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2024 AAPS 360 Annual Meeting: Highlights in the Area of In Vitro Release and Dissolution

Sanjaykumar Patel[1*], Niloufar Salehi[2], Jie Shen[3], Lynne S. Taylor[4], Aleksander Mendyk[5], Sandra Klein[6], Fady Ibrahim[7], Yasuhiro Tsume[1], Stephen D. Stamatis[2], Vivian A. Gray[8], Andre Hermans[1], and Sandip Tiwari[9]

[1]Merck & Co., Inc., Rahway, NJ, USA.
[2]Eli Lily & Company, Indianapolis, IN, USA.
[3]Northeastern University, Boston, MA, USA.
[4]Purdue University, West Lafayette, IN, USA.
[5]Jagiellonian University-Medical College, Kraków, Poland.
[6]University of Greifswald, Greifswald, Germany.
[7]Sanofi, Cambridge, MA, USA.
[8]Dissolution Technologies, Hockessin, DE, USA.
[9]BASF Pharma Solutions - North America, Tarrytown, NY, USA.

e-mail: sanjaykumar.patel@merck.com

INTRODUCTION

The American Association of Pharmaceutical Scientists (AAPS) successfully hosted its PharmSci 360 Annual Meeting and Exposition from October 20–23, 2024, at the Salt Place Convention Center in Salt Lake City, UT. This annual event provides a platform for pharmaceutical scientists from across the globe to gather, facilitating interactions among professionals from academia, industry, and regulatory bodies.

The AAPS PharmSci 360 Annual Meeting featured a productive In-Vitro Release and Dissolution Testing (IVRDT) community meeting. Sanjaykumar Patel, the community chair, and Tahseen Mirza, the chair-elect, effectively led the meeting with strong support from past chairs and community members. During the meeting, they shared the community's accomplishments from 2024 and outlined potential plans for 2025. The in-person format allowed for interactive discussions, which enhanced participant engagement and facilitated the generation of ideas and possible topics for community events in 2025.

In 2024, the IVRDT community within the American Association of Pharmaceutical Scientists (AAPS) achieved several notable accomplishments and collaborations. The community organized two significant webinars hosted by AAPS:

1. "Capsule Dissolution and Related Quality Attributes," co-hosted with the Excipient community and presented by Dr. Margareth Marques from USP. This webinar provided extensive insights into the quality attributes of capsule dissolution, attracting a substantial audience and fostering an interactive question-and-answer session.

2. "New Methods for Absorption Profiling of Advanced Drug Delivery Systems," co-hosted with the Oral Biopharmaceutics and Absorption Modeling community and presented by Dr. Christel Bergström, PhD, from Uppsala University, Sweden. This session delved into novel methodologies for absorption profiling, engaging participants in a highly interactive discussion.

Both webinars attracted a substantial audience and included highly interactive discussion sessions that enhanced participant engagement and knowledge exchange.

In 2024, the IVRDT community accomplished several publishing goals, achieving three notable publications in the journal, *Dissolution Technologies*. These publications include:

- A detailed summary report on the outreach workshop organized in collaboration with the University of the Philippines Manila, which focused on topics related to dissolution testing (*1*).
- Highlights from the 2023 AAPS 360 Annual Meeting, particularly concerning the area of in vitro release and dissolution (*2*).

*Corresponding author

- A comprehensive summary of the webinar hosted by the community to share insights on the new USP Dissolution Performance Verification Standard, which included frequently asked questions (*3*).

During the AAPS 360 annual meeting, the IVRDT community presented a symposium titled "Accelerated Development of Poorly Soluble Drugs Using Predictive Tools," moderated by Niloufar Salehi, the communit''s secretary. The symposium aimed to address the challenges associated with formulating low-solubility active pharmaceutical ingredients (APIs) and explored how in vivo predictive in vitro methods can expedite drug development while reducing the necessity for extensive preclinical and clinical studies. The symposium featured a comprehensive array of topics, including the utilization of biorelevant media, the implementation of predictive tools in the early stages of drug product development, the significance of multi-compartment systems, and the correlation between predictive dissolution and preclinical and clinical outcomes. The session was well-attended and facilitated extensive discussions, highlighting the ongoing challenges within the pharmaceutical industry concerning the formulation of low-solubility APIs. Participants acknowledged the potential of predictive tools to offer viable solutions to these critical issues, thus emphasizing the importance of continued innovation and research in this domain.

