General Considerations for Dissolution Methods: Development, Validation, and Transfer

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“Dissolution Concepts and Applications” provides a forum for sharing information about topics associated with in vitro dissolution testing. Our objective for this feature: useful and practical information applicable to daily work situations.

Reader comments, questions, and suggestions are needed to help us fulfill the column objective. Case studies illustrating actual experiences associated with dissolution testing are also welcome. Please send your comments and suggestions to column coordinators Vivian Gray at vagray@rcn.com or Greg Martin at greg.martin@complectors.com, or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS
The following key points are discussed:
• The dissolution method is important because it is the only test that addresses product performance.
• Dissolution methods may be used for different purposes, and the method development process should address these specific goals.
• The validity of the dissolution test must be demonstrated. This is generally accomplished by examining the ruggedness of the method and conducting a series of validation experiments.
• Because the implications of a failing dissolution result can be huge, it is important to have a rugged method with appropriate discriminating power.
• Changes encountered during the product lifecycle may present challenges to the ongoing validity of the method. These include changes to both the drug product and the testing laboratory.

INTRODUCTION
Dissolution is an important test for pharmaceutical products, because it is the only test that addresses product performance. While most dissolution tests are used for quality control purposes, there are several potential applications for dissolution methods, such as aiding in formulation selection, developing a correlation between in vitro data and in vivo data (IVIVC) or justifying post-approval product changes. Dissolution method development should be linked to the intended purpose of the method. Once method conditions have been established, and an understanding of method ruggedness generated, the method must be validated. When sufficient data have been generated with the validated method, a specification can be proposed (which will ultimately require regulatory approval). Over the lifetime of the method (from development to production to site transfer to generic product), there are likely to be multiple changes to both the drug product and the testing laboratory. With each change, the validity of the method may be challenged and must be reestablished.

ABOUT THE AUTHORS
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A quality-by-design (QbD) approach to method lifecycle, which can be very useful for dissolution methods, has been described recently (1). This approach identifies the following stages that occur during the method lifecycle:

- Method design
- Method development
- Method understanding
- Method validation
- Method transfer.

Additionally, product changes, such as composition or batch size, may occur.

**METHOD DESIGN**
What is the purpose of the method? Traditionally, dissolution methods have been developed as quality control tests. More recently, biorelevant dissolution has been useful as a formulation selection tool during drug product development (2). Dissolution tests may be developed in pursuit of an in vivo-in vitro correlation (IVIVC) to justify scale up or post-approval changes or to obtain biowaivers when introducing a lower potency. Hence, it is important to identify the purpose before developing a dissolution method.

What type of dosage form will be tested? Test conditions for an immediate release product will be different from those for an extended release or delayed release product, and the apparatus used for a tablet might be different from one used for a transdermal patch or medicated stent.

One approach is to identify the analytical target profile, incorporating some of the expectations for the method. For example, expectations might include use of a commonly available apparatus for the testing, completion of the release within an hour, variability within a stated tolerance, and rapid or automated assay of samples.

**METHOD DEVELOPMENT**
Dissolution methods always include an apparatus, a dissolution medium, test conditions, and an analytical procedure for testing the samples (3). In most cases, there may be several different methods that could be chosen for dissolution testing. Therefore, a systematic approach for selection of the method may be useful.

**Apparatus**
United States Pharmacopeia (USP) apparatus 1 and 2 (described in USP, General Chapter <711> Dissolution) are used most frequently. These are simple, robust, well standardized, available worldwide, and flexible enough to allow testing for a variety of drug products. The US Food and Drug Administration recommends using these unless they have been shown to be unsatisfactory. Five other official apparatuses are described in USP, and several others have been approved for certain products (with justification).

**Medium**
Generally, dissolution testing should be carried out under physiological conditions (4). Buffers in the physiological range (pH 1.2-6.8 for immediate release, pH 1.2-7.5 for extended release) are recommended. Selection of the medium requires an understanding of the drug substance solubility and solution stability over this pH range. Sink conditions, described as a volume of medium at least three times that required to form a saturated solution of the drug substance, are recommended but not always required (5). Water is generally avoided because test conditions such as pH and surface tension can vary depending on source and may change during the dissolution test itself (4). Surfactants may be used if necessary, either as a wetting agent or to solubilize the drug substance, at concentrations above the critical micelle concentration (CMC) (5). Use of hydroalcoholic medium is discouraged by FDA (4).

