dx.doi.org/10.14227/DT290422P230

Dissolution Best Practices and International Harmonization - AAPS Workshop Report

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The AAPS In-Vitro Release and Dissolution Testing (IVRDT) Community and Stability Community jointly organized the virtual workshop "Dissolution Best Practice and International Harmonization," held on August 16th, 2022. The workshop was designed to bring awareness to differences in dissolution testing and acceptance criteria between international pharmacopoeias, discuss how to address these differences, develop science-based dissolution design strategies, and meet the needs of the international market. The workshop consisted of two sessions – dissolution in pharmacopeias and dissolution best practices.

Many compendial procedures and chapters have been established, including *United States Pharmacopeia* (USP), *European Pharmacopoeia* (EP), and *Japanese Pharmacopoeia* (JP), to establish standards for quality control of drug products, e.g., dissolution testing. Although the International Conference on Harmonization (ICH) has expended a great effort to standardize technical measurements of pharmaceuticals for human use, differences exist among the pharmacopeias, especially from new ICH members, such as Chinese Pharmacopoeia (ChP). There are differences in acceptance criteria and specifications that impact the dissolution design strategy and drug release profile. Considerable retooling of the dissolution methods and specifications may be required when a company plans to release product in other countries that have different standards for dissolution testing.

PART 1: DISSOLUTION IN PHARMACOPEIAS

The first session was moderated by Xujin Lu, PhD (Bristol-Myers Squibb, New Brunswick, NJ, USA). The first speaker was Mark Alasandro, PhD (MZA Pharmaceutical Consulting, San Diego, CA). The talk title was "Dissolution Best Practices – Understanding the acceptance criteria in different Pharmacopeia." He explained the differences in dissolution testing requirements provided in the ChP, JP, EP, and USP pharmacopeias (*1*). He also shared the results from AAPS survey on awareness of these differences along with strategies to address these differences. These strategies are critical to avoid last minute retooling of methods, specifications, and delaying product launch. He explained the need for a globally accepted dissolution method with a single specification. Such a method would streamline generation of dissolution data to support formulation, process, and raw material changes globally. Coupling such a method with the knowledge active pharmaceutical ingredients (API) solubility, permeability, and pharmacokinetics would also help secure biowaivers. This knowledge can also be used to build Bayesian and other statistical modeling approaches to predict the impact of changes on product performance, safety, and efficacy.

For the dissolution test, there are similarities between ChP, USP and ICH Q4b, such as dimensions of 1-liter dissolution vessel and paddle size, but there are many differences.

- The definition of the ChP Q differs from the USP Q.
  - The Q_{ChP} is the same as USP Q + 5%, so the dissolution specification for China is listed as Q_{ChP} + 5%, whereas, for the US and other ICH region it is listed as Q.

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- ChP only has 2 stages of testing whereas USP and ICH have 3 stages.
  - ChP maintains the original two-stage approach of the JP and EP even though JP and EP have aligned with the USP three-stage approach as noted in ICH Q4B. USP has always had a 3-stage approach since the first publication of the USP General Chapter Dissolution <711>.
- The ChP stages of testing are *Stage 1*: mean of 6 units must be ≥ Q_{ChP} and no two units can be less than Q_{ChP} – 10%; if one unit is < Q – 10%, then go to stage 2 and test another 6 units. *Stage 2*: mean of 12 units is ≥ Q_{ChP} and not more than three units are < Q_{ChP} – 10% and only one unit is < Q_{ChP} – 10% but ≥ Q_{ChP} – 20%.
- Total number of units tested is 12, not 24 as allowed in the USP, JP and EP. Same applies for extended and delayed released formulations, where only 12 total units can be tested.
- For performance verification testing, ChP uses salicylic acid not prednisone tablets.
- The use of enzymes is not allowed by the ChP to address gelatin capsule shell crosslinking.
- ChP has only adopted the 1-liter vessel, not 2- or 4-liter vessels (which are not part of ICH).

Based on the AAPS survey, 50% of the AAPS community surveyed were unaware of the differences and about 30% had problems filing in China. Some of these problems were addressed by adopting the ChP guidance, or by working with the regulatory agency to gain acceptance of their USP-based method or use a modified USP approach, or by showing that their company's data meets ChP guidance using statistical analysis.

