DISSOLUTION TECHNOLOGY IN PHARMACEUTICAL SCIENCE
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ABSTRACT

Drug dissolution testing plays an important role as a routine quality control test, for characterizing the quality of the product, for accepting product sameness under SUPAC (Scale-Up and Post-Approval Changes) related changes, in waiving bioequivalence requirements for lower strengths of a dosage form and in supporting waivers for other bioequivalence requirements. Absorption of a drug is possible only after dissolution i.e. when drug molecule is present in solution form. Thus, dissolution is a prerequisite step for the drug absorption. It can help to identify potential problems of in vivo release and bioavailability/absorption following administration and thereby guiding the selection of prototype formulations. This review article is focus on the history of dissolution, importance and application of dissolution, mathematical concept and validation method of dissolution study. This review article is also focus on the construction and specification of dissolution test apparatus and its acceptance criteria as per different pharmacopoeias like Indian pharmacopoeia, US pharmacopoeia, British pharmacopoeia and international pharmacopoeia.

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INTRODUCTION

A drug is expected to be released from the solid dosage forms (granules, tablets, capsules etc.) and immediately go into molecular solution. This process is called dissolution. Dissolution is a critical step for the performance of a drug as well as dosage form, because it is a prerequisite for the drug absorption [1].

History of Dissolution

Dissolution testing has almost had a century of development. It expanded over years beyond the ordinary tablets and capsules, first to extended-release and delayed-release (enteric-coated) articles, then to transdermal, multivitamin and minerals products, and to class monographs for non-prescription drug combinations. It was in the year 1897 that Noyes and Whitney published a paper on “Rate of solution of solid substances in their own solution” which gave the first known reference to dissolution testing. In this paper, they suggested that a layer of saturated solution that forms instantly around a solid particle controls the dissolution rate. Later in 1900, Brunner and Tolloczko proved and listed the factors determining the dissolution rate as chemical and physical structures of the solid, the surface area exposed to the medium, agitation speed, medium temperature and the overall design of the dissolution apparatus. In 1904, Nernst and Brunner established a relationship between the dissolution rate and the diffusion coefficient by developing a modified Noyes-Whitney equation with the application of Fick’s law of diffusion to it. In 1930, Experiments on dissolution testing began with in vivo-In vitro correlations and in 1931; Hixon and Crowell developed the cube-root law of diffusion. In 1934, disintegration test was introduced for tablets by the Swiss pharmacopoeia Helvetica but it became an official United States pharmacopoeia (USP) method only in 1950. During this period, the emphasis also moved from studying the effects of physicochemical properties of drug on dissolution to correlation of dissolution to bioavailability of dosage forms. In 1958, a rotating bottle dissolution method was developed for extended release formulations. The USP recognized a need for a standardized dissolution test and began experimenting with a variety of basket and stirring devices during the 1960s. Levy and Hayes utilized a beaker blade stirrer at 30-60rpm and found significant differences in the in vitro dissolution rates of different brands of aspirin tablets, which linked to the incidence of gastric irritation caused by various brands due to their slow dissolution rates. USP 18 incorporated the first official dissolution test for solid dosage forms using a rotating basket in 1970. In 1975, the USP began developing of calibrators for dissolution testing and in 1978, it proposed three calibrator tablets – prednisone (disintegrating), salicylic acid (non-disintegrating) and nitrofurantoin (disintegrating), but no predefined calibration frequency was made. In the same year 1978, the Food Drug Administration (FDA) published guidelines for dissolution testing. In 1990, the paddle over disk, rotating cylinder and the reciprocating disk dissolution apparatus models were developed and later in 1995, the reciprocating cylinder and the flow-through cell were developed [18].

Importance of Dissolution

Dissolution is a prerequisite for the drug absorption. Absorption of a drug is possible only when it is present in solution form, wherein the molecules are independent and assume molecular dispersion. Each molecule is absorbed independently through biological membranes. Thus dissolution (molecular dispersion) is a prerequisite for drug absorption.

Absorption is a serious problem for:
1. Poorly water soluble drugs owing to poor dissolution
2. Acidic drugs, which are absorbed from the gastric region. Delayed release of these drugs may lead to decreased absorption.
Hence, dissolution focuses on these two categories. Basic drugs readily go into solution in gastric fluids, but absorbed from the small intestine [1].

**Applications of Dissolution**

1. This test is used to measure the release of an active substance (usually single ingredient) from the product in solid oral, tablet or capsule dosage forms.
2. It is one of the most important and useful *in vitro* tests for assuring product quality. *In vitro* dissolution often aids in guiding the selection of prototype formulations.
3. It helps to determine optimum amounts of ingredients needed to achieve requisite drug release profiles.
4. It is one of the most important and useful *in vitro* tests for assuring product quality batch-batch consistency.
5. Provides information on the impact of changes in composition, process or site of manufacture.
6. Can help to identify potential problems of *In vivo* release and bioavailability/absorption following administration.
7. *In vitro* dissolution is a valuable tool to assess drug product stability and shelf-life [1].

**Types of Dissolution**

Two types of dissolution are there:
1. In vitro dissolution
2. In vivo dissolution

Dissolution methods provide a convenient means of testing a drug product, when a proper dissolution method is chosen; the rate of dissolution of the product may be correlated to the rate of the absorption of the drug in the body. A number of examples of drugs have shown excellent correlations as discussed in the topics dissolution-drug absorption and factors influencing the dissolution.

**Correlations**

These correlations may be established for the following parameters.

**Table 1 in Vitro in Vivo Correlation**

<table>
<thead>
<tr>
<th>SR.NO</th>
<th>IN VITRO</th>
<th>IN VIVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dissolution rate</td>
<td>Absorption rate (or absorption time)</td>
</tr>
<tr>
<td>2.</td>
<td>Percent of drug dissolved</td>
<td>Percent of drug absorbed</td>
</tr>
<tr>
<td>3.</td>
<td>Percent of drug dissolved</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>4.</td>
<td>Percent of drug dissolved</td>
<td>Serum drug concentration</td>
</tr>
</tbody>
</table>

The absorption time refers to the time for a constant amount of a drug to be absorbed. The dissolution method, medium and experimental conditions should be selected so that in vivo conditions are approximated to the in vitro method [1].
Mathematical Concepts of Dissolution \(^{(1)}\)

**Dissolution of Particles**

Eq. (1) is one of the oldest expressions used to describe the dissolution process of a particle:

\[
\frac{dW}{dt} = \frac{D}{h} S (C_s - C_t) \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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systems; for example, Lai and Carstense derived shape factors to modify cube root behavior. In reality, dissolution from multiparticulate systems requires more complex mathematical approaches to dissolution. Associated problems include correctly assigning the particle size distribution to the powders, the fact that small particles have higher solubility than larger ones, and account for changes in both the size and the number of particles during dissolution.

![Dissolution data of a hypothetical solid plotted as cumulative amount released (Right axis) and after cube root law data treatment (left axis) (1)](image)

**Dissolution of Disintegrating Tablets and Capsules**

The development of theories of dissolution from disintegrating tablets and capsules becomes very difficult because disintegration produces vast changes in surface area. Attempts have been made to develop models to describe dissolution rates from tablets using complex mathematical approaches [15].

