FACTORS AFFECTING DRUG ABSORPTION

List of content :--

(3) Age

[B] CLINICAL FACTORS

- **STUDY QUESTIONS**
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Introduction

- **Definitions**

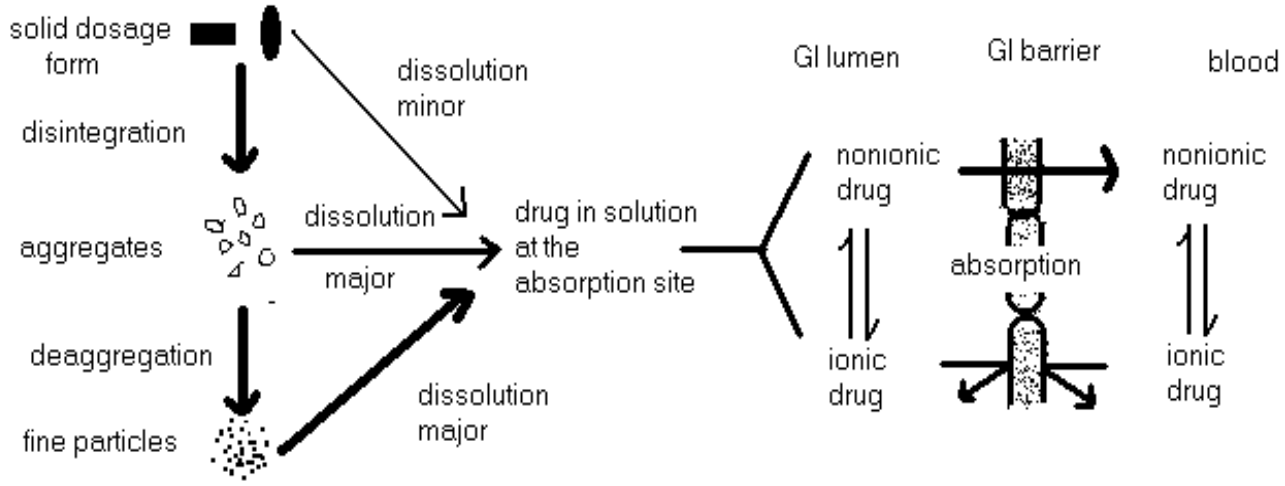
Pharmacokinetics

- Evaluate the way in which a drug interacts with various barriers within a biological system

Pharmacodynamics

- Study of the relationship between systemic exposure of a drug and it's biological effects on tissue

- **Absorption** can be defined as the movement of active drug (or prodrug) from the site of administration across biologic barriers into a site where it is measured in the **blood.** This site of measurement is not specified.
- **Bioavailability** can be defined as the fraction of administered drug that reaches the **systemic circulation**
- Note the difference in endpoint measurement sites



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

FACTORS INFLUENCING GI ABSORPTION OF A DRUG FROM IT'S DOSAGE FORM

I PHARMACEUTICAL FACTORS:

It include factors relating to the-

[A] Chemical Factors

- A variety of chemical options can be used to improve the stability and systemic availability of drugs.
- For example, esters can be prepared of both acids and bases to produce more stable derivatives, which hydrolyse to the active parent once absorbed. The stability and solubility of both acids and bases tend to increase when they are in the form of salts.

- Typically, administration of soluble salts of penicillin give rise to higher circulating antibiotic levels than the free acid. When the salt of a weak acid dissolves in the stomach, it generates a diffusion layer of relatively high pH which,in turn, promotes further dissolution. The same argument could theoretically be used for basic drugs.
- However, the pH effect in this case is swamped by the very low pH present in stomach fluids.
- Thus, salts of basic drugs are used primarily for handling and solubility rather than for improved dissolution.

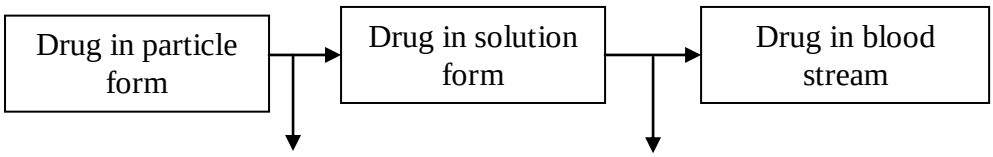
B] Physicochemical properties of drug substances

1.Drug solubility and dissolution rate –

- The rate determining steps in absorption of orally administered drugs are**:**

II.Rate of dissolution

III.Rate of drug permeation through the biomembrane.



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

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

- Imp prerequisite for the absorption of a drug is that it must be present in aq solution & this is depends on drug's aq solubility &its dissolution rate.

