DISSOLUTION METHODS, FORMULATION & PROCESSING FACTORS, CORRELATION OF IN-VIVO DATA WITH IN VITRO DISSOLUTION DATA:-

SUBMITTED TO
DEPARTMENT OF PHARMACEUTICS

Dissolution is a process of mass transfer of solid into the solvent. It is a multiple process involving heterogeneous swinging reaction/interaction between the phases of solute-solute, solute-solvent and solvent-solvent interface.

Dissolution Methods:-

Categorized into two methods:-

- Official methods
- Non official methods

➢*OFFICIAL METHODS:-*

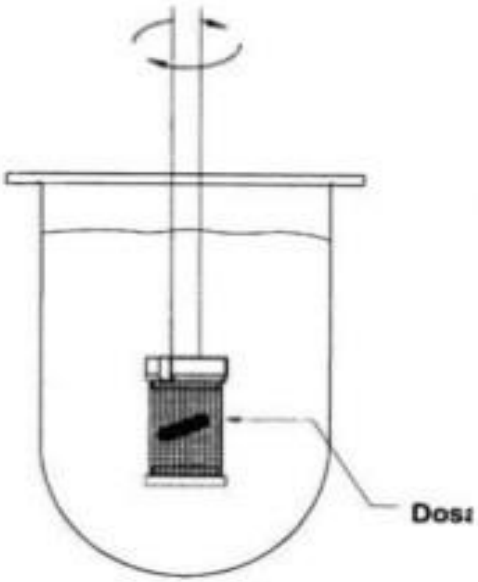
Apparatus are used according to standards specified. The USP includes seven apparatus design for drug release and dissolution testing of immediate release and for oral dosage form, for extended release, enteric coated, transdermal drug delivery system.

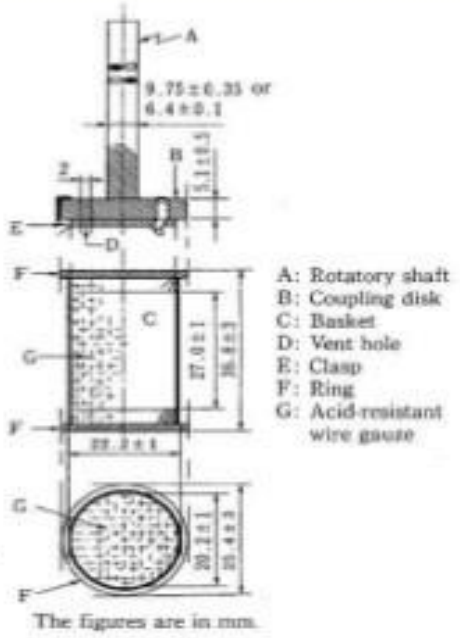
Methods are listed below:-

- Rotating basket method
- Paddle method
- Flow-through method
- Reciprocating cylinder method
- Paddle over disk method
- Rotating cylinder method
- Reciprocating disk method