**Dissolution of Non-Disintegrating Tablets**

For systems where drug release involves the dissolution of a soluble drug at high concentrations from an insoluble matrix, the Higuchi equation adequately describes release rates [Eq. (3)].

\[
\frac{W_t}{t^{1/2}} = 2W_0 \frac{S}{V} \left(\frac{D}{\pi \tau}\right)^{1/2}
\]

Where \(W_t\) is the amount of drug dissolved in time \(t\); \(W_0\) is the dose of the drug; \(S\) is the effective diffusional area; \(V\) is the volume of the hydrated matrix; \(D\) is the diffusion coefficient of the drug in the hydrated matrix; and \(\tau\) is the tortuosity of the matrix. An analogous equation was developed for drugs of limited water solubility [16].

**Intrinsic Dissolution Rate**

The intrinsic dissolution rate (IDR) of a pure substance is the rate at which it dissolves from a constant surface area whilst the temperature, agitation, pH, and ionic strength of the dissolution medium are kept constant. Thus, for a drug substance, the IDR is independent of formulation factors and measures the inherent solubility of the drug in the dissolution medium. Thus, IDR determinations can be used to characterize bulk drug substances and excipients and to test the chemical equivalence of active pharmaceutical ingredients.
synthesized by different processes. They can also provide an important insight into the dissolution behavior of a drug in physiological conditions or distinguish whether changes in the dissolution profile of a drug product in various bio relevant media are due to interactions between the medium and formulation excipients or medium and drug substance or both. Subsequently, this test has a place in the screening process of drug candidates for further development. Yu et al. have discussed the feasibility of using IDR as opposed to saturation solubility data to place drugs in a Biopharmaceutics Classification System (BCS) class as in vivo drug dissolution is a dynamic rate controlled process rather than an equilibrium process [17]. The IDR is a key indicator of the potential bioavailability of a candidate drug where an IDR 1.0 mg/min/cm² suggests that drug dissolution will not be the rate-limiting step to absorption while an IDR 0.1mg/min/cm² suggests that drug dissolution will be the rate-limiting step to absorption. An intermediate value suggests that drug dissolution may be the rate-limiting step to absorption [17].

Development of Dissolution Method and Its Validation (10)

The USP dissolution procedure is a performance test applicable too many dosage forms. It is one test in a series of tests that constitute the dosage form’s public specification (tests, procedures for the tests, acceptance criteria). To satisfy the performance test, USP provides the general test chapters. These chapters provide information about conditions of the procedure. For dissolution, these include information about (1) medium, (2) apparatus/agitation rate, (3) study design, (4) assay, and (5) acceptance criteria. Overall the dissolution procedure yields data to allow an accept/reject decision relative to the acceptance criteria, which are frequently based on a regulatory decision. This chapter provides recommendations on how to develop and validate a dissolution procedure [10].

Observations

Visual observations and recordings of product dissolution and disintegration behavior are very useful because dissolution and disintegration patterns can be indicative of variables in the formulation or manufacturing process. To accomplish visual observation, proper lighting (with appropriate consideration of photo degradation) of the vessel contents and clear visibility in the bath are essential. Documenting observations by drawing sketches and taking photographs or videos can be instructive and helpful for those who are not able to observe the real time dissolution test. Observations are especially useful during method development and formulation optimization. Examples of typical observations include, but are not limited to, the following:

1. Uneven distribution of particles throughout the vessel. This can occur when particles cling to the sides of the vessel, when there is coning or mounding directly under the apparatus, when particles float at the surface of the medium, when film-coated tablets stick to the vessel land/or when off-center mounds are formed.
2. Air bubbles on the inside of the vessel or on the apparatus or dosage unit. Sheen on the apparatus is also a sign of air bubbles. This observation would typically be made when assessing the need to deaerate the medium.
3. Dancing or spinning of the dosage unit, or the dosage unit being hit by the paddle
4. Adhesion of particles to the paddle or the inside of the basket, which may be observed upon removal of the stirring device at the end of the run.
5. Pellicles or analogous formations, such as transparent sacs or rubbery, swollen masses surrounding the capsule contents.
6. Presence of large floating particles or chunks of the dosage unit.
7. Observation of the disintegration rate (e.g., percentage reduction in size of the dosage unit within a certain time frame).

8. Complex disintegration of the coating of modified or enteric-coated products—for example, the partial opening and splitting apart (like a clamshell) or incomplete opening of the shell accompanied by the release of air bubbles and excipients.

**Sampling**

Manual sampling uses plastic or glass syringes, a stainless steel cannula that is usually curved to allow for vessel sampling, a filter, and/or a filter holder. Auto sampling is a useful alternative to manual sampling, especially if the test includes several time points. However, because regulatory labs may perform the dissolution test using manual sampling, auto sampling requires validation with manual sampling. If coning (mounding) under the paddle at 50 rpm, the coning can be reduced by increasing the paddle speed to 75 rpm, thus reducing the artifact and improving the data. 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. Selection of the agitation and other study design elements for modified-release dosage forms is similar to that for immediate-release products[10].

**Study design**

Time points for immediate-release dosage forms, the duration of the procedure is typically 30 to 60 minutes in most cases, a single time point specification is adequate for Pharmacopeial purposes. Industrial and regulatory concepts of product comparability and performance may require additional time points, which may also be required for product registration or approval. A sufficient number of time points should be selected to adequately characterize the ascending and plateau phases of the dissolution curve. According to the Biopharmaceutics Classification System referred to in several FDA Guidance, highly soluble, 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 drug substance within 15 minutes. For these types of products a one-point test will suffice. However, most products do not fall into this category. Dissolution profiles of immediate-release products typically show a gradual increase reaching 85% to 100% at about 30 to 45 minutes. Thus, dissolution time points in the range of 15, 20, 30, 45, and 60 minutes are usual for most immediate-release products. For rapidly dissolving products, including suspensions, useful information may be obtained from earlier points, e.g., 5 to 10 minutes. For slower-dissolving products, time points later than 60 minutes may be useful. Dissolution test times for compendial tests are usually established on the basis of an evaluation of the dissolution profile data.

So-called infinity points can be useful during development studies. To obtain an infinity point, the paddle or basket speed is increased at the end of the run for a sustained period (typically 15 to 60 minutes), after which time an additional sample is taken. Although there is no requirement for 100% dissolution in the profile, the infinity point can provide data that may supplement content uniformity data and may provide useful information about formulation characteristics during initial development or about method bias.

For an extended-release dosage form, at least three test time points are chosen to characterize the in vitro drug release profile for Pharmacopoeial purposes. Additional sampling times may be required for drug approval purposes. An early time point, usually 1 to 2 hours, is chosen to show that there is little probability of dose dumping. 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.

Volume can be increased from the typical 900 to 1000 mL by using 2- and 4-L vessels to assist in meeting sink conditions for poorly soluble drugs. A noncompendial apparatus may have some utility with proper justification, qualification, and documentation of superiority over the standard equipment. For example, a small-volume apparatus with mini paddles and baskets may be considered for low-dosage strength products. The rotating bottle or static tubes (jacketed stationary tubes enclosed with a water jacket and equipped with a magnetic stirrer) may also have utility for microspheres and implants, peak vessels for eliminating coning, and modified flow-through cells for special dosage forms, including powders and stents.

Sinkers

When sinkers are used, a detailed description of the sinker must be stated in the written procedure. It may be useful to evaluate different sinkers, recognizing that sinkers can significantly influence the dissolution profile of a dosage unit when transferring the procedure; the sinkers should be duplicated as closely as possible in the next facility. There are several types of commercially available sinkers. A method for making sinkers by hand, sinkers that are similar to ‘a few turns of wire helix. Materials- Use 316 stainless steel wire or other inert material, typically 0.032 inch 20 gauge and cylinders of appropriate diameter (e.g., cork borers).

