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Method development and validation for dissolution testings

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ABSTRACT

Dissolution is a qualitative and quantitative tool which can provide valuable information about biological availability of a drug as well as batch to batch consistency, new formulation development guide and ensure product quality and performance after changes in the manufacturing process. Like many performance tests in regulated environment, the dissolution is considered to be one of the most important control tests performed on pharmaceutical dosage forms and developing and validation of dissolution methods is an important part of good manufacturing practices. This article discusses the general concepts and highlights of some specific method development and validation guidelines used in developing and validating dissolution test methods.

Keywords: Dissolution, Validation, Medium, pH, rpm (Rotation per minute) and Surfactant.

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INTRODUCTION

Dissolution is a common characterization test used by the pharmaceutical industry to guide formulation design and to control product quality. It is often a required performance test for solid dosage forms, transdermal patches, and suspensions. Dissolution is also the only test that measures in vitro drug release as a function of time, which may reflect the reproducibility of the manufacturing process and, in some cases, the drug's in vivo performance. Dissolution is defined as the process by which solid substance enters in solvent to yield a solution. Simply, dissolution is a mass transfer from a solid surface to liquid phase. It clearly states that dissolution is a dynamic property. To guide satisfy dissolution requirements, the United States Pharmacopeia (USP) [1,2] and British Pharmacopeia [5] provides information in the way of a general chapters on dissolution, as well as on disintegration and USP additional provide guidance on drug release. The USP and Food and Drug Administration (FDA) also provide guidelines on development and validation of dissolution procedures [3,4, 10-12]. This article will draw the information and will discuss the available guidance in some detail.

Dissolution testing is used as an in vitro surrogate in formulation development and bioequivalence. Dissolution testing is an in vitro laboratory test method that is designed to demonstrate how efficiently an active drug substance is extracted out of a solid oral dosage form. In vitro dissolution testing is an important physicochemical tool used to measure drug release rates during both early and late stages of drug development. Also dissolution is a very appropriate parameter to monitor and provides very useful information on the performance capabilities of solid oral dosage forms that may be used within development to assist in the selection of suitable formulations, and it serves as a quality control test in support of routine manufacture to establish lot-to-lot performance consistencies. In fact, this test method is considered so useful that it is a standard compendial method published by the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP) and other Pharmacopeias.

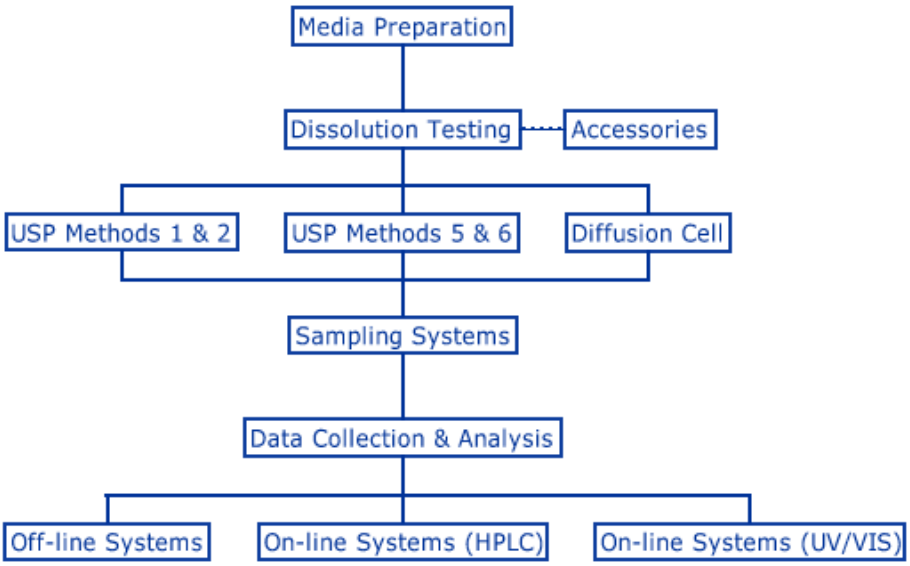

Figure1: Stages in the dissolution testing process [20]

