# Drug Absorption

**Presented by Dr. Areen Alshweiat**

# 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

↳ if the drug stays in the stomach (acidic media) for a long time, it will loose its' effect.

# Absorption

**Main factors affecting oral absorption:**

I. Physiological factors

**II. Physico-chemical factors**

III. Formulation factors

# A. pH - Partition Theory

Determains the suitable PH which affects the absorption

*Ionization and unionization: affects on absorption + solubility

- 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.

- 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.

* since the membranes are lipophilic, then lipophilic drugs + small hydrophilic particles can go through.

* drugs should be soluble to to get absorbed

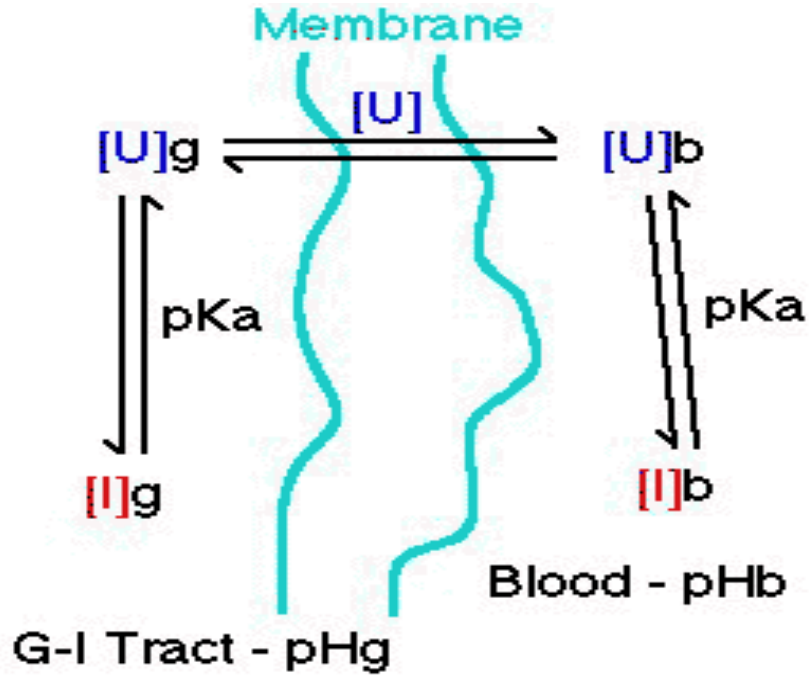
* lipophilic drugs: ↑ Permeability

↑ 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
- 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**
**U: unionized drug**

**Diagram Showing Transfer Across Membrane**

* $HA \rightleftharpoons H^+ + A^-$
* ↑Ka → ↑acidity → ↓pH
* $-\log ka = pKa$ → ↑pka → ↓acidity → ↑pH

*Basic: $A^- + H^+ \rightleftharpoons HA$

* ↑ Ka → ↑ basicity

*Kb + Ka relasionship = $1 \times 10^{-14}$ = Kw

# 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: -

تطبيق الحسابات في صادة الفين بحلل.

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

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

**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.

*Pka and pH positive relation: ↑pka → ↑ pH → ↓ acidity → ↑ Basicity.

* ↑ pH → ↑ Dissociation constant

| 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 cromoglycate | < 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 |

if pH > PKa:

$\frac{[A]}{[HA]} > 1$

So the ionized is more than the ionized which means its' solubility is high

Absorption occurs in the stomach because it is an acidic media and has lower ph value

Absorption occurs in the intestine because it is a basic media and has higher ph value

# 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: Unionized form of weakly acidic drugs can be absorbed from the small intestine for the following reasons:

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

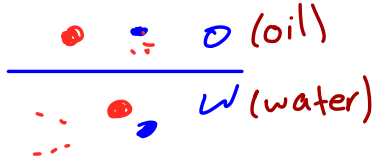
→ Has lower PH than the intestine

For permeability, drugs should have lipophilic characteristics as well as hydrophilic ones

# 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**.

* to test solubility:




Each has small particles in the opposite media

↑ p → ↑ Solubility in lipids → ↑ Absorption

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

Lipid concentration

Aqueous concentration

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

To test the ratio, usually: oil / Water

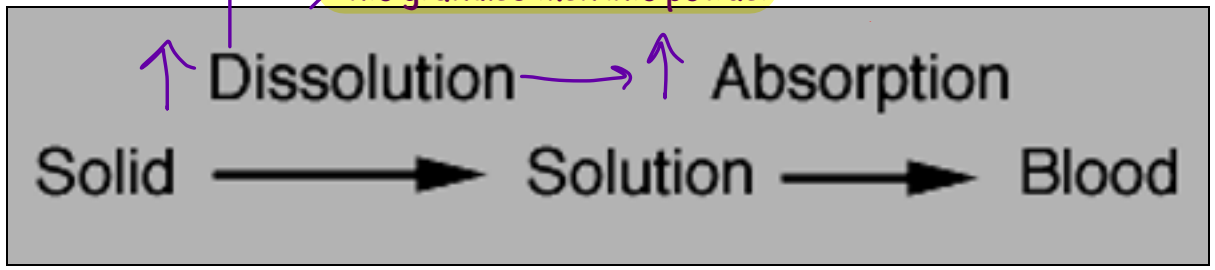
**The higher p value, the more absorption is observed**

Higher in lipids

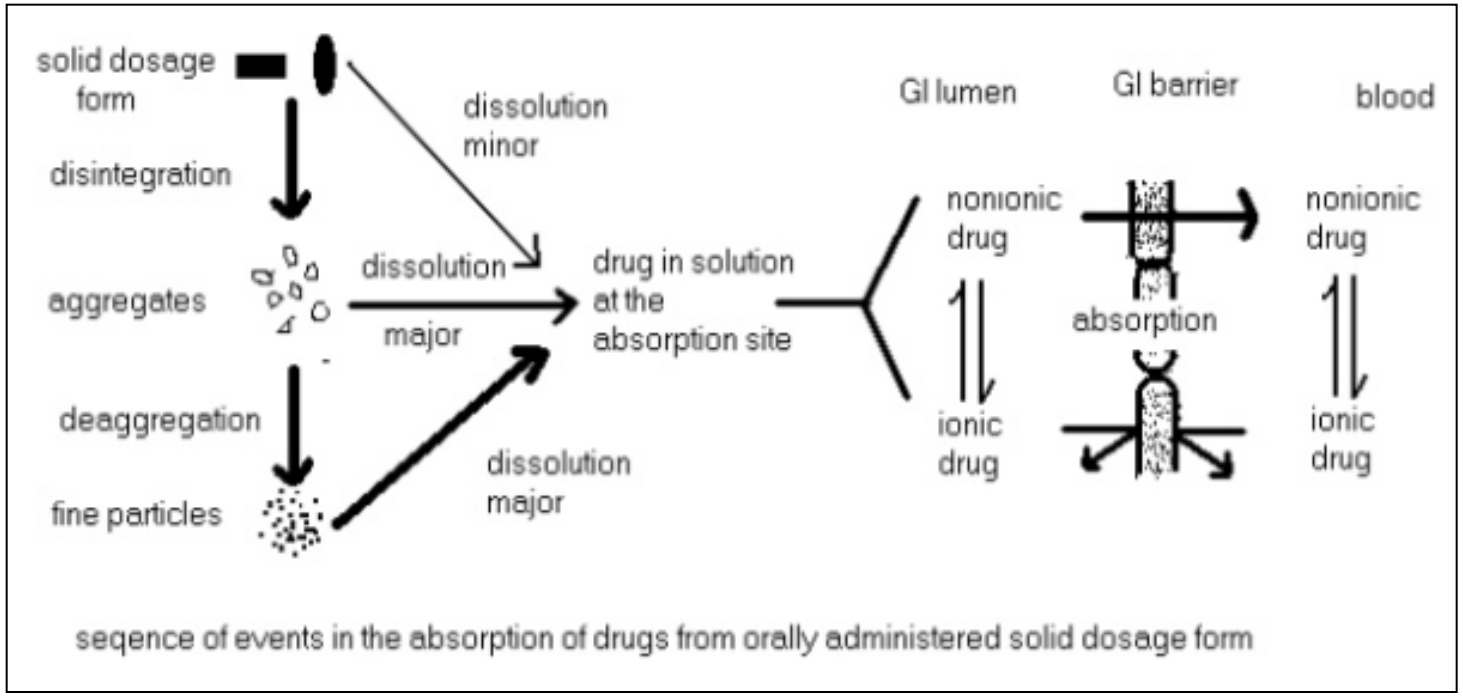
# C. Drug Dissolution

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

* Rate of dissociation affects the rate of absorption (positive relation)




