Pharmaceutical Quality Management

CHAPTER 2

Quality Control Test for Solid Dosage Forms

By:

Dr. Fahad Pervaiz

Dosage Forms:

Completed forms of the pharmaceutical preparation in which prescribed doses of medication are included. They are designed to:

- 1- Accurate dose.
- 2- Protection e.g. coated tablets, sealed ampules.
- 3- Protection from gastric juice.
- 4- Masking taste and odour.
- 5- Placement of drugs within body tissues.
- 6- Sustained release medication.
- 7- Controlled release medication.
- 8- Optimal drug action.
- 9- Insertion of drugs into body cavities (rectal, vaginal)
- 10- Use of desired vehicle for insoluble drugs.

Solid dosage forms include

- *Tablets*
- *Capsules*
- *Granules*
- *Powders*

Tablets:

- *Tablets are solid dosage forms containing one or more active ingredients. They are unit dosage form. They are obtained by single or multiple compression and may be coated or uncoated. They are usually intended for oral applications but sometime they also have some alternative applications such as implants, tablets for injection, irrigation or external use, vaginal tablets etc.*

Quality Control Tests for oral solid dosage form (TABLETS)

Two types of tests

- ***PHYSICAL TESTS***
- ***CHEMICAL TESTS***

PHYSICAL TESTS

- *1. Disintegration*
- *2. Weight Variation*
- *3. Hardness*
- *4. Friability*
- *5. Thickness & Diameter*

CHEMICAL TESTS

- *Drug Content or Assay*
- *CONTENT UNIFORMITY TEST*
- *DISSOLUTION TEST*

Complete list of test performed for tablets

1. Appearance, odor, color, taste
2. Hardness
3. Disintegration
4. Friability
5. Thickness uniformity
6. Weight uniformity
7. Assay of the active ingredient
8. Moisture content
9. Light stability
10. Identification tests for the active ingredient and possible contaminants
11. Content uniformity
12. Dissolution
13. Microbial limits, e.g., total microbial count
14. Stability of the active ingredient in the formula and marketed container

Table USP/NF Requirements for Tablets

Test		Procedure
1.	Identification	Specific color test, infrared spectrum, UV spectrum
2.	Impurities or degradation products	See Table 17
3.	Weight variation	Sec. III.A
4.	Content uniformity	For tablet that contains highly toxic or 50 mg or less of active ingredient
5.	Disintegration	Sec. III.C
6.	Dissolution	Sec. III.D
7.	Moisture	See Table 3
8.	Microbial limit	Negative salmonella as in digitalis, pancreatin, and Rauwolfia serpentina tablets
9.	Assay	See Table 14
10.	Packaging and storage	Well-closed container, e.g., codeine phosphate tablets
		Tight-closed container, e.g., diazepam tablets
		Light-resistant container, e.g., colchicine tablets
		Avoid exposure to excessive heat, e.g., tetranitrite tablets
		Preferably in glass containers, e.g., nitroglycerine tablets
		Protect from heat and moisture, e.g., oxytriphyline tablets

Source: U.S. Pharmacopeia/National Formulary.

A) PHYSICAL TESTS

1) General Appearance:

1.1 *Size and Shape:*

- Difficulty swallowing tablets and capsules can be a problem for many individuals and can lead to a variety of adverse events and patient noncompliance with treatment regimens.
- It is estimated that over 16 million people in the United States have some difficulty swallowing, also known as dysphagia.
- Size and shape of tablets and capsules affect the transit of the product through the pharynx and esophagus and may directly affect a patient's ability to swallow a particular drug product.
- Larger tablets and capsules have been shown to have a prolonged esophageal transit time. This can lead to disintegration of the product in the esophagus and/or cause injury to the esophagus, resulting in pain and localized esophagitis and the potential for serious sequelae
- Researchers specifically compared the transit time of 8 mm diameter round tablets to 11 mm diameter round tablets and 14 mm x 9 mm oval tablets and found the transit times for the 8 mm round tablet to be significantly shorter than for 11 mm round and 14 mm x 9 mm oval tablets ($p<.02$ and $p<.04$, respectively). In addition, significantly more patients were aware of the larger round tablets (>8 mm) sticking in the esophagus compared with the 8 mm round tablets.
- For any given size, certain shapes may be easier to swallow than others. In vitro studies suggest that flat tablets have greater adherence to the esophagus than capsule-shaped tablets. Studies in humans have also suggested that oval tablets may be easier to swallow and have faster esophageal transit times than round tablets of the same weight.

FDA Recommendation on Size and Shape of Tablets

- ❑ If the RLD is less than 17 mm in its largest dimension, the generic product should be:

- No more than 20 percent larger than the RLD in any single dimension (the resulting single dimension of the generic should not exceed 17 mm)
- No more than 40 percent larger than the volume of the RLD

❑ If the RLD is equal to or greater than 17 mm in its largest dimension, the generic product should be:

- No larger than the RLD in any single dimension
- No larger than the volume of the RLD

❑ Generic have a similar shape or have a shape that has been found to be easier to swallow compared with the shape of the RLD. Evaluating and comparing the largest cross sectional areas of the RLD and generic product is one strategy to quantify changes in shape

1.2. Color:

- Color specification is helpful for the identification of specific product during manufacturing process.
- There should be equal distribution of color as uniform distribution of color increases the ethical appeal.
- Sometime during manufacturing the problem of mottling (unequal and uneven distribution of color) occur that shows poor quality product.

1.3. Odor:

- Presence or absence of odor in a batch of tablet is also tested.
- Some drugs produce characteristic odor e.g. multivitamins and it is helpful for the detection of material.
- While in some drugs presence of odour show the unstable drug or degradation e.g. aspirin has vinegar like odour if degraded.

1.4. Surface texture:

- The surface of tablet should be smooth and there must be no chips, cracks, contamination from external substances, capping and sticking.

2. *DISINTEGRATION TEST*

- The state in which any residue of the unit, except fragment of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.

Theories of disintegration:

1. Evolution of gas: If the gas is evolved by a chemical reaction, when the tablet comes into contact with water, then the tablet will disintegrate. This is the basis for manufacture of effervescent tablets. Example of such a reaction is sodium bicarbonate with citric and tartaric acid, which yields carbon dioxide.

2. Heat of wetting: The heat produced when a tablet is immersed in water causes the entrapped air in the tablet to expand and exert sufficient pressure to disintegrate the tablet.

3. Effect of water absorption: The water absorbed by the tablet initiate disintegration, but this depends upon the solubility of the drug and other ingredients present.

4. Swelling: The grains of the disintegrate, particularly of starches, swell in the present of water and exert pressure on the granules to force them apart.

5. Porosity of tablets: It has been shown that penetration of water into a tablet is proportional to its mean pore diameter or porosity. The porosity and permeability of tablets decrease as the tableting pressure increased, and as the porosity decrease, the disintegration time increases

Purpose:

- This test is performed to determine that whether the tablets or capsules disintegrate within the prescribed time when placed in a liquid medium under the specified experimental conditions

Apparatus:

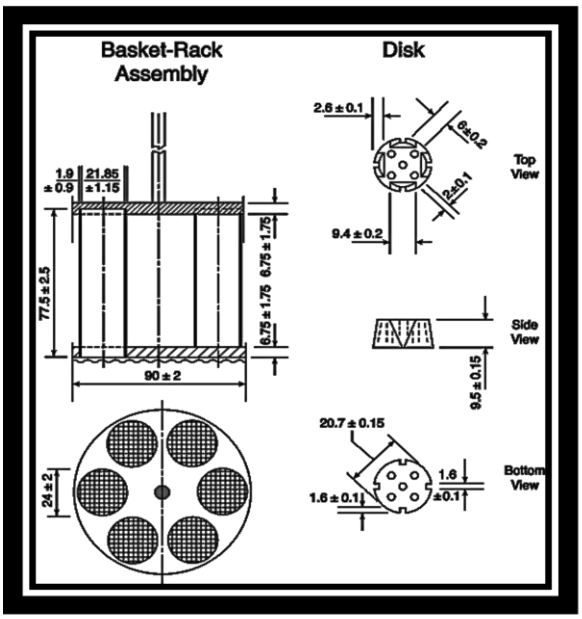
Two types of apparatus are used:

Apparatus-A:

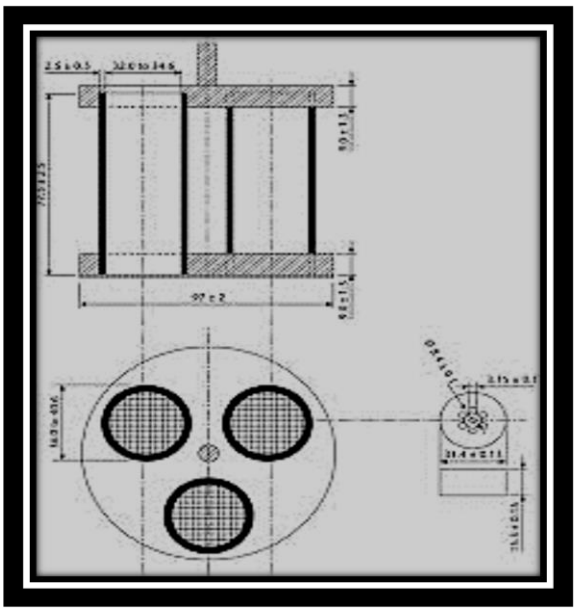
Most commonly used for tablets which are less than 18 mm long

Apparatus-B:

Most commonly used for tablets which are more than 18 mm long

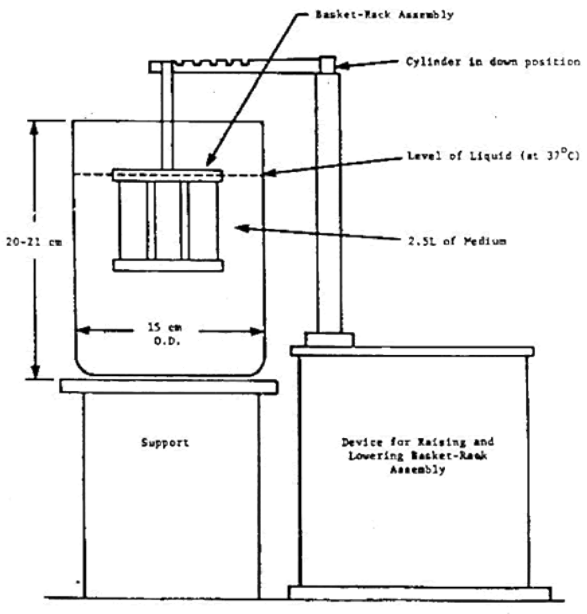


Apparatus A



Apparatus B

Diagram of Assembled Apparatus



Apparatus construction (Basket-rack assembly)

- Circular basket rack assembly
- Suitable vessel for immersion fluid (1 liter beaker)
- Thermostatic arrangement for maintaining the temperature at 37+2℃
- A device for rising and lowering of basket rack in immersion fluid at constant frequency of 28-32 cycles/min through a distance of 50-60 mm.
- The basket-rack assembly consists of 6 open-ended transparent tubes and a rack for holding these tubes in vertical direction.
- Each tube is 77.5 ± 2.5 mm long and having an inside diameter of 21.5 mm and a wall 1 to 2.8 mm thick
- The tubes are held in a vertical position by two plastic plates which are circular in shape and made up of transparent material having six holes of a diameter that allow the tube to be inserted.
- Attached to under surface of the lower plate is a woven stainless steel wire cloth, which has a plane square weave with 1.8 to 2.2 mm mesh apertures and with a diameter of 0.63±0.03 mm.
- The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the 2 plastic plates.
- A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

Medium used in disintegration:

- *Water*
- *Simulated gastric fluid (PH = 1.2)*
- *Simulated intestinal fluid (PH = 7.5)*

Procedure:

- Place 1 tablet in each of the six tubes of basket and operate the apparatus using water maintained at 37±20.

- At the end of time limit, lift the basket from the fluid and observe the tablets, if all of the tablets have disintegrated, test is clear, if 1-2 tablets fail to disintegrate, repeat the test with 12 additional tablets

Acceptance criteria:

- All the 6 tablets or capsules must be disintegrated. If 1 or 2 dosage units fails to disintegrate than repeat the test with additional 12 tablets. The requirements of the test are met if not less than 16 of the 18 dosage units tested are disintegrated.

i. Uncoated tablets:

If one or two of 6 tablets fails to disintegrate completely, repeat the test on 12 additional tablets, not less than 16 of total 18 tablets disintegrate completely.

According to USP & BP disintegration time must be less than 15 min.

ii. Film coated tablets :

Prescribed time and acceptance/rejection criteria are the same as to the uncoated tablets.

According to USP & BP disintegration time must be less than 30 min.

iii. Enteric coated tablets:

Place one tablet in each tube. Operate the apparatus using simulated gastric fluid till 1-2 hours. Lift the basket from fluid and observed the tablets. There should be no evidence of disintegration, cracking and softening. Operate the apparatus using simulated intestinal fluid for one hour or the time specified in the monograph. Acceptance/rejection criteria are same as of the uncoated tablets.

iv. Buccal tablets:

Place one tablet in each tube. Operate the apparatus using water or specified medium, if prescribed. After 4 hours all the tablets should have disintegrated. Acceptance/rejection criteria are same as of the uncoated tablets.

v. Sublingual tablets:

Apply the test for un-coated Tablets. Omit the use of disc. Observe the tablets for time specified in monograph. For the most of the sublingual tablets time limit is within 2min.

Apparatus-A	**Apparatus-B**
For tablets and capsules less than 18 mm long Tubes: • 6 open ended tubes • 77.5 ± 2.5 mm long • 21.5 mm internal diameter • 2 mm wall thickness Plates: • 2 superimposable plates • 90 mm diameter' • 6 mm thick • 6 holes Discs: • Cylindrical discs • 20.7 ± 0.15 mm diameter • 9.5 ± 0.15 mm thick • Transparent plastic material • Density 1.18-1.20 • Weighing 3.0 ± 0.2g • Each disc with 5 holes & 4 groves • Diameter of perforation is 2.0 mm	For tablets and capsules more than 18 mm long Tubes: • 3 open ended tubes • 77.5 ± 2.5 mm long • 33.5 ± 0.5 mm internal diameter • 2 mm wall thickness Plates: • 2 superimposable plates • 97 mm diameter' • 9 mm thick • 3 holes Discs: • Cylindrical discs • 31.4 ± 0.13 mm diameter • 15.3 ± 0.15 mm thick • Transparent plastic material • Density 1.18-1.20 • Weighing 3.0 ± 0.2g • Each disc with 7 holes & without groves • Diameter of perforation is 3.15 ± 0.1mm

3. Weight Variation Test

The purpose of this test is to measure uniformity in weight of tablets in a batch and to get estimate of active content in each unit of dosage form. It also give estimation of important vital excipients. If active content is more than 25% then usually weight variation test can be performed

Apparatus:

- Digital Weighing balance

Procedure:

- Take 20 units of dosage form randomly.
- Weigh each unit individually on digital weighing balance.
- Take an average weight of all 20 unit dosage forms.
- Calculate deviation of each individual tablet from average weight.
- Take percentage deviation of each unit of dosage form.

