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The scope of articles is limited to dissolution or disintegration topics as the major focus. Articles on formulation development where dissolution is just one test of many should not be submitted.

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The November 2026 issue will include a *Stimuli* article for operation of USP apparatus 4; research articles on azithromycin tablets, paracetamol tablets, dynamic stomach-intestine system, profile comparisons using Weibull fitted parameters and global biowaiver guidelines; as well as the Q and A feature.

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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

*Corresponding author

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.

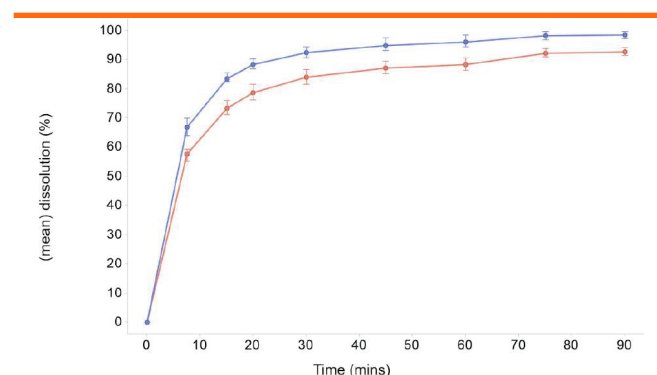


Figure 1. Impact of deaeration on the dissolution performance of an immediate-release product with 0.1% CTAB in the medium. Red = no deaeration; blue = with deaeration).
CTAB: cetyltrimethylammonium bromide.

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 ($\text{mol}/\text{cm}^2/\text{s}$) 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.

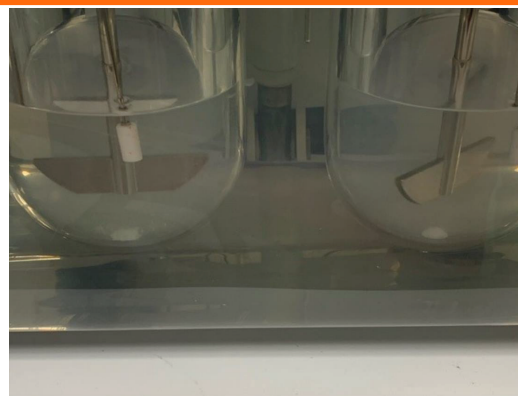


Figure 2. Two immediate-release tablets with the same API and formulation but different secondary manufacturing processes. **Left:** Process A exhibits dynamic coning, acceptable variability and complete release. **Right:** Process B exhibits static coning, unacceptable variability and incomplete release. 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 Sinkers 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.

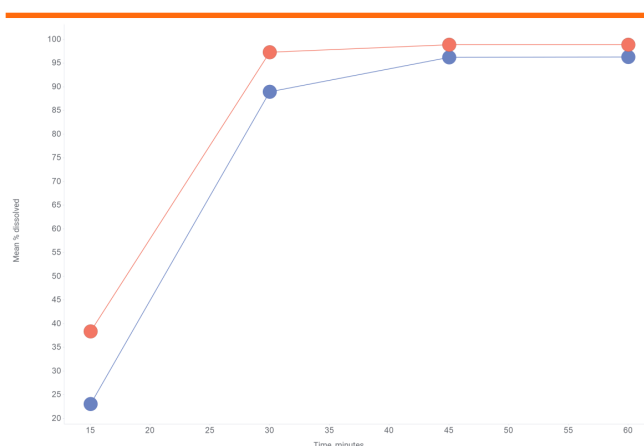


Figure 3. Impact of sinker type on mean dissolution of HPMC capsule product containing a semisolid matrix. Red = 8 coil helical sinker; blue = Sotax style sinker (15.5 x 5.0 mm). HPMC: hydroxypropyl methylcellulose.

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 $\geq 85\%$ 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 ($\geq 85\%$) 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 $\geq 85\%$ 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 $\geq 90\%$. 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.

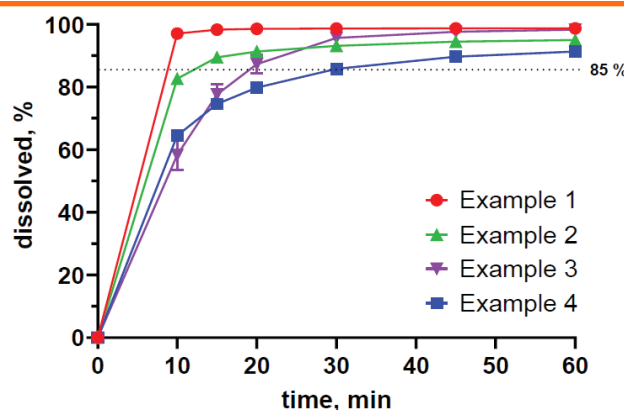


Figure 4. Examples for different dissolution profiles typically seen in immediate-release formulations.

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).

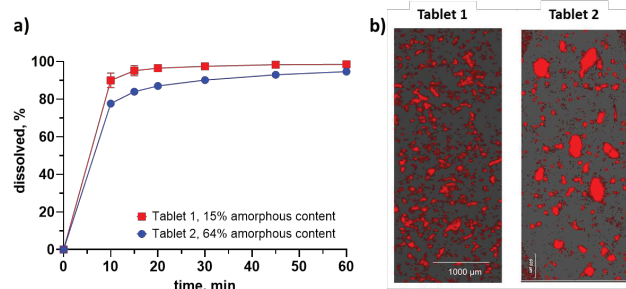


Figure 5. (a) Dissolution profiles of two 10-mg tablets containing API with 15% (tablet 1, red) and 64% (tablet 2, blue) amorphous content. (b) Raman mapping of cross-sections of tablets 1 and 2.

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, μ DISS 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	Brivacetam 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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Variability in Quality Attributes of Commercial Alpha-Lipoic Acid Dietary Supplements: Evidence from Pharmacopoeial Testing

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ABSTRACT

Introduction: Alpha-lipoic acid (ALA) is a bioactive compound marketed as a dietary supplement (DS) worldwide.

Methods: This study assessed the quality of nine commercial ALA DS formulations (seven hard capsules, two gastro-resistant capsules) from the Serbian market using *European Pharmacopoeia* tests for solid dosage forms: uniformity of mass (2.9.5), content determination by UV–Vis spectrophotometry, disintegration (2.9.1), and dissolution (2.9.3) in 0.5% sodium lauryl sulfate medium at 37 °C (United States Pharmacopeia apparatus 1 [basket], 900 mL, 100 rpm). **Results:** Measured ALA content ranged from 77.79% to 120.39% of the declared amount, with notable intrabatch variability in some products. Five formulations failed at least one test: two failed uniformity of mass (C, D), two failed content uniformity (B, D), one did not disintegrate within 30 min (H), and three failed dissolution criteria (B, F, H). Our findings reveal an inconsistent quality of ALA DS. **Conclusion:** There is a need for a transparent and credible quality signal that would inform consumers, guide clinicians, and motivate manufacturers to meet higher standards and more consistent product performance.

KEYWORDS: alpha-lipoic acid (ALA), dietary supplements, dissolution testing, UV–vis spectrophotometry

INTRODUCTION

Alpha-lipoic acid (ALA), also known as thioctic acid, is a naturally occurring antioxidant globally marketed for its potential health benefits in metabolic disorders and oxidative stress-related conditions (1–4). In Serbia, as well as in other European countries, ALA is registered both as a drug and a dietary supplement (DS), even at the same doses (5). In contrast, in the USA, ALA is marketed solely as a DS and is not approved as a prescription or over-the-counter drug (4).

In most jurisdictions, DS are regulated as a category of food (6), with regulatory oversight focused primarily on safety and labeling rather than on efficacy or pharmaceutical quality. These products can be registered and marketed without prior demonstration of therapeutic

efficacy or formal quality control testing (7). As a result, the responsibility for ensuring quality, such as content uniformity, disintegration, and dissolution, lies primarily with the manufacturer, and pharmacopoeial standards are not matched by the regulations (7, 8).

According to the USP, a high-quality DS is one that, besides being safe (free from harmful levels of contaminants) and labelled accurately, contains the listed ingredients in the declared potency and amounts, ensures bioavailability, and is manufactured according to established current Good Manufacturing Practices (cGMP) (8). However, adherence to USP standards is voluntary, and the U.S. Food and Drug Administration (FDA) does not require DS to meet USP quality benchmarks (7, 9, 10). Instead, the United States Pharmacopeia (USP) provides a third-party

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verification program as a tool for manufacturers to ensure DS quality (10).

Multiple studies have documented discrepancies between declared and actual active ingredient content in commercially available DS raising concerns about their quality, safety, and efficacy (4, 11–15). ALA, in particular, presents formulation challenges due to its poor water solubility, instability in gastric acid, and extensive hepatic metabolism, resulting in an estimated oral bioavailability of only 30% (16). Therefore, the pharmaceutical and technological characteristics of ALA dosage forms can significantly affect its bioavailability and, consequently, its clinical effects (7).

The quality control of DS is important because they easily cross international borders in today's increasingly globalized marketplace (17). The global use of DS is on the rise and with the lack of mandatory quality testing in most regulatory systems, there is a pressing need for independent, evidence-based assessments of their quality (18–20).

The aim of the study was to investigate the quality of commercially available DS containing ALA by evaluating mass and content uniformity, disintegration time, and dissolution profiles, using analytical methods and regulatory acceptance criteria for solid dosage forms prescribed by the *European Pharmacopoeia*, 11th edition (EP).

METHODS

The experimental part of the research was conducted in the laboratories of the Department of Pharmacy, Faculty of Medicine, University of Novi Sad. A total of nine formulations of DS containing ALA (randomly labeled A–I) were analyzed in the study, including two gastro-resistant capsule formulations (B and I) and seven hard capsule formulations. The investigated DS were purchased from local pharmacies in Novi Sad, Serbia, and some samples were donated by the manufacturers. All samples were stored in their original packaging, in a dry and dark place at room temperature (20–25 °C).

Uniformity of Mass

Uniformity of mass was conducted according to EP 2.9.5. Uniformity of mass of single-dose preparations (21). For each sample, 20 randomly selected units were weighed using an analytical balance (Radwag, Radom, Poland). The samples were considered to comply with the specification if not more than two of the individual masses deviated from the average mass by more than the permitted percentage deviation: $\pm 10\%$ for capsules

with an average mass of less than 300 mg, and $\pm 7.5\%$ for capsules with an average mass of 300 mg or more. No units were allowed to deviate by more than twice the specified percentage (21).

Determination and Uniformity of Content

The content of ALA was determined by a previously published method (22). The stock standard solution of ALA was prepared by dissolving ALA standard (Farmalabor, Canosa di Puglia, Italy) in methanol (Lach-Ner, Neratovice, Czech Republic) at a concentration of 30 mg/mL. Seven working standard solutions were prepared by diluting the stock solution to obtain concentrations ranging from 0.046875 to 3 mg/mL. The absorbance of each solution was measured, and the calibration curve exhibited linearity within the observed concentration range ($R^2 = 0.9975$).

