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MEETING REPORT

Drug Dissolution in Oral Drug Absorption: Workshop Report

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Abstract
The in-person workshop "Drug Dissolution in Oral Drug Absorption" was held on May 23–24, 2023, in Baltimore, MD, USA. The workshop was organized into lectures and breakout sessions. Three common topics that were re-visited by various lecturers were amorphous solid dispersions (ASDs), dissolution/permeation interplay, and *in vitro* methods to predict *in vivo* biopharmaceutics performance and risk. Topics that repeatedly surfaced across breakout sessions were the following: (1) meaning and assessment of "dissolved drug," particularly of poorly water soluble drug in colloidal environments (*e.g.*, fed conditions, ASDs); (2) potential limitations of a test that employs sink conditions for a poorly water soluble drug; (3) non-compendial methods (*e.g.*, two-stage or multi-stage method, dissolution/permeation methods); (4) non-compendial conditions (*e.g.*, apex vessels, non-sink conditions); and (5) potential benefit of having both a quality control method for batch release and a biopredictive/biorelevant method for biowaiver or bridging scenarios. An identified obstacle to non-compendial methods is the uncertainty of global regulatory acceptance of such methods.

Keywords absorption · amorphous · dissolution · food · permeability · solubility

Abbreviations

ABS	Acid-base supersolubilization
ASD	Amorphous solid dispersion
A/V	Area-to-volume
BE	Bioequivalent
BCS	Biopharmaceutics Classification System
BioGIT	*In vitro* biorelevant gastrointestinal transfer system
CMC	Chemistry, Manufacturing, and Controls
CDMO	Contract development and manufacturing organization
CBA	Critical bioavailability attribute
CMA	Critical material attribute
CPP	Critical process parameter
CQA	Critical quality attribute
Cyd	Cyclodextrin
DoE	Design of experiments
$C_{dissolved}$	Drug-dissolved concentration
DGM	Dynamic gastric model
DLS	Dynamic light scattering
FaSSGF	Fasted state–simulated gastric fluid
FaSSIF	Fasted state–simulated intestinal fluid
FedGAS	Fed state–simulated gastric fluid
FeSSIF	Fed state–simulated intestinal fluid
FDA	Food and Drug Administration
GIT	Gastrointestinal tract
GDUFA	Generic Drug User Fee Act
ICH	International Conference on Harmonization
IVIVC	*In vitro–in vivo* correlation
IVIVR	*In vitro–in vivo* relationship
MRI	Magnetic resonance imaging
NCE	New chemical entity
NDA	New Drug Application
PLS	Partial least squares
PSD	Particle size distribution
pH_{max}	pH of maximum solubility

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PBPK	Physiological based pharmacokinetic
PBBM	Physiologically based biopharmaceutics modeling
PDUFA	Prescription Drug User Fee Act
PPI	Proton pump inhibitor
QC	Quality control
RTRT	Real-time release testing
SUPAC	Scale up and post-approval change
S(N)EDDS	Self-(nano)emulsifying drug delivery systems
SSA	Specific surface area
TFF	Tangential flow filtration
USP	United States Pharmacopeia

Introduction

The in-person workshop "Drug Dissolution in Oral Drug Absorption" was held on May 23–24, 2023, in Baltimore, MD, USA, and was organized by the University of Maryland Center for Excellence in Regulatory Science and Innovation (M-CERSI). The workshop was organized into lectures and breakout sessions. The purpose of the workshop was to facilitate dialog between academic, industrial, and regulatory drug development scientists about current phenomena and methods in oral drug product dissolution method development and application. The lecture notes from this workshop are posted at: https://cersi.umd.edu/drug-dissolution-oral-drug-absorption-workshop. The workshop agenda is included in Supplementary materials.

Topics included *in vivo* dissolution and drug absorption; *in vivo* gastrointestinal tract (GIT) imaging and dynamics; regulatory considerations for dissolution method development, including non-compendial methods; and critical amorphous solid dispersion (ASD) properties and dissolution method development. Over 100 attendees participated.

The objective of this workshop report is to summarize the lectures and breakout session discussions. The workshop included 13 lectures on advances in drug dissolution. In this workshop report, lectures are briefly described in three subsections: Lectures involving supersaturation; lectures involving dissolution/permeation systems; and lectures involving oral biopharmaceutics prediction and understanding. This sectioning of lecture content reflects the three common topics that were re-visited by various lecturers and via several breakout discussions.

The workshop included 10 breakout sessions to provide opportunities to discuss in small groups the current challenges and limitations, including emerging approaches and techniques for complex oral formulations. Table I lists breakout session topics and main questions addressed. Common themes across breakout sessions were the following: (1) meaning and assessment of "dissolved drug," (2) issues of requiring sink conditions for a poorly water soluble drug; (3) non-compendial methods, (4) non-compendial conditions; and (5) potential benefit of a biopredictive/biorelevant method that supplements a quality control (QC) method. An identified obstacle to non-compendial methods is the uncertainty of global regulatory acceptance of such methods.

Lectures Involving Supersaturation

Supersaturation via Acid-Base Interactions

Abu Serajuddin presented a novel approach to greatly increase aqueous solubility and dissolution rates of poorly water-soluble basic and acidic drugs. According to the classical pH-solubility theory (1), the solubility of a free base and its salt with an acidic counterion may be described by two independent curves, one where the free base is the equilibrium species and the other where the salt is the equilibrium species; the point where the two curves intersect is the pH of maximum solubility (pH_{max}). When an acid is used to reduce pH of the suspension of a basic drug in water, the solubility of drug increases until pH_{max} is reached, and upon further lowering of pH to < pH_{max}, a phase transition of the drug occurs resulting in the crystallization of its salt form. Acids used to adjust pH of the suspensions must be strong enough to lower pH below pH_{max}; if relatively weaker acids are used, pH_{max} may never be reached, and solubility of the drug in aqueous medium keeps increasing according to the Henderson-Hasselbalch equation without any salt precipitation until a very high solubility is attained. Singh *et al.* reported that, while aqueous solubilities of phosphate and HCl salts of haloperidol are 1 and 4 mg/mL, respectively, the solubility of the compound could be increased to >300 mg per gram of solution by adjusting pH with such weak acids as malic acid, succinic acid, and citric acid, which did not form haloperidol salts (2). Similar increases in aqueous solubility of other basic drugs like itraconazole and cinnarizine have also been reported in presence of weak acids like glutaric acid and malic acid (3). Serajuddin and associates also demonstrated very high solubility (>350 mg/g) of flurbiprofen, an acidic drug, by raising pH with the weak base meglumine. The phenomenon has been named acid-base supersolubilization (ABS) since extremely high aqueous solubility was obtained via interactions between basic drugs and weak acids, or acidic drugs with weak bases.

Serajuddin presented how ABS may be applied to the development of amorphous solid dispersions (ASD). When the supersolubilized solution of a basic or acidic drug is dried, the material forms an ASD that neither crystallizes into salt nor converts back to the crystalline free base or acid, thus giving a physically stable ASD with high drug content. Such conversions of drug to the amorphous form

Table I List of Breakout Sessions. Key Questions used to Guide Session Discussions are also Provided

Breakout session	Key questions
In vitro approaches to interpret/predict food effects	What *in vitro* dissolution or dissolution/permeation methods can anticipate positive, negative, or a lack of food effects?
Ionizable drugs or excipients: buffer capacity considerations	At what stage during the product development process are dissolution medium modified to take into consideration ionizable drugs and excipients?
	What different buffer systems are investigated for ionizable drugs and excipients? Are buffer systems used for dissolution testing part of quality control dissolution method or are they used exclusively for product development/research activities?
	What are the major gaps in developing/leveraging *in silico* tools to predict performance of ionizable drugs and drug products with ionizable excipients?
Drug dissolution from amorphous solid dispersions	What basic and applied laboratory methods provide the best insights into drug dissolution from amorphous solid dispersions?
Non-compendial testing for ASDs from industry and regulatory perspective	For ASDs, what compendial and non-USP dissolution methods are most useful, and what are the challenges?
Drug dissolution from nano-formulations	What are key technical challenges presented by nanoparticle formulations?
	What critical bioavailability attributes (CBAs) affect the *in vitro* drug release from nano-formulations?
	What are the key considerations or strategies for achieving a clinically relevant dissolution method for nano-formulations?
	What are potential benefits of methods that add a permeation component, such as dialysis, microdialysis, or dissolution-permeation?
	What options exist for automating dissolution methods?
	For nanocrystalline oral dosage forms, can disintegration be used as a proxy QC method instead of dissolution?
Drug dissolution from lipid-based formulations	What kind of lipid-based formulations have you been developing and what strategy have you applied?
	What are some challenges you have encountered when developing/validating dissolution methods for lipid-based formulations?
Drug dissolution from co-crystals	What are the current roles of co-crystals in drug development?
	Do they require any special considerations for dissolution testing?
Non-compendial methods	What is the definition of non-compendial methods?
	Under what conditions has any particular non-compendial method been helpful, and why?
	Are such non-compendial methods complementary or potential replacements for compendial methods?
Non-USP methods *versus* regulatory methods: biopharmaceutic risk assessment	How do you initiate developing a dissolution method for your proposed product? For 505(b)(1) *vs* 505(b)(2) *vs* ANDA products?
	What leads you to pursue or not pursue a non-USP method as your ultimate regulatory method?
	Have you filed a non-USP method and gained approval from regulatory agencies worldwide?
	What can be the potential risk/benefits and technical challenges in adopting and transferring a non-compendial method to commercial testing sites, especially for a non-NME?
Real-time release testing (RTRT) to replace *in vitro* dissolution	What are the best real-time release testing practices to establish confidence in the model?
	What are the challenges to implementing dissolution RTRT?
	What future improvements are needed?

may also be obtained by the melt extrusion of the acid-base mixture without the need of any water to dissolve drug (4). However, ASDs formed by interaction between only acids and bases could be semisolid and viscous and difficult to process into tablets and capsules. The issue was resolved by adsorbing aqueous solutions onto silicates before drying or by melt extrusion along with polymers. ASDs produced using haloperidol, cinnarizine, and itraconazole were converted to tablets and capsules that dissolved rapidly and provided supersaturation in dissolution media. Thus, the application of ABS not only greatly increased solubilities of basic and acidic drugs in aqueous media, but also formed rapidly dissolving and supersaturating ASDs.

