تفريغ بيوفارما

اسم الموضوع: L3+L4 drug absorption

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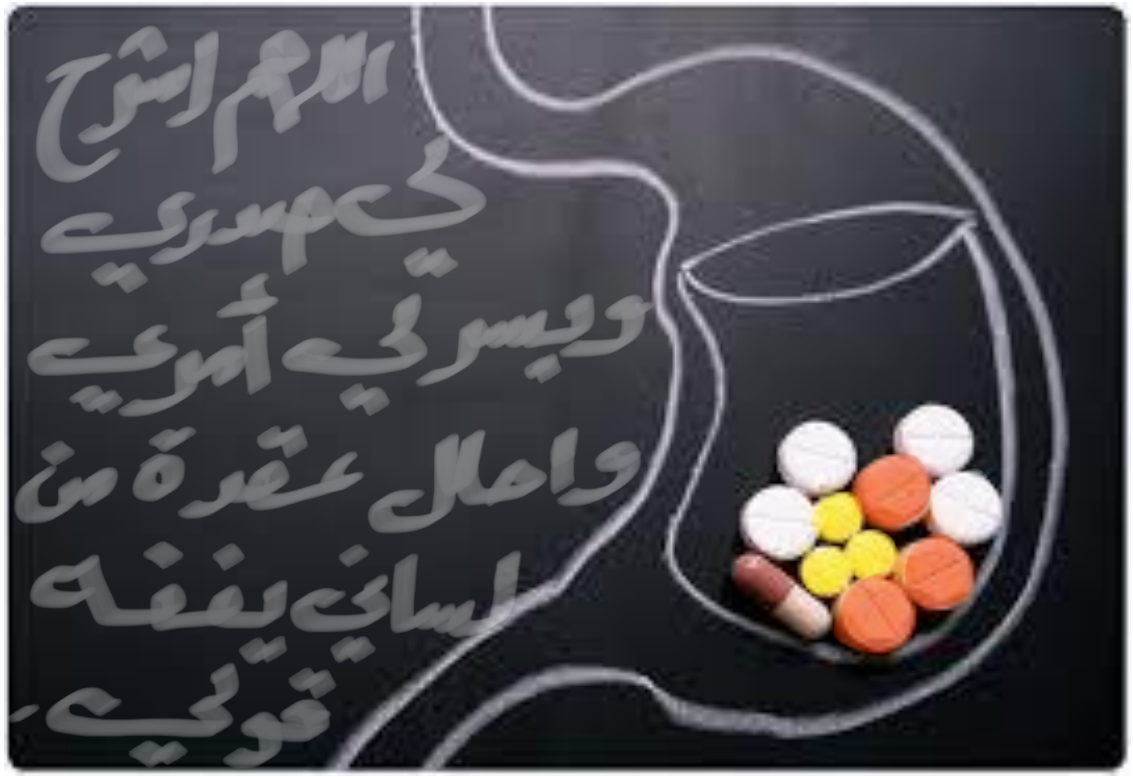
Soul Academy

لجان الدُّفعات

Drug Absorption



Presented by Dr. Muna Oqal

Absorption

Main factors affecting oral absorption:

I. Physiological factors

II. Physico-chemical factors

III. Formulation factors

Physico-Chemical Factors Affecting Oral Absorption

DRUG ABSORPTION: It is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.

A- pH-partition theory
B- Lipid solubility of drugs
C- Dissolution and pH
D- Drug stability and hydrolysis in GIT
E- Complexation
F- Adsorption

يعني الدواء يفضل على سطح الخلية أو
absorption في الدواء رح يدخل لجوا الخلية.

A. pH - Partition Theory

unionized ← absorption
ionized ← distribution

- According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier.

- As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (the lipid-soluble form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (poorly-lipid soluble) form of such drugs.

الدواء المتأين (ionized) يذوب في الماء
أما الغير متأين (unionized) يذوب في lipid .

- Consequently, the absorption of a weak electrolyte will be determined by the extent to which the drug exists in its unionized form at the site of absorption.

- The larger the fraction of drug is in the unionized form at a specific absorption site, the faster is the absorption.

A. pH - Partition Theory

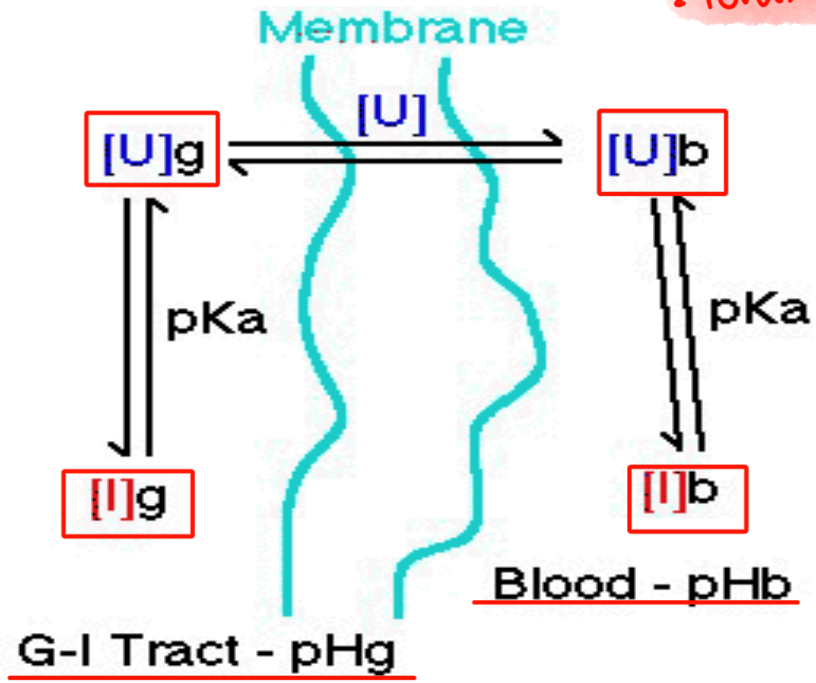
- Brodie proposed the partition theory to explain the influence of GI pH and drug pKa on the extent of drug transfer or drug absorption → dissotiation constant.
- The theory states that the process of absorption is governed by:

1. The dissociation constant (pKa) of the drug.
2. The lipid solubility of the unionized drug.
3. The pH at the absorption site.

Ionization state:

Unionized state is important for passive diffusion through membrane so important for **absorption**.

Ionized state is important for **solubility**.



I: ionized drug water soluble
U: unionized drug lipid soluble

Diagram Showing Transfer Across Membrane

Drug pKa and GI pH

- The fraction of drug in solution that exist in the unionized form is a function of both dissociation constant of the drug and the pH of the fluid at the absorption site and it can be determined by Henderson- Hasselbach equation: -

low pKa ← strong acid
high pKa ← strong base

$$pH = pKa + \log \frac{[\text{ionized form}]}{[\text{Unionized form}]}$$ For, Acidic drugs

$HA \rightleftharpoons H^+ + A^-$ (pKa ↓)

$$pH = pKa + \log \frac{[\text{unionized form}]}{[\text{ionized form}]}$$ For, Basic drugs (pKa ↑)

Where quantities in square brackets represent the concentrations of the species at equilibrium

- The dissociation constant is often expressed for both acids and bases as pKa (the basic logarithm of the acidic dissociation constant).
- The lower the pKa of an acidic drug, the stronger the acid i.e., greater the proportion of ionized form at a particular pH. The higher the pKa of a basic drug, the stronger the base.

Drugs	PKa	PH/site of absorption
Very weak acids e.g. pentobarbital Hexobarbital	>8	Unionized at all pH values; Absorbed along the entire length of GIT
Moderately weak acids e.g. aspirin Ibuprofen	2.5 – 7.5	Unionized in gastric pH& ionized in intestinal pH; better absorption from stomach
Stronger acids E.g. disodium cromoglylate	< 2.0	Ionized at all pH values; Poorly absorbed from GIT
Very weak bases e.g. theophylline Caffeine	< 5.0	Unionized at all pH values; Absorbed along entire GIT
Moderately weak bases e.g. codeine	5 – 11	Ionized at gastric pH, unionized at intestinal pH; better absorption from intestine.
Stronger bases e.g. guanethidine	> 11	Ionized at all pH values; Poorly absorbed from GIT

Limitations of the pH-partition Hypothesis

- Despite their high degree of ionization, ionized and unionized forms of weak acids are highly absorbed from the small intestine and this may be due to:

1. The large surface area that is available for absorption in the small intestine.
2. A longer small intestine residence time.
3. The unstirred layer (a layer of fluid overlying the surface cells of the mucosa of the small intestine).
4. Microclimate pH, that exists on the surface of intestinal mucosa and is lower than that of the luminal pH of the small intestine

B. Lipid Solubility of Drugs

- Ideally for optimum absorption, a drug should have sufficient aqueous solubility to dissolve in fluids at absorption site and lipid solubility high enough to facilitate the partitioning of the drug in the lipoidal membrane i.e. drug should have perfect Hydrophilic–lipophilic balance (HLB) for optimum Bioavailability.
- Some drugs are poorly absorbed after oral administration even though they are non-ionized in small intestine. Low lipid solubility of them may be the reason.
- The best parameter to correlate between water and lipid solubility is **partition coefficient**.

Partition coefficient (p) = [L] conc / [W] conc

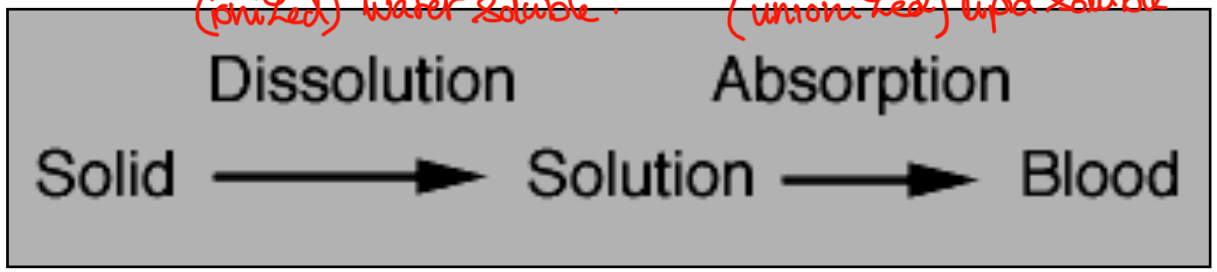
where, [L] conc is the concentration of the drug in lipid phase.
[W] conc is the concentration of the drug in aqueous phase.

