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Dissolution Testing for Solid Oral Dosage Forms

By Tanya Tadey, PhD, and Geoffrey Carr, PhD

New applications of this testing bolster importance as quality control step

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Dissolution is an important test method that is carried out on solid oral dosage forms like capsules, tablets, and oral suspensions. For these dosage forms to be efficacious, the active drug substance must be absorbed into the systemic circulation so that it can be transported to its site of activity. The overall efficiency of this process contributes to the bioavailability of the drug substance and involves two steps, dissolution and absorption, or permeability, as defined within Food and Drug Administration (FDA) guidelines concerned with the Biopharmaceutics Classification System (BCS).

Step one, dissolution, is the process of extracting the drug substance out of the dosage form solid-state matrix into solution within the gastrointestinal tract. Step two, absorption, is the process of transporting the drug substance from the gastrointestinal tract into the systemic circulation. Dissolution testing is an in vitro laboratory test method that is designed to demonstrate how efficiently an active drug substance is extracted out of a solid oral dosage form. Therefore, it can provide an indication of the efficiency of in vivo dissolution (step one) but does not provide any information on drug substance absorption (step two), so it can only provide limited information on potential bioavailability.

However, since step one performance is very much dependent on product formulation and the details of manufacture, whereas step two performance is generally not greatly affected by either of these factors, dissolution is a very appropriate parameter to monitor and provides very useful information on the performance capabilities of solid oral dosage forms that may be used within development to assist in the selection of suitable formulations, and it serves as a quality control test in support of routine manufacture to establish lot-to-lot performance consistencies. In fact, this test method is considered so useful that it is a standard compendial method published by the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP).

A systematic approach, based on sound scientific and regulatory principles, should be applied in developing a dissolution method.

Types of Dissolution Apparatus

Any dissolution test method involves immersing the dosage unit in a suitable medium, which is kept in motion at a constant speed and requires the determination of the rate at which the drug substance is extracted from the dosage unit and dissolves in the medium. Results of this type of determination are dependent on system hydrodynamics, which, in turn, depend on apparatus details. In view of this, the various compendia provide strict details of all dissolution apparatus dimensions; fortunately, the chapters on dissolution published in USP, EP, and JP are harmonized. Various designs of apparatus are included in the compendia, as described below, and, typically, in each case, single dosage units are tested in a number of vessels or cells (usually six).

For orally administered immediate and delayed release dosage forms, including tablets, capsules, and suspensions, USP Apparatus 1 (basket) or 2 (paddle) is recommended. Apparatus 2 is generally the first choice for immediate release due to ease of use, reproducibility, hydrodynamics, and general acceptance.

For extended release dosage forms designed to deliver the drug to site absorption at a controlled rate over an extended period of time, USP Apparatus 3 and Apparatus 4 (flow-through cell) should also be considered during method development because they allow for changes in the medium pH during dissolution testing. USP Apparatus 3 offers advantages such as ease of setup, operation, and sampling relative to USP Apparatus 4, and is generally preferred when a pH gradient is required. It should be noted, however, that USP Apparatus 3 is not currently recognized by the JP and should therefore not be considered for products intended for the Japanese market. USP Apparatus 4 is particularly applicable to very poorly soluble drug substances because it allows for continuous introduction of fresh medium during the test.

Figure 1. USP Apparatus 2 is generally the first choice for measuring the dissolution of immediate release dosage forms.

Selection of Dissolution Conditions

A systematic approach, based on sound scientific and regulatory principles, should be applied in developing a dissolution method. Both the FDA and USP have published guidelines on developing suitable dissolution methodology. Sufficient information about the drug substance properties (solution stability, solubility, particle size, polymorphism, permeability, and site of absorption) that are likely to affect the in vitro dissolution behavior should be obtained. Drug product characteristics, such as the type of dosage form (tablet, capsule, suspension), the number of strengths, and the desired release mechanism and profile (immediate, delayed, or extended release) will determine some decisions regarding method parameters. It is also extremely important for dissolution method development chemists to work closely with input from their counterparts in pharmaceutics and process development. Failure to do this during method development may result in a method that is not relevant for the dosage form.