Overall, ChP requirements are more stringent if the data shows variability and ICH Q4B stage 2 and 3 testing is needed. Some regulatory flexibility may be allowed through discussions about the data and specifications with regulators. Moving forward, there may be more alignment with the ICH Q4B in the next 2025 ChP edition. Other opportunities for further discussion include the use of in vitro in vivo correlation, physiologically based biopharmaceutical modeling (PBBM), biowaivers, enzymes, and more.

The second speaker was Kevin Moore, PhD (USP, Rockville, MD, USA) who spoke on the topic, "Pharmacopeial Convergence and Harmonization." He is the USP delegate to the ICH Assembly, and in his talk introduced the role of USP in international harmonization with a specific focus on the Pharmacopeial Discussion Group (PDG) and ICH. The talk focused on describing USP's approach to pharmacopeial convergence and harmonization as critical tools to promote the alignment of quality standards to ensure consistent global access to quality medicines for the benefit of public health. An overview was provided for the PDG, which brings together USP, EP, and JP, with WHO as an observer in the harmonization of broad impact general chapters and excipients monographs, with a total of 31 general chapters and 60 excipient monographs on the PDG workplan. In addition, the history of interaction between PDG with ICH was provided, with a synopsis of the activities of the ICH Q4B Expert Working Group, which evaluated regulatory interchangeability of 15 general chapters on the PDG workplan. Also, the talk chronicled the first major reforms of the PDG (in its 32 years of existence) to integrate additional pharmacopoeias from regions not yet represented through the establishment of a pilot for expansion, set to begin this fall. This milestone decision marks a critical step in the PDG's commitment to expanding recognition of harmonized pharmacopeial standards. Lastly, the history of dissolution harmonization in PDG and interchangeability of the chapter through ICH Q4B was presented in detail, including the example of how harmonized text is distinguished from local requirements in the USP text and how PDG Sign Off cover sheets are written, which are publicly available and provide information on non-harmonized and local requirements in PDG pharmacopeias. Detailed information on the PDG including workplan, purpose, process, statement on harmonization policy, and the PDG working procedure and interaction with ICH Q4B can be found on the USP website at https://www.usp.org/harmonized-standards/pdg.

The third speaker was Margareth Marques, PhD (USP, Rockville, MD, USA) who spoke on "USP General Chapter Dissolution <711>." This chapter describes the apparatus and test conditions for dissolution of the most common pharmaceutical dosage forms (tablets, capsules, and suspensions). This chapter is partially harmonized with the EP and JP.

The USP national text is easily identified by the symbol: ♦,♦; text within these symbols is applicable to USP only. One example of USP national, not harmonized, text is the section "For Dosage Forms Containing or Coated with Gelatin," where use of enzymes in the dissolution medium when there is evidence of crosslinking in

gelatin is described. Another example is the use of USP Prednisone Tablets for the qualification of the dissolution apparatus 1 (basket) and apparatus 2 (paddle), which is applicable only to USP. Also, the text describing USP apparatus 3 (reciprocating cylinder) has a footnote stating that this apparatus is not accepted by the JP. The USP has hundreds of individual monographs for pharmaceutical dosage forms. These monographs have dissolution test conditions that are specific for products approved for the USA market, with few exceptions.

The dissolution, disintegration, or drug release test conditions, including the acceptance criteria, in any USP monograph are the conditions approved by FDA for products marketed in the USA. There are a few exceptions in which the monographs were developed upon request from the WHO. One example is the monograph for zinc sulfate tablets. This product is not approved for the USA market, and the monograph was developed based on a product approved for the European market.

USP <711> contains the acceptance criteria used in the evaluation of dissolution results for different release mechanisms (immediate, delayed, and extended release). If a particular product was approved with a product-specific acceptance table, this table is included in the particular monograph. Some examples can be found in the monographs for Clarithromycin extended-release tablets, Divalproex sodium extended-release tablets, and Extended phenytoin capsules. Two useful tools that can be a starting point in the development of dissolution tests are the FDA Dissolution Methods database, available at https://www.accessdata.fda.gov/scripts/cder/dissolution/index/cfm, and the USP Dissolution Methods database, available at https://www.usp.org/resources/dissolution-methods-database.

Proposals for revisions to any USP general chapter or monograph are published in *Pharmacopeial Forum*, available free of charge at www.uspnf.com. New proposals are posted bimonthly and are open for public comment for 90 days. Each proposal, including those being harmonized with EP and JP, has a brief explanation of the reasons for revision. Comments and suggestions for revisions to any part of the USP–NF are welcome. Comments should be supported by data, have a scientific justification, and be an improvement to the standard.