Release Mechanisms of Amorphous Solid Dispersions

Lynne Taylor described release mechanisms of ASDs. The dissolution of small molecules is well understood, and typically described using equations based on the Noyes-Whitney model. However, drug release from ASDs is less explored, and fundamental mechanisms of transfer from the solid ASD into solution are unknown. While the "amorphous solubility advantage" of drugs is well established, this cannot account for the very rapid drug release into the solution phase observed from ASDs with low drug loadings. Instead, it appears that the drug release rate is controlled by the polymer dissolution rate, at least below a critical drug

loading. Furthermore, for neutral, high molecular weight polymers such as copovidone, formation of a gel layer during ASD hydration, as well as the phase behavior within this gel layer appear important for understanding how drug loading impacts release performance. Copovidone-based ASDs typically show a "falling-off-the-cliff" phenomenon, where release is rapid at low drug loadings, but decreases dramatically once a critical drug loading is exceeded. Using microscopy, it can be demonstrated that for some drugs at low drug loadings, phase separation occurs in the gel layer formed by hydration, leading to dispersed drug-rich domains. These are released into solution as the polymer dissolves. At higher drug loadings, water ingress also leads to phase separation, but now the insoluble phase is continuous, leading to a low-solubility surface layer, that impedes release from the ASD. For enteric polymer based ASDs, solution pH is an additional critical parameter. Hypromellose acetate succinate HF (HPMCAS-HF) grade solubility is highly sensitive to pH variations relevant to the gastrointestinal tract. A negative food effect observed in monkeys for an ASD of (pH independent) pretomanid and HPMCAS-HF was attributed to a low intestinal pH where the polymer showed limited solubility. The compromised solubility and release rate of the ASD was not readily detected using fed state–simulated intestinal fluid with a pH of 5.8, but could be better observed by conducting additional release studies over a wider range of pH values. In summary, as ASDs increase in popularity as a formulation strategy for poorly soluble drugs, improved understanding of release as a function of formulation and media variables will underpin *in vivo* performance predictability which is currently lacking for these systems.

Food and Drug Administration perspective on QC Dissolution Test for Oral Drug Products Containing ASDs

Kevin Wei discussed a perspective on QC dissolution testing for oral drug products containing ASDs. In general, the preparation of an ASD-based drug product involves the conversion of a poorly water-soluble crystalline drug substance into its amorphous form with higher solubility. After oral administration of a drug product containing an ASD, it can display significantly increased apparent solubility when compared to its crystalline form, which allows it to generate a supersaturated state in the GIT and, in turn, improve its dissolution, absorption, and bioavailability. From a QC perspective, the biopharmaceutical risks for an ASD-based drug product can be mitigated by developing a dissolution method with optimal discriminating ability toward the product's critical bioavailability attributes (CBAs). CBAs are formulation or process attributes which are expected to critically impact the bioavailability (absorption rate and extent) of the drug product.

For ASD-based drug products, one of the most significant quality concerns is the lack of thermodynamic stability, which is reflected by its conversion to the crystalline form during the manufacturing process and/or storage (product's shelf-life), which could lead to inadequate bioavailability and clinical performance due to sub-therapeutic dosing, posing a high risk to the patient. Therefore, to ensure that the bioavailability and clinical performance will not be affected, it is very important to have an adequate QC for the crystalline content in ASD-based drug products. In addition, critical formulation variables (*e.g.*, levels and/or grade of polymer, surfactant, disintegrant) and critical process parameters (*e.g.*, ASD particle size, compression force/hardness) may also impact the dissolution and bioavailability of ASD-based drug products. When developing a dissolution test for QC purposes for ASD-based drug products, the discriminating ability of the dissolution method toward crystalline content, critical formulation variables, and process parameters should be evaluated. Both the dissolution method and the acceptance criterion/criteria should be considered when the discriminating ability of a proposed dissolution test is demonstrated. An optimal discriminating dissolution test should be able to mitigate the biopharmaceutical risks that may/could negatively impact the *in vivo* performance of a proposed drug product.

Additionally, it is advised that for ASD-based drug products, sponsors submit to FDA the dissolution method development and validation report(s) prior to their New Drug Application (NDA) submission, and request feedback/comments from FDA, specifically from the Office of Pharmaceutical Quality (OPQ) / Office of New Drug Products (ONDP)/ Division of Biopharmaceutics.

Lectures Involving Dissolution/Permeation Systems

"Dissolved" Species: Biopharmaceutical Roles and Ways to Measure

Martin Brandl presented on drug species that may be considered dissolved and related analytical testing. In recent years, differentiating between molecularly dissolved state and "other dissolved" states such as colloidal or colloid-associated states has drawn greater attention. Many candidate-enabling formulations have been demonstrated to give rise to such "other dissolved" states such as micelles, submicron amorphous or crystalline nanoparticles, or cyclodextrin complexes (5). Also, poorly water-soluble drugs in human luminal or biomimetic environments tend to associate with a variety of colloids arising from bile salts and (phospho) lipids (6).

It appears that micelle-associated drugs are less prone to overcome biological barriers (7). With amorphous solid dispersions, dissolution is more complex: binding of drug to micelles; surfactant, irrespective whether surfactant is from the formulation or biomimetic media, apparently leads to enhanced apparent solubility but not to enhanced permeation. The simultaneous formation of another dissolved species, namely, amorphous sub-micron drug-rich particles during dissolution (5), play a different role; they appear to be the root-cause for molecular supersaturation (8) and thus enhanced absorption, as the drug-rich particles cannot pass biomimetic barriers.

Such roles of various "other dissolved" species were elucidated via equilibrium states and during combined dissolution/permeation experiments. A recent approach focuses on molecularly dissolved drug concentration through microdialysis sampling in parallel with micelle-associated drug concentration through nano-filtration and drug concentration in the form of drug-rich submicron particles over time (9). The combination of all three approaches appears to allow unprecedented mechanistic insights into mechanisms of candidate enabling formulations. Combined dissolution/permeation experiments may serve as a surrogate approach for performance-ranking of enabling formulations. However, techniques to follow molecularly dissolved drug concentrations such as microdialysis sampling have potential for wider use.

In vitro Evaluation of Drug Presence in the Micellar Phase of Contents of Upper Small Intestine: Rationale, Challenges, Opportunities

Christos Reppas presented on *in vitro* evaluation of drug presence in the micellar phase of contents of the upper small intestine. After oral administration of enabling drug products or conventional lipophilic drug products with weakly alkaline characteristics, drug concentrations in the micellar phase of contents of the upper small intestine can be crucial for the overall luminal product performance. Drug concentrations in the micellar phase of contents of the upper small intestine are highly sensitive to total drug presence in the lumen of the upper small intestine, *i.e.*, the total drug arrival and elimination (intestinal transit and epithelial transport) rates, and to the physical state of the drug that enters the upper small intestine from the stomach, *i.e.*, solid state, aqueous solution, and/or non-aqueous solution.

In vitro evaluations under conditions simulating drug administration in the fasted state are possible, after considering the appropriate level of simulation of the system and after confirming the usefulness of *in vitro* data against luminal data in humans. Micellar drug concentrations in the duodenal compartment of the *in vitro* biorelevant gastrointestinal transfer (BioGIT) system are in line with micellar drug concentrations in the upper small intestine (10). The BioGIT system has been shown to be useful for evaluating the impact of formulation and/or dose on early exposure, after oral administration of conventional or enabling drug products with a glass of water to fasted adults (11).

Significant gaps in understanding key luminal drug/drug product related processes do not yet allow for *in vitro* evaluations of drug presence in the micellar phase of contents of the upper small intestine under non-fasting conditions. Current investigations aim to identify the gastric contents characteristics which relate to the frequently delayed disintegration of drug products, to characterize drug gastrointestinal transfer process, and to evaluate the importance of drug in the micellar *versus* colloidal (liquid) phase of contents of the upper small intestine.

