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Myth-Busting Dissolution: An IQ Consortium Perspective on Common Misunderstandings in the Practice and Science of Dissolution Testing

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ABSTRACT

Dissolution testing is a foundational analytical tool in pharmaceutical development, critical for assessing the quality and performance of various dosage forms. Despite its long-standing role, the field is hampered by widely held myths and legacy practices that can jeopardize data integrity and hinder efficient development. This article, authored by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) dissolution working group, systematically examines and dispels persistent misconceptions underlying common laboratory practices when testing oral dosage forms using the basket or paddle dissolution apparatus. Key areas addressed include myths about dissolution media selection, such as the inappropriate use of sonication for deaeration and assumptions about universal surfactant concentrations. The authors challenge default approaches to hydrodynamics, including paddle speeds and apparatus configurations, and highlights the necessity of method optimization tailored to each formulation. Additionally, misunderstandings relating to filters, sinkers, sampling techniques, and the transferability of methods between product strengths or populations are critically evaluated. By presenting technical evidence, the authors highlights the risks of relying solely on empirical approaches without establishing a sound scientific understanding of the dissolution behavior of the product. The article underscores the importance of adaptability, thorough validation, and robust rationale in dissolution method development, enabling greater discrimination and clinical relevance. Through myth-busting and evidence-based recommendations, this review aims to foster critical thinking and continuous improvement among pharmaceutical scientists. By dispelling outdated beliefs and promoting rigorous science, this article supports the development of dissolution methods that are reliable, discriminative, and ultimately supportive of both innovation and patient safety.

KEYWORDS: Dissolution, myths, dissolution medium, hydrodynamics, filters, sinkers, method development, oral dosage forms, basket apparatus, paddle apparatus

INTRODUCTION

Dissolution testing is a cornerstone of pharmaceutical development, providing critical insight into the performance of oral dosage forms. Despite its longstanding utility, the field is rife with misconceptions or bad practices that can lead to misinterpretation of data and suboptimal formulation decisions. These myths, often perpetuated by outdated practices or a lack of comprehensive understanding, can impede innovation and prolong pharmaceutical development which can be detrimental to the patient.

This article aims to debunk some of the most pervasive myths in dissolution testing, offering a clearer perspective based on scientific evidence, contemporary best practices and the experiences of the experts within the International Consortium for Innovation & Quality (IQ) dissolution working group. The IQ

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Dissolution Working Group is composed of dissolution specialists from pharmaceutical member companies with extensive experience across numerous development and commercial programmes.

The myths presented in this manuscript were identified during focused working group discussions in which commonly encountered misconceptions were collated from members' collective experience across internal projects and interactions with external partners, including contract research organizations (CRO), contract development and manufacturing organizations (CDMO), and biotechnology companies. Only topics encountered by multiple members across different settings were included, with the aim of addressing recurring misconceptions and providing clarity based on the group's combined scientific and practical experience. By addressing these misconceptions, this review supports a more informed approach to dissolution method development and justification of test conditions, ultimately enhancing the reliability and relevance of this essential development and quality control (QC) tool.

The myths explored in this article will focus on the following key areas of dissolution testing, including:

- **Dissolution media**: Myths surrounding the preparation, selection, and composition of dissolution media.
- **Hydrodynamics**: Misconceptions about the vessel hydrodynamics and coning phenomena (*1*).
- **Filters and sinkers**: How a lack of control of these common method elements can lead to technical challenges.
- **Sampling and analysis**: Misunderstandings related to the analytical method particularly involving dissolution automation and interpretation of data.
- **Formulation development**: Lack of alignment between formulation characteristics and dissolution behavior.

Each of these areas will be examined, with a focus on the scientific principles and empirical data that challenge these myths. By dispelling these myths, the authors aim to enable a more accurate and efficient pathway to developing clinically relevant and robust dissolution methods.

DISSOLUTION MEDIA

Myth: Sonication is an Effective Deaeration Technique for Dissolution Media

The significance of deaeration of the dissolution medium is routinely investigated during method development as the presence of bubbles can adversely impact the dissolution rate or increase method variability. An oxygen concentration below 6 mg/L has been identified as a marker for adequate deaeration of water for the *United States Pharmacopeia* (USP) Performance Verification Test (PVT) (*2*). The example degassing technique in the USP is to heat the medium, while stirring gently at 41 °C, and then immediately filtering under a vacuum using a filter with a 0.45 µm membrane or less, with vigorous stirring and continue stirring under vacuum for about 5 minutes (*3*). Other validated deaeration techniques are allowed and are employed routinely in dissolution testing, often provided in the form of commercial off the shelf units. One technique that is often erroneously used for dissolution medium deaeration is sonication with or without heating. Sonication is a common technique used to degas mobile phases for liquid chromatography; however, those mobile phases typically contain organic solvents as opposed to the 100% aqueous dissolution medium. Rohrs and Stelzer showed conclusively that sonication has no measurable effect on dissolved oxygen levels when applied to room temperature aqueous medium (*4*). For this reason, it is critical that sonication is not a laboratory's routine deaeration technique. Ideally, any technique that is performed should be validated against the pharmacopeial standard technique.

Myth: The Critical Micelle Concentration (CMC) of Sodium Lauryl Sulphate (SLS) is 0.18–0.23% w/v

USP chapter <1092> The Dissolution Procedure: Development and Validation lists the critical micelle concentration (CMC) of sodium lauryl sulphate (SLS) (sometimes known as sodium dodecyl sulphate or SDS) as 0.18–0.23% (w/v) and provides references to literature (*2*, *5*). In practice, when SLS is added to common dissolution medium below the quoted CMC an apparent solubility increase relative to the neat buffer is observed. This is because the CMC is a function of the ionic environment and temperature of the medium. For that reason, it may be necessary to determine the CMC in the dissolution medium. Table 1 presents work by AstraZeneca using the pendant drop technique to experimentally determine the CMC for both SLS and polysorbate 80 (Tween80) in the three most common dissolution media (USP simulated gastric fluid [SGF] without enzymes pH 1.2, 50 mM sodium acetate pH 4.5 buffer, and 50 mM sodium phosphate pH 6.8 buffer). Although absolute values may vary depending on the measurement technique, the observed media and temperature dependent trends are informative for the present discussion.

