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**Review Article**

# ADVANCES IN DISSOLUTION TECHNOLOGIES: A REVIEW

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**ABSTRACT**

*In vitro* performance tests, such as dissolution tests, are performed for orally administered non-solution dosage forms for a variety of reasons. It is one of the quality control tests for oral solid dosage forms that are performed on a regular basis. Dissolution research began around 100 years ago as a field of physical chemistry and significant progress has been made since then. Aside from its significance in pharmaceutical analysis, it is also significant in pharmaceutical formulation technology and drug discovery. In this review paper, we will concentrate on various mathematical aspects of the dissolution process and the various dissolution apparatuses that are in use. We will go over some non-traditional dissolution testing methods. The main applications of the dissolution testing include biopharmaceutical characterization of the drug product, as a tool to ensure consistent product quality and to predict *in vivo* drug bioavailability. Dissolution testing was initially developed for solid orals, but its application has since expanded to a variety of novel dosage forms. The goal of this review is to represent all of the potential standardized test methods that are required to characterize the dissolution properties of a wide range of dosage forms, from traditional to novel delivery.



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## 1. INTRODUCTION

The process by which a solid solute enters a solution is known as dissolution. Dissolution is the process by which a solid solute enters a solution in the pharmaceutical industry. It is defined in the pharmaceutical industry as the amount of drug substance that enters solution per unit time under standardized liquid/solid interface, temperature, and solvent composition conditions. Drug dissolution testing is important as a routine quality control test for characterizing product quality and also plays an important role in drug development(1). Pharmacopeias use dissolution testing to evaluate drug release from solid and semisolid dosage forms. The first dissolution tests were developed to quantify the amount and extent of drug release from solid oral dosage forms such as immediate/sustained release tablets and capsules(2). Dissolution has recently become important in testing drug release from dosage forms such as buccal and sublingual tablets, chewing gums, soft gelatin capsules, suppositories, transdermal patches, aerosols, and semisolids have all been studied by physical chemists since the end of the nineteenth century. The goal is to have a complete set of USP performance tests for all dosage forms(3).

Despite advances in invitro dissolution in chemical engineering sciences, the concept was not widely used in pharmaceutical sciences until the early 1950s. Until then, it was assumed that the drug's *in vivo* availability was determined solely by tablet disintegration, ignoring the dissolution process. *In vitro* performance test procedures such as dissolution and disintegration are used for orally administered non-solution dosage forms to I guide drug development and select formulations for further *in vivo* studies, ii) evaluate comparability between products before and after changes in formulation and/or manufacturing, and iii) serve as a surrogate for *in vivo* bioequivalence studies, with suitable *in vitro*/*in vivo* correlations and/or use of the Biopharmaceutics Classification System approach, and iv) ) ensure batch-to-batch consistency for product performance(4). A dissolution test measures the rate of release of the drug. The objective is to develop a discriminatory method that is sensitive to variables that affect the dissolution rate. Such variables may include characteristics of the active pharmaceutical ingredient (API) (e.g., particle size, crystal form, bulk density), drug product composition (e.g., drug loading, and the identity, type, and levels of excipients), the drug product manufacturing process (e.g., compression forces, equipment), and the effects of

stability storage conditions (e.g., temperature, humidity)(5). At early stages of formulation development, *in vitro* dissolution testing provides guidance on optimizing drug release from formulations. Such variables may include characteristics of the active pharmaceutical ingredient (API) (e.g., particle size, crystal form, bulk density), drug product composition (e.g., drug loading, and the identity, type, and levels of excipients), the drug product manufacturing process (e.g., compression forces, equipment), and the effects of stability storage conditions (e.g., temperature, humidity). At early stages of formulation development, *in vitro* dissolution testing provides guidance on optimizing drug release from formulations. While at later stages, it may be employed as an indicator of the *in vivo* performance of drug products to potentially reduce the number of bioavailability/ bioequivalence studies(6). The connection between the dissolution test and *in vivo* performance is based on the fact that before an active pharmaceutical agent can be absorbed, it must first be dissolved in the aqueous contents of the gastrointestinal (GI) tract. Because there is no other *in vitro* performance test with such a close link to *in vivo* performance, dissolution and drug release studies are a regulatory requirement for the development, and ultimate approval, of all solid oral drug products(7, 8, 9). It is evident that the release profile and thus absorption of drug may be influenced by design and operation of the apparatus, and the selection of medium, USP describes the various apparatuses used in dissolution studies, and has been recently harmonized with the European Pharmacopoeia and the Japanese Pharmacopoeia(10). Several guidelines are available for the development and application of dissolution testing in various FIP position papers and regulatory guideline are also available. Dissolution research started to develop about 100 years ago as a field of physical chemistry and since then important progress has been made(11). History on developments with dissolution testing is given in **Table 1.**

