

Dissolution Equipment Excerpt



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DISSOLUTION THEORY, METHODOLOGY, AND TESTING



EDITED BY
Anthony Palmieri III



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**Edited by
Anthony Palmieri III**

Dissolution Technologies, Incorporated

Hockessin, Delaware

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Introduction

The definition of dissolution is deceptively simple. It is the process in which a solid substance goes into solution. For dosage forms containing an active solid ingredient, the rate of dissolution may be critical to absorption. Obviously, in most instances, dissolution of the active solid material is affected by a variety of factors such as the media in which the drug is dissolving, the temperature of the media, and the affinity for the solid particles to dissolve in the media. There are numerous other factors, such as excipients, coatings, and pH, which have an effect on the rate of dissolution. While the most rapid absorption is from a solution, most dosage forms are solids, either tablets or capsules. One must also consider dissolution from suspensions and suppositories. Several chapters in this text cover various dosage forms as the theme for the discussion on dissolution. The theory is the same regardless of the dosage form design, but obviously, the rate of dissolution and the limitations are different for each individual dosage form.

Any process of drug release and subsequent absorption into the blood stream must consider dissolution of the solid. Wetting of the material, be it hydrophilic or hydrophobic, is the first critical step and precedes deaggregation. This process may also be considered disintegration. The drug then dissolves into the dissolution media, be it *in vitro* or *in vivo*. As a rule, suspensions dissolve faster than capsules since some deaggregation has already occurred. Tablets usually have the slowest dissolution rate, either by design to allow a sustained, controlled release or by the nature of the wetting process.

The earliest obvious reference to dissolution (1897) was by Noyes and Whitney, where they stated that the dissolution rate is governed by the rate of diffusion of a saturated thin layer forming instantly around the dissolving material. The work of Noyes and Whitney concentrated on physico-chemical aspects and not bioavailability. In 1951, Edwards showed that aspirin tablets would have poor analgesic activity due to poor dissolution.

Theoretical models of dissolution continued to be developed in the early 1900s by Brunner, when he adapted Fick's Law of diffusion. In the 1930s the cube root law, which describes a linear relationship between dissolution rate and cube root of time, came into favor. By the 1950s, dissolution was further studied and began to be recognized as a factor in bioequivalence, although it was not until the 1960s

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that dissolution and absorption rates would be correlated. Beginning in the 1960s a multitude of research papers reported a correlation between dissolution and bioavailability. During this time, many researchers believed and hoped that dissolution would directly relate to, and predict, bioavailability. However, even forty years later, we realize that although we can often correlate *in vivo*–*in vitro* activity with dissolution, it does not predict biologic or therapeutic activity.

There are a myriad of factors that have an effect on dissolution such as agitation rate, vessel shape, wobble of the equipment, temperature, and others. The most one can expect is an equivalence test on different products, assuming all variables are held equal or, as in most cases, the slight variations in the tests cancel one another.

Today dissolution is readily identified as a quality control issue and used to prove batch-to-batch relationships and equivalence. For many drugs, similar dissolution profiles are generally accepted as producing bio-equivalent lots. It is generally accepted that the last 30 years have seen the science of dissolution become mature, and it is recognized that there are limits to what dissolution testing can scientifically prove. It is universally accepted as a quality control tool. We now understand the factors that have an effect on and control the rate of dissolution. Solubility, particle size, and crystalline states are all intrinsic factors that have an effect on the rate of dissolution. Diluents, excipients, binders, granulating agents, and lubricants all play a role in dissolution as well. Obviously, the dosage form itself is critical. All of these factors will be addressed in this text.

Rapid dissolution is not always the goal in formulation. If one desires a controlled- or sustained-release dosage form, the factors that affect the dissolution rate may be manipulated to obtain the desired effect. The pharmaceutical formulator can use methods of controlling dissolution to readily obtain a desired release profile.

While the remainder of the book is divided into chapters by dosage form, many factors remain the same regardless of the dosage form while some are specific to the individual dosage form and dosage form design.

ANTHONY PALMIERI III

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DISSOLUTION THEORY, METHODOLOGY, AND TESTING

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Dissolution Equipment

G. Bryan Crist

DISSOLUTION APPARATUS OVERVIEW

Over the past forty years, two basic techniques have evolved for in vitro dissolution testing, the stirred beaker method and the flow-through procedure.

The stirred beaker system places the test specimen and a fixed volume of fluid in a vessel, and stirring provides mechanical (hydrodynamic) agitation. This system was adopted as the official dissolution method in *USP XVIII* in 1970 and described as the rotating basket method, USP Apparatus 1.

The rotating paddle method was adopted as an official dissolution method by the USP several years later and became USP Apparatus 2. The origin of official equipment developed from a number of basket and stirring devices (1) is shown in Figure 1.

Some of the needs for the flow-through type apparatus included a change of pH or any other change in the dissolution medium. Difficulties had also arisen for a number of sparingly soluble drugs, which were difficult to investigate with a limited volume of media. The flow-through system was first adopted by the Deutscher Arzneimittelcodex (German Pharmaceutical Codex, DAC) in 1981.

Two flow-through apparatus were eventually added to the *USP* in 1990 to overcome some of the experimental difficulties from the use of the single vessel methodology. They became known as USP Apparatus 3, Reciprocating Cylinder, and USP Apparatus 4, Flow-Through Cell.

The most common dissolution apparatus used throughout the world are the basket and the paddle. These methods are simple and robust and are generally flexible enough to allow dissolution testing for a wide variety of drug products. For this reason, Apparatus 1 and 2 should be used for dissolution method development unless shown to be unsatisfactory. Other in vitro dissolution apparatus such as the reciprocating cylinder and the flow-through cell system described in the *USP* may be considered, if needed.

More drug release equipment, USP Apparatus 5 and 6, deal with transdermal systems. USP Apparatus 7 (Alza-type) was developed for the analysis of transder-

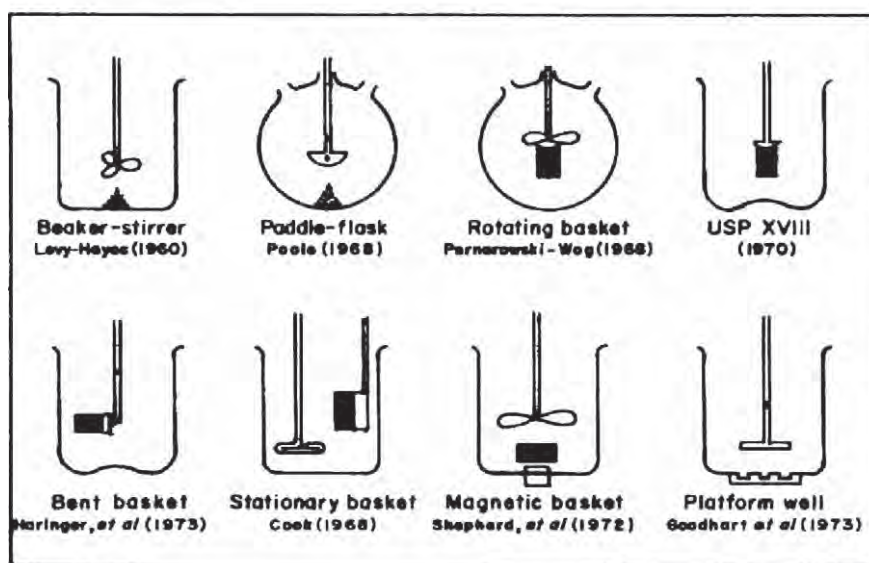
Dissolution, Bioavailability and Bioequivalence

Figure 1. Different designs of dissolution vessels and stirrers that have been utilized in major nonofficial methods. (Reprinted with permission from ref 1. Copyright 1982 Advanstar Communications, Inc.)

mal systems as well as a variety of drug release systems such as osmotic pumps and implants. Because of the diversity of delivery systems and the evolving nature of understanding in the area of drug release, different experimental modifications may be needed to obtain a suitable in vivo correlation with in vitro release data. Alternatives or modifications to established methodology should be considered on the basis of proven superiority for a particular product. If the release of the active drug substance from an individual drug product cannot be accommodated by one of the major compendial apparatus, appropriate modifications have to be developed. However, unnecessary proliferation of alternative dissolution apparatus should not be encouraged due to the reproducibility problems that plagued early dissolution equipment; this will also hinder regulatory acceptance.

USP APPARATUS 1 AND 2—ROTATING BASKET AND PADDLE

USP Apparatus 1 and 2 are described officially in USP Physical Test Chapter <711> Dissolution (2). USP Apparatus 1 is called the rotating basket apparatus and USP Apparatus 2 is called the rotating paddle apparatus. They are also de-

scribed in pharmacopeia throughout the world, but for purposes of discussion, references will be made to the *USP* regarding specifications and operation.

Rotating Basket

A general description of the rotating basket apparatus consists of shaft and basket component fabricated from 316 stainless steel. Unless otherwise specified in a test method or official monograph, a 40-mesh basket is used. The basket shaft assembly containing the product is lowered into a 1000-mL vessel and rotated at a specific speed within media, which is maintained at a specific temperature. The rotating basket method is routinely used for capsule formulations at an agitation speed of 50–100 rpm. Rates outside a range of 50–150 rpm are generally unacceptable because of irreproducibility associated with the hydrodynamics below 50 rpm and turbulence above 150 rpm. High turbulence in the vessel leads to a loss of discriminatory power associated with the dissolution method.

The vessel used for Apparatus 1 and 2 is typically a 1000-mL hemispheric-shaped vessel made of glass or suitably inert material. Vessel volume should be between 500 and 1000 mL with 900 mL used historically. One-liter vessels are tubing-based with dimensions of 98–106 mm i.d. and 160–210 mm in height. Larger vessels have been developed over the years to allow more volume for poorly soluble compounds. The USP 2-L vessel has dimensions of 98–106 mm i.d. and 280–300 mm in height. The USP 4-L vessel has dimensions of 145–155 mm i.d. and 280–300 mm in height.

The official basket used for Apparatus 1 is a 40-mesh design, meaning there are 40 openings per linear inch. Openings are equal in both directions producing a standard square weave. *USP* specifies that 40-mesh (40×40) screen be manufactured with wire having a 0.010" diameter. Dissolution baskets are fragile and require proper handling and care. Attachment to or removal from the basket shaft requires holding the upper rim. When not in use, baskets should be stored in protective cases. Baskets should be carefully inspected for damage or excessive wear since defective or misshaped baskets will affect test results. The standard 40-mesh basket with a 0.01" wire size results in a 0.381-mm square aperture. For comparison, the *Japanese Pharmacopeia* specifies 0.011" wire diameter resulting in 0.425-mm square hole resulting in a 36-mesh basket. The baskets are not interchangeable and could result in a 24% difference in *USP*, *EP*, and *JP* baskets when testing the USP disintegrating calibrator, Prednisone.

