

# Dissolution

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## 18.1 Introduction

A dissolution test, as a release test, is required for virtually all pharmaceutical products that are not true solutions. Dissolution testing monitors the rate at which a solid or semisolid pharmaceutical dosage form releases the active ingredient(s) into a liquid medium at liquid/solid interface, under standardized conditions of temperature, agitation, flow rate, volume, and media composition. Dissolution, or in vitro release, of the drug substance from the product into a typically aqueous-based medium, is linked to the release of the drug into the body, making it available for absorption, and then efficacy or clinical outcome. Scientists have been conducting dissolution studies for many years. However, it was not until 1970 that dissolution testing was officially recognized as an indicator of product quality when it was incorporated into 12 monographs in the United States Pharmacopeia/National Formulary (USP/NF), USP XVIII/NF XIII.<sup>1</sup> In the current US Pharmacopeial edition, USP 42, nearly all monographs for solid dosage form include a dissolution test.<sup>2</sup> Dissolution is defined as a Category III test by the USP, i.e., an “Analytical method for the determination of performance characteristics ...”<sup>3</sup> Dissolution testing is primarily used in industry as a quality control tool to monitor the consistency

of formulation and manufacturing processes of the dosage form. Dissolution is considered by most regulatory agencies as a highly critical quality characteristic for most solid dosage forms.

The regulatory agencies use the dissolution test to provide a quality connection from a pivotal biobatch, if available, to the commercialized product. For this reason, the dissolution test development and validation are critical factors in insuring that the test is robust and clinically relevant. Clinical relevance comes from developing a test that provides understanding of the product release mechanism(s) and, in the highest form, an in vivo–in vitro correlation (IVIVC). The acceptance criteria in the drug product (DP) specification or compendial monograph attributed to a clinically relevant test are most important and useful.

An important regulatory development has been the FDA Guidance for Industry, “*Waiver of In Vivo Bioavailability and Bioequivalent Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)*.”<sup>4</sup> This guidance is extremely significant because it affirms that under some circumstances the dissolution testing can be used in lieu of bioavailability (BA) and/or bioequivalence (BE) clinical studies. Whereas this guidance applies only to immediate release products, the general

principles therein may be also be applicable to controlled release (CR), or extended release (ER) under certain circumstances. The guidance defines the four classes of the biopharmaceutics classification system and the methods for determining the three aspects—solubility, permeation, and dissolution.

Development and validation of dissolution methods require a good understanding of the theory of dissolution and the roles of the key parameters of the dissolution test. A complete dissolution validation package would consider at a minimum the dissolution apparatus used, equipment qualification requirements, and any appropriate governmental or regulatory guidelines. Therefore, it is important to address these issues here in the context of dissolution test validation.

## 18.2 The dissolution test

In order for a dissolution test to demonstrate the unique dissolution characteristics of the dosage form, the dissolution procedure should be based on the physical and chemical properties of the drug substance as well as the dosage form design. Some of the physical–chemical properties of the drug substance and media which influence the dissolution characteristics are

- solubility in water and other appropriate solvents
- ionization constants
- solution stability
- particle size/surface area
- crystal form
- common ion effects
- ionic strength
- buffer effects
- octanol/water partition coefficients
- effect of temperature on solubility

Once the drug substance properties have been determined, the actual dosage form needs to be

considered. The analyst developing the dissolution test needs to know, for example, whether the dosage form is a tablet, capsule, semisolid (ointment or cream), or transdermal, and whether it is designed for immediate release or controlled release of the drug product. Of key importance is the potency of the dosage form or the amount of drug to be delivered and the rate at which the drug is to be delivered. This is related directly to the mathematical expression of dissolution rate, which is defined by the Noyes–Whitney equation:

$$\frac{dW}{dt} = k_1 S (C_{\text{sat}} - C_{\text{sol}}) \quad (18.1)$$

where

$dW/dt$  = the dissolution rate

$k_1$  = the dissolution rate constant

$C_{\text{sat}}$  = the concentration of a saturated solution

$C_{\text{sol}}$  = the concentration of the solution at any given time

$S$  = the surface area of the solid

In vivo, the gastrointestinal tract acts as a natural sink, provided the drug is rapidly absorbed as it dissolves. In vitro, sink conditions are simulated by using either a large volume of dissolution medium or by replenishing the medium with fresh solvent at a specific rate. By keeping the volume of dissolution medium at least three times greater than the saturation volume, sink conditions are approximated. When sink conditions are achieved,  $C_{\text{sat}} \gg C_{\text{sol}}$ , and Eq. (18.1) simplifies to

$$\frac{dW}{dt} = k_2 S \quad (18.2)$$

where

$k_2$  = a dissolution constant =  $k_1 C_{\text{sat}}$

In this case (Eq. 18.2), the dissolution rate is characteristic of the release of active ingredient from the dosage form rather than the solubility in the dissolution medium. Therefore, sink

conditions are one of the main experimental parameters to be controlled in dissolution testing. Sink conditions can be achieved by the appropriate selection of the dissolution apparatus and dissolution medium.

## 18.2.1 Apparatus

The USP General Chapter <711> *Dissolution*<sup>5</sup> describes several apparatus types used in dissolution testing. Other compendia such as the Pharmacopoeia of Japan (JP),<sup>6</sup> the British Pharmacopoeia (BP),<sup>7</sup> and the European Pharmacopoeia (Ph. Eur.)<sup>8</sup> all include the Apparatus 1 and 2 dissolution equipment as described in the USP. The USP Apparatus 1 (basket) and Apparatus 2 (paddle) are by far the most frequently used for immediate release and most extended-release dosage forms. The USP Apparatus 1, 2, 3, and 4 are described in detail below. The USP Apparatus 3, 4, 5, 6, and 7 are used less frequently than Apparatus 1 and 2, but are being used more frequently for characterizing the release of the active ingredient from novel dosage forms.<sup>9</sup> Descriptions of USP Apparatus 5, 6, and 7 are found in the USP General Chapter <724> *Drug Release*<sup>10</sup>; these are devoted to transdermal patches. In vitro release of transdermals is described in more detail in Chapter 19.