**Table 1:** History on developments with dissolution testing

| Year | Contributor (s) | Major contribution |
|---|---|---|
| 1897 | Noyes AN and Whitney WR | Conducted the first dissolution experiments and published an article entitled "the rate of solution of solid substances in their own solutions". Noyes- Whitney equation |
| 1900 | Brunner E and von Tolloczko S | Showed that the rate of dissolution depends on the exposed surface, the rate of stirring, temperature, structure of the surface and the arrangement of the apparatus. |
| 1904 | Nernst W and Brunner E | Nernst–Brunner equation based on the diffusion layer concept and Fick's second law. |
| 1931 | HixsonAW and Crowell JH | Dependence of reaction velocity upon surface and agitation. Hixson and Crowell reported that the Noyes–Whitney equation in its original form and without any details about the mechanism of the process had been sufficiently validated with a wide range of experiments, as opposed to the various mechanistic explanations that had appeared, none of which was entirely satisfactory. |
| 1951 | Edwards LJ | First to appreciate that following the oral administration of solid dosage forms, if the absorption process of drug from the gastrointestinal tract is rapid, then the rate of dissolution of that drug can be the step which controls its appearance in the body. |
| 1957 | Nelson E | First to explicitly relate the blood levels of orally administered drugs (theophylline salts) to their *in vitro* dissolution rates. |
| 1961 | Higuchi T | Reviewed the interfacial barrier model proposed by Wilderman in 1909 and Danckwerts model (1951). |
| 1962 | Levich VG | Improved the theoretical model of the dissolution experiment using rotating disks, taking into account the centrifugal force on diffusion. |
| 1970 | | The basket-stirred-flask test (USP apparatus 1) was adopted as an official dissolution test in 6 monographs of the United States Pharmacopeia (USP) and National Formulary (NF). |
| 1978 | | Adoption of the paddle method (USP apparatus 2). |
| 1981 | | The first guidelines for dissolution testing of solid dosage forms were published as a joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists of the FIP. |
| 1991 | | Adoption of the reciprocating cylinder (USP apparatus 3) for extended-release products. |
| 1995 | | Adoption of the flow-through cell in (USP apparatus 4) for extended-release products. |

Major contributions and events in the development of dissolution testing

## 2. Interrelation between Dispersion and Drug Dissolution/Absorption

Dispersion is a technique that results in the dispersion or embedding of one substance in another molecule or continuous phase. A dispersion can be classified in several ways based on the size and state of the dispersed matter(12). Dispersions are classified into three types: coarse dispersions (suspensions), colloidal dispersions (nanoparticles), and molecular dispersions (true solution, liquid or solid state). The term "dispersion" refers to the formation of reversible agglomerate containing two or more substances via van der Waals forces, hydrogen bonds, hydrophobic interaction, and/or physical entanglement rather than covalent bonds. Dispersing a drug in another material is an efficient method of overcoming the intermolecular force between drug molecules and achieving rapid dissolution(12, 13). Preparing dissolution-unconfined dispersions for BCS II medicines is a viable technique to increase oral absorption. However, for BCS IV medicines, simply exceeding the solubility limit using a dispersion approach is insufficient to boost absorption. It must overcome both dissolution and absorption barriers at the same time(14). Formulation strategies that have both a dispersion and an absorption-promoting impact are fundamentally necessary to create. Because of their excellent biocompatibility and contact with the cell membrane, lipid-based formulations have shown considerable promise in improving absorption(15).

## 3. Biopharmaceutics Classification System

The drugs are classified in BCS on the basis of solubility, permeability, and dissolution.

Solubility class boundaries are based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5(16).

Permeability class boundaries are based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. A drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose(17).

For dissolution class boundaries, an immediate release product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 15 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900 ml or less in the following media: 0.1 M HCl

or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid(18).

