
Bio Pharma
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3- Gastrointestinal (GI) Physiology

- The gastrointestinal tract is a muscular tube approximately 6 m in length with varying diameters.

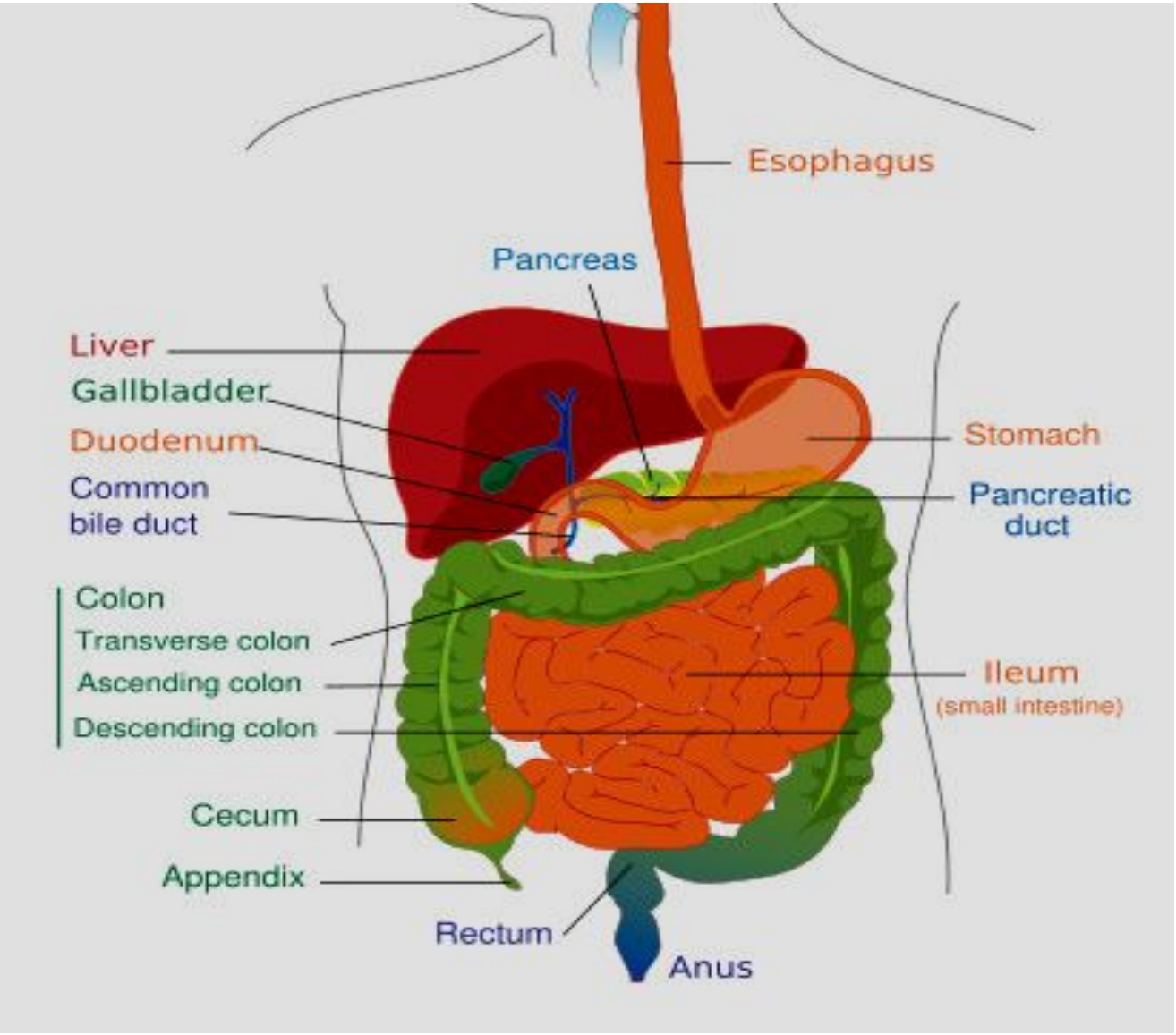
- It stretches from the mouth to the anus and consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon.

- The majority of the gastrointestinal epithelium is covered by a layer of mucous. This is a viscoelastic translucent aqueous gel that is secreted through out the GIT, acting as a protective layer and a mechanical barrier.

هسا زي ما حكينا انو ال GIT هو muscular tube بدأ من ال mouth وبنتهي بال anus بتبع قانون ficks first law وهاد القانون هو اللي بتحكم بموضوع ال diffusion وال absorption في ال GIT .

فمتل ما حكينا بالقانون بالمحاضرة الماضية انو كل ما كان ال thickness قليل رح يكون ال absorption عالي كمان surface area الها دخل كل ما كانت أكبر كل ما كان ال absorption أعلى .

Gastrointestinal (GI) Physiology



Gastrointestinal (GI) Physiology

I. Characteristics of GI physiology and Drug Absorption:

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Buccal	approx 6	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
Oesophagus	5-6	Very thick no absorption	-	small	short, typically a few seconds, except for some coated tablets	-

رح نحكي عن ال buccal هو باطن الخد وال thickness لإلو بتكون قليلة يعني ال absorption عالي وزي ما بنعرف انو كل الأدوية سواء كانت IV أو Oral رح تمر ب metabolism and excretion بس أدوية ال oral بتمر بكمان metabolism إسمو first bass metabolism بس إذا أنا أخدت الدواء عن طريق ال buccal بتروح على ال blood circulation على طول فزي كأنو أعطيت الدواء IV وال bioavailability بتكون الو 100٪ .

I. Characteristics of GI physiology and Drug Absorption

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Stomach	1.7-3.5	normal	good	small	min (liquid) 30 - 120 min (solid food)	no
Duodenum	7 - 5	normal	good	Very large	,very short	no

I. Characteristics of GI physiology and Drug Absorption

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Small Intestine	7.5 – 6	normal	good	Very large	About 3 hours	no
Large intestine	7 - 6.8	-	good	Not very large	long, up to 24 hours	Lower colon, rectum yes

I. Characteristics of GI physiology and Drug Absorption

The environment within the lumen:

Gastrointestinal pH

- As we observed from the previous tables, the pH of fluids varies along the length of the GIT.
- The gastrointestinal pH may influence the absorption of drugs in a variety of ways:

A- It may affect the chemical stability of the drug in the lumen e.g. penicillin G, erythromycin

B- affect the drug dissolution or absorption e.g. weak electrolyte drug

Luminal enzymes

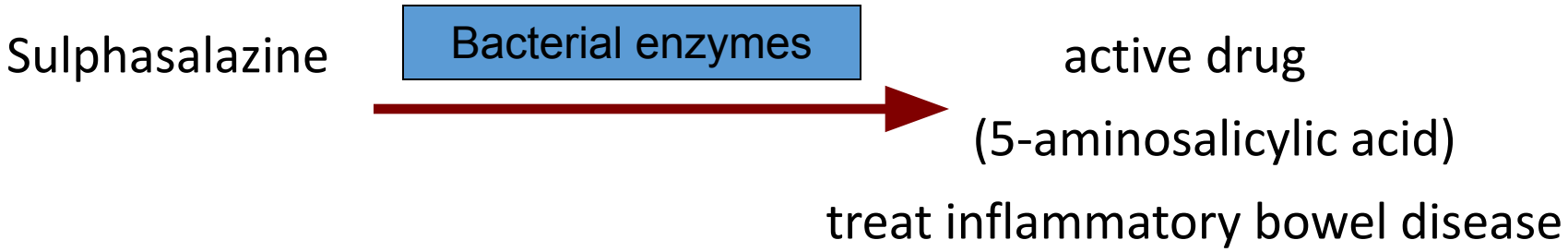
- The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine.
- Pepsins and proteases are responsible for the digestion of protein and peptide drugs in the lumen.

هسا في أكتر من أشي بأثر على موضوع ال absorption منها ال environment within the lumen

العامل الأول هو ال ph : ال PH أقل أشي بكون بال stomach ولما نروح على ال intestine بتزيد ال PH وكمان في بكتيريا اسمها notmal flora وإنزيمات داخل ال GIT اللي بتساعد على ال degradation وال absorption للأدوية .

