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A key approach on dissolution of pharmaceutical dosage forms

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Abstract
Dissolution testing is a critical methodology which is widely utilized in the development of a new pharmaceutical product. The test, in its simplest form, consists of placing the formulation in a dissolution apparatus containing suitable dissolution medium, allowing it to dissolve over a specified period of time and then assaying the resultant solution using appropriate analytical method to determine the amount of drug. Dissolution tests are relevant for an array of investigations like drug degradation profiles, stability and shelf life studies, physical and mechanical testing of dosage forms, incoming QC testing on raw materials etc. The present review outlines the recent findings on various dissolution apparatuses, their modifications, methods for degassing of media like Helium sparging, Heating and filtering, Vacuum degassing, sonication and dissolution testing of various dosage forms like Immediate Release (IR) Dosage forms, Delayed Release Dosage Forms, Extended Release Dosage Forms, Transdermal Delivery Systems, Powders, Chewable Tablets, Buccal Tablets, Chewing Gums, Soft Gelatin Capsule, Aerosols, Suppositories and other Semisolids. This article presents, a short review on guidelines for dissolution profile testing, particularly focusing on the recommendations regarding statistical methods for assessing profile similarly. In this context, the guidelines on *in vitro/in vivo* correlations and on granting bio waivers are outlined briefly. The goal of this article is to give a survey of the current guidelines, including a description and discussion of the recommended methods for data analysis.

Keywords: dissolution test, quality control test, stability, bioequivalence, paddle, validation, quantitation, diverse factors

Introduction
Dissolution
The definition of dissolution is deceptively simple. It is the process in which a solid substance goes into solution. For dosage forms containing an active solid ingredient, the rate of dissolution may be critical to absorption. Obviously, in most instances, dissolution of the active solid material is affected by a variety of factors such as the media in which the drug is dissolving, the temperature of the media, and the affinity for the solid particles to dissolve in the media. There are numerous other factors, such as excipients, coatings, and pH, which have an effect on the rate of dissolution. While the most rapid absorption is from a solution, most dosage forms are solids, either tablets or capsules. One must also consider dissolution from suspensions and suppositories. Several chapters in this text cover various dosage forms as the theme for the discussion on dissolution [1].

The theory is the same regardless of the dosage form design, but obviously, the rate of dissolution and the limitations are different for each individual dosage form. Any process of drug release and subsequent absorption into the blood stream must consider dissolution of the solid. Wetting of the material, be it hydrophilic or hydrophobic, is the first critical step and precedes deaggregation. This process may also be considered disintegration. The drug then dissolves into the dissolution media, be it *in vitro or in vivo*. As a rule, suspensions dissolve faster than capsules since some deaggregation has already occurred [1].

Tablets usually have the slowest dissolution rate, either by design to allow a sustained, controlled release or by the nature of the wetting process. The earliest obvious reference to dissolution was by Noyes and Whitney, where they stated that the dissolution rate is governed by the rate of diffusion of a saturated thin layer forming instantly around the dissolving material [2]. The work of Noyes and Whitney concentrated on physico-chemical aspects and not bioavailability. In 1951, Edwards showed that aspirin tablets would have poor analgesic activity due to poor dissolution. Theoretical models of dissolution continued to be developed

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in the early 1900s by Brunner, when he adapted Fick's Law of diffusion [1].

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

the dosage form itself is critical. All of these factors will be addressed in this text. Rapid dissolution is not always the goal in formulation [2]. Salt or ester formation: Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents [4]. If one desires a controlled- or sustained-release dosage form, the factors that affect the dissolution rate may be manipulated to obtain the desired effect. The pharmaceutical formulator can use methods of controlling dissolution to readily obtain a desired release profile. While the remainder of the book is divided into chapters by dosage form, many factors remain the same regardless of the dosage form while some are specific to the individual dosage form and dosage form design.
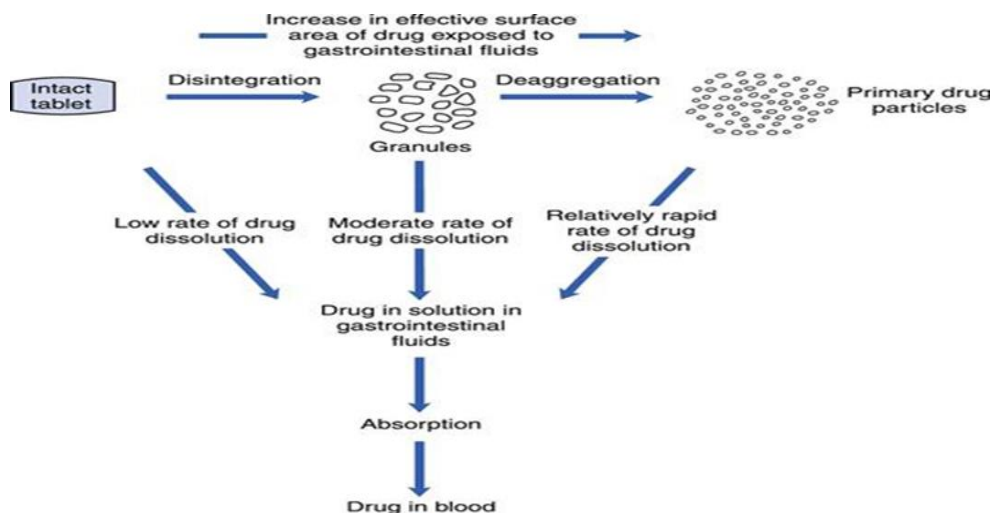

2 Importance and Applications of Dissolution Test
Oral dosage form of tablets or capsules are one of the most effective ways of current treatment. The efficacy of such dosage forms is dependent on the dissolution of the drug in the gastrointestinal fluids prior to absorption into the systemic circulation; therefore, the rate of dissolution of the tablet or capsule is critical. Dissolution can be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition [3]. It is well thought-out as one of the most important quality control tests performed on pharmaceutical dosage forms. It is also developed as a predictor bioavailability, replacing human studies to establish

bioequivalence. A direct relationship between *in vitro* dissolution rate of several drugs and their bioavailability has been established and is known as *in vitro-in vivo* correlation, IVIVC [4].

