Biopharmaceutics

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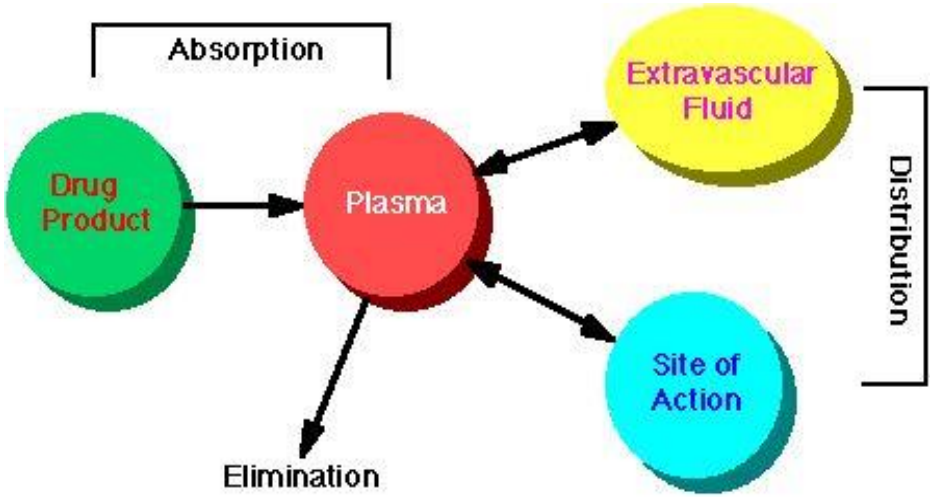
Definition : The science dealing with the physicochemical properties of the drug in the dosage form and its therapeutic response.



To give therapeutic effect; drug should undergo:

1- release from the dosage form to the physiological fluids.

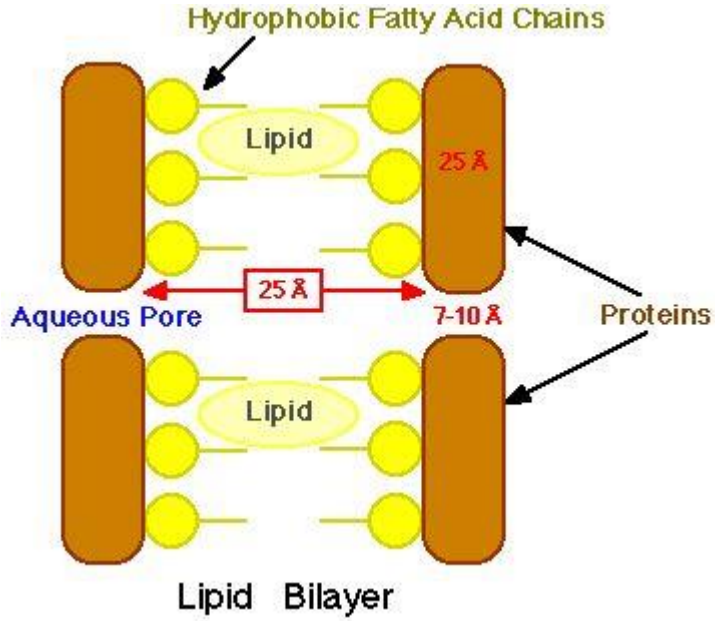
2- crossing the biological membranes to reach the blood circulation

Structure of Gastro-intestinal Tract:

Almost 90% of marketed drugs are administered orally and absorbed through the GIT.

	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
BUCCAL	approx 7	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
ESOPHAGUS	5 - 6	Very thick, no absorption	-	small	short	-
STOMACH	1 - 3 decomposition, weak acid unionized	normal	good	small	30 - 40 minutes, reduced absorption	no
DUODENUM	6 - 6.5 bile duct, surfactant properties	normal	good	very large	very short (6" long), window effect	no
SMALL INTESTINE	7 - 8	normal	good	very large 10 - 14 ft, 80 cm^2/cm (due to presence of villi and microvilli)	about 3 hours	no
LARGE INTESTINE	5.5 - 7	-	good	not very large 4 - 5 ft	long, up to 24 hr	lower colon, rectum yes

Passage of Drugs Across Cell Membranes:



For the drug to be absorbed, it should pass the membranes of the apical cells in the small intestine as follows:

1- Non ionic drugs can pass cell membranes more readily than ionized drugs.

2- Small molecular weight drugs can pass cell membranes more readily than large molecular weight drugs and that are bound to the proteins.

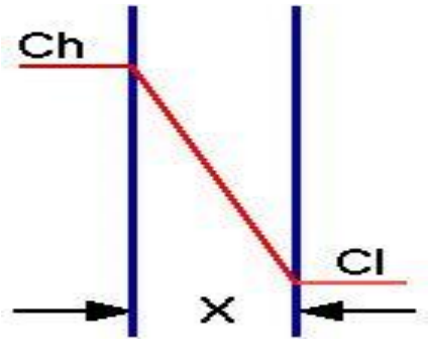
3- Water soluble drugs of small molecular weight pass through simple diffusion through the water pores. E.g..: urea and small molecular weight sugars.

Mechanisms of Drug Absorption

1- Passive Diffusion:

Drugs move from the high concentration (Ch) to the low concentration (Cl) across the membrane according to Fick's law of diffusion:

$$dQ/dt = -[(Ch-Cl).\ D.\ A.\ K] / h$$



dQ/dt → Diffusion rate

(Ch-Cl) → Concentration gradient

D → Diffusion Coefficient

A → Surface area

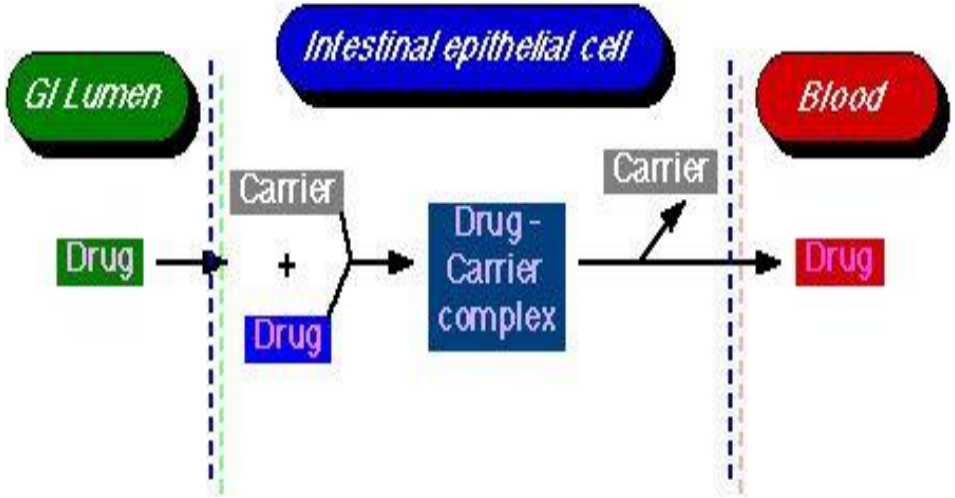
K → Oil/Water Partition Coefficient

h → Thickness of the biological membrane

2- Carrier-mediated transport:

i) Active transport:

The body has a number of specialized mechanisms for transporting particular compounds; for example, glucose and amino acids. Sometimes drugs can participate in this process; e.g. 5-fluorouracil. Active transport requires a carrier molecule and a form of energy.