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Types of Dissolution Apparatus

A systematic approach, based on sound scientific and regulatory principles, should be applied in developing a dissolution method. The dissolution procedure requires an apparatus, a dissolution medium, and test conditions (like RPM, time points etc). Various designs of apparatus are included in the compendia, as described here. The USP has 7 different apparatus that can be used for dissolution testing [2]. For orally administered immediate and delayed release dosage forms, including tablets, capsules, and suspensions, USP Apparatus 1 (basket) or 2 (paddle) is recommended. Apparatus 2 is generally the first choice for immediate release due to ease of use, reproducibility, hydrodynamics, and general acceptance. These two apparatus were developed through the 1960s and adopted by the USP in the 1970s. For extended release dosage forms designed to deliver the drug to site absorption at a controlled rate over an extended period

Figure 2: Dissolution Apparatus 1 and 2 is generally the first choice for measuring the dissolution of immediate release dosage forms [7]

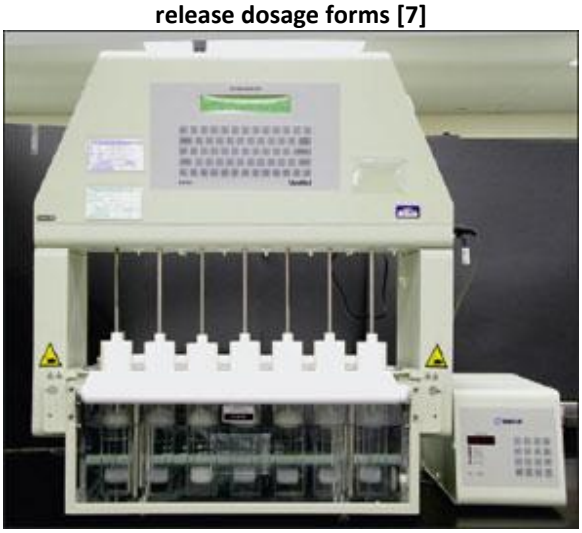

Figure 3: The advantages of USP Apparatus 3 include ease of setup, operation, and sampling. It is generally preferred when a pH gradient is required [7].

of time, USP Apparatus 3 (Reciprocating Cylinder, which is not accepted by the Japanese pharmacopoeia) and Apparatus 4 (flow-through cell) should also be considered during method development because they allow for changes in the medium pH during dissolution testing. Apparatus 5 is Paddle over Disk, apparatus 6 is Cylinder and apparatus 7 is Reciprocating Holder. Before using the apparatus, the dissolution apparatus should be appropriately calibrated to ensure compliance with regional good manufacturing practice (GMP) requirements. For example, an appropriately designed and executed mechanical calibration strategy should be in compliance with good manufacturing practice requirements. Because of these parameters may affect the hydrodynamics within the vessels.

Dissolution Development procedure

A systematic approach, based on sound scientific and regulatory principles, should be applied in developing a dissolution method. Both the FDA and USP have published guidelines on developing suitable dissolution methodology [2, 12]. Sufficient information about the drug substance properties (solution stability, solubility, particle size, polymorphism, permeability, and site of absorption) that are likely to affect the in vitro dissolution behavior should be obtained. Drug product characteristics, such as the type of dosage form (tablet, capsule, and suspension), the number of strengths, and the desired release mechanism and profile (immediate, delayed, or extended release) will determine some decisions regarding method parameters.

Dissolution medium selection

Before selecting the dissolution medium physical and chemical data for the drug substance and dosage unit need to be determined. The selection of dissolution medium is guided by drug substance solubility and solution state stability of the drug as a function of the pH value. When selecting the composition of the medium, the influence of buffers, pH value, and surfactants on the solubility and stability of the drug need to be evaluated. The choice of dissolution medium is an important consideration. Whenever possible, testing should be performed under sink conditions to avoid artificially retarding the dissolution rate due to approach of solute saturation of the medium. The sink conditions are defined as concentrations that yield a saturation solubility of the drug substance at least three times the highest dose of the drug substance dissolved in the volume of medium used for dissolution. Sink conditions are preferred because they are more likely to result in dissolution that reflects kinetics of the drug release from the dosage form rather than from solubility limitations. When sink conditions are present, it is more likely that dissolution results will reflect the properties of the dosage form. A medium that fails to provide sink conditions may be acceptable if it is shown to be more discriminating or otherwise appropriately justified.

