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Meeting Report

Dissolution Testing in Drug Product Development: Workshop Summary Report

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Abstract. This publication summarizes the proceedings and key outcomes of the first day ("Day 1") of the 3-day workshop on "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development." The overall aims of the workshop were to foster a productive dialog between industry and regulatory agencies and to discuss current strategies toward the development and implementation of clinically relevant dissolution specifications as an integral part of enhanced drug product understanding and effective drug product life-cycle management. The Day 1 podium presentations covered existing challenges and concerns for implementing highly valuable, yet often unique and novel experimental dissolution setups as quality control tools. In addition, several podium presentations highlighted opportunities to replace conventional dissolution testing with surrogate test methods to enable robust drug product and process understanding within the context of quality by design (QbD), new manufacturing technologies, and real-time release testing (RTRT). The topics covered on Day 1 laid the foundation for subsequent discussions which focused on the challenges related to establishing an *in vitro–in vivo* link and approaches for establishing clinically relevant drug product specifications which are becoming an expectation in regulatory submissions. Clarification of dissolution-related terminology used inconsistently among the scientific community, and the purpose of various testing approaches were key discussion topics of the Day 1 breakout sessions. The outcome of these discussions along with creative ways to overcome challenges related to bridging "exploratory dissolution approaches" with methods suitable for end-product control testing are captured within this report.

KEY WORDS: biorelevant; biopredictive; clinically relevant dissolution; discriminating power; surrogate for dissolution.

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Abbreviations API, Active pharmaceutical ingredient; AUC, Area under curve; BA, Bioavailability; BCS, Biopharmaceutical Classification System; BE, Bioequivalence; C_{max}, Maximum concentration; cGMP, Current good manufacturing practices; CMA, Critical materials attribute; CPP, Critical process parameter; CQA, Critical quality attribute; CRDPS, Clinically relevant drug products specification(s); CSOP, Engineering Research Center for Structured Organic Particulate Systems at the New Jersey State University at Rutgers, NJ; EMA, European Medicines Agency; ER, Extended release; FDA, Food and Drug Administration; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IQ, International Consortium for Innovation & Quality in Pharmaceutical Development; IR, Immediate release; IVIVC, *In vitro–in vivo* correlation; IVIVR, *In vitro–in vivo* relationship; M-CERSI, Maryland-Center for Excellence in Regulatory Sciences and Innovation; M&S, Modeling and simulation; NIR, Near infrared; SUPAC, Scale-up and postapproval changes; PAT, Process analytical techniques; PBPK model, Physiologically based pharmacokinetic model; PBAM, Physiologically based absorption model; PCA, Principal component analysis; PK, Pharmacokinetic; PLS, Partial least square; PSD, Particle size distribution; QC, Quality control; QbD, Quality by design; QRA, Quality risk assessment; RTRT, Real-time release testing; RTQA, Real-time quality analysis; TPP, Target product profile; USP, United States Pharmacopeia

INTRODUCTION

In May 2017, a 3-day workshop titled "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Drug Product Development" convened at the University of Maryland's School of Pharmacy in Baltimore, MD. The meeting was led by the Center for Excellence in Regulatory Sciences and Innovation (M-CERSI) and co-organized by members of the United States Food and Drug Administration (US FDA), European Medicinal Agency (EMA), and the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ). A high-level workshop summary describing the overall challenges of patient-centric drug product development and strategies for linking *in vitro* testing and *in vivo* performance was recently published (1). In short, this 3-day meeting provided a discussion forum for scientists working in the industry, academia, and regulatory agencies to debate and advance the understanding of the following critical topics:

1. The Role of Dissolution Testing Throughout Drug Product Development (Day 1)
2. The Need for Establishing the *In Vitro–In Vivo* Link (Day 2)
3. Regulatory Applications of Clinically Relevant Dissolution Testing (Day 3)

The agenda for all 3 days included a balanced mix of presentations from the industry, academia, and regulators highlighting the utility of *in vitro* dissolution testing in product development as well as concerns related to its use for product performance understanding. Most importantly, the breakout sessions provided a forum for participants to elaborate, rationalize, and challenge current industry practices as well as regulatory expectations. These breakout sessions were designed to provoke new ideas related to *in vivo* product performance understanding and to develop meaningful drug product specification approaches in the context of current and

emerging new technologies as well as regulatory trends. The outcomes of Day 2 and Day 3 discussions are the subject of separate publications (2,3).

In the opening presentation, Dr. Lawrence X. Yu, from the US FDA, briefly elaborated about the history of dissolution testing and the need for *patient-centric dissolution testing* in product development. Since its development in the late 1950s and early 1960s, and its acceptance by the United States Pharmacopeia (USP) Convention in 1970 (4,5), *in vitro* dissolution testing has been used as a quality control measure for solid oral dosage forms. In recent times, it has been evolving as an invaluable tool to forecast *in vivo* performance of drug products and to ascertain the need for *in vivo* comparative bioavailability and bioequivalence studies. According to Dr. Yu, dissolution can link product quality to *in vivo* performance through *in vitro–in vivo* correlations/relationships (IVIVC/IVIVR) developed either *via* conventional paths or using physiologically based pharmacokinetic absorption modeling (PBAM).[1] Therefore, it is an essential test to realize quality by design for solid oral dosage forms (6,7). Recent developments in the simultaneous measurement of *in vivo* solubility/dissolution in the gastrointestinal tract and drug concentration in plasma provide opportunities to better design *in vitro* dissolution methods and development of improved mechanistic oral drug absorption models (8). Dr. Yu remarked that the FDA has recently granted biowaivers and standardized the dissolution testing requirements for highly soluble drugs designed as immediately release dosage forms (9). However, for poorly soluble drugs designed as immediate release or modified release products—although IVIVC is possible—in practice, it is difficult to achieve. Therefore, in Dr. Yu's opinion, future drug product development efforts should focus on the measurement of *in vivo* solubility and dissolution as input toward the development of *in vitro* dissolution methods and mechanistic absorption models.