Formula:

D = deviation = average – individual weight

$$\%\text{age deviation} = \frac{Deviation}{Average\ weight} \times 100$$

Acceptance Criteria:

Average weight : BP	**Average weight : USP**	**%age deviation**
< 80 mg	< 130 mg	±10 %
80-250 mg	130-324 mg	± 7.5 %
>250 mg	>324 mg	±5 %

- Not more than 2 tablets can deviate from the limit.
- Not a single unit can deviate twice the limit given in monograph

4. *FRIABILITY:*

- It is the resistance of the tablets against the mechanical shock during packaging, handling and transportation and helpful for checking the lamination and capping
- *Friability is defined as a "percentage of weight loss by tablets due to mechanical action during test. Tablets are weighed before and after testing and friability is percent loss"*
- It is the tendency of tablets to powder, chip, or fragment and this can affect the elegance appearance, consumer acceptance of the tablet, and also add to tablet's weight variation or content uniformity problems.

Significance

- Check breakability
- Check drug loss
- Check capping and hardness

Apparatus: (Roche Friabilator)

- An instrument called friabilator consisting of drum is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping.
- Internal diameter 283-291mm
- Depth 36-40mm
- Made of transparent synthetic polymer with internal surface polished.
- A curved projection with an inside radius b/w 75.5-85.5mm that extent from middle of the drum to outer wall from where tablets are tumbled.
- Drum is rotated at 25± 1rpm.
- Thus at turn, tablets rolls or slide, and fall onto the drum wall or onto each other.

Procedure:

- For tablets weighing upto 0.65g, take a sample of tablets corresponding to weigh approximatelty 6.5 g.
- For tablets weighing more than 0.65g, take a sample of 10 tablets.
- Place the tablet on a sieve no. 100 and remove any loose dust with the aid of air pressure or a soft brush.
- Accurately weigh the tablet samples and place the tablet in the drum.
- Rotate the drum 100 times (25 rpm for 4 minutes) and remove the tablets.
- Remove any loose dust from the tablets as before. If no tablets are cracked, split or broken, weigh the tablets to the nearest mg.
- If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.
- Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned. In the case of hygroscopic tablets, a humidity-controlled environment is required for testing. A drum with dual scooping projections, or apparatus with more than one drum, for the running of multiple samples at one time, is also permitted.

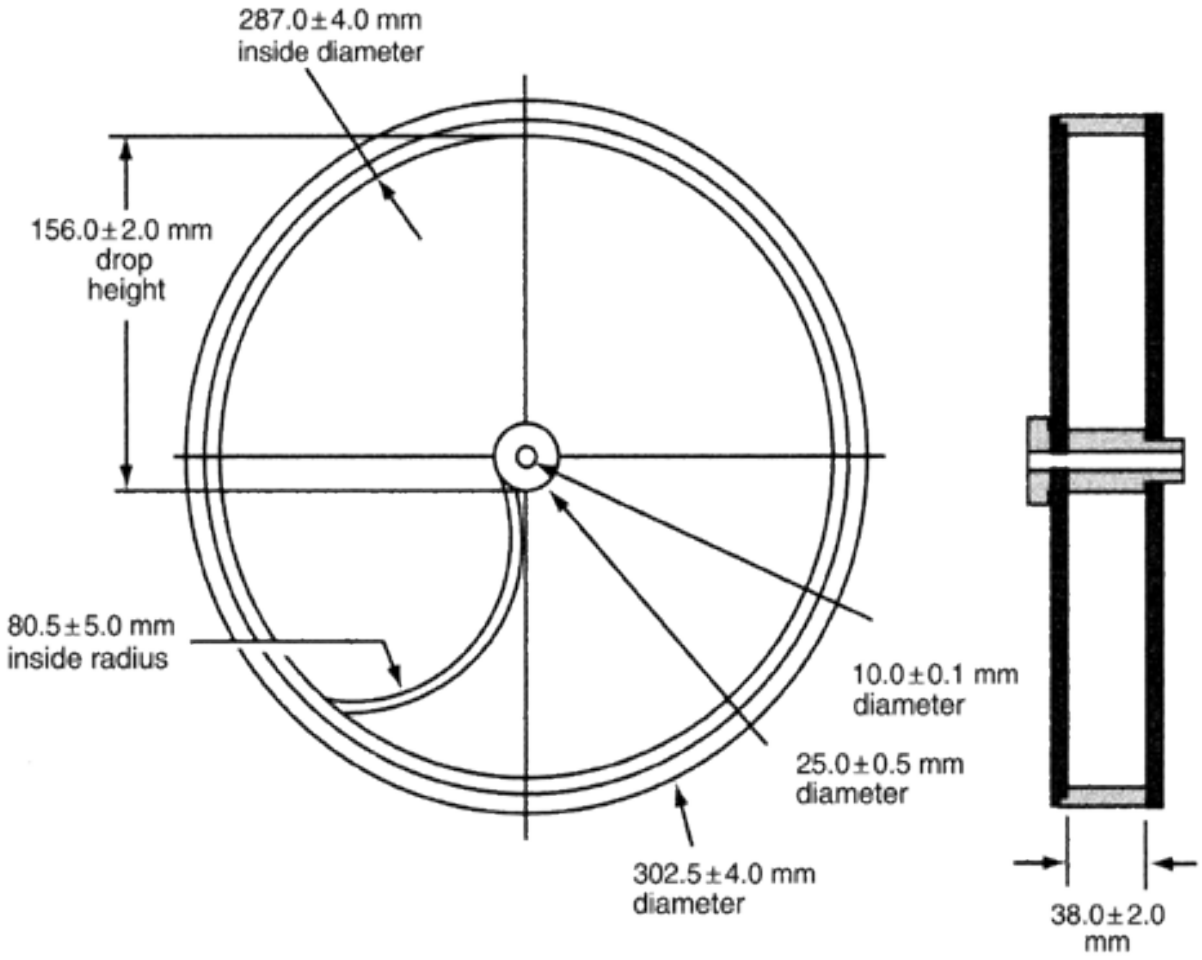
Acceptance Criteria:

- Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test is repeated twice and the mean of the 3 tests determined. A maximum loss of mass (obtained from a single test or from the mean of 3 tests) not greater than 1.0 %
- *Not more than 1% USP & BP*
- *Not more than 0.8% New Product*

Formula:

$$F = 100\ (1 - W1/\ Wo\ )$$

- Wo = Weight before test
- W1 = Weight after test



5. Tablet Hardness Test:

- Hardness is synonym for breaking force or resistance to crushing strength.
- According to USP it is tablet breaking force, and according to BP it is resistance to crushing of tablets.
- Hardness test ensures mechanical integrity and it defines optimum physical characteristics.

Purpose:

- Hardness test is performed to determine need for pressure adjustments. Hardness can effect disintegration. If tablets have high hardness then disintegration time will be also high and vice versa.
- It will also serve as guideline in handling, packaging and storage of formulation.

Factors Affecting the Hardness:

- Compression of the tablet and compressive force.
- Amount of binder. (More binder a more hardness)
- Method of granulation in preparing the tablet (wet method gives more hardness than direct method, Slugging method gives the best hardness).
- Particle size
- Mechanical interlocking

Types of hardness testers:

1. Manual or mechanical

- Strong-Cobb tester
- Monsanto Hardness tester
- Pfizer Hardness tester

2. Motor driven

- Schleuniger Hardness tester
- Erweka Hardness tester
- Pharma test hardness tester

PROCEDURE

i. Stoker-Monsanto Hardness Tester (manual):

- It is a small potable hardness tester, manufactured by Monsanto chemicals.
- Select 6 tablets randomly according to USP
- Place the tablets, diametrically, between the moving and fixed jaw one by one.
- Gradually increase the force applied to the edge of tablet by moving the screw knob forward until the tablet breaks.
- The reading is noted from the scale which indicates the pressure required in kg to break the tablet.

ii. Erweka hardness tester(mechanical):

- In this instrument the breaking force is applied by a beam fastened to one end to a pivot.
- The motor moves a weight along the beam at a constant speed and increase the force against the tablet.
- When the tablet breaks, a micro switch is activated that stop the motor.
- An indicator is fastened to the weight shows the breaking strength on a scale in kg.

Orientation of Tablet:

- Round tablets without scoring: Diametral compression
- Unique or complex shape: No obvious orientation. In general : Across the diameter or parallel to the longest axis.

- Scored tablets : Scores perpendicular to platen faces, it is for the strength of matrix
- Scores parallel to platen faces, it is breaking force required to break tablet at score

Units:

- Kg (SI unit)
- Newton (SI unit) 9.807 Newtons = 1 kilogram.
- Pound (lb) 1 kilogram = 2.204 pounds.
- Kilo pound (kp)
- Strong Cobb (SC) an ad hoc unit of force, 1 Strong-Cobb represented roughly 0.7 kilogram of force or about 7 newtons

Acceptance Criteria:

- Force of about 5-8 kg is considered a minimum requirement for satisfactory tablet.

6. THICKNESS AND DIAMETER:

- It is important for the tablets and capsules to undergo quality test to make sure all tablets and capsules in the same type are uniform in physiochemical properties (such as diameter, thickness and hardness) to provide the same pharmacological effects and to prevent incorrect dose given to the patients.

Devices:

- Micrometer Screw gauge, Vernier calipers or Digital hardness tester

Significance:

- Proper packaging of solid dosage form, i.e. in blister, strip, bulk or bottle packaging's.

Factors Affecting the thickness & diameter:

Following factors are there:

- Tablet compression or force
- Amount of material in punch or die
- Depth and diameter of die

Procedure:

1. 10 tablets of Uphamol Cold and Flu are selected and then, the test for diameter uniformity and thicknessis carried out by using the apparatus

2. Then the value of the diameter and thickness is taken. The deviation of each is calculated

$$\text{Deviation of diameter \%} = \frac{\text{Average of diameter for the tablets} - \text{diameter of each tablet}}{\text{Average of diameter for the tablets}}$$

Acceptance criteria

The deviation of individual unit from the mean diameter should not exceed ± 5% for tablets with diameter of less than 12.5 and ± 3% for diameter of 12.5 mm or more.

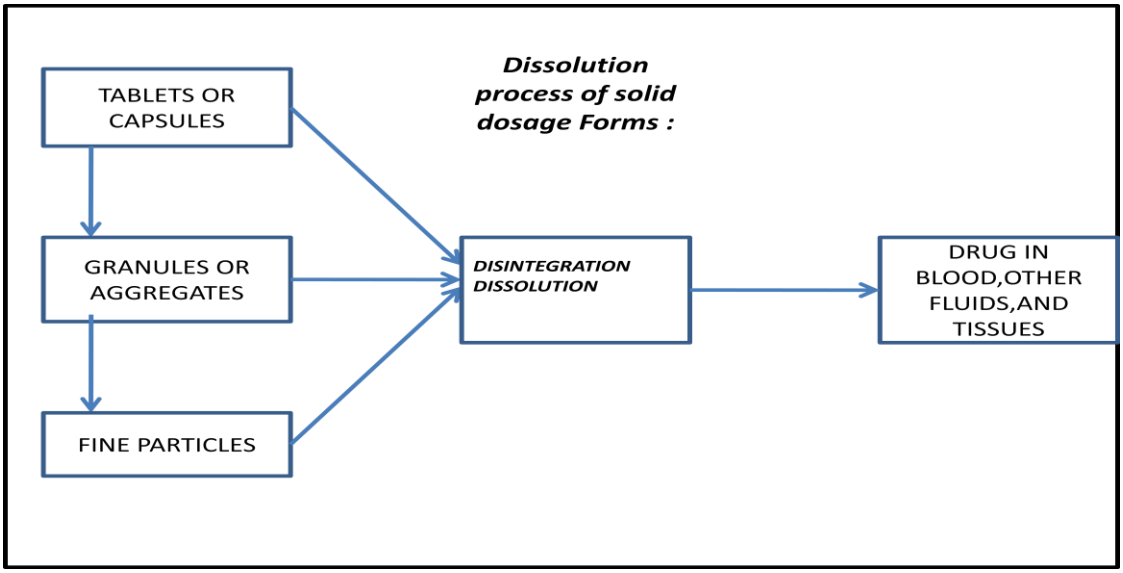
B) CHEMICAL TESTS

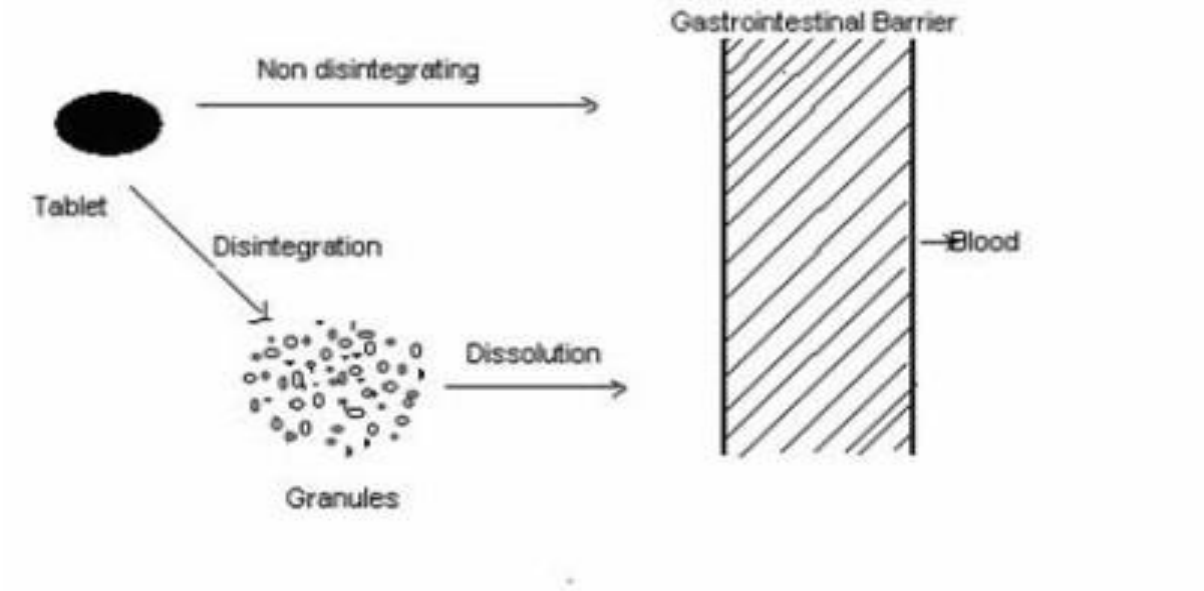
1. DISSOLUTION TESTING

DEFINITION:

- Dissolution is the process by which a solid solute enters in to a solution i.e mass transfer from solid surface to liquid phase.
- In the pharmaceutical industry, it may be defined as "the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface and temperature.
- Solid dosage forms may or may not disintegrate when they interact with gastrointestinal fluid following oral administration depending on their design.