In spite of IVIVC, dissolution is a qualitative and quantitative tool which can offer important information about biological availability of a drug and also lot-to-lot consistency of products. Hence, dissolution tests are used for the conformity with compendial specifications and are also required for the license application of the product. Moreover, they are used during the development and stability testing as part of product specifications [5].
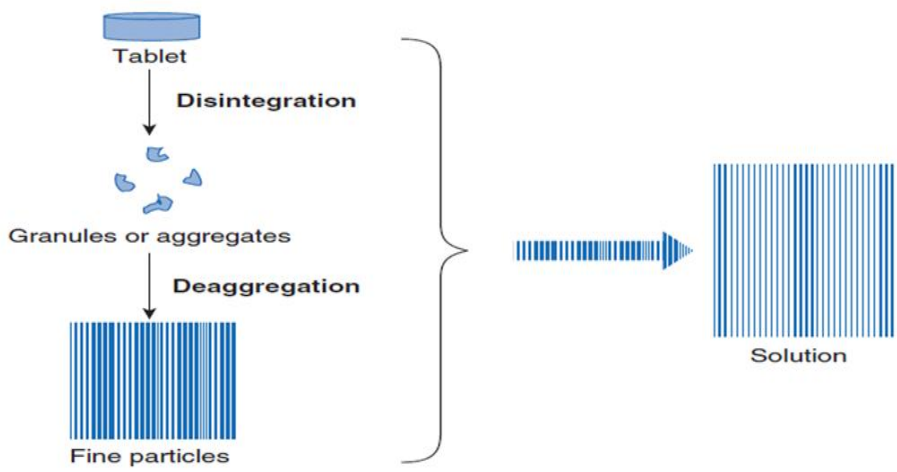
Fig: Disintegration, Deaggregation, Solution.

Importance

Tablet dissolution is a regular method to measure the rate of release of drug from a product [7]. The major functions of the dissolution test may be as under:

- Results from in-vitro dissolution rate experiments can be used to explain the observed differences in in-vivo availability.
- Dissolution testing provides the means to evaluate critical parameters such as adequate
  bioavailability and provides information necessary to formulator in development of more efficacious and therapeutically optimal dosage forms.
- Most sensitive and reliable predictors of in-vivo availability.
- Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.
- It can ensure bioavailability of product between batches that meet dissolution criteria.
- Ensure batch-to-batch quality equivalence both in-vitro and in-vivo, but also to screen formulations during product development to arrive at optimally effective products.
- Physicochemical properties of model can be understood needed to mimic in-vivo environment.
- Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.
- Serve as quality control procedures, once the form of drug and its formulation have been finalized.
- The function of the dissolution test is now been comprehensive from oral dosage forms on a range of other dosage forms such as trans dermal systems and suppositories [8].

Product Stability

In-vitro dissolution also used to assess drug product quality with respect to stability and shelf life.

As product age, physicochemical changes to the dosage form may alter dissolution characteristics of drug product over time. For some products, polymorph transformations to more stable, and hence less soluble crystalline forms may result in reduced dissolution rates [7].

Comparability Assessment

Also useful for assessing the impact of pre- or post- approval changes to drug product such as changes to formulation or manufacturing process. . A situation in which use of, or exposure to, a violate product is not likely to cause adverse health

Consequences [6]. Thus, in-vitro comparability assessment is critical to ensure continued performance equivalency and product similarity [7].

Waivers of in-vivo bioequivalence requirements

In-vitro dissolution testing or drug release testing may be used for seeking waiver of required

Product to conduct in-vivo bioavailability or bioequivalence studies [7].

Dissolution Mechanism

Dissolution test assesses the collective amount of drug that goes into solution as a function of time. It involves:

- release of drug from the formulation matrix i.e. disintegration
- solubilization of the drug particles (drug dissolution) in the liquid medium [10].

The overall rate of dissolution cohesive properties of solid dosage form plays a major role in disintegration. The dissolution rate is considered to be disintegration controlled if the first step of dissolution is rate-limiting [11]. Careful evaluation of the intrinsic rate of dissolution and different aspects of the formulation (e.g., release profiles from pre-compressed granules, compression force, porosity, etc) can disclose the virtual contribution of the disintegration step to the cumulative dissolution of the drug [12].

In the second step of dissolution-solubilization, the physicochemical properties of the drug like its chemical form i.e. salt, free acid/free base and physical form like amorphous or polymorph, etc play a significant role. If the latter step is rate limiting, then dissolution rate is intrinsic dissolution controlled (SUPAC–MR, 1997). .For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration [9]. It is evident generally for poorly soluble compounds in immediate release formulations [13]. *In vivo* precipitation needs to be considered when developing a dissolution test method for poorly soluble compounds in solubilized formulations, especially to establish an *in vivo–in vitro* relationship (IVIVR) or correlation (IVIVC) [14].

Dissolution Testing
Various dissolution tests

Dissolution means dissolving. It is a vital first step when medicinal drugs are taken in the form of tablets and capsules. Rate of dissolution is an important property of a medicine as it indicates how quickly the drug in a formulation is released in the body and made available for absorption [15]. Because dissolution tests provide the Compendial correlation to drug product performance.

- Dosage forms to be tested are
1) Immediate release dosage forms: Powders, Granules / Beads, Capsules
2) Controlled release dosage forms: Powders, Granules / Beads, Capsules
3) Transdermal System
4) Implants
- The dissolution apparatus has evolved gradually & considerably from a simple beakertype to a highly versatile & fully automated instrument. Based on absence or presenceof sink conditions, there are three principal types of dissolution apparatus:
1. Closed-compartment- Basically a limited volume apparatus operating under non-sink conditions. E.g. App-I & II.
2. Open compartment- One in which dosage form is contained in a column which is brought in continuous contact with fresh, flowing dissolution medium (perfect sink condition)
3. Dialysis type system- Used for very poorly aqueous soluble drug for which maintenance of sink conditions would otherwise require large volume of dissolution fluid.