### 18.2.1.1 USP Apparatus 1 (basket)

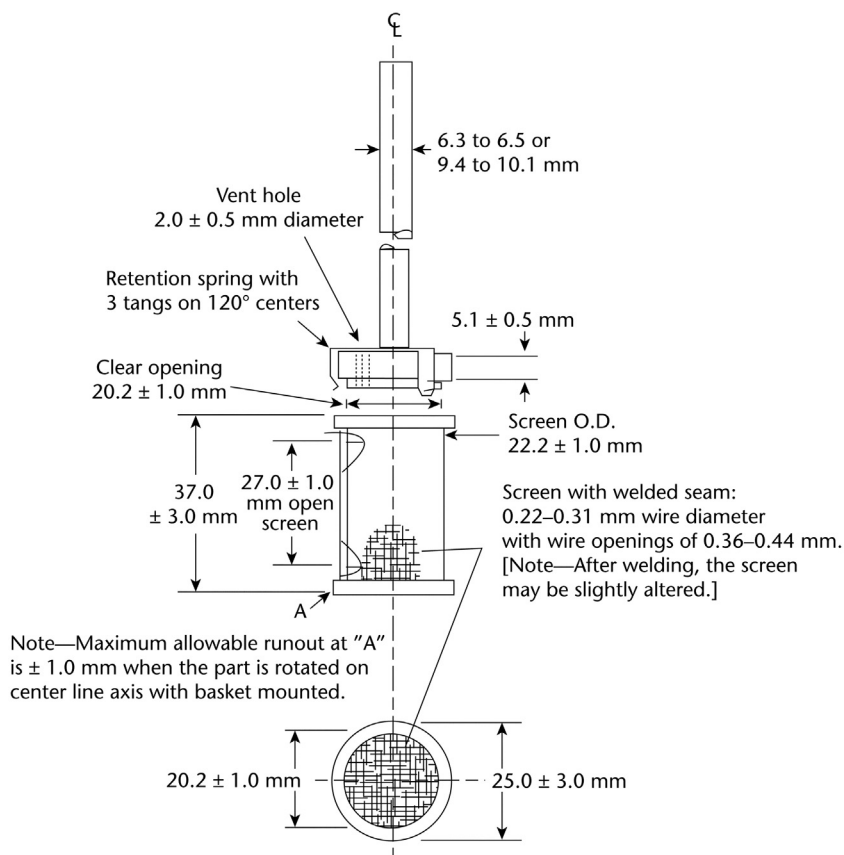
The USP Apparatus 1, shown schematically in Fig. 18.1, consists of a covered vessel of specified shape and dimensions and capacity of 1000 mL, a metallic shaft one end of which attaches to a motor, and a cylindrical metallic mesh basket that attaches to the opposite end of the shaft. The dosage form is placed inside of the basket and the basket assembly is immersed in the dissolution vessel containing a minimal volume of dissolution medium and rotated at a specified speed.

### 18.2.1.2 USP Apparatus 2 (paddle)

The USP Apparatus 2 is currently the most frequently used apparatus for the dissolution testing of solid dosage forms. The dissolution vessel used with this apparatus is the same as for the USP Apparatus 1. However, the basket assembly is replaced by a paddle of specified dimensions as shown in Fig. 18.2. With this apparatus, the dosage form is dropped directly into the vessel containing the dissolution medium and allowed to sink to the bottom; the paddle is then rotated at a specified speed but can be immersed in the vessel when the dosage form is dropped as long as the rotation device is switched off; this is the common industry practice. The USP specifies placing the dosage form in the apparatus and immediately operating at a specified rotational speed. The USP does not state whether the paddle can or cannot be immersed prior to addition of the dosage form, only that the rotation be started after the dosage form has been added. However, experience has shown that care should be taken to ensure that the dosage form sinks to the bottom of the vessel and does not stick to the sides, which can result in different dissolution profiles. Dosage units that float should be weighed down with a sinker (see Section 18.3.3. Sinkers) or tested with USP Apparatus 1.

### 18.2.1.3 USP Apparatus 3 (Reciprocating Cylinder)

The Reciprocating Cylinder, shown in Fig. 18.3, is often used as a research tool where a change of pH in the media during the test is necessary, for example, when testing enteric coated tablets. The dosage unit can be moved from row to row, with the vessels in each row containing media of different pH or composition. The equipment has a special configuration for beaded products; the beads are contained by the screens in the upper and lower parts of the cell, yet the reciprocating motion allows for good mixing. The typical media volume is 200–250 mL.



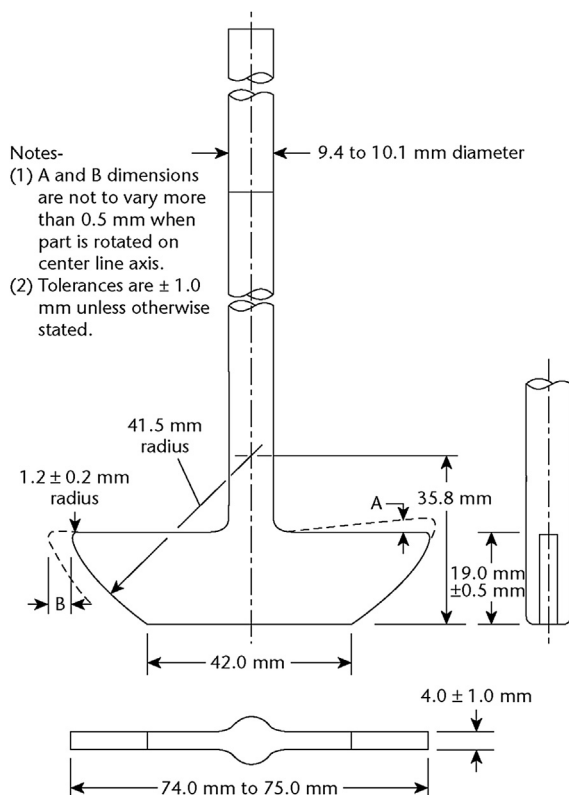
**FIGURE 18.1** USP Apparatus 1, basket. Reproduced with permission from *The United States Pharmacopeial Convention (USP)* ©2017.

#### 18.2.1.4 USP Apparatus 4 (flow-through-cell)

In USP Apparatus 4, the drug product is positioned in a cell through which the dissolution medium flows constantly, dissolving the drug dosage unit. The liquid passes through a filter at the top of the cell and is then collected in a reservoir. Because of the constant flow of media, an extended-release product matrix can be monitored, or a poorly soluble product can continually be in a sink environment. A diagram of a unique flow-through-cell is shown in Fig. 18.4.

## 18.3 Method development

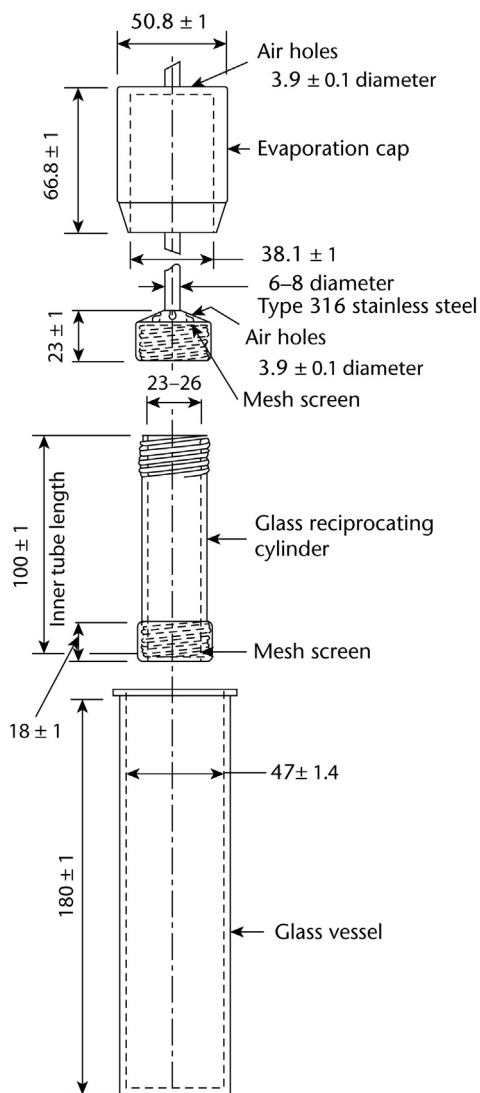
The reader is referred to a number of seminal articles describing the development of dissolution methods in the literature.<sup>11–15</sup> There is also a comprehensive chapter in the USP, General Chapter <1092>, titled *USP General Informational Chapter, The Dissolution Procedure: Development and Validation*, which is an excellent resource for method development and validation.<sup>16</sup> The ICH Harmonized Tripartite Guideline Q2A: *Text on Validation of Analytical Procedures* is also a useful resource.<sup>17</sup>



**FIGURE 18.2** USP Apparatus 2, paddle. Reproduced with permission from *The United States Pharmacopeial Convention (USP)* ©2017.