The higher p value, the more absorption is observed

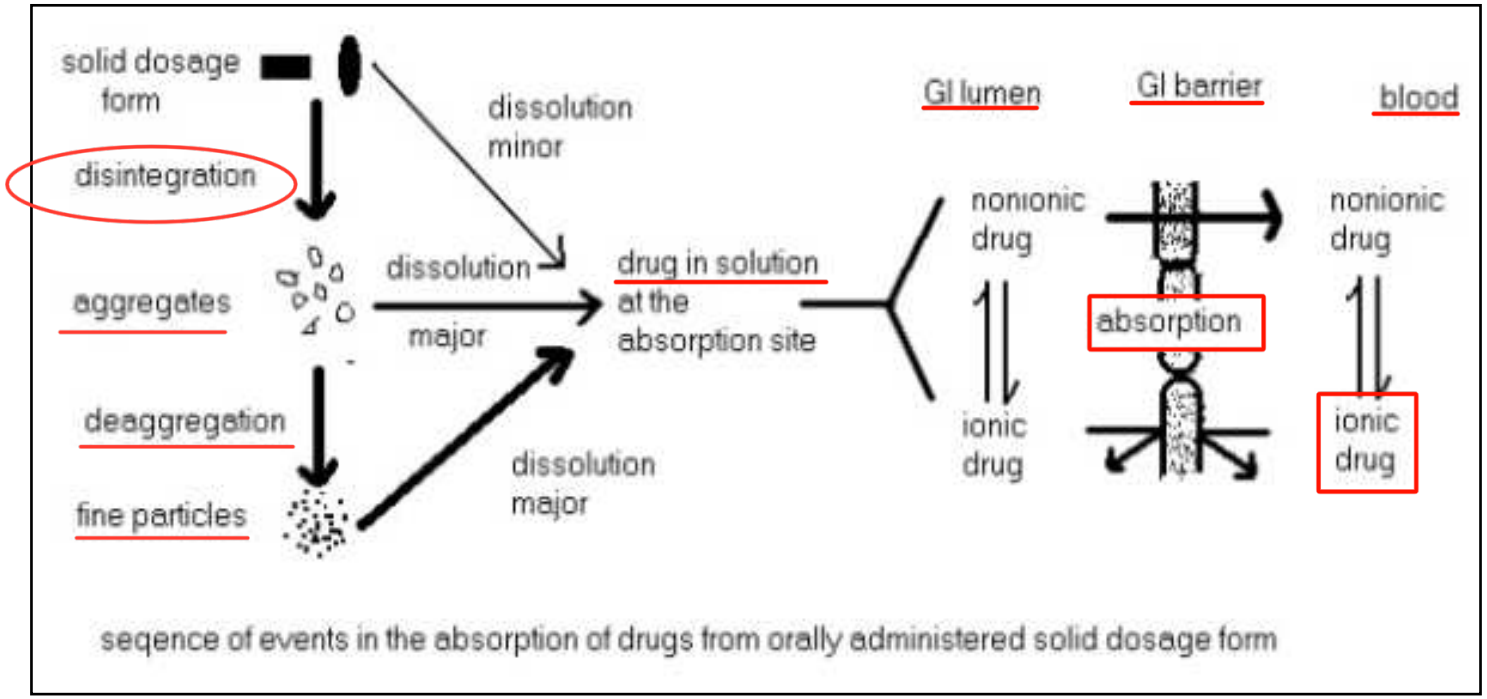
C. Drug Dissolution

- Many drugs are given in solid dosage forms and therefore must dissolve before absorption can take place (dissolution step).

(ionized) water soluble · (unionized) lipid soluble



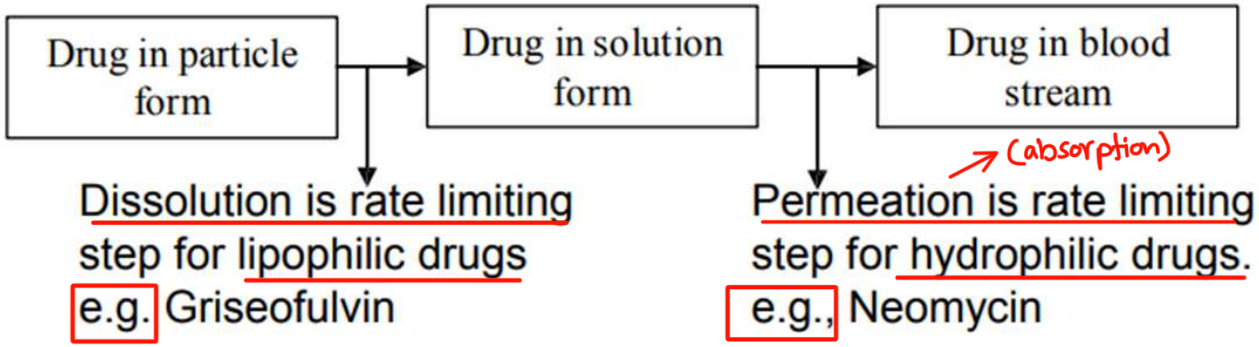
- Dissolution is the process of solubilization of a substance in a given solvent.



seqence of events in the absorption of drugs from orally administered solid dosage form

C. Drug Dissolution

- Drug dissolution rate is the amount of drug that goes into solution per unit time under the standard conditions of temperature, pH, solvent composition and constant solid surface area.
- If dissolution is the slow, it will be the rate determining step (the step controlling the overall rate of absorption) then factors affecting dissolution will control the overall process.
- Drug dissolution is considered to be diffusion controlled process through a stagnant layer surrounding each solid particle.
- Solutions > Suspensions > Capsules > Tablets > Coated tablets



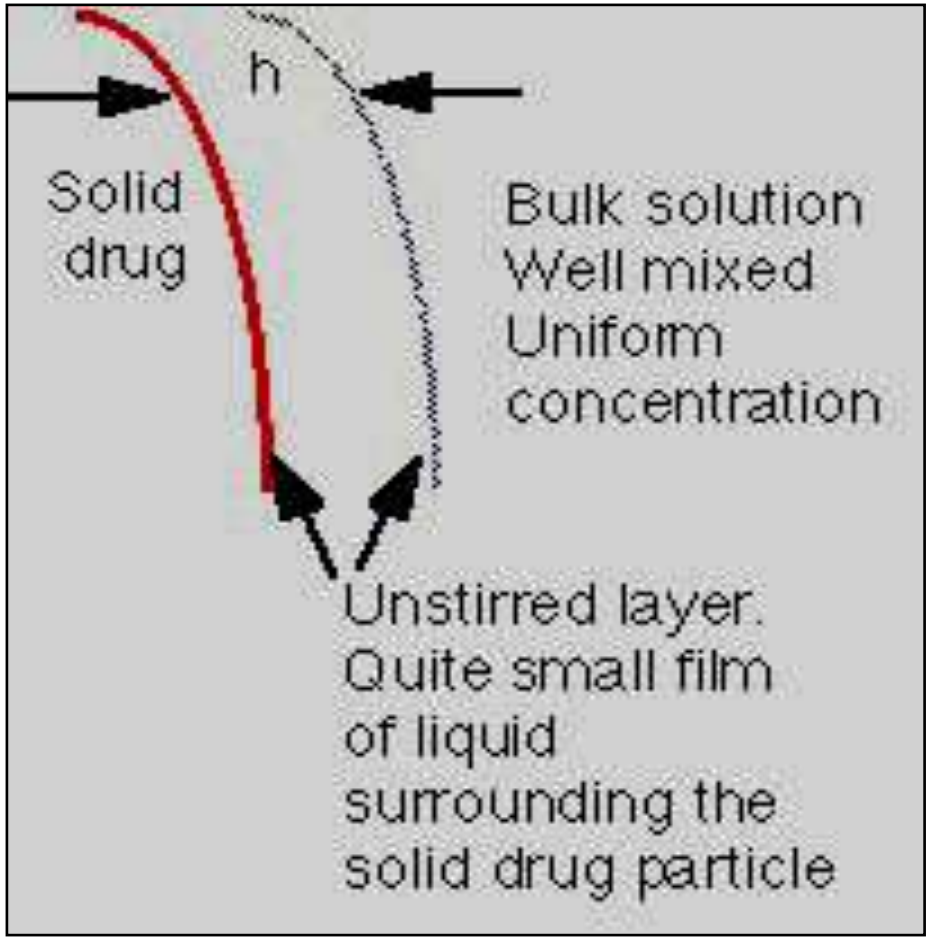


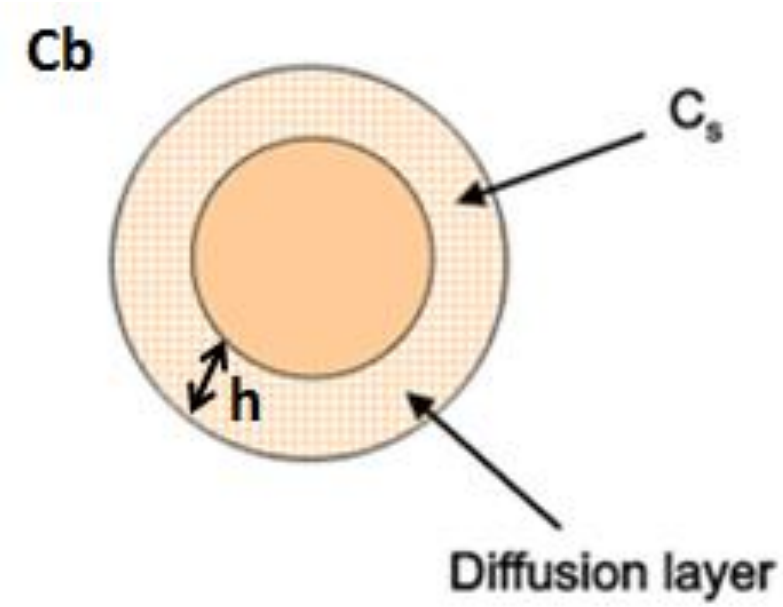
Diagram Representing Diffusion through the Stagnant Layer