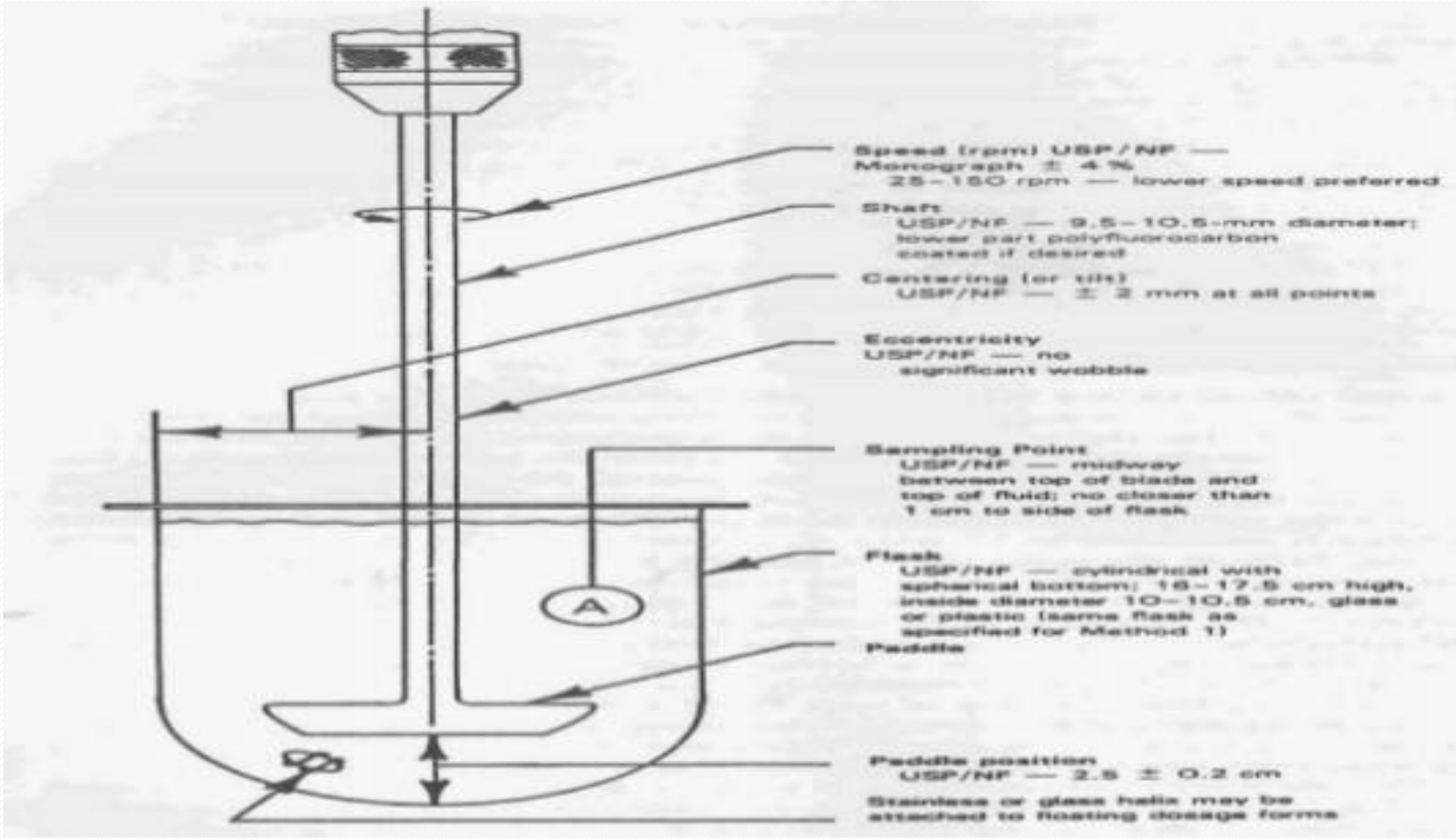
Apparatus 1 - Basket

- **Useful for**
  - capsules
  - beads
  - delayed release / enteric coated dosage forms
  - floating dosage forms
  - surfactants in media
- **Standard volume**
  - 900/1000 mL
  - 1, 2, 4 L vessels





Apparatus 2–Paddle

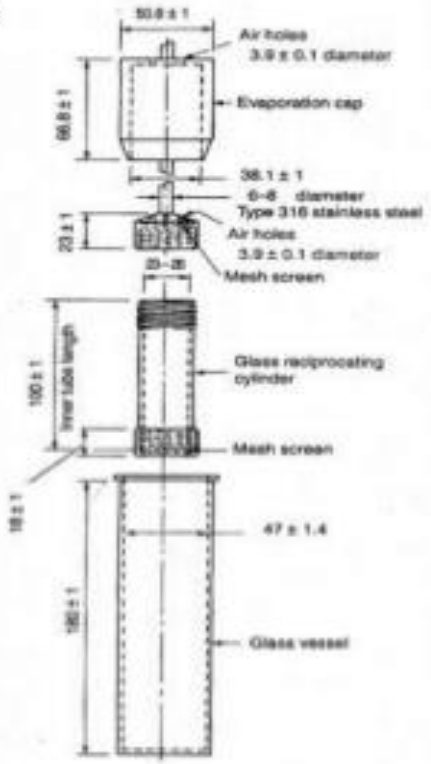


APPARATUS-3(RECIPROCATING CYLINDER)