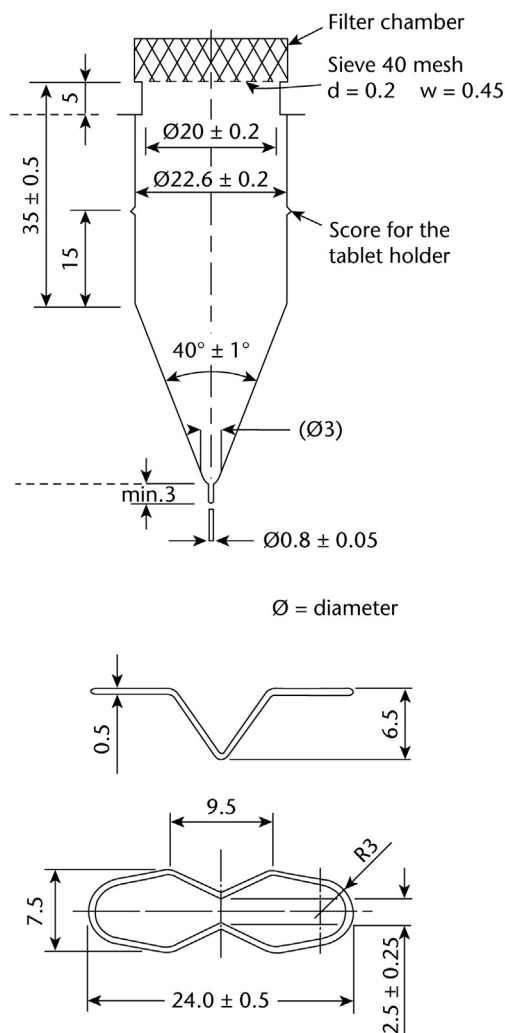
### 18.3.1 Solubility

The solubility of the drug substance is an important, though not the only, driving force in the dissolution test (Eqs. 18.1 and 18.2). It is, however, important first to know the solubility in three physiologically relevant media: 0.1 M HCl, 4.5 pH buffer, and 6.8 pH buffer. Therefore, the analyst should be familiar with the BCS classification system<sup>4</sup> and characterize the drug according to the criteria provided (solubility and permeability). Poorly soluble drugs may require using alternative media, typically ones containing surfactants. Following an understanding the solubility of the drug substance, the dissolution rate of the drug



**FIGURE 18.3** USP Apparatus 3, Reciprocating Cylinder. Reproduced with permission from *The United States Pharmacopeial Convention (USP)* ©2017.

substance in the formulation becomes the focus of the method development. Proteolytic enzymes may also be needed to dissolve pellicles formed during the dissolution testing of gelatin capsules, which can impede the release of the drug.



**FIGURE 18.4** USP Apparatus 4, flow-through-cell. Reproduced with permission from *The United States Pharmacopoeial Convention (USP)* ©2017.

### 18.3.2 Choice of media

The evaluation of dissolution media starts with the medium or media in which the drug is most readily soluble. The type of formulation then is considered. For fast dissolving drugs, the current FDA Guidance<sup>18</sup> recommends

0.1 M HCl. For an extended-release product, typically a pH 6.8 buffer is used because it most resembles the pH of the small intestine. For a delayed release formulation, the medium typically consists of an acidic stage followed by a pH 6.8 buffer stage.<sup>5</sup> For poorly soluble drugs where a solubility enhancer may be necessary, there are a range of surfactants that may be suitable. The most commonly used surfactants are sodium lauryl sulfate (SLS) and polysorbate solutions, used at concentrations of 0.5%–2%. The chosen concentration of surfactant must be justified scientifically to be used in a regulatory test.

### 18.3.3 Sinkers

Dosage forms that tend to float or move around during the course of a dissolution test can result in variability and bias. Sinkers are often used to hold such dosage forms in place during a dissolution test. There are many types of sinkers that may be used in dissolution testing, including custom-made sinkers, and commercially manufactured sinkers. However, it is important that the construction of the sinker is well-defined because it can contribute to variability of the results. Therefore, when sinkers are necessary, detailed descriptions and an explanation of why a sinker is necessary must be stated in the method. When comparing different sinkers (or sinker vs. no sinker), tests must be run concurrently with each sinker. Each sinker type must be evaluated based on its ability to maintain the dosage at the bottom of the vessel without inhibiting drug release. A comparison of the different sinker types (or no sinker) is performed using the same criteria for intermediate precision described in USP General Chapter <1092>.<sup>16</sup> The variability at all time points should be evaluated when the method calls for the generation of a dissolution profile rather than a single point determination.

When transferring a method, the sinkers must be duplicated as closely as possible in any subsequent testing facility.

### 18.3.4 The “infinity point”

The final time point selected for a dissolution test does not necessarily correspond to complete dissolution of drug. However, it is important to establish that, at some point, or under some conditions, all of the drug material can be accounted for. This can be particularly useful when investigating out-of-specification results obtained by Assay or Uniformity of Dosage Units (see Chapter 11 for further discussion). Performing an “infinity point,” or fast-stir, test in the early product development phases or routinely on samples in testing can give an indication of the recovery/accuracy, assuming that the drug is present at or around 100% of the label claim in the dosage unit. To obtain an infinity point, during the normal test after the last time point is pulled, the paddle or basket speed is increased to at least 150 rpm for 30–60 min without stopping the test, after which time a further sample is taken. Although there is no requirement for 100% dissolution in the profile, the infinity point can provide supportive data when compared to the content uniformity data. The infinity point data for all six vessels can be compared to the Assay and the Uniformity of Dosage Units (weight uniformity or content uniformity) values in terms of the mean and the variability. This may also provide useful information as to any artifacts from the dissolution method and/or the dosage form interacting with the media.

### 18.3.5 Determination of discriminatory power

The regulatory agencies often ask sponsors to support the discriminatory ability of the selected dissolution method. This discriminatory ability may be demonstrated by comparing dissolution

profiles of formulations that are intentionally manufactured with deliberate, meaningful variations of the most relevant critical manufacturing parameters (e.g.,  $\pm 10\%$ – $20\%$  change to the ranges of selected parameters).<sup>19,20</sup>

In the past, dissolution tests have generally been conducted at a single time point resulting in fast dissolution rates. However, unless the product is a very rapidly dissolving BCS Class 1 or BCS Class 3, a slower profile test is typically needed to give pertinent information about any change in the product. Regulatory agencies prefer a method that is clinically relevant, that is, one that shows an IVIVC or certain discriminatory power. Since clinically relevant specifications are becoming a requirement for the characterization and regulation of drug products, laboratories are putting more resources into method development and the establishment of an IVIVC or at least some relationship between dissolution and in vivo performance.

