GASTROINTESTINAL ABSORPTION

Syllabus: Different factors affecting GIT absorption. Physical, Chemical, Dietary and Dosage form factors.

Questions:
1. Write the dosage form factors affecting drug absorption from GIT. How binding agent affect the GIT absorption.
2. Describe the physiology of the different parts of the GIT. Discuss the role of pH on the GIT absorption of drugs.
3. Discuss the physiochemical factors affecting drug absorption from gut and significance of pH-partition hypothesis.
4. Describe the physico-chemical factors affecting drug absorption from GIT.
5. Enlist factors affecting gastro intestinal absorption. Discus in detail effect of gastric empting time on drug absorption.
6. What is gastric empting? Describe its role in drug absorption.
7. Enlist factors affecting gastro intestinal absorption. Discuss in detail effect of gastric emptying of on drug absorption.
8. *Hydrophilicity and lipophylicity property of a drug decide its absorption.* Comment with justification.

FACTORS INFLUENCING GASTROINTESTINAL ABSORPTION OF A DRUG FROM ITS DOSAGE FORM

A. PHARMACEUTICAL FACTORS
      This includes factors relating to the physicochemical properties of the drug, and dosage form characteristics and pharmaceutical ingredients.
1. *Physicochemical properties of drug substances:*
      (i)   Drug solubility and dissolution rate
      (ii) Particle size and effective surface area
      (iii) Polymorphism and amorphism
      (iv) Pseudopolymorphism (hydrates / solvates)
      (v)   Salt form of the drug
      (vi) Lipophilicity of the drug – (pH partition hypothesis)
      (vii) pKa of the drug and pH – (pH partition hypothesis)
      (viii)Drug stability
2. *Dosage characteristics and pharmaceutical ingredients*
      (i)   Disintegration time (tablets / capsules)
      (ii) Dissolution time
      (iii) Manufacturing variables
      (iv) Pharmaceutical ingredients (excipients / adjutants)
      (v)   Nature and type of dosage form
      (vi) Product age and storage conditions

B. PATIENT RELATED FACTORS
      These includes factors relating to the anatomic, physiologic and pathologic characteristics of the patient.
(i)   Age
(ii) Gastric emptying time
(iii) Intestinal transit time
(iv) Gastrointestinal pH
(v)   Disease states

(vi) Blood flow through the GIT
(vii) Gastrointestinal contents
a) Other drugs   b) Food   c) Fluids   d) Other normal GI contents
(viii) Pre-systemic metabolism by
a) Luminal enzymes   b) Gut wall enzymes   c) Bacterial enzymes   d) Hepatic enzymes
A. PHARMACEUTICAL FACTORS

1. Drug solubility and dissolution rate

         Orally administered solid dosage form are first disintegrated or deaggregated, then the solid particles are dissolved; drugs in solution then permeate across biomembrane to be absorbed in the body.
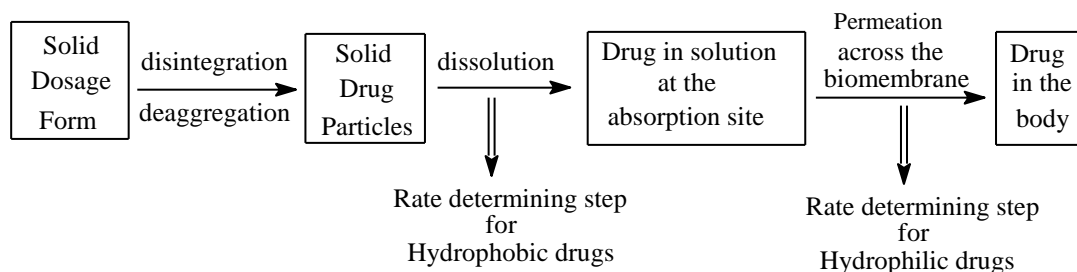
Two critical processes in the absorption of orally administered drugs are:
         1. Rate of dissolution, and
         2. Rate of drug permeation through the biomembrane (i.e. gastrointestinal membrane)

- For poorly water-soluble drugs rate of dissolution is the rate determining step hence the absorption is called to be <u>dissolution rate limited</u>. e.g. griseofulvin, spironolactone.
- For highly water-soluble drugs dissolution is rapid so the rate determining step is permeation hence, the absorption is called to be <u>permeation rate limited</u>. e.g., cromlyn sodium, neomycin sulfate etc.