Medium selection should begin with aqueous-based media in the range of pH 1.2 to 6.8 (or pH 7.5 in the case of modified release dosage forms). Purified water is often used as the dissolution medium, but is not ideal for several reasons. First, the quality of the water can vary

depending on the source of the water, and the pH value of the water is not controlled. Water is inexpensive, readily available, easily disposed of, ecologically acceptable, and suitable for products with a release rate independent of the pH value of the medium. The dissolution characteristics of an oral formulation should be evaluated in the physiologic pH range of 1.2 to 6.8 (1.2 to 7.5 for modified-release formulations)[3]. Where multiple strengths of the drug substance are available, the highest strength should be used for initial medium selection. During the dissolution method development the dissolution medium temperature and pH must be controlled. Selection of the most appropriate conditions 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. Typical media for dissolution may include the following (not listed in order of preference): dilute hydrochloric acid, simulated gastric or intestinal fluid (with or without enzymes), water, and surfactants (with or without acids or buffers). Commonly the surfactants were used for very poorly soluble compounds, aqueous solutions may contains a percentage of surfactant that is used to enhance drug solubility. Commonly used surfactants are include the anionic surfactant sodium dodecyl sulfate, cationic cetyl trimethylammonium bromide, and neutral surfactant Polysorbate 80. The need for surfactants and the concentrations used can be justified by showing profiles at several different concentrations. Surfactants can be used either as wetting agents or to solubilize the drug substance. For purposes of medium selection, the minimum concentration above CMC(critical micelle concentration) that meets sink condition criteria should be determined and selected for further optimization. For ionizable compounds, variation of both pH and surfactant can be used to select an appropriate medium. Addition of organic solvent such as alcohols is generally not recommended and may lead to regulatory delays. Enzymes are also sometimes used in the media when testing gelatin capsule products.

Normally, for apparatus 1 and apparatus 2, the volume of the dissolution medium is 500 mL to 1000 mL. 900 mL as the most common volume for dissolution test[7]. The volume can be raised up 2L and 4 L, using larger vessels and depending on the concentration and sink conditions of the drug; justification should be required for these procedure. The volume specified refers to measurements made between 20 °C and 25 °C. If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0.05 units of the specified pH. The significance of degassing of the medium should be determined, because the dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases must be removed prior to testing.

Choice of Apparatus and Agitation

The choice of apparatus should be based on knowledge of the formulation design and the practical aspects of dosage form performance in the in vitro test system[1, 2, 22]. For solid oral dosage forms, Apparatus 1 and Apparatus 2 are used most frequently. When Apparatus 1 or 2 is not suitable, another official apparatus may be used. Apparatus 3 (Reciprocating Cylinder) has been found to be especially useful for bead-type modified-release dosage forms. Apparatus 4 (Flow-Through Cell) may be offer advantages for modified-release dosage forms that contains

limited solubility active ingredients. Apparatus 5 (Paddle over Disk) and Apparatus 6 (Rotating Cylinder) have been shown to be useful for evaluating and testing transdermal dosage forms. Apparatus 7 (Reciprocating Holder) has been shown to have application to nondisintegrating oral modified-release dosage forms, as well as to transdermal dosage forms.

For some dosage forms, particularly capsules that might float on the media surface when dissolution apparatus 2 used, "sinkers" may be required to sink the dosages forms. If sinkers are required, steps must be taken in method development to evaluate different types and construction, as sinkers can significantly affect dissolution. If the sinker is handmade, the sinker material and construction procedure instructions should be documented; if a commercial sinker is used, the vendor part number should be reported.