Predicting Food Effects on Drug Absorption

Anette Müllertz lectured on food effects. Upon intake of a meal, a multitude of events are triggered, especially in the GIT. The presence of food itself (*e.g.*, chyme) will delay gastric emptying and change motility and thereby GIT hydrodynamics. In addition, stomach pH increases, and bile salts and phospholipids will be secreted from the gall bladder, and enzymes from the pancreas. GI volume and viscosity will increase as the composition of the GI fluids change.

These events can influence drug absorption at different levels. Delayed gastric emptying often delays absorption and thereby T_{max} of a drug. Secondly, food components such as undigested lipid and digesting/digested lipid can increase drug solubilization and consequently increase the absorption, *i.e.*, positive food effect. However, in some cases, a drug can bind to chyme components and cause a negative food effect, *i.e.*, a reduction of drug absorption in the fed state. A negative food effect can also be a consequence of the changed pH profile in the fed state, as the neutral forms of a drug molecule is preferentially absorbed.

During drug development, it is important to elucidate if a drug has a food effect, and this is also required by FDA. Many *in vitro* models have been developed to try to predict food effects on a drug or drug product. It should be emphasized that there is a difference between a drug and a drug product, as a food effect can be dependent on the physicochemical characteristics of the drug, but it can also be a consequence of the formulation. Formulations or dosages forms with reduced food effect may possibly be developed.

Most *in vitro* models are relatively simple and are based on USP methods where the media is changed to simulate the fed state bile and phospholipid levels. In some cases, these media predict whether there is a potential food effect on a drug molecule; however, they cannot accommodate for an entire meal.

For this purpose, several more advanced *in vitro* models have been developed, *e.g.*, the Dynamic Gastric Model (DGM) (12). The DGM can accommodate an entire chewed meal (*e.g.*, the FDA high-fat breakfast). Chewing and addition of saliva and amylase is important for chyme rheology, and therefore, the behavior of the dosage forms when ingested in the fed state. Food is therefore subjected to simulated chewing prior to addition to the DGM.

The DGM includes a physiologically relevant dynamic addition of acid and gastric enzymes (pepsin and lipase) from the gastric wall, and it also displays the same pH profile as seen in the human stomach. DGM hydrodynamics simulates gastric sheer and peristalsis. Samples are ejected from the DGM to the duodenal module at the same rate as from the human stomach to the duodenum. Pancreatic enzymes, bile salts, and phospholipids are added to the duodenum module to mimic the *in vivo* activity and concentration in the duodenum. Samples are collected from the duodenal module to assess dissolved drug over time. A point-by-point *in vivo in vitro* correlation has been obtained for drugs with positive and negative food effect. Thus, the DGM is a useful model to predict and understand the food effect on drugs and drug products.

Considering Free-Drug Concentrations in the GI Tract: Impact of Cyclodextrin and Food

Shinji Yamashita discussed free-drug concentrations in the GIT, with a focus on cyclodextrin and food effects. After oral administration, most drugs are absorbed from the small intestine. Drug absorption rate from the small intestine can be expressed as the product of drug-dissolved concentration ($C_{dissolved}$), intestinal membrane permeability, and membrane surface area. Although $C_{dissolved}$ is defined as a total dissolved concentration, it should be noted that only the drug existing as in free (unbound) and unionized form at the vicinity of the small intestine membrane can be absorbed, assuming drug permeates the membrane through the intracellular lipid pathway.

Various factors affect the time-profile of $C_{dissolved}$ in the small intestine. Solubilizers such as surfactant or cyclodextrin can enhance the total $C_{dissolved}$, but they sometimes fail to improve the absorption due to the decrease in the free fraction of the dissolved drug. Results of *in vitro* dissolution/permeation studies concerning cyclodextrin effects on the free concentration and membrane permeation of poorly soluble drugs were discussed. In addition, effects of food intake on the drug absorption from cyclodextrin-containing formulation were demonstrated.

Combined Dissolution/Permeation: Input for Rationalized Drug Formulation Development

Annette Bauer-Brandl presented on the use of combined dissolution/permeation systems as input for rationalized drug formulation development. Oral bioavailability enhancement for enabling formulations is typically due to transient drug supersaturation. However, not all drug dissolved states are equally prone to boost absorption. The interplay between dissolution, solubilization, phase separation (*e.g.*, precipitation), re-dissolution, and simultaneous absorption determines the extent and duration of molecular supersaturation and thus bioavailability. Predictive *in vitro* experiments need to reflect this interplay, which requires selection of the following: (i) barrier types in terms of transmittance, biomimetic transport mechanism, and robustness in different media; (ii) setups with potentially widely different volumes (*e.g.*, microtiter plates, inserts, United State Pharmacopeia (USP) paddle apparatus), hydrodynamics, and area-to-volume (A/V) ratios; and (iii) experimental conditions (*e.g.*, media compositions, gastric steps, flow rates, and transit times).

Classical dissolution/permeation setups such as Franz cells, side-by-side diffusion cells, and paddle apparatus inserts tend to show insufficient permeation rates. Recent additions to the dissolution/permeation toolbox with high area-to-volume ratios are most promising. Three case studies presented were the following: (a) ranking of amorphous formulations of tadalafil in a microtiter plate (13); (b) *in vitro–in vivo* relationship (IVIVR) for dipyridamole enabling formulations in PermeaLoop™ with high A/V ratio (14); and (c) comparison of IVIVR for posaconazole commercial formulations from experiments in µFLUX™ and PermeaLoop™ (15).

For ranking of formulations, microtiter plates have successfully been used in a high throughput screening "black box" fashion comparing amount permeated at a certain time point. For a deeper mechanistic understanding, which is crucial for prediction and prospective pharmacokinetic modeling, permeation over time, in-depth analysis of supersaturation states, and dynamic equilibria in the donor were demonstrated in more advanced setups.

Lectures Involving Oral Biopharmaceutics Prediction and Understanding

Gastrointestinal Imaging with MRI: Providing Information about Conditions at the Site of Drug Delivery

Werner Weitschies presented on gastrointestinal imaging. The use of modern non-invasive techniques such as magnetic

resonance imaging (MRI) and ingestible telemetric sensors has significantly improved our understanding of the conditions under which drug forms act in the gastrointestinal tract after ingestion (16). This is especially true for the situation in the stomach, which is central to the release of active ingredients during the ingestion of immediate-release dosage forms. When a drug is taken under fasting conditions according to the FDA guideline (240 ml of water), volume and pH decrease to baseline over 30 min after ingestion (17).

The situation for intake under fed conditions is even more complex due to the inhomogeneity of gastric filling and the phenomenon of the "Magenstrasse" (stomach road) as a rapid evacuation process for fluids ingested after a solid meal, such as the high-calorie breakfast commonly used in food effect studies (18). After a test meal of approximately 1000 kcal (along with 240 mL of water) and no further meal or fluid intake for the next 5 h, gastric volume and pH conditions decline over 5 h.

In vivo Formulation Behavior and Drug Absorption

Patrick Augustijns lectured on *in vivo* formulation behavior and drug absorption. Despite significant progress, our current understanding of drug and formulation behavior inside the human GIT is incomplete. In particular, important knowledge gaps remain concerning the dynamic nature of the intraluminal environment. In the GIT, drugs are exposed to a constantly changing chemical and physical environment, which varies depending on the site in the GIT and the time relative to, for instance, food intake or the gastrointestinal motility cycle. A direct and effective way to improve our insight into the complex relationship between gastrointestinal drug disposition and systemic drug exposure is the collection of gastrointestinal fluids (via oral and/or nasal intubation) at specific time intervals after oral drug administration, followed by characterization of the collected aspirates in terms of physicochemical properties (*e.g.*, pH, bile salt content, osmolality) and drug/metabolite concentrations. Furthermore, the impact of food and the concomitant intake of other medication on drug(product) behavior can be investigated. Several case examples were presented studying the influence of gut physiology on the intraluminal behavior of orally administered drug products. These case examples were grouped according to five underlying mechanisms:

Firstly, the intake of proton pump inhibitors (PPIs) can impact the solubility of basic compounds in the stomach, potentially leading to reduced dissolution in the stomach. Upon transfer to the small intestine, this reduced dissolution may result in a decreased degree of supersaturation as the driving force for absorption (19). Secondly, the gastrointestinal environment can be influenced by the volume of water used for drug intake, potentially leading to variations in solubilization, supersaturation, and precipitation of weakly basic drugs (20). Thirdly, the intake of PPIs can lead to a reduction of fluid volume in not only the stomach but also the small intestine (21). Fourthly, after food intake, the process of lipolysis constantly alters the colloidal structures in intestinal fluids and, consequently, the interplay between drug solubilization and permeation (22). Fifthly, the timing of drug intake relative to the cyclic gastrointestinal motility pattern (alternating periods of active motility and quiescence) contributes to variability in gastrointestinal formulation behavior and drug absorption (23). Monitoring of the dynamic intraluminal environment and local drug concentrations provides valuable insights into understanding the influence of gut physiology on formulation behavior. Additionally, it aids in guiding the optimization of *in vitro* and *in silico* simulation models.

