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International Journal Of Pharma Professional's Research

Review Article

DISSOLUTION:- Life line of Pharmaceutics

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ISSN NO:0976-6723

Abstract

In this present review we studied the different dissolution parameters which are required for the dissolution. Different types of dissolution apparatus in detail with the help of diagram to understand it well. The validation procedures for the dissolution apparatus and its devices. we also study the different types of buffers which are used in dissolution their preparation methods are also included in it. From this study we concluded that anyone can go familiar with the dissolution, its apparatus and the buffers.

Keywords: - Dissolution, Dissolution Apparatus, Validation, Buffers.

Introduction

Dissolution testing is a requirement for all solid oral dosage forms and is used for drug product release and stability testing. The dissolution test is the most important analytical test for detecting physical changes in an API and in the formulation. The two commonly used dissolution apparatus are the basket (USP Apparatus 1) and the paddle (USP Apparatus 2).

Both apparatus have been widely accepted by the pharmaceutical community for measuring the rate of dissolution of an API from a given pharmaceutical solid dosage form. The setup of dissolution Apparatus 1 and 2 requires control over many variables as defined in USP <711> (*1)*, European Pharmacopoeia 2.9.3 (*2*), and Japanese Pharmacopoeia 15 (*3*). The variables in both of these apparatus are vessels, shaft dimensions, shaft wobble, rotation speed, shaft height from the bottom of the vessel, vessel centering and tilt, temperature, leveling of the dissolution apparatus at its base, vibration, and so forth. Many literature articles describe methods to control these variables (*4–20*). However, none of these address control of basket variability (refer to USP <711>).

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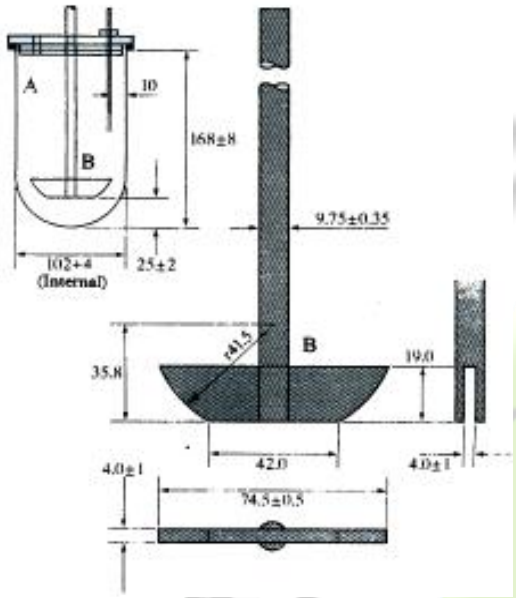
USP and FDA Requirements for Basket Apparatus

The basket apparatus consists of a wire-mesh basket that is attached to a rotation shaft, which is then immersed into a dissolution vessel for the duration of the dissolution test. Since the dosage unit is in direct contact with the basket, the physical dimensions and motion of the basket can have a dramatic effect on the dissolution rate of the solid dosage unit. Because of the critical nature of the basket, it is tightly controlled by several mechanisms. First, the dimensions of basket height, i.d. and o.d. of the basket opening, height of the open screen, and size of the mesh are specified in USP <711>. Next, the amount of wobble at the bottom of the basket while rotating is checked with a wobble meter at periodic intervals, anywhere from time of use to once a year, to ensure that it is within the 1-mm specification indicated in USP.Finally, a functional test using standardized performance-verification tablets is executed. The rate of release of the standardized calibrator tablet is measured and compared to the acceptance criteria. The performance verification tablets and acceptance criteria are designed so that if the apparatus is not set up in accordance with the tight USP specifications, it will not pass this final test.(21-23)

Dissolution Test

This test is designed to determine compliance with the dissolution requirements for solid dosage forms administered orally. The test is intended for a capsule or tablet. Use Apparatus 1 unless otherwise directed. All parts of the apparatus that may come into contact with the preparation under examination or with the dissolution medium are chemically inert and do not adsorb, react or interfere with the preparation under examination. All metal parts of the apparatus that may come into contact with the preparation or the dissolution medium must be made from

stainless steel, type 316 or equivalent or coated with a suitable material to ensure that such parts do not react or interfere with the preparation under examination or the dissolution medium. 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 smoothly rotating element. An apparatus that permits observation of the preparation under examination and the stirrer during the test is preferable.



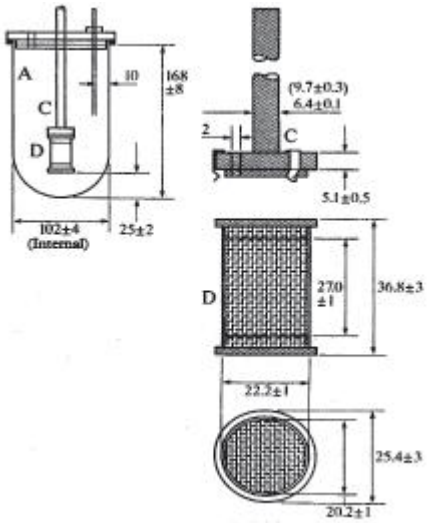
An assembly consisting of the following:

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 . 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.

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 insuch a way that the paddle rotates smoothly and without significant wobble.

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



The assembly is the same as in Apparatus 1 except that in the stirring element the paddle is replaced by a basket, D . 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 0.381mm 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 2.5m m 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 27mm during the test.[24]

The two components of the dissolution test are simple: sample preparation, which takes place within the dissolution apparatus, and sample analysis, primarily via chromatographic or spectrophotometric techniques. The two components of the dissolution test, sample preparation and assay, are separated by a filtration step. Filters must be validated to prove their efficiency in removing undissolved active pharmaceutical ingredient (API) from the sample and to verify that they do not adsorb dissolved API, which affects the integrity of the sample concentration. The first step taken to overcome concentration and sensitivity issues is usually modification of the analytical method by taking advantage of a larger path length for a spectrophotometer or a larger injection volume for high performance liquid chromatography (HPLC). When success with these techniques is limited, we must focus on the dissolution apparatus where a reduction in media volume may be a more rugged solution.[25]

Only a few of the compendial dissolution and drug-release apparatus are designed for low-dose compounds and volume requirements less than 100 mL present additional challenges to the traditional paddle and basket apparatus. Rugged dissolution

methods should quantify the low levels of analyte accurately and precisely, especially in the initial stages of drug release in the dissolution profile. Accurate analytical concentration in the presence of reliable and consistent agitation is the primary requirement of any dissolution test but demands extreme precision in low-volume conditions to ensure data accuracy. The dissolution apparatus must operate under conditions of controlled temperature, agitation rate, precise hydrodynamics, and volume. To maintain precise hydrodynamics, the apparatus must maintain overall physical uniformity and alignment throughout the test.

Standard dissolution apparatus may be obtained from manufactures that produce the equipment according to the specification and tolerances outlined in General Test Chapter <711> Dissolution (*26*). For low concentrations of API, official compendia apparatus may be incapable of maintaining quantitative levels of analyte during the dissolution of oral dosage units containing microgram or nanogram levels. Dissolution of typical high-potency, low-dose compounds may require a reduction in vessel volume accompanied by an alteration in apparatus design due to limitations in detection and quantitation. If a reduction in volume is considered and the apparatus is modified, the operating conditions of the modified apparatus should maintain the same degree of precision and alignment required for any other compendial dissolution apparatus. Small-volume apparatus are desired not only for high-potency, low-dose formulations. Small-volume dissolution utilizing a mini paddle has been suggested as an alternative to standard paddle methods that require large volumes of biorelevant medium. This can be very expensive, and there may be limitations of large sample size or active drug availability in the early stages of drug development (*27*).