- 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

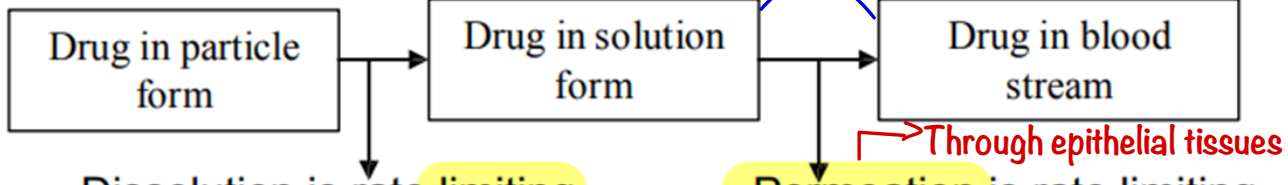
No breaking down into particles

Powder in shell, faster than tablets

Dispersed particles, faster than capsules

Dissolution is completed, but no absorption yet

Rate of dissolution

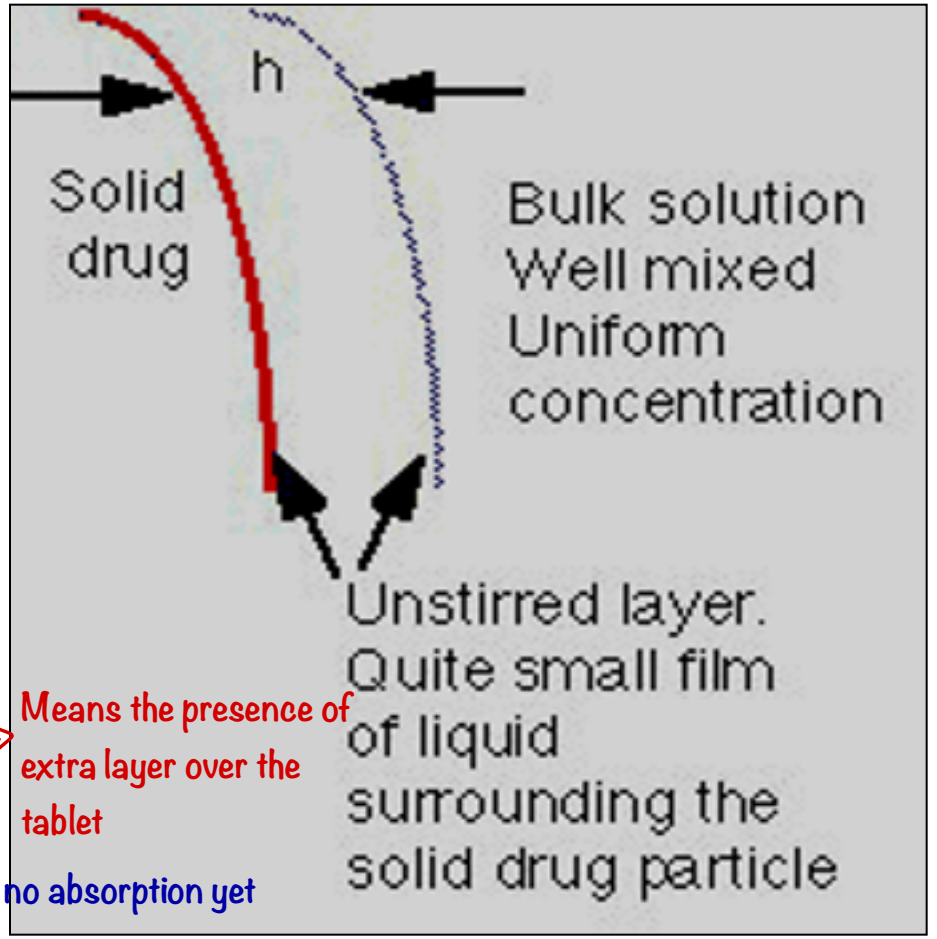



Through epithelial tissues

Dissolution is rate limiting step for lipophilic drugs e.g. Griseofulvin

Determains the absorption rate

Permeation is rate limiting step for hydrophilic drugs. e.g., Neomycin




Means the presence of extra layer over the tablet

Diagram Representing Diffusion through the Stagnant Layer

# C. Drug Dissolution

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

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

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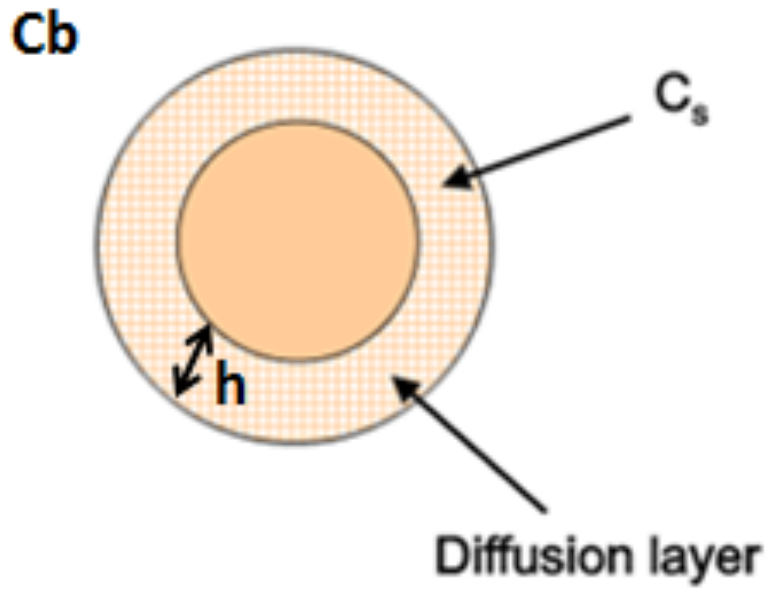



- Where D: is the diffusion coefficient
- A: the surface area
- Cs: the solubility of the drug
- Cb: the concentration of drug in the bulk solution
- h: the thickness of the stagnant layer.
- If Cb is much smaller than Cs then we have so-called "Sink Conditions" and the equation reduces to

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

# 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:

↑ Viscosity ↑ Diffusion ↑ Dissolution ↑ Absorption

- 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.

*Powder has higher surface area than tablets

*Surfactants act as wetting agents

*Cocoa in milk needs wetting agent to complete the dissolution

# 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.

↳ ↑ Dissolution.

## 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:

*Example: one gram of sugar has higher surface area than one gram of cubed sugar

- 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.

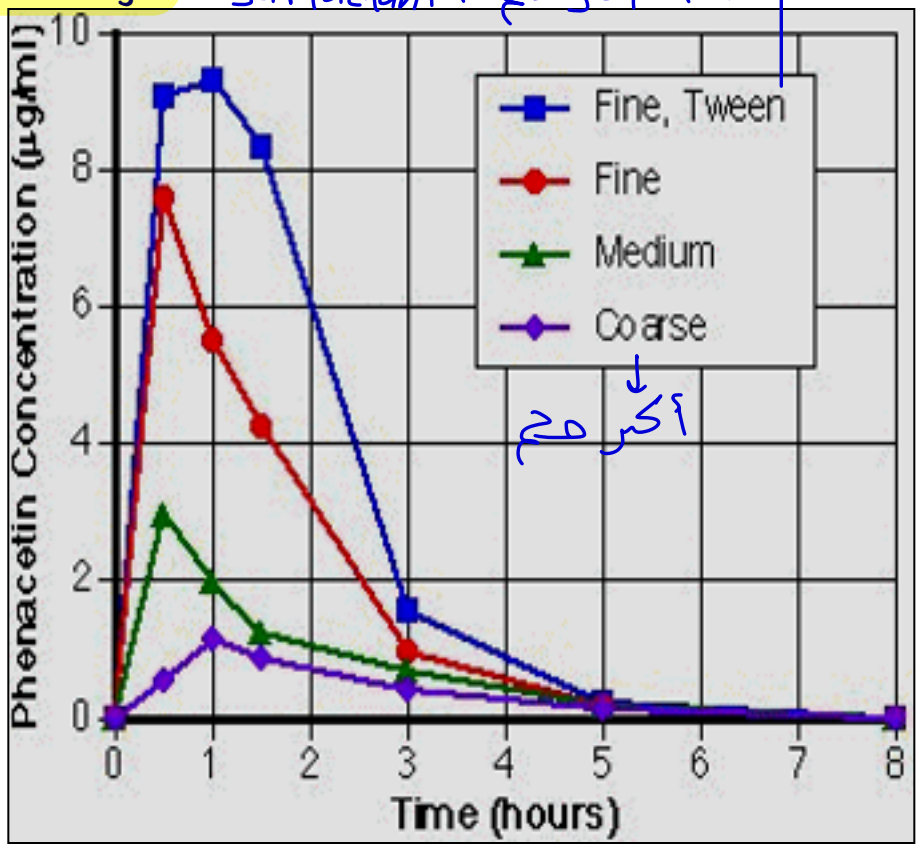
Eg: homogenisers

- Methods of particle size reduction include: mortar and pestle, mechanical grinders, mills, solid dispersions in readily soluble materials (PEG's).

simplest way.

