dx.doi.org/10.14227/DT130206P6

# Challenges to the Dissolution Test, including Equipment Calibration

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The dissolution test has been under scrutiny in several areas: the quality-by-design initiative has called for the end to dissolution testing along with all end-product testing (1-3); there is a push for more clinically relevant specifications (4); the potential flaws in the hydrodynamic fluid flow patterns that emerge from the vessel and paddle interaction are being closely examined (5-8), and the use of the calibrator tablets has been questioned (9).

The US Food and Drug Administration's Quality by Design and Process Analytical Technology (PAT) initiatives urge manufacturers to know their drugs and drug products much more thoroughly than is the present practice. Nothing is more disheartening than to see a significant change in the dissolution results on stability of a Phase III product or on a release batch of a commercial product. It is even more discouraging when no assignable cause is forthcoming. The increased knowledge expected from PAT may prevent these "surprises," and that would be a welcome change. The dissolution test is sensitive to a nearly infinite number of parameters, from characterizations of the drug to formulation changes to, most importantly, manufacturing parameters. The dissolution test's ability to show changes in so many parameters is its power and its frustration. The power of the test outweighs the frustration for one simple reason: the dissolution test is the only test that has some degree of relevance to the drug's therapeutic effect in vivo.

Eliminating dissolution as an end-product test would be problematic from several angles. Can you be sure in-process testing has detected all of the many sources of potential change in the final product? How do you measure the stability of the finished product unless you test it at release and then over its shelf life? What is the value of eliminating a proven indicator of stability?

The push for more clinically relevant dissolution specifications and methods is laudable, and in this effort, the method-development stage is particularly critical. Many a naïve manager has viewed the dissolution test as simple…until a problem occurs. Only then does the manager discover that the staff is too inexperienced to understand the test's nuances or sources of error (10). A separate dissolution-testing group is the optimal way to handle both dissolution method development and routine testing. A group allows for better training, accumulation of direct product experience, and useful collaboration. Also, a separate lab devoted to dissolution testing will better avoid equipment problems stemming from vibration and other related issues.

Finding the appropriate method and specifications, especially with the typical low drug solubility, takes time and resources. Cutting corners at this stage is very risky. The robustness and variability of the method should be examined thoroughly. Guidance on method development is available through the literature (11, 12), FDA guidances (13–15), a new proposed informational general chapter from US Pharmacopeia: <1092> The Dissolution Procedure: Development and Validation (16), the AAPS in Vitro Release and Dissolution Testing Focus Group, books (17, 18), and websites that offer chat rooms, bulletin boards, or interactive Q and A (19–21).

Variability should be examined early in method development. High variability is problematic, making trend analyses and F2 (similarity factor) calculations difficult. It is vital to isolate and understand the sources of variability. Observe the physical dissolution process for any anomalous stirring—the test should show gentle homogenous mixing. Note the hydrodynamic flow of the fluid and look for any coning (a concentrated gathering of excipients and drug under the paddle), tablet-sticking, air bubbles, or off-center placement of the dosage form, and examine the dissolution rate to see if there is a correlation. If so, the method developers should make every effort to minimize this anomalous behavior. Our ultimate nightmare is a recall due to dissolution failures. At the method-development stage, all aspects of the mechanical or physical dissolution test that can affect the results should be illuminated and minimized, so that if a dissolution test failure occurs later on, the failure can, with confidence, be attributed to some change in the dosage form.

When the time comes to set specifications, the sponsor and FDA need to collaborate to make the specifications appropriate. The specification must describe a very fine line, preventing bioinequivalent batches from passing, while not being so tight as to fail good (meaning fully effective in vivo) batches that may vary slightly. In some instances, a specification is borderline: over time, the product goes more and more to stage 2 retesting. While batches may

initially pass after retesting, this scenario may produce later failures and recalls. Again, special care should be taken to understand critical parameters and, in particular, the stability behavior of the product.

In later phases of the product's life, method development and validation should include robustness of the method, examining the aspects of the test (as opposed to the product) that may influence the dissolution rate results. Typical parameters such as temperature changes, changes in media concentration, basket attachment type, paddle height, changes in media pH, and many other aspects should be altered within small tolerance ranges to see if the dissolution rate is sensitive to them. Other factors such as the presence of air bubbles or dosage form position in the bottom of the vessel should be examined. This helps in understanding where the method is robust and where it may be overly sensitive, and developers can expand test-method instructions or modify the test itself. The importance of the method development and validation stage cannot be overemphasized; it assists in knowing and characterizing the product well and even predicting the in vivo behavior when an in vivo-in vitro correlation is developed (22). Problems with variability, poor mixing, or fluid flow can usually be overcome with appropriate change in apparatus type, speed of rotation, sinkers, or even media choice.