In the current regulatory environment, our dissolution methods must be accurate, sensitive, and specific, and the reproducibility of the test method employed must be established, verified, and documented (*28*). Additionally, the method must maintain limits of detection and quantitation, range, and linearity and discriminate variation from batch to batch. Small-volume apparatus components should be precisely designed, rugged, and commercially available to aid in the approval of the noncompendial method and analytical transferability. Regulatory expectations of the small-volume dissolution method should continue to:

- Characterize the in vitro release early in development.
- Evaluate release with various conditions of agitation, media composition, pH, and temperature.
- Establish optimum test conditions.
- Demonstrate a release of 80% or an asymptote.

The method should also be capable of showing discrimination, rejecting lots, and ultimately demonstrating consistency of performance from lot to lot. In terms of dissolution specifications for modified release products, expectations are high for in vitro–in vivo correlation (IVIVC), and the small-volume dissolution apparatus should provide data needed to support scale-up and post-approval changes for modified-release (SUPAC-MR) (*29*). Additionally, the dissolution test should be approvable based on meaningful methodology and specifications, and in general, the method must be relevant, predictable, specific, and discernable (*30*).

Dissolution medium. Use the dissolution medium specified in the individual monograph. If the medium is a buffered solution, adjust the solution so that its pH is within 0.05 units of the pH specified in the monograph. The dissolution medium should be deaerated prior to testing. [31]

Method

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 36.5º to 37.5º. Unless otherwise stated, place one dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit. When 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.

Acceptance criteria

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 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

Level	Number Tested	Acceptance criteria
S_1	**6**	Each unit is not less than D* + 5 percent**.
S_2	**6**	Average of 12 units (S1 +S2) is equal to or greater than D, and no unit is less than D –15 per cent**.
S_3	**12**	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**.

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

**Percentages of the labelled content.

Level	Number Tested	Acceptance criteria
L_1	**6**	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.
L_2	**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 labelled content outside each of the stated ranges; and none is more than 10 per cent of labelled amount below the stated amount at the final test time.
L_3	**12**	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 labelled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10 per cent of labelled content below the stated amount at the final test time; and none of the units is more than 20 per cent of labelled content outside each of the stated ranges or more than 20 per cent of labelled content below the stated amount at the final test time.

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. 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.

Modified-release dosage forms. Use method A or Method B.

MethodA

Acid stage. Place 750 ml of 0.1M hydrochloric acid in the vessel, and assemble the apparatus. Warm the dissolution medium to 36.5º to 37.5º. 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. 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 36.5º to 37.5º. 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 36.5º to 37.5º. 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 36.5º to 37.5º. 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.[32]

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 labelled content of active substance dissolved from the units tested conform to Table . Continue the testing through the 3 levels unless the results of both acid and buffer stages conform at an earlier level.

Level	Number Tested	Acceptance criteria
A_1	**6**	No individual value exceeds 10 percent dissolved.
A_2	**6**	The average value of the 12 units (A1 + A2) is not more than 10 per cent dissolved, and no individual unit is greater than 25 per cent dissolved.
A_3	**12**	The average value of the 24 units (A1 + A2 + A3) is not more than 10 per cent dissolved, and no individual unit is greater than 25 per cent dissolved.

Buffer stage. Unless otherwise specified, the requirements of this part of the test are met if the quantities, based on the percentage of the labelled content of active substance dissolved from the units tested conform to Table . 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 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 labelled content.[33]

Level	Number Tested	Acceptance criteria
B_1	**6**	No unit is less than D + 5 per cent*
B_2	**6**	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*
B_3	**12**	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*.

* percentages of the labelled content.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—

Place the stated volume of the Dissolution Medium (+1%) in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the Dissolution Medium to 37+0.58, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate 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 basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution Medium at 378 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. Repeat the test with additional dosage form units. If automated equipment is used for sampling and the apparatus is modified, validation of the modified apparatus is needed to show that there is no change in the agitation characteristics of the test.

Where capsule shells interfere with the analysis, remove the contents of not fewer than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of Dissolution Medium. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets— Use this procedure where Procedure for a Pooled Sample is specified in the individual monograph. Proceed as directed under Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets. Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of the active ingredient dissolved in the pooled sample.

Dissolution Medium

Dissolution testing should be carried out under physiological conditions, if possible. This allows interpretation of dissolution data with regard to in vivo performance of the product. However, bstrict adherence to the gastrointestinal environment need not be used in routine dissolution testing. The testing conditions should be based on physicochemical characteristics of the drug substance and the environmental conditions the dosage form might be exposed to after oral administration.

The volume of the dissolution medium is generally 500, 900, or 1000 mL. Sink conditions are

desirable but not mandatory. An aqueous medium with pH range 1.2 to 6.8 (ionic strength of

buffers the same as in USP) should be used. To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0. To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. Recent

experience with gelatin capsule products indicates the possible need for enzymes (pepsin with SGF and pancreatin with SIF) to dissolve pellicles, if formed, to permit the dissolution of the drug. Use of water as a dissolution medium also is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients. For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulfate is recommended (34,35). The need for and the amount of the surfactant should be justified. Use of a hydro alcoholic medium is discouraged.

Discussion of Dissolution Apparatus

Over the years, the traditional paddle and basket dissolution apparatus with 1-L vessels has been an important tool for characterizing the biopharmaceutical quality of a product at different stages in the product life cycle. Our discussion will focus on those official apparatus
contained in the current USP (*36*,*37*).

Apparatus mentioned in the following sections contain recognized minimum operational volumes. Consultation with the manufacturers of these apparatus is recommended to obtain the latest performance specifications if further reductions in vessel volume are desired. Apparatus will be discussed according to their USP apparatus numbers, and additional information will follow each apparatus regarding its noncompendial modifications to achieve small-volume dissolution.

USP Dissolution Apparatus

- Apparatus 1 - Basket (37º)
- Apparatus 2 - Paddle (37º)
- Apparatus 3 - Reciprocating Cylinder (37º)
- Apparatus 4 – Flow-Through Cell (37º)
- Apparatus 5 – Paddle over Disk (32º), Transdermal Delivery System, use paddle and vessel from Apparatus 2 with a stainless steel disk assembly to hold the transdermal on the bottom of vessel.
- Apparatus 6, Cylinder (32º), Transdermal Delivery System, use Apparatus 1 except replace the basket shaft with a stainless steel cylinder element.
- Apparatus 7, Reciprocating Holder, for transdermal delivery systems and also a variety of dosage forms.

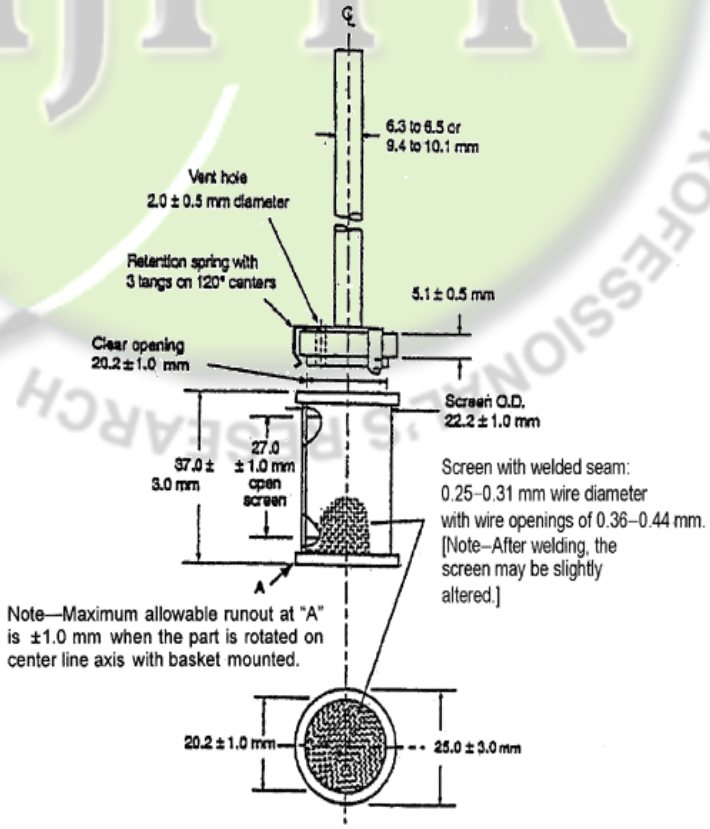
USP Apparatus --- Rotating Basket and Paddle

The traditional basket and paddle apparatus utilize a 1000-mL hemispheric bottom vessel.

