# DRUG DISSOLUTION

**Delivered by**
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# CONTENTS

- Definition
- Theories of Drug Dissolution
- Noyes-Whitney's Dissolution rate law
- Factors affecting Drug Dissolution
- Study of various approaches to improve dissolution of poorly soluble drug
- In-vitro dissolution testing models
- In-vitro-In-vivo correlation
- References

## Definition-

- Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.

- Rate of dissolution is the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

# 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.

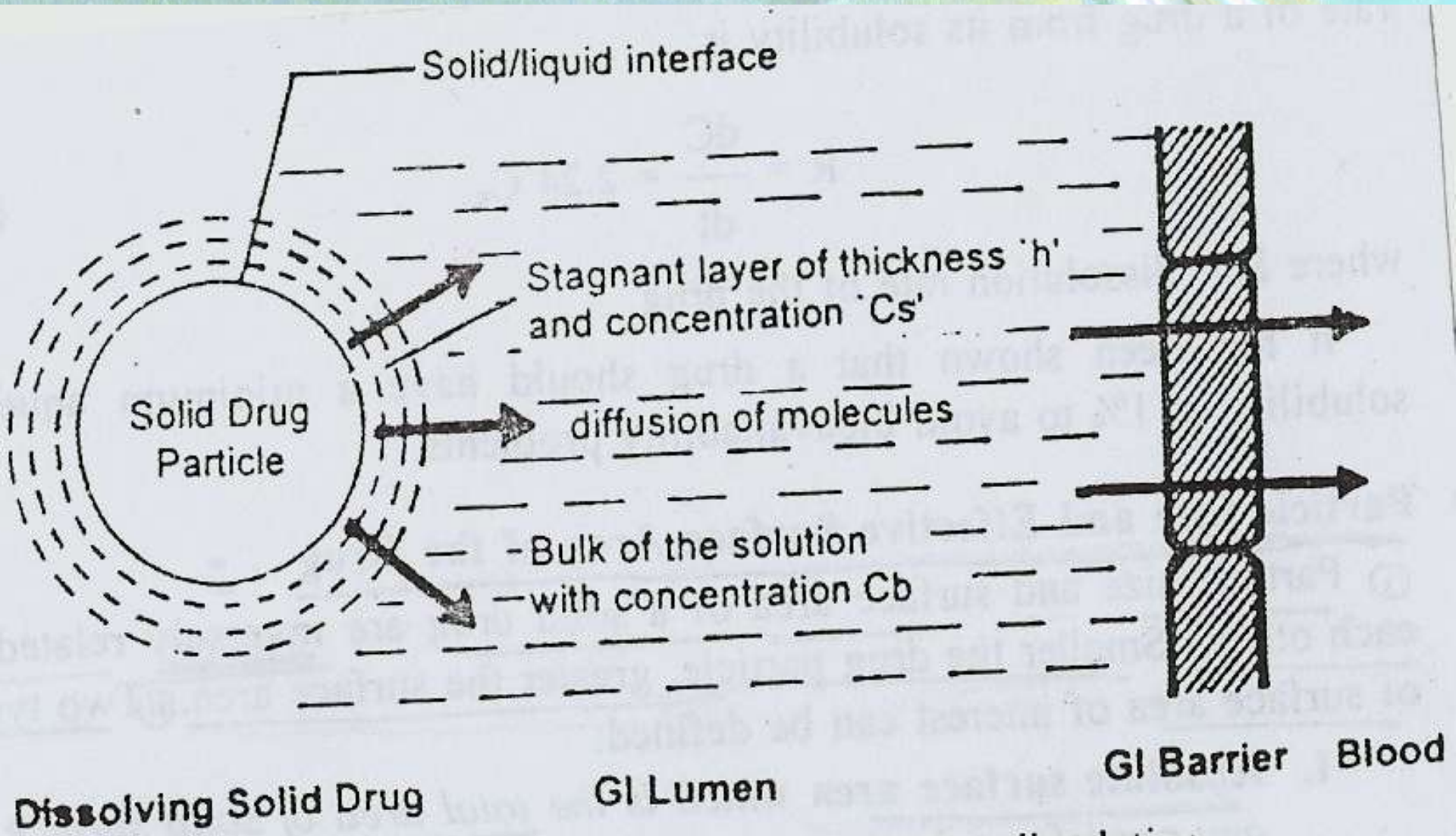



**Fig. 2.11** Diffusion layer model for drug dissolution

- 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 -

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

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.

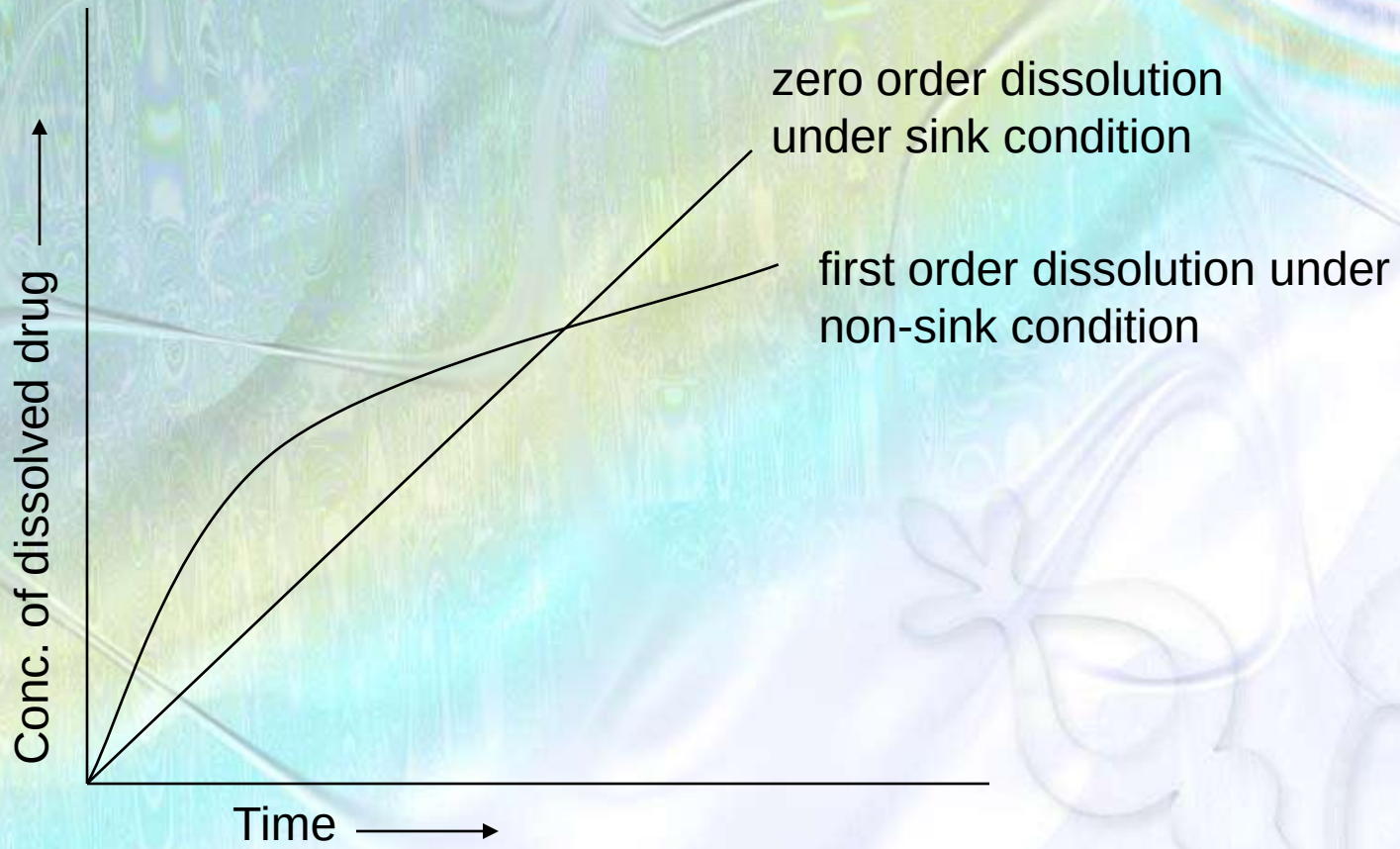
- This is first order dissolution rate process, for which the driving force is concentration gradient.
- This is true for *in-vitro* dissolution which is characterized by non-sink conditions.
- The *in-vivo* dissolution is rapid as sink conditions are maintained by absorption of drug in systemic circulation 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 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's 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.

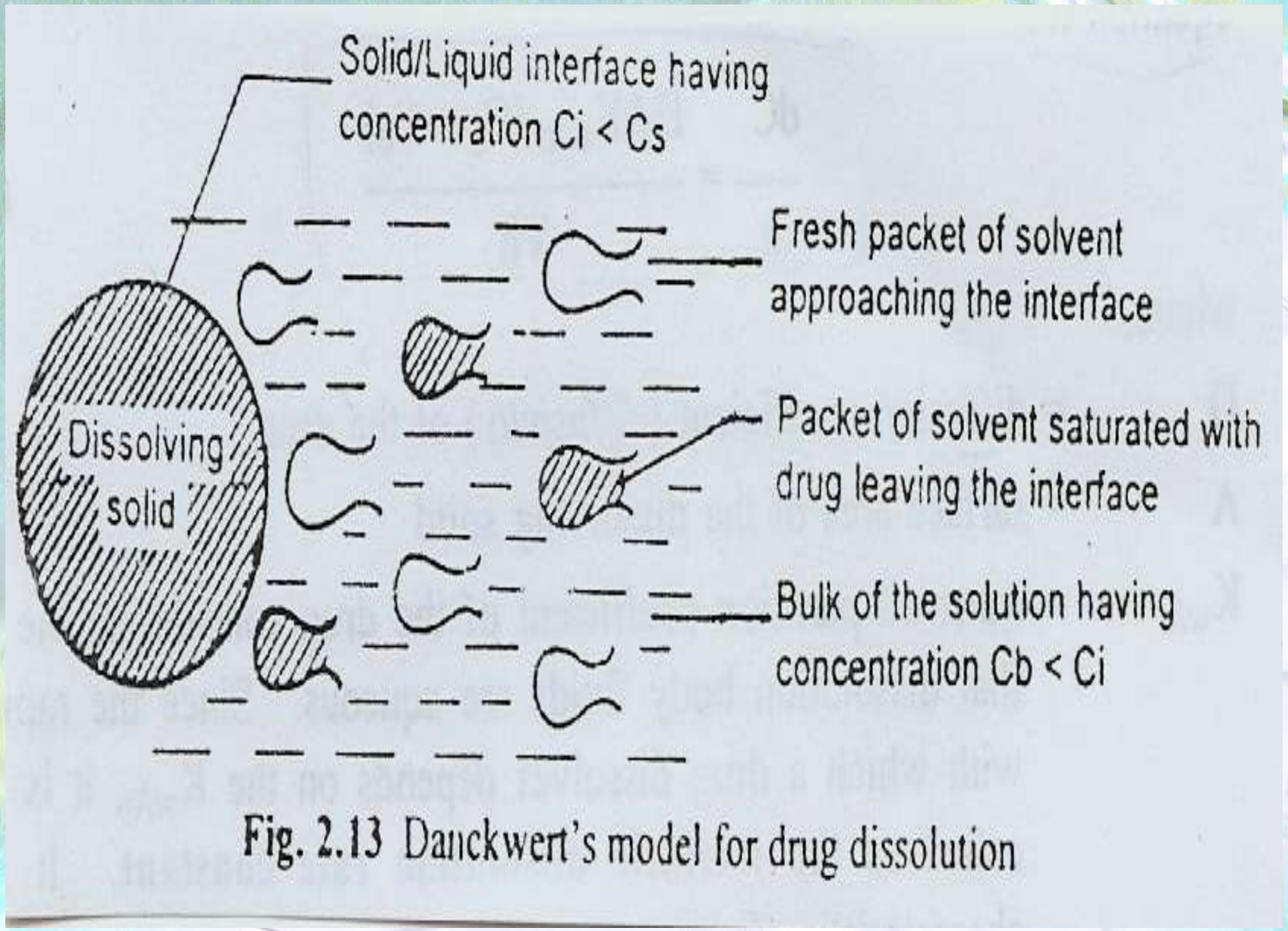



Fig. 2.13 Danckwert's model for drug dissolution

- 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 :-

- The concept of this theory is explained by following equation-

$$G = K_i (C_s - C_b)$$

Where,

G = dissolution rate per unit area,

$K_i$ = effective interfacial transport constant.

- Factors affecting Drug Dissolution :-

A. Factors relating to the physicochemical properties of drug.

B. Factors relating to the dosage forms.

A. Factors relating to the physicochemical properties of drug-

i. Solubility-

- Solubility plays important role in controlling dissolution from dosage form.

- From Noyes-Whitney equation it shows that aqueous solubility of drug which determines its dissolution rate.

ii. Particle size and effective surface area of the drug –

- Particle size and surface area are inversely related to each other.