C. Drug Dissolution

- The dissolution of drugs can be described by the **Noyes-Whitney equation:**

particle size & viscosity تتأثر بال ← تعتمد على particle ←

$$\text{Rate of Solution} = \frac{D \bullet A \bullet (Cs - Cb)}{h}$$



- Where D: is the diffusion coefficient طردية
- A: the surface area طردية
- Cs: the solubility of the drug (in diffusion layer) طردية
- Cb: the concentration of drug in the bulk solution
- h: the thickness of the stagnant layer. عكسية
- If Cb is much smaller than Cs then we have so-called "Sink Conditions" and the equation reduces to

كلما قل حجم الـ particle كلما زادت الـ surface area كلما زاد الـ dissolution rate.

$$\text{Rate of Solution} = \frac{D \bullet A \bullet Cs}{h}$$

C. Drug Dissolution

Factors affecting drug dissolution in the GIT:

I. Physiological factors affecting the dissolution rate of drugs:

- The environment of the GIT can affect the parameters of the Noyes-Whitney equation and hence the dissolution rate of a drug.

A- Diffusion coefficient, D:

- Presence of food in the GIT → increase the viscosity of the gastrointestinal fluids → reducing the rate of diffusion of the drug molecules away from the diffusion layer surrounding each undissolved drug particles **(↓ D)**

  → decrease in dissolution rate of a drug.

C. Drug Dissolution

B- Drug surface area, A:

Surfactants in gastric juice and bile salts → increase the wettability of the drug so this would increase the drug solubility via micellization.

C. The thickness of diffusion layer, h:

An increase in gastric and/or intestinal motility → decrease the thickness of diffusion layer around each drug particle → increase the dissolution rate of a drug.

D. The concentration, C, of drug in solution in the bulk of the gastrointestinal fluids:

Increasing the rate of removal of dissolved drug by absorption through the gastrointestinal-blood barrier and increasing the intake of fluid in the diet will decrease in C → rapid dissolution of the drug.

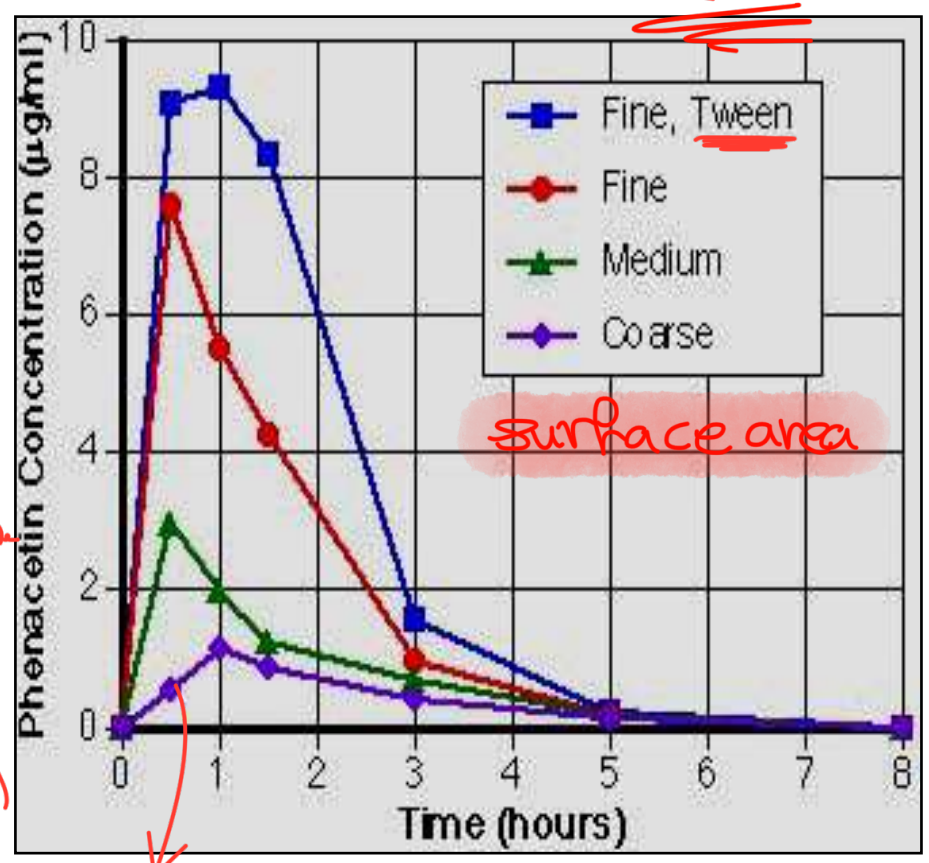
C. Drug Dissolution

II. Physicochemical factors affecting the dissolution rate of drugs:

A- Surface area, A:

- The smaller the particle size → the greater the effective surface area of drug particle (More intimate contact between solid surface and aqueous solvent), the higher the dissolution rate.

- Methods of particle size reduction include: mortar and pestle, mechanical grinders, mills, solid dispersions in readily soluble materials (PEG's).
- However very small particles can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption.



polyethelinglycol

surfactant (surface active agent)

surface area

large particle size

C. Drug Dissolution

B-Diffusion coefficient, D:

The value of D depends on the size of the molecule and the viscosity of the dissolution medium.

C- Solubility in the diffusion layer, C_s

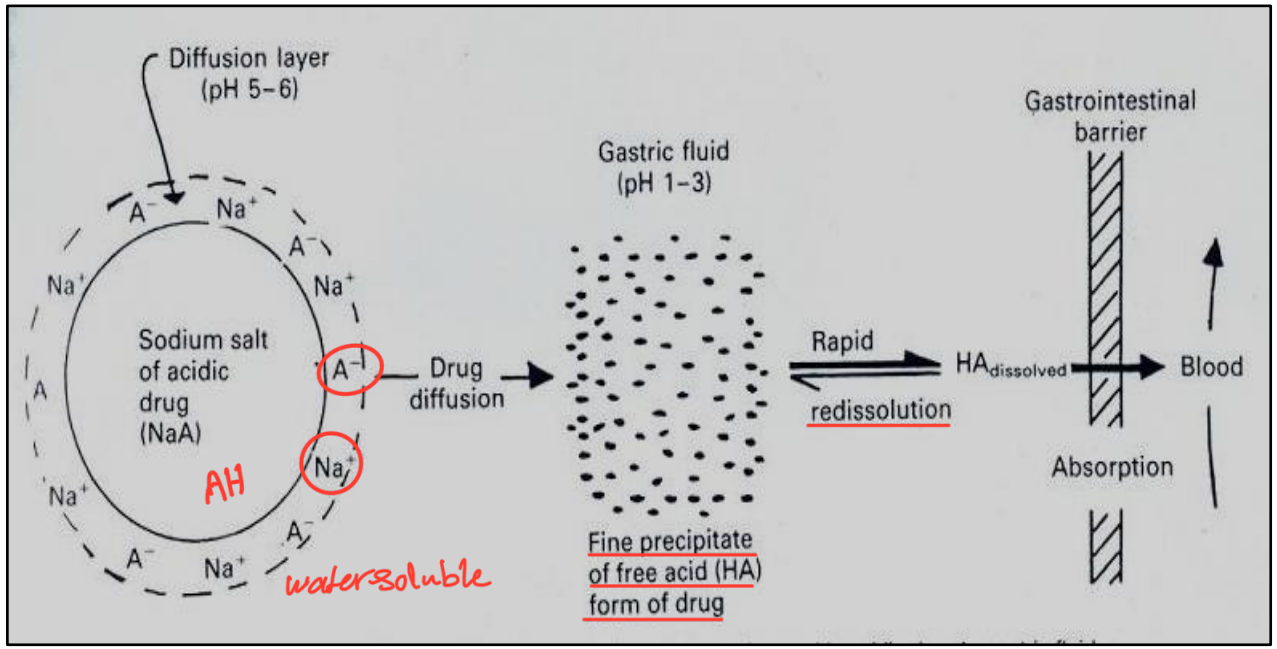
- The dissolution rate of a drug is directly proportional to its intrinsic solubility in the diffusion layer surrounding each dissolving drug particle.

D- Salt forms of the drugs:

- **Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.**
- The dissolution rate of a weakly acidic drug in gastric fluid (pH 1 – 3.5) will be relatively low.
- If the pH in the diffusion layer increased, the solubility, C_s, of the acidic drug in this layer, and hence its dissolution rate in gastric fluids would be increased.

C. Drug Dissolution

- The pH of the diffusion layer would be increased if the chemical nature of the weakly acidic drug was changed from that of the free acid to a basic salt (the sodium or potassium form of the free acid).
- The pH of the diffusion layer would be higher (5-6) than the low bulk pH (1-3.5) of the gastric fluids because of the neutralizing action of the strong (Na^+, K^+) ions present in the diffusion layer.
- The drug particles will dissolve at a faster rate and diffuse out of the diffusion layer into the bulk of the gastric fluid, where a lower bulk pH.
- Thus the free acid form of the drug in solution, will precipitate out, leaving a saturated solution of free acid in gastric fluid.