According to USP 30 dissolution apparatus used are:

Usp app	Description	Rot. Speed	Dosage form
1	Basket	50-120 Rpm	Ir, Dr, Er
2	Paddle	25-50 Rpm	Ir, Dr, Er
3	Reciprocating Cylinder	6-35 Rpm	Ir, Er
4	Flow-Thru Cell	N/A	Er, Poorly Soluble Api
5	Paddle Over Disk	25-50 Rpm	Transdermal
6	Cylinder	N/A	Transdermal
7	Reciprocating Holder	30 Rpm	Er

Conditions (for all in general)
1. Temp. - 37 ± 0.5^0 C
2. PH - ±0.05 unit in specified monograph
3. Capacity – 1000 ml
4. Distance between inside bottom of vessel and paddle/basket is maintained at 25 ± 2 mm.
5. For enteric coated dosage form it is first dissolved in 0.1 N HCl& then in buffer of pH 6.8to measure drug release. (Limit – NMT 10% of drug should dissolve in the acid after2hr.and about 75% of it should dissolve in the buffer after 45 min [16].
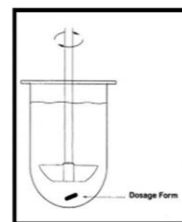
USP apparatus

40 mesh basket   20 mesh basket   10 mesh basket   suppository basket
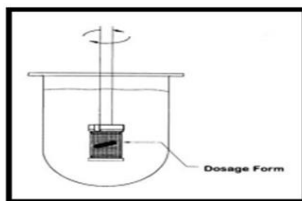
1. Apparatus I- Basket Apparatus
- Unless otherwise specified in the individual monograph, use 40-mesh cloth.
- Useful for:
  Capsules, Beads, Delayed release / Enteric Coated dosage forms
  , Floating dosage forms
- Standard volume: 900/1000 ml
  1, 2, 4 liter vessels
- Advantages:
  1) more than 200 monographs.
  2) Full pH change during the test
  3) Can be easily automated which is important for routine investigation.
- Disadvantages:
  1) Disintegration-dissolution interaction
  2) Hydrodynamic Dead jone under the basket.
  3) Degassing is particularly important
  4) Limited volume-----sink condition for poorly soluble drugs

2. Apparatus-II - Paddle Apparatus
Method of First Choice
- The dosage unit is allowed to sink to the bottom of the vessel before rotation of theblade is started.
- A small, loose piece of no reactive material such as not more than a few turns of wirehelix may be attached to

dosage units that would otherwise float.
- Other validated sinker devices may be used [16].

PTFE coated paddle   Solid PTFE coated paddle

Useful for
Tablets, Capsules, Beads, Delayed release, enteric coated dosage forms

Standard volume: 900/1000 ml
Advantages
1. Easy to use
2. Robust

3. Can be easily adapted to apparatus 5
4. long experience
5. pH change possible
6. Can be easily automated which is important for routine investigations.

Disadvantages
1. pH/media change is often difficult
2. Hydrodynamics are complex, they vary with site of the dosage form in the vessel (sticking, floating) and therefore may significantly affect drug dissolution.
3. Coning.


Sinkers for floating dosage forms

Limitations of USP Apparatus 1and 2
1. USP2 (and USP1) Apparatus has plenty of HYDRODYNAMICS.
2. Complicated 3-dimensional flow generated by the paddle.
3. Significant impact of convective transport –Conditions used (50 – 100 rpm) highly Exaggerates flow in the GI.
4. If Static-tank model used – sink conditions artificially generated to simulate sink in GI.
5. Use of solvents and surfactants non-native to GI.

Apparatus III – Reciprocating cylinder
• The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glassreciprocating cylinders; stainless steel fittings (type 316 or equivalent) and screens thatare made of suitable non-sorbing and nonreactive material (polypropelene) and that aredesigned to fit the tops and bottoms of the reciprocating cylinders; and a motor anddrive assembly to reciprocate the cylinders vertically inside the vessels.
• The vessels are partially immersed in a suitable water bath of any convenient size thatpermits holding the temperature at 37 ± 0.5 during the test.
• The dosage unit is placed in reciprocating cylinder & the cylinder is allowed to move inupward and downward direction constantly. Release of drug into solvent within

thecylinder measured [16].
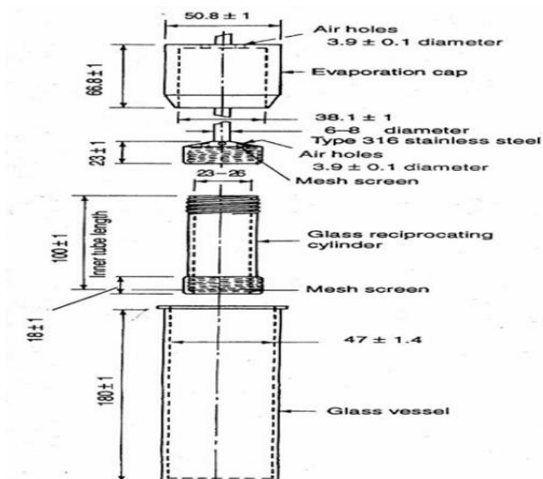
Useful for: Tablets, Beads, controlled release formulations

Standard volume: 200-250 ml/station
Advantages
1) Easy to change the pH-profiles
2) Hydrodynamics can be directly influenced by varying the dip rate.