According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability:

- **Class I - high permeability, high solubility**
  - Example: metoprolol, paracetamol
  - Those compounds are well absorbed and their absorption rate is usually higher than excretion.
- **Class II - high permeability, low solubility**
  - Example: Glibenclamide, bicalutamide, ezetimibe, aceclofenac
  - The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found.
- **Class III - low permeability, high solubility**
  - Example: cimetidine
  - The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
- **Class IV - low permeability, low solubility**
  - Example: Bifonazole
  - Those compounds have a poor bioavailability. Usually, they are not well absorbed over the intestinal mucosa and a high variability is expected.

## 4. *IVIVC* AND BIOPHARMACEUTICAL CLASSIFICATION SYSTEMS

The BCS is defined as "the scientific basis for identifying pharmacological compounds based on their aqueous solubility and intestinal permeability," according to FDA standards. The BCS considers three primary parameters that affect the rate and degree of drug absorption from Immediate Release (IR) Solid Oral dosage forms, including dissolution, solubility, and intestinal permeability, when paired with drug product dissolution(19- 21).

The BCS is a key guideline for evaluating the conditions under which in-vitro in-vivo correlations are likely to occur(22). It is also employed in the development of the in-vitro dissolution specification. The classification is linked to the drug dissolution and absorption model, which specifies the essential parameters that influence drug absorption as a set of dimensionless numbers called the Absorption, Dissolution, and Dose numbers(23).

### 4.1. Dissolution number

The Absorption number is the ratio of the mean residence time to the absorption time. The Dissolution number is a ratio of mean residence time to mean dissolution time. The Dose number is the mass divided by an uptake volume of 250 ml and the drug's solubility(24).

### 4.2. Characteristics of Drugs of Types BCS classes

Class I drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. (25) Bioavailability and dissolution are very rapid. So, bioavailability and bioequivalence studies are unnecessary for such product. IVIVC cannot be expected. These compounds are highly suitable for design the SR and CR formulations(26).

Class II drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number. These drugs exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. IVIVC is usually accepted for class II drugs(27).

For Class III drugs permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement in permeability(28).

For Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability and gastric emptying form the rate limiting steps for the drug absorption. These are unsuitable for controlled release(29).

For Class V drugs are those ones that do not come under the purview of BCS classification but includes the drugs whose absorption is limited owing to their poor stability in the GI milieu(30)

- Gastric instability
- Complication in GI lumen
- High first pass metabolisms

## 5. *IN VITRO* DISSOLUTION

The release of the drug substance from the drug product, the dissolving or solubilization of the drug under physiological conditions, and the permeability throughout the

gastrointestinal system all influence drug absorption from a solid dosage form after oral administration. Because the first two phases are so important, the *in vitro* dissolution could be useful in predicting *in vivo* performance(31).

*In vitro* dissolution studies are used in the drug development process to assess a drug product's lot-to-lot quality, guide the development of new formulations, and ensure that product quality and performance are maintained after certain changes, such as changes in the formulation, manufacturing process, manufacturing site, and manufacturing process scale-up(32). Dissolution, on the other hand, is used by the IVIVC as a substitute for drug bioavailability. As a result, more stringent dissolution conditions for the *in vivo* waiver may be required. To construct an IVIVC, a dissolving methodology that can discriminate between study formulations with varied release patterns and best reflects *in vivo* behavior should be adopted(33).

## 6. COMPENDIAL METHODS

According to USP 30, the official dissolution apparatus are classified into 7 types: USP Apparatus 1-basket, USP Apparatus 2-paddle, USP Apparatus 3-reciprocating cylinder, USP Apparatus 4-flow-through cell, USP Apparatus 5-paddle-over-disk, USP Apparatus 6-rotating cylinder, and USP Apparatus 7-reciprocating holder(34). In Indian Pharmacopoeia, only two apparatuses are official: IP Apparatus 1-paddle, and IP Apparatus 2-basket(35). In British and Japanese Pharmacopoeia apparatuses 1, 2 and 4 Pharmacopoeia apparatuses 1, 2 and 4 official, whereas in European Pharmacopoeia apparatus 1, 2, 3, 4, 5 and 6 are official, Selection of dissolution apparatus and method depends upon the dosage form and intention of dissolution(36).