Dr. Sarah Pope Miksinski[2] discussed the overall context for clinical relevance (10) by tying the five strategic priorities of the Office of New Drug Products to the broader priorities of the Office of Pharmaceutical Quality (11). In addition, she reinforced the importance of the "link to the patient," both in terms of various ongoing initiatives as well as regulatory decision-making and general operations. Her presentation focused on the fundamental link to patient expectations for quality, which include a product being safe and effective, exhibiting performance as labeled, maintaining expected performance throughout the shelf life, being manufactured in a manner that assures quality, and being available as needed. Dr. Pope-Miksinski also outlined the essential concepts of the current dialog on clinical relevance, including data requirements and recommendations, robust and transparent risk communication, the presence/acknowledgement of uncertainty, the efficiency of interactions, and paying appropriate attention to "the big picture." She discussed the

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[1] The term PBAM applied to drug product quality is evolving. The terms PBAM and physiologically based biopharmaceutics modeling (PBBM) were used interchangeably in the subsequent manuscripts following the workshop and are part of the theme.

[2] At the time of the workshop, a director at the US FDA

penultimate benefit–risk framework, which balances potential risks to quality with availability to patients/consumers. Dr. Pope-Miksinski concluded her presentation by outlining five key concepts of clinical relevance, each relating to context, connections, and collaboration in the regulatory landscape.

Companies represented by IQ are, in principle, aligned with the position presented by Dr. Yu that dissolution testing plays a critical role in enhanced product understanding (*e.g.*, QbD) (12). Dissolution testing under physiologically relevant conditions is common practice in many companies especially in early development. When such methods are applied, a link between *in vitro* dissolution testing and *in vivo* performance can be achieved in many cases. However, expectations for implementing these methods for routine quality control purposes are concerning to the pharmaceutical industry, as these methods may lack the robustness expected for QC methods (13). In addition, there is general concern over global regulatory acceptance due to the fact that these methods are frequently noncompendial in nature. Current industry practices using biorelevant dissolution in early stages of development and strategies toward bridging these methods with globally acceptable dissolution specifications for routine product release and stability testing are highlighted in the first two summaries of the Day 1 podium presentations.

Additionally, there is an emerging trend in the industry to explore alternatives to dissolution testing and to apply them during product development to ensure product quality instead of relying on traditional dissolution testing. This goal can be achieved by focusing on a combination of in-process and/or at-line analytical tests and *in silico* modeling resulting in predictive dissolution models. In many instances, it can be demonstrated that these tests and/or models are as predictive of *in vivo* performance as traditional or nontraditional dissolution methods. Hence, they support establishing both clinically relevant drug product specifications and robust manufacturing control strategies. There is currently limited experience both in the industry and within regulatory agencies to use these tests instead of traditional dissolution. However, such alternative approaches, underpinned by a deep understanding of the interrelationship between *in vitro* dissolution testing, other quality attributes/in-process controls, and *in vivo* drug product performance assessment, are also expected to be enablers of continuous manufacturing and RTRT. Compared to the other CQAs required to empower RTRT (*i.e.*, content uniformity, purity, etc.), modeling dissolution performance may be the most challenging, as tablet dissolution is often influenced by several material attributes and process parameters. Examples of the use of surrogates for dissolution testing as well as predictive dissolution modeling are described in the sections following the summaries about dissolution testing under physiologically relevant conditions.

SUMMARY OF PODIUM PRESENTATIONS

The Role of Dissolution Testing in Early Formulation Screening (14)

The principal driver behind conducting *in vitro* dissolution studies in the early phase of product development is to predict *in vivo* performance of formulation candidates entering phase I clinical trials. With the assumption that *in vivo* dissolution is meaningful for PK performance in humans, the minimum expectations for early stage dissolution methodology are to identify what aspects of the drug substance, formulation composition, and process are most important to achieve the desired *in vivo* performance of the drug product. The *in vitro* dissolution studies may complement or substitute preclinical (animal) models, and they are performed to guide formulation development and optimization and to select the best candidates for BA studies.

When it is known that *in vivo* dissolution is the rate-limiting step in the absorption process, one approach for formulation candidate screening is to conduct dissolution at the solubility limit of the drug substance (15). This "1X dissolution" (16) means that the target drug concentration of the *in vitro* dissolution experiment is equal to the solubility limit of the API. Since the dissolution rate is meaningful for *in vivo* performance, formulation differences that make a measurable impact on the rate at which the drug reaches its solubility limit are explored.

In the example shown in Fig. 1, 1X biorelevant dissolution was conducted using prototype formulations where *in vivo* performance was known to be dependent on the dissolution rate of the API. Spray-dried intermediates with varied formulation attributes were prepared with drug A and a polymer (copovidone), both with and without sodium lauryl sulfate (SLS) in the amorphous solid dispersion. These intermediates were then processed into tablets (FM 1 tablet and FM 2 tablet). In addition, one tablet (FM 3 tablet) and one capsule formulation (FM 3 capsule) containing only amorphous API with traditional excipients were prepared, in order to investigate if dosage forms containing amorphous API give comparable *in vivo* exposures to formulations containing the amorphous API in a spray-dried intermediate. Dissolution testing was performed using a two-stage "1X" dissolution approach on the three tablet formulations. The dissolution rate of the formulations in the second stage (FaSSIF) of the two-stage biorelevant dissolution experiment is dependent upon the ability of the formulation to form amorphous particles in the first stage (SGF) of the test. The dissolution results clearly revealed a difference in these formulations' ability to deliver amorphous particles in the SGF stage and therefore differentiated dissolution rate in the second stage. The observed rank–order relationship between dissolution rate demonstrated a clear correlation with systemic exposure, further supporting that for this drug, dissolution is critical for drug product *in vivo* performance (16).