I. Characteristics of GI physiology and Drug Absorption

- The lipases may affect the release of drugs from fat / oil – containing dosage forms.
- Bacteria which are localized within the colonic region of the GIT secrete enzymes which are capable of a range of reactions.
- e.g. Sulphasalazine which is a prodrug used to target the colon.



I. Characteristics of GI physiology and Drug Absorption

Disease state and physiological disorders

- Local diseases can cause alterations in gastric pH that can affect the stability , dissolution and absorption of the drug.

- Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals. This may result in an increased overall rate of absorption of drugs that are absorbed in the small intestine.

- However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients.

هسا في عنا اشي اسمو ال gastrectomy وهو إنو تنشال جزء من المعدة وهاد رح يقلل وجود الدواء داخل ال stomach ورح يسرع وصول الدواء لل small intestine فرع يزيد ال absorption وال bioavailability لكن هاد الأشي مش مطلق لأنو في بعض الأودية بتحتاج تقعد بالمعدة فترة أطول فبالتالي هاي الأدوية اللي بحاجة تقعد بالمعدة فترة ما رح يصير الها degradation.

I. Characteristics of GI physiology and Drug Absorption

The unstirred water layer

- It is a more or less stagnant layer of water and mucous adjacent to the intestinal wall.

- This layer can provide a diffusion barrier to drugs.

- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption.

II Gastric emptying and motility

- The time a dosage form takes to traverse the stomach is usually termed: the gastric residence time, gastric emptying time or gastric emptying rate.

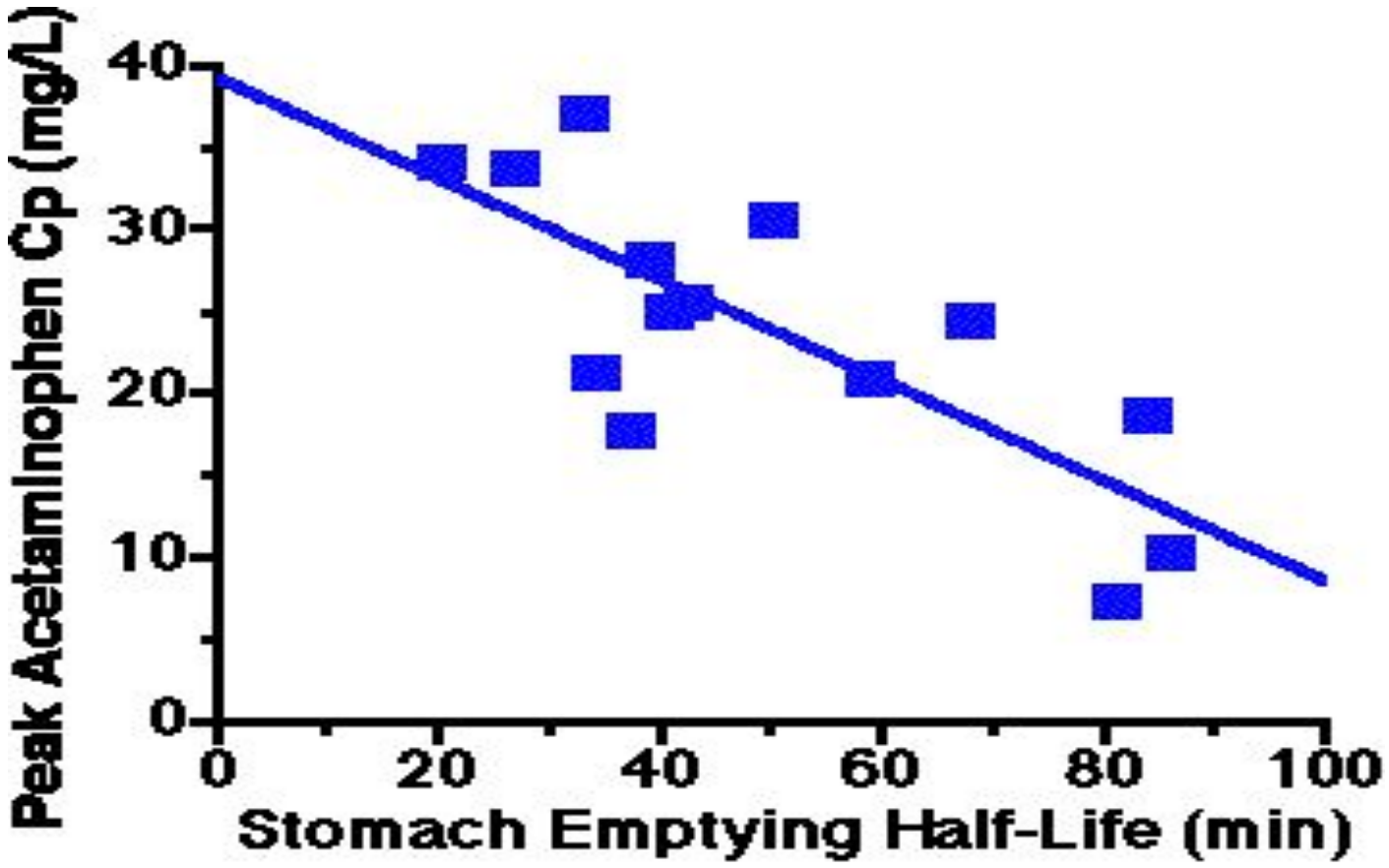
- Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption.
- For example, a good correlation has been found between stomach emptying time and peak plasma concentration for acetaminophen. The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration.
- Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.

هسا ال unstirred water layer هي طبقة راكدة مكونة من ال mucous وال water ممكن تعمل complex مع ال tetracycline وتقلل ال absorption لالو .

gastric emptying Time :

كل ما قعد الدواء بالمعدة أكثر كل ما كان ال gastric emptying rate أقل ال absorption أقل يعني العلاقة عكسية بينهم

II Gastric emptying and motility



Dependence of peak acetaminophen plasma concentration as a function of stomach emptying half-life

II Gastric emptying and motility

Factors Affecting Gastric Emptying

Volume of Ingested Material	As volume increases initially an increase then a dcrease. Bulky material tends to empty more slowly than liquids
Type of Meal	
Fatty food	Decrease
Carbohydrate	Decrease
Temperature of Food	Increase in temperature, increase in empyting rate
Body Position	Lying on the left side decreases emptying rate. Standing versus lying (delayed)
Drugs	
Anticholinergics (e.g. atropine)	Decrease
Narcotic (e.g. morphine)	Decrease
Analgesic (e.g. aspirin)	Decrease

II Gastric emptying and motility

Factors Affecting Gastric Emptying

Viscosity	Rate of emptying is greater for less viscous solutions
Emotional states	- Stressful emotional states increase stomach contraction and emptying rate - Depression reduces stomach contraction and emptying
Disease states	-Rate of emptying is reduced in: Some diabetic patients, hypothyrodism -Rate of emptying is increased in: hyperthyrodism
Excercise	Reduce emptying rate

الأكل ممكن يأثر على ال absorption فممكن يعمل
complex متل ال tetracycline مع ال calcium وال
iron وممكن يقلل ال PH وبالتالي رح يقلل ال absorption
للأدوية اللي بتحتاج وسط حمضي أو واحد متناول Fat بدها
وقت هضم أكبر ال emptying time أكثر ووصوله لل
plasma أقل وال onset of time يكون قليل وممكن يأثر
على ال the secreation of intestine.

هسا ال viscosity ممكن تأثر على emptying rate وبعض الأكل ممكن يأثر على ال metabolism فمثلا في بعض الأكلات بتعمل induction وبالتالي بتحفز الإنزيمات إنها تعمل metabolism وبالتالي رح يقل ال absorption وال bioavailability وبعض الأكلات بتعمل inhibition متل Grapefruit اللي بعمل inhibition ل CYP3A إحدى Cytochrome P450 substrate فبقلل ال metabolism وبزيد ال absorption وبالتالي بزيد ال bioavailability.