- However very small particles can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption.

surfactant + جروب




أكبر حجم

*Glass beads are put with the drug to increase friction and get smaller particles

*Sometimes extra small particles need to stick together a little bit for better dissolution

# 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, $C_s$

It's nature: ionized, unionized, etc...

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

Salts that form from weak acids and weak bases are charged which increases their solubility

## D- Salt forms of the drugs:

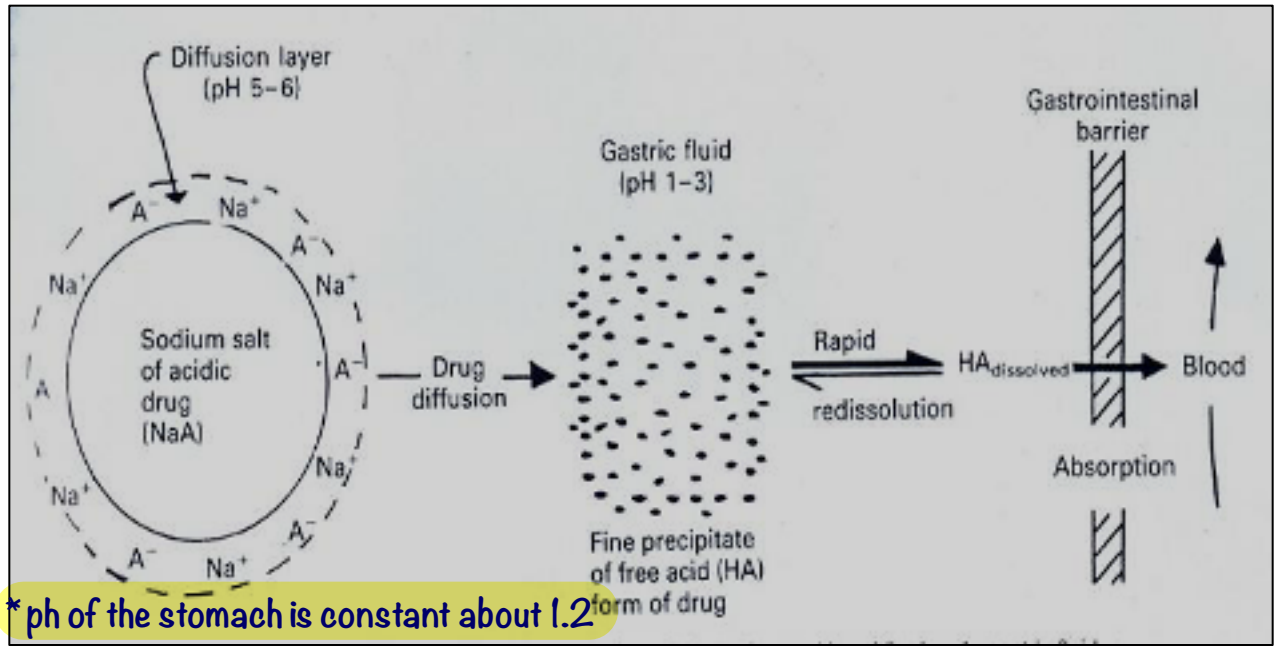
- **Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.**
- The dissolution rate of a weakly acidic drug in gastric fluid (pH 1 – 3.5) will be relatively low.
- If the pH in the diffusion layer increased, the solubility, $C_s$, of the acidic drug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

* Acidic drugs will not be soluble at low ph, since the unionized is much more than the ionized

# C. Drug Dissolution

* Salt formation will increase the ph of the diffusion layer, so it will then become soluble

- 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.




* ph of the stomach is constant about 1.2

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

* If the ph of the diffusion layer decreases again, particles will precipitate

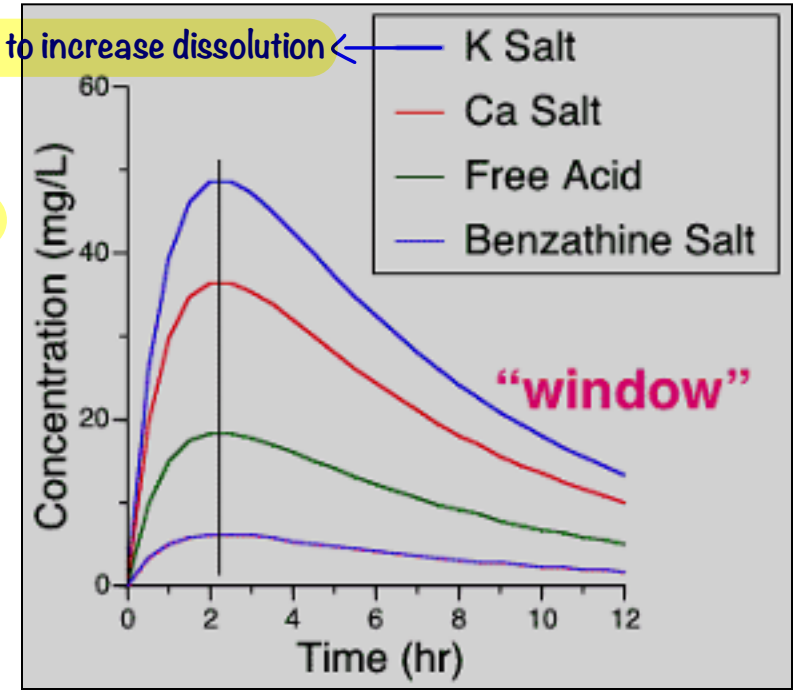
**This precipitated free acid will be in the form of:**
**- very fine, non-ionized, wetted particles which have a very large surface area in contact with gastric fluids, facilitating rapid re-dissolution when additional gastric fluid is available.**

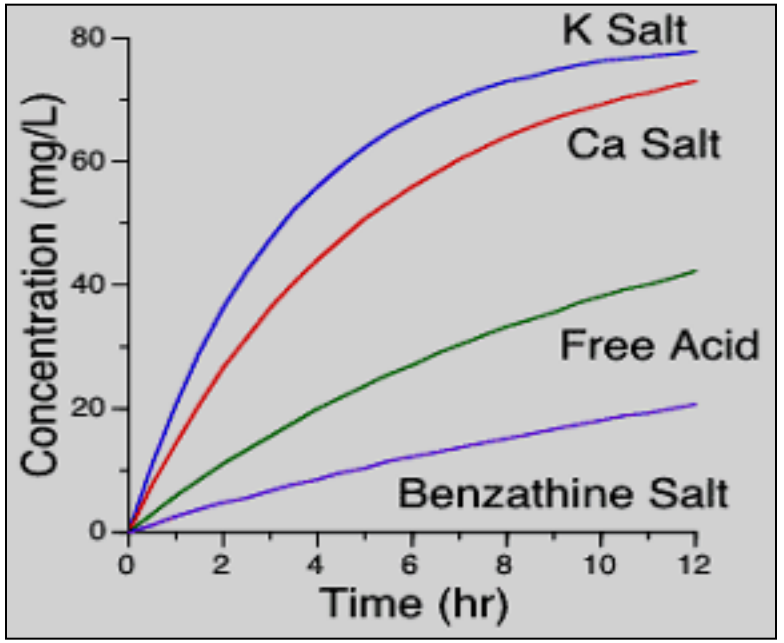
# C. Drug Dissolution

- **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.