Table 1. Measured CMC of SLS and Polysorbate 80 Using Pendant Drop Technique in Common Dissolution Media

Medium	Temp (°C)	SLS		Polysorbate 80	
		CMC (%w/v)	CMC (mM)	CMC (%w/v)	CMC (mM)
Water	25	0.19	6.6	0.11	0.9
Water	37	0.22	7.5	0.06	0.5
USP SGF pH 1.2	37	0.16	5.6	0.04	0.3
50 mM pH 4.5 sodium acetate buffer	37	0.09	3.1	0.12	1.0
50 mM pH 6.8 sodium phosphate buffer	37	0.05	1.9	0.14	1.1

CMC: Critical micelle concentration; SLS: sodium lauryl sulphate. USP SGF: United States Pharmacopoeia Simulated Gastrointestinal Fluid

This information is important during the selection of surfactant concentration for the dissolution medium for a poorly soluble compound. Concentrations around the quoted USP CMC are often mistakenly avoided due to robustness concerns. Levels in the region of 0.05–0.15% (w/v) are also often avoided due to being below the CMC, and thus are not expected to impact solubilization. This can result in more SLS than is needed to provide adequate sink conditions in the medium composition, which has a knock-on effect of reducing the method's discrimination potential. As shown in Table 1, the CMC are heavily media dependent. For example, utilizing an SLS concentration of 0.1% (w/v) in a typical phosphate buffer would still increase solubility due to the presence of micelles and could be accurately weighed to give a robust and reproducible level and still be 2-fold above the CMC. Surfactants can be used below the CMC in dissolution medium to reduce surface tension and improve the wettability of dosage units.

Overall, it is important to remember that a CMC of a surfactant is dependent on the temperature and buffer selected, and the values quoted in the USP are specific to the medium and temperature.

Myth: SLS is Always the Best Surfactant

SLS is the most frequently used surfactant in dissolution media due to its solubility and wetting enhancing properties, widespread availability, ease of use. A search in the U.S. Food and Drug Administration (FDA) Dissolution Methods Database reveals that SLS is used in more than half of dissolution media containing surfactants (*6*). Polysorbates (Tween 20, 40, and 80) are close to 30% combined, and cetyltrimethylammonium bromide (CTAB) is about 8%. Other surfactants used include Triton X-100 and Brij 35. Although this list clearly identifies SLS as the most used surfactant, the sum of all other surfactants adds up to about 46%, and USP <1092> lists 13 commonly used surfactants (*2*, *6*).

In most cases, surfactants are added to dissolution media to enhance the active pharmaceutical ingredient's (API) solubility during the dissolution test and subsequent analysis and/or to improve wettability of the dosage unit. The surfactant type and amount added to the chosen dissolution medium needs to be justified, e.g., via solubility measurements including various media in different pH values as well as multiple surfactant types in different concentrations (*2*). API solution stability during and after the dissolution run as well as interactions with formulation ingredients also need to be considered (*7*).

SLS is known for its precipitation reaction in the presence of potassium ions (*8*). Consequently, when SLS is selected as the surfactant in a phosphate buffered medium, potassium phosphate buffers are typically replaced by sodium phosphate buffers. However, this substitution is not feasible if the formulation, i.e., the API and/or other excipients, contains potassium.

The use of SLS might not always result in better solubility compared to other surfactants. In a case study presented by Fotaki et al., a five- to sixfold increase in triamterene dissolution was observed in 0.1 M acetic acid with 1 % Tween 20 compared to 1 % Tween 20 or 0.1 M acetic acid, respectively (*7*). This synergistic effect was attributed to the pH dependent increase in triamterene solubility at lower pH levels combined with the higher micellar concentration and excellent molar solubilization capacity of Tween 20 due to its low CMC value. Further, about 40% triamterene dissolved in acetate buffer, pH 4.5 + 0.5% Tween 20, whereas 0.5% SLS in acetate buffer, pH 4.5 resulted in less than 1% dissolution. Here, the SLS anion may have interacted with the cationic drug species, forming an insoluble salt that hindered dissolution. Similarly, Huang et al. reported de-solubilization caused by ion-pairing interactions between ionic drugs and SLS, leading to inconsistent and incomplete drug release for poorly soluble cationic drugs (*9*). In another study, Park and Choi found that cationic surfactants such as CTAB significantly increase the solubility and dissolution rate of acidic drugs, including mefenamic acid, nimesulide, and ibuprofen compared to SLS and Tween 80 (*10*).

In some cases, however, surfactant addition to dissolution media has nothing to do with solubility enhancement but rather limiting undesirable interaction, e.g., API surface absorption to glass or tubing. For electrostatic interactions with glass surfaces or polypropylene, hydrophobic surfactants such as Tween 20 can be

effective due to their low CMC value, which facilitates micellar formation or adsorption to surfaces, thereby blocking API adsorption and ensuring consistent drug release (*11*).

In summary, although SLS is the most widely used surfactant in dissolution media, its application, like that of all surfactants, must be carefully evaluated, and a clear rationale must be established.

Myth: Surfactant Medium Does Not Require Deaeration

The USP chapter <1092> The Dissolution Procedure – Development & Validation states that surfactant media typically are not deaerated because the process results in foaming and the impact of dissolved air on the dissolution process is usually mitigated by the reduced surface tension (*2*). The key elements of that statement are the words "typically" and "usually". Figure 1 illustrates a case where a dissolution medium containing a surfactant, CTAB, showed a significant impact of medium deaeration on the dissolution profile due to the material floating to the surface and being unavailable for dissolution. When deaeration of surfactant medium is required, a commercial system is advised to minimize foaming. Alternatively, the medium may be deaerated and dispensed to the vessel at 37 °C prior to addition of the surfactant. This example demonstrates that there are occasions where degassing of surfactant medium may be required.

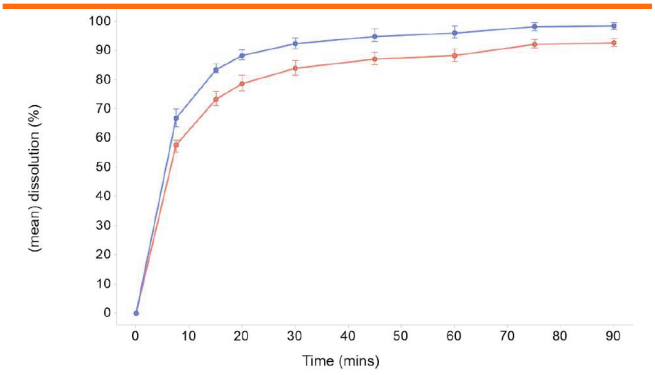

Figure 1. Impact of deaeration on the dissolution performance of an immediate-release product with 0.1% CTAB in the medium. Red = no deaeration; blue = with deaeration).
CTAB: cetyltrimethylammonium bromide.

Myth: pH Selection Rather Than Surfactant Addition is the Best Way to Manipulate Sink Conditions

The choice of appropriate dissolution medium is not always a straightforward one. In general, solubility measurements serve as the basis. If adequate solubility can be achieved at any pH value in the physiological range, using pH to fine tune for the intended formulation should be pursued. However, finding the optimal medium pH value can be tricky and result in a change in drug solubility from very soluble at one pH to insufficient with only a small change in pH. The widespread assumption that pH adjustment is inherently superior to surfactant addition for achieving sink conditions can lead to overly sensitive, non-robust dissolution methods. Small, often unavoidable shifts in pH, e.g. either due to buffer capacity, preparation variability, or scale-up, may result in disproportionate changes in solubility and thereby compromise method robustness and reproducibility (*7*).