### 18.3.6 Design of experiments and quality by design concepts and variations

Development of a dissolution method should be a team effort. Formulators provide information on the critical quality attributes (CQAs) and provide the prototype dosage forms that reflect important formulation and processes variables studied by DoE studies. The principles of quality by design (QbD) can also be applied to assessment of dissolution methods. The DoE studies may be useful to establish the critical factors that influence the dissolution rate. The DoE can evaluate the dissolution operational parameters<sup>21,22</sup> or the product formulation release attributes.<sup>23,24</sup> They may provide understanding of the release mechanisms and determine if the dissolution method can show change to the CQAs. As an application of a QbD approach to dissolution, Li, et al. were able to demonstrate the ability to predict changes in drug dissolution rate over time as a function of



temperature and humidity for two active ingredients in an immediate release dosage form using ASAP<sup>prime</sup>®, an accelerated stability assessment program.<sup>25</sup> Such applications could be useful in setting specifications to cover the shelf life of a product. More detailed information on DoE is found in Chapters 2 and 4.

### 18.3.7 Drug substance properties

Knowledge of drug substance properties, especially the pH-solubility profile and the effects of surfactant, is essential. The effects of excipients in the formulation on the solubility of the drug should also be well-understood. One needs to anticipate precipitation of the drug as the pH changes in the dissolution media, or as the amount of drug in solution increases. When the drug substance is poorly soluble, complete dissolution in the standard may not be possible without long sonication or mixing; therefore, it is common practice to use a small amount of alcohol to completely dissolve the drug substance in the standard solution. There is a limit of 5% alcohol in the final solution so that the final measurement is not adversely affected.

### 18.3.8 Drug product properties

Assuming the drug product is manufactured consistently, highly variable dissolution results may indicate that the dissolution method is not robust, which can result in difficulty identifying trends and effects of formulation changes. There are two major causal factors that influence variability: mechanical and formulatory. Mechanical contributions to variability can arise from the dissolution method conditions chosen, such as incomplete deaeration and inappropriate paddle speed. Careful visual observation of the dissolution process in the vessel can often help identify whether mechanical conditions, such as rotational speed, need to be altered (visual and/or

video recording of the dissolution experiments can also be particularly useful in this regard).

Contributions to variability in the dissolution results from the formulation can arise from poor uniformity of dosage units (either weight variability or content variability), and reactions in the dissolution solution leading to drug degradation *in situ*. Film coating may cause sticking of the dosage form to the vessel walls, thereby changing the hydrodynamics of the test. Upon aging, gelatin capsule shells are known to form pellicles. Tablets may become harder or softer over time, depending upon the excipients and interaction with moisture, which may affect disintegration and hence the dissolution rate.

### 18.3.9 Method and equipment parameters

The final dissolution method used for routine analysis should reflect the optimum choice of medium, apparatus, and the sampling time points. The apparatus can be operated using various speeds (typically 50–100 rpm with Apparatus 1 and 2), dip rate (Apparatus 3), and flow rate (Apparatus 4). The sampling time points may vary from 5 min with a rapidly disintegrating tablet or suspension to many hours with extended-release products.

### 18.3.10 Manufacturing process

The various processes involved in the manufacture of the dosage form should be investigated to determine which factors will affect the release mechanism. The factors most likely to affect the dissolution of tablets are compression force, blending time, lubrication time, and temperature.

## 18.4 Method validation

As mentioned above, the USP General Informational Chapter <1092><sup>16</sup> is an excellent

resource for dissolution method validation. Validation of a dissolution test method consists of two parts. The first part, and the part that will be given the most emphasis in this section, is the validation of the dissolution test method, that is, the actual dissolution run and the removal of the samples for analysis. The second part is the analytical method used to determine the concentration of the drug, which is usually UV spectrophotometry or HPLC with UV detection.

There are numerous aspects of the dissolution procedure that require validation and there are different levels of validation depending on the phase of development. In early development, filtration, deaeration, linearity, precision, solution stability, selectivity, and accuracy/recovery should be considered as part of the validation. During later development (Phase III and beyond) full validation studies, to include intermediate precision, automation and robustness are added. This chapter focuses on validation of methods used in later stages of development, when full method validation is necessary.

It is presumed that full validation will be conducted on the final dissolution test method established for a new drug application or a marketing authorization application. The ideal dissolution method should exhibit a low variability in the dissolution results, the solutions should be stable in the dissolution media, and there should be an established dissolution profile, using a minimum of three time points. The dissolution profile should be gradual with at least two points at or below 85% of the active dissolved to satisfy the rules for an  $f_2$  analysis.<sup>26</sup> The  $f_2$ , or similarity factor, is a critical tool for demonstrating bioequivalence, although it is not needed for BCS Class I drugs where the product dissolves rapidly, e.g., 85% in 15 min within the relevant range of pH. The dissolution test method should be discriminating and capable of detecting changes in the product CQAs, as these attributes would influence the release of

the drug and can be characteristics of the drug substance, the formulation, the manufacturing process, or stability.

Once the appropriate dissolution conditions have been established, the analytical method should be suitably validated. The validation parameters may vary depending on the intended use, but will typically include, at a minimum, linearity and range, accuracy, precision, specificity, solution stability, and robustness. Each of these analytical parameters is discussed in detail elsewhere in this book in various contexts, and the general principles are the same for dissolution. This section will discuss the validation of parameters unique to dissolution testing. All dissolution testing must be performed on a qualified dissolution apparatus meeting the specified mechanical and performance standards and with qualified associated analytical instrumentation for the determination of sample concentrations.

### 18.4.1 Linearity and range

Linearity and range demonstrate the ability of the dissolution method to obtain test results over the range of expected concentrations that are proportional to the concentration of the analyte in the sample. Analytical detector linearity should be established over the entire range of concentrations expected during the procedure. For immediate release formulations, a concentration range of at least 50% of the lowest concentration expected in the dissolution vessel to 120% of the highest concentration is sufficient. For extended-release products, the concentration range should extend from approximately 10%–120% of that expected from dissolution of the entire dose. If an extended-release product is formulated in multiple strengths, the detector linearity should be confirmed from 10% of the lowest strength concentration to 120% of the highest strength concentration. When justified, it may be acceptable to use different dissolution conditions to

cover a product where there is a large range of dosage strengths. For fixed dose combination products, it may be acceptable to use different dissolution methods for the analysis of the individual drugs provided suitable justification is provided.<sup>25</sup> Typically, the concentration range is divided into five evenly spaced concentrations. All samples should be heated to 37°C (or the specified dissolution temperature). The temperature is especially important if the samples are poorly soluble and/or near sink conditions in the vessel.

Solutions of drug substance used in determining linearity and range can be prepared with placebo to show if the sample solution is reflective of a real dissolution sample. Whenever possible, all solutions should be made from a common stock, using the dissolution media as the diluting solvent. As mentioned earlier, alcohol may be used to enhance the solubility of the poorly soluble drug. No more than 5% organic is allowed in the final solution. Linearity is generally considered acceptable if the linear regression correlation coefficient is  $\geq 0.997$ , and the y-intercept not significantly different from zero at the 95% confidence limit.