<table>
<thead>
<tr>
<th>Capsule Shell Type</th>
<th>Length of Wire (cm)</th>
<th>Diameter Size (cm)</th>
<th>Cork Bore Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>#0, elongated</td>
<td>12</td>
<td>0.8</td>
<td>4</td>
</tr>
<tr>
<td>#1 and #2</td>
<td>10</td>
<td>0.7</td>
<td>3</td>
</tr>
<tr>
<td>#3 and #4</td>
<td>8</td>
<td>0.55</td>
<td>2</td>
</tr>
</tbody>
</table>

Procedure

Cut the specified length of wire, coil around a cylinder of the appropriate size, and use small pliers to curve in the ends. Use caution, because wire ends may be rough and may need to be bled. 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

For immediate-release capsule or tablet formulations, Basket type Apparatus at 100 rpm or Paddle type Apparatus at 50 or 75 rpm are most commonly used. Other agitation speeds and apparatus are acceptable with appropriate justification. Rates outside 25 to 150 rpm are usually inappropriate because of the inconsistency of hydrodynamics below 25 rpm and because of turbulence above 150 rpm. Agitation rates between 25 and 50 rpm are generally acceptable for suspensions. For dosage forms that exhibit coning (mounding) under the paddle at 50 rpm.

Medium

Physical and chemical data for the drug substance and dosage unit need to be determined before selecting the dissolution medium. Two key properties of the drug are the 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. Key properties of the dosage unit that may affect dissolution include release mechanism (immediate, delayed, or modified) and disintegration rate as affected by hardness, friability, presence of solubility enhancers, and presence of other excipients.

Generally, when developing dissolution procedure, one goal is to have sink conditions, defined as the volume of medium at least three times that required in order to form a saturated solution of drug substance. 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. Using an aqueous—organic solvent mixture as a dissolution medium is discouraged however, with proper justification this type of medium may be acceptable.

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. Second, the pH value can vary from day to day and can also change during the run, depending on the active substance and excipients. Despite these limitations, 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). During method development, it may be useful to measure the pH before and after a run to discover whether the pH changes during the test. Selection of the most appropriate conditions for routine testing is then based on discriminatory capability, ruggedness, stability of the analyze in the test medium, and relevance to in vivo performance, where possible label claim level, especially for a single-point analysis.

Preparation of the placebo samples for the HPLC analysis is to be performed in the same way as in the spectrophotometric analysis. Examine the chromatogram for peaks eluting at the same retention time as the drug, if there are extraneous peaks. Inject the standard solution, and compare retention times. If the retention times are too close, spike the placebo solution with the drug Chromatograms may also be obtained over an extended run time using the blank (dissolution medium), standard, and sample solution to identify late eluters that may interfere with subsequent analyses.

The validation documentation may include overlaid representative chromatograms or spectra of blank dissolution medium, a filtered placebo solution, a standard solution, and a filtered dissolution sample. Absence of interfering peaks in the placebo chromatogram or lack of absorbance by the placebo at the analytical wavelength demonstrates specificity.

**Validation**

The validation topics described in this section are typical but not all-inclusive. The validation elements addressed may vary, depending on the phase of development or the intended use for the data. The acceptance criteria are presented as guidelines only and may differ for some products. Firms should document the appropriate acceptance criteria for their products in pertinent SOPs. Other considerations may be important for special dosage forms. The extent of validation depends on the phase of the product development. Full validation takes place by the time of Phase III clinical studies. Validation studies should address the variations associated with different profile time points. For products containing more than a single active ingredient, the dissolution method needs to be validated for each active ingredient.

It is necessary to demonstrate that placebo constituents, other active drugs, do not unduly affect the results or degrades. The placebo consists of all the excipients and coatings (inks, sinker, and capsule shell are also included when appropriate) without the active ingredient. Weighing samples of the placebo blend and
dissolving or dispersing them in dissolution medium at concentrations that would be encountered during testing may determine placebo interference. It may be desirable to perform this experiment at 37°C by comparing it to the 100% standard by the formula: 100°C(A P / A S)(V / L) in which C is the concentration, in mg per mL, of the standard; A P and A S are the absorbance of the placebo and the standard, respectively; V is the volume, in mL, of the medium; and L is the label claim, in mg.

The interference should not exceed 2%. For extended-release products, a placebo version of the finished dosage form may be more appropriate to use than blends, because this placebo formulation will release the various excipients in a manner more nearly 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. When other active drugs or significant levels of degrade is present, it is necessary to demonstrate that these do not significantly affect the results. One procedure for doing this is to measure the matrix in the presence and absence of the other active drug or degrade; any interference should not exceed 2%.

1. **Linearity and Range**

   Linearity and range are typically established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during release. This may be done in conjunction with accuracy/recovery determination. The scheme may be altered if different flow-cell sizes or injection volumes are used. 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. Organic solvents may be used 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, unless validated. Linearity is typically calculated by using an appropriate least-squares regression program. Typically, a square of the correlation coefficient (r² = 0.98) demonstrates linearity. In addition, the y-intercept must not be significantly different from zero.

2. **Accuracy/Recovery**

   Accuracy/recovery are typically 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. In cases of 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 diluting to the final concentration with dissolution medium. An amount of stock solution equivalent to the targeted label claim may be added to the vessel instead of the drug powder. 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. Bracketing or matrixing of multiple strengths may be useful. A special case for validation is the Acid Stage procedure described in Delayed-Release Dosage Forms. The limit of not more than 10% needs to be validated. If the compound degrades in acid, the validation experiment must address this fact.

3. **Precision**

   Repeatability is determined by replicate measurements of standard and/or sample solutions. It can be measured by calculating the RSD of the multiple injections or spectrophotometric readings for each standard solution, or from the accuracy or linearity data. Intermediate Precision—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 precision can be across the range of product strengths. Typical variations to study include days, analysts, and equipment. The use of an experimental matrix design is encouraged for evaluation of intermediate precision. If possible, intermediate precision can be evaluated using a well-characterized lot of drug product of tight content uniformity. In cases where a well-characterized product is not available, placebo and active ingredient may be used to identify intermediate precision.

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 each strength; instead, bracketing with high and low strengths may be acceptable. A typical 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.

4. Robustness

The evaluation of robustness, which assesses the effect of making small, deliberate changes to the dissolution conditions, typically is done later in the development of the drug product. The number of replicates (typically 3 or 6) is dependent on the intermediate precision. Parameters to be varied are dependent on the dissolution procedure and analysis type. They may include medium composition (e.g., buffer or surfactant concentration), pH, volume, agitation rate, and temperature. For HPLC analysis, parameters may include mobile phase composition (percentage organic, buffer concentration, pH), flow rate, wavelength, column temperature, and multiple columns (of the same type). For spectrophotometric analysis, the wavelength may be varied.

Standard and Sample Solution Stability

The standard solution is stored under conditions that ensure stability. The stability of the standard is analyzed over a specified period of time, using a freshly prepared standard solution at each time interval for comparison. The acceptable range for standard solution stability is typically between 98% and 102%. The sample solution is typically stored at room temperature. The sample is analyzed over a specified period of time using the original sample solution response for comparison. The typical acceptable range for sample solution stability may be between 98% and 102% compared with the initial analysis of the sample solutions. If the solution is not stable, aspects to consider could be temperature (refrigeration may be needed), light protection, and container material (plastic or glass). The procedure may state that the standards and samples need to be analyzed within a time period demonstrating acceptable standard and sample solution stability.