In these cases, additions of the right type and concentration of surfactant can help in selecting the best medium composition (*12*). For compounds with a pH dependent solubility, but not enough to rely on pH alone for sink conditions, it might also be easier to use conditions with low solubility and add surfactant. With this approach, the solubility enhancing effect is solely triggered by the surfactant. This can reduce the risk of abrupt solubility changes and improve method robustness across development stages and laboratories. Finally, the stability of API and formulation must be ensured at the chosen pH value and can eliminate the switch to a pH value with better solubility (*7*). In practice, stability constraints frequently limit the usable pH range, further reducing the feasibility of pH-based optimization alone.

Adjusting pH is often a primary strategy, but the addition of surfactant, rather than changing the pH of the medium, can also be an effective approach for developing a robust dissolution method. Rather than prioritizing pH adjustment by default, pH and surfactant effects should be evaluated in parallel during method development (*2*). pH optimization should be favored when solubility changes are gradual, well controlled, and compatible with API and formulation stability. Surfactants should be considered when pH-driven solubility is highly sensitive, insufficient to ensure sink conditions, or limited by stability concerns. A careful, data-based choice between pH and surfactant use supports the development of robust, discriminating, and clinically relevant dissolution methods.

Myth: Surfactants Are Only Added to Dissolution Medium to Improve Sink Conditions

Commonly, surfactants are added to dissolution media to enhance the solubility of poorly soluble compounds. Surfactant choice and concentration must be justified in the dissolution method by conducting appropriate experiments (*2*). However, as it is essential to develop a robust dissolution method for quality control, sometimes the addition of surfactant can also be justified for reasons other than API solubility. For APIs with surface adhering tendencies, first, material alternatives, e.g. filter material or elimination of tubing, for all points of contact should be considered. In some instances, e.g., API adsorption

to the vessel surface, the addition of a small amount of surfactant may eliminate the effect. Additional cases for surfactant addition include media surface tension reduction, improved API wettability and reduced reaeration of the dissolution medium (*13*).

As with the use of any kind of surfactant with dissolution media, surfactant type and amount must be chosen carefully and full justification provided.

Myth: 500–900 mL of 0.1N HCl (pH 1.0) is Representative of Human Fasted State Gastric Conditions

When performing dissolution testing in gastric media, it is important to know that neither the volume used nor the pH are typical of actual human gastric conditions. In adult humans, resting fasted gastric volume is highly variable, but average volume is about 25 mL, which is more than an order of magnitude lower than volumes typically used in a pharmacopeial basket or paddle apparatus (*14*). Gastrointestinal (GI) volumes are also highly dynamic, in contrast to the static volumes typically used in vitro. The stomach will have stomach wall secretions and saliva as dynamic inputs, and gastric emptying to the intestine as an output. Any co-administered water taken with a dosage form will temporarily increase gastric volume, but is then rapidly emptied, with about 85% of administered water emptied in 30 minutes (*14*). Fasted gastric pH has high intra and intersubject variability and is typically significantly less acidic than 0.1 N hydrochloric acid (HCl); pH 1.0 can be regarded as a low-end physiological extreme (potentially useful as a worst case) of the gastric pH likely to be experienced in a human population, rather than typical.

Myth: Pharmacopeial Buffer Strength Can Be Used Without Justification

A brief analysis of the dissolution test conditions listed in FDA dissolution database indicates that approximately 25% of all test conditions include phosphate salt as one of the buffering components. More than 70% of the phosphate buffered solution utilized 50 mM as the phosphate salt concentration. The widely used 50 mM phosphate buffer concentration certainly complies with USP <711> Dissolution chapter, which mentions this buffer at pH 6.8 as a buffer condition for extended-release dosage forms. However, whether this buffer concentration or ionic strength is generally appropriate for providing good discrimination power or is a robust condition for immediate-release (IR) dosage forms is not discussed in USP <711>.

In practice, the salt concentration in a buffered solution does impact the drug release rate of both API and excipients in drug product. Drug solubility, as one of the most important parameters being considered during the determination of dissolution conditions, and its impact from salts and counter-ions are well defined in USP <1236> Solubility Measurements (*15*). Studies on the intrinsic dissolution rate tests of naproxen API using Wood's apparatus in multiple buffer systems with different ionic strengths indicate a strong drug flux rate (mol/cm^2/s) dependence on the buffer concentration strengths (*16*). Another key example of drug excipient sensitivity to buffer strength is the use of poly(lactic-co-glycolic) acid (PLGA) polymer as a commonly used excipient in controlled-release formulations. The degradation rate (reflected by the molecular weight over time) of PLGA polymer is altered by buffered solutions with different phosphate concentrations. These differences further extend to different drug release rates within the same formulation (*17*). With all those examples, screening of buffer concentration and solution ionic strength should be considered when there is evidence that the product is highly sensitive to changes in buffer composition.

HYDRODYNAMICS

Myth: Screening Paddle Stirrer Rate by Increments of 25 rpm will Always Be Okay

Proper hydrodynamic conditions lay the foundation of a good discriminative drug release method against various dosage forms. Agitation speeds of 50, 75, and 100 rpm are the most used for the basket and paddle apparatus according to USP <1092>, and lower rotation speeds have been commonly used for suspension products (*2*). Lower speeds are preferred for higher discriminative power, but method robustness issues brought by insufficient agitation, e.g., coning effect under a paddle, requires evaluation during method development. Often, both good discrimination power and method robustness can be met by choosing 50, 75, or 100 rpm; however, there are many cases in the FDA Dissolution Method Database using rotation speeds that are not in a 25-rpm increment. A case example illustrating this was published where the rotation speed in the paddle apparatus was evaluated with fine-tuned rotation speed because of coning at 50 rpm and loss of discrimination at 75 rpm using a standard vessel (case 5) (*1*). Multiple design of experiment (DOE) studies with rotation speed as one of the important parameters eventually indicated that 55 rpm in an apex vessel provided the desired balance of discrimination and method robustness.

While screening speeds of 50–100 rpm in 25 rpm increments is generally appropriate, using smaller increments (5–10 rpm) may be necessary to achieve the

right balance of method robustness and discrimination power when the product demonstrates high sensitivity to hydrodynamic changes. It should be noted that for paddle apparatus most methods should be in the range of 50–75 rpm, whereas 100 rpm is only normally acceptable for basket methods.

