. He is a fellow of the American Association of Pharmaceutical Scientists (AAPS) and is a past chair of the Teachers of Pharmaceutics Section of the American Association of Colleges of Pharmacy. Sury is a member of the Academy of Distinguished Teachers at the University of Minnesota. He the recipient of the Outstanding Educator Award and the David Grant Research Achievement Award in Physical Pharmacy, both from AAPS, the PhRMA Foundation Award and the Michael Pikal Distinguished Scholar Award from The National Institute of Pharmaceutical Technology and Education. He is an Associate Editor of *Molecular Pharmaceutics*.

Novel Total Diffraction Methods for Amorphous Material Characterization

Simon Bates. Ph.D.

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Abstract. With the general trends of increasing complexity of active molecules and decreasing solubility, amorphous forms have continued to grow in importance. Yet despite their importance, they have remained challenging to fully characterize using available laboratory tools. In this presentation, I will discuss some novel X-ray Total Diffraction approaches using laboratory equipment that can provide enhanced analytical capabilities. The first makes use of a modified component analysis method for precise and accurate quantitative analysis of intermediates and drug products containing multiple amorphous forms. The same methodology can be used to evaluate novel amorphous forms that may appear during processing or storage. The second approach I will present makes use of PDF modeling of Cu X-ray data to determine changes in molecular packing density in an amorphous form under differing processing conditions.

Biography. Simon Bates is V.P. of Science and Technology at Rigaku Americas Corp., where he nurtures collaborative relationships between industry partners and academia in the discovery of new technologies and methodologies for the next generation analytical systems. His fascination with materials science and analytics has led Dr. Bates on an interesting career path. Having received his Ph.D. from the University of Hull for his neutron diffraction studies on the magnetic properties of rare earth materials, Dr. Bates completed his postdoctoral work at the University of Edinburgh where he first started to design and build specialized high resolution X-ray diffraction system for materials characterization. He continued working on X-ray analytical systems and software design throughout his career at Philips, Shimadzu (Kratos), Bede Scientific, and Rigaku. However, before joining Rigaku, Dr. Bates explored a different career direction and spent 17 years working in pharmaceutical contract research at SSCI and then Triclinic Labs., where he expanded his toolkit for materials analysis to embrace thermal methods and IR/Raman spectroscopy while experimenting in organic chemistry and molecular modeling. Dr. Bates has continued his relationship with academia, volunteering as an Adjunct Professor at Purdue University, University of Hawaii Hilo and more recently at the University of Long Island.

Oral Delivery of BCS IV Compounds: 50+% Drug Loaded Formulations of Redispersal Amorphous Nanoparticles

Devalina Law, Ph.D.

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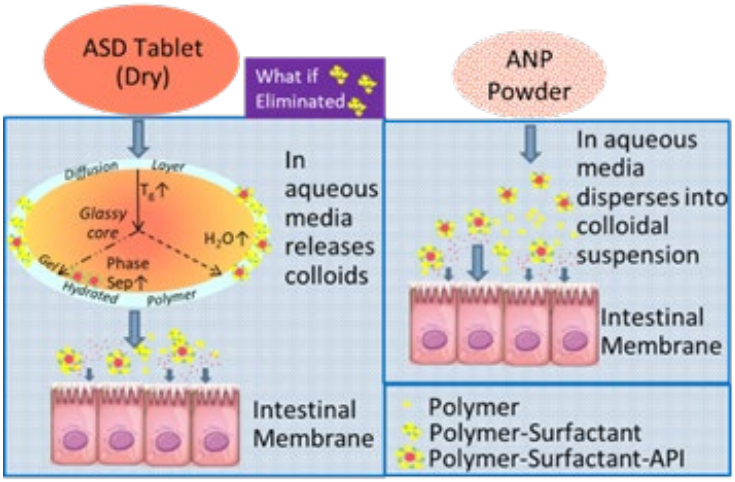
Abstract. In the past two decades there have been five times more Amorphous Solid Dispersion (ASD) Formulations approved by FDA compared to the two decades prior to it, representing a shift in the pipeline and the need for enabling formulations. It has been demonstrated that these ASD formulations when in contact with aqueous media release droplets of amorphous nanoparticles (ANP) that maintain supersaturation in the lumen. This *in situ* ANP generation during dissolution requires large amounts of polymer and surfactants leading to <25% drug loading thus significant pill burden. The goal of this research was to eliminate the excess excipients thus improve drug loading. Using 2 model compounds ABT-530 and Compound X, the process entailed developing a dilute nanosuspension using impinging jet technology, concentrating it using various methods such as rotary evaporation, thin film evaporation or tangential flow filtration then finally drying/solidifying by spray drying or lyophilizing. Although this research is still at proof-of-concept stage the presentation will use both *in vitro* (DLS, SEM, HPLC, NMR, DSC etc.) and *in vivo* (animal and human) data to demonstrate the value of this approach.



Biography. Devalina Law is Senior Research Fellow at AbbVie Inc. She received her B.Pharm. and M.Pharm from Jadavpur University, Kolkata India and Ph.D. from University of Minnesota. After graduating from Dr. Grant's Lab she joined Pharmaceutical Research & Development at Abbott Laboratories, now AbbVie Inc. supporting Discovery in candidate nomination and Development in formulation characterization. Then moved to Global Pharmaceutical Operations supporting on-market products and new product launches. In 2016 she moved back to R&D where her team is responsible for Phase 1-Phase 3 oral solid dosage form development. Her research interest focuses on the delivery systems for overcoming poor oral bioavailability and the impact of physical stability of drug substance on drug product development. Currently Dr. Law serves on the Editorial Advisory Board of J. Pharm. Sci., as the Chair of Chicagoland Pharmaceutical Discussion Group and as a Chair of AAPS-MSE Community. In 2015 she received the Outstanding Service and Leadership Award from AAPS MSE Community.

Manifold Embedding of Molecular Quantum Information for Chemical Deep Learning

Tonglei Li, Ph.D.

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Abstract. It takes more than a decade and billions of dollars to put a new drug product on the market. The essence of drug discovery and development is to characterize molecular interactions and realize wanted interactions by molecular engineering. The astronomical drug development process is attested by dismal failure rates moving from hits to leads and from leads to final products. The processes have nonetheless produced vast troves of data, ranging from high-throughput screening assays to clinical trials. “Big Data” is coined to accentuate the sheer magnitude of data collections; in drug research, it underscores the plea to develop new drugs by exploiting and learning from existing databases. The recent advance in artificial intelligence (AI) software and hardware facilitates the application of machine and deep learning (ML/DL) to mine molecular data. The power of AI has yet to be fully unleashed in accelerating drug development timelines and cutting costs. A major hurdle is molecular description for learning. Because the electronic structures of a molecule bear the ground truth of molecular interactions, there is an urgent need to utilize electronic attributes in AI models. We have recently developed a novel route of capturing the quantum information (QI) of a molecule, coined Manifold Embedding of Molecular Surface (MEMS). MEMS is readily computable and can be further featurized as input for machine learning. Our results of several predictions (solubility, drug-induced liver toxicity, and CPY P405 binding) have demonstrated its feasibility and prowess as molecular representations in predictive and generative deep learning.

Biography. Dr. Tonglei Li is Professor and Allen Chao Endowed Chair in the Department of Industrial and Physical Pharmacy at Purdue University. He received BS and MS in Chemistry and Computational Chemistry, respectively, from Nankai University, China. He obtained Ph.D. in Pharmaceutics, as well as MS in Computer Science, from Purdue University. He joined the faculty at the University of Kentucky and became Associate Professor before returning to his alma mater and holding his current title. His research interests include computational chemistry and mathematics, multiscale modeling and simulation, high-performance computing, and drug development. Over the last few years, Dr. Li has ventured into deep neural networks and data learning by Bayesian inference through Gaussian Process, aiming to solve challenging problems in molecular engineering. He currently serves as Editor-in-Chief of Pharmaceutical Research.

What atomic force microscopy can see on organic crystals

Igor Sokolov, Ph.D.

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Abstract. A recent development of novel modes of operation of atomic force microscopy (AFM), Ringing mode, allows imaging of the distribution of physical and mechanical properties of materials down to the nanoscale. In this talk, I will describe the application of this mode to image organic crystals, in particular, MOF Hybrid ZIF-8-9. As an example, we demonstrate the imaging of multiple physical properties of the organic phase of MOF, which is impossible to see by any other exiting techniques. The described approach is expected to be instrumental to study the mechanisms of formation of organic crystals, their aging, degradation, fusion, etc.