Current Physical Parameters and Tolerances:

Wobble	± 1 mm basket lower rim
Dimensions	per USP
Height	25 ± 2 mm
Centering	± 2 mm center line
Speed	$\pm 4\%$ of set speed
Vessel Temp.	37 ± 0.5 °C
Timepoints	$\pm 2\%$ of specified time

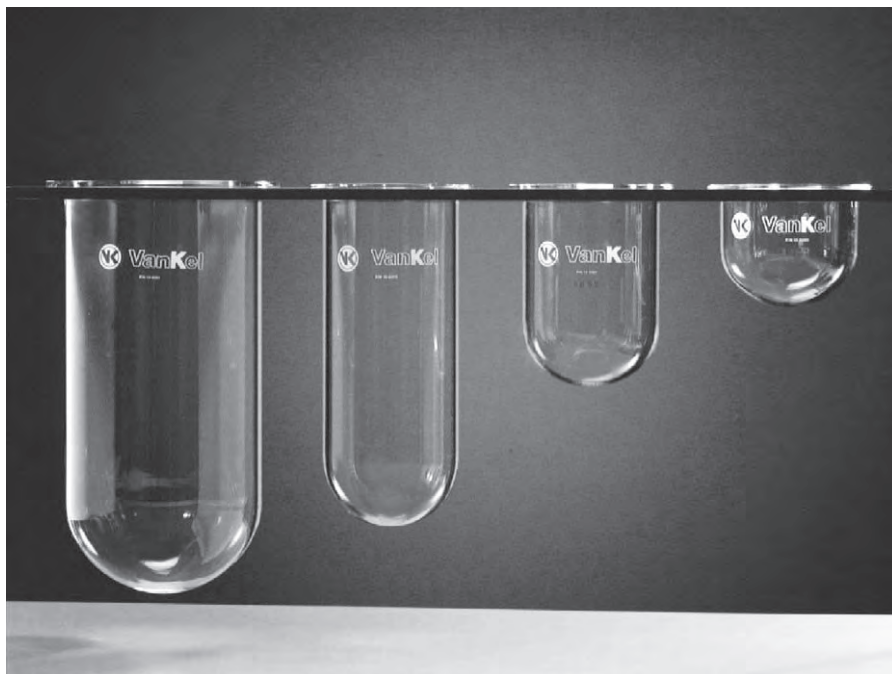


Figure 2. Various dissolution vessels.

In addition to the current physical parameters, some pharmaceutical laboratories have adopted more stringent parameters gleaned from a PhRMA Subcommittee on Dissolution Calibration proposal to the *USP* (3) to maintain a higher degree of control over the rotating basket apparatus:

Optional Parameters and Tolerances:

Shaft wobble	≤ 0.5 mm total runout
Basket wobble	≤ 1.0 mm total runout
Basket exam	No defects at time of use
Shaft verticality	Vertical using bubble level
Speed	$\pm 2\%$ set speed
Vibration	≤ 0.2 -mil displacement

Typical products tested with the rotating basket are capsules, tablets, floaters, modified-release products, beads, and suppositories. Suppository testing may be performed with a slotted Palmieri basket with or without glass beads.

Several allowable variations of the standard 40-mesh basket exist including a basket with a gold coating 2.5- μm thick (0.0001-inch). Larger vessels accommodating up to two and four liters are now allowable variations in the *USP*. Such vessels are advantageous for poorly soluble drugs.

Some non-official variations of the rotating basket include Teflon baskets, o-ring

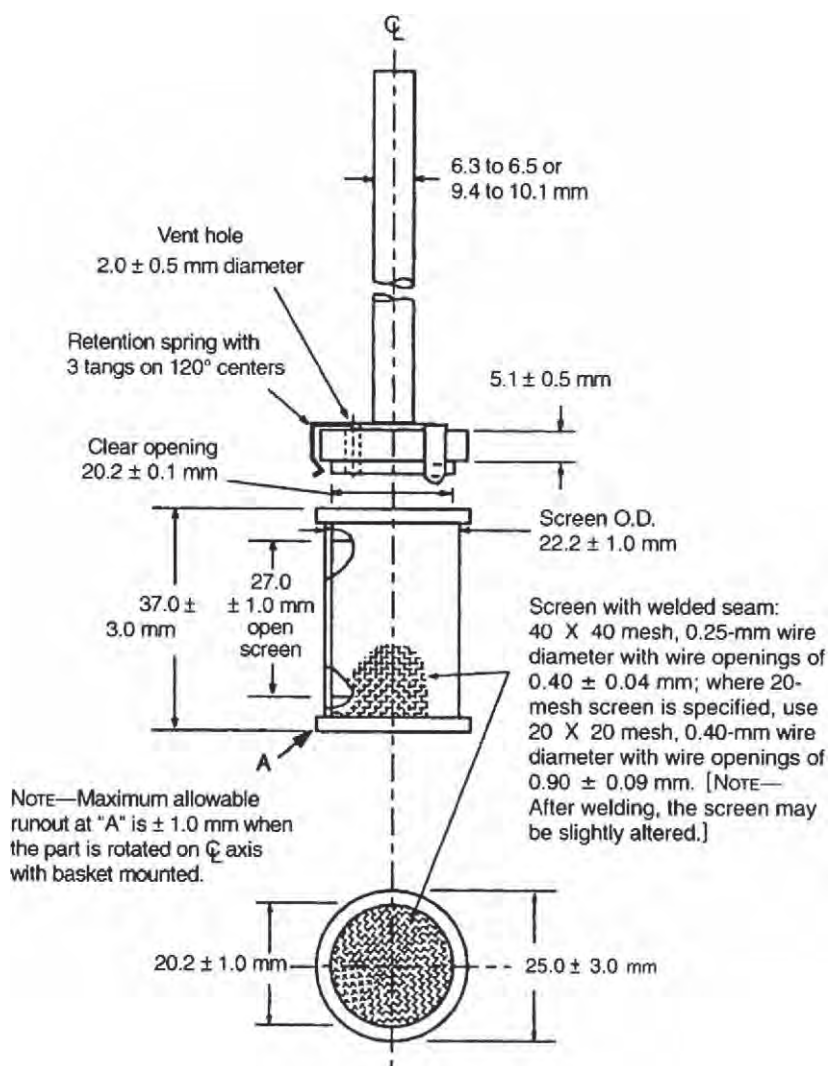


Figure 3. Official basket used for USP Apparatus 1.

baskets, 10-mesh through 2300-mesh (5-micron), three-fin, mini, and bolus baskets for veterinary products. Examples of these baskets are shown in Figure 4.

Occasionally a small volume apparatus may be required for low-dose, high-potency products. Such a variation consists of a mini-basket apparatus based on USP Apparatus 1 with 100- or 200-mL vessels. Small volume apparatus has a typical operational minimum volume of 30-mL. Shown in Figure 5 are a mini basket and an official rotating basket.



Figure 4. Examples of non-official variations of the rotating basket.

Rotating Paddle

General Apparatus 2 Description

USP Apparatus 2, the rotating paddle method, followed the development of the rotating basket method with better stirring characteristics. The paddle blade is fixed to the bottom of the shaft and rotates at a height of 25 mm from the inner bottom of the vessel. The paddle consists of a metallic or suitably inert, rigid blade and shaft composing a single entity. The paddle blade and shaft may be coated with a suitable inert material.

The paddle is lowered into a 1000-mL vessel and rotated at a specific speed within media, which is maintained at a specific temperature. The rotating paddle method is routinely used at an agitation speed of 25 to 75 rpm. Rates outside a

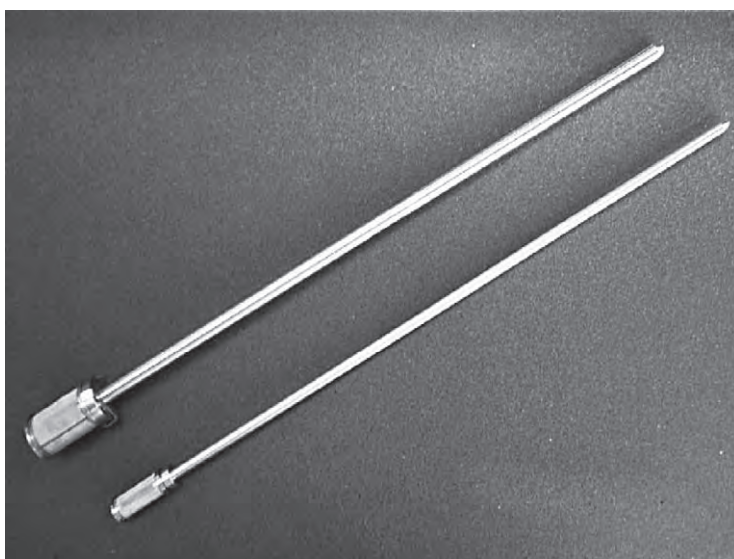


Figure 5. Mini basket and official rotating basket.



Figure 6. Typical dissolution setup.

range of 25 to 75 rpm are generally unacceptable because of irreproducibility of the hydrodynamic effects below 25 rpm and turbulence above 100 rpm. High turbulence in the vessel leads to a loss of discriminatory power associated with the method. Agitation rates around 25 rpm but less than 50 rpm are acceptable for suspensions. For solid dosage forms with excessive coning, rotational speeds around 75 rpm may be necessary to improve the data. As with any variance from normal operating parameters, atypical conditions must be supported with data from normally accepted conditions for justification of USP Apparatus 2. When dissolution profiles exhibit inappropriately dissolving drug substance during method development, adjustments outside the normal rotational speed may be warranted.

Any time a method references *USP* General Chapter <711>, the dosage unit must be allowed to settle to the bottom of the vessel before rotation of the paddle begins. To aid the dosage unit settling to the bottom of the vessel, a small, loose piece of stainless steel wire consisting of a few turns may be attached to a dosage unit that would otherwise float.

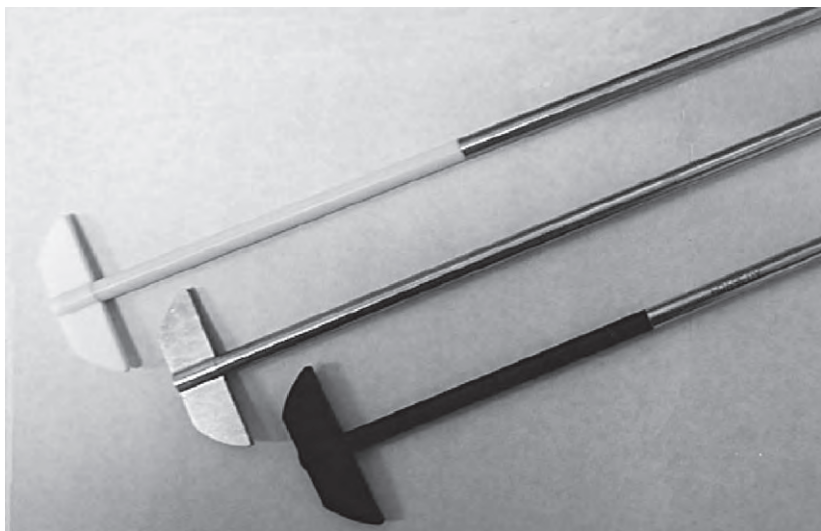


Figure 7. Examples of Apparatus 2 paddles.