These accomplishments and collaborations highlight the significant contributions and active engagement of the IVRDT community within the AAPS organization and the broader field of pharmaceutical science.

The IVRDT community leadership team held an active session during the in-person meeting to collect and compile feedback at the AAPS 360 annual event. This feedback will be used to identify key focus areas for future events and proposals for the 2025 IVRDT community effort and for the AAPS 360 annual meeting. The proposed topics for consideration included biorelevant and biopredictive dissolution, clinically relevant dissolution methods, predictive methods for pediatric formulations, and alcohol-induced dose dumping for modified-release formulations. The in-person community meeting was highly successful, promoting scientific engagement within AAPS and reinforcing the commitment to advancing dissolution science, with the goal of achieving another productive year in 2025.

This article provides a summary of the key presentations at PharmSci 360 in October 2024.

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SUB-TRACK: TURBOCHARGING THE EFFICIENT DELIVERY OF PEPTIDE THERAPEUTICS THROUGH MOLECULAR UNDERSTANDING

Dr. Lynne Taylor from Purdue University (USA) gave a presentation on the topic "Release rate of peptides from the formulations containing permeation enhancers." Oral peptides formulations are of increasing interest given the recent development of the GLP-1 agonist semaglutide as an oral tablet formulation, Rybelsus, as well as the capsule formulation of octreotide, Mycapssa. Inherent to the successful oral delivery of hydrophilic peptides, is the inclusion of permeation enhancers (PE) in the formulation, typically in relatively high amounts. Furthermore, it is widely considered critical that the PE and peptide are released at the same time, at the correct location in the gastrointestinal tract, whereby the PE achieves a sufficiently high local concentration at the membrane to enhance peptide permeability. We have initiated studies of how PEs and peptides release from solid oral dosage forms. Initial studies with insulin as the model peptide, and sodium decanoate or salcaprozate sodium as the PEs, formulated into tablets with microcrystalline cellulose, revealed that the PE released faster than the peptide. However, the presence of the PE promoted the peptide release at near-neutral pH conditions, relative to tablets that contained no PE. The enhanced release was attributed to a local pH effect caused by the basic PEs, such that the pH in the close vicinity of the tablet was higher than the bulk pH. Insulin, in turn, has a higher solubility at pH conditions higher than its isoelectric point of 5.3, driving its release. These release studies highlighted important considerations around microenvironmental pH changes, and the synchronicity of peptide and PE release from a

solid oral dosage form. Follow-up studies evaluated the use of a gel-forming polymer to improve the synchronicity of the peptide and PE release. Cyclosporine, a lipophilic peptide, and octreotide, a hydrophilic peptide, were used as model systems with the same PEs as discussed above. Copovidone was employed as a gel-forming polymer. The inclusion of copovidone into the formulation was found to enable rapid and synchronous release of the peptide and the PE for octreotide. In the case of cyclosporine, synchronous peptide, and PE release could be achieved at a low drug loading in the formulation, but the peptide release rate slowed down as the drug loading increased, and the PE released faster than the drug. Thus, the use of a gel-forming polymer is an interesting approach to enable simultaneous delivery of peptide and PE.

Collaborators for this work include: Andrew Fagan, Lorraine M. Bateman, Abina M. Crean, and Joseph P. O'Shea from the Research Ireland Centre for Pharmaceuticals, School of Pharmacy, University College Cork, Cork, Ireland; and Pradnya Bapat, Sheena Luy, and Neha Panchabhai from Purdue University.

KEYNOTE: USING ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING (AI/ML) IN THE DRUG DISCOVERY AND DEVELOPMENT PROCESSES

Prof. Aleksander Mendyk from Jagiellonian University-Medical College (Poland) gave a keynote presentation entitled "Using AI/ML: What is Lacking to Make AI/ML Really Successful in the Drug Discovery/Development Processes.". He raised the topic of an overestimation of artificial intelligence (AI) capabilities and, at the same time, of an oversimplification of AI understanding via a hype-based focus on artificial neural networks only.

His talk outlined a general evolution of the term "AI" and biological foundations of machine learning (ML) tools, invoking father figures of the field, like 2024 Nobel Prize winners John Hopfield and Geoffrey Hinton. Prof. Mendyk criticized the current popular understanding of the whole AI field on the grounds of Alan Turing's test and its colloquial application to judgment of the scope and application domain of AI.