Agitation (RPM speed) is also an important part of the dissolution procedure. For immediate-release dosage form formulations, Apparatus 1 (baskets) at 100 rpm or Apparatus 2 (paddles) at 50 or 75 rpm are most commonly used [8]. Other agitation speeds and apparatus are acceptable with appropriate justification obtained during method development. Because of inappropriate of the inconsistency of hydrodynamics lower and higher rpm are usually unaccepted, below 25 rpm and increased turbulence above 150 rpm. Coning or mounding problems can be reduced by increasing the rpm of paddle. If justified, 100 rpm may be used, especially for extended-release products. Decreasing or increasing the apparatus rotation speed may be justified if the profiles better reflect in vivo performance and/or the method results in better discrimination without adversely affecting method reproducibility.

Table 1: Apparatus Recommendations for Novel or Special Dosage Forms [8]

Type of Dosage form	Dissolution release method apparatus
Conventional solid oral dosage form	Basket, paddle, reciprocating cylinder or flow through cell
Oral suspensions	Paddle
Orally disintegrating tablets	Paddle
Chewable tablets	Basket, paddle, or reciprocating cylinder with glass beads
Transdermal patches	Paddle over disk
Semi-solid topical preparations	Franz cell diffusion system
Suppositories	Paddle, modified basket, or dual chamber flow through cell

Design of Dissolution study

Dissolution testing is evaluated frequently by determining the rate release profiles, or the amount dissolved over the period of time. It plays many important roles throughout drug product development. Single or multiple points in time can be measured, depending upon the dosage type or data desired. For immediate-release dosage forms, the duration of the method

is typically 30 to 60 minutes; in most cases, a single time point specification is adequate for regulatory purposes. For formulation comparison with Reference Listed Drug product (RLD) [21, 22] to support phase of clinical development purposes, profiles (multi-points) are required. It is common to collect data from numerous time points (like 10,20,30,45 and 60 min). Single-point data collection at 30 or 60 min was used for release testing in the QC laboratory. For profile comparisons, a sufficient number of time points should be selected to adequately characterize the dissolution curve ascending and plateau.

A profile may not be required for immediate release products in which the drug substance is known to be Class 1 (high solubility and high permeability) as defined by BCS[21]. For this class of drugs, the FDA guidance suggests that dissolution of 85% in 15 minutes ensures that bioavailability of the drug is not limited by dissolution. However, most products do not fall into this category. If really want to study the dissolution characteristics of this kind of products, can reduction in RPM and time may helpful. Dissolution time points in the range of 15, 20, 30, 45, and 60 minutes are usual for most immediate-release products [3]. Dissolution test times for compendial tests are usually established on the basis of an evaluation of the dissolution profile data. For slower-dissolving products, time points later than 60 minutes may be useful. However there is no requirement for 100% dissolution in the profile.

For an extended-release dosage form, at least three test time points are chosen to characterize the in vitro drug release profile for regulatory purposes. Additional profiles may be required for drug registration and get approval purposes. An early time point, usually 1 to 2 hours, is chosen to show that there is little probability of dose dumping (a phenomenon of drug metabolism in which environmental factors can cause the premature and exaggerated release of a drug). 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 the 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.

During these early method development runs, it is imperative to observe the behavior of the dosage form visually throughout the run.

Generally sampling is very important element in all the analytical methods. Similarly sampling is an important experimental design consideration in dissolution studies. For many tests, particularly immediate release formulation tests using one time point over a short (less than 1 hour) period, sampling can be done manually. For extended tests, tests with multiple sampling times, or to increase throughput, automated sampling is a useful. When automated sampling is employed, it is important to determine that no bias versus the manual method has been introduced. However, because regulatory labs may perform the dissolution test using manual sampling, autosampling requires validation with manual sampling. Any hydrodynamic disturbance of the vessels by the sampling probes also should be considered, and adequate

validation should be performed to ensure that the probes are not introducing a significant change in the dissolution rate.

Comparison between manual and automated procedures should be conformed to evaluate the interchangeability of the procedures. This can be done by comparing the data from separate runs or, in some cases, by sampling both ways from the same vessel. If the results are consistent with the requirements for intermediate precision (described this in Validation chapter), the procedures are to be considered interchangeable.