ليش الواحد بعد الأكل بحس حالو مصدع لإنو كل ال blood بروح GIT وبالتالي كل ما كانت كمية الدم اللي زاصلة كبير كل ما وصل لل liver كمية دم أكتر كل ما saturation أعلى فبتضل الكية الباقية اللي ما ارتبطت بال substrate بالدم وبالتالي ال absorption عالي وال bioavailability عالية

III Effect of Food

- The presence of food in the GIT can influence the rate and extent of absorption, either directly or indirectly via a range of mechanisms.

A- Complexation of drugs with components in the diet

e.g.Tetracycline forms non-absorable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies, at the same time of day as the tetracycline.

B- Alteration of pH

Food tends to increase stomach pH by acting as a buffer. This liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one.

III Effect of Food

C- Alteration of gastric emptying

Fats and some drugs tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

D- Stimulation of gastrointestinal secretions

- Gastrointestinal secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence a reduction in their bioavailability.
- Fats stimulate the secretion of bile. Bile salts are surface active agents which increase the dissolution of poorly soluble drugs (griseofulvin).

  Bile salts can form insoluble and non-absorbable complexes with some drugs, such as neomycin and kanamycin.

III Effect of Food

E-Competition between food components and drugs for specialized absorption mechanisms

There is a possibility of competitive inhibition of drug absorption in case of drugs that have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist.

F- Increased viscosity of gastrointestinal contents

The presence of food in the GIT provides a viscous environment which may result in:

- Reduction in the rate of drug dissolution
- Reduction in the rate of diffusion of drug in solution from the lumen to the absorbing membrane lining the GIT.

Hence, there is reduction in drug bioavailability.

III Effect of Food

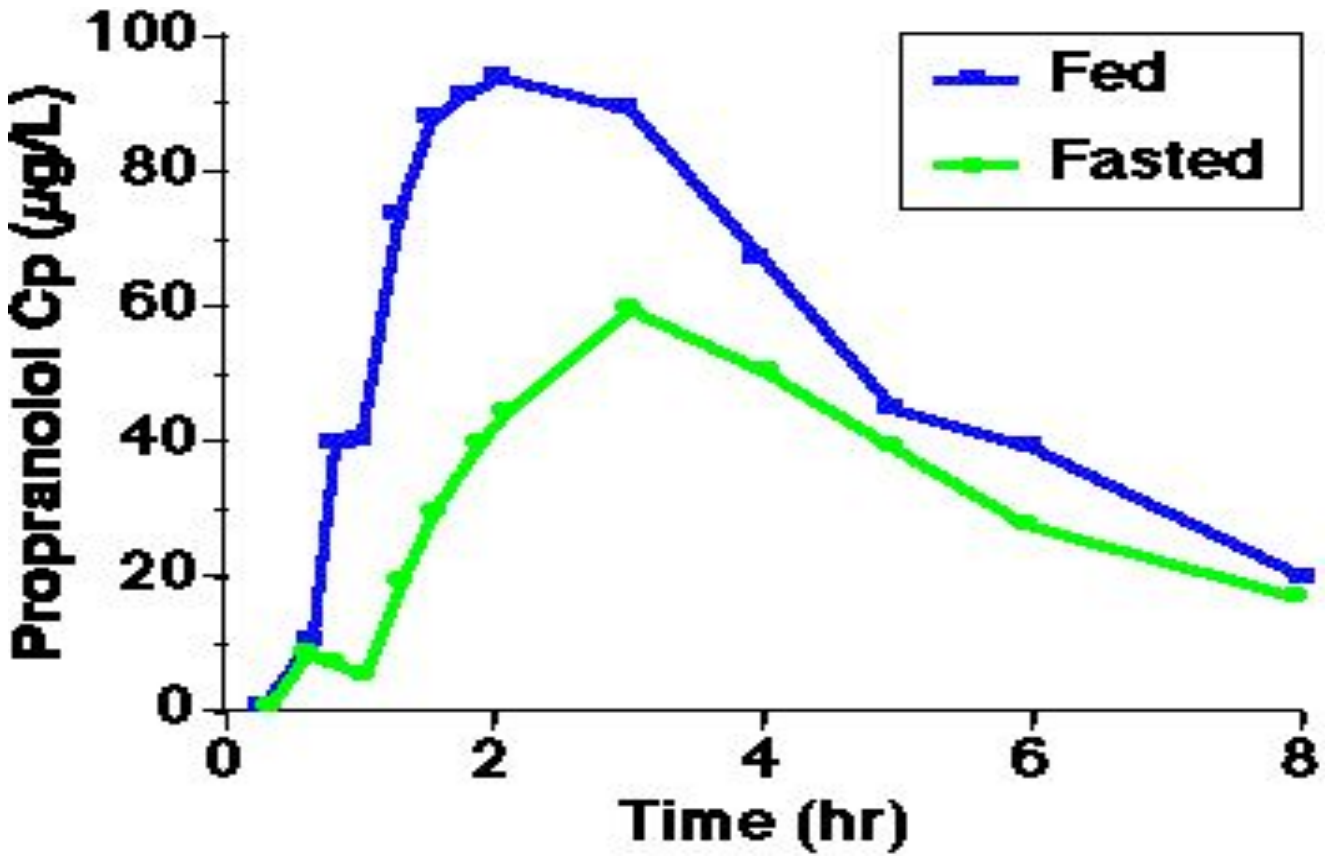
G- Food-induced changes in presystemic metabolism

- Certain foods may increase the bioavailability of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.
- E.g. Grapefruit juice is capable of inhibiting the intestinal cytochrome P450 (CYP3A) and thus taken with drugs that are susceptible to CYP3A metabolism which result in increase of their bioavailability.

H- Food-induced changes in blood flow

- Food serve to increase the bioavailability of some drugs (e.g. propranolol) that are susceptible to first-pass metaolism.
- Blood flow to the GIT and liver increases after a meal. The faster the rate of drug presentation to the liver; the larger the fraction of drug that escapes first-pass metabolism. This is because the enzyme systems become saturated.

III Effect of Food



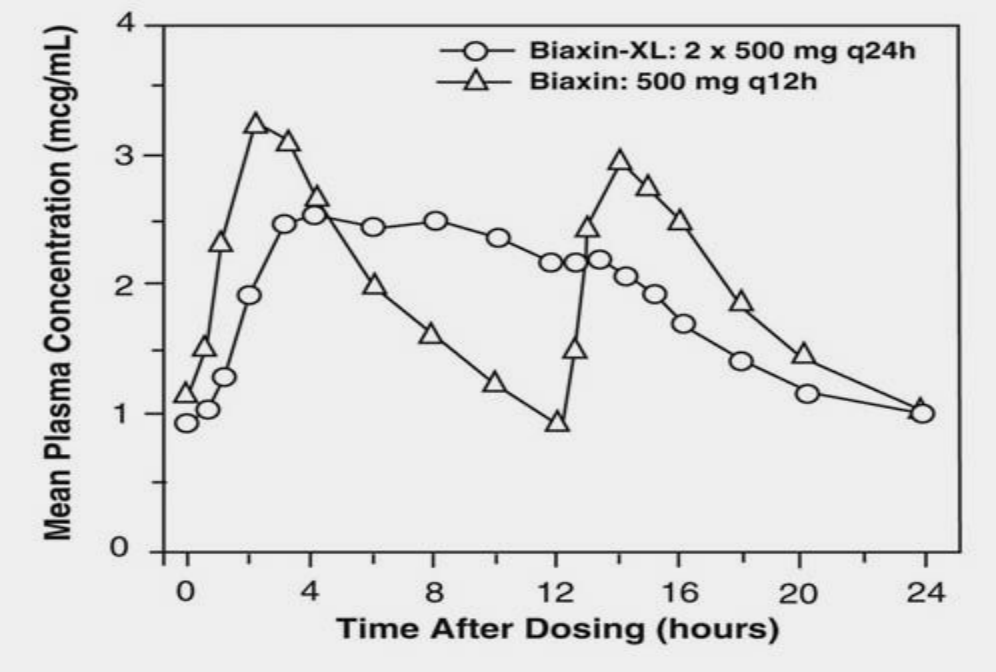
Effect of Fasting *versus* Fed on Propranolol Concentrations

Double peak phenomena

- Some drugs such as cimetidine and ranitidine, after oral administration produce a blood concentration curve consisting of two peaks.

- The presence of double peaks has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic cycle or failure of a tablet dosage form.