The final speaker of this session was Fasheng Li, PhD, (Pfizer, Groton, CT, USA). His topic was "USP <711> vs ChP (0931) dissolution acceptance criteria comparison and challenges to the industry." The in vitro dissolution test has been routinely used by pharmaceutical companies for commercial productions of solid dosage forms for quality control and prediction of in vivo drug release. However, there are large gaps between the different pharmacopeias with respect to dissolution test methods and acceptance criteria.

The presentation focused on the comparisons the dissolution test acceptance criteria between USP <711> and ChP (0931) using Monte Carlo simulation modelling. Operating characteristic curves were used to evaluate the probabilities of satisfying the respective acceptance criteria in two seemingly distinct compendial guidances.

When comparing USP <711> and ChP (0931) for testing the same product, ChP (0931) criteria are more stringent than USP <711> if using the same Q value for the same product. It was suggested that a standard deviation threshold for a drug product batch might be established. For results below that threshold, it would not be necessary to test against other compendial criteria.

The session ended with a panel discussion joined by Dr. Baoming Ning from the Chinese National Institute for Food and Drug Control. There was a discussion on why ChP only has two-stage testing. Dr. Ning explained that ChP adopted the EP and JP at a time when only two-stage testing was allowed. Although EP and JP have since adopted a three-stage approach, ChP has not. Dr. Ning also shared that ChP is making efforts to align with ICH. The agency has transformed and implemented a number of ICH guidelines by recommending them and publishing the Chinese version of original ICH guidelines and by assigning experts to participate in the in-depth coordination of ICH issues, including dissolution issues. ChP is open for discussion and are flexible to alternative approaches.

PART 2: DISSOLUTION BEST PRACTICES

The second part of the workshop was moderated by Yan Wu, PhD (Merck & Co., Inc, Rahway, NJ, USA). The first speaker was Andreas Abend, PhD (Merck & Co., Inc, Rahway, NJ, USA), who spoke on the topic of "Designing a Science Based Approach." Pharmaceutical scientists perform dissolution testing primarily to 1) rank formulation prototypes with varying compositions and/or made under different processing conditions, 2) assess product sameness as part of quality control; or 3) gauge the impact of formulation and manufacturing changes on product quality (*2*). These tasks often require testing under a variety of experimental conditions. The selection of the appropriate methodology is usually based on drug substance physicochemical properties, formulation composition, manufacturing/process conditions, and

drug product design (i.e., immediate, delayed, or extended release, etc.). There are no regulatory provisions restricting the choice or experimental conditions when dissolution is used in support of formulation candidate selection (*3*). Hence, companies can choose an experimental method based on prior knowledge or publications found in peer literature that are deemed appropriate to drive rational formulation and process selection. Approaches currently used in industry range from simple multimedia dissolution experiments performed in standard compendial dissolution apparatus to highly complex transfer models like the Gastro-Intestinal Simulator (GIS) or TNO Gastro-Intestinal Model (TIM). At the beginning of product development, where formulation prototype performance is solely evaluated in vitro or in preclinical species, the risk of making poor formulation or process choices as a result of relying on tests with unknown in vivo relevance is entirely with the development teams.

Once a formulation is used in the clinic or when the product is on the market, consistent product performance is critical. As a result, companies pivot their dissolution strategy towards methods and experimental conditions that ensure product quality as well as acceptance of a single specification in a complex and misaligned global regulatory environment. During market application review, many regulatory agencies challenge dissolution specifications for products containing poorly soluble drug substances if a company fails to demonstrate the ability of the specification to reject product that may not perform in patients as claimed in the product label. In an effort not to delay product approval and launch, companies often file specifications that are sensitive to small variations in materials attributes that are unlikely to impact in vivo performance. This practice often results in unnecessarily tight manufacturing process controls. Furthermore, companies may have to accept different dissolution specifications proposed by different agencies, and as a result they may have to apply different acceptance criteria for the same product (*4*). This dissolution specification development and filing approach, which until recently was common practice in the industry, is not considered "best science," as the proposed method and acceptance criterion are not capable of reliably distinguishing good from bad product, which is exactly what a specification is intended to do. Depending on drug substance physicochemical properties and formulation complexity, industry is encouraged to develop clinically relevant dissolution specifications (CRDS). A clinically relevant dissolution specification requires the dissolution method to demonstrate that changes in rate and extent of in vitro dug release produces similar changes in rate and extent of in vivo (PK) release of the drug into the systemic circulation. Thus, the specification is based on acceptable in vivo performance as opposed to some manufacturing parameter that is assumed to be in vivo relevant.

