Dissolution Concepts and Applications
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Validation of Dissolution Methods
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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 journal managing editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS
The following key points are discussed:

- Validation of analytical methods in the pharmaceutical industry is a well-known requirement of current good manufacturing practices, and dissolution methods fall under this requirement.
- The validation exercise for dissolution methods addresses key areas including product performance reproducibility, solutions stability, and detection of changes in formulation, process, and product performance on stability.
- The approach to method validation must be based on good science and a defined strategy. This includes identification of the analytical target profile and associated modern expectations for dissolution testing methods.
- Traditional analytical performance characteristics including specificity, accuracy, precision, linearity, and range are discussed.
- Other considerations based on risk evaluation, including deaeration, volume, use of sinkers, filtration, solution stability, carryover from sampling devices, and automation are also discussed.
- Validation of a dissolution method provides documented evidence that the method will be suitable for its intended use and serve as needed during the product lifecycle.

INTRODUCTION
The validation of analytical methods in the pharmaceutical industry is a well-known requirement of the current good manufacturing practice guidelines (CGMPs), and dissolution methods fall under this requirement. While the current regulatory guidances on method validation such as United States Pharmacopeia (USP) general chapters <1225> and <1092>, and International Conference on Harmonisation (ICH) guidance Q2 (R1) (1-3) provide valuable information, the validation of dissolution methods may require investigation into analytical performance characteristics that goes beyond what is included in the guidance documents. This article discusses some practical approaches for addressing both the traditional analytical performance characteristics and some of those that may be unique to dissolution methods.

The validation exercise for dissolution methods actually aims to answer the following questions:

- Is the variability of the method satisfactory and will replicate tests of the same sample result in profiles that are similar to one another?
- Are there any significant analytical solutions stability issues?
- Can the method detect changes in formulation or the manufacturing process?
- Does the method have the capability to detect changes on stability?

ABOUT THE AUTHORS
Gregory P. Martin is president of Complectors Consulting (www.complectors.com), which provides consulting and training in the area of pharmaceutical analytical chemistry. He may be contacted at greg.martin@complectors.com. Vivian A. Gray has 35 years experience in all aspects of dissolution testing and began a consulting business in 2002, V.A. Consulting, Inc., in dissolution testing and related areas. She may be contacted at vagray@rcn.com.
STRATEGY AND APPROACH
As always, the approach to method validation starts with applying good science. Validation should be an exercise that builds on a firm foundation. Considering the lifecycle of a dissolution method, there may be multiple validation exercises. There is an expectation that even before validation begins, a well-defined analytical target profile (4) has been documented and the method has been developed using sound practices based on an understanding of technology and expectations with regard to dissolution (5, 6). These are useful in establishing the acceptance criteria that will be used to evaluate the validation exercises. Additionally, it is useful to carry out experiments to enhance the understanding of the capabilities of the dissolution method. These include investigating the impact of various parameters on dissolution results such as lot-to-lot variability, the influence of different analysts or instruments, or the effect of stability. It is also valuable to have experience with genuine samples that are characteristic of those that will be tested by the method and not just lab samples.

ANALYTICAL PERFORMANCE
Traditional analytical performance characteristics are described in USP general chapter <1225> and in ICH guidance document Q2. These include specificity, accuracy, precision, linearity, and range. It is generally appropriate to consider all of these for dissolution methods, although the extent to which they are evaluated may depend on the phase of the project (7).

Specificity
Specificity is an important characteristic that should be considered early during the method development process (8). This is because specificity requirements often drive the runtime for a chromatographic analysis or the selection of wavelength for a spectrophotometric analysis. There has been a lot of discussion within the pharmaceutical community about the specificity requirements for a dissolution method. Keep in mind that dissolution results are typically reported as integer values. For this reason, interference from small peaks, such as impurities or degradations that are controlled to levels well below 1%, may have no impact on reported dissolution values. However, it is important to demonstrate that there is no significant interference (e.g., >2%) from the dissolution medium, the placebo, or sample manipulation, such as the effect of filters.

Accuracy
When assessing accuracy, the goal is to evaluate the recovery of the active ingredient from the dosage form in the dissolution medium. These experiments generally include multiple replicates that may be carried out at the nominal concentration of 100% dissolved or at several different concentrations covering the range of interest. Some chemists perform these experiments in volumetric flasks while others prefer to perform the experiment in the vessel, using the actual dissolution apparatus. Typical acceptance criteria for recovery in dissolution methods are 97-103%.

Precision
Precision is probably the analytical performance characteristic that generates the most interest and complexity for dissolution methods. Recognize that this actually incorporates a number of different parameters, which we will address in increasing levels of magnitude. For instance, it incorporates the variability from the actual determination, whether we are talking about injection precision for high-performance liquid chromatography (HPLC) or replicate measurements on a UV spectrophotometer. Next is the variability associated with testing multiple replicates of the sample. Usually dissolution testing is performed on multiples of six dosage forms to be consistent with the USP staged acceptance criteria. If the variability associated with these replicates is too high, it could result in the need to perform additional testing. Another aspect that can contribute to the variability is called intermediate precision or ruggedness, and refers to the effects of testing on different days, by different analysts, or on different instruments. Sometimes intermediate precision is simulated by performing robustness testing, in which some of the parameters that may be anticipated to change are intentionally varied. Finally, in some cases, it is necessary to evaluate inter-laboratory variability. It is not uncommon, in the lifecycle of an analytical method, to anticipate that the testing will be performed by more than one laboratory. In these cases, it is important to evaluate the effects of transferring a method from one laboratory to another. The general expectation is that variability at all but the early time points is relative standard deviation (RSD) less than 10% (9). Often the variability is much less than this.