2. Particle size and effective surface area –

- Smaller the particle size (by micronization) → greater is the effective surface area → more intimate contact b/w solid surface and aq solvent → higher is the dissolution rate → increase in absorption efficiency
- e.g. poorly aq soluble nonhydrophobic drugs like Griseofulvin, chloramphenicol whose dissolution is rate limited.
- Particle size reduction has been used to increase the absorption of a large number of poorly soluble drugs, such as bishydroxycoumarin, digoxin, griseofulvin, nitrofurantoin,and tolbutamide.

- Griseofulvin has extremely low aqueous solubility, and material of normal particle size gave rise to poor and erratic absorption.
- Microsize particles improve absorption, but it is improved even more when it is formulated in ultramicrosize particles as a monomolecular dispersion in polyethylene glycol.

3. Polymorphism and amorphism –

- When sub exist in different crystalline form i.e. in polymorphic form then diff forms are Many compounds form crystals with different molecular arrangements, or polymorphs. These polymorphs may have different physical properties, such as dissolution rate and solubility.

Stable form	Metastable form
- Lowest energy state - Highest m.pt. - Least aq solubility - Dissolution rate limited	- Less stable form - Highest energy state - Lowest m.pt. - Higher aq solubility - Better absorption and Bioavailability

- e.g The vitamin riboflavin exists in several polymorphic forms, and these have a 20-fold range in aqueous solubility.
- Polymorphs that have no crystal structure, or amorphic forms, have different physical properties from the crystalline forms.
- Absorption of many orally administered drugs is controlled by dissolution rate.
- Amorphous forms generally dissolve faster than crystalline forms because no energy is needed to break up the crystal lattice. For this reason, the amorphous form is often preferred over the crystalline form and several drugs, including hydrocortisone and prednisolone, are marketed in the amorphic form.
- E.g. novobiocin

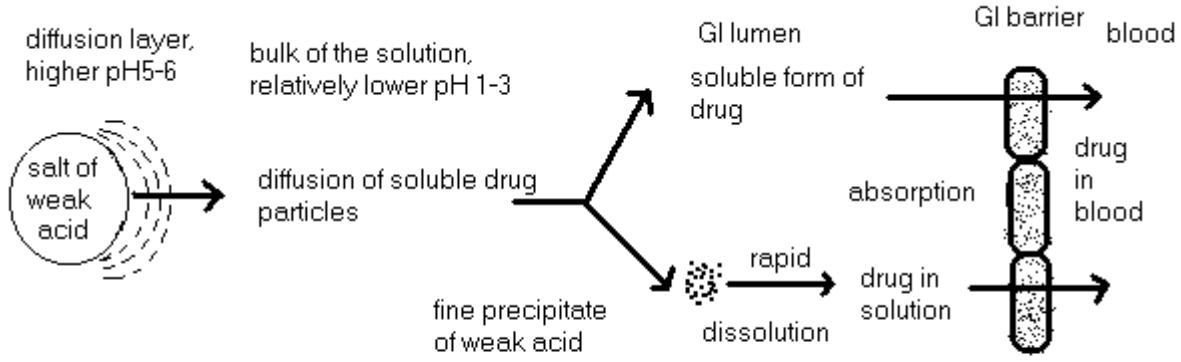
Amorphous form	Crystalline form
→ More soluble → Rapidly dissolving → Readily absorbed	→ Less soluble → Slower dissolving → Not absorbed to significant extent

4. Solvates/hydrates –

- During their preparation, drug crystals may incorporate one or more solvent molecules to form solvates.
- The most common solvate is water. If water molecules are already present in a crystal structure, the tendency of the crystal to attract additional water to initiate the dissolution process is reduced, and solvated (hydrated) crystals tend to dissolve more slowly than anhydrous forms.
- Significant differences have been reported in the dissolution rate of hydrated and anhydrous forms of ampicillin, caffeine, theophylline, glutethimide, and mercaptopurine
- The clinical significance of these differences has not been examined but is likely to be slight.
- Solvates have greater solubility than their nonsolvates.e.g. chloroform solvates of Griseofulvin, n-pentanol solvate of fludrocortisone.

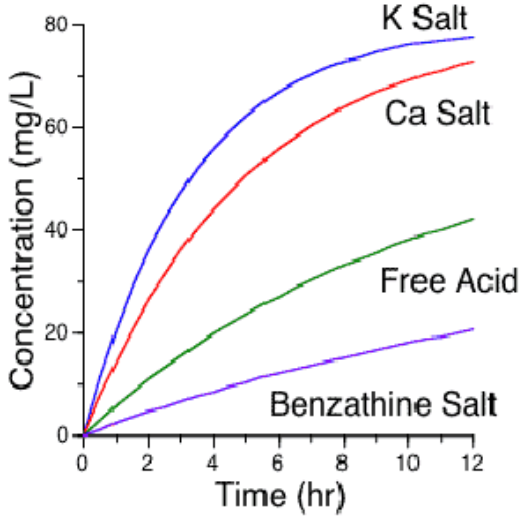
5. Salt form of drug: --

- 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 imp 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.