* the process can be saturated

* transport can proceed against a concentration gradient

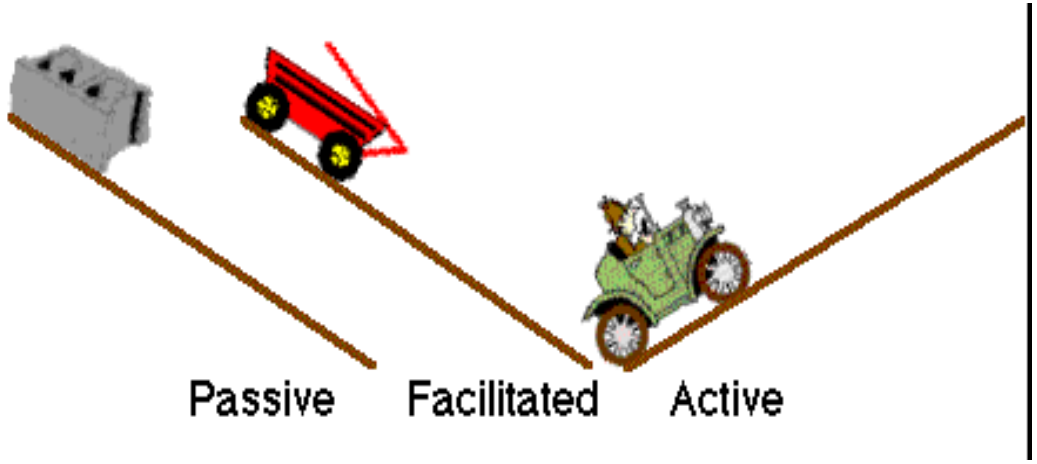
* competitive inhibition is possible (e.g. penicillin and probenicid)

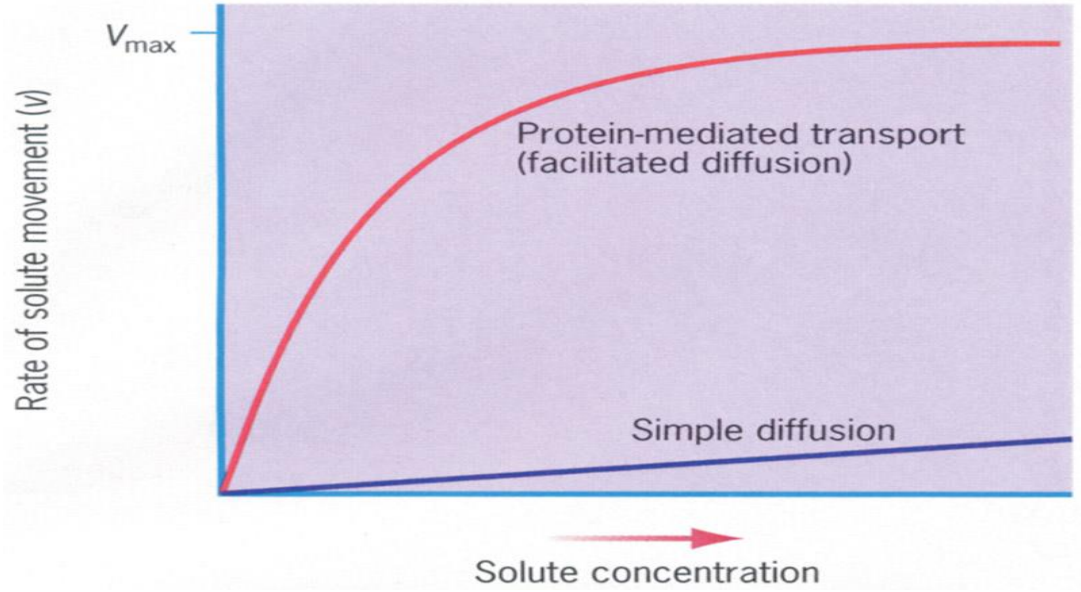
ii) Facilitated Diffusion:

A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport

** Saturable if not enough carrier

** no transport against a concentration gradient, downhill but faster.





3- Ion-pair Transport:

The mechanism can explain the absorption of drugs like; Tetracycline HCl and Quaternary amm. Compounds which are;

1- Highly ionized in pH of GIT

2- Too hydrophilic drugs

3- Too large molecules to pass through the water pores.

4- don`t partition through the membrane

4- Convective absorption (pore transport):

For very small molecules (e.g urea; water and low molecular weight sugars)

5- Pinocytosis:

For example Vitamin A, D, E, and K. … by invagination of drug globules to the membrane.

Factors Affecting Drug Absorption From GIT

I- Physiological Factors:

1) Surface Area of GIT Site:

** According to Fick's law → increasing SA → increase in Diffusion rate and absorption.

*** Small intestine with its folds, villi and microvilli → high absorption extent.

** Small intestine is the main site for absorption:

1- Large surface area

2- Most drugs are absorbed from small intestine even its pH is not suitable for absorption (e.g. weak acids)

3- The small intestine is the site with highest carrier density.

N.B. in case of large intestine → main site for drugs that are activated by bacterial flora (e.g. sulfasalazine)

2) pH of GIT site:

** pH of the GIT differs according to site and time.

Site → Stomach (acidic) & Intestine (basic)

Time → Diurnal cycle of gastric acidity (increase in day and decrease at night)

*** pH affect the absorption of drugs as most drugs are either weak acids or weak bases.

*** Some drugs may decompose in low pH of stomach and need to be protected with enteric coating

3- Gastric emptying rate (G.I.T)

1-Most drugs are absorbed from small intestine , hence any delay in gastric emptying rate →→reduction in the drug absorption →delay in onset of of action→reduction in therapeutic response of the drug.

2-Drugs exposed to chemical decomposition in stomach by its low pH or enzymes , the delay in gastric emptying i.e. most time exposure→more decomposition→reduced bioavailability.

