Addressing Compliance Concerns During Dissolution Method 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. 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 managing editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:
- Dissolution testing is important because it is the only test that addresses product performance
- Dissolution methods may be developed for different purposes and must be appropriately validated
- As with other methods, it is important to consider the entire method lifecycle
- When developing, validating, or transferring a dissolution method, there is always a potential to encounter compliance issues
- By identifying and addressing these potential compliance issues, the risk of regulatory or inspection questions or non-compliance can be minimized.

INTRODUCTION

Dissolution is an important test for pharmaceutical products. Dissolution 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 that are vital during the
entire product lifecycle. These include activities 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. The product dissolution specification 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.

Due to the importance of the dissolution test, regulators often pay close attention to the entire lifecycle for dissolution methods. Several guidance documents are available (1-5), and it is prudent to address the points raised in these documents to minimize compliance issues.

A quality-by-design (QbD) approach to method lifecycle, which can be very useful for dissolution methods, has been described by Nethercote et al. (6). This approach identifies several stages that occur during the method lifecycle: design, development, method understanding, method validation, and transfer. Additionally, product changes, such as composition or batch size, may occur. At each stage, it can be valuable to identify the regulatory expectations and assure that they are addressed.

**METHOD DEVELOPMENT**

Dissolution methods always include an apparatus, a dissolution medium, test conditions, and an analytical procedure for testing the samples (8). In most cases, there may be several different methods that could be chosen for dissolution testing. A systematic and logical approach must be used.

**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. FDA recommends using these apparatuses 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.

From a compliance perspective, it is important that the apparatus is official as described in the compendia—otherwise significant justification may be required. The apparatus must be appropriated,
qualified, and successfully calibrated (performance verification test [PVT] or mechanical calibration) (9, 10). As with any analytical technique used in a current good manufacturing practice (CGMP) environment, analysts must be appropriately trained.

**Medium**

Dissolution testing should generally be carried out under physiological conditions (1). 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 (11). 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) (11). Use of hydroalcoholic medium is discouraged by FDA (1).

Demonstrating the solubility of the drug over the pH range of interest is a regulatory expectation. If the dissolution is performed to support scale-up or post-approval changes, generally testing at three pH values is expected. If the dissolution medium is not made using standard USP buffer compositions, the composition should be justified. If a surfactant (e.g., sodium lauryl sulfate or Polysorbate 80) is used, there are generally fewer questions if the surfactant has been successfully filed for products containing other poorly-water-soluble drugs. It is important to clearly specify the grade of the surfactant because there can be significant variations in composition and levels of impurities between grades.

**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 degrees C for oral products, and 32 degrees 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 speeds for apparatus 1 and 2 are 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. Deaeration should be investigated and, if necessary, controlled as part of the documented dissolution procedure. 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.

Compliance questions will be minimized if any deviation from the most common conditions (e.g., temperature of 37 degrees C, medium volume of 500 to 1000 mL, and rotation speed of 100 rpm for apparatus 1 [baskets] or 50 rpm for apparatus 2 [paddles]) is justified. The effect (or lack of effect) of deaeration should be demonstrated empirically and the method of deaeration or specific dissolved gas requirements documented. Time points used during development should adequately characterize the dissolution profile, including the ascending slope and the plateau (area where concentration is no longer changing with time).

In addition, sample-handling characteristics such as filtering or automation (including autosamplers) should be well documented. Because there is the potential for significant impact from these operations, providing the results from carefully planned experiments that investigate the potential impact will likely reduce regulatory questions.
**Analysis**

Most 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 to automate the analytical procedure. Other techniques have been used such as derivatization and gas chromatography (GC), usually because the nature of the analyte is not amenable to the simpler techniques.

As with the dissolution apparatus, there is a regulatory expectation that any instrument used for analysis should be qualified and calibrated, and that personnel will be trained.

**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. This work should anticipate the variations that can be expected in the application of the method, such as with 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. During method validation and method transfer, all profile points should be used in the comparisons. 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 (8).

Investing the time and effort to understand and evaluate the potential sources of variability may reap significant benefits from a regulatory or compliance perspective. This evaluation can be particularly valuable when investigating out-of-specification (OOS) or laboratory incidents, which will help in distinguishing between typical variability and atypical situations.