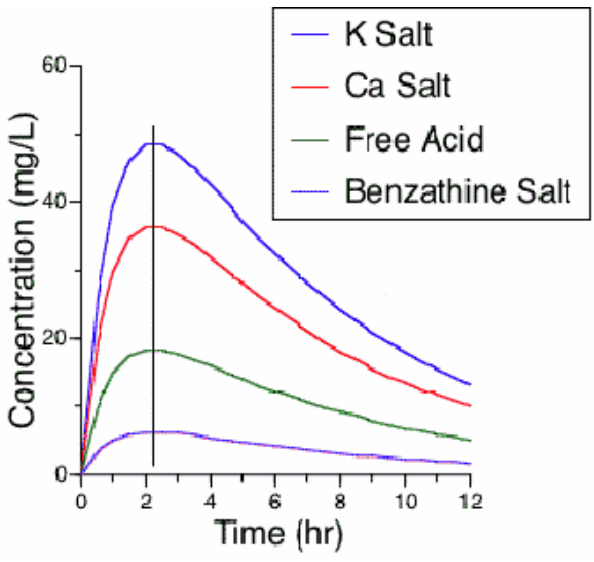


dissolution &absorption of an acidic drug administered in a salt from

- Reverse in the case of salts of weak bases, it lowers the pH of diffusion layer and the promoted the absorption of basic drugs.
- Other approach to enhance the dissolution and absorption rate of certain drugs is by formation of in – situ salt formation i.e. increasing in pH of microenvironment of drug by incorporating buffer agent.e.g. aspirin, penicillin
- But sometimes more soluble salt form of drug may result in poor absorption.e.g. sodium salt of phenobarbitone and phenobarbitone, tablet of salt of phenobarbitone swelled, it did not get disintegrate thus dissolved slowly and results in poor absorption.



A) It shows the dissolution Profile of various salts



B) It shows the Penicillin plasma Conc. in fasting subjects, after oral Administration of 4×10^5 units of Penicillin in different forms.

- Dissolution profile of various salts, where A) shows that potassium salt has the highest solubility B) shows the dissolution profile of various penicillin salts.

6. Ionization state :-

➔ Unionized state is imp for passive diffusion through membrane so imp for absorption.

➔ Ionized state is imp for solubility.

7. Drug pKa & lipophilicity & GI pH --- pH partition hypothesis: --

➔ pH – partition theory states that for drug compounds of molecular weight more than 100, which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by

- pKa of drug
- The lipid solubility of the unionized drug
- pH at the absorption site.

a) pKa of drug

➔ Amount of drug that exist in unionized form and in ionized form is a function of pKa of drug & pH of the fluid at the absorption site and it can be determined by Henderson-hesselbach equation: -

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

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

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

b) Lipophilicity and drug absorption: -

- Ideally for optimum absorption, a drug should have sufficient aq solubility to dissolve in fluids at absorption site and lipid solubility (Ko/w) high enough to facilitate the partitioning of the rug in the lipoidal biomembrane i.e. drug should have perfect HLB for optimum Bioavailability.

- And $\frac{\text{Ko/w = Distribution of drug in organic phase (octanol)}}{\text{Distribution of drug in aq phase}}$
- As Ko/w i.e. lipid solubility i.e. partition coefficient increases percentage drug absorbed increases.

[C] Formulation Factors:-

1. **Disintegration time: -**

- Rapid disintegration is important to have a rapid absorption so lower D.T is required.
- Now D.T of tablet is directly proportional to –amount o f binder
  -Compression force.
- And one thing should be remembered that in vitro disintegration test gives no means of a guarantee of drugs B.A. because if the disintegrated drug particles do not dissolve then absorption is not possible.