3-Enteric coated drugs showing release in duodenum fluids→show delay therapeutic action if delayed gastric empty occurs.

Factors promoting gastric emptying rate :

1-Hunger 2-Anxiety

3-Patient`s body position (laying on right side)

4-Intake of fluids

5- Antiemetic drugs such as meteclopramid.

Factors retarding gastric empyting rate :

1-Fatty foods 2-High bulk diet (viscous)

3-Mental depression

4-Gastric ulcers 5-Hyperthyroidism

6-Patient`s body position (laying on left side).

4- *Intestinal motility :*

There are two types of intestinal movements : -**propulsive** and **mixing .**

The propulsive determine the intestinal transit rate and the residence time of the drug in the small intestine.

The greater the intestinal motility, the shorter the time of residence and less time for dissolution and absorption leading to less activity.

Intestinal residence time will be important for :

1-sustained and prolonged dosage forms.

2-Enteric coated dosage forms.

3-Slowly dissolving drugs in the intestinal fluids.

5- Drug stability in G.I.T :

The drug may be chemically degraded and/or metabolized in G.I.T leading to incomplete bioavailability. This occurs in the G.I.T fluid for drugs pH dependent and affected by hydrolysis. Examples: erythromycin →acid
catalytic hydrolysis in G.I.T. Also polypeptides, nucleotides and fatty acids undergo enzymatic hydrolysis in G.I.T.

Hepatic metabolism :

All drugs absorbed from stomach , small intestine and colon pass into hepatic portal system and presented to the liver before reaching systemic circulation .This means that the liver is the primary site of drug metabolism hence a significant portion of the absorbed dose may never reach systemic circulation . This phenomenon is called ***first –pass effect*** . Examples such as: propranolol and propoxyphenol .

6- *Influence of food and diet* :

The rate and extent of drug absorption can be influenced by the presence of food in G.I.T.

Food influence drug bioavailability by these mechanisms **:**

1) Alteration in the rate of gastric emptying:

The diet containing high proportion of fats decreases gastric emptying rate.

2) Stimulation of gastric secretion .

Food stimulate gastric secretions →hydrolysis or enzymatic metabolism for unstable drug . for example :

a-Fat stimulate bile secretion , the bile salts are S.A.A→ increase dissolution of some poorly soluble drugs →increase in their absorption e.g. grisofulvin .

b- Bile salts form insoluble non absorbable complexes with neomycin, kanamycin and nystatin ,hence not administered with fatty foods .

3) Competition between food components and drugs having specialized absorption mechanism :

e.g. l-dopa which competes with some amino acids resulted from ingested proteins .

4) Complexation of drugs with components in the diet :

a-Tetracycline absorption is decrease when administrated with milk since a complex is formed with calcium , non absorbable.

b-If the complex formed is water soluble →readily dissociate →liberate the drug →absorption is noted.

5) Increased viscosity of G.I.T.

The increased viscosity of G.I.T contents→ reduction in the rate of diffusion of the drug from the lumen to the absorbent membrane →decrease bioavailability

6) Food induced changes in the blood flow to the liver .

After meals ,the blood flow to G.I.T and liver is increased →increase rate of presenting the drug to the liver →large fraction of the drug that escapes from first pass metabolism.

II- physicochemical factors influencing drug absorption from G.I.T

i. Partition co-efficient and extent of ionization

DEFINITION : partition coefficient of a drug is the ratio of its solubility in an aqueous solvent to its solubility in a non aqueous solvent.

- **Hydrophilic drugs** → higher water solubility →faster dissolution rate than hydrophobic drugs showing poor solubility.
- Weak electrolyte drugs exist as ionized (salt) form and non-ionized (weak acid or weak base) forms. The extent of ionization depend on pka of the weak electrolyte and on the PH of the solvent .
- For weak acids : PH=PKa +log (salt/non-ionized acid).
- For weak base : PH = PKa +log (non-ionized base/salt).

ii. Dissolution

- **Definition**: Dissolution is the process by which a chemical or drug become dissolved. It is the rate limiting step of poorly soluble substances.
- **Dissolution rate**: is the amount of active ingredient in a solid dosage form dissolved in unit time under standard conditions of liquid/solid interface temperature and media composition.

Mathematically it is expressed by:

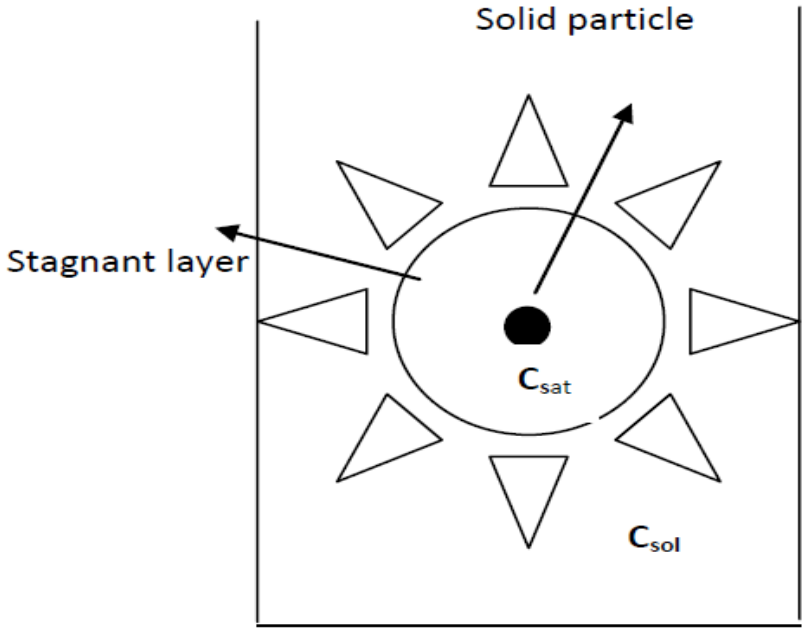
- **Noyes-whitney equation** :
- **$Dc/dt = KS (C_{sat}-C_{sol})$**
- where : Dc/dt = dissolution rate

k = dissolution constant.

s = surface area of the solid.

C_{sat} = concentration of saturated solution.

C_{sol} = concentration of any given time .



By keeping one volume of solvent large with respect to solution point (at least 5- 10 times as large) sink conditions are approximated as Csat >> Csol.

Dissolution profile: is a graph representing the relationship between percentage of drug dissolved and time

-***Sink condition****:* this expression is originated from the theory that G.I.T is a natural sink i.e. the drug instantly absorbed at moment it dissolves.