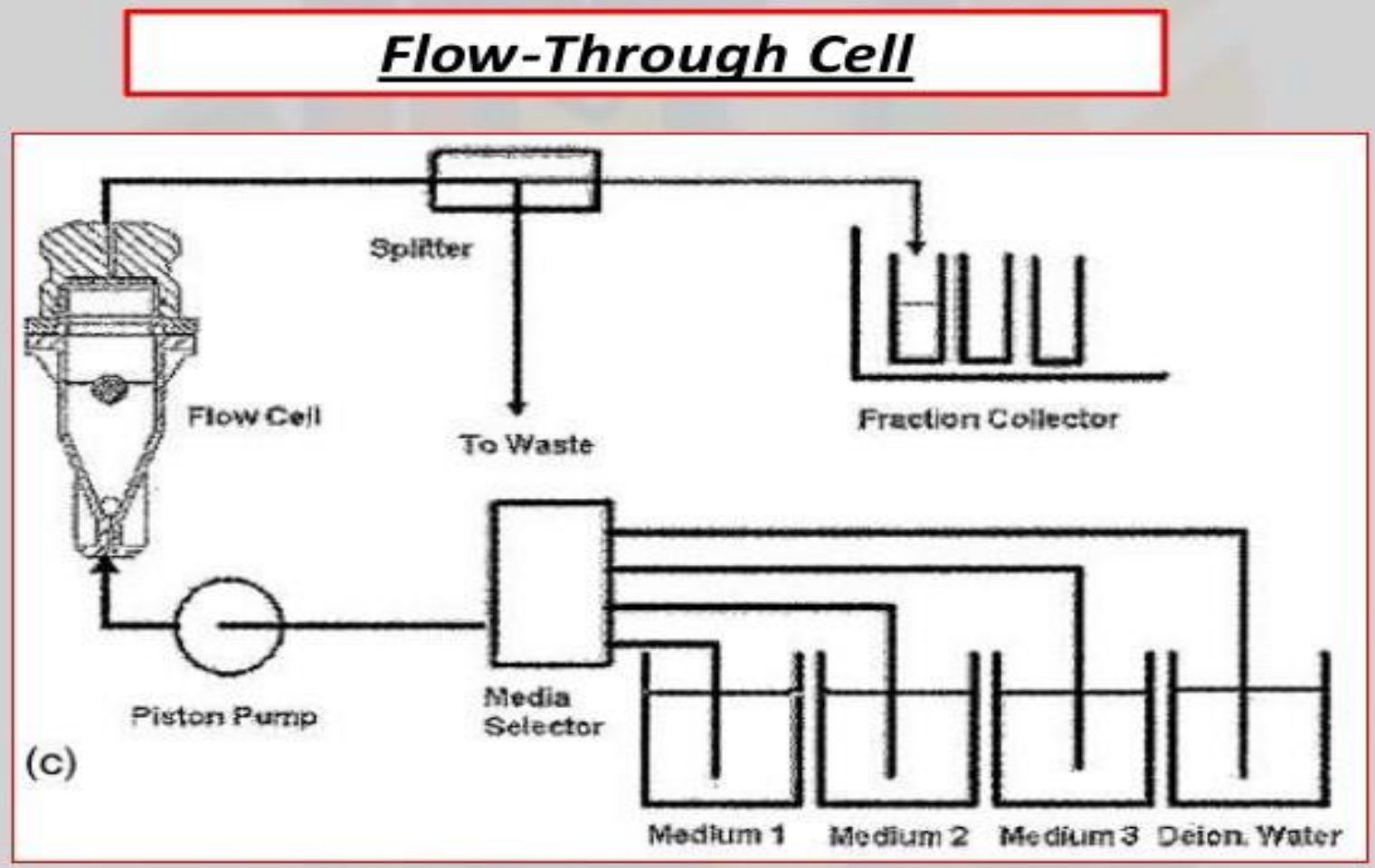
❖ **DESIGN:**

- Vessel: -Set of cylindrical flat bottom glass vessels
  -Set of reciprocating cylinders
  -stainless steel fittings(type 316) and 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, controlled and extended release formulations



Apparatus four:-flow through cell



ADVANTAGES:-

•Infinite sink condition can be achieved hence low soluble drugs studies can be done.

•It is easy to change pH of media during test, avoiding hot spots as seen in basket method.

•Minimum dwell time, avoiding problems of degradation of drug during process.

•Ease of sampling and automation of data reduction.
•Adaptability to current USP calibrators.

DIS-ADVANTAGES:-

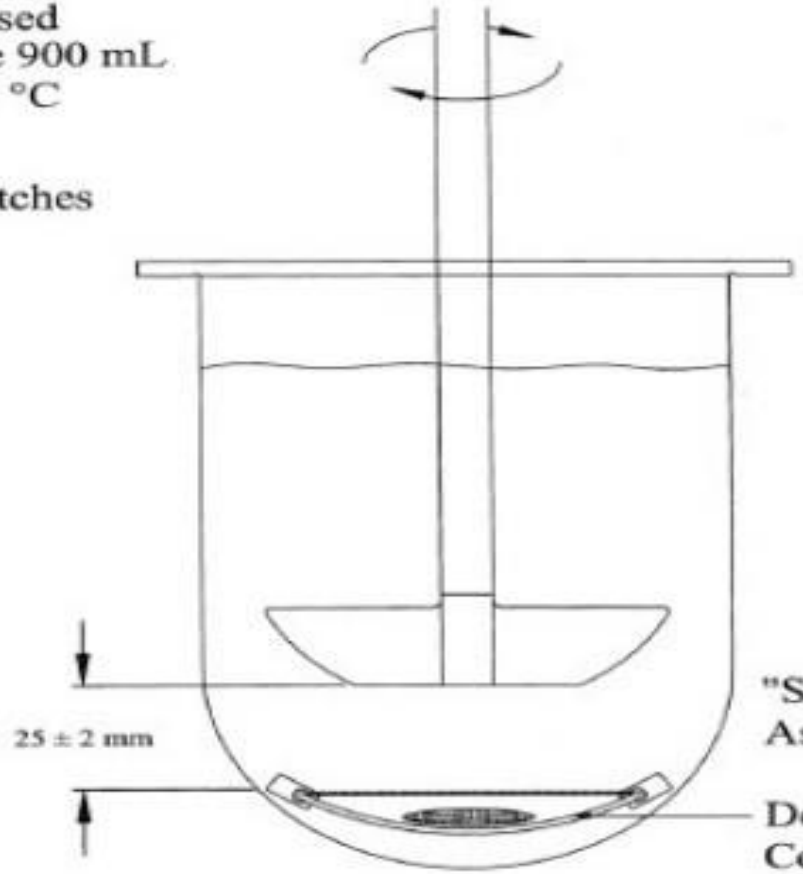
- Large volume of media is required.
- Control of constant flow rate is difficulty.
- Clogging results in damage to equipment.
- Pump should produce pulse free flow.
- Pressure may build up due to clogging hence pressure transducer should used to regulate pressure and to maintain constant flow rate.

USP Apparatus 5 - Paddle Over Disk

Standard Paddle Used
- Typical Volume 900 mL
- Temperature 32 °C

Useful for
- Transdermal Patches
- Ointments
- Floaters
- Emulsions
- Bolus

Modifications
- Disk Design
- Volume



APPARATUS-6(ROTATING CYLINDER)

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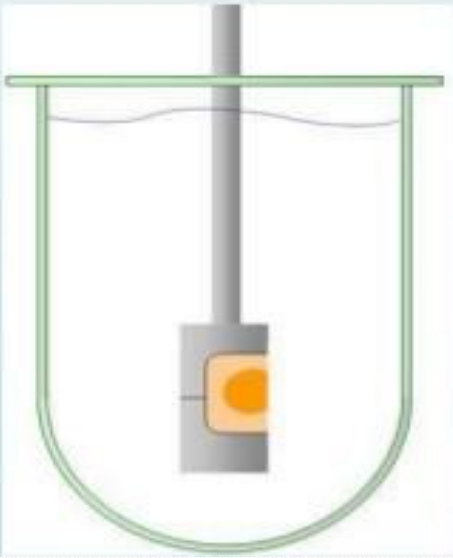
- **DESIGN:**
  - Vessel:- same as apparatus 1.
  - Shaft :-Stainless steel 316, basket is replaced with cylinder is used
  - Sample :- Mounted to inner porous cellulosic material and adheres to cylinder.
    - Dosage unit is placed in cylinder and release from side out.
  - Water-bath: maintained at 32±0.5°C
- **USE:**
  - Transdermal patches cannot be cut into small size.
  - Solid dosage forms,



