Importance, Objectives & Factors Affecting Dissolution Rate, Theories of Dissolution And Official Dissolution Tests (Equipments of Dissolution Study)

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INTRODUCTION

Definition:- Dissolution rate may be defined as amount of drug substance that goes in the solution per unit time under standard conditions of liquid/solid interface, temperature and solvent composition. It can be considered as a specific type of certain heterogeneous reaction in which a mass transfer results as a net effect between escape and deposition of solute molecules at a solid surface.
The processes involved in dissolution of solid dosage forms:

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(Schematic illustration of dissolution process of solid dosage forms)

**IMPORTANCE AND APPLICATIONS**

**IMPORTANCE (Need of dissolution)……..

1. Results from in-vitro dissolution rate experiments can be used to explain the observed differences in in-vivo availability.
2. 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.
4. Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.
5. It can ensure bioavailability of product between batches that meet dissolution criteria.
6. 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.
7. Physicochemical properties of model can be understood needed to mimic in-vivo environment.
8. Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.
9. Serve as quality control procedures, once the form of drug and its formulation have been finalized.

**NOTE:**
- Simulated test modification done as per need
• If hydrophobic drug than the sodium lauryl sulphate can be added into simulated fluid to solublize the drug.
• For erodible tablet speed of agitation is bit high because it requires external force.
• HGC capsule shell forms swollen rubbery mass when comes in contact with physiological fluid so dissolve the shell by using enzyme like pepsin & pancreatin.
• In case of SGC capsule where content is oily we add tween 80.
• To study the effect of food we can add vegetable oil.
• In case of encapsulated product, material first removed & then studied separately. E.g. spenshul.

APPLICATIONS

1. PRODUCT DEVELOPMENT
   • Important tool during development of dosage form.
   • Aids in guiding the selection of prototype formulations and for determining optimum levels of ingredients to achieve drug release profiles, particularly for extended release formulations.
   • Also guides in selection of a “market-image” product to be used in pivotal in-vivo bioavailability or bioequivalence studies.

2. QUALITY ASSURANCE
   D.T. performed on future production lots and is used to assess the lot-to-lot performance characteristics of drug product and provide continued assurance of product integrity/similarity.
3. 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.

4. 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. Thus, in-vitro comparability assessment is critical to ensure continued performance equivalency and product similarity.

5. 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.

FACTORS AFFECTING DISSOLUTION RATE

1. Physicochemical Properties of Drug
2. Drug Product Formulation Factors
3. Processing Factors
4. Factors Relating Dissolution Apparatus
5. Factors Relating Dissolution Test Parameters

1. PHYSICOCHEMICAL PROPERTIES OF DRUG

1) DRUG SOLUBILITY
   - Solubility of drug plays a prime role in controlling its dissolution from dosage form. Aqueous solubility of drug is a major factor that determines its dissolution rate. Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems.
   - Studies of 45 compound of different chemical classes and a wide range of solubility revealed that initial dissolution rate of these substances is directly proportional to their respective solubility.
   - Fig shows a log-log plot of solubility of several drug Vs their corresponding intrinsic rates of dissolution at infinite rotation speed. Evident from graph that compounds with high solubility exhibit significantly higher dissolution rates.

2) SALT FORMATION
   - It is one of the common approaches used to increase drug solubility and dissolution rate. It has always been assumed that sodium salts dissolve faster than their corresponding insoluble acids. Eg. sodium and potassium salts of Penicillin G, sulfa drugs, phenytoin, barbiturates etc.
   - While in case of Phenobarbital dissolution of sodium salt was slower than that of weak acid. Same is the case for weak base drug, strong acid salts, such as hydrochlorides and sulphates of weak bases such as epinephrine, tetracycline are
commonly used due to high solubility. However, free bases of chlortetracycline, methacycline were more soluble than corresponding hydrochloride salt at gastric pH values, due to common ion suppression.

3) PARTICLE SIZE
- There is a direct relationship between surface area of drug and its dissolution rate. Since, surface area increases with decrease in particle size, higher dissolution rates may be achieved through reduction of particle size.
- Micronization of sparingly soluble drug to reduce particle size is by no means a guarantee of better dissolution and bioavailability.
- Micronization of hydrophobic powders can lead to aggregation and floatation when powder is dispersed into dissolution medium. So, mere increase in S.A. of drug does not always guarantee an equivalent increase in dissolution rate. Rather, it is increase in the “effective” S.A., or area exposed to dissolution medium and not the absolute S.A. that is directly proportional to dissolution rate.
- Hydrophobic drugs like phenacetin, aspirin shows decrease in dissolution rate as they tend to adsorb air at the surface and inhibit their wettability. Problem eliminated by evacuating surface from adsorbed air or by use of surfactants. So these drugs in-vivo exhibit excellent wetting due to presence of natural surfactants such as bile salts.