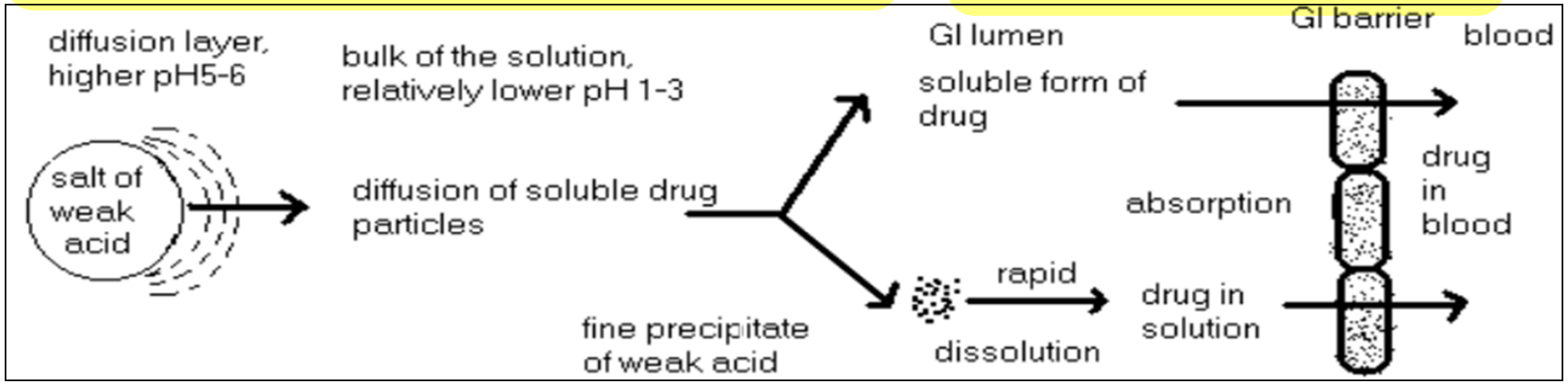
* Increasing solubility also depends on the salt its self

The best salt to increase dissolution




* The aim of decreasing dissolution is increasing the release time. → بعض الأدوية ما بدنا يتم امتصاصها بشكل سريع



# C. Drug Dissolution

(Packing)

## 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

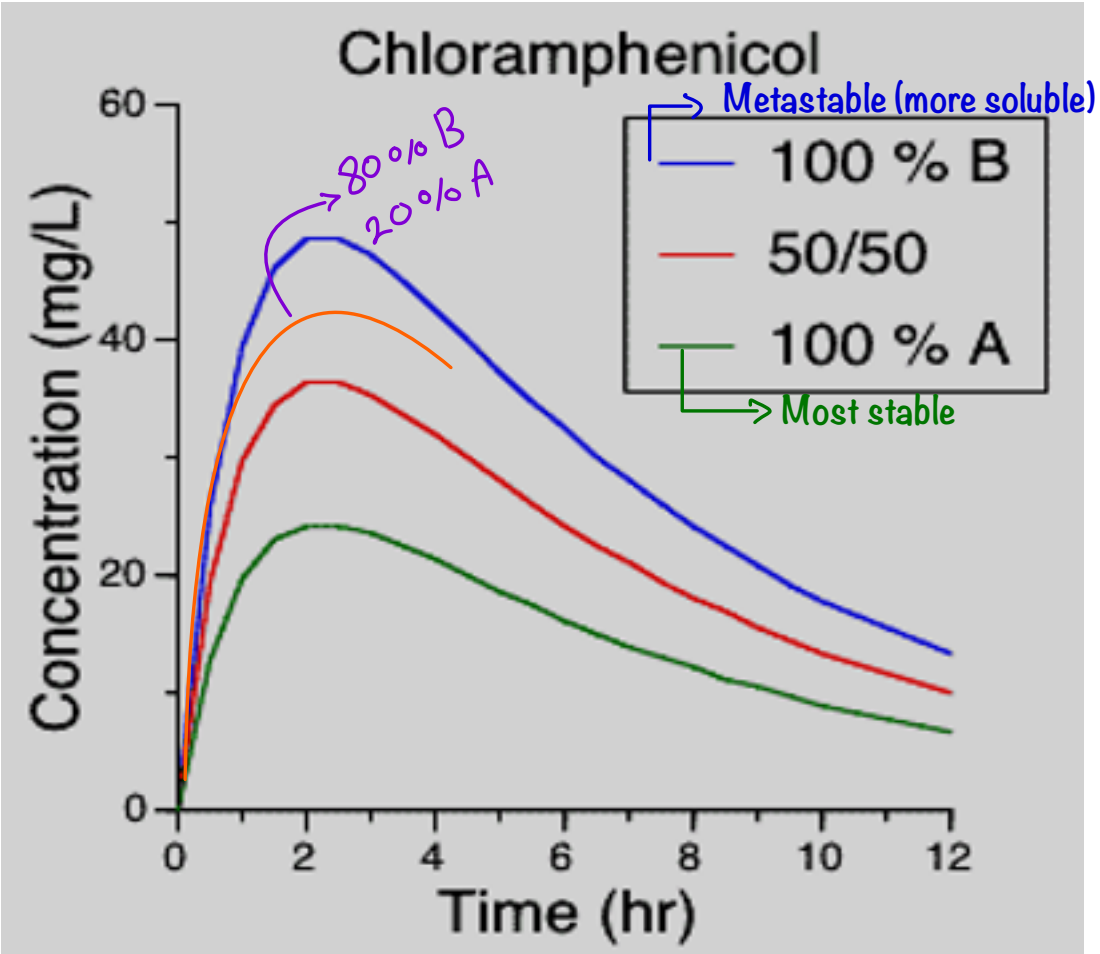
B → is the metastable (Mid stability) polymorph (more soluble)

C → is the unstable polymorph

↳ Becomes stable with time

# 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).
  - B becomes A (more stable)



# C. Drug Dissolution

* Generally speaking: unstable = ↑ Soluble ↑ energy

* exception: metastable

Not ordered

## 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.

Loss of solubility

# C. Drug Dissolution

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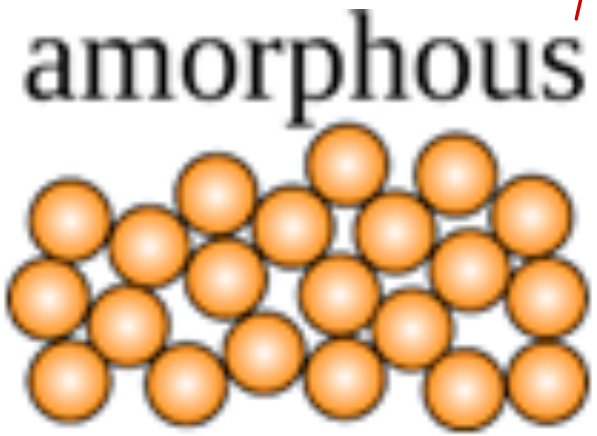
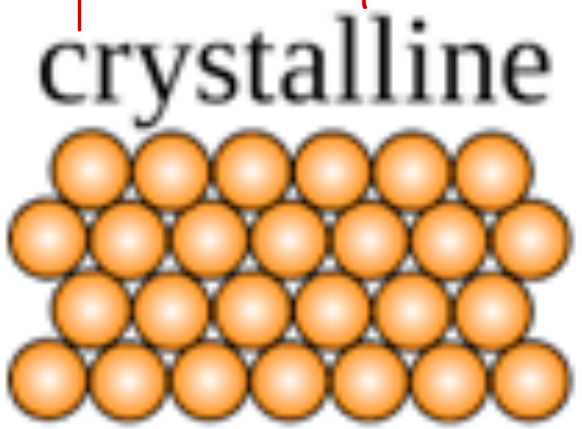



Packed in a specific order




## Amorphous form

More soluble
Rapidly dissolving
Readily absorbed

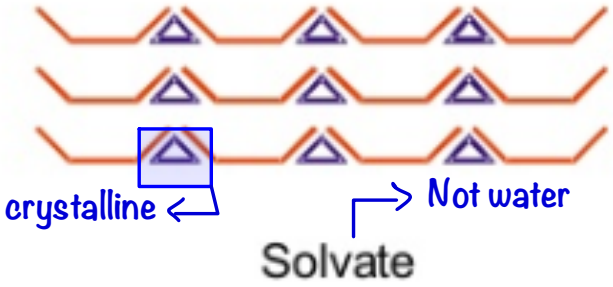
## Crystalline form

Less soluble
Slower dissolving
Not absorbed to significant extent

# C. Drug Dissolution

## 3- Solvates and hydrates:

- **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.