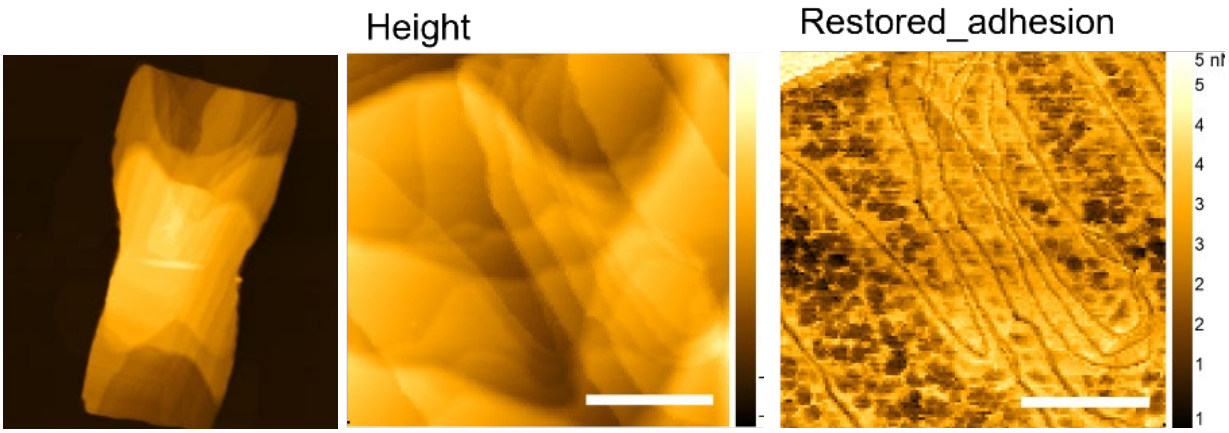

Figure: A single hybrid Zif 8-9 crystal visualized with AFM. Topography of single crystal is shown on the left (10x10 microns) and a zoomed part in the middle. A restored adhesion is shown in the right. Scale bar of the zoomed area is 500 nm.

Biography. Igor Sokolov has 34 years of experience in atomic force microscopy. He received his B.S. in Physics from St. Petersburg State University (Russian Harvard) and Ph.D. from D.I. Mendeleev Central Research Institute for Metrology, both in the Soviet Union. Sokolov worked as a Research Associate at the University of Toronto 1994-2000. In 2000 he joined Clarkson University, where he achieved the title of full professor and served as director of the Nanoengineering and Biotechnology Laboratories Center. He is now professor and Gordon Senior Fellow at Tufts University, with about 200 referred papers, including publications in elite journals like Nature, Nature Nanotechnology, PRL, PNAS, Advanced Materials, Materials Today, etc. He has 21 patents issued and pending. His interests are in Engineering for Health, which includes the development of novel imaging modalities of physical and mechanical properties at the nanoscale and the development of novel nanomaterials, optical nanosensors, and drug carriers.

Material Sparing Estimation of Bioavailability And Drug Precipitation Using An Artificial Gut Simulator

Ronald A. Siegel[1] and Helen H. Hou[2]

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Abstract. Amorphous solid dispersions (ASDs) inhibit crystallization of poorly soluble drugs during storage, and retard precipitation following release into the GI fluids. Standard USP dissolution tests do not adequately assess the performance of ASDs. The large volume of the dissolution medium is physiologically unrealistic, and may overestimate the capacity of the medium to prevent precipitation of released drug. On the other hand, the USP apparatus does not simulate absorption of free drug, and is likely to overestimate the actual degree of precipitation that would occur *in vivo*. Finally, drug/polymer interactions in solution increase the apparent solubility of the drug, which may not be free to cross the intestinal membrane. In recent years, several "bio-relevant" testing systems have appeared. We review the strengths and weaknesses of such systems. We then discuss our own artificial gut simulator (AGS), which consists of a manifold of hollow fibers (HFs) suspended in the extraluminal fluid of a spectrophotometer cuvette. The ASD is introduced into the cuvette, and the dissolved drug crosses the HF membranes into the intraluminal fluid, which flows out of the HFs. Concentrations of dissolved drug in both fluids are monitored, permitting the assessment of absorption and precipitation. By regulating the extraluminal fluid volume, the intraluminal fluid flow, and the permeability area (PA) product of the HF membranes, we can tune the AGS to match the *in vivo* absorption rate constant of the drug. Overall, this system provides a cheap, convenient, and material sparing means to predict the absorption kinetics of drugs formulated as ASDs.

Dr. Ronald A. Siegel is Professor and Department Head of Pharmaceutics, and Professor of Biomedical Engineering at the University of Minnesota (UMN). He received his ScD in Electrical Engineering and Computer Science from MIT in 1984, and taught and carried out research at UCSF from 1984-1998, before joining UMN. Dr. Siegel is Past President of the Controlled Release Society (CRS), and is Fellow of CRS, AAPS, and the American Institute for Medical and Biological Engineering (AIMBE). His research areas have included protein release from polymers, rhythmic pulsed delivery from hydrogels, hard and soft microfabricated sensors and drug delivery systems, mathematical modeling of membrane transport, pharmacokinetics/pharmacodynamics, prodrug/enzyme systems for intranasal administration of benzodiazepines to treat seizure emergencies, and amorphous solid dispersions.

Dr. Helen Hou is Distinguished Scientist in the Department of Small Molecule Pharmaceutical Sciences at Genentech. She has 17 years of pharmaceutical development experiences across several big Pharma companies. At Genentech, Dr. Hou leads drug product development to allow fast entry into human and the definition of market image formulation/process. She leads a group of scientists in pipeline support, strategic initiatives, and research innovation. Dr. Hou specializes in the development of oral solid dosage forms and sterilized ophthalmic products. Her research interests include amorphous solid dispersions, particle dry coating, and integrated drug substance and drug product development. Dr. Hou received her PhD in Materials Science and Engineering from the University of Minnesota. She is a member of the International Consortium for Innovation and Quality (IQ) Amorphous Solid Dispersion Working Group, the lead of the Enabling Technologies Consortium (ETC) Solid Formulation Screening project, and serves as the Industry Advisory Board (IAB) chair of the Center for Integrated Material Science and Engineering for Pharmaceutical Products (CIMSEPP).

The Membrane Permeability of Nonpermeable Drug Particles

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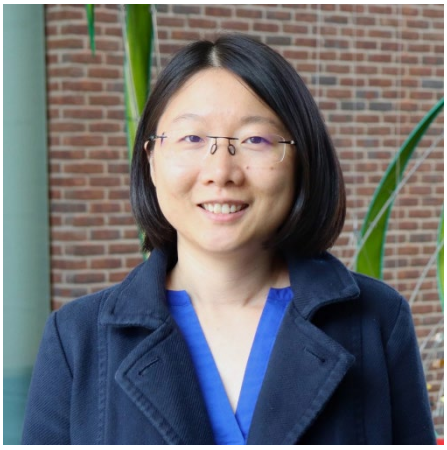
Abstract. Nanosized drug particles and colloidal species improve the permeability and bioavailability of poorly soluble drugs by increasing the local drug concentration near the mucosal surface, termed as the particle drifting effect. However, discrepancies were often observed in different drugs, colloids, and formulations. Thus, the aim of this project was to gain insights on the mechanisms and extent of enhanced absorption by colloidal particles. Various experimental setups, including artificial membranes, biphasic diffusion, cell culture models, and animal tissues were used to investigate this phenomenon, and colloidal particles of different size, type, and compositions were tested. Our results suggested minimal contribution from endocytosis, whereas passive permeation is the main mechanism of enhanced absorption by drug nanoparticles. Colloidal drug particles readily dissolve/dissociate and replenish the consumed free drug concentration within the diffusional boundary layer, leading to increased local concentration in the aqueous solution adjacent to the membrane surface. The extent of such enhancement was found to be dependent on both the particle dissolution/dissociation and membrane permeation processes, where colloidal and drug properties as well as the relative contribution of diffusional boundary layer appeared to be key factors. Mass transport analyses were performed to provide more quantitative understanding of this phenomenon. This work provides insight on the permeability advantages by drug particles and colloidal species, and may contribute to improved bioavailability prediction of colloid containing formulations.



Biography. Na Li is an assistant professor in the Department of Pharmaceutical Sciences at the University of Connecticut (UConn). She received her bachelor's degree in Food Science and Engineering from South China University of Technology, and Ph.D. degree in Food Chemistry at Purdue University, followed by postdoctoral training in Industrial and Physical Pharmacy at Purdue. Prior to joining UConn, she also worked at Crystal Pharmatech Inc. working on solid-state chemistry and crystal form selection of small molecule drugs. Her lab group, started in 2019 at UConn, focuses on understanding the permeability and absorption of poorly soluble drugs, process stability and phase behavior, as well as microbial metabolism of oral drugs. She currently serves on the editorial board of Molecular Pharmaceutics.

Solid Form Landscape: Changes and Challenges in Last Decade

Z. Jane Li, Ph.D.

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Abstract. Drug discovery and development have been continuously evolving over the last few decades. With expansion of chemical space and more diverse structures, the solid-state landscape of NCEs has been increasing in complexity and selection of acceptable crystalline form for development has become more challenging. We have collected the data from solid form screens of ~400 compounds in the last 5-6 years, and analyzed the data in terms of MW, selected chemical descriptors, occurrence of crystalline forms, assessment of stable forms, hydrates and solvates. In this talk, the results from this preliminary survey will be presented, the trend of solid form characteristics, and technical challenges in crystallization and selection of appropriate form for development and scale-up will be discussed.