4) SOLID STATE CHARACTERISTICS
- Solid phase characteristics of drug, such as amorphicity, crystallinity, state of hydration and polymorphic structures have significant influence on dissolution rate.
- Anhydrous forms dissolve faster than hydrated form bcz they are thermodynamically more active than hydrates. Eg. Ampicillin anhydrate faster dissolution rate than trihydrate.
- Amorphous forms of drug tend to dissolve faster than crystalline materials. E.g. Novobiocin suspension, Griseofulvin.
- Where in the dissolution rate of amorphous erythromycin estolate is markedly lower than the crystalline form of erythromycin estolate.
- Metastable (high activation energy) polymorphic forms have better dissolution than stable forms.

5) CO-PRECIPITATION
- Dissolution rate of sulfathiazole could be significantly increased by co-precipitating the drug with povidone.
2. DRUG PRODUCT FORMULATION FACTORS

- Dissolution rate of pure drug can be altered significantly when mixed with various adjuncts during manufacturing process such as diluents, dyes, binders, granulating agents, disintegrants and lubricants.
- Generically identical tablet or capsules exhibited differences in their dissolution rates of their active ingredients.

1) DILUENTS

- Diluents in capsule & tablet influence the dissolution rate of drug.
- Studies of starch on dissolution rate of salicylic acid tablet by dry double compression process shows three times increase in dissolution rate when the starch content increase from the 5 – 20 %.
- Here starch particles form a layer on the outer surface of hydrophobic drug particles resulting in imparting hydrophilic character to granules & thus increase in effective surface area & rate of dissolution.
- Different types of dissolution apparatus utilized affect ranking of different varieties of starch. With stirring type of agitation, order was potato starch>cornstarch>arrowroot starch>rice starch. With oscillating type, a different order observed. Corn>rice>arrowroot>potato.
- The dissolution rate is not only affected by nature of the diluent but also affected by excipient dilution (drug/excipient ratio).

- E.g. in quinazoline comp. dissolution rate increases as the excipient /drug ratio increases from 3:1 to 7:1 to 11:1.

2) DISINTEGRANTS

- Disintegrating agent added before & after the granulation affects the dissolution rate.
- Studies of various disintegrating agents on Phenobarbital tablet showed that when copagel (low viscosity grade of Na CMC) added before granulation decreased dissolution rate but if added after did not had any effect on dissolution rate.
- Microcrystalline cellulose is a very good disintegrating agent but at high compression force, it may retard drug dissolution.
- Starch is not only an excellent diluent but also superior disintegrant due to its hydrophilicity and swelling property.
- Disintegration and dissolution rate of disintegrants with moderate swelling capacity depend to a large extent on mixing time of drug/excipient preblende.
- With lubricant. On other hand, disintegrants with strong swelling capacity such as sodium starch glycolate were hardly affected by mixing time with lubricant.
3) BINDERS AND GRANULATING AGENTS

- The hydrophilic binder increase dissolution rate of poorly wettable drug.
- Large amt. of binder increase hardness & decrease disintegration /dissolution rate of tablet.
- Non aqueous binders such as ethyl cellulose also retard the drug dissolution.
- **Phenobarbital tablet granulated with gelatin** solution provide a faster dissolution rate in human gastric juice than those prepared using Na – carboxymethyl cellulose or polyethylene glycol 6000 as binder.

![Graph showing dissolution rate of tablets with different binders](image)

- Gelatin imparted hydrophilic character to hydrophobic drug surface whereas PEG 6000 formed a poorly soluble complex while NA-CMC was converted to its less soluble acid form at the low pH of gastric fluid.
- In Phenobarbital tablet, faster dissolution rate was observed with 10% gelatin whereas decrease in dissolution rate with 20% gelatin. This was due to higher concentration which formed a thick film around tablet.
- Water soluble granulating agent Plasdone gives faster dissolution rate compared to gelatin.