2. **Manufacturing variables: -**

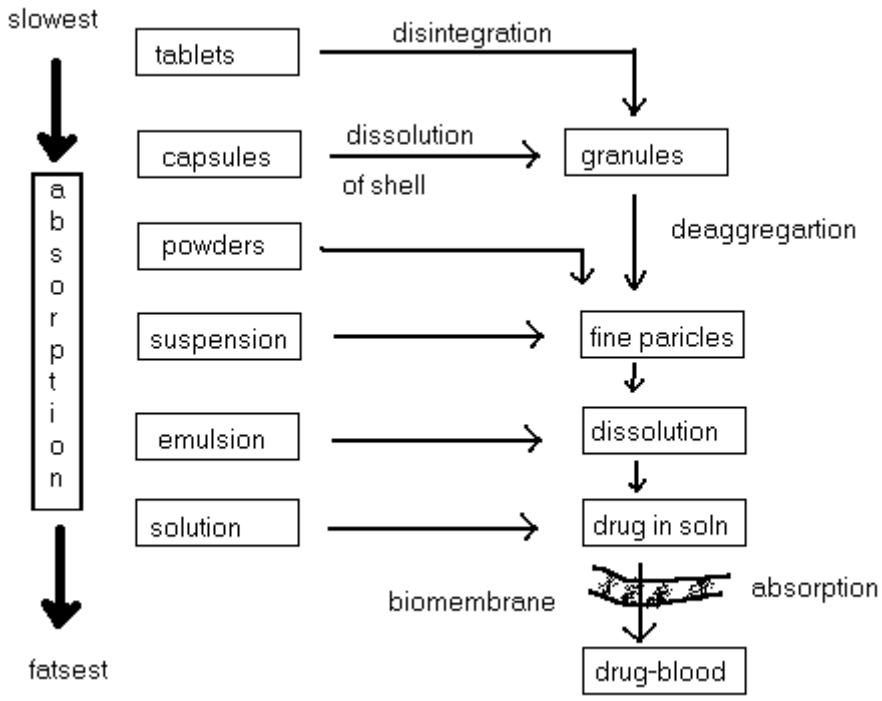
a). Method of granulation

- Wet granulation yields a tablet that dissolves faster than those made by other granulating methods. But wet granulation has several limitations like formation of crystal bridge or chemical degradation.
- Other superior recent method named APOC (agglomerative phase of communition) that involves grinding of drug till spontaneous agglomeration and granules are prepared with higher surface area. So tablet made up of this granules have higher dissolution rate.

b) Compression force: -

- Higher compression force yields a tablet with greater hardness and reduced wettability & hence have a long D.T. but on other hand higher compression force cause crushing of drug particles into smaller ones with higher effective surface area which in decrease in D.T.
- So effect of compression force should be thoroughly studied on each formulation.

3. **Nature and type of dosage form –**



Drug formulations are designed to provide an attractive, stable, and convenient method to use products. Conventional dosage forms may be broadly characterized in order of decreasing dissolution rate as solutions, solid solutions, suspensions, capsules and tablets, coated capsules and tablets, and controlled release formulations.

A.Solutions

- Aqueous solutions, syrups, elixirs, and emulsions do not present a dissolution problem and generally result in fast and often complete absorption as compared to solid dosage forms. Due to their generally good systemic availability, solutions are frequently used as bioavailability standards against which other dosage forms are compared.

B.Solid solutions

- The solid solution is a formulation in which drug is trapped as a solid solution or monomolecular dispersion in a water-soluble matrix. Although the solid solution is an attractive approach to increase drug absorption, only one drug, griseofulvin, is currently marketed in this form.

C.Suspensions

- A drug in a suspension is in solid form, but is finely divided and has a large surface area. Drug particles can diffuse readily between the stomach and small intestine so that absorption is relatively insensitive to stomach emptying rate.
- Adjusting the dose to a patient's needs is easier with solutions and suspensions than with solid dosage forms. Liquid dosage forms, therefore, have several practical advantages besides simple dissolution rate.
- However, they also have some disadvantages, including greater bulk, difficulty in handling, and perhaps reduced stability.

D.Capsules and tablets

- These formulations differ from each other in that material in capsules is less impacted than in compressed tablets. Once a capsule dissolves, the contents generally disperse quickly. The capsule material,
- Although water soluble, can impede drug dissolution by interacting with the drug, but this is uncommon.
- Tablets generally disintegrate in stages, first into granules and then into primary particles. As particle size decreases, dissolution rate increases due to of increased surface area.
- Tablet disintegration was once considered a sufficient criterion to predict in vivo absorption.

As a general rule,the bio-availability of a drug from various dosage forms decrease in the following order:Solutions>Emulsions>Suspensions>Capsules>Tablets>Coated Tablets>Enteric coateds Tablets>Sustained Release Products.

4. Pharmaceutical ingredients/Excipients: -

❖ More the no. of excepients in dosage form, more complex it is & greater the potential for absorption and Bioavailability problems.

❖ Changing an excipient from calcium sulfate to lactose and increasing the proportion of magnesium silicate, increases the activity of oral phenytoin.

❖ Systemic availability of thiamine and riboflavin is reduced by the presence of Fuller's earth.

❖ Absorption of tetracycline from capsules is reduced by calcium phosphate due to complexation.