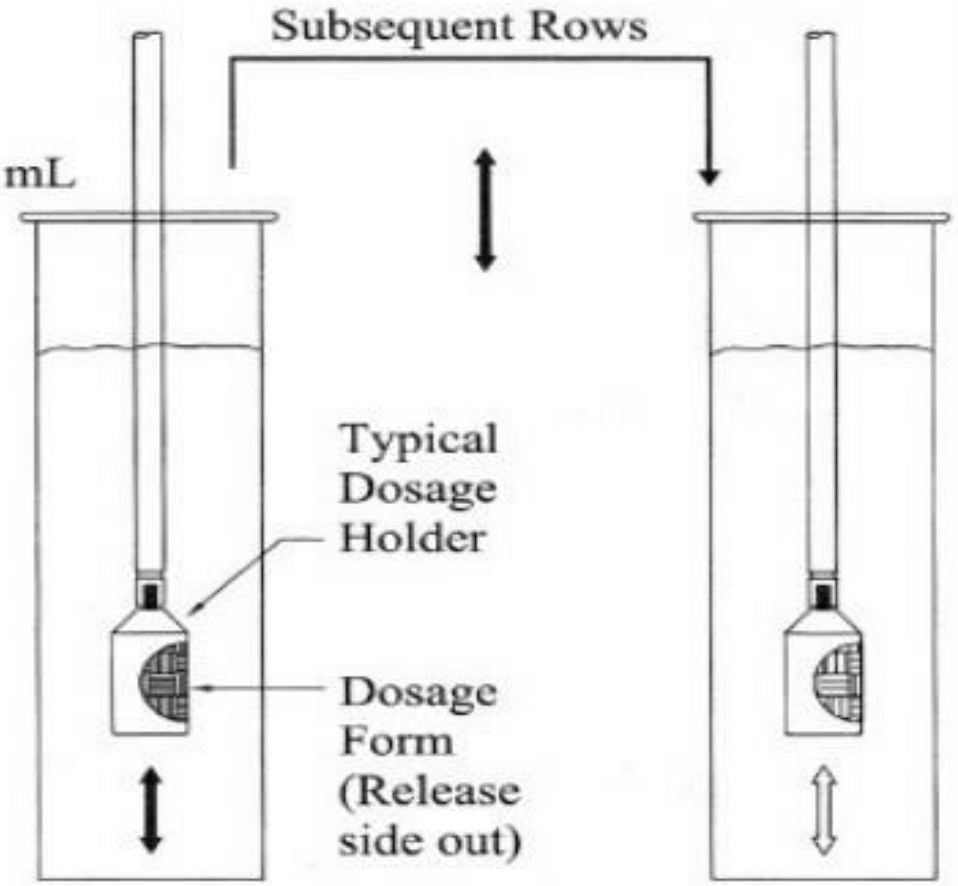
USP Apparatus 7 – Reciprocating Holder

Reciprocating Holder
- Sample Holder
- Temperature 32 °C

Sequential Media Tubes
- Typical Volumes 50 to 200 mL

Useful for
- Transdermal Patches
- Solid Dosage Forms
- pH Profile
- Small Volumes

Modifications
- Dosage Form Holder



➢*NON- OFFICIAL METHODS:-*

Tracking of dissolution from different dosage form is some times is not possible with the existing official methods. So several non-official methods are designed for dissolution testing.

These includes,

- Percutaneous absorption technique.
- Rotating bottle method for sustained release dosage form.
- Dialysis system.

PERCUTENOUS ABSORPTION TECHNIQUE:

•Percutaneous absorption is related to the absorption across the skin.

Percutaneous absorption methods are currently used to study transfer kinetics through membranes.

•These are useful in testing membrane characteristics and studying absorption through skin.

•These are generally use for patches, the patches generally mounted in same position as the simulated skin membrane and serves as the donor side of the system.

•Some of the tech. that are used in percutaneous absorption measurement includes side-by-side, the Franz cell, and flow through cell design.

ROTATING BOTTLE METHOD:-

•This is probably the oldest method used for sustained release dosage forms.

•The system consists of 12 small bottle attached to a horizontal shaft that rotates at a slow rate of 6-50 rpm.

•The whole assembly is placed in a constant water bath.

•Each bottle consists of 60 ml of dissolution fluid that is decant through a 40-mesh screen after each sampling period and is replaced by fresh fluid.

DIALYSIS SYSTEM:-

•In this case very poorly soluble drugs, where perfect sink condition would necessitate a huge volume of solvent with conventional methods, a different approaches utilizing dialysis membranes, was tried as a selective barrier between the fresh solvent and the cell compartment containing the dosage form.

•It has been used with some success in case of other dosage form such as suspensions, creams and ointments.

Factors affecting dissolution rate:-

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

Factor related to physicochemical properties of drug:-

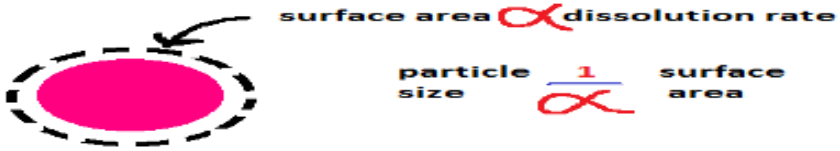
1. Particle size of drug

- 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.

- E.g. Micronisation of non-hydrophobic drug like griseofulvin leads to increase in dissolution rate.

- Micronisation of hydrophobic powders can lead to aggregation and floatation, when powder is dispersed into dissolution medium.