To stimulate in –vivo condition: (C sat – Csol) known as the retarding affect should be minimal as Csol = 0 i.e Csat – C sol = Csat To stimulate in –vivo Csat >>> Csol , or at any time :

C sol = 10 % C sat.

To maintain sink conditions use :

a- Large volume of dissolution medium.

b- High flow rate of dissolution medium.

Advantages;

1-determination of bio- equivalency of different batches of solid dosage forms (dissolution is rate limiting step).

2-Monitoring formulation and manufacturing process by quality control

3-Evaluation of the intrinsic dissolution rate which is useful in screening new compounds

In – vitro dissolution testing :

A- *official methods :*

1- The rotating basket (USP , BP , EP) apparatus 1 .

2- The rotating paddle (USP , BP) apparatus 2 .

3- Flow- through cell dissolution method .

4- The modified disintegration (USP) apparatus 3 .

The rotating basket – apparatus 1 (USP , BP , EP).

The apparatus mainly consists of a basket held by a motor shaft, the basket holds the sample and rotates in around flask containing the dissolution medium. The entire flask is immersed in a constant temperature bath, set at 37 °c. The dissolution medium is 900 ml (USP) or 1000 ml (BP).

The rotation speed 25-100 r.p.m.

Special dissolution media:

a- Simulated gastric fluid: (0.1 N HCl + Pepsin + 0.9 % NaCl)

b- Simulated intestinal fluid: (phosphate buffer pH 7.4 + pancreatin)

Disadvantages of rotating basket method :

a. Gummy substance can clog the basket screen

b. Inadequate flow rates when particles leave the basket and float in the medium.

c. Sensitivity to dissolved gases in dissolution fluid.

d. Difficulty in construction and automation

uses :

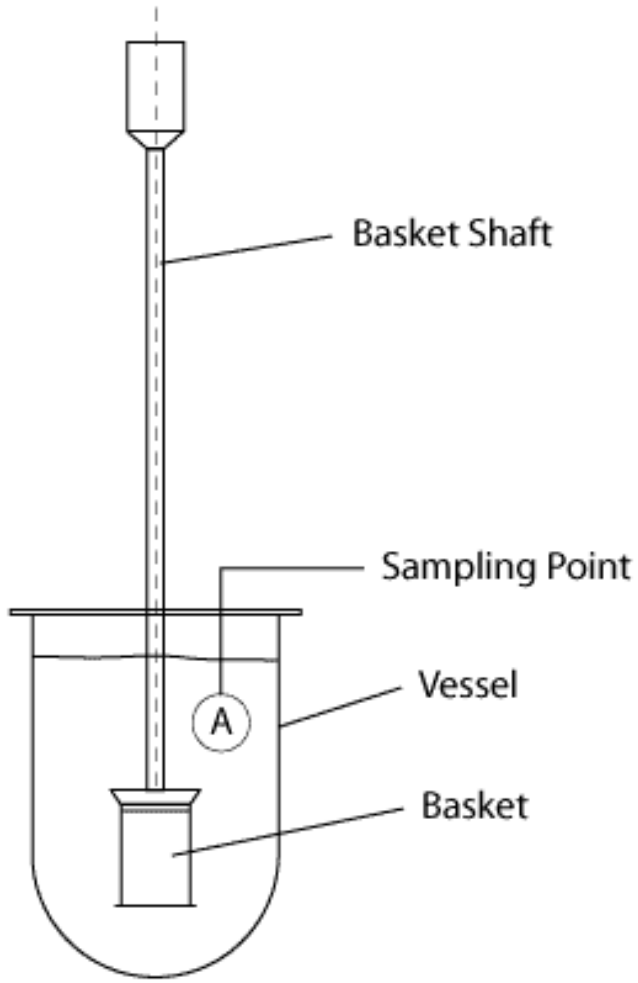
A- for tablets and capsules.

B- Special basket made from plastic with pores 10 mesh basket for use in case of suppositories.

C-Used for microencapsulated products e.g. controlled release beads (80 mesh basket).

D-Gradient pH dissolution medium (reactive dissolution media) must be used

for testing of sustained or delayed release dosage forms (this can be achieved by using a simulated gastric fluid then gradual addition of few mls of alkali).



The rotating paddle (USP apparatus 2):

It consists of a special coated paddle that minimizes turbulence due to

stirring and stainless steel or glass helix attached to floating dosage form.

Paddle geometry is important for precise dissolution data. Suits automated

systems.

Disadvantages of using sinkers:

1- Glass helix can be hardly seen in the media and metallic wires may be

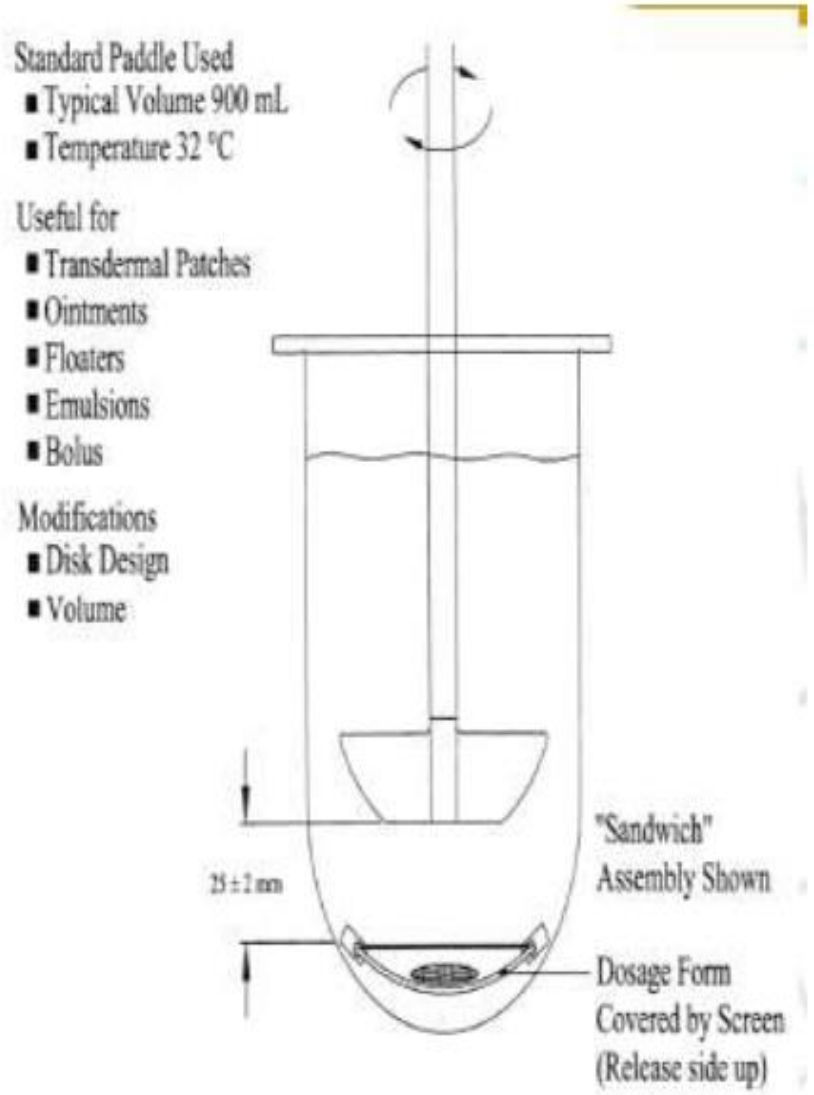
reactive with the dissolution media

2- Gummy excipients may clog the helix, leading to non-uniform release

and changed physical form of dosage forms.