Two types of surface area –

- Absolute surface area which is the total surface area of any particle.
- Effective surface area which is the area of solid surface exposed to the dissolution medium.

- Effective surface area is directly related to the dissolution rate.

- Greater the effective surface area, more intimate the contact between the solid surface and the aqueous solvent and faster the dissolution.

## iii. Polymorphism and 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.

- Amorphous form of drug which has no internal crystal structure represents higher energy state and greater aqueous solubility than crystalline forms.
- E.g.- amorphous form of novobiocin is 10 times more soluble than the crystalline form.

- Thus, the order for dissolution of different solid forms of drug is –

amorphous > metastable > stable

# IV. Salt form of the drug-

- Dissolution rate of weak acids and weak bases can be enhance by converting them into their salt form.

- With weakly acidic drugs, a strong base salt is prepared like sodium and potassium salts of barbiturates and sulfonamides.

- With weakly basic drugs, a strong acid salt is prepared like the hydrochloride or sulfate salts of alkaloidal drugs.

# iv. Hydrates/solvates –

- The stoichiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates.
- When the solvent in association with the drug is water, the solvate is known as hydrate.
- The organic solvates have greater aqueous solubility than the nonsolvates.
- E.g. – chloroform solvates of griseofulvin is more water soluble than their nonsolvated forms

- Factors contributing to the faster dissolution rate of a drug

a. Reduction of particle size.
b. An increase in drug solubility
c. Absence of aggregation and agglomeration between the fine crystallites of pure drug.
d. Excellent wettability and dispersibility of a drug as the encircling soluble carrier readily dissolves and causes the water to contact and wet the particles.
e. Crystallization of the drug in metastable form after solidification from the fused solution which has high solubility

B. Factors relating to the dosage forms –

i. Pharmaceutical excipients –

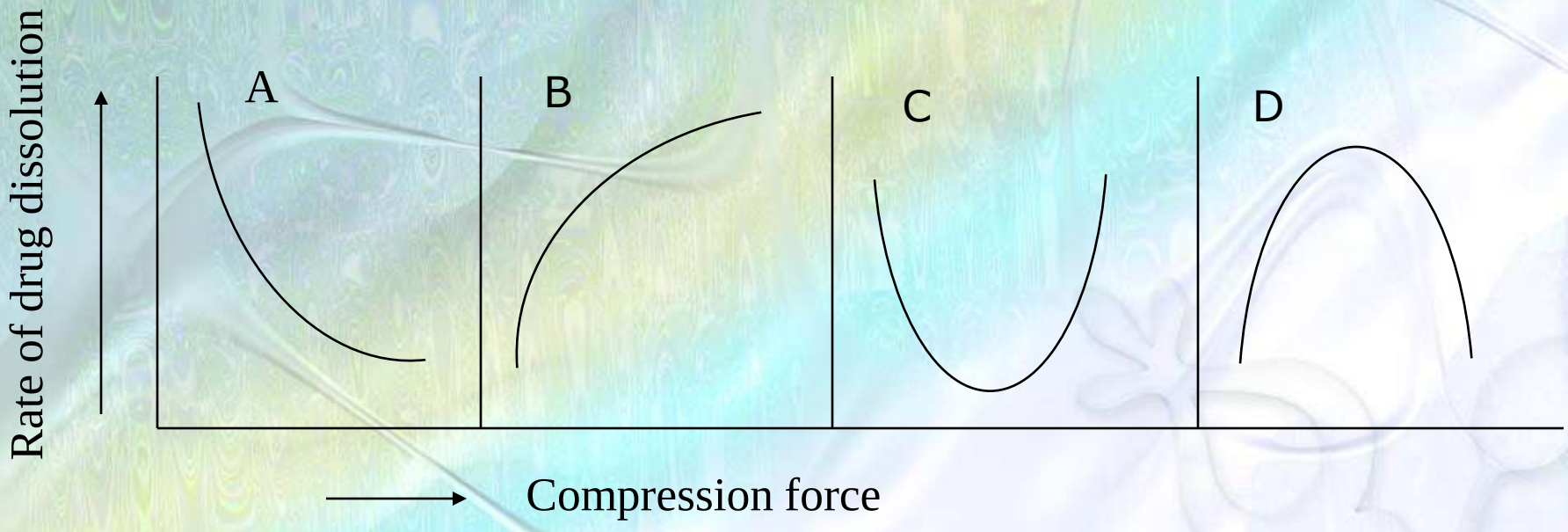
- Vehicle
- Diluents
- Lubricants
- Binders
- Surfactants
- colorants

## ii. Manufacturing processes -

- Method of granulation –

- ☑ Wet granulation
- ☑ Direct compression
- ☑ Agglomerative phase of communication (APOC)

- Compression Force :-




Influence of compression force on dissolution rate of tablet

## ➢ Intensity of packing of capsule contents –

- Diffusion of GI fluids into the tightly filled capsules creates a high pressure within the capsule resulting in rapid bursting and dissolution of contents.

- On other hand, it shows that capsule with finer particles and intense packing have poor drug release and dissolution rate due to decrease in pore size of the compact and poor penetrability by the GI fluids.

# IN-VITRO DISSOLUTION TESTING MODELS

# INTRODUCTION

- Alternative to *in vivo* bioavailability determination
- Dissolution testing – Official in pharmacopeias
- Quantify the extent of release of drug
- Routinely used by Q.C. and R&D
- Q.C. → Evaluate – batch consistency
- R&D → Prediction of drug release

# FACTORS TO BE CONSIDERED WHILE DESIGNING OF A DISSOLUTION TEST

# Factors relating to the dissolution apparatus

- Design of the container
- Size of the container
- Shape of the container
- Nature of agitation
- Speed of agitation
- Performance precision of the apparatus

# Factors relating to the dissolution fluid

- Composition
- Viscosity
- Volume
- Temperature
- Sink condition

| DISSOLUTION MEDIUM | EXAMPLE |
|---|---|
| Water | Ampicillin caps., butabarbital sodium tabs. |
| Buffers | Azithromycin caps., paracetamol tabs. |
| HCL solution | Cemetidine tabs. |
| Simulated gastric fluid | Astemizole tabs., piroxicam caps. |
| Simulated intestinal fluid | Valproic caps., Glipizide tabs. |
| Surfactant solution | Clofibrate caps, danazol caps |

# Process parameters

- Method of introduction of dosage form
- Sampling techniques
- Changing the dissolution fluid

# OFFICIAL METHODS

# Classification

- There are basically three general categories of dissolution apparatus :

1. Beaker methods
2. Open flow-through compartment system
3. Dialysis concept

# 1. BEAKER METHODS

# Rotating Basket Apparatus (Apparatus 1)

- It is basically a closed-compartment, beaker type apparatus.
- It comprising of a cylindrical glass vessel with hemispherical bottom of one litre capacity partially immersed in a water bath.
- A cylindrical basket made of #22 mesh is located centrally in the vessel at a distance of 2 cm from the bottom and rotated by a variable speed motor through a shaft.

## Contd…..

- All metal parts like basket and shaft are made of stainless steel 316.

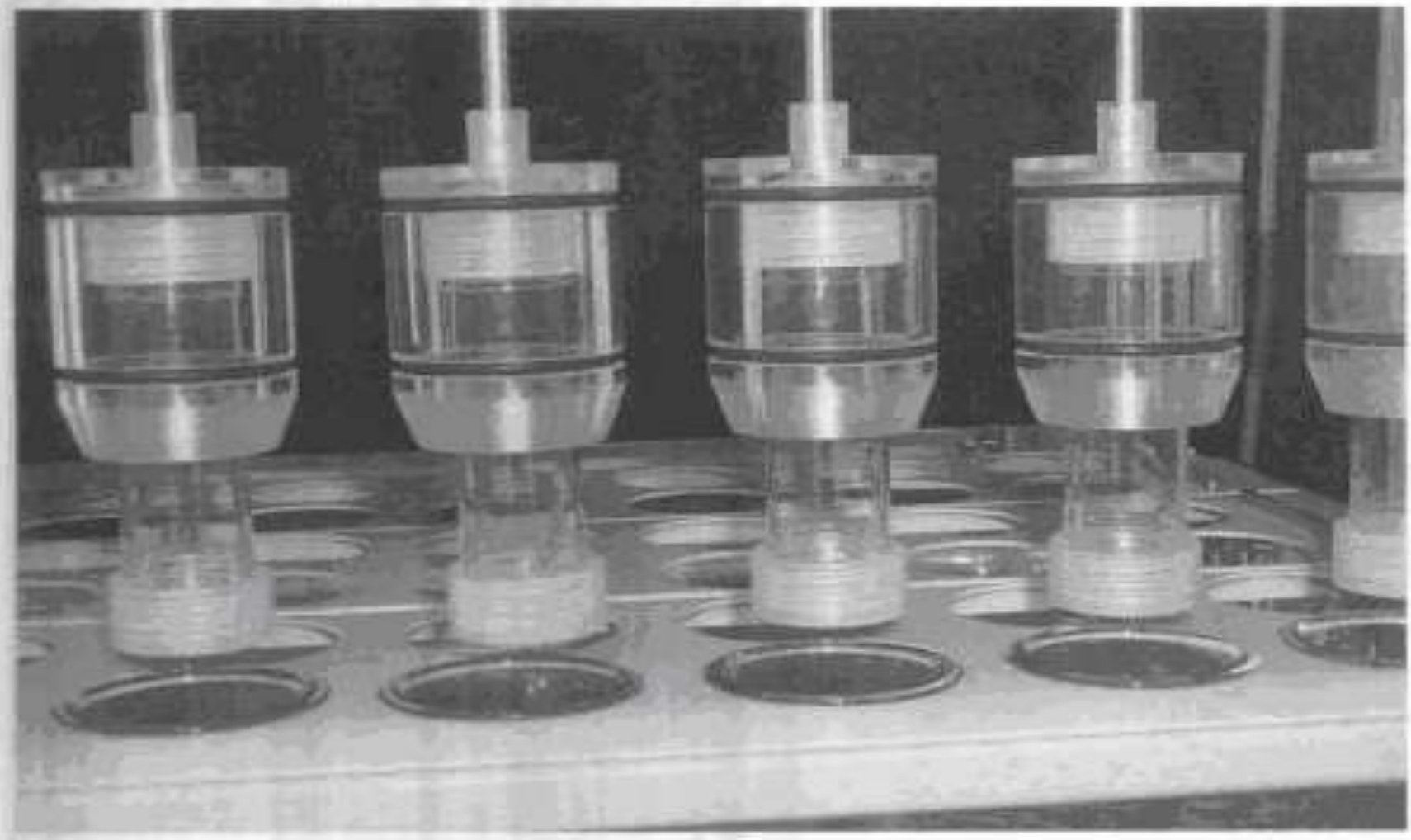
# Rotating Paddle Apparatus (Apparatus 2)

- Here, basket is replaced with a stirrer.
- A small, loose, wire helix may be attached to the dosage form that would otherwise float.
- The position and alignment of the paddle are specified in the official books.

# The Reciprocating Cylinder Method (Apparatus 3)

- This method adopts the USP disintegration "basket and rack" assembly for the dissolution test.
- The disks are not used.
- This method is less suitable for precise dissolution testing due to the amount of agitation and vibration involved.
- E.g. Chlorpheniramine ER tablets, Carbamazepine chewable tablet

(c) The reciprocating cylinder (USP III) dissolution apparatus.



# Paddle over Disk method (Apparatus 5)

- Modification of Apparatus 2.
- Here, stainless steel disk designed for holding transdermal system at the bottom of the vessel.
- The disk/device should not sorb, react with, or interfere with the specimen being tested.
- The disk holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade.