- E.g. hydrophobic drugs like aspirin, phenacetin and phenobarbital shows decrease in dissolution rate, as they tend to adsorb air at the surface and inhibit their wettability



2. DRUG SOLUBILITY

- Solubility of drug plays a prime role incontrolling its dissolution from dosage form. Aqueous solubility of drug is a major factor that determines its dissolution rate.
- E.g. Poorly soluble drug :griseofulvin, spironolactone
Hydrophilic drug :neomycin

3. Solid state characteristics

-Solid phase characteristics of drug, such as amorphicity, crystallinity, state of hydration and polymorphic structures have significant influence on dissolution rate.

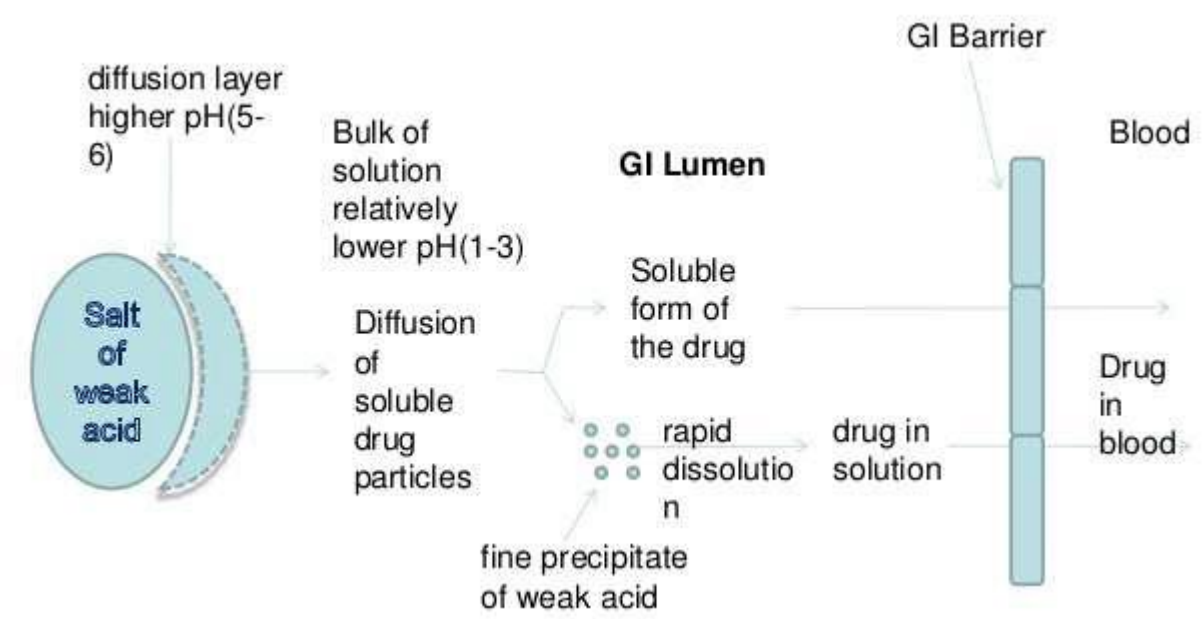
-Anhydrous forms dissolve faster than hydrated form because they are thermodynamically more active than hydrates. E.g. Ampicillin anhydrate faster dissolution rate than trihydrate.

- Amorphous forms of drug tend to dissolve faster than crystalline materials. E.g. Novobiocin suspension, Griseofulvin.
- Metastable(high activation energy) polymorphic form have better dissolution than stable form.

4. Salt formation:-

-It is one of the common approaches used to increase drug solubility and dissolution rate. E.g. sodium and potassium salts of Penicillin G, phenytoin, barbiturates etc.

- While in case of Phenobarbital, dissolution of sodium salt was slower than that of weak acid.

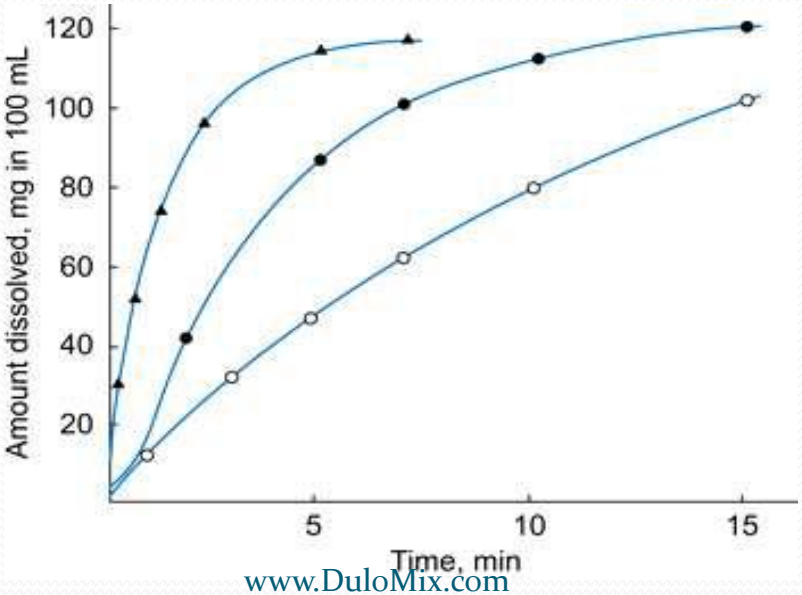


Dissolution and absorption of an acidic drug administered in salt form

Factors related to drug product formulation:-

1. Binders and granulating agents:-

- In general, the hydrophilic (aqueous) binders show better dissolution profile with poorly wettable drugs like phenacetin by imparting hydrophilic properties to the granule surface.
- Large amounts of such binders increase hardness and decrease disintegration / dissolution rates of tablets.