❖ Most of these types of interactions were reported some time ago and are unlikely to occur in the current environment of rigorous testing of new dosage forms and formulations.

a) Vehicle-

- Rate of absorption – depends on its miscibility with biological fluid.
- Miscible vehicles (aq or water miscible vehicle) –rapid absorption e.g. propylene glycol.
- Immiscible vehicles - absorption –depends on its partitioning from oil phase to aq body fluid.

b) Diluents-

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

c) Binders & granulating agent -

- Hydrophilic binders – imparts hydrophilic properties to granule surface – better dissolution of poorly wettable drug. e.g. starch, gelatin, PVP.
- More amount of binder – increases hardness of tablet – decrease dissolution & disintegration rate.

d) Disintegrants -

- Mostly hydrophilic in nature.
- Decrease in amount of disintegrants – significantly lowers B.A.

e) Lubricants -

- Commonly hydrophobic in nature – therefore inhibits penetration of water into tablet and thus dissolution and disintegration.

f) Suspending agents/viscosity agent –

- Stabilized the solid drug particles and thus affect drug absorption.
- Macromolecular gum forms unabsorbable complex with drug e.g. Na CMC.
- Viscosity imparters – act as a mechanical barrier to diffusion of drug from its dosage form and retard GI transit of drug.

g) Surfactants –

- May enhance or retards drug absorption by interacting with drug or membrane or both.
- Surfactants have been considered as absorption enhancers, again mostly in animals. Polyoxyethylene ethers have been shown to enhance gastric or rectal absorption of lincomycin,penicillin, cephalosporins, and fosfomycin in rats and rabbits.
- However, in humans, oral polyoxyethylene-20-oleyl ether resulted in poor and variable insulin absorption.
- In general, unionic surfactants have little effect on membrane structure but cationic surfactants have been associated with reversible cell loss and loss of goblet cells.
- Physiologic surfactants – bile salts – promotes absorption – e.g. Griseofulvin, steroids
- It may decrease absorption when it forms the unabsorbable complex with drug above CMC.

h)Bile salts-

- Bile contains conjugates of cholic acid and chenodeoxycholic acid, which emulsify dietary fat, facilitate lipolysis, and transport lipid molecules through the unstirred layer of the intestinal mucosa by micellar solubilization. The ability of bile salts to promote lipid absorption has prompted their investigation as absorption enhancers for drugs, with modest success.
- Absorption of insulin can be increased by bile salts, both in experimental animals and in humans.

i) Colourants

- Even a low concentration of water soluble dye can have an inhibitory effect on dissolution rate of several crystalline drugs.
- The dye molecules get absorbed onto the crystal faces and inhibit the drug dissolution. For example: Brilliant blue retards dissolution of sulfathiazole.

5. <u>Product age and storage conditions –</u>

- Product aging and improper storage conditions adversely affect B.A.
- E.g. –precipitation of drug in solution
  particle size of suspension
  & Hardening of tablet → decrease rate of Change in drug dissolution & absorption.

II PATIENT RELATED FACTORS

Physiologic Factors Related to Drug Absorption:

The systemic absorption of a drug is dependent on

(1) the physicochemical properties of the drug,
(2) the nature of the drug product, and
(3) the anatomy and physiology of the drug absorption site.

1) Membrane Physiology

A) Nature of Cell Membrane

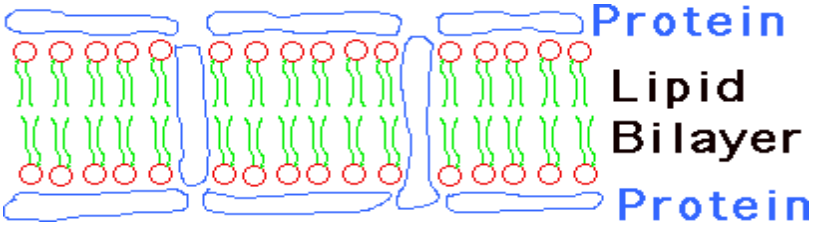


Fig 1.1 Cell Membrane Structure (Fluid Mosaic Model)

✓ The fluid mosaic model, proposed by , explains the transcellular diffusion of polar molecules.
✓ According to this model, the cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix ().
✓ These proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier.
✓ As shown in , transmembrane proteins are interdispersed throughout the membrane. Two types of pores of about 10 nm and 50 to 70 nm were inferred to be present in membranes based on capillary membrane transport studies (). These small pores provide a channel through which water, ions, and dissolved solutes such as urea may move across the membrane.

B) Trasport Processes

Passive Diffusion

- ✓ lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.
- ✓ *Passive diffusion* is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is *passive* because no external energy is expended.

Carrier-Mediated Transport

- ✓ Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.
- ✓ In the intestine, drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism. Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

Active Transport

- ✓ Active transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites.
- ✓ A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are absorbed from the gastrointestinal tract by this process. Active transport is characterized by the transport of drug against a concentration gradient—that is, from regions of low drug concentrations to regions of high concentrations.
- ✓ Therefore, this is an energy-consuming system. In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane

Vesicular Transport

- ✓ An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

Pore (Convective) Transport

- ✓ Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. Although such pores have never been directly observed by microscopy, the model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.

Ion-Pair Formation

✓ Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pK_a values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membranes poorly. When the ionized drug is linked up with an oppositely charged ion, an *ion pair* is formed in which the overall charge of the pair is neutral. This neutral drug complex diffuses more easily across the membrane.