Since the construction of the sinker has such an impact on the hydrodynamics in the bottom of the vessel, individuals have sought to standardize the USP design. A unique standardization utilizing cork borers was presented in the *Pharmacopeial Forum* as a stimuli article (4). The guidance suggested a method to construct sinkers by hand with the use of a cork borer which would minimize the variability resulting from different interpretations of the construction of a USP sinker.

In addition to sinking floating dosage forms, sinkers may assist in keeping a dosage form from sticking to the vessel inappropriately as in the case with some film-coated tablets. Sinkers must be adequately described in laboratory standard operating procedures to eliminate hydrodynamic variation associated with different sinker devices. Sinkers of other descriptions may be used if properly validated. Many different sinkers have evolved, some of which are based on the wire helix design.

Current Physical Parameters and Tolerances:

Wobble	Not specified in USP
Dimensions	per USP
Height	25 ± 2 mm
Centering	± 2 mm center line
Speed	$\pm 4\%$ of set speed
Vessel Temp.	37 ± 0.5 °C
Timepoints	$\pm 2\%$ of specified time

As mentioned in the previous section on physical parameters for basket, some

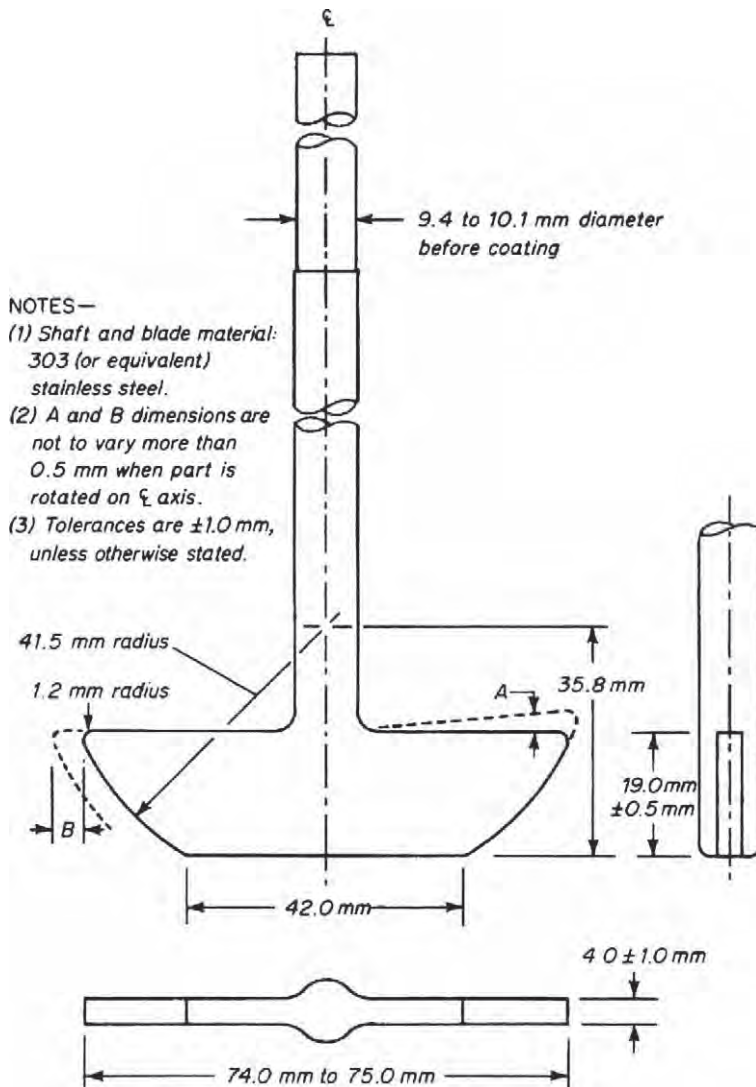


Figure 8. USP Apparatus 2 paddle specifications.

laboratories have adopted more stringent parameters for the paddle apparatus to maintain a higher degree of control.

Optional Parameters and Tolerances:

Shaft wobble	≤ 0.5 mm total runout
Paddle exam	No defects at time of use
Shaft verticality	Vertical using bubble level



Figure 9. Sinker constructed of stainless steel wire.

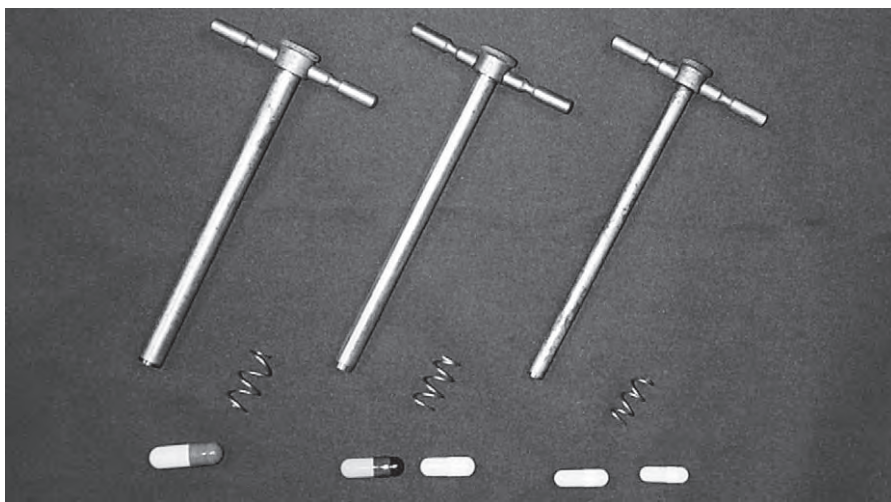


Figure 10. Sinkers constructed using cork borers.

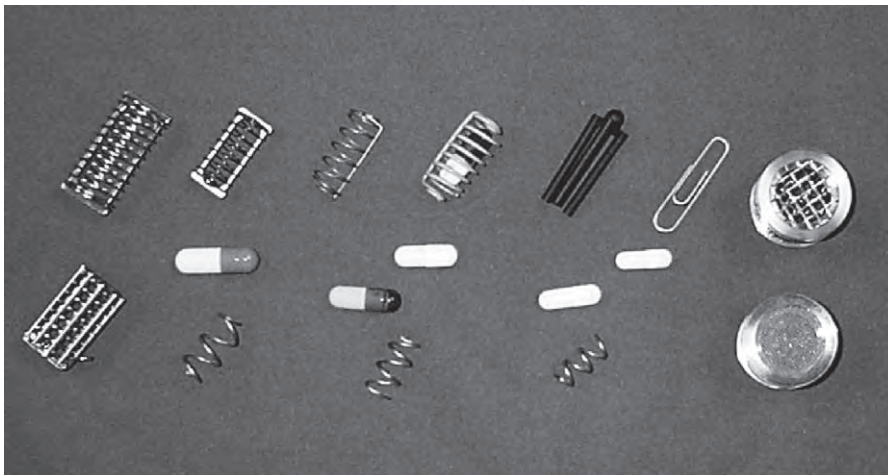


Figure 11. Examples of sinker designs.

Speed	± 2 RPM of set speed
Vibration	≤ 0.2 -mil displacement

Typical products tested by the paddle method are tablets, capsules (with sinkers), hydrogel tablets, suspensions, powders, microparticles, and transdermals (paddle-over-disk method).

Calibration of USP Apparatus 1 and 2

In the early 1970s, scientists began to evaluate significant apparatus-to-apparatus differences in dissolution results. Monograph specifications could not be enforced due to variability in results from lab to lab and apparatus to apparatus. In 1978, the USP established and issued the first official dissolution calibrator tablets and reference standards. The primary purpose was to control vibration since most other parameters could be controlled by mechanical measurements.

Since that time, dissolution apparatus used under current Good Manufacturing Practices (cGMPs) should be challenged with an apparatus suitability test as outlined in the *USP* Chapter <711> Dissolution. At the time of this printing, the suitability test must be conducted with USP dissolution calibrators of the disintegrating and non-disintegrating type, Prednisone and Salicylic Acid tablets, respectively. The word calibration is somewhat of a misnomer since the “calibrator” tablets do not actually calibrate anything, as a weight would be used to calibrate an analytical balance. At this time there is no predefined period of calibration; however, our current Good Manufacturing Practices as outlined in 21 CFR Parts 210 and 211 require calibration of analytical equipment according to prescribed schedules. These prescribed schedules are generally established by various organizations to limit the liability originating from test results obtained on apparatus

that may fall out of calibration as a result of age, environmental factors, or relocation.

In the event of obtaining an outside-of-target dissolution result or a suspect result during calibration or routine analysis, a detailed review of the equipment, method, materials, and analyst documentation should take place. The investigation should be thoroughly documented and include all observations and explanations for the aberrant result by showing a cause-and-effect relationship, corrective action, and eventually the retest. One change at a time should be made prior to retesting to isolate the cause of the aberrant result. Recheck all physical parameters after any adjustments are made and perform retesting on a set of six tablets.

A laboratory review checklist consisting of the following areas should be implemented to perform a thorough evaluation: check calculations, reread samples that were non-conforming, examine spectrophotometer and any automatic sampling equipment, review sampling technique, review standard preparation, review media preparation. Documentation of the investigation should include a description of the failure with a full data summary, the laboratory review checklist, description of the findings, corrective actions, additional physical adjustment of the apparatus, specific reasons for the run to be invalidated such as a crack in the vessel, and the retest(s).

Aberrant Dissolution Data Investigation

The most common sources of error in dissolution testing for the rotating basket and paddle methods are deaeration, paddles and baskets conformance, condition of vessels, vibration and environmental issues, sampling technique, and filtering issues.

Deaeration

While numerous deaeration techniques have been utilized, some are better than others. The USP recommends heating media to approximately 41 °C followed by vacuum filtration through a 0.45- μ m filter under vigorous stirring. After filtration, continue to draw the vacuum for five additional minutes. In theory, the best way to remove dissolved gases is through boiling, but this is a waste of energy and time resources. However, heating media to 41 °C and applying a vacuum can achieve boiling at a lower temperature. The filter is simply used to provide a pressure gradient. Once the media passes through the filter, air is immediately and efficiently stripped out. Media is then measured and gently poured into the dissolution vessel and allowed to equilibrate to 37 °C in the vessel. Alternate deaeration techniques have been used such as helium sparging or vacuum ultrasonication. Critical parameters for helium-sparging methods include gas flow rate, type of diffuser, and time per volume. The efficiency of alternate deaeration techniques must be demonstrated and documented through validation.