Rate of dissolution of phenacetin from ▲powder, ● granules, and ○ tablet in diluted gastric juice.

2. Disintegrants:-

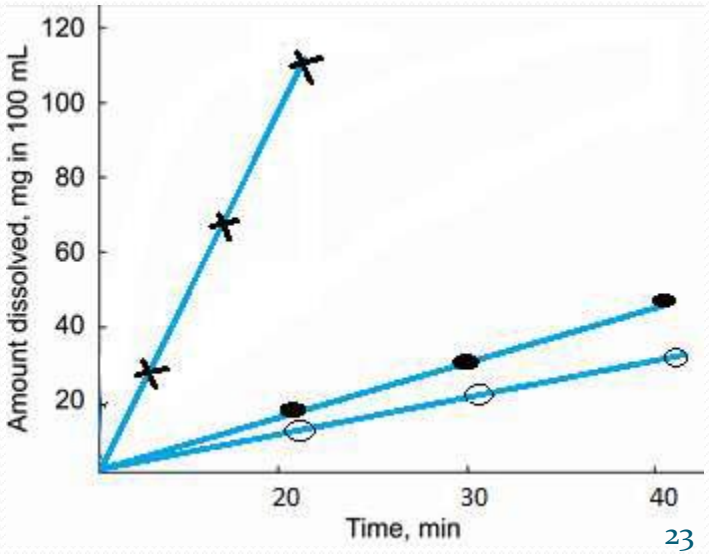
- Disintegrating agent added before & after the granulation affects the dissolution rate.

-E.g. 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

Effect of starch content on dissolution rate of salicylic acid tablet, ○ 5 %, ● 10 % and × 20 % starch in granules.



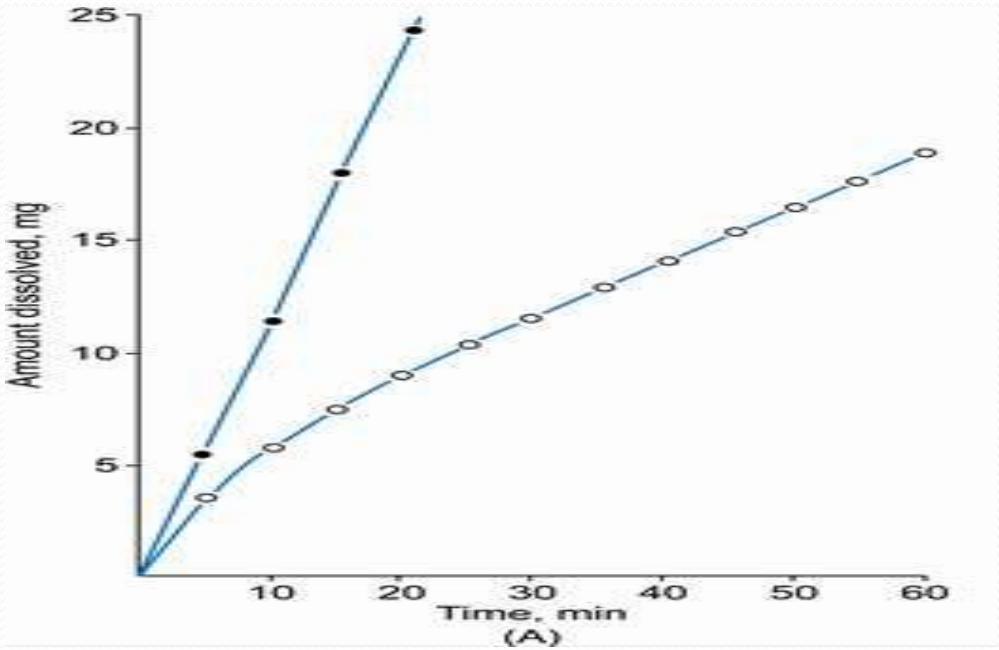
3. Effect of lubricants / anti-frictional agents:-

-The nature, quantity, and quality of lubricants added can affect the dissolution rate.

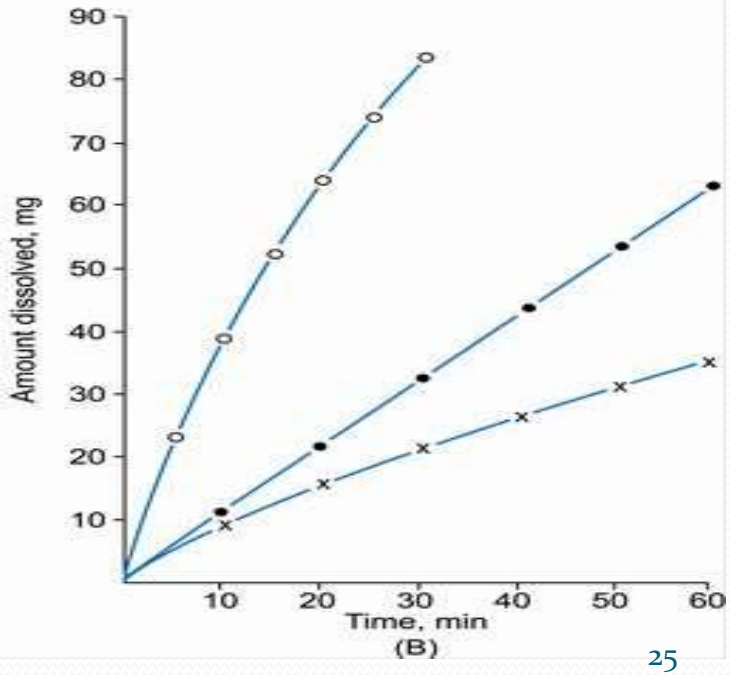
-Lubricants are hydrophobic in nature (several metallic stearate & waxes) which inhibit wettability, penetration of water into tablet so decrease in disintegration and dissolution.