For disintegrating solid oral dosage forms, disintegration usually plays a vital role in the dissolution process since it determines to a large extent the area of contact between the solid and liquid.





1.1 Mechanism of Dissolution

Dissolution test determines the cumulative amount of drug that goes into solution as a function of time

Steps involved

- STEP 1: liberation of the solute or drug from the formulation matrix (disintegration)
- STEP 2: dissolution of the drug (solubilization of the drug particles) in the liquid medium

The overall rate of dissolution depends on the slowness of these two steps

First Step:

Cohesive properties of the formulated solid dosage form drug play a key role disintegration and erosion

Semi- solid or liquid formulations, the dispersion of lipids or partitioning of the drug from the lipid phase is the key factor. If the first step of dissolution is rate-limiting, then the rate of dissolution is considered to be *disintegration controlled*

Second Step

Solubilization of the drug particles depends on the physicochemical properties of the drug such as its chemical form (*e.g.,* salt, free acid, free base) and physical attributes

1.2 Theories of Drug Dissolution

I. Diffusion layer model/Film Theory

II. Danckwert's model/Penetration or surface renewal Theory

III. Interfacial barrier model/Double barrier or Limited solvation theory

I. Diffusion layer model/Film Theory

It involves two steps:

a. Solution of the solid to form stagnant film or diffusive layer which is saturated with the drug

b. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution; this is r.d.s in drug dissolution.

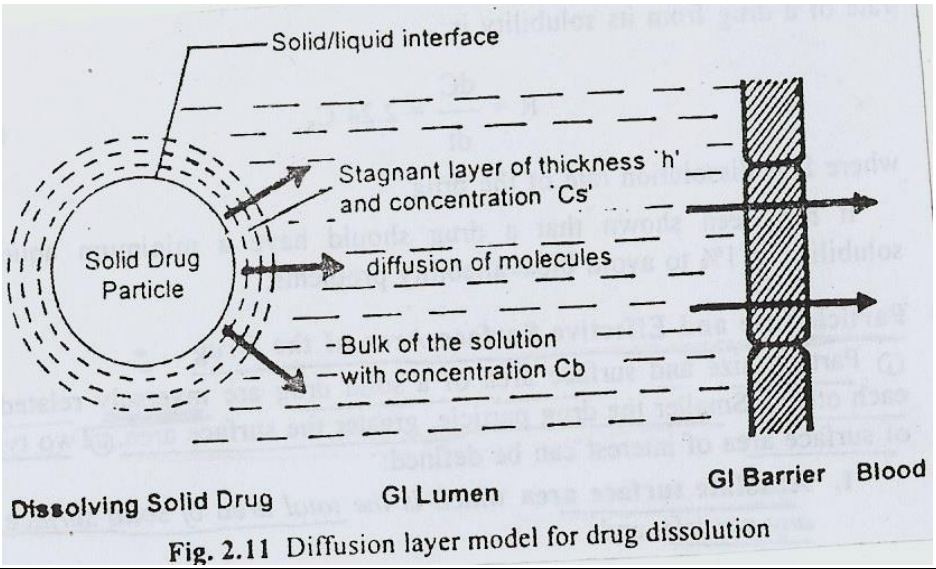


Fig. 2.11 Diffusion layer model for drug dissolution

Noyes-Whitney equation:

- The rate of dissolution is given by Noyes and Whitney:

$$\frac{dc}{dt} = k\,(C_s - C_b)$$

Where,

dc/dt= dissolution rate of the drug

K= dissolution rate constant

C_s= concentration of drug in stagnant layer

C_b= concentration of drug in the bulk of the solution at time t

---

Modified Noyes-Whitney's equation:

Modified Noyes-Whitney's Equation -

$$\frac{dC}{dt} = \frac{DAKw/o\,(C_s - C_b)}{Vh}$$

Where,

D= diffusion coefficient of drug.

A= surface area of dissolving solid.

Kw/o= water/oil partition coefficient of drug.

V= volume of dissolution medium.

h= thickness of stagnant layer.

$(C_s - C_b)$= conc. gradient for diffusion of drug.

- This is first order dissolution rate process, for which the driving force is concentration gradient.
- This is true for *in-vitro* dissolution which is characterized by non-sink conditions.

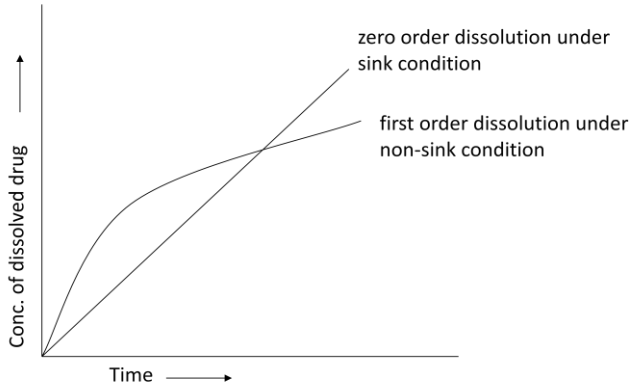
- The *in-vivo* dissolution is rapid as sink conditions are maintained by absorption of drug in systemic circulation i.e. C_b=0 and rate of dissolution is maximum.

  - Under sink conditions, if the volume and surface area of the solid are kept constant, then

$$\frac{dC}{dt} = K$$

  - This represents that the dissolution rate is constant under sink conditions and follows zero order kinetics.

Dissolution rate under non-sink and sink conditions.



- **Hixon-Crowell's cubic root law of dissolution:** It takes into account the particle size decrease and change in surface area,

$$W_0^{1/3} - W^{1/3} = K_t$$

Where,

W_0=original mass of the drug

W=mass of drug remaining to dissolve at time t

K_t=dissolution rate constant.

II. Danckwert model/Penetration or surface renewal Theory

- Dankwert takes into account the eddies or packets that are present in the agitated fluid which reach the solid-liquid interface, absorb the solute by diffusion and carry it into the bulk of solution.
- These packets get continuously replaced by new ones and expose to new solid surface each time, thus the theory is called as surface renewal theory.

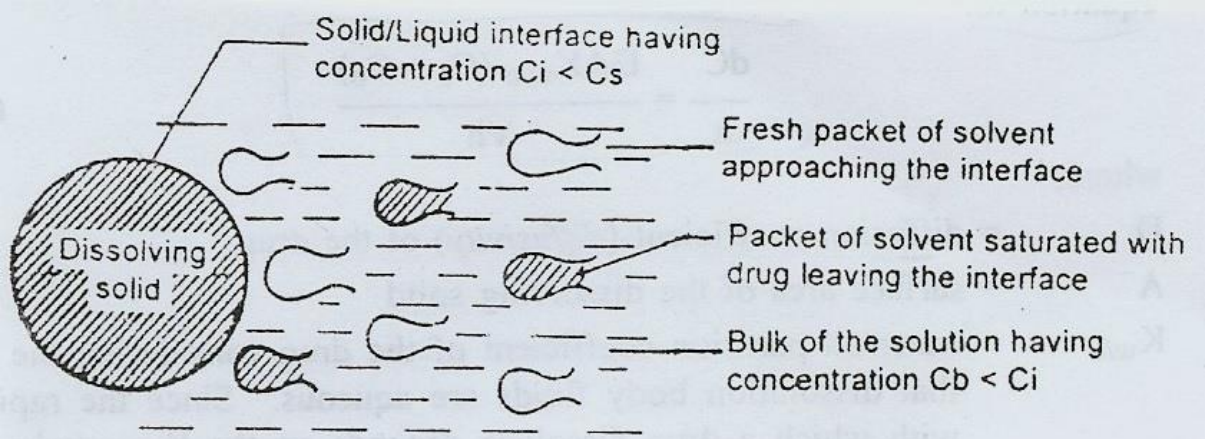


Fig. 2.13 Danckwert's model for drug dissolution

- The Danckwert's model is expressed by equation

$$V\frac{dC}{dt} = \frac{dm}{dt} = A\,(Cs\text{-}Cb).\sqrt{\gamma D}$$

Where,

m = mass of solid dissolved

Gamma (γ) = rate of surface renewal

III. Interfacial barrier model/Double barrier or Limited solvation theory

- Based on solvation mechanism, and it is function of solubility rather than diffusion
- When considering dissolution of the crystal have different interfacial barrier , given by the following equation

  $G = K_i (C_s - C_b)$

  Where,

  G = dissolution rate per unit area,

  K_i = effective interfacial transport constant.

- model can be extended to both the diffusion layer model and danckwert's model

1.3 Factors Influencing Dissolution And Dissolution Studies

I. Physicochemical Properties of Drug
II. Factors related with formulation
III. Processing Factors of Formulation
IV. Factors Relating Dissolution Apparatus
V. Factors relating Dissolution test parameters

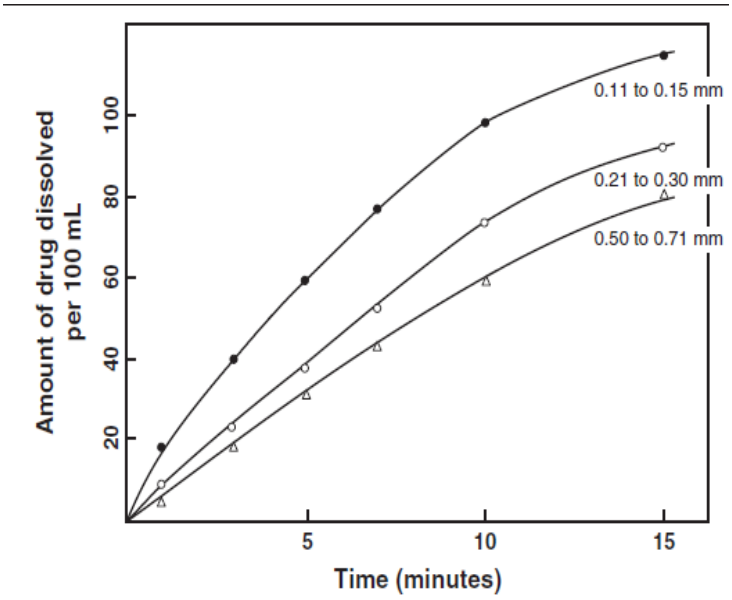
I. PHYSICOCHEMICAL PROPERTIES OF DRUG

A) DRUG SOLUBILITY:

- Solubility of drug plays a prime role in controlling its dissolution from dosage form.
- Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems.
- The drug might be considered 'poorly soluble' when its dissolution rate is slower than the time it takes to transfer past its absorption sites, resulting in incomplete bioavailability.
- This generally is the case for drugs where aqueous solubility is less than 100 mg/ml

B) 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.
- For poorly soluble drugs and many hydrophobic drugs, reduction in the particle sizes of about 3–5 mm is frequently employed as a successful strategy for enhancing drug dissolution rate. It is important to note that for some drugs too much reduction in the particle size can lead to exposure of surface charges, which can retard the drug dissolution rate.
- Micronization of sparingly soluble drug to reduce particle size is by no means a guarantee of better dissolution and bioavailability.



C) 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 Pencillin- G, sulfa drugs, phenytoin, barbiturates etc.

D) SOLVATES & HYDRATES:

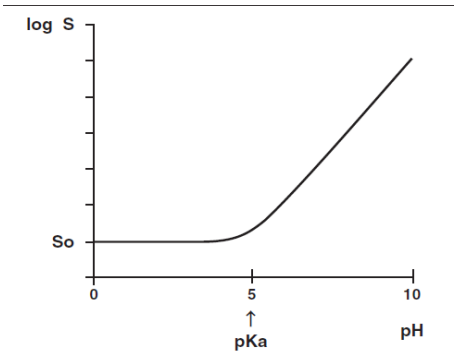
- A solvate is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice.
- If the solvent is water, it is called a hydrate.
- Anhydrous compounds are highly soluble than hydrate compounds.eg: anhydrous and hydrate forms of ampicillin.

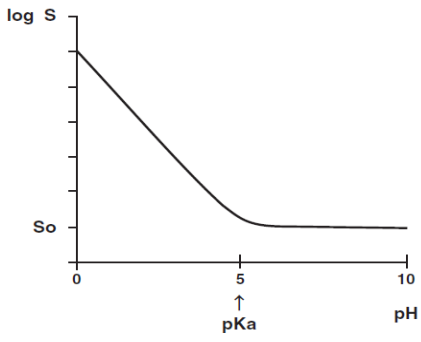
E) EFFECT OF pH:

- The solubility of a weak acidic drug or weak basic drug is influenced by the pH of the fluid.
- Therefore, differences are expected in the solubility and the dissolution rate of such drugs in different regions of the GIT.
- Rate of dissolution is increases while increasing the pH solution.

  Ex: Pencillin , Aspirin alkaline buffered tablets dissolution

- The solubility of weak acids and bases depends on their ionization constants, pKa as well as the pH of the dissolution medium. Intrinsic solubility can be defined as the solubility of a compound in its free acid or base form. For weak acids this is approximated by the solubility at pH values greater than one unit below its pKa. As the pH of the fluid increases, the solubility of the weak acid increases owing to the contribution from the ionized species. At pH values greater than pH = pKa + 1, a linear relationship between the logarithm of the solubility and the pH is observed, until the limiting solubility of the ionized form is reached





F) ADSORBENTS:

- The concurrent administration of drugs and medicinal products containing solids adsorbents (e.g: antidiarrhoeal mixtures) may result in the adsorbents interfering with the absorption of such drugs from the GIT.eg: Promazine adsorbs on to attapulgite decreases absorption.

G) CO-PRECIPITATION:

- Dissolution rate of sulfathiazole could be significantly increased by co-precipitating the drug with povidone.