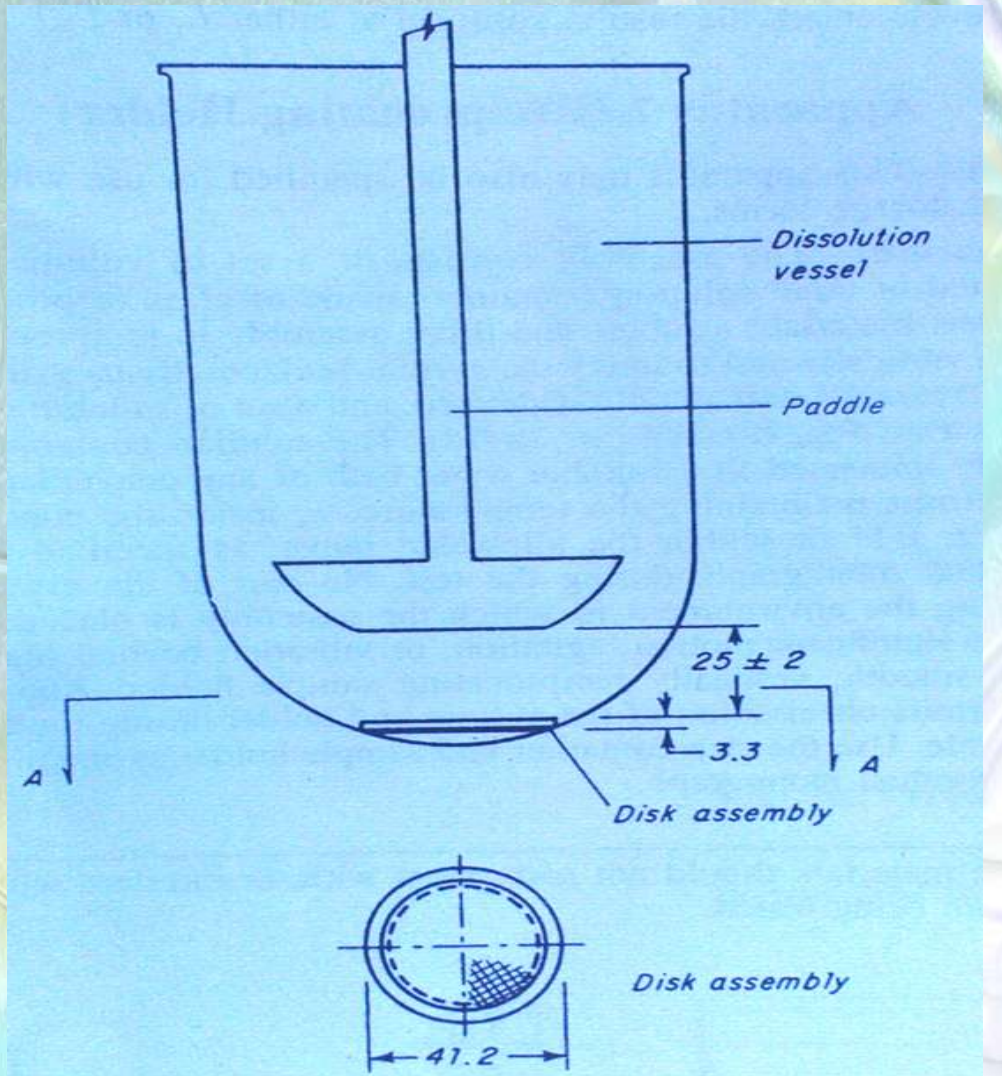



Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

# Cylinder method (Apparatus 6)

- Same as apparatus 1,except to replace the basket and shaft with a S.S. cylinder stirring element.
- Temperature - 32 ± 0.5°
- The dosage unit is placed on the cylinder.
- Distance between the inside bottom of the vessel and cylinder is maintained at 25 ± 2 mm.

# Reciprocating Holder method (Apparatus 7)

- The assembly consists of a set of calibrated solution containers, a motor and drive assembly to reciprocate the system vertically.

- Various type of sample holder are used.

# Advantages of the Beaker Methods

- The basket method is the most widely used procedure which confines the solid dosage form to a limited area which is essential for better reproducibility.
- It is advantageous for capsules as they tend to float at the surface thus minimizing the area exposed to the dissolution fluid.

# Limitation of the Beaker Methods

- Clogging of the basket screen by gummy particles.
- Tendency of the light particles to float.
- Sensitivity of the apparatus to variables such as vibration, eccentricity, etc.
- Rapid corrosion of the SS mesh in presence of HCl.
- Sensitivity of the apparatus to any slight changes in the paddle orientation.
- Non-reproducible position of the tablets at the bottom of the flask.

# 2. OPEN FLOW-THROUGH COMPARTMENT SYSTEM

- The dosage form is contained in a small vertical glass column with built in filter through which a continuous flow of the dissolution medium is circulated upward at a specific rate from an outside reservoir using a peristaltic or centrifugal pump.
- Dissolution fluid is collected in a separate reservoir.
- E.g. lipid filled soft Gelatin capsule

(d) Flow-through cell (USP IV).

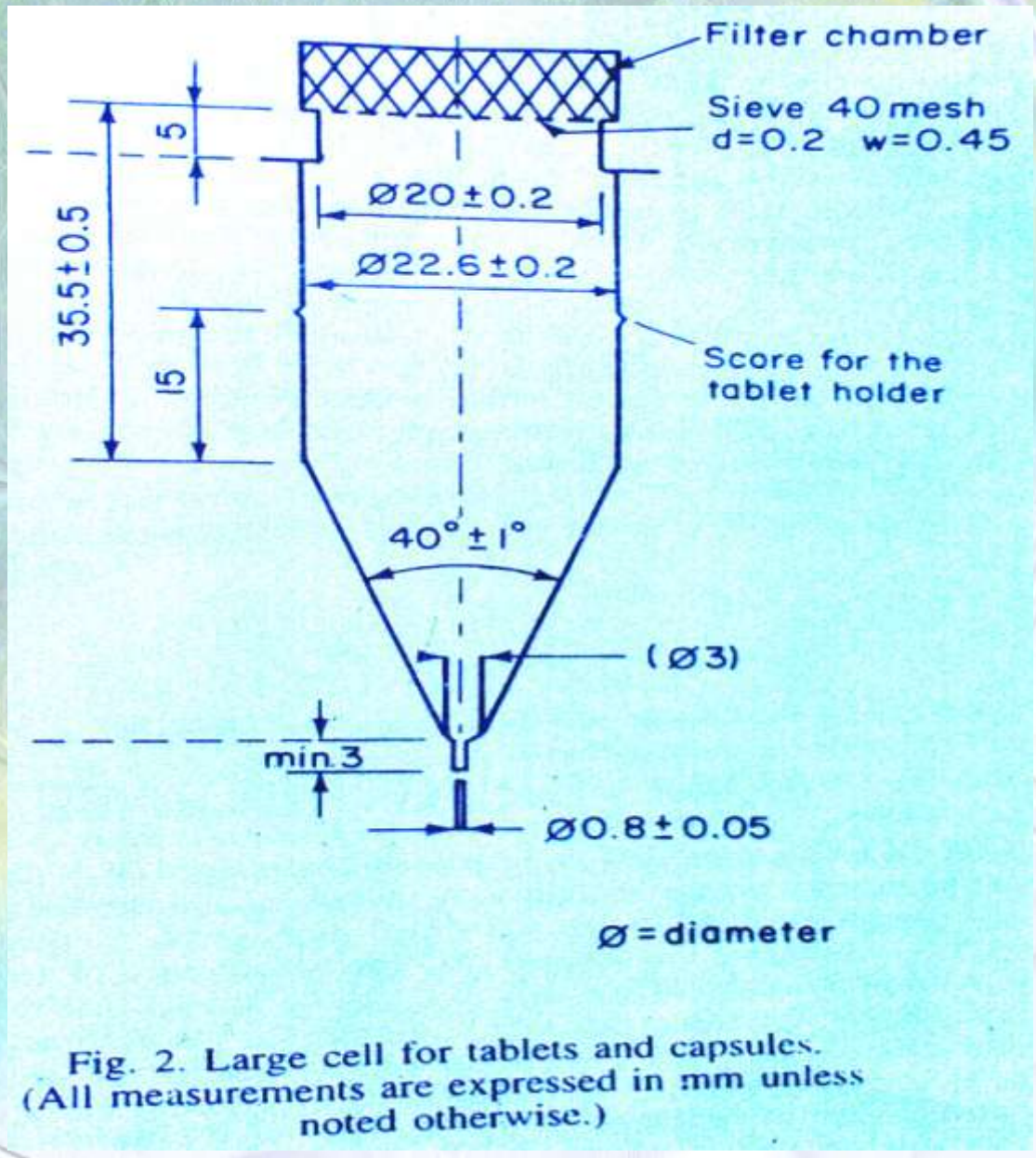



Fig. 2. Large cell for tablets and capsules. (All measurements are expressed in mm unless noted otherwise.)

## ⇨ Advantages

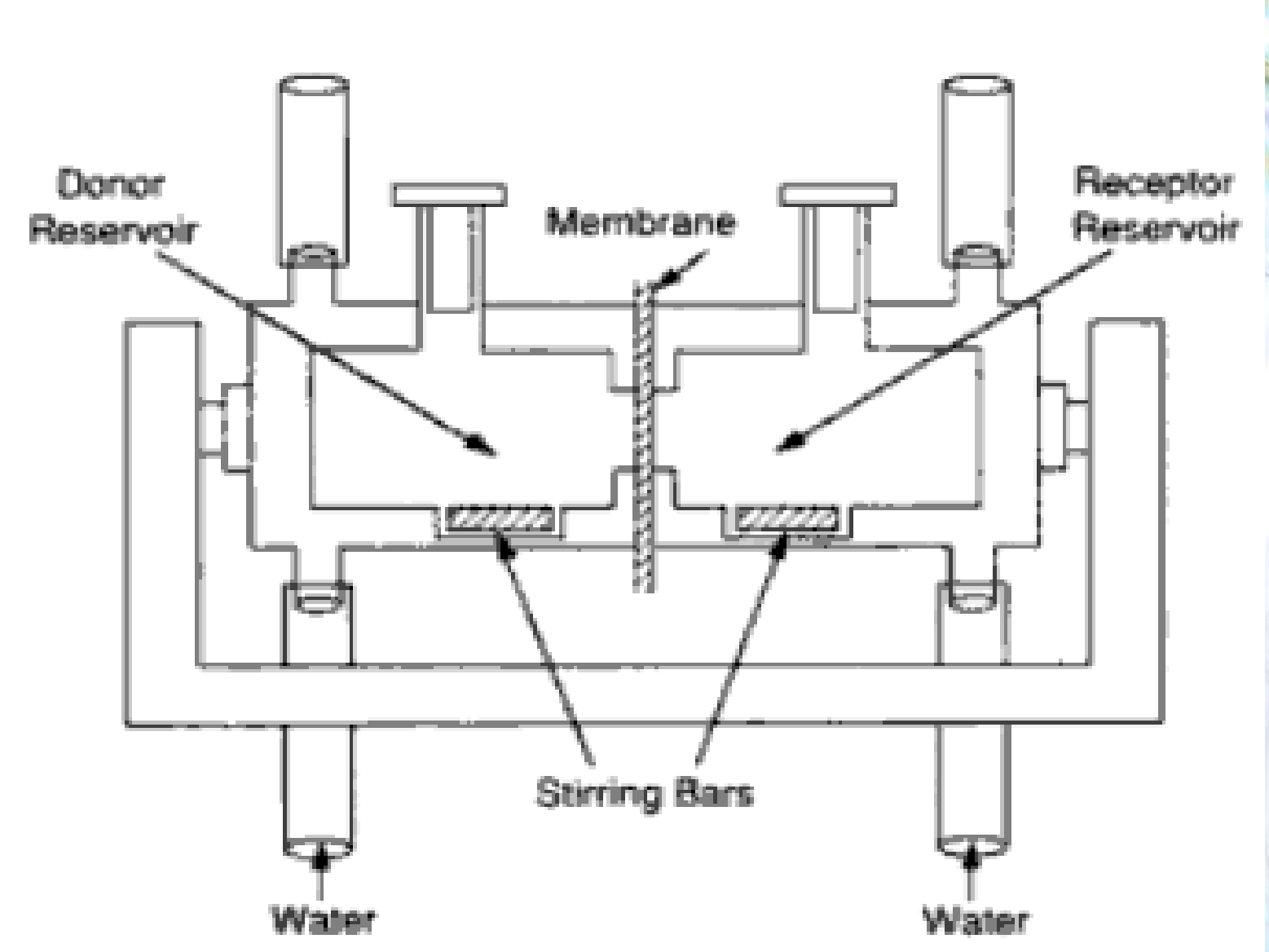
- No stirring and drug particles are exposed to homogeneous, laminar flow that can be precisely controlled. All the problems of wobbling, shaft eccentricity, vibration, stirrer position don’t exist.
- There is no physical abrasion of solids.
- Perfect sink conditions can be maintained.

## ⇨ Disadvantages

- Tendency of the filter to clog because of the unidirectional flow.
- Different types of pumps, such as peristaltic and centrifugal, have been shown to give different dissolution results.
- Temperature control is also much more difficult to achieve in column type flow through system than in the conventional stirred vessel type.

# 3. DIALYSIS SYSTEM

- Here, dialysis membrane used as a selective barrier between fresh solvent compartment and the cell compartment containing dosage form.
- It can be used in case of very poorly soluble drugs and dosage form such as ointments, creams and suspensions.