Disadvantages
1) small volume (max. 250 ml)
2) Little experience
3) Limited data

4) Apparatus IV – flow through cell
The assembly consists of a reservoir and a pump for the Dissolution Medium; a flowthrough
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.
• Assemble the filter head, and fix the parts together by means of a suitable clamping device.
• Introduce by the pump the Dissolution Medium warmed to 37 ± 0.5 through the bottom of the cell to obtain the flow rate specified in the individual monograph.
• Collect the elute by fractions at each of the times stated.
• Perform the analysis as directed in the individual monograph [16].
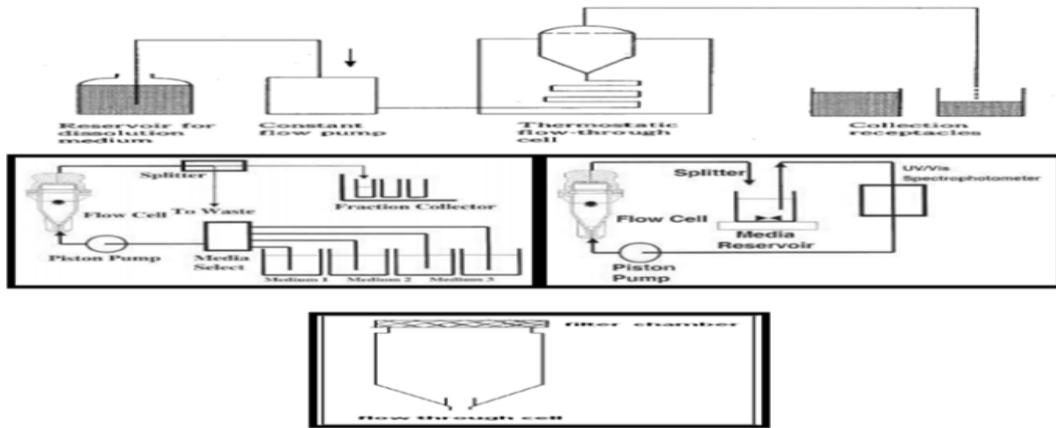
Useful for
Low solubility drugs, Micro particulates, Implants, Suppositories, Controlled release formulations

Variations
(A) Open system & (B) Closed system

Advantages
1. Easy to change media pH
2. PH-profile possible
3. Sink conditions

Disadvantages
1. Deaeration necessary
2. High volumes of media
3. Labor intensive

5) Apparatus V – Paddle over disk
- Use the paddle and vessel assembly from Apparatus 2 with the addition of a stainless
- steel disk assembly designed for holding the transdermal system at the bottom of the vessel.
- Other appropriate devices may be used, provided they do not sorb, react with, or
- interfere with the specimen being tested
- The disk assembly for holding the transdermal system is designed to minimize any

- "dead" volume between the disk assembly and the bottom of the vessel.
- The disk assembly holds the system flat and is positioned such that the release surface is
- parallel with the bottom of the paddle blade
- The vessel may be covered during the test to minimize evaporation [16].

Useful for: Transdermal patches
Standard volume: 900 ml

Disadvantages: Disk assembly restricts the patch size.

6) Apparatus VI – cylinder
- Use the vessel assembly from Apparatus 1 except to replace the basket and shaft with a
- stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5 during the test.
- The dosage unit is placed on the cylinder at the beginning of each test, to the exterior of
- the cylinder such that the long axis of the system fits around the circumference of the cylinder & removes trapped air bubbles.
- Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph [16].

7) Apparatus VII – reciprocating holder
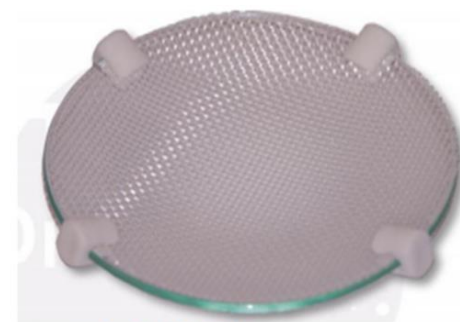
US 724 APPARATUS
Transdermal Patch Retainer (Hanson Style)

- The assembly consists of a set of volumetrically calibrated solution containers made of glass or other suitable inert material, a motor and drive assembly to reciprocate the system vertically and a set of suitable sample holders.
- The solution containers are partially immersed in a

suitable water bath of any convenient size that permits maintaining the temperature, inside the containers at 32 ±0.5
- For Coated tablet drug delivery system attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyano acrylate glue onto the

end of aplastic rod or by placing the system into a small nylon net bag at the end of a plastic rodor within a metal coil attached to a metal rod).

- For Transdermal drug delivery system attach the system to a suitable sized sampleholder with a suitable O-ring such that the back of the system is adjacent to andcentered on the bottom of the disk-shaped sample holder or centered around thecircumference of the cylindrical-shaped sample holder. Trim the excess substrate with asharp blade.
- For Other drug delivery systems attach each system to be tested to a suitable holder asdescribed in the individual monograph [16].

3.3 Dissolution Testing Method
Dissolution means dissolving. It is a vital first step when medicinal drugs are taken in the form of tablets and capsules. Rate of dissolution is an important property of a medicine as it indicates how quickly the drug in a formulation is released in the body and made available for absorption [15].
There are two main methods
- The rotating basket
- The paddle.

The rotating basket method
The tablet or capsule is placed ina stainless steel cylindrical mesh basket. The basket is placed in a vessel kept at a constant temperature. The basket is rotated at a constant speed (between 25 and 150 revolutions per minute).Samples are withdrawn for analysis from the same position each time.

Fig 1: A bank of eight vessels for measuring rate of dissolution using the paddle method. The paddles can be replaced by mesh baskets, allowing the apparatus to be used for the rotating basket method [17].

The paddle method
The apparatus for the paddle method is similar to that for the rotating basket method. The design of the paddle and the speed at which is rotates are important. The paddle must rotate smoothly with no wobbling and no vortex should form when the paddle is turning. The tablet or capsule is allowed to sink to the bottom of the vessel before the paddle starts rotating. The apparatus may seem a little crude for making such an important measurement. However, it is a precisely defined, close tolerance instrument.

3.5 Acceptance Criteria
3.5a Conventional-release (or immediate-release) dosage forms
Unless otherwise specified in the individual monograph the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 1. Continue testing through the three levels unless the results conform at either S 1 or S2. The quantity, Q, is the specified amount of dissolved active ingredient expressed as a percentage of the labelled content; the 5%, 15% and 25% values in the acceptance table are percentages of the labelled content so that these values and Q are in the same terms [19].