4) LUBRICANTS

- Lubricants are hydrophobic in nature (metallic stearates) and prolong tablet disintegration time by forming water repellant coat around individual granules. This retarding effect is most imp factor in influencing rate of dissolution of solid dosage forms.
- Both amount and method of addition affect the property. It should be added in small amount (1% or less) and should be tumbled or mixed gently for only very short time. Prolonged mixing the dissolution time.
- However, if an enhancing effect in dissolution of hydrophobic granules is desired, water soluble lubricant such as SLS or CARBOWAXES may be used.
5) SURFACTANTS
- They enhance the dissolution rate of poorly soluble drug. This is due to lowering of interfacial tension, increasing effective surface area, which in turn results in faster dissolution rate.
- E.g Non-ionic surfactant Polysorbate 80 increase dissolution rate of phenacetin granules. The increase was more pronounced when the surfactant was sprayed on granules than when it was dissolved in granulating agent.

6) WATER-SOLUBLE DYES-
- Dissolution rate of single crystal of sulphathiazole was found to decrease significantly in presence of FD&C Blue No.1. The inhibiting effect was related to preferential adsorption of dye molecules on primary dissolution sources of crystal surfaces. They inhibit the micellar solubilization effect of bile salts on drug.
- Cationic dyes are more reactive in lower conc. than are anionic dyes.

7) COATING POLYMERS-
- Tablets with MC coating were found to exhibit lower dissoln profiles than those coated with HPMC at 37ºC. The differences are attributed to thermal gelation of MC at temp near 37º, which creates a barrier to dissoln process & essentially changes the dissoln medium. This mechanism is substantiated by the fact that at temp below the gel point & at increased agitation, the effect disappears.

3. PROCESSING FACTORS

1) METHOD OF GRANULATION-
- Granulation process in general enhances dissolution rate of poorly soluble drug. Wet granulation is traditionally considered superior. But exception is the dissolution profile of sodium salicylate tablets prepared by both wet granulation and direct compression where the dissolution was found more complete and rapid in latter case.
- A newer technology called as APOC “Agglomerative Phase of Commination” was found to produce mechanically stronger tablets with higher dissolution rates than those made by wet granulation. A possible mechanism is increased internal surface area of granules produced by APOC method.

2) COMPRESSION FORCE
- The compression process influence density, porosity, hardness, disintegration time & dissolution of tablet.
- First condition, higher compression force increase the density & hardness of tablet, decrease porosity & hence penetrability of solvent into the tablet retard the wettability by forming a firmer & more effective sealing layer by the lubricant and in many case tighter bonding between the particle so decrease dissolution rate of tablet.
• Second condition, higher compression force cause deformation, crushing or fracture of drug particles into smaller ones or convert spherical granules into disc shaped particles with a large increase in the effective surface area so increase in dissolution rate.

• Combination of both conditions can occur

• In short dissolution decrease at lower pressure (better bonding), then increase at higher pressure (crushing effect) and decrease again with further increase in pressure bcz of extra rebonding and formation of denser tablets with poorer dissolution characteristics.

3) DRUG EXCIPIENT INTERACTION
• These interactions occur during any unit operation such as mixing, milling, blending, drying, and/or granulating result change in dissolution.
• The dissolution of prednisolone found to depend on the length of mixing time with Mg-stearate
• Similar as increase in mixing time of formulation containing 97 to 99% microcrystalline cellulose or another slightly swelling disintegrant result in enhance dissolution rate.
• Polysorbate-80 used as excipient in capsules causes formation of formaldehyde by autoxidation which causes film formation by denaturing the inner surface of capsule. This causes decrease in dissoln rate of capsules.

4) STORAGE CONDITIONS
• Dissolution rate of Hydrochlorothiazide tablets granulated with acacia exhibited decrease in dissolution rate during 1 yr of aging at R.T. A similar decrease was observed in tablets stored for 14 days at 50-80ºC or for 4 weeks at 37ºC.
• For tablets granulated with PVP there was no change at elevated temperature but slight decrease at R.T.
• Tablets with starch gave no change in dissoln. rate either at R.T. or at elevated temperature.
4. FACTORS RELATING DISSOLUTION APPARATUS

1) AGITATION
   - Relationship between intensity of agitation and rate of dissolution varies considerably acc. to type of agitation used, the degree of laminar and turbulent flow in system, the shape and design of stirrer and physicochemical properties of solid.
   - Speed of agitation generates a flow that continuously changes the liq/solid interface between solvent and drug. In order to prevent turbulence and sustain a reproducible laminar flow, which is essential for obtaining reliable results, agitation should be maintained at a relatively low rate.
   - Thus, in general relatively low agitation should be applied.
     I. BASKET METHOD- 100 rpm
     II. PADDLE METHOD- 50-75 rpm