For each tested product, 10 randomly selected units were extracted with 10 mL of methanol (Lach-Ner, Neratovice, Czech Republic) using an ultrasonic bath (Velleman, VTUSC2, Gavere, Belgium) for 16 minutes without heating. The extracts were centrifuged at room temperature for 5 minutes at 4000 rpm (SL 16R Thermo Fisher Scientific, Osterode am Harz, Germany). Depending on the declared ALA dose per dosage unit, the solutions were further diluted: 10-fold for 100 mg and 150 mg ALA products, 20-fold for 200 mg and 300 mg ALA products, and 40-fold for 600 mg ALA products.

The absorbance of the prepared solutions was measured using a single-beam UV-Vis spectrophotometer (8453 G1103A, Agilent Technologies, Santa Clara, CA, USA) at 333 nm (22). Quartz cuvettes with a 1 cm path length were used for all UV-Vis measurements. The ALA content was determined for 10 individual dosage units, and the mean value and standard deviation were calculated.

The formulation was considered to comply with the pharmacopoeial requirement if not more than one out of 10 units deviated from the average content by more than $\pm 15\%$, and none deviated by more than $\pm 25\%$ (21).

Disintegration Testing

The disintegration testing of capsules was performed according to the EP 2.9.1. using a standard disintegration apparatus (Erweka ZT3, Langen, Germany). Test A was conducted on six units per sample. The immersion fluid was distilled water, maintained at 37 ± 2 °C. Disintegration was monitored visually, and the disintegration time was recorded as the time when the last unit disintegrated completely.

According to the general monographs of the EP, the disintegration time limit for hard capsules was 30 minutes (21).

Dissolution Testing

The dissolution rate of ALA from the tested formulations was determined using USP apparatus 1 as described in EP 2.9.3 (21).

Compliance with pharmacopoeial criteria was evaluated according to EP 2.9.3 and 5.17.1. A formulation met the acceptance criteria at stage S1 if all six units released at least 80% of the determined amount of ALA within 45 minutes. To eliminate variability caused by deviations between the declared and the actual content of the active substance, dissolution results were calculated based on the determined content of each formulation.

Calibration

The calibration curve was constructed using ALA standard (Farmalabor, Canosa di Puglia, Italy). The initial UV-Vis absorption spectrum of the standard ALA solution was recorded in the range of 200–400 nm, with a maximum absorption observed at 334 nm. For calibration, the stock solution was prepared by dissolving ALA in 0.5% (w/v) sodium lauryl sulfate (SLS) solution at a concentration of 1 mg/mL. Serial dilutions were made to obtain working standard solutions with concentrations ranging from 0.0625 to 1 mg/mL. The calibration curve exhibited linearity across the entire concentration range with a correlation coefficient $R^2 = 0.9989$.

Dissolution Procedure

The dissolution medium was prepared by dissolving SLS (Lach-Ner, Neratovice, Czech Republic) in purified water obtained by laboratory distillation (AC-L8, Optic Ivymen System, J.P. Selecta, Barcelona, Spain) to a final concentration of 0.5% (w/v). This medium was selected due to the known low water solubility of ALA to ensure complete and reproducible dissolution suitable for quantitative analysis.

Dissolution testing was performed using a dissolution tester (DT 600, ERWEKA GmbH, Langen, Germany) with USP apparatus 1 (basket) and a volume of 900 mL of dissolution medium, maintained at $37 \pm 0.5^\circ\text{C}$, with a stirring speed of 100 rpm for all formulations.

Sampling was performed using an autosampler equipped with cannula filters of 10 μm porosity (ERWEKA GmbH, Langen, Germany), enabling immediate and consistent filtration of samples to eliminate undissolved particles prior to spectrophotometric analysis. Aliquots of 5 mL

were withdrawn at time points of 5, 15, 25, 35, 45, and 60 minutes, with immediate replacement by the same volume of fresh, preheated medium. The amount of dissolved ALA was determined by UV-Vis spectrophotometry at 334 nm. Dissolution testing was conducted on six dosage units for each tested product.

A full analytical method validation was not performed. However, the UV-vis method applied for dissolution sample analysis was based on a previously published procedure for ALA determination and was considered fit for purpose for comparative dissolution testing (7).

RESULTS

Uniformity of Mass and Content

Out of the nine ALA DS, formulation C failed the uniformity of mass test, as 8 out of 20 capsules deviated from the average mass by more than $\pm 7.5\%$. Formulation D failed the test due to 11 individual capsules deviating from the average mass by more than $\pm 10\%$.

According to test B for uniformity of content of single-dose preparations (EP 2.9.6), formulations B and D failed to comply with the acceptance criteria, as more than three individual dosage units fell outside the limits of 85–115% of the average content. All other formulations (A, C, E, F, G, H, and I) complied with the specified acceptance criteria. These results are presented in Table 1.

Disintegration and Dissolution Test

All disintegration times are shown in Figure 1. Only one formulation (H) failed to disintegrate within 30 minutes.

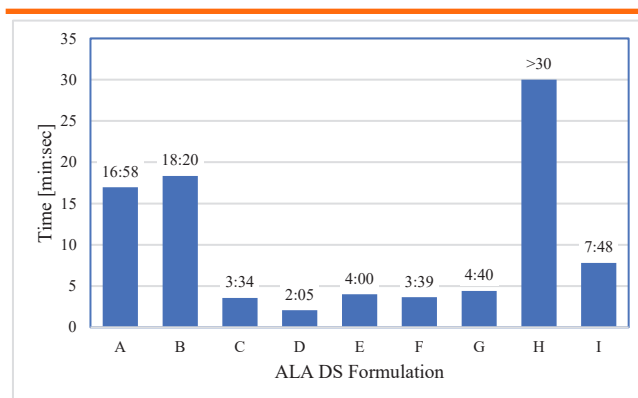


Figure 1. Disintegration times for the alpha-lipoic acid dietary supplement (ALA DS) formulations in distilled water at 37°C .

The dissolution profiles of the nine tested DS formulations containing ALA are presented in Figure 2. According to the EP dissolution criteria for conventional-release dosage forms, formulations B, F, and H did not meet the acceptance criteria (21). Marked differences in dissolution behavior were observed among the tested formulations.

Table 1. Uniformity of Mass and Content for ALA DS Formulations

Formulation	Lot No.	Expiry Date	Declared Content (mg)	Measured Content (mg)	
				Mean $\pm$ SD	% of Declared
A	L0724061	7/27	300	240.97 $\pm$ 17.49	80.32 $\pm$ 5.83
B	0124501	1/26	600	490.69 $\pm$ 46.89	81.78 $\pm$ 7.81
C	300067	8/26	300	277.11 $\pm$ 25.55	92.37 $\pm$ 8.52
D	C47S460724	7/27	200	192.66 $\pm$ 25.27	96.33 $\pm$ 12.64
E	046426	8/27	100	111.55 $\pm$ 2.80	111.55 $\pm$ 2.80
F	0403	5/27	300	361.18 $\pm$ 39.06	120.39 $\pm$ 13.02
G	0081024	10/26	300	290.14 $\pm$ 13.11	96.71 $\pm$ 4.37
H	0324115	3/27	300	311.80 $\pm$ 25.19	103.93 $\pm$ 8.40
I	1023012	10/25	150	116.68 $\pm$ 10.19	77.79 $\pm$ 13.59

ALA DS: Alpha-lipoic acid dietary supplement.

The highest dissolution was observed in formulation A (123.97%), and formulation H reached only 7.15%.

Standard deviation values for dissolution profiles varied considerably among formulations and across time points, reflecting intra-formulation variability in dissolution behavior. Formulations A and B exhibited particularly high SD values at early time points (e.g., SD up to 29.24% for formulation A at 25 minutes and 16.00% at 5 minutes), suggesting inconsistent initial release kinetics within the tested units. In contrast, formulations such as E, G, and H generally demonstrated lower SD values across most sampling points, indicating more consistent dissolution performance.

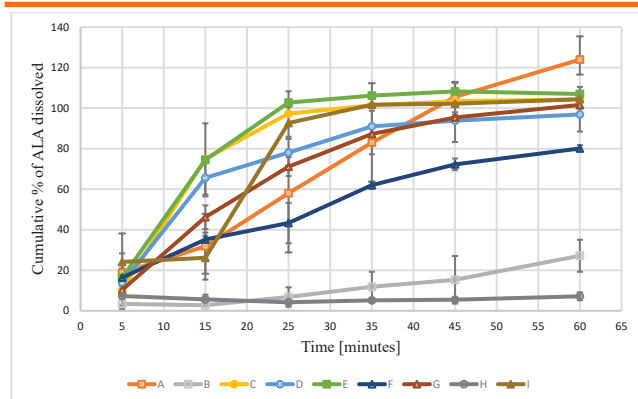


Figure 2. Dissolution profiles of commercial alpha-lipoic acid (ALA) formulations at 37 °C in 0.5% sodium lauryl sulphate medium. Values represent mean $\pm$ SD ($n = 6$).

DISCUSSION

Generally, although various analytical methods for ALA, such as high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), UV-Vis spectrophotometry, capillary electrophoresis, and electrochemical detection have been developed,

relatively few studies have applied these techniques to analyze commercially available ALA DS (12, 14, 23–26).

As highlighted by Durazzo et al., the dissemination of such findings remains an area in need of further improvement and attention (17). Despite analytical methods being transferable internationally through standardized scientific channels, reports concerning the actual quality of DS are rarely communicated globally, limiting transparency and consumer awareness (17).

In the present study, mass and content uniformity testing identified inconsistencies, with three of nine formulations failing to meet mass uniformity, content uniformity, or both. Variability in ALA content (77.79% $\pm$ 13.59%–120.39% $\pm$ 13.02%) is consistent with Ravanic et al., who reported a wide range (53–100%), whereas Lalić-Popović et al. reported 98–107%, and Sitton et al. also observed 98% relative to label claims (12, 14, 26). Both consumers and health professionals expect that DS contain the ingredients and amounts listed on their labels (17). Thus, variability in average ALA content indicates a potentially misleading declaration, which may compromise consumer trust and underscores the need for stricter quality control and regulatory enforcement in the DS market.

In addition to the average content, variability between individual units within the same batch is a critical quality parameter. High intrabatch variability can lead to uneven therapeutic effects or suboptimal outcomes. In this study, formulations D, F, and I exhibited relatively high standard deviations (12.64%–13.59%), indicating notable intrabatch variability.

Capsule content uniformity depends on several key formulation and processing factors, including filler-binders, compatibility between the active pharmaceutical

ingredient (API) and excipients, and the particle size compatibility among all components (29). Significant particle size differences can cause segregation and uneven distribution. Although segregation is less likely when the API constitutes a large portion of the capsule fill weight, particle size compatibility with added excipients remains vital to maintain uniformity. In the current study, all analyzed formulations contained 150–600 mg of API per capsule, indicating that the API constituted a substantial proportion of the total fill weight. Proper blending techniques and flow optimization are therefore essential to ensure consistent capsule mass and content. Additionally, attention must be paid to possible chemical incompatibilities between excipients and the API, particularly under high-speed filling conditions where heat may promote undesired interactions (29).