Filtration also is an important for all the analytical techniques. Filtration studies should be done at the time of method development. Filtration of dissolution samples usually is necessary to prevent un-dissolved drug particles from entering the analytical test sample and further dissolving and skewing the test result. Also, filtration removes insoluble excipients that may cause high background or turbidity in the dissolution assay technique. Adsorption of the drug(s) onto the filter should 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 may use or centrifuge method may be suitable.

Acceptance Criteria for Dissolution Test Method

Once the medium, apparatus, optional agitation rate, medium ionic strength and surfactant concentration fixed, further specification limits (acceptance criteria) for the dissolution have to be defined to ensure the batch-to-batch consistency during the test development. Setting acceptance criteria is important for many reasons. If criteria are too restrictive, results may fail the study even if they are acceptable. If criteria are set too wide, then the methods may not be adequately demonstrated. Acceptance criteria for dissolution tests are set on the basis of requirements for a percent quantity of drug to be released after a certain period of time in the dissolution apparatus. The acceptance criteria should be representative of multiple batches from the same nominal composition and manufacturing process, include key batches used in pivotal studies, and batches that are representative of the drug product performance in stability studies. Acceptance criteria in the form of "Q-factors," or the percentage of the labeled amount, are derived, that specify a certain amount dissolved at a given time point. Dissolution tests can have a single Q-factor, or multiple Q-factors. A formulation is regarded as an immediate release drug, when at least 80% of the drug substance is dissolved in about 20-30 minutes, corresponding to "Q" = 75%. For immediate release products, acceptance criteria are based on a single time point and a single value, expressed as a Q value. Then, at each of the three stages, the specification requires that mean values not be less than Q, but a set number of individual units are allowed to release a percent quantity of active which may be as low as Q - 25% for one unit at stage three[3,5,7]. For extended release products, specifications are based on three or four time points. For the intermediate time points, the requirements are based on ranges; for the final time point, they are usually based on a single value. Therefore, the acceptance criteria at each stage are expressed in terms of variances around ranges for intermediate time points and minimum acceptable release at the

final time point. The acceptance criteria are presented as guidelines only and may differ for some products.

In general to distinguish significant change in a composition or manufacturing process, the discriminating dissolution test methods are capable in vivo performance. These kinds of methods are very useful to compare the test results with Reference Listed Drugs (RLD). A properly designed dissolution test method should result in reproducible data. Too much result variability can make it difficult to identify trends, true batch differences, or effects of formulation changes. If too much variability is observed, the usual remedies include changing the apparatus type, speed of agitation, or deaeration (degassing). A relative standard deviation of less than 20% at early time points and less than 10% at other time points is recommended. During routine testing of the product, variability outside the expected range should be investigated from analytical, formulation, and processing perspectives.

ASSAY AND RESULTS

There are two common accurate possibilities of analyzing dissolution test samples, ultraviolet/visible (UV/VIS) Spectrophotometry method and HPLC determinations. Spectrophotometric determinations are the most common method of routine quality release analysis because it is faster, simpler, and require less solvent than HPLC. Diode array UV/VIS spectrophotometers capable of multi-component analysis can even be used to analyze multiple actives in the same sample and, in many cases, formulations with interfering excipients. HPLC methods are used when there is potential interferences from the formulation matrix or medium or even degradation of the active drug substance can be separated by HPLC. HPLC also has the advantage of many modes of detection (for example conductivity, fluorescence, and MS) for both sensitivity (molecules of non-chromophores) and selectivity purposes. Further, large variations in sample concentration can often be dealt with simply by adjusting injection volume. When developing a dissolution procedure that includes an HPLC assay, the compatibility of the dissolution media with the mobile phase must be considered, especially if large injector volumes (over 100 µL) are needed. Systems for automated sampling and analysis by either HPLC or UV/VIS are commercially available. The application of these systems must be validated against manual sampling and analysis to demonstrate that they do not introduce any bias to the results. Single injections of each vessel time point with standards throughout the run constitute a typical run design. Regardless of the mode of assay utilized, however, the procedure must be validated