Setting up Dissolution Studies to Reflect Product Performance in the GI Tract

Jennifer Dressman discussed dissolution setup to reflect product performance in the GITs. Biorelevant dissolution testing has become widely accepted to better understand how orally administered pharmaceuticals release their drug payload. The original media have been updated and extended in a number of different directions over the years (24, 25). Many suggestions have been put forward to maximize their physiological relevance, such as using bicarbonate instead of standard buffers, while accounting for practical considerations in the laboratory (26). In recent years, dosing conditions have been identified for which the dissolution test needs to be customized. This presentation focused on three of these areas: How do we test whether *in vivo* dissolution will be influenced by concomitant intake of acid-reducing agents (ARA)? How can we better mimic food effects *in vitro*? Is it possible to set up a dissolution test to predict how oral products will release the drug in an overdose situation?

Segregur *et al*. published a review on changes in upper GI physiology associated with ARA intake, focusing on H2-receptor antagonists and proton pump inhibitors (27). Media were presented to reflect these changes using a bracketing approach to cover the range of potency and dosing of these drugs. Subsequently, the media were applied to drugs in clinical development, dipyridamole, and potassium raltegravir (28). By combining dissolution results in the media with physiological based pharmacokinetic (PBPK) models, it was shown that the PBPK-generated plasma profiles reproduced the clinical data well. The key take-home message was that low-buffer capacity media were required to reflect H2-receptor antagonist/PPI therapy, while standard pharmacopeial buffers were not suitable.

Most drugs can be administered before or after meals. But, how can we test whether they will be just as effective in both scenarios? Recently, a new series of media (fed

state–simulated gastric fluid, FedGAS) has been introduced to represent fed state conditions in the stomach to help understanding of how a high-fat meal, such as those used in food effect studies, can influence bioavailability (29). In a collaboration between University of Florida and FDA, such media detected important differences in the behavior of three different amorphous solid dispersions of itraconazole. Combining the dissolution data with PBPK, it was possible to show which products would have positive or negative food effects.

Lastly, overdosing has become a major problem in the USA and abroad. To better treat those who overdose, it is important to understand what happens to drug release *in vivo* when many dosage units have been ingested. In work at Fraunhofer ITMP, a dissolution method has been set up in USP 3 equipment to mimic drug release from up to 50 units. Four different marketed products of acetaminophen (IR tablets, hard capsules, soft capsules, and ER tablets) were tested in the method, revealing that the rate and extent of release of acetaminophen from the different formulations varied widely. The method could be a way forward to predicting plasma profiles from other drugs that are often involved in overdose cases.

Biorelevant *in vitro* Testing-Dissolution Method Development Beyond Compendial Approaches

Zongming Gao discussed biorelevant *in vitro* testing-dissolution method development that span beyond compendial approaches. Dissolution testing is used throughout the life cycle of drug development, from product release throughout its shelf-life stability. It is a commonly employed test in the pharmaceutical industry and a pivotal analytical test used for detecting physical changes in an active pharmaceutical ingredient (API) and formulated drug product. *In vitro* dissolution results are one criterion to control product quality and essential for FDA review and approval. The presentation provided case studies based on review and published dissolution results to show challenges on being able to discriminate bioequivalent (BE) or non-BE batches. It is imperative that the dissolution test is both robust and reproducible, with the ability to detect any key changes in product performance that will have impacts to the patients. Current USP methods may be fit for QC purpose (*e.g.*, Chemistry, Manufacturing, and Controls (CMC) purpose), but may be not relevant to *in vivo* conditions. To address these potential issues, FDA - which is also responsible to accelerate innovations - has made great efforts on scientific developments of *in vitro* dissolution testing methods (30, 31). The presentation included case studies that detailed the development and application of biorelevant *in vitro* dissolution methods in FDA laboratories.

Summary of Breakout Sessions

The workshop included 10 breakout sessions to provide opportunities to discuss current challenges and limitations, including emerging approaches and techniques for complex formulations. Table I lists breakout session topics and main questions addressed. Overall, topics that repeatedly rose across sessions were the following: (1) meaning and assessment of “dissolved drug,” particularly of poorly water soluble drug in colloidal environments (*e.g.*, fed conditions, ASDs); (2) potential limitations of a test that requires sink conditions for a poorly water soluble drug; (3) non-compendial methods (*e.g.*, two-stage or multi-stage method, dissolution/permeation methods); (4) non-compendial conditions (*e.g.*, apex vessels, non-sink conditions); and (5) potential benefit of having both a QC method for batch release and a biopredictive/biorelevant method for biowaiver or bridging scenarios. An identified obstacle to non-compendial methods is the uncertainty of global regulatory acceptance of such methods.

In vitro Approaches to Interpret/Predict Food Effects

This breakout was facilitated by Martin Brandl, Annette Bauer-Brandl, and Kimberly Raines. The main question was the following: What *in vitro* dissolution or dissolution/permeation methods can anticipate positive, negative, or a lack of food effects?

In vitro methods to assess the effects of food often aim to provide insights for formulation optimization, typically with the aim to minimize food effects or to create robust formulations, the performance of which is independent of food. Several *in vitro* and *in silico* tools are being explored to predict the direction and extent of food effects. However, the complexity of different interactions within the GIT and the inter-individual variability *in vivo* makes a reliable prediction of food effect challenging. Furthermore, food intake changes physiologic factors such as luminal hydrodynamics, splanchnic blood-flow, and induction of metabolic enzymes, which are difficult to capture *in vitro*.

Thus, simple bio-predictive tools typically consider drug/bile-salt interactions and range from simple equilibrium solubility studies in media mimicking the bile-salt and lipid composition of the intestinal fluid in different prandial states to “biorelevant” *in vitro* dissolution testing, to combined dissolution-permeation models base on tissue, cells, or cell-free systems. Approaches may use real-time analytics and biopharmaceutics modeling-simulation approaches.

Food effects should be assessed by comparing the dissolution of the drug product in two media. A higher drug release under fed state–simulated intestinal fluid (FeSSIF) conditions over fasted state–simulated intestinal fluid (FaSSIF) conditions indicates a higher drug dissolution in the media with the higher concentration of bile salts that are released in the intestine in fed sate. However, when determining food effects *in vitro*, multiple factors need to be investigated beyond dissolution and solubility, namely permeability, and the interplay between dissolution and permeation, as well as metabolism.

One example discussed was the investigation of a cyclodextrin (Cyd)-formulation of itraconazole which revealed moderately negative food effects based on the AUC ratio under fed and fasted conditions. The solubility of itraconazole in phosphate buffer solution, and in different concentrations of FaSSIF and FeSSIF media (which represent different concentration of bile salts) provided an insight into the interaction between itraconazole and bile salt micelles. The presence of bile salts resulted in the displacement of itraconazole from Cyd complex. This finding could serve as a starting point in understanding the need for additional types of dissolution studies, considering the interplay between Cyd, the drug, and bile salts. Two-stage dissolution/permeation methods and combined dissolution/permeation studies provided a greater understanding of the food effects. Such studies should be aimed at utilizing high-throughput techniques and also at developing a roadmap for *in vitro* studies.

Currently, FDA recommends an *in vivo* clinical food effect study for all extended-release oral products using the to-be-marketed formulation irrespective of the solubility and permeability of drug substance. Although there are no standardized *in vitro* tools nor an FDA requirement for assessing food effects during the drug approval process, such studies, would be assessed on a case-by-case basis, and would be beneficial in obtaining an insight into these effects prior to submission. An understanding of the food effects could potentially impact clinical trials, and early knowledge would guide formulation development through the clinical stages.

Ionizable Drugs or Excipients: Buffer Capacity Considerations

This breakout was facilitated by Rohit Jaini and Parnali Chatterjee. Four questions were addressed. This breakout session was focused on buffer capacity considerations while developing dissolution methods for drug products that contain ionizable drugs (especially weak acids and weak bases that would be considered Biopharmaceutics Classification System (BCS) Class IIa/IIb drug substances) or ionizable excipients (*e.g.*, polymers, pH modifiers, solubilizers). The discussion was structured into four phases, (i) understanding current practices in the industry and academia when developing dissolution methods for ionizable compounds; (ii) gauging industry stance on the importance of buffer capacity on dissolution, delving into buffer concentration and buffer type; (iii) influence on developing QC dissolution method *versus* biorelevant dissolution method; and (iv) leveraging *in silico* tools to predict *in vitro* dissolution of drug products with ionizable molecules or excipients.

Firstly, at what stage during the product development process are dissolution media modified to take into consideration ionizable drugs and excipients? The general sentiment, concurrent with prior literature on *in vitro* dissolution of ionizable compounds, was that method development is highly compound specific and drug product specific. The group noted that, in most cases, a single dissolution medium under sink conditions is used for dissolution testing of development formulations of weak acids or weak bases. For weak acids or weak bases, dissolution is influenced by a variety of factors including dose/solubility ratio, stability of the drug substance in the dissolution medium, intrinsic solubility, acid/basic nature of the drug, media pH, pKa of the molecule, particle size distribution, buffer species and concentrations, and hydrodynamics. Solid-state properties (*e.g.*, thermodynamic stability) of the weak acids/weak bases are an additional criterion that can play a pertinent role in the selection of a suitable dissolution medium. At early stages of product development, the thermodynamically stable form is not known. Through form screening studies, the thermodynamically stable form is identified. At the same time, solid-form conversion is monitored using dissolution testing so that it is of less concern during later stages of the product development. If however, solid-form conversion does occur and dissolution testing cannot discern the two forms, the method development will then have to be initiated from the beginning.