Donor
Reservoir
Membrane
Receptor
Reservoir
Stirring Bars
Water
Water

# NON OFFICIAL METHODS

# THE ROTATING FILTER METHOD

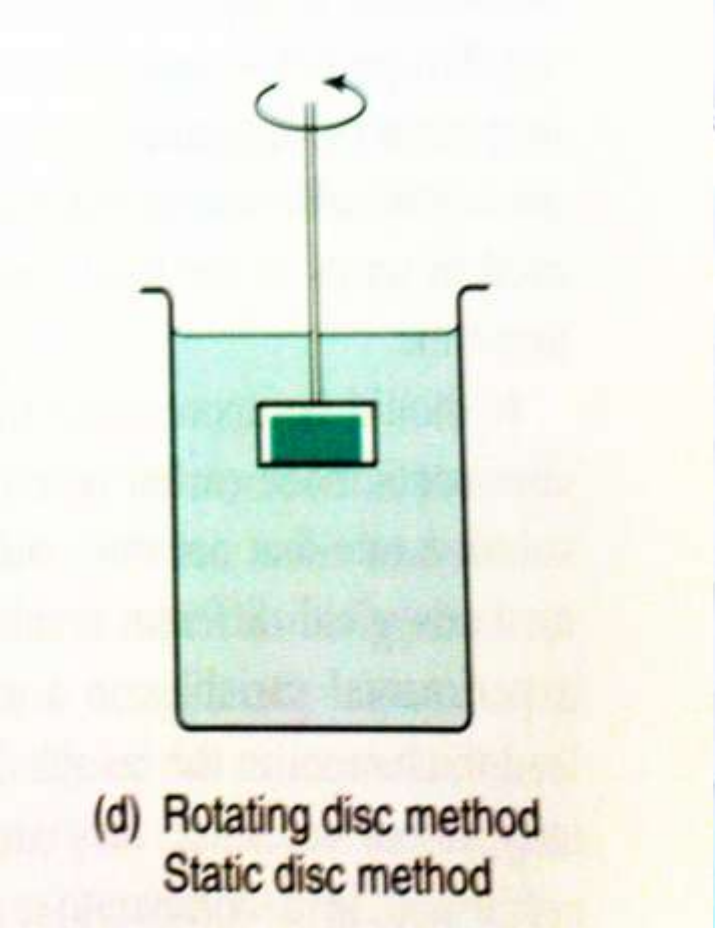
- It consists of a magnetically driven rotating filter assembly and a 12 mesh wire cloth basket.
- The sample is withdrawn through the spinning filter for analysis.

# ROTATING FLASK DISSOLUTION METHOD

- This consists of a spherical flask made of glass and supported by a horizontal glass shaft that is fused to its sides.
- The shaft is connected to a constant speed driving motor.
- The flask is placed in a constant temperature water bath and rotates about its horizontal axis.

# ROTATING AND STATIC DISK METHODS

- The compound is compressed into non disintegrating disc
- Mounted – One surface is exposed to medium
- Assumption – Surface area remains constant
- Used to determine the intrinsic dissolution rate

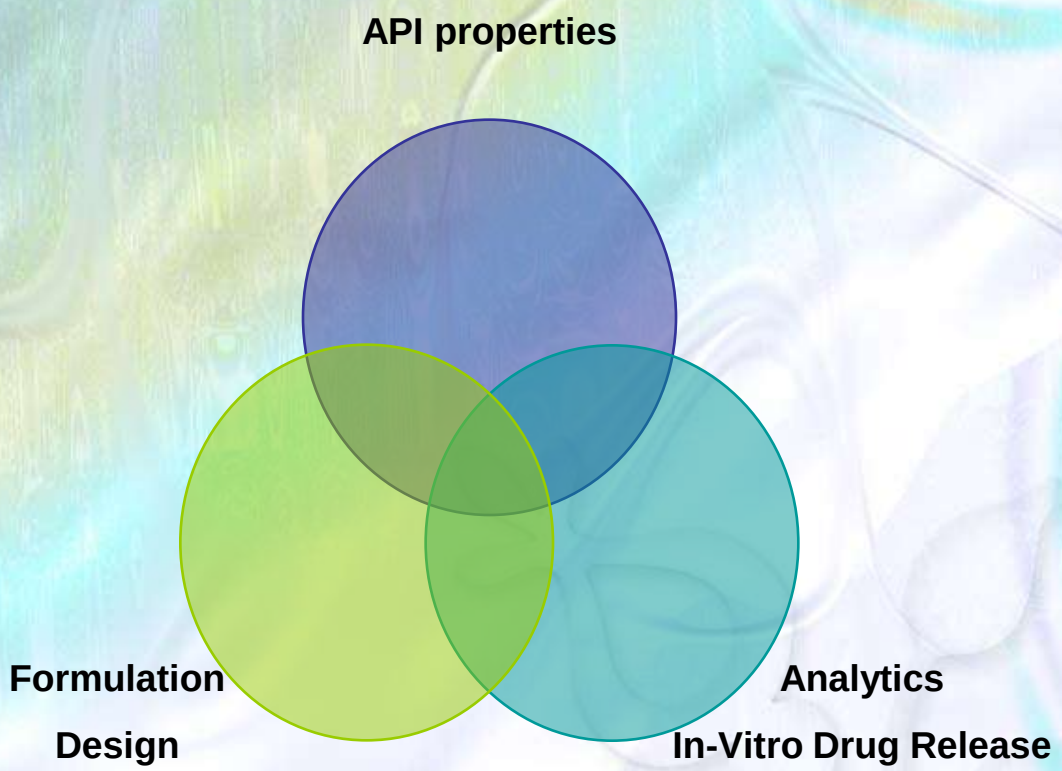


(d) Rotating disc method
Static disc method

# Dissolution, Pharmaceutical Product Interchange ability and Biopharmaceutics Classification

## Dissolution:

**An interplay of three groups of factors**



# Applications of Dissolution in the Pharmaceutical Industry

**1. As a formulation design aid (since formulation can profoundly affect dissolution behaviour)**

**2. As a quality control measure immediately after production for batch release**

**3. As a quality control measure to check performance during the shelf life**

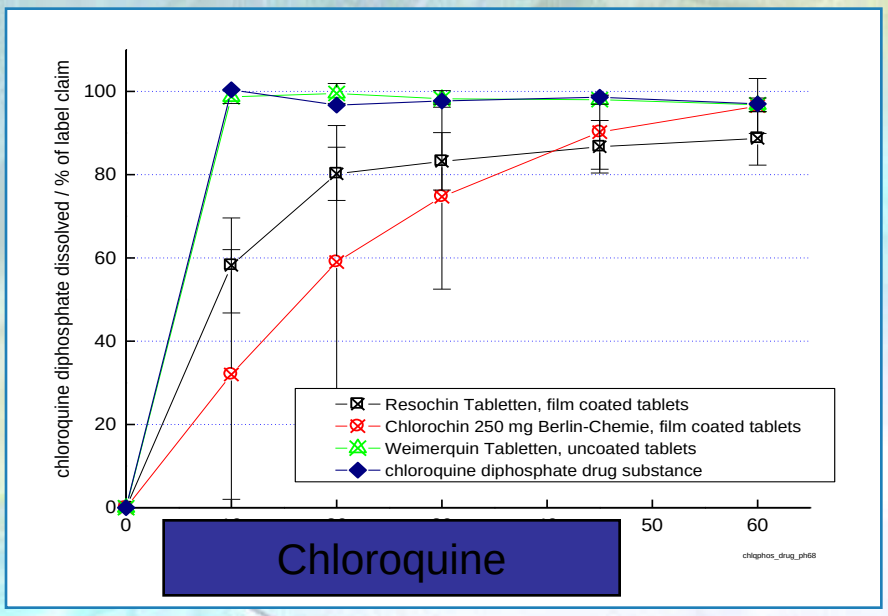
**4. To predict performance under various dosing conditions („biorelevant“ methods)**

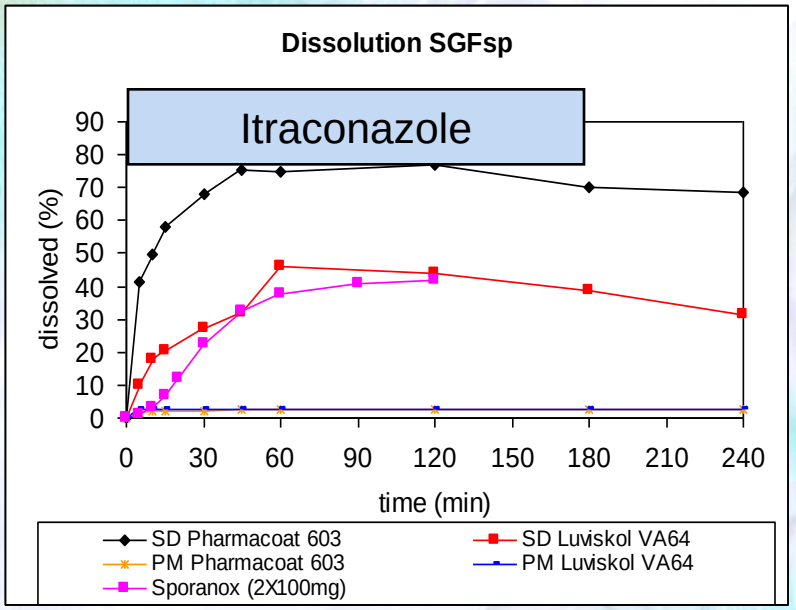
**5. To verify that the quality of a product is not adversely affected when there is a change in excipients or manufacturing method (can sometimes be used instead of a pharmacokinetic study)**

**6. To obtain approval for a multisource drug product („generic“ version of an existing drug product) – in certain cases a pharmacokinetic study is not required.**

# 1. Dissolution as an aid to formulation in the Pharmaceutical Industry

**The dissolution of the pure API is determined. If this is too slow for the target release rate from the API, the formulation has to be enhanced to improve the release characteristics.**



# 2&3 . Dissolution as a quality control measure for batch release, and to ensure continued quality during the shelf life.

**Here it is important to have a well-designed dissolution test that can detect batches with poor quality without rejecting batches of adequate quality.**

**The USP and, recently, the International Pharmacopeia, make recommendations for specific drug products**

USP®
U.S. Pharmacopeia
The Standard of Quality℠

# WHO Standard dissolution method for highly soluble APIs

- Paddle Apparatus
- 500 mL
- SIFsp/IP Phosphate Buffer pH 6.8
- 75 Rpm
- 37 °C
- Sampling at 30 min.

- **Specification:**
  - ≥85 % release within 30 min.

# Dissolution, Pharmaceutical Product Interchangeability and Biopharmaceutics Classification

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# *Why the Paddle Apparatus?*

**Widely used for:**

- **Tablets and capsules (can also be used for pellets, MR dosage forms)**

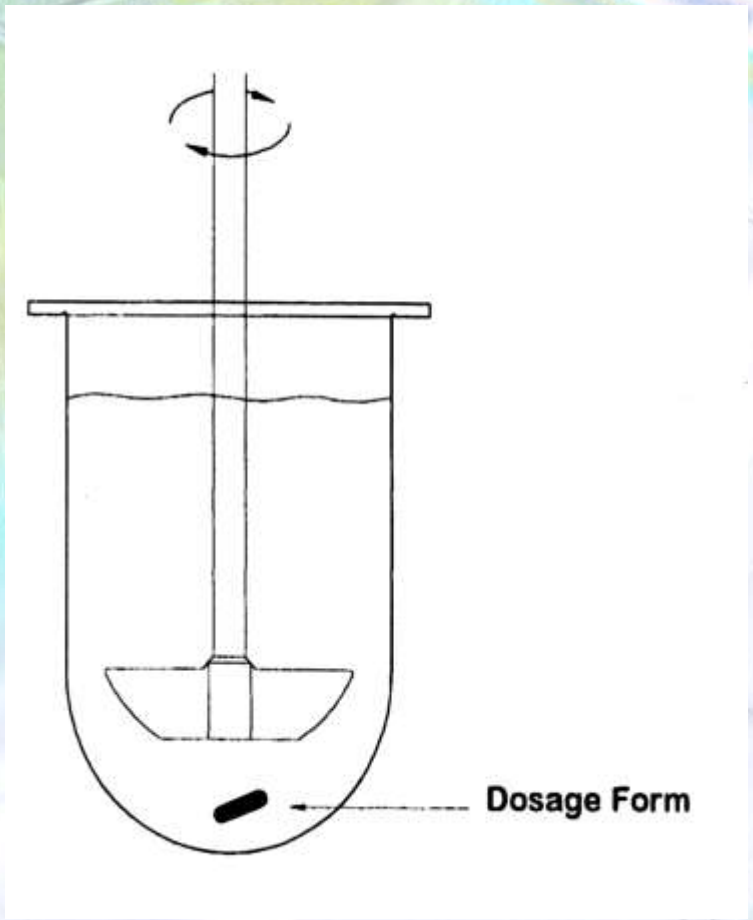
**Advantages:**

- **easy to use, robust**
- **long experience**
- **Many examples in USP**

**Disadvantages:**

- **possibility of coning**

***Method of choice for IR – dosage forms***



- ***Why 500 mL medium?***
  - Corresponds approximately to the volume of the contents in the upper GI tract in the fasting state plus a glass of water.
- ***Why 75 rpm?***
  - Avoids coning problems in most cases
  - For most drugs and drug products studied to date, if there is no coning, the results are very similar at 50 and 100 rpm.