H) POLYMORPHISM & AMORPHISM:

- When a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as Polymorphism.
- Stable polymorphs has lower energy state, higher M.P. and least aqueous solubility.
- Metastable polymorphs has higher energy state, lower M.P. and higher aqueous solubility.
- Generally, the metastable form is preferred because it exhibits the faster dissolution rate. There are a number of methods available for obtaining the metastable form that include recrystallization from different solvents, melting or rapid cooling. Polymorphism has been shown to influence solubility and, therefore, dissolution rate and bioavailability of drugs. Enhanced dissolution rate as a result of the right polymorph selection, however, does not always translate into improved bioavailability

I) COMPLEXATION:

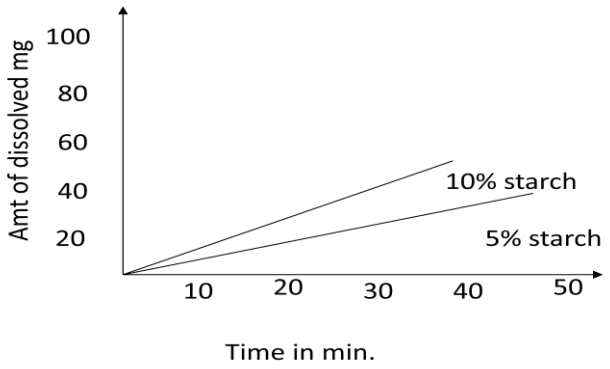
- Complexation of a drug in GIT fluids may alter the rate and the extent of absorption.eg: streptomycin, tetracyclines.

  Eg: -Diakylamides -prednisone

II) FACTORS RELATED TO DRUG PRODUCT FORMULATION

A) DILUENTS:

- 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 increases 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
- 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.



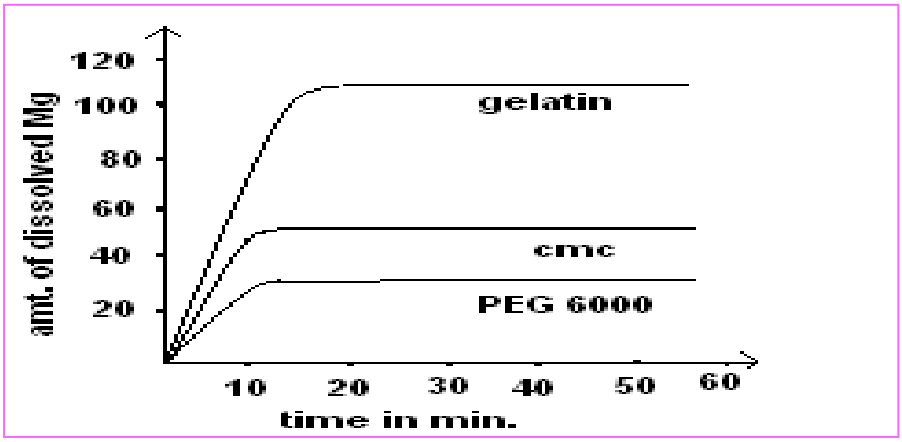
B) DISINTEGRANTS:

Disintegrating agent added before & after the granulation affects the 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.

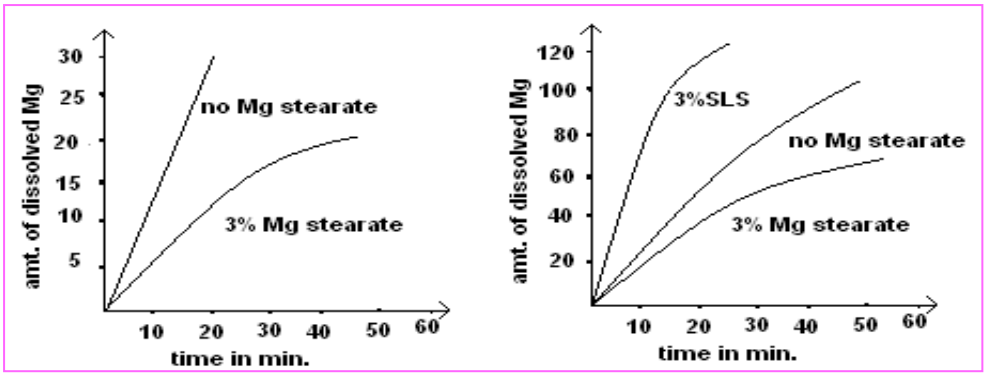
C) BINDERS & GRANULATING AGENTS:

- 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**.
- Water soluble granulating agent **Plasdone** gives faster dissolution rate compared to gelatin.



D) LUBRICANTS:

- Lubricants are hydrophobic in nature (several metallic stearate & waxes) which inhibit wettability, penetration of water into tablet so decrease in disintegration and dissolution.
- The use of soluble lubricants like SLS and Carbowaxes which promote drug dissolution.



E) 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.

F) EFFECT OF COATING:

- Coating ingredients especially shellac & CAP etc. Also have significant effect on the dissolution rate of coated tablet. Tablets with MC coating were found to exhibit lower dissolution profiles than those coated with HPMC at 37ºC.

G) EFFECT OF SOLUBILTY ENHANCERS:

- Cyclodextrins: The renewed interest of the past 25 years in cyclodextrins has provided an additional avenue for improving the solubility of poorly soluble drugs. Cyclodextrins are torus-shaped oligosaccharides composed of glucose molecules, which can form inclusion complexes by accepting a guest molecule into the central cavity. A positive feature of cyclodextrin complexes is that they are stable in aqueous solution. The earlier natural cyclodextrins included a-, b- and g-cyclodextrins containing 6, 7 and 8 glucose units, respectively.

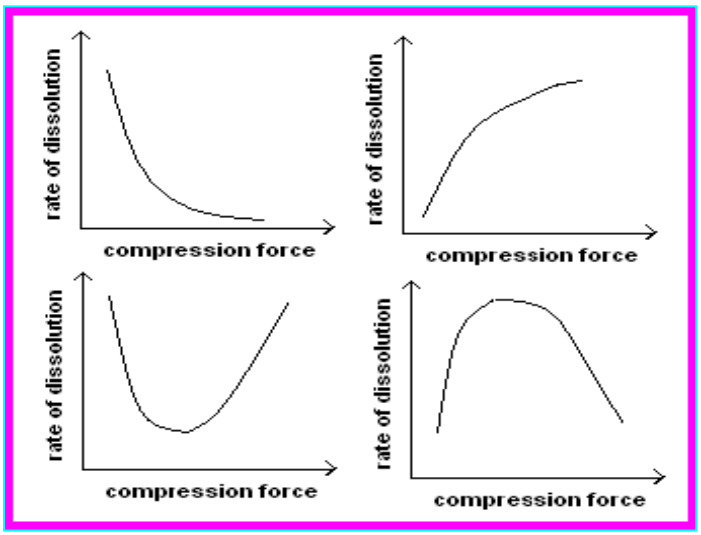
III) PROCESSING FACTORS OF FORMULATION

A) 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 Comminution"** 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.

B) COMPRESSION FORCE

- The compression process influence density, porosity, hardness, disintegration time & dissolution of tablet.



- In the above graphs:

1. Tighter bonding

2. Higher compression force cause deformation crushing or fracture of drug particle or convert a spherical granules into disc shaped particle

3. & 4. Both condition

C) 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.

D) STORAGE CONDITIONS

- Dissolution rate of hydrochlorothiazide tablets granulated with acacia exhibited decrease in dissolution rate during 1 yr of aging at R.T
- For tablets granulated with PVP there was no change at elevated temperature but slight decrease at R.T.

IV) FACTORS RELATING DISSOLUTION APPARATUS

A) AGITATION

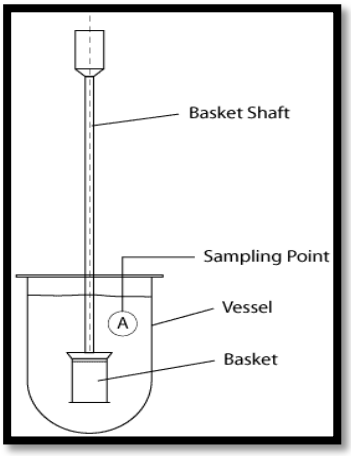
- Relationship between intensity of agitation and rate of dissolution varies considerably according to type of agitation used, the degree of laminar and turbulent flow in system, the shape and design of stirrer and physicochemical properties of solid.
- Speed of agitation generates a flow that continuously 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.

B) 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.

C) SAMPLING PROBE POSITION

- Sampling probe can affect the hydrodynamic of the system & so that change in dissolution rate.
- For position of sampling, USP 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.



V) FACTORS RELATING DISSOLUTION TEST PARAMETERS

A) Temperature

- Drug solubility is temperature dependent, therefore careful temperature control during dissolution process is extremely important.

B) Dissolution Medium

- Altering PH
- Dissolved air tends to release slowly in form of tiny air bubble that circulate randomly and affect hydrodynamic flow pattern

- Specific gravity decrease thus floating of powder thus wetting and penetration problem.
- Surface tension
- Viscosity
- Nature of medium

1.4 DISSOLUTION TESTING

- Dissolution and drug release tests are in-vitro tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually aq.medium under specified conditions.
- It is an important QC procedure for the drug product and linked to product performance in-vivo.

Need for dissolution testing:

- Evaluation of bioavailability.
- Batch to batch drug release uniformity.
- Development of more efficacious and therapeutically optical dosage forms.
- Ensures quality and stability of the product.
- Product development, quality control, research and application.

DISSOLUTION APPARATUSES:

	U.S.P	B.P	E.P
TYPE 1	Basket apparatus	Basket apparatus	Basket apparatus
TYPE 2	Paddle apparatus	Paddle apparatus	Paddle apparatus
TYPE 3	Reciprocating cylinder	Reciprocating cylinder	Reciprocating cylinder
TYPE 4	Flow through cell	Flow through cell	Flow through cell
TYPE 5	Paddle over disk	Disk assembly method Paddle over disk	Disk assembly method Paddle over disk
TYPE 6	Rotating cylinder	Extraction cell method	Extraction cell method
TYPE 7	Reciprocating disk	Rotating cylinder	Rotating cylinder
		The chewing apparatus	The chewing apparatus
		Punch and die Apparatus	Punch and die Apparatus

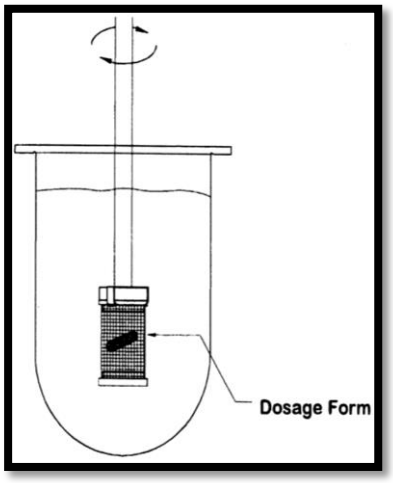
USP.APPARATUS	DESCRIPTION	ROT.SPEED	DOSAGE FORM
TYPE 1	Basket apparatus	50-120 rpm	IDR,DR,ER
TYPE 2	Paddle apparatus	25-50 rpm	IDR,DR,ER
TYPE 3	Reciprocating cylinder	6-35 rpm	IDR,ER
TYPE 4	Flow through cell	N/A	ER,Poorly soluble API
TYPE 5	Paddle over disk	25-50 rpm	TRANSDERMAL
TYPE 6	Rotating cylinder	N/A	TRANSDERMAL
TYPE 7	Reciprocating holder	30 rpm	ER

I. OFFICIAL METHODS:

APPARATUS-1 (ROTATING BASKET)

❖ ***DESIGN:***

- Vessel: -Made of borosilicate glass.
  -Semi hemispherical bottom
  -Capacity 1000ml
- Shaft : -Stainless steel 316
  -Rotates smoothly without significance wobble (100 rpm)
  -Speed regulator
- Water bath:-Maintained at 37±0.5ºC



❖ ***USE:***

Tablets, capsules, delayed release, suppositories, and floating dosage forms.

❖ ***METHOD:***

- Place the stated volume of the dissolution medium (±1 %) in the vessel and equilibrate dissolution medium to 37±0.5°C.
- Place 1 tablet or capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage form unit and immediately operate the apparatus at the rate specified (100rpm).
- Withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating basket, not less than 1cm from the vessel wall at each times stated.
- Replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37°C.
- Keep the vessel covered for the duration of the test and verify the temperature of the mixture under test at suitable times.
- Perform the analysis as directed in individual monograph and repeat the test with additional dosage form units.

❖ ***ADVANTAGES:***

- Can do pH change during the test
- Can be easily automated which is important for routine investigations.

❖ ***DISADVANTAGES:***

- Basket screen is clogged with gummy particles.

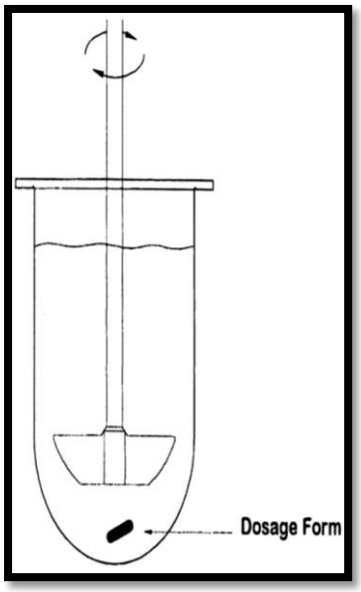
- Hydrodynamic dead zone under the basket.
- Degassing is particularly important.
- Mesh gets corroded by HCl solution.

