Pharmaceutical Dissolution Testing

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Edited by

Jennifer Dressman
Johann Wolfang Goethe University
Frankfurt, Germany

Johannes Krämer
Phast GmbH
Homburg/Saar, Germany

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Dissolution Method Development: An Industry Perspective

CYNTHIA K. BROWN

Eli Lilly and Company, Indianapolis, Indiana, U.S.A.

INTRODUCTION

In today's pharmaceutical industry, dissolution testing is a valuable qualitative tool that provides key information about the biological availability and/or equivalency as well as the batch-to-batch consistency of a drug. Therefore, a properly designed dissolution test is essential for the biopharmaceutical characterization and batch-to-batch control of the drug product. During drug development, dissolution testing is used to select appropriate formulations for in vivo testing, guide formulation development activities, and assess stability of the drug product under various packaging and storage requirements. For the dissolution test to be a useful drug

characterization tool, the methodology needs to be able to discriminate between different degrees of product performance and thus, the collection of a multi-time point dissolution profile is useful. At present, almost all solid oral dosage forms require dissolution testing as a quality control check before a product is introduced into the market place. For the dissolution test to be a useful quality control tool, the methodology should be simple, reliable and reproducible, and ideally be able to discriminate between different degrees of product performance (1).

Dissolution testing is also used to identify bioavailability (BA) problems and to assess the need for further bioequivalence (BE) studies relative to scale-up and post-approval changes (SUPAC), where it can function as a signal of bioinequivalence (2,3). The issuance of the Food and Drug Administration (FDA) guidance document, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*, allows dissolution testing to be used as a surrogate for in vivo BE testing under certain circumstances (4). The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that influence the rate and extent of drug absorption from immediate-release solid oral dosage forms: dissolution, solubility, and intestinal permeability (5). Based on the BCS framework, drug manufacturers may request waivers from additional in vivo studies (biowaivers) if their drug product meets certain criteria. In addition, the FDA's guidance on BA and BE (6) allows biowaivers for additional strength(s) of immediate-release as well as modified-release drug products based on formulation proportionality and dissolution profile comparison.

These changes in BE requirements that move away from the in vivo study requirement in certain cases and rely more on dissolution test results, emphasize the significance of dissolution test applications. In all cases where the dissolution

test is used as a BE test, a link with a bioavailable product is established. With the advances in dissolution testing and the increased understanding of the scientific principles and mechanisms of dissolution testing, a clear trend has appeared where the dissolution test is not solely a traditional quality control test but may also be used as a surrogate to the in vivo BE test (7).

For the dissolution test to be used as an effective drug product characterization and quality control tool, the method must be developed with the various end uses in mind. In some cases, the method used in the early phase of product and formulation development could be different from the final test procedure utilized for control of the product quality. Methods used for formulation screening or BA and/or bioequivalency evaluations may simply be impractical for a quality control environment. It is essential that with the accumulation of experience, the early method be critically re-evaluated and potentially simplified, giving preference to compendial apparatus and media. Hence, the final dissolution method submitted for product registration may not necessarily closely imitate the in vivo environment but should still test the key performance indicators of the formulation.

To facilitate the development of appropriate dissolution tests several regulatory, pharmacopeial, and industrial organizations have issued dissolution-related guidelines that provide information and recommendations on the development and validation of dissolution test methodology, the establishment of dissolution specifications, and the regulatory applications of dissolution testing (8–16). This chapter describes a systematic approach for the development of a dissolution method. The information is organized and presented in sections that follow the chronological sequence of the method development process. These include the assessment of relevant physical and chemical properties of the drug, determination of the appropriate dissolution apparatus, selection of the dissolution medium, determination key operating parameters, method optimization, and validation of the methodology.

PHYSICAL AND CHEMICAL PROPERTIES

The first step in the development of a new dissolution test is to evaluate the relevant physical and chemical data for the drug substance. Knowledge of the drug compound's physical–chemical properties will facilitate the selection of dissolution medium and determination of medium volume.