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

Present of hydrate

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

Comparing to anhydrous

* Anhydrous material doesn't contain water

| | |
|---|---|
| Solvent is water | Hydrates |
| Solvent is other solvents | Solvates |

# C. Drug Dissolution

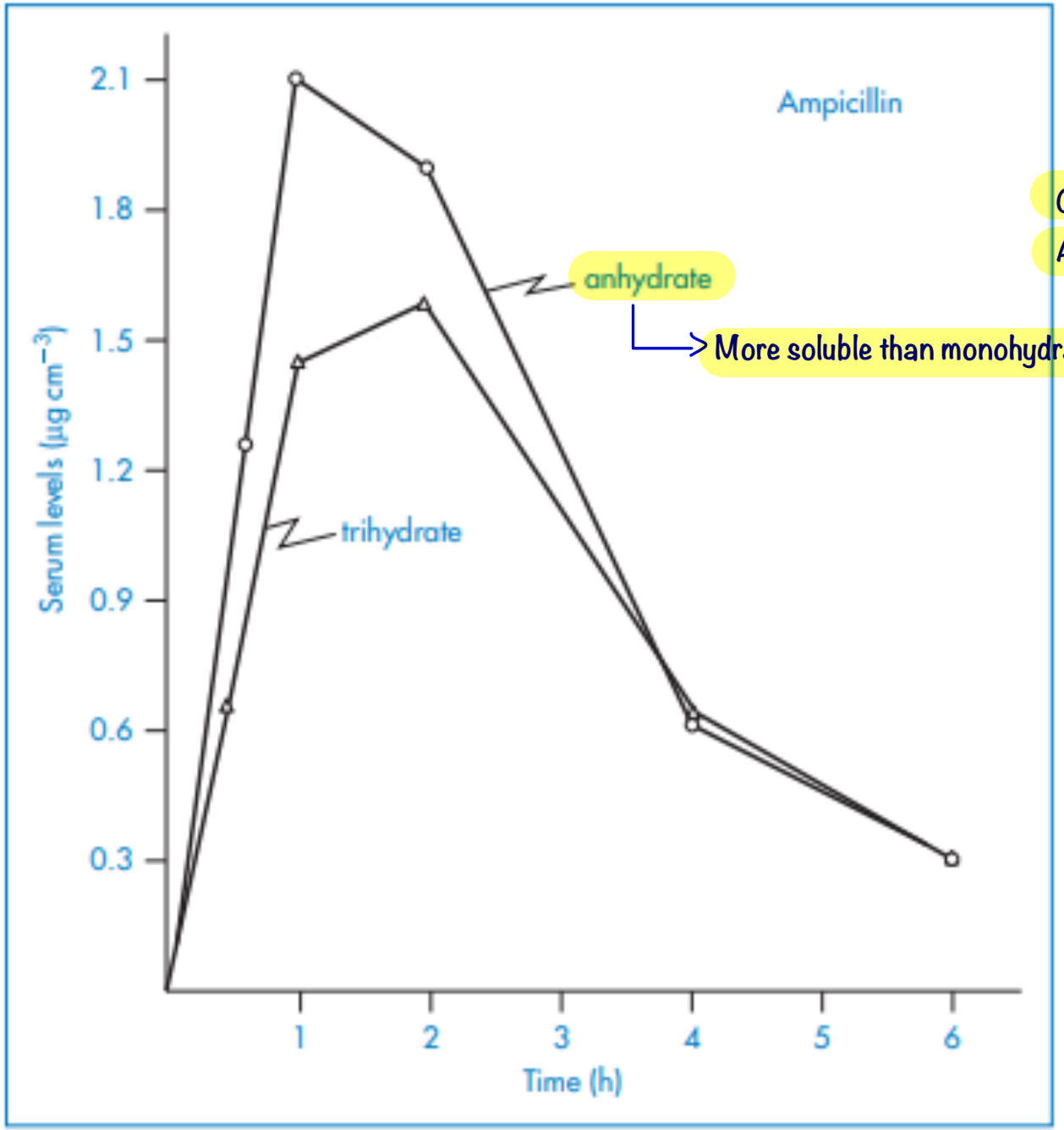
**4-Anhydrous:** Drug is not associated with water

- 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.

Higher solubility than trihydrate.

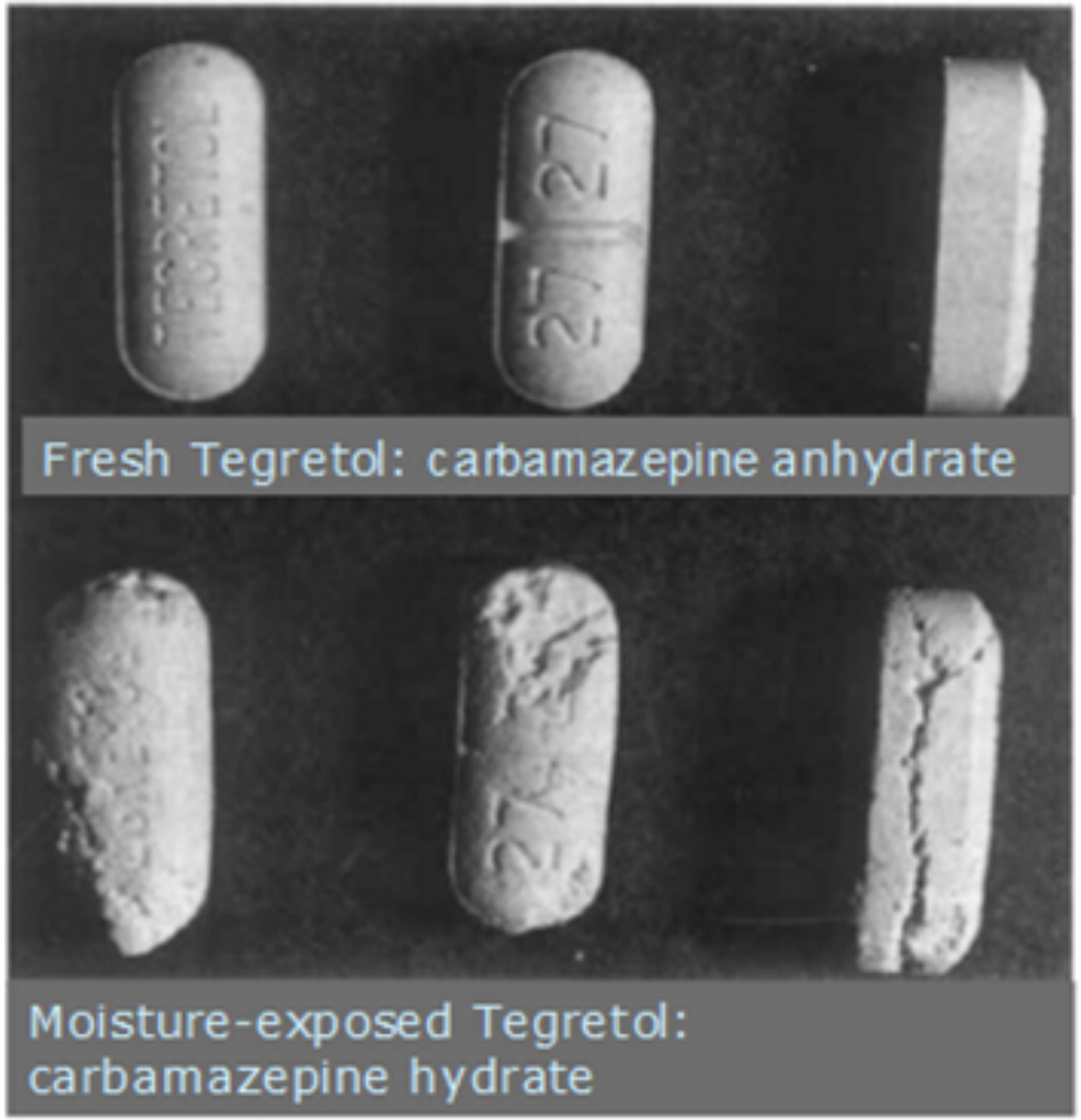



Order from highest to lowest solubility:

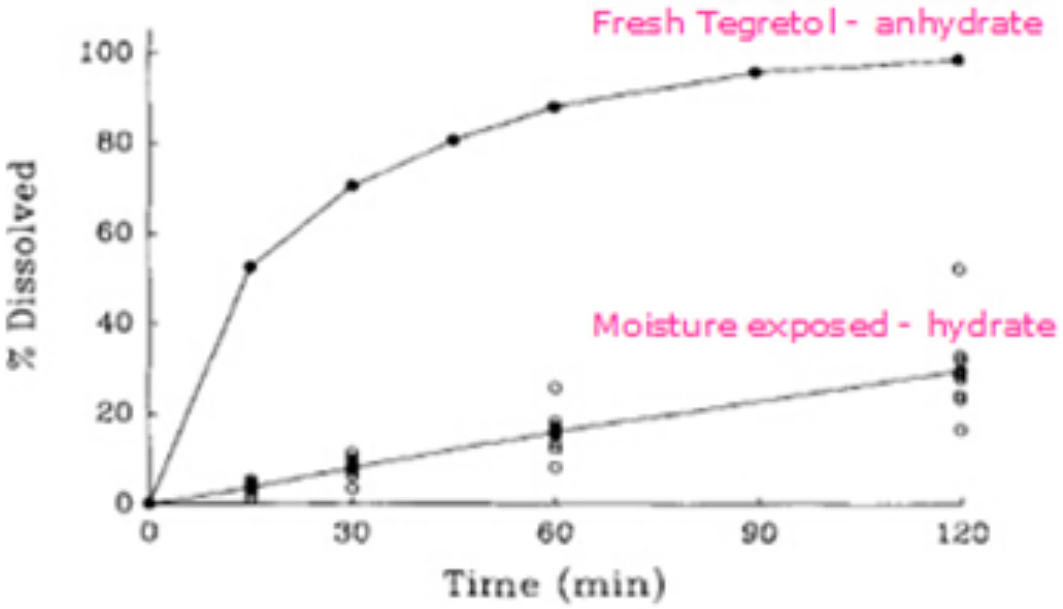
Anhydrous > monohydrous > dihydrous > trihydrous

→ More soluble than monohydrate

# C. Drug Dissolution




- Hydrates may reduce
  - solubility
  - dissolution rate



# D- Drug Stability and Hydrolysis in GIT

Must be protected from both enzymes and acidic media

- 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 ??

Must be coated to prevent degradation in acidic media

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.

*Ethyl cellulose can be the coat polymer

Reduces solubility, so reduces absorption

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.

Release erythromycin in the small intestine, giving the drug alone which allowed absorption

*Prodrug must breakdown to give the drug alone for absorption

* Some complexations can have positive effect on absorption

# 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.

ضل مرتبط مع الدواء مما منعه من الامتصاص

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

As milk

Type of an antibiotic

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

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

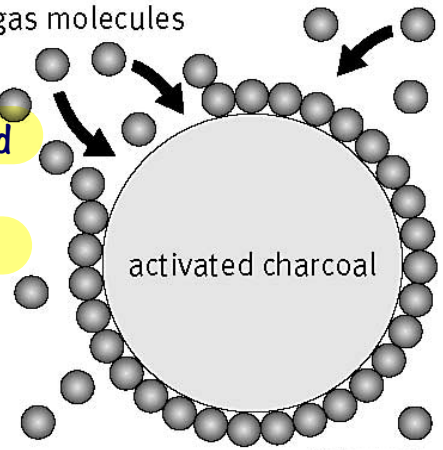
4- Lipid soluble drug + water soluble complexing agent = well-absorbed water soluble complex ( cyclodextrin)

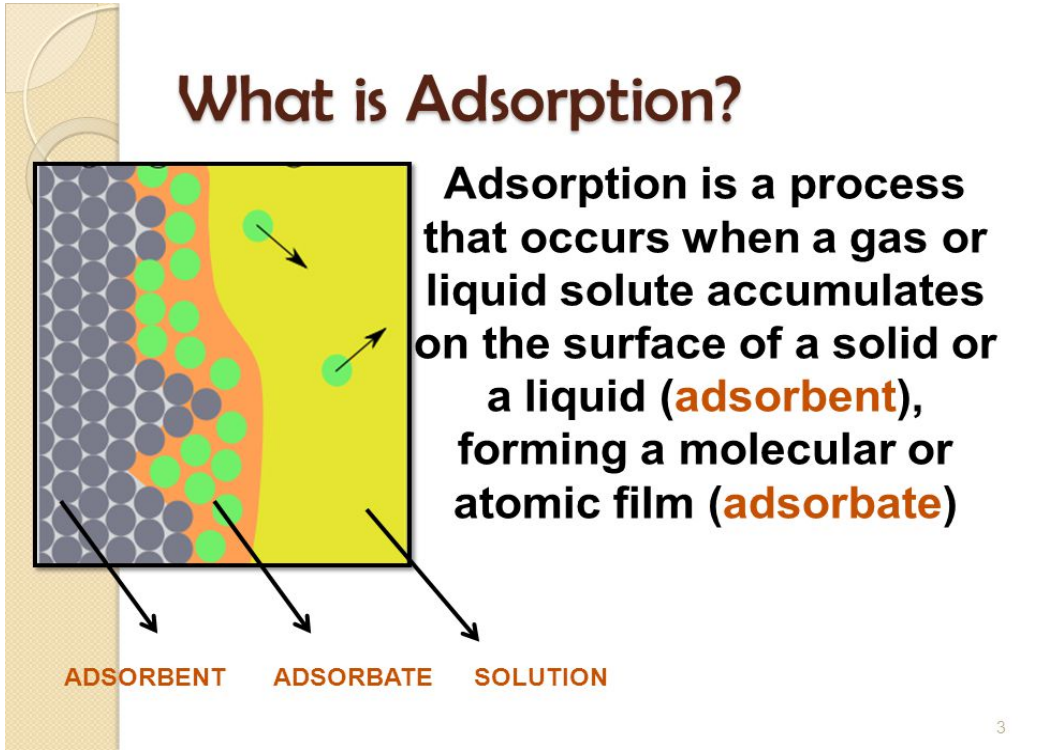
بعمل على ترتيب polar molecules للداخل و non-polar molecules للخارج، وبالتالي بعمل على تحسين امتصاص lipid soluble drug

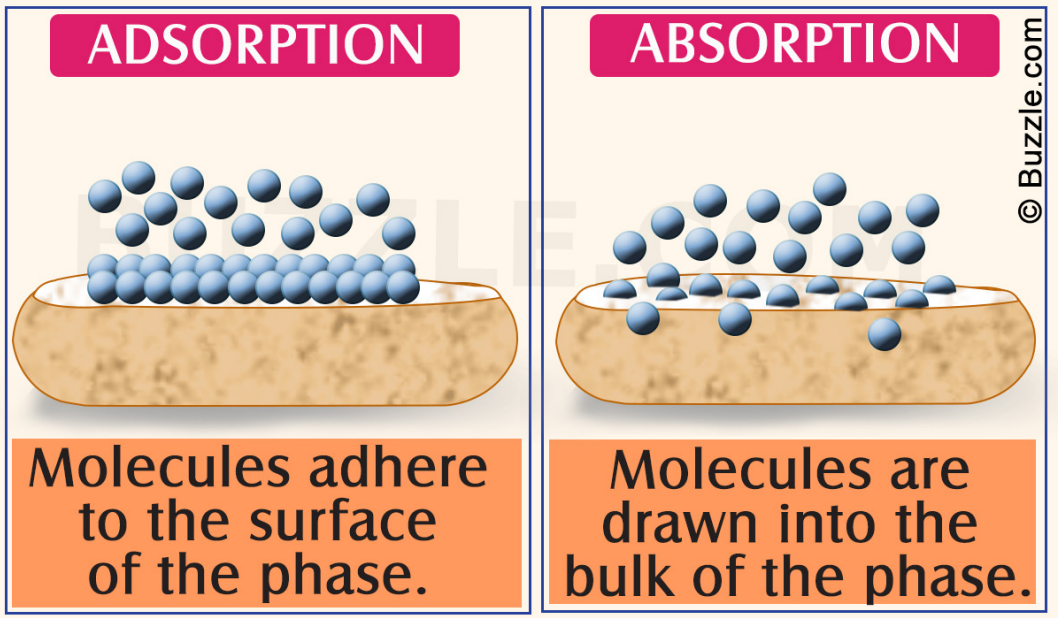
# F- Adsorption ادمصاص، التصاق المادة على السطح

- Certain insoluble substances may adsorbed co-administrated drugs leading to poor absorption.
- Charcoal (antidote in drug intoxication). Counteract a form of poisoning
- Kaolin (antidiarrheal مضاد للإسهال mixtures)
- Talc (in tablets as glidant مزلق)

Links to drug particles, during manufacture to make sure it is filled with material, as well as absorbing moisture



**Main factors affecting oral absorption:**

I. Physiological factors

II. Physico-chemical factors

**III. Formulation factors**

الاختصارات حفظ

# 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.

*Disintegration time has an opposite relationship with disintegration, as disintegration is faster then we have less disintegration time

### 1. Disintegration time (DT):

Time needed for the tablet to breakdown into smaller fragments, which leads to higher surface area.