أكبس على الصح لحتى يطلع التفريغ



Presystemic metabolism

Definition:

The metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation.

Gut wall metabolism

- This effect is known as first-pass metabolism by the intestine.
- Cytochrome P450 enzyme, CYP3A, that is present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme e.g. cyclosporin.

Presystemic metabolism

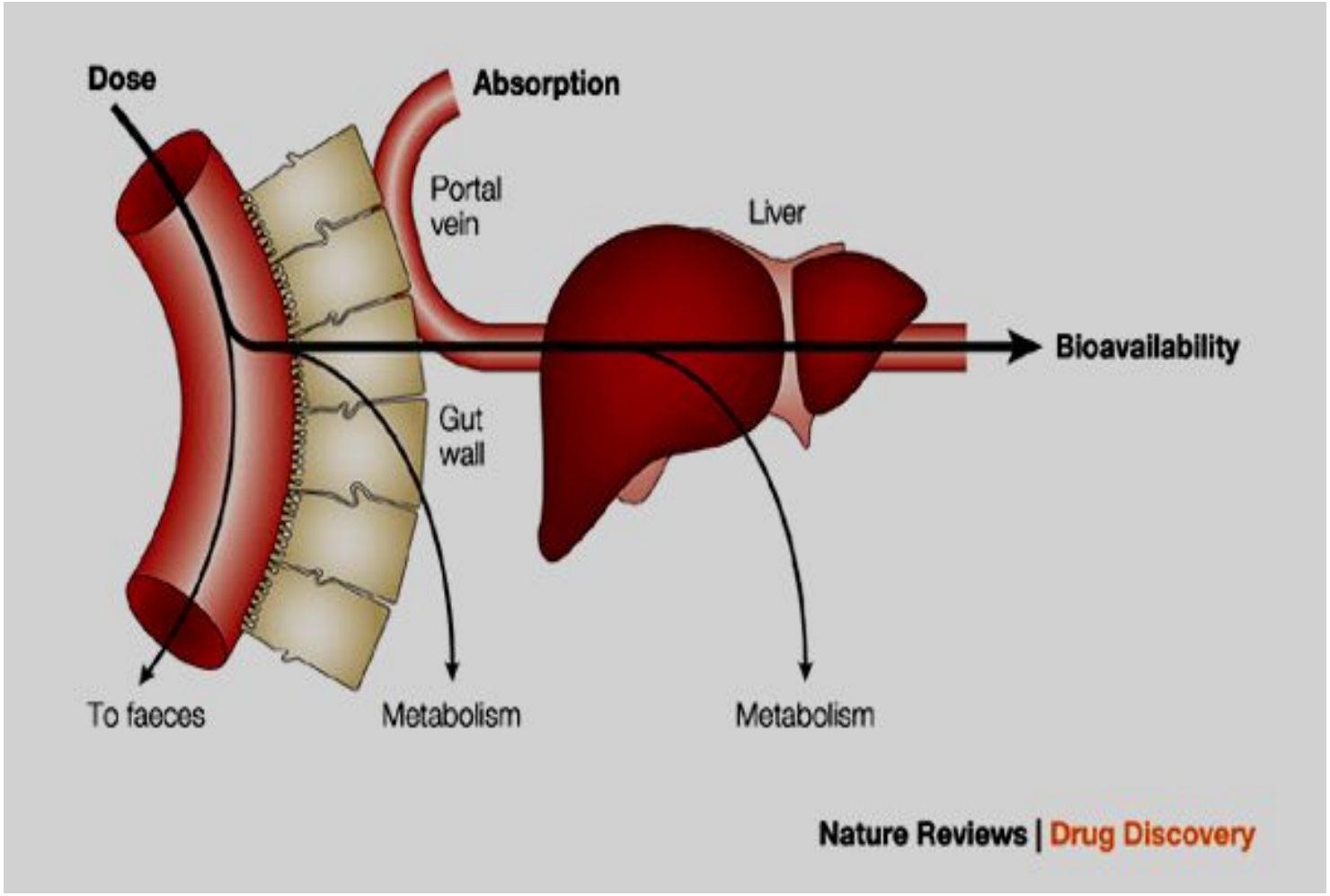
Hepatic metabolism

- After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body.

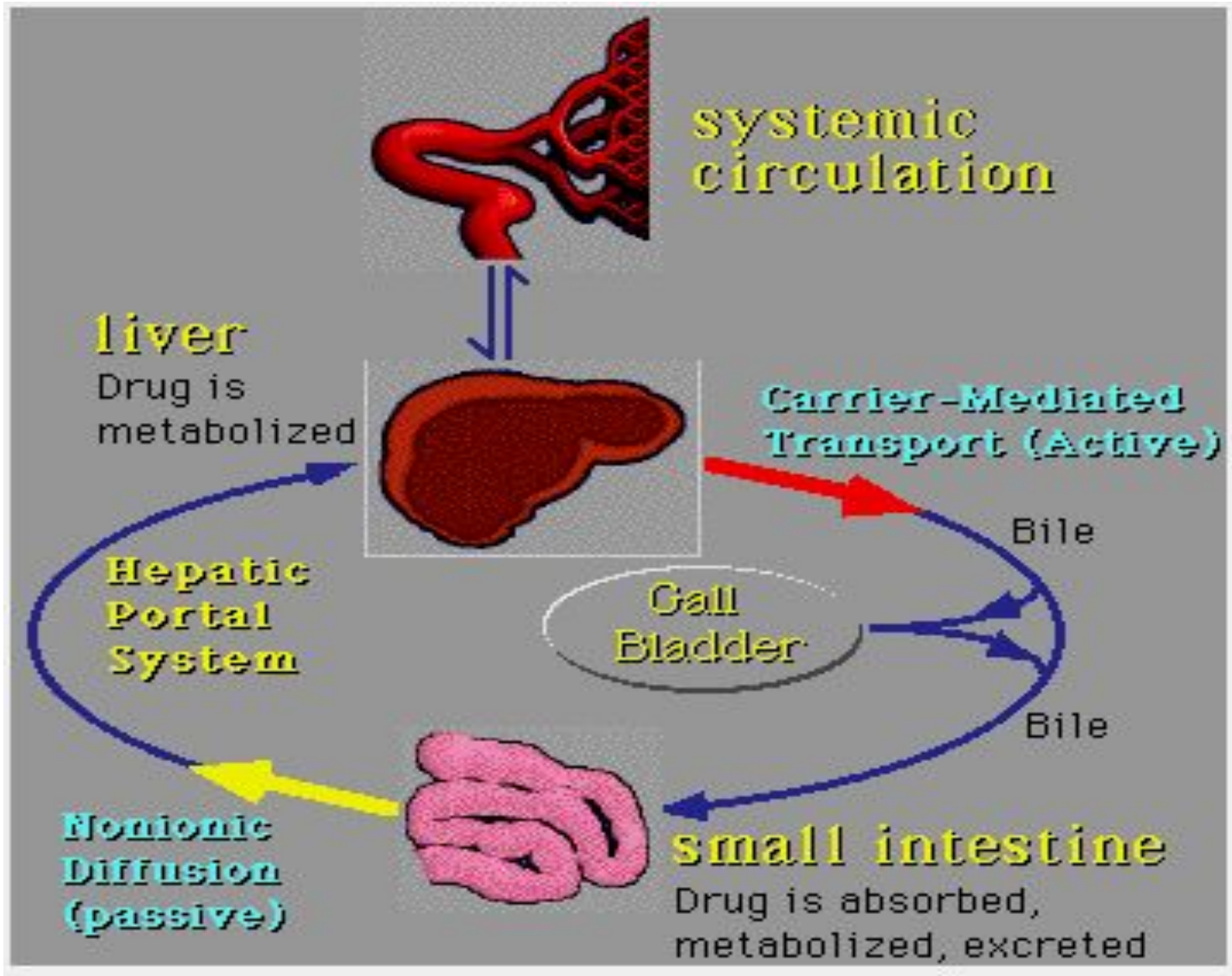
- The liver metabolizes many drugs (e.g. propranolol), sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system.

- This *first pass* through the liver thus greatly reduces the bioavailability of the drug.