Shaft with Conical Head and Basket

APPARATUS-2 (PADDLE)

❖ ***DESIGN:***

- Vessel: -Same as basket apparatus
- Shaft: -The blade passes through the shaft so that the bottom of the blade fuses with bottom of the shaft.
- Stirring elements: -Made of tefflon
  For laboratory purpose
  -Stainless steel 316
- Water-bath: -Maintains at 37±0.5°C
- Sinkers : -Platinum wire used to prevent tablet/capsule from floating

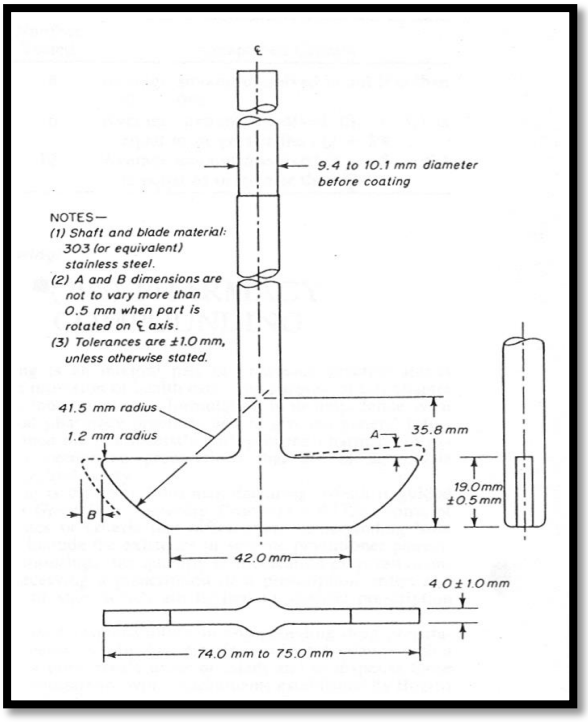


❖ ***METHOD:***

- It consists of a special coated paddle formed from a blade and a shaft that minimizes turbulence due to stirring.
- The coated material is inert.
- The paddle is attached vertically to a variable -speed motor that rotates at a controlled speed.
- The tablet or capsule is placed into a round-bottom dissolution flask and the apparatus is housed in a constant temperature water bath maintained at 37°C.
- Most common operating speeds are 50rpm for solid oral dosage forms and 25 rpm for suspensions.
- A sinker, such as few turns of platinum wire may be used to prevent a capsule or tablet from floating
- Used for film coated tablets that stick to the vessel walls or to help to position tablet/capsule under the paddle.

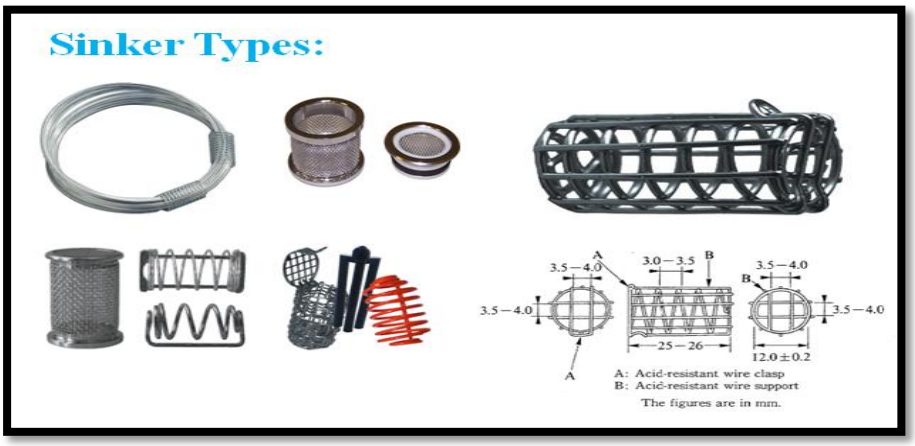
❖ ***ADVANTAGES:***

- Easy to use
- Robust
- Can be easily automated which is important for routine investigations



❖ ***DISADVANTAGES:***

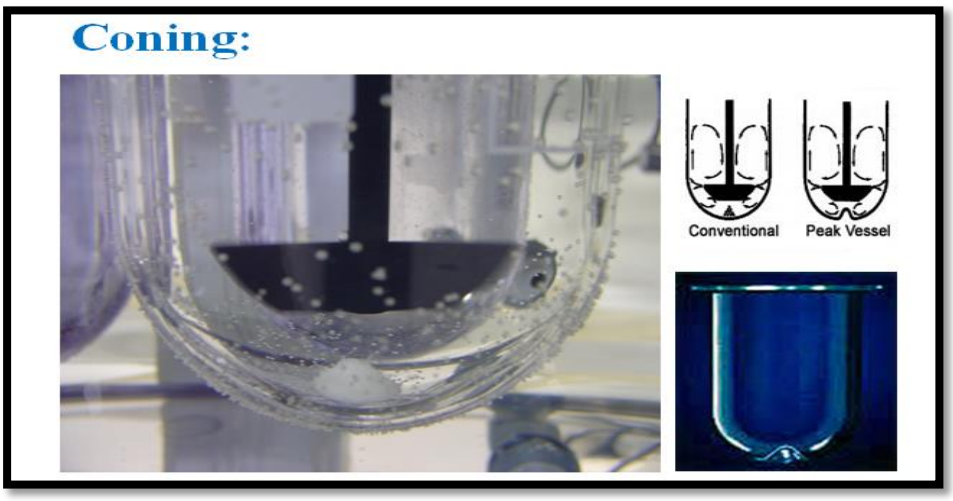
- pH/media change is often difficult
- Hydrodynamics are complex, they vary with site of the dosage form in the vessel (sticking,floating) and therefore may significantly affect drug dissolution
- Sinkers for floating dosage forms



- Coning

❖ ***CONING:***

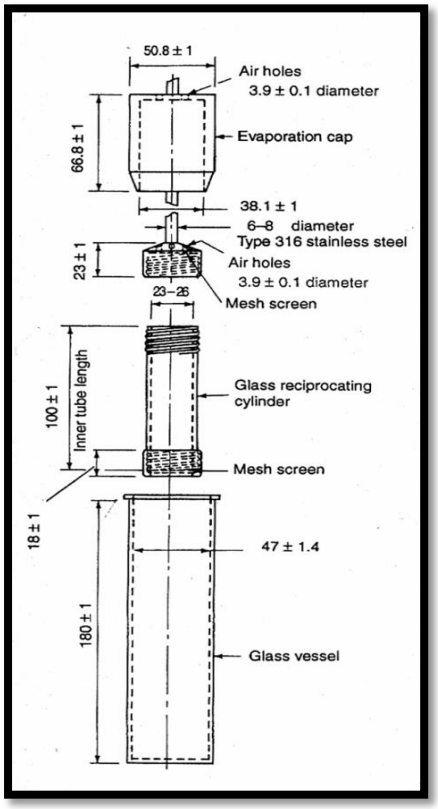
However, this configuration often causes accumulation of particles near the bottom of the vessel due to insufficient agitation underneath the paddle. This phenomenon is often referred as “coning” or “heap formation”. Once the coning phenomena occurred, the dissolution rate of a drug could become slower and more variable compared to well-suspended cases. The occurrence of coning phenomena depends on the particle size, the particle density, the fluid viscosity, the fluid density, the apparatus configurations and the agitation strength.

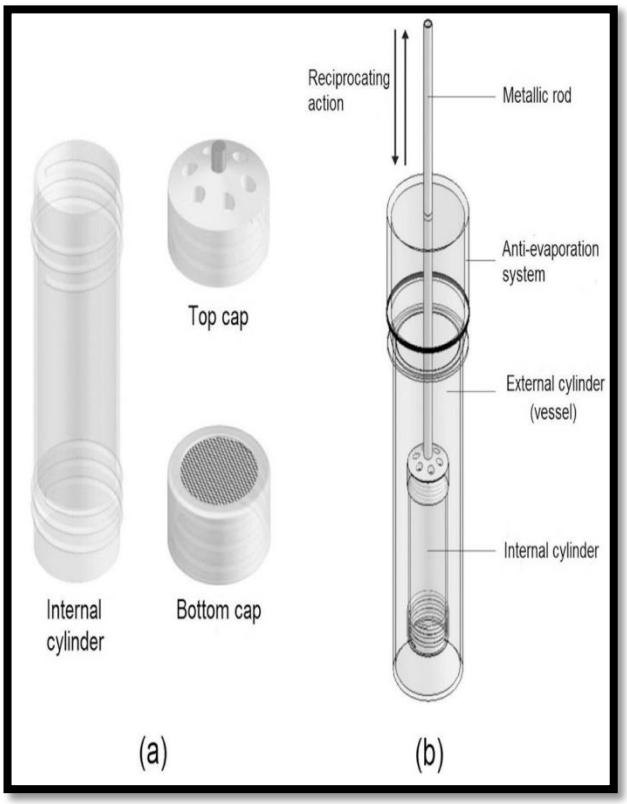


APPARATUS-3 (RECIPROCATING CYLINDER)

❖ ***DESIGN:***

- Vessel: -Set of cylindrical flat bottom glass vessels
  -Set of reciprocating cylinders
  -Stainless steel fittings (type 316)
  - Screens made of nonsorbing or non-reactive materials.
- Agitation type: -Reciprocating
  -5-35 rpm
- Volume of dissolution medium:-200-250ml
- Water bath:- Maintain at 37±0.5°C





❖ ***USE:***

Tablets, beads, pallets controlled and extended release formulations

❖ ***METHOD:***

- Place the stated volume of dissolution medium in each vessel of the apparatus, assemble the apparatus, equilibrate the dissolution medium to 37±0.5 and remove the thermometer
- Place one dosage form unit in each of the cylinders taking care to exclude the air bubbles from the surface of each dosage unit and immediately operate the apparatus as specified in the monograph.

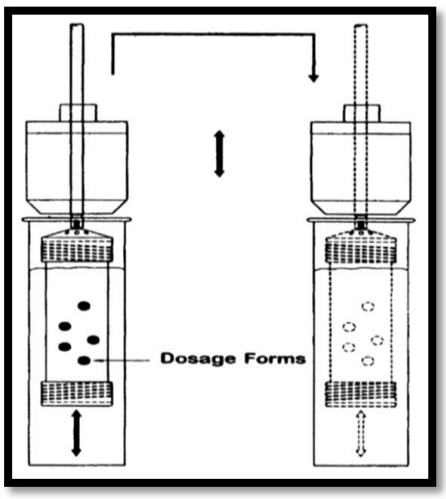
- During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1cm.
- Within the time interval specified raise the cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the dissolution medium and bottom of each vessel.

❖ ***ADVANTAGES:***

- Easy to change the pH
- pH-profiles
- Hydrodynamics can be directly influenced by varying the dip rate

❖ ***DISADVANTAGES:***

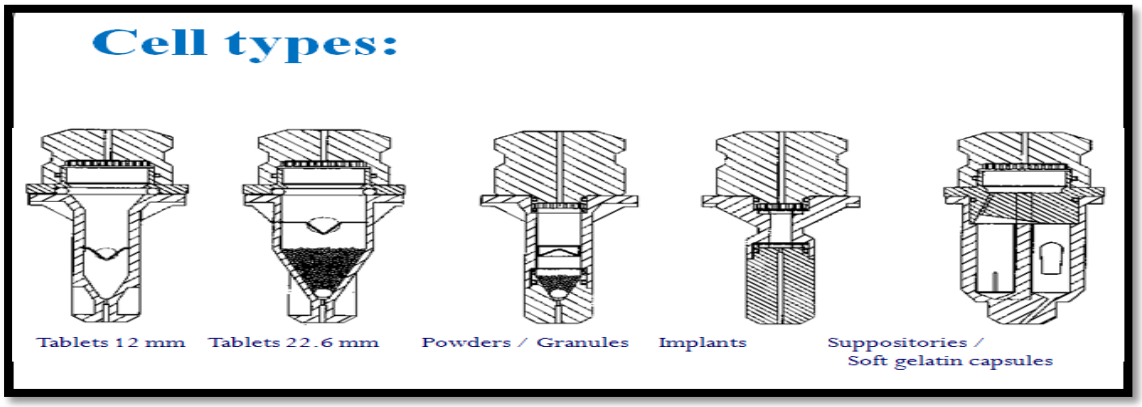
- Small volume (max. 250 ml)
- Little experience
- Limited data



APPARATUS-4 (FLOW THROUGH CELL)

❖ ***DESIGN:***

- Reservoir : -For dissolution medium
- Pump : -Forces dissolution medium through cell
  - -Holding a sample
  - -Flow rate 10-100ml/min
  - -Laminar flow is maintained
  - -Peristaltic/centrifugal pumps are not recommended
- Water bath:- Maintain at 37±0.5°C



❖ ***USE:***

- Low solubility drugs, microparticulates, implants, suppositories and controlled release formulations

❖ ***METHOD:***

- The flow through cell is transparent & inert mounted vertically with filters.
- Standard cell diameters are 12 & 22.6 mm.
- The bottom cone usually filled with glass beads of 1 mm diameter.
- Tablet holder used for positioning special dosage form

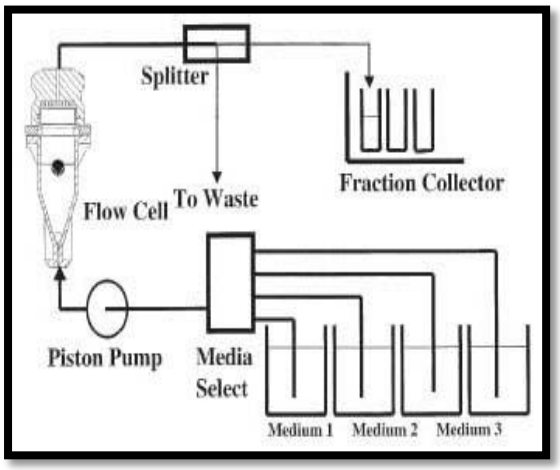
- Place the glass beads into the cell as specified in the monograph.
- Place one dosage unit on top of the beads or on a wire carrier.
- Assemble the filter head and fix the parts together by means of a suitable clamping device.
- Introduce by the pump of the dissolution medium warmed to 37±0.5 through the bottom of the cell to obtain the flow rate specified and measured with an accuracy of 5%.
- Collect the eluate by fractions at each of the times stated.

❖ ***ADVANTAGES:***

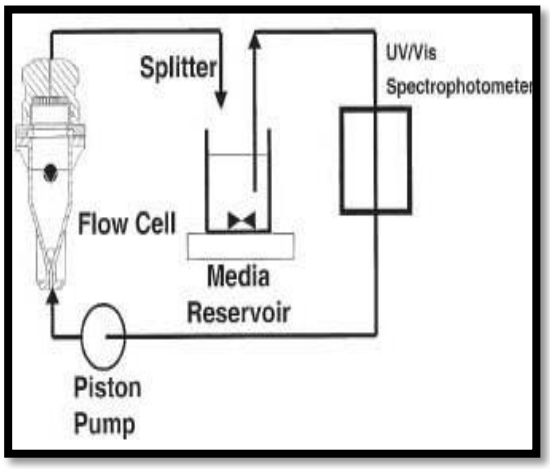
- easy to change media pH
- pH-profile possible
- Sink conditions maintained.
- different modes

  a) open system

  b) closed system



a) Open system



b) Closed system

❖ ***DISADVANTAGES:***

- Deaeration necessary
- high volumes of media
- labor intensive

APPARATUS-5 (PADDLE-OVER-DISK)

❖ ***DESIGN:***

- Vessel
- Shaft
- Stirring elements: -Rotating speed 25-50 rpm

- Sample holder: -Disk assembly that hold a product in such a way that release surface is parallel with paddle.
  -Paddle is directly attached over disk assembly.
  -Samples are drawn between surfaces off the medium and top of the paddle blade.
- Volume:900ml
- Temperature:32°C

❖ ***USE:***

Transdermal patches, ointments, floaters, emulsions.