Spectrophotometric Analysis

Samples may be automatically introduced into the spectrophotometer using auto sippers and flow cells. Routine performance checks, cleaning, and maintenance as described in the standard operating procedures or metrology documents are useful for reliable operation of these instruments. Cells with path lengths ranging from 0.02 to 1 cm are typically used. Cell alignment and air bubbles could be sources of error. The smaller path length cells are used to avoid diluting the sample; however, acceptable linearity and standard error need to be demonstrated. During analysis, standard solutions are typically prepared and analyzed at just one concentration at 100% (or the selected Q value) of the dosage strength. During profile analysis, other concentrations may be
useful. A typical blank, standard, and sample may be analyzed in a sequence that brackets the sample with standards and blanks, especially at the beginning and end of the analysis. In most cases, the mean absorbance of the dissolution medium blank may not exceed 1% of the standard. Values higher than 1% must be evaluated on a case-by-case basis. The typical RSD for UV analysis is usually not more than 2%. The absorptivity is calculated by dividing the mean standard absorbance by the concentration, in mg per mL, divided by the flow-cell path length in cm. After enough historical data are accumulated, an acceptable absorptivity range for the analyte (using the appropriate flow cell) may be determined. This value may be useful in troubleshooting aberrant data. Fiber optics as a sampling and determinative method, with proper validation, is an option. It may be useful to examine the UV spectrum of the drug in solution to select the optimum wavelength.

HPLC

For HPLC analysis, the compatibility of dissolution media and mobile phase may be examined, especially if large injector volumes (over 100 µL) are needed. Samples are normally analyzed with HPLC using a spectrophotometric detector and an auto-injector. Single injections of each vessel time point with standards throughout the run constitute a typical run design. System suitability tests include, at a minimum, the retention window and injection precision. Typically, the repeatability of an HPLC analysis should be less than or equal to 2% RSD for five or six standard determinations. The standard level is typically at the 100% label claim level, especially for a single-point analysis. Preparation of the placebo samples for the HPLC analysis is to be performed in the same way as in the spectrophotometric analysis. Examine the chromatogram for peaks eluting at the same retention time as the drug. If there are extraneous peaks, inject the standard solution, and compare retention times. If the retention times are too close, spike the placebo solution with the drug. Chromatograms may also be obtained over an extended run time using the blank (dissolution medium), standard, and sample solution to identify late eluters that may interfere with subsequent analyses. The validation documentation may include overlaid representative chromatograms or spectra of blank dissolution medium, a filtered placebo solution, a standard solution, and a filtered dissolution sample. Absence of interfering peaks in the placebo chromatogram or lack of absorbance by the placebo at the analytical wavelength demonstrates specificity.

Acceptance criteria

Typical acceptance criteria for the amount of active ingredient dissolved, expressed as a percentage of the labeled content (0), are in the range of 75% to 80% dissolved. A 0 value in excess of 80% is not generally used, because allowance needs to be made for assay and content uniformity ranges. Acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Acceptance criteria should be consistent with historical data, and there is an expectation that acceptable batches (e.g., no significant differences in in vivo performance, composition, or manufacturing procedure) will have results that fall within the acceptance criteria [10].
Dissolution Test Apparatus as per pharmacopoeias

Table 3. List of Dissolution test Apparatus as per Pharmacopoeias

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paddle Type</td>
<td>Basket type</td>
<td>Basket type</td>
<td>Paddle type</td>
<td>Paddle type</td>
</tr>
<tr>
<td>2</td>
<td>Basket type</td>
<td>Paddle type</td>
<td>Paddle type</td>
<td>Basket type</td>
<td>Basket type</td>
</tr>
<tr>
<td>3</td>
<td>#Reciprocating cylinder type</td>
<td>Reciprocating cylinder type</td>
<td>Flow through cell type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Flow through cell type</td>
<td>Flow through cell type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*Paddle over disk type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>*Rotating disk type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>*Reciprocating holder type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*GIVEN ONLY IN USP24, NF19, 2000
#GIVEN IN BP 2010, NOT IN BP 2005

Construction and Specifications of Dissolution Test Apparatus

1. Paddle Type Apparatus

An assembly consisting of the following:

a) A cylindrical vessel, A, made of borosilicate glass or any other suitable transparent material, with a hemispherical bottom and with a nominal capacity of 1000ml and an inside diameter of 98-106 mm (Fig.2). The vessel has a flanged upper rim and is fitted with a lid that has a number of openings, one of which is central.

b) A motor with a speed regulator capable of maintaining the speed of rotation of the paddle within 4 per cent of that specified in the individual monograph. The motor is fitted with a stirring element, which consists of a drive shaft and blade forming a paddle, B (Fig.2). The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The shaft is positioned so that its axis is within 2 mm of the axis of the vessel and the lower edge of the blade is 23 to 27 mm from the inside bottom of the vessel. The apparatus operates in such a way that the paddle rotates smoothly and without significant wobble.

c) A water-bath set to maintain the dissolution medium at 36.5° to 37.5°. The bath liquid is kept in constant and smooth motion during the test. The vessel is securely clamped in the water bath in...
such a way that the displacement vibration from other equipment, including the water circulation device, is minimize

![Diagram](image1)

**Fig.2. Paddle type dissolution test apparatus** (12)

2. Basket Type Apparatus (12)

The assembly is the same as in Apparatus 1 except that in the stirring element the paddle is replaced by a basket, D (see Fig. 3.). The metallic shaft rotates smoothly and without significant wobble. The basket consists of two components. The top part, with a vent, is attached to the shaft C, it is fitted with three spring clips, or other suitable means that allow removal of the lower part for introduction of the preparation under examination and that firmly hold the lower part of the basket concentric with the axis of the vessel during rotation. The lower detachable part of the basket is made of welded-steam cloth, with a wire thickness of 0.254 mm diameter and with 0.381 mm square openings, formed into a cylinder with narrow rim of sheet metal around the top and the bottom. The basket may be plated with a 2.5 mm layer of gold for use with acidic media. The distance between the inside bottom of the vessel and the basket is maintained at 23 to 27 mm during the test.

![Diagram](image2)

**Fig.3. Basket Type Dissolution Test Apparatus** (12)
3. Reciprocating Cylinder Type Apparatus\textsuperscript{(12)}

The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material), and screens that are made of suitable nonsorbing and nonreactive material and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5 during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. A device is used that allows the reciprocation rate to be selected and maintained at the specified dip rate given in the individual monograph within ±5%. An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The vessels are provided with an evaporation cap that remains in place for the duration of the test. The components conform to the dimensions shown in fig.4 unless otherwise specified in the individual monograph\textsuperscript{[7]}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig4.png}
\caption{Reciprocating cylinder type dissolution test apparatus\textsuperscript{(12)}}
\end{figure}

NOTE: 1.) Reciprocating cylinder type dissolution test apparatus is not accepted by Japanese pharmacopoeia

2.) British pharmacopoeia 2010 has included reciprocating cylinder Apparatus as apparatus III which is not described in BP’05

3.) Not given in Indian Pharmacopoeia

4. Flow-Through Cell Type Apparatus\textsuperscript{(12)}

The assembly consists of a reservoir and a pump for the Dissolution Medium; a flow-through cell; and a water bath that maintains the Dissolution Medium at 37 ± 0.5. Use the specified cell size as given in the individual monograph. The pump forces the Dissolution Medium upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must deliver a constant flow (±5% of the nominal flow rate); the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute. The flow-through cell (see Figures 5 and 6), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the
apex to protect the fluid entry tube; and a tablet holder (see Figure 5 and 6) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath, and the temperature is maintained at 37 ± 0.5.