Some of the physicochemical properties of the active pharmaceutical ingredient (API) that influence the dissolution characteristics are:

Ionization constants (pK_a),
Solubility as a function of pH,
Solution stability as a function of pH,
Particle size,
Crystal form, and
Common ion, ionic strength, and buffer effects.

Two key physicochemical API properties to evaluate are the solubility and solution-state stability of the drug substance as a function of pH. Knowledge of the pK_a (or pK_a's) is useful because it defines the charge of the molecule in solution at any given pH. Ideally, the drug substance's solubility in the dissolution medium should not be the rate-limiting factor for the drug substance's dissolution from the drug product. Hence, the dissolution rate should be characteristic of the release of the active ingredient from the dosage form rather than the drug substance's solubility in the dissolution medium. When adjusting the composition of the medium to insure adequate solubility for the drug substance, the influence of surfactants, pH, and buffers on the solubility and stability of the drug substance need to be evaluated. The solution-state stability of the API must also be considered in the design of a dissolution test because the molecule's stability in various dissolution media may limit the pH range over which the drug product's dissolution can be evaluated. Typically, the drug's solution stability should be determined at 37°C for 2 hr for immediate-release formulations and twice the designated testing time for sustained-release formulations (17).

During the initial stages of a drug product's development, a dissolution test should facilitate the formulation development and selection. During this phase of the drug development process bioavailability data is usually not available. In the absence of BA, the dissolution medium selection should be based on the physicochemical properties, the formulation design, and the intended dose. The BCS provides a good framework for determining if the dissolution of the drug will be the rate-limiting factor in the in vivo absorption process. Hence, the pH solubility of the drug and the intended dose are essential parameters to consider early in the dissolution method development process.

Once you have a good understanding of the physical–chemical properties of the drug substance, the key properties of the dosage form, i.e., type, label claim, and release mechanism, need to be considered. The most appropriate dissolution testing apparatus and dissolution medium can be selected based on the physical–chemical properties of the drug substance and the key properties of the dosage form. Dosage forms can be designed to provide immediate release, delayed release, or extended (controlled) release. Determining the type of release and anticipated site of in vivo absorption will facilitate the selection of dissolution media, testing apparatus, and test duration.

DISSOLUTION APPARATUS SELECTION

The choice of apparatus is based on knowledge of the formulation design and practical aspects of dosage form performance in the in vitro test system. Dissolution testing is conducted on equipment that has demonstrated suitability, such as described in the 2003 United States Pharmacopeia (USP) under the general chapters of *Dissolution* and *Drug Release* (10,11). The basket method (USP Apparatus 1) is routinely used for solid oral dosage forms such as capsule or tablet formulations at an agitation speed of 50–100 rpm, although speeds of up to 150 rpm have been used. The paddle method (USP Apparatus 2) is frequently used for solid oral dosage forms such as tablet

and capsule formulations at 50 or 75 rpm. The paddle method is also useful for the testing of oral suspensions at the recommended paddle speed of 25–50 rpm. The reciprocating cylinder (USP Apparatus 3) has been found to be especially useful for bead-type modified-release dosage forms. The flow-through cell (USP Apparatus 4) may offer advantages for some modified-release dosage forms, especially those that contain active ingredients with limited solubility. Additionally, the reciprocating cylinder or the flow-through cell may be useful for soft gelatin capsules, bead products, suppositories, or poorly soluble drugs. By design, both the reciprocating cylinder and the flow-through cell allow for a controlled pH change of the dissolution medium throughout the test, which allows the apparatus to be easily utilized for physiological evaluations of the dosage form during development. The paddle over disk (USP Apparatus 5) and the cylinder (USP Apparatus 6) have been shown to be useful for evaluating and testing transdermal dosage forms. The reciprocating holder (USP Apparatus 7) has been shown to have application to non-disintegrating oral modified-release dosage forms, as well as to transdermal dosage forms.

In general, compendial apparatus and methods should be used as a first approach in drug development. To avoid unnecessary proliferation of equipment and method design, modifications of compendial equipment or development and use of alternative equipment should be considered only when it has been proven that compendial set up does not provide meaningful data for a given dosage form. In these instances, superiority of the new or modified design has to be proven in comparison to the compendial design.