# Volumes in the upper GI tract after two types of meals

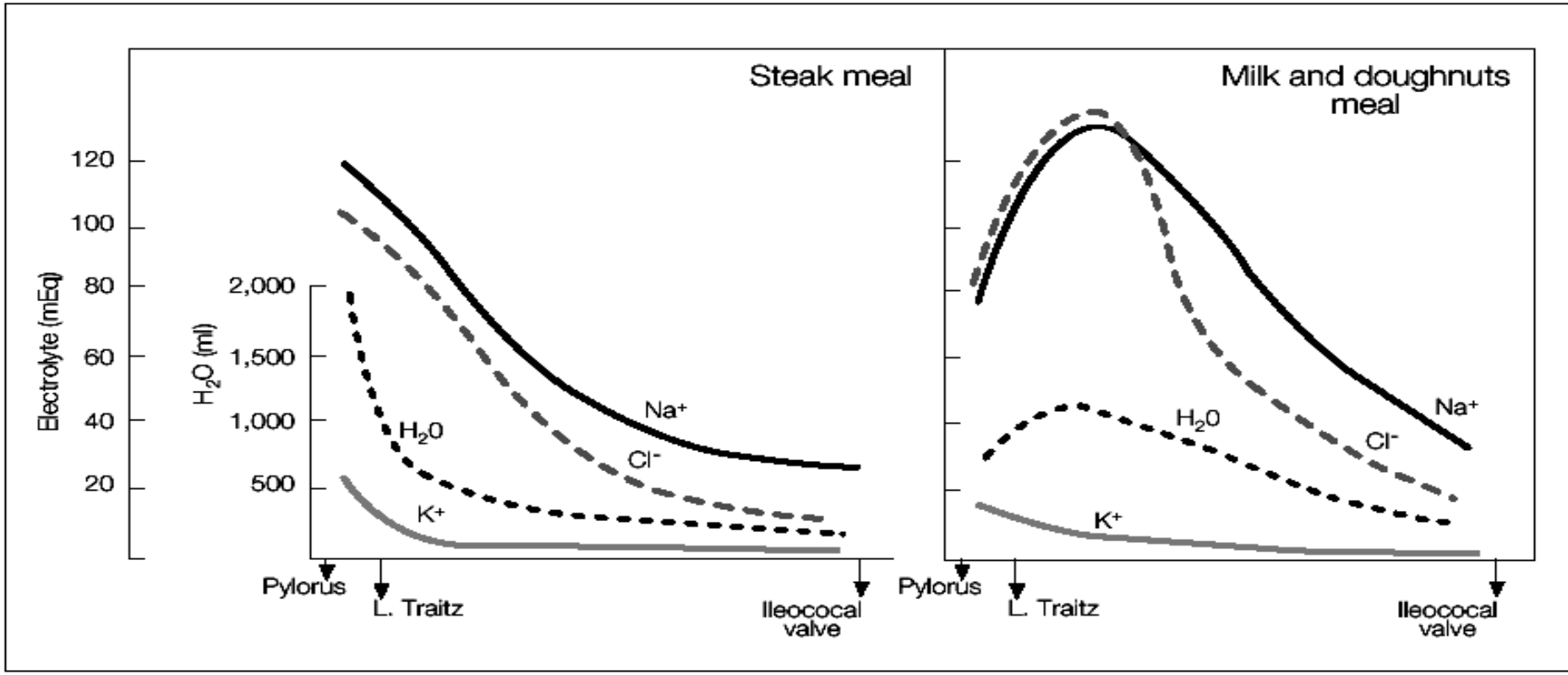



*Figure 5: Water volumes and electrolyte concentrations in the small intestine following ingestion of a hypo tonic steak/water meal (Panel A), and a hypertonic milk/doughnuts meal (Panel B) [Fordran and Locklea Am. J. Dig. Dis.* ***11****:503-521 (1966)].*

- ***Why 37°C?***
  - Corresponds to the temperature of the GI fluids
  - For transdermal products a lower temperature, usually 32°C is used, since this is closer to skin temperature.

- ***Why a pH 6.8 Phosphate buffer?***
  - Corresponds to one of the three pH values stipulated by the FDA in its biowaiver guidance
  - Both the USP and IP buffers have good buffer capacity. Nevertheless, the pH should be checked at the end of the experiment.

# Case Example: Doxycycline hyclate

- **Solubility:**
  - **SGFsp pH 1.2** **40.1 mg/mL**
  - **Aq. puricata** **> 50.0 mg/mL**
  - **SIFsp pH 6.8** **28.7 mg/mL**
- **Dose – 230 mg**
- **Permeability:**
  - **Bioavailability:** **95 %**
  - **$C_{max}$, p.o. admin.** **2–3 h**

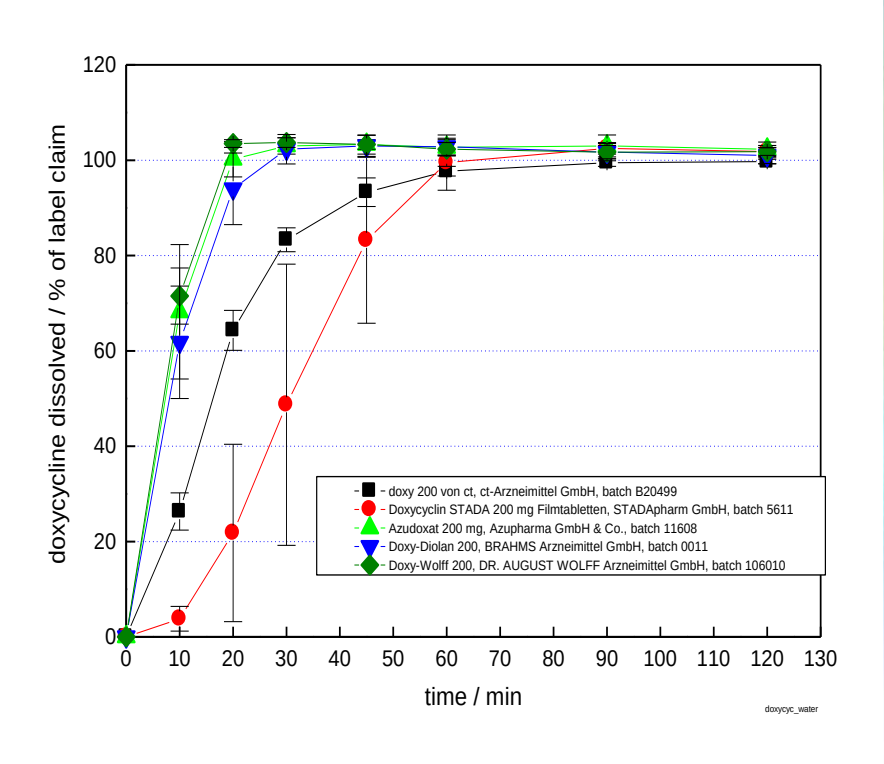
**USP Method**

**Paddle Apparatus, 75 rpm**
**Paddle 4.5 cm above the vessel bottom**
**900 mL de-ionized water**
**30 min. for Capsules, 90 min. for Tablets**

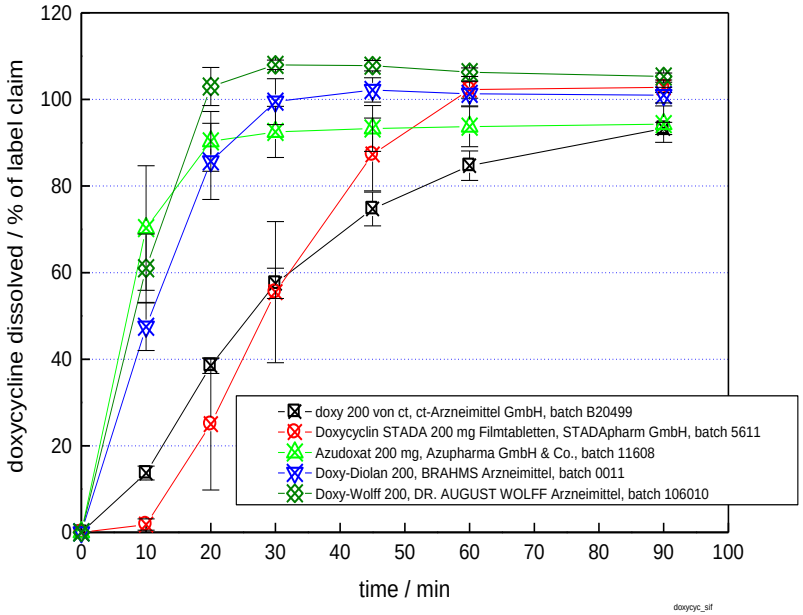
**WHO Method**

**Paddle Apparatus, 75 rpm**
**Standard paddle position**
**500 ml pH 6.8 phosphate buffer**
**>85% release in 30 min.**

# Comparison of dissolution results for products that contain 230.8 mg Doxycycline hyclate




**USP Method**

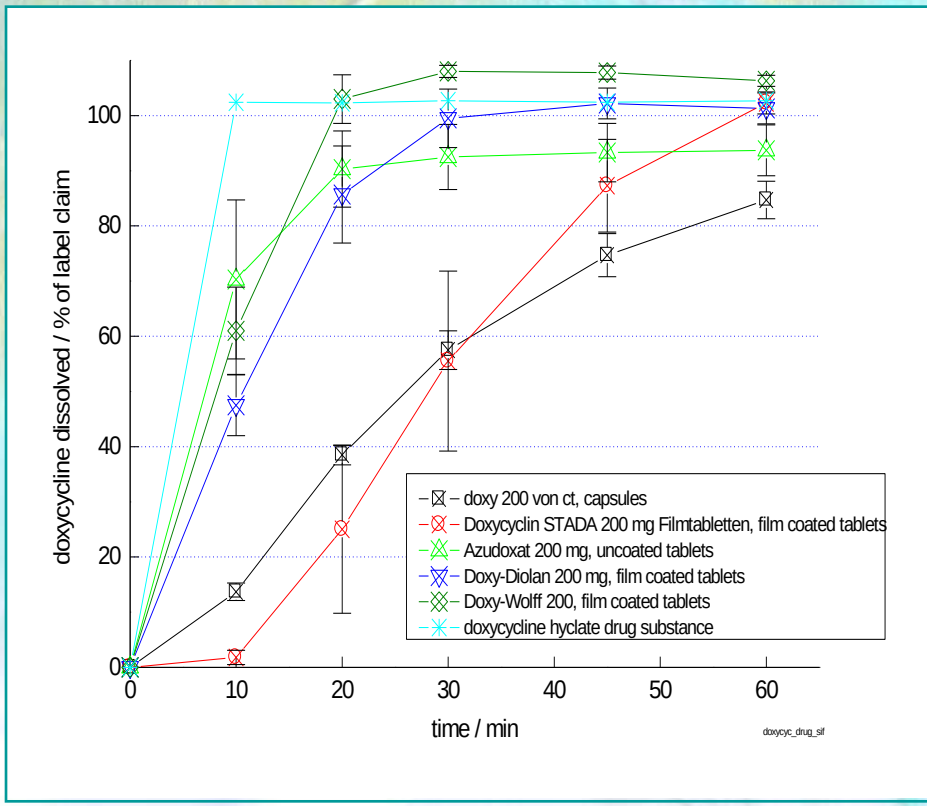



WHO Method

- ***Why a specification of 85% in 30 min?***
  - Corresponds to the specification stipulated by the FDA in its biowaiver guidance
  - During development of the method, it is advisable to generate a dissolution profile (e.g. samples at 10, 20, 30, 45 and 60 mins) so that the dissolution is adequately characterized
  - For determination of **bioequivalence**, it must be shown that the dissolution profile of the test product varies by less than 10% from the comparator product (usually by f2 comparison)

# Dissolution tests proposed for Pharm. Int.

- **Chloroquine phosphate and sulfate**
- **Doxycyline hyclate**
- **Ethambutol dihydrochloride**
- **Isoniazid**
- **Metronidazole**
- **Primaquine diphosphate**
- **Pyrazinamide**
- **Rifampicin**



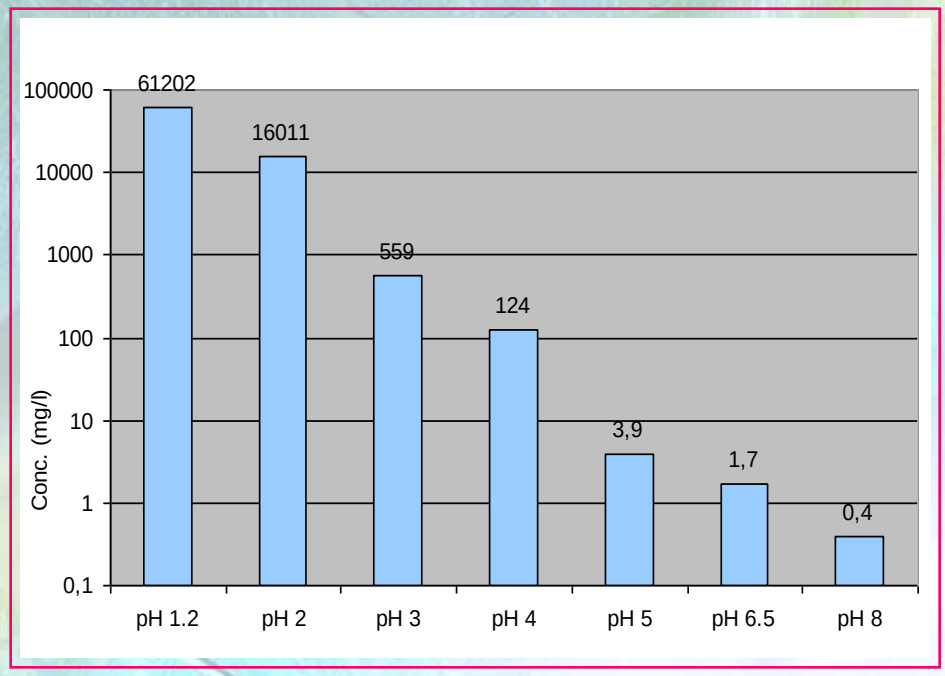
However, many APIs are **poorly soluble**, creating dissolution problems