3- Variations in dissolution results due to variable size, material, number

of coils and positions of helix



The flow –through cell dissolution method:

The dosage form sample is held in a fixed position while the dissolution medium is pumped through the sample holder using a pulseless pump. The dissolution medium may be fresh or recirculated. It is easily automated and it allows the convenience of changing the PH during the operation.

Advantages of flow through cell dissolution system:

1- Maintenance of sink condition

2- Built-in filtration

3- Possibility of changing pH during dissolution

4- No change in sample position

5- Mathematically definable flow patterns

6- Easily automate into an open or closed systems

7- The amount dissolved can be determined at any time using direct connection with a spectrophotometer or HPLC.

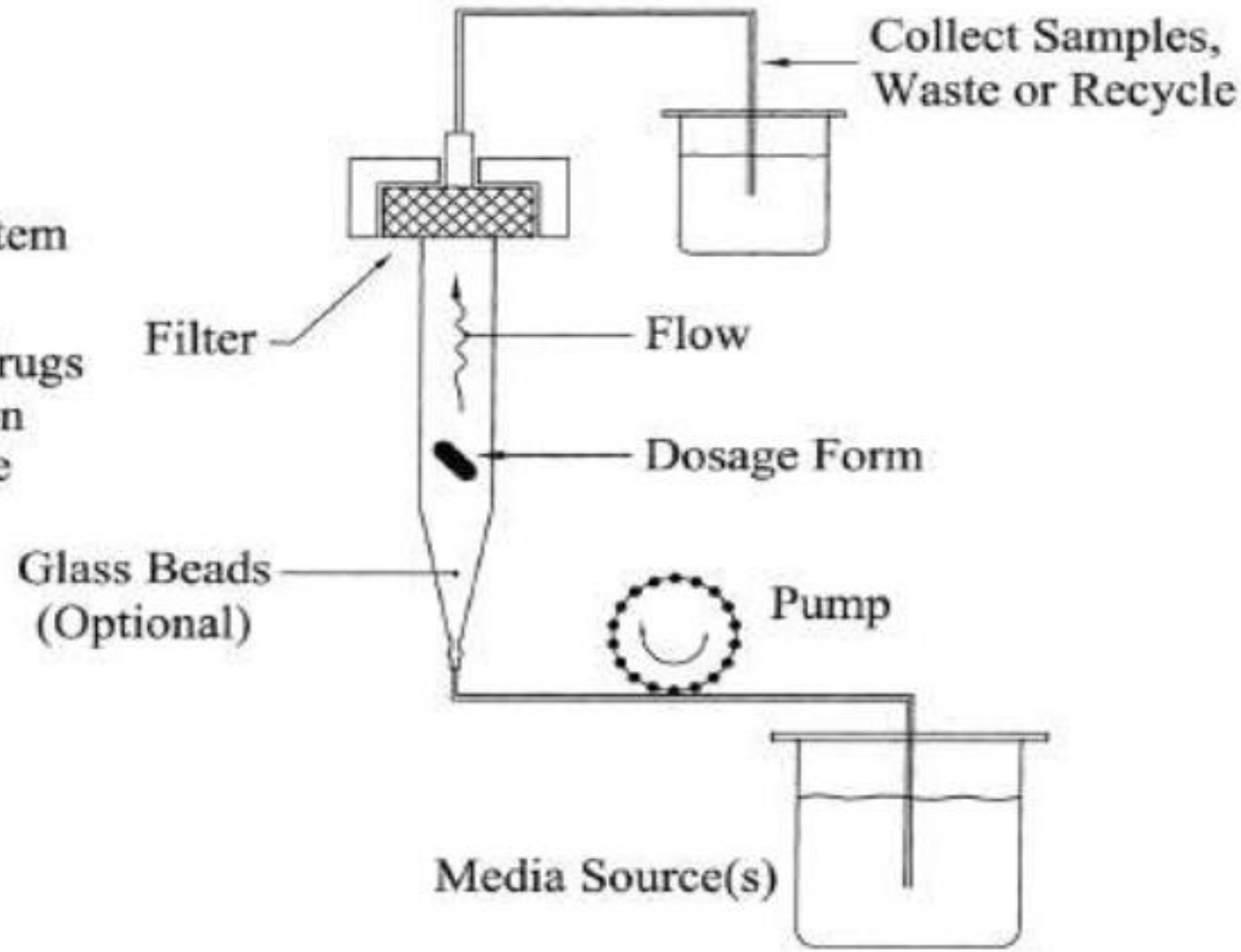
Flow-Through Cell

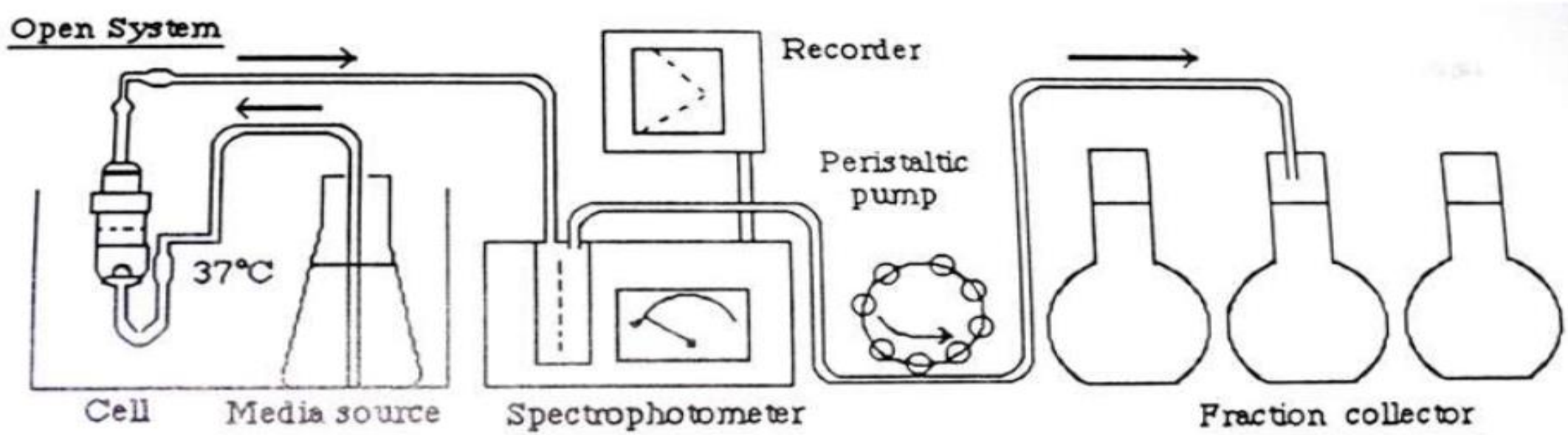
Variations

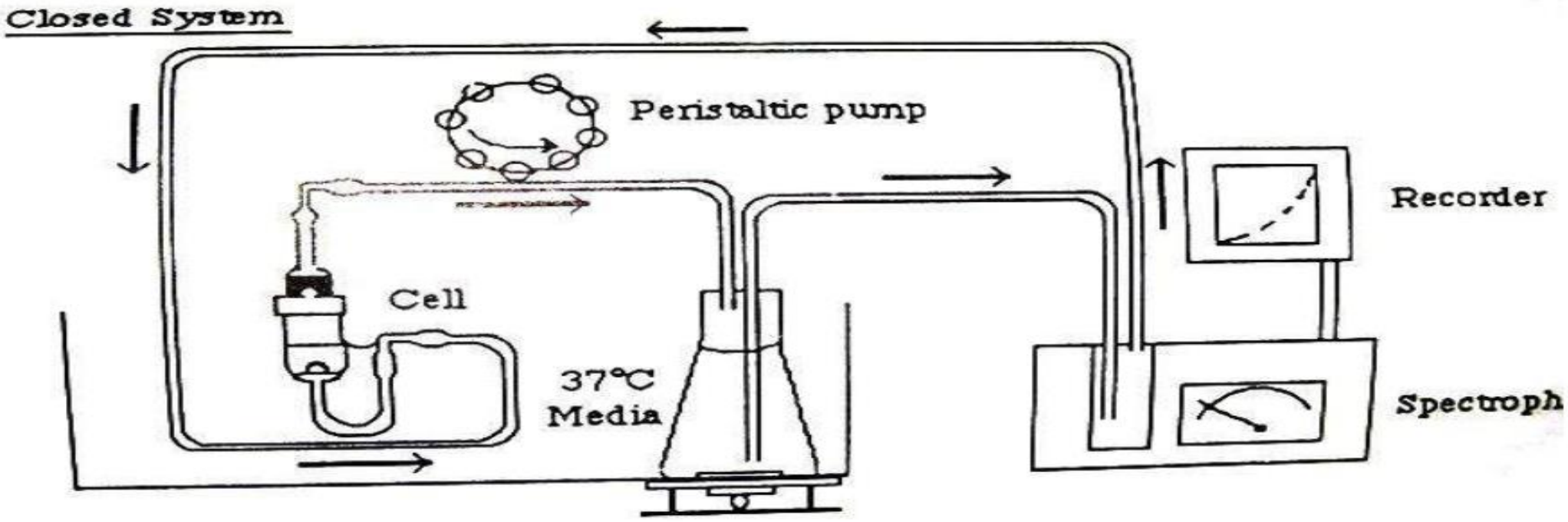
- Size
- Flow Rate
- Filter
- Open/Closed System

Useful for

- Low Solubility Drugs
- Rapid Degradation
- Media pH Change




Open System
Recorder
Peristaltic pump
37°C
Cell
Media source
Spectrophotometer
Fraction collector


Closed System
Peristaltic pump
Recorder
Cell
37°C
Media
Spectroph

The modified Disintegration (USP apparatus 3)

This method is a modification of the USP basket and rack disintegration method. The modification includes removal of the plastic disc on the reciprocating cylinder and replacing the 10-mesh screen by 40-mesh.

Used for Drug products such as:

– Solids (mostly non disintegrating)

• Monodisperse (tablets)

• Polydisperse (encapsulated beads)

– Originally used for extended release products, particularly beads in capsule

• Reciprocating agitation

– Reciprocating cylinder

– Usual speed 5 to 35 rpm (reciprocations per minute)

- **Disadvantages**

– Disintegrating dosage forms too low results

– Surfactant cause foaming

– Small volume

- **Advantages**