Table 1 outlines the current status of scientific development for the dissolution or release testing from various dosage forms and recommends, where possible, the dissolution apparatus of "first choice" (13). Refer also to Chapter 2 for further description of the USP apparatus.

DISSOLUTION MEDIUM SELECTION

For batch-to-batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose

Table 1 Apparatus Recommended Based on Dosage Form Type

Type of dosage form	Release method
Solid oral dosage forms *(conventional)*	Basket, paddle, reciprocating cylinder, or flow-through cell
Oral suspensions	Paddle
Oral disintegrating tablets	Paddle
Chewable tablets	Basket, paddle, or reciprocating cylinder with glass beads
Transdermals—patches	Paddle over disk
Topicals—semisolids	Franz cell diffusion system
Suppositories	Paddle, modified basket, or dual chamber flow-through cell
Chewing gum	Special apparatus [European Pharmacopoeia (PhEur)]
Powders and granules	Flow-through cell (powder/granule sample cell)
Microparticulate formulations	Modified flow-through cell
Implants	Modified flow-through cell

range of the drug product in order to ensure that sink conditions are met. The term sink conditions is defined as the volume of medium at least greater than three times that required to form a saturated solution of a drug substance. A medium that fails to provide sink conditions may be justifiable if it is shown to be more discriminating or if it provides reliable data which otherwise can only be obtained with the addition of surfactants. When the dissolution test is to indicate the biopharmaceutical properties of the dosage form, it is more important that the test closely simulate the environment in the GI tract than necessarily produce sink conditions for release. Therefore, it is not always possible to develop one dissolution test or select one dissolution medium that ensures batch-to-batch control as well as monitoring the biopharmaceutical aspects of the drug product.

The dissolution characteristics of oral formulations should be evaluated over the physiologic pH range of 1.2–6.8 [1.2–7.5 for modified release (MR) formulations]. During method development, it may be useful to measure the pH before and after a run to see if the pH changes during the test,

especially if the buffer capacity of the chosen medium is low. Selection of the most appropriate medium for routine testing is then based on discriminatory capability, ruggedness, stability of the analyte in the test medium, and relevance to in vivo performance where possible.

For very poorly soluble compounds, aqueous solutions may contain a percentage of a surfactant (e.g., sodium lauryl sulfate, Tween 80 or CTAB) that is used to enhance drug solubility. The need for surfactants and the concentrations used should be justified. Surfactants can be used as either a wetting agent or, when the critical micelle concentration (CMC) is reached, to solubilize the drug substance. The surfactant's CMC depends upon the surfactant itself and the ionic strength of the base medium. The amount of surfactant needed for adequate drug solubility depends on the surfactant CMC and the degree to which the compound partitions into the surfactant micelles. Because of the nature of the compound and micelle interaction, there is typically a linear dependence between solubility and surfactant concentration above the CMC. If a compound is ionizable, surfactant concentration and pH may be varied simultaneously, and the combined effect can substantially change the solubility characteristics of the dissolution medium. Table 2 lists dissolution medium selection criteria as defined in regulatory, industry, and compendial guidances.

The BCS describes the classification of compounds according to solubility and permeability (6). Biorelevant medium is a term used to describe a medium that has some relevance to the in vivo dissolution conditions for the compound. Choice of a biorelevant medium is based on a mechanistic approach that considers the absorption site, if known, and whether the rate-limiting step to absorption is the dissolution or permeability of the compound. In some cases, the biorelevant medium will be different from the test conditions chosen for the regulatory test and the time points are also likely to be different. If the compound dissolves quickly in the stomach and is highly permeable, gastric emptying time may be the rate-limiting step to absorption. In this case, the dissolution test is to demonstrate that the drug is released quickly under

Table 2 Recommended Dissolution Medium Composition and Volume for Rotating Basket or Rotating Paddle Apparatus