5. **Paddle Over Disk Apparatus** \(^{(12)}\)

Use the paddle and vessel assembly from apparatus 2 as described under dissolution, with the addition of a stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel. Other
appropriate devices may be used, provided they do not sorb, react with, or interfere with the specimen being
tested. The temperature is maintained at 32± 0.5°C.

A distance of 25±2mm between the paddle blade and the surface of the disc assembly is maintained
during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for
holding the transdermal system is designed to minimize any “dead” volume between the disk assembly and the
bottom of the vessel the disk assembly holds the system flat and is positioned such that release surface is
parallel with the bottom of the paddle blade[8].

6. Cylinder Type Apparatus[12]

Use the vessel assembly from Paddle type apparatus except to replace the basket and shaft with a
stainless steel cylinder-stirring element and to maintain the temperature at 32 ± 0.5 during the test. The shaft
and cylinder components of the stirring element are fabricated of stainless steel. The dosage unit is placed on
the cylinder is maintained at 25±2mm during the test.

Dissolution Medium:
Use the medium specified in the individual monograph.

Procedure:
Place the stated volume of the dissolution medium in the vessel of the apparatus specified in the
individual monograph, assemble the apparatus, and equilibrate the dissolution medium to 32±0.5°C. Unless
otherwise directed in the individual, prepare the test system prior to test as follows. Remove the protective liner
from the system, and place the adhesive side on a piece of cuprophan that is not less than 1 cm larger on all
sides than the system. Place the system, cuprophan-covered side down, on a clean surface, and apply a suitable
adhesive to the exposed cuprophan borders. If necessary, apply additional adhesive to the back of the system.
Dry for one minute. Carefully apply the adhesive coated side of the system to the exterior of the cylinder such
that the long axis of the system fits around the circumference of the cylinder. Place the cuprophan covering to
remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in
the individual monograph. Within the time interval specified, or at each of the time stated, withdraw a quantity
of dissolution medium for analysis from a zone midway between the surface of the dissolution medium and the
top of the rotating cylinder, not less than 1 cm from the vessel. Perform the analysis as directed in the individual
monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug
delivery system[8].

7. Reciprocating Holder Type[12]
Apparatus: the assembly consists of a set of volumetrically calibrated or tared solution containers made of glass
or other suitable inert material, motor and drive assembly to reciprocate the system vertically and to index the
system to horizontally to a different row of vessels automatically if desired, and a set of suitable sample holders
the solution containers are partially immersed in a suitable water bath of any suitable convenient size that
permits maintaining the temperature, T, inside the containers at 32±0.5°C or within the allowable range, as
specified in the individual monograph, during the test. No part of the assembly including the environment in
which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the
smooth, vertically reciprocating sample holder. Apparatus that permits observation of the system and holder
during the test is preferable. Use the size container and sample holder as specified in the individual monograph
[8].
Dissolution Medium: Use the dissolution medium specified in the individual monograph.[8]

General Methods to Perform Dissolution Test for Different Types of Dosage Forms and Its Acceptance Criteria as Per Different Pharmacopoeias

1. Indian Pharmacopoeia 2010[5]

1.1. Conventional and prolonged-release solid dosage forms

Place the stated volume of the dissolution medium, free from dissolved air, into the vessel of the apparatus. Assemble the apparatus and warm the dissolution medium to 36.5° to 37.5°. Unless otherwise stated, place one dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit. When Paddle type Apparatus 1 is used, allow the tablet or capsule to sink to the bottom of the vessel prior to the rotation of the paddle. A suitable device such as a wire of glass helix may be used to keep horizontal at the bottom of the vessel tablets or capsules that would otherwise float. When Apparatus 2 is used, place the tablet or capsule in a dry basket at the beginning of each test. Lower the basket into position before rotation. Operate the apparatus immediately at the speed of rotation specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10 mm from the wall of the vessel. Except in the case of single sampling, add a volume of dissolution medium equal to the volume of the samples withdrawn. Perform the analysis as directed in the individual monograph. Repeat the whole operation five times. Where two or more tablets or capsules are directed to be placed together in the apparatus, carry out six replicate tests. For each of the tablet or capsule tested, calculate the amount of dissolved active ingredient in solution as a percentage of the stated amount where two or more tablets or capsules are placed together, determine for each test the amount of active ingredient in solution per tablet or capsules and calculate as a percentage of the stated amount[5].

1.2. Prolonged-release dosage forms

Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units conform to Table 2. If the results do not conform to the requirements at stage L1 given in the table, continue testing with additional dosage units through stages L2 and L3 unless the results conform at stage L2. The limits embrace each value of D, the amount dissolved at each specified dosing interval. Where more than one range is specified, the acceptance criteria apply to each range[5].

1.3. Modified-release dosage forms.

Use Method A or Method B.

Method A

Acid stage: Place 750 ml of 0.1M hydrochloric acid in the vessel, and assemble the apparatus. Warm the dissolution medium to 36.5° to 37.5°. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in the acid medium, withdraw an aliquot of the liquid and proceed immediately as directed under Buffer stage. Perform the analysis of the aliquot using a suitable assay method. Buffer stages complete the operations of adding the buffer and adjusting the pH within 5 minutes. With the apparatus operating at the rate specified, add to the medium in the vessel 250 ml of a 0.2 M solution of trisodium phosphate dodecahydrate that has been warmed to 36.5° to 37.5°. Adjust, if necessary, with 2M hydrochloric acid or 2M sodium hydroxide to a pH of 6.8 ± 0.05. 2M hydrochloric acid or 2M sodium hydroxide to a pH of 6.8 ± 0.05.
Method B

Acid stage: Place 1000 ml of 0.1M hydrochloric acid in the vessel and assemble the apparatus. Warm the dissolution medium to 36.5° to 37.5°. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in the acid medium, withdraw an aliquot of the liquid and proceed immediately as directed under Buffer stage. Perform the analysis of the aliquot using a suitable assay method.

Buffer stage: Use buffer that has previously been warmed to 36.5° to 37.5°. Drain the acid from the vessel and add 1000 ml of pH 6.8 phosphate buffer, prepared by mixing 3 volumes of 0.1M hydrochloric acid with 1 volume of 0.2 M solution of trisodium phosphate dodecahydrate and adjusting, if necessary, with 2M hydrochloric acid or 2M sodium hydroxide to a pH of 6.8 ± 0.05. This may also be done by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer. Continue to operate the apparatus for 45 minutes, or for the specified time. At the end of this period, withdraw an aliquot of the liquid and perform the analysis using a suitable assay method[5].

Acceptance Criteria

1.4. Conventional-Release Dosage Forms

Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units conform to Table D. If the results do not conform to the requirements at stage S1 given in the table, continue testing with additional dosage units through stages S2 and S3 unless the results conform at stage S2. Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of the dissolution medium. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors should not be greater than 25 per cent of the stated amount[5].

Table 4

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6</td>
<td>Each unit is not less than D* + 5 percent**.</td>
</tr>
<tr>
<td>S2</td>
<td>6</td>
<td>Average of 12 units (S1 +S2) is equal to or greater than D, and no unit is less than D –15 per cent**.</td>
</tr>
<tr>
<td>S3</td>
<td>12</td>
<td>Average of 24 units (S1+S2+S3)is equal to or greater than D, not, More than 2 units are less than D – 15 per cent** and no unit is less than D – 25 per cent**.</td>
</tr>
</tbody>
</table>

* D is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

**Percentages of the labeled content.
Table 5

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>6</td>
<td>No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>L2</td>
<td>6</td>
<td>6 The average value of the 12 units (L1 + L2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10 per cent of labeled content outside each of the stated ranges; and none is more than 10 per cent of labeled amount below the stated amount at the final test time. The average value of the 24 units (L1 + L2 + L3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10 per cent of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10 per cent of labeled content below the stated amount at the final test time; and none of the units is more than 20 per cent of labeled content outside each of the stated ranges or more than 20 per cent of labeled content below the stated amount at the final test time.</td>
</tr>
<tr>
<td>L3</td>
<td>12</td>
<td>No individual value exceeds 10 percent dissolved.</td>
</tr>
</tbody>
</table>

Acceptance criteria

Acid stage: Unless otherwise specified, the requirements of this part of the test are met if the quantities, based on the percentage of the labeled content of active substance dissolved from the units tested conform to Table 5. Continue the testing through the 3 levels unless the results of both acid and buffer stages conform at an earlier level.