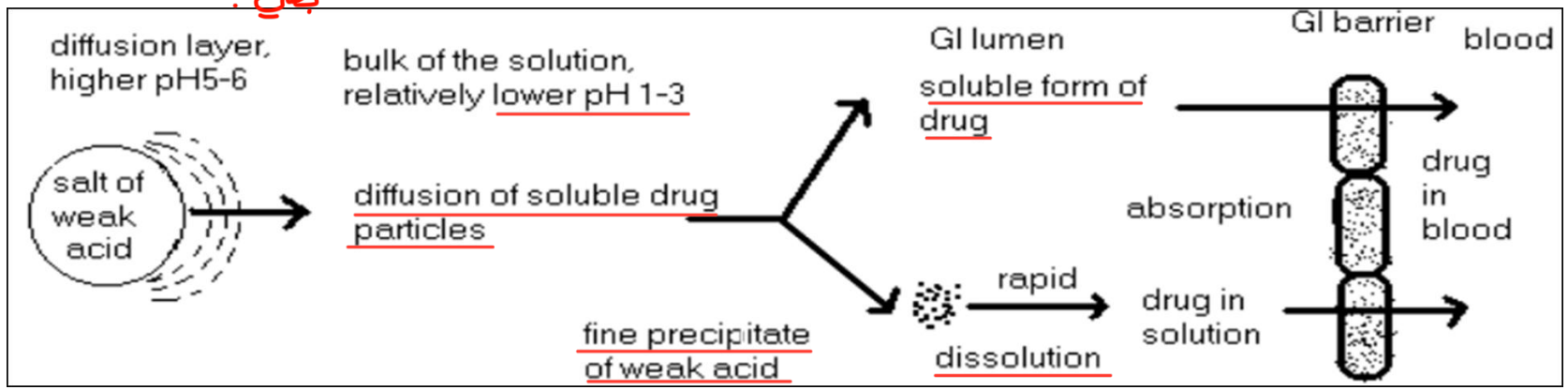


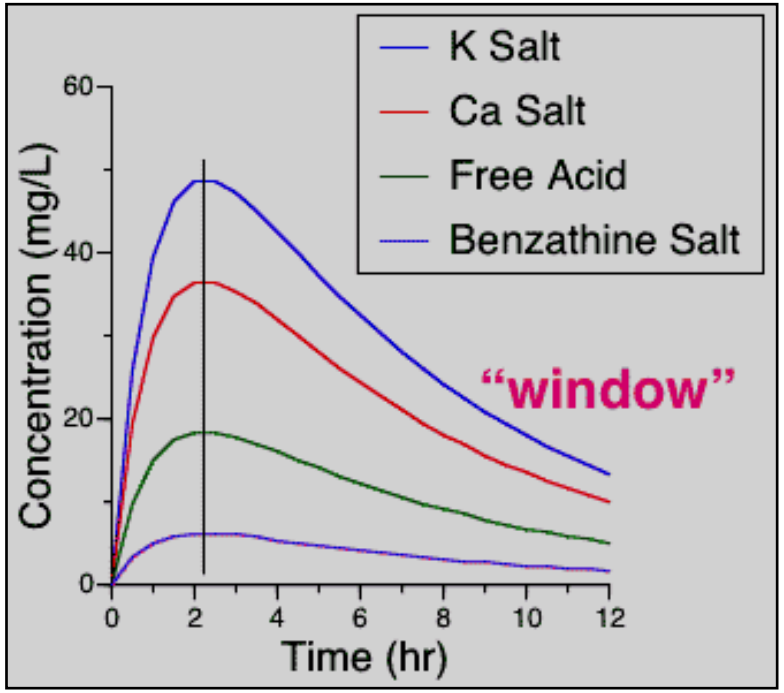
Dissolution process of a salt form of a weakly acidic drug in gastric fluid.

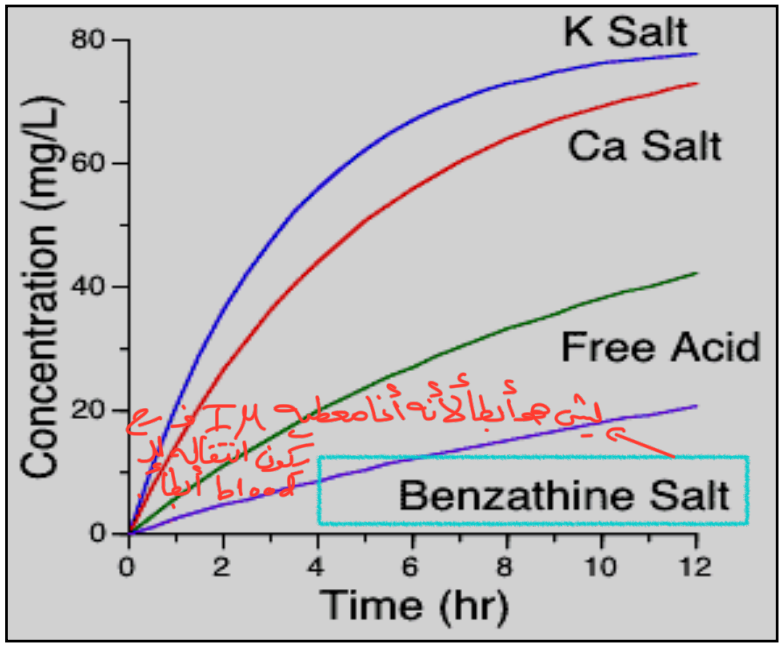
This precipitated free acid will be in the form of:
- very fine, non-ionized, wetted particles which have a very large surface area in contact with gastric fluids, facilitating rapid re-dissolution when additional gastric fluid is available.

C. Drug Dissolution

- **Salt form of drug:** At given pH, the solubility of drug, whether acidic/basic or its salt, is a constant. While considering the salt form of drug, pH of the diffusion layer is important not the pH of the bulk of the solution.
- E.g. of salt of weak acid. ---Which increases the pH of the diffusion layer, which promotes the solubility and dissolution of a weak acid and absorption is bound to be rapid.
- One example for the effect of salt form on the dissolution rate of drug is the dissolution and bioavailability profiles of Penicillin V with various salts.
- These results might support the use of the benzathine or procaine salts for IM depot use and the potassium salt for better absorption orally.







C. Drug Dissolution

E- Crystal form:

1- Polymorphism:

- Some drugs exist in a number of crystal forms or polymorphs. These different forms may have different physical properties include solubility properties and thus different dissolution characteristics.
- Chloramphenicol palmitate is one example which exists in three crystalline forms A, B and C.

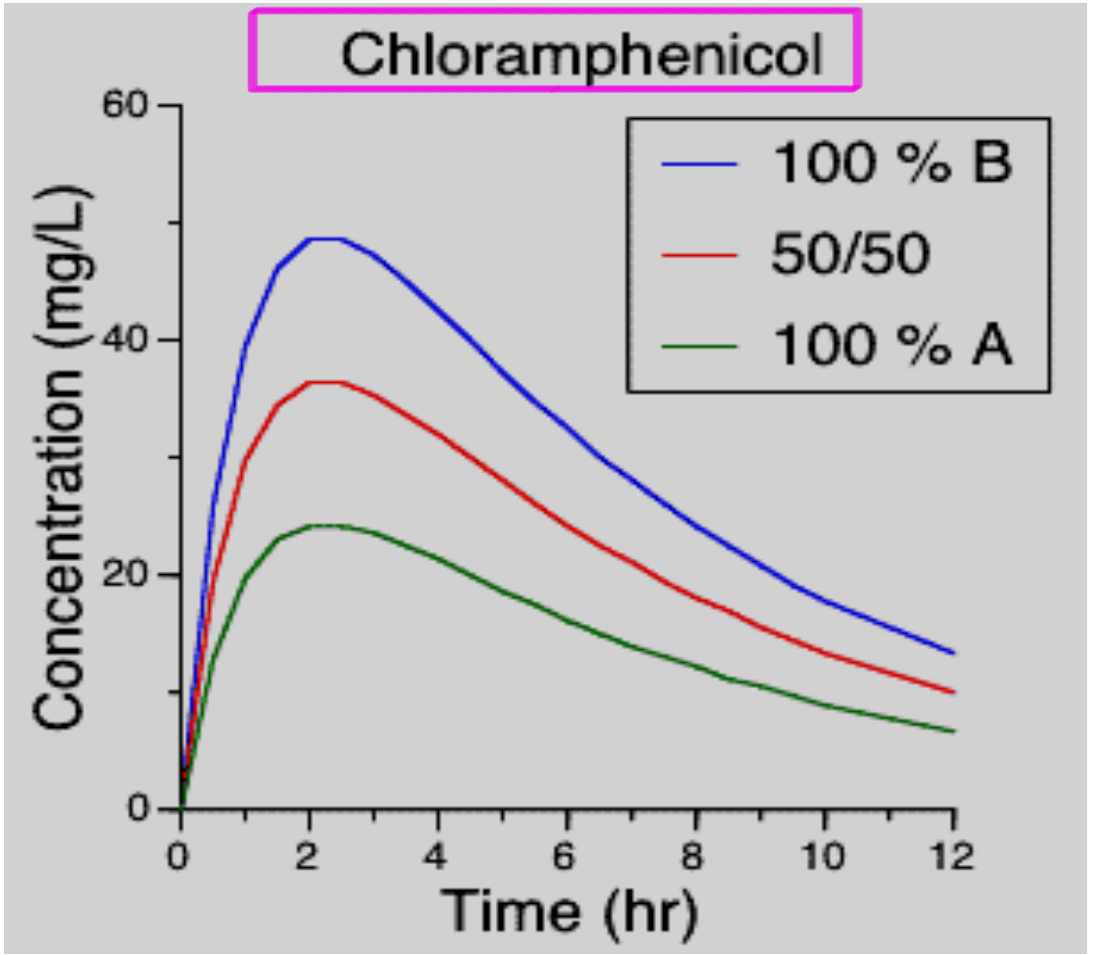
A → is the stable polymorph (low dissolution)

B → is the metastable polymorph (more soluble)

C → is the unstable polymorph (high dissolution / high bioavailability)

C. Drug Dissolution

- The plasma profiles of chloramphenicol from oral suspensions containing different proportions of polymorphic forms A and B were investigated.
- The extent of absorption of Chloramphenicol increases as the proportion of the polymorphic form B is increased in each suspension.
- This is attributed to the more rapid dissolution of the metastable polymorphic form B.
- Shelf-life could be a problem as the more soluble (less stable) form may transform into the less soluble form (more stable).