Consequently, this makes developing biorelevant or biopredictive dissolution methods a formidable challenge, more specifically for ionizable drugs or dosage forms containing ionizable excipients. It indeed is essential to understand the key limiting factors controlling drug dissolution when developing dissolution methods.

Industry representatives provided anecdotal instances where a certain zwitterionic molecule exhibited slower *in vitro* dissolution while exhibiting good *in vivo* absorption. This was largely due to common ion effect with a specific ionic species present in compendial buffer media, but not encountered by the molecule *in vivo*. Consequently, dissolution was performed in an alternative buffer system to have more representative dissolution of the molecule. It was suggested to comprehensively evaluate common ion effect, not just with sodium or chloride ions, but all ionic species that the molecule may encounter *in vitro* and *in vivo*. The discussion was then focused on the buffer capacity

consideration when developing dissolution methods for ionizable molecules.

Secondly, what different buffer systems are investigated for ionizable drugs and excipients? Are buffer systems used for dissolution testing part of quality control dissolution method or are they used exclusively for product development/research activities? Two schools of thought were evident. One side presented that the influence of buffer capacity may be overplayed and may not be as limiting a factor as generally expected. This view held that, despite lower buffer capacity, physiologically, there is excessive amounts of continuous secretion of bicarbonate buffer in the body that maintain a bulk pH of 6.8, unlike under *in vitro* conditions that work with a fixed volume of media. Moreover, the implication was that the *in vivo* buffer system makes up for lower buffer capacity in its sheer volume. An alternative view presented that buffer capacity is indeed essential for compounds where dissolution is highly sensitive to changes in surface pH in the unstirred boundary layer around dissolving particles. This is a function of pKa and intrinsic solubility of the molecule or excipient. It would be pertinent to use a buffer type or buffer concentration to replicate the lower *in vivo* buffer capacity when developing a more biorelevant dissolution method to aid formulation selection and drug product design. Other physiologically relevant buffer systems were discussed including fasted state–simulated gastric fluid (FaSGF), FaSSIF, and FeSSIF that are used for formulation selection and for physiologically based biopharmaceutics modeling (PBBM). However, these systems suffer from stability issues (~1 week), are generally expensive, and not scalable. Taking both arguments into consideration, the trade-off between reducing buffer capacity and maintaining the bulk pH (as is well regulated *in vivo*) is crucial to consider. Additionally, the group advised considering buffer capacity considerations for enteric coated dosage forms and for molecules with high precipitation tendencies.

Thirdly, the group was then asked whether considerations of buffer capacity were influential in developing QC methods. The group appeared unanimous in its opinion of keeping the QC dissolution methods as close to the conventional compendial methods whenever possible to facilitate ease of testing at manufacturing facilities. It is possible for some molecules that the QC method and biorelevant dissolution method might end up being identical. Nevertheless, the preference seemed to be to use a more complex biorelevant method primarily to aid drug product design and formulation selection. Lastly, gaps in currently available *in silico* tools to predict *in vitro* dissolution were discussed.

Fourthly, what are the major gaps in developing/leveraging *in silico* tools to predict performance of ionizable drugs and drug products with ionizable excipients? The group considered this to be the 'holy grail' of dissolution. Research groups are striving toward developing more mechanistic *in silico* dissolution models with a focus on capturing species effects (*e.g.*, pH, pKa, bile mixed micelles, surfactants). Lacking a full consideration of these interactions in a PBBM model limits scientists' capability in mechanistically describing the drug absorption, distribution, metabolism, and elimination. As these *in silico* tools are new and need to be validated, the consensus was to encourage greater collaborations between industries and academia to facilitate data sharing to improve and validate *in silico* tools. The more accurate the *in silico* predictions of *in vitro* dissolution are, the easier it will be for method development and translatability to predict *in vivo* performance.

Non-Compendial Testing for ASDs from Industry and Regulatory Perspective

This breakout was facilitated by Lynne Taylor, Andre Hermans, and Rajesh Savkur. The main question was the following: For ASDs, what compendial and non-USP dissolution methods are most useful, and what are the challenges? It was acknowledged that a common, fundamental challenge to assessing ASD dissolution is the lack of clarity about what it means for a poorly water-soluble drug to be dissolved from an ASD; even in favorable conditions, ASDs result in significant amounts of drug being "dissolved" as colloidal species, rather than true molecular solutions. Correspondingly, given limitations to the current understanding of drug dissolution from ASDs, there is no universal *in vitro* "biopredictive/biorelevant" dissolution method to guide ASD formulation optimization. Three techniques that were discussed, with an eye on measuring or assessing "dissolved" drug, were the filtering method (*i.e.*, separate dissolved from undissolved drug), dissolution/permeation system, and centrifugation to isolate polymer and drug in undissolved particles.

A discussion point initiated around how to define sink conditions for QC methods. Sink conditions are not well defined for ASDs, including whether to consider crystalline or amorphous solubility should be considered a basis for sink conditions. It was noted that sink conditions are not required by regulatory agency and that procedures to measure amorphous solubility are not uniformly well defined, since amorphous solubility depends upon a phase separation process which is time-dependent and can change based on composition. Similarly, a single value for crystalline solubility can be challenging, since the presence of excipients (*e.g.*, polymers) may impact measured solubility. For example, surfactant either from formulation or dissolution medium can interact with drug, polymer, or other excipients to modulate the amount of molecularly dissolved drug. The use of buffers as a dissolution media without surfactant may reduce this complexity.

Given these complexities, more standardized approaches to assess ASD formulations, in terms of measuring

dissolution or solubility *versus* time for ASD (*e.g.*, how much excess drug; what time points) would be beneficial. However, identifying standardized approaches for ASDs would be challenging at this time. It should also be taken into consideration that ASDs are typically different from neat amorphous drug, since the polymer (and surfactant) impact the measured solubility. Amorphous solubility or "kinetic solubility" implies not a true equilibrium, but rather a snapshot in time. While a regulatory perspective encouraged the examination of the concentration profile *versus* time, it was recognized that during such an experiment that different species will be present (*e.g.*, nanoprecipitate, drug-rich domains formed following Liquid-Liquid Phase Separation), in part depending on quantities of drug, polymer, surfactant, and their interactions (*e.g.*, drug-polymer interactions). In practice, even when drug from ASD is already considered to be in solution, drug concentration determination from filtered samples *versus* centrifuged samples will typically yield different results. Additionally, drug can crystallize from supersaturation in samples subjected to filtration at high pressure.

Two common, but opposing, observations of ASD dissolution are fast drug release, as well as very slow disintegration/dissolution due to gelling. In many cases, fast release has been observed regardless of formulation changes, potentially limiting the utility of the test conditions. Also, depending on the polymer and drug load, gelling can cause very slow dissolution with unknown *in vivo* relevance.

In the context of early formulation development, an important dissolution test capability is *in vivo* sensitivity to impact of polymer type, drug load, and process parameters in *in vivo* performance. A dissolution test employing a single dissolution compartment will often over-estimate the degree of drug precipitation. A useful approach may be application of a range of non-compendial methods (*e.g.*, a single dissolution compartment, a two-stage or multi-stage method, and a dissolution/permeation system) to select formulations for subsequent development in human studies. When the ASD composition is finalized, the focus moves to identifying a QC dissolution method.

Discussions about early formulation development also noted that different dissolution approaches can be applied to address differing issues or phenomena, such as spring effect, or parachute/precipitation kinetics. Non-sink methods offer opportunity to screen formulations using a simple method. Relatedly, early formulation development studies may use smaller drug amounts, such that larger dissolution systems are only used when a more final dosage form is available.

Discussions about later formulation development acknowledged two potential dissolution methods: a QC method for batch release and a biopredictive/biorelevant method for biowaiver or bridging scenarios. It was acknowledged that non-compendial approaches have potential to enrich modeling, including PBBM, to improve *in vivo* prediction. However, such biopredictive/biorelevant methods will need to be effective in adding value beyond the QC test and robustness in terms of being transferable across site locations. Some contract development and manufacturing organizations (CDMOs) may have limited ability to apply non-compendial approaches to formulation development. Concerns whether a manufacturing site can repeat what has been observed in the research laboratory setting, using a more complex non-compendial method were raised.

A final discussion concerned potential for non-compendial methods to be acceptable to regulatory authorities. Feedback indicated flexibility and willingness of regulators to consider non-compendial methods, with appropriate scientific justification (*e.g.*, test results are concordant with pharmacokinetic exposure). However, it was acknowledged that harmonization uncertainties tend to force sponsors to a common QC approach. Also, a more complex non-compendial methods can be expected to present greater challenges for method transfer to multiple sites throughout the world.