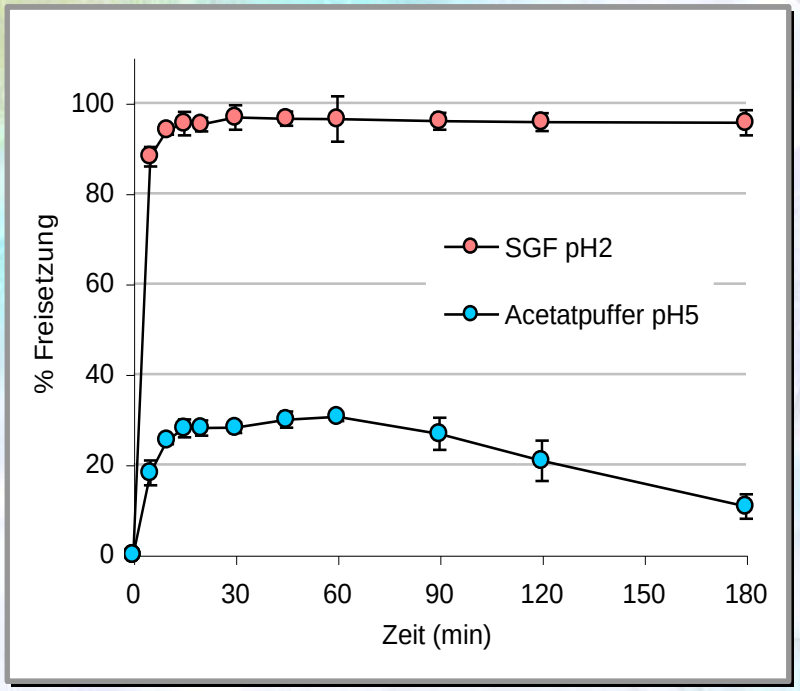
Some dissolution test options for poorly soluble drugs

1. Adjust the pH of the medium
2. Add a surfactant to the medium
3. Increase the volume of the dissolution medium
4. Increase the duration of the dissolution test

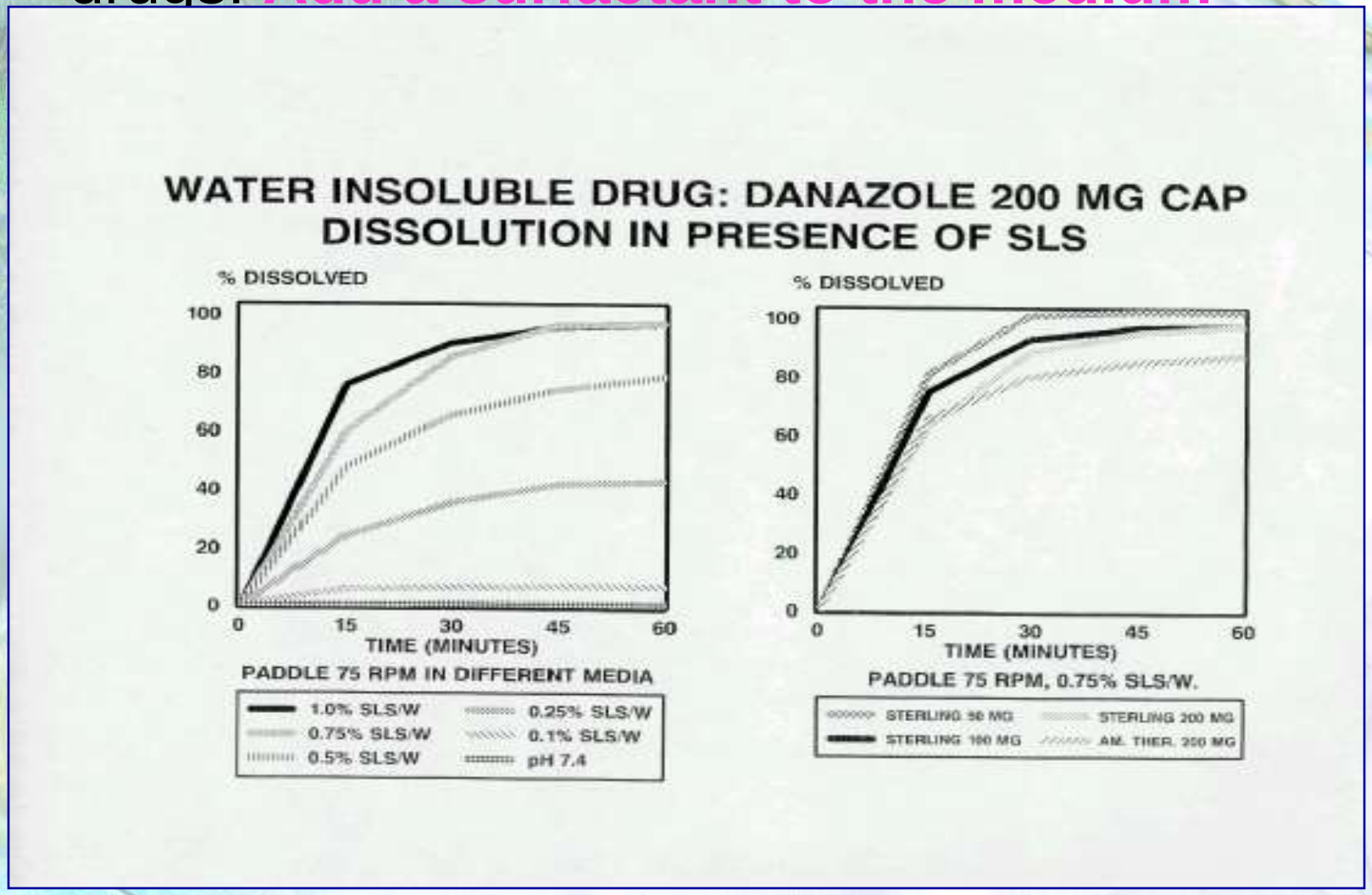
Some dissolution test options for poorly soluble drugs: **Adjust the pH of the medium**

***pH-dependent solubility: weak base***



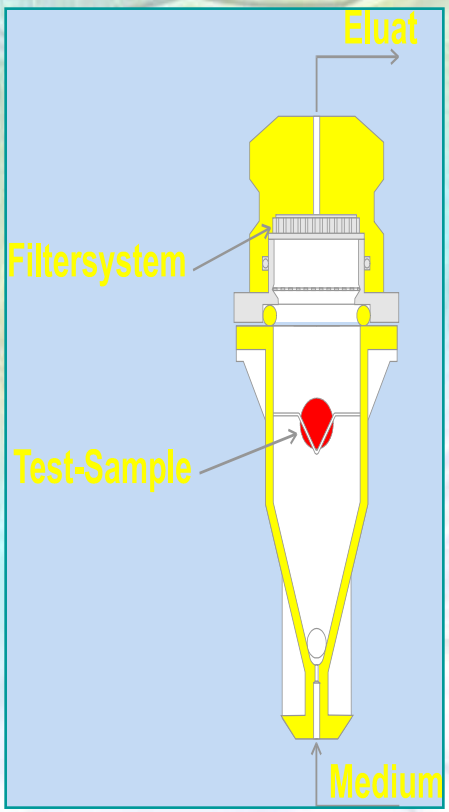



# Some dissolution test options for poorly soluble drugs: **Add a surfactant to the medium**




***Increasing levels of sodium lauryl sulfate (0.1-1%) increase dissolution of danazol (left panel)***

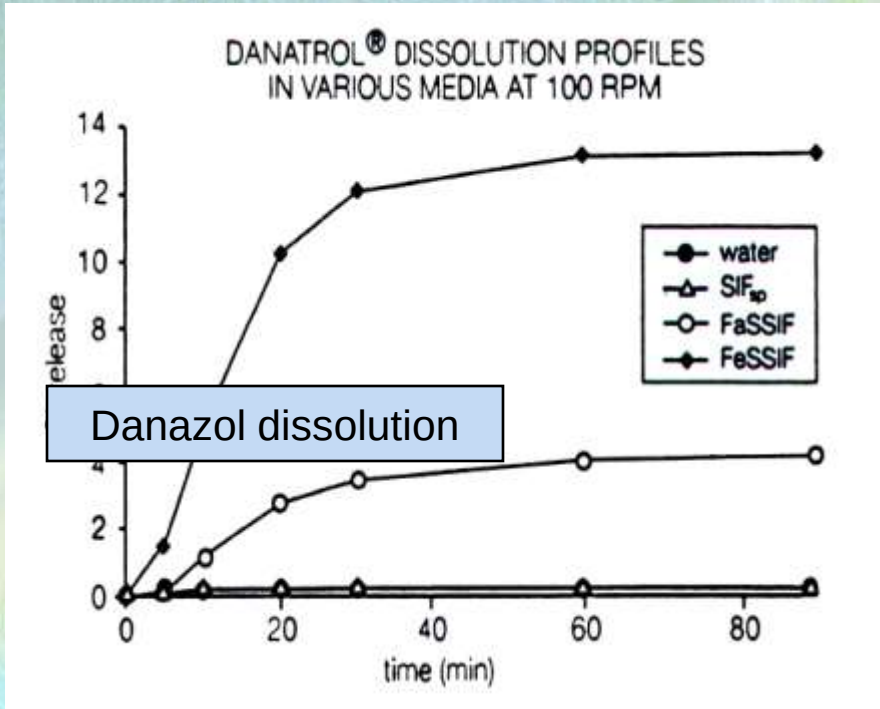
# Some dissolution test options for poorly soluble drugs: **Increase the volume of the medium**



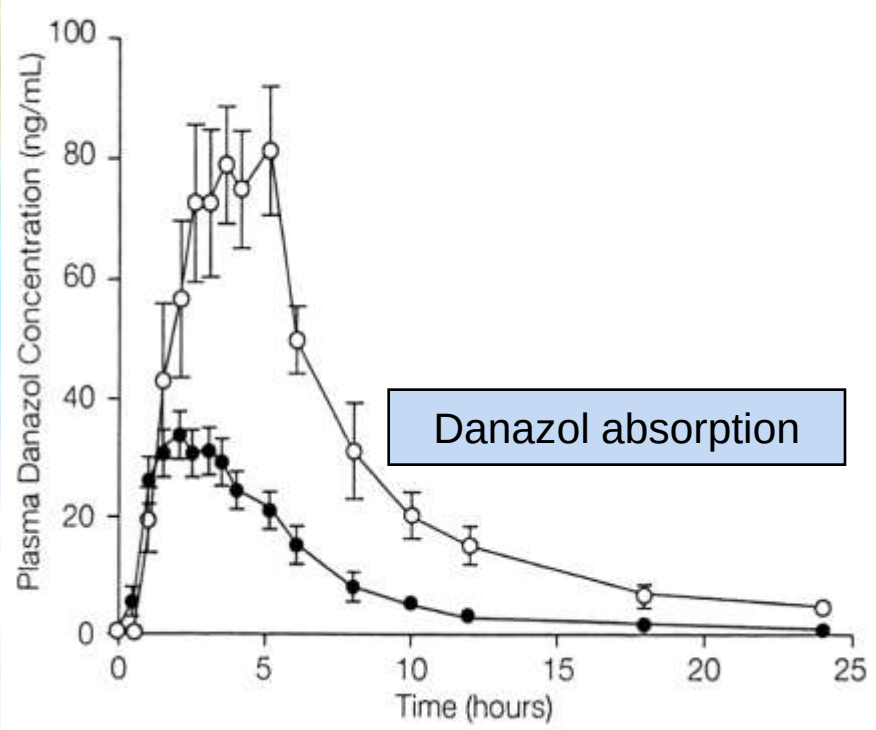

***Using the Flow-Through tester, volumes of up to several liters can be used.***

# 4. Dissolution to predict performance under various dosing conditions:

**One question that often comes up is whether the API release is affected by coadministration of a meal.**




Danazol dissolution




Danazol absorption

# 5.&6. Dissolution to obtain (continued) approval to market a drug product

**In certain circumstances, dissolution testing can serve as a surrogate for a bioequivalence study in humans. This is referred to as a „biowaiver“.**