– Reciprocating cylinder programmed for dissolution in various media for various time

– Can change the media easily

– May start at pH 1 and then pH 4.5 and then at pH 6.8

– Attempt to mirror pH changes and transit times in the GI tract

Dissolution requirements :

1- *USP requirements :*

" the amount of drug dissolved in a given time period Q is expressed as a percentage of the label contents" .

For many products the passing of Q is set at 75% in 45 min.

For each dissolution run (six) tablets or capsules are tested and the dissolution test continues till the specifications are fulfilled or all the stages are exhausted.

-**Stage one** → 6 dosage units →each dosage unit not less than Q+5%.

-**Stage two** → 6 dosage units → average of 12 dosage units from stage 1 and 2 = or ≥ Q and no single unit is less than Q-15 %.

-**Stage three** → 12 dosage unit → average of 24 dosage units = or ≥ Q and no more than 2 units are less than Q-15%.

2- BP Requirements :

-Five dosage units .

-The labeled amount in solution not less than 70% of labeled amount appear in solution in 45 minutes.

3-EP Requirement :

Such as BP requirement

B- Non –official methods :

1- Beaker method : (levy method)

400 ml beaker containing 250 ml of dissolution medium was agitated by three blade stirrer rotated at 60 r.p.m. The stirrer should be immersed to a depth of 27 mm into the medium. Samples removed at specified intervals, filtered and assayed.

2- Flask stirrer method : (Poole method)

This method is similar to the previous beaker method, but a flask with rounded bottom is used instead. This prevents the formation of elevated residues of particles on the flat bottom (mounds).

3- Rotating bottle apparatus :

" mainly used for controlled release beads . The bottles used holded on a rotating shaft at speed 30 r.p.m in water bath (37°C).

At the end of each sampling period the apparatus is stopped and each bottle is decanted through 40 –mesh screen and the residue is retained. The bottles are exposed to new extracting fluid for specific period of time.