### 18.4.2 Bias and accuracy

The bias of a method is a measure of the agreement between the measured value and the true value. The accuracy of the dissolution method, which is determined from the recovery of drug spiked into the dissolution medium, is a measure of the agreement between measured value and a reference (or standard) value. In general, accuracy is determined by preparing multiple samples containing the drug and other constituents present in the dosage form (e.g., excipients, coating materials) ranging in concentrations from below or at the expected concentration of the lowest profile point to above the highest concentration upon full release. The samples can be prepared either

in situ or in a flask with media heated to 37°C. The drug must be fully dissolved before an accuracy aliquot is taken. The order of addition of the drug substance to the media, either before or after the excipients, may be critical. For example, some drugs need to be added to the media without the excipients to wet properly, or vice versa where the excipients need to mix first before the drug substance is introduced. For poorly soluble drugs, the mixing process may take some time before the drug is fully dissolved. In some cases, drug powder cannot be added directly, and addition of a diluted stock solution is appropriate: for example, when the amount of drug required is too small to weigh accurately or the drug is electrostatic. The generally acceptable measured recovery is 95%–105% of the amount added. Low recoveries may be due to excipient interference<sup>27</sup> or incomplete dissolution.

### 18.4.3 Intermediate precision and reproducibility

Intermediate precision evaluates the effects of random events or variations in the laboratory on the precision of the dissolution method. If possible, it is advisable to change the environmental conditions in the laboratory to the extent possible to anticipate potential issues during method transfer to other laboratories. Many times, method transfer studies are not successful because insufficient emphasis was placed on the intermediate precision study to rigorously challenge the method to intra-laboratory and inter-laboratory variations. Intermediate precision should be evaluated at all time points of the dissolution profile using the drug product for evaluation.

The dissolution profiles on the same drug product should be determined by at least two different analysts, with each analyst individually preparing standard solutions and media (with different lots of reagents, if available).

The analysts should use different dissolution baths, different HPLC systems (including columns and mobile phases), and the tests should be performed on different days. Each analyst should test and analyze 12 dosage unit samples from the same lot. The mean values and the relative standard deviations at each time point of the dissolution test between each analyst are compared. The results are generally considered acceptable if the absolute mean difference does not exceed 10% at time points when less than 85% of the drug is dissolved and does not exceed 5% for time points equal to or above 85% dissolved drug.<sup>16</sup> The 10% acceptance criteria may appear generous, but high variability of some products, especially at the earlier time points, is well established because it is sensitive to variability in tablet disintegration as well as dissolution. However, if variability of individual values is low and a 10% difference in means obtained, it may be prudent to look for causes of the bias. It is also useful to look for individual values that appear to be significantly outside the values for the other samples. Box-plots and quantitative statistical tests for differences between the two analysts should also be considered. It is important to note the same acceptance criteria should be used for method validation and method transfer. Method reproducibility is a measure of inter-laboratory variability and is best measured during method transfer. Inclusion of the receiving laboratory in the method validation studies and training of the analysts at the receiving laboratory can significantly improve the chances of successful transfer of dissolution methods. Even seemingly simple steps, such as how the tablets are added to the dissolution vessels, can affect the test results. For example, a difference in dissolution results may be observed if one analyst adds the tablets while the paddles are rotating and the other analyst adds the tablets before rotation of the paddles is started (the correct procedure).

#### 18.4.4 Repeatability/method precision

A third form of precision, repeatability, or method precision, is determined by replicate measurements of standard and sample solutions prepared at five concentrations by a single analyst on a single instrument. To show the precision of the sample solution, the DS may be prepared in a solution with placebo as a substitute. It is important that the drug be completely in solution for this evaluation and preparation of a standard solution may be facilitated by first dissolving the drug in small amount of alcohol if necessary. However, the alcohol content in the final solution should not exceed 5% when the samples are measured by UV spectrophotometry to avoid shifts in the absorption spectrum. General acceptance criteria for repeatability for HPLC procedures are <1% RSD and for UV analysis <2% RSD. Higher RSDs may be acceptable when working with low concentrations.

#### 18.4.5 Specificity

Specificity is the ability of the method to determine the analyte of interest in the presence potential interferences. Whereas it is not an absolute requirement that the analytical procedure used for the analysis of dissolution samples, it is convenient to use the same stability indicating HPLC method used for Assay (see Chapters 9–11) because the validation of the Assay method can incorporate experiments that simultaneously demonstrate the dissolution method is fit for purpose. UV spectrophotometry is simpler and faster than HPLC; however, the absence of interference from excipients, inks, dyes, and capsule shells should be demonstrated. Interference from impurities related to the drug can be ignored provided they do not exceed 2% of the drug concentration in the sample.

If UV spectrophotometry is used for the analysis of dissolution samples, it is good practice to

demonstrate by HPLC that the drug does not degrade significantly during the dissolution experiment producing degradation products with different UV spectra. The USP allows for a correction for the capsule shell interference provided the interference does not exceed 25% of the labeled drug concentration, in which case the analytical method should be modified to reduce the interference.<sup>5</sup>

### 18.4.6 Solution stability

Solution stability is the determination of stability of sample and standard solutions over time under normal laboratory conditions. The standard solution and the sample solution are stored under representative conditions over a reasonable period of time and the results are compared with those obtained with freshly prepared standard solutions. The standard solution should be at expected profile point concentrations not exceeding 120% of the dosage form dissolved. Sample solutions should also be compared in the same manner to a freshly prepared sample; a placebo plus drug solution could be used instead of an actual sample. The acceptable range for standard and sample stability samples is 98.0%–102.0% of the freshly prepared solutions (note: both increases and decreases in concentration can occur due to solvent evaporation or chemical degradation, respectively).<sup>16</sup> An expiration date and storage conditions should be established based on the results of the experiments, ideally at least 8 days, which would allow storage of the standard and sample solutions for up to 1 week at room temperature. The sample and standard solutions should be tested at regular intervals over the preferred expiration period in the event that shorter storage times are necessary. It is also good practice to store the solutions in the refrigerator in the event that the drug is not sufficiently stable for room temperature storage. Very occasionally, storage of frozen samples

may be necessary for very unstable drugs. If storage under refrigerated or frozen conditions is necessary, the samples must be allowed to come to room temperature and inspected very carefully for particulate matter to ensure that any precipitated materials are redissolved before analysis.

### 18.4.7 Robustness

The robustness is the ability of the method to resist small changes in instrument settings and the experimental conditions. As discussed in Chapter 10, the preferred approach to robustness testing in dissolution is by a statistical design of experiments (DoEs) approach, in which relatively large changes to the instrument settings (notably stir rate, filters and temperature, flow rate of the sampling device), composition of the dissolution medium (pH, volume, buffer concentration, surfactant concentration, aeration), as well as sample position in the apparatus, and the design of the sinkers (if applicable), are made in a systematic fashion to define the design space of the method. Mathematical treatment of the experimental data allows for the prediction of the control space within which smaller changes to the instrument settings and the composition of the dissolution media will not significantly affect the rate of dissolution. The control space should never be more restrictive than the specifications of the instrumentation or the total errors of the analytical measurements (see Chapters 2 and 9 for a more detailed explanation of total analytical errors). Thorough evaluation of the robustness of the dissolution method is essential for successful method transfer and to ensure that the performance of the method is maintained over long periods of routine application. If the analysis of dissolution samples is performed by HPLC, typically using the Assay procedure, the nature of the dissolution samples should be taken into account during validation.