2) STIRRING ELEMENT ALIGNMENT
   - The USP / NF XV states that the axis of the stirring element must not deviate more than 0.2 mm from the axis of the dissolution vessel which defines centering of stirring shaft to within ±2 mm.
   - Studies indicant that significant increase in dissolution rate up to 13% occurs if shaft is offset 2-6 mm from the center axis of the flask.
   - Tilt in excess of 1.5° may increase dissolution rate from 2 to 25%.

3) SAMPLING PROBE POSITION & FILTER
   - Sampling probe can affect the hydrodynamic of the system & 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.

5. FACTORS RELATING DISSOLUTION TEST PARAMETERS

1) TEMPERATURE
   - Drug solubility is temperature dependent, therefore careful temperature control during dissolution process is extremely important.
   - Generally, a temp of 37° ± 0.5 is maintained during dissolution determination of oral dosage forms and suppositories. However, for topical preparations temp as low as 30° and 25° have been used

2) DISSOLUTION MEDIUM
   - It is very imp factor affecting dissolution and is itself affected by number of factors such as:
A. Effect of pH

- Weak acids, dissoln. rate increases with increase in pH whereas for weak bases, increase with decrease in pH.

B. Volume of dissolution medium and sink conditions

- Volume generally 500, 900 or 1,000 ml.
- Simulated gastric fluid (SGF) - pH 1.2.
- Simulated intestinal fluid (SIF) - pH 6.8 (not exceed pH 8.0).
- The need for enzymes should be evaluated case-by-case like…. (Pepsin with SGF and pancreatin with SIF)
- If drug is poorly soluble, a relatively large amount of fluid should be used if complete dissolution is to be expected.
- In order to minimize the effect of conc. gradient and maintain sink conditions, the conc. of drug should not exceed 10-15% of its max. Solubility in dissoln. medium selected. For most of the drugs about 1 L is more than sufficient to maintain sink conditions.
- However, some insoluble drug present a problem as to handling of huge volume of dissoln. medium that would be required to maintain the sink conditions. For these, different approaches have been tried like:
  1. Continuous flow method where fresh solvent is pumped continuously into dissoln flask at a fixed flow rate while maintaining a constant volume.
  2. Use of non-ionic surfactant in conc. above CMC.
  3. Use of alcoholic solution (10-30%).

C. Deaeration of dissolution medium

- Dissolved air in distilled water could significantly lower its pH and consequently affect the dissolution rate of drugs that are sensitive to pH changes, weak acids.
- Another effect is to be released from the medium in form of tiny air bubbles. These bubbles collect at the surface of the dosage forms, thereby acting as a hydrophobic barrier between solvent and solid surface. This inhibits wetting and reduction of S.A. and lower dissoln. rate.

THEORIES OF DISSOLUTION

1) Diffusion Layer Model (Film Theory)
2) Danckwert’s Model (Penetration or Surface Renewal Theory)
3) Interfacial Barrier Model (Double Barrier Mechanism OR Limited Solvation Theory)

DIFFUSION LAYER MODEL (FILM THEORY):

- It is a simplest model where dissolution of crystal, immersed in liquid takes place without involving reactive or electrical forces. Consist of two consecutive steps:
Solution of the solid to form a thin film or layer at the solid / liquid interface called as stagnant film or diffusion layer which is saturated with the drug this step is usually rapid (instantaneous).  
Diffusion of the soluble solute from the stagnant layer to the bulk of the solution this step is slower and is therefore the rate determining step in the drug dissolution. The model is depicted in following fig.