Presystemic metabolism



Hepatic metabolism



II **Physical-Chemical Factors Affecting Oral Absorption**

Physical-chemical factors affecting oral absorption include:

A- pH-partition theory

B- Lipid solubility of drugs

C- Dissolution and pH

D- Drug stability and hydrolysis in GIT

E- Complexation

F- Adsorption

A. pH - Partition Theory

- 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.

هسا ال membrane هو المسؤول عن العبور بسمح بمرور ال lipid soluble مش ال water soluble وهو اللي بحدد كمية ال absorption .

وحكينا كمان عن ionization وبهمنا انو يكون الدواء nonionized حتى يدخل ال membrane لانو ال nonionized بتمثل ال lipid soluble اما ال ionized بتمثل ال water soluble فبالتالي كل ما كان non ionized كل ما كان ال absorption الو اعلى .

في أكتر من عامل بعتمد عليهم الدواء حتى يصير ألهم absorption
وهما disassociation وال soulble وال PH هسا soluble تعني
ال ionized فبالتالي فبهمني يكون الدواء ionized حتى يكون
soluble وبهمني يكون nonionized حتى يصير الو absorption
حتى يكون soluble بدو يتحول من nonionized ل ionized
حتى يصير soluble والعكس اذا بدي أدخلو عن طريق ال
membrane وبالدم لازم يكون بال ionized form حتى يكوب
بالدم .

A. pH - Partition Theory

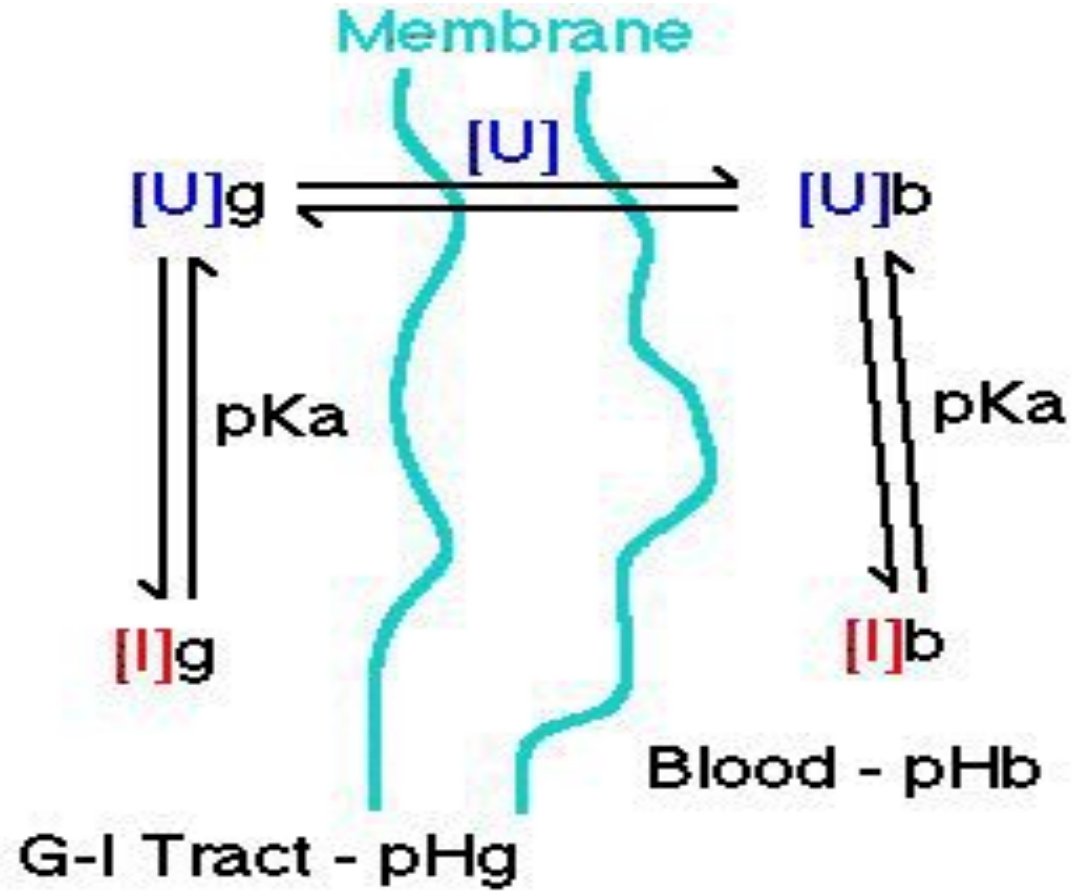


Diagram Showing Transfer Across Membrane

A. pH - Partition Theory

- The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using ***Henderson - Hasselbalch equation.***

**** Weak acids (e.g. aspirin):**

$$HA \rightleftarrows H^+ + A^-$$

$$Ka = \frac{a_{H^+} \bullet a_{A^-}}{a_{HA}} \approx \frac{[H^+] \bullet [A^-]}{[HA]}$$

Dissociation Constant equation - Weak Acids

taking the negative log of both sides

حتى الدواء يصير إلو absorption لازم يكون nonionized فبالتالي لازم يكون في عندي H كتير لحتى ترتبط مع ionized وبصير nonionized وبكون ال absorption عالي .

نيجي على ال acid كل ما كان ال pka قليل رح تكون strong acid وال absorption قليل لانو رح يكون ionized.

نبجي لل base كل ما ال pka قليلة رح تكون weak base كل ما كان ال absorption عالي .

هسا بال weak acid بترتبط ال H بال stomach فال absorption بكون عالي لل weak base لكن هاد الحكي مش مطلق لأنو بعض ال weak acid بصير الها absorption بال intestine لانو ال transit time عالي وبالتالي بعطي absorption أكتر داخل ال intestine في ال epithelial layer فيها بكون ال PH قليل فهناك بتحول لل non ionized.

A. pH - Partition Theory

$$-logKa = -log[H^+] - log\frac{[A^-]}{[HA]}$$

Rearranging gives the following equation:

$$pKa - pH = log\frac{[U]}{[I]} = log\frac{[HA]}{[A^-]}$$

Henderson - Hasselbalch Equation - Weak Acids

A. pH - Partition Theory

Weak Bases:

$$pKa - pH = log\frac{[I]}{[U]} = log\frac{[HB^+]}{[B]}$$

Henderson - Hasselbalch Equation - Weak Bases

Limitations of the pH-partition hypothesis:

-Despite their high degree of ionization, 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.

A. pH - Partition Theory

3- A 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

- 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.

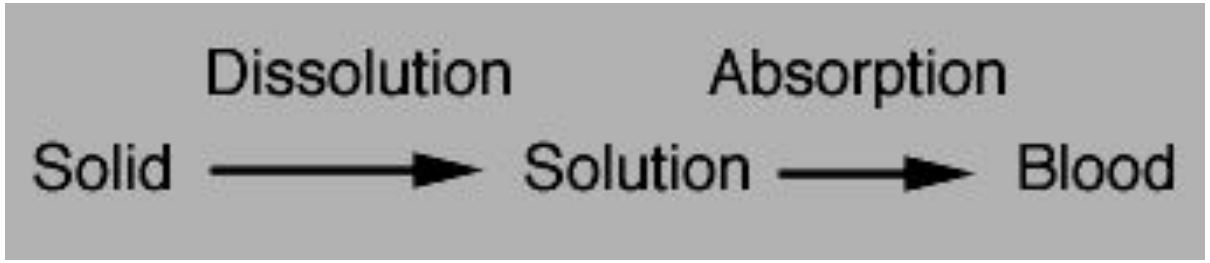
[W] conc is the concentration of the drug in aqueous phase.

- The higher p value, the more absorption is observed.

هسا بهمنا يكون الدواء يكون lipid soluble حتى يسهل
نوضوع الإمتصاص لكن إذا كان lipid كيف بدو يدوب بالدم
والGIT فعشان هيك لازم يكون الدواء lipid soluble و
water soluble فعندي نسبة بتحدد هاد الاشي هي ال
partition coefficient وكل ما زاد بكون الدواء lipophilic
وبالتالي ال absorption عالي الو بس ليش بكون بعض
الادوية lipid soluble لكن ما بتدوب لانو حجمو بكون كبير

C. Drug Dissolution

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



- 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.