### 18.4.8 Other validation parameters

Other aspects of validation may include carryover of residual drug, effect of an in-residence probe (e.g., auto-sipper or fiber optic probe), adsorption of drug onto the vessel, tubing and filters, and cleaning and/or rinse cycles. Evaluation of the filter generally includes preparation of a suitable standard solution (lowest and highest profile concentrations are recommended) and a completely dissolved sample solution. For the standard solutions, results of the filtered solution (appropriate discard volumes should be determined beforehand) are compared to those of the unfiltered standard. For the filtered sample solution, results should be compared to a fully dissolved and centrifuged sample solution. The acceptable range for standard and sample filtration efficiency is generally between 98% and 102% of the unfiltered standards solutions and unfiltered but centrifuged sample solution.

## 18.5 Automation

Automated sample collection has become much more widely used in recent years. If possible, when conducting a validation of an automated method, there should be a comparison to a manual sampling method for the same dissolution conditions. All profile time points should be evaluated. This validation can be done in one of two ways: (1) when the drug dissolution results are not highly variable, and understanding the effect of an in-residence probe is desired, two concurrent runs (same sampling intervals,  $n = 6$ ) using manual and automated sampling methods are compared using the criteria established for intermediate precision, or (2) if the dissolution results are highly variable (i.e., the RSD is above 20% at time points of 10 min or earlier and 10% RSD or above at later time points), the analysis can be performed by

pulling the sample from the vessel simultaneously by manual and automated sampling methods for each time point. Note that the correction for the volume withdrawn from the medium is doubled in the latter case.

## 18.6 Sources of error in dissolution testing

Several factors can contribute to errors and bias in a dissolution test, arising from the equipment (apparatus and dissolution vessels), dissolved gases, standard solutions, and reference standards, vibration and other mechanical aberrations. Critical factors related to running the method that are not well documented in the written procedure can be a common cause of failed method transfers.

### 18.6.1 The dissolution apparatus

USP Apparatus 1 and 2 can be sources of error if not closely inspected before using. Obviously, dimensions should be as specified.<sup>5</sup> In cases of both baskets and paddles, shafts must be straight and true. The paddles are sometimes partially coated with Teflon. This coating can peel and partially shed from the paddle, causing flow disturbance of hydrodynamics within the vessel. Paddles can rust and become nicked or dented; this can adversely affect dissolution hydrodynamics and also be a source of contamination. Thorough cleaning of the paddles is important to preclude carryover of drug or medium.

The baskets need special care and examination. The basket mesh/screen can become frayed, misshapen, or warped with use. Screen mesh size may change over time, especially when used with acidic medium. There are different designs for attaching baskets to shafts. The attachment can be with clips or with O-rings. These attachment variations can affect dissolution results, depending upon the product;

therefore, this factor should be taken into consideration when evaluating the robustness of a dissolution method.<sup>28</sup> Baskets are especially prone to gelatin or excipient build-up if not thoroughly cleaned immediately after use.

The major components of dissolution equipment are the housing for the spindle assembly (sometimes called the tester head), water bath, paddles, baskets and shafts, vessels, samplers, and analyzers. Mechanical aspects of the equipment, such as media temperature, paddle or basket speed, shaft centering and wobble, and vibration can all have a significant impact on the rate of dissolution of the drug.

### 18.6.2 Dissolution vessels

Problems caused by vessel irregularities are often overlooked. Vessels are manufactured from large glass tubing, from which the vessel bottom is molded. Depending upon techniques of the molding process, irregular surfaces of the vessels can occur and the uniformity of vessel bottom roundness can vary. Cheaply made vessels are notorious for this problem. Close examination of vessels when newly purchased is very important, as surface irregularity can cause dissolution results to differ significantly.<sup>21,29,30</sup> Another common problem with vessels is residue build-up either from oily products or sticky excipients. Insoluble product, if not rinsed well from previous testing, can cause contamination in subsequent tests. Vessels that become scratched and etched after repeated washing should be discarded. Lids always need to be in place during a dissolution run to prevent evaporation. As mentioned before, vessels should be locked down to avoid vibration. The bath water level should always be maintained at the top of the vessels to ensure uniform heating of the medium. Monitoring of the temperature of the media in all the vessels used in a test (rather than just one) can assure the temperature uniformity.

### 18.6.3 Vibration and mechanical aberration

A common problem with dissolution equipment is vibration,<sup>31–33</sup> which can be minimized by ensuring that the top plate and lids for Apparatus 1 and 2 are properly leveled. External sources of vibration include other equipment on bench tops, especially shakers, centrifuges, or sonicators. Local construction in the area or within the building is a common, though often overlooked, source of vibration. The testers should not be near hoods or significant air flow sources. Heavy foot traffic and door slamming also should be avoided. The water bath itself is rarely a source of vibration because the water bath designs have evolved to eliminate noisy circulators near the bath.

Careful maintenance of the equipment is equally critical. For example, the spindle bearings of Apparatus 1 and 2 can become worn over time, and causing vibration and wobble of the shaft. In addition, the drive belts should be checked regularly for wear and the presence of dirt and the tension of belt should be adjusted for smooth operation. Although difficult to detect without very close observation of the testers, surging of spindles can also cause spurious results. Vessels need to be locked in place so they do not move during operation.

### 18.6.4 Dissolved gases

Dissolved atmospheric gases in the dissolution medium can adversely affect dissolution, and thorough deaeration of the dissolution media is essential for generation of reproducible results. Dissolved oxygen and other gases can result in presence of bubbles, which are commonly observed in nondeaerated medium. USP General Chapter <711>, *Dissolution*,<sup>5</sup> states that bubbles can interfere with dissolution test results and should be avoided. Dissolved air can slow down dissolution by creating a barrier; either adhering to the tablet surface or to basket

screens or particles can cling to bubbles on the glass surface of the vessel or shafts.

The dissolution test should be performed as soon as practical after deaeration of the medium. It is common practice to rotate the paddle to equilibrate the temperature of the dissolution medium. However, excessive stirring prior to starting the experiment can result in redissolution of atmospheric gasses. The paddle should always be stopped prior to adding the test article, and great care should be taken to ensure that the test article falls in the same place every time at the bottom of the vessel and does not stick to the sides.

There are several methods for deaeration of medium, some manual and some automated. The method described in USP General Chapter <711><sup>5</sup> uses heat, filtration, and vacuum. Helium sparging is also frequently used for deaeration of the dissolution medium; however, recent shortages of helium have made this approach less practical and commonplace.

### 18.6.5 Standard solutions

Great care should be taken when preparing standard solutions, especially if the standard must be dried before weighing, as well as ensuring that the drug powder is completely dissolved. Notably, prednisone USP RS becomes very hard upon drying and difficult to dissolve in water. Dissolving the powder first in a small amount of alcohol often helps to eliminate this problem. A history of the typical absorptivity range of the standard can also be very useful to determine if the standard has been prepared properly.