Myth: Use of Resident Sampling Probes Will Not Influence Drug Release Profiles

A resident probe is a sampling cannula that remains present in the dissolution vessel for the duration of the test. By definition, this is a deviation from the harmonized pharmacopeia for both basket and paddle apparatus and USP <1092> The Dissolution Procedure – Development & Validation states that such deviations should be validated, which means that the resident probe should give similar dissolution performance to sampling performed as per the pharmacopeia with non-resident probes (*2*). Issues with cannulas causing method robustness issues have been highlighted in case studies by Mann et al., so the importance of their impact should not be underestimated (*18*). Many automated systems now have manifolds that mimic a manual sampling process and so this is not an issue, but if a fiber optic probe for instance is used then the impact of that probe should be understood. In summary, if the sampling cannula is present in the medium for the duration of the test, it can have an impact on the vessel hydrodynamics and a subsequent impact on the dissolution of the product. With that in mind, the sampling procedure should be routinely studied as part of method development.

CONING

Myth: Sinkers Can Be Used to Overcome Coning

The International Council on Harmonization (ICH) M9 Guideline mentions that when high variability or coning is observed in the paddle apparatus that the use of the basket apparatus is recommended or suitably justified alternative approaches to overcome coning can be used if scientifically substantiated (*19*). ICH M9 specifically mentions the use of sinkers without any reference to supporting data. In practice, sinkers often make no improvement to the coning phenomenon as the powder cone remains in place, albeit now with a sinker in place. This is an area that has limited study in literature. A recent publication in 2024 by Terashima and Ozeki has attempted to address this statement by the assessment of a BCS I drug product or cellulose particles of varying sizes in the paddle apparatus at 50 rpm in the presence and absence of sinkers (*20*). The authors looked at three sinker types: pharmacopeial basket sinkers, helical coil sinkers and the so-called "CLIPS" sinkers. They found that the effect of sinkers on coning varied depending on their shape and characteristics of the particles that constituted coning, with the CLIPS sinker alleviating some coning elements but the pharmacopeial sinker exacerbating the coning. The conclusion from this work was to choose the most appropriate sinker for the formulation. A more universal solution to alleviate coning is the adoption of an apex vessel, which changes the fundamental position of the powder (*1*). The use of a sinker may help, but as shown by Terashima and Ozeki, sinkers can improve the coning or make the situation worse.

Myth: All Coning is the Same, All Coning is Bad

Coning is a phenomenon that can occur in the paddle apparatus when solid particulate material such as from a disintegrated tablet forms a pile or cone in the bottom center of the vessel. As mentioned above, this phenomenon can increase variability or lead to incomplete release, as some active ingredient may become trapped in the cone.

Although coning is sometimes observed, complete release is achieved with acceptable variability. On close visual examination across multiple products that exhibit coning, a pattern has been observed to emerge. When the particulate matter is loose and freely moving into and out of the cone, coning tends to not have significant adverse effects. When the cone appears to be rigid or sticky, then variability and incomplete release tend to emerge. The first case may be called dynamic coning (possibly acceptable), whereas the second case may be called static coning (probably unacceptable). Refer to Figure 2 for examples of dynamic and static coning.

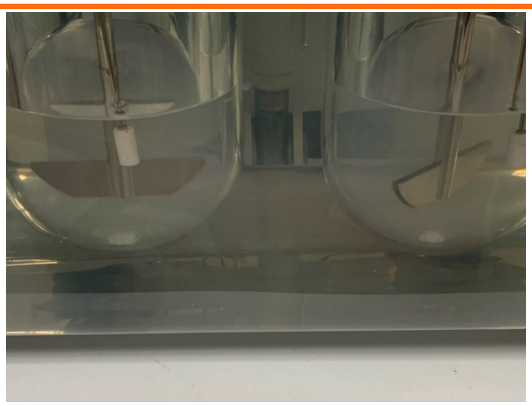

*Figure 2. Two immediate-release tablets with the same API and formulation but different secondary manufacturing processes. **Left**: Process A exhibits dynamic coning, acceptable variability and complete release. **Right**: Process B exhibits static coning, unacceptable variability and incomplete release. The products produced by both processes are bioequivalent in vivo, underscoring that coning is a phenomenon of the in vitro system and might not imply performance in vivo. API: active pharmaceutical ingredient.*

Myth: Coning Means an Increase in Drug Release at Infinity Spin Will Always Occur

It is commonly assumed that the cone of sedimented material at the bottom of the standard hemispherical dissolution vessel is associated with trapping of some drug within the cone that can only dissolve once a higher rotation speed is applied at the end of the test to disturb the cone. This use of the so-called "infinity spin" is good practice during method development, as under these conditions the dissolution test is a pseudo content uniformity test assuming one is operating under sink conditions. It is sensible to collect two timepoints during the infinity spin to ensure a plateau is reached. It is also good practice to reduce the rotation speed back to normal levels to remove any vortex effects particularly if using automated sampling systems. However, examples are known within the dissolution IQ community where the visual presence of coning does not always translate into the jump post infinity spin in the dissolution profile. Formulations containing highly soluble APIs with dense excipients may visually have a cone present but due to high solubility, the API can dissolve prior to the sedimentation forming or the drug can solubilize and diffuse through the cone. Therefore, a visual assessment of coning is not enough evidence alone to justify an increase in rotation speed or a switch to an alternative apparatus or vessel.

FILTERS AND SINKERS

Myth: Filters Are Only There to Protect the Liquid Chromatography Column

Dissolution filters are a heavily under-appreciated element of a dissolution test; however, the incorrect filter material selection and/or inadequate filter validation can lead to real issues (*21*). A previous IQ publication by Mann et al. (*18*) describes the best practices around filter validation and the potential issues that can arise if not performed correctly. To summarize, the filter discard volume, filter efficiency and filter leachable interferences should all be assessed at the most appropriate concentration for each test (*18*). It is also important to note that centrifugation should be avoided in pharmacopeial dissolution sampling where possible, as it is not possible to perform the centrifugation within the standard sampling window.

Myth: A Sinker is Always Needed, and All Sinkers Are Equal

It is common practice to use a sinker for dosage forms like capsules which tend to become buoyant. It is also common to use a sinker for dosage forms that do not disintegrate such as hydroxypropyl methylcellulose (HPMC) modified-release tablets that dissolve via erosion or diffusion processes. The use of a sinker in these cases helps minimize variability by ensuring a consistent position in the vessel for these products where small differences in landing position on the bottom of the vessel impact the dissolution profile. Alternatives that also help with this are the felodipine stationary basket, which again provides a standardization of the tablet position relative to the paddle. For many rapidly disintegrating dosage forms though, a sinker is not required and would not be included in initial stages of method development.

If a sinker is used, then during the robustness and ruggedness studies the impact of a change in sinker or sinker dimensions could be a potential variable to study. In one example case study for an HPMC capsule product that contains a semisolid matrix, it was shown that the sinker type impacted the dissolution at early timepoints (see Fig. 3), so the exact sinker used in the method needs to be controlled carefully.