**One example is when a change has to be made to the formulation or manufacture of an existing product**

**Another example is in the approval of a new multisource product.**

# „*Must have“ Literature*

- „Handbook of Dissolution Testing 3. Auflage“
  Roy Hanson & Vivian Gray
  Published by Dissolution Technologies (2005)
  www.dissolutiontechnologies.com
- „Pharmaceutical Dissolution Testing“
  Edited by J. Dressman & J. Krämer
  Published by Taylor and Francis
  www.taylorandfrancis.com
- General Chapter on Dissolution Testing (United States Pharmacopeia)

# IN VITRO IN VIVO CORRELATION

# INTRODUCTION

- Key goal in development of dosage form is good understanding of *in vitro* and *in vivo* performance of dosage form
- Formulation optimization requires altering some parameters – bioavailability studies
- Delay in marketing, added in time and cost
- Regulatory guidance developed to minimize the additional bioavailability studies
- The guidance is referred as *in vitro in vivo* correlation

# IVIVC BASIC

- Simply a mathematical model describing the relationship b/w *in vitro* and *in vivo* properties of drug
- In vitro – in vivo correlation can be achieved using

⍓Pharmacological correlation

⍓Semi quantitative correlation

⍓Quantitative correlation

# DEFINITION

- **USP** definition

"The establishment of rational relationship b/w a biological property or a parameter derived from a biological property produced by a dosage form and physicochemical property of same dosage form"

- **FDA** definition

"It is predictive mathematical model describing the relationship b/w in vitro property of dosage form and a relevant in vivo response"

# IMPORTANCE

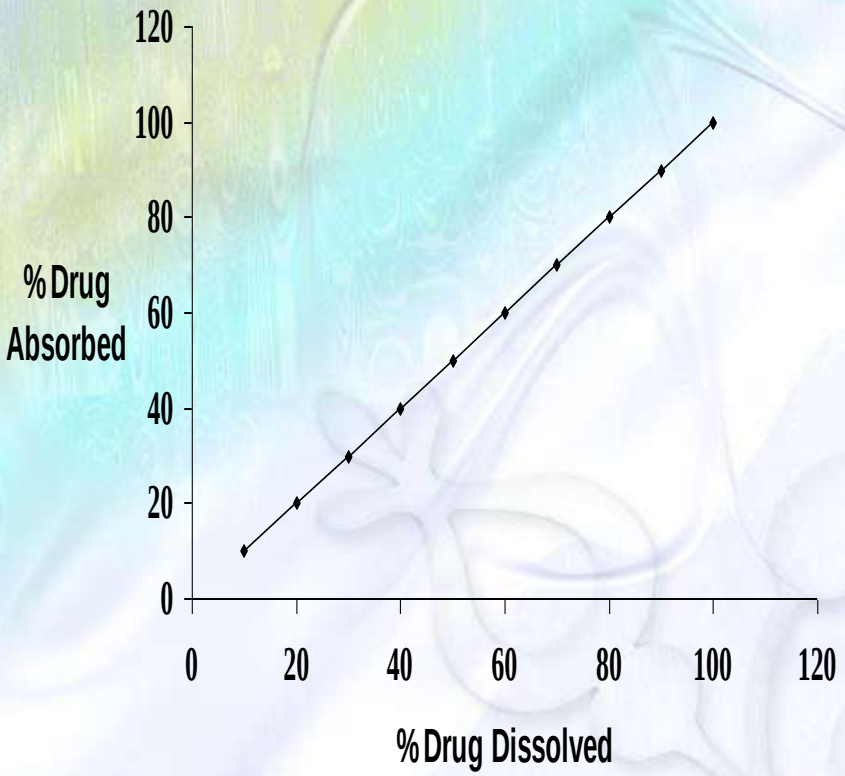
- Serves as a surrogate of in vivo and assist in supporting biowaivers
- Validates the use of dissolution methods and specification
- Assist in QC during mfg and selecting the appropriate formulation

# LEVELS OF CORRELATION

- Level A correlation
- Level B correlation
- Level C correlation
- Multiple level C correlation
- Level D correlation

# Level A correlation

- Highest category correlation
- Represents point to point relationship
- Developed by two stage procedure
- ✓ Deconvulation
- ✓ Comparison
- Purpose – define direct relationship



# Level B correlation

- Utilizes the principle of statistical moment analysis

  MDTvitro is compared with MRTvivo
- No point to point correlation
- Does not reflect the actual in vivo plasma level curves
- Thus we can not rely to justify the formulation modification, mfg site change and excipient source change.

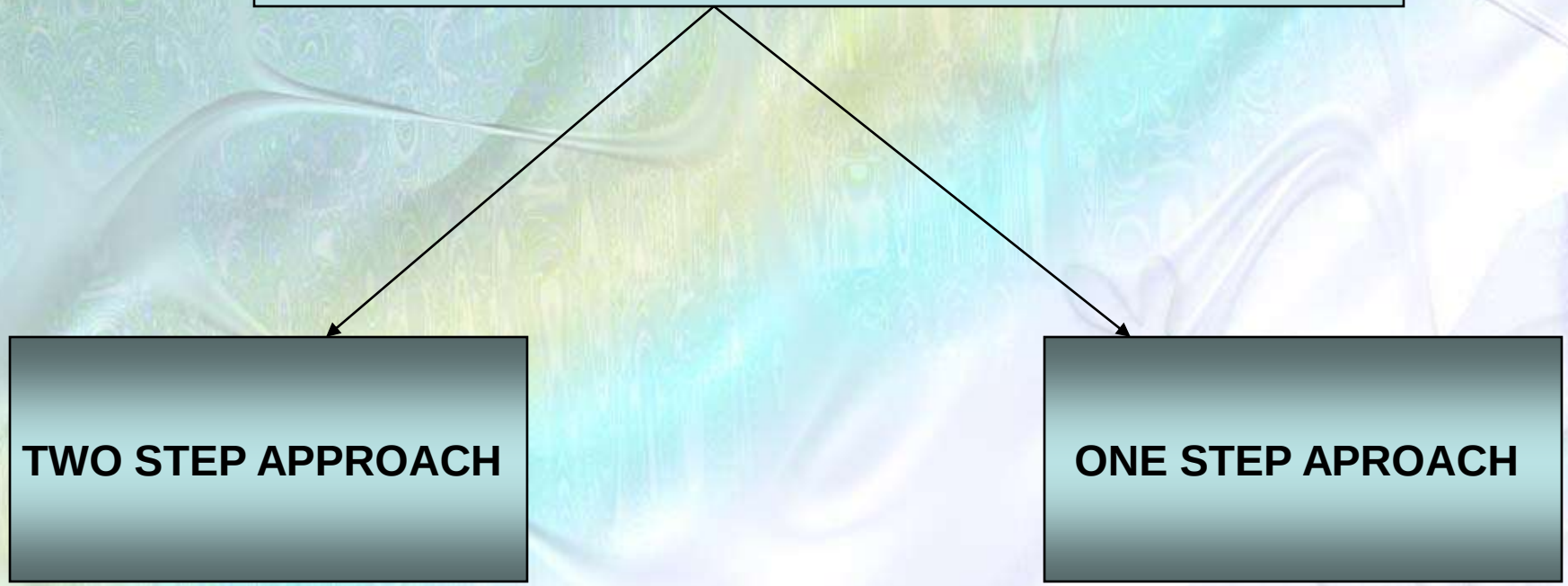
# Level C correlation

- Dissolution time point ($t_{50\%}$,$t_{90\%}$ ) is compared to one mean pharmacokinetic parameter ( $C_{max}$ ,$t_{max}$ ,AUC)
- Single point correlation
- Weakest level of correlation as partial relationship b/w absorption and dissolution is established
- Useful in the early stages of formulation development

# Multiple level C correlation

- It reflects the relationship b/w one or several pharmacokinetic parameter of interest and amount of drug dissolved at several time point of dissolution profile
- Base on
  - ◊ Early
  - ◊ Middle
  - ◊ Late stage

1. Develop formulation with different release rates
2. Obtain *in vitro* dissolution profile and *in vivo* concentration profile of these formulation



## ❖Approaches to improve dissolution of poorly soluble drug –

### ➢Lipid based formulations –

- These include lipid solutions, micro-emulsions.
- Lipid solutions consist of drug dissolved in vegetable oil or in triglycerides.
- The high lipophilicity facilitates absorption into the intestinal lymphatics and then to the systemic circulation.
- The presence of surfactant in this formulation causes the enhanced absorption due to membrane induced permeation changes.

## ➢ Size reduction technology –

- Surface area increases by decreasing particle size which results in higher dissolution rate.

- Reduction in particle size can be accomplished by micronization, cryogenic and supercritical fluid technology.

## ➢ Functional polymer technology –

- This technique enhance the dissolution rate of poorly soluble drug by avoiding the lattice energy of the drug crystal.

- These polymers (amberlite, duolite) are ion exchange materials that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly.

- The resultant complex, known as resinate can be formulated as suspension, dry powder or tablet.

## ➢ Porous microparticle technology –

- The poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix. when mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles.

- This is the core technology applied as HDDS (Hydrophobic Drug Delivery System). These drug particles provide large surface area for increased dissolution rate.

- The hydrophilic solubilization technology (HST) for poorly soluble drugs uses a lecithin and gelatin based water soluble coating to improve dissolution and hydration of lecithin-gelatin coat forms micelles which improve oral bioavailability of the insoluble drugs.

## ➢ Controlled precipitation technology –

- In this process, the drug is dissolved in a water miscible organic solvent and then dispersed into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin)

- The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystal

- The stabilizers control particle growth and enhances the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer.

## ➢ Inclusion complexes –

- These complexes can be prepared with β-cyclodextrin and HP-β-CD.
- The required quantity of β-CD is weighed and water added to get consistancy.
- To the mass weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for 1 hr. and then completely dried in hot air oven at 60$^{o}$C for 2 hrs. The dried mass is sieved through mesh no. 120

## ➢Solid dispersions –

- It is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the fusion or melting solvent method.

- Carriers for solid dispersion-

✓ Sugars- dextrose, sorbitol, mannitol.

✓ Acids- Citric acid, tartaric acid, succinic acid.

✓ Polymeric materials- PEG 4000, PEG 6000, HPMC, polyvinyl pyrrolidone.

- Methods of preparation –

1. Melting method/Fusion method –

- In this method, the physical mixture of a drug and water soluble carrier was heated directly until it is melted, which was then cooled and solidified rapidly in an ice bath.
- To facilitate faster dissolution, the melt was poured in the form of thin layer onto a stainless steel plate and cooled by flowing air or water on opposite side of plate.
- The final solid mass is then crushed, pulverized and sieved.

## 2. Solvent method –

- Solid solutions or mixed crystals can be prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent.

- Thermal decomposition of drugs or carriers can be prevented because of low temperature.

- E.g. – solvent dispersions of β-carotenes-PVP, griseofulvin –PVP, tolbutamide-PVP, etc.

# 3. Melting-Solvent method –

- The drug is first dissolved in a solvent and then the solution is incorporated directly into the melt of the carrier.

- A liquid drug such as methyl salicylate, Vitamin-E, clofibrate can be formulated as a solid dosage form and mixing it with melted liquid of PEG-6000 and cooling the mixture.

## ➢ Simple Eutectic mixtures –

- Rapid solidification of fused liquid of two components which shows complete liquid miscibility and negligible solid-solid solubility yields a simple eutectic mixture.

- When a eutectic is exposed to GI fluids, both poorly soluble drug and carrier may crystallize out in very small particulate size.

## ➢ Solid solution :-

- It is made up of a solid solute molecularly dispersed in a solid solvent. The two components crystallize together in a homogenous one-phase system and thus they are referred to as mixed crystals or molecular dispersions.

- They are generally prepared by fusion method where a physical mixture of solute and solvent are melted together followed by rapid solidification.

- The two mechanisms suggested for rapid dissolution of molecular dispersions –

i. When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles.

ii. Solute and solvent molecules randomly arranged themselves to form crystal lattice, when dissolution fluid is exposed to such crystal, soluble solvent molecules get dissolved in dissolution fluid and leaves behind insoluble drug molecules.

## ➢ Glass solutions and glass suspensions –

- It is a homogenous glassy system in which a solute dissolves in a glassy solvent.
- Glass solution is metastable and it amorphous to x-ray diffraction.
- Polyhydroxy molecules like sugars form glasses which may be due to strong hydrogen bonding prevent crystallization.

- Amorphous precipitations in a crystalline carrier –

- The drug precipitate out in an amorphous form in the crystalline carrier from a melting or solvent method of preparation.

- Amorphous form produces faster dissolution rate than crystalline form.