Historically, media has been measured and gently added to the vessel with the aid of a cylinder or other calibrated “to deliver” device. Media should be delivered with an accuracy of $\pm 1\%$, which currently rules out most “class A” graduated

cylinders because they are calibrated in 10-mL increments and are not capable of measuring the ± 9 -mL tolerance for the typical 900-mL media volume. Alternately, media could be measured in a “to deliver” class A volumetric flask if it has been calibrated at the intended measuring temperature. An alternate media-measuring technique employed by many automated systems is gravimetric measurement.

Dissolution media at a controlled elevated temperature may also be weighed by correcting for pre-determined density. This is how many automated delivery systems measure and transfer media to the vessel.

Vibration

For dissolution equipment to operate correctly, the area must be maintained free from excessive vibration from sources such as centrifuges, vacuum pumps, fume hoods, shakers, ultrasonic cleaners, and unstable bench top and construction. All such sources of external vibration must be eliminated. Internal sources of vibration may be caused by tension or dirt on drive belt, worn parts and bearings, and turbulence in the water bath. Make sure the deflector shield is in place in the water bath.

Preferably use a vibration meter during calibration periods to obtain a baseline measurement. If suspect or aberrant dissolution results are obtained on the apparatus, current vibration measurements may be compared to the level obtained during calibration to see if this could have contributed to the suspect data. Vibration measurements should be part of the routine physical calibration of the apparatus to detect vibration from unwanted sources prior to obtaining data.

Sampling and Filtering

The filter is essential to stop the dissolution test by removing undissolved drug product as well as particulate matter and turbidity from the sample. Filters must be tested for drug adsorptivity to show that they do not bind drug substance. Filters should also be evaluated for efficiency to demonstrate that drug substance did not pass through the filter and continue to dissolve. Separate, clean, dry filters and glassware must be used when sampling each vessel. Generally, the first several milliliters should be discarded prior to sample collection for analysis but the specific amount discarded must be determined through validation. Sample aliquots must be filtered immediately after the sample is drawn, otherwise the dissolution process continues.

Baskets and Paddles

Basket and paddle stirring elements must be checked for USP conformance. Routine physical observations of baskets and shafts should be conducted to ensure integrity of the stirring element. Physical observation of basket and shafts should include that they are straight and roll evenly on a flat surface. Any Teflon coating must not be chipped or peeling, which adds to the turbulence in the vessel. Check surfaces for corrosion or discoloration due to prolonged exposure to hydrochloric acid. Stainless steel, while resistant to rust and corrosion, will be attacked by chlo-

ride ions, which will cause pitting in the surfaces and a reduction in the wire diameter used in the baskets. A basket will maintain specifications of 40-mesh unless it is misshapen, but the basket micron rating will change over its lifetime due to corrosion. A non-lustrous pewter appearance is an indication that the basket integrity is failing. Particles may fall out of the basket too early causing lower results if the wire diameter is significantly reduced due to corrosion. Gold coating up to 2.5- μm thick is an allowable variation for baskets to inhibit corrosion associated with a stainless steel basket. The basket surface must be smooth, not wrinkled or misshapen, and must not have a frayed appearance; the basket should be replaced, if necessary.

USP basket clips must be tight since loose clips impart excessive wobble. Non-USP baskets such as o-ring attachments without clips must be validated to show that there is no change in test results. USP Prednisone calibrator tablets run in o-ring baskets have exhibited up to a 10% suppressed result over the USP clip-type basket.

Regarding air bubbles, several observations should be made when starting a dissolution run. Bubbles occasionally form underneath the disk and sometimes hold a tablet in the upper portion of the basket and do not allow one side of the dosage unit to contact the media for several minutes. If this is not noticed, a non-disintegrating dosage form similar to the salicylic acid calibrator tablet will produce results on the low side of the expected range. Bubbles that form under a basket will alter the performance of the basket and cause failures since dissolution media will not circulate through the basket properly. Bubbles forming in the mesh will also change the characteristics of the basket by blocking the openings and virtually changing the mesh of the basket. The latter condition is usually a result of poor media deaeration.

Vessels

Dissolution vessels should be serialized or numbered and maintained in their original positions. This reduces the opportunity for a defective vessel to be moved from one apparatus to another, causing random failures. The inner surface of vessels should be routinely checked for irregularities, scratches, cracks, pits, and unevenness or surface aberrations. Vessels should be acquired from a reputable manufacturer since the inner surface must have a defect-free hemispheric bottom. Vessels manufactured with poor quality control will exhibit shallow, protruding, or asymmetrical bottoms, which will greatly affect the dissolution results due to increased turbulence.

Vessels need to be checked for cleanliness. Scum, film, or sticky residues build up over time and can greatly affect dissolution rates. Vessels must be scrupulously clean. Tablets are to be dropped into non-rotating medium and allowed to settle to the bottom of the vessel prior to starting the rotation of paddles. Observe the dosage unit after introduction and record unusual observations such as sticking, floating, bubbles, and irregular shape of the cone.



Figure 12. Cone formation (12a) and Peak vessel configuration (12b).

Non-Compendial Variations

Several unofficial modifications have developed to provide advantages over traditional dissolution apparatus. These have been occasionally implemented to improve the hydrodynamics of the dissolution test but only when the modification has proven to be superior to traditional dissolution apparatus.

Peak Vessel

The peak vessel reduces the inherent inconsistencies in the hydrodynamics of standard hemispherical dissolution vessels. An inverted peak is incorporated into the bottom of the vessel, displacing the unstirred zone, preventing cone formation.

Small-Volume Dissolution

To maintain quantitative levels of analyte during the dissolution test, a reduction in vessel volume accompanied by an alteration in apparatus design may be required. For oral dosage units containing concentrations of analyte at the microgram or nanogram level resulting from highly potent, low dose compounds, small-volume dissolution apparatus may be required and are generally quantitation limited. The justification for the small-volume dissolution apparatus is primarily due to the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions.

Mega Paddle

Another device that was introduced to overcome some of the hydrodynamic anomalies associated with the dissolution test is the mega paddle. The mega paddle was introduced as a stimuli article in the *Pharmacopeial Forum* (5). Its primary

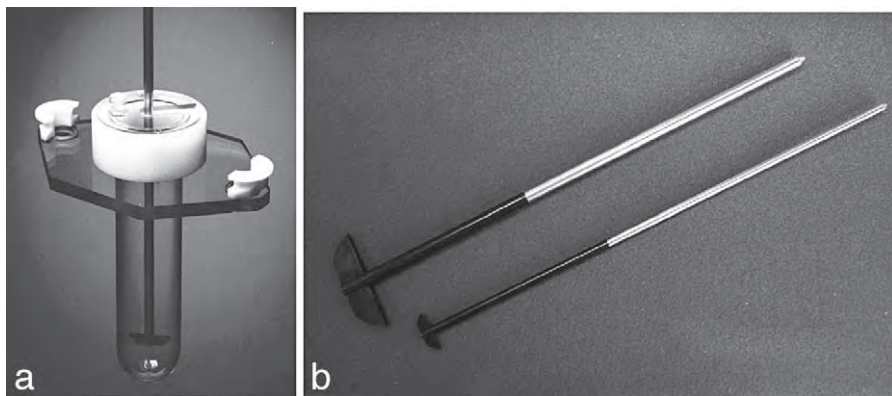


Figure 13. Small-volume dissolution apparatus.

purpose was to improve the mixing characteristics within the vessel, eradicate coning, and produce better stirring from a low energy system that will not cause particle shear. The mega paddle may also be useful for 2-L and 4-L vessels where greater fluid movement is required. This modified paddle has not been as widely accepted as the peak vessel for improving hydrodynamics within the vessel.

Stationary Basket

The stationary basket assembly is used with traditional rotating paddle apparatus. This modification suspends the dosage unit contained in a basket device just above

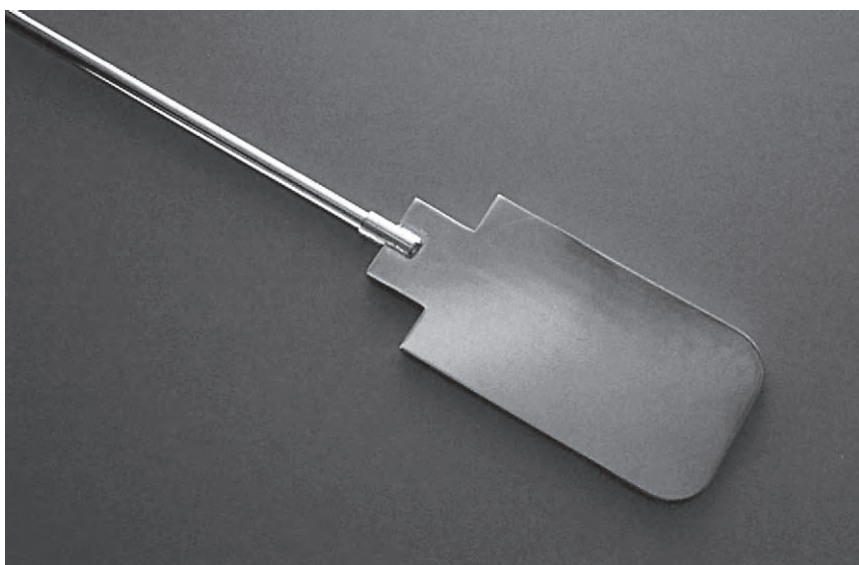


Figure 14. Mega paddle.

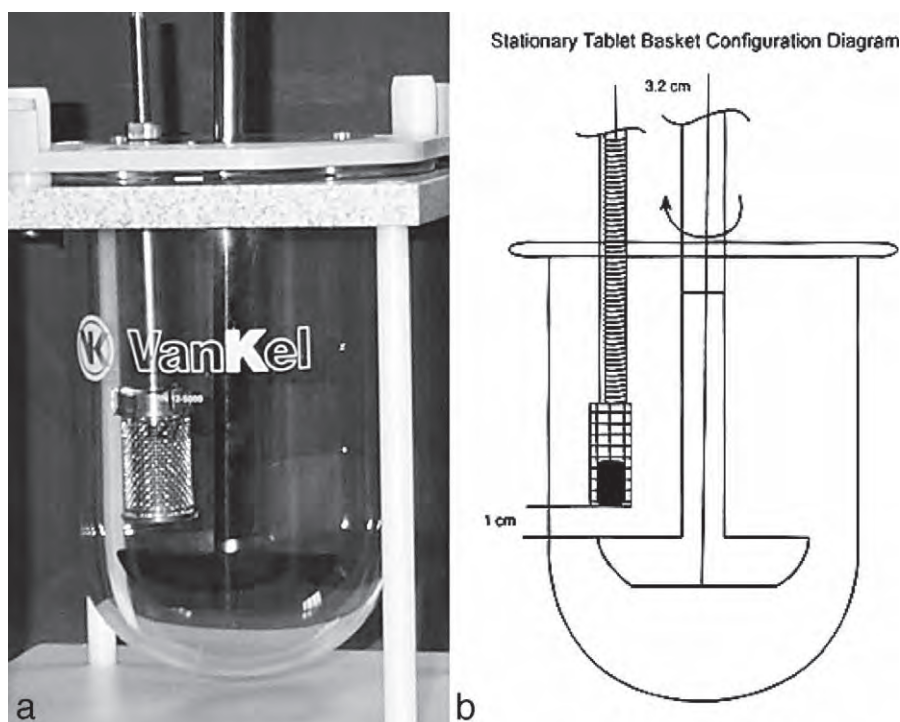


Figure 15. Stationary basket design.

the rotating paddle. Several variations of the stationary basket have evolved. One system utilizes a basket held in place by a disk with clips similar to the rotating basket apparatus with the exception that a 0.25-inch shaft mounts the stationary basket to the evaporation cover. In addition to a standard USP 40-mesh basket, 10- and 20-mesh baskets have been used. Another variation was introduced in the *USP 26 First Supplement* for a Felodipine monograph. This design utilizes a quadrangular basket of stainless steel wire gauze, which is suspended 1 mm above the rotating paddle.