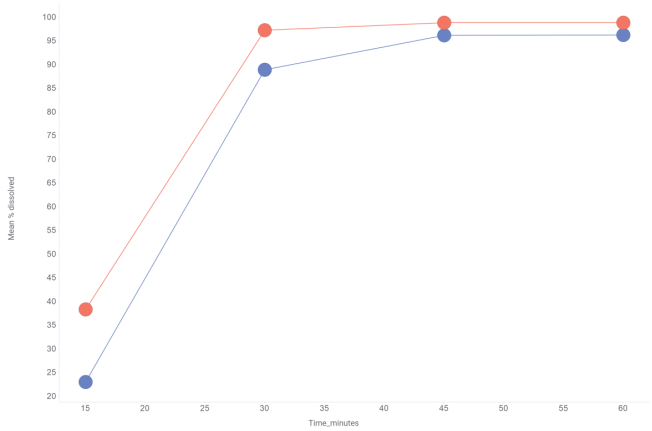

Figure 3. Impact of sinker type on mean dissolution of HPMC capsule product containing a semisolid matrix. Red = 8 coil helical sinker; blue = Sotax style sinker (15.5 x 5.0 mm). HPMC: hydroxypropyl methylcellulose.

SAMPLING AND ANALYSIS

Myth: Autosamplers Are Equivalent to Manual Sampling, and the Same Settings Can Be Used for all Products

It is commonly believed that differences exist between autosampling and manual sampling approaches in various ways such as sampling cannula shapes and time spent on sampling process. Drug release rate differences caused by different fluid flow dynamics between manual sampling and automated sampling was observed and discussed by Mann et al. (*18*). Additional validation is suggested by USP <1092> The Dissolution Procedure – Development & Validation if full automated sampling is used in dissolution test development (*2*). Generally, autosamplers may cause deviation from compendial procedures and provide different dissolution profiles from manual sampling. Additional validation of the autosamplers should be carried out.

Additionally, differences also exist among different brands of autosamplers. For example, autosampling systems can have two cannulas (one sampling and one return), single cannulas, or even no cannulas (sample port was built in stirring shaft), leading to different hydrodynamic effects on drug release rate. Different prime volume for rinsing the sample tube is another parameter to consider. In addition, whether the medium used for priming sampling tubes is returned to the dissolution vessel, or whether there is a waste drop volume (the amount of sample that is pushed through the needles before the sample is dispensed into the collection vials) should be considered. In the latter case, these need to be inspected carefully before calculating the percentage of drug release. Thus, the same settings cannot typically be used for different autosampler systems.

FORMULATION

Myth: Immediate-Release (IR) Formulations Should Dissolve Very Rapidly, and Slower Release Profiles Are Always Overdiscriminating

During the development of a dissolution method for IR formulations, rapid dissolution might be expected. However, there can be misconceptions on what a rapid dissolution profile represents, and if it is suitable for the respective formulation, as it may be different case by case. Dissolution method development and especially media selection are influenced by solubility measurements and in consequence, by drug solubility. Biopharmaceutics Classification System (BCS) class I and III compounds tend to have high solubility and are less likely to be dissolution-rate limited. They often, but not always, display a very fast release behavior across the entire physiological pH range, resulting in ≥ 85% release in ≤ 15 minutes (see Fig. 4, example 1). For such formulations, a simplified dissolution method development, e.g., according to the FDA guideline, can be used or dissolution may even be replaced by disintegration (*22, 23*). However, these profiles are frequently mistaken as examples of dissolution profiles for (all) IR formulations.

For other cases and especially BCS class II and IV compounds, a dissolution method, which is discriminative for key quality attributes must be developed. Generally, dissolution profiles for IR formulations are measured over 60 minutes and full release (≥ 85%) should be achieved within 45 minutes. Based on these measurements and experiences gained during drug product development, dissolution specifications (Q value) are set. In contrast to the European Medicines Agency (EMA), which also accepts Q = 75%, the FDA generally requests a Q = 80% or higher (*24*). Hence, dissolution method development should aim for at least 90% released after 45 minutes.

Differences between dissolution profiles are often assessed by calculation of the similarity factor, f_2 (*25*). Although specific calculation requirements differ from country to country, it is advisable to have at least three timepoints for test and reference formulation each, with no more than one timepoint ≥ 85% to perform f_2 calculations based on criteria set by most countries (*26*). Ideally, all these criteria for f_2 testing should be reflected in the final dissolution method for such IR formulations.

In Figure 4, examples 2–4 represent dissolution profiles of three different BCS II/IV IR formulations, which illustrates how individual drug substance and formulation attributes can impact in vitro performance. Example 2 has a very rapid release rate, exceeding 90% in 15 minutes. While this method may still be suitable to detect quality attributes, formal f_2 calculations to assist comparative dissolution profile analysis, may not be possible. In contrast, examples 3 and 4 formally meet all criteria expected for IR dissolution profiles, but visually this may be perceived differently. Both profiles include at least three timepoints suitable for f_2 calculations and achieve a mean dissolution of ≥ 90%. Since all examples were developed under sink conditions, additional measurements, especially for cases like example 4, should aim to clarify the final dissolved amount after 60 minutes, i.e., in the context of low intrinsic dissolution rates or to omit reasons such as coning.

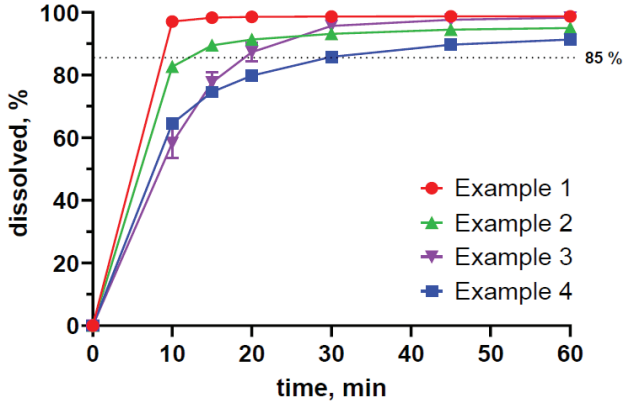

Figure 4. Examples for different dissolution profiles typically seen in immediate-release formulations.

Nevertheless, dissolution profiles with slower release characteristics can result from a well-designed and appropriate dissolution method and should not be dismissed solely based on their slower release kinetics.