Table 1. Acceptance criteria of conventional-release (or immediate-release) dosage forms

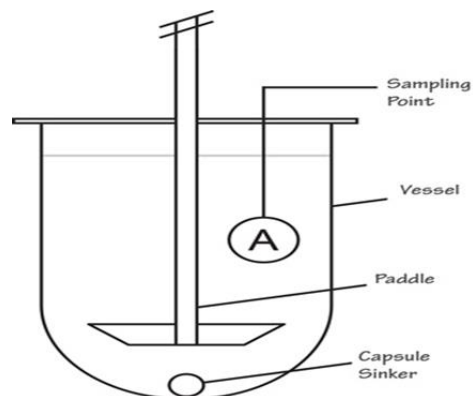| Level	Samples tested	Acceptance criteria
S1	6	Each value is not less than Q + 5%
S2	6	Average value of the 12 dosage units (S1 + S2) is equal to or greater than Q and no unit is less than Q-15%
S3	12	Average value of 24 dosage units (S1 + S2 + S3) is equal to or greater than Q; not more than 2 units are less than Q - 15%; no unit is less than Q - 25%.

3.5b Sustained release dosage forms
Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 2.

Table 2: Acceptance Criteria of Sustained Release Dosage Forms

Level	Samples tested	Acceptance criteria
L1	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
L2	6	The average value of the 12 dosage 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% of the labelled content outside each of the stated ranges; and none is more than 10% of labelled content below the stated amount at the final test time
L3	12	The average value of the 24 dosage units (L1 + L2 + L3) lies within the stated ranges and is not less than the stated amount at the final test time; not more than 2 of the 24 dosage units are more than 10% of labelled content outside each of the stated ranges; not more than 2 of the 24 dosage units are more than 10% of labelled content below the stated amount at the final test time; and none of the 24 dosage units is more than 20% of labelled content below the stated content at the final test time; none of the units are more than 20% of labelled content outside each of the stated ranges or more than 20% of labelled content below the stated amount at the final test time

3.5c Delayed-release dosage forms

Acid stage. Unless otherwise stated in the individual monograph the requirements of this part of the test are met if the quantities, based on the percentage of the labelled content of active ingredient(s) dissolved from the dosage units tested conform to Table 3

Table 3: Acceptance Criteria ofDelayed-release dosage forms

Level	Samples tested	Acceptance criteria
A1	6	No individual value exceeds 10% dissolved
A2	6	Average value of the 12 dosage units (A1 + A2) is not more than 10% dissolved, and no individual value is greater than 25% dissolved
A3	12	Average value of 24 dosage units (A1 + A2 + A3) is not more than 10% dissolved, and no individual value is greater than 25% dissolved.

Unless otherwise specified in the individual monograph the requirements are met if the quantities of active ingredients dissolved from the units tested conform to Table 4

Table 4: Acceptance Criteria of Delayed-release dosage forms

Level	Samples tested	Acceptance criteria
B1	6	No value is less than Q + 5%
B2	6	Average value of the 12 dosage units (B1 + B2) is equal to or greater than Q, and no unit is less than Q - 15%
B3	12	Average value of the 24 dosage units (B1 + B2 + B3) is equal to or greater than Q; not more than 2 units are less than Q - 15%, and no unit is less than Q - 25%.

3.6 Dissolution media

The selection of an appropriate dissolution medium is a fundamental stage of the dissolution test.

- It is more important that the test closely simulate the environment in the GI tract than necessarily produce sink condition [20].

Sink Condition

The dissolution rate may be given by Novey-Whitney equation.

$$\frac{dW}{dt} = \frac{D}{h}S(C_s - C_t)$$

Where,

S : surface area

T : time

$C_s – C_t$: concentration gradient between the concentration of solute in the stagnantlayer.

- This is first order dissolution rate process, for which the driving force is concentrationgradient.
- This is true for in-vitro dissolution which is characterized by non-sink conditions.
- The in-vivo dissolution is rapid as sink conditions are maintained by absorption of drug in systemic circulation i.e. Cb=0 and rate of dissolution is maximum.
- Under sink conditions, if the volume and surface area of the solid are kept constant, then,dW/dt = K
- This represents that the dissolution rate is constant under sink conditions and follows zero order kinetics
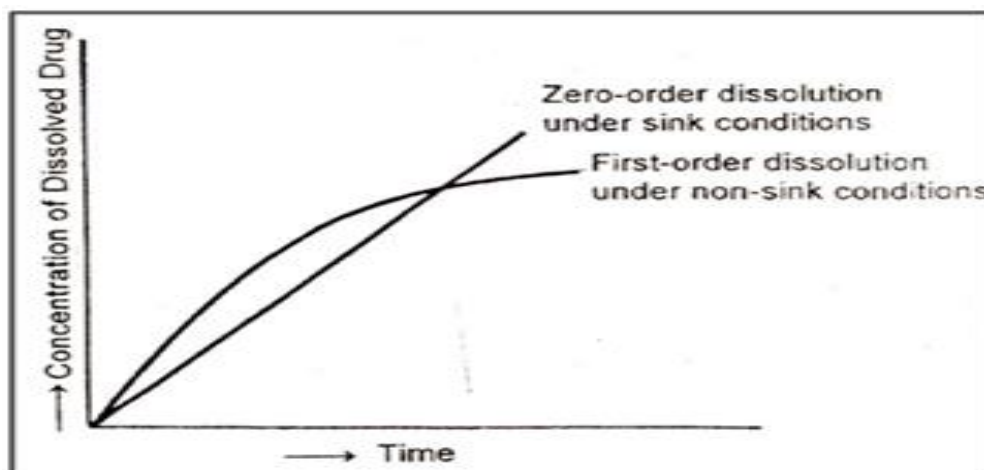
Fig: So, we have to maintain sink condition in in-vitro. This is can be achieved by,

i. Bathing the dissolving solid in fresh solvent from time to time
ii. Increasing the volume of dissolution fluid
iii. Removing the dissolved drug by patitioning it from the aqueous phase of the dissolution fluid into an organic phase placed either above or below the fluid, for example, hexane or chloroform
iv. Adding a water miscible solvent such as alcohol to the dissolution medium
v. By adding selected adsorbent to remove the dissolved drug.
- A sink condition occurs when the drug that can be dissolved in the dissolution medium is 3 times greater than the amount of drug to be dissolved.