The efficacy of a DS is determined not only by the amount of the active ingredient but also by the formulation's performance and design. DS formulation can influence the fraction absorbed, delivery to the target within a defined period, and, ultimately, the benefits it may provide to the users (17).

ALA, a compound with low solubility and high permeability, is classified as a Biopharmaceutics Classification System (BCS) class II substance. For compounds in this class, dissolution testing is the most appropriate and informative tool, as dissolution is the rate-limiting step in their absorption (14, 29, 30). Without appropriate disintegration or dissolution rates, ALA will not be available at the absorption site and thus will not be absorbed despite its good permeability.

The results of this study showed that disintegration outcomes varied, with one hard capsule (formulation H) failing to disintegrate within the 30-minute limit. The exact formulation did not pass the dissolution test, indicating that poor disintegration substantially impairs dissolution and downstream bioavailability. Besides formulation H, two more formulations (B and F) failed to meet dissolution criteria. These observations are consistent with Lalić-Popović et al., who reported that at a speed of 100 rpm, two out of five ALA DS dissolved 80% of their content within 45 minutes (14).

Among the nine analyzed DS, two pairs demonstrated similar dissolution profiles. This finding indicates that, despite the general variability in formulation and manufacturing practices across products, certain formulations may share comparable technological. However, given the overall heterogeneity of the remaining products, these matching profiles appear more

coincidental than the result of standardized formulation practices across manufacturers.

Although in vitro disintegration and dissolution tests do not directly predict absorption or bioavailability (unless such a link has been experimentally established for a specific product), they remain important tools for assuring DS quality and consistency. Products that fail these tests may not properly disintegrate or release their active ingredients, leading to reduced or absent absorption and, consequently, failure to achieve the expected health benefits (17).

In the United States, FDA oversight focuses on safety, but monitoring the rapidly growing number of DS on the market exceeds available resources. At the same time, consumers and clinicians can consult the Dietary Supplement Label Database (DSLDB) and look for evidence of third-party testing to verify label accuracy and performance (31, 32). For example, the USP Verified Mark indicates a DS has passed USP's voluntary, third-party verification program, confirming identity, strength, purity, performance, and cGMP-compliant manufacturing (33).

Limitations

DS included in this study were purchased on the Serbian market, but most of these products are widely available internationally, and the findings are therefore informative for evaluating DS quality and consistency beyond the local context. However, a relatively small number of products and a one-batch-per-product design may limit the results of our study.

CONCLUSION

The findings of our study reveal heterogeneity in some of the critical quality attributes: mass uniformity, content uniformity, disintegration, and dissolution across commercial ALA DS. Out of nine tested formulations, five did not pass one or more pharmacopoeial tests for solid dosage forms, revealing variability in product quality, consistency, and performance. For the DS industry, this underscores the importance of formulation characteristics and process control to ensure ALA DS quality.

While stronger statutory control and harmonized enforcement would be the most direct route to improving DS quality, achieving such reforms is slow, politically complex, and in some settings not feasible in the near term. Establishing an independent third-party verification program in Europe could be one way to provide a quality signal for consumers and clinicians, as well as to motivate manufacturers to meet higher standards.

DISCLOSURES

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Comparative Analysis of Statistical Methods for Modelling the Dissolution Profile of a Bentonite-Based Suppository

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ABSTRACT

Introduction: The advancement of modified-release pharmaceutical forms, such as bentonite-based suppositories, requires accurate modeling of the active ingredient's release kinetics. This study aimed to evaluate the capacity of four canonical release-kinetics models (Weibull, Higuchi, first-order, and Korsmeyer–Peppas) to define and describe the release profile of tramadol from bentonite-based suppository mixtures. **Methods:** Seventeen bentonite-based tramadol suppository mixtures were prepared according to a design comprising polyethylene glycol (PEG) and bentonite. All dissolution profiles were acquired using a USP basket apparatus. The release-kinetics models were fitted within both frequentist and Bayesian hierarchical frameworks. The frequentist analysis employed Akaike information criterion (AIC)-based selection to rank model performance, and the Bayesian approach incorporated informative priors and a hierarchical structure to capture intermixture variability. The comparison of the models employed leave-one-out cross-validation (LOO) and the widely applicable information criterion (WAIC). **Results:** The frequentist and Bayesian approaches both identified the Weibull model as the most suitable descriptor of the release behavior for tramadol. The Weibull model showed better performance in describing tramadol release. The hierarchical Bayesian method proposes many advantages in terms of uncertainty quantification and robustness. The complementary use of frequentist and Bayesian techniques offers a rigorous paradigm for sustained-release mixture development. **Conclusion:** Our study affirms the applicability of bentonite as a biocompatible, functional excipient for modifying drug release behavior of suppositories.

KEYWORDS: Bentonite, tramadol, suppository, dissolution profile, Bayesian statistics

INTRODUCTION

Tramadol is an analgesic drug indicated for moderate to severe pain (1, 2). This synthetic opioid drug discovered in 1962 and marketed as Tramal in 1977 by Grünenthal GmbH (3). In the United States, the total number of tramadol prescriptions exceeded 30 million in 2021, making it one of the most

prescribed opioids in the country (4–7). The need for therapeutically effective drug delivery systems has led researchers to develop new strategies (8). Rectal drug delivery uses pharmaceutical technology to control the release and delivery of active pharmaceutical ingredients (APIs) in the rectal ampoule (9–11). Suppositories remain among the most commonly used dosage forms. Many

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studies have focused on accelerating or slowing API release from suppositories by using coatings, emulsions, hydrogels, layering, nanoparticles, osmotic systems, thermoreversible matrices, and gelling agents (10, 12). These sustained-release mixtures are especially valuable for patients who cannot tolerate oral dosage forms or require long-acting preparations (13).

Bentonite is a natural clay composed mainly of montmorillonite (14, 15). It serves as a nontoxic, nonirritating matrix in topical gels and, on occasion, oral suspensions. Previous work has shown that alginic-acid-incorporated bentonite matrices can sustain morphine release in rabbits to manage nocturnal pain (16). A bentonite-based tramadol suppository could similarly provide prolonged analgesia compared to commercially available mixtures (16).

The study of active molecule dissolution kinetics and their optimization is traditionally based on frequentist statistics to select the best model. Special cubic polynomial fitting and Akaike information criterion (AIC)-driven model selection via DDSolver produce point estimates and rank candidate models by fit quality. Although these frequentist methods are well established, they yield limited insight into parameter uncertainty and batch variability (17).

Bayesian hierarchical modeling overcomes these limitations by treating kinetic parameters as random variables with prior distributions and by explicitly modeling variability at multiple levels (18, 19). Informative priors leverage existing knowledge of release-rate constants, while Markov Chain Monte Carlo sampling yields full posterior distributions that capture uncertainty (20, 21). Model comparison via leave-one-out (LOO) and WAIC balances fit and complexity, enabling rigorous ranking (18).

This study will analyze dissolution data for 17 tramadol suppository mixtures, varying in PEG molecular weights and bentonite content, using both frequentist and Bayesian hierarchical approaches. Four competing kinetic models will be implemented within each framework and compared for their performance.

METHODS

Materials and Reagents

All chemicals used in this study were of analytical grade and suitable for pharmaceutical research applications. The details of each material, including manufacturer, catalog reference, and reagent grade, are summarized in Table 1.

Table 1. Chemicals Used in the Study

Chemical	Manufacturer	Reagent grade
Tramadol hydrochloride	Merck, Germany	Pharmaceutical grade
PEG 1540, 4000, and 6000	Hoechst Chemikalien (Werk Gendorf), Germany	Analytical / pharmaceutical grade
Bentonite	Sigma-Aldrich, England	Analytical grade
Ethanol 96%	Sigma-Aldrich, England	HPLC grade
Mono-sodium phosphate	Sigma-Aldrich, England	Analytical grade
Di-sodium phosphate	Sigma-Aldrich, England	Analytical grade

PEG: polyethylene glycol

Preparation of Suppositories

The tramadol suppositories were prepared following a systematic mixture design aimed at assessing how variations in matrix composition influence drug release behavior. Seventeen formulations were developed by adjusting the ratios of polyethylene glycol (PEG 6000, 4000, and 1540) and bentonite, while maintaining a constant amount of tramadol to assess matrix composition effects on drug release. The formulations covered a wide range of PEG and bentonite proportions, including matrices without bentonite and balanced compositions combining equal PEG ratios. A detailed description of all formulations and their respective component ratios is presented in Table 2.

Table 2. Composition of Tramadol Suppository Formulations

Formulation	PEG 6000 (g)	PEG 4000 (g)	PEG 1540 (g)	Bentonite (g)
1	1.33	1.47	0.00	0.20
2	1.00	1.47	0.33	0.20
3	0.67	1.47	0.67	0.20
4	0.33	1.47	1.00	0.20
5	1.33	1.50	0.00	0.17
6	1.00	1.50	0.33	0.17
7	0.67	1.50	0.67	0.17
8	0.33	1.50	1.00	0.17
9	1.33	1.58	0.00	0.08
10	1.00	1.58	0.33	0.08
11	0.67	1.58	0.67	0.08
12	0.33	1.58	1.00	0.08
13	1.00	1.50	0.50	0.00
14	0.50	1.50	1.00	0.00
15	1.00	0.83	1.00	0.17
16	0.50	0.83	1.50	0.17
17	0.99	0.99	0.99	0.03

PEG: polyethylene glycol

The tramadol suppositories were produced using the conventional fusion molding technique under controlled temperature and stirring conditions to ensure homogeneity and stability. The detailed preparation steps are illustrated schematically in Figure 1.

The preparations were analyzed for appearance and hardness according to the *European Pharmacopoeia* guidelines. Appearance was evaluated visually for color, shape, and surface uniformity. Hardness was measured using a tablet hardness tester (Erweka, Germany), and all formulations met the acceptable limit of ≥ 1800 g.

In Vitro Dissolution Testing

The USP basket apparatus for tablets was used for dissolution testing. Three suppositories were tested for each formulation. Dissolution method parameters were presented in Table 3.

Table 3. Dissolution Method Parameters

Apparatus	USP Type 1- Basket
Brand	PHARMA TEST Apparatebau GmbH (Hainburg, Germany)
Medium volume	500 mL
Rotation speed	50 rpm
Medium	Phosphate buffer pH 7.2
Temperature	37 ± 0.5 °C
Sampling times	5, 20, 30, 50, and 60 min

Samples (5 mL) were collected at 5, 10, 20, 30, 50, and 60 mins during dissolution and replaced with fresh medium at 37 ± 0.5 °C to maintain sink conditions (22). The samples analyzed without dilution by UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan), and the concentration was determined at 270 nm according to the tramadol calibration range. The calibration range of tramadol (20–150 $\mu\text{g/mL}$) covered the concentration range of the tramadol product, which is 100 $\mu\text{g/mL}$ (100 ppm) (Fig. 2).

Diffusion Model Fitting

Adsorption kinetics were evaluated using the dissolution profile (16). This study focused on diffusion by evaluating four mathematical models most commonly used in biopharmaceutics (first-order, Higuchi, Korsmeyer-Peppas, and Weibull) (23), independent of physicochemical properties such as the ratio of polymer components and molecular weight of the polymer.

