Compendial Methods of Dissolution
dissolution and drug release testing may be used for:

- Batch-to-batch drug release uniformity
- Stability
- Scale-up and postapproval changes (SUPAC)
- Predicting in-vivo performance
Official methods for dissolution tests

- The USP-NF provides several official methods for carrying out dissolution tests of tablets, capsules and other special products such as transdermal preparations.

- Tablets are grouped into uncoated, plain-coated, and enteric-coated tablets.
Table 14.7 Dissolution Apparatus

<table>
<thead>
<tr>
<th>Apparatus&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Name</th>
<th>Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparatus 1</td>
<td>Rotating basket</td>
<td>Tablets</td>
</tr>
<tr>
<td>Apparatus 2</td>
<td>Paddle</td>
<td>Tablets, capsules, modified drug products, suspensions</td>
</tr>
<tr>
<td>Apparatus 3</td>
<td>Reciprocating cylinder</td>
<td>Extended-release drug products</td>
</tr>
<tr>
<td>Apparatus 4</td>
<td>Flow cell</td>
<td>Drug products containing low-water-soluble drugs</td>
</tr>
<tr>
<td>Apparatus 5</td>
<td>Paddle over disk</td>
<td>Transdermal drug products</td>
</tr>
<tr>
<td>Apparatus 6</td>
<td>Cylinder</td>
<td>Transdermal drug products</td>
</tr>
<tr>
<td>Apparatus 7</td>
<td>Reciprocating disk</td>
<td>Extended-release drug products</td>
</tr>
<tr>
<td>Rotating bottle</td>
<td>(Non-USP-NF)</td>
<td>Extended-release drug products (beads)</td>
</tr>
<tr>
<td>Diffusion cell (Franz)</td>
<td>(Non-USP-NF)</td>
<td>Ointments, creams, transdermal drug products</td>
</tr>
</tbody>
</table>

Apparatus 1-7 refer to compendial dissolution apparatus in USP-NF.
Rotating Basket Method (Apparatus 1)

consists of a cylindrical basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing the dissolution medium. The entire flask is immersed in a constant-temperature bath set at 37°C.
The rotating speed and the position of the basket must meet specific requirements set forth in the current USP.

Apparatus 1 is generally preferred for capsules and for dosage forms that tend to float or disintegrate slowly.
Paddle Method (Apparatus 2) consists of a special, coated paddle that minimizes turbulence due to stirring. The paddle is attached vertically to a variable-speed motor that rotates at a controlled speed. The tablet or capsule is placed into the round-bottom dissolution flask, which minimizes turbulence of the dissolution medium.
A constant-temperature water bath maintained at 37°C

The position and alignment of the paddle are specified in the USP

The most common operating speeds for Apparatus 2 are 50 rpm for solid oral dosage forms and 25 rpm for suspensions.

Apparatus 2 is generally preferred for tablets.
A *sinker*, such as a few turns of platinum wire, may be used to prevent a capsule or tablet from floating.

The sinker should not alter the dissolution characteristics of the dosage form.
Reciprocating Cylinder Method (Apparatus 3)

The reciprocating cylinder apparatus (Apparatus 3) consists of a set of cylindrical, flat-bottomed glass vessels equipped with reciprocating cylinders.
Reciprocating Cylinder Method (Apparatus 3)

- for dissolution testing of extended-release products, particularly bead-type modified-release dosage forms.
- Six units are tested, and the dissolution medium is maintained at 37°C.
Flow-Through-Cell Method (Apparatus 4)

The flow-through-cell apparatus (Apparatus 4) consists of a reservoir for the dissolution medium and a pump that forces dissolution medium through the cell holding the test sample.
Flow-Through-Cell Method (Apparatus 4)

- Flow rate ranges from 4 to 16 mL/min.
- Six samples are tested during the dissolution testing.
- The medium is maintained at 37°C.
- Apparatus 4 may be used for modified-release dosage forms that contain active ingredients having very limited solubility.
Flow-Through-Cell Method (Apparatus 4)

There are many variations of this method. Essentially, the sample is held in a fixed position while the dissolution medium is pumped through the sample holder, thus dissolving the drug. Laminar flow of the medium is achieved by using a pulseless pump.
Flow-Through-Cell Method (Apparatus 4)

- The dissolution medium may be fresh or recirculated.
- In the case of fresh medium, the dissolution rate at any moment may be obtained.
- Whereas in the official paddle or basket method, cumulative dissolution rates are monitored.
Flow-Through-Cell Method (Apparatus 4)

- A major advantage of the flow-through method is the easy maintenance of a sink condition for dissolution.
- A large volume of dissolution medium may also be used, and the mode of operation is easily adapted to automated equipment.
Paddle-over-Disk Method (Apparatus 5)