Two multicompartment models were also discussed in this presentation. In the first example, a transfer model system was established to investigate the *in vivo* behavior of weakly basic compounds. Preliminary data showed promising results to support a transfer model as an alternative way to estimate *in vivo* precipitation in the intestinal compartment for these compounds (Fig. 2) (17). This model accurately simulates the gastric retention time and transfer rate of drugs into the intestinal tract. The transfer rate is especially important for compounds that may precipitate in the stomach due to possible pH changes of the gastric fluid. A couple of opportunities for this methodology were described. For example, the transfer model enabled the development of an *in silico* model, including a full mathematical model to describe simultaneous transfer/precipitation process as well as methodology to describe formulations and drugs using enabling formulation strategies.
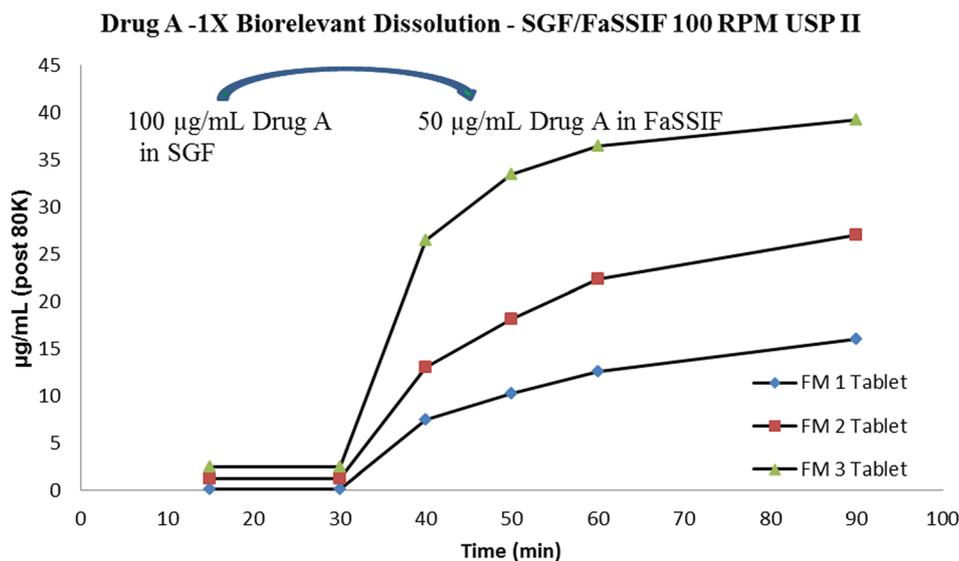
Drug A -1X Biorelevant Dissolution - SGF/FaSSIF 100 RPM USP II

Fig. 1. "1X" dissolution of tablets and capsules used in clinical studies in biorelevant media and their associated PK data

The second multicompartment model discussed was an artificial stomach duodenum (ASD) *in vitro* system that mimics the dynamic conditions of the human gastrointestinal tract, as well as the biorelevant fluids present in these systems ([18]). In the schematic shown in Fig. [3], the green circles represent pumps that introduce biorelevant fluids at each stage. The drug concentration is measured in the stomach and duodenum compartment *via* UV fiber optic probes. The ASD concept captures supersaturation, precipitation, and dissolution phenomena as they occur *in vitro* and relates them to how they may occur *in vivo*. Several enhancements for the ASD methodology were suggested, including standardization of fluid compositions, solids transport, agitation rate, and fed *vs*. fasted simulations. Also discussed were enhancements to the physical system including additional compartments, the ability to adjust transit time, automated low-volume sampling, and methods to simulate removal of aqueous drug from the system (absorption).

Dissolution Methodologies from Biorelevant to Quality Control ([19])

As discussed earlier, biorelevant dissolution plays a key role in early development for formulation screening, biopharmaceutics risk assessment, and formulation development toward achieving the targeted product profile (TPP) ([20]). In addition to the properties of the drug substance and the drug product, both biorelevant media and hydrodynamics need to be considered when applying these dissolution methods. As a result, the experimental conditions one may use range from simple (*i.e.*, SGF and using USP apparatus I or II for tablets containing highly soluble drug substances) to highly sophisticated setups (for example TIM-TNO ([21])) with different biorelevant media for tablets formulated with poorly soluble drug substances.

On the other hand, dissolution is also a key test to confirm batch-to-batch consistency and drug product quality at release and throughout its shelf life. Companies therefore implement dissolution specifications following current

regulatory guidance in routine quality control laboratories using standard equipment and under conditions described in applicable compendia.

The coexistence of several sets of dissolution tests—a set of internal tests to enable product development and an "official" test to ensure product quality control—begs the questions of the degree of alignment between these sets, and which set represents the best description of the dissolution behavior of the product. To answer these, and perhaps additional related questions, close examination of both current industry practice with regard to dissolution testing approaches and their significance toward *in vivo* drug performance understanding is necessary.

A comparison of key attributes for the two sets of methods is depicted in Table [I].

Traditionally, GMP-compliant QC methods are performed in compendial dissolution devices and simple buffered media, with a regulatory expectation for "sink conditions" and complete drug substance release within a meaningful timeframe. In contrast, biorelevant dissolution methods are often performed in "noncompendial" equipment using complex biorelevant media. These methods are "universal" (*i.e.*, nonproduct specific) and companies implement them as part of their formulation development technology platform to assess *in vivo* performance and bioperformance risks. Multiple biorelevant methods may be part of the platform technology and thus may be applied to understand *in vivo* performance of a given formulation considering, for example, drug–drug interactions or food effects. The *in vitro* release profiles may be monitored at nonsink conditions and allow formulation ranking even in cases where full release is not achieved (see for example Fig. [1]).