✓ For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms ion pair with hexylsalicylate

2) Gstero-Intestinal Physiology

(A) Gastric emptying rate:-

➔ Anatomically, a swallowed drug rapidly reaches the stomach.

➔ Eventually, the stomach empties its contents into the small intestine. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time for the drug to reach the duodenum will slow the rate and possibly the extent of drug absorption, thereby prolonging the onset time for the drug.

➔ Some drugs, such as penicillin, are unstable in acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact.

➔ Gastric emptying rate is faster in case of solution & suspensions than solid & nondisintegrating dosage forms.

✘ Factors that influence gastric emptying rate are: -

a. Volume of meal
b. Composition of meal
c. Physical state and viscosity of meal
d. Temperature of meal
e. Gastrointestinal pH
f. Electrolyte and osmotic pressure
g. Body posture
h. Emotional state
i. Disease state.

(B) Intestinal motility: -

➔ Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells.

➔ The drug must have a sufficient time (*residence time*) at the absorption site for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

(C) Drug stability in GIT: -

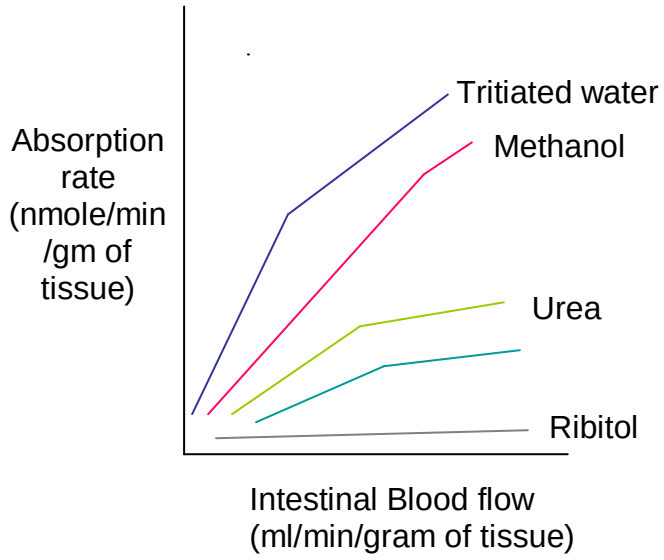
◈ Metabolism or degradation by enzymes or chemical hydrolysis may adversely affect the drug absorption and thus reduces B.A.
◈ Destruction in gastric acid.
◈ Generally a problem with orally administered drugs.

(D) Intestinal transit: -

◈ Long intestinal transit time is desirable for complete absorption of drug e.g. for enteric coated formulation & for drugs absorbed from specific sites in the intestine.
◈ Peristaltic contraction promotes drug absorption by increasing the drug membrane contact and by enhancing dissolution especially of poorly soluble drugs.
◈ Influenced by food, disease and drugs. e.g. metoclopramide which promotes intestinal transit &thus enhance absorption of rapidly soluble drugs while anticholinergic retards intestinal transit and promotes the absorption of poorly soluble drugs.

(E) Blood flow to GIT:

- Once the drug is absorbed from the small intestine, it enters via the mesenteric vessels to the hepatic-portal vein and the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of drug removal from the intestinal tract, thereby reducing the rate of drug bioavailability
- GIT has higher perfusion rate because it is extensively supplied by blood capillary network.
- Therefore help in maintaining sink conditions &concentration gradient for drug absorption by rapidly removing of drug from site of action.
- Blood flow is imp for actively absorption of drugs.
- Highly permeable drugs or drugs that absorbed through pores –GI perfusion is rate limiting while the drugs with poor permeability GI perfusion is not imp.
- Perfusion increases after meals & persist for few hours but absorption is not affected.



Graph representing the absorption rate of various drugs affected by intestinal blood flow.

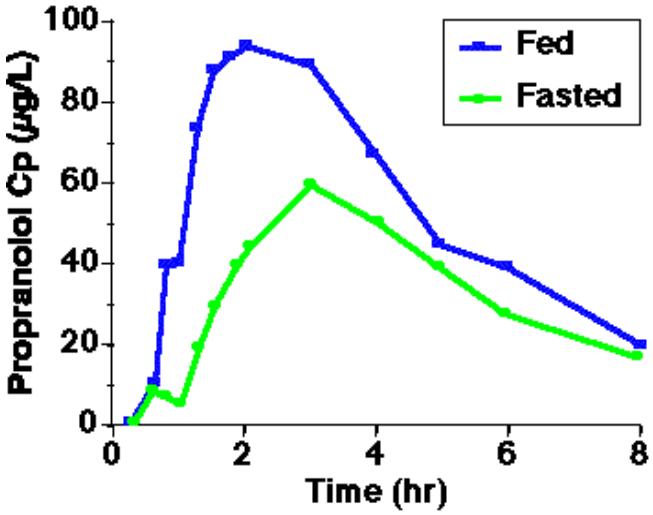
(F) Effect of Food

➢ The presence of food in the GI tract can affect the bioavailability of the drug from an oral drug product (). Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs. The effects of food are not always predictable and can have clinically significant consequences. Some effects of food on the bioavailability of a drug from a drug product include ():