Qualification of Non-Compendial Equipment

While no USP specifications or calibration procedure are available for small and large volume vessels, peak vessels, mega paddles, or stationary baskets, the pertinent physical characteristics should be measured. Detailed specifications of the modified equipment must be documented and reliable sources for the equipment should be available. Apparatus should be calibrated with one-liter vessels to indicate that the apparatus is suitable under standard conditions. Physical parameters of height, centering, speed, wobble, and temperature need to be measured against current USP criteria and documented.

Non-compendial dissolution apparatus are only to be used in extraordinary conditions with demonstrated and documented superiority over conventional “official” dissolution apparatus. Non-compendial dissolution apparatus should also demonstrate discrimination of variation from batch to batch, utilize sufficient volume to be analytically quantifiable, be rugged (transferable), precisely and reproducibly manufactured, and commercially available. Additional calibration regimens should be implemented whenever practical.

USP APPARATUS 3 AND 4—RECIPROCATING CYLINDER AND FLOW-THROUGH CELL

These apparatus are found in *USP* Physical Test Chapter <724> Drug Release (6). USP Apparatus 3 is called the reciprocating cylinder apparatus, and USP Apparatus 4 is called the flow-through cell.

Reciprocating Cylinder

General Apparatus 3 Description

A presentation at the 1980 Federation Internationale Pharmaceutique (F.I.P.) drew attention to acute problems associated with USP Apparatus 1 and 2 dissolution results. The conference inspired the concept for the USP Apparatus 3. The USP Apparatus 3, also known as the Bio-Dis, is an excellent apparatus for developing controlled-release products because it can quickly and easily expose products to mechanical and physiochemical conditions which may influence the release of the products in the GI tract. The Bio-Dis Extended Release Tester was designed to test the dissolution rates of extended-release products or any dosage form requiring release profiling at multiple pH levels. The capability for product transfer from one pH to another makes it an excellent candidate for delayed-release products.

USP Apparatus 3 has seven inner tubes, which mechanically traverse six rows of corresponding, media-filled outer tubes. Six of the tubes are for testing drug product while the seventh row is maintained for blank media or standard solutions. The reciprocating cylinder apparatus consists of sets of cylindrical, flat-bottom glass vessels with corresponding sets of reciprocating cylinders. A motor and drive assembly reciprocate the cylinders vertically inside the vessels. The cylinders are allowed to move from row to row to expose the undissolved drug product to various pH levels.

When the reciprocating cylinder test begins, the inner tubes descend slowly into the first row of the vessels, then the reciprocating motion starts. After the programmed time for this row expires, the inner tubes rise above the vessels, drain for the programmed time, and automatically move to the next row. The process is repeated for each row.

The reciprocating cylinders are glass tubes fitted with top and bottom caps containing screens designed to contain the product under evaluation. As the cylinder reciprocates vertically the drug product is constantly exposed to media contained

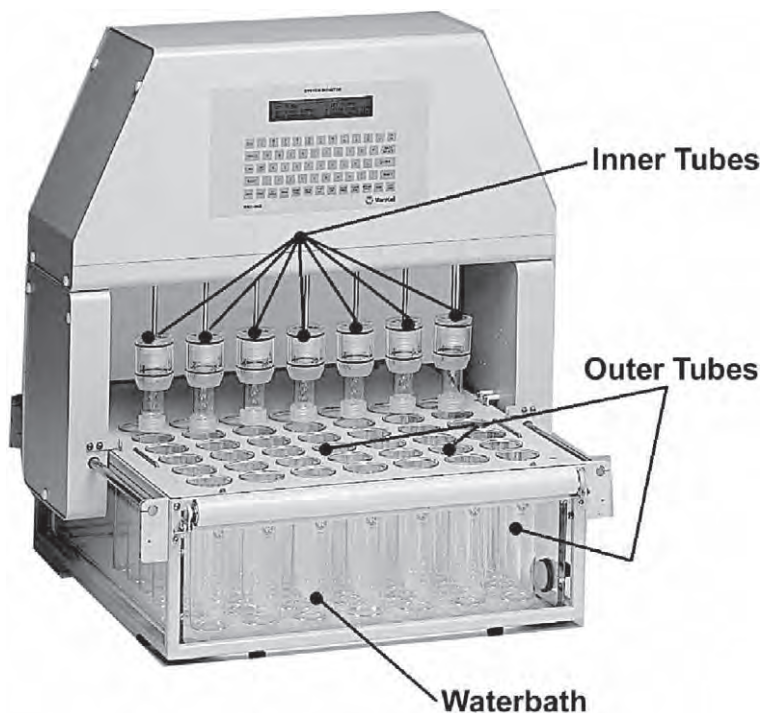


Figure 16. USP Apparatus 3: Bio-Dis Tester.

in the vessel. The 300-mL outer tubes remain in contact with the water bath to maintain the medium temperature at 37 °C.

The seventh position of the reciprocating cylinder apparatus may be modified for each row to contain a blank and standard at the specified pH, to be sampled for automated analysis.

Current Physical Parameters and Tolerances:

Temperature	37 ± 0.5 °C
Dip rate (DPM)	±5% of set speed
Stroke Distance	10.0 ± 0.1cm
Bottom screen	per method
Top screen	per method (optional)
Timepoints	±2% of specified time

USP Calibration Requirements

The reciprocating cylinder apparatus does have a calibration program as outlined in the *USP* utilizing Chlorpheniramine Maleate tablets as the single-unit calibrator.



Figure 17. Bio-Dis reciprocating cylinder inner tubes.

Flow-Through Cell

General Apparatus Description

The flow-through cell was primarily developed for poorly soluble solid dosage forms. Limitations of volume and pH change associated with traditional rotating paddle and basket apparatus prompted the development of the flow-through cell. The flow-through cell is made up of three transparent parts, which fit into each other. The lower part consists of two adjacent chambers connected to an overflow device. The dissolution media passes into the lower part of the chamber then flows upward to an exit in the upper chamber, which leads to a filter assembly.

The middle part of the cell has a cavity and holder designed to contain the dosage unit. Typical flow rates from 4 mL/min up to 16 mL/min are traditionally used.

With a flow-through system, the specimen is placed in a small column, which is continuously flushed with a stream of fluid, simultaneously providing the medium and the mechanical agitation for dissolution of the drug substance.

USP Apparatus 4 can be run as an open or closed system. The open system provides a large volume of multiple solvents as needed. An open system provides media from one or multiple pH sources and collects separate discrete samples as they elute from the flow-through cell.

The closed systems circulate the media through the cell from a reservoir. A closed system with a small media reservoir could reduce volume to below 100 mL for low-dose compounds. The closed system is easily automated as shown in Figure 22.

Products that may be tested in Apparatus 4 include extended-release dosage forms, beads, suppositories, powders, and implants.



Figure 18. Typical Bio-Dis setup.

Current Physical Parameters and Tolerances:

Temperature	37 ± 0.5 °C
Pump rate	240–960 mL/hr
Std flow rates	4, 8, 16 mL/min
Flow rate accuracy	$\pm 5\%$
Pulsation	120 ± 10 pulses/min
Cell Diameters	12 and 22.6 mm

USP APPARATUS 5, 6, AND 7—PADDLE OVER DISK, ROTATING CYLINDER, AND RECIPROCATING HOLDER APPARATUS

These apparatus were originally designed and are primarily used for the analysis of transdermal delivery systems. However, the reciprocating holder apparatus has been utilized for a number of extended-release products other than transdermal

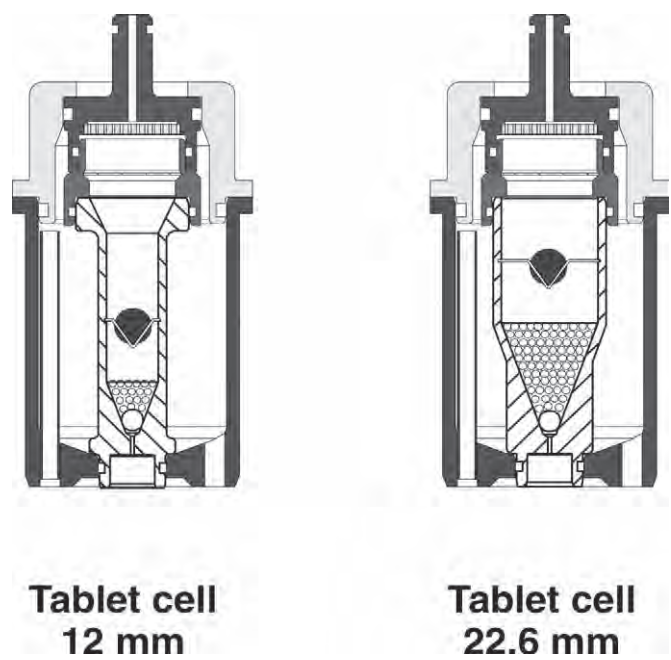


Figure 19. USP Apparatus 4: Flow-through cells.

delivery devices. These apparatus are fully described in the *USP* (6) as follows: paddle over disk as USP Apparatus 5, the rotating cylinder as USP Apparatus 6, and the reciprocating holder as USP Apparatus 7.

The analysis of transdermal delivery systems occurs typically at 32 °C, similar to the temperature of the skin. Before the 1980s, the skin was seldom regarded as a suitable route for administration of drugs to systemic circulation. However, the transdermal route offered several potential advantages for the systemic delivery of drugs. Drugs with narrow therapeutic indices can be good candidates for transder-



Figure 20. Set of USP Apparatus 4 flow-through cells.