Typical QC and biorelevant methods are not only different with respect to their purpose and experimental conditions under which they are performed, but the requirements and anticipated variabilities in individual data points may be significantly different, as discussed above. In particular, data generated under biorelevant method conditions
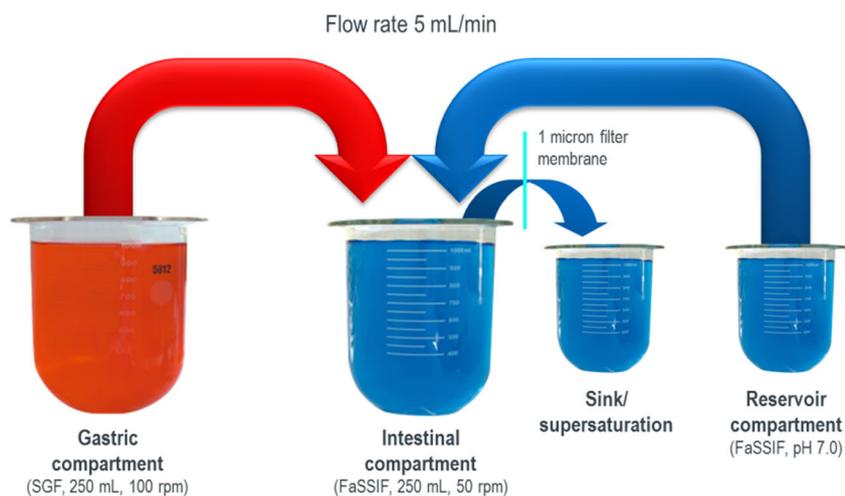
Fig. 2. Example of a simple dissolution transfer model to study the *in vivo* behavior of drug products containing weakly basic compounds

often reveal a high degree of variability (13), and therefore, the methods may not be sufficiently robust for transfer to a routine QC lab. Additionally, since the equipment and the reagents are not standardized, implementing "system suitability" or other meaningful performance criteria may not be practical. Nevertheless, in some cases, a biorelevant method may be applied as a routine QC test upon consideration of a few questions, including regulatory expectation for qualifying and justifying noncompendial equipment, setting acceptance criteria in the absence of full drug release, the appropriate use of the standard staged criteria (*e.g.*, Q+5 for Stage 1), and the potential for a biorelevant method with higher variability to meet nonstandard analytical validation criteria.

Efforts continue to be made by both industry and the regulatory authorities to build a bridge across the significant gaps from the biorelevant method(s) to a QC method that can detect and control for changes in CPPs and CMAs thereby ensuring acceptable *in vivo* performance (clinically relevant) for BCS 2 and BCS 4 drugs and modified release formulations. In order to close the gap between biorelevant and QC methods, several approaches have been explored including (a) proactive collaboration between functional areas involved in pharmaceutical product development, (b)

phase-appropriate "fit-for-purpose" dissolution methodology, (c) application of QbD principles during development, and (d) systematic transition or evolution from biorelevant dissolution to QC dissolution.

When the goal is to work toward the development of dissolution methods that are clinically relevant, a decision tree may help in the development process (see example in Fig. 4). The process starts with the selection of biorelevant methods to evaluate prototype formulations, and then narrows them down to one method that can detect the key risks related to *in vivo* performance. The evolution of the biorelevant method(s) to the QC method is largely driven by systematic simplification of the testing procedure while maintaining or building discrimination for the product attributes that can be measured by *in vitro* dissolution and are most likely to impact PK.

The Use of Surrogates for Dissolution Testing for Immediate Release Formulations—When Is It Feasible? (22)

When investigating the sensitivity of dissolution methods toward changes in CPPs and CMAs, companies frequently use an array of analytical tools in an attempt to correlate the data to the rate and extent of *in vitro* drug
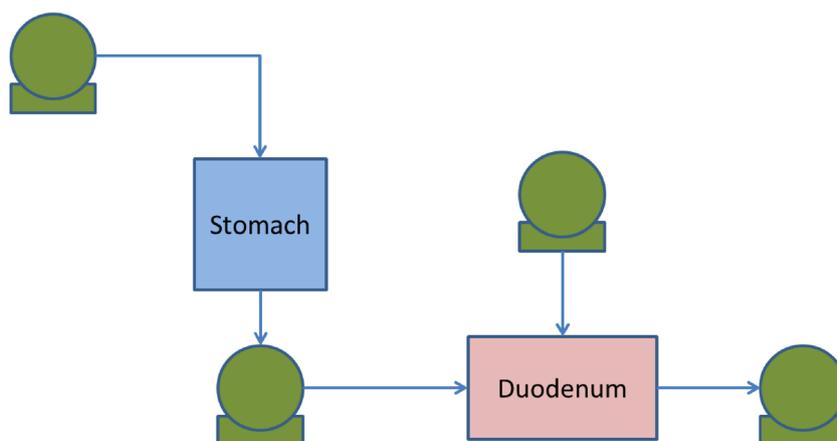

Fig. 3. Schematic of the artificial stomach duodenum (ASD) system

Table I. Purpose and Key Attributes of Biorelevant and QC Dissolution Methods

	Biorelevant dissolution	Quality control dissolution
Purpose	Predicting *in vivo* performance	Ensuring batch-to-batch consistency
Device	Compendial and noncompendial	Compendial
Medium	Biorelevant media	Conventional buffers w/ or w/o surfactant
Method development	Conditions chosen to mimic the environment of the GI tract	Conditions chosen to detect process and stability changes specific for a given product
Profile	Drug substance amount released varies under nonsink condition; used to rank order	Full release expected within a defined amount of time; usually at 3–5 sink
Early phase	Formulation selection, CMA, CPP, and CQA identification	Clinical batch release as required by specification
Later phase	Potential to establish IVIVC/IVIVR; guide design of BA or BE studies if necessary	Clinical batch release; justification of commercial drug product specifications and if possible, use to establish IVIVC/IVIVR

Refer to the breakout summary for the participants'/authors' assessment on the differences among several dissolution terminologies

release. In case these measurements demonstrate a correlation to drug product dissolution, companies may implement these analytical methods as part of manufacturing process controls, or finished product testing. Some of these techniques as well as the specific steps which are a subset in the overall *in vitro* dissolution event and the potential CPPs and CMAs they are probing are shown in Fig. 5. Since these measurements are typically readily available, sensitive, accurate, precise, robust, and rapid, it is highly desirable from an industry perspective to apply them instead of traditional dissolution while maintaining the same level of quality assurance. Examples of the use of these novel analytical tools as surrogates for dissolution testing either by themselves or as part of a predictive dissolution model are discussed in the following section.