C. Drug Dissolution

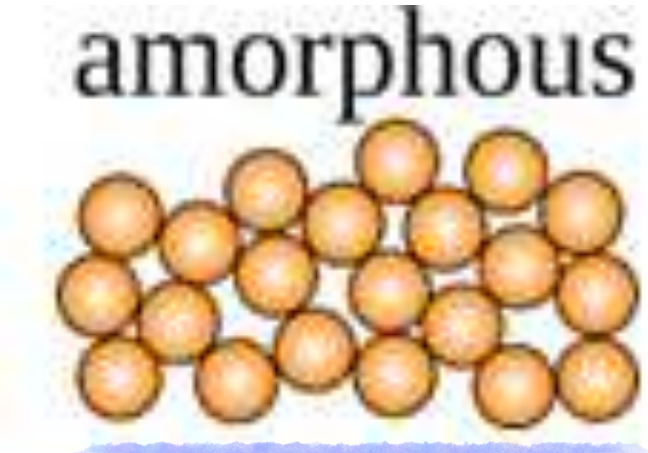
2- Amorphous solid:

- The amorphous form dissolves more rapidly than the corresponding crystalline form, because no energy is needed to break up the crystal lattice.

- The more soluble and rapidly dissolving amorphous form of novobiocin antibiotic was readily absorbed following oral administration of an aqueous suspension to humans. However, the less soluble and slower-dissolving crystalline form of novobiocin was not absorbed (therapeutically ineffective).

- The amorphous form of novobiocin slowly converts to the more stable crystalline form, with loss of therapeutic effectiveness.

C. Drug Dissolution



More effectivenesss

Amorphous form

- More soluble
- Rapidly dissolving
- Readily absorbed

Crystalline form

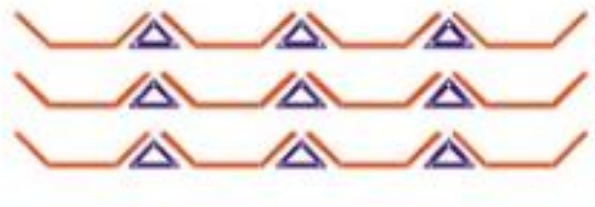
- Less soluble
- Slower dissolving
- Not absorbed to significant extent

C. Drug Dissolution

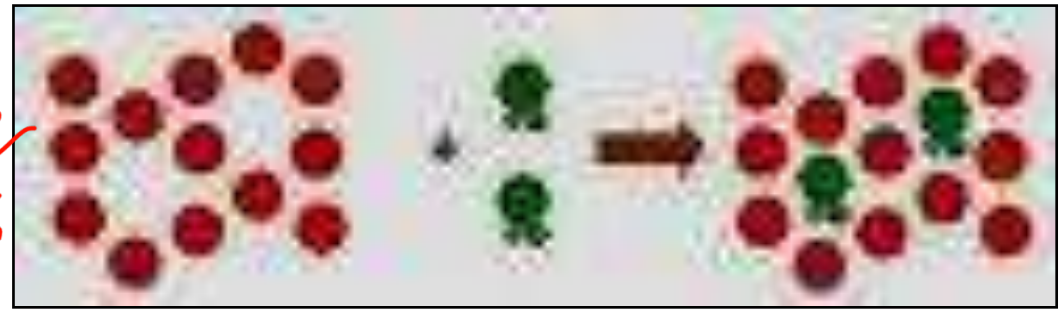
3- Solvates and hydrates:

يؤثر بشكل سلبي على dissolution و bioavalability للدواء

- **Solvates:** If the drug is able to associate with solvent molecules to produce crystalline forms known as solvates.
- The solvent trapped is known as solvent of crystallization.
- The solvates may exists in varying crystalline forms known as pseudopolymorphs and the phenomenon is known as pseudopolymorphism.



Solvate



- **Hydrates:** drug associates with water molecules.

- The greater the solvation of the crystal, the lower are the solubility and dissolution rate in a solvent identical to the solvation molecules.

Solvent is water	Hydrates
Solvent is other solvents	Solvates

C. Drug Dissolution

4-Anhydrous: Drug is not associated with water

- The anhydrous forms have higher energy states, higher aqueous solubilities, dissolves at faster rate and hence exhibit higher bioavailability.

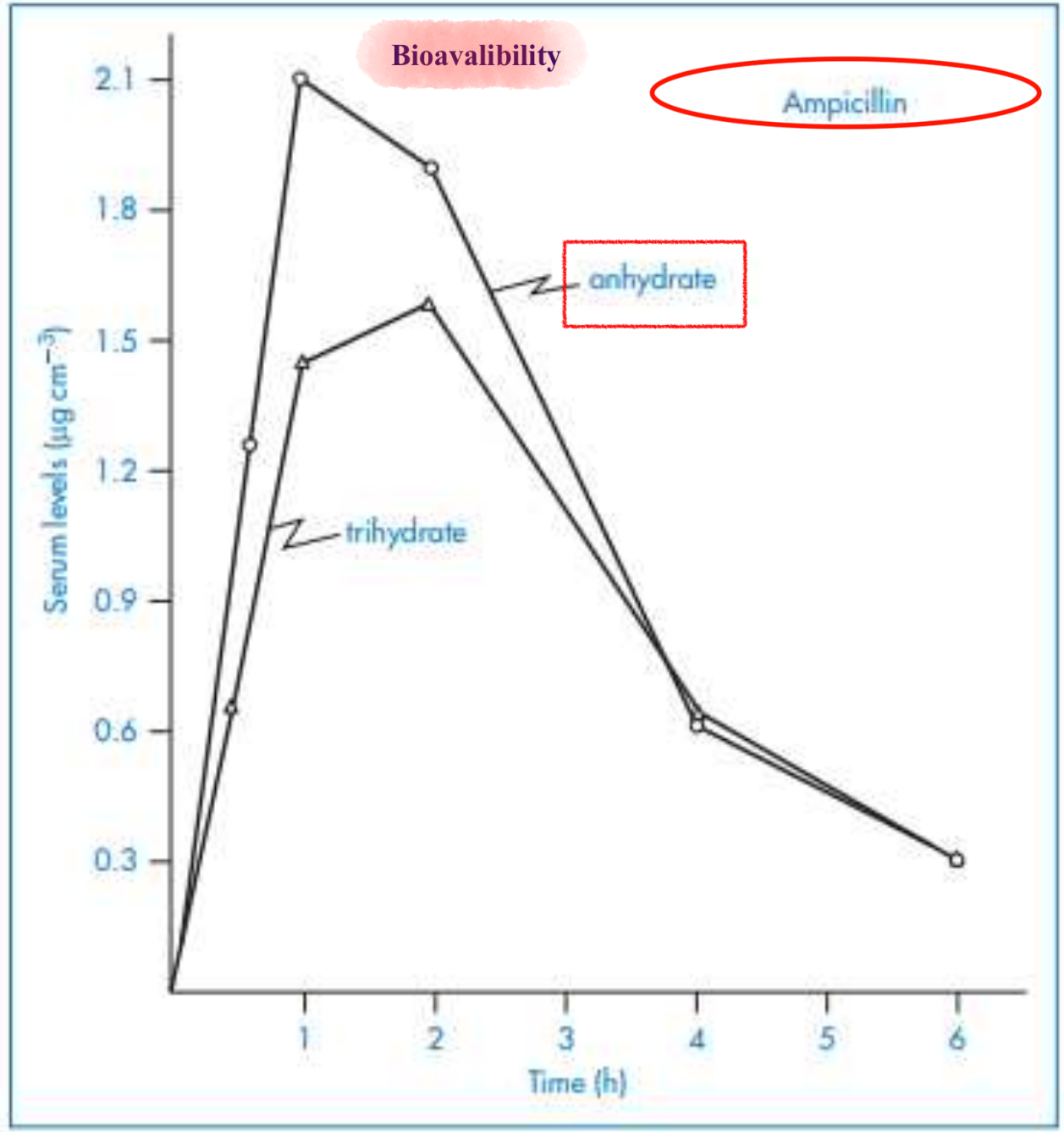
  Ex: anhydrous ampicillin more soluble than their hydrous form

- Monohydrate and Dihydrated : drug is associated with one and more water molecules respectively.
- The faster-dissolving anhydrous form of ampicillin was absorbed to a greater extent from both hard gelatin capsules and an aqueous suspension than was the slower-dissolving trihydrate form.