- Fick’s law covers only diffusions under steady state conditions. Modifying it Noyes & Whitney established another equation
  \[
  \frac{dC}{dt} = k ( C_s - C_b ) \quad \text{(A)}
  \]
  \[
  \frac{dC}{dt} = \text{dissolution rate of the drug} \\
  k = \text{dissolution rate constant \ (first order)} \\
  C_s = \text{conc. of drug in stagnant layer (saturation or max. drug solubility)} \\
  C_b = \text{conc. of the drug in bulk of the solution at time } t
  \]
- Brunner & Tolloczko incorporated surface area ‘A’ in Noyes & Whitney equation.
  \[ dc/dt = k_1 A \ ( C_s - C_b ) \]
- Afterwards Brunner, incorporated Fick’s law of diffusion & expanded his given eq to include diffusion coefficient ‘D’, thickness of stagnant diffusion layer ‘h’ & volume of dissolution medium ‘V’.
  \[
  \frac{dC}{dt} = \frac{D A k_{w/o} ( C_s - C_b )}{V h} \quad \text{(B)}
  \]
  \[
  D = \text{diffusion coefficient of the drug} \\
  A = \text{surface area of dissolving solid} \\
  k_{w/o} = \text{water / oil partition coefficient of the drug considering the fact that dissolution body fluid are aqueous since the rapidity with which a drug dissolved depend on the } k_{w/o}, \text{it is also called as the intrinsic dissolution rate constant} \\
  V = \text{volume of dissolusion medium} \\
  h = \text{thickness of stagnant layer} \\
  (C_s - C_b) = \text{conc. gradient for diffusion}
  \]
- This eq describes a first – order dissolution kinetics. It represents dissolution under non-sink conditions.
• If volume is relatively large such that

\[ \frac{dC}{dt} = \frac{A K_{w/o}}{Vh} Cs \]

Cs & D are constant for each specific chemical substance

\[ \frac{dC}{dt} = k_1 \frac{A}{Vh} \quad (\because k_1 = K_{w/o} D Cs) \]

V & A kept constant during dissolution test

\[ \frac{dC}{dt} = k \quad \text{(C)} \]

• Dissolution rate under sink condition follow zero order dissolution rate.

• For obtaining IVIVC sink condition can be achieved by:
  1) Bathing the dissolving solid in fresh solvent from time to time.
  2) Increasing the volume of dissolution fluid.
  3) Removing the dissolved drug by partitioning it from the aqueous phase of dissolution fluid into the organic phase placed either above or below the dissolution fluid for e.g. hexane or chloroform.
  4) Adding a water miscible solvent such as alcohol to the dissolution fluid.
  5) By adding selected adsorbents to remove the dissolution drug.

• In vitro sink condition is so maintain that Cb always less than 10% of Cs.

**HIXON-CROWELL CUBE ROOT RELATIONSHIP**

• Major assumptions in Noyes-Whitney relationship is that the S.A.(A) term remains constant throughout dissoln process. This is true for some formulations, such as transdermal patches.
• However, size of drug particles from tablets, capsules and suspensions will decrease as drug dissolves.
• This decrease in size of particles changes the effective S.A.
Thus, Hixon & Crowell modified the eq to represent rate of appearance of solute by weight in solution by multiplying both sides of volume term.

\[ W_0^{1/3} - W^{1/3} = kt \]

- \( W_0 \) = original mass of drug
- \( W \) = mass of drug remaining to dissolve at time \( t \)
- \( K \) = dissolution rate constant

DANCKWERT’S MODEL (PENETRATION OR SURFACE RENEWAL THEORY)

- This theory assumes that solid-soln equilibrium is achieved at interface and mass transport is slow step in dissoln process.
- The model could be visualized as a very thin film having a conc. \( Ci \) which is less than saturation, as it is constantly being exposed to fresh surfaces of liquid having a conc. much less than \( Ci \). Acc. to model, the agitated fluid consist of mass of eddies or packets that are continuously being exposed to new surfaces of solid and then carried back to bulk of liquid.
- Diffusion occurs into each of these packets during short time in which the packet is in contact with surface of solid.
- Since turbulence actually extends to surface, there is no laminar boundary layer and so no stagnant film exists. Instead, surface continually being replaced with fresh liquid.

\[ V \frac{dC}{dt} = \frac{dm}{dt} = A(Cs - Cb) \int rB \]

where
- \( m \) = mass of solid dissolution
- \( r \) = rate of surface renewal (or the interfacial tension)

![Diagram](Image)
INTERFACIAL BARRIER MODEL (DOUBLE BARRIER OR LIMITED SOLVATION THEORY)

The Diffusion layer model and the Dankwert’s model were based on two assumptions:

1) The rate determining step that controls dissolution is the mass transport.
2) Solid solution equilibrium is achieved at the solid/liquid interface.