From a regulatory standpoint, currently only BCS class 1 and 3 compounds allow for surrogate testing in the form of disintegration as defined by the ICH Q6 decision tree (23). The main rationale for limiting surrogate tests to highly soluble compounds stems from the fact that overall tablet dissolution is largely independent of the rate of API solubilization and the overall dissolution profile is dictated by tablet disintegration. Hence, in many cases, a dissolution–disintegration relationship can be established. It has been shown that for certain IR tablets, disintegration is more sensitive toward process factors such as hardness, as compared to dissolution. In case a clear correlation for hardness and disintegration can be established, tablet hardness can replace disintegration as part of RTRT, which has been accepted for several products, albeit only in some markets.
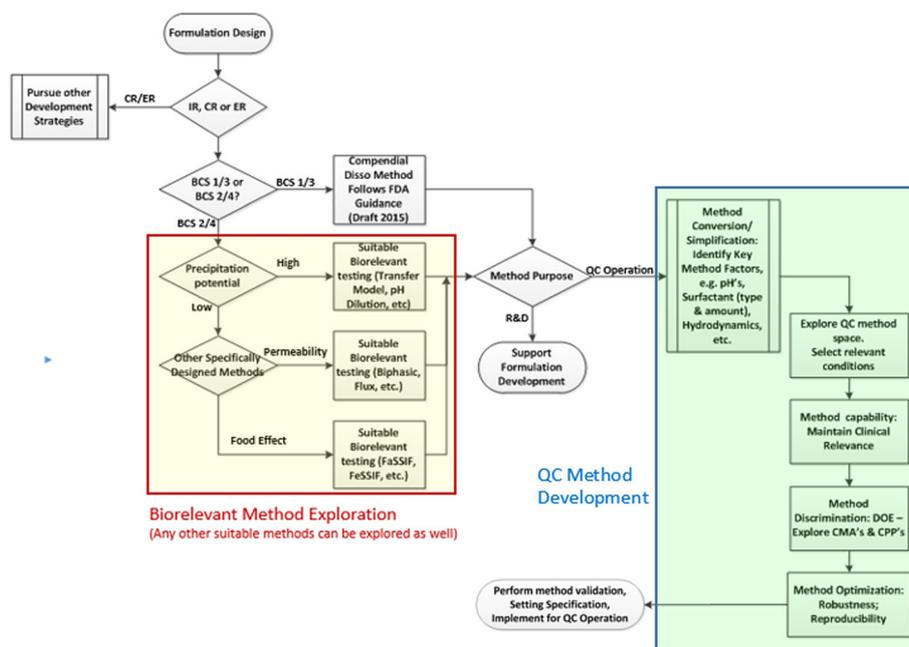

Fig. 4. Flowchart for the systematic transition from biorelevant dissolution methods to a single QC dissolution method

However, for BCS class 2 and 4 products, the API dissolution rate is assumed to be a major factor in the overall tablet dissolution event. Thus, disintegration might not be the overall rate-limiting step for low-solubility compounds and cannot be used to ensure consistent release of the API from the drug product. Regardless of the solubility of the API—and as a general approach—it was proposed to use mechanistic dissolution understanding of the drug product as a guiding principle to determine the dissolution rate-limiting step and to select proper surrogate characterization tests. Figure 5 depicts the overall dissolution mechanism of immediate release solid oral dosage forms as well as potential surrogate tests for each dissolution step along with examples of raw materials and drug product material attributes impacting these steps.

To demonstrate the potential application of surrogate testing approaches for BCS class 2 and 4 compounds, case studies where enhanced product understanding justifies the use of disintegration or CMAs/or CPPs as quality predictors for dissolution testing were presented. The presented examples included applications from the industry and academia on using first principle modeling as well as empirical methods such as fitting of experimental data to a Weibull function or multivariate approaches for dissolution modeling of dosage forms containing low-solubility drugs. It was demonstrated that first principle modeling based on mass transfer models utilizing commercially available software (DDD Plus™) can result in good predictability of dissolution performance in various surfactant-containing media. This approach can be especially useful during dissolution method development where simulated dissolution profiles could replace actual dissolution experiments to predict *in vitro* dissolution performance of the drug under study.

Two case studies where disintegration was a suitable surrogate for dissolution testing for low-solubility compounds when formulated as amorphous solid dispersion formulations were presented to demonstrate that a surrogate method can be more sensitive than dissolution testing and is appropriate for enhanced product understanding as well as assurance of product quality. In these examples, it was demonstrated that the tablet disintegration rate was rate limiting and dictated the overall dissolution profile. In addition to surrogate approaches, case studies on using first principles such as a modified Noyes–Whitney dissolution model and empirical dissolution models such as a modified Weibull to predict dissolution performance of drug products with fast- and slow-release profiles were presented and discussed. The development of a dissolution model requires extensive efforts to correlate the CMA and CPP with model parameters which allows for the development of an enhanced product control strategy justifying the elimination of dissolution testing for product release.

Enabling Real-Time Quality Assurance with NIR-Based Prediction of Dissolution for Tablets Made by Continuous Direct Compression (24)