The selection of dissolution medium is guided by drug substance solubility and establishment of sink conditions. Sink conditions are defined as concentrations that yield a saturation solubility of the drug substance at least three times the highest dose of the drug substance dissolved in the volume of medium used for dissolution. For example, if dissolution of a 100 mg strength tablet is being performed in 900 mL of medium, a saturation solubility greater than 0.33 mg/mL in the medium is required to maintain sink conditions. Sink conditions are preferred because they are more likely to result in dissolution that reflects kinetics of the drug release from the dosage form rather than from solubility limitations. In some cases, though, a medium that does not meet the strict requirements for sink condition may be justified if it is demonstrated to result in a more discriminating profile.

Figure 2. The advantages of USP Apparatus 3 include ease of setup, operation, and sampling. It is generally preferred when a pH gradient is required.

Medium selection should begin with aqueous-based media in the range of pH 1.2 to 6.8 (or pH 7.5 in the case of modified release dosage forms). Water is generally not recommended because its ionic strength and pH can be variable and difficult to control. Typically, 0.1 N HCl (pH 1.2), acetate (pH 4.5), and phosphate buffers (pH 6.8 and 7.5) at USP-recommended ionic strength are evaluated. The exception is delayed release dosage forms, which are designed to release the drug substance at an intestinal pH of 6.8. Where multiple strengths of the drug substance are available, the highest strength should be used for initial medium selection.

For drug substances that exhibit low solubility in aqueous media throughout the pH range, the addition of surfactants is

recommended due to their physiological role in solubilizing drugs in vivo. Commonly used surfactants include the anionic surfactant sodium dodecyl sulfate, cationic cetyl trimethylammonium bromide, and neutral surfactant Polysorbate 80.

At concentrations below the critical micelle concentration (CMC), surfactants can increase the rate of dissolution by acting as wetting agents. Above the CMC, drug substance can be solubilized in the hydrophobic interior of the micelle and, as a result, solubility increases with increasing concentration of surfactant. For purposes of medium selection, the minimum concentration above CMC that meets sink condition criteria should be determined and selected for further optimization. For ionizable compounds, variation of both pH and surfactant can be used to select an appropriate medium. Addition of organic solvent such as alcohols is generally not recommended and may lead to regulatory delays.

Table 1. USP Dissolution Requirements for Immediate Release Products.

STAGE	NUMBER TESTED	ACCEPTANCE CRITERIA
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

Table 1. USP Dissolution Requirements for Immediate Release Products (Click to Enlarge).

Comparative dissolution profiles of the dosage form should be performed to select final media conditions. A single dissolution run using two to three tablets in each of the selected media can be used to select the medium that provides the most desirable profile. For immediate release dosage forms, this profile is usually generated in 900 mL of media using USP Apparatus 2 (paddle method) at 50 revolutions per minute (RPM). A lower volume of medium (500 mL) may be required for very low strengths to achieve an adequate concentration for detection. Sampling should occur at five- to 15-minute intervals for 60 minutes or until an asymptote is reached. For ionizable compounds, the pH in each vessel should be measured at the end of the run to determine if the medium has sufficient buffer capacity to maintain the same pH throughout the run.

The results of percent dissolved versus time in each medium should be plotted on the same graph for comparison. A medium resulting in a gradual increase of released drug leading to 100% release of the drug is preferred because it is more likely to detect differences in formulation or processing parameters. Obtaining dissolution profiles of dosage forms with known formulation, manufacturing, or bioavailability differences can aid in optimizing for the most discriminatory condition. A profile may not be required for immediate release products in which the drug substance is known to be Class 1 (high solubility and high permeability) as defined by BCS. For this class of drugs, the FDA guidance suggests that dissolution of 85% in 15 minutes ensures that bioavailability of the drug is not limited by dissolution.