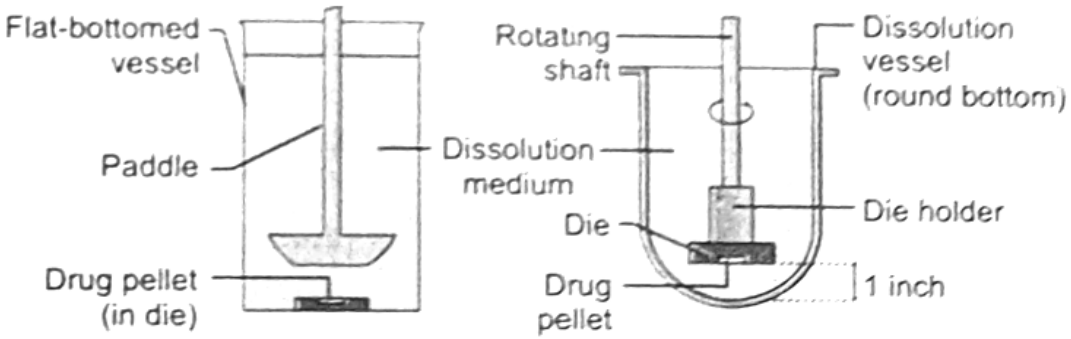
### 6.1. Basket Apparatus (USP Apparatus 1)

The basket method was first described in 1968 by Pernarowski, Woo, and Searl. The apparatus consists of a motor, a metallic drive shaft, a cylindrical basket and a covered vessel made of glass or other inert transparent material. The contents are held at 37°0.5°C. The bath liquid is kept in constant and smooth motion during the test and there should be no significant motion, agitation, or vibration caused by anything other than the smoothly rotating stirring element. Ideally, the apparatus should provide clear observation of the stirring element and sample. The vessel is cylindrical with a hemispherical bottom and flanged upper rim. It is 160–175 mm high and has an inside diameter of 98-106 mm, and a nominal capacity of 1000 ml. A fitted cover may be used to retard evaporation but should provide sufficient openings to allow ready insertion of a shaft and a thermometer, and allow withdrawal of samples.

The shaft is positioned so that its axis is within 2 mm of the axis of the vessels and the lower edge of the blade is 23 to 27 mm from the inside bottom of the vessel, and should rotate smoothly, without significant wobble. The shaft rotation speed should be main individual monograph using motor with a speed regulator. The shaft has a vent and three spring clips to fit the basket into position. Basket is fabricated of stainless steel, type 316 or equivalent. Welded seam, stainless steel cloth (40 mesh or 425 mm) is used, unless an alternative is specified. For acidic media, 2.5 mm thick gold coating on the basket may be used(40).

**6.2. Paddle Apparatus (USP Apparatus 2)**

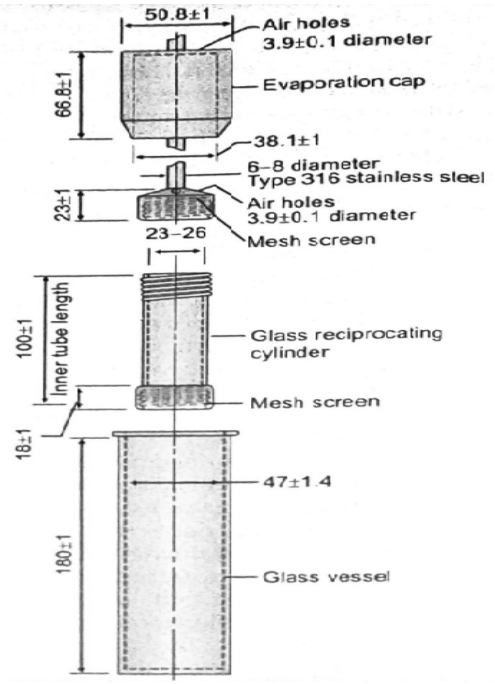
In this apparatus, a paddle replaces the basket as the source of agitation. As with the basket apparatus, the shaft should be positioned no more than 2 mm at any point away from the vertical axis of the vessel and rotate without any significant wobble. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating to prevent corrosion. The dosage form is allowed to sink to the bottom of the flask before rotation of the blade commences(41).