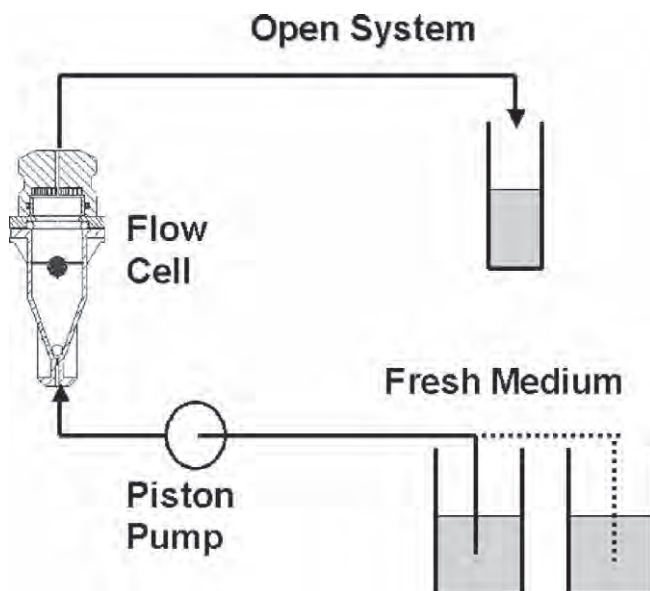


Figure 21. USP Apparatus 4 open system.

mal route because of the absence of the peak-and-valley feature associated with the in vivo absorbance of conventional oral dosage forms. Transdermal systems provide controlled blood levels of potent drugs. Lastly, because of its noninvasive delivery, a transdermal patch may be removed easily if toxicity or side effects

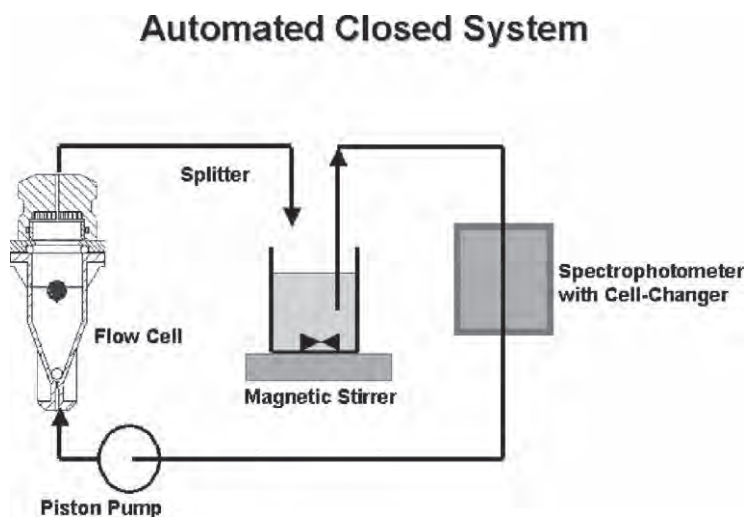


Figure 22. USP Apparatus 4 closed system.

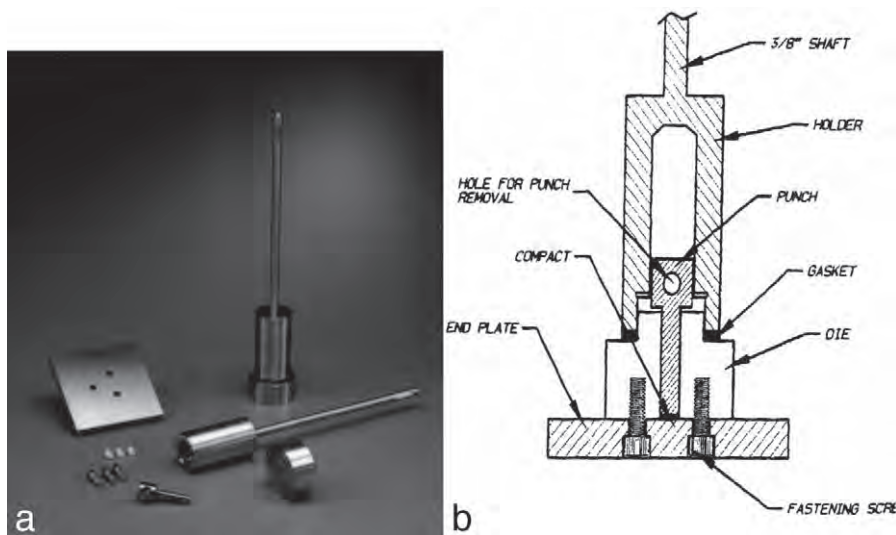


Figure 29. Modified Woods apparatus for intrinsic dissolution.

constant surface method in the form of the modified Woods apparatus, which compresses the active pharmaceutical ingredient into a disk of known surface area (0.5 cm^2). The Woods apparatus is found under *USP* General Chapter <1088> Intrinsic Dissolution (7). The dissolution rate obtained by this method is termed the *intrinsic dissolution rate*, and is characteristic of each solid compound in a given solvent under the fixed experimental conditions. The modified Woods apparatus consists of a punch and die which contains the compressed pellet of bulk drug substance. The die is attached to the holder, which is inserted into the dissolution apparatus capable of holding the device. The test begins by lowering the intrinsic device containing the drug substance into the dissolution vessel and rotating.

Samples are obtained to a point where at least 10% of the drug contained in the device has dissolved. The intrinsic dissolution may be calculated by plotting the cumulative amount of the drug substance dissolved per the constant surface area against time until 10% has dissolved. The cumulative amount of drug substance dissolved for a specific area is obtained by dividing the amount dissolved at each time point by 0.5 cm^2 . Performing a linear regression on the data points up to the point that 10% has dissolved will yield the intrinsic dissolution rate from the slope of the regression line. The value obtained is based on the Noyes-Whitney equation and is generally expressed as milligrams dissolved per minute per centimeter squared ($\text{mg}/\text{min}/\text{cm}^2$). Intrinsic rates greater than $1.0 \text{ mg}/\text{min}/\text{cm}^2$ have negligible problems with dissolution rate limitations, but rates less than $0.1 \text{ mg}/\text{min}/\text{cm}^2$ suggest problems with dissolution rate.

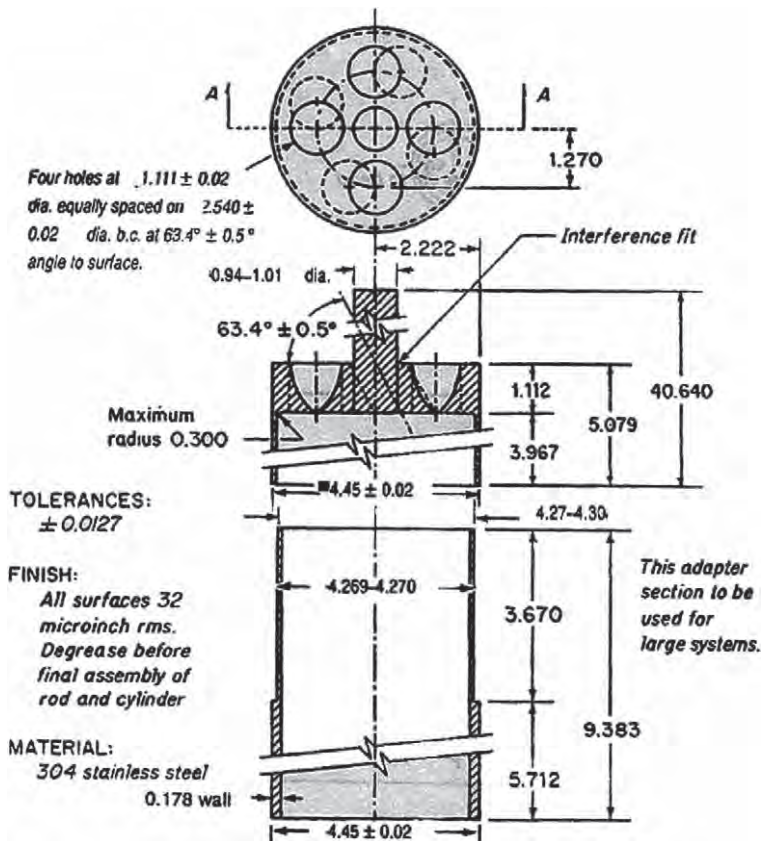


Figure 24. USP Apparatus 6: Rotating cylinder.

Centering	± 2 mm centerline
Speed	$\pm 4\%$ of set speed
Vessel Temp.	$32 \pm 0.5^\circ \text{C}$
Timepoints	$\pm 2\%$ or ± 15 min of the specified time (lesser)

Rotating Cylinder

This apparatus utilizes the typical dissolution apparatus and vessel configuration with the exception of rotating cylinder stirring elements that are used in place of paddle or basket stirring elements. The shaft consists of a stainless steel cylinder-stirring element with a removable extension, which is used for larger transdermal systems.

The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

To attach the transdermal system, remove the system from the package and

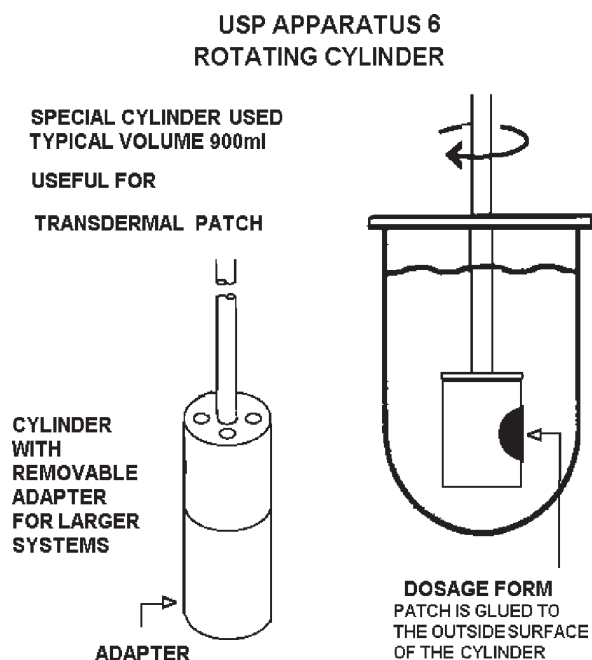


Figure 25. USP Apparatus 6 dosage unit placement.

remove the protective liner from the system. Place the adhesive side on a piece of Cuprophane that is not less than 1 cm larger on all sides of the system perimeter.