Myth: BCS I/III Drugs Are Never Sensitive to Particle Size or Dissolution Rate Limited

This risk means that for some BCS I/III drugs, sensitivity to dissolution rate may be overlooked or not anticipated. Low-dose drugs like digoxin and levothyroxine can counterintuitively be highly sensitive to dissolution rate

in vivo, despite being classed as BCS class I/III molecules (*27, 28*). This is because BCS solubility class is determined by dose to solubility ratio, not solubility alone. Therefore, it is possible to have a low-dose BCS I/III drug product that still has dissolution rate/particle size sensitivity. However, as BCS I/III drugs will not approach saturation solubility and will not typically need surfactant addition in the dissolution method, underdiscrimination in a dissolution test is less of a risk than for a typical BCS II drug.

It is also worth noting that a wider range of BCS I/III drugs have the potential to be dissolution rate sensitive if the particle size of the API is large enough.

Myth: BCS II/IV Drugs Tend to Dissolve Slowly

Like the previous myth, this misunderstanding is partly based on the misconception that BCS class is related directly to solubility rather than dose to solubility ratio. In addition, whether a drug product dissolves slowly or not is critically dependent upon how it has been formulated, the extent to which drug particle size has been controlled, and upon the media selected for the dissolution test.

When dose/solubility ratio is very high, drug absorption will be limited by drug solubility in the GI tract. To manage this, drugs are typically formulated to solubilize the drug beyond its crystalline solubility, resulting in supersaturation and/or significantly enhanced dissolution rates. Amorphous solid dispersions (ASDs) are the most common approach currently used to formulate these drugs. The combination of rapid dissolution and supersaturation needs to be carefully considered when developing a suitable dissolution method for ASDs. In addition, the impact of undesirable crystallinity in the drug product (even when not typically observed under normal storage conditions) and attempting to find a method capable of detecting its impact, has become a key focus of dissolution method development for ASDs. This has been the topic of a recent IQ dissolution paper (*29*).

Myth: Amorphous Containing Drug Products Will Always be Faster Than Crystalline

A common and persistent assumption in the dissolution and formulation community is that increasing the amorphous fraction of an API will inevitably result in faster dissolution and improved performance. Amorphization of an API, e.g., by formulation design, is typically aimed at enhancing the solubility of the API compared to its crystalline form, thereby improving its bioavailability. This expectation, however, is often applied simplistically, without sufficient consideration of how amorphous content is distributed, stabilized, and processed within the final drug product. However, this assumption does not always hold true, as preventable formulation defects during the manufacturing of ASDs, such as inhomogeneous distribution and stabilization of the API within the ASD or tablet matrix, can significantly influence the dissolution performance. Additionally, process parameters like tableting pressure may induce further amorphous API formation, and storage conditions can lead to redistribution or changes in API form.

The following example illustrates how dissolution data can directly contradict the widely held belief that amorphous materials necessarily dissolve faster and, thereby, highlight a common misconception rather than a formulation abnormality. The investigated drug product contains an API with variable amorphous content, which undergoes further amorphization during drug product manufacturing. Dissolution testing was used to evaluate the impact of varying amorphous content on the release profiles. Contrary to common expectations, API with an amorphous content far exceeding the specified range (e.g., 64%) showed a significantly slower dissolution, particularly within the first 30 minutes, compared to the control (Fig. 5a).

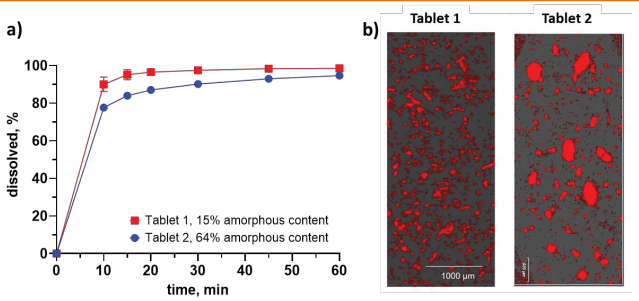

*Figure 5. (**a**) Dissolution profiles of two 10-mg tablets containing API with 15% (tablet 1, red) and 64% (tablet 2, blue) amorphous content. (**b**) Raman mapping of cross-sections of tablets 1 and 2.*

Solubility studies comparing API with 100% amorphous content to fully crystalline samples showed only a 1.4-fold increase in solubility for the amorphous API in the QC dissolution medium relative to the crystalline form. Therefore, the presumed solubility advantage of the amorphous material was marginal under the test conditions. Moreover, µDISS experiments conducted with API containing amorphous content ranging from 0% to 100% demonstrated comparable release profiles in the QC medium, except for the 100% amorphous sample, which exhibited an eightfold slower release (10 vs 80 minutes).

Raman mapping of cross sections of film-coated tablets provided critical insight: tablets containing high amorphous content showed distinct amorphous API

agglomerates, in contrast to a more homogeneous distribution of finer API particles in tablets with the standard amorphous content (Fig. 5b). Thus, the commonly cited benefit of higher amorphous solubility was outweighed by poor spatial distribution and reduced effective surface area for dissolution.

Overall, this example directly challenges the myth that amorphous drug products will inherently dissolve faster than their crystalline counterparts. Dissolution testing here does not merely identify a formulation issue but reveals the pitfalls of relying on amorphous content as a surrogate for dissolution performance without considering microstructure and processing history. This underscores the need for careful interpretation of dissolution data and a more nuanced understanding of amorphous behavior beyond simplified assumptions.

Myth: Keeping the Dissolution Test Temperature at 37 °C Matches the In Vivo Temperature if the Gastrointestinal (GI) Tract

In a dissolution test, 37 °C is used to mimic body temperature. The use of a constant temperature is an important control measure for the generation of consistent dissolution data. However, in the stomach, temperature will deviate from 37 °C as it takes a short time for co-administered fluids (up to 20–30 minutes depending upon their temperature) taken with a dosage form to equilibrate to body temperature. Although this temperature lag time is typically not used in the in vitro test, it does occasionally matter to the in-vivo formulation performance, with the most obvious case being that of gelatin capsule dissolution and rupture in the stomach. This is due to the temperature dependence in gelatin solubility, which needs to approach body temperature for efficient dissolution (*30*). This need is important if comparing with HPMC capsules, which are typically slower to dissolve at 37 °C but do not have temperature dependence, unlike gelatin capsules.

Myth: Dissolution Should be Able to Pick Up All Formulation Failure Modes

No, the dissolution method does not need to pick up on all failure modes. What the dissolution method should pick up on should be subject to a risk assessment that not only considers the critical quality attributes (CQAs), but also which tests, alongside dissolution, are most appropriate for detecting which failure mode.