Z. Jane Li is Vice President of Material Science at Pharmaron. She obtained her PhD from the University of Minnesota under Prof. Grant. Dr. Li worked 10 years at Pfizer Global Research and Development (Groton, CT) where she became Associate Research Fellow, and then at Boehringer Ingelheim for 10 years being promoted to a Distinguished Research Fellow prior to joining Pharmaron in May of 2017. At Pharmaron, she has developed Material Science capabilities in Discovery support, preformulation, solid form selection and crystallization process development for scale-up and expanded business significantly. In her 30+ years career in pharmaceutical R&D, she has gained broad knowledge in solid-state pharmaceuticals, drug delivery, formulation development and CMC, contributed in problem-solving for several commercial products and actively involved in advancing pharmaceutical research in DS/DP interface, co-crystal, crystal engineering and solubilization. Dr. Li has been taken on roles in solid-state pharmaceutical field, as an associate editor of *J. Pharm. Sci.* for ~6 years and an adjunct faculty at U of MN Pharmaceutics and has ~30 publications/presentations and 30+ patents on pharmaceutical salt/cocrystals and polymorphs.

Development of ASD Formulation for Clinical Studies – From Amorphous Theoretical Solubility Calculation to ASD Tablet Development

Wei Zhang, Ph.D.

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Abstract. Amorphous formulation becomes an attractive strategy to deliver poorly water soluble drugs owing to its higher solubility than its crystalline counterpart. This presentation will cover three major topics for actual amorphous drug product development. In the first topic, the evaluation of different methods of calculating amorphous drug solubility will be briefly introduced. Different calculation methods are compared against each other and with experimental solubility measurement. According to the evaluation outcome, one of them is recommended for industrial application based on its overall accuracy and complexity. Extensive research has been conducted to demonstrate the advantages of amorphous formulation at ASD powder/intermediate state, but to successfully apply an amorphous formulation in clinical studies, final dosage forms (e.g. ASD tablets) are needed. Owing to the potential large amount of polymers in the ASD composition, the disintegration and drug release from ASD tablets could become a challenge, especially at relatively high ASD loading in tablet. The second topic will discuss how polymer type, ASD loading in tablet and polymer-drug ratio in ASD affect the disintegration and drug release of ASD tablets. At last, the third topic will present an actual example of developing an ASD tablet to simultaneously improve bioavailability and mitigate the mechanical instability risk of the selected crystalline form to support a Phase 1 clinical study of a Genentech development compound. The development example covers ASD composition screening, compatibility study of ASD prototypes with common tablet excipients, and *in vitro*/*in vivo* evaluation of the developed final ASD tablets. To summarize, the overall goal of this presentation is to provide an industrial perspective for the design and development of final amorphous drug products based on the fundamental understanding of amorphous materials.

Biography. Wei Zhang received his Ph.D. degree in Pharmaceutical Sciences under the guidance of Prof. Lian Yu from the University of Wisconsin-Madison in 2016. Since then, Wei has been working in the Small Molecule Pharmaceutical Sciences Department at Genentech Inc. as a research scientist. His research interest focuses on development of ASD formulation to deliver poorly water soluble drugs especially its actual application in clinical studies. Wei's work in this area covers the evaluation of amorphous solubility calculation, amorphous formulation stability evaluation, downstream processing and evaluation of ASD tablet etc. Wei has in total published 20 research papers. He also serves as an active peer reviewer and has reviewed close to 100 manuscripts to date.

Drug Product Manufacturing Challenges for Amorphous Solid Dispersions And Hydrated APIs

Kapil Arora, Ph.D.

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Abstract. Part 1: Compound A is developed as a spray-dried dispersion (SDD) to provide improved solubility and oral bioavailability. The lead SDD composition is 50:50 % (w/w) Compound A: HPMCAS-M and is used to manufacture a solid oral dosage form for clinical use. During a recent SDD manufacture, the GMP API batch was not fully dissolved in the spray solution which led to a physical mixture consisting of the SDD and crystalline material. The goal of the presentation is to go through the team's forensic investigation and how the SDD batch was salvaged such that project timelines are not impacted.

Part 2: In recent years, continuous tablet manufacturing technology has been used to obtain regulatory approval for several new drug products. While a significant fraction of active pharmaceutical ingredients exist as hydrates (wherein water is incorporated stoichiometrically in the crystal lattice), the impact of processing conditions and formulation composition on the dehydration behavior of hydrates, during continuous manufacturing, has not been investigated. Using solid-state analytical tools, we monitored the dehydration kinetics of a model compound in formulations containing dicalcium phosphate anhydrous (DCPA), mannitol, or microcrystalline cellulose. The presentation will focus on the key results and implications on the drug product.

Biography. Dr. Kapildev Arora is currently working at Pfizer Inc. in the Pharm Sci Small Molecule, Drug Product Design Group, located in Groton, Connecticut, USA. Dr. Arora received his Ph.D. in Chemistry from National Chemical Laboratory, Pune, India in 2007. Before joining Pfizer in 2012, Dr. Arora worked as a post-doctoral fellow at the University of South Florida, Tampa, USA (2007-2009) and at the University of Minnesota, Minneapolis, USA (2009-2012). To upskill his business acumen Dr. Arora completed his Master of Business Administration (MBA) degree in 2020 from the University of Rhode Island, Rhode Island, USA. Dr. Arora has built and maintained strong incumbent leadership skills with 15+ years of comprehensive R&D experience and knowledge working on candidate profiling from Discovery-to-Commercialization. Dr. Arora works in the areas of pre-formulation and formulation that include the selection of solid-state forms for development (e.g., salts, polymorphs, hydrates, and cocrystals), and the characterization of the drug substance in a drug product (i.e., in the presence of excipients) to support the stability and development of a robust formulation for both clinical trials and product safety assessments. Dr. Arora is also a key member of the multidisciplinary team of pharmaceutical scientists primarily focused on establishing the intellectual property portfolio for Pfizer's NCEs and involved with research activities on the mitigation of nitrosamines impurities in the drug products.

Poster and Flash Presentations

#1

The Crystal Structure Prediction and Process De-risking of an Unusual API:Epimer Cocrystal in the Commercial Synthesis of Belzutifan

C. Scott Shultz, Luca Iuzzolino, Lorenzo Codan, Justin A. Newman, Michael Pirnot and Melissa Tan

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During the commercial process development of belzutifan, a novel treatment for von Hippel−Lindau (VHL) disease-associated renal cell carcinoma (RCC), we observed the crystallization of a previously unknown 1:1 cocrystal of belzutifan with its epimer (inversion of stereochemistry at the hydroxyl position). Observations such as this bear particular relevance with respect to controlling the purity of the active pharmaceutical ingredient (API) in the commercial manufacturing process. After the discovery of the cocrystal, the crystal structure was determined initially through a combination of crystal structure prediction (CSP) and powder x-ray diffraction and later by single crystal X-ray diffraction. The only lattice interaction between the API and the epimer is a □-□□ stacking arrangement created by alternating fluorobenzonitrile groups from each molecule. The formation of this complex, while unexpected, is a reminder that unexplored crystal forms can pose a significant risk to the robustness of chemical manufacturing processes. At present, the cost of leveraging CSP tools across the entirety of a synthetic process is significant. However, discoveries such as the belzutifan:hydroxy epimer cocrystal highlight why current investments for *in silico* tools are necessary and justify expanding their use to de-risk commercial synthetic routes to expedite the development of life-saving medications.

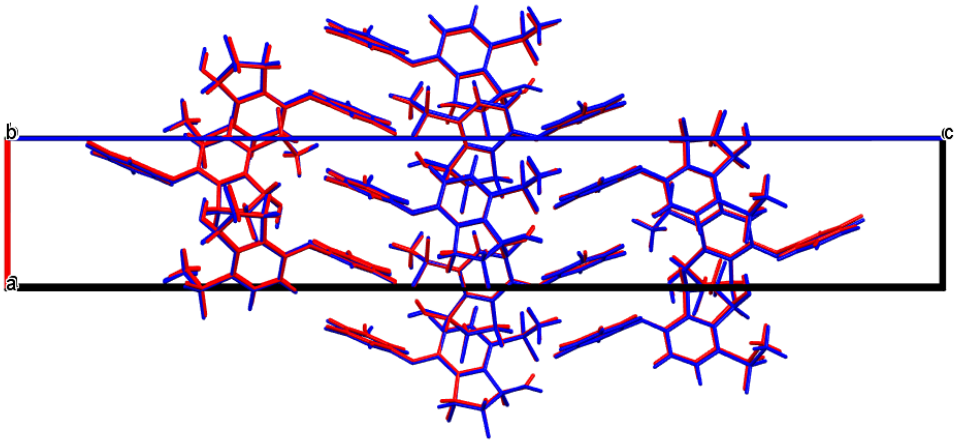

Figure 1. 20-molecule overlay of the structure determined by SCXRD (red) and the refined CSP Rank 1 structure (blue), with an $RMSD_{20}$ of 0.175 Å.