هسا أنا بهمني الدواء ما يضل solid فلازم يصير إله degradation بعدها
dissolution بعدها absorption فعشان هيك بنسمي ال dissolution ال
rate limiting step فهو خطوة بتحدد كمية ال absorption....

C. Drug Dissolution

- Drug dissolution is considered to be diffusion controlled process through a stagnant layer surrounding each solid particle.

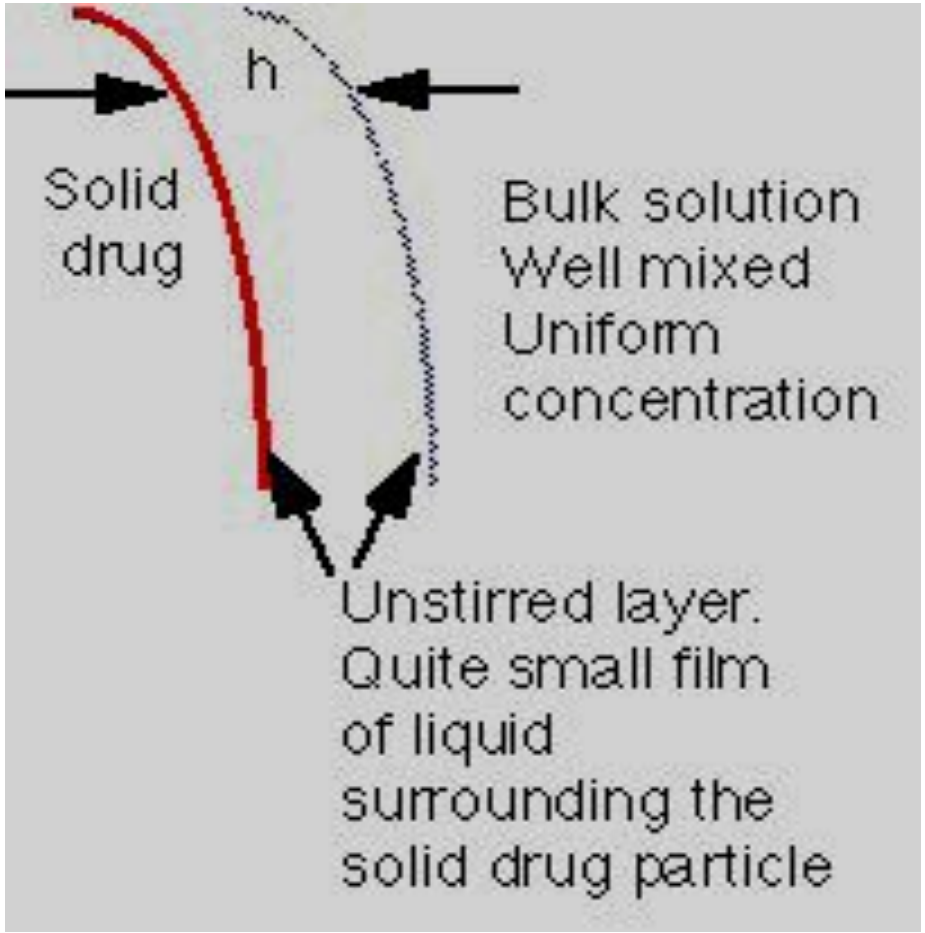


Diagram Representing Diffusion Through the Stagnant Layer

C. Drug Dissolution

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

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

- 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, and 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:

- 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 → 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:

C. Drug Dissolution

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.

II Physicochemical factors affecting the dissolution rate of drugs:

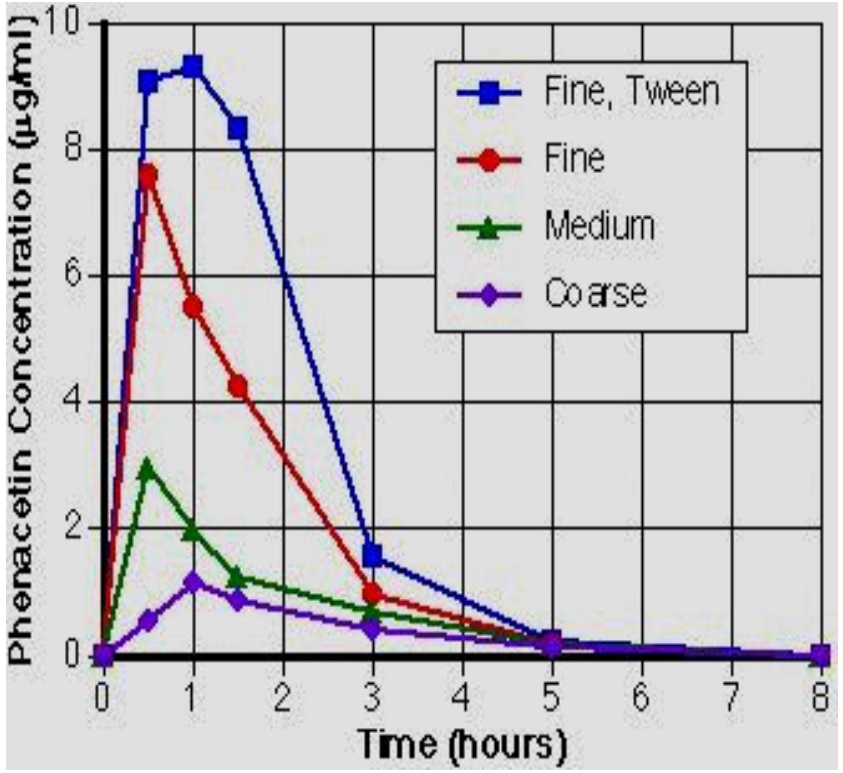
A- Surface area, A:

- The smaller the particle size → the greater the effective surface area of drug particle → the higher the dissolution rate.

C. Drug Dissolution

- *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.



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.

C. Drug Dissolution

D- Salts:

- **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.