Guidance or compendial reference	Volume	pH	Additives
Federation International Pharmaceutique (FIP) (23)	500–1,000 mL; 900 mL historical; 1,000 mL recommended for future development	pH 1–6.8; above pH 6.8 with justification—not to exceed pH 8	Enzymes, salts, surfactants with justification
United States Pharmacopeia (USP) (10–12)	500–1,000 mL; up to 2,000 mL for drug with limited solubility	Buffered aqueous solution pH 4–8 or dilute acid solutions (0.001 N HCl to 0.1 N HCl)	Enzymes, salts, surfactants balanced against loss of discriminatory power; enzymes can be used for cross-linking of gelatin capsules or gelatin-coated tablets
World Health Organization (WHO) (16), European Pharmacopoeia (PhEur) (14), Japanese Pharmacopoeia (JP) (15)	Determined per product	Adjust pH to within ±0.05 units of the prescribed valued	Determined per product
FDA (8,9)	500, 900, or 1,000 mL	pH 1.2–6.8; higher pH justified case-by-case—in general not to exceed pH 8	Surfactants recommended for water poorly soluble drug products—need and amount should be justified; enzymes use need case-by-case justification; utilized for the cross-linking of gelatin capsules or gelatin-coated tablets

typical gastric (acidic) conditions. On the other hand, if dissolution occurs primarily in the intestinal tract (e.g., a poorly soluble, weak acid), a higher pH range (e.g., simulated intestinal fluid with a pH of 6.8) will be more appropriate (18).

The fed and fasted state may also have significant effects on the absorption or solubility of a compound. Compositions of media that simulate the fed and fasted states can be found in the literature (19) (see also Chapter 5). These media reflect changes in the pH, bile concentrations, and osmolarity after meal intake and therefore have a different composition than that of typical compendial media. They are primarily used to establish in vitro–in vivo correlations during formulation development and to assess potential food effects and are not intended for quality control purposes. For quality control purposes, the substitution of natural surfactants (bile components) with appropriate synthetic surfactants is permitted and encouraged because of the expense of the natural substances and the labor-intensive preparation of the biorelevant media.

KEY OPERATING PARAMETERS

Media: Volume, Temperature, Deaeration

As shown in Table 2, the recommended volume of dissolution medium is 500–1000 mL, with 900 mL as the most common volume when using the basket or paddle apparatus. The volume can be raised to between 2 and 4 L, depending on the concentration and sink conditions of the drug, but proper justification is expected.

The standard temperature for the dissolution medium is $37 \pm 0.5^{\circ}C$ for oral dosage forms. Slightly increased temperatures such as $38 \pm 0.5^{\circ}C$ have been recommended for dosages forms such as suppositories. Lower temperatures such as $32 \pm 0.5^{\circ}C$ are utilized for topical dosage forms such as transdermal patches and topical ointments.

The significance of deaeration of the medium should be determined on a case-by-case basis, as air bubbles can interfere with the test results and act as a barrier to dissolution

if present on the dosage unit or basket mesh. Additionally, air bubbles can cause particles to cling to the apparatus and vessel walls. On the other hand, bubbles on the dosage unit may increase the buoyancy and lead to an increase in the dissolution rate, or decrease the dissolution rate by decreasing the available surface area. Consequently, the impact of medium deaeration may be formulation dependent, such that some formulations will be sensitive to the presence of dissolved air in the dissolution while other formulations will be robust. To determine if deaeration of the medium is necessary, a comparison between dissolution data generated with non-deaerated medium vs. dissolution data generated with deaerated medium should be performed.

The following deaeration method is described as a footnote in the 2003 United States Pharmacopeia (USP) under the general chapter *Dissolution* (10). The USP deaeration method requires heating of the medium, followed by filtration, and drawing of a vacuum for a short period of time. Other deaeration methods such as room temperature filtration, sonication, and helium sparging are described in literature (20,21) and are routinely used throughout the industry. The deaeration method needs to be clearly characterized, since the method chosen might impact the dissolution release rate (13). It should be noted that dissolution tests using the flow-through cell method could be particularly sensitive to the deaeration of the medium. Media containing surfactants are not usually deaerated after the surfactant has been added to the medium because of excessive foaming. In some laboratories, the base medium is deaerated prior to the addition of the surfactant.