- Delay in gastric emptying
- Stimulation of bile flow
- A change in the pH of the GI tract
- An increase in splanchnic blood flow
- A change luminal metabolism of the drug substance
- Physical or chemical interaction of the meal with the drug product or drug substance

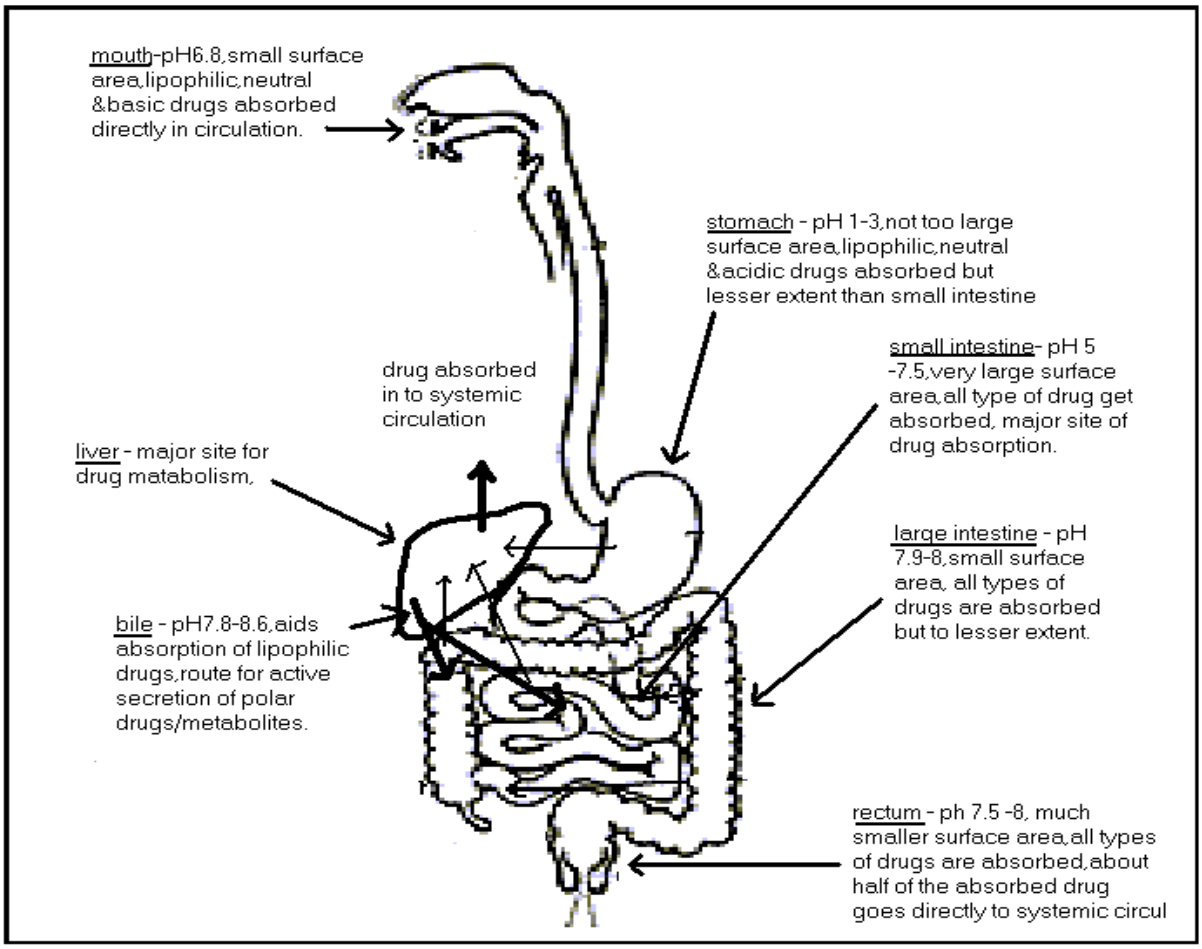
The absorption of some antibiotics, such as penicillin and tetracycline, is decreased with food; whereas other drugs, particularly lipid-soluble drugs such as griseofulvin and metazalone, are better absorbed when given with food containing a high fat content.

✓ Propranolol plasma concentrations are larger after food than in fasted subjects. This may be an interaction with the components of food.



Effect of fasting vs food on propranolol concentrations

(G) pH and surface area of GIT:



3) Age

- In infants, the gastric pH is high and intestinal surface and blood flow to the GIT is low resulting in altered absorption pattern in comparison to adults.
- In elderly persons, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area and GI blood flow, higher incidents of achlorhydria and bacterial over growth in small intestine.