❖ ***Modification:***

Disk design and volume

❖ ***METHOD:***

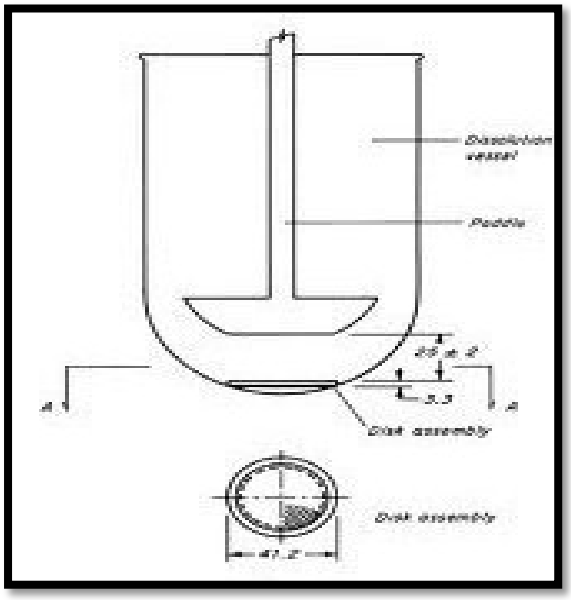
- This method is used for testing the release of drugs from transdermal products.
- The apparatus consists of a sample holder or disc assembly that holds the product.
- The entire preparation is placed in a dissolution flask filled with specified medium maintained at 32ºC.
- The paddle is placed directly over the disc assembly.
- The disk assembly holds the system flat and is positioned such that release surface is placed parallel with the bottom of the paddle blade. Vessel is covered to minimize evaporation during test.
- Samples are drawn midway between the surface of dissolution medium and the top of the paddle blade at specified times.

❖ ***ADVANTAGES:***

- Easy to handle
- Sink conditions are maintained
- Membrane effect is minimum
  I.e. drug is placed on a disc at the bottom.

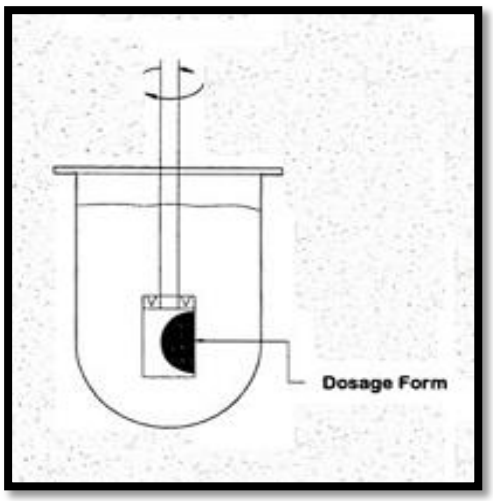
❖ ***DISADVANTAGES:***

- Disk assembly restricts the patch size
- Borosilicate glass
- 17 mesh is standard(others available)
- Accommodates patches up to 90mm



APPARATUS-6 (ROTATING CYLINDER)

- ***DESIGN:***
  - Vessel: In place of basket, cylinder is used.
  - Shaft : Stainless steel 316
  - Sample :- Mounted to cuprophan (inner porous cellulosic material) an entire system adheres to cylinder.
    - Dosage unit is placed in cylinder and release from side out.
  - Water-bath: maintained at 32±0.5°C



❖ **USE:**

- Transdermal patches cannot be cut into small size.
- Solid dosage forms, pH profile , small volumes

❖ ***METHOD:***

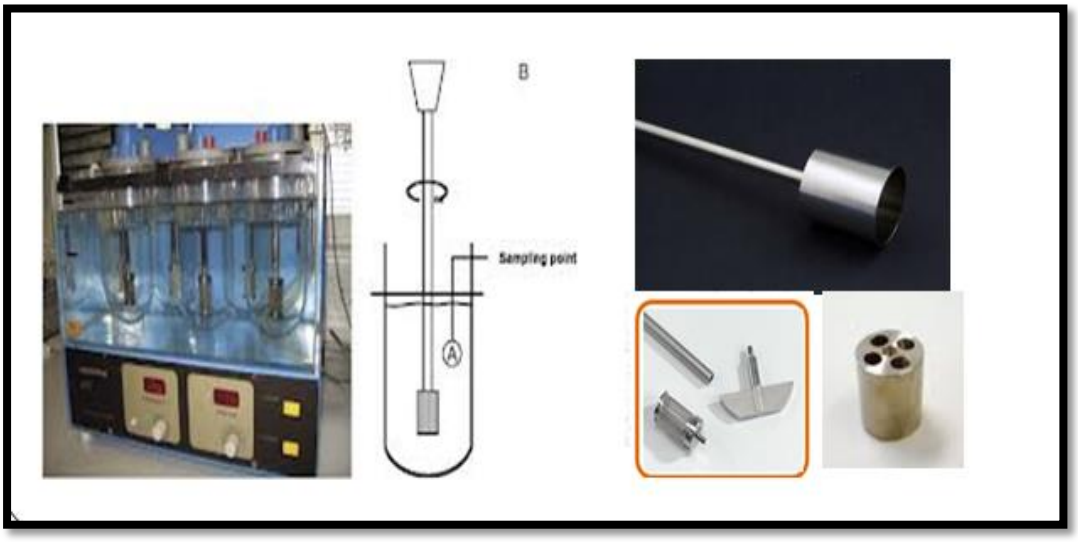
- Use the assembly from apparatus 1 except to replace the basket and shaft with a stainless steel cylinder stirring element.
- The temperature is maintained at 32±0.5°C.
- The dosage unit is placed on the cylinder with side out.
- The dosage unit is placed to the exterior of the cylinder such that long axis of the system fits around the circumference of the cylinder and removes trapped air bubbles.
- Place the cylinder in the apparatus and immediately rotate at the rate specified in the individual monograph.
- Samples are drawn midway between the surface of the dissolution medium and the top of the rotating cylinder for analysis.

❖ ***ADVANTAGES:***

- Equipment (apparatus 1) available with the manufacturers can be used with modification as apparatus 6.

❖ ***DISADVANTAGES:***

- Large volume of medium is required.
  - Drug gets diluted & causes difficulties in analysis
  - Difficult to clean the cylinder.

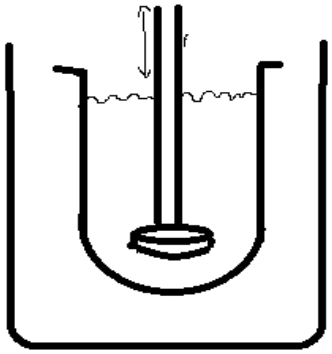


APPARATUS-7 (RECIPROCATING-HOLDER)

- ***DESIGN:***
  - Vessel: Flat bottomed cylindrical vessel

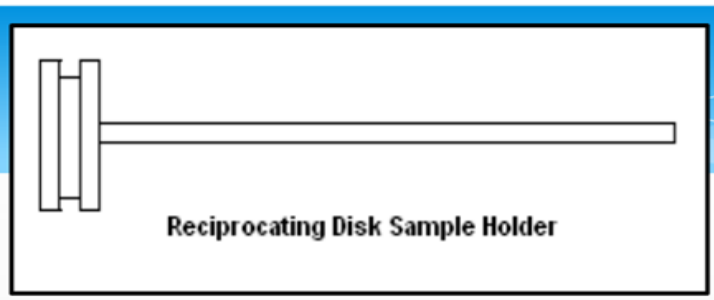
    -Volume of dissolution medium
  - Shaft :
  - Sample : -Placed on disk shaped holders
  - Agitation: -Reciprocation

    -Reciprocating frequency 30 cycle/sec
  - Water-bath: -Maintain at 32±0.5°C

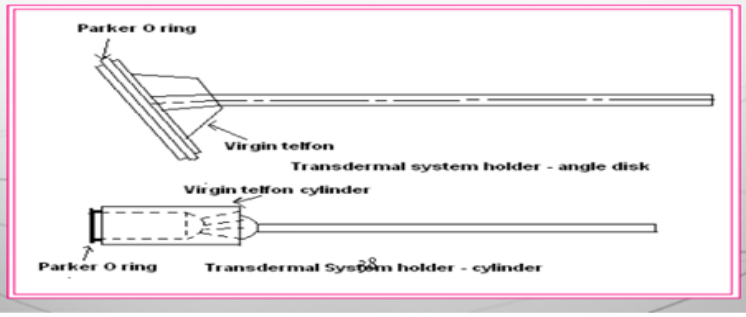


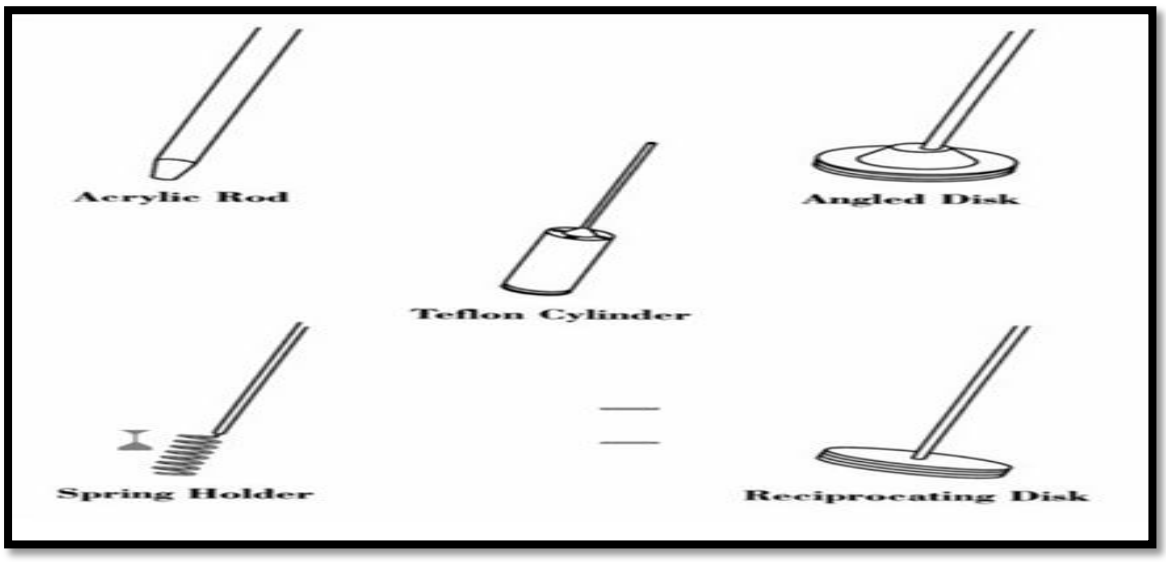
- ***USE:***

  Transdermal patches
- ***METHOD:***
  - The assembly consists of a set of volumetrically calibrated solution containers made of glass or suitable inert material, a motor, a drive assembly used to reciprocate the system vertically.
  - The samples are placed on the disk shaped holders using cuprophan supports
  - The test is carried out at 32°C.
  - The reciprocating frequency is 30cycles/min.
- ***ADVANTAGES:***
  - Convenient method for selecting the volume of the medium.
  - Sink conditions can be maintained.
  - More sensitivity
- ***DISADVANTAGES:***
  - Investment is high because the design is totally different from standard equipment already available in industry.



•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.



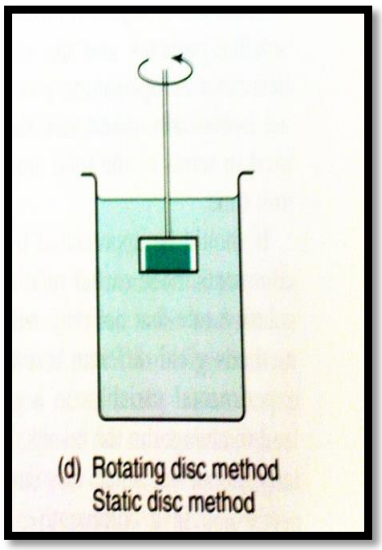


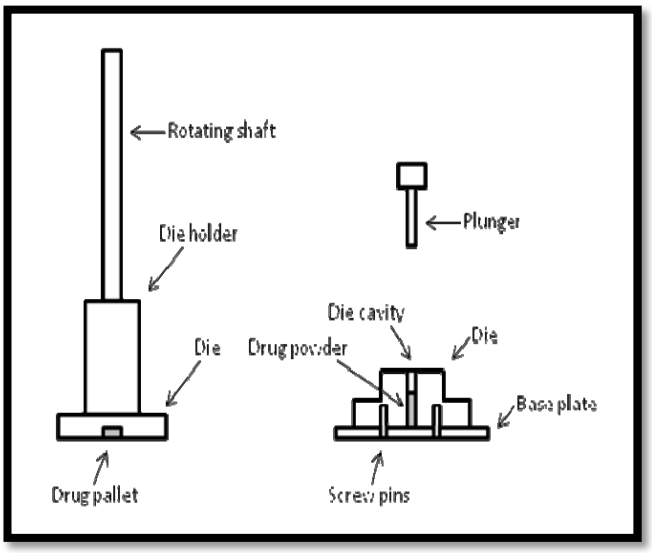
II. UNOFFICIAL METHODS

1. ROTATING/STATIC DISK METHOD

- Developed by late Eino nelson and described by Levy and Sahli.
- In this method,the drug is compressed in a non-disintegrating disc without excipients.
- The disc is mounted in a holder so that only one face of the disc is exposed to the dissolution medium.

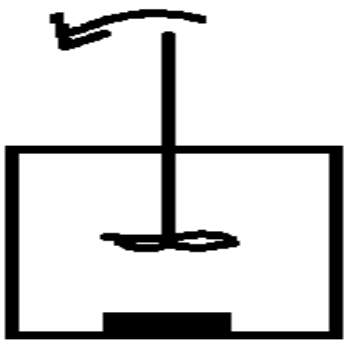
- The holder and disc are immersed in medium and held in a fixed position as in static disc method and rotated at a given speed in rotating disc method.
- Samples are collected at predetermined times.
- Surface area of the drug through which dissolution occurs is kept constant –intrinsic dissolution rate.