Sinker Evaluation

Currently, the Japanese Pharmacopoeia (JP) is the only pharmacopeia that requires a specific sinker device for all capsule formulations. The USP recommends a few turns of a nonreactive material wire when the dosage form tends to float (12) (see Chapter 2 for illustrations of the Japanese and USP sinkers). Because sinkers can significantly influence the dissolution

profile of a drug product, detailed sinker descriptions and the rationale for why a sinker is used should be stated in the written procedure. When comparing different sinkers (or sinkers versus no sinkers), a test should be run concurrently with each sinker. Each sinker type should be evaluated based on its ability to maintain the dosage at the bottom of the vessel without inhibiting drug release.

Sinkers can significantly influence the dissolution profile of a drug. Therefore, the use of sinkers should be part of the dissolution method validation. If equivalent sinkers are identified during the sinker evaluation and validation, the equivalent sinkers should be listed in the written dissolution test procedure. When a dissolution method utilizes a dissolution sinker and is transferred to another laboratory, the receiving laboratory should duplicate the validated sinker design(s) as closely as possible.

Analytical Detection

For determination of the quantitative step in the dissolution method, information regarding the spectral, chromatographic, electrochemical, and/or chemical characteristics of the drug substance should be considered. The quantitative method needs to provide adequate sensitivity for the accurate determination of the analyte in the dissolution medium. Since formulations are likely to change during product development, it is usually advantageous to use high-performance liquid chromatography (HPLC) detection procedures. However, because of the ease of automation and faster analysis time, UV detection methods are more desirable for the routine quality control testing of products.

Filtration of the dissolution sample aliquot is usually needed prior to quantitation. Filtration of the dissolution samples is usually necessary to prevent undissolved drug particles from entering the analytical sample and dissolving further. Also, filtration removes insoluble excipients that may otherwise cause a high background or turbidity. Prewetting of the filter with the medium is usually necessary. Filters can be in-line, at the end of the sampling probe, or both. The

pore size can range from 0.45 to 70 μm. The usual types are depth, disk, or flow-through filters. However, if the excipient interference is high, or the filtrate has a cloudy appearance, or the filter becomes clogged, an alternative type of filter or pore size may need to be evaluated.

Adsorption of the drug(s) to the filter needs to be evaluated. If drug adsorption occurs, the amount of initial filtrate discarded may need to be increased. If results are still unsuitable, an alternative filter material should be sought. Centrifugation of samples is generally not recommended, as dissolution can continue to occur during centrifugation and there may be a concentration gradient in the supernatant. A possible exception might be compounds that adsorb to all common filters.

Sampling Time Points and Specifications

Key operating parameters that may change (or be optimized) throughout a product's development and approval cycle are dissolution sampling time points and dissolution limits or specifications by which the dissolution results should be evaluated. The results generated from the dissolution test need to be evaluated and interpreted based on the intended purpose of the test. If the test is used for batch-to-batch control, the results should be evaluated in regard to the established limits or specification value. If the test is being utilized as a characterization test (i.e., biopharmaceutical evaluations, formulation development studies, etc.) the results are usually evaluated by profile comparisons.

For immediate-release dosage forms, the dissolution test duration is typically 30–60 min, with a single time point specification being adequate in most cases for routine batch-to-batch quality control for approved products. Typical specifications for the amount of active ingredient dissolved, expressed as a percentage of the labeled content (Q), are in the range of 75–80% dissolved. A Q value in excess of 80% is not generally used, as allowances need to be made for assay and content uniformity ranges. Since the purpose of specifying dissolution limits is to ensure batch-to-batch consistency

within a range that guarantees comparable biopharmaceutical performance in vivo, specifications including test times are usually established based on an evaluation of dissolution profile data from pivotal clinical batches and confirmatory BA batches (8).