VALIDATION OF DISSOLUTION METHODS

Methods validation is the process of demonstrating that analytical method or procedures are suitable for their intended use. The methods validation process for analytical procedures begins with the planned and systematic collection by the applicant of the validation data to support the analytical procedures. Typical analytical performance characteristics that should be considered in the validation of the types of procedures described below in the **Table**

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2. Because dissolution is a quantitative test, all of the analytical performance characteristics apply, with the exception of the detection of limit. In addition, for Chromatographic based assays, system suitability is always required. However, in a dissolution test, in addition to the procedure used to perform and assay the test results, some individual "sub tests" (for example, filtration and solution stability) also must be validated. The various validation performance characteristics listed in USP chapter 1225 [4] are well defined in a general sense, the specifics of how the analytical performance characteristics apply to dissolution testing deserves a little more focus.

Table 2: Data elements required for general procedure validation (from USP Chapter 1225). Type- I: Identification tests. An asterisk indicates the parameter may be required, depending upon the nature of the test. Type-II: Analytical procedures for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests. Type-III Analytical procedures for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products. Type-IV Analytical procedures for determination of performance characteristics. For additional details see reference:4 and 10

Type of Tests / Characteristics	Type-I Identification	Type -II Impurities		Type -III Assay Dissolution (Measurement Only), Content/Potency	Type-IV Specific tests
		Quantity	Limit		
Specificity	Yes	Yes	Yes	Yes	Yes
Linearity	No	Yes	No	Yes	No
Range	No	Yes	No	Yes	No
Accuracy	No	Yes	No	Yes	Yes
Precision Repeatability	No	Yes	No	Yes	Yes
Precision Intermediate Precision	No	Yes	No	Yes	Yes
Detection limit	No	No	Yes	No	No
Quantification limit	No	Yes	No	No	No
Robustness	No	Yes	No	Yes	Yes

Specificity/Placebo Interference

To demonstrate specificity/placebo Interference in dissolution methods, it is necessary to evaluate that the results are not affected by placebo constituents, other active drugs, or degradants in the formulated product. A proper placebo should consists of everything in the formulation, except the active drug substance; all the excipients and coatings (inks, sinker, and capsule shell are also included when appropriate), other actives, etc. In some instances, placebo interference may be studied by weighing samples of a placebo blend and dissolving or dispersing it into the dissolution medium at concentrations that would normally be encountered during testing. The interference generally should not exceed 2%.

For extended-release products, a placebo version of the actual drug product may be more appropriate to use than blends, because this placebo formulation will release the various excipients over time in a manner more closely reflecting the product than will a simple blend of

the excipients. In this case, it may be appropriate to evaluate potential interference at multiple sampling points in the release profile.

If the placebo interference exceeds 2%, then method modification, such as: (1) choosing another wavelength, (2) baseline subtraction using a longer wavelength, or (3) using HPLC, may be necessary in order to avoid the interference.

Absence of interfering peaks in the placebo chromatogram or lack of absorbance by the placebo at the analytical wavelength demonstrates specificity. One procedure for doing this is to measure the matrix in the presence and absence of the other active drug or degradate: any interference should not exceed 2%.

Linearity and Range

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample[11]. The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

Linearity and range are generally established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during release. Typically, solutions are made from a common stock if possible. For the highest concentration, the determination may not exceed the linearity limits of the instrument.

Some cases organic solvents may necessary to enhance drug solubility for the preparation of the standard solutions; however, no more than 5% (v/v) of organic solvent in the final solution should be used. Linearity is typically calculated by using an appropriate least-squares regression program. Typically, a square of the correlation coefficient ($r^2 \geq 0.98$) demonstrates linearity. In addition, the *y*-intercept must not be significantly different from zero Typically to calculate and report the Linearity by least-square linear regression analysis of the curve, a minimum of five points are recommended. Typically, a square of the correlation coefficient (r2≥0.98) demonstrates linearity. In addition, the y-intercept must not be significantly different from zero. According to International Conference on Harmonization (ICH) for dissolution testing, linearity should be demonstrated ±20% over the range of the dissolution test. For example, for a controlled release drug product with a multiple Q-factor of 20% after one hour, and 90% after 24 hours, the validated range should be from 0-110% of label claim [11].