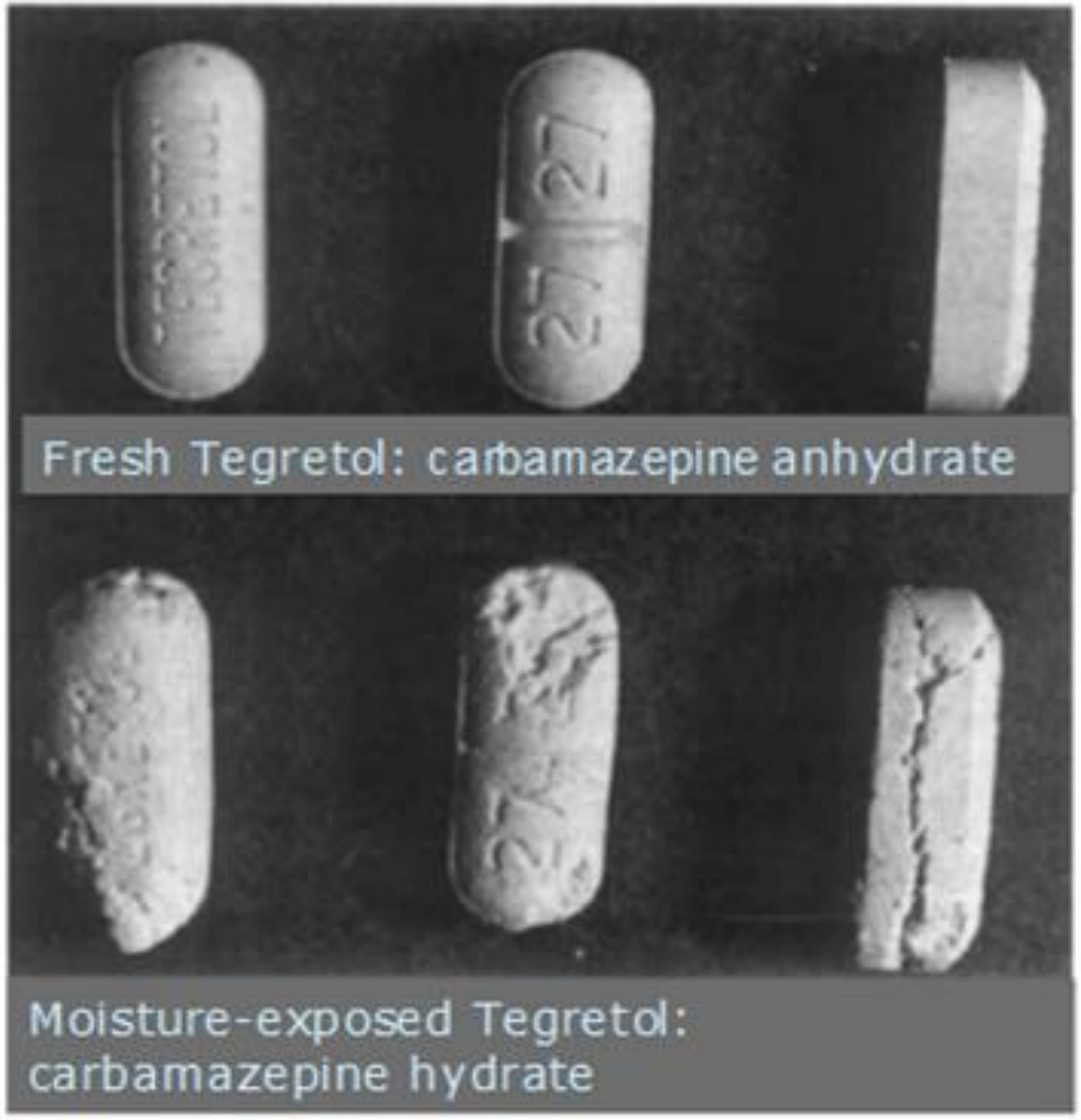
Trihydrate < Dihydrate < Monohydrate < Anhyrous

(bioavailability)

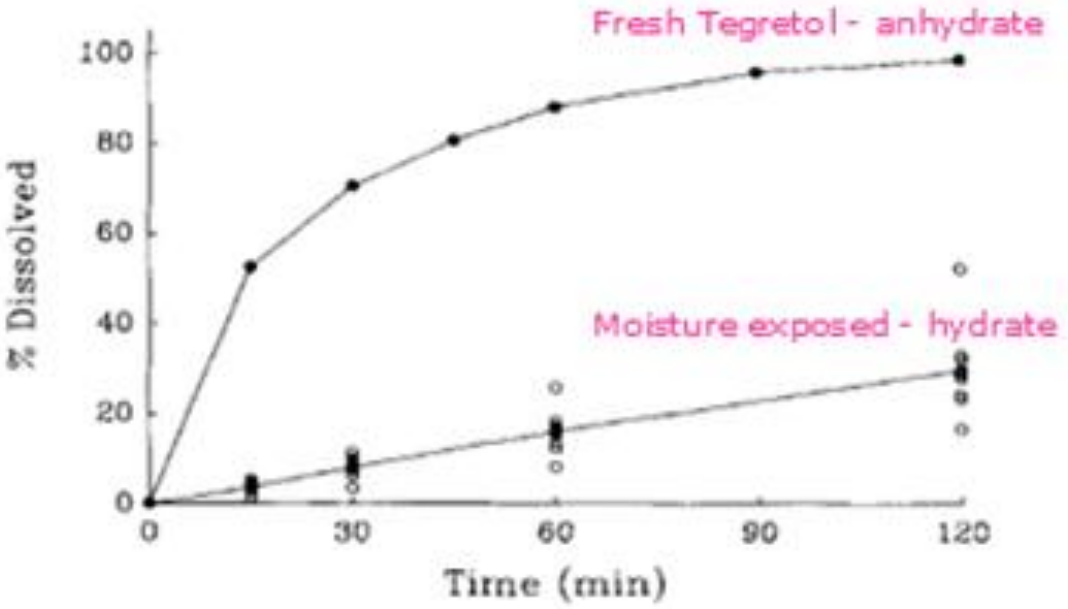
Bioavalibility



C. Drug Dissolution



- Hydrates may reduce
  - solubility
  - dissolution rate



D- Drug Stability and Hydrolysis in GIT

- Drugs that are susceptible to acidic or enzymatic hydrolysis in the GIT, suffer from reduced bioavailability.
- How to protect drugs (erythromycin) from degradation in gastric fluid ??

يتكسر بالمعدة

1- Preparing enteric coated tablets containing the free base of erythromycin. The enteric coating resists gastric fluid but disrupts or dissolves at the less acid pH range of the small intestine.

2- The administration of chemical derivatives of the parent drug. These prodrugs (erythromycin stearate) exhibit limited solubility in gastric fluid, but liberate the drug in the small intestine to be absorbed.

E- Complexation

- **Complexation** of a drug may occur within the dosage form and/or in the gastrointestinal fluids, and can be beneficial or detrimental to absorption.

1- Intestinal mucosa (mucin) + Streptomycin = poorly absorbed complex

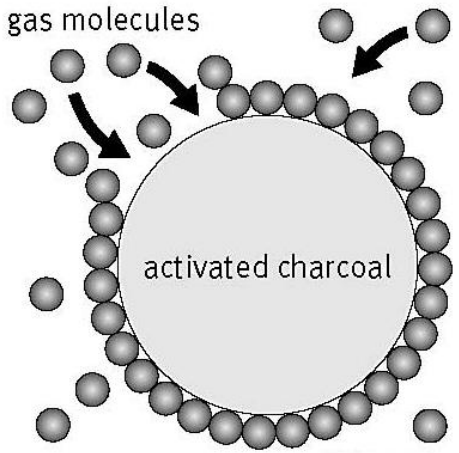
2- Calcium + Tetracycline = poorly absorbed complex (Food-drug interaction)

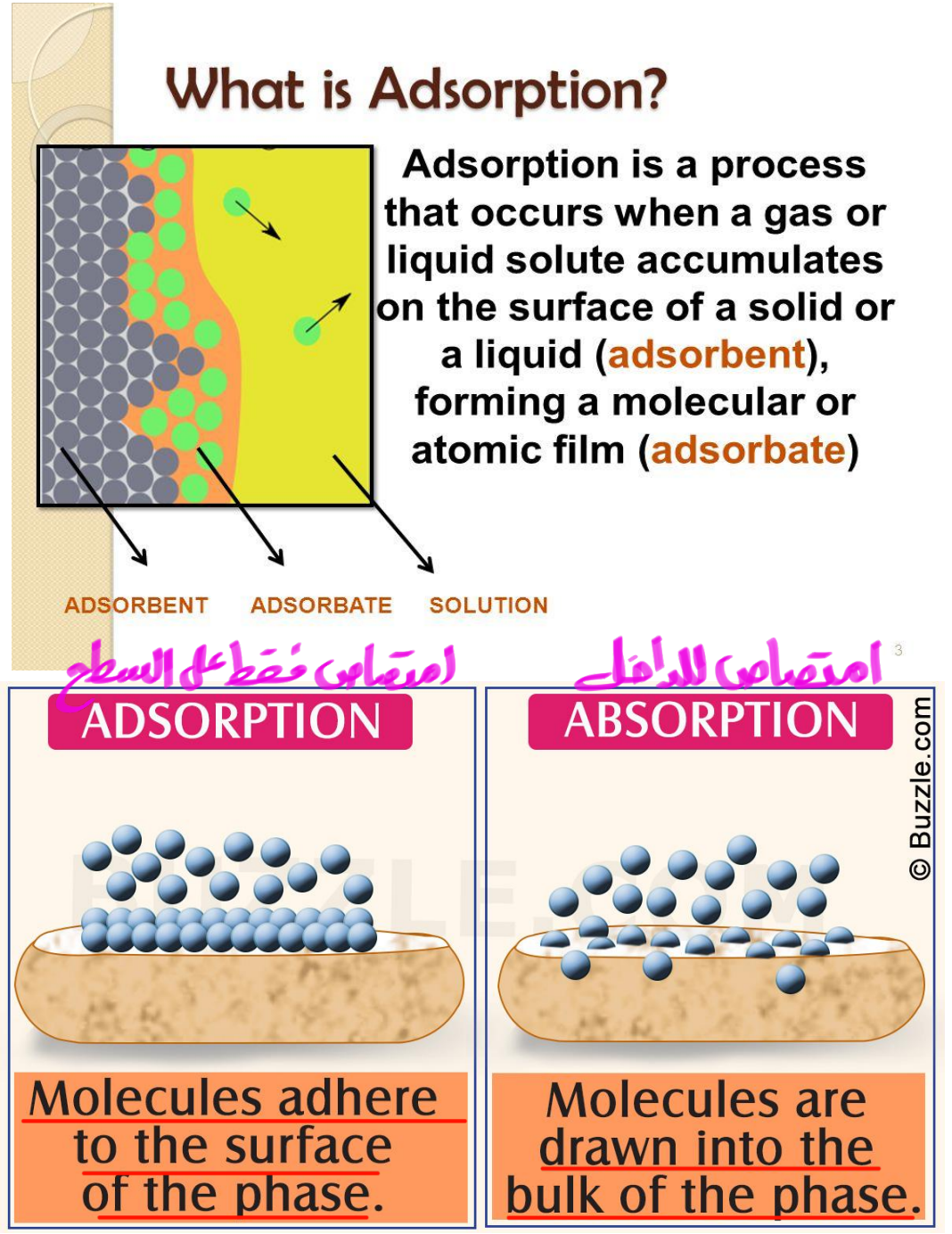
3- Carboxyl methylcellulose (CMC) + Amphetamine = poorly absorbed complex (tablet additive – drug interaction)