Drug Dissolution from Amorphous Solid Dispersions

This breakout was facilitated by Dana Moseson and Debasis Ghosh. The main question was the following: What basic and applied laboratory methods provide the best insights into drug dissolution from amorphous solid dispersions? Focus was on using dissolution testing as a method to assess performance failures in amorphous solid dispersions, specifically with respect to crystalline content. As an amorphous solid dispersion provides a bioavailability benefit over its crystalline counterpart due to its higher solubility, any crystalline content present in the formulation reduces the solubility advantage or serves as a substrate for crystal growth and further supersaturation loss. Crystallinity within an amorphous solid dispersion may result from nucleation and growth pathways (*i.e.*, during stability storage) or incomplete crystalline-to-amorphous phase transformation (*i.e.*, during hot melt extrusion) (32). Key attributes of crystals formed by these pathways when compared to bulk crystalline material include small crystallite size, high surface area, high surface energy, and possibly a different polymorphic form. Additionally, these sorts of endogenous crystals are encased within an amorphous polymeric matrix, which may prevent extensive crystal growth depending on its properties as well as environmental conditions.

In vitro dissolution testing to study the impact of crystallinity on amorphous solid dispersion supersaturation profiles may have two main purposes. First, the method may seek to quantitate crystallinity. Second, the method may serve to predict the potential bioavailability implications of crystallinity within an amorphous solid dispersion.

Detecting crystallinity in a QC dissolution method is possible only under very few circumstances, due to inherent dissolution test variability, selection of appropriate sink/non-sink conditions, media selection, and the propensity of the drug for crystal growth under selected conditions (33). Dissolution test design can be done by introducing crystallinity created in one of several ways: (i) Directly adding additional crystalline content (spiking experiment) (34); (ii) Stress the ASD formulation through high temperature/humidity exposure with the intent of crystallizing some or all of the amorphous drug (35); and (iii) Creating crystallinity within the ASD by altering the manufacturing process. For spray drying, this could be done by modifying the spray solvent system with an anti-solvent (such as water). For hot melt extrusion, this could be done by reducing the processing temperature or residence time (36).

While method 1 (spiking) appears to be the most straightforward, it may not accurately mimic crystal properties which may form in the ASD formulation in terms of crystal particle size/surface area, surface energy, and polymorphic form. Designing experiments that mimic different crystal properties to study their impact on supersaturation profiles is challenging (37). There is a lack of practical tools to assess the surface area of the crystalline particles when inside the ASD matrix. Microscopy-based methods, such as polarized light microscopy, transmission electron microscopy, and micro computed tomography may be used as non-quantitative surrogate methods to identify crystal attributes (depending on length scale) within an amorphous polymer matrix, but no current bulk property techniques are available. Solid state methods such as powder X-ray diffraction (PXRD) or other spectroscopic techniques are suitable methods for quantifying crystallinity on a mass basis, but are limited by dilution, crystal attributes, and method parameters (32).

Practical difficulties with spiking studies were highlighted. Since crystal growth occurs on a surface area basis, addition of bulk crystals on a mass basis underestimates the impact on supersaturation and crystal growth. Additionally, whether additional crystalline API material is added to the full quantity of ASD (*e.g.*, 10% crystalline API + 100% amorphous API in the ASD) or it is replaced (10% crystalline API + 90% amorphous API in the ASD), the driving force for dissolution and crystal growth is changed. Even the use of micronized spiked crystals does not provide for an unequivocal improvement in dissolution test design over bulk crystals. Two conflicting examples can be given. In a study by Moseson *et al.*, the use of bulk crystals followed a concentration dependent solubility advantage decrease. However, in samples containing residual crystals remaining from the hot melt extruded manufacturing process, greater supersaturation loss was detected than expected based on the quantification of crystals on a mass basis from a PXRD method (36). In a study by Hermans *et al.*, the use of bulk *versus* micronized crystals were used in spiking studies. When 10% bulk crystalline material was used, the dissolution method was able to detect and provide an approximate quantification of crystalline content (34). However, when micronized crystals were used, rather than over-estimating crystalline content (as a surface area-based crystal growth hypothesis would suggest), no concentration difference was detected between this experiment and the 100% amorphous sample, speculated to be due to the greater solubility found in high surface energy small particle size crystals.

Crystallinity as a general critical quality attribute for ASD formulations was also discussed. A risk-based approach should be used when determining the risk of crystallinity occurring within the ASD drug product. For example, not all amorphous drugs are likely to crystallize based on their high glass transition temperature, or when drug-polymer interactions persist during storage. Orthogonal tools should be used to characterize, detect, and/or quantify crystallinity within the amorphous solid dispersion drug product. Regulators recommend that drug manufacturers/sponsors perform a risk assessment and investigate the impact of crystallinity in dissolution and *in vivo* performance. Sponsors should thoroughly characterize their drug product performance and drug manufacturing processes and justify their control strategy.

Drug Dissolution from Nano-Formulations

This breakout was facilitated by David Curran and Anitha Govada and proceeded via six questions (Table I). Firstly, what are key technical challenges presented by nanoparticle formulations? There is a terminological discrepancy with "nanoformulations" between filing institutions, which describe formulations with particles between 1 and 1000 nm as nanoformulations. A size range of approximately 1–100 nm is commonly used in various working definitions or descriptions regarding nanotechnology proposed by the regulatory and scientific community. However, FDA does not have an established regulatory definition, and considers any material or end product with at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1–100 nm), or material/end product which exhibit dimension-dependent properties or phenomena up to 1 µm (38, 39).

Differentiating if drug species are solubilized or not is challenging. Filtration of nanoparticles on the benchtop using Anotop 20 nm syringe filters can present issues with backpressure and filter clogging, and they are not compatible with automated dissolution systems. A proposed solution is to characterize particle size distribution (PSD) with dynamic light scattering (DLS) prior to filtration or analytical characterization, as the smallest particles in the distribution may dissolve before sampling; therefore, filtration at the 20 nm

level may not be necessary in all cases. However, DLS is generally low-throughput and does not integrate easily into automated dissolution systems. Characterizing the PSD of nanoparticles in the formulation is challenging, since the size distribution may be dynamic during processing and dissolution characterization.

Secondly, what CBAs affect the *in vitro* drug release from nano-formulations? Nanoformulation PSD impacts its *in vitro* dissolution, especially when the API is hydrophobic. In the discussed case of fenofibrate, transitioning from conventional to micronized to nanosized forms improved bioavailability due to decreased PSD. While specific surface area (SSA) is a better indicator, practical challenges limit its use and PSD is commonly used as a CBA.

Permeation was also suggested as a CBA, since ultimately *in vivo* performance is determined by permeation rather than dissolution. However, it was argued that nano-formulated APIs are typically BCS class II, and are generally not permeation-limited, motivating dissolution as a more important CBA.

The process history of the nanoformulation was also offered as an important CBA. For example, wet milling and drying of nanoformulations can create an amorphous layer that may necessitate additional surfactant in the dissolution test. For nanoformulations produced from antisolvent precipitation, the identity of the antisolvent should also be considered a CBA.

Thirdly, what are the key considerations or strategies for achieving a clinically relevant dissolution method for nanoformulations? Conventional dissolution sample timings may not be fast enough for nanoformulations. For nanoformulations with rapid disintegration, a dissolution method must be able to sample on the order of 1 min, suggesting *in situ* analytics may be necessary.

A continuous, *in situ* method such as UV fiberoptics may be useful for characterizing dissolution, but also may be distorted due to effects from particle aggregation and non-sink conditions. To account for aggregation, academicians suggested using the zero-intercept method to detect aggregation or derivative spectra to compensate for scatter by nanoparticles.

Fourthly, what are potential benefits of methods that add a permeation component, such as dialysis, microdialysis, or dissolution-permeation? Many suggested that dialysis sampling times are too slow for nanoformulation assessment. However, others suggested that two-stage dialysis can sustain supersaturation. Additionally, regulators commented that microdialysis can obtain measurement time-scales around 2–3 min.

Dissolution-permeation was promoted by some since it may be more predictive and can maintain supersaturation without precipitation. However, regulators again suggested that bioavailability of drugs likely to be nanonized (*e.g.*, BCS Class II) is not permeation-limited. Continuous microdialysis was also proposed as a potential method. However, challenges in executing this method with biorelevant media and artificially enhanced dissolution from micelle formation were reported. Reverse dialysis and the dispersion releaser were suggested as potential non-standard methods.

There was an open debate about whether any dissolution method utilized for nanoformulations should be under sink or non-sink conditions. Another open question was whether permeation enhancers should be considered in any of these methods. It was concluded that for orally-delivered peptides, permeation enhancers become important in dissolution-permeation characterization, but these therapeutics are hydrophilic and unlikely to benefit from being formulated in a nanoformulation.

Fifthly, what options exist for automating dissolution methods? All participants expressed interest in an FDA-developed automated compartment model based on tangential flow filtration (TFF). However, this promising method is still in development. Successful use of Agilent's NanoDis System, which uses USP Apparatus 1 and 2, was reported. Challenges with adsorptive loss onto fibers were discussed, which may limit the effectiveness of this tool with precious samples, depending on method and molecule attributes. Methods based on *in situ* analytics with fiber optics were favorably discussed, since these methods do not require sample removal. Regulators noted that for some drug products, this may also be only the method listed in the FDA dissolution method database. However, reviewers still must monitor and validate these automated methods before being approved as an analytical method.