To accomplish sink conditions required for bolus and poorly soluble dosage forms, vessels up to 4000 mL have been incorporated into the USP, but the operational minimum of the 1000-mL vessel is around 500 mL. Although smaller volumes have been used for various purposes such as the dissolution of esomeprazole magnesium and omeprazole magnesium, which are carried out in the acid stage using only 300 mL of 0.1 M HCl (*8*), in general, the hydrodynamics below 500 mL become too unstable for routine dissolution testing. The traditional vessel has handled routine oral dosage tablets, capsules, suspensions, suppositories, and chewable tablets, but smaller-volume vessels with scaled-down basket and paddles (Figure 1) have been developed to handle volumes capable of nano- and picogram levels of drug. The operational minimum for small-volume vessels of 100 mL and 200 mL is approximately 30 mL.

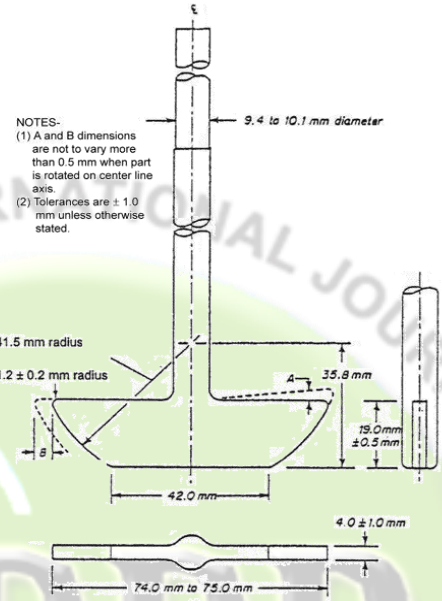
USP Apparatus 1 —Rotating Basket

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material1; a motor;



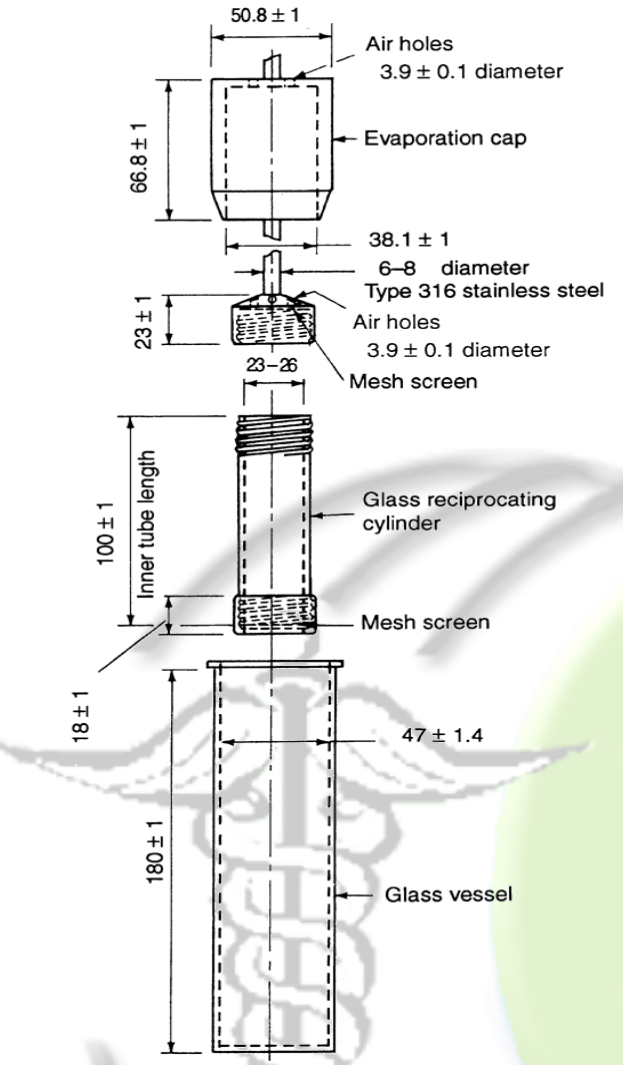
a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or placed in a heating jacket. The water bath or heating jacket permits holding the temperature inside the vessel at 37+0.58 during the test and keeping the bath fluid in constant, smooth motion. 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 smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 L, the height is 160 mm to 210 mm and its insidediameter is 98 mm to 106 mm; for a nominal capacity of 2 L, the height is 280mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 L, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within +4%.Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 mm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25+2 mm during the test.

Apparatus 2 paddle type —Use the assembly from Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25+2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float. Other validated sinker devices may be used.



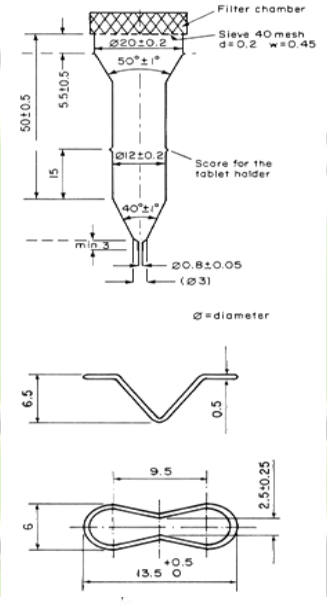
USP Apparatus 3—Reciprocating Cylinder

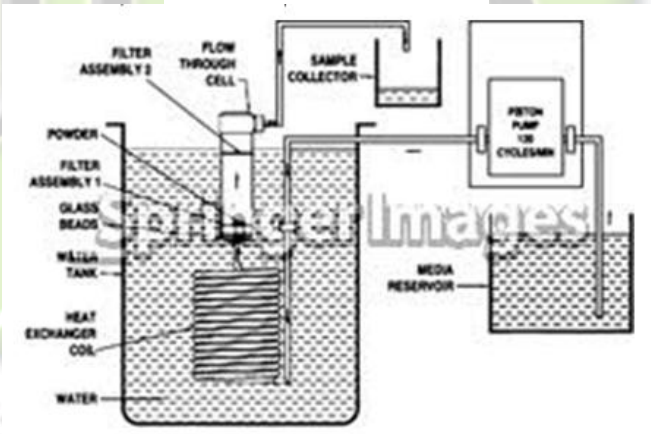
The reciprocating cylinder apparatus has six or seven inner tubes, which mechanically traverse six rows of corresponding media-filled outer tubes. Also called the Bio-Dis, for biorelevant dissolution, the apparatus has been successfully used for tablets, capsules, beads (Figure 2), and other extended-release dosage forms that require exposure to various media representing conditions in the gastrointestinal tract. The traditional configuration utilizes a 300-mL vessel, which is an advantage for products requiring a small volume. The reciprocating cylinder has an operational minimum of about 150 mL. A noncompendial version has been developed; it utilizes a 100-mL vessel with a scaled-down reciprocating inner tube that can run at an operational minimum of about 50 mL