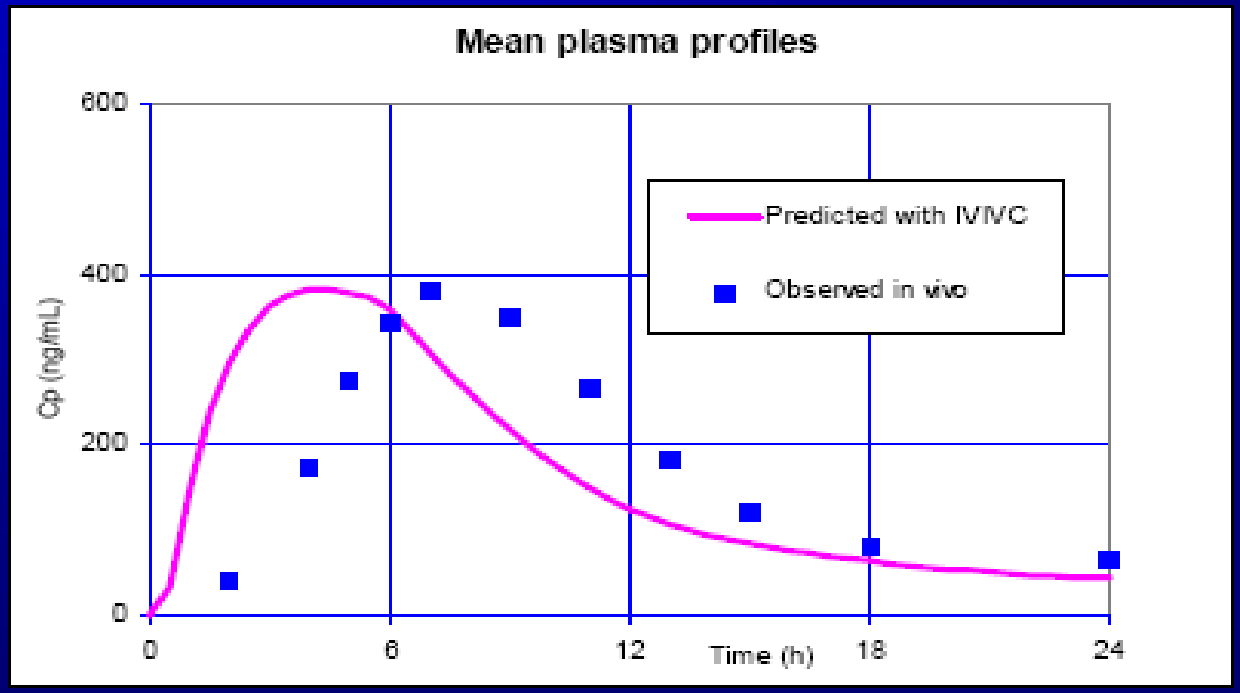
# EVALUTION OF PREDICTIBILITY CORRELATION

- Demonstrate – in vitro dissolution characteristic is maintained
- They focus the predictive performance or prediction error
- Depending of intended application of IVIVC and therapeutic index
  - Internal evaluation
  - External evaluation

$$\%\ PE = \frac{(C_{max}\ \text{observed} - C_{max}\ \text{predicted}) \times 100}{C_{max}\ \text{predicted}}$$

# Weakness of the Predictability Metrics

$C_{max}$ predicted ~ $C_{max}$ observed, but $T_{max}$ different



# Biopharmaceutics Classification System

| Class | Solubility | Permeability | IVIVC Expectations |
|---|---|---|---|
| 1 | High | High | IVIVC posible if dissolution rate (DR) is slower than gastric emptying rate. Otherwise limited or no IVIVC. |
| 2 | Low | High | IVIVC expected if *in vitro* DR is similar to *in vivo* DR. |
| 3 | High | Low | Absorption (permeability) is rate determining, therefore limited IVIVC with DR to be expected. |
| 4 | Low | Low | Limited or no IVIVC expected. |

# Biopharmaceutics Classification System

## Absorption Number

*A function of GI Permeability to Drug Substance*

$$An = \left( \frac{P_{eff}}{R} \right) \left( T_{GI} \right) = \frac{T_{GI}}{T_{ABS}}$$

# Biopharmaceutics Classification System

*Effective permeability*

$$An = \left( \frac{P_{eff}}{R} \right) \left( T_{GI} \right) = \frac{T_{GI}}{T_{ABS}}$$

*Residence time in GI*

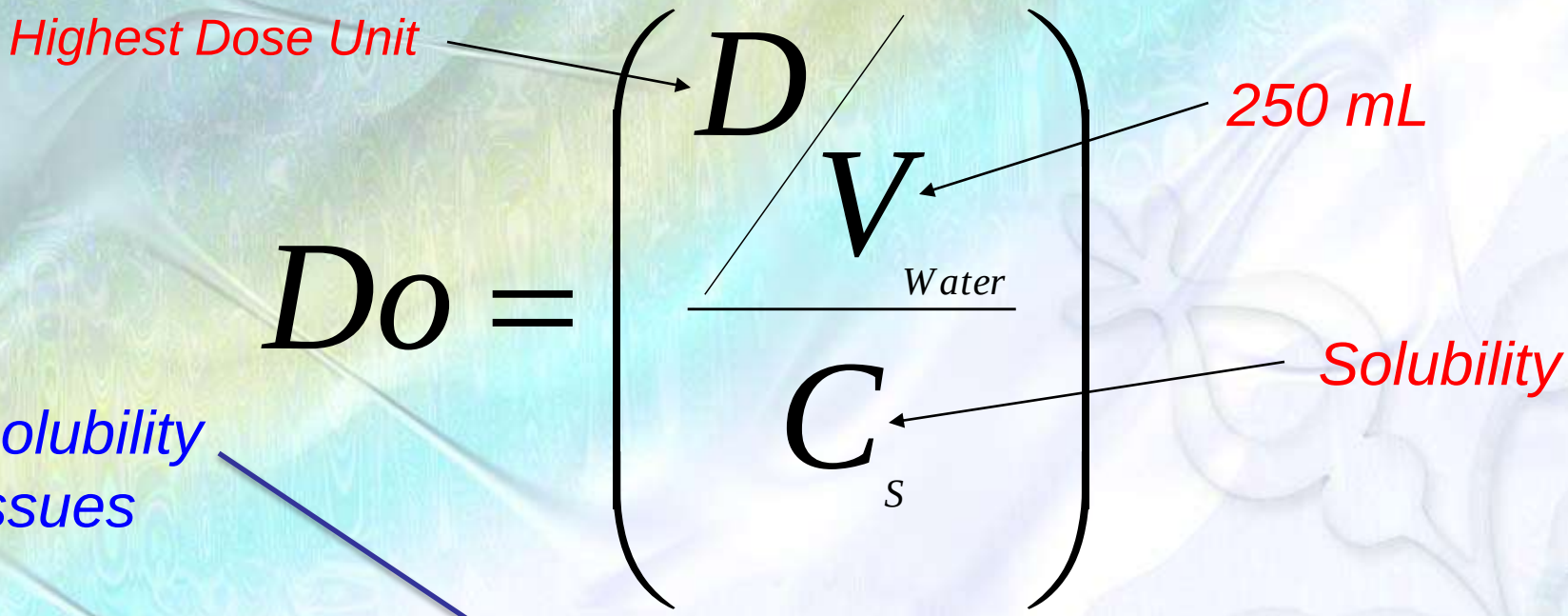
*Radius of GI*

*Time required for complete absorption*

# Biopharmaceutics Classification System

## Dose Number

*A function of solubility of drug substance*




$D / V_{water} >> C_S$ ~ High Do  $D / V_{water} << C_S$ ~ Low Do

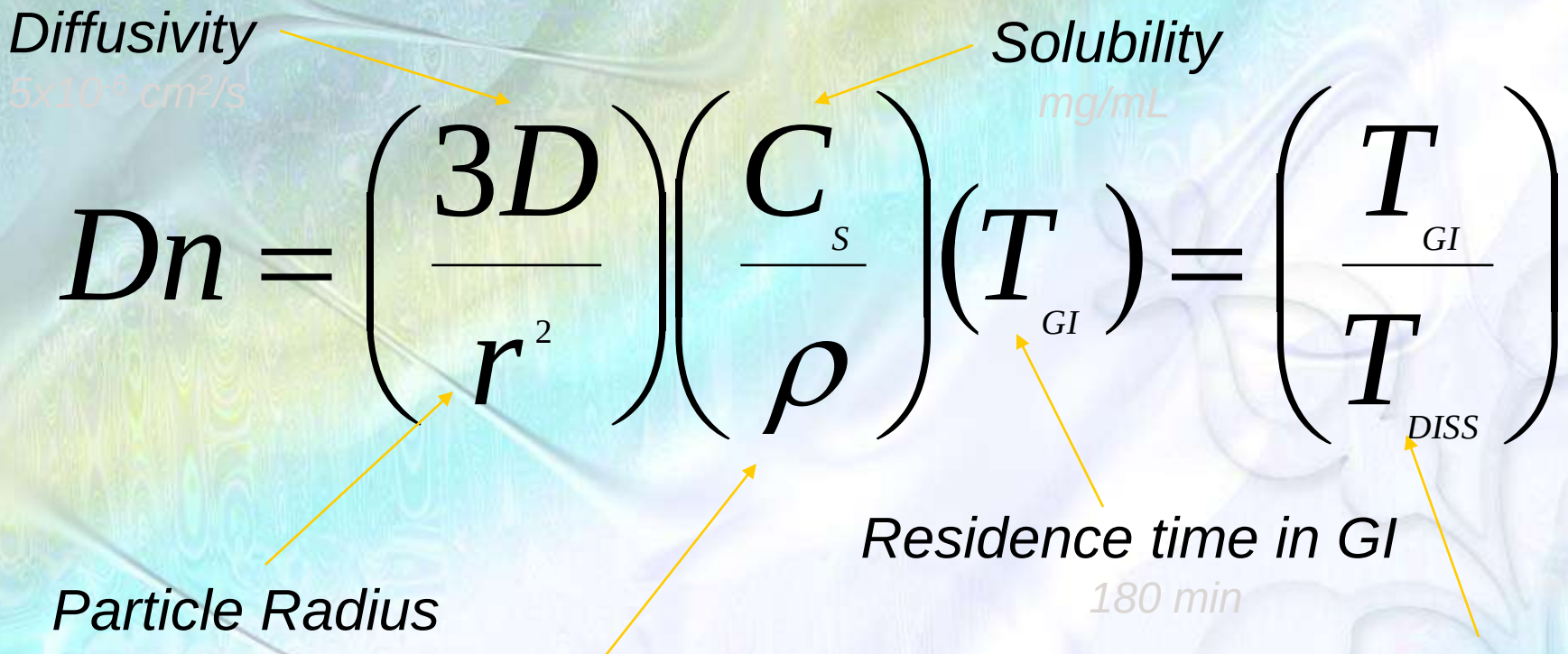
# Biopharmaceutics Classification System

## Dissolution Number

*A function of drug release from formulation*

$$Dn = \left(\frac{3D}{r^2}\right)\left(\frac{C_S}{\rho}\right)\left(T_{GI}\right) = \left(\frac{T_{GI}}{T_{DISS}}\right)$$

# Biopharmaceutics Classification System



# Dissolution and IVIVC

- It has high discriminating power and able to detect minor changes in manufacturing process
- Purpose
  - Batch consistency
  - Quality performance
  - Guide to new formulation
- **Dissolution apparatus**

| | |
|---|---|
| Apparatus 1 | Rotating basket |
| Apparatus 2 | Paddle method |
| Apparatus 3 | Reciprocating cylinder |
| Apparatus 4 | Flow through cell |

- For IVIVC purpose dissolution profile of at least 12 dosage form each lot should be carried out

$$f_2 = 50 \log\{[1 + 1/n \sum_{t=1}^{n} (Rt - Tt)^2 ]^{-0.5} \times 100 \}$$

- Where $R_t$ and $T_t$ = cumulative % dissolved for reference and test
- Values range from 0 to 100

# Bioavailability studies in developing IVIVC

- Performed to characterize the plasma conc. versus time profile
- Performed with sufficient no. of subjects
- Appropriate deconvulation technique is to be applied for IVIVC

$$F_T = \frac{C_T + K_E \int_0^T C dt}{K_E \int_0^\infty C dt}$$

**Wegner Nelson method**

$$F_T = \frac{C_T + K_{10} \int_0^T C dt + (X_p)_T / V_c}{K_{10} \int_0^\infty C dt}$$

**Loo – Riegelman method**

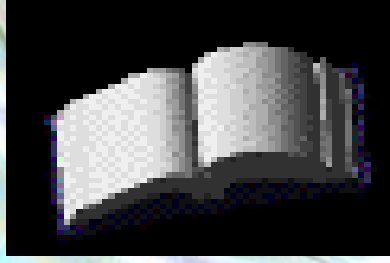
# Factors to be considered while developing IVIVC

1. Stereochemistry
2. First pass effect
3. Food effect

# APPLICATION OF IVIVC

- **Early development of drug product and optimization**
- **Bio waiver for minor formulation and process changes**
- **Setting dissolution specification**

# References

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# Any Question ?

# THANK YOU

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