#2

Predicting Critical Water Activity As a Function of Temperature of Hydrates And Anhydrates Using IDR/solubility Ratio And DSC Data

Xin Yao

Molecular Profiling and Drug Delivery, Small molecules CMC Dev, AbbVie
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Critical water activity (aw_c) changes with temperature (T) and decides the cutoff of water content for crystallizing a hydrate or anhydrate. For measuring this essential value in crystallization process development, the conventional methods include competitive slurry with a series of variable aw or T, and solubility extrapolation against aw or T. Those experiments usually are material-and-time-consuming. Recently, methods with light activities were developed using intrinsic dissolution rate (IDR) extrapolation and solubility ratio. Different from the previous work, this work provides two facile and complementary ways to predict aw_c at any temperature based on a thermodynamic model for any pair of hydrates and anhydrates. The thermodynamic model and the two prediction methods were exemplified on carbamazepine and theophylline. At a given temperature, only the IDR or solubility ratio of the interested two forms in pure water or dilute buffer is required to predict aw_c within an error of ±0.03. Moreover, this study investigates the possibility of predicting aw_c against T of anhydrate and hydrates from their DSC data. Heat capacity differences were measured and indicate an approximately linear relationship between $ln\ aw_c$ and $1/T$ of anhydrate and hydrates within a normal temperature range (5-70 °C), consistent with the previous solubility data with variable temperature. All the data from different sources (IDR, solubility, slurry, and DSC data) is consistent under the thermodynamic model. Comparable to the interfering thermodynamic stability relationship of true polymorphs of Yu, the relationship against water activity is interfered. The theoretical cases of aw_c *vs.* T and the critical temperature concept are discussed.

Disclosures: All authors are employees of AbbVie and may own AbbVie stock. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

#3

Chiral Separation by Seeded Crystallization

Kennedy A. Borchardt-Setter, Junguang Yu, Ilia A. Guzei, Xin Yao, and Lian Yu

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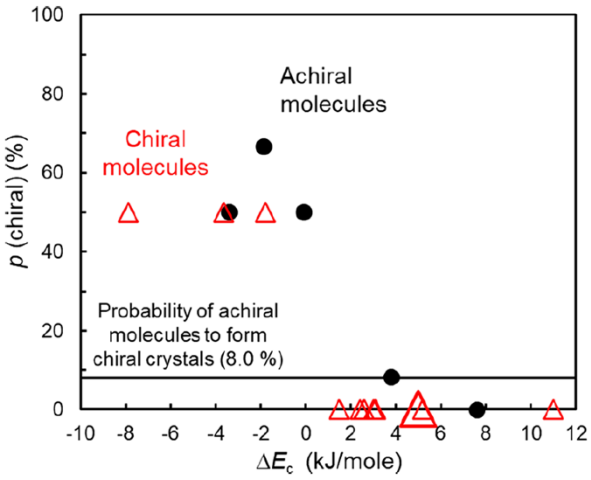
Chirality is everywhere in nature. The natural amino acids are the L form, while the natural sugars are the D form. When a drug interacts with a living system, a change of chirality can make a medicine into a toxin. Among the methods to obtain enantiopure compounds, crystallization is the most economical. In Part 1 of this talk, we show that the relative energies of the chiral and achiral crystals influence the success of chiral separation by crystallization. In the cases where crystallization can generate chirality, the chiral crystal usually has lower energy than the achiral, while the opposite is true if no chiral separation occurs. This simple result helps assess the potential for a given system to undergo chiral separation by crystallization. In Part 2 of this talk, we show that arabitol satisfies the rule developed in Part 1 and indeed shows chiral separation by crystallization. For this system, chiral separation does not occur spontaneously, but can be induced by seeding the liquid with an enantiopure crystal. Overall, this work has developed a method to screen candidates for chiral resolution by crystallization and for promising candidates, a seeding method to control the course of crystallization for chiral separation. Ongoing efforts involve obtaining a conglomerate through solution crystallization, and future efforts aim to ultimately separate the chiral forms.



#4

Surface Enrichment and Depletion of Components in Amorphous Solid Dispersions and Its Impact on Stability and Release

Junguang Yu, Kennedy Ann Borchardt-Setter, Yuhui Li, Xin Yao, Chailu Que, Lian Huang, Ho-Wah Hui, Yuchuan Gong, Feng Qian, and Lian Yu

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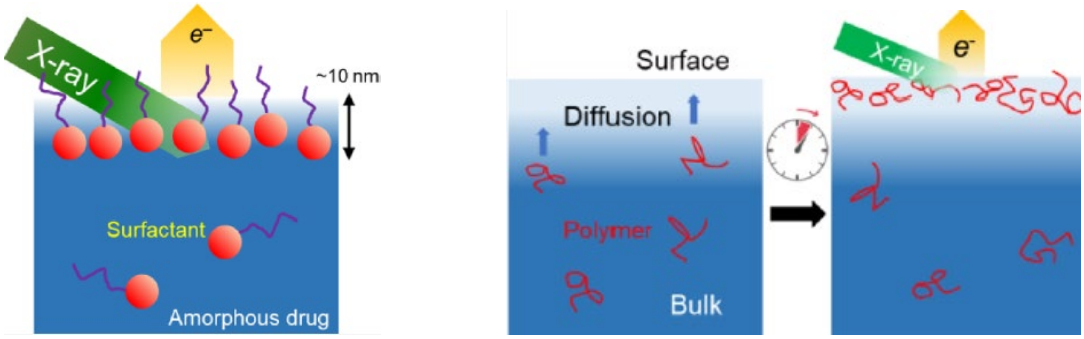
Every material has an interface with its surrounding where molecules have different organization and dynamics from those in the interior. Using X-ray Photoelectron Spectroscopy (XPS), we show that surface composition can be vastly different from bulk composition in an amorphous solid dispersion (ASD), which is increasingly used to deliver poorly soluble drugs. Besides the drug, an ASD usually contains a surfactant and a polymer. We show that a surfactant can enrich strongly on the surface of an ASD to near purity, controlled by the relative surface activities of the components.[1] A polymer in an ASD can also surface-enrich and the rate of enrichment is governed by polymer diffusion through the bulk, which enables prediction of kinetics of surface enrichment process.[2] The presence of a hydrophilic polymer can drive a hydrophobic surfactant toward the surface. The surface enrichment and depletion of components play a major role in drug stability and release. For example, a polymer layer on the surface can inhibit the otherwise rapid crystal nucleation and improve the wetting and dissolution.[3] Our finding highlights the importance of surface chemistry in developing high-quality ASDs.



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#5

Amorphous Drug-Polymer Salts with High Stability under Tropical Conditions and Improved Release

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An amorphous drug-polymer salt (ADPS) is formed through an acid/base reaction between a drug and oppositely charged polymer. ADPS have extraordinary stability against crystallization due to the strong ionic interactions between the drug and polymer without sacrificing release. Previous work has introduced a slurry conversion method for synthesizing ADPS containing a basic drug and an acidic polymer that can be implemented in basic global health facilities [1,2]. Neusaenger et al. used X-ray photoelectron spectroscopy (XPS) to measure the degree of proton transfer in an ADPS and showed that slurry conversion can achieve higher degrees of salt formation than common manufacturing methods such as hot-melt extrusion (HME) and rotary evaporation (RE), resulting in enhanced drug stability and release [3]. In this work, we show that the slurry conversion method works equally well to form an ADPS between a poorly-soluble acidic drug, indomethacin (IMC) or naproxen (NPX), and a basic polymer, Eudragit EPO. XPS measurements indicate that the extent of deprotonation of the acidic drug increases with increasing EPO concentration. Our work demonstrates the widespread application of the slurry conversion method to synthesize ADPS from small molecule drugs and oppositely charged polyelectrolytes to increase stability and solubility.

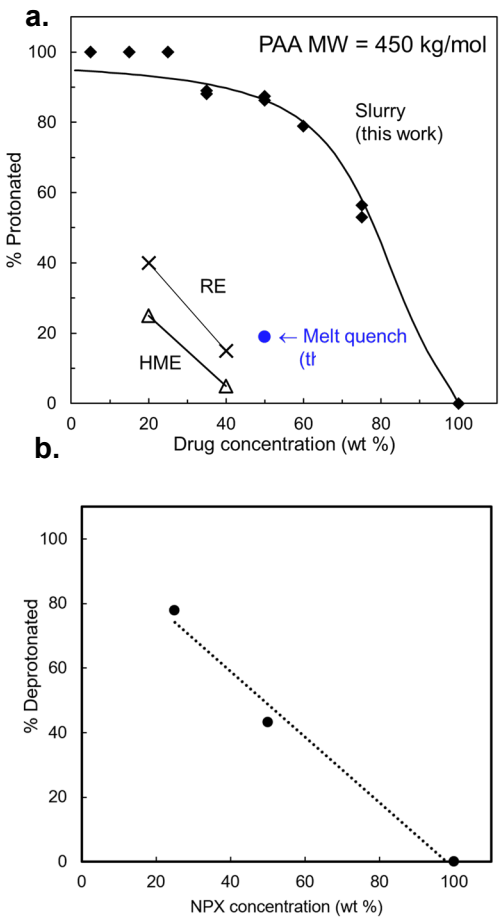

Fig. 1. (a) Comparison of protonation profiles of basic drug lumefantrine formulated with the acidic polymer poly(acrylic acid) (PAA 450 kg/mol by slurry conversion, hot-melt extrusion (HME) and rotary evaporation (RE). (b) Deprotonation profile of acidic drug NPX formulated with Eudragit EPO.