**METHOD VALIDATION**

The analysis step should be validated as any other analytical method. This will typically 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%. 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 a potency 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 for methods used for quality control. These methods typically undergo more rigorous validation than methods that may be used infrequently, such as those for justifying scale-up or post-approval changes (12-15).

When there are multiple active drugs in the dosage form, the method must be validated for each of the actives.

Compliance issues with validation of dissolution methods are similar to those for any analytical procedure. These include a documented validation protocol including well-documented test procedures and clearly identified acceptance criteria, and a final report that documents conformance and addresses any OOS or unexpected results.

**ESTABLISHING THE DISSOLUTION SPECIFICATION**

After method development and testing of multiple lots of the dosage form, the quality control dissolution specification for product release may be determined. The specification must be appropriate for the dosage form. The specification may include a single timepoint for a highly soluble and rapidly dissolving drug product. The specification may include multiple
timepoints in the case of a poorly soluble drug or a product that is not rapidly dissolving. Multiple timepoints specifications are typical for extended release products. There is a minimum of three time-point specifications for extended release products. The first time point is designed to control potential dose dumping (i.e., not more than X% can be dissolved). The second time-point is characteristic of the dosage form release rate. The final time-point specification controls the extent of dissolution (i.e., not less than X% dissolved).

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.

Acceptance criteria for dissolution tests often involve extended discussions with regulatory authorities. Having a complete and well documented database of dissolution results is often helpful for establishing the acceptance criteria. Once the acceptance criteria are established, conformance to the compendial acceptance tables is expected, and any deviations should be thoroughly investigated. Note that occasional progression to second stage testing is not considered a deviation, unless it represents a significant change from historical data.

**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.

**CHANGE CONTROL**

Any changes to the dissolution method over its lifecycle, whether related to formulation changes or analytical methodology, are likely to attract the attention of those evaluating compliance. Establishment of an appropriate change control procedure, including documentation of changes, the rationale for the change, and risk analysis of the impact of the changes is an expectation in a modern regulated laboratory.

**METHOD TRANSFER**

Dissolution methods are often transferred multiple times during the product lifecycle. These include transfers from the developer to routine quality control testing lab, from research and development to quality control, from one site to another, from innovator company to contract lab, and so on. 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.

Expectations for method transfers include providing a transfer protocol listing the analytical procedure, the samples to be tested, and acceptance criteria for the data. After completion of the transfer, a transfer report including documented results in relation to the acceptance criteria should address many of the compliance questions. Responsible personnel must also be prepared to answer questions about instrument qualification and training of analysts at the receiving laboratory.

**CONCLUSIONS**

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. Changes may occur to either the drug product or to the execution of the dissolution method. There is potential that the validity of the dissolution test can be challenged for any of these changes. Evaluation of changes must be conducted, including additional validation experiments as necessary to demonstrate that the method continues to function as intended and that the data are reliable.
Due to the importance of the test in characterizing performance of the dosage form and the many places where compliance issues can be encountered, dissolution testing is often a target for regulatory or compliance questions. Evaluating dissolution testing provides an inspector with insight into procedures in a laboratory related not only to the dissolution results, but instrument qualification and calibration, method validation procedures, employee training, laboratory investigations, and change control procedures. For this reason, inspectors often target dissolution results and reports. This also provides a laboratory an opportunity to showcase its procedures. Laboratory personnel must be well acquainted with regulatory expectations and have addressed those expectations in the generation of the dissolution data.

REFERENCES
8. USP, United States Pharmacopeia 34, General Chapter <1092> The Dissolution Procedure Development and Validation.
12. USP, United States Pharmacopeia 34, General Chapter <1058> Analytical Instrument Qualification.
13. USP, United States Pharmacopeia 34, General Chapter <1225> Validation of Compendial Procedures.
14. ICH, Q2(R1) Validation of Analytical Procedures: Text and Methodology, November 1996.

ARTICLE ACRONYM LISTING
CMC Critical Micelle Concentration
FDA US Food and Drug Administration
IVIVC In Vitro and In Vivo Correlation
OOS Out of Specification
QbD Quality by Design
SUPAC Scale-up and Post-Approval Change
USP United States Pharmacopeia

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