The first-order model refers to a system where the release rate of the API is only a function of the remaining concentration of the API ($F = 100 \times (1 - e^{-k_1 \times t})$). The Higuchi model suggests that the amount of API released from the dosage form is a function of the square root of time ($F = k_H \times t^{0.5}$). Korsmeyer-Peppas is another comprehensive semi-empirical model, which can, in general, define separate release phenomena involving either diffusion or swelling ($F = k_{HP} \times t^{0.5}$).

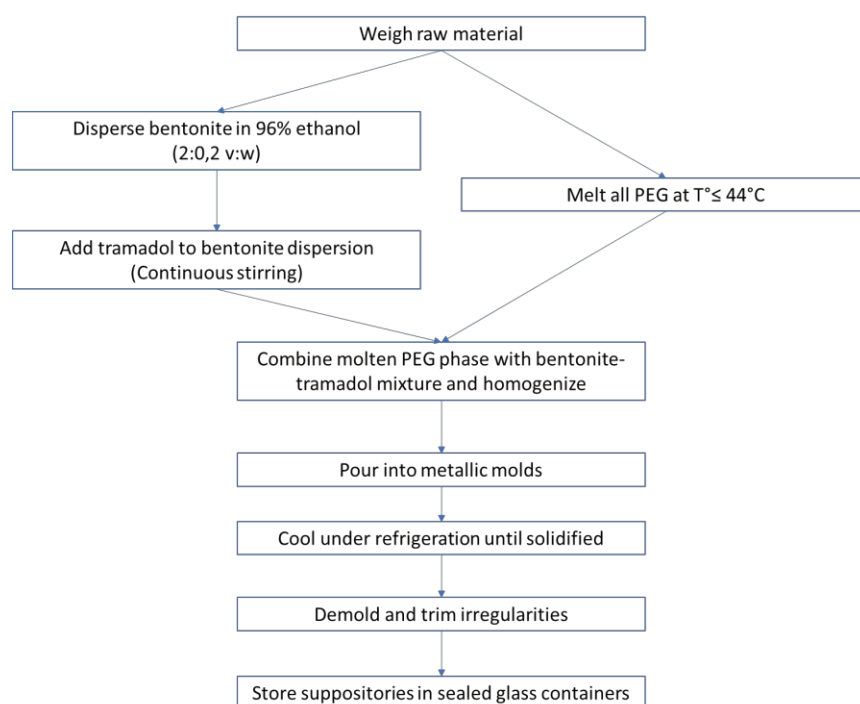


Figure 1. Flowchart for suppositories preparation. PEG: polyethylene glycol.

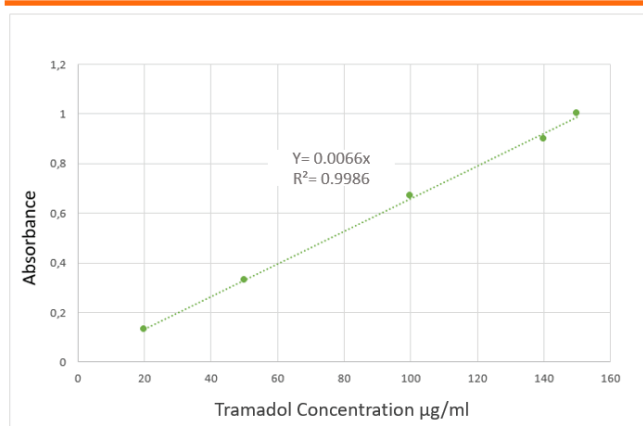


Figure 2. Calibration range of tramadol assay.

According to Weibull model, the logarithm of released ingredient and the logarithm of time have a linear relationship (24). It is initiated on a function originally proposed by Weibull in 1951, and Langenbucher in 1972 adapted the function permitting to describe drug release curves (25). The equation can be expressed as a function (F) of the fraction of drug accumulated in the solution at time (t):

$$F = 100 \times (1 - e^{-(\frac{t-T_i}{\alpha})^\beta})$$

α (the scale parameter) describes the time scale of the process, however, T_i (the localization parameter) defines the latency time of the release process, i.e., how many times being zero (24). β (the exponent of time of Weibull function) is, according to the cited equation, linearly related to the exponent (n) of the power law derived from the analysis of the first 60% of the release curves. The value of β is considered as an indicator that describes the mechanism of transport of a drug through the matrix. $\beta \leq 0.75$ generally indicates Fickian diffusion in either fractal or Euclidian spaces, whereas a combined mechanism is associated with β values in the range of 0.75–1. When the β value is > 1 , we estimate that drug transport corresponds to a complex release mechanism.

Statistical Analysis

DDSolver (add-in tool for Microsoft Excel) was used to determine the best fitting model based on the dissolution profile (based on R_{sq} (Adjust) and AIC) and the API release mechanism from the matrix (26, 27).

In addition to DDSolver, a Bayesian hierarchical modeling approach was used to compare the fit of four models to the release kinetics of all the formulations. PyMC and ArviZ, Python libraries specialized in Bayesian modeling and analysis, were used for model specification, sampling, and evaluation (28).

For the four candidate models (Weibull, Higuchi, first order, and Korsmeyer–Peppas), each model defined a likelihood function based on the respective kinetic equation and incorporated informative prior distributions for the parameters. A hierarchical structure was implemented to account for potential run-to-run variability.

Markov Chain Monte Carlo (MCMC) methods were used to draw samples from the posterior distributions of the model parameters. Convergence of the chains was assessed visually and statistically. Model fit was evaluated by using the LOO cross-validation in addition to WAIC metrics, allowing for objective comparison and selection of the best-fitting model (29). MCMC convergence was assessed using trace plots and the Gelman-Rubin statistic.

RESULTS AND DISCUSSION

The appearance of the suppositories varied between a whitish and yellowish coloration depending on whether they contained only PEGs or the PEGs-Bentonite mixture. For the hardness, all preparations met the requirement of 1800 g according to the *European Pharmacopoeia*.

Dissolution Testing

Table 4 summarizes the dissolution data for the 17 preparations used in the experiments. After 5 minutes of dissolution, the mean percentage of drug release varied from 7.54% to 34.48%, then was 12.58–46.55% at 10 mins, 20.45–68.71% at 20 mins, 27.58–88.14% at 30 mins, 38.03–99.17% at 50 mins, and 41.82–100.89% at 60 mins.

Adsorption Diffusion Models

Table 5 provides a summary of the results of fitting the four models to the dissolution data obtained. Of the 17 formulations, 10 fit the Weibull model, five fit the Korsmeyer-Pappas model, and two fit the linear and Higuchi model.

The Weibull model is an empirical model that explains both delayed and immediate releases of various drug delivery systems. The AIC, which is now considered as a standard measure of model and data fit based on maximum likelihood, displays the best-fitting model when comparing a group of models, and the model with the lowest AIC is the best fit (30). As shown by the the lowest AIC values, the Weibull model best defines the release behavior of active pharmaceutical ingredients from bentonite-based matrix. Nonetheless, slight deviations suggest that the Weibull model may not always be the right model for tramadol release. All parameters affecting the API release should be defined and controlled.

Table 4. Mean Percentage Dissolved of the Experimental Formulations

Formulation	5 min	10 min	20 min	30 min	50min	60 min
	T1 %	T2 %	T3 %	T4 %	T5 %	T6 %
1	7.54	15.76	20.45	40.00	44.24	62.27
2	6.62	12.58	20.61	27.58	42.73	59.55
3	13.18	22.12	42.88	46.82	58.33	69.55
4	29.64	33.91	44.26	64.77	67.24	74.30
5	29.64	33.91	44.26	64.77	67.24	74.30
6	23.76	30.11	39.55	51.64	55.06	67.14
7	29.12	36.50	51.47	62.83	73.70	78.20
8	34.48	49.20	68.71	84.03	84.29	89.36
9	30.68	46.55	55.76	69.85	89.76	92.76
10	28.11	39.68	60.94	70.85	92.56	94.47
11	34.70	42.61	62.98	76.26	92.24	93.26
12	32.97	45.42	60.11	76.05	96.58	97.56
13	24.18	35.64	60.45	80.38	96.52	100.89
14	25.73	41.71	68.89	88.14	99.17	98.83
15	6.82	14.39	18.33	28.79	38.03	41.82
16	23.79	34.55	55.15	66.52	69.39	72.27
17	24.55	36.36	55.61	68.94	70.30	71.06

T: Content of dissolved tramadol

Table 5. Release Kinetics of 17 Formulations of Tramadol Using Different Mathematical Models Obtained by DDSolver

PARAMETERS		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FIRST ORDER MODEL	R ² Adj	0.94	0.96	0.94	0.92	0.63	0.80	0.89	0.92	0.97	0.94	0.95	0.95	0.98	0.98	0.94	0.75	0.70
	K1	0.014	0.013	0.021	0.015	0.022	0.033	0.061	0.047	0.005	0.053	0.054	0.054	0.051	0.06	0.01	0.032	0.033
	AIC	30.75	28.06	31.77	30.87	39.08	37.75	35.55	34.84	28.39	32.30	32.65	32.65	28.83	25.67	25.24	39.24	40.22
HIGUCHI MODEL	R ² Adj	0.87	0.83	0.95	95.02	0.90	0.93	0.95	0.77	0.97	0.98	0.95	0.98	0.97	0.93	0.94	0.87	0.82
	KH	6.67	6.06	8.56	7.01	10.55	8.67	10.75	13.07	12.57	12.75	13.06	13.37	13.37	13.98	5.104	10.42	10.53
	AIC	36.29	36.68	29.41	28.38	33.23	28.53	29.01	39.93	27.98	24.29	31.54	27.27	31.62	36.23	25.93	35.24	36.92
KORSMEYER-PEPPAS	R ² Adj	0.79	0.97	0.96	0.96	0.93	0.96	0.99	0.90	0.98	0.98	0.98	0.98	0.97	0.92	0.98	0.90	0.87
	K	2.77	1.21	6.52	4.80	14.73	11.90	15.19	23.46	15.93	13.81	17.84	16.30	11.50	15.59	2.77	15.38	16.66
	N	0.79	0.93	0.57	0.60	0.39	0.42	0.40	0.33	0.43	0.47	0.41	0.44	0.54	0.47	0.66	0.39	0.37
	AIC	32.36	26.37	29.53	27.32	31.44	26.00	19.68	35.39	24.00	25.48	26.98	24.55	32.68	37.92	19.41	34.27	35.56
WEIBULL MODEL	β	1.14	2.80	0.68	0.596	0.59	0.56	0.63	0.69	0.79	0.88	0.79	0.85	2.31	1.93	0.76	0.48	0.44
	R ² Adj	0.90	0.97	0.96	0.96	0.93	0.95	0.99	0.96	0.95	0.98	0.97	0.95	0.99	0.99	0.98	0.97	0.93
	AIC	34.60	27.00	28.96	26.31	31.41	27.31	18.51	28.65	32.88	27.59	27.86	32.44	28.48	9.52	20.75	30.31	25.73

Adj: adjusted; AIC: Akaike Information Criterion; β, Weibull shape parameter; K1, first-order rate constant; KH, Higuchi rate constant; K, Korsmeyer-Peppas rate constant; N, Korsmeyer-Peppas release exponent.