- The USP-NF also lists a paddle-over-disk method for testing the release of drugs from transdermal products.
- The apparatus (Apparatus 5) consists of a sample holder or disk assembly that holds the product.
Paddle-over-Disk Method (Apparatus 5)

- The entire preparation is placed in a dissolution flask filled with specified medium maintained at 32°C.
- The paddle is placed directly over the disk assembly.
- Similar to dissolution testing with capsules and tablets, six units are tested during each run. Acceptance criteria are stated in the individual drug monographs.
Cylinder Method (Apparatus 6)

- For testing transdermal preparation is modified from the basket method (Apparatus 1).
- In place of the basket, a stainless steel cylinder is used to hold the sample.
- The sample is mounted onto cuprophan (an inert porous cellulosic material) and the entire system adheres to the cylinder.
Cylinder Method (Apparatus 6)

Testing is maintained at 32°C. Samples are drawn midway between the surface of the dissolution medium and the top of the rotating cylinder for analysis.
Reciprocating Disk Method (Apparatus 7)

- for testing transdermal products
- a motor drive assembly (Apparatus 7) is used to reciprocate the system vertically,
- the samples are placed on disk-shaped holders using cuprophan supports.
- The test is also carried out at 32°C
- reciprocating frequency is about 30 cycles per minute.
- The acceptance criteria are listed in the individual drug monographs.
Methods for Testing Enteric-Coated Products

USP-NF lists two methods (Method A and Method B) for testing enteric-coated products. The latest revision of the USP-NF should be consulted for complete details of the methods.
Both methods require that the dissolution test be performed in the apparatus specified in the drug monograph (usually Apparatus 2 or Apparatus 1). The product is first tested with 0.1 N HCl for 2 hours and then changed to pH 6.8 buffer medium.
The buffer stage generally runs for 45 minutes or for the time specified in the monograph. The objective is that no significant dissolution occurs in the acid phase (less than 10% for any sample unit), and a specified percentage of drug must be released in the buffer phase. Specifications are set in the individual drug monographs.
Meeting Dissolution Requirements

The dissolution test time points should be selected to characterize adequately the ascending and plateau phases of the dissolution curve. USP-NF sets dissolution requirements for many products.
Meeting Dissolution Requirements

- The amount of drug dissolved within a given time period \((Q)\) is expressed as a percentage of label content.
- The \(Q\) is generally specified in the monograph for a drug product to pass the dissolution test.
- Three stages (S1, S2, and S3) of testing are allowed by USP-NF.
Meeting Dissolution Requirements

Initially, six tablets or capsules are tested for the dissolution test. If the dissolution test fails to meet the criteria for S1, then six more units are tested. Dissolution testing continues until the dissolution criteria are met or until the three stages are exhausted.
Meeting Dissolution Requirements

Acceptance Table 1

<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 $Q + 5%$.</td>
</tr>
<tr>
<td>S₂</td>
<td>6</td>
<td>Average of 12 units ($S₁ + S₂$) 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 $Q - 25%$.</td>
</tr>
</tbody>
</table>
Meeting Dissolution Requirements

- For many products the passing value for $Q$ is set at 75% in 45 minutes.
- Some products require a $Q$ of 85% in 30 minutes,
- others 75% in 60 minutes.
- For a new drug product, setting the dissolution specification requires a thorough consideration of the physical and chemical properties of the drug.
Dissolution

Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of C₈H₉NO₂ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 243 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Acetaminophen RS in the same Medium.

Tolerances—Not less than 80% (Q) of the labeled amount of C₈H₉NO₂ is dissolved in 30 minutes.
FOR TABLETS LABELED AS CHEWABLE—

Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Procedure— Proceed as directed for Procedure for Acetaminophen Tablets.

Tolerances— Not less than 75% (Q) of the labeled amount of C₈H₉NO₂ is dissolved in 45 minutes.
Intrinsic Dissolution Method

- A new drug or substance may be tested for dissolution without the effect of excipients or the fabrication effect of processing.
- The dissolution of a drug powder by maintaining a constant surface area is called intrinsic dissolution.
- Intrinsic dissolution is usually expressed as mg/cm²/min.
Intrinsic Dissolution Method

In one method, the basket method is adapted to test dissolution of powder by placing the powder in a disk attached with a clipper to the bottom of the basket.
Peristalsis Method

- attempts to simulate the hydrodynamic conditions of the gastrointestinal tract in an *in-vitro* dissolution device.
- The apparatus consists of a rigid plastic cylindrical tubing fitted with a septum and rubber stoppers at both ends.
Peristalsis Method

- The dissolution chamber consists of a space between the septum and the lower stopper.
- The apparatus is placed in a beaker containing the dissolution medium. The dissolution medium is pumped with peristaltic action through the dosage form.
Peristalsis Method
Problems of Variable Control in Dissolution Testing