Range and Linearity
The analytical range for the method should include the entire range of anticipated results from the testing.
During validation, it is important to control deaeration. Dissolved oxygen or dissolved gases may be useful in helping to control deaeration. A device for measuring deaeration has a significant effect on dissolution results, and potentially increase the dissolution rate. When integrated tablets, causing them to rise to the surface have also been observed attached to granules of dissolution medium while there may be significant affects to dissolution testing and the magnitude of the impact of automation.

Robustness
With regard to robustness, in addition to the usual parameters that are normally investigated associated with the determinative step, several parameters may be of interest for dissolution methods. These include the buffer concentration, the pH of the medium, the temperature of the medium in the vessels, the rotation speed of the apparatus, and the timing of the samples (10).

Other Considerations—Risk Analysis
There are several other parameters that should be investigated when validating a dissolution method. A rigorous risk assessment is helpful in identifying parameters that may be important. Some of these include deaeration, medium volume, effect of sinkers, filter qualification, solutions stability, carryover during sampling, and impact of automation.

Deaeration. The effect of deaeration is fairly unique to dissolution testing and the magnitude of the impact may vary significantly from one dissolution method to another. Deaeration refers to the process of removing dissolved gases, primarily air, from the dissolution medium. This may be accomplished in a variety of ways, including vacuum filtration, sparging with a less soluble gas such as helium or passing the medium by a gas permeable membrane (11). Some products seem to be unaffected by the presence of gases in the dissolution medium while there may be significant affects with other products. The presence of air bubbles has been observed on the surface of solitude since forms, which might slow down the rate of dissolution, and have also been observed attached to granules of disintegrated tablets, causing them to rise to the surface and potentially increase the dissolution rate. When deaeration has a significant effect on dissolution results, it must be carefully controlled. A device for measuring dissolved oxygen or dissolved gases may be useful in helping to control deaeration.

Volume. It is important to control the volume of the dissolution medium because any changes in volume will affect the concentration of the samples removed. Many laboratories use a graduated cylinder to measure the dissolution medium. There is variability associated both with the measurement in the graduated cylinder and with the transfer process, because there may be some liquid that is not transferred from the graduated cylinder.

Sinkers. Sinkers are sometimes used in dissolution methods, most often to maintain the dosage form at the bottom of the vessel but also to prevent dosage forms from sticking to the vessel. When sinkers are used, it is important to assure consistency from run to run (12). This requires that the sinkers be carefully described in the analytical procedure. When using commercial sinkers, this can be accomplished by specifying the manufacture and part number. When sinkers are fabricated in the laboratory, as is the case when a simple wire coil is used, including adequate descriptions will help to minimize run-to-run variability. Recognize that when a method is being used for multiple potencies, the same sinker may not be appropriate for all of the potencies. For instance, larger capsules may not fit well into a sinker that is optimized for smaller capsules.

Filtration. During validation, it is important to evaluate the impact of the filters used to clarify samples. First, it should be demonstrated that the use of the filter does not cause any interference in the determinative step. Second, it should also be demonstrated that there is no loss of active drug during the filtration process.

Stability. Solution stability should be evaluated for all analytical methods, but is even more important for dissolution methods. Because the dissolution test is normally performed at 37°C, the elevated temperature has the potential to decrease solution stability. Furthermore, because dissolution testing is normally carried out in aqueous media, compounds that are poorly water-soluble may have decreased solution stability, and the solution stability may be affected by the pH of the medium. Acceptance criteria for solution stability vary from lab to lab, and may depend on a number of factors such as the likelihood of needing additional testing, but are generally in the range of 1 to 3% loss.

Sampling device carryover. Carryover effects have been observed when using the same sampling device for multiple vessels or for multiple time points. This practice has been used in many laboratories,
because it is sometimes impractical to use a fresh sampling device for every vessel and for every time point. In these situations, it is important to evaluate any potential carryover effects. Carryover is usually controlled at less than 2%. 

**Automation.** Automation has been used in a variety of ways to assist with dissolution testing. This makes sense because dissolution testing is a time-consuming test. However, it is important to be aware that the introduction of automation has the potential to significantly affect dissolution results (13). It is beyond the scope of this article to address the subject comprehensively. It should be sufficient to point out that dissolution testing is unique in that the concentration of active ingredient in the dissolution vessel may be changing rapidly during the execution of the test. Therefore, introduction of automation has significant potential to affect the results. It is important to remember that regulatory agencies, when testing a commercial product, are likely to use manual procedures, and therefore, a correlation between manual and automated results should be well characterized.

**CONCLUSIONS**
The goal of validation of a dissolution method is to provide documented evidence that the method will be suitable for its intended use. Validation builds on a foundation of identified requirements, sound development practices, and good science. Risk analysis aids in the identification of additional parameters that may need to be evaluated, and the analytical target profile can inform the acceptance criteria for evaluating whether or not the method meets the goals.

**REFERENCES**