4- Lipid soluble drug + water soluble complexing agent = well-absorbed water soluble complex (cyclodextrin)

F- Adsorption

- Certain insoluble substances may adsorbed co-administrated drugs leading to poor absorption.
- Charcoal (antidote in drug intoxication).
- Kaolin (antidiarrheal mixtures)
- Talc (in tablets as glidant)



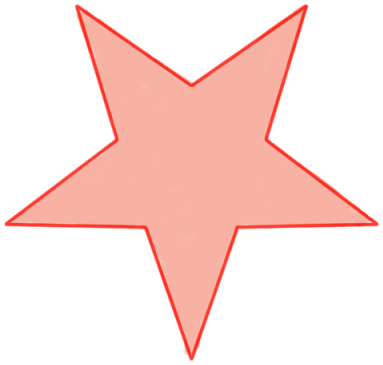


Main factors affecting oral absorption:

I. Physiological factors

II. Physico-chemical factors

III. Formulation factors

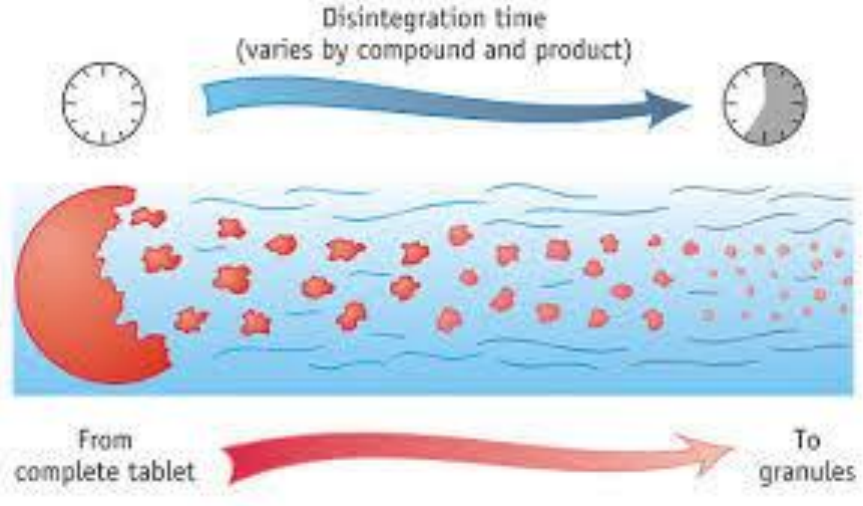


III Formulation Factors Affecting Oral Absorption

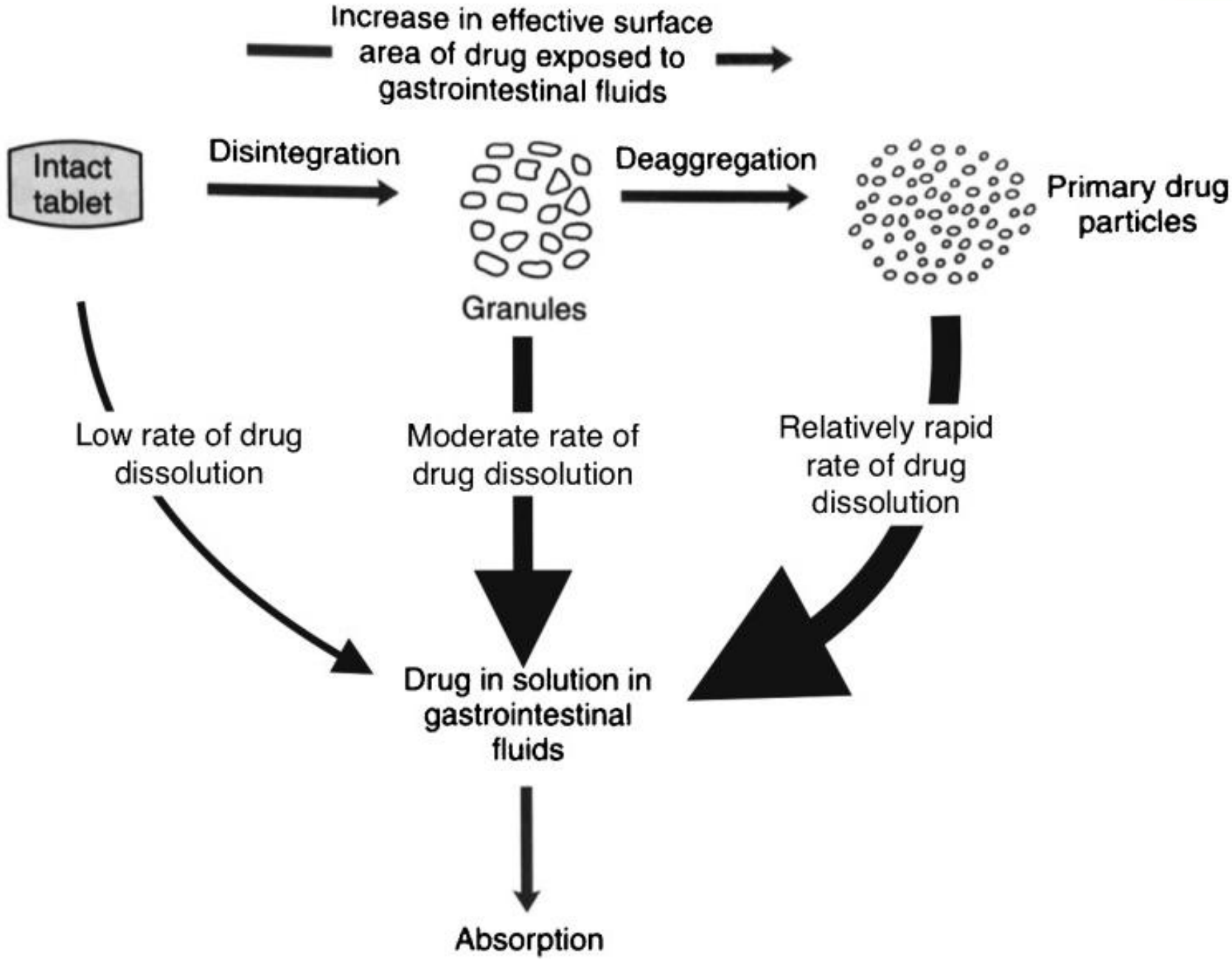
The role of the drug formulation in the delivery of drug to the site of action should not be ignored.

1. Disintegration time (DT):

- It is defined as the time taken by the solid dosage form to breakdown into smaller particles in the body after their ingestion.
- Order of disintegration of the solid dosage forms: Capsules > Tablets > Coated tablets > Enteric coated tablets > sustained release tablets.
- It Harder the tablet, greater is its disintegration time.
- Disintegration of solid dosage forms can be enhanced by incorporating appropriate amounts of disintegrants in the formulation.



* زيادة الـ disintegrant بتقلل من الـ disintegration time


Increase in effective surface area of drug exposed to gastrointestinal fluids
Intact tablet
Disintegration
Granules
Deaggregation
Primary drug particles
Low rate of drug dissolution
Moderate rate of drug dissolution
Relatively rapid rate of drug dissolution
Drug in solution in gastrointestinal fluids
Absorption

III Formulation Factors Affecting Oral Absorption

2. Manufacturing variables:

a) Method of granulation:

Wet granulation: enhance the dissolution rate of insoluble drugs by selecting a suitable granulating liquid.

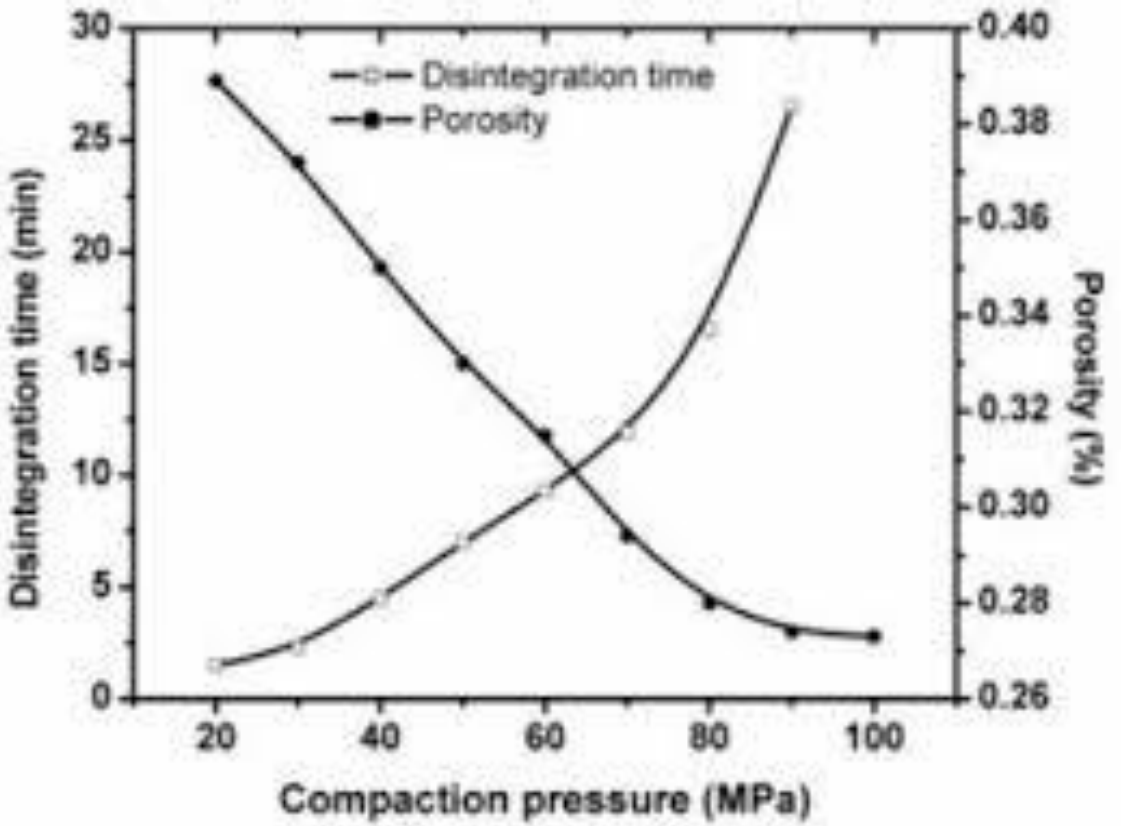
b) Compression force:

- Direct compression: dissolution rate of tablets prepared by this method are higher than the wet granulation method.