### 18.6.6 Method considerations

#### 18.6.6.1 Sample introduction

The best way to avoid errors and data “surprises” is to put a great deal of effort into the development and validation of methods. Some

areas of testing are especially troublesome. Sample introduction can be difficult and sometimes impossible to control and some products have dissolution profiles that are “position dependent.” For example, if the tablet is off-center, the dissolution rate may be higher due to shear forces. Conversely, placing the sample close to the center can result in coning and a decrease in dissolution rate. Film-coated tablets can be sticky when wetted, resulting in inconsistent positioning of the test article in the vessel. Replacement of the paddle with a basket or the use of a sinker is the best way to minimize the effects of position provided build-up of gelatinous matter does not impair the dissolution.

Suspensions can be introduced into the dissolution vessel in a variety of ways: manually, using syringes or pipettes, pouring from a tared beaker, or automated delivery using calibrated pipettes. Each method has its own set of limitations, although automated sample introduction tends to reduce variability. Mixing of a suspension sample can generate air bubbles; therefore, the mixing time of suspension samples must be strictly controlled to reduce erroneous or biased results.

#### 18.6.6.2 Dissolution media

The dissolution medium is a critical component of the test that can cause problems if not carefully controlled. One cause of inaccurate results is the volume of medium withdrawn through multiple sampling if not replaced carefully to maintain sink conditions.

Surfactants can be difficult to clean from the surface of the vessel, especially if the concentration is high (>0.5%). Surfactants, such as SLS, can accumulate on the surfaces of the sampling lines, carboys, other glass containers, and plastic bottles, which may require extensive rinsing to assure complete removal. Batch-to-batch variability of surfactants, SLS in particular, in terms of grade, age, impurities (especially electrolytes) can significantly and affect solubility.<sup>34</sup> The foaming properties of surfactants can make it



very difficult to effectively deaerate the medium as well and some peristaltic pumps used in automated equipment are not adequate for surfactant medium. Therefore, deaeration of the dissolution medium prior to addition of the surfactant can reduce some of the problems associated with foaming. One caution when lowering a basket into surfactant medium is that surface bubbles can adhere to the bottom of the basket and decrease the dissolution rate substantially. Several sources of error may be encountered when performing HPLC analysis if surfactants are present in the medium. Auto-injectors may need repeated needle washing to be adequately cleaned, and solutions containing high concentrations of surfactants may be too viscous for accurate delivery and may need to be diluted before injection. Surfactants can also build up on the surface of column packing material leading to extraneous peaks and changes in chromatographic behavior.<sup>35</sup> Basic media (pH > 8) can cause hydrolysis of some HPLC packing materials, which can be avoided by either diluting the samples with a suitable buffer or choosing a column that can operate at higher pH values.

### 18.6.6.3 Sinkers

Sinkers are defined in USP as “*not more than a few turns of a wire helix...*” Other sinkers may be used, but the analyst should be aware of the effect different types of sinkers may have on mixing.<sup>36</sup> Sinkers can be barriers to dissolution when the wire is wound too tightly around the dosage unit.

### 18.6.6.4 Filters

Filters are used invariably in the preparation of dissolution samples to prevent undissolved particles from entering the analytical sample and further dissolving. Filtration is also essential to prevent the introduction of particulate matter into the analytical instrument; this is particularly important when the samples are analyzed by HPLC to avoid blockage of the column. Many types or different filter materials are used in

automated and manual sampling.<sup>37</sup> The filtration step is a critical yet underestimated source of problems in the dissolution test and needs to be adequately evaluated with both the standard solution and sample solution. Care should be taken that the filter pore size is not larger than the drug particle size; this is especially important with micronized or nanoparticles. Filtration also removes insoluble excipients that may otherwise cause a high background.

Validation of the prewetting or discard volume is critical for both the sample and standard solutions. Plugging of filters is a common problem, especially with automated sampling devices.

Manual sampling techniques can introduce error by virtue of variations in strength and size of the human hand from analyst to analyst. Therefore, the pulling velocity through the filter may vary considerably. Too rapid a movement of liquid through the filter can compromise the filtration process itself.

### 18.6.6.5 Automation

While automation of dissolution sampling is very convenient and labor-saving, errors often occur with automated devices when potential problem areas are overlooked. Sampling lines are often a source of error for a variety of reasons: unequal lengths between the dissolution vessels and the analytical instrument, crimping, wear beyond limits, disconnection, carryover, line mix-ups or crossing, and inadequate cleaning. The volume dispensed, purged, recycled, or discarded should be checked routinely. Pumping tubes can wear out through normal use or repeated organic solvent rinsings and may require replacement.

Flow cells in UV-spectrophotometric analysis can be a source of error due to air bubbles that become caught in the flow cell, either introduced via a water source containing bubbles or by air entering inadvertently into poorly secured sample lines. Flow rate and dwell time should be evaluated, to ensure the absorbance readings have reached a steady state. Detector cells need

to be cleaned frequently to avoid buildup of drug, excipients, surfactants, or buffer salts from the dissolution medium.

A common source of error can derive from a different filter type being used in the automated dissolution test versus the manual dissolution test. If the same filter type and pore size cannot be used, then filter validation is essential.

#### 18.6.6.6 *Cleaning*

The analyst should take special care to examine this aspect when validating the method. In many laboratories, where different products are tested on the same equipment, this is a critical issue that, if inadequately monitored, may be a cause of inspection failures and erroneous results.

#### 18.6.6.7 *Method transfer*

Problems occurring during transfer of methods can often be traced to not having used exactly the same type of equipment, such as baskets/shafts, sinkers, dispensing apparatus, sampling method, or difference in the testing environment. The sampling technique (manual vs. automated), and sample introduction, should be uniform. A precise description of medium and standard preparation, including grade of reagents, in the method is essential and should go well beyond simply stating the method should be conducted according to the relevant pharmacopeial general chapter. Video recording may be useful to detect differences between sites.

## 18.7 Visual observations

One of the most useful tools for identifying sources of error is close visual observation of the dissolution test. Trained analysts can pinpoint many problems because they have developed a knowledge and understanding of the cause and effect relationships of well-known issues that can occur during the

dissolution test. Video recording of the dissolution process can be an invaluable approach in diagnosing anomalous or poor reproducibility of dissolution results. Accurate, meaningful dissolution occurs when the product dissolves without disturbance from barriers to dissolution, or disturbance of vessel hydrodynamics from any source. The particle disintegration pattern must show freely dispersed particles. Anomalous dissolution usually involves one or more of the following observations:

- floating chunks of tablet
- spinning
- coning
- mounding
- gumming
- swelling
- capping
- “clam shell” erosion
- off-center position
- sticking of particles adhering to apparatus or vessel walls
- sacs
- swollen/rubbery mass
- clear pellicles

Along with good documentation, familiarity with the dissolution behavior of a product is essential in quickly identifying changes in stability or changes associated with a modification of the formulation. One may notice a change in the size of the dissolving particles, excipients floating upward, or a slower erosion pattern. Changes in the formulation or an increase in strength may produce previously unobserved basket screen clogging. If the contents of the basket immediately fall out and settle to the bottom of the vessel, a spindle assembly surge might be indicated. If the medium has not been properly deaerated, the analyst may see particles clinging to vessel walls. The presence of bubbles always indicates that deaeration is necessary. Lastly, the water bath should contain clean water so visual observations of the dissolution test can be made clearly and easily.