-The use of soluble lubricants like SLS and Carbowaxes promote drug dissolution.

- E.g. Magnesium stearate, a hydrophobic lubricant, tend to retard the dissolution rate of salicylic acid tablet, whereas sodium lauryl sulfate enhances its dissolution, due to its hydrophobic but surface activity, which increases wetting and better solvent penetration into tablet.



(A) Effect of magnesium stearate ondissolution rate of salicylic acid from rotating disc made from fine salicylic acid powder, ○ 3 % Mg. Stearate, ● no lubricant added



(B) Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablet, × 3 % Mg. Stearate
, ● no lubricant, and ○ 3 % Sodium lauryl sulphate.

4. Coatings:-

- In general, the deleterious effect of various coatings on drug dissolution from a tablet dosage form is in the following order: Enteric coat > Sugar coat > Non- enteric film coat.

5. Buffers:-

- Buffers are sometimes useful in creating the right atmosphere for drug dissolution, e.g. buffered aspirin tablets.

6. Complexing agents:-

- A complexed drug may have altered stability, solubility, molecular size, partition coefficient and diffusion coefficient.
- E.g. Enhanced dissolution through formation of a soluble complex of ergotamine tartarate-caffeine complex and hydroquinone-digoxin complex.

Processing factors:-

1. Method of granulation:-

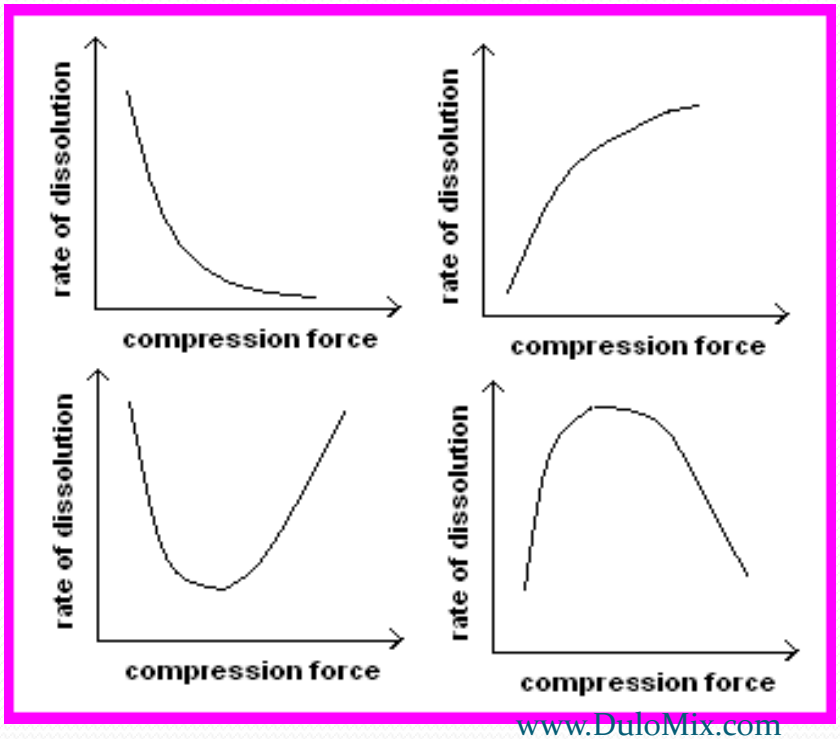
- Wet granulation has been shown to improve the dissolution rate of poorly soluble drugs by imparting hydrophilic properties to the surface of granules.

- 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.

2. Compression force:-

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

- The curve obtained by plotting compression force versus rate of dissolution can take one of the 4 possible shapes:-



1. tighter bonding increases hardness
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

Factors related to dissolution apparatus:-

1. AGITATION:-

-Rate of dissolution depends on type of agitation used, the degree of laminar and turbulent flow in system, the shape and design of stirrer.

- Speed of agitation should be such that it prevent turbulence and sustain a reproducible laminar flow, which is essential for obtaining reliable results.

- So, agitation should be maintained at a relatively low rate.

2. SAMPLING PROBE POSITION & FILTER:-

-Sampling probe can affect the hydrodynamic of the system.

-USP states that sample should be removed at approximately half the distance from the upper surface of basket or paddle and surface of dissolution medium and not closer than 1 cm to the side of the flask.

3. STIRRING ELEMENT ALIGNMENT:-

- The USP / NF states that the axis of the stirring element must not deviate more than 0.2 mm from the axis of the dissolution vessel.

Factors related to dissolution test parameters:-

1. Vibration:-

-The excessive vibration of dissolution apparatus increases dissolution rates.

2. Vessel design and construction:-

-Plastic vessels provide more perfect hemisphere than glass vessels.

3. Temperature control:-

-Should be maintained at 37 ± 0.5 º C

4. Dissolution medium parameters:-

- Surface tension, pH, Viscosity, De-aeration

CORRELATION OF IN-VIVO DATA WITH IN-VITRO DISSOLUTION DATA:- (IVIVC)

According to Food & Drug administration:
IVIVC is a predictive mathematical model describing therelationship between an in-vitro property of a dosageform and a relevant in-vivo response.

According to FDA 1977 on bioavailability & bioequivalence stated that dissolution test the preferred in-vitro test should be correlated with in-vivo data.

•The in-vitro property is the rate or extent of drug dissolution or release while the in-vivo response is the plasma drug concentration or amount of drug absorbed.

• It establishes relationship between biological property (pharmaco-dynamic effect & plasma drug concentration) and physicochemical property of drug substance such as dissolution rate.