The dissolution universal strategy tool (DUST) discusses the need at an early stage of product development to consider all key risks related to the drug product and manufacturing process that could impact the dissolution of the product (question 3) (*31*). This should be full consideration of all potential CQAs, be they critical material attributes (CMAs) or critical process parameters (CPPs). The answer to this question normally comes from the quality risk assessment of the product. However, as development progresses and the knowledge of the product increases, the overall control strategy for the product will evolve and it could be that the point of control for a particular CMA or CPP is derived at a different place within the control strategy. The DUST process tries to elucidate this by asking at the current stage of development, what does the dissolution *need* to discriminate for (question 5) (*31*). This can be informed by the outcome of any relative bioavailability studies or the particle size control strategy for a project. For instance, if a decision has been made that the API will be milled and controlled via a specification on the API, then the dissolution method may no longer need to discriminate across a wide range of particle sizes. On the other hand, it may be that the dissolution method is the most sensitive technique to a particular CMA, such as crystalline content in an ASD product, and so is the key control point; hence, the dissolution method must be able to suitably identify batches that would provide unacceptable bioperformance.

Myth: The Same Dissolution Method Can Always Be Used for Adult and Pediatric Products

Although some pharmaceutical formulations are solely developed for diseases prevalent in children, most pediatric formulation development is initiated in parallel of an adult formulation development around phase II. Incentives such as patent extension and pediatric exclusivity resulted in a significant increase in pediatric formulation development over the last decade (*32*). Children are among the most sensitive and diverse patient groups and several considerations to ensure a safe and effective drug product must be made. Among others these include scalable age-appropriate dosage forms, administration with or without manipulation as well as palatability and acceptability (*33, 34*). Oral pediatric formulations for children up to 6 years include liquid formulations such as solutions or suspensions (ready-to-use or powder/granules for re-constitution) as well as solid oral dosage forms such as mini-tablets/granules, orally dispersible tablets, sprinkle powders, oral powders, and oral granules (*32, 35*). From around 6 years of age, children are safely able to swallow small tablets and scaled down versions of the adult formulation can be used.

From a dissolution method development point of view,

it might be obvious that different analytical focal points could be applied for formulations that differ significantly from the adult formulation. However, this might not be the case, e.g., for mini-tablets or granules that might have the appearance of a miniaturized adult formulation. Although formulation development may start with the adult formulation, pediatric formulations may have a higher drug load, may need formulation adjustment with regards to processability, or may require a change in excipients as not all are safe for children and overall are more sensitive to blend uniformity (*34*).

A typical aim for dissolution method development is to provide a QC tool, which is discriminative for specific quality attributes of the API and pharmaceutical formulation. The lower dosage strength and smaller formulation sizes in pediatric formulations can pose a significant analytical challenge. In dissolution experiments, where usually only one dosage unit is measured, small dose strengths can result in difficulties in capturing all timepoints due to limitations in analytical sensitivity. For scalable formulations such as minitablets or granules, it is important to define the tested dose, e.g., the content of a stick pack or a defined spoon of granule. Unlike adult tablets, these small formulations may display coning like behavior, sticking, or floating that require adjustments in the dissolution setup.

For media type and volume selection BCS classification and overall solubility is usually considered. Smaller dose strengths might not require the same amount of surfactant as the adult formulation. In contrast, however, a changed formulation behavior or release mechanism, e.g., agglomeration or sticking either within the drug product itself or to the dissolution apparatus, might result in the need for surfactants, which are not used in the adult dissolution method. For BCS classification, the solubility of the highest dose in 250 mL is measured. For parallel developed pediatric and adult formulations, the adult BCS classification is often used. However, the fluid volume (250 mL) is not representative for the fluid intake volume during pediatric drug administration. Although pediatric approaches for the BCS have been proposed and discussed for some time now, so far, no official consensus has been reached (*36–39*). However, as different fluid volumes and/or the use of the largest pediatric dose strength often would result in a change in BCS, it still may make sense to at least discuss this topic during formulation development.

Myth: Multiple Strengths Will Always Use the Same Method

Although with sufficient justification it is possible to apply the same dissolution method conditions across varying product strengths, this will not always be the case, and it is important that those developing dissolution methods do not make this assumption without adequate testing and justification. As with the other myths, applying the same method across strengths during development without proper testing could lead to robustness or method discrimination concerns. As USP <1092> recommends being at sink conditions for a developed method, different strengths may have different media requirements (i.e., composition or volume) (*2*). For example, a higher strength may need the introduction of higher surfactant level to fully solubilize the active, or less surfactant may be suitable as the active strength is decreased. Media volumes may also need to be adjusted, which can result in changes to the hydrodynamics/fluid flow, which then impact the dissolution behavior (*40*). As additional strengths are developed, the formulation, drug load, dosage form and/or manufacturing process may all potentially change which could impact the API release and therefore the necessary dissolution method conditions. However, it may also be possible that different strengths may perform similarly, and use of the same method could therefore be justifiable.

The FDA Dissolution Methods Database summarizes dissolution method conditions for approved products (*6*). Within this compiled database there are several products for which the same dissolution method conditions have been applied across varying strengths. For example, 20 and 40 mg indomethacin capsules both have the same basket method. Candesartan cilexetil tablets at 4, 8, and 16 mg strengths also all have the same paddle method, with 0.35% polysorbate 20 in 0.05 M phosphate buffer pH 6.5 as the medium. In comparison, there are also many examples for which different conditions have been developed for different product strengths. Although 4, 8, and 16 mg candesartan cilexetil tablets have the same method conditions as mentioned above, when the tablet strength was increased to 32 mg, a new method using 0.70% polysorbate 20 in 0.05 M phosphate buffer pH 6.5 was developed. Table 2 summarizes some additional examples where method conditions were altered for varying strengths. Examples selected show that parameters such as media composition, media volume, paddle speed and apparatus have all been altered across developed product strengths.

In summary, a change in strength does not necessitate the use of the same dissolution method, although using the same conditions is not atypical and is acceptable if justifiable (i.e., different strengths have comparable

Table 2. Extracts From U.S. FDA Dissolution Database (6) Showing Method Modifications for Different Product Strengths