- According to interfacial barrier model, an intermediate conc. can exist at the interface as a result of solvation mechanism and is a function of solubility rather than diffusion.
- When considering the dissolution of the crystal will have a different interfacial barrier given by following equation,

\[ G = k_i (C_s - C_b) \]

Where \( G \) = dissolution per unit area  
\( k_i \) = effective interfacial transport constant

- In this theory, the diffusivity \( D \) may not be independent of saturation conc. \( C_s \).
- The interfacial barrier model can be extended to both Diffusion layer model and the Dankwert’s model.

VARIOUS OFFICIAL DISSOLUTION TESTS

- 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 beaker type to a highly versatile & fully automated instrument. Based on absence or presence of sink conditions, there are three principal types of dissoln 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 dissoln 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 dissoln fluid.
OFFICIAL DOSSOLUTION MONOGRAPHS

According to I.P. & E.P. for solid dosage forms (tablets and capsules) dissolution apparatus used are:

1. Apparatus I – PADDLE APPARATUS
2. Apparatus II – BASKET APPARATUS

According to B.P. apparatus used are:

1. Apparatus I – BASKET APPARATUS
2. Apparatus II – PADDLE APPARATUS
3. Apparatus III – FLOW THROUGH CELL APPARATUS

According to USP 30 dissolution apparatus used are:

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<th>DESCRIPTION</th>
<th>ROT. SPEED</th>
<th>DOSAGE FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>BASKET</td>
<td>50-120 rpm</td>
<td>IR, DR, ER</td>
</tr>
<tr>
<td>II</td>
<td>PADDLE</td>
<td>25-50 rpm</td>
<td>IR, DR, ER</td>
</tr>
<tr>
<td>III</td>
<td>RECIPROCATING CYLINDER</td>
<td>6-35 dpm</td>
<td>IR, ER</td>
</tr>
<tr>
<td>IV</td>
<td>FLOW-THRU CELL</td>
<td>N/A</td>
<td>ER, POORLY SOLUBLE API</td>
</tr>
<tr>
<td>V</td>
<td>PADDLE OVER DISK</td>
<td>25-50 rpm</td>
<td>TRANSDERMAL</td>
</tr>
<tr>
<td>VI</td>
<td>CYLINDER</td>
<td>N/A</td>
<td>TRANSDERMAL</td>
</tr>
<tr>
<td>VII</td>
<td>RECIPROCATING HOLDER</td>
<td>30 rpm</td>
<td>ER</td>
</tr>
</tbody>
</table>

CONDITIONS (for all in general)

1. Temp. - 37±0.5°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 6.8 to measure drug release. (Limit – NMT 10% of drug should dissolve in the acid after 2hr. and about 75% of it should dissolve in the buffer after 45 min.)
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 the blade is started.
- A small, loose piece of no reactive 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.

**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.

Limitations of USP Apparatus 1 and 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.

3) Apparatus III – Reciprocating cylinder

- The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and screens that are made of suitable nonsorbing and nonreactive material (polypropylene) and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels.

- The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5°C during the test.
- The dosage unit is placed in reciprocating cylinder & the cylinder is allowed to move in upward and downward direction constantly. Release of drug into solvent within the cylinder measured.
**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

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4) **Apparatus IV – flow through cell**

- 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 $37 \pm 0.5^\circ$.
- 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°C 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.

**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.

Useful for: Transdermal patches
Standard volume: 900 ml
Disadvantages: Disk assembly restricts the patch size.

US 724 APPARATUS
Transdermal Patch Retainer (Hanson Style)

- Borosilicate Glass
- 17 mesh is standard (others available)
• Accommodates patches of up to 90mm

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°C 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.

7) Apparatus VII – reciprocating holder

- 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°C.
- 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 a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).
For Transdermal drug delivery system attach the system to a suitable sized sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade.

For Other drug delivery systems attach each system to be tested to a suitable holder as described in the individual monograph.

Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of Dissolution Medium within a calibrated container.

Reciprocate at a frequency of about 30 cycles per minute with amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point.

Perform the analysis as directed in the individual monograph.

QUESTION BANK
1. What is dissolution? Give its application & importance. (2005)
2. Explain factors affecting dissolution. (2006)
3. Explain in detail the theories of dissolution.
4. What is sink condition? How can it be achieved?
5. Give detail on film theory.
6. Give official dissolution tests of different dosage form.
7. Explain Danckwert’s model of solubility.(2006)
8. What is the need of dissolution testing?

References

1. Pharmaceutical dissolution testing by Umesh V. Banakar.
3. Dissolution, Bioavailability & Bioequivalence by M. Abdou.