**Test Conditions**
Test conditions for the dissolution method include temperature, volume and deaeration of the medium, rotation speed of the apparatus, and sampling time point(s). Temperature of the medium is normally 37°C for oral products and 32°C for transdermal products. Medium volumes of 500, 900, or 1000 mL are common when using apparatus 1 or 2, and volumes up to 4000 mL and as low as 100 mL may be used with non-standard vessels. Rotation speed for apparatus 1 and 2 is generally between 25 and 150 rpm, with 100 rpm typical for apparatus 1 and 50 rpm typical for apparatus 2. Deaeration of the medium may or may not affect the dissolution characteristics of a drug product, so this should be investigated and, if necessary, controlled during testing. Time points for the dissolution method are generally 15, 30, 45, and 60 minutes for rapidly dissolving products. For products that dissolve very rapidly, 10- or 20-minute time points may be used. For extended release products, sampling time points will generally continue until full release has been attained. While a quality control test for an immediate release product might have only one
time point, during development, it is often desirable (or required) to collect samples at several time points to characterize the dissolution profile.

**Analysis**
Most common samples are analyzed by spectrophotometry or by high-performance liquid chromatography (HPLC). Both techniques are commonly available in pharmaceutical laboratories. Spectrophotometry is generally faster; HPLC may be chosen when there is interference from the placebo, to address sensitivity issues, or so that the analysis can be automated. Other techniques have been used, including derivatization and gas chromatography, usually because the nature of the analyte is not amenable to the simpler techniques.

**METHOD UNDERSTANDING**
Once a preliminary choice of method conditions has been made, it is valuable to develop an understanding of the method characteristics and ruggedness. This typically includes running the method multiple times, with real samples, and anticipating the variations that can be expected in the application of the method. These include different lots of drug product, testing on multiple days, use of multiple apparatuses, and testing by different analysts. Observing within test and between test variability may help in the evaluation of future results and may lead to method improvements. In evaluating dissolution method ruggedness, results are generally acceptable when mean values differ by less than 10% absolute when less than 85% is dissolved, and by less than 5% when greater than 85% is dissolved (3).

**METHOD VALIDATION**
The analysis step should be validated as any other analytical method. Typically, this will include specificity, linearity, range, accuracy, precision, and solution stability. In this case, specificity implies no significant interference from the placebo. The range should extend from the lowest expected value to greater than 100%, and typical requirements for linear regression analysis are $r^2 > 0.98$, with a y-intercept not significantly different from zero (3). Accuracy requirements may not be as strict as those for an assay. Precision determinations should include both repeatability and intermediate precision, with expectations for the latter typically <20% relative standard deviation (RSD) at early timepoints and <10% RSD at later timepoints. For the results to be meaningful, it is necessary for the sample solutions to be stable at least for the period of the analysis.

The extent of validation experiments during development may depend on the phase of development of the drug product, with full validation expected by Phase 3.

When there are multiple actives, the method needs to be validated for each of the actives.

**METHOD TRANSFER**
Dissolution methods are often transferred multiple times. Transfers may occur from the developer to routine testing lab, from research and development to quality control, and from one laboratory site to another. Each change requires evaluation of whether the method continues to perform as intended. Options for this evaluation include comparative testing, co-validation between laboratories, method validation or revalidation, or a transfer waiver.

**PRODUCT CONSIDERATIONS**

**Establishing the Specification**
For product release, the specification may include a single time point for a highly soluble, rapidly dissolving drug product. The specification may include multiple time points in the case of a poorly-soluble drug or a product that is not rapidly dissolving, including extended release products. For extended release products, typically there is a minimum of three time points. The first time point is designed to show potential dose dumping, the second is characteristic of the release rate, and the final time point shows the extent of dissolution.

The acceptance criteria generally follow the algorithms described in the Acceptance Tables in USP <711> Dissolution or USP <724> Drug Release. These tables allow multiple stages of testing. A drug product that meets the requirements of any of the three stages is considered to be acceptable.

A drug product is expected to meet the specification throughout its shelf life.

**Formulation Changes**
During the lifecycle of a drug product (including development), there may be many changes, including composition, production processes, scale up, and introduction of new potencies. Each of these requires re-examination of the dissolution method (is the method still appropriate?) and may require redevelopment or revalidation.
CONCLUSION
The performance of a drug product is usually characterized by the dissolution method, making it one of the critical tests in a product specification. Assuring the method is valid for its intended purpose throughout the lifecycle of the product requires an approach that starts with the design of the method and continues through each change that may occur, either to the drug product or to the execution of the dissolution method. At each step, with the potential that the validity can be challenged, it is necessary to do an evaluation. This may include additional validation experiments to demonstrate that the method continues to function as intended and that the data are reliable.

REFERENCES
3. USP, United States Pharmacopeia, <1092> The Dissolution Procedure Development and Validation.

ARTICLE ACRONYM LISTING
CMC Critical Micelle Concentration
FDA United States Food and Drug Administration
HPLC High-Performance Liquid Chromatography
IVIVC In vitro and in vivo Correlation
QbD Quality by Design
RSD Relative Standard Deviation
USP United States Pharmacopeia