Among the models considered, Weibull is a favorable model that comprises parameters sensitive to all the ranges of the API release profile. In the Weibull equation, T_i is the localization parameter that defines the latency time of the release process, and the exponent β , a shape parameter, characterizes the shape of the API release curve and may be related to some physiological effects. For equations with $\beta = 1$, the curve has an exponential

shape, $\beta > 1$ has a sigmoidal shape, and $\beta < 1$ is a parabolic curve. This suggests that the Weibull model is flexible with great potential to be applied to a variety of API release patterns.

The experimental response is explained by the Weibull model mathematical equation, where variations in tramadol release rates are described by the calculation

of its natural logarithm. In other words, although the Weibull model does not disregard the alteration of the API release rate between successive phases of the same release model, it deactivates the effect of these changes on the pattern by calculating their natural logarithm.. Otherwise, the exponent β could be employed to predict and optimize the release conditions of a drug delivery system in the development process and provide more necessary release profiles, though further in vivo studies would be required to confirm the clinical relevance of these findings.

Numerous APIs are adsorbed into bentonite by interacting with the surface of the clay sheets. These adsorptions vary depending on the type of the ingredient, nevertheless, the main mechanism is cation exchange. The surface of bentonite sheets is negatively charged ($\text{Al}_2\text{H}_2\text{Na}_2\text{O}_{13}\text{Si}_4$), which is why the surface charge is permanently balanced by cation exchange. Particularly, cationic API are adsorbed into the surface by these electrostatic interactions; this is the case of tramadol HCl. Thus, the release mechanism of tramadol from a bentonite-based suppository is by diffusion. Other factors including solvent pH, solvent temperature, ionic strength, and the initial concentration of active ingredient can also influence the results (31).

The dissolution profile of the optimal formulation after 24 h gave satisfactory results, which can only be explained by the Weibull model ($R_{sq}(\text{Adjust}) = 99\%$ and $\text{AIC} = 14.7861$).

Bayesian Model Selection Approach

In evaluating the model comparisons based on the LOO and WAIC criteria, distinct trends emerge in the ranking and performance of the models. For the LOO comparison

(Table 6), the Weibull model secures the top position ($\text{elpd_loo} = -292.85$), indicating its superior predictive ability compared to other models. Notably, the Korsmeyer-Peppas and Higuchi models follow closely, demonstrating competitive performance (-321.53 and -323.001 , respectively). The first order model had the lowest value (-402.41) but showed a substantial difference in expected log predictive density (elpd_diff), suggesting a notable deviation in predictive accuracy. In the WAIC comparison (Table 7), a similar pattern emerges, with the Weibull model leading, closely pursued by the Korsmeyer-Peppas and Higuchi models. Interestingly, the first order model exhibits a pronounced elpd_diff , emphasizing its inferior performance.

The β parameter of the Weibull model followed a normal distribution in all cases, as indicated by Figure 3. Estimated β values were $0.56\text{--}1.16$, with standard error values of $0.071\text{--}0.16$. Standard error values were 5.11 for LOO and 4.82 for WAIC.

The pooled and hierarchical Bayesian models were compared using the Weibull model as a reference. The hierarchical model outperformed the pooled model in both LOO and WAIC comparisons (ranked first in both metrics [LOO rank: 0; WAIC rank: 0]). The hierarchical model boasts significantly lower values (elpd_loo : -292.77 vs. -404.01 and elpd_waic : -289.57 vs. -404.00), indicating superior predictive accuracy and model fit compared to the pooled counterpart, which received negligible weight in both comparisons. This reinforces the conclusion that the hierarchical Bayesian approach offers substantial advantages for Weibull model.

Table 6. Ranking of Hierarchical Models Based on LOO Metrics

Model	Rank	elpd_LOO	p_LOO	elpd_diff	weight	SE
Weibull	0	-292.9	29.45	0.00	1.00	5.11
Korsmeyer-Peppas	1	-321.54	19.94	28.68	0.00	6.46
Higuchi	2	-323.00	18.23	30.14	0.00	6.57
First order	3	-402.41	2.22	109.56	0.00	5.60

LOO: leave-one-out cross validation; diff: difference; elpd: expected log predictive density; p: p-value; SE: standard error.

Table 7. Ranking of Hierarchical Models Based on WAIC Metrics

Model	Rank	elpd_WAIC	p_waic	elpd_diff	weight	SE
Weibull	0	-289.72	26.31	0.00	1.00	4.82
Korsmeyer-Peppas	1	-319.92	18.32	30.20	0.00	6.20
Higuchi	2	-321.69	16.92	31.97	0.00	6.33
First order	3	-402.41	2.21	112.69	0.00	5.60

WAIC: widely applicable information criterion; diff: difference; elpd: expected log predictive density; p: p-value; SE: standard error.

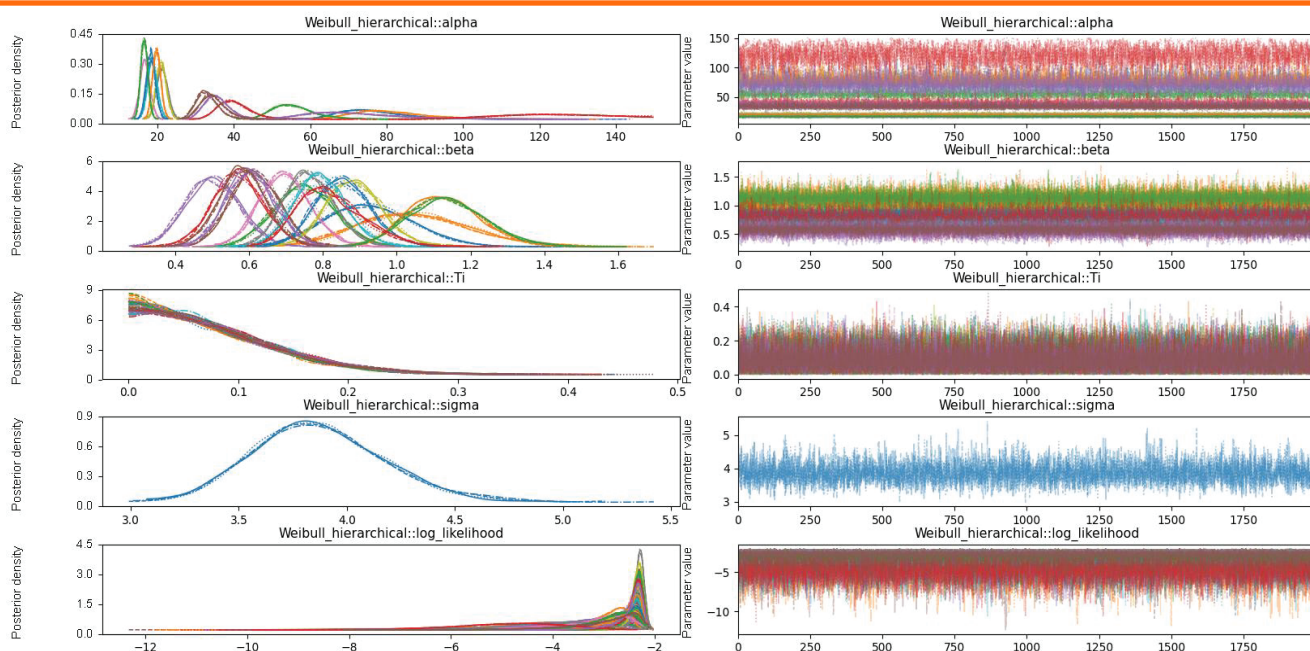


Figure 3. Trace plots and posterior distribution of the best model parameters and its standard deviation (σ).

The hierarchical Bayesian method's strength lies in its consistent selection of a reliable model (Weibull) for the formulation series. The frequentist approach provides a range of possibilities, but the Bayesian method shines in its accurate representation of the observed data (Fig. 4).

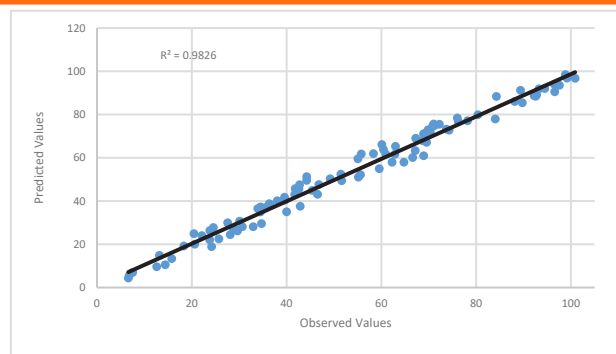


Figure 4. Observed versus predicted cumulative release mean values (%) by the hierarchical Bayesian method (Weibull model).

A posterior predictive plot was generated (Fig. 5) to delve deeper into the compatibility between our hierarchical model and the observed data. The model generally aligned well with the data, capturing the major features and distributions of the observed cumulative percentage of tramadol released at each time point across all formulations ("y_obs_hierarchical"). Although some minor deviations exist, these nuances do not detract from the overall positive assessment. The model provides a robust and reliable representation of the observed phenomena.

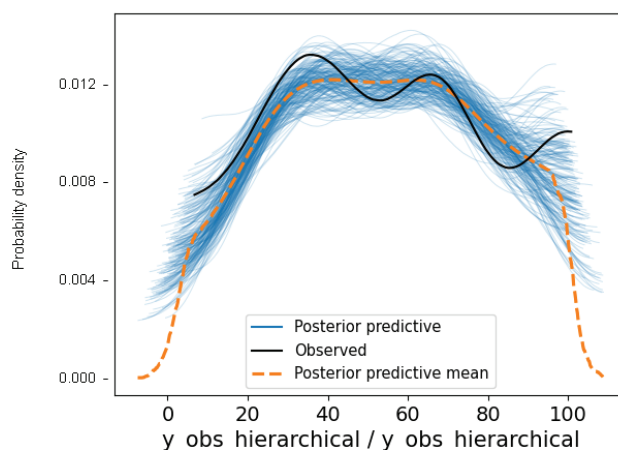


Figure 5. Plot of the posterior predictive checks for the best fit model. $y_{\text{obs hierarchical}}$: observed cumulative release (%) used as the response variable in the hierarchical Bayesian model.

CONCLUSION

Our study effectively proved the potential of bentonite-based sustained-release tramadol suppositories formulated through systematic mixture design. The incorporation of bentonite as a matrix-forming agent, combined with varying PEG compositions, allowed modulation of the drug release profiles, highlighting the clay's functional role in controlled delivery systems.