The longer the DT the later the absorption and effect

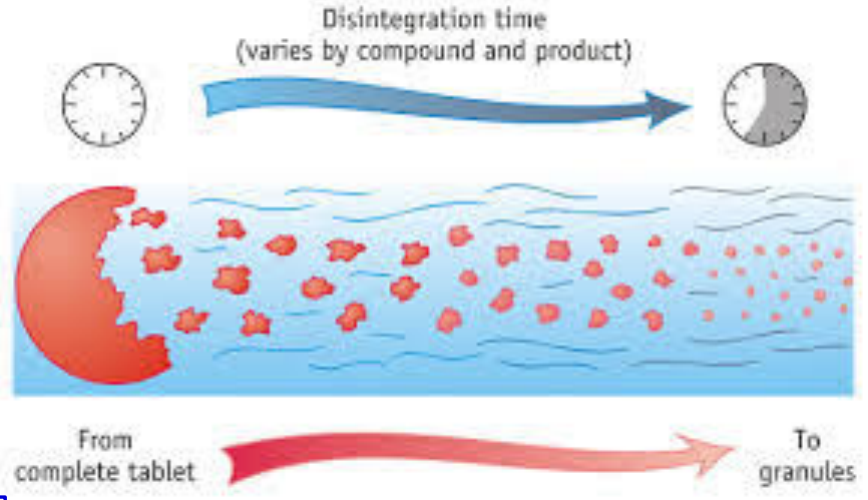
- It is defined as the time taken by the solid dosage form to breakdown into smaller particles in the body after their ingestion.
- Order of disintegration of the solid dosage forms: Capsules > Tablets > Coated tablets > Enteric coated tablets > sustained release tablets.

Faster ←

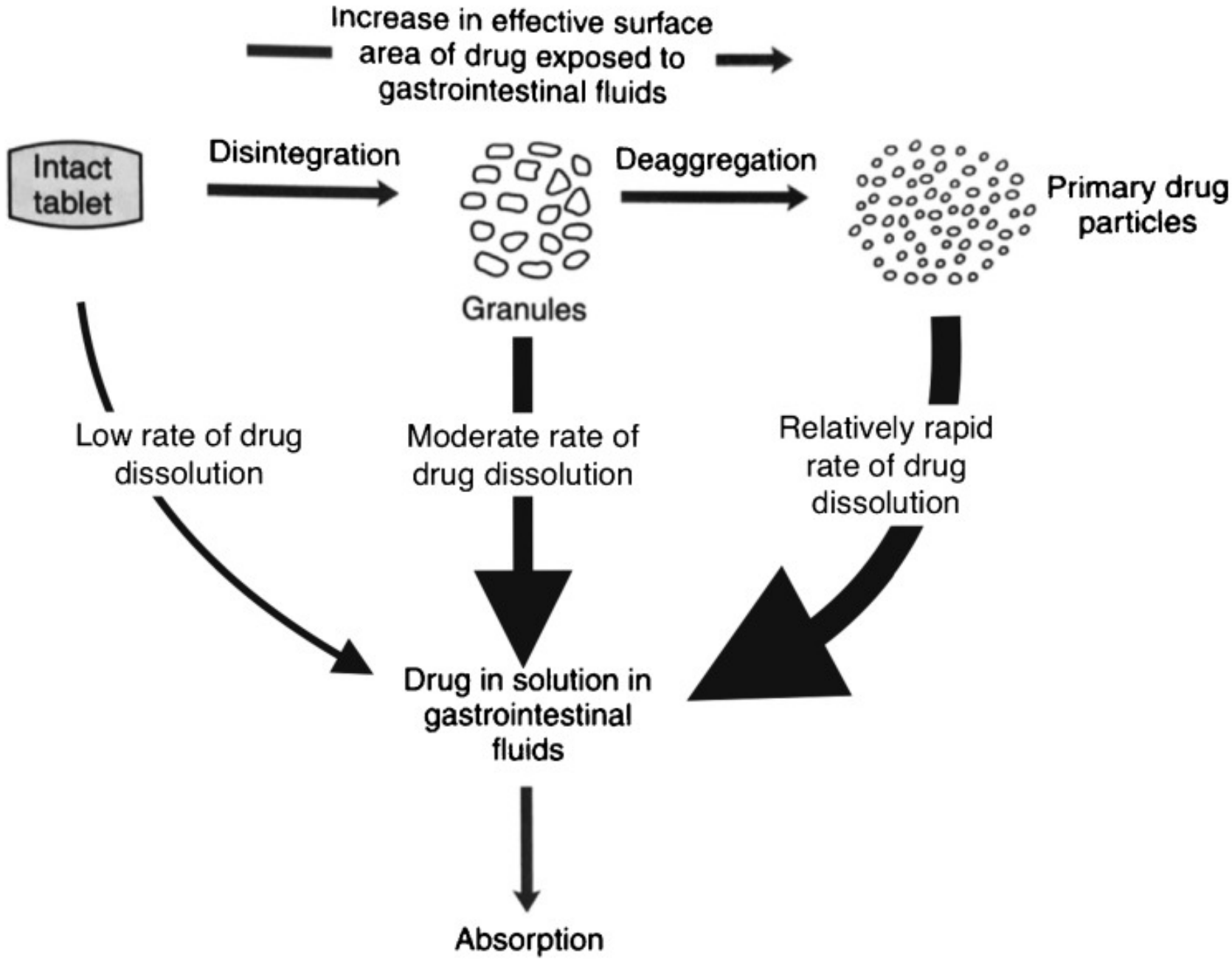
Designed to be slow ←

- 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.

*Adding disintegrants such as cellulose the disintegration process




*Needs higher pH to release the drug and takes longer time to increase the pH


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:

*Granules are larger than fine powder, can be said that each small group of fino powder ave granules

**Wet granulation**: enhance the dissolution rate of insoluble drugs by selecting a suitable granulating liquid. The additive will affect on disintegration and to affect on absorption

→ If oil is used is will reduce the rate of dissolution

### b) Compression force:

↑ Compression force ↑ Hardness ↓ Surface area ↓ Disintegration

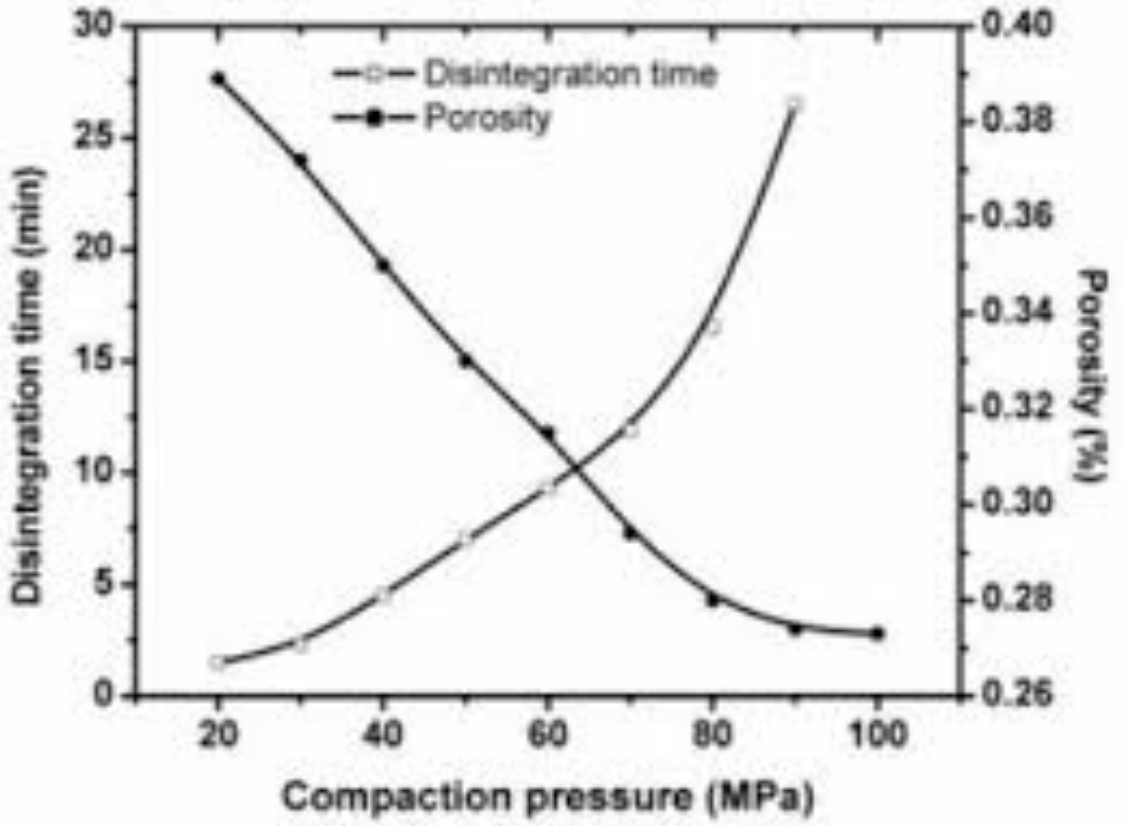
- Direct compression: dissolution rate of tablets prepared by this method are higher than the wet granulation method.