USP Apparatus 4—Flow-Through Cell

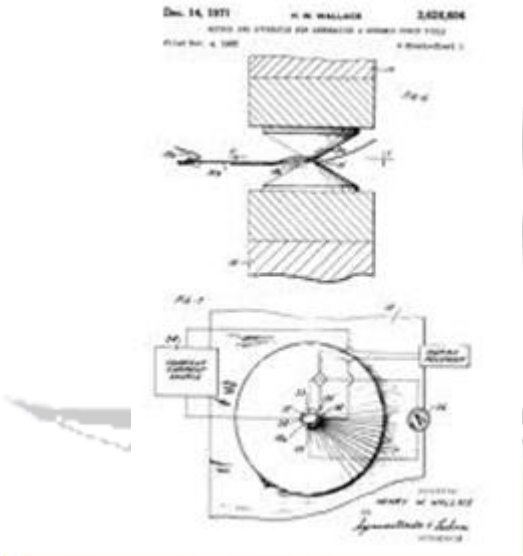
The flow-through cell was originally developed to simulate gastrointestinal conditions by exposing extended-release and poorly soluble dosage forms to media of varying pH. The apparatus has been used for capsules, powders, tablets, implants, and suppositories and has been used with a wide range of media volume. A compendial closed system with a small media reservoir could traditionally reduce volume to less than 100 mL for the official USP 12- and 26-mm cells. Noncompendial cells that allow dissolution of nanoparticles and suppositories have been developed. Small-volume applications have been refined for the flow-through apparatus, resulting in closed cells handling dissolution volumes less than 15 mL. These smaller cells have been developed for implants and other low-dose products.





USP Apparatus 5 and 6—Paddle Over Disk and Rotating Cylinder

These two methods were developed for transdermal systems, and the official vessel is the traditional 1000-mL hemispheric bottom dissolution vessel mentioned previously. The minimum vessel volume is 500 mL due to the hydrodynamic issue mentioned for the paddle apparatus. No smaller vessels have been developed or applied to USP Apparatus 5 or 6 to the author's knowledge at this time.



USP Apparatus 7—Reciprocating Holder

Originally introduced in the USP as a small-volume option for small transdermal patches, the reciprocating disk apparatus was later renamed the reciprocating holder apparatus with the adoption of four additional holders for transdermal systems, osmotic pumps, and other low-dose delivery systems. The agitation rate for the reciprocating holder apparatus has been typically 30 cycles per minute at an amplitude of 2 cm, but a specific vessel size has not been stated in the USP General Chapter <724> Drug Release (37). The original reciprocating holder apparatus commonly used 50–400-mL vessels and was not initially designed for extremely low volumes. The reciprocating cylinder apparatus has become a good candidate for modification due to the emergence of numerous low-dose compounds that have challenged traditional dissolution equipment. These dosage forms include subcutaneous implants and combination products such as drug-eluting stents (Figure 3). Currently, Apparatus 7 can accommodate a dissolution environment as low as 5 mL.

Validation of a Dissolution Apparatus:-

Dissolution is defined as the process by which a known amount of drug substance goes into solution per unit of time under standardized conditions. The primary goal of dissolution testing is to be used as a qualitative tool to provide measurements of the bioavailability of a drug as well as to demonstrate bioequivalencefrom batch-to-batch. The bioavailability and bioequivalence data obtained as a result of dissolution testing can be used to guide the development of a new formulation and product development processes toward product optimization,as well as to ensure continuing product quality and performance of the manufacturing process. In addition,dissolution is a requirement for regulatory approval for product marketing and is a vital

component of the overall quality control program [38].

Dissolution testing is conducted using a dissolution apparatus that conforms to the specifications outlined in the United States Pharmacopeia. There are seven types of dissolution apparatus; the apparatus chosen to perform dissolution testing depends primarily on the drug dosage form. In order to have a high degree of assurance that the dissolution apparatus is consistent and accurate in its performance,validation is required. Validation is defined as documented evidence that provides a high degree of assurance that a specific instrument performs according to manufacturer's specifications and user requirements. Validation is achieved by performing a series of validation activities; for a dissolution apparatus,validation is obtained through installation qualification and operational qualification.

Installation Qualification

Installation qualification consists of documented verification that all key aspects of the dissolution apparatus are in working condition and have been properly installed in accordance with manufacturer's specifications in the proper operating environment. The installation qualification of a dissolution apparatus should include the following verifications:

• Preventive maintenance

The installation qualification should document that the dissolution apparatus is enrolled in a preventive maintenance program to assure that the system continues to operate properly and no component part of the system becomes inoperable due to wear and use.

• Calibration

The installation qualification should document that specific devices contained within the dissolution apparatus (e.g., speed, time, and temperature displays) have been calibrated to traceable standards.Documentation should include the date calibration was performed and when calibration is due.

• SOPs

The installation qualification should document that all SOPs pertaining to the dissolution apparatus are approved and in place. Applicable SOPs may include preventive maintenance, calibration, operation, document archival, and equipment logbook usage.

• Utilities

The installation qualification should document the manufacturer's specifications for required utilities and verify that the appropriate utilities are available for the system. For example, utility verification may include confirming that the appropriate electrical power requirements

(voltage, amperage, safety cut-offs) are documented and comply with manufacturer's specifications.

• Computerized System

If the dissolution apparatus is computerized, the installation qualification should document the manufacturer's specifications for the computer system and verify that the computer system in place complies with manufacturer's specifications. Documentation should include model and serial number of associated hardware, operating system name and version, software name and version, location of master and back-up files, and CPU requirements such as speed and hard drive capacity.

• Environmental Conditions

The installation qualification should document the environmental conditions that surround the dissolution apparatus conform to USP standards, which require that 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 smoothly rotating stirring element.

• Equipment Information

The installation qualification should document equipment information including the manufacturer, model number, and serial number of the dissolution apparatus, and verify that the information complies with purchase orders and user requirements. In addition, verification of the unit's compliance with requirements outlined by the USP <711> Dissolution General Chapter,and specific to each dissolution apparatus, should be performed. Requirements to be verified are summarized below .[39]

Apparatus 1

• Vessel: cylindrical, 160-210 mm high, inside diameter 98-106 mm, nominal capacity is 1000 mL; sides are flanged at the top.

• Shaft: positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble.

• Materials of Construction: Shaft and basket components are stainless steel, type 316 or equivalent.

• Basket position: the distance between the inside bottom of the vessel and the basket is maintained at 25 +/- 2 mm during the test.

Apparatus 2

• Vessel: cylindrical, 160-210 mm high, inside diameter 98-106 mm, nominal capacity is 1000 mL; sides are flanged at the top.

• Shaft: positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble.

Materials of Construction: Shaft and blade are a single entity that may be coated with a suitable inert coating.

• Blade position: the distance between the inside bottom of the vessel and the blade is maintained at 25 +/- 2 mm during the test. The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft.

Apparatus 3

• Reciprocating Cylinder: positioned so that during the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9- 10.1 cm.

• Materials of Construction: Fittings are stainless steel, type 316 or equivalent.

Apparatus 4

• Materials of Construction: Flow-through cell, composed of transparent and inert material, is mounted vertically with a filter system that prevents escape of undissolved particles from the top of the cell. Tube connections are of polytef tubing with 1.6-mm diameter and chemically inert flanged-end connections.

• Cell Assembly: Cell diameters are 12 and 22.6 mm; the apparatus uses a clamp mechanism and two O-rings for the fixation of the cell assembly.

Apparatus 5

• Vessel: cylindrical, 160-210 mm high, inside diameter 98-106 mm, nominal capacity is 1000 mL; sides are flanged at the top.