Place the system on a clean surface with the Cuprophane side down. Apply a suitable adhesive (Dow Corning, 355 medical adhesive 18.5% in Freon® 113, or equivalent) to the exposed Cuprophane borders and back, if necessary. Carefully

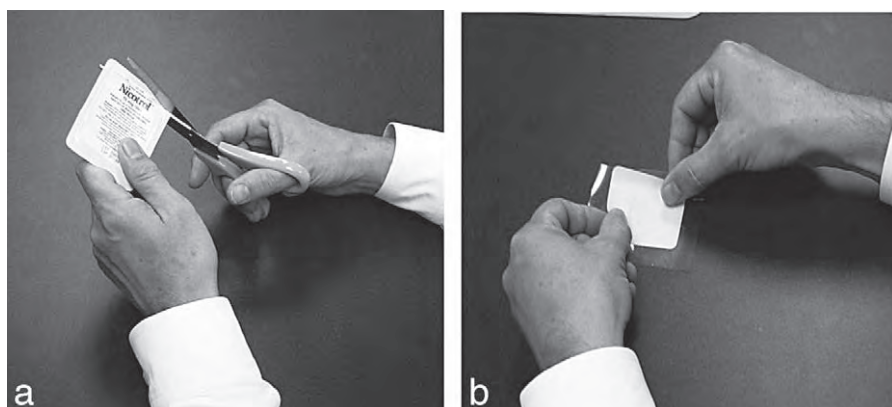


Figure 26. Transdermal dosage unit preparation.

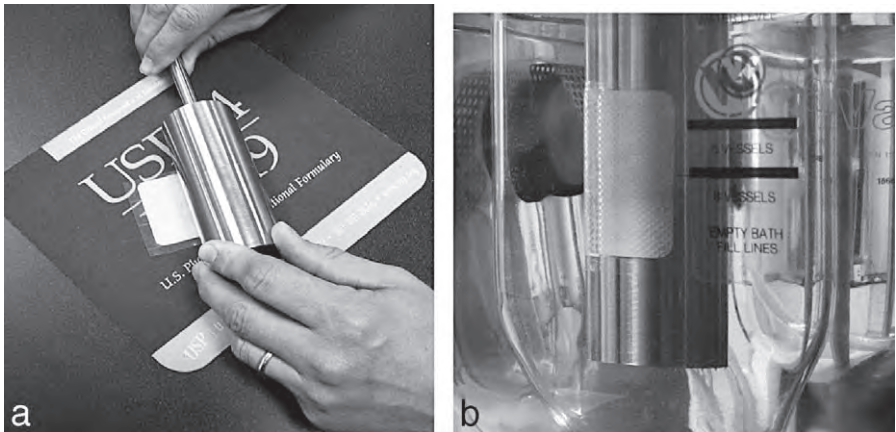


Figure 27. Transdermal dosage unit attachment.

apply the adhesive-coated side of the system to the exterior of the cylinder with the long axis of the system fitting around the circumference of the cylinder. The use of a soft pad or a computer mouse pad will help to attach the system to the cylinder without trapping air bubbles or damaging the patch. Place the cylinder in the dissolution apparatus, lower into the media, and immediately rotate at the specified speed.

Current Physical Parameters and Tolerances:	
Dimensions	per USP
Height	25 ± 2 mm
Centering	±2 mm centerline
Speed	±4% of set speed
Vessel Temp.	32 ± 0.5 °C
Timepoints	±2% or ±15 min of the specified time (lesser)

Reciprocating Holder

Also known as the “Alza apparatus” and USP Apparatus 7, the reciprocating holder apparatus has evolved to handle not only transdermal products, but also other sustained-release products. The apparatus utilizes sets of volumetrically or gravimetrically calibrated tubes and a mechanical device capable of reciprocating the specific holders vertically in the tubes containing dissolution medium. Typical vessel volumes of 50–75 mL are used. Vessels are usually 50 mL with an operational minimum around 25 mL. Adaptations have been made to accommodate 100- and 300-mL vessels. Products typically tested in the reciprocating holder apparatus are transdermal delivery systems, osmotic pumps, and other non-disintegrating extended-release dosage forms such as implants and drug-eluting stents.

The holder apparatus consists of five different reciprocating holder configurations. The disk, cylinder, and angled disk are used for transdermal delivery systems.

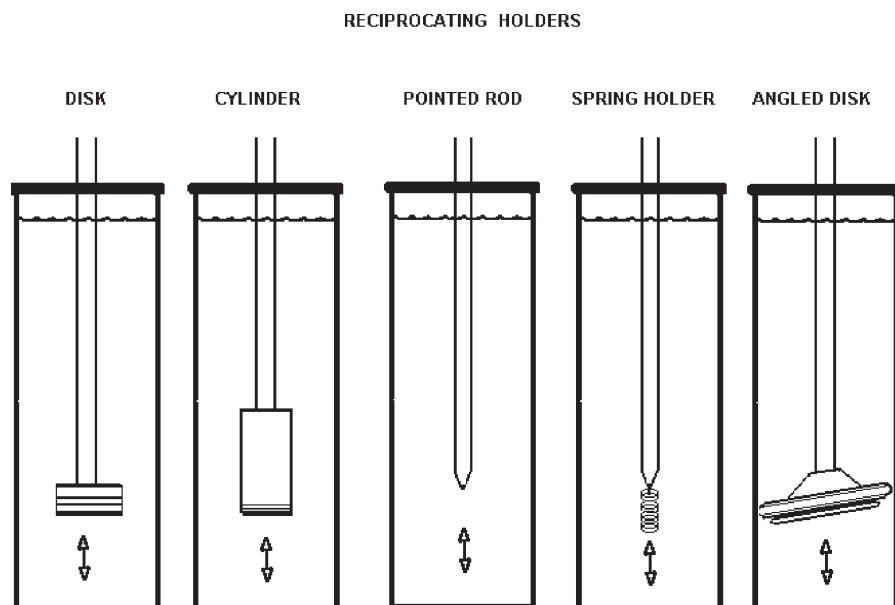


Figure 28. USP Apparatus 7 reciprocating holder configurations.

The pointed acrylic rod operates with an osmotic pump dosage unit or implant glued to the tip. The spring holder contains a non-disintegrating dosage unit or osmotic pump as it reciprocates vertically in the vessel. Illustrations of the vessels and reciprocating holders are shown in Figure 28.

Current Physical Parameters and Tolerances:

Temperature	32 ± 0.5 °C
Dip rate	30 DPM
Stroke Distance	2 cm
Holder	per USP
Timepoints	$\pm 2\%$ of specified time

INTRINSIC DISSOLUTION

During the development process for new oral dosage pharmaceutical products, drug substances must be evaluated to show consistent physical characterization as represented by their dissolution rate constants. The drug substances, sometimes available from multiple techniques and sources, must demonstrate uniformity in the manufacturing process as well as in their physiochemical properties. The intrinsic dissolution rate is defined as the dissolution rate of pure substances under the condition of constant surface area. Intrinsic dissolution apparatus utilizes a

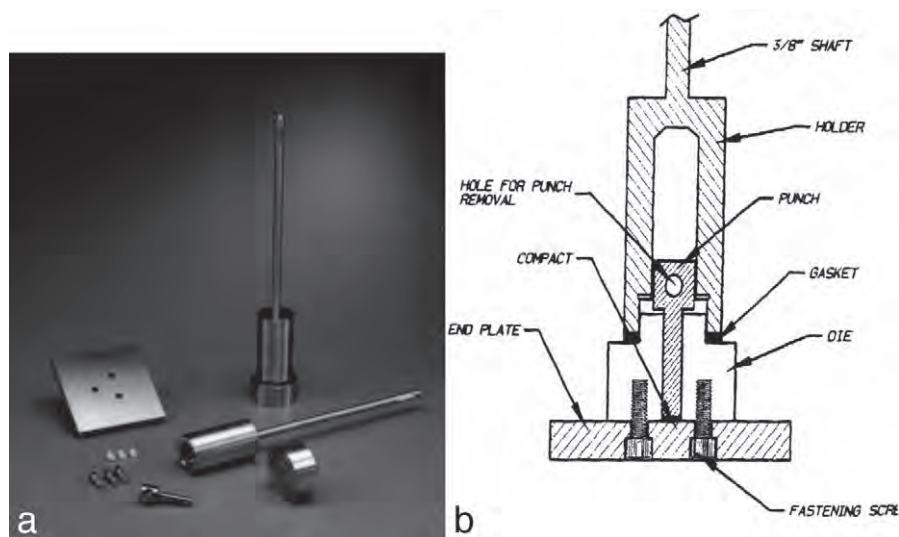


Figure 29. Modified Woods apparatus for intrinsic dissolution.

constant surface method in the form of the modified Woods apparatus, which compresses the active pharmaceutical ingredient into a disk of known surface area (0.5 cm^2). The Woods apparatus is found under *USP* General Chapter <1088> Intrinsic Dissolution (7). The dissolution rate obtained by this method is termed the *intrinsic dissolution rate*, and is characteristic of each solid compound in a given solvent under the fixed experimental conditions. The modified Woods apparatus consists of a punch and die which contains the compressed pellet of bulk drug substance. The die is attached to the holder, which is inserted into the dissolution apparatus capable of holding the device. The test begins by lowering the intrinsic device containing the drug substance into the dissolution vessel and rotating.

Samples are obtained to a point where at least 10% of the drug contained in the device has dissolved. The intrinsic dissolution may be calculated by plotting the cumulative amount of the drug substance dissolved per the constant surface area against time until 10% has dissolved. The cumulative amount of drug substance dissolved for a specific area is obtained by dividing the amount dissolved at each time point by 0.5 cm^2 . Performing a linear regression on the data points up to the point that 10% has dissolved will yield the intrinsic dissolution rate from the slope of the regression line. The value obtained is based on the Noyes-Whitney equation and is generally expressed as milligrams dissolved per minute per centimeter squared ($\text{mg}/\text{min}/\text{cm}^2$). Intrinsic rates greater than $1.0 \text{ mg}/\text{min}/\text{cm}^2$ have negligible problems with dissolution rate limitations, but rates less than $0.1 \text{ mg}/\text{min}/\text{cm}^2$ suggest problems with dissolution rate.

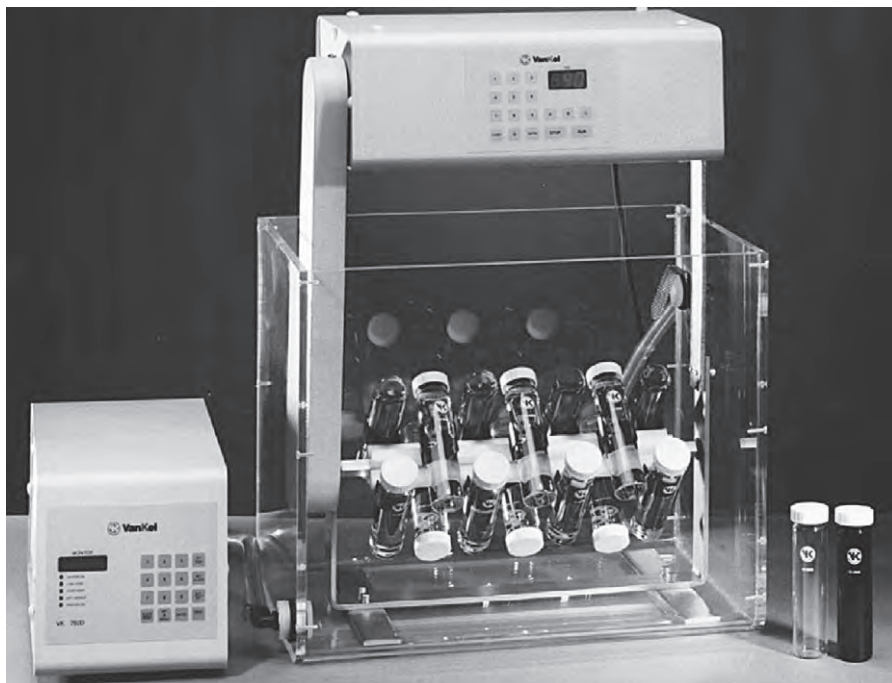


Figure 30. Rotating bottle apparatus.