A discussion of the dissolution equipment is important: the dissolution rate is generated by the stirring mechanism interacting with the dosage form in the media. But always be aware that the dissolution equipment is a machine. The initial quality of the device and its subsequent care and maintenance will influence both operational reliability and product dissolution rate results. Almost any industrial process will produce a lemon occasionally, and any machine will wear out over time. The environment in which it operates will affect performance, and it needs to be running properly at all times. Current practice requires calibrator-tablet tests every six months to assess the performance of the dissolution equipment.

Historically, the calibrator tablets were developed because representatives from the FDA, USP, and the Pharmaceutical Manufacturers of America (now PhRMA) all agreed that vibration (internal and external) was influencing the dissolution results of products (23). The USP was charged with the responsibility of developing calibrator tablets. In the late 70s, the calibrator tablets were put in place and required in <711> USP General Chapter on Dissolution. Today, we still cannot assess vibrational effects except by calibrator tablet tests. A PhRMA study (24) assessing the value of the calibrator tablets concluded that "…some type of calibrator tablets should be maintained until enhanced mechanical calibration is further defined (e. g., establishing a definitive vibration tolerance)." We have to give credit to many of the equipment manufacturers who have diligently designed testers that have less and less internal vibration. Even well designed equipment that is used for years for 1 hour, 8 hours, or even 24 hours a day will eventually show signs of wear, however. Also, the external environment can subject the equipment to vibration from heavy foot traffic, nearby construction, or nearby equipment on the same bench top, to name just a few sources. We must also acknowledge that not all equipment on the global market is solidly designed. With no mechanical means to test vibration other than calibrator tablets, eliminating calibrator tablets from the equipment performance assessment raises great concern. It is well documented that vibration affects the dissolution results (25-29); in some cases, vibration biases the results high, giving a false passing result. The consequences of false passing results should be of great regulatory concern.

Vessel asymmetry is another equipment aspect that is only detected at the present time by calibrator tablets. The glass dissolution vessel is not made from a mold but from a combination of individual hemispheres shaped from standard tubing (30). The irregularities in the vessel shape can cause a change in the fluid flow pattern and hence change the dissolution results. In the early days of dissolution testing, FDA lab scientists pointed this out in a 1982 publication (31). Since then, other publications and practical lab experience in many reputable laboratories have substantiated the finding (32). There are now no available mechanical means of detecting flaws in the vessel design, although there may be some devices on the horizon. Until then, the calibrator tablets are the only appropriate tool for detecting this problem.

Some recent articles suggest that new apparatus for dissolution testing may be better designed to give less variability and more homogenous mixing, and might even produce better correlations with in vivo performance of the product (33, 34). New technology has added to the utility of the dissolution test. Fiber optics have increased automation of on-line testing. Premixed media also increases test efficiency. With novel dosage forms, the other official Apparatus 3, 4, and 7 are becoming more suitable as are modifications of this equipment. There are some performance tests for unique dosage forms that may not use the official equipment; this is fitting and should not be resisted if the advantages are truly apparent. For immediate-release and extended-release dosage forms, however, Apparatus 1 and 2 can typically provide appropriate methods with special care and study during the method-development stage. There are probably 700 compendial tests that use the present apparatus, and these tests are being used for very large numbers of product brands. New products are constantly being approved with dissolution methods using

Apparatus 1 or 2. The investment of resources and scientific data backing these apparatus is indisputable. Newly designed equipment will have to go through the same rigorous qualification and will be sensitive to the same parameters that influence the present equipment. Industry will resist a move away from the equipment it already owns, and the regulatory agencies have many times discouraged, from the podium, proliferation of new equipment types.

Though these arguments may appear to support the status quo, this is not exactly the case. A more thorough understanding of active pharmaceutical ingredients and finished drug products in the early development stages, as recommended, would undoubtedly benefit the industry. More careful training and analyst experience are of paramount importance to minimize sources of variability and maximize sensitivity to critical parameters during the method development stage. New equipment that significantly adds to generation of a proper in vitro release test is a worthy endeavor. Until there are appropriate mechanical means to detect vibration and vessel asymmetry, calibrator tablets are our best tool, though a search for better ways to characterize the equipment should continue.

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*Note: This article has also been published in Analytical Methods, A Technology Primer, a Supplement to Pharmaceutical Technology, 2006 edition, pages 4-13.*