2. BEAKER METHOD:

- Reported by Levy and Hayes (1960).
- Dissolution medium, 250ml of 0.1N HCl at 37°C placed in a 400ml beaker.
- Agitation by three blade polyethylene stirrer, 5cm diameter and rotates at 60 rpm.
- Stirrer immersed to a depth of 2.7 cm in medium and in the center.
- Tablets are placed in a beaker and test was carried out.
- Samples are removed and assayed for the content. Stagnant studies are also performed.



3. STIRRER METHOD

- Developed by Poole (1969).
- It includes RBF and a stirring element similar to that of beaker method.
- RBF used to avoid the formation of moulds of particles in different positions on the flat bottom of a beaker.

4. PERISTALSIS METHOD:

- To stimulate hydrodynamic condition of GIT tract in an in-vitro dissolution device.
- It consists of rigid plastic cylindrical tubing fitted with septum and rubber stopper at both ends.
- Dissolution chamber consists of a space between septum and lower stopper.
- Dissolution medium is pumped with peristaltic action through the dosage form.

5. ROTATING BOTTLE METHOD:

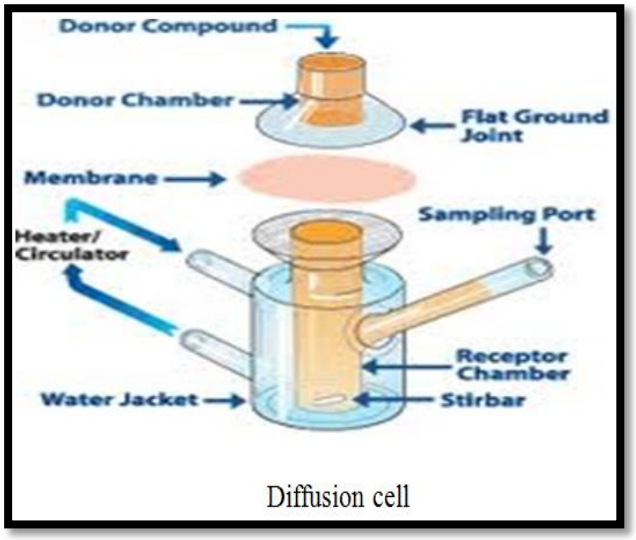
- It consists of rotating rack to hold sample drug products in bottles and they are capped tightly & rotated in 37°C temperature bath.
- Samples are decanted through a 40 mesh screen and residue is assayed.

6. DIALYSIS METHOD:

- Cell consists of 32mm inflated membrane.
- Plugged at the lower end by tight fitting cylindrical perspex box.
- Upper end of the tube held by thin perspex ring inserted into the tube and secured by an elastic band.
- The cell suspended, from the arm of the tablet disintegration apparatus and containing the dosage form in 150ml of distilled water at 37°C.
- The cell is raised or lowered 30times a min, into 150ml of distilled water at same temperature.
- Agitation by slight flexing and stretching of the dialysis membrane as it enters and leaves the bath. Rotated at 60rpm.

7. DIFFUSION CELL

- Static or flow through diffusion cells are used to characterize in-vitro drug release and drug permeation kinetics from a topical drug product eg: Ointment, cream or transdermal drug product.
- The Franz diffusion cell is static diffusion system used to characterize drug permeation through skin model.
- The skin is mounted on the Franz diffusion cell and the drug product is placed on the skin surface.
- The drug permeates across the skin into a receptor fluid compartment that may be sampled at various times.
- This system is used for selection of appropriate formulation that has optimum drug delivery.



Diffusion cell

ACCEPTANCE CRITERIA

Table 1. USP Acceptance Criteria

Stage	Number units	Acceptance Criteria
S1	6	Each unit is not less than Q* +5%
S2	6	Average of the 12 (S1+S2) units is ≥ Q and no uni is less than Q–15%
S3	12	Average of 24 (S1+S2+S3) units is ≥ Q and not more than 2 units are less than Q–15% and no unit is less than Q–25%

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

2. Content Uniformity Test

- The content uniformity test is to ensure that every dosage form contains equal amount of drug substance i.e. active pharmaceutical ingredient within a batch.
- Mainly it is used for testing the consistency of Amount of active pharmaceutical ingredient within individual units of tablets or capsules.
- Normally testing is confirmed by
  performing specific assay to determine the content of drug material contained in particular dosage form.

Content Uniformity Tests: Pharmacopoeial Comparison

- The major pharmacopoeias used widely are:
- The International Pharmacopoeia (IP)
- The British Pharmacopoeia (BP)
- The United States Pharmacopoeia (USP)
- The European Pharmacopoeia (Ph. Eur.)

United States Pharmacopoeia (USP): Procedure For Content Uniformity Test

- ***Stage1:**
  Take 10 units randomly and perform the assay.

  It passes the test if the relative standard deviation (RSD) is less than 6% and no value is outside 85-115%. And it fails the test if one or more values are outside 75-125%.

- ***Stage2:**

  But if one unit is outside the limits of 85% to 115% and within 75% to 125% take 20 more units and perform the assay procedure. Passes the test if RSD of all the 30 tablets is less than 7.8%, not more than one value is outside 85-115%, and no value is outside 75-125%. Or else the batch fails the test.

RELATIVE STANDARD DEVIATION (RSD)

- In probability theory and statistics, the coefficient of variation (CV), also known as relative standard deviation (RSD), is a standardized measure of dispersion of a probability distribution or frequency distribution. It is

often expressed as a percentage, and is defined as the ratio of the standard deviation to the mean (or its absolute value). The CV or RSD is widely used in analytical chemistry to express the precision and repeatability of an assay.

FORMULA FOR EXCEL

= [STDEV(Data Range) / AVERAGE(Data Range)]*100

APPLICATIONS:

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers and into soft capsules			WV	WV
Others			CU	CU

Quality Control Test for Solid Dosage Forms

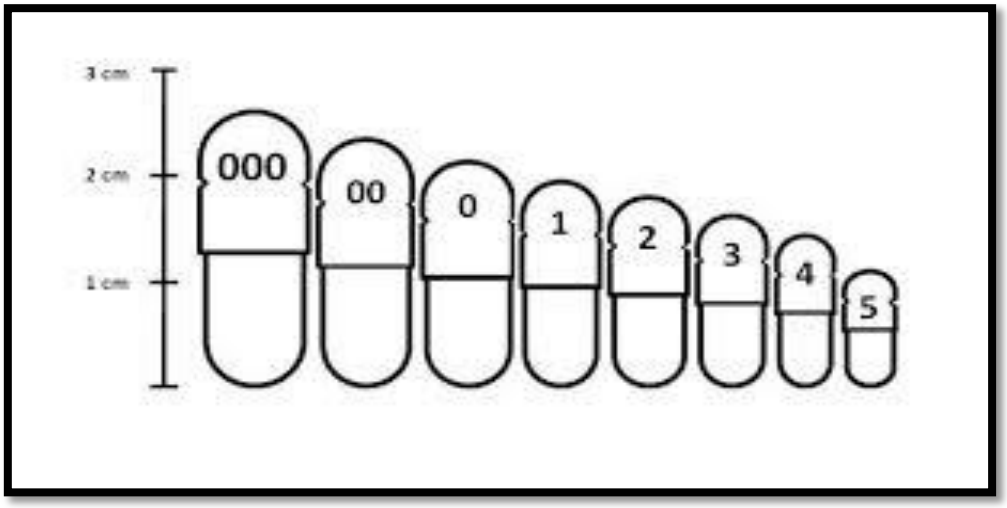
Part (B)

Quality Control of Capsules & Capsules Shells

Quality Control of Capsules & Capsules Shells

DEFINITION

Capsule is the Most versatile of all dosage forms. Capsules are solid dosage forms in which one or more médicinal and inert ingrédients are enclosed in a Small Shell or container usually made of gelatin.



ADVANTAGES OF CAPSULES

- *Capsules mask the taste and odour of unpleasant drugs and can be easily administered.*
- *They are slippery when moist and hence easy to swallow with a draught of water.*
- *As compared to tablets less adjuncts are required.*
- *The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.*
- *They are economical .*
- *They are easy to handle and carry.*
- *The shells can be opacified (with titanium dioxide) or coloured, to give protection from light.*

DISADVANTAGES OF CAPSULES

- *The drugs which are hygroscopic absorb water from the capsule shell making it brittle and hence are not suitable for filling into capsules.*
- *The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of stomach.*

QUALITY CONTROL OF CAPSULES

Whether capsules are produced on a small scale or large scale all of them are required to pass through certain tests i.e., quality control tests to test the quality of the finished product.

Quality control tests are divided into

PHYSICAL TEST	***CHEMICAL TEST***
Disintegration test	*Dissolution test*
Weight variation	*Assay*
	Content uniformity
	Stability testing

PHYSICAL TESTS OF CAPSULES

APPEARANCE

Capsule colour

- The capsules are fed to a pneumatic conveyer. In this unit, any capsule whose colour does not conform to the reference colour standard for that particular product is discarded others passes the test.

DISINTERATION TEST-

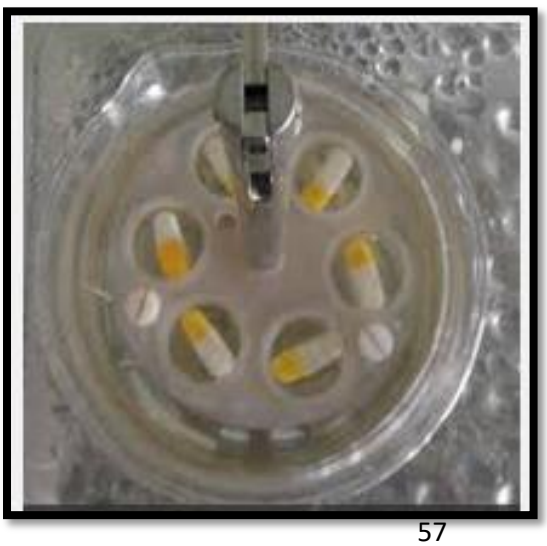
The disintegration test determines the whether capsules disintegrated with a prescribed time when placed in a liquid medium under the prescribed integral conditions.

METHOD-

According to B.P and which applies to both hard and soft capsules

1. Introduce one capsule in each tube and suspend the apparatus in a beaker containing water at 37 ^{0} C. If hard capsules float on surface of water, the disc may be added.

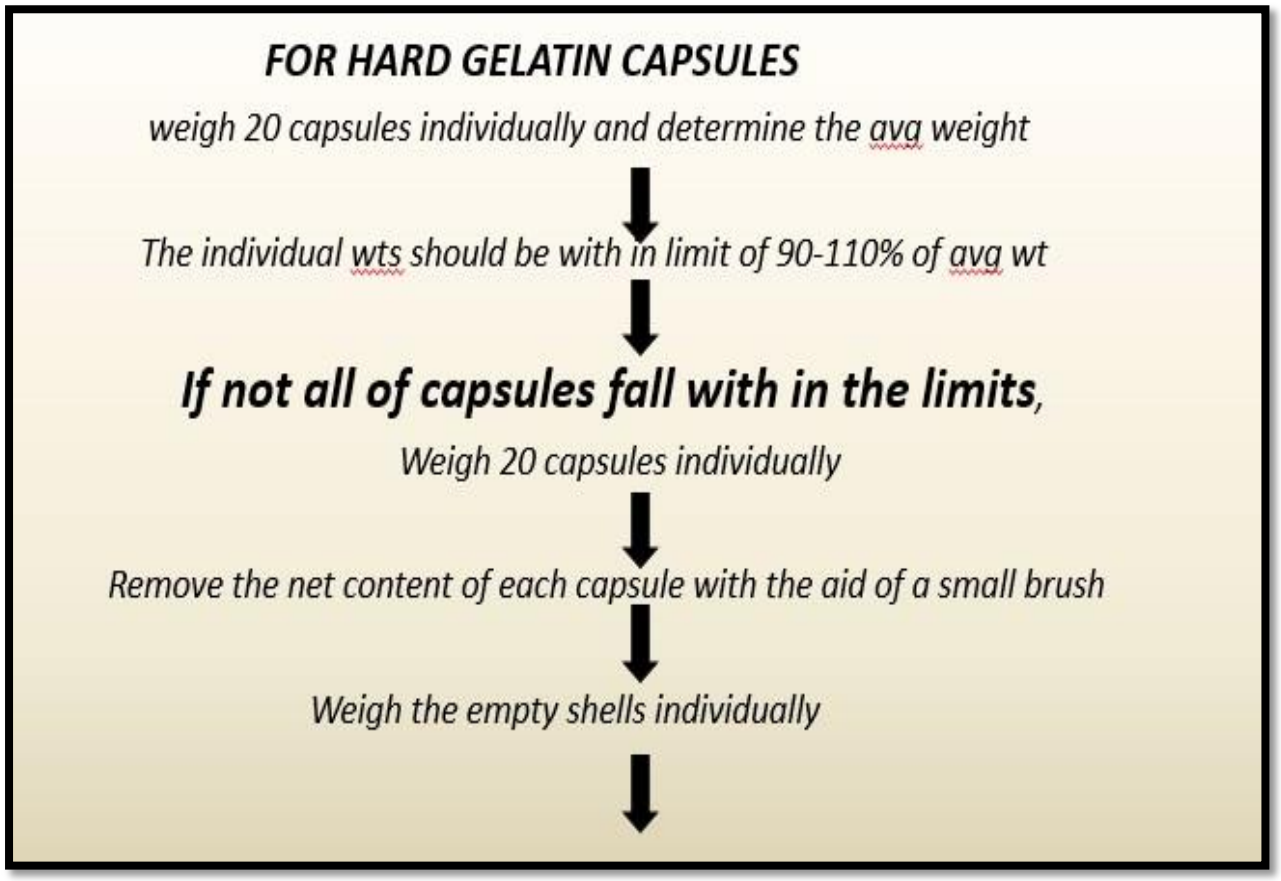
2. Operate the apparatus for 30 min, remove the assembly from the liquid.