Assessing the impact of manufacturing (i.e., formulation and or process) changes on product quality for approved drugs is highly regulated, and the battery of tests to justify these changes depend on the nature of the change and drug substance solubility and permeability, i.e., the Biopharmaceutics Classification System (BCS). The level of dissolution testing a company needs to perform depends on the expected impact on product quality. Accordingly, for minor changes (unlikely to have in vivo impact) falling within the scope of current guidance, passing the approved dissolution specification may be sufficient. For moderate changes (e.g., there may be an impact in vivo performance), dissolution testing often requires dissolution profile similarity assessment. The latter may range from assessing profile similarity using the approved dissolution method or testing in as many as four pH levels of aqueous media and water (without surfactant). However, as with non-clinically relevant dissolution specifications, there's no guarantee that such dissolution profile assessments are indicative of acceptable or unacceptable in vivo performance. Here again, a clinically relevant dissolution method provides the link between in vitro rate and extent of drug release and in vivo performance and should therefore replace the above-mentioned multimedia assessment.

The next speaker in the second session of the symposium was Tessa M. Carducci, PhD (Merck & Co., Inc., Rahway, NJ, USA), who gave a talk on "Global Best Practices." As more pharmaceutical companies are filing drug products globally, Dr. Carducci emphasized that there is a strong business driver for universal acceptance of quality control dissolution methods and specifications for products in global markets. Additional sampling, results assessment, and/or testing an additional method extends the product release time and analysts needed, also adding supply risk and complexity. Optimizing the chance of global acceptance of the dissolution method often involves selecting the most discriminating method without sacrificing method robustness. Although adhering to multiple country-specific guidelines can be overwhelming, there are common themes underlying the principles governing dissolution method development in various markets, such as appropriate discriminating power (*5*–*7*). Furthermore, more markets are embracing scientific justifications including clinically relevant arguments (*7*). Pharmaceutical companies can help continue to drive

global acceptance by presenting innovative, science-based, and clinically relevant justifications to the agencies.

Dr. Carducci presented a case example for a Biopharmaceuticals Classification System (BCS) class IV immediate-release tablet made by direct compression. Although the equilibrium solubility of the active compound is low in pH 6.8 media, the dissolution is rapid due to high apparent solubility of the API, and the supersaturated solution is stable. Two main quality control dissolution method options were considered, either 0.1 N HCl or pH 6.8 buffer. Both options demonstrate robustness for routine commercial testing, and both are sensitive to process parameters and considered discriminating; the pH 6.8 method has greater sensitivity to process parameters and is additionally sensitive to the API form. Although this method could be considered over-discriminating due to there being no risk of API form change in the drug product even on stability, the 0.1 N HCl method could be seen as under-discriminating. Therefore, the pH 6.8 method was proposed universally to ensure global acceptance as it is more discriminating without having execution risks in supply. As with the dissolution method proposal, Dr. Carducci explained that we can optimize our chance of global acceptance of the dissolution specification by selecting the most discriminating specification per relevant regulatory guidances or preferences and providing a strong justification that includes linkage to clinical relevance. Another case example was given where the specification following the EMA reflection paper would be set at 30 minutes based on the dissolution of batches used in pivotal clinical studies, but a tighter specification at 20 minutes was proposed to align with the FDA expectation for the specification to be set where 80% release is achieved (*3*, *5*). The specification at 20 minutes does not significantly increase risk of failing acceptable batches as compared to 30 minutes and has increased chance of global acceptance.

Dr. Carducci closed with a proposal for leveraging the procedures in ICH M9 as a path towards a universal multimedia dissolution procedure for demonstrating in vitro dissolution comparison for both post-approval product changes and changes made during development (*8*).

The next speaker was Beverly Nickerson, PhD (Pfizer, Groton, CT, USA), and the topic was "Dissolution Testing with Apex Vessels." Dr. Nickerson highlighted challenges associated with coning during dissolution testing and the benefits of using apex vessels to address these issues. Coning is an artifact that may be observed during dissolution testing of some solid oral dosage forms due to insoluble excipients in the formulation. This can lead to the presence of a cone of dense undissolved excipients at the bottom of the dissolution vessel under the paddle. The cone of material prevents dissolution of drug that is trapped in the cone.