- Cs/Cd≤3 [20]

Below are some examples of dissolution media
- **Dissolution buffer pH 1.3, TS**
  Dissolve 2 g of sodium chloride R in 800 mL of water R, adjust the pH to 1.3 with hydrochloric acid (~70 g/l) TS and dilute to 1000mL with water R.
- **Dissolution buffer pH 2.5, TS**
  Dissolve 2 g of sodium chloride R in 800 mL of water R, adjust the pH to 2.5 with hydrochloric acid (~70 g/l) TS and dilute to 1000mL with water R.
- **Dissolution buffer pH 3.5, TS**
  Dissolve 7.507 g of glycine R and 5.844 g of sodium chloride R in 800 mL of water R, adjust the pH to 3.5 with hydrochloric acid(~70 g/l) TS and dilute to 1000 mL with water R.
- **Dissolution buffer pH 4.5, TS**
  Dissolve 6.8 g of potassium di hydrogen phosphate R in 900 mL of water R, adjust the pH to 4.5 either with hydrochloric acid (~70g/l) TS or sodium hydroxide (~80 g/l) TS and dilute to 1000 mL with water R.
- **Dissolution buffer, pH 6.8, TS**
  Dissolve 6.9 g of sodium di hydrogen phosphate R and 0.9 g of sodium hydroxide R in 800 mL of water R, adjust the pH to 6.8with sodium hydroxide (~80g/l) TS and dilute to 1000 mL with water R.
- **Dissolution buffer, pH 6.8, 0.25% SDSTS**
  Dissolve 6.9 g of sodium di hydrogen phosphate R, 0.9 g of sodium hydroxide R and 2.5 g of sodium dodecyl sulfate R in 800 mL of water R, adjust the pH to 6.8 with sodium hydroxide (~80g/l) TS and dilute to1000 mL with water R.
- **Dissolution buffer pH 7.2, TS**
  Dissolve 9.075 g of potassium dihydrogen phosphate R in water R to produce 1000 mL (solution A). Dissolve 11.87 g of disodium hydrogen phosphate R in sufficient water R to produce 1000 mL (solution B). Mix 300 mL of solution A with 700 mL of solution B.
- **Gastric fluid, simulated, TS**

Dissolve 2.0 g of sodium chloride R and 3.2 g of pepsin R in 7.0 mL of hydrochloric acid (~420 g/l) TS and sufficient water R to produce 1000mL. This test solution has a pH of about 1.2.
- **Intestinal fluid pH 6.8, simulated, TS**
  Mix 77.0 mL of sodium hydroxide (0.2 mol/l) VS , 250.0 mL of a solution containing 6.8 g potassium di hydrogen phosphate R and500 mL of water R. Add 10.0 g pancreatin R, mix and adjust pH to 6.8 ± 0.1. Dilute to 1000 mL with water R [19].

Dissolution Method Development & Validation
4.1 Dissolution Method Development
The dissolution procedure has several distinct components. These components include a dissolution medium, an apparatus, the study design (including acceptance criteria) and the mode of assay. The easy accessibility and higher surface area makes the nose a potentially viable drug delivery organ [17]. All of these components must be properly chosen and developed to provide a method that is reproducible for within laboratory day-to-day operation and robust enough to enable transfer to another laboratory.

4.1a The Dissolution Medium
When selecting the dissolution medium, physical and chemical data for the drug substance and drug product need to be considered, e.g. the solubility and solution state stabitilyof the drug as a function of pH value. The problem is how to deliver drugs right where we need it [18].Other critical drug product properties include the release mechanism (immediate, delayed or modified) and disintegration rate as affected by formulation hardness, friability, presence of solubility enhancers and other excipients. The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc [19]. When selecting the composition of the medium (Refer Table No.1), the influence of buffers, molarity, pH, and surfactants on the solubility and stability of the drug also need to be evaluated.

Table 1: Dosage forms with specific recommended dissolution medium [23]

S. No.	Dosage form	Modulation in dissolution medium
1	Semi-solid Topical Dosage forms (Creams,ointments,Gels)	Depending upon the solubility of the drug substance, the receptor medium may need to contain alcohol and/or surfactant. De-aeration is critical to avoid bubble formation at the interface with the membrane. As with transdermal products the test temperature is typically set at 32 °C to reflect the usual skin temperature.
2	Suppositories	Lipophilic suppositories release the drug after melting in rectal cavity and are significantly affected by rectal temperature (36.0-37.5°C). The test temperature should take into consideration physiological conditions but may also be at or slightly above the melting point, e.g. at 37.0 – 38.5 °C (e. g. Suppositories, used for patients with fever).
3	Oral Suspensions	Rotating paddlemethod utilizing an aqueous dissolution medium. Sample introduction and agitation rate should be established on the basis of the viscosity and composition of suspension matrix.
4	Buffered or Effervescent Tablet	Consider the physicochemical characteristics of the active ingredient (solubility, pKa or pKb, etc), buffered medium. Verify buffering capacity and ionic strength of the media.
5	Lipid filled Capsules	An enzyme (lipases) in addition to surfactants to simulate digestion if this is a rate-limiting step for dissolution. Lipases more closely reflect physiological conditions, but it is costly.
6	Chewing Gums	Test media with a pH 6.0 are commonly used, since this pH corresponds to saliva pH values of 6.4 (adults) or 7.3 (children).
7	Parenterals: Implants and Microparticles	The flow rate of the medium has to be set very slow. As tests are often run over a very long time period (e.g. Several weeks) measures have to be taken to compensate against evaporation and to prevent microbial growth in the medium. The composition of the medium should be taken into account forosmolarity, pH and buffer capacity of the fluids at the site of application, which are usually assumed to resemble to that of plasma

8	Transdermal Patches	The patch should be properly positioned so that the drug-loaded surface is exposed to the medium. The pH of the medium ideally should be adjusted to 5.0-6.0, reflecting physiological skin conditions. For the same reason, test temperature is typically set at 32.0□C
9	Dosage form with more than one active ingredient	Depending on the differences of the solubilitiesof the active ingredients, it may be necessary to have separate sets of dissolution conditions, one for each API