Clinical Factors:-

1) Diseases

Parkinson's disease may have difficulty swallowing and greatly diminished gastrointestinal motility. A case was reported in which the patient could not be controlled with regular oral levodopa medication because of poor absorption. Infusion of oral levodopa solution using a j-tube gave adequate control of his symptom.

Patients on tricyclic antidepressants (imiprimine, amitriptyline, and nortriptyline) and **antipsychotic drugs** (phenothiazines) with anticholinergic side effects may have reduced gastrointestinal motility or even intestinal obstructions. Delays in drug absorption, especially with slow-release products, have occurred.

Achlorhydricpatients may not have adequate production of acids in the stomach; stomach HCl is essential for solubilizing insoluble free bases. Many weak-base drugs that cannot form soluble salts will remain undissolved in the stomach when there is no hydrochloric acid present and are therefore unabsorbed. Salt forms of these drugs cannot be prepared because the free base readily precipitates out due to the weak basicity.

Dapsone, itraconazole, and ketoconazole may also be less well absorbed in the presence of achlorhydria. In patients with acid reflux disorders, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption. Co-administering orange juice, colas, or other acidic beverages can facilitate the absorption of some medications requiring an acidic environment.

HIV-AIDSpatients are prone to a number of gastrointestinal (GI) disturbances, such as increased gastric transit time, diarrhea, and achlorhydria. Rapid gastric transit time and diarrhea can alter the absorption of orally administered drugs. Achlorhydria may or may not decrease absorption, depending on the acidity needed for absorption of a specific drug. Indinavir,

for example, requires a normal acidic environment for absorption. The therapeutic window of indinavir is extremely narrow, so optimal serum concentrations are critical for this drug to be efficacious.

Congestive heart failure (CHF) patients with persistent edema have reduced splanchnic blood flow and develop edema in the bowel wall. In addition, intestinal motility is slowed. The reduced blood flow to the intestine and reduced intestinal motility results in a decrease in drug absorption. For example, furosemide (Lasix), a commonly used loop diuretic, has erratic and reduced oral absorption in patients with CHF and a delay in the onset of action.

Crohn's disease is an inflammatory disease of the distal small intestine and colon. The disease is accompanied by regions of thickening of the bowel wall, overgrowth of anaerobic bacteria, and sometimes obstruction and deterioration of the bowel. The effect on drug absorption is unpredictable, although impaired absorption may potentially occur because of reduced surface area and thicker gut wall for diffusion.

2) Drugs

- Anticholinergic drugs in general may reduce stomach acid secretion. Propantheline bromide is an anticholinergic drug that may slow stomach emptying and motility of the small intestine. Tricyclic antidepressants and phenothiazines also have anticholinergic side effects that may cause slower peristalsis in the GI tract. Slower stomach emptying may cause delay in drug absorption.
- Metoclopramide is a drug that stimulates stomach contraction, relaxes the pyloric sphincter, and, in general, increases intestinal peristalsis, which may reduce the effective time for the absorption of some drugs and thereby reduce the peak drug concentration and the time to reach peak drug concentration. For example, digoxin absorption from a tablet is reduced by metoclopramide but increased by an anticholinergic drug, such as propantheline bromide. Allowing more time in the stomach for the tablet to dissolve generally helps with the dissolution and absorption of a poorly soluble drug, but would not be helpful for a drug that is not soluble in stomach acid.
- Antacids should not be given with cimetidine, because antacids may reduce drug absorption. Antacids containing aluminum, calcium, or magnesium may complex with drugs

such as tetracycline, ciprofloxacin, and indinavir, resulting in a decrease in drug absorption. To avoid this interaction, antacids should be taken 2 hours before or 6 hours after drug administration. As mentioned, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption.

- Cholestyramine is a nonabsorbable ion-exchange resin for the treatment of hyperlipemia. Cholestyramine adsorbs warfarin, thyroxine, and loperamide, similar to activated charcoal, thereby reducing absorption of these drugs.
- Absorption of calcium in the duodenum is an active process facilitated by vitamin D, with calcium absorption as much as four times more than that in vitamin D deficiency states. It is believed that a calcium-binding protein, which increases after vitamin D administration, binds calcium in the intestinal cell and transfers it out of the base of the cell to the blood circulation.

QUESTIONS

Ten mark question –

1. What is absorption? How pharmaceutical parameters affect the absorption of drugs?
2. Enlist the factors affecting drug absorption. Write in detail about the factors that are related to the physiological conditions and formulation of dosage form.
3. Write in brief about factors affecting drug absorption.(2003)
4. Discuss Physiological & Clinical factors Affecting drug absorption.(2007)

One-mark` questions –

1. What is important of pKa of drug in absorption?
2. Does food have any effect on drug absorption? How it affects it?
3. What is the relation between drug absorption & gastric emptying rate?

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