• The in-vitro dissolution characteristics are dependent on the physical properties of active pharmaceutical ingredients, the drug dissolution, hydrodynamics of dissolution apparatus & dissolution media.

▪ UNLESS THE INVITRO DISSOLUTION REFLECTS THE INVIVO PERFORMANCE THE RESULTS OBTAINED WILL HAVE NO RELEVANCE.

OBJECTIVES:-

1) To ensure batch to batch uniformity in physiological performance by utilizing in-vitro experimental data.

2) To serve as a tool in developing new, efficacious and safe dosage form.

3) It assumes great imp. Especially for such formulations which contains drugs having narrow therapeutic window.

(Eg: Diltiazem , carbamazepine& Nifedipine) or variable therapeutic response (Eg: Theophylline, digoxin etc.,)

IVIVC CAN BE ACHIEVED USING:-

A) Pharmacological correlations based on clinical observations.

B) Semi-quantitative correlation based on drug blood level or urinary excretion data.

C) Quantitative correlation arising from absorption kinetics & calculation of an invivo absorption rate constants.

DIFFERENT METHODS OF IVIVC:-

- Simple point type
- Comparison of Profiles
- *Simple Point Type:-* The percentage of drug dissolved in a given time is correlated with the bioavailability of the drug product.

COMPARISON OF PROFILES:-

In vivo Data:

- Plasma concentration time profile.
- Pharmacokinetic parameters.
- Percent drug absorbed time profile.
- Statistical movement analysis.

In vitro Data:

- Percent drug dissolution profile.
- Kinetic parameters.
- Percent drug dissolved time profile.
- Statistical movement analysis.

IN VIVO DATA

- Plasma concentration time profile
- Pharmacokinetic parameters.
- Percent drug absorbed time profile.
- Statistic Plasma concentration time profile:
- ·Plasma concentration at time t.
- ·Peak plasma concentration (Cmax).
- ·Time taken for Cmax (tmax).
- AUC0 t , AUC0 ∞
- Time for a certain percentage of drug to reach al movement analysis

IN VITRO DATA

- Percent drug dissolution profile.
- Kinetic parameters.
- Percent drug dissolved time profile.
- Statistical movement analysi Percent drug dissolution profile:
- ·Percent drug dissolved at time t.
- ·Maximum drug dissolved at tmax.
- ·Time taken for maximum amount of drug to dissolve.
- ·Total amount of drug dissolved.
- ·Time for a certain percentage of drug to
- dissolve such as t30%, t50%, t90%, etc. s.

IN VIVO DATA

- the blood such as t30%, t50%, t90%Pharmacokinetic parameters:
- ·Absorption rate constant.
- ·Elimination rate constant., etc·Absorption half life.
- ·Elimination Percent drug absorbed time profile:
- ·Percent drug absorbed at time Statistical movement analysis:
- ·Mean Residence Time (MRT).
- ·Mean Absorption Time (MAT).half life.

IN VITRO DATA

- Kinetic parameters:
- ·Dissolution rate constant.
- ·Dissolution Percent drug dissolved time profile:
- ·Percent drug dissolved at time Statistical movement analysis:
- ·Mean Dissolution Time (MDT). half life

PERCENT OF DRUG DISSOLVED VERSUS PERCENT OF DRUG ABSORBED:-

• If a drug is absorbed completely after dissolution, a linear correlation may be obtained and by comparing the percent drug absorbed to the percent drug dissolved.

• In choosing the dissolution medium and use a slow dissolution stirring rate so that invivo dissolution is approximated.

Eg: The drug Aspirin is absorbed rapidly and completely from GIT. Therefore a change in the dissolution rate from a dosage form may be reflected in a change in the amount and rate if drug absorption during the period of observation.

•Differences in the dissolution rates of dosage forms will be reflected in the rate and extent of the drug only if the drug absorption is dissolution rate limited.

DISSOLUTION RATE V/S ABSORPTION RATE:-

• If dissolution of the drug is rate limiting, a faster dissolution rate may result in a faster rate of appearance of drug in the plasma. It may be possible to establish a correlation between rate of dissolution and rate of absorption of the drug.

• The absorption is more difficult to determine then peak absorption time. Therefore, the absorption time may be used in correlating dissolution data to absorption data.

•In the analysis of invitro invivo drug correlation rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the preparation.

❑ Eg: In study involving three sustained released Aspirin products, the dissolution time for the preparations were linearly correlated to the absorptions times for various amounts aspirin absorbed.

• The results from this study demonstrated that aspirin was rapidly absorbed and it was very much depended on the dissolution rate for absorption.

DIFFERENT STAGES IN IVIVC:-

Stage 1 IVIVC:

•represents a point-to-point relationship between in vitro dissolution rate and in vivo rate of the drug from the dosage form.

•Super imposable absorption rate curves and mathematical descriptions are similar.

•Alternative to in vivo method.

•Manufacturing method changes, formula,modification performed without in vivo data.

Stage 2 IVIVC:

•level B IVIVC utilizes the principles of statistical moment analysis.

In this level of correlation, the mean in vitro dissolution time (MDTvitro) of the product is compared to either mean in vivo residence time (MRT)

Not point to point correlation

This level is not reliable to justify changes in manufacturing or formula changes.

Stage 3 IVIVC:

➢Single point correlation

Relates dissolution time with pharmacokinetic property like AUC (AREA UNDER CURVE).

Helps to develop formulations.

Stage 4 IVIVC: (multiple stage 4):

❑Amount of drug dissolved at different time intervals can be correlated with many pharmacokinetic parameters.

❑Scale up and post approval changes(SUPAC) can be made to the formulation.

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THANK YOU