- The centering and alignment of the paddle is critical in the paddle method.
- Turbulence can create increased agitation, resulting in a higher dissolution rate.
- The basket method is less sensitive to the tilting effect.
- However, the basket method is more sensitive to clogging due to gummy materials.
Problems of Variable Control in Dissolution Testing

- Pieces of small particles can also clog up the basket screen and create a local non-sink condition for dissolution.
- Furthermore, dissolved gas in the medium may form air bubbles on the surface of the dosage form unit and can affect dissolution in both the basket and paddle methods.
Problems of Variable Control in Dissolution Testing

- The interpretation of dissolution data is probably the most difficult job for the pharmacist.
- In the absence of in-vivo data, it is generally impossible to make valid conclusions about bioavailability from the dissolution data alone.
Problems of Variable Control in Dissolution Testing

For example:
In a study of sustained-release theophylline tablets compressed at various degrees of hardness, found that, at 50 rpm, dissolution with the paddle method was faster than that of the basket method for tablets of 4.0-kg hardness.

However, with tablets of 6.8-kg hardness, similar dissolution profiles were obtained at 125 rpm for the basket and paddle methods over a period of 6 hours.
Problems of Variable Control in Dissolution Testing

- Apparently, the composition of the formulation as well as the process variables in manufacturing may both be important.
- No simple correlation can be made for dissolution results obtained with different methods.
Problems of Variable Control in Dissolution Testing

- In the absence of *in-vivo* data, the selection of the dissolution method is based on the type of drug product to be tested.
Problems of Variable Control in Dissolution Testing

For example:

- A low-density preparation may be poorly wetted in the basket method.
- A gummy preparation may clog up the basket screen; therefore, the paddle method is preferred.
Problems of Variable Control in Dissolution Testing

A floating dosage form (e.g., suppository) may be placed in a stainless steel coil (sinker) so that the dosage form remains at the bottom of the dissolution flask.

For many drugs, a satisfactory dissolution test may be obtained with more than one method by optimizing the testing conditions.
Diffusion Cells

Static and flow-through diffusion cells are commercially available to characterize in-vitro drug release and drug permeation kinetics from a topical drug product (eg, ointment, cream) or transdermal drug product.
Diffusion Cells

The Franz diffusion cell is a static diffusion system that is used for characterizing drug permeation through a skin model.
The source of skin may be human cadaver skin or animal skin (e.g., hairless mouse skin).

Anatomically, each skin site (e.g., abdomen, arm) has different drug permeation qualities.

The skin is mounted on the Franz diffusion cell system.
The drug product (eg, ointment) is placed on the skin surface and the drug permeates across the skin into a receptor fluid compartment that may be sampled at various times.

The Franz diffusion cell system is useful for comparing *in-vitro* drug release profiles and skin permeation characteristics to aid in selecting an appropriate formulation that has optimum drug delivery.
In-Vitro-In-Vivo Correlation

It establishes a relationship between a biological property of the drug (such as pharmacodynamic effect or plasma drug concentration) and a physicochemical property of the drug product containing the drug substance, such as dissolution rate.
An IVIVC should be evaluated to demonstrate that predictability of \textit{in-vivo} performance of a drug product from its \textit{in-vitro} dissolution characteristics is maintained over a range of \textit{in-vitro} dissolution release rates and manufacturing changes.
The *in-vitro* dissolution characteristics are dependent on:

- physical properties of the active pharmaceutical ingredient (API)
- drug formulation
- hydrodynamics of the dissolution apparatus, and the dissolution medium.
dissolution tests for immediate-release solid oral drug products may be over discriminating and a clinically acceptable product might perform poorly in the dissolution test.

Well-defined *in-vitro-in-vivo* correlations have been reported for modified-release drug products.
It is important to note that multisource, pharmaceutically equivalent drug products may not be bioequivalent even if these drug products meet the same USP-NF monograph specifications.
**In-Vitro-In-Vivo Correlation**

For example,

- USP-NF includes 10 separate dissolution tests for theophylline extended-release capsules that are labeled for dosing every 12 hours.

- USP-NF has separate and distinct dissolution test requirements for two different phenytoin sodium capsules.
For extended-release phenytoin sodium capsules, USP-NF states that "not more than 35%, between 30% and 70% and not less than 85% of the labeled amount of C15H11N2NaO2 in the Extended Capsules dissolves in 30 minutes, 60 minutes, and 120 minutes, respectively, under the specified dissolution conditions"
In contrast, about tolerances for "Prompt Phenytoin Sodium Capsules," USP states "not less than 85% of the labeled amount of C15H11N2NaO2 in the Prompt Capsules dissolves in 30 minutes."
It is important to note that multisource, pharmaceutically equivalent drug products may not be bioequivalent even if these drug products meet the same USP-NF monograph specifications.
In-Vitro-In-Vivo Correlation

- In the United States, only FDA-approved generic, bioequivalent drug products that meet the requirements for *therapeutic equivalence* may be interchanged.