The development of predictive dissolution models to enable RTRT (sometimes referred to as "real-time quality assurance" or RTQA) of pharmaceutical solid dosage forms is essential in continuous manufacturing systems to enable closed-loop process control.
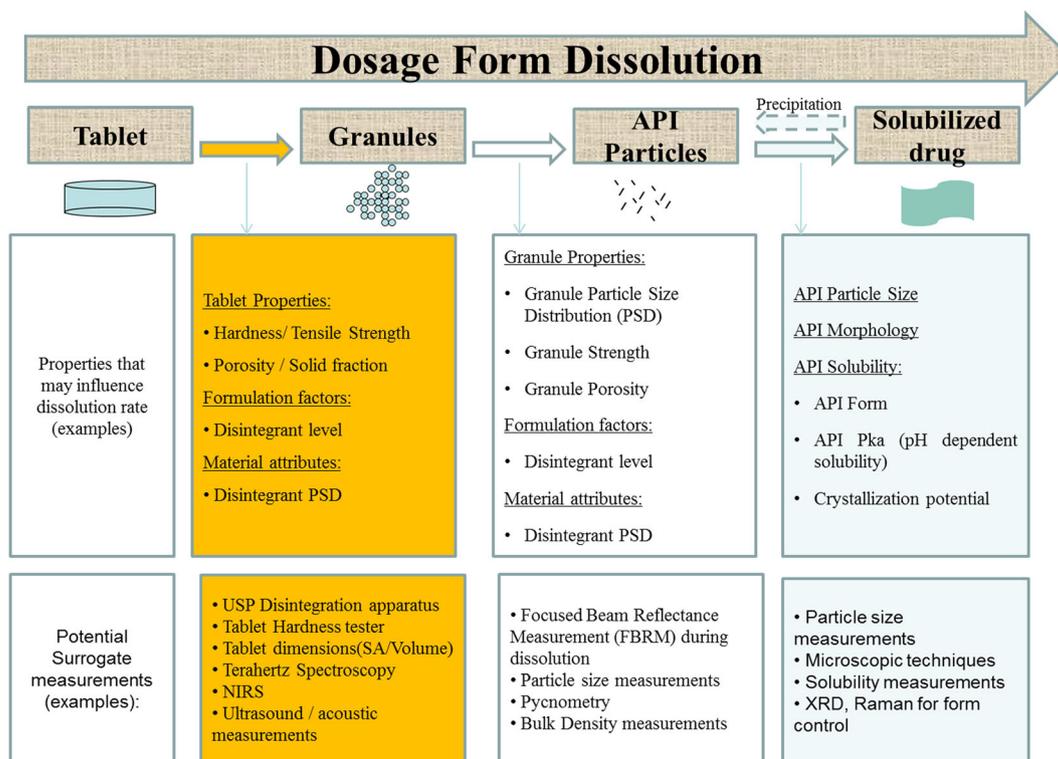

Fig. 5. Schematic of the dissolution of an IR tablet containing granulated API and associated rate constants: tablet disintegration into granules, dissolution (disintegration) of granules, and release of API particles followed by API solubilization

A general method to develop formulation-dependent statistical models that rely on nondestructive spectral measurements as well as process parameters to predict the dissolution profile of individual pharmaceutical tablets was established at the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS). The step-by-step method is summarized below for an immediate release formulation of a highly soluble API; however, it was noted that an analogous procedure was successfully followed for an ER formulation.

Stage 1. *Design of experiments*. First, it is necessary to determine the target processing conditions of the solid tablets, including formulation composition. For example, tablets composed of 9% acetaminophen, 90% lactose, and 1% magnesium stearate by weight were investigated. The target compression force was 24 kN for 350 mg tablets. Other processing variables included the blender speed (200 rpm) and the feed frame speed (25 rpm). A more detailed description of the continuous manufacturing process in this case can be found in Pawar *et al.* (25). Then, the initial step consists of designing the necessary experiments to explore the effect that variations in formulation and/or processing conditions would have on dissolutions performance. It is crucial to identify the most important variables that could result in changes to the dissolution profile. In the case discussed, several factors including API concentration, compaction force, blender speed, and the rotation speed of the feed frame were varied. In each case, three different levels for each variable were explored.

Stage 2. *Dissolution and spectral measurements*. The tablets manufactured under the conditions determined in step 1 are then scanned in transmission mode using NIR spectroscopy. It was noted that alternative spectral methods, such as Raman spectroscopy, could be used depending on the formulation and tableting process under consideration. It is also possible, depending on formulation, to use reflectance NIR from both sides of each tablet. Following the spectroscopy studies, dissolution profiles for all the tablets were obtained using standard compendial methodologies described in the USP.

Stage 3. *Model development*. First, each dissolution profile is fitted to an *ad hoc* dissolution model. In the case discussed here, a Weibull model with two parameters provided a good fit to the experimental data. The application of an alternative *model independent* approach is also possible (see Pawar *et al.* (25)—for a model independent approach based on the *level* and *shape* of the dissolution curves). At the same time, principal component analysis was performed on the spectral data obtained from the tablets. Finally, a multilinear regression was performed between the principal components identified from the spectral data (retaining the first 3 components) and the fitting parameters of the dissolution curves. This provided a statistical model to predict dissolution profiles for individual tablets.

Stage 4. *Validation*. The model was finally used to predict the dissolution profile of six independent tablet variants manufactured at the target conditions. In all cases, good agreement was obtained between the predicted and actual dissolution profiles. The profiles were then compared using the standard f_1 and f_2 factors with excellent results. The measured f_2 values *for individual tablets* ranged from 75 to 79 and the f_1 values ranged from 3 to 10.

The methodology described here can be utilized for other formulations and the C-SOPS is actively pursuing other case studies, including ER tablets. A remarkable advantage of the proposed approach is its nondestructive nature, which would enable investigating and correlating other critical properties with dissolution as well as testing for dissolution performance at multiple times during the manufacture and product shelf life. Note that the same methodology could be applied to batch processing.

Dissolution Modeling in Support of Real-Time Release Testing for a Fixed-Dose Combination Product (26)

In this case study, dissolution modeling of a fixed-dose combination (FDC) tablet with two APIs was presented. Although the FDC tablets were made through a co-granulation process, two separate offline dissolution methods were applied for the two APIs, respectively. Correspondingly, two RTRT dissolution models have been developed. A comprehensive understanding of the drug product formulation and manufacturing process was essential to establish the RTRT model. As depicted in the fishbone diagram below (Fig. 6), the inputs of factors for dissolution modeling outlined in the boxes are outputs of many process parameters.

For each input factor that could potentially influence tablet dissolution, process analytical techniques (PAT) have been implemented, with measurements taken at different stages of the process, as shown in Table II.