Table 6

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>6</td>
<td>No individual value exceeds 10 percent dissolved.</td>
</tr>
<tr>
<td>A2</td>
<td>6</td>
<td>The average value of the 12 units (A1+A2) is not more than 10 percent dissolved, and no individual unit is greater than 25 per cent dissolved.</td>
</tr>
<tr>
<td>A3</td>
<td>12</td>
<td>The average value of the 24 units (A1+A2 + A3) is not more than 10 percent dissolved, and no individual unit is greater than 25 per cent dissolved.</td>
</tr>
</tbody>
</table>
Buffer stage: Unless otherwise specified, the requirements of this part of the test are met if the quantities, based on the percentage of the labeled content of active substance dissolved from the units tested conform to Table G. Continue the testing through the 3 levels unless the results of both acid and buffer stages conform at an earlier level. The value of \( D \) in Table G is 75 per cent dissolved unless otherwise specified. The quantity, \( D \), is the specified total amount of active substance dissolved in both the acid and buffer stages, expressed as a percentage of the labeled content.

Table 7

<table>
<thead>
<tr>
<th>Level</th>
<th>Number</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>6</td>
<td>No unit is less than ( D + 5 ) per cent*</td>
</tr>
<tr>
<td>B2</td>
<td>6</td>
<td>The average value of the 12 units (B1+ B2) is equal to or greater than ( D ) and no unit is less than ( D - 15 ) per cent*.</td>
</tr>
<tr>
<td>B3</td>
<td>12</td>
<td>The average value of 24 units (B1 + B2 + B3) is equal to or greater than ( D ), not more than 2 units are less than ( D - 15 ) per cent*, and no unit is less than ( D - 25 ) per cent*.</td>
</tr>
</tbody>
</table>

2. British Pharmacopoeia 2010\(^{(7)}\)

2.1. Test conditions and acceptance criteria

Test conditions

Pharmacopoeial tests using either the basket or the paddle are based on the principle of operating under 'sink conditions', that is, in a manner such that material already in solution does not exert a modifying effect on the rate of dissolution of the remainder. ‘Sink conditions’ normally occur in a volume of dissolution medium that is at least 5 to 10 times the saturation volume. The standardized conditions have been chosen to provide a gentle hydrodynamic regimen. ‘Physiological’ media are preferred to water/organic solvent mixtures or solutions incorporating surfactants.

In the interests of International Harmonization the British Pharmacopoeia Commission reviewed the testing condition specified in the British Pharmacopoeia and adopted a dissolution medium volume of 900 ml instead of 1000 ml as the norm and now requires the analyst to test 6 individual tablets or capsules instead of 5. Following consultation of manufacturers, the published tests, wherever appropriate, were also amended to conform to the revised standardized conditions. However, changes to the volume of the dissolution medium were not made in cases such as Digoxin Tablets, where there was an indication of correlation between the results of in-vivo bioavailability and the established pharmacopoeial test and in other justified cases. The revised standardized BP conditions for published tests using either the basket or the paddle are:

Rotation speed: 100 rpm (basket), 50 rpm (paddle) dissolution medium volume: 900 ml dissolution medium composition: aqueous, commonly 0.1 M hydrochloric acid or phosphate buffers of pH 6.8 to 7.6 number of units tested: 6 (plus 6, if retest).
2.2. Acceptance Criteria

The standardized BP criteria for published tests using either the basket or the paddle are that, for each unit tested, not less than 70% of the active ingredient or ingredients dissolve within 45 minutes. If one unit fails to meet this requirement, a retest may be carried out using the same number of units.

It should be noted that the 70% dissolution requirement must be met by each of the tablets or capsules tested (or by all but one of the total number of units if a retest is performed) and that the percentage is in terms of the stated amount (that is, the labeled claim). Taking account of permissible assay ranges and content uniformity, this pharmacopoeial (that is, shelf-life) dissolution requirement is considered to offer an acceptable degree of assurance of 'total dissolution'. The choice of a time is, of necessity, somewhat arbitrary but 45 minutes is considered satisfactory for the majority of conventional-release (non-modified-release) products.

Standardized conditions and limits are considered appropriate for a pharmacopoeial test that is intended for application to monographs covering products from different manufacturers. It might be argued that non-standardized conditions and limits would be more discriminatory but 'tailor-made' test conditions and limits may introduce product bias and may discriminate unnecessarily between products that are equally acceptable from a clinical viewpoint. Similarly with sufficient manipulation of the test conditions dissolution of almost any product can be achieved. Ideally the test should reflect clinically significant differences in bioavailability arising from differences in dissolution in such a way those clinically acceptable formulations will pass whereas clinically unacceptable formulations will fail.

Another issue that has been considered in relation to test conditions and criteria is that of multiple-point dissolution profiles as opposed to single-point dissolution tests. It has been concluded that for conventional-release preparations such an extension of testing is not generally necessary or appropriate for pharmacopoeial purposes.

2.3. Low-solubility Preparations

Certain BP monographs for tablets or capsules containing active substances of low solubility in aqueous media were originally identified as requiring dissolution specification. Progress in developing suitable specifications for these preparations has been difficult. One way of resolving the problem is use of media modified by the addition of an organic solvent, such as ethanol, or a surfactant. This approach has been adopted by the USP and as an interim measure in certain BP monographs. Dissolution tests based on those in the USP using modified media were published for griseofulvin sodium dodecyl sulphate and Spironolactone Tablets (0.1% sodium dodecyl sulphate), following laboratory work to demonstrate applicability to products on the UK market and in the knowledge that, in the absence of a published BP test, the requirement in the USP was usually cited[7].

While such an approach may be validated by in vivo correlation on a product-specific basis, doubt has continued to be expressed as to its validity for pharmacopoeial purposes. Departure from the gentle hydrodynamic regimen represented by the aqueous media normally used in BP tests calls into question the relevance of the specification especially as an indicator of bioavailability and in relation to product comparisons. With respect to the modifiers, some have argued that the use of surfactants is more likely to give problems of product bias while others have suggested that water/organic solvent mixtures can adversely affect the initial disintegration of the tablet. A consensus has emerged, however, that in circumstances where use of a modified medium is unavoidable, a low concentration of sodium dodecyl sulphate is the modifier of choice.

Another approach to dealing with low-solubility preparations is to use a flow-through cell apparatus. This is described in the European Pharmacopoeia and this method has yet to be investigated as a possible
method of choice for low-solubility preparations since it would overcome the objections to the use of 'non-physiological' media.

2.4. Modified-Release Preparations

Any consideration of the quality of modified-release preparations in relation to their safety and efficacy must include attention to the release characteristics of these products. A manufacturer must be able to provide the licensing authority with an assurance that the dissolution profile reflects in vivo performance, which in turn is compatible with the recommended dosage schedule for the specific product. The general monographs for Capsules and Tablets include a Production requirement that a suitable test is carried out to demonstrate the appropriate release of the active ingredient or ingredients. With respect to providing tests in individual monographs, however, it has been concluded, following detailed discussion, that it is not possible to provide satisfactory pharmacopoeial control of the dissolution profile of the majority of modified-release preparations [7].