Acceptance Criteria

- *No residue remains on the screen of the apparatus or,*
- *If the residue remains, it consists of fragments shells ,*
- *If a soft mass with no palpable core ,*
- *If the disc is used any residue is remaining on its lower surface should only consists of soft fragments of shells.*

WEIGHT VARIATION



net wt of contents individually = gross wt - the wt of shell

Determine the avg net content from the sum of individual net wt

Then determine the percentage deviation b/w individual net content and avg net content

LIMITS-

- *Not more then 2 of the differences are greater then 10% of the avg net content*
- *No case is the difference greater then 25% wt range*

If more then 2, but not more then 6 capsules deviate from the avg b/w 10-25%

Determine the net contents of an additional 40 capsules

Determine the avg content of entire 60 capsules

Determine the 60 deviations from the new avg

LIMITS-

- *NMT 6 of 60 capsules does the difference exceed 10% of the avg net content*
- *No case does the difference exceed 25%*

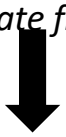
FOR SOFT CAPSULES

Proceed as directed under hard capsules, but determine the net wt of the contents of individual capsules as follows:

Weigh the capsules individually then cut and open the capsules

Remove the contents by washing with the suitable solvent

Allow the solvents to evaporate from the shells at room temp



Weigh the individual shells

Calculate the net contents

CHEMICAL TESTS OF CAPSULES

DISSOLUTION TEST-

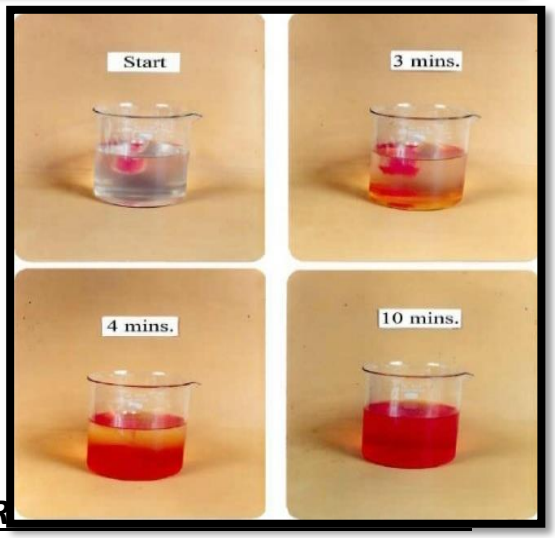
- *The dissolution test is carried out using the dissolution apparatus official U.S.P.*
- *The capsule is placed in a basket, and the basket is immersed in the dissolution medium and caused to rotate at a specified speed.*
- *The dissolution medium is held in a covered 1000ml glass vessel and maintained at 37 C by means of a constant temperature suitable water bath.*
- *The stirrer speed and type of dissolution medium are specified in the individual monograph*

Table 1. USP Acceptance Criteria

Stage	Number units	Acceptance Criteria
S1	6	Each unit is not less than Q* +5%
S2	6	Average of the 12 (S1+S2) units is ≥ Q and no uni is less than Q–15%
S3	12	Average of 24 (S1+S2+S3) units is ≥ Q and not more than 2 units are less than Q–15% and no unit is less than Q–25%

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

DISSOLUTION PROFILE



FACTORS AFFECTING DRUG DISSOLUTION FR

Overall Dissolution Rate is a Function of:

- *Dissolution Rate of the Shell*
- *Rate of Penetration of Dissolution Medium*
- *Rate of Disaggregation of Powder Mass*
- *Nature of Primary Drug Particles*
- *Normally, shell ruptures and dissolves within about 4 minutes.*
- *Rupture occurs first at the shoulders where shell wall is thinnest.*

- *Ends fall away and as liquid penetrates and disaggregation*
- *occurs, formulation tend to spill out of the two ends*

CONTENT UNIFORMITY

10 capsules are taken and subjected to assay

↓

9 of 10 capsules should be in the range of ± 15% (85-115%)

↓

And 10th capsule are beyond ± 15% range then 20 capsules are assayed

↓

All capsules within range of ± 25% (75-125%)

QUALITY CONTROL OF CAPSULES SHELLS

BLOOM STRENGHT OF GELATIN

RAW MATERIALS-

The gelatin of the capsule shells should be assayed for varies physical properties like bloom strength, viscosity etc..

CAPSULES PHYSICAL STABILITY

- *The capsule manufacturers routinely conduct accelerated physical stability tests on all new capsule products as an integral part of the product development program. The following tests have proved adequate for determining the effect of the capsule shell content on the*

PROCEDURE

gelatin is weighed into water to typically create a 6.67% soln in standard bloom bottles

↓

The mix is then stirred and keep it for 3 hours at room temp

↓

gelatin shell. The tests are strictly relevant to the integrity of the gelatin shell and should not be confused as stability tests for the active ingredients in the capsule content.

- *The results of such tests are used as a guide for the reformulation of the capsule content or the capsule shell, or for the selection of the proper retail package.*
- *The capsules at these stations are observed periodically for 2 weeks. Both gross and subtle effects of the storage conditions on the capsule shell are noted and recorded. The control capsule should not be affected except at the 80 percent RH (relative humidity) station, where the capsule would react as described under the effects of high humidity*

Table 8. Test conditions for accelerated stability tests for capsule dosage forms [34]

Test conditions	Observation
80% RH at room temperature in an open container. 40℃ in an open container. 40℃ in a closed container (glass bottle with tight screw-cap).	Capsules are observed periodically for 2 weeks, both gross and subtle effects of the storage conditions are noted and recorded. The control capsule should not be affected except at the 80% RH station.

Table 2: Effect of Temperature and Humidity on Capsule shell

Temperature	Humidity	Effect on Capsule shell
21-24°C	60%	Capsules become softer,tackier and bloated
Greater than 24°C	Greater than 45%	More rapid and pronounced effects – unprotected capsules melt and fuse together

Loss on drying (LOD)

- *Loss on drying (LOD) is determined according to European Pharmacopoeia (7th Ed). Loss on drying (d) based on ~3 g of capsules. The capsules were placed on a previously dried weighing dish and dried in an oven at 105±2°C to constant mass and cooled down to room temperature in a desiccator over silica gel before weighing. Loss on drying is the loss of mass expressed as volume percent.*

- *The water content of hard gelatin capsules should be within the specification limit between 13 and 16% water content*

SULFATED ASH (Residue on Ignition)

- *Heat a silica or platinum crucible to redness for 10 minutes, allow to cool in a desiccator and weigh. Unless otherwise specified in the individual monograph, transfer to the crucible 1 g of the substance under examination and weigh the crucible and the contents accurately. Ignite,*

gently at first, until the substance is thoroughly charred. Cool, moisten the residue with 1 ml of sulphuric acid, heat gently until the white fumes are no longer evolved and ignite at 800° ± 25° until all black particles have disappeared. Conduct the ignition in a place protected from air currents. Allow the crucible to cool, add a few drops of sulphuric acid and heat. Ignite as before, allow to cool and weigh. Repeat the operation until two successive weighing do not differ by more than 0.5 mg.

- *Colored capsules upper limit (7%)*
- *transparent body and an opaque cap (5% upper limit)*
- *Transparent capsules (2%)*

MICROBIOLOGICAL TESTING

- *The microbiological testing is performed according to the European Pharmacopoeia (7th Ed.) Chapter 2.6.12 Microbiological examination of non sterile products: Microbial enumeration tests and Chapter 2.6.13 Microbiological examination of non sterile products: Test for specified microorganisms.The specifications are listed in Table*

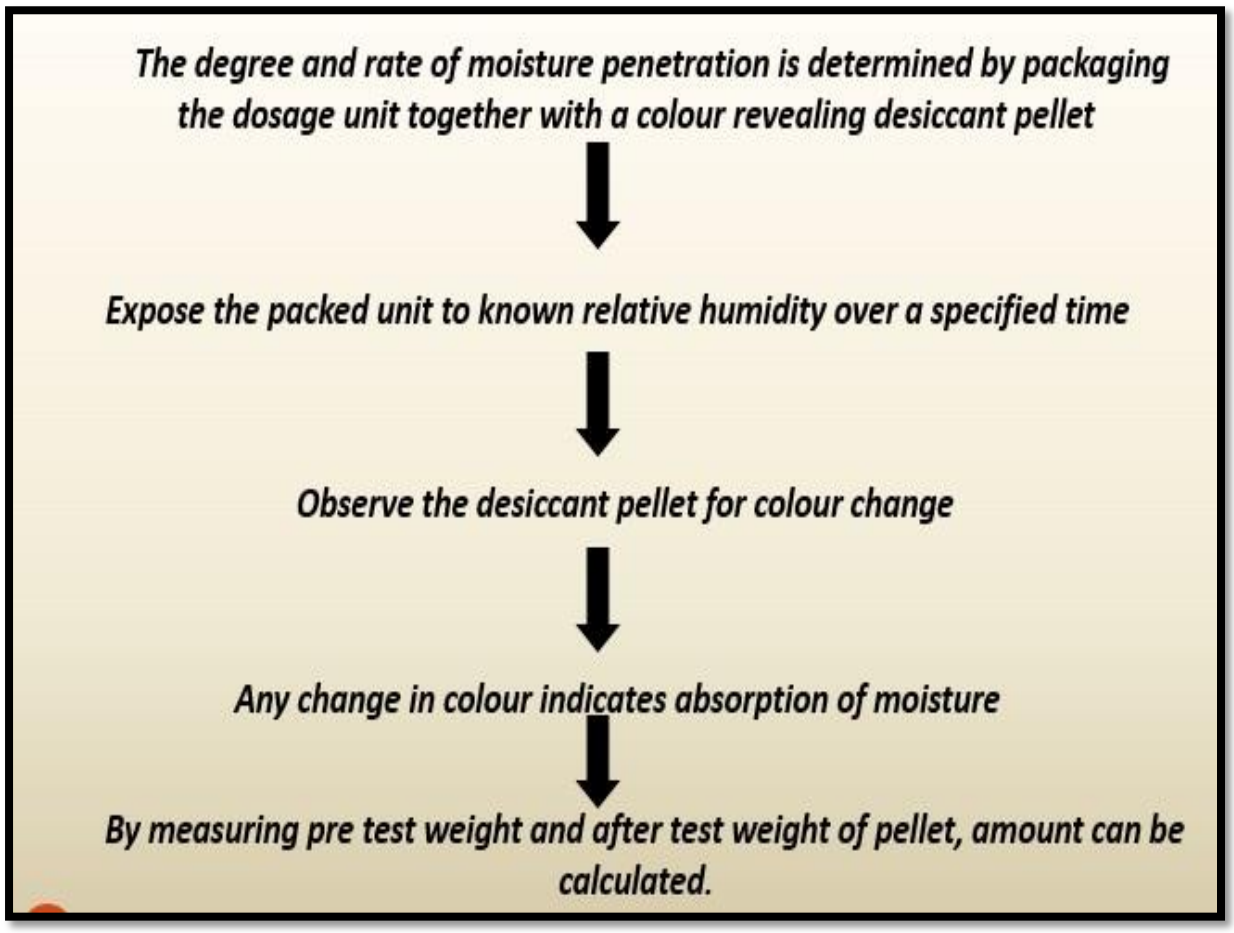
Table II. Microbiological specification for capsules according to the European Pharmacopoeia

Test	Specification
Total aerobic microbial count	Maximum 1,000/g
Total yeasts/molds count	Maximum 100/g
Escherichia coli	Absence in 1 g
Salmonella species	Absence in 10 g
Staphylococcus aureus	Absence in 1 g
Pseudomonas aeruginosa	Absence in 1 g

LUBRICANT CONTENT

- *Lubricant content is measured in 4 g of capsules separated into cap and body. Methylene chloride is added to the capsules until completely covered and then the capsules are agitated for 5 min minimum. The extract is transferred to a previously dried and tarred flask and the operation is repeated once more with a further sufficient amount of methylene chloride. The solvent is gently evaporated avoiding any boiling, the flask is dried in the oven (103–107°C) for about 2 h before cooling down to room temperature in a desiccator. The residue is weighed and calculated as a percentage of capsule weight. The lubricant content should not exceed 0.5%.*

MOISTURE PERMEATION TEST (For Capsule Packaging)



SULFUR DIOXIDE CONTENT

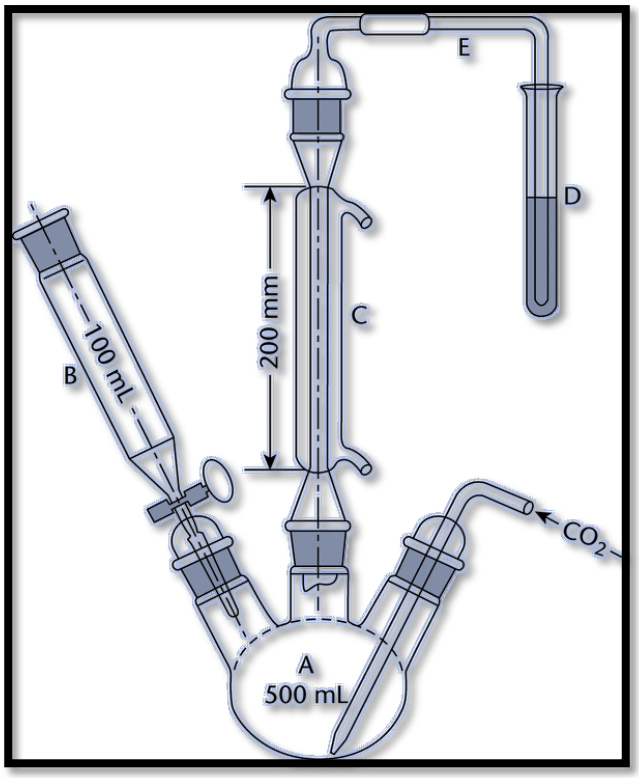
Method

Apparatus

A 500-ml three-necked round-bottomed flask is fitted with a water-cooled reflux condenser, 200 mm long, the upper end of which is connected to an absorption tube. The flask is fitted with a 100-ml dropping funnel and a gas inlet tube which reaches nearly to the bottom of the flask. The absorption tube contains 10 ml of hydrogen peroxide solution previously neutralized to bromophenol blue solution.

Procedure

Place 150 ml of water in the flask and pass a stream of carbon dioxide at a rate of 100 ml per minute for 15 minutes. Connect the absorption tube and without interrupting the flow of carbon dioxide introduce through the funnel the prescribed quantity of the substance under examination and 80 ml of 2 M hydrochloric acid. Boil for 1 hour, disconnect the absorption tube and stop the flow of carbon dioxide. Wash the contents of the absorption tube into a 250-ml conical flask, heat on a water-bath for I5 minutes and allow to cool. Titrate with 0.1 M sodium hydroxide using bromophenol blue solution as indicator until the color changes from yellow to violet-blue. 1 ml of 0.1M sodium hydroxide is equivalent to 0.003203 g of SO_2.



SULFUR DIOXIDE CONTENT

- *25 g of capsules are used for each analysis*
- *upper limit is (50 ppm)*