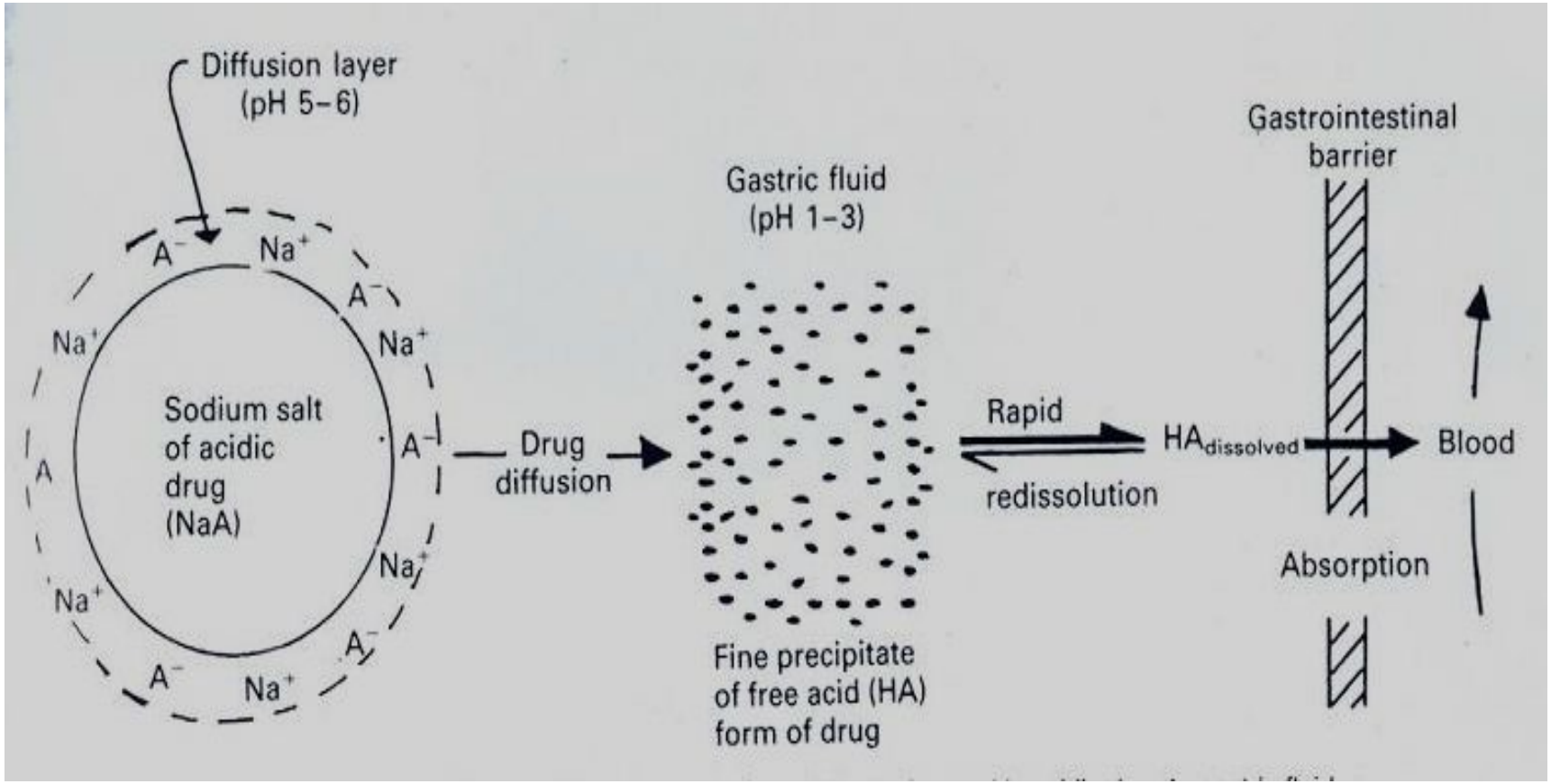
C. Drug Dissolution

- Thus the free acid form of the drug in solution, will precipitate out , leaving a saturated solution of free acid 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 redissolution when additional gastric fluid is available.

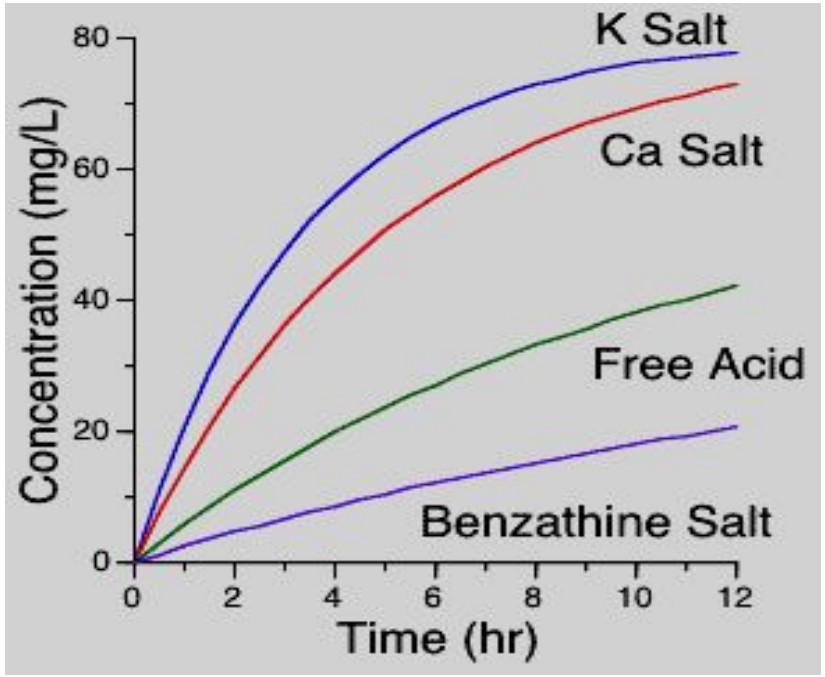
Drug Dissolution

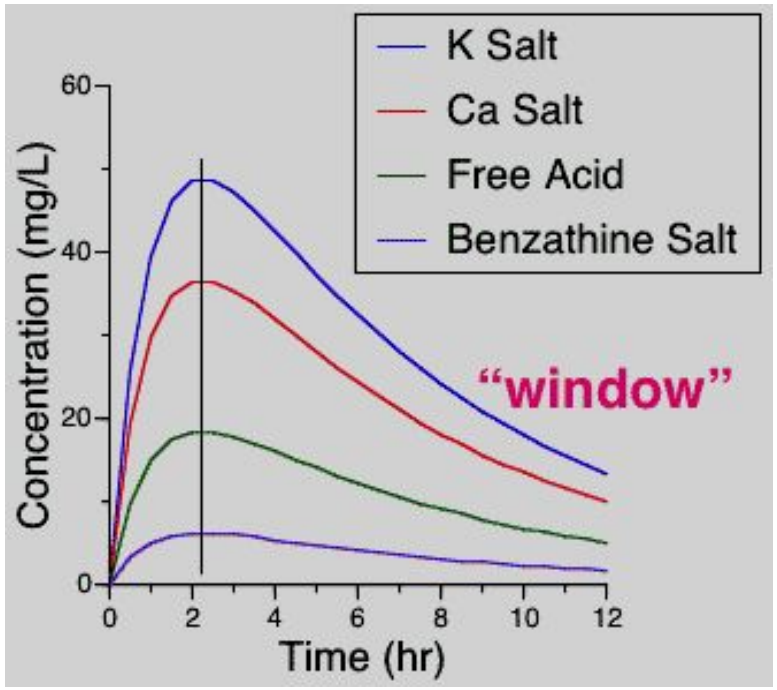


Dissolution process of a salt form of a weakly acidic drug in gastric fluid.

Drug Dissolution

- One example 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.

Drug Dissolution

E- Crystal form:

1- Polymorphism:

- Some drugs exist in a number of crystal forms or polymorphs. These different forms may have different 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 polymorph (more soluble)

C → is the unstable polymorph

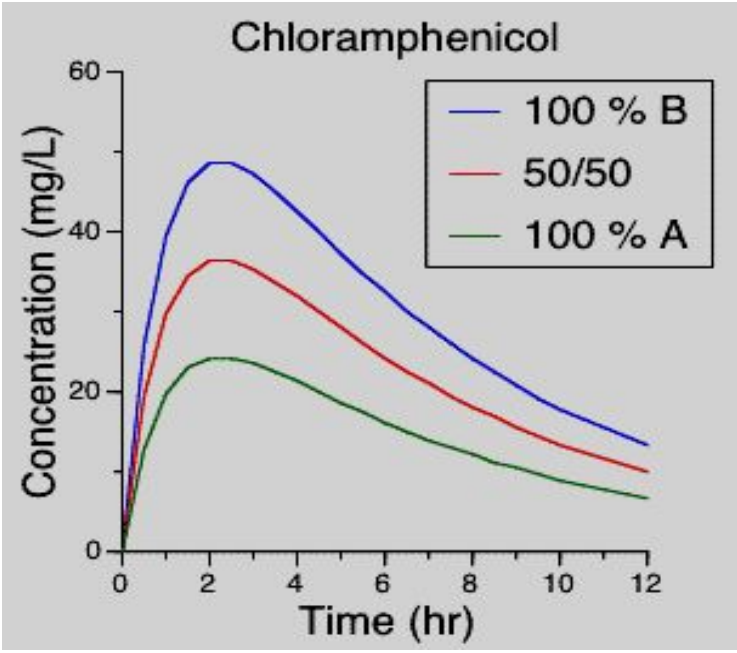
- The plasma profiles of chloramphenicol from oral suspensions containing different proportions of

Drug Dissolution

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).

Drug Dissolution

2- Amorphous solid:

- The amorphous form dissolves more rapidly than the corresponding crystalline form.

- 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.

Drug Dissolution

3- Solvates:

Solvates: If the drug is able to associate with solvent molecules to produce crystalline forms known as solvates.

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.

Drug Dissolution

- 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.

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 ??

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.

هسا ال stability بعض الادوية ما رح تتحمل ال acidity الموجودة داخل المعدة.
فبالتالي رح يقلل كمية الادوية اللي رح توصل داخل ال intestine وبالتالي رح يقل ال absorption.

متل ال erythromycin ما بتحمل حموضة المعدة فبعملو enteric coating لالو يعني بغلفو باشي يتحمل ال acidityأو ممكن يعطو دواء يخفض الجموضة بعدهاةيعطو ال erythromycin.