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#6

Calculating Elastic Strain with Surface Tension: A Highly Flexible Single Crystal of Celecoxib Form I Obtained through Melt Crystallization

*Zhengzheng Zhou,[a,b] Vikram Joshi,[b] Yiwang Guo,[b] Tianyi Xiang,[b] Zijian Wang,[b] and Changquan Calvin Sun[b]**

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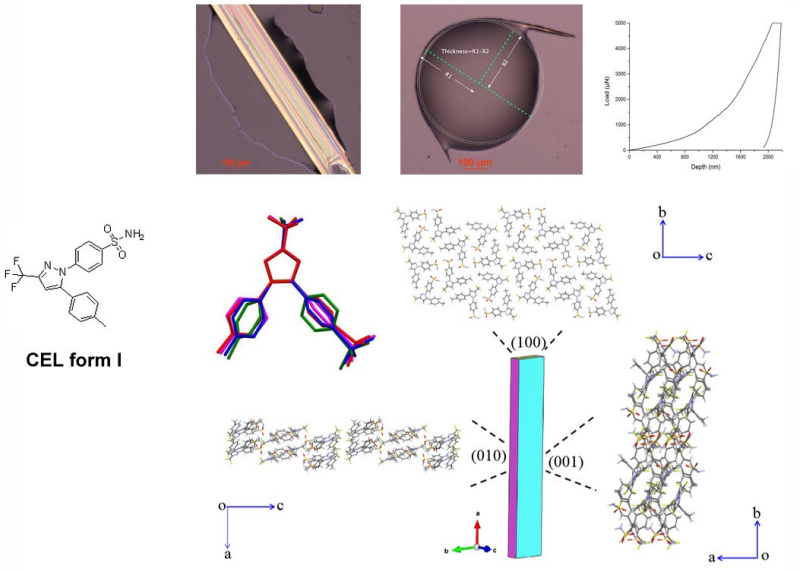
Elastic strain limit is a parameter used to gauge the flexibility of a material, indicating its ability to restore its original shape once stress is removed. Currently, the prevailing method for inducing elastic strain in organic single crystals is three-point bending, which involves physical manipulation of crystals using forceps and a needle to perform. However, this approach poses difficulties as it is challenging and imprecise to ensure that a single crystal reaches its maximum elastic deformation without fracturing solely through manual handling. This study introduces a novel approach to calculate elastic strain in highly flexible single crystals using surface tension as an external stress. We applied this method to a single crystal of celecoxib (CEL) form I, a well-known non-steroidal anti-inflammatory drug, which has been marketed since 1998. This crystal form has been known for decades but its crystal structure has not been determined. By employing a novel gradient-cooling melt crystallization technique, we successfully obtained the elusive single crystal and determined its crystal structure by single crystal X-ray diffraction.It is a rare crystal structure with high Z' = 3, accounting for only 0.51% of crystal structures in Cambridge Structural Data (updated Nov. 2022). Notably, the CEL Form I crystal exhibited exceptional flexibility, achieving a remarkable maximum elastic strain of 8.66%, surpassing most known elastically flexible molecular crystals. The high elastic strain is consistent with its low Young's modulus (E = 3.18 ± 1.01 GPa) and hardness (H = 39.8 ± 15.6 MPa), determined by nanoindentation, as well as low mean yield pressure (P_y = 41.73 ± 3.00 MPa) by in-die Heckel analysis.



#7

Co-Crystal Formation and Evaluation of RORγ Antagonist Candidate BI 730460: From Drug Substances to Drug Products

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BI 730460 is an active pharmaceutical ingredient (API) candidate for Retinoic acid receptor-related orphan receptor γ (ROR γ) antagonist. The drug substance exhibits two free base forms (Form I and II), and solid form screening indicates that Form II is thermodynamically stable at room temperature. However, further salt/co-crystal assessment reveals that the fumaric acid co-crystal of API (BI 730460 FU) has a better aqueous solubility at pH 6.8 with 16-fold increase compared with free base Form II as well as doubled bioavailability. In rat pharmacokinetic (PK) studies at 3mg/kg dose, BI 730460 FU suspension formulation shows 49% increase in bioavailability compared to the free base Form II. The co-crystal formation of BI 730460 FU is confirmed with stoichiometry of 2:1 of API: FU with unique hydrogen bonding interaction which revealed by single crystal X-ray diffraction (SC-XRD) as well as solid state NMR spectroscopy (ssNMR). Moreover, the good crystallinity and other properties of this co-crystal drug substance exhibits great stability, manufacturability and most importantly, significantly dissolution and oral adsorption compared with free base solid forms. The dissolution profile of BI 730460 FU co-crystal exhibits great stability of supersaturation in FaSSIF condition (pH 6.5) at 37 °C for over 20 hours. The co-crystal dissociation of API occurs under different formulations and stress stability conditions have been determined by Raman spectroscopy as well as direct characterization of two-dimensional X-ray diffraction (2D-XRD).

#8

Differentiating and Quantifying Two Different Amorphous Phases of API in Tablet Formulation by ^{15}N Solid State NMR: Derisking the Drug's Chemical Liability

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A sensitive solid state ^{15}N NMR method was developed to allow for differentiation and quantification of **amorphous API potassium salt**, **amorphous API free form, and their crystalline counterparts** in the presence of excipients in a tablet formulation. To achieve the desired sensitivity, ^{15}N enriched API crystalline potassium salt was used to prepare tablets. The tablets were stressed at multiple elevated temperature and relative humidity conditions to assess the extent of API amorphization and ensuing salt disproportionation with the goal to determine if any free API form (amorphous or crystalline) was generated. In contrast to the potassium salt, free API form was known to present a chemical degradation liability. This work confirmed the mechanism of the API degradation being the amorphization-mediated salt disproportionation and, by evaluating the routes to amorphization, determined the risk of degradation during the life cycle of the drug product.

#9

Mechanism and Generality of the Tabletability Flip Phenomenon

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It has been commonly assumed that a solid form of an API with better tabletability also exhibits better tabletability when formulated with excipients. However, it was recently shown API solid forms with poorer tabletability could exhibit better tabletability in formulations, i.e., tabletability flip. This work is aimed at: 1) exploring the mechanism by visualizing the deformation of particles and their bonding areas in a tablet; and 2) investigating the generality of the tabletability flip phenomenon using six different systems. By visually showing the plastic deformation of particles in a mixture consisting of soft and hard particles, we have demonstrated a possible mechanism of the tabletability flip phenomenon. The mechanism entails that softer excipient particles conform to the shape of harder API particles during compaction, resulting in a larger bonding area and higher tensile strength (Figure 1). We have also demonstrated the generality of the tabletability flip phenomenon, which occurred in all six systems tested in this work.

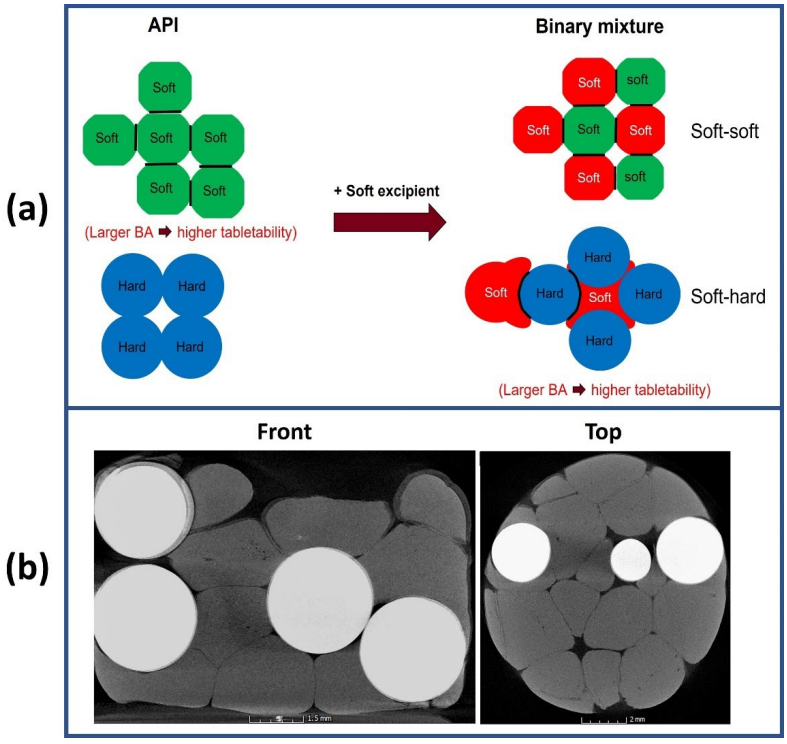

Figure 1. a) The hypothesized mechanism of tabletability flip, where a soft API develops a larger bonding area (BA) between particles when a pure API powder was compressed but smaller BA when the API is formulated with a soft excipient. b) The micro-CT images (2D slices) of a PlayDoh-glass bead tablet.