Based on that, Prof. Mendyk introduced a few examples of the discovery of some new drugs and identified major obstacles to the development of the field as data-related: both data quantity and quality. The latter is understood mostly as a lack of negative results that heavily bias our current systems, as ML is a data-driven approach.

His presentation sparked a vivid discussion about how data sets could (or should?) be curated, what are the possibilities to empower AI with the correct data, and what are the alternatives to artificial neural networks, as focusing solely on these was identified as an oversimplification of AI understanding.

SYMPOSIUM: ACCELERATED DEVELOPMENT OF POORLY SOLUBLE DRUGS USING PREDICTIVE TOOLS

The first lecture of the symposium, titled "Biorelevant Media and Relevance in Current Time," was delivered by Sandra Klein from the University of Greifswald (Germany). Sandra completed her PhD under the supervision of Dr. Jennifer Dressman at the University of Frankfurt, Germany, making her part of the team that pioneered biorelevant media. Her journey with these tools began 25 years ago, when biorelevant media were still in their infancy. Sandra shared that, at the beginning of her doctoral studies, the fasted- and fed-state simulated intestinal fluids (FaSSIF and FeSSIF, respectively) had just been introduced. During Sandra's time as a PhD student, she and Dr. Dressman worked closely with Dr. Christos Reppas' research group at the University of Athens to develop additional biorelevant media. She noted that many of the PhD students involved in these early efforts have continued to contribute to this field. Among these notable researchers are Drs. Nikoletta Fotaki and Maria Vertzoni, who, like Sandra, remain highly active members of the IVRDT community.

The first biorelevant media, developed shortly before and after the turn of the century, were designed to simulate the conditions in the upper gastrointestinal tract of an adult after the administration of an oral dosage form with a glass of water in the fasted state or after the ingestion of a standardized meal, i.e., under conditions mimicking a clinical study setting. The goal was to create physiologically relevant dissolution and release profiles that, ideally, would allow the prediction of in the vivo drug release of poorly soluble drugs in an average healthy adult. The introduction of these media initially sparked mixed reactions. Many researchers were enthusiastic about this innovative approach, but some were skeptical. Some doubted that biorelevant media, which cannot claim the reproducibility of standard buffer solutions, would ever gain a foothold in the pharmaceutical industry or be accepted by regulatory authorities. However, these doubts were not to be confirmed, and Sandra's presentation offered an insightful overview of the development of biorelevant media – from a conceptual idea to a carefully refined set of dissolution media enabling analysts to closely mimic the gastrointestinal

conditions in a clinical study setting using biorelevant in vitro models. She emphasized that in the field of oral drug development biorelevant media has become a cornerstone in reducing risks in clinical development. Use of biorelevant media has significantly reduced reliance on animal testing, which was traditionally employed to evaluate the in vivo release behavior of drugs at various stages in formulation development. Additionally, regulatory authorities worldwide are increasingly acknowledging their importance, leading to the official inclusion of several biorelevant media in the United States Pharmacopeia. This achievement highlights their pivotal role in advancing pharmaceutical research and fostering more efficient and ethical drug development processes.

In addition to the now widely known biorelevant media for simulating conditions in the gastrointestinal tract of adult humans, several analogs have already been established, such as those for simulating gastrointestinal conditions in dogs or pigs to evaluate how data from pharmacokinetic studies in these animals correlate with those from human studies. However, when it comes to completely eliminating animal pharmacokinetic studies from formulation development in the future and predicting in vivo drug release using biorelevant in vitro models, it is necessary to focus not only on the conditions in the gastrointestinal tract of an adult in a clinical study setting, but other potential patients, dosing conditions, sites of application, and routes of administration. This is precisely why it is not surprising that, in recent times, considerable research activity has been observed focusing on the development of biorelevant media for special patient groups, as well as for non-oral dosage forms and their respective routes and sites of administration. Sandra is actively addressing such questions herself, both in the field of oral and non-oral drug delivery. At the symposium, she presented her recently developed biorelevant pediatric dissolution media toolbox, which allows the simulation of conditions in the gastrointestinal tract of children of various ages under different (age-appropriate) drug administration conditions, based on the current state of knowledge. Through a series of tests with pediatric dosage forms containing poorly soluble drugs, Sandra was able to effectively demonstrate the discriminatory power of the pediatric biorelevant media used. Overall, the experiments revealed clear trends that correlated well with bioavailability data reported for the respective dosage forms, further validating the relevance of biorelevant media in predicting in vivo drug release in this special population.