A comprehensive modeling approach was undertaken to characterize the dissolution kinetics using both frequentist and Bayesian frameworks. The comparative analysis revealed that the Weibull model consistently provided the best fit for most formulations in both

frameworks, effectively capturing the complexity of the release behavior. While the frequentist approach (using AIC-based ranking) served as a reliable initial screening tool, the Bayesian hierarchical modeling approach offered superior advantages, including robust uncertainty quantification, explicit handling of inter-formulation variability, and rigorous model ranking through LOO and WAIC metrics. This comparison underscores that, for complex formulations with inherent batch-to-batch variability, hierarchical Bayesian methods provide a more informative and generalizable model selection strategy.

The estimated Weibull shape parameter (β) suggested that diffusion remains the predominant release mechanism for tramadol from these bentonite-based matrices, consistent with theoretical expectations for clay-polymer systems. The flexibility of the Weibull model, capable of describing both Fickian and anomalous release kinetics, underscores its suitability for evaluating complex drug delivery platforms.

Collectively, these findings advocate for the integration of Bayesian hierarchical modeling as a robust, informative tool in the development of sustained-release formulations. Moreover, the results affirm the applicability of bentonite as a biocompatible, functional excipient for modifying drug release behavior. Future investigations should incorporate compatibility studies, advanced physicochemical characterization, and in vivo validation to further substantiate these preliminary conclusions and optimize clinical translation.

DISCLOSURES

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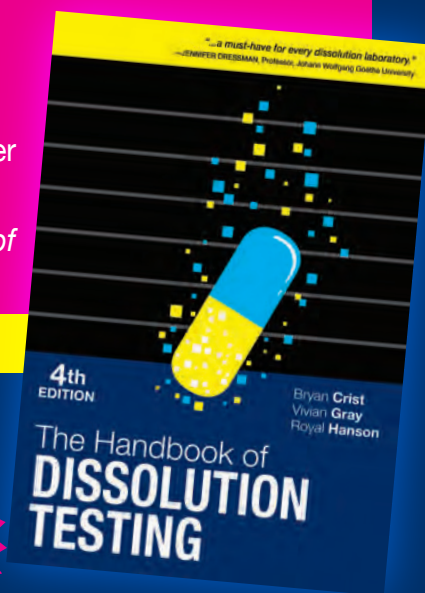
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Distek Turns 50 – Reflections on Leadership, Legacy, and Looking Ahead

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INTRODUCTION

In 2016, when Distek celebrated its 40th anniversary, I wrote about my family's journey and reflected on what it meant to grow up in a business founded by my parents. Ten years later, I find myself reflecting again and appreciating just how intertwined my story is with Distek's story.

I was born in 1974. Distek was incorporated in 1976. This year, Distek turns 50. I am in my 50s. Many have joked that I grew up with the company, and the older I get, the truer that feels, both literally and figuratively. Both milestones have caused me to think about where we've been and, more importantly, about where we're going.

The last decade has been defined by growth and transformation. We have continued to invest in and strengthen our core dissolution business while simultaneously expanding our bioprocessing product line. We've also invested heavily in software and cloud technologies that complement our instrumentation and create new value for our customers. It's been exciting to watch our products evolve into increasingly connected, software-enabled platforms while staying true to what has always been at the heart of Distek: designing and building great laboratory instruments.

That journey has also been humbling. Like many ambitious initiatives, expansion into new areas has taken longer and proven more complex than originally imagined. Yet I could not be prouder of what our team has accomplished: new products, new markets, new expertise, and a foundation built to support future growth for years to come.

Now, the parallel...just as the company was growing, and so was I – as a leader. Early in my career, I was in the weeds, hyper-focused on the day-to-day operation. The turning point came when we implemented EOS (Entrepreneurial Operating System). It provided a structured framework for aligning priorities, accountability, and execution across our organization.

For the first time, we had a system that allowed me to step back and work on the business rather than just in it. But here's what I've come to understand: a system like EOS only works if the people are ready for it. So yes, EOS gave us structure, but our team gave it life. They embraced it because they are the kind of people who take ownership, welcome accountability, and are genuinely open to changing the way we do things (for the better).

That adaptability and trust made change (for both the organization and me) possible. And it is also the foundation for what lies ahead. The opportunities in front of Distek are real and significant. Bioprocessing continues to grow as biologics become an increasingly important part of the pharmaceutical landscape. Our software and cloud-based capabilities are opening doors to new ways of supporting customers and helping them make better use of the data our instruments generate. And artificial intelligence is beginning to change what is possible in laboratory environments, from how instruments operate to how data is interpreted and acted upon. We are not standing on the sidelines watching these shifts happen. We are actively building toward them, and the discipline and people we have in place are what make that possible.

In addition to the Distek team (Fig. 1), I am grateful for our customers, who continue to push us, challenging us to innovate, holding us to a high standard, and growing alongside us. Together, our employees and customers are what make this company special.

When I reflect on all of this, I keep coming back to my parents, Gerry and Pearl (Fig. 2), because those qualities did not appear by accident. They were instilled from the very beginning by what my parents built nearly 50 years ago. What began as a small family business grew through hard work, perseverance, and a genuine commitment to customers and employees. The products have changed. The systems have changed. The markets have changed. But the values they instilled from the very beginning,

integrity, quality, care for the people around us, have not. In many ways, those values are what made all of this change possible.

As I've gotten older, I've found myself thinking more about stewardship than ownership. For the first generation, building a company often means figuring things out one day at a time. The second generation has the responsibility of growing and strengthening what was created. Through YPO (Young Presidents' Organization) and my exposure to how other family businesses operate, I've learned that thinking carefully about what comes next (i.e., putting the

right structures in place, developing the right people) is itself a form of leadership. My goal is simple: leave the business stronger than I found it and ensure the people who come after us are set up to take it further than I could.

I am excited about what lies ahead. Technology is evolving, the markets are growing, and the people we have in place give me real confidence in what this company can become. Fifty years in, and I still feel like we're just getting started.



Figure 1. Distek Office Team.



Figure 2. Gerry, Jeff, and Pearl Brinker.

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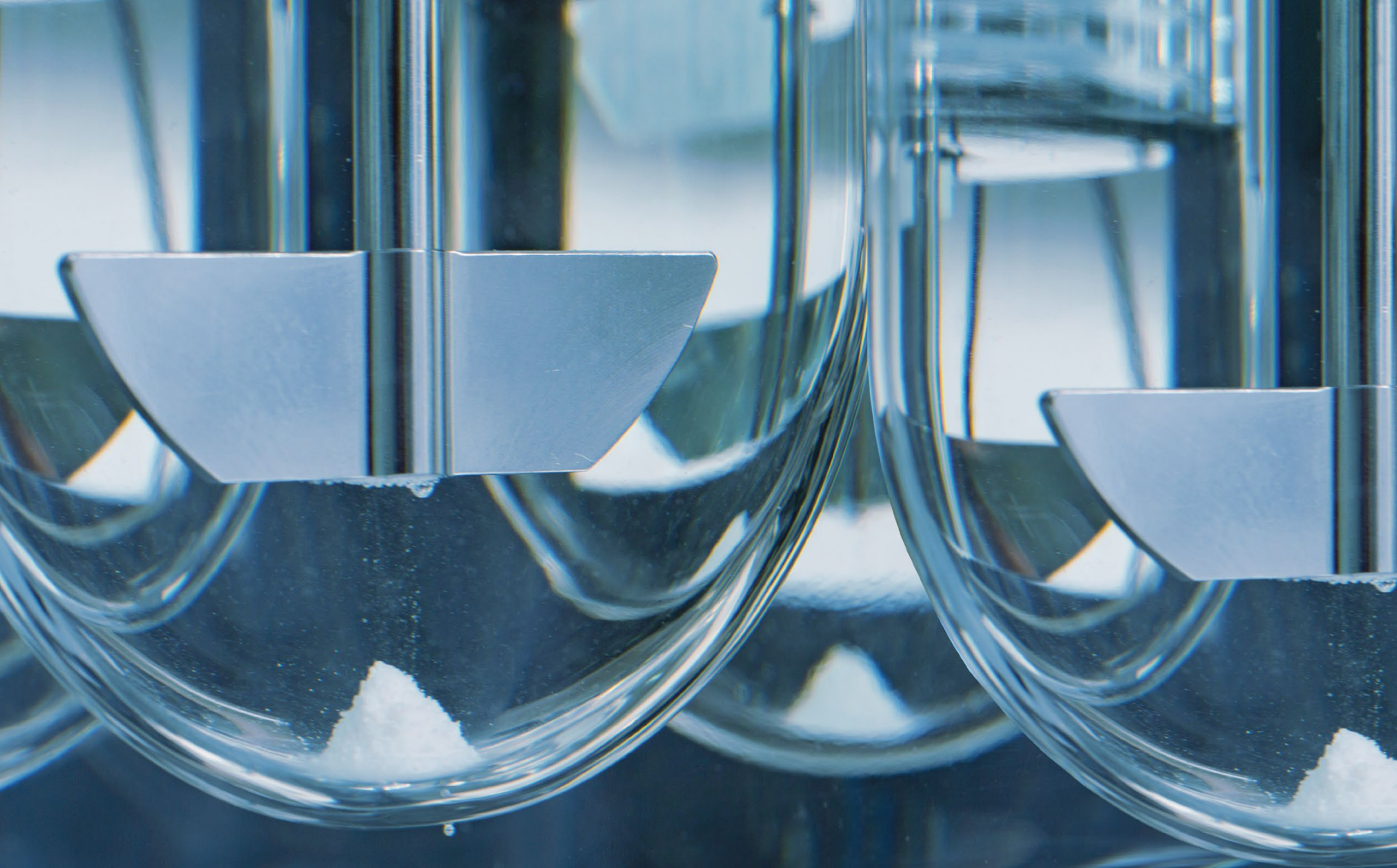
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Question & Answer Section

The following questions have been submitted by readers of *Dissolution Technologies*. Margareth R. Marques, Ph.D. and Mark Liddell, Ph.D., United States Pharmacopeia (USP), authored responses to each of the questions. *Note: These are opinions and interpretations of the authors and are not necessarily the official viewpoints of the USP. E-mail for correspondence: mrm@usp.org.

Q In the USP general chapter <1724> Semisolid Drug Products – Performance Tests, the vertical diffusion cell (VDC) rack is typically connected to a thermostatically controlled water bath recirculatory. Can the water bath be considered a regulated heating system, meaning that an alternative heating system cannot be used (e.g., a heating block)?

A There are no restrictions on the heating system for the cells. A water bath or any other approach can be used as long as the temperature is maintained and controlled at the appropriate temperature. Keep in mind that the temperature is $32 \pm 1^\circ\text{C}$ for products applied to the skin and $37 \pm 1^\circ\text{C}$ for products intended for internal application.

Q For Models B and C described in the USP general chapter <1724> Semisolid Drug Products – Performance Tests, what is the volume of the vertical diffusion cell (VDC)? The FDA Guidance for Industry – Nonsterile Semisolid Dosage Forms—Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation” (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ss-nonsterile-semisolid-dosage-forms-scale-and-post-approval-changes-chemistry-manufacturing>), describes a diffusion cell system with a standard open cap ground glass surface with 15-mm diameter orifice and total diameter of 25 mm. Does this correspond to any specific USP apparatus (A, B, or C)?