- The effect of compression force should be thoroughly studied on each formulation:

➢ Increasing compression force yields a tablet with greater hardness and reduced wettability & hence have a long disintegration time (D.T).

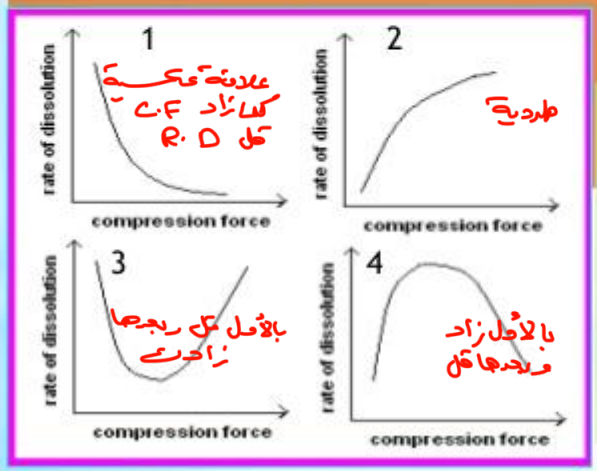
➢ Whereas, using higher compression force cause crushing or fracturing of drug particles into smaller ones or convert the spherical granule into a disc-shaped particle with higher effective surface area, which result in decreasing in D.T, and increasing the dissolution rate of the tablet.



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

Method of granulation:

سلايد إضافي موجود على التميز

C) Dry granulation

- Dry granulation is typically used in the manufacture of tablets if the formulation ingredients are too fluffy or too susceptible to flowability problems for direct compression or too susceptible to degradation from heat and/or moisture for wet granulation.
- The process is sometimes chosen as an alternative to wet granulation when direct compression is not feasible not because wet granulation is not feasible but because the manufacturer is more experienced with dry granulation or to reduce processing time and/or equipment requirements to reduce costs.

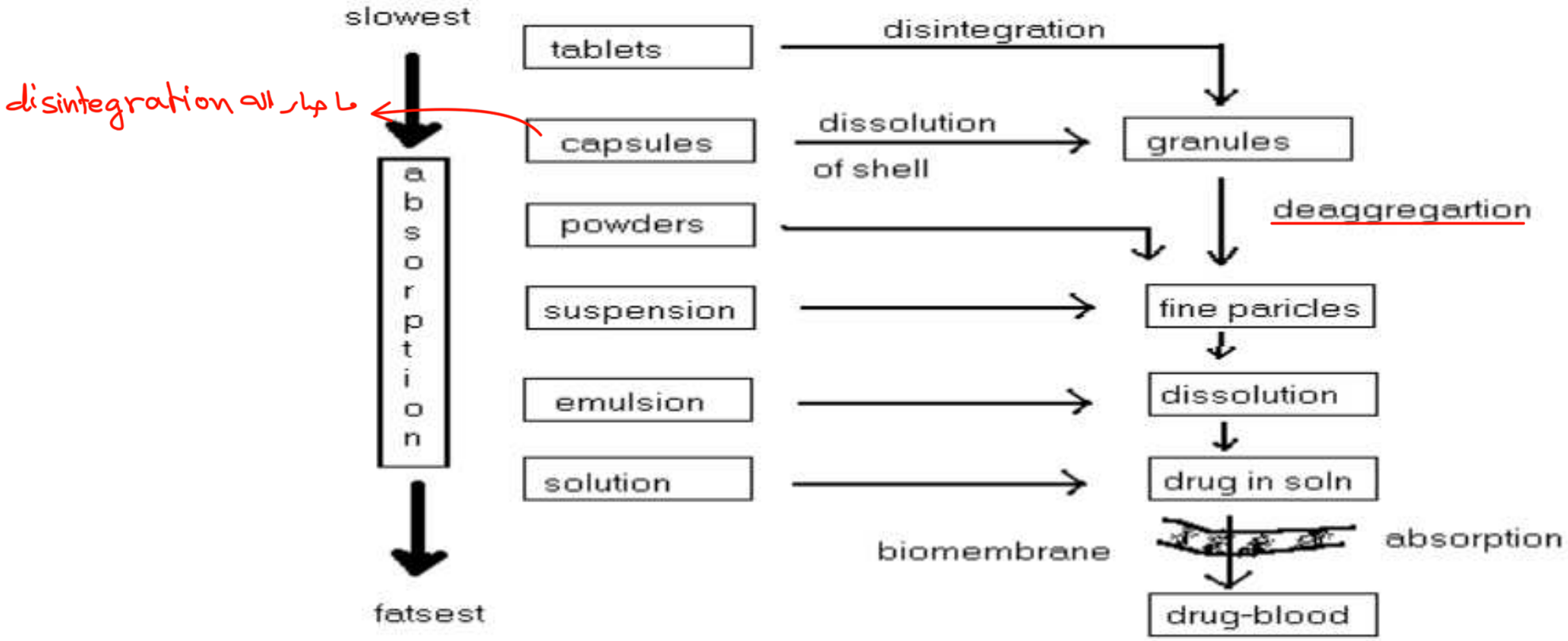
- The manufacture of tablets by dry granulation method eliminates a number of unit operations but still include milling of drugs, weighing, mixing, slugging, dry screening, lubrication, and compression of granules into tablets.

- For successful manufacture of tablets using dry granulation, either the active ingredient or the diluent must have sufficient inherent binding or cohesive properties.

III Formulation Factors Affecting Oral Absorption

3. Nature and type of dosage form

- Depending upon the nature and type of dosage form, the absorption pattern of a drug decreases in the following order
- Solutions > Emulsions > Suspensions > Capsules > Tablets Coated tablets > Enteric coated tablets > Sustained release tablets



III Formulation Factors Affecting Oral Absorption

A. Solution dosage form

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

- Some drugs which are poorly soluble in water may be:

1. Dissolved in mixed water/alcohol or glycerol solvents (cosolvency).
2. Given in the form of a salt (in case of acidic drugs).
3. An oily emulsion or soft gelatin capsules have been used for some compounds with lower aqueous solubility to produce improved bioavailability.

III Formulation Factors Affecting Oral Absorption

B. Suspension dosage forms:

- A well formulated suspension is second to a solution in terms of superior bioavailability.
- A suspension of a finely divided powder will maximize the potential for rapid dissolution.
- A good correlation can be seen for particle size and absorption rate.
- The addition of a surface active agent (surfactant) will improve the absorption of very fine particle size suspensions.

III Formulation Factors Affecting Oral Absorption

C. Capsule dosage forms:

- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the GI tract contents.

- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.

- Tightly packed capsules may have reduced dissolution bioavailability.

III Formulation Factors Affecting Oral Absorption

D. Tablet dosage forms:

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.

4. Pharmaceutical ingredients (excipients)

- Excipients (eg. Lubricants, granulating agent, etc.) are added to a formulation to enhance functional properties to the drug and dosage form such as:
  - ➢ Improve the compressibility of the active drug.
  - ➢ Stabilize the drug against degradation.
  - ➢ Decrease gastric irritation, etc.
- Excipients should be pharmacodynamically inert

sudden release ← dose dumping

- As more the no. of excipients being added in the dosage form, as more complexation and greater the potential for absorption and bioavailability problems.

Formulation Factors

4. Pharmaceutical ingredients (excipients)

السائل الحامل الدواء

a) Vehicle:

- Vehicles are used in parenteral and oral liquids preparations.
- Rate of absorption depends on its miscibility with biological fluid.
- Miscible solvents-rapid absorption of drug.
- Immiscible solvent-slow absorption of drug.

مخفف

b) Diluents

Diluents are added to increase the bulk of the dosage form, especially in tablets and capsules.

Hydrophilic diluents-form the hydrophilic coat around hydrophobic drug particles – thus promotes dissolution and absorption of poorly soluble hydrophobic drug.

III Formulation Factors Affecting Oral Absorption

c) Binding Agents

- Although binders are incorporated to produce cohesive bonding between granules during the process of compaction of tablets.
- Hydrophilic binders are for enhancing the dissolution rate of poorly soluble drug. e.g. starch, gelatin, polyvinylpyrrolidone (PVP).
- More amount of binder increases hardness of tablet and decrease dissolution & disintegration rate.

d) Disintegrating Agents

- They are added to the tablet to disrupts the cohesive forces between the granules, thereby causing the breakdown of the tablet to attain faster dissolution.
- Mostly hydrophilic in nature, increase in disintegration increase the bioavailability.
- e.g.: Guar gum, Starch, Microcrystalline cellulose

III Formulation Factors Affecting Oral Absorption

e) Lubricating Agents

- These agents when added to a tablet formulation to decrease the friction between the granules and die wall of the tablet press.
- Commonly hydrophobic in nature therefore inhibits penetration of water into tablet and thus dissolution and disintegration.

f) Surfactants

They are commonly used in the formulations as solubilizers, emulsifiers, wetting agents etc.

At lower concentrations, they increase the rate of absorption of poorly water soluble drugs.

Physiologic surfactants like bile salts they promotes absorption

e.g.: Griseofulvin, steroids

g) Complexing Agents

They increase the absorption rate of other drugs due to

- Formation of soluble complexes which enhances the dissolution.
- Increased the lipophilicity which enhances membrane permeability

h) Colorants

Water-soluble dyes even in least concentrations get adsorbed on the crystal faces and delay their dissolution rate.

e.g.: Brilliant blue retards dissolution of sulfathiazole.

III Formulation Factors Affecting Oral Absorption

5. Product age and storage Conditions:

Alterations in storage conditions and prolonged duration of storage of drug products may modify their physicochemical properties resulting in altered drug absorption patterns.