Similar to the presentation earlier (24), a stepwise approach was also taken in developing the dissolution model. Tablets made from a DOE run, where the input factors are purposefully varied, were first measured by the offline dissolution method, *i.e.*, USP dissolution. From the reference dissolution profiles collected, dissolution rates (Z) were determined by fitting through a modified Noyes–Whitney equation, as shown below:

$$Z = \frac{dLC}{dt} = z(p-LC)^n \left(S - \frac{Dose}{Vol}LC\right) \tag{1}$$

LC = % dissolved at time t, Dose = target dose, Vol = volume of the dissolution medium (fixed parameter), S = solubility of the API (fixed parameter), n = shape factor (fixed parameter), z = rate factor (fitted parameter), and p = plateau (fitted parameter).

Step 2 of the model development was to take the measured attribute data by PAT (as in Table II) and build a chemometrics (partial least square or "PLS") model to predict the dissolution rate (Z). The goodness of fit was measured by comparing the PLS model predicted dissolution rate and the reference dissolution rate determined in step 1. With the predicted dissolution rate and the modified Noyes–Whitney equation, the predicted dissolution profiles were reconstructed as shown for example in Fig. 7.

The stepwise approach shown above was included in recent market applications, and the proposed incorporation of the predictive dissolution model as part of the product's RTRT has obtained regulatory approval in several markets.

SUMMARY OF BREAKOUT SESSIONS

A comprehensive list of potential topics and questions was collected prior to the meeting from IQ member companies, the FDA and EMA. These were prioritized and split into two groups with the intent to allow adequate time for discussions. The topics selected for the Day 1 breakout sessions represented a balanced mix of questions from industry and regulatory agencies, focusing mainly on terminology and challenges related to bridging biorelevant and QC methods. Note that the focus of these discussions was to gain an understanding of best practices to define the experimental conditions under which the dissolution methods are used. Nevertheless, the definitions of the various dissolution methods and their applicability in product development are similar to the definitions outlined in the recent high-level summary of this workshop (1).

Breakout session subgroups A1 and A2 concluded their discussions with proposed definitions for commonly used dissolution-related terminology:

1. Biorelevant dissolution method(s): a set of experimental *in vitro* method conditions (media and equipment) that mimic the physiological environment the drug encounters upon ingestion. The participants' opinion was to avoid the term biorelevant but rather call these *physiologically based dissolution (test) methods*.

2. Discriminating dissolution method: an *in vitro* dissolution method that can detect variations in CPPs and CMAs that potentially have an impact on *in vivo* performance. This method is used to establish quality control dissolution specifications.

3. Quality control method: method conditions that are based on a discriminating dissolution method. To avoid confusion of the term "quality control" for dissolution methods used in product development, it was decided to avoid this term altogether. The quality control aspect of the dissolution specification is meaningful in a commercial environment but seems to be of little value during development. The term QC method should be replaced therefore with *regulatory approved method*.

4. Clinically relevant dissolution method: a set of experimental *in vitro* dissolution conditions which are sensitive toward changes in CPPs and CMAs with a demonstrated link to *in vivo* drug product performance (*e.g.*, C_{max}, AUC). This link can be based on modeling (*e.g.*, IVIVC or PBAM), or the dissolution method and resulting dissolution profiles (*i.e.*, fastest and slowest profiles) may provide a safe space within which similar clinical performance has been demonstrated.

Breakout session subgroups B1 and B2 deliberated several specific questions related to bridging "biorelevant" and QC methods:

1. *Is it ever feasible to use a biorelevant method for QC? Is there any rationale to implement two different methods (QC and biorelevant)? How does one link biorelevant testing to QC testing during product development?*

   a. Dissolution performed in SGF using USP Apparatus 1 or 2 for BCS 1 and 3 drug products can be considered biorelevant. Thus, for these drug products, the QC method can be considered "biorelevant." Using biorelevant dissolution methods for poorly soluble drug products in a QC environment is challenging mainly due to concerns over lack of method robustness, not achieving full drug product
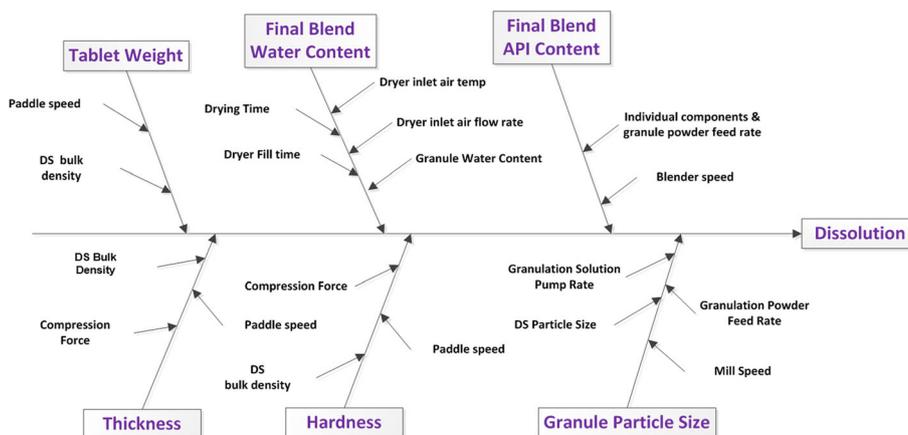

Fig. 6. Fishbone diagram of input factors that may impact *in vitro* dissolution

Table II. PAT Technologies, Applied RTRT Methods, and Targeted Materials for Measurements

PAT technology	RTRT method	Material measured
Laser diffraction	Granule particle size	Milled granules
NIR	API content, water content	Final blend
Weight, thickness, hardness	Tablet weight, hardness, thickness	Core tablet

release (*e.g.*, Q of 80%), and general global regulatory acceptance.

b. Biorelevant methods are mainly used to rank order formulation prototypes and to identify potential biopharmaceutics risk. They can also be used to identify CMAs and CPPs early in development. In practice, companies perform biorelevant and QC type dissolution in development and then switch to a QC method in late stage development and use information from biorelevant dissolution to establish appropriate discrimination of the QC method toward CPPs and CMAs.