## 18.8 Performance verification of dissolution equipment

In order for a dissolution method to be considered valid, the dissolution apparatus must be set up, qualified, and operated in compliance with appropriate compendia, as applicable. USP General Chapter <711>, *Dissolution*, lists apparatus specifications, the apparatus suitability test (now called Performance Verification Testing (PVT)), the dissolution medium requirements, as well as specific procedure requirements for USP Apparatus 1 and 2.<sup>5</sup> The PVT informs the analyst whether the equipment is operating properly, and it is always preceded by mechanical calibration. The acceptance criteria of the PVT for Apparatus 1 and Apparatus 2 were revised in 2010. The current acceptance criteria include a geometric mean and standard deviation. There is a “single-stage” test consisting of two consecutive runs of six (or eight, depending on the apparatus’s configuration) and a “two-stage” test in which one run is evaluated and, if it does not pass either or both criteria, another run or runs are performed. A detailed explanation of these criteria was published in 2009.<sup>38</sup> A “toolkit” that contains a calculation for evaluating whether a PVT passes or fails is available at the USP website.<sup>39</sup> This toolkit also provides comprehensive information on how to perform mechanical calibration.

Valid use of the PVT requires choosing either the one-stage or two-stage test before testing begins. The instructions clearly state that choosing which test to use **after** examining the data invalidates the use of this compendial tool/worksheet.

Despite recent efforts of the pharmacopeia to standardize procedures to reduce errors, including training courses, the major sources of dissolution variability continue to be vibration, centering, vessel design, and deaeration. A detailed look at the PVT and industry trends on the use of mechanical tests and PVT was published in a special edition of *Dissolution Technologies* in May 2010.<sup>40–43</sup> There is also an FDA

guidance: “Use of mechanical calibration of dissolution apparatus 1 and 2 – current good manufacturing practice (CGMP).”<sup>44</sup>

This guidance has created considerable controversy as it states that an *enhanced* mechanical calibration (MC) can be used as an alternative to the current Apparatus Suitability procedure (PVT) for Apparatus 1 and 2 described in the USP General Chapter <711>. Both procedures executed according to a written protocol will satisfy the cGMP requirements for calibration of laboratory apparatus and mechanical equipment for manufacturing, as set forth in CFR §§ 211.160(b) and 211.68, respectively.

## 18.9 Regulatory aspects and specifications

The regulatory agencies for the various global regions generally address dissolution guidelines in terms of the particular testing necessary to demonstrate the appropriate or intended release from a dosage form. These guidelines relate more to the development of an appropriate dissolution method than the validation procedure itself. As a rule, the specifics of the analytical validation for dissolution procedures are not separated from the discussions of general method validation as most of the critical validation analysis parameters do not differ between dissolution methods, and, for example, assay methods. As the regional regulatory and ICH guidelines are discussed in detail elsewhere in this book, the reader is referred to those chapters.

Clearly, the final dissolution specification for a drug product needs to reflect the optimal dissolution test developed and validated according to the discussions throughout this chapter. Acceptable limits for dissolution results are dependent on the type of dosage form and the desired release characteristics, e.g., immediate release versus extended release.

The FDA has provided some guidance on setting acceptable dissolution specifications that take into account the desired product release characteristics and, in particular, BCS

classification considerations.<sup>4,26</sup> A recent FDA guidance shows a further breaking down of immediate release formulations to cover specifically immediate release drug products containing high solubility drug substances.<sup>18</sup> It should be noted that the FDA provides only guidance and the recommendations posed in the various guidances are not legally binding. That said, it is recommended that proposed specifications be discussed with FDA prior to presenting in a formal submission. Specifications that are within the FDA guidance for a specific dosage form are likely to receive less resistance than those which are outside the guidance, but in any case, the specifications must be justified with appropriate supportive data. All dissolution specifications must apply to a given drug product over its entire shelf life.

### 18.9.1 Immediate release drug products

Specifications for immediate release dosage forms are intended to assure a quality measure of batch-to-batch consistency and in some cases an indicator of acceptable bioavailability. For drug products containing drug substances with high solubility over the physiological pH range, dissolution is primarily used as a quality control check for batch-to-batch consistency, and a single point specification is most often considered sufficient. In such cases, a generally acceptable specification is not less than 85% (Q = 80%) dissolved in 30 min. Acceptance criteria other than this can be proposed but must be accompanied by appropriate supportive data.<sup>26</sup>

For poorly soluble drugs, a two-point specification is sometimes needed. It is also possible that in some cases an IVIVC can be established. If that is the case, specification limits should be set based on the IVIVC and the dissolution test can be used to distinguish between bioequivalent and bioinequivalent formulations or batches. However, since IVIVC for immediate release

drug products are rare, the specifications are usually based on dissolution data from pivotal batches and other important lots, including stability data.

### 18.9.2 Extended-release drug products

Extended-release formulations are, in essence, designed such that release from the dosage form, and hence the dissolution of the drug substance, is controlled and occurs over an extended period of time. As such, single point, or in most cases two-point, specifications are insufficient to adequately characterize the quality and batch-to-batch consistency of the drug product. In addition, because of the designed drug release characteristics, it is often possible to establish an IVIVC for these formulations. Whether or not an IVIVC can be established, the specification should reflect results from biobatches designed to determine acceptable clinical behavior. The dissolution specification for extended-release formulations should include a minimum of three time points, one early time point to establish the absence of dose dumping, one time point in the middle of the release profile, and one at the end where at least 80% of the dose has been released.

Approaches to IVIVC for extended-release products are discussed in detail in the FDA guidance: Extended-release solid oral dosage forms: development, evaluation, application of in vitro/in vivo correlations,<sup>45</sup> and USP General Chapter <1088>, *In Vitro and In Vivo Evaluation of Dosage Forms*<sup>46</sup> A well-established correlation will allow for a reasonable prediction of the in vivo behavior of formulations without performing a bioavailability study. Finding the appropriate correlation has been the focus of numerous studies.<sup>47–49</sup> The establishment of an IVIVC has been the subject of much discussion recently in the arena of QbD and setting clinically relevant specifications.<sup>50</sup>

### 18.9.3 Generic drug products

There are essentially three scenarios that guide the approach to setting dissolution specifications for generic products.<sup>26</sup> For many generic products, a compendial monograph is available. In such cases, it is expected that the generic product meets the specification provided in the monograph. If a compendial dissolution test is not available but a dissolution test for the Reference Listed Drug Product (RLD) is publicly available, the dissolution test and specification should be consistent with the RLD. There is also an FDA database of dissolution methods which provides methods FDA prefers for a drug product.<sup>51</sup> If neither a compendial test nor a test for the RLD are publicly available, comparative dissolution testing between the generic product and the RLD should be presented and specification considerations should include testing data under a variety of test conditions as well as bioequivalence data.

## 18.10 Conclusions

This chapter has provided current GMPs in the area of dissolution testing method validation and method development for the purpose of filing drug products with regulatory agencies. There are extensive references and further reading provided so the reader can research the subject in more depth if desired.

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