A The FDA guidance indicates “One possible in vitro release study design is summarized below...,” meaning that other designs are allowed. The actual volume of each cell needs to be determined to calculate the mass balance and flux rates in the system. From <1724> (text reprinted with permission of USP):

should be inspected for any cracks or other damage which they detect and have done.

2. Qualification of Volume of Receptor Solution Compartment/Vessel: In the case of a VDC, the volume of the receptor solution should be empirically determined for each cell, individually, and recorded in a manner that can be uniquely associated with each diffusion cell thereafter, for use in calculations. The volume should be filled in a consistent manner for all diffusion cells (some cells may have a fill line marked on the cell which can be utilized) and the procedure used should consider whether the displacement by a stir bar (or other mechanism) may impact the volume measured such that the measured volume would not be relevant to that diffusion cell if a different size stir bar was used during the test. The nominal volume of the diffusion cells provided by the manufacturer should be used only as a guide.

For immersion cells, the volume of receptor solution to be filled in the dissolution vessel should be accurately measured with the appropriate volumetric glassware and transferred to the dissolution vessel.

Q Could simulated intestinal fluid be used with a product where cross-linking due to the gelatin cross-linking is evident, or in what cases could it be used? Compared to the USP general chapter <711> Dissolution, there is a substantial difference in the amount of pancreatin added to the medium.

A Information regarding the enzymes and amounts to be used when there is evidence of cross-linking in gelatin capsules can be found in <711> Dissolution. The enzyme to be used should be selected based on the pH of the dissolution medium. In <711> Dissolution, the activity of the enzyme is specified in units/L of media. In contrast, the composition of simulated intestinal fluid as described in USP Test Solutions and Indicator Solutions (Intestinal Fluid, Simulated, TS) does not take into account the proteolytic activity of pancreatin. More information about cross-linking in gelatin capsules can be found in the USP general chapter <1094> Capsules – Dissolution Testing and Related Quality Attributes and in the paper by M. Marques entitled “Enzymes in the Dissolution Testing of Gelatin Capsule” (*AAPS PharmSciTech*, 2014, DOI: 10.1208/s12249-014-0162-3).

Q Regarding delayed-release dosage forms, in the USP general chapter <711> Dissolution, Method A, where it starts with 750 mL of acid medium and, in the buffer stage, 250 mL of buffer medium is added to the vessel containing the acid medium. If the sampling time in the buffer stage is 45 minutes, will this time start after adding buffer medium to the last vessel?

A No. The test time for the buffer stage of the dissolution experiment begins after the addition of the buffer medium to each individual vessel containing the 750 mL of the acid medium. Depending on whether the sampling is manual or automated, the addition of the buffer medium may be done in such a way to allow each vessel to be sampled at the appropriate time after the buffer medium is added to the vessel.

Q We have a dissolution instrument with seven vessels. We use the seventh vessel for the blank. Is it necessary to

evaluate this seventh vessel when doing the performance verification test of the dissolution equipment?

A The seventh vessel and position need to be qualified only if used to test samples. In this case, make sure that you compare the acceptance criteria for the six-vessel dissolution system. There may be slight differences in the %CV upper limit based on the number of vessels used in the dissolution run.

Q How do you apply Acceptance Table 2 for extended-release dosage forms as described in <711> Dissolution for the time points where the acceptance criteria is not a range? As an example, the tablet label claim is 500 mg and at the first time point the acceptance criteria is not more than (NMT) 40% and the last time point is not less than (NLT) 80%.

A The amount released for an extended-release dosage form is typically calculated based on the product label claim. In practice, the acceptance criteria is always a range. Consider the example provided. The range for the first time point is actually 0–40% of the product label claim, and the range for the last time point is 80–100% of the product label claim. Even when the acceptance criteria are stated as NLT or NMT a single value, in practice, the acceptance criteria represent a range of acceptable values.

Q When performing the performance verification test using USP Dissolution Performance Verification Standard

(DPVS) – Prednisone tablets, do the tablets need to be weighed prior to performance of the dissolution experiment?

A No. The tablets do not need to be weighed before the dissolution experiment. DPVS – Prednisone tablets are packaged in blister cards with push-through foil lidding. As with other pharmaceutical dosage forms, the label claim of the content, 10 mg of prednisone, should be used to calculate the percent release values, which are then used to determine the geometric mean and %CV.



Every issue of *Dissolution Technologies* features a Question and Answer section. This section is designed to address general dissolution questions submitted by our readers.

Please send your questions to:

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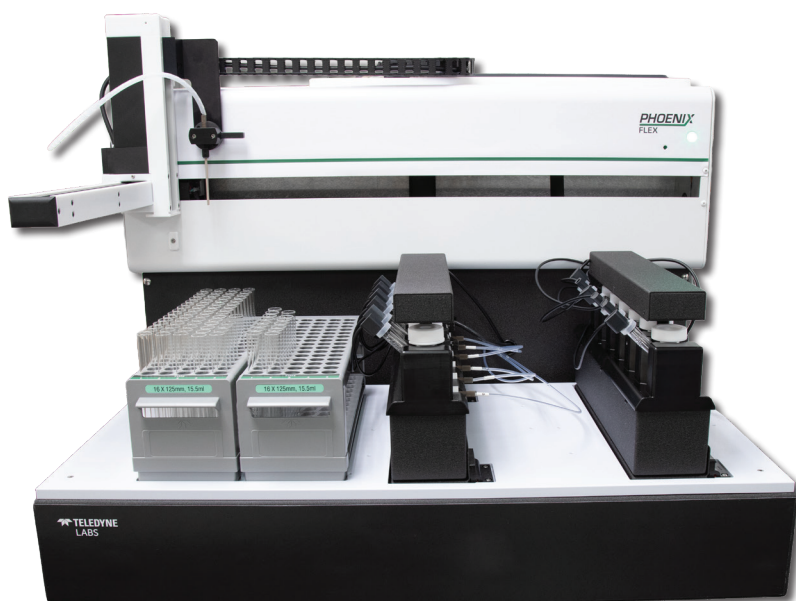
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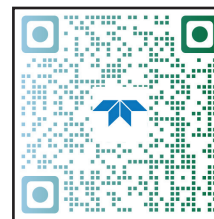


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Calendar of Events

October 7–8, 2026

INSIGHT 2026 Pharmaceutical Conference

Location: Dublin, Ireland

For information, visit www.insight2026.com

October 14–15, 2026

Advancing Bioequivalence Frameworks for Inhalation Drug Products: Optimizing In Vitro, In Vivo, and In Silico Methods

Location: The Universities at Shady Grove; Rockville, MD and virtual

Registration: <https://www.complexgenerics.org/education-training/advancing-bioequivalence-frameworks-for-inhalation-drug-products-optimizing-in-vitro-in-vivo-and-in-silico-methods/>

October 25–28, 2026

PharmSci 360 AAPS Meeting

Location: Ernest N. Morial Convention Center, New Orleans, LA

For information, visit <https://www.aaps.org/pharmsci/annual-meeting>

November 5, 2026

Let's talk - From Dissolution Sample Preparation to LC Finish

Location: DDG Online Meeting at 10:30 am ET

Registration: <https://www.agilent.com/chem/dissolution-webinars>

November 16–18, 2026

Eastern Analytical Symposium and Exhibition

Location: Crowne Plaza Princeton-Conference Center, Plainsboro, NJ, USA

For information, visit eas.org

December 1–2, 2026

Long-Acting Injectable (LAI) Generics: Navigating Technical Hurdles in Product Development and Regulatory Assessment

Location: The Universities at Shady Grove, Rockville, MD and virtual

Registration: <https://www.complexgenerics.org/education-training/long-acting-injectable-lai-generics-navigating-technical-hurdles-in-product-development-and-regulatory-assessment/>

On Demand Events

- ***Powder Flow Testing***
<https://www.copleyscientific.com/events/webinar-foundations-of-powder-flow-testing/>
- ***dissoLab Software: Predictive Dissolution Simulated from Microscopic Images***
<https://vimeo.com/1054617734?share=copy>
- ***Fiber Optic UV: Better Dissolution Testing On Demand***
<https://www.distekinc.com/watch/fiber-optic-uv-better-dissolution-testing/>
- ***Advances in In Vitro Bioequivalence Assessment for Topical Products Part 2***
<https://youtu.be/iqphypToHZ0?si=mn9FJLDhm-VBoWMm>
- ***Ocular Administration (OCAT™) in GastroPlus® On Demand***
<https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-ocular-administration-ocat-virtual/>

- **Oral Cavity Administration (OCCAT™) in GastroPlus® On Demand**
<https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-oral-cavity-administration-occat-virtual/>
- **Pulmonary Administration (PCAT™) in GastroPlus® On Demand**
<https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-pulmonary-administration-pcat-virtual/>
- **GastroPlus® ADR – 4 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™)**
<https://www.simulations-plus.com/events/gastroplus-adr-4-course-bundle-tcat-ocat-occat-pcat/>
- **GastroPlus® ADR – 5 Course Bundle (TCAT™ / OCAT™ / OCCAT™ / PCAT™ / Injectables)**
<https://www.simulations-plus.com/events/gastroplus-adr-5-course-bundle-tcat-ocat-occat-pcat-injectables/>
- **Transdermal Administration (TCAT™) in GastroPlus®**
<https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-transdermal-administration-tcat-virtual/>
- **Injectables (IM, SQ, IA) in GastroPlus® Including Biologics and LAIs**
<https://www.simulations-plus.com/events/gastroplus-additional-dosage-routes-workshop-injectables-incl-lai-biologics-virtual/>
- **GastroPlus® X Tutorial Series**
<https://www.simulations-plus.com/events/gastroplus-x-tutorial-series/>
- **GastroPlus® X Tutorial Series I – Panels and Start-up Essentials**
<https://www.simulations-plus.com/courses/gastroplus-x-tutorial-series1/>
- **GastroPlus® X Tutorial Series II – Modules**
<https://www.simulations-plus.com/courses/gastroplus-x-tutorial-series-ii-modules/>
- **GastroPlus® X Tutorial Series III – New Features in GastroPlus X.2**
<https://www.simulations-plus.com/courses/gastroplus-x-tutorial-series-iii-new-features-in-gastroplus-x-2/>

- **Complimentary Introduction to GastroPlus® for up to v.9.9**
<https://www.simulations-plus.com/events/complimentary-introduction-to-gastroplus-v-9-9/>
- **Complimentary Introduction to GPX™**
<https://www.simulations-plus.com/events/complimentary-introduction-to-gpx/>

Free Tutorials (AI Language Translation)

- **GastroPlus® Tutorial in French**
https://www.youtube.com/watch?v=h-_4m8xpDg8&list=PLQuCii74Pfd327VslFvlp_IRxqJlfzEF0
- **GastroPlus® Tutorial in Japanese**
<https://www.youtube.com/watch?v=IkTsLRPVlms&list=PLQuCii74Pfd317she0RsVTFVCyl2yvvz9X>
- **GastroPlus® Tutorial in Mandarin**
<https://www.youtube.com/watch?v=XabV2jiAsVU&list=PLQuCii74Pfd3LojzBlatK7mnbLxPvqFDa>
- **GastroPlus® Tutorial in Portuguese**
<https://www.youtube.com/watch?v=idkaPR6av9M&list=PLQuCii74Pfd0zttMQdhy6sv97OIK9MyE5>
- **GastroPlus® Tutorial in Spanish**
<https://www.youtube.com/watch?v=kEmj98nnpx8&list=PLQuCii74Pfd2oVl6tsQNvxZs6sX0Ww9FT>

Free Live Workshops

- **GastroPlus® Summer School: Practical API Skills for Basic and Advanced Modeling**
https://www.simulations-plus.com/events/gastroplus-summer-school-practical-api-skills-for-basic-and-advanced-modeling/?mtm_campaign=Dissolution_Technologies&mtm_source=digital%20newsletter&mtm_medium=cpc

SOTAX Releases q-doc® Version 4n, Advancing Digitalization and Automation in Pharmaceutical Quality Control

New release introduces DataLink™ for Waters Empower®, DataLink™ for Körber PAS-X MES, standardized system connectivity, and enhanced dissolution workflows

June 2026 - SOTAX announced the release of q-doc® Version 4n, the latest version of its modular software suite for seamless, traceable, and compliant laboratory data management. The new release strengthens q-doc® connectivity with standardized DataLink™ import/export functionalities, including integrations with Waters Empower® CDS, Körber PAS-X MES, and LIMS/MES/ERP systems.