Accuracy/Recovery

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

Accuracy and recovery are commonly established by preparing multiple samples containing the drug and any other constituents present in the dosage form (e.g., excipients, coating materials, capsule shell) ranging in concentration from below the lowest expected concentration to above the highest concentration during release.

For poor drug solubility, it may be appropriate to prepare a stock solution by dissolving the drug substance in a small amount of organic solvent (typically not exceeding 5%) and final concentration of the solution should be diluted with dissolution medium.

ICH guidelines recommend a minimum of nine determinations over a minimum of three concentrations [11], e.g. three concentrations, three replicates each. Instead of adding the drug powder directly to the vessel, an amount of stock solution equivalent to the target label claim recommended. Similarly, for very low strengths, it may be more appropriate to prepare a stock solution than to attempt to weigh very small amounts. The measured recovery is typically 95% to 105% of the amount added. Often accuracy and recovery experiments are carried out at the same time as linearity, using data from the same samples

Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. For analytical method validation, precision is measured over two levels, repeatability and intermediate precision. The same will be applicable for dissolution method validation also. Repeatability expresses the precision under the same operating conditions over a short interval of time by one analyst using one instrument. Repeatability is determined by replicate measurements of standard and/or sample solutions. It can be measured by calculating the RSD of the multiple HPLC injections (peak area and retention time) or spectrophotometric readings for each standard solution. Repeatability can also be measured from the same samples used in the accuracy, recovery and linearity experiments.

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc .Intermediate precision may be evaluated to determine the effects of random events on the precision of the analytical procedure. This evaluation is typically done later in the development of the drug product.

The dissolution profiles on the same sample may be run by at least two different analysts, each analyst preparing the standard solutions and the medium. Typically, the analysts use different dissolution baths, spectrophotometers or HPLC equipment (including columns), and auto samplers; and they perform the test on different days. This procedure may not need to be performed for every strength; instead, bracketing with high and low strengths may be acceptable. Acceptance criterion is that the difference in the mean value between the dissolution results at any two conditions using the same strength does not exceed an absolute 10% at time points with less than 85% dissolved and does not exceed 5% for time points above 85%. Acceptance criteria may be product-specific, and other statistical tests and limits may be used.

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters [4, 11, 14]. For dissolution testing, parameters to be varied include medium composition (e.g., buffer or surfactant concentration), pH, volume, agitation rate, and temperature. These parameters would be investigated in addition to those typically evaluated during validation of the assay method, either spectrophotometric or HPLC.

Additional validation Tests

In addition to the common analytical performance characteristics normally evaluated for method validation, standard and sample solution stability and filter validation must also be evaluated [3]. Solution stability is important given the conditions and length of time of some dissolution tests. The standard and sample solution should be stored under conditions that ensure stability. Solution stability is analyzed over a specified period of time, using freshly prepared solutions at each time interval for comparison. The acceptable range for solution stability is typically between 98% and 102%. If the solution is not stable, aspects to consider could be temperature (refrigeration may be needed), light protection, and container material (plastic or glass). A time period for analysis should also be specified. Filter validation is accomplished by preparing a suitable standard solution or a completely dissolved sample solution at the appropriate concentrations. For standard and sample solutions, the results for filtered solutions (after discarding the appropriate volume) to those for the unfiltered solutions can be compared.

CONCLUSION

An appropriate drug release test is required to characterize the drug product and ensure batch-to-batch reproducibility and consistent pharmacological/biological activity. The efficient dissolution method development and validations are critical elements in the development of pharmaceuticals. Success in these areas can be attributed to several important factors, which in turn will contribute to regulatory compliance. However, a systematic and methodical approach

taking into account all the components that make up the dissolution test procedure, including the dissolution medium, the choice of apparatus, the test design (including the acceptance criteria), and determining the assay mode will pay great dividends in the end.

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