- These generic drug products are listed in the FDA publication, Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the *Orange Book*.
Failure of Correlation of *In-Vitro* Dissolution to *In-Vivo* Absorption

- there are many published examples of drugs with dissolution data that correlate well with drug absorption in the body
- there are also many examples indicating poor correlation of dissolution to drug absorption.
Failure of Correlation of *In-Vitro* Dissolution to *In-Vivo* Absorption

- There are also instances where a drug has failed the dissolution test and yet is well absorbed.
- The problem of no correlation between bioavailability and dissolution may be due to the complexity of drug absorption and the weakness of the dissolution design.
For example, a product that involves fatty components may be subjected to longer retention in the gastrointestinal tract.

The effect of digestive enzymes may also play an important role in the dissolution of the drug in vivo.

These factors may not be adequately simulated with a simple dissolution medium.
Failure of Correlation of *In-Vitro* Dissolution to *In-Vivo* Absorption

Example: quinidine gluconate sustained-release tablets

- Dissolution tests using four different dissolution media were performed for two quinidine gluconate sustained-release tablets.
- Brand BE was known to be bioavailable, whereas product BO-1 was known to be incompletely absorbed.
It is interesting to see that using acid medium as well as acid followed by pH 7.4 buffer did not distinguish the two products well.
Failure of Correlation of *In-Vitro* Dissolution to *In-Vivo* Absorption

- whereas using **water** or **pH 5.4 buffer** as dissolution medium clearly distinguished the "good" product from the one that was not completely available.
In this case, the use of an acid medium is consistent with the physiologic condition in the stomach, but this procedure would be misleading as a quality control tool.

It is important that any new dissolution test be carefully researched before being adopted as a method for predicting drug absorption.
The USP dissolution procedure is a performance test applicable to 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 "Disintegration\(^ {701}\)\), "Dissolution\(^ {711}\)\), and "Drug Release\(^ {724}\).
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.
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).
Volume

Normally, for basket and paddle apparatus, the volume of the dissolution medium is 500 mL to 1000 mL, with 900 mL as the most common volume. The volume can be raised to between 2 and 4 L, using larger vessels and depending on the concentration and sink conditions of the drug; justification for this procedure is expected.
Deaeration

The significance of deaeration of the medium should be determined, because air bubbles can interfere with the test results, acting as a barrier to dissolution if present on the dosage unit or basket mesh. Further, bubbles can cause particles to cling
Enzymes

The use of enzymes in the dissolution medium is permitted in accordance with *Dissolution* (71) when dissolution failures occur as a result of cross-linking with gelatin capsules or gelatin-coated products.
Apparatus

The choice of apparatus is based on knowledge of the formulation design and the practical aspects of dosage form performance in the in vitro test system. For solid oral dosage forms, *Apparatus 1* and *Apparatus 2* are used most frequently.
Sinkers

When sinkers are used, a detailed description of the sinker must be stated in the written procedure. It may be useful to evaluate
Agitation

For immediate-release capsule or tablet formulations, Apparatus 1 (baskets) at 100 rpm or Apparatus 2 (paddles) at 50 or 75 rpm are most commonly used. Other agitation speeds and apparatus are acceptable with appropriate justification.
Agitation

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.
Study Design

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.
Study Design

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.
Study Design

According to the Biopharmaceutics Classification System referred to in several FDA Guidances, 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.
Observations

Uneven distribution of particles throughout the vessel.
Air bubbles on the inside of the vessel or on the apparatus or dosage unit.
Dancing or spinning of the dosage unit,
Adhesion of particles to the paddle or the inside of the basket,
Observations

Observation of the disintegration rate

Complex disintegration of the coating of modified or enteric-coated products-
Sampling:
- manual
- Autosampling

Filters:
- filtration of the dissolution samples

Centrifugation of the sample

Assay

Validation
Validation:

- Specificity/Placebo interference
- Linearity and range
- Accuracy/Recovery
- Precision/Repeatability
- Robustness
- Standard and sample solution stability
- Sample analysis: Spectrophotometric, HPLC
Acceptance Criteria

Typical acceptance criteria for the amount of active ingredient dissolved, expressed as a percentage of the labeled content \((Q)\), are in the range of 75% to 80% dissolved. A \(Q\) value in excess of 80% is not generally used, because allowance needs to be made for assay and content uniformity ranges.
Acceptance Criteria

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.