Sixthly, for nanocrystalline oral dosage forms, can disintegration be used as a proxy QC method instead of dissolution? Using disintegration as a proxy QC method is promising for formulations where disintegration is rate-limiting rather than dissolution. However, this approach requires substantial upfront investment from filers to establish a correlation between dissolution and disintegration for a given product.

Drug Dissolution from Lipid-Based Formulations

This breakout was facilitated by Anette Müllertz and Leah Falade and proceeded via two questions.

- What kind of lipid-based formulations have you been developing and what strategy have you applied?

It was identified that the four most common types of lipid-based formulations for poorly soluble drugs were type 1 composed mainly of triglyceride, type 2 composed of oil/triglyceride + lipophilic surfactant, type 3 self-(nano)emulsifying drug delivery systems (S(N)EDDS)

with lipids and high amount of hydrophilic surfactant, and type 4 containing hydrophilic surfactant and co-solvent. Type 4 formulations were the most widely used among the discussion group, mainly because these often provide the highest drug solubility (load). The goal of any given development of a lipid-based formulation is to obtain an isotropic lipid formulation (non-phase separating), to increase drug load and prevent precipitation during dispersion in the GI fluids. Predictive *in vitro* methods for this formulation include dispersion tests in water, and also *in vitro* digestion models, simulating the environment the lipid formulation is subjected to in the GIT. In type 4 formulations, a small amount of ethanol can be added to increase drug loading as high as possible, and here *in vitro* digestion is not relevant.

Nano-emulsion forming lipid formulations (type 3), such as S(N)EDDS, have been formulated for both oral and injectable dosage forms. S(N)EDDS have also been designed for oral proteins/peptides delivery, and here it is important to include medium chain lipids, that can act as permeation enhancers. In addition, the need to depend on bile salts for emulsification of lipid systems can be eliminated by addition of surfactants in the formulations. This further ensures uniform particle size of the emulsion droplets and consistent lipid digestion *in vivo* and could potentially eliminate one variable caused by food effect.

- What are some challenges you have encountered when developing/validating dissolution methods for lipid-based formulations?

Challenges include drug precipitation, interactions with bile salts, the presence of high content of co-solvents, and developing lipid systems with high enough drug loading and less surfactants/co-surfactants. For drugs dissolved in lipid-based formulations, rupture tests of the capsule, dispersion tests for batch uniformity, and later disintegration tests have also been proposed as valuable QC control tests. In addition, droplet size tests have been utilized. It was mentioned that droplet size tests can also be adequate for QC purposes specifically for an emulsion-based drug product, but a dissolution/dispersion method may be necessary for scale up and post-approval change (SUPAC) guidance purposes.

Formulation challenges include the presence of too much co-solvent, which can cause the drug substance to precipitate upon dispersion if drug solubility in the lipid formulation is due to co-solvent presence; co-solvent will partition into the aqueous phase during dispersion, thereby reducing drug solubility in the emulsion droplets. Such challenges are current issues to enhance the potential of lipid-based formulations as a prominent delivery strategy.

Drug Dissolution from Co-Crystals

This breakout was facilitated by Abu Serajuddin and Alaadin Alayoubi. The main question was the following: What are the current roles of co-crystals in drug development? Co-crystals are defined as crystalline materials composed of two or more different molecules, typically the API and co-crystal formers (coformers) in the same crystal lattice, according to the FDA guidance "Regulatory Classification of Pharmaceutical Co-Crystals" definition (40). Unlike salts, where the API forms an ionic complex with an acid or base in the same crystal structure, co-crystals rely on weaker intermolecular interactions such as hydrogen bonds, π bonds, and van der Waals forces. One advantage of co-crystals over salts is that they are not restricted by the pKa of the API. While salts usually require a pKa difference greater than two between the API and the counterion for successful formation, co-crystals can be formed based on these weaker interactions.

Co-crystals, similar to salts, are useful for improving the physicochemical properties of APIs, to enhance solubility and dissolution rate, which can increase systemic exposure. Additionally, co-crystals can mitigate the negative effects of high pH on solubility and dissolution for basic drugs. The dissolution behavior of co-crystals under different pH conditions was discussed by briefly reviewing highlights of two papers on ketoconazole co-crystals published in the literature. Like salts, co-crystals demonstrated microenvironmental pH effects in increasing dissolution rates under certain pH conditions (41, 42). For example, at pH 5.0, ketoconazole co-crystals formed with fumaric, succinic, and adipic acids demonstrated a parachute effect (supersaturation) and enhanced dissolution over the free base. The dissolution rates, however, decrease with further increase in pH to pH 6.5. These findings hint that co-crystals can reduce the impact of food effect, since the gastric pH increases with food intake, which may decrease dissolution rate of the free base; increased dissolution rates of co-crystals observed at relatively high pH may minimize such effects.

One interesting point was whether a co-crystal may be considered a NCE. The FDA does not consider a co-crystal as NCE but rather analogous to a new polymorph of the API given that dissociation of the API from its co-crystal form occurs before reaching the site of pharmacological activity. However, some indicated that if salts are considered NCE, co-crystals should also be viewed as NCE because they possess different physical and chemical properties (*e.g.*, melting point, solubility) that are more favorable over the free base or acid form of API. Dissolution testing of co-crystals requires considering the dose at a given pH, and if a parachute effect is observed, alternative approaches may need to be explored. Overall, the participants felt that cocrystals may be treated similar to salts for the purpose of developing dissolution methodologies. While co-crystals are generally

not believed to have an effect on the intrinsic permeability property of the drug substance, further studies are needed to confirm it. However, co-crystals can help achieve supersaturation, which could result in a higher drug permeation rate. Some co-crystals may not dissolve in a 1:1 ratio, and the use of dissolution-permeation models may be helpful for their development.

A new perspective was also discussed regarding the use of co-crystals as a tool to reduce the formation of nitrosamines (N-nirosodimethylamines; NDMAs) in drug products. Some nitrosamines may be carcinogenic and may form when vulnerable amines (secondary, tertiary, and quaternary) react with nitrosating agents (N_2O_3 and NO^-). Vulnerable amines may be a constituent part of the drug molecule, and nitrosating agents may be found in some excipients. Therefore, NDMAs may be formed in drug products. Recently, various research papers have shown that using antioxidants such as ascorbic acid as excipients may inhibit NDMA formations or even reduce existing NDMA levels in drug products via redox reaction. Co-crystal formation may play a role in this area, particularly by exploring co-crystals with antioxidants possessing potent nitrite scavenging properties.

Lastly, it was acknowledged that successful co-crystal formation is drug-dependent and can be challenging due to its reliance on weak intermolecular forces. Over the years, the interest in co-crystal development has diminished, possibly because more straightforward alternatives such as salt formation and amorphous solid dispersion (ASD) have emerged to address undesirable physicochemical properties of drug substances. Furthermore, the formation of co-crystals requires additional efforts to study the human safety of coformers. Nonetheless, co-crystals remain a useful tool for drug delivery and may be valuable in mitigating NDMA formation.

Non-Compendial Methods

This breakout was facilitated by Kerstin Schaefer and Hansong Chen and proceeded via three questions (Table I). Firstly, what is the definition of non-compendial methods? There was a consensus that non-compendial methods are not listed in the USP. In addition, modified compendial apparatuses like the use of mini or peak vessels or non-compendial conditions used with compendial apparatuses (*e.g.*, uncommon stirring speeds, high surfactant concentrations) can be considered non-compendial methods. Hence, non-compendial methods use specialized equipment or modified USP setups as well as non-compendial media and settings.

Secondly, under what conditions has any particular non-compendial method been helpful, and why? Non-compendial methods are usually not pursued for QC dissolution testing, as they often use complex setups and media. These setups aim to help in formulation development, such as use of biorelevant media to bridge between *in vitro* dissolution and *in vivo* data. Ideally, non-compendial methods can help build simulation models and reduce or eliminate animal testing.

Thirdly, are such non-compendial methods complementary or potential replacements for compendial methods? Ideally, every QC dissolution method should be biopredictive and help in establishing *in vitro–in vivo* correlation (IVIVC) or IVIVR. However, in reality, this is often not possible. Methods used for QC testing have to be robust and deliver reproducible results. It might not be possible and feasible to apply all criteria required in QC dissolution methods to non-compendial methods. Setups like the tiny-TIM system are highly complex and require a set of specialized media. Hence, currently compendial and non-compendial approaches are used for different purposes. QC dissolution testing is a product-specific quality test, whereas non-compendial methods can help to better understand underlying mechanisms. Currently, some pharmaceutical companies have used non-compendial methods in authority interactions. However, very limited to no feedback was received back from authorities. Both industry and regulatory authorities are open to using non-compendial methods. It was discussed that a database containing (all) case studies would be helpful due to the novelty and lack of expertise in industry and at regulatory authorities in the use of data generated with non-compendial methods *e.g.*, in submission documents. A future goal should be to devise a mechanism to generate and share a database.