#10

The Synergy of Computation and Experiment in Pharmaceutical R&D

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The importance of computational modeling and machine learning are well known in pharmaceutical drug discovery; however, modeling is underappreciated in drug development. This work highlights how virtual screening, crystal structure prediction (CSP), crystallization strategy recommendation, and morphology prediction calculations guide and enhance the experimental work performed for drug development projects. Specifically, the screening and selection of solid forms can be accelerated while increasing confidence that the best solid form has been discovered. Furthermore, modeling data obtained from CSP and morphology predictions combined with crystal structures from microcrystalline electron diffraction (MicroED) provide molecular level insights that explain challenging or ambiguous experimental results.

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#11

Worsened Punch Sticking by External Lubrication with Magnesium Stearate

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External lubrication of tooling with magnesium stearate was found to aggravate punch sticking at low compaction pressures. Qualitatively similar punch-sticking profiles were observed for all four model compounds. With increasing pressure, the weight of adhered mass initially increased and then decreased to eventually reach a net loss (Figure 1). We hypothesized that, whether or not API particles are transferred to punch tip depends on relative strengths of three forces pertaining to powder compaction, i.e., 1) MgSt and API (F_{MA}); 2) punch and MgSt (F_{PM}); and 3) API and API (F_{AA}). When MgSt is more plastic than API, the highly plastic MgSt layer can deform readily to develop a larger bonding area with the API particles in contact than that between API particles. Hence, F_{MA} rises more sharply than F_{AA} to reach a plateau (Figure 2). On the other hand, F_{PM} is independent of pressure as the bonding area between MgSt and punch has already reached a maximum before compression. Therefore, the condition of $F_{PM} > F_{MA} > F_{AA}$ is satisfied in a low-pressure range (Figure 2), under which API particles will be transferred to the MgSt layer, leading to punch sticking. The weight would increase with increasing pressure till $F_{MA} = F_{AA}$, which corresponds to a maximal weight gain. As F_{AA} surpasses F_{MA} with further increase in pressure, the peeling-off of MgSt from punch tip results in a negative weight change. The observation that all four model powders are less plastic than MgSt, based on their in-die P_y values (Table 1), provides strong support to the hypothesized punch-sticking mechanism.

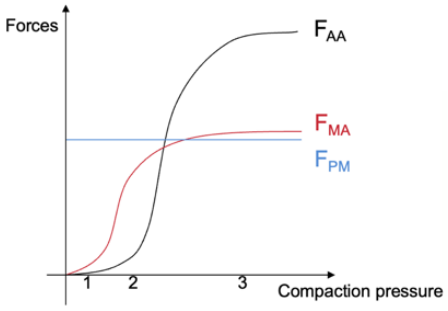

Figure 1. Interplays among F_{AA}, F_{MA}, and F_{PM}.

Materials	In-die P_y (MPa)
Ibuprofen	40.5 ± 9.9
Celecoxib	47.1 ± 8.3
Sodium cyclamate	108.3 ± 4.7
Acetaminophen	89.5 ± 2.7
Magnesium stearate	25.8 ± 4.5

Table 1. In-die Py values of APIs and MgSt.

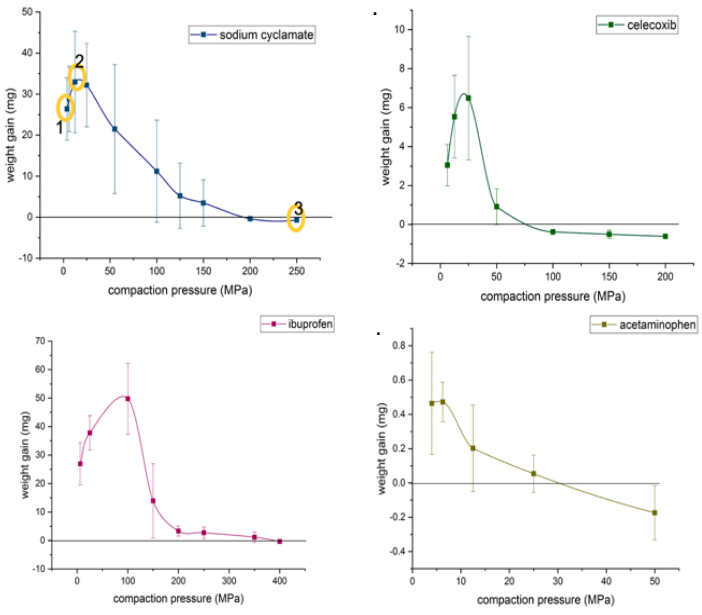

Figure 2. The weight gain plots versus compaction pressure.

#12

Predicting Tabletability of Powder Mixtures

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The ability to accurately predict the tabletability of powder mixtures from that of pure materials would facilitate the development of tablet formulations in a time and material-sparing manner. It is, in fact, essential for successful digital design of tablets. A powder tabletability equation was recently derived by Vreeman & Sun.[1] Non-linear regression of tabletability data, tensile strength vs. pressure, using the tabletability equation leads to three tabletability parameters, $\sigma_{max}, \alpha, \text{and } \beta$.

$$\sigma = \sigma_{max} e^{\alpha W\left(-e^{-\frac{P}{\beta}-1}\right)}$$

Binary mixtures of two plastic excipients, microcrystalline cellulose (MCC, Avicel PH102) and Kollidon (VA64), in 20% (w/w) increments were compressed at a dwell time of 103 ms and their tabletability profiles were determined. We obtained the tabletability parameters of MCC and Kollidon by curve-fitting first. The tabletability profiles of four mixtures were obtained from tabletability parameters predicted using a power law mixing model from parameters of the two pure powders and composition,. The predicted tabletability profiles are in excellent agreement with the experimental tabletability profiles (Figure 1), indicating applicability of the power law mixing model for this system.

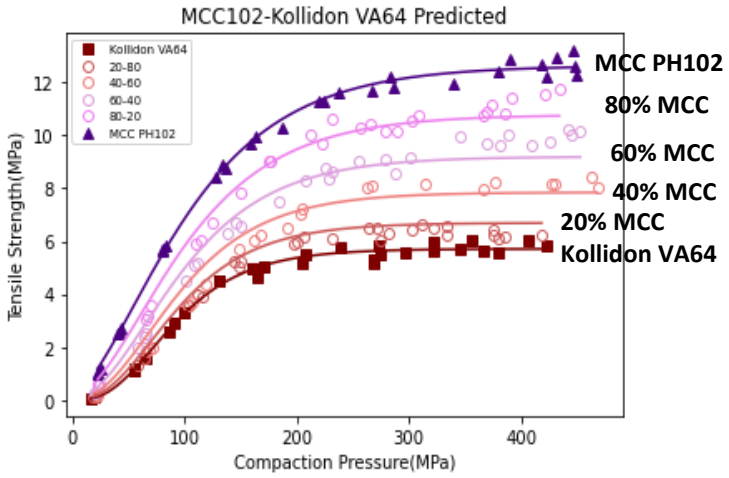

Figure 1. Tabletability profiles of four MCC - Kollidon mixtures (in 20% increments) along with pure MCC and Kollidon. Open symbols are for experimental data points of mixtures. Lines are predicted using power law from those of MCC and Kollidon.

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#13

Surface Enrichment of Polymer Component in an Amorphous Drug and its Effect on Surface Crystallization

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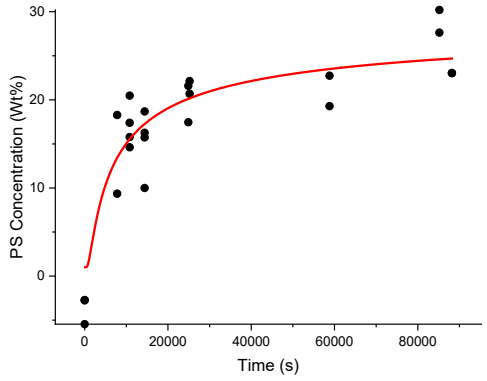
Amorphous formulations are increasingly used to deliver poorly soluble drugs. An amorphous formulation generally contains a polymer as dispersion matrix. Two recent developments in this area are (1) surface crystallization can be vastly faster than bulk crystallization leading to failure of an amorphous formulation[1] and (2) a polymer component can enrich at the surface of an amorphous drug.[2,3] These phenomena have strong influence on the stability and performance of amorphous drugs. In this work, we investigate the effect of polymer surface enrichment on the surface crystallization process. The surface composition of indomethacin containing 1 wt % polymer has been measured using X-ray Photoelectron Spectroscopy (XPS). Strong surface enrichment effect was observed up to a factor of 40 for polystyrene, at a rate controlled by bulk diffusion of the polymer. The slow diffusion of the polymer meant that the surface composition of a freshly prepared surface is stable in the glassy state but evolves rapidly in the liquid state and in the presence of plasticizers. This enabled us to vary to the surface concentration of a polymer and investigate its effect on the surface crystallization process of the drug. Our result is relevant for understanding and predicting the stability of amorphous formulations that contain fractures and milling-induced fresh surfaces.