Rotating bottle sampling intervals :

a) One hour with an extracting fluid pH 1.2.

b) One additional hour with an extracting fluid pH 2.5.

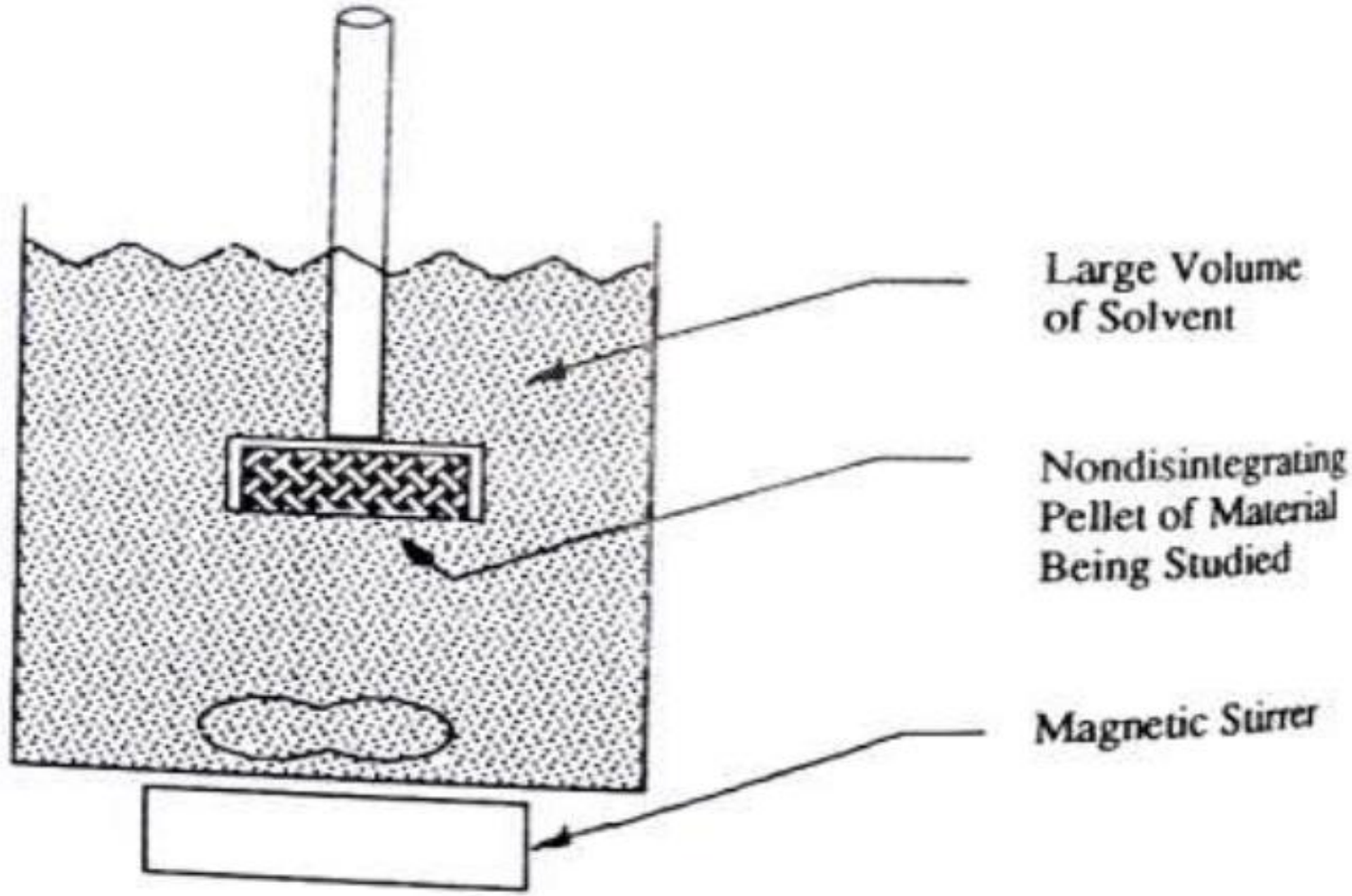
c) 1.5 hour additional with an extracting fluid pH 4.5.

d) 1.5 hour additional with an extracting fluid pH 6.8.

e) Two hours additional with an extracting fluid pH 7.4

4- Intrinsic dissolution method:

This means dissolution at constant surface area. i.e. the surface of a tablet exposed to dissolution medium is kept constant during the test. The powder is compressed into pellets or plugs then placed in an adapter which is attached to the drive rode. The whole assembly is then immersed into a large volume of dissolution medium. This method is used for screening new compounds considered for new applications. Not for finished products. **Drugs with dissolution rates greater than 1 mg/min/cm2 have no problem, but those with less than 10 % of this value indicate rate limited dissolution.**


Large Volume
of Solvent
Nondisintegrating
Pellet of Material
Being Studied
Magnetic Stirrer

Variables affecting the accuracy of dissolution testing results:

1- Selection of dissolution medium and method is based on the drug product to be tested. E.g. for gummy products the paddle method is preferred.

2- The alignment and centering of the paddle is critical to prevent vortex formation

3- Dissolved gases or those adhering to the basket can affect dissolution and may interfere with solid/liquid affinity

4- Many drug products show higher dissolution rates with the paddle method

5- No correlation can be made for dissolution results obtained from different methods

6- To express bioavailability, there must be in-vivo data that correlates with in-vitro dissolution data

7- Dissolution medium, temperature and rate of agitation must be controlled.

Other physicochemical factors affecting drug absorption from G.I.T :

iii. Solid dispersion

This technique facilitates absorption of poorly absorbed drugs by incorporation of a readily soluble carrier e.g. Urea or a water soluble polymer e.g. Polyethylene glycol (such as griseofulvin dispersed in PEG). The advantages of these systems include:

1- Increased solubility of drugs by finely subdivided particle size

2- Solubilization by the carriers

3- Prevention of agglomeration or aggregation during dissolution

4- Facilitated dispersability and wettability

5- Possibility of formation of the more soluble metastable polymorphic forms during preparation of solid dispersion.

iv. Crystal form

Many drugs have more than one polymorphic form. Each form has different solubility and stability. The metastable polymorphic forms are more water soluble than other stable forms. E.g. **Chloramphenicol palmitate** has three polymorphic forms A, B and C. the C polymorph is unstable while A and B are stable and metastable respectively. When A and B were administered in suspension form and subjected to dissolution, the metastable form (B) is dissolved rapidly and ha higher bioavailability after being hydrolysed to free chloramphenicol. The stable form (A) undergoes slow dissolution and hence slow bioavailability.