During these early method development runs, it is imperative to observe the behavior of the dosage form visually throughout the run. For dosage forms that are observed to float, sinkers described in USP <1092> can be used in Apparatus 2. Alternatively, USP Apparatus 1 can also be evaluated. Coning, which results in a cone-shaped mass of disintegrated solids at the bottom of a vessel, can occur in Apparatus 2, especially for higher weight dosage units or products containing a large quantity of insoluble excipients. Coning can prevent dissolution of drug particles inside the cone and lead to incomplete dissolution and poor reproducibility of results. Coning can often be eliminated by increasing the paddle speed to 75 RPM. Additionally, the basket method or commercially available PEAK vessels designed with a convex bottom may help to minimize coning issues. Because PEAK vessels are not recognized by the USP, however, their use must be appropriately justified. Dosage forms that stick to the vessel interior may show better behavior in USP Apparatus 3.

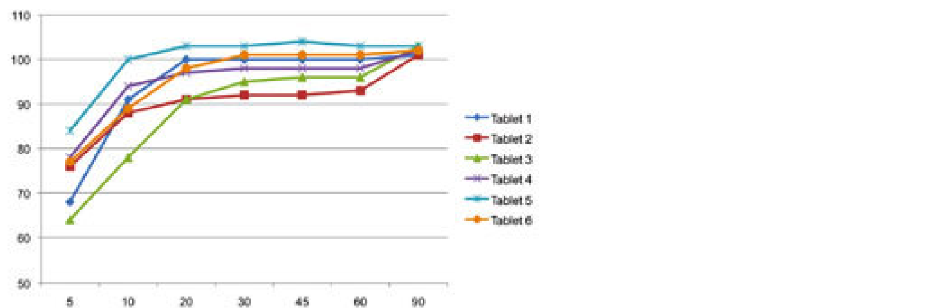

Figure 3. Representative Example of Dissolution Profiles (Click to Enlarge)

For modified release dosage forms, medium selection runs are analogous to those for immediate release with the exception that the sampling time points will depend on the desired release profile of the dosage form. Samples should be taken throughout the run to adequately characterize the release profile. Initial dissolution in acidic medium for one to two hours, followed by a change to buffer at pH 6.8 or 7.5, should be considered for extended release drugs because this more closely resembles the physiological pH exposure and improves the chance for a successful correlation of in vivo and in vitro data.

A change in medium pH can be achieved in Apparatus 2 by starting with 750 mL of acidic media and adding a buffering reagent at a designated time point as described in the USP<711> procedure for delayed release dosage forms designed to release the drug only at intestinal pH. The same procedure can be applied to change the medium pH for extended release dosage forms in Apparatus 2. Apparatus 3 should also be evaluated for extended release dosage forms.

Once the medium and apparatus are selected, the method should be further optimized for parameters such as optimal agitation rate, medium ionic strength, and surfactant concentration if applicable. The final conditions should demonstrate optimal discriminatory power along with sufficient reproducibility and robustness. A relative standard deviation of less than 20% at early time points and less than 10% at other time points is recommended.

Direct ultraviolet/visible (UV/VIS) spectrophotometry and high pressure liquid chromatography (HPLC) are most commonly applied to the analysis of dissolution samples. UV/VIS should be considered as a first choice for routine quality control release testing because it is faster and more efficient. Current diode array UV/VIS spectrophotometers capable of multi-component analysis can even be used to analyze multiple actives in the same sample and, in many cases, formulations with interfering excipients. During

early phase development in which multiple formulations and strengths are screened, however, HPLC is often the method of choice even though it is less efficient than UV/VIS. Potential interferences from the formulation matrix or medium or even degradation of the active can be separated by HPLC. Further, large variations in sample concentration can often be dealt with simply by adjusting injection volume. Systems for automated sampling and analysis by either HPLC or UV/VIS are commercially available. The application of these systems must be validated against manual sampling and analysis to demonstrate that they do not introduce any bias to the results. For extremely low dose compounds or those without sufficient UV chromophore, HPLC with mass spectrometric detection can be used to achieve rapid analysis with extremely high sensitivity.