Non-USP Methods *versus* Regulatory Methods: Biopharmaceutic Risk Assessment

This breakout was facilitated by Yi Gao and Tapash Ghosh. The USP methods (*i.e.*, USP apparatuses 1 to 6) and non-USP methods (*i.e.*, non-USP standardized apparatuses or methods that are not yet well defined) were reviewed. It was concluded that developing and filing a non-USP method has not become a well-established practice. For example, a QC method that combines dissolution and permeability concepts is a current research topic, may result in clinically relevant approaches for conducting dissolution and setting dissolution specifications of certain supersaturating formulations, but has not been developed and implemented in QC. Discussions proceeded via four questions.

Firstly, how do you initiate developing a dissolution method for your proposed product? For 505(b)(1) *vs* 505(b)(2) *vs* ANDA products? For NDA products, the dissolution method is often developed from scratch. For Abbreviated New Drug Application (ANDA) products, the previously known method (*i.e.*, found in the database or regulatory filing documents) was the basis for starting the method development.

Secondly, what leads you to pursue or not pursue a non-USP method as your ultimate regulatory method? Except for one sponsor applying the apex vessel method (*e.g.*, peak vessels) during developing commercial dissolution testing for one drug product, no other company in the audience has developed a non-USP method. The most common non-compendial methods that have been used are those with apex vessels to overcome coning issues. Although the variability due to coning was reduced, there is still a lot of variability from vessel to vessel due to apex vessels not being standardized. Significant differences existed among the apex rising angles and heights manufactured by different vendors. USP is actively working on standardizing the dimensions of the apex vessels, like other compendial apparatuses with specific dimensions and configurations. Once completed, USP will publish their proposal for apex vessels in the Pharmacopeial Forum which will remain open for public comments for 90 days. There was a consensus and interest in moving to make apex vessels compendial. Before the availability of USP apex vessels, coning may be addressed by adjusting agitation speed. Though paddle speeds of 50 and 75 rpm are recommended for USP apparatus 2, sometimes it becomes necessary to apply higher speeds. In those cases, it is important to provide data to justify the proposed higher speed, and especially important to demonstrate discriminating ability.

Thirdly, have you filed a non-USP method and gained approval from regulatory agencies worldwide?

The above sponsor did not file the apex vessel method due to the concerns of vessel QC problems, as discussed above.

Fourthly, what can be the potential risk/benefits and technical challenges in adopting and transferring a non-compendial method to commercial testing sites, especially for a non-NME? Since no one in the audience had filed and gained approval of a non-USP method, a thorough discussion on this question was not carried out, beyond the above comments about apex vessels. However, general risks were discussed. If non-compendial approaches are pursued in dissolution method development, the conditions should be well characterized, and all specifications need to be provided for review. These details are essential to ensure that data can be replicated, and have the ability to transfer the method to other sites.

Approaches to, and risks concerning, dissolution method development and selection were discussed. One discussion centered around the FDA and USP Dissolution Method Databases. These databases give a general outline of the methods previously used for similar drug molecule and dosage forms. Once a method is included in the FDA dissolution methods database, if subsequent generics or other sponsors deviate from the method, the company is encouraged to petition the USP to include the conditions in the USP database, and the specific USP Dissolution Test utilized will be listed in the product labels. It was noted that dissolution methods in the FDA and USP databases are provided as a suggested starting point to assist industry in method development. However, the dissolution specifications (*i.e.*, method and acceptance criteria) are product specific. FDA encourages an applicant to exercise due diligence before they take an unusual measure, like increasing paddle speed to 200 rpm. The goal of FDA is to work alongside industry to ensure that the Prescription Drug User Fee Act (PDUFA) and Generic Drug User Fee Act (GDUFA) timelines are met, and that proposed dissolution conditions and methods are justified (*e.g.*, exhibit discriminating ability) to support medications are safe and effective. The FDA is open to receiving data from studies in which a safe space could be defined. This concept of a safe space can be built based on established IVIVC, IVIVR, and/or PBPK models and can be used to extend the approved dissolution acceptance criterion.

Another discussion concerned non-USP methods used for specialized products such as chewing gums, buccal tablets, and orally disintegrating tablets. There is a European apparatus developed for medicated chewing gum; however, the equipment is very expensive and not readily available. Buccal tablets are designed to stick to the cheek pouch and therefore release the drug from one side. Given this mechanism, it was debated whether it is scientifically meaningful to subject such a product to dissolution vessel-based testing to quantify drug release. It was discussed that disintegration is a test that can be used for QC and therefore replace dissolution studies if conditions are qualified in the International Conference on Harmonization (ICH) guidance (*e.g.*, orally disintegrating tablets that disintegrate quickly).

Real-Time Release Testing to Replace *in vitro* Dissolution

This breakout was facilitated by Hanlin Li and Haritha Mandula. Real-time release testing (RTRT) is the "ability to evaluate and ensure the quality of in-process and/or final drug product based on process data, which typically includes a valid combination of material attributes and process controls" (43). RTRT, if utilized, becomes a powerful tool in implementing Control Strategy and allows for increased manufacturing flexibility and efficiency, enhanced process understanding for real time corrective actions or segregations (in instances of continuous manufacturing), and added assurance of product quality. With respect to replacing *in vitro* dissolution, RTRT needs to be coupled with a predictive model. This leads us to the following questions: (1) What are the best RTRT practices to establish confidence in the model, (2) What are the challenges to implementing dissolution RTRT, and (3) What future improvements are needed?

The discussion first centered around the importance of the QC dissolution method. The QC method is the foundation

for RTRT development. A clinically relevant QC dissolution method is critical for RTRT success. The confidence in the predictive dissolution model is limited by the robustness and discriminatory ability of the QC dissolution method. There was debate about the challenge to develop a clinically relevant QC method. Many times, the QC method is solely designed for discriminating capabilities with respect to manufacturing process; however, the manufacturing changes may not be relevant to *in vivo* situation. One reasoned that manufacturing design spaces are often so tightly controlled, that it may be near impossible to manufacture a non-bioequivalent drug product batch within the confines of those controls. In that case, the factors found relevant to *in vitro* dissolution performance should still be included in the RTRT dissolution model to support formulation robustness and manufacturing process.

Nevertheless, to truly harness the flexibility of the safe space for which a drug product is still expected to be 'bioequivalent,' one needs to have a firm understanding of the RTRT design space. A very tightly controlled manufacturing process can consistently produce a drug product that meets the target quality profile. However, it may not provide much flexibility for manufacturing operations or regulatory specifications. Clinical relevance of Critical Quality Attributes (CQAs), critical process parameters (CPPs), and critical material attributes (CMAs) is crucial for establishing the flexibility. For dissolution RTRT, an understanding of the dissolution process is required to ascribe relevant factors in the raw materials and process parameters to changes in the *in vitro*, and thus *in vivo*, dissolution. There is also a need to understand the level of interaction with CMAs and CPPs. Proper design of experiments (DoE) and risk assessment is paramount to the holistic approach for RTRT. The RTRT dissolution model can be used to predict a single time point or the entire dissolution curve. In the case of full dissolution profile prediction, it typically involves a partial least squares (PLS) model, predicting the dissolution rate "Z," followed by using Noyes-Whitney or Weibull equation to predict the dissolution curve.

Open conversation is needed between regulators and industry to successfully implement a dissolution model for RTRT. While regulators assess the risk (*i.e.*, what is the risk of relying on RTRT to predict dissolution for this drug product), the industry (or sponsor) is knowledgeable about their drug product and therefore could share the critical aspects and explain how the process knowledge is built into the dissolution RTRT. To reduce the risk from the pharmaceutical development perspective, it is important to test the limits of the model with respect to the extremes of the material attributes and operating ranges of the process parameters. The dissolution model should be challenged with an external data set and the model's ability to detect non-conforming batches also needs to be demonstrated. It was emphasized that appropriate model maintenance (*e.g.*, via regulatory commitment of annual parallel testing and internal QC that triggers model updates) is also required for the longevity of dissolution RTRT.

Finally, to encourage broader use of dissolution RTRT, publications of successful case studies are needed to help identify a structured approach as well as to move RTRT into prediction of more complex formulations. This brought the discussion full circle as it was determined that the biggest challenge for expanding the use of RTRT as a surrogate for *in vitro* dissolution is the need for an appropriate QC dissolution method on which to build the predictive model.

Summary

In summary, the workshop "Drug Dissolution in Oral Drug Absorption" was held on May 23–24, 2023, at the University of Maryland and hosted by M-CERSI met the expectations of the organizers, invited speakers/panelists, and attendees. The workshop included lectures and breakout sessions led by leaders from academia, industry, and regulators on relevant drug dissolution topics. Lecture themes were ASDs, dissolution/permeation interplay, and *in vitro* methods to predict *in vivo* biopharmaceutics performance and risk. Common breakout session topics were on the meaning and assessment of "dissolved drug" in fed conditions and from ASDs; limitations of a test that employs sink conditions; non-compendial methods and conditions (*e.g.*, two-stage method, dissolution/permeation methods, apex vessels); and potential benefit of having both a QC method and a biopredictive/biorelevant dissolution method. The workshop identified an obstacle to general application of non-compendial methods due to the uncertainty of global regulatory acceptance of such methods as ongoing work needed to move forward in the area.

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Author Contribution This is a workshop report which included parallel breakout sessions. Nevertheless, all co-authors agree this report captures the most meaningful discussions.

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Declarations

Conflict of Interest The authors declare no competing interests.

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