3.1. Immediate-release dosage forms

Dissolution Medium - A suitable dissolution medium is used. Use the solvent specified. The Apparatus Suitability Test, Apparatus 1 and 2—individually test 1 tablet of the USP Dissolution Calibrator, Disintegrating Type and 1 tablet of USP Dissolution Calibrator, Non disintegrating Type, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Apparatus Suitability Test, Apparatus 3- Individually test 1 tablet of the USP Drug Release Tablets (Single Unit) according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate.

Place the stated volume of the Dissolution Medium (±1%) in the vessel of the specified apparatus given in the individual monograph, assemble the apparatus, equilibrate the Dissolution Medium to 37 ± 0.5, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate given in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the Dissolution Medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall.

[NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution Medium at 37 or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.]

Perform the analysis as directed in the individual monograph using a suitable assay method. Repeat the test with additional dosage form units. If automated equipment is used for sampling or the apparatus is otherwise modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this general chapter is necessary in the individual monograph. If the Dissolution Medium is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH given in the individual monograph.

[NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.] Proceed as directed for Immediate-Release Dosage Forms.
Time— the test-time points, generally three, are expressed in hours.

Method A—

Procedure
Perform an analysis of the aliquot using a suitable assay method in the individual monograph.

3.2. Extended-Release Dosage Forms

Dissolution Medium— Proceed as directed for Immediate-Release Dosage Forms. Delayed-release dosage forms (Not Accepted by the Japanese Pharmacopoeia)

Use Method A or Method B and the apparatus specified times stated are to be observed within a tolerance of ±2%, unless otherwise specified. (Unless otherwise directed in the individual monograph)

Time— where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%.

Procedure for a Pooled Sample for Immediate-Release Dosage Forms —Use this procedure where Procedure for a Pooled Sample is specified in the individual monograph. Proceed as directed in Procedure for Apparatus 1 and Apparatus 2 in Immediate-Release Dosage Forms. Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the pooled sample as the test specimen. Determine the average amount of the active ingredient dissolved in the pooled sample.

Acid stage— Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate given in the monograph.

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under Buffer Stage. The procedure is specified in buffer stage.

With the apparatus operating at the rate specified vessel 250 mL of 0.20 M Tribasic sodium phosphate that has been equilibrated to 37 ± 0.5 Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time given in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the Buffer Stage if the requirement for the minimum amount dissolved is met at an earlier time [12].

Method B—

Procedure
As given in the individual monograph
Perform an analysis of the aliquot using a suitable assay method.

3.3. Apparatus 3 (Reciprocating Cylinder)

I. Immediate-Release Dosage Forms

Place the stated volume of the Dissolution Medium in each vessel of the apparatus, assemble the apparatus, equilibrate the Dissolution Medium to 37 ± 0.5, and remove the thermometer. Place 1 dosage form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating
cylinders and withdraw a portion of the solution under test from a zone midway between the surface of
the Dissolution Medium and the bottom of each vessel. Perform the analysis as directed in the individual
monograph. If necessary, repeat the test with additional dosage-form units.

II. Delayed-release dosage forms

a. Proceed as described for Delayed-Release Dosage Forms, Method B under Apparatus 1 and
Apparatus 2 using one row of vessels for the acid stage media and the following row of vessels
for the buffer stage media and using the volume of medium specified (usually 300 mL).

Time — proceed as directed for Immediate-Release Dosage Forms under Apparatus 1 and Apparatus 2.

III. Immediate-release dosage forms

a. Place the glass beads into the cell specified the beads or, if specified in the monograph the parts
together by means of a suitable clamping device. Introduce by the pump the dissolution medium
warmed to 37 ± 0.5 through the bottom of the cell to obtain the flow rate specified in the
monograph, on a wire carrier. Assemble the filter head, and fix the individual monograph at each
of the times stated. Perform the analysis as directed Repeat the test with additional dosage-form
units. Proceed as directed for Immediate-Release dosage forms under Apparatus 4 and measured
with an accuracy of 5%. Collect the elute by fractions in the individual monograph.

3.4. Interpretation

1. Immediate-Release Dosage Forms

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active
ingredient dissolved from the dosage units tested conform to A Table D. Continue testing through the three
stages unless the results conform at either S 1 or S 2. The quantity, Q, is the amount of dissolved active
ingredient specified in the individual monograph, expressed as a percentage of the labeled content of the
dosage unit; the 5%, 15%, and 25% values in Acceptance Table Dare percentages of the labeled content so that
these values and Q are in the same terms\textsuperscript{[12]}

<table>
<thead>
<tr>
<th>STAGE</th>
<th>NUMBER TESTED</th>
<th>ACCEPTANCE CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6</td>
<td>Each unit is not less than Q + 5%/o.</td>
</tr>
<tr>
<td>S2</td>
<td>6</td>
<td>Average of 12 units (S + S2) is equal to or greater than Q, and no unit is less than Q 15%.</td>
</tr>
<tr>
<td>S3</td>
<td>12</td>
<td>Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q 15%, and no unit is less than Q 25%/o.</td>
</tr>
</tbody>
</table>

Immediate-Release Dosage Forms Pooled Sample— unless otherwise specified in the individual monograph,
the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the
accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the
results conform at either S 1 or S 2. The quantity, Q, is the amount of dissolved active ingredient specified in
the individual monograph, expressed as a percentage of the labeled content\textsuperscript{[10]}. 
Table 9 (for a Pooled Sample)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6</td>
<td>Average amount dissolved is not less than Q + 100/0.</td>
</tr>
<tr>
<td>S2</td>
<td>6</td>
<td>Average amount dissolved (S1 + S2) is equal to or greater than Q + 50/0.</td>
</tr>
<tr>
<td>S3</td>
<td>12</td>
<td>Average amount dissolved (S1 + S2 + S3) is equal to or greater than Q.</td>
</tr>
</tbody>
</table>

2. Extended release dosage forms

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to Acceptance Table J. Continue testing through the three levels unless the results conform at either L 1 or L 2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q i, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.

Table 10

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L 1</td>
<td>6</td>
<td>No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>L2</td>
<td>6</td>
<td>6 The average value of the 12 units (L 1 + L 2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.</td>
</tr>
<tr>
<td>L3</td>
<td>12</td>
<td>The average value of the 24 units (L 1 + L 2 + L 3) lies within each of the stated ranges, and is not less than the stated amount at the final test time.</td>
</tr>
</tbody>
</table>

3. Delayed-Release Dosage Forms

Acid Stage— Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to Acceptance Table K. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Table 11

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>6</td>
<td>No individual value exceeds 10% dissolved.</td>
</tr>
<tr>
<td>A2</td>
<td>6</td>
<td>Average of the 12 units (A 1 + A 2) is not more than 10% dissolved and no individual unit is greater than 25% dissolved.</td>
</tr>
<tr>
<td>A3</td>
<td>12</td>
<td>Average of the 24 units (A 1 + A 2 + A 3) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.</td>
</tr>
</tbody>
</table>
Buffer Stage— Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to Acceptance Table L. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of $Q$ in Acceptance Table L is 75% dissolved unless otherwise specified in the individual monograph. The quantity, $Q$, specified in the individual monograph is the total amount of active ingredient dissolved in both the Acid and Buffer Stages, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in Acceptance Table L are percentages of the labeled content so that these values and $Q$ are in the same terms \[10\].