The most common dissolution medium is dilute hydrochloric acid, however other media commonly used includes buffers in the physiologic pH of 1.2 to 7.5, simulated gastric or intestinal fluid (with or without enzymes), water and surfactants(with or without acids or buffers) such as polysorbate 80, sodium lauryl sulfate and bile salts. Physicochemical properties of the inserts were evaluated like uniformity of thickness, drug content, weight, swelling index and surface pH [20]. The use of aqueous-organic solvent mixtures, while generally discouraged, can also be used if justified. Enzymes are also sometimes used in the media when testing gelatin capsule products. Media volumes are typically in the range of 500-1000 ml, with 900 ml the most common volume. Volumes as high as 2-4 L have been used and as low as 100 ml for high potency (low dosage strength) drug formulations. Media deaerationis usually required, and can be accomplished by heating the medium or (more commonly) filtering the medium or placing it under vacuum for short period of time. USP chapter 711 contains additional information on deaeration(USP 32-NF 27). During method development, results from dissolution samples run in nondeaerated medium versus a deaerated medium should be compared to determine whether deaeration is necessary. When developing dissolution procedure, one general goal is to have "sink" conditions. Sink conditions are defined as the volume of medium that is at least three times that required in order to form a saturated solution of drug substance. Dissolution results will more accurately reflect the properties of the dosage form when sinkconditions are present. This is current technology; a lot of it is determined by the price point [21].

Table 3: USP Dissolution Apparatus Selection For Various Dosage Forms

Dosage form	Apparatus (USP)
Solid dosage form (Immediate release, Modified release Products), chewable tablet	Type I -Basket apparatus Type II -Paddle apparatus
Bead type Modified release dosage form	Type III -Reciprocating cylinder apparatus
Modified release dosage form that Contain active ingredients with limited solubility.	Type IV -Flow through cell apparatus.
Soft gelatin capsules, suppositories, poorly soluble drugs, implants	Type III & IV (Reciprocating cylinder and Flow through cell apparatus)
Transdermal dosage form	Type V -Paddle over disk Type VI –Cylinder apparatus
Nondisintegrating oral modified dosage form as will as traditional dosage form	Type VII -Reciprocating holder apparatus

4.1c Dissolution study design

Dissolution is evaluated by measuring rate release profile or the amount dissolved over time. Single or multiple points in time can be measured, depending upon the dosage type or data desired.

Table 4: USP Apparatus and Agitation Criteria

USP App	Description	Rot. Speed	Dosage Form
1	Basket	50-120 rpm	IR, DR, ER
2	Paddle	25-50 rpm	IR, DR, ER
3	Reciprocating Cylinder	6-35 rpm	IR, ER
4	Flow-Thru Cell	N/A	ER, POORLY SOLUBLE API
5	Paddle Over Disk	25-50 rpm	TRANSDERMAL
6	Cylinder	N/A	TRANSDERMAL
7	Reciprocating Holder	30 rpm	ER

Where, IR= Immediate Release, DR= Delayed Release, ER= Extended Release

For immediate release dosage forms, the procedure duration is usually 30 to 60 minutes and in most cases, a single time point specification is adequate. However for formulation development comparison purposes, profile comparison is required and it is common to collect data from numerous time pointsFor extended release dosage forms, at least three test time points are typically chosen to characterize the *in vitro* drug release profile. Once an inactive ingredient has been approved for a product through a particular route of administra-tion, it can be used in any new drug [22]. Sampling probe can affect the hydrodynamic of the system and so that change in dissolution rate. For position of sampling, USP / NF states that sample should be removed at approximately half the distance from the basket or paddle to the dissolution medium and not closer than 1 cm to the side of the flask. Filter material must be saturated with the drug by repeated passage to avoid losses that might go undetected during the test sampling. Accumulation of the particulate matter on the surface may cause significant error in the dissolution testing. Acceptance criteria must also be considered during test development. The acceptance criteria should be representative of multiple batches from the same nominal composition and manufacturing process, include key batches used in pivotal studies and batches that are representative of the drug product performance in stability studied. Acceptance criteria are derived in the form of "Q-factors" a minimum amount

dissolved at a given time as a percentage of the labeled content. Dissolution tests can have a single Q-factor, or may have multiple Q-factors. A Q value in excess of 80% is not generally used, because allowance needs to be made forassay and content uniformity ranges. Finally, the dissolution test procedure should be discriminating enough to be capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect *in vivo* performance. In general, a properly designed dissolution test should result in reproducible data. Too much result variability can make it difficult to identify trends, true batch differences or effects of formulation changes. If too much variability is observed, theusual remedies include changing the apparatus type, speed of agitation, or deaeration; consideration and/ or examination of sinker type; and changing the composition of the medium. During routine testing of the product, variability outside the expected range should be investigated from analytical formulation and processing perspectives.

4.1d Assaying the results
There are two common ways of analyzing dissolution test samples, spectrophotometric (UV) determinations and HPLC. Typically the drug substance UV spectrum is observed to choose the optimum wavelength for analysis. Cells with path lengths ranging from 0.02 to 1 cm are used. Buffering agents used were having buffering capacity NMT 0.05% and pH was adjusted at which prednisolone acetate was stable [23]. HPLC methods, however, have distinct advantages, particularly when there is significant interference from excipients or between multiple active ingredients in the formulation. It also requires less sample volume.

4.2d Accuracy and Recovery
Accuracy expresses the closeness of agreement between the values which are accepted either as a conventional true value or an accepted reference value and the value found practically. Accuracy is measured by (1) Use of reference standard with known purity and (2) Comparison with independent, well-characterized procedure. Accuracy and recovery can be established by preparing samples containing the drug and any other constituents present in the dosage form ranging in concentration from below the lowest expected concentration to above the highest concentration during release. ICH recommends a minimum of nine determinations over a minimum of three concentrations, e.g. three concentrations, three replicates each. The measured recovery is typically 95% to 105% of the amount added.

4.2f Limit of Detection& Quantitation
Limit of Detection
It is defined as a lowest amount of an analyte in a sample which can be detected but not necessarily quantitated. Detection methods like visual evaluation, signal-to-noise ratio (3:1) andstandard deviation (SD) of response and slope (DL=3.3xSD/S).

Limit of Quantitation
It is defined as a lowest amount of an analyte in a sample which can bequantitatively determined with a suitable precision and accuracy. Quantitation methods like visual evaluation, signalto -noise ratio (10:1) and standard deviation (SD) of response and slope (DL=10xSD/S).