Over compaction may give opposite result as it may cause fracturing of the drug particles as a result of very high pressure

- 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.



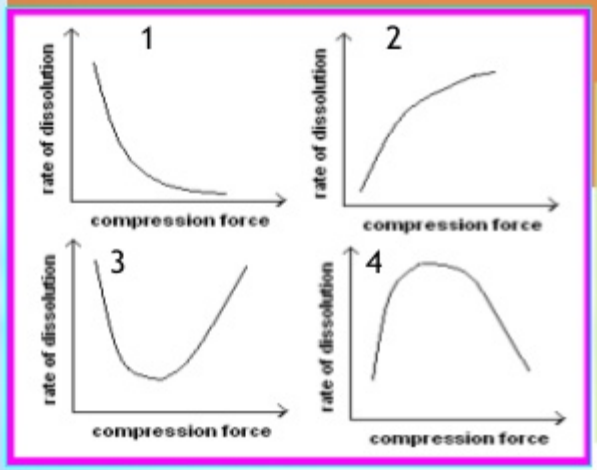

*After disintegration, powder may be aggregated since it doesn't have enough water

May also affect the spaces between particles

## 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

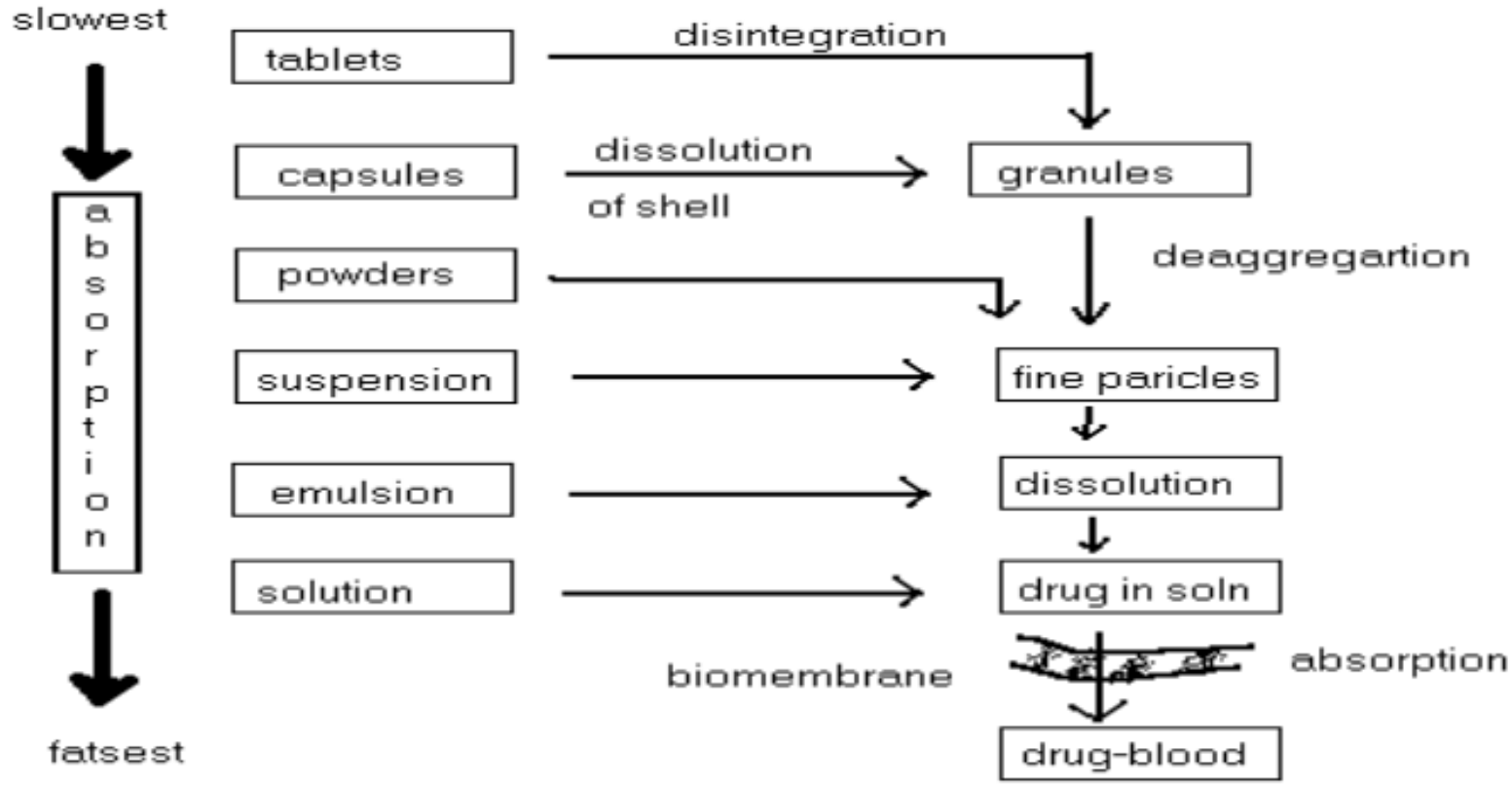
3.& 4. both condition

# 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.

*Like dissolves like so water dissolves polar substances, and that's why nonpolar drugs are less soluble in water

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

*co-solvents should be miscible with water

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

* suspensions should be shaken well before used to get accurate dose

## B. Suspension dosage forms:

*Suspended fine powder in liquid makes up the suspension

- 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.

* lower particle size increases the surface area which then increases the absorption

- A good correlation can be seen for particle size and absorption rate.

* by reducing tension between particles, so it does not allow the aggregation of the fine powder

- 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.

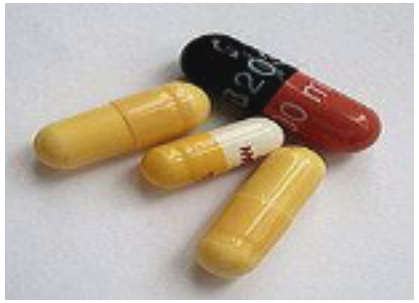
It is water soluble

- 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.

To give the maximum absorption possible

- Tightly packed capsules may have reduced dissolution bioavailability.

Caused via adding excess amounts of powder than needed which makes it harder to dissolute



# 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.


Additives other than the active pharmaceutical constituents

## 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

Should not use any pharmaceutical effect, either good or bad, especially not inhibiting the action of the active ingredient

- 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)

**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.

* acts in increasing the size of very small tablets to be able to deal with it, for example: a 5 mg tablets is very small, so we should increase the size of it to become in a size of a normal tablet.

**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.

* calcium carbonate: inorganic
* sugars: hydrophilic (increasing size)

# 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.

Increases disintegration time

Not to be hydrophobic, because we want to increase not decrease disintegration

## 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

To avoid sticking to the mould

- 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.

→ ↓ Dissolution

## f) Surfactants

↓ Surface area ↓ Dissolution

Unless using lower concentration

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

*As micelles are used as solubilizers to increase the absorption of drugs

Cyclodextrin is a soluble complex that increases the absorption

## 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

Used to help patients with discrimination

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

Can cause a decrease in the bioavailability as it affects degradation

**5. Product age and storage Conditions:** Storage may also affect the stability of the drug

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