Method Difference	Drug & Strength	USP Apparatus	Speed	Dissolution Medium	Medium Volume	Sampling Timepoints
Media volume	Baclofen tablets (10 & 20 mg)	II (paddle)	25	50 mM acetate buffer, pH 4.5	500 mL (10 mg) 1000 mL (20 mg)	5, 10, 15, 30 min
Media volume	Brivaracetam tablets (2.5, 5, 10, 25, 50, 75, & 100 mg)	II (paddle)	50	Phosphate buffer, pH 6.4	500 mL (2.5 & 5 mg) 900 mL (10, 25, 50, 75, & 100 mg)	5, 10, 15, 20, & 30 min
Media volume	Elacestrant dihydrochloride tablets (100 & 400 mg)	II (paddle)	75	0.01N HCl	500 mL (100 mg) 1000 mL (400 mg)	5, 10, 15, 30, 45, & 60 min
Surfactant level	Dolutegravir sodium tablets (10, 25 & 50 mg)	II (paddle)	50	10 mg: 0.01 M PB, pH 6.8 25 mg: 0.01 M PB, pH 6.8 & 0.15% (w/v) SLS 50 mg: 0.01 M PB, pH 6.8 & 0.25% (w/v) SLS	900 mL	5, 10, 15, 20, 30, & 45 min
Surfactant level	Ibrutinib tablets (140, 280, 420, & 560 mg)	II (paddle)	75	140 & 280 mg: 3.0% (w/v) polysorbate 20 in 50 mM PB, pH 6.8 420 & 560 mg: 6.0% w/v polysorbate 20 in 50 mM PB, pH 6.8	900 mL	10, 20, 30, 45, & 60 min
Paddle speed	Clozapine tablets (12.5, 25, 100, 150, & 200 mg)	II (paddle)	50 rpm (12.5, 25, & 100 mg) 75 rpm (150 & 200 mg)	Acetate buffer, pH 4.5	900 mL	5, 10, 15, 20, & 30 min
Combined changes	Levetiracetam tablets (1 & 1.5 g, 500 & 750 mg)	1 & 1.5 g: III (reciprocating cylinder)	15 dips/min	Sodium acetate buffer, pH 4.5	900 mL	1, 2, 4, 6, 8, 10 & 12 hours
		500 & 750 mg: I (basket)	100 rpm	0.05 M phosphate buffer, pH 6.0	900 mL	1, 2, 4, 6, 8 and 12 hours

HCl: hydrochloric acid; PB: phosphate buffer; USP: United States Pharmacopeia; SLS: sodium lauryl sulphate.

profiles under specified method conditions). The examples provided here as well as the full summary in the compiled Dissolution Methods Database point to the need to fully assess method conditions across strengths (*6*).

GENERAL

Partial Myth: The Basket or Paddle Apparatus Can/ Cannot Be Used to Mimic Dissolution In Vivo

Typical paddle/basket methods cannot reflect some key aspects influencing dissolution in vivo, most notably dynamic media change and the motility patterns in the GI tract. However, despite this, over recent decades significant progress has been made in the development of dissolution media that at least mimic the key in vivo environments experienced by a dosage form/drug in the GI tract, maximizing the opportunity to mimic in vivo performance.

In the late 1990s, the introduction of biorelevant media marked the beginning of evaluating how dosage forms perform within the GI lumen (*41*). Since that time, various new media have been put forward, which now allows for the simulation of nearly every section of the GI tract in both fasted and fed conditions. Current findings suggest that the level of complexity and biorelevance essential for anticipating in vivo release is influenced by the API, the dosage form, and the conditions under which it is given (*42*). The biorelevant compositions can be as simple as water (level 0) or as complex as mixtures containing physiologically relevant substances like enzymes, products of fat digestion, and bile components (level 3), with their biopredictive potential being contingent on the drug and the formulation's robustness and sensitivity to GI conditions.

The levels concept can be combined with the different types of dissolution testing equipment that are commercially available to come up with a wide variety of potential dissolution tests. In this context, the OrBiTo Dissolution Decision Tree provides a helpful guide to selecting an appropriate dissolution method, based on dosage form type, drug characteristics and availability of equipment (*43*). The proposed methods can be biorelevant and/or biopredictive (*44*). In principle,

biorelevant methods are designed to closely mimic various physiological processes including dissolution in relevant biological fluids, while biopredictive methods produce dissolution profiles which can predict pharmacokinetic profiles.

For biorelevant methods, it is often required to apply lower volumes than in the compendial methods, closer hydrodynamics to physiology (e.g., with peristaltic contractions), and transfer of fluids, as well as use of an absorption system (*45*). For instance, poorly soluble weak bases pose a greater risk than neutral compounds for precipitation in the GI tract. Consequently, it is suggested to select a biorelevant pH shift dissolution method, where drug release is measured to mimic gastric then intestinal conditions sequentially (*46*, *47*). Further complexity arises with the implementation of the dissolution-transfer methodologies which allow for simulating the kinetics of gastric emptying, motility, digestion, intestinal secretion, and/or permeation (*48*). Those physiological processes may synergistically influence oral drug absorption.

In the case where a biorelevant method is biopredictive, the in vitro dissolution profiles can then be used to predict pharmacokinetic profiles. Although this is traditionally achieved by establishing a classical in vivo-in vitro correlation, more recently it has been shown that physiologically-based biopharmaceutics models (PBBMs) can also verify the clinical relevance of the dissolution method (*49*). In principle, these models mimic physiological conditions and incorporate dissolution information while accounting for relevant physicochemical and physiological factors leading to a prediction of systemic exposure versus time. Furthermore, they are extensively utilized in industry for examining whether a dissolution QC method is indicative of the drug product performance. Successful validation of these models may enable the development of a dissolution "safe" space (*50*). Those are the boundaries defined by in vitro specifications, within which drug product batches are anticipated to be bioequivalent to one another, or less optimally, but still possible, bioequivalent to the pivotal clinical batch(es).

CONCLUSION

Dissolution testing remains a pivotal tool in pharmaceutical development, yet its effective application is frequently hampered by enduring myths and outdated practices. As discussed throughout this article, misconceptions surrounding dissolution media selection, hydrodynamics, analytical sampling, filters and sinkers, and formulation-specific approaches can significantly impact data interpretation, method robustness, and ultimately, the development timeline of pharmaceutical products. This myth-busting examination, grounded in the collective experience and current best practices of the IQ Consortium experts, underscores the necessity for critical evaluation of historical assumptions and continuous method validation.

Crucially, dissolution method development should be viewed as a scientific endeavour that demands thoughtful justification for every procedural choice—ranging from media composition to apparatus configuration and analytical techniques. Surfactant selection must account for physicochemical properties, matrix interactions, and true in vivo relevance, rather than relying on generic concentrations or default to the most used components. Similarly, hydrodynamic conditions, whether it is rotation speed, vessel design, or the use of sinkers and filters, must be systematically optimized for each formulation to ensure both discriminative power and robustness, rather than following arbitrary conventions.

The persistence of myths—such as universal applicability of standard pH and buffer strengths, or the belief that rapid dissolution is always ideal—demonstrates a pressing need for greater dissemination of experimental evidence over established dogma. Moreover, the diversity in formulation strategy, particularly when extrapolating methods across product strengths or paediatric/adult indications, highlights the inadequacy of one-size-fits-all solutions. Instead, dissolution method development must remain adaptable, data-driven, and relevant to the evolving landscape of drug products and regulatory expectations. By addressing these prevalent misunderstandings, the authors hope to empower scientists to build more reliable, biorelevant, and informative dissolution methods. This enhanced rigor will in turn support more efficient formulation development, better risk mitigation, and, ultimately, the delivery of safer and more effective medicines to patients. Embracing continual learning and evidence-based practice is key to overcoming the inertia of tradition and promoting true innovation in dissolution science.

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