### Table 12

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>6</td>
<td>Each unit is not less than $Q + 5%$.</td>
</tr>
<tr>
<td>B2</td>
<td>6</td>
<td>Average of 12 units ($B1 + B2$) is equal to or greater than $Q$, and no unit is less than $Q – 15%$.</td>
</tr>
<tr>
<td>B3</td>
<td>12</td>
<td>Average of 24 units ($B1 + B2 + B3$) is equal to or greater than $Q$, not more than 2 units are less than $Q – 15%$, and no unit is less than $Q – 25%$.</td>
</tr>
</tbody>
</table>

### 4. European Pharmacopoeia \[13\]

#### 4.1. Paddle and basket apparatus

Place the prescribed volume of dissolution medium in the vessel, assemble the apparatus, warm the dissolution medium to $37 \pm 0.5 \, ^\circ\mathrm{C}$ and remove the thermometer. Place one unit of the preparation to be examined in the apparatus. For the paddle apparatus, place the preparation at the bottom of the vessel before starting rotation of the blade; dosage forms that would otherwise float are kept horizontal at the bottom of the vessel using a suitable device, such as a wire or glass helix. For the basket apparatus, place the preparation in a dry basket and lower into position before starting rotation. Take care to avoid the presence of air bubbles on the surface of the preparation. Start the rotation of the apparatus immediately at the prescribed rate (± 4 per cent) \[13\].

#### 4.2. Flow-through apparatus

Place 1 bead of 5 mm (± 0.5 mm) diameter at the bottom of the cone to protect the fluid entry of the tube and then glass beads of suitable size, preferably 1 mm (± 0.1 mm) diameter. Introduce 1 unit of the preparation in the cell on or within the layer of glass beads, by means of a holder. Assemble the filter head. Heat the dissolution medium to $37 \pm 0.5 \, ^\circ\mathrm{C}$. Using a suitable pump, introduce the dissolution medium through the bottom of the cell to obtain a suitable continuous flow through an open or closed circuit at the prescribed rate (± 5 per cent).

Place 1 unit of the preparation to be examined in chamber A. Close the cell with the prepared filter assembly. At the beginning of the test, chamber A requires air removal via a small orifice connected to the filter assembly. Heat the dissolution medium to an appropriate temperature taking the melting point of the preparation into consideration. Using a suitable pump, introduce the warmed dissolution medium through the bottom of the cell to obtain a suitable continuous flow through an open or closed circuit at the prescribed rate (± 5 per cent). When the dissolution medium reaches the overflow, air starts to escape through the capillary and chamber B fills with the dissolution medium.
The preparation spreads through the dissolution medium according to its physico-chemical properties. In justified and authorized cases, representative fractions of large volume suppositories may be tested. Dissolution medium if a buffer is added to the dissolution medium, adjust its pH to within ±0.05 units of the prescribed value. Prior to testing if necessary, remove any dissolved gases that could cause the formation of bubbles.

Recommended procedure Ensure that the equipment has been calibrated within the past 6-12 months. Place the volume of dissolution medium, as stipulated in the individual monograph, in the vessel; assemble the apparatus and place it in the water-bath; allow the temperature of the dissolution medium to reach 37±0.5°C and remove the thermometer.

When apparatus Paddle is used, allow either one tablet or one capsule of the preparation to be tested to sink to the bottom of the vessel before starting the rotation of the blade, taking care that no air bubbles are present on the surface of the dosage form. In order to stop the dosage form from floating, anchor it to the bottom of the vessel using a suitable device such as a wire or glass helix. When apparatus Basket is used, place either one tablet or one capsule of the preparation to be tested in a dry basket at the beginning of each test. Lower the basket into position before rotation.

Immediately start rotation of the blade or basket at the rate specified in the individual monograph. Withdraw a sample from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10 mm below the surface & and at least 10mm from the vessel wall, at the time or time intervals specified. Either replace the volume of dissolution medium with a volume equal to that of the liquid removed, or compensate for the loss of liquid by calculation, except where continuous measurement is used.

For filtration of the removed liquid, use an inert filter with a suitable pore size. Use a filter that does not cause significant adsorption of the active ingredient from the solution, and does not contain substances extractable by the dissolution medium that would interfere with the specified method of analysis. Use centrifugation as an alternative with conditions depending on the sample being tested\[13\]. Unless otherwise indicated, proceed in parallel with five additional tablets or capsules. Determine the quantity of active ingredient dissolved in the specified time limit indicated in the individual monograph. The result should be expressed as a percentage of the content stated on the label\[13\].

5.5. International Pharmacopoeias\[14\]

Table 13

<table>
<thead>
<tr>
<th>Stage</th>
<th>Samples Tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6</td>
<td>Each unit is not less than Q+5%</td>
</tr>
<tr>
<td>S2</td>
<td>6</td>
<td>Average of 12 units is equal to or greater than Q; and no unit is less than Q-15%</td>
</tr>
<tr>
<td>S3</td>
<td>12</td>
<td>Average of 24 units is equal to or greater than Q; no: more than 2 units are less than Q-15%; no unit is less than Q-25%</td>
</tr>
</tbody>
</table>

Continue testing through the three stages unless the results conformat either S1 or S2. The quantity, Q, is the released labeled content of active ingredient as a percentage as specified in the individual monograph; both the 5% and 15% values in the acceptance table are percentages of the labeled content so that these values arid Q are in the same terms\[14\].
Table 14 Lists of Some Marketed Dissolution Test Apparatus

<table>
<thead>
<tr>
<th>MANUFACTURER</th>
<th>MODEL NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNILAB</td>
<td>TSD 408 (TOUCH SCREEN)</td>
</tr>
<tr>
<td>Dr. SCHLEUNIGER PHARMATRON</td>
<td>DIS 6000</td>
</tr>
<tr>
<td></td>
<td>DIS 8000</td>
</tr>
<tr>
<td>ERWEKA</td>
<td>DT 820</td>
</tr>
<tr>
<td></td>
<td>DT 727</td>
</tr>
<tr>
<td></td>
<td>DT 826</td>
</tr>
<tr>
<td></td>
<td>DT 728</td>
</tr>
<tr>
<td></td>
<td>DT 827</td>
</tr>
<tr>
<td></td>
<td>DT 600</td>
</tr>
<tr>
<td></td>
<td>DT 828</td>
</tr>
<tr>
<td></td>
<td>DT 607</td>
</tr>
<tr>
<td></td>
<td>DT 720</td>
</tr>
<tr>
<td></td>
<td>DT 608</td>
</tr>
<tr>
<td></td>
<td>DT 726</td>
</tr>
<tr>
<td></td>
<td>FRL 804</td>
</tr>
<tr>
<td>ELECTRO LAB</td>
<td>EDT 08 Lx</td>
</tr>
<tr>
<td></td>
<td>EDT 14 Lx</td>
</tr>
<tr>
<td>JASCO</td>
<td>DT 810</td>
</tr>
<tr>
<td>COPLEY</td>
<td>DIS EMC 6000</td>
</tr>
<tr>
<td>PHARMA TEST</td>
<td>PT DT 70</td>
</tr>
</tbody>
</table>

CONCLUSION

Drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, i.e., to assess batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development, i.e., to predict in vivo drug release profiles. Dissolution testing should be able to predict in-vivo performance of drug product and thus reduce unnecessary human studies, accelerate drug product development and hasten validation of post-approval changes. The designs of the dissolution apparatuses and the ways of operating dissolution apparatuses have huge impacts on the hydrodynamics, thus the performances.

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