• Shaft: positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble.

• Materials of Construction: Shaft and blade are a single entity that may be coated with a suitable inert coating. Disk assembly is stainless steel.

• Blade Position: the distance between the surface of the disk assembly and the blade is maintained at 25 +/- 2 mm during the test. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade.

Apparatus 6

• Vessel: cylindrical, 160-210 mm high, inside diameter 98-106 mm, nominal capacity is 1000 mL; sides are flanged at the top.

• Shaft: positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble.

• Materials of Construction: Cylinder stirring element is stainless steel, type 316 or equivalent.

• Cylinder Position: the distance between the inside bottom of the vessel and the cylinder is maintained at 25 +/- 2 mm during the test.

Operational Qualification

Operational Qualification consists of documented evidence that the equipment operates as intended and is capable of consistent operation within established specifications. The operational qualification of a dissolution apparatus should include the following verifications:

• System Suitability (Calibration)

A system suitability test using USP calibrators should be conducted during operational qualification testing. The procedure for dissolution and sampling is outlined in the Certificates supplied with each USP Calibrator tablet for each apparatus. The calibrators used for the test are disintegrating tablets (Prednisone) and non disintegrating tablets (Salicylic Acid). The test is considered successful if the percent of drug released at 30 minutes falls within a pre-established range. The ranges for each combination of apparatus and calibrators at 50 or 100 RPM are established by the USP and are different for each lot of calibrators. This test must be conducted for each of the vessels contained within a dissolution apparatus. For a vessel to be acceptable, it must, individually, provide acceptable drug release from the calibrator [40]. For sample aliquots withdrawn from the vessels, the solutions are analyzed using previously validated HPLC or UV/Vis methods (depending on the monograph) that yield acceptable peak resolution and elution time. The analysis can then be used to create a profile of percent drug released vs. time.

• Validation of Automated Versus Manual Procedures

At a minimum, the following verifications should be included in the operational qualification of an automated dissolution system [41]:

• *Software/hardware Communication*

Verify that the software accurately controls the hardware.

• *Operator Interface Functions*

Verify that the system can be accurately controlled through functions pre-defined by the manufacturer. For example, operator interface testing may include confirming that all menu options are available and that a file can be successfully created and modified.

• *Stress/boundary/challenge Testing*

Verify that the system successfully performs under stress and/or challenge conditions that may be present during operation. For example, stress/boundary/ challenge testing may include confirming that a maximum number of files can be processed simultaneously, or that the system can perform simultaneous functions.

In addition, if the dissolution apparatus employs a computerized system, 21 CFR Part 11 requirements must be considered. At a minimum, the following verifications should be included in the operational qualification:

• *Report Printing/handling*

Verify that all reports defined by the manufacturer are available and accurate.

• *Audit Trail*

Verify that the audit trail accurately captures changes to the system, including file creation, modification, deletion, and data processing.

• *Electronic Signatures*

Verify that electronic signatures are operational and accurate.

Data archival and restoration

Verify that data is successfully archived and restored.

• *Data Integrity*

Verify that data integrity is not compromised during data backup, archival, or restoration functions.

• *System Security*

•Verify that all applicable system security measures are operational (e.g., user name, password, screen saver, automatic time-outs, user level definitions, etc.)

• Validation of Analytical Methods Employed in Quantitative Analysis of Dissolution Samples

Analytical methods used to perform analysis of dissolution should be validated. Generally, this method validation is not part of the operational qualification of the dissolution apparatus. However, validated methods should be employed to analyze the samples withdrawn as part of the system suitability testing performed during the operational qualification.[42]

• Temperature Distribution Study

A temperature distribution study should be conducted during the operational qualification. The study should include temperature mapping of each vessel contained within the dissolution apparatus. Temperature should be mapped using a data acquisition system for a minimum time that is based on the monograph or 1 hour,whichever is greater. The temperature of Apparatus 1, 2, 3, and 4 must remain at 37°C ± 0.5°C; the temperature of Apparatus 5 and 6 must remain at 32°C ± 0.5°C.

• Rotation Speed Study

A rotation speed study should be conducted during the operational qualification. The study should include a measurement of the speed of the shaft rotation for each vessel contained within the dissolution apparatus. Speed should be measured using a photo tachometer for 30 minutes or the time specified in the individual monograph, whichever is greater. The speed of the shaft rotation should be verified to be within 4% of the speed specified in the monograph.[43]

Buffer solutions are solutions which resist to changes in pH. Usually, buffer solutions
consist of a weak acid and its conjugate base (for example CH3COOH/CH3COO□) or
a weak base and its conjugate acid (for example NH_3/NH_4^+.

A buffer solution is formed by partial neutralization of a weak acid with a strong base or of a weak base with a strong acid. Alternatively, buffer solutions can be prepared by mixing the
precalculated concentrations of each of the constituents. The pH of a buffer solution, which is composed of a weak acid HA and its conjugate base A^- is calculated by the Henderson-Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

where Ka is the acid dissociation constant of the weak acid HA and [HA] and [A□] are
the concentrations of HA and A□ in the buffer solution, respectively.

Preparation of a Buffer Solution

Solutions called buffers are remarkably resistant to pH changes caused by the addition of an acid or base.These solutions always contain both the salt of a weak acid or base, as well as the parent acid or base. For example, a buffer solution containing a weak acid, HA, and the anion, A− from its salt, will establish the following equilibrium: $HA(aq) \leftrightarrow H^+(aq) + A^-(aq)$

and the [H+] can be calculated as follows:

$$[H^+] = K_a \frac{[HA]}{[A^-]}$$

If a small amount of strong acid were added to that solution, the H+ ion would tend to react with the A− ion present, forming HA:
$H+ (aq) + A^-(aq) \leftrightarrow HA(aq)$
Similarly, a small amount of strong base added to the solution will react with the HA present to form water and A− ions:
$HA(aq) + OH^-(aq) \leftrightarrow H2O(l) + A^-(aq)$
In both cases, if the ratio [HA]/[A−] changes only slightly, the [H+], and the pH, will remain
approximately constant. If instead similar quantities of strong acid or base are added to the same volume of water, the pH changes by several units.

The objective of this experiment is to prepare a buffer solution and to investigate the changes in pH that occur when known amounts of strong acid and strong base are added to it. These changes will be compared to the pH changes that occur in an identical volume of water.

To prepare a buffer that would tend to have and maintain a given pH value, a solution of a weak acid or base and a solution of the salt of that acid or base is needed. Given the value of Ka of the acid, and the [H+] required in an acid buffer, the formula below can be used to determine the [HA]/[A−] ratio in the buffer.

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

By mixing appropriate volumes of the acid and salt solutions the concentration ratio can easily be obtained and thus the buffer can be made. Buffers will typically have H+ ion concentrations near the Ka values for the weak acid used: if the buffer is to be effective against the addition of both acid and base, the ratio [A−]/[HA] should be approximately one as indicated by the Henderson-Hasselbalch equation:

$$pH = pK + \log \frac{[A^-]}{[HA]}.$$

Preparation of Buffer Solutions

Dilute each of the mixtures to 1 L with distilled water. (NOTE: the pH will not be affected if the volumes are slightly more or less than 1 L.)

Important: The pH of each buffer must be checked and adjusted before being bottled.