(a) Polymer surface concentration vs. time



(b) Halftime for polymer surface enrichment

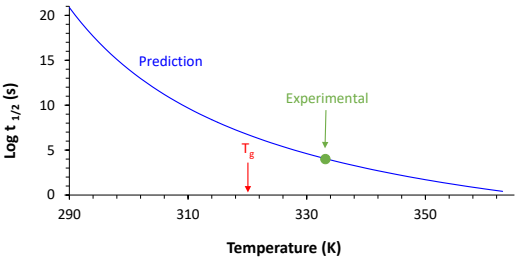


Figure 1. (a) Evolution of polymer (PS) surface concentration at 60 °C. (b)

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#14

Role of Poloxamer 188 in Preventing Ice Surface Induced Protein Aggregation During Freeze Thawing

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During freezing, ice crystallization can potentially induce protein adsorption at ice surfaces leading to protein denaturation. Surfactants, by replacing protein from the interfaces and/or forming protein-surfactant complexes, can stabilize proteins. Although widely used, the chemical instability of polysorbates (PS) limits its use as a surfactant. Poloxamer 188 (P188) is considered an alternative to PS due to its chemical stability and low toxicity profile. P188 exhibited a high crystallizing propensity during the freeze-thaw cycles. As a stabilizer, P188 is expected to be surface active and function as a stabilizer only when it is amorphous. Thus, in order to exploit the potential of P188 as a surfactant in frozen protein formulations, we hypothesize that (i) non-crystallizing solutes, including disaccharides and proteins, can inhibit P188 crystallization during cooling and heating and (ii) when retained amorphous, P188 can prevent protein from surface-induced denaturation. The freeze-thaw cycles were conducted at controlled (cooling and heating at 1 °C/min) and uncontrolled (cooling to -80 °C, heating to room temperature) rates. The phase behavior of solutes in frozen aqueous solutions was characterized using low temperature differential scanning calorimetry (DSC) and synchrotron X-ray diffractometry (XRD). After freeze-thawing, the particle size was determined using dynamic light scattering (DLS). Non-crystallizing solutes, including proteins (lactate dehydrogenase as model proteins) and trehalose, could inhibit P188 crystallization during cooling. By maintaining amorphous during cooling, P188 prevented the surface-induced aggregation of lactate dehydrogenase after freeze-thawing. However, a P188 rich phase appeared and resulted in substantial crystallization during heating making it a potential bulking agent for freeze-dried formulations. The results highlighted the influence of non-crystallizing solutes on the phase behavior of P188, and the significance of the physical state of P188 as a surfactant in protein formulation.

#15

Dual Functionality of Poloxamer 188 in Freeze Dried Protein Formulations: A Stabilizer in Frozen Solution and a Bulking Agent

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Poloxamer 188 (P188) is an alternative to polysorbates in preventing ice surface-induced protein denaturation. It has a high crystallization propensity in frozen state, rendering its role as a potential bulking agent in freeze-dried formulations. Multifunctional excipients can potentially reduce the complexity during formulation design and prevent undesirable drug-excipient and excipient-excipient interactions. We hypothesize that P188 can be a dual functional excipient – a cryoprotectant in frozen systems and a bulking agent in freeze-dried formulations. As the crystallization of P188 can potentially undermine its stabilization effect, sugars (sucrose and trehalose) can be added to inhibit its crystallization. However, as the crystallization of P188 can undermine its stabilization effect, the impact of its crystallization on protein stability, both during processing and storage, warrants careful investigation. The phase behavior of P188-sugar in frozen aqueous solutions was characterized using differential scanning calorimetry. Lactate dehydrogenase (LDH) was used as the model protein (200 µg/mL). The total solute concentration in the prelyophilzation solution was 3% (w/v). The freeze-drying parameters were: (i) Freezing: -45 °C, 3 h; (ii) Primary drying: -25 °C, 200 mTorr for 12 h; (iii) Secondary drying: 20 °C, 200 mTorr, 6 h; (iv) Annealing (optional): -30 °C, 6 h. P188 crystallinity in the final lyophiles was determined by X-ray diffractometry. Besides, the freeze-dried products were also evaluated based on their appearance, reconstitution time and water content. The LDH activity in the reconstituted solution was determined. Sucrose, in a concentration-dependent manner, inhibited P188 crystallization in freeze-dried formulations. However, trehalose did not have such an effect. Annealing did not improve P188 crystallinity in the final lyophiles. Cake collapse was observed in the 1:2 (w/w) P188-sucrose lyophile. All the lyophiles exhibited a rapid reconstitution time of ~ 30 s. The water content of pure P188 cake was < 1% (w/w). The addition of sugar increased the water content to 2% ~ 4% (w/w). Surfactants played a substantial role in preventing ice surface induced LDH destabilization during freeze-drying. The low LDH recovery in pure P188 cake indicated its poor stabilization effect during drying. P188-sugar systems exhibited similar LDH recovery to mannitol-sucrose-polysorbate systems, revealing the dual functionality of P188. In conclusion, P188 could serve as a cryoprotectant as well as a bulking agent in freeze-dried formulations.

#16

Relative Bioavailability Assessment of Solid Forms by an Artificial Stomach and Duodenum

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In this work, a model BCS II compound under development, characterized by low aqueous solubility and high permeability, was employed to evaluate the reliability of an artificial stomach and duodenum (ASD) in predicting *in vivo* bioavailability. The *in vitro* dissolution profiles of five forms of the compound, including a solution in an oral dosing vehicle and four different solid forms, were investigated using an ASD apparatus. The area under the curve (AUC) of the concentration–time profile in the duodenum chamber was considered as a proportional measure of bioavailability. The relative bioavailability estimated based on ASD data demonstrated a consistent rank order with the *in vivo* bioavailability in rats, with the solution > salicylic acid cocrystal > malic acid cocrystal > maleate salt > monohydrate (Figure 1). This study showcased a strong correlation between ASD results and the *in vivo* bioavailability of this model compound. If this correlation can be extended to other BCS II compounds, as well as to other animal species and humans, ASD exhibits great potential as a valuable tool for solid form selection and formulation development in the context BCS II compounds.

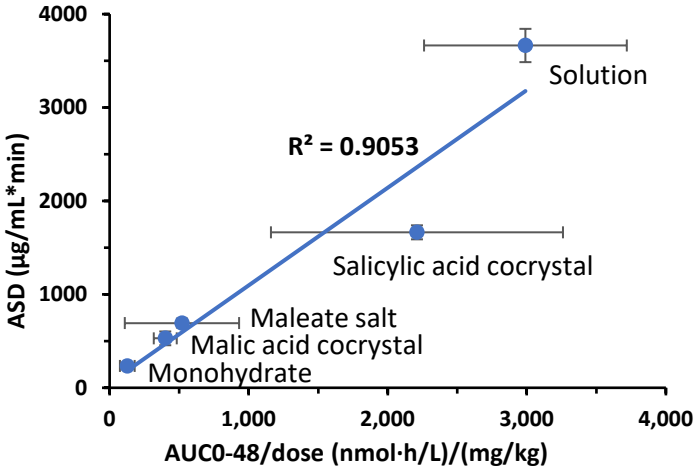

Figure 1. Correlation between the area under the curve (AUC) obtained through an *in vitro* ASD study and an *in vivo* rat study

#17

Time and Temperature Dependence of Nucleation and Crystallization in Amorphous Pharmaceuticals

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Amorphization of crystalline drugs serves as a potential strategy to improve bioavailability. However, the amorphous form can crystallize, negating the solubility advantage. Hence, understanding the factors influencing the physical stability of amorphous pharmaceuticals is critical. The amorphous-to-crystalline transformation typically occurs through two steps: nucleation and crystal growth. The time and temperature dependence of the first evidence of crystallization forms the time-temperature-transformation (TTT) diagram. The TTT curves are the boundary between the completely amorphous and crystal growth regions (amorphous + crystalline). The TTT curves reveal the role of molecular mobility and thermodynamic driving force on crystallization (Figures 1a and 1b)[1].
In amorphous solid dispersions (ASDs), crystallization onset time increased significantly with polymer concentration. With an increase in polymer concentration, the TTT curves shift progressively in the time axis (Figure 1b)[2]. The molecular mobility decreased as a function of polymer concentration, revealing its role in reducing the crystallization onset time. Further, we developed a method to obtain the nucleation TTT diagram, based on the accelerated crystallization of the nucleated systems. With a decrease in temperature, nucleation was facilitated until the temperature was reached with the shortest nucleation time. Further decrease in temperature increased the nucleation time as mobility limitations inhibit the rate of nuclei formation (Figure 1c). Nucleated ASDs are “ticking time-bombs”, with the potential for crystallization during product storage. Utilizing the time and temperature dependence of nucleation propensity offers a viable approach for the preparation of stable ASDs.