(A) Stationary disk apparatus (B) Rotating disk apparatus

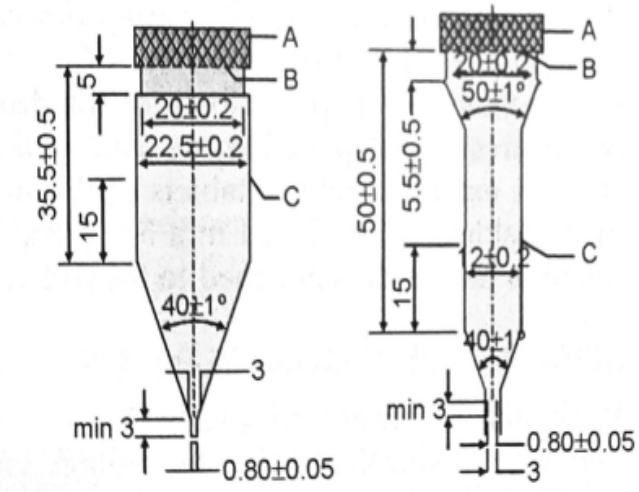
**6.3. Reciprocating Cylinder Apparatus (USP Apparatus 3)**

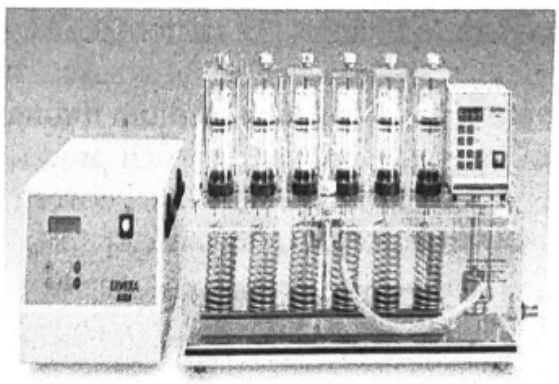
Reciprocating Cylinder Apparatus consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material), and screens that are made up of suitable non-sorbing and non-reactive material and that are designed to fit into the tops and bottoms of the reciprocating cylinders. It has been designed to allow the tubes to be dipped sequentially in up to six different media vessels, using programs that vary the speed and duration of immersion. It allows automated testing for up to six days and the manufacturers advocate its use in the testing of extended-release dosage forms.




**6.4. Flow through cell Apparatus (USP Apparatus 4)**

The assembly consists of a reservoir and a pump for the Dissolution Medium; a flow through cell; a water bath that maintains the Dissolution Medium at 37 ± 0.5. The cell size is specified in the individual monograph. The pump forces the Dissolution Medium upwards through the flow-through cell. Place the glass beads into the cell specified in the monograph, Place 1 dosage unit on top of the beads or, if specified in the monograph, on a wire carrier and then assemble the filter head, and fix the parts together by means of a suitable clamping device. By introducing the pump, the Dissolution Medium warmed to 37 ± 0.5 through the bottom of the cell to obtain the flow rate specified in the individual monograph.



**6.5. Paddle-over-disk Apparatus (USP Apparatus 5)**

This uses the paddle apparatus (USP 2) with the sample, usually a transdermal delivery system, being attached to a stainless-steel disk, which is then placed at the bottom of the vessel, directly under the paddle(42).

### 6.6. Rotating Cylinder Apparatus (USP Apparatus 6)

This is a modification of the basket apparatus a with the basket being replaced by a stainless-steel cylinder. This apparatus is generally used for transdermal delivery systems by attaching to the outside of the cylinder.

### 6.7. Reciprocating Holder Apparatus (USP Apparatus 7)

Apparatus consists of a sample holder that oscillates up and down in the medium vessel. The sample holder may take the form of a disk, cylinder, or a spring on the end of a stainless steel or acrylic rod, or it may simply be a rod alone. This apparatus may be used for transdermal products, coated drag delivery systems, or osmotic pump devises. The sample is attached to the outside of 5 sample holder. It is prescribed for the tree release testing of pseudoephedrine hydrochloride extended-release tablets USP, when in the tablets are enclosed in a 5 x 5 cm nylon, which is then attached to the rod(43).