4.2gRobustness
The robustness of an analytical procedure is the measure of its capacity to remain unaffected by small deliberate variations in parameters internal to the procedure [26]. For dissolution testing, parameter to be varied includes medium composition, pH, volume, agitation rate and temperature. These parameters would be investigated in addition to those typically evaluated during validation of assay method, either spectrophotometric or HPLC.

4.2h System Suitability Test
The test requires a set of parameters and criteria thereof to ensure the system is working properly. It depends on type of test. For chromatographic methods: tailing factor, relative retention times, resolution factor, relative standard deviation and number of theoretical plates should be calculated. The number of theoretical plates to be checked before start of run and to be verified afterwards. The suitable test is also described in Pharmacopoeias.

Enhancement of Dissolution Rate of Tablet
6.1 Factors that Influence Dissolution Testing
A variety of factors can affect the *in vitro* rate of dissolution considerably and a great part of literature is concerned with identification and evaluation of these factors [25]. Many factors affecting the rate of drug dissolution from a dosage form comprise six core classes [26].
1. Factors associated with the drug's physicochemical properties.
2. Factors associated with product formulation.
3. Factors associated with the dosage form of drug.
4. Factors associated with dissolution testing apparatus.
5. Factors associated with test parameters of dissolution.
6. Diverse factors.

i. Factors associated with the drug's physicochemical properties.
The physicochemical properties of the drug can play a major role to control its dissolution from the product. The dissolution rate can be determined by the aqueous solubility of the drug [26]. Some of the main physicochemical properties of the drug that may alter the dissolution rate are as follows [27].

- Factors affecting solubility include polymorphism, amorphous state and salvation, free base, or salt form, complications, etc [28] Apart from the particle size, particle characteristics that affect the rate of dissolution include particle shape and particle density. These properties indirectly affect the effective surface area byaltering the rate of shear of the solvent coming in contact with the solid (Abdou H, 1989).
- Factors disturbing surface area available for dissolution include particle size and production variables (Brahamankar DM and Sunil B. Jaiswal).
- Factors related to the composition and method of manufacture include amount and type of excipients, granule size and its distribution, amount and type of disintegrant or surfactant and compression. An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility [29].
- Environmental factors involved include humidity during production, storage conditions and age of products [31].
- A metastable polymorph generally shows a greater dissolution rate than the corresponding stable polymorph.

A typical example showing effects of polymorphism on the bioavailability of drug is of chloramphenicol palmitate, which exists in three crystalline forms A, B and C. At normal temperature and pressure, "A" is the stable polymorph, "B" is the metastable polymorph and "C" is the unstable polymorph [31].

- The dissolution rate is directly proportional to the surface area of the drug. Hence, higher dissolution rates can be achieved by particle size reduction as the surface area increases. Various transdermal drug delivery technologies are described including the use of suitable formulations, carriers and penetration enhancers [30]. The effective surface area is the one that is accessible to the dissolution fluid. If the drug is hydrophobic and the dissolution medium has poor wetting properties then particle size reduction may have decreased effective surface area and a "slower" rate of dissolution

Diverse factors
The *in vivo* and *in vitro* dissolution of oral solid dosage forms is affected by variations in the GIT fluid (e.g. pH, surfactants); physical factors such as hydrodynamic flow and mechanical stress [32]. The physiological conditions that can influence the release of the drug include:

- Intestinal transit time,
- gastric emptying
- variable pH
- Food effects
- Effect of metabolism

If the dosage form is non-disintegrating then there is variability of retention times in the stomach between the fed and fasted states. For example, if the patient is in the fasted state, gastric emptying generally occurs within two hours and is delayed noticeably in the fed state [32]. When this occurs, gastric emptying controls drug release and if the dosage form has a delayed release element, the drug may not be adequately confined for residence time greater than 2 hours in the gastric pH of 1.2 (Katori N *et al*, 1996).
If the target of the dosage form is to release the drug in the duodenum then the dissolution test should reflect the possibility of a short residence time. The enteric coating must not erode at irrelevant pH and an appropriate dissolution test for pH sensitive release mechanism is required simultaneously [32].
Food can affect a number of factors and hence dissolution also. Dissolution media for water insoluble drugs usually include a surfactant to support dissolution [33]. Formulae of dissolution media with mixed micelles are designed to mimic the fed state but can be very expensive [34]. These formulae usually comprise mixtures of sodium taurocholate and egg lecithin.
The use of oil/water emulsions as dissolution medium to mimic a fatty meal cannot be easy to work with. Moreover, extraction of the drug from the oil phase may extend the analytical time and operational cost. For *in vivo* observation of the food efffects, dissolution media with higher lipid content are required if an IVIVC is the desired endpoint. Using different synthetic surfactants, research was done to study the solubilization and dissolution of water insoluble drugs in emulsions [35]. A detailed but comprehensive perception of the stability of the drug and dosage form in the presence of gastrointestinal enzymes is essential when shaping the necessity of enzymes in the media. The use of

lumenal enzymes is compulsory if the goal is an IVIVC but it is expensive akin to the use of lecithin and bile salts.

Conclusion
This brief review on the dissolution testing hereby concludes with a note that dissolution testing is considered as a most important test. There are different dissolution media and apparatuses for dissolution testing of both conventional and novel dosage forms. However, some of these methods and dissolution media which are reviewed in this article are intended to be used in research and development only and might not be suitable for routine quality control. The discussion provided should help in making a choice for an appropriate dissolution medium and dissolution apparatus. For oral products, the dissolution test is recognized as a valuable *in vitro* tool as a measure of performance test. Similarly, for topical and dermal drug products sufficient advances have been made to propose *in vitro* release test. A paddle over disk is suggested for drug release from transdermal patches or delivery through skin. For semi-solid preparations, drug release using vertical diffusion cell assembly is recommended. For other dosage forms, parenteral and mucosal, a significant progress has been made towards the development of drug release from release from the formulations. However, more work needs to be performed and validated before standard method/tests are measuring aerodynamics particle size distribution and uniformity of dose delivered.

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