• If the pH is too high, adjust the pH to the correct value by adding

1 M HCl, with stirring.
• If the pH is too low, adjust the pH to the correct value by adding 1 M NaOH, with stirring

pH	Mixture
3	10.21 g of potassium hydrogen phthalate + 223 mL of 0.10 M HCl
4	10.21 g of potassium hydrogen phthalate + 1 mL of 0.10 M HCl
5	10.21 g of potassium hydrogen phthalate + 226 mL of 0.10 M NaOH
6	6.81 g of potassium phosphate monobasic + 56 mL of 0.10 M NaOH
7	6.81 g of potassium phosphate monobasic + 291 mL of 0.10 M NaOH
8	6.81 g of potassium phosphate monobasic + 467 mL of 0.10 M NaOH
9	4.77 g of sodium tetraborate + 46 mL of 0.10 M HCl
10	4.77 g of sodium tetraborate + 183 mL of 0.10 M NaOH
11	2.10 g of sodium bicarbonate + 227 mL of 0.10 M NaOH

Composition of Buffer Solutions

In normal water (non-buffered solution) if you add a small amount of a strong acid or base, it will cause the pH of the water to change significantly. Two drops of 1 mol dm-3 HCl added to water will change the pH from 7 to 4.

Acidic buffers

Composition

An acidic buffer is composed of a weak acid (HA) and its conjugate base (A-) or a weak acid and the salt of the weak acid and a strong base.

How to make an acidic buffer

1) Start with a weak acid and strong base of the same concentration (e.g. 0.10 moldm-3).

Take about 25cm3 of a strong base and add an excess moles of a weak acid (50cm3) so that

there is a sufficient number of moles of the weak acid to completely neutralize all the moles of strong base

.Excess weak acid is added so that the resulting solution contains the salt (conjugate base), water and excess weak acid.

OH- (aq) + H+(aq) → A-(aq) + H+(aq)
Limiting excess salt excess weak acid

buffer solution in the buffer the [HA] = [A-]

Or

2) Add equal concentration and volume (equal moles) of a weak acid (HA) and the salt of the weak acid and a strong base (A-).

Alkali / Basic Buffer

Composition

A basic buffer is composed of a weak base (B) and its conjugate acid (BH+) / weak base and the salt of the weak base and a strong acid.

How to make a basic buffer

1) Start with a weak base and strong acid of the same concentration (e.g. 0.10 moldm-3).

Take about 25cm3 of a strong acid and add an excess of weak base (about 50 cm3) so that

there are sufficient moles of the weak base to neutralize all of the strong acid, leaving

excess base in the solution.

OH- (aq) + H+(aq) → A-(aq) + OH-(aq)
excess limiting salt excess weak base

buffer solution in the buffer the [OH-] = [A-]

OR

2) Add equal concentration and volume (equal moles) of a weak base and the salt of the weak base and a strong acid.(38)

Buffer Solutions

A. Standard Buffer Solutions

Standard Buffer Solutions are solutions of standard pH. They are used for reference purposes in pH measurements and for carrying out many pharmacopoeial tests which require adjustments to or maintenance of a specified pH. They may be prepared by the methods described below. The preparation of special buffer solutions is described in the sections in which their use is specified as in the microbiological assay of antibiotics or in the individual monographs where the use of such solutions is indicated. The reagents required for the preparation of standard buffer solutions are described in Appendix 4.2. All the crystalline reagents except boric acid should be dried at 110º to 120º for 1 hour before use. Carbon dioxide-free water should be used for preparing buffer solutions and wherever water is mentioned for preparation of such solutions the use of carbon dioxide-free water is implied. The prepared solutions should be stored in chemically resistant, glass-stoppered bottles of alkakli-free glass and used within 3 months of preparation. Any solution which has become cloudy or shows any other evidence of deterioration should be discarded. Standard buffer solutions for various ranges of pH values 1.2 to 10.0 may be prepared by appropriate combinations of 0.2 M hydrochloric acid or 0.2 M sodium hydroxide and of solutions described below, used in the proportions shown in the accompanying tables. The standard pH values given in the tables and elsewhere in the Appendix are considered to be reproducible within ± 0.02 Unit at 25º.

1. Boric Acid and Potassium Chloride, 0.2 M: Dissolve 12.366 g of boric acid and 14.911 g of potassium chloride in water and

dilute with water to 1000 ml.

2. Disodium Hydrogen Phsophate, 0.2 M: Dissolve 71.630 g of disodium hydrogen phosphate in water and dilute with water to 1000 ml.

3. Hydrochloric Acid, 0.2 M: Hydrochloric acid diluted with water to contain 7.292 g of HCl in 1000 ml. Standardise as directed in Appendix 4.4.

4. Potassium Chloride, 0.2 M: Dissolve 14.911 g of potassium chloride in water and dilute with water to 1000 ml.

5. Potassium Dihydrogen Phosphate, 0.2 M: Dissolve 27.218 g of potassium dihydrogen phosphate in water and dilute with water to 1000 ml.

6. Potassium Hydrogen Phthalate, 0.2 M: Dissolve 40.846 g of potassium hydrogen phthalate in water and dilute with water to 1000 ml.

7. Sodium Hydroxide, 0.2 M: Dissolve sodium hydroxide in water to produce a 40 to 60 per cent w/v solution and allow to stand. Taking precautions to avoid absorption of carbon dioxide, siphon off the clear supernatant liquid and dilute with carbon dioxide-free water a suitable volume of the liquid to contain 8.0 g of NaOH in 1000 ml. Standardise as directed in Appendix 4.4.

Composition of Standard Buffer Solutions

Hydrochloric Acid Buffer: Place 50.0 ml of the 0.2 M potassium chloride in a 200-ml volumetric flask, add the specified volume of 0.2 M hydrochloric acid (see Table 1) and then add water to volume.

TABLE 1.

SNO.	PH	0.2 M HCL , ml
1	1.2	85.0
2	1.3	67.2
3	1.4	53.2
4	1.5	41.4
5	1.6	32.4
6	1.7	26.0
7	1.8	20.4
8	1.9	16.2
9	2.0	13.0
10	2.1	10.2
11	2.2	7.8

Acid Phthalate Buffer: Place 50.0 ml of 0.2 M potassium hydrogen phthalate in a 200-ml volumetric flask, add the specified volume of 0.2 M hydrochloric acid (see Table 2) and then add water to volume.

TABLE 2.

SNO.	PH	0.2 M HCL , ml
1	2.2	49.5
2	2.4	42.2
3	2.6	35.4
4	2.8	28.9
5	3.0	22.3
6	3.2	15.7
7	3.4	10.4
8	3.6	6.3
9	3.8	2.9
10	4.0	0.1

Neutralised Phthalate Buffer; Phthalate Buffer: Place 50.0 ml of 0.2 M potassium hydrogen phthalate in a 200-ml volumetric flask, add the specified volume of 0.2 M sodium hydroxide (see Table 3) and then add water to volume.

TABLE:-3

SNO.	PH	0.2M NaOH, ml
1	4.2	3.0
2	4.4	6.6
3	4.6	11.1
4	4.8	16.5
5	5.0	22.6
6	5.2	28.8
7	5.4	34.1
8	5.6	38.1
9	5.8	42.3

Phosphate Buffer: Place 50.0 ml of 0.2 M potassium dihydrogen phosphate in a 200-ml volumetric flask, add the specified volume of 0.2 M sodium hydroxide and then add water to volume.(TABLE 4

SNO.	PH	0.2M NaOH, ml
1	5.8	3.6
2	6.0	5.6
3	6.2	8.1
4	6.4	11.6
5	6.6	16.4
6	6.8	22.4
7	7.0	29.1
8	7.2	34.7
9	7.4	39.1
10	7.6	42.4
11	7.8	44.5
12	8.0	46.1

Alkaline Borate Buffer: Place 50.0 ml of 0.2 M boric acid and potassium chloride in a 200-ml volumetric flask, add the specified volume of 0.2 M sodium hydroxide (see Table 5) and then add water to volume.

TABLE 5.