## 7. Bio-relevant Dissolution Media

Compendial dissolution media often fail to yield IVIVC's for class 2 drugs because relevant physiological parameters are not taken into account. A suitable *in vitro* model should include a medium that mimics as much as possible the GIT contents after food intake. Biorelevant *in vitro* dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs(44). These biorelevant media can be used to assess the performance of different formulations for poorly water-soluble compounds. Biorelevant media have been successfully applied over the past decade to obtain IVIVCs. Two bio-relevant dissolution media simulating conditions in the proximal small intestine FaSSIF and FeSSIF were proposed in 1998(45). Bio-relevant dissolution methods, combined with permeability measurements and computational simulations, were used to predict the oral absorption of drug. Due to their complex composition, these media are expensive and need to be prepared on the day of the experiment.

The properties of GI fluid change in both fasted and fed states, affecting solubility. Several physiochemical and physiological properties of GI fluids, such as pH, buffer capacity, bile component content, aggregation state, and enzyme activity, have a significant impact on the dissolution process(45). The composition of GI fluid is important for GI fluid simulation because a convenient alternative may aid routine and experimental *in vitro* dissolution work after mimicking biological(46).

| Media constituents | Quantity |
|---|---|
| **FaSSGF,pH 1.8** | |
| Sodium chloride | 2g |
| Hydrochloride acid, conc. | 3g |
| Triton X 100 | 1g |
| Deionized water qs ad gs | 1L |
| **Blank FaSSIF, pH 6.5** | |
| NaH2PO4 x H2O | 3.4.38g |
| NaCl | 6.186g |
| NaOH | 0.348g |
| Deionized water qs ad | 1L |
| **Blank FeSSIF, pH 5.0** | |
| Glacial acetic acid | 8.56g |
| NaCl | 11.874g |
| NaOH pellets | 4.04g |
| Deionized water qs ad | 1L |
| **SCOF, pH 5.8** | |
| 1M Acetic acid | 170ml |
| 1M NaOH | 157ml |
| Deionized water qs ad | 1L |
| **SGFsp, pH 1.2** | |
| Sodium chloride | 2g |
| Hydrochloric acid con | 7g |
| Deionized water qs ad | 1L |
| **FaSSIF** | |
| Sodium taurocholate | 8.25g |
| Lecithin | 2.954g |
| Blank FeSSIF qs ad | 1L |

## 7. Modernization in Dissolution Testing

### 7.1. Automation in dissolution testing

Laboratories automate dissolution tests to increase capacity, improve accuracy and reduce costs per test. These factors lead one to consider automation as a method of choice for a quality-control laboratory as well as for a research laboratory. In addition, the emerge of service laboratories testing samples outsourced from pharmaceutical companies calls for automation to offer clients an economic service. With the widespread acceptance of dissolution testing in pharmaceutical industry various automated procedures have been developed(47).

### 7.2. Fiber optics technology

Proposals for a new general chapter on dissolution in the USP have highlighted the use of this technology and a regulatory perspective has also been published. These developments suggest that fiber optic technology is likely to emerge as a common analytical tool in future. Bynum et al reported of the development of a UV Fiber Optic Probe Dissolution System for the analysis of solid dosage forms(48). The system uses 12 dip-type fiber optic probes coupled to 12 separate PDA spectrophotometers to acquire continuous dissolution curves in real time. The system is applicable to the analysis of both immediate and controlled release formulations. The system is accurate, quicker, and easier to set up when compared with conventional HPLC or UV-sipper systems. Zolnik et al and his co-workers reported that fiber optic UV probes can be used in conjunction with USP apparatus 4 to monitor the release from

dispersed systems, such as microspheres, since the dispersed system is in an isolated chamber (flow through cell) and therefore does not interfere with UV analysis. The fiber optic probes allow ease of collection of multiple data points and therefore can be useful to achieve a comprehensive characterization of the release profile(49).

**8. Conclusions**

Noyes and Whitney derived their equation in the course of their dissolve studies on benzoic acid and lead chloride in 1897, and this was the beginning of dissolution research. As a result, dissolution began as a topic in physical chemistry and continues to be a major research area in numerous branches of physical science. (50) The rate of oral absorption of weakly water-soluble medications is determined by drug dissolution, and solubility is also a basic criterion for the formulation and development of different dosage forms of different drugs. For oral solid dosage forms such as tablets and capsules, dissolution testing is a typical task for pharmaceutical quality control. It's also required by transdermal drug delivery methods(51). Every day, the science of dissolution testing advances. Improvements in through scientific trials conducted around the world, technology has made the technique simple, quick, and reliable. It's a must-have tool for pharmaceutical research and development(52).

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