LEVEL	NUMBER TESTED	CRITERIA
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Table 2. USP Dissolution Requirements for Extended Release Products (Click to Enlarge).

Dissolution Test Acceptance Criteria

Acceptance criteria for dissolution tests are set on the basis of requirements for a percent quantity of drug to be released after a certain period of time in the dissolution apparatus. Since each test is usually conducted using six individual dosage units, acceptance criteria must be established on this basis. The compendia recognize that reasonable tolerances are required to ensure that criteria are not prohibitive, but at the same time, they need to discriminate between acceptable and unsatisfactory batches of products. The approach developed within various compendia is now harmonized for immediate release and extended release —though not for delayed release—and allows for three levels of staged testing.

For immediate release products, acceptance criteria are based on a single time point and a single value, expressed as a Q value. Then, at each of the three stages, the specification requires that mean values not be less than Q, but a set number of individual units are allowed to release a percent quantity of active which may be as low as Q - 25% for one unit at stage three.

For extended release products, specifications are based on three or four time points. For the intermediate time points, the requirements are based on ranges; for the final time point, they are usually based on a single value. Therefore, the acceptance criteria at each stage are expressed in terms of variances around ranges for intermediate time points and minimum acceptable release at the final time point .

Further Applications of Dissolution tests

Apart from applications for development of new products and as a routine specification test method, dissolution data has value for a number of applications. To support scale up and post approval changes (SUPAC) for commercial immediate release and modified release products, the amount of dissolution and bioequivalence data required is dependent on the magnitude of the changes, which are defined as levels one to three within SUPAC guidelines.

For the development of immediate release generic products, the FDA requires demonstration of bioequivalence of the potential generic version with the innovator product. It is possible to obtain a biowaiver under the following circumstances, however:

- The product is immediate release and there are multiple strengths; or
- It has been demonstrated that the highest strength shows bioequivalence with the innovator product.

For new products, clinical trials are often conducted using an established commercial product as a comparator. Because it is important that neither the investigators nor clinical trial subjects are able to distinguish among the product under investigation, the clinical comparator, and any placebo, the various products are made to look alike, or blinded. Achieving this with a commercial product usually involves some form of manipulation such as over-encapsulation and then addition of a backfill. Recognizing that any such manipulation could affect the bioavailability of the comparator, the European Medicines Agency, in its "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials," requires that dissolution testing be conducted to demonstrate that manipulations of comparator products have not compromised their performance.

Both of the latter applications are recommended to be based on comparisons of dissolution profiles (between innovator and generic versions or "un-manipulated" and blinded clinical comparator). So although, as indicated above, specification dissolution testing for immediate release products is usually based on a single time point, profiles require that additional earlier dissolution samples be analyzed. Profile comparisons are then based on the difference factor (F1), which calculates the percent difference between the two curves at each time point, and the similarity factor (F2), which is a logarithmic reciprocal square root transformation of the sum of

squared error and is a measurement of the similarity in the percent dissolution between the two curves. For dissolution curves to be considered appropriate for comparison analysis:

- they should only include a single point after 85% dissolution for both products; and
- the coefficient of variation at each time point should not be more than 10%, except that for the earliest time point it may be not more than 20%.

If dissolution profile matching cannot be conducted or if unacceptable results are observed, then bioequivalence data may be required by regulatory agencies. n

Dr. Tadey *is associate director of analytical development and* ***Dr. Carr*** *is director of analytical development at Patheon Inc. For more information, contact Dr. Carr at geoff.carr@patheon.com or (905)812-6628.*

RESOURCES

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