SNO.	PH	0.2M NaOH, ml
1	8.0	3.9
2	8.2	6.0
3	8.4	8.6
4	8.6	11.8
5	8.8	15.8
6	9.0	20.8
7	9.2	26.4
8	9.4	32.1
9	9.6	36.9
10	9.8	40.6
11	10.0	43.7

Other Buffer solutions

Acetate Buffer pH 2.8: Dissolve 4 g of anhydrous sodium acetate in about 840 ml of water, add sufficient glacial acetic acid to adjust the pH to 2.8 (about 155 ml) and dilute with water to 1000 ml.

Acetate Buffer pH 3.4: Mix 50 ml of 0.1 M sodium acetate with 950 ml of 0.1 M acetic acid.

Acetate Buffer pH 3.5: Dissolve 25 g of ammonium acetate in 25 ml of water and add 38 ml of 7 M hydrochloric acid. Adjust the pH to 3.5 with either 2 M hydrochloric acid or 6 M ammonia and dilute with water to 100 ml.

Acetate Buffer pH 3.7: Dissolve 10 g of anhydrous sodium acetate in 300 ml of water, adjust to pH to 3.7 with glacial acetic acid and dilute with water to 1000 ml. Before use adjust to pH 3.7, if necessary, with glacial acetic acid or anhydrous sodium acetate, as required.

Acetate Buffer pH 4.0: Place 2.86 ml of glacial acetic acid and 1.0 ml of a 50 per cent w/v solution of sodium hydroxide in a 1000-ml volumetric flask, add water to volume and mix. Adjust the pH, if necessary.

Acetate Buffer pH 4.4: Dissolve 136 g of sodium acetate and 77 g of ammonium acetate in water and dilute with water to 1000 ml. Add 250 ml of glacial acetic acid and mix.

Acetate Buffer pH 4.6: Dissolve 5.4 g of sodium acetate in 50 ml of water, add 2.4 ml of glacial acetic acid and dilute with water to 100 ml. Adjust the pH, if necessary.

Acetate Buffer pH 4.7: Dissolve 8.4 g of sodium acetate and 3.35 ml of glacial acetic acid in sufficient water to produce 1000 ml. Adjust the pH, if necessary.

Acetate Buffer pH 5.0: Dissolve 13.6 g of sodium acetate and 6 ml of glacial acetic acid in sufficient water to produce 1000 ml. Adjust the pH, if necessary.

Acetate Buffer pH 5.5: Dissolve 272 g of sodium acetate in500 ml of water by heating to 35º, cool and add slowly 50 ml of glacial acetic acid and sufficient water to produce 1000 ml. Adjust the pH, if necessary.

Acetate Buffer pH 6.0: Dissolve 100 g of ammonium acetate in 300 ml of water, add 4.1 ml of glacial acetic acid, adjust the pH, if necessary, using 10 M ammonia or 5 M acetic acid and dilute with water to 500 ml.

Acetate Buffer Solution: Dissolve 14 g of potassium acetate and 20.5 ml of glacial acetic acid in sufficient water to produce 1000 ml.

Acetic Acid-Ammonium Acetate Buffer: Dissolve 77.1 g of ammonium acetate in water, add 57 ml of glacial acetic acid and dilute with water to 1000 ml.

Acetic Ammonia Buffer pH 3.7, Ethanolic: To 15 ml of 5 M acetic acid add 60 ml of ethanol (95 per cent) and 24 ml of water. Adjust the pH to 3.7 with 10 M ammonia and dilute with water to 100 ml.

Acetone Solution, Buffered: Dissolve 8.15 g of sodium acetate and 42 g of sodium chloride in water, add 68 ml of 0.1 M hydrochloric acid and 150 ml of acetone and dilute with water to 500 ml.

Albumin Phosphate Buffer pH 7.2; Phosphate-albumin Buffered Saline pH 7.2: Dissolve 10.75 g of disodium hydrogen phosphate, 7.6 g of sodium chloride and 10 g of bovine albumin in sufficient water to produce 1000 ml. Before use adjust to pH 7.2 with 2M sodium hydroxide or a 10 per cent w/v solution of phosphoric acid as required.

Ammonia-Ammonium Chloride Buffer: Dissolve 67.5 g of ammonium chloride in about 200 ml of water, add 570 ml of strong ammonia solution and dilute with water to 1000 ml.

Ammonia Buffer pH 9.5: Dissolve 33.5 g of ammonium chloride in 150 ml of water, and 42 ml of 10 M ammonia and dilute with water to 250 ml. Store in polyethylene containers.

Ammonia Buffer pH 10.0: Dissolve 5.4 g of ammonium chloride in 20 ml of water, add 35 ml of 10 M ammonia and dilute with water to 100 ml.

Ammonia Buffer pH 10.9: Dissolve 67.5 g of ammonium chloride in sufficient 10 M ammonia to produce 1000 ml.

Barbitone Buffer pH 7.4: Mix 50 ml of solution containing 1.944 per cent w/v of sodium acetate and 2.946 per cent w/v of barbitone sodium with 50.5 ml of 0.1 M hydrochloric acid, add 20 ml of an 8.5 per cent w/v solution of sodium chloride and dilute with water to 250 ml.

Barbitone Buffer pH 8.6, Mixed; Barbitone Buffer pH 8.6: Dissolve 1.38 g of barbitone, 8.76 g of barbitone sodium and 0.38 g of calcium lactate in sufficient water to produce 1000 ml.

Boric Buffer pH 9.0; Borate Buffer pH 9.0: Dissolve 6.20 g of boric acid in 500 ml of water, adjust to pH 9.0 with 1 M sodium hydroxide (about 41.5 ml) and dilute with water to 1000 ml.

Buffer Solution pH 2.5: To 25.0 ml of 0.2 M potassium hydrogen phthalate add 37.0 ml of 0.1 M hydrochloric acid and dilute with sufficient water to produce 100.0 ml.

Buffer (HEPES) solution pH 7.5: Dissolve 2.38 g of 2[4-(hydroxyethyl)piperazin-1-yl]ethanesulphonic acid in about 90 ml of water. Adjust the pH to 7.5 with sodium hydroxide

solution. Dilute to 100 ml with water.

Carbonate Buffer pH 9.7: Dissolve 8.4 g of sodium bicarbonate and 10.6 g of sodium carbonate in sufficient water to produce 500 ml.

Chloride Buffer pH 2.0: Dissolve 6.57 g of potassium chloride in water, add 119.0 ml of 0.1 M hydrochloric acid and dilute with water to 1000 ml.

Citro-phosphate Buffer pH 5.0: Mix 48.5 ml of 0.1 M citric acid with sufficient 0.2 M disodium hydrogen phosphate to produce 100 ml.

Citro-phosphate Buffer pH 6.0: Mix 36.8 ml of a 2.1 per cent w/v solution of citric acid with 63.2 ml of a 7.15 per cent w/v solution of disodium hydrogen phosphate.

Citro-phosphate Buffer pH 7.0: Mix 17.6 ml of a 2.1 per cent w/v solution of citric acid with 82.4 ml of a 7.15 per cent w/v solution of disodium hydrogen phosphate.

Citro-phosphate Buffer pH 7.2: Mix 13.0 ml of a 2.1 per cent w/v solution of citric acid with 87.0 ml of a 7.15 per cent w/v solution of disodium hydrogen phosphate.

Citro-phosphate Buffer pH 7.6: Dissolve 1.33 g of citric acid and 67.1 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml.

Cupric Sulphate Solution pH 2.0, Buffered: Mix 5.3 ml of 0.2 M hydrochloric acid and 25 ml of 0.2 M potassium chloride, add 4 ml of a 0.393 per cent w/v solution of cupric sulphate and dilute to 100 ml of water.