After this brief insight into one of her current research areas, Sandra encouraged researchers to build on past achievements in the field of biorelevant media by directing their future efforts toward the development and optimization of media tailored to different populations, routes of administration, and sites of application. Based on the experience gained so far with established biorelevant media, such initiatives have the potential to become one of the mainstays of successful and innovative pharmaceutical research in the future.

Next, Dr. Fady Ibrahim from Sanofi (USA) discussed the limitations of compendial dissolution methods and explored advanced in vitro testing approaches for early drug product development. Key points include:

1. Dissolution testing serves as a surrogate for product quality and has various applications throughout drug development, from pre-formulation to post-approval changes.

2. Challenges with dissolution testing include over-discrimination (flagging differences in clinically bioequivalent products) and under-discrimination (failing to reject non-bioequivalent products).

3. Quality control (QC) dissolution media may not always be physiologically relevant or biopredictive. There is large variability among subjects in gastrointestinal conditions, which is not captured by standard methods.

4. Advanced in vitro testing approaches include:

- Combined dissolution and permeation systems (e.g., IDAS2, MacroFLUX, Microflux)
- Transfer models simulating different gastrointestinal compartments (e.g., GIS device)
- Fed-state models (e.g., fed stomach model, GastroDuo, TIM system)

5. A case study on counter-ion selection for a salt form of a weakly basic compound was presented. The study utilized in vitro precipitation tests and biorelevant media to screen formulation attributes and predict in vivo performance.

The presentation emphasized the importance of understanding the limiting processes of oral absorption for each molecule to select appropriate biopredictive systems. Complex systems are not always necessary for simple tasks, and variability in vivo necessitates multiple testing conditions and risk assessment. Although biopredictive systems are diverse and no single system

can fully replicate physiological conditions, they offer valuable tools for predicting in vivo performance beyond traditional compendial methods in early drug product development.

Dr. Tsume from Merck (USA) presented "Role of multi-compartment systems for low solubility weak base drugs." Poorly soluble, weakly basic drugs like ketoconazole dissolve in acidic conditions like the stomach. Those dissolved drugs in the stomach will precipitate or appear to be supersaturated levels once they are moving from the stomach to the small intestine. This observation is important to evaluate the oral absorption of test compounds and the development of oral formulation. Those phenomena cannot be observed in single vessel setups with one fixed pH in the experimental condition, like compendial dissolution apparatus USP I and 2. With USP apparatus 3 and 4, the dissolution media and those pHs can be changed and the drug dissolution rate in each media can be observed. However, those dissolution studies cannot trace the dissolved drug solution and cannot observe the precipitation and/or supersaturation of test compounds. Therefore, it is important to use a multi-compartment dissolution setup with a minimum of two different pHs, such as two-stage dissolution and transfer dissolution models, to gain a comprehensive understanding of bioperformance of oral dosage forms. He presented the results through his research and his collaborative efforts with the PQRI consortium to demonstrate the importance of multi-compartment dissolution testing to study the bioperformance of weakly basic drugs.

Dr. Stephen Stamatis from Eli Lilly (USA) presented "Linking in-vivo predictive dissolution data with pre-clinical and clinical studies." The talk began with a high-level introduction to mechanistic absorption/physiologically based biopharmaceutics modeling (PBBM) to serve as the link between in vitro and in vivo dissolution performance. A hypothetical case study followed wherein a discovery program team needed to select between various solid forms to advance to the clinic. By leveraging a small-scale two-stage dissolution experiment, the team was able to rationalize the in vivo performance in both rats and dogs to make a confident selection of the form to advance. He concluded with an example of how later-phase dissolution modeling data can be incorporated in a PBBM to enable a robust description of performance across varied formulations. The methods required for this (i.e., Z-factors or product-particle size distribution [P-PSD]) require additional information warranted for later stage analysis. The key takeaway from the presentation was that phase-appropriate experiments coupled with model-driven hypotheses allow a team to drive mechanistic understanding and more informed decision-making.

PICTURES OF THE IVRDT COMMUNITY MEETING