When the test is utilized as a characterization tool (i.e., biopharmaceutical evaluations, formulation development studies, etc.) the results are usually evaluated by profile comparisons. In this case, the product's comparability and performance are evaluated by collecting additional sampling time points. For registration purposes, a plot of the percentage of the drug dissolved vs. time should be determined. Enough time points are to be selected to adequately characterize the ascending and plateau phases of the dissolution curve. According to the BCS referred to in several FDA guidance documents, highly soluble and highly permeable drugs formulated with rapidly dissolving products need not be subjected to a profile comparison if they can be shown to release 85% or more of the active ingredient within 15 min. For these types of products, a one-point test will suffice. When an immediate-release drug product does not meet the rapidly dissolving criteria, dissolution data from multiple sampling time points ranging from 10 to 60 min or longer are usually collected.

So-called infinity points can be useful during development studies. To obtain an infinity point, the paddle or basket speed is increased significantly (e.g., 150 rpm) at the end of the run and the test is allowed to run for an extended period of time (e.g., 60 min), and then an additional sample is taken. Although there is no requirement for 100% dissolution in the profile, the infinity point can provide data that may provide useful information about the formulation characteristics during the initial development.

For an extended-release dosage form, at least three test time points are chosen to characterize the in vitro drug-release profile for the routine batch-to-batch quality control for approved products. Additional sampling times may be required for formulation development studies, biopharmaceutical evaluations, and drug approval purposes. An early time

point, usually 1–2 hr, is chosen to show that there is little probability of dose dumping. Release at this time-point should not exceed values expected according to the mechanism of release and the intended overall-release profile. An intermediate time point is chosen to define the in vitro-release profile of the dosage form, and a final time point is chosen to show essentially complete release of the drug. Test times and specifications are usually established on the basis of an evaluation of drug-release profile data. For products containing more than a single active ingredient, drug release is to be determined for each active ingredient. Extended-release specifications are addressed in the USP under the general chapter *In Vitro and In Vivo Evaluation of Dosage Forms* (12) and the FDA's guidance document *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (9).

METHOD OPTIMIZATION

When human BA data are available from several formulations, the dissolution test should be re-evaluated and optimized (if needed). The goal of dissolution method optimization is to identify in vitro test conditions that adequately discriminate critical formulation differences or critical manufacturing variables. During the method optimization process, the biostudy formulations are tested using various medium compositions (e.g., pH, ionic strength, surfactant composition). The effect of hydrodynamics on the formulations should also be evaluated by varying the apparatus agitation speed. If a non-bioequivalent batch is discovered during a bioequivalency study and the in vivo absorption is dissolution rate limited (BCS Class 2), the dissolution methodology should be optimized to differentiate the non-bioequivalent batches from the bioequivalent batches by dissolution specification limits. This would ensure batch-to-batch consistency within a range that guarantees comparable biopharmaceutical performance in vivo. Once a discriminating method is developed, the same method should be used to release product batches for future clinical studies.

VALIDATION

Once the appropriate dissolution conditions have been established, the method should be validated for linearity, accuracy, precision, specificity, and robustness/ruggedness. This section will discuss these parameters only in relation to issues unique to dissolution testing. All dissolution testing must be performed on a calibrated dissolution apparatus meeting the mechanical and system suitability standards specified in the appropriate compendia.

Linearity

Detector linearity should be checked over the entire range of concentrations expected during the procedure. The ICH recommendation for range of dissolution methods is ±20% of the specification limits (22). For example, if the specification for an immediate-release tablet is "no tablet less than 80% in 45 min," then the range to be checked would be from 60% to 100% of the tablet's label claim. For controlled or extended-release product, the range should be extended to include values 20% less than the lowest specification limit to values 20% higher than the upper specification limit. Typically, the concentration range is divided into five evenly spaced concentrations. Linearity testing of the dosage form should cover the entire range of the product.

Linearity is evaluated by appropriate statistical methods such as the calculation of a regression line by the method of least squares. The linearity results should include the correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares as well as a plot of the data. Also, it is helpful to include an analysis of the deviation of the actual data points for the regression line to evaluate the degree of linearity.