Cupric Sulphate Solution pH 4.0, Buffered: Dissolve 0.25 g cupric sulphate and 4.5 g of ammonium acetate in sufficient water to produce 100 ml.

Cupric Sulphate Solution pH 5.2, Buffered: Dissolve 1.522 g of anhydrous disodium hydrogen phosphate in sufficient water to produce 53.6 ml and add a 2.1 per cent solution of
citric acid until the pH of the solution is between 5.15 and 5.25 (about 46 ml). Mix 98.5 ml of the resulting solution with 1.5 ml of a 0.393 per cent solution of cupric sulphate.

Diethanolamine Buffer pH 10.0: Dissolve 96.4 g of diethanolamine in sufficient water to produce 400 ml. Add 0.5 ml of an 18.6 per cent w/v solution of magnesium chloride, adjust the pH to 10.0.with 1 M hydrochloric acid and dilute with water to 500 ml.

Glycine Buffer pH 11.3: Mix a solution containing 0.75 per cent w/v of glycine and 0.58 per cent w/v of sodium chloride with an equal volume of 0.1 M sodium hydroxide. Adjust the pH if necessary.

Glycine Buffer Solution: Mix 42 g of sodium bicarbonate and 50 g of potassium bicarbonate with 180 ml of water and add a solution containing 37.5 g of glycine and 15 ml of strong ammonia in 180 ml of water. Dilute with water to 500 ml and stir until solution is complete.

Imidazole Buffer pH 6.5: Dissolve 6.81 g of imidazole and 1.23 g of magnesium sulphate in 752 ml of 0.1 M hydrochloric acid, adjust the pH if necessary and dilute with water to produce 1000 ml.

Imidazole Buffer pH 7.4: Dissolve 3.40 g of imidazole and 5.84 g of sodium chloride in water, and 18.6 ml of 1 M hydrochloric acid and dilute with water to produce 1000 ml.

Palladium Chloride Solution, Buffered: To 0.5 g of palladium chloride add 5 ml of hydrochloric acid and warm on a waterbath. Add 200 ml of hot water in small portions with continued heating until solution is complete. Cool and dilute with sufficient water to produce 250.0 ml. To 50.0 ml of the resulting solution add 10.0 ml of 1 M sodium acetate, 9.6 ml of 1 M hydrochloric acid and sufficient water to produce 100.0 ml.

Phosphate-albumin buffered saline pH 7.2: Dissolve 10.75 g of disodium hydrogen phosphate, 7.6 g of sodium chloride and 10 g of bovin albumin in water and dilute to 1000.0 ml with the same solvent. Immediately before use adjust the Ph (2.4.24)using dilute sodium hydrogen solution or dilute phosphoric acid.

Phosphate Buffer pH 2.0: Dissolve 0.136 g of potassium dihydrogen phosphate in 800 ml of water, adjust the pH to 2.0 with hydrochloric acid and add sufficient water to produce 1000 ml.

Phosphate Buffer pH 2.5: Dissolve 100 g of potassium dihydrogen phosphate in 800 ml of water, adjust the pH to 2.5 with hydrochloric acid and add sufficient water to produce
1000 ml.

Phosphate Buffer pH 3.6: Dissolve 0.900 g of anhydrous disodium hydrogen phosphate and 1.298 g of citric acid monohydrate in sufficient water to produce 1000 ml.

Phosphate Buffer pH 4.0, Mixed: Dissolve 5.04 g disodium hydrogen phosphate and 3.01 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml. Adjust the pH with glacial acetic acid.

Phosphate Buffer pH 4.9: Dissolve 40 g of sodium dihydrogen phosphate and 1.2 g of sodium hydroxide in sufficient water to produce 100 ml. If necessary, adjust the pH with 1 M
sulphuric acid or 1 M sodium hydroxide as required.

Phosphate Buffer pH 5.0: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 ml of water and adjust the pH to 5.0 with 10 M potassium hydroxide.

Phsophate Buffer pH 5.5, Mixed

SOLUTION I — Dissolve 13.61 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

SOLUTION II — Dissolve 35.81 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml.

Mix 96.4 ml of solution I with 3.6 ml of solution II.

Phosphate Buffer pH 6.5: Dissolve 60.5 g of disodium hydrogen phosphate and 46 g of potassium dihydrogen phosphate in water, add 100 ml of 0.02 M disodium edentate and 20 mg of mercuric chloride and dilute with water to produce 1000 ml.

Phosphate Buffer pH 6.8, Mixed: Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Phosphate Buffer pH 6.8, 0.2 M Mixed: Dissolve 13.872 g of potassium dihydrogen phosphate and 35.084 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml. Store in a cold place.

Phosphate Buffer pH 7.0, Mixed: Dissolve 0.50 g of anhydrous disodium hydrogen phosphate 0.301 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Phosphate Buffer pH 7.0 with Azide, Mixed: To 1000 ml of a solution containing 1.8 per cent w/v of disodium hydrogen phosphate and 2.3 per cent w/v of sodium chloride, add sufficient of a solution containing 0.78 per cent w/v of sodium dihydrogen phosphate and 2.3 per cent w/v of sodium chloride (about 280 ml) to produce a pH of 7.0. Dissolve sufficient sodium azide in the resulting solution to give a 0.02 per cent w/v solution.

Phosphate Buffer pH 7.0, 0.067 M Mixed: Dissolve 3.532 g of potassium dihydrogen phosphate and 14.542 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml.

Phsophate Buffer pH 7.5, 0.33 M Mixed

SOLUTION I — Dissolve 119.31 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml.

SOLUTION II — Dissolve 45.36 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Mix 85 ml of solution I and 15 ml of solution II and adjust the pH if necessary.

Phosphate Buffer pH 8.0, 0.02 M: Mix 50 ml of 0.2 M potassium dihydrogen phosphate with 46.8 ml of 0.2 M sodium hydroxide and add sufficient water to produce 500 ml.

Phosphate Buffer, 0.025 M Standard: Dissolve 3.40 g of potassium dihydrogen phosphate and 3.55 g of anhydrous disodium hydrogen phosphate, both previously dried at 110º to 130º for 2 hours, in sufficient water to produce 1000 ml.

Saline, Phosphate-buffered: Dissolve 2.5 g of sodium dihydrogen phosphate, 2.523 g of disodium hydrogen phosphate and 8.2 g of sodium chloride in sufficient water to produce 1000 ml.

Saline pH 6.4, Phosphate-buffered: Dissolve 1.79 g of disodium hydrogen phosphate, 1.36 g of potassium dihydrogen phosphate and 7.02 g of sodium chloride in sufficient water to produce 1000 ml.

Saline pH 7.4, Phosphate-buffered: Dissolve 2.38 g of disodium hydrogen phosphate, 0.19 g of potassium dihydrogen phosphate and 8.0 g of sodium chloride in sufficient water to produce 1000 ml. Adjust the pH if necessary.

Tris-acetate buffer solution pH 8.5: Dissolve 0.294 g of calcium chloride of tris(hydroxymethyl)aminomethane in water. Adjust the pH(2.4.24) with acetic acid. Dilute to 1000.0 ml with water.

Tris(hydroxymethyl)aminomethane buffer solution pH 7.4: Dissolve 30.3 g of tris(hydroxymethyl)aminimethane in approximately 200 ml of water. Add 183 ml of 1 M hydrochloric acid. Dilute to 500.0 ml with water.[45]

NOTE — The pH is 7.7-7.8 at room temperature and 7.4 at 37º. This solution is stable for several months at 4º.

Conclusion:- In this above study we get familiar with the different dissolution apparatus the buffers which are used in it and we now know that how dissolution is very much necessary and how we have to make the different types of buffers.

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