PEAK vessels (now commonly referred to as apex vessels) were introduced by VanKel in the 1990s to minimize the effect of coning (*9*). These vessels have an inverted cone at the bottom of the vessels to prevent material from accumulating under the paddle. Despite the availability of these vessels for so many years, there are very few methods listed in the FDA dissolution database that use PEAK or apex vessels, and there is continued reluctance by companies to use the vessel due to fears of lack of regulatory acceptance.

Dr. Nickerson also discussed a *Stimuli* article that was published in *Pharmacopeial Forum* in collaboration with members of IQ Dissolution Working Group, AAPS In Vitro Release and Dissolution Testing Community, and apex vessel manufacturers (*10*). The goal of the article was to seek acceptance of the apex vessel as an alternative to the standard 1-L vessel to be used when scientifically justified. This article compared apex vessels from various major manufacturers through an interlaboratory study and through computational fluid dynamics modeling. In addition, specifications and qualification procedures for apex vessels were proposed. Dr. Nickerson presented an example of a project she worked on that included the use of apex vessels to develop a discriminating and robust method for an immediate-release tablet.

The next speaker was Bryan Crist (DissoAssist, Wilmington, NC, USA), and his topic was "Dissolution Apparatus Qualification Criteria." Mr. Crist provided elements of dissolution apparatus performance qualification as defined by the US FDA, USP, ASTM, and various international pharmacopeias. Reflecting on best practices for analytical instrument qualification (AIQ) from USP general chapter <1058> Analytical Instrument Qualification, he differentiated between the holistic qualification requirements of the USP Performance Verification Test (PVT) included in USP <711> and modular qualification requirements of the enhanced mechanical qualification (eMQ) procedure in ASTM-E2503-13 for the basket and paddle dissolution apparatus. Elements of dissolution apparatus qualification parameters contained in the ChP (0931) were also compared to USP and ASTM specifications and tolerance.

A historical perspective was provided for the various apparatus qualification procedures along with review of

advantages and limitations of the USP PVT and ASTM eMQ. Mr. Crist ended with reminders that either the PVT or eMQ will satisfy cGMP requirements for performance qualification of the dissolution apparatus but cautioned that the goal of a proper AIQ was that the apparatus remain in a qualified state between performance qualification intervals. There were three advantages that the eMQ approach had for accomplishing this by 1) reducing the intervals between periodic qualification based on risk; 2) requiring analyst's documentation of observational checks prior to each run; and 3) replacing damaged or out-of-specification components with certified components.

The final speaker for this session was Piero Armenante, PhD (New Jersey Institute of Technology, Newark, NJ, USA). His topic was "The Hydrodynamics of the USP Apparatus 1 (Basket Apparatus)." He presented results of experimental work that he and his students conducted to study in detail the hydrodynamics of the USP apparatus 1. They used particle image velocimetry to determine the fluid velocities in the dissolution vessel on a vertical central plane through the basket and on a number of horizontal planes for three different basket rotational speeds and with different mesh openings (*11*, *12*). They found that flow field was dominated by the tangential velocity component and was approximately symmetrical in all cases. However, despite all precautions taken, small flow asymmetries were observed in the axial and radial directions which appears to be an unavoidable characteristic of the fluid flow in apparatus 1. The magnitudes of axial and radial velocity components varied significantly with location in the vessel, basket rotational speed, and mesh opening, but were always much lower to the tangential velocities. Interestingly, a small vertically angled jet emanating radially near the top edge of the basket was observed. This jet contributes significantly to the vertical recirculation of the fluid inside the vessel and especially to the flow through the basket and around the dosage form within, having major implications on the drug dissolution rate. The results of this work provide insight into the flow field inside USP apparatus 1 and how operating and geometric variables affect the system hydrodynamics and hence the dissolution process.

The session ended with a panel discussion where there was some discussion on strategies to support formation changes during development, such as going from drug in a capsule to a capsule formulation and then to a tablet formulation for phase 3. Depending on the specific case, possible strategies include comparison of the dissolution profiles to support the new formulation, an IVIVC study, or small (e.g., 12 patients) in vivo comparability study.

SUMMARY

The recordings of the meeting, including panel discussions, are available on the AAPS website. The workshop was well received, with more than 60 people in attendance and active participation in two panel discussion sessions. The workshop accomplished its goal as a forum to learn and discuss strategies for dealing with different dissolution methods and acceptance criteria in different pharmacopeia, developing the dissolution method and setting specifications with global acceptance in mind. These strategies will benefit the industry for global marketing effort and enhance international best practices by presenting innovative, science-based, and clinically relevant dissolution justifications to the agencies.

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