E- Complexation

- Complexation of a drug may occur within the dosage form and/or in the gastrointestinal fluids, and can be benefecial or deterimental 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)

لما يتحد الدواء مع أي اشي بكون complex ممكن يكون مفيد وممكن يكون لا
ويقلل ال absorption الأدوية اللي بتكون lipid بضيف الها water soluble
material وبزيد ال solubility داخل ال GIT وال Blood ..
او متل ال calcium وال tetracycline بقلل ال absorption لالو .

F- Adsorption

- Certain insoluble susbstances may adsorbed co-administrated drugs leading to poor absorption.

- Charcoal (antidote in drug intoxication).
- Kaolin (antidiarrhoeal mixtures)
- Talc (in tablets as glidant)

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.

- Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

A. Solution dosage forms:

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

III Formulation Factors Affecting Oral Absorption

- 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

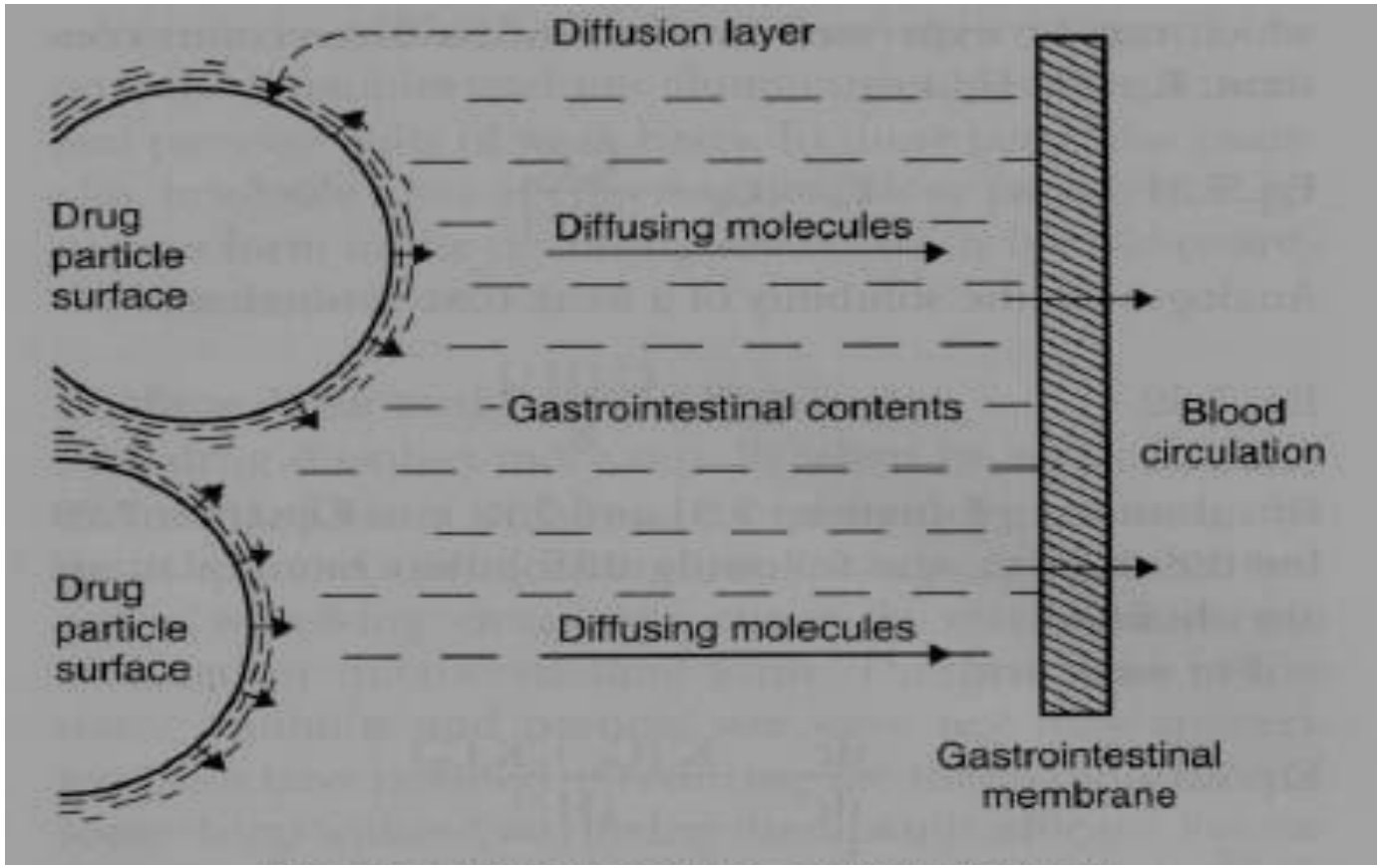
B. Suspension dosage forms:

- 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 will improve the absorption of very fine particle size suspensions.

III Formulation Factors Affecting Oral Absorption



Absorption of drugs from aqueous suspensions

III Formulation Factors Affecting Oral Absorption

C. Capsule dosage forms:

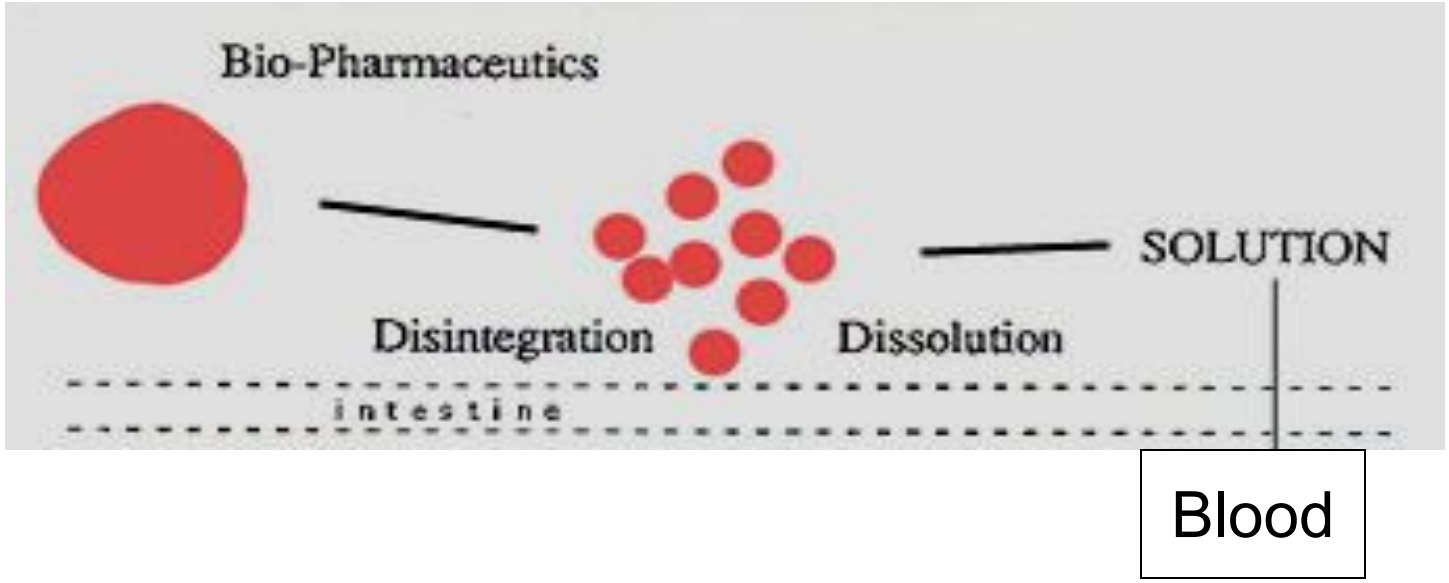
- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.

- 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 and bioavailability.

III Formulation Factors Affecting Oral Absorption

D. Tablet dosage forms:



III Formulation Factors Affecting Oral Absorption

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

1-Ingredients

Drug : may be poorly soluble, hydrophobic

Lubricant : usually quite hydrophobic

Granulating agent : tends to stick the ingredients together

Filler: may interact with the drug, etc., should be water soluble

Wetting agent: helps the penetration of water into the tablet

Disintegration agent: helps to break the tablet apart