2. Particle size and effective surface area of the drug particles.

From Noyes-Whitney's equation of dissolution:

$$\frac{dC}{dt} = \frac{DAK_{W/O}(C_S - C_B)}{Vh}$$

where,   D   = diffusion coefficient or diffusivity of the drug molecule
         A   = surface area of the dissolving solid exposed to the dissolution medium
         $K_{O/W}$ = water/oil partition coefficient of the drug
         V   = volume of dissolution medium
         h   = thickness of the stagnant layer
         $C_S - C_B$ = concentration gradient of the diffusing drug molecule.

From this equation it can be concluded that the greater the surface area, A, faster the distribution. When the particle size of a certain mass of a drug is reduced the surface area is increased, hence, if particle size is reduced dissolution rate increases.
Two types of surface area can be defined:
1. <u>Absolute surface area</u>: Which is the total area of solid surface of any particle, and
2. <u>Effective surface area</u>: Which is the area of solid surface exposed to the dissolution medium.
e.g.   <u>Micronization</u> of poorly water soluble drugs like griseofulvin, chloramphenicol and several salts of tetracycline results in superior dissolution rates.
However, size reduction has some limitation. In case of hydrophobic drugs like aspirin, phenacetin and phenobarbital micronization actually results in a decrease in effective surface area due to the following reasons.

(i)   The hydrophobic surface of the drugs absorb air onto their surface which inhibit their wettability, such powders float on the dissolution medium.
(ii) The particle reaggregate to form larger particles due to their high surface free energy.
(iii) Extreme particle size reduction may impart surface charges that may prevent wetting; moreover electrically induced agglomeration may prevent intimate contact of the drug with the dissolution medium.

3. Polymorphism and amorphism
        Depending on the internal structure, a solid can exist either in a crystalline or amorphous form.
*   When, a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as polymorphism.
N.B. Various polymorphs can be prepared by crystallizing the drug from different solvents under diverse conditions. Depending on their relative stability, one of the several polymorphic forms will be physically more stable than the others. Such a stable polymorph represents the lowest energy state, has highest melting point and least aqueous solubility. The remaining polymorphs are called metastable forms which represents higher energy state, the metastable forms have a thermodynamic tendency to convert to the stable form. A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.
*   So the metastable forms have higher aqueous solubility and hence higher bioavailability than the stable polymorphs.
e.g. Chloramphenicol palmitate has three polymorphs A, B and C. The B -form shows best
      bioavailability and A form is virtually inactive biologically.
e.g. Polymorphic form-III of riboflavin is 20 times more water soluble than the form-I.
*   Due to aging of dosage forms containing metastable forms of the drug results in the formation of less soluble, stable polymorph.
e.g. more soluble crystalline form-III of cortisone acetate converts to less soluble form-V in an
      aqueous suspension resulting in caking of solid.

Amorphous form (i.e. having no internal structure)
        Such drugs represents the highest energy state and can be considered as supercooled liquids.
They have greater aqueous solubility than their crystalline form.
e.g. the amorphous form of the novobiocin is 10 times more soluble than the crystalline form.
Thus the order for dissolution of different solid forms of drug is amorphous > metastable > stable.

4. Pseudopolymorphism (Hydrates / Solvates)
        During crystallization process the solvent molecules may be incorporated into the crystal lattice of the solid in *stoichiometric* proportion – these type of crystals are called