Accuracy

Accuracy samples are prepared by spiking bulk drug and excipients in the specified volume of dissolution fluid. The concentration ranges of the bulk drug spikes are the same

as those specified for linearity testing. If the dosage form is a capsule, the same size and color of capsule shell should be added to the mixture. The solutions should be tested according to the parameters specified in the method, i.e., temperature, rotation speed, filters, sampling mode, and detection mode. If accuracy solutions are prepared at five concentrations levels across the range, aliquots can be collected at the sampling interval(s) specified in the method and analyzed according to the quantitative method procedure. An alternative approach is to collect at least three sampling aliquots from the low-, middle-, and high-accuracy solutions.

Precision

According to the dissolution method, precision is determined by testing at least six aliquots of a homogenous sample for each dosage strength. The precision should be assessed at each specification interval for the dosage form. The precision can be determined by calculating the relative standard deviation (RSD) of the multiple aliquots from each solution.

Two unique sample tests (e.g., different analysts, instruments, reagents, and standard preparations) performed within the same laboratory would establish the method's intermediate precision. If the dosage form requires the use of a sinker, the sinker specified in the method should be used in precision testing.

Specificity

The dissolution analysis method must be specific for the bulk drug substance in the presence of a placebo. A mixture of dissolution fluid and the excipients (including the capsule shell if applicable) should be tested to specificity. Stability of the drug in the dissolution medium should be considered since the dissolution test exposes the drug to hydrolytic media at 37°C for specified time spans. Simply monitoring the UV spectra of the solutions is not sufficient in determining degradation since many degradation products will have the same UV spectrum as the parent compound. Therefore, specificity testing should be confirmed by analyzing accuracy samples

with a selective analysis mode such HPLC. If the capsule shell interferes with the bulk drug detection, the USP allows for a correction for the capsule shell interference. Corrections $>25\%$ of labeled content are unacceptable (10).

Robustness/Ruggedness

Robustness testing should determine the critical parameters for a particular dissolution method. By subjecting each dissolution parameter to slight variations, the critical dissolution parameters for the dosage form will be determined. This will facilitate method transfer and troubleshooting. Robustness testing should evaluate the effect of varying media pH, media volume or flow rate, rotation speed, apparatus sample position, sinkers (if applicable), media deaeration, temperature, and filters. Ruggedness of the methods should be evaluated by running the method with multiple analysts on multiple systems. If the analysis is performed by HPLC, the effect of columns and mobile conditions should also be addressed.

AUTOMATED SYSTEMS

Validation of automated systems must demonstrate a lack of contamination or interference that might result from automated transfer, cleaning, or solution preparations procedures. Equivalency between the results generated from the manual method and the data generated from the automated system should be demonstrated. Since sensitivity to automated dissolution testing may be formulation related, qualification and validation of automated dissolution equipment needs to be established on a product-by-product basis (8,13) (see also Chapter 12 for a more detailed description of automation issues).

CONCLUSIONS

Regulatory changes in BE requirements (that move away from the in vivo study requirements in certain cases and rely

more on dissolution testing) emphasize the significance of dissolution test applications. A clear trend has appeared with the advances in and increased understanding of the scientific principles and mechanisms of dissolution testing. The dissolution test is not solely a traditional quality control test but may also be used as a product characterization test that can serve as a surrogate to the in vivo BE test. For the dissolution test to be used as an effective drug product characterization and quality control tool, the method must be developed with the final application for the test in mind. A properly designed dissolution test can be used to characterize the drug product and assure batch-to-batch reproducibility for consistent pharmacological and biological activity.

Therefore, the development and validation of a scientifically sound dissolution method requires the selection of key method parameters that provide accurate, reproducible data that are appropriate for the intended application of the methodology. It is important to note that while more extensive dissolution methodologies may be required for bioequivalency evaluations or biowaivers (i.e., multiple media, more complex dissolution media additives, and multiple sampling time points), it is also essential for the simplified, routine quality control dissolution method to discriminate batch-to-batch differences that might affect the product's in vivo performance.

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