The release supports SOTAX's broader objective to help pharmaceutical manufacturers advance digitalization, automation, and continuous assurance across critical quality workflows. As outlined in the SOTAX perspective paper Global Pharmaceutical Digitalization, the industry is shifting from retrospective quality-by-inspection toward data-centric, continuously assured manufacturing models supported by interoperable data, governed computerized systems, and inspection-ready decision records.

A key highlight of q-doc® Version 4n is DataLink™ for Waters Empower®, which enables q-doc® to automatically create high-performance liquid chromatography (HPLC) sample sets in Waters Empower® CDS for dissolution workflows. By linking dissolution data with analytical LC results, laboratories can reduce manual handoffs, improve data consistency, and strengthen traceability from testing through evaluation.

"q-doc® Version 4n is another step in SOTAX's commitment to digitalization and automation in pharmaceutical quality control. With DataLink™ for Empower®, we are helping customers connect dissolution testing with chromatographic analysis, reduce manual data handling, and build more efficient, compliant laboratory workflows," said Patrick Ballmer, Vice President, SOTAX.

q-doc® Version 4n also includes DataLink™ for Körber PAS-X MES, a certified interface that connects in-process control test data with manufacturing execution systems. This functionality helps create a digital bridge between IPC laboratories and production environments.

"With DataLink™ for PAS-X, q-doc® extends traceable laboratory data management beyond the IPC lab and into the manufacturing environment. The certified interface with Körber PAS-X MES helps customers reduce manual data handling, improve operational efficiency, and maintain stronger data integrity across connected GMP workflows," said Rui Fraga, Product Manager, SOTAX.

The new release also expands standardized connectivity through DataLink™ for SQL Import, Job Import, SQL Export, and LIMS Export, supporting automated batch and test run registration, file-based data exchange, paperless batch record export, and automated output as PDF or Microsoft Excel®-compatible files.

For dissolution testing, q-doc® Version 4n introduces new features for Xtend™ systems, including staging for immediate-release products, staging for extended and delayed-release products, and f1 and f2 dissolution profile comparison with seamless access to archived tests. The release also supports built-in UV-Vis qualification workflows directly from q-doc®, helping laboratories standardize qualification routines from an installed and validated software platform.

Together with platforms such as Xtend™ for fully automated dissolution, JetX™ for automated assay and content-uniformity sample preparation, AT50 for automated online and at-line physical testing, and q-doc® for integrated data management, SOTAX provides a focused instrumentation and data layer that supports repeatable measurements, standardized workflows, and governed data across laboratory and manufacturing environments.

With q-doc® Version 4n, SOTAX continues to advance its vision of “Data without Borders” by helping laboratories integrate instruments, processes, and existing IT ecosystems for more efficient, paperless, and compliant data management.

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About Sotax

The SOTAX Group is the leading global provider of complete testing solutions for Research and Development (R&D), Quality Control (QC), and In-Process Control (IPC) departments of the pharmaceutical industry. SOTAX's instruments, software, and services are recognized by their customers worldwide as the industry benchmark for best-in-class solutions. It is also the only pharmaceutical services supplier specialized in R&D for dissolution and release testing. The company is offering a high level of expertise for complex dosage forms testing as well as an FDA-inspected facility for routine cGMP testing. Its laboratories, located all over the globe, operate for clients worldwide ranging from virtual companies to big Pharma including generic.



Simulations Plus Announces Collaboration with Lonza and U.S. FDA to Advance Predictive Frameworks for Complex Oral Drug Products

Simulations Plus, Inc. (“Simulations Plus” or the “Company”), a global leader in model-informed and AI-accelerated drug development that advances biopharma innovation, announced a funded research collaboration with Lonza Group AG (“Lonza”), a leading contract development and manufacturing organization (CDMO) dedicated to serving the healthcare industry, and the U.S. Food and Drug Administration (FDA) to develop and validate a mechanistic, predictive framework for assessing the in vivo performance of amorphous solid dispersion (ASD) drug products.

“Complex oral formulations such as amorphous solid dispersions present significant scientific and regulatory challenges due to their sensitivity to physiological and manufacturing variables,” said Dr. Viera Lukacova, Chief Scientific Officer of Simulations Plus. “Through this funded collaboration, we aim to integrate advanced in vitro systems with mechanistic modeling to improve prediction of in vivo performance, support regulatory decision-making, and enable more efficient development pathways for these high-impact therapies that deliver faster dissolution and more drug absorption.”

Advancing Mechanistic, Model-Informed Approaches for Complex Products

ASDs are among the most powerful yet complex oral drug delivery systems, with performance influenced by factors such as food intake, gastric pH, formulation composition, and manufacturing processes. Current regulatory approaches often require multiple clinical bioequivalence (BE) studies, which can be resource-intensive while still carrying uncertainty.

The collaboration evaluates whether advanced in vitro dissolution systems—particularly those incorporating dynamic gastrointestinal physiology—combined with mechanistic physiologically based biopharmaceutics modeling (PBBM), can reliably predict key in vivo outcomes, including food effects and the impact of elevated gastric pH conditions. By establishing and validating these predictive capabilities, the collaboration aims to provide a scientific foundation for reducing reliance on certain clinical BE studies while maintaining the rigor and transparency required by regulators.

Integrating Experimental and Mechanistic Modeling Expertise

The collaboration brings together complementary capabilities across experimental science and computational modeling.

Lonza will lead experimental work, including in vitro dissolution testing under fasted, fed, and elevated gastric pH conditions using advanced systems such as Controlled Transfer Dissolution (CTD), as well as the characterization and, where needed, manufacturing of ASD formulation variants.

Simulations Plus will lead the development and validation of in vitro–in vivo extrapolation (IVIVE) frameworks using its DDDPlus® and GastroPlus® platforms, translating experimental data into predictions of in vivo pharmacokinetics and supporting virtual bioequivalence assessments. At the same time, it creates new opportunities to extend these capabilities into grounded AI-enabled workflow environments, where data, mechanistic models, and simulation outputs will be more directly connected. The company will also contribute to interpretation within a regulatory context, ensuring alignment with evolving expectations for model-informed drug development (MIDD).

Francois Ricard, Head of R&D, Lonza Advanced Synthesis, said, “This collaboration reflects Lonza’s commitment to advancing more predictive, science-driven approaches as the leader in the field of bioavailability enhancement. By combining advanced in vitro experimentation with mechanistic modeling, and working closely with Simulations Plus and the FDA, we aim to strengthen the scientific foundation that underpins regulatory decision-making for complex oral drug products. Ultimately, this type of collaboration should help accelerate development for our customers requiring bioequivalence during clinical development.”

Alignment with Regulatory Priorities and Industry Needs

This work is supported in part through FDA funding and includes ongoing engagement with FDA scientists to directly align with regulatory priorities to advance MIDD, modernize bioequivalence assessment for complex products, and reduce unnecessary reliance on human studies. By combining regulatory collaboration with open, non-proprietary data and validated methods based on real-world, FDA-approved ASD products, the initiative is intended to inform future regulatory approaches and support broader adoption of science-based alternatives.

“The industry is moving toward a future where decisions are informed earlier, with greater confidence and scientific transparency,” added Lukacova. “Our role is to ensure those decisions are grounded in validated science—while enabling more efficient ways to connect data, models, and insight.”

Simulations Plus and NVIDIA Collaborate to Scale GPU-Accelerated, AI-Assisted Modeling Workflows

Simulations Plus, Inc. (“Simulations Plus” or the “Company”), a global leader in model-informed and AI-accelerated drug development that advances biopharma innovation, announced the launch of a technical collaboration with NVIDIA focused on enabling graphics processing unit (GPU)-accelerated simulation and AI-assisted workflows for computationally intensive modeling applications within the drug development lifecycle.

The collaboration brings together Simulations Plus’ validated scientific engines across physiologically-based pharmacokinetics (PBPK), pharmacokinetics/pharmacodynamics (PK/PD), and quantitative systems pharmacology (QSP) with NVIDIA AI infrastructure to accelerate and scale simulation cycles, parameter exploration, and virtual population studies. Together, these capabilities address two core constraints in model-informed drug development (MIDD): reducing manual, expertise-driven work and enabling large-scale exploration of model structures and parameters in parallel—shifting modeling from a sequential process to a more iterative, data-informed workflow operating at program-relevant timelines.

NVIDIA contributes advanced computing infrastructure and expertise in accelerated inference and GPU-native optimization to improve simulation performance and enable interactive, AI-assisted workflows. NVIDIA also brings access to its life sciences ecosystem, including the NVIDIA BioNeMo platform and a global network of pharmaceutical partners, supporting broader engagement and adoption.

“For 3 decades, Simulations Plus has helped pharmaceutical and biotechnology organizations apply modeling and simulation with confidence across drug development. Our collaboration with NVIDIA brings together validated science, accelerated computing, and AI capabilities in a way that expands what scientific teams are able to explore and accomplish,” said Shawn O’Connor, Chief Executive Officer of Simulations Plus.

The collaboration is initially focused on two areas:

Next-generation scientific engines

Simulations Plus has begun developing GPU-optimized simulation capabilities for QSP and PK/PD applications, reducing runtimes and enabling broader exploration of complex biological systems. This enables scientists to evaluate a broader range of hypotheses without pre-pruning models, increasing confidence in model selection and supporting more robust program decisions.

AI-assisted scientific workflows

Simulations Plus is applying AI-assisted approaches, informed by NVIDIA’s expertise in accelerated inference and agentic AI, to support model construction, parameter fitting, diagnostics, and refinement—reducing manual effort and accelerating iteration from question to analysis. By reducing manual, time-intensive steps, these workflows will allow scientists to focus more on scientific interpretation and decision-making, significantly accelerating iteration cycles within drug development programs.

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