ADDITIONAL “UNOFFICIAL” APPARATUS: ROTATING BOTTLE APPARATUS AND DIFFUSION CELLS

Rotating Bottle

Approximately ten years before the development of the rotating paddle and basket apparatus, the rotating bottle method was developed to study timed-release formulations. The original chapter in the *National Formulary* where references are made to the operation of the equipment is entitled *Timed-Release Tablets and Capsules In Vitro Test Procedure*. Originally, the apparatus used various “extracting fluids” composed of a mixture of simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) over five pH ranges: 1.2, 2.5, 4.5, 7.0, and 7.5.

The apparatus is constructed to hold sets of bottles, 150 mm in length with a 30-mm diameter, containing a dosage unit and attached to a rotating bar while submerged in a water bath to maintain the extracting fluid within the bottle at 37.0 °C. After specified periods of time, the apparatus is removed from the water bath, the bottles are removed, and samples are generally acquired through total media exchange. After samples are taken and 37.0 °C media added back to the vessels, the bottles are recapped, reattached to the apparatus, and the apparatus is lowered back into the water bath.

The rotating bottle apparatus was first introduced as an official apparatus in the

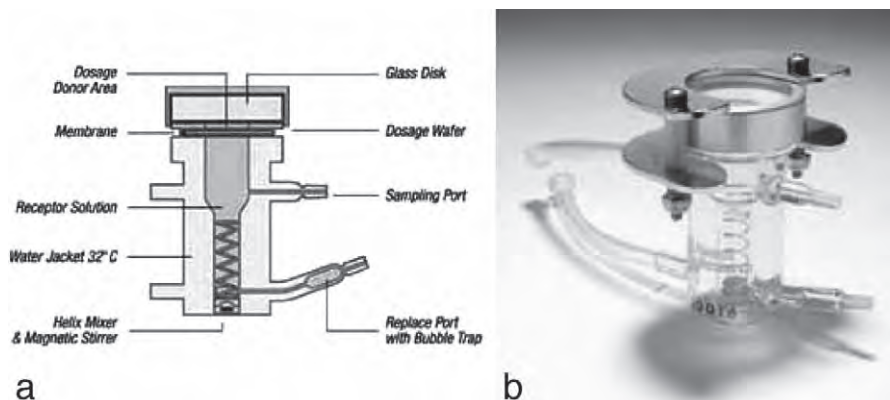


Figure 31. Franz cell.

United States National Formulary but was not carried over to the *United States Pharmacopeia*, which presently contains the seven “official” dissolution apparatus used in the United States. While it is no longer an official apparatus, it does possess several distinguishing characteristics. It is the only dissolution apparatus that has no evaporative loss and therefore can run for extended periods of time without loss of media. This is especially helpful for implants, which may need to run for days or even weeks to acquire in vitro dissolution data for regulatory approval or even quality control over the manufacturing process. The rotating bottle method is a labor-intensive method and this may be part of the reason that it has never become as popular as other, more efficient and easy to use apparatus.

Diffusion Cells

Over the past decade, the use of an in vitro release test to evaluate drug release from semisolid formulations has received increased attention. Two in vitro apparatus have evolved over this period, the Franz Cell and the Enhancer Cell. Both systems have been developed to monitor formulation performance or changes in batch-to-batch uniformity. Both apparatus produce similar results in response to formulation changes, but preference to using one device over the other depends on the application technique desired. The methodology consists of either diffusion cell, an appropriate synthetic membrane, appropriate receptor phase, at least 5 data points over a six-hour period to determine the release rate, and an analytical method to determine the concentration at a given time. These diffusion cells should be capable of providing manufacturing process control and ultimately a quality control test to ensure batch-to-batch uniformity. The diffusion cells are also quite useful in the development of transdermal systems. Both diffusion systems have various surface sizes depending on the analytical need.

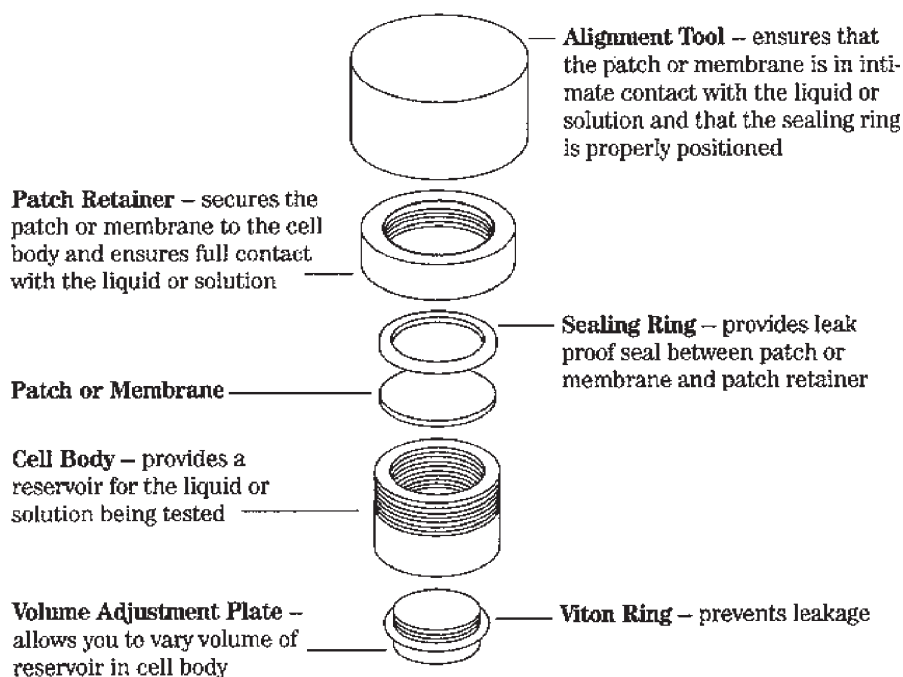
Enhancer Cell – Exploded View

Figure 32. Enhancer cell-exploded view.

Franz Cell

The Franz cell is a vertical diffusion cell system developed by Dr. Thomas Franz. It has been used historically to determine the release of active from topical preparations and has been modified to analyze potential transdermal drug delivery formulations. The glass cell system consists of a receptor chamber, donor chamber with clamp, sampling and media replacement ports, temperature-controlled heating jacket, and a stirrer. The Franz cells may be sampled manually or automatically. A top cap seals the donor compartment from air to minimize reverse diffusion associated with automatic samplers.

Enhancer Cell

The Enhancer Cell is a device that can be used to study the drug release profiles of topical formulations. It is made of Teflon, an inert and non-reactive material. The main idea behind the development of the enhancer cell was to develop a simple, affordable, reliable, and reproducible quality control method that could be used to discriminate variations in the release characteristics of topical dosage forms. The Enhancer Cell consists of a cap, a washer, membrane, an o-ring, and a drug reservoir. The outer diameter of the body and the solid ring are identical to the

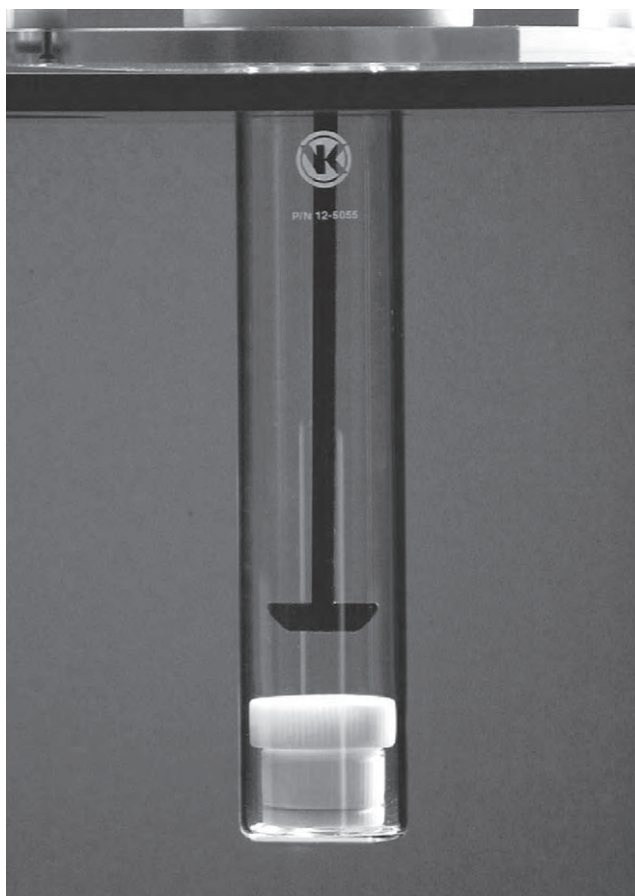


Figure 33. Enhancer cell in vessel.

inner diameter of the cap, which aids in keeping the membrane in place while tightening the cell. A typical six-spindle dissolution tester may be used. The apparatus must be modified to hold 200-mL capacity vessels instead of the standard 900-mL vessel. It is essential to use smaller receptor volumes to obtain samples with detectable concentration of drug for HPLC analysis. Additional required equipment includes an adapter plate to position the vessel in the center, an evaporation cover, a smaller-sized shaft, and collet to hold the shaft firmly in place. The operational minimum volume is about 50 mL. Transdermal membrane candidates may also be evaluated with the Enhancer Cell.

Regarding the qualification and use of “unofficial” dissolution apparatus, the FDA encourages the development and use of the most appropriate instrumentation (8). However, the use of rare or exotic systems not only places undue burden on the regulatory laboratory, but also may delay the approval process for new drug

products. When noncommercial instrumentation is used, the instrumentation should be capable of being constructed from commercially available components at a reasonable cost, if possible. For unique methodologies or instrumentation requiring contract fabrication, the applicant's cooperation with the FDA laboratories in helping facilitate duplication of the analytical equipment and procedure is important. In addition to design and equipment specifications, complete performance assessment procedures should be provided. Such systems may be found suitable for regulatory use. However, unnecessary proliferation of alternative dissolution apparatus should not be encouraged, and alternatives or modifications to established dissolution apparatus should be considered on the basis of proven superiority for a particular product.

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