The amorphous forms are more water soluble than the crystalline forms. For example, the antibiotic **novobiocin** is more absorbed from oral suspension in the amorphous form. However, the amorphous form is thermodynamically unstable and is gradually converted to the more stable less soluble crystalline form leading to unacceptable variations in therapeutic effects.

Association of some drugs with solvent molecules to form crystalline forms is called **solvates formation. When water is the solvent, the solvates are called hydrates**. Generally the greater the solvates are in a crystal, the lower the solubility in a solvent identical to the solvation molecules. **For example, anhydrous ampicillin is more bioavailable than the trihdrate.**

v. Complexation

Complexation between drugs and components of the G.I.T affects drug concentrations available for absorption and hence its effectiveness.

G.I.T mucous called **mucin forms unabsorbable complexes with some drugs such as streptomycin, dihydrostreptomycin and quaternary ammonium compounds used as hypotensives**. **Food containing calcium such as dairy products forms insoluble complexes with tetracyclines.**

Complexation can **occur inside the dosage form or between drug and excipients e.g amphetamine and sodium carboxymethyl cellulose or between phenobarbitone and polyethylene glycol 4000.**

vi. Adsorption

The process of adsorption of certain drugs on the surface of some adsorbents is noted in cases of treatment of diarrhea. **Kaolin, attapulgite, charcoal and kaopectate** are famous adsorbents. Drugs such as **promazine and lincomycin** are examples of drugs susceptible to adsorption. If the process of adsorption is irreversible this leads to great reduction of free drug concentration available for absorption.

vii. Chemical stability of drugs in G.I.T

Many drugs are unstable in the acidic pH of the stomach due to its acid catalyzed hydrolysis. **Penicillin G and erythromycin are two famous examples**. **Enteric coated** tablets of these drugs protect them from hydrolysis in the stomach until they release the drug in the intestine. Another approach to increase the stability of drugs in G.I.T, is to use a more **stable derivative** of the parent drug called prodrug. For example **erythromycin stearate, which doesn't dissolve in the stomach but dissolves in the intestine and liberates the free base erythromycin**.

Factors affecting rate of dissolution of drugs from tablets , capsules and suppositories .

1- Environmental factors during dissolution :

a- Intensity of agitation, rate, and type of flow of fluids and geometrical factors.

b- Difference in concentration between the solubility of drug in dissolution medium and concentration in bulk fluids (concentration gradient).

c- Composition of dissolution medium (pH, ionic strength, surface tension and viscosity).

d- Temperature of dissolution medium.

2-Factors related to the physicochemical properties of the drug:

1-Polymorphism.

2-free acid ,free base or salt form .

3-complexation, solid dispersions and eutictics .

4-particle size .

5-surfactant .

6-mannufacturing variables .

7-amorphous, crystalline or solvates

3-Factors related to the composition and method of manufacturing :

1-Tablets

1- Amount and type of diluents .

2-Type of tablet machine used.

3-Granule size and granule size distribution.

4-Amount and type of disintegrant

5-Compression force and speed of compression

6-Method used in preparation ,wet or dry.

7-amount and type of surfactant

2-Capsules :

1- Amount and type of diluents used .

2- Method used to reduce the bulk (granulation or slugging).

3- Granule, or powder size and size distribution.

4- Amount and type of lubricant.

5- Applied pressure during filling.

6- Amount and type of surfactant

7- Composition and properties of capsule shell.

3-Suppositories :

8- Type of base and nature of drug in suppository.

9- Relative affinity of the drug to the base and to the dissolution medium.

10- Presence of surfactant.

4- Factors related to dosage form environment

1- Humidity during manufacture.

2- Storage condition for dosage forms.

3- Shelf-life or aging of the dosage form. For example, hard gelatin capsules stored for long time at high temperature and humidity may undergo gelatin crosslinking and swelling leading to difficulty in opening.

III-Dosage form factors influencing drug absorption from the gastrointestinal tract .

The bioavailability of administered drug in a dosage form can be influenced by factors associated with formulation and production of dosage forms.

1-*Influence of excepients :*

"excepients include disintegranting agents, diluents , lubricants , suspending agents , emulsifying agents , flavoring agents , coloring agents , chemical stabilizer ……etc.

a- Diluents :

The effect of diluents on bioavailability is shown from this example:

-**Sodium phenytoin** capsules used in treating epilepsy contain the diluent **calcium sulfate dehydrate**. When **lactose** was used instead of calcium sulfate as new diluent, drug absorption from GIT was increased markedly leading to **accumulation of drug in blood**. The drug level exceeded the maximum safe drug concentration and toxic side effects were observed. This is due to the fact that part of the drug forms a poorly absorbable complex with calcium sulphate dehydrate. Therefore, when lactose was used as the diluents the dose of phenytoin should have been reduced.

b- lubricants and glidants :

It has been shown that **talc** as a lubricant for **cyanocobalamin** tablets make interference with absorption of the vitamin. Also, **magnesium stearate** may retard drug dissolution leading to slower absorption.

c- Surfactants :

Surfactants are employed as emulsifying agents, solubilizing agents, suspending, stabilizer as well as wetting agents. The surfactants have been shown to be capable of **either increase or decrease or exert no effect on the transfer of drug to the biological membranes**.

The release of poorly soluble drugs from tablets and hard gelatins capsules is increased by surfactants inclusion due to increased wettability. For example, **polysorbate 80 added to a suspension of phenacetin resulted in prevention of aggregation, facilitated dissolution in GIT.**

d- *Viscosity enhancing agents*:

These are often used in liquid dosage forms. Examples such as hydrophilic polymers and many sugars are used as sweetening agents and viscosity enhancing agents.

The changes appearing in G.I.T drug absorption affected by the presence of viscosity enhancing agents such as complex formation between the drug and the hydrophilic polymer → reduce the drug concentration in solution available for absorption.

Administration of viscous solution leads to increase in viscosity of G.I.T contents which leads to:

-↓ in gastric empty rate (i.e. increase in gastric residence time)

-↓ in rate of movement of drug molecules to absorption membrane.

- decrease in dissolution rate of drugs

-decrease in intestinal motility

2- Influence of the type of dosage form

Generally the drug must be in solution in G.I.T fluid before the start of absorption. Steps of drug release from dosage form such as disintegration, dissolution and diffusion can delay drug absorption especially for poorly soluble drugs. Therefore, selection of the appropriate dosage form to deliver the drug rapidly to the site of absorption is greatly critical. The bioavailability of drugs, in these types of dosage forms, tends to decrease in the following order: **aqueous solution > aqueous suspension > soft gelatin capsules > hard gelatin capsules > uncoated tablets > coated tablets.**