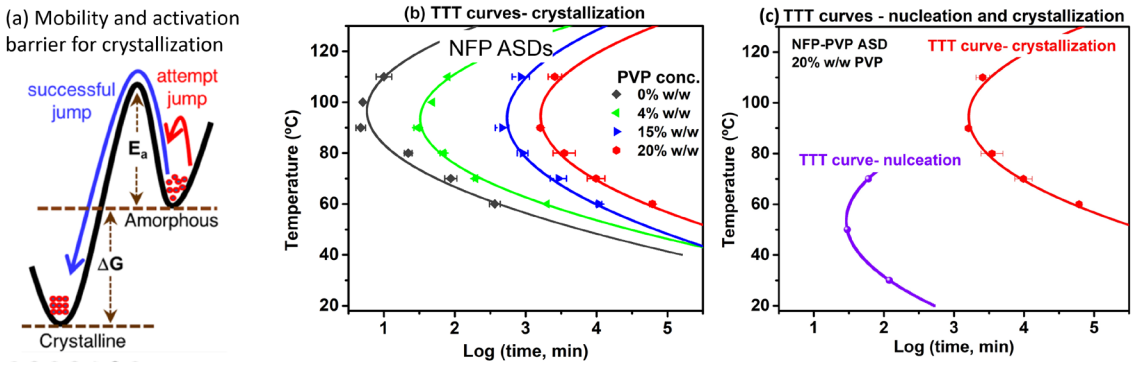

Figure 1. (a) Schematic representing the role of mobility and activation barrier for crystallization, (b) TTT curves for crystallization of NFP-PVP ASD as a function of polymer concentration, (c) TTT curves of nucleation and crystallization of nifedipine (NFP) ASD with 20% PVP (w/w).

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#18

Initial Considerations in Designing Pharmaceutical Co-crystals: A Case Study of Naringenin

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The purpose of this study is to investigate and assess predictive and screening tools for co-crystal formation with naringenin (NAR), a model flavonoid with poor aqueous solubility and potential treatment for Alzheimer's disease. Around 250 molecules collected from safe-for-human-use databases were scrutinized with respect to pharmaceutical and pharmacological selection criteria to identify a pool of NAR-specific coformers. An initial set of 24 NAR-compatible co-formers (Group A) underwent a thorough solid-form screening that includes, liquid-assisted grinding (LAG), slurry at equimolar and non-equimolar stoichiometric ratios, reaction crystallization, and solvent evaporation. Critical method parameters e.g., solvent, volume of solvent, and time were also varied to maximize opportunity for co-crystal formation. However, based on the limited co-crystal yield from Group A, a second group of 16 co-formers (Group B) was chosen following a statistical analysis of co-crystals in the Cambridge Structural Database (CSD) along with safety criteria consistent with Group A. Powder X-ray Diffraction (PXRD) and Differential Scanning Calorimetry (DSC) were used to determine co-crystal formation. The success of predicting co-crystal formation with NAR and all 40 coformers was evaluated by (1) calculating hydrogen bonding propensity using CSD version 2020.5.43, (2) the molecular complementarity tool in Mercury version 2022.3.0 and (3) molecular miscibility using DSC. The assessment of other predictive tools such as Hansen Solubility Parameters based on drug-coformer miscibility, the ΔpKa rule and intermolecular energy calculations to determine the likelihood of cocrystal formation is under the development.

NAR is a weakly ionizable compound with poor aqueous solubility and low bioavailability, and thus cocrystallization is a reasonable option for potentially improving its performance. A total of 9 NAR co-crystals, six previously reported and three new co-crystals with gallic acid, succinimide and tetramethyl pyrazine were generated in this work. Our co-crystals have potential as novel drug products because both physicochemical and pharmacological selection criteria were established at the outset; however, the success rate observed for new co-crystal formation using experimental screening was around 10%. Our observed success rate for co-crystal formation from Group B is around 13% despite leveraging probable hydrogen-bonding interactions. The prediction accuracy of the molecular complementarity tool was better at 25%, however, molecular properties such as shape, size, dipole moment of drug and coformer need to be refined to better predict co-crystal formation. Lastly, the molecular miscibility screen using DSC showed the best correlation, successfully predicting co-crystal outcomes with success rate more than 80%. Overall, new tools/descriptors to predict and/or screen probable co-crystal formation are necessary to advance co-crystal engineering in pharmaceutical solid-form discovery.

#19

Discriminative Dissolution Method Development through An AQbD Approach

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A two-stage workflow for the dissolution method development and demonstration of discrimination power was developed through an analytical quality by design (AQbD) approach. In the first stage, the dissolution method development follows the procedure of 1) understanding the properties of drug substance and drug product, 2) evaluating sink conditions, 3) conducting dissolution testing using a design of experiments (DoE), and 4) determining a method operable design region (MODR). In the second stage, the discrimination power was demonstrated through 1) performing a risk assessment to identify formulation and process variables of interest, 2) setting of a meaningful range for each variable, 3) conducting dissolution testing of a formulation DoE, 4) determining a formulation-discrimination correlation diagram (Figure 1), and 5) demonstrating method discrimination power.

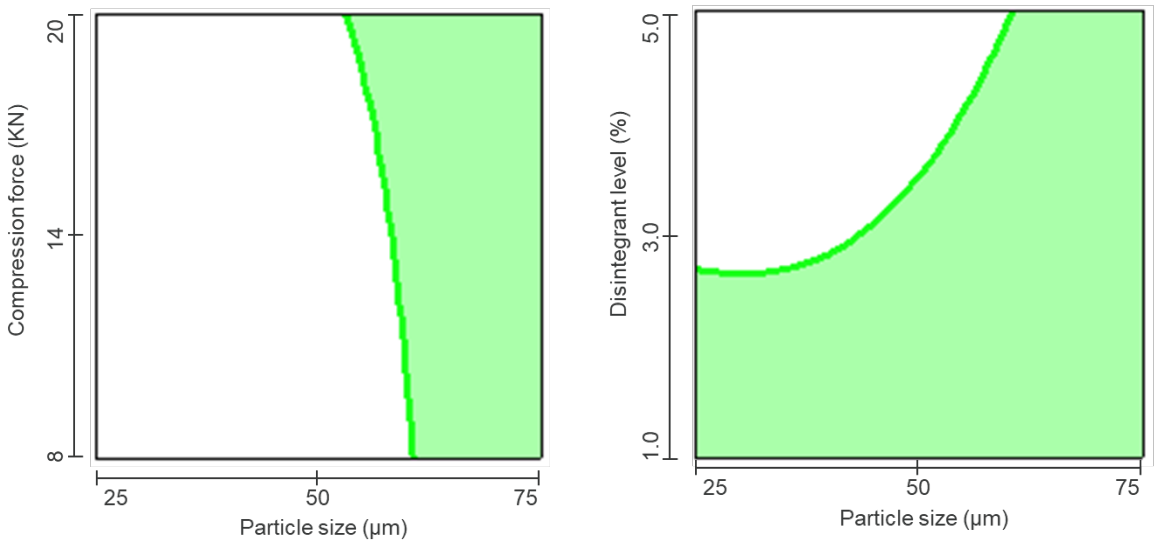

Figure 1. Formulation-discrimination correlation diagram.

#20

Impact of Solid Content on Micromeritics, Flowability, and Compaction Properties of Lyophilized Products

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The lyophilization process is frequently used to solidify and stabilize labile drug substances, especially in the development of biological products intended for parenteral delivery. However, there is a growing interest in exploring oral administration for delivering biological products such as proteins, antibodies, peptides, microbiomes, probiotics, nucleic acids, vaccines and extracellular vesicles. The solid state and powder properties of powders resulting from the freeze-drying process play a vital role in designing high-quality oral dosage forms like tablets, powders in bottles or capsules. These properties impact downstream processes such as powder handling, package selection, encapsulation, content uniformity, storage stability, and efficacy during reconstitution.

In this work, we evaluated the effect of solid content on the properties of lyophilized powders using common bulk agents of sucrose, mannitol, and trehalose. Both 5% and 10% solid content solutions underwent the same lyophilization cycle and the formed cake was milled by same process. We evaluated drying time, cake appearance, water content, particle size distribution, particulate morphology, hygroscopicity, flowability, bulk density tapped density, compaction properties, as well as reconstitution time influenced by bulk agent concentration. Additionally, we examined solid-state properties of powders using powder X-ray diffraction, differential scanning calorimetry, polarized light microscopy. Surprisingly, raising the solid content from 5% to 10% had a significant impact on the solid state of lyophilized products, resulting in various changes, including distinct thermal properties and hygroscopicity. However, all of the powders displayed inadequate flowability and low bulk density, which necessitated the implementation of formulation approaches to address these issues.