2. *Is it critical that the extent of dissolution meet a Q of 80%? There's a tension between biorelevance and complete release for poorly soluble products.*

a. Incomplete dissolution profiles are likely concerning from a regulatory perspective and may be called into question if these profiles are inconsistent with the systemic concentration–time profile of the product. Incomplete dissolution maybe acceptable provided that the sponsor provides additional supporting data (*i.e.*, from BE studies or based on IVIVC).

b. Adding surfactant to the dissolution medium to achieve full release on the other hand may sacrifice discriminating power of the dissolution method toward CPPs and CMAs.

3. *In your experience, do you mostly use biorelevant dissolution as tool in early stage drug development? Do you have comments on additional roles of biorelevant dissolution?*

a. Yes, biorelevant dissolution is mainly applied in early development.

b. Some companies may use biorelevant dissolution in decision-making related to formulation and process

changes and as input toward bioequivalence study design.

4. *How do you determine the appropriate level of discrimination for biorelevant, clinically relevant, and QC dissolution methods?*

a. Clinical relevance of the dissolution method implies that a correlation between CMAs and CPPs exists. The magnitude of *in vitro* discrimination should ideally be aligned with *in vivo* differences. Therefore, the method is considered appropriately discriminating with regard to rejecting batches that are not bioequivalent to batches used in pivotal clinical trials. In the case of an established safe space, the dissolution method conditions may be overly discriminating.

b. Biorelevant dissolution methods used in early product development often follow a "generic" approach. Therefore, in the absence of a link to *in vivo* performance, the degree of discriminating power is often not known. Biopharmaceutics risk assessment and prior knowledge, as well as modeling and simulation, may be helpful to inform the need and guide approaches to adjust the sensitivities toward certain CMAs (*i.e.*, API particle size) or CPPs.

c. The discriminating power of a QC method may be established based on a biopharmaceutics risk assessment aimed at identifying CPPs and CMAs. In the absence of clinical relevance, the appropriate magnitude and significance of discrimination is unclear.

5. *If direct correlations such as those shown in the Day 1 afternoon presentations (22,24,26) show a direct link of process parameters and materials attributes and PK, what is the value of in vitro dissolution? What if these parameters or material attributes are a better predictor of in vivo performance?*
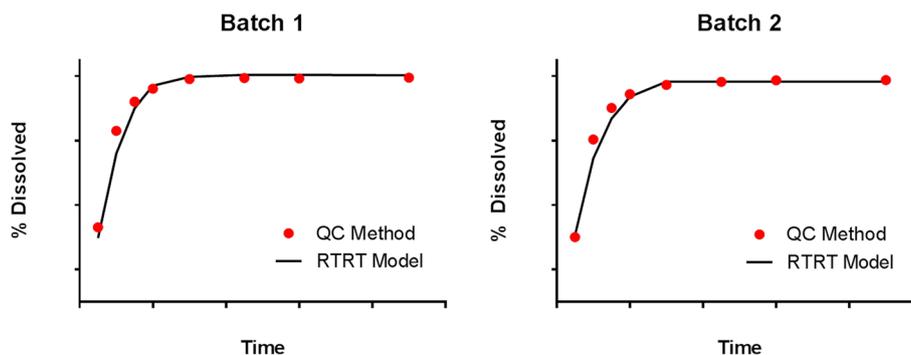

Fig. 7. Predicted (solid line) and measured dissolution rates for batches 1 and 2 demonstrating the agreement of measured and modeled data

Development of dissolution models and surrogate testing should be performed in parallel with a clinically relevant QC method. Once a clear correlation between the surrogate test(s), dissolution, and *in vivo* performance is established, surrogate testing can be used.

Detailed outcomes of the breakout sessions are provided in the Supplemental Material.

CONCLUSIONS

In vitro dissolution testing continues to play a major role in drug product development, quality control, and to support postproduct approval formulation and manufacturing changes. Today, scientists have increasing access to *in vitro* tools which can be used to build a link to *in vivo* performance and to guide formulation candidate selection, formulation process development and to assess and respond to biopharmaceutics risks including informing the success of necessary formulation bridging studies and ultimately for the routine release of product. The new and expanding set of diagnostic tools which includes modeling and simulation for both *in vitro* dissolution and PBAM also creates a dilemma for the industry and regulators. Both parties want to ensure that product released to patients meets the claims in the product label; however, the lack of robustness of nontraditional methods used for example in early development often presents a challenge in utilizing those in a routine QC environment. Product development is usually performed by highly skilled scientists who are competent to work with novel technology and trained to interpret development data in the context of biopharmaceutics risks. Transferring nontraditional methods to a routine QC environment with strict adherence to procedures and where data are usually judged "pass" or "fail" is concerning, as failing results due to method variability are likely to cause major disruptions in the release of product and thus supply of product to patients.

One of the key objectives of the Day 1 discussions was to engage scientists in productive dialog to share experiences, new opportunities, and concerns over the current state of product understanding especially in the context of using dissolution testing as an integral component of robust control strategies to ensure product quality and to enable emerging formulation and manufacturing technology. In this respect, the technical presentations provided excellent background information, while the breakout sessions highlighted major differences in the use of dissolution-related terminology, utilization and the limitations of novel approaches, and interpretation of regulatory guidance. As the discussions during the breakout sessions indicated, the meeting was a success with respect to gaining a better understanding of terminology, the potential use of dissolution technology including surrogates and modeling to enhance product understanding, and the need to develop clinically relevant dissolution specifications especially for poorly soluble drugs. The challenges to overcome current limitations with the available *in vitro* toolkit and with novel approaches such as PBAM are part of the broader effort to develop strategies to implement CRDPS in product development and, if appropriate, as part of the control strategy culminating in RTRT and

the desired regulatory flexibility for product life-cycle management. Details about the current state and challenges related to PBAM and establishing traditional IVIVC as well as strategies to develop CRDPS are detailed in Day 2 and Day 3 meeting summary reports.

Clearly, one of the shortcomings of Day 1 was the limited time that was set aside for the breakout sessions with respect to the significance and the number of topics that were discussed. It may be advantageous for future workshops to dedicate considerably more face-to-face time to discuss topics that concern scientists working in the industry and regulatory agencies to advance product understanding as it relates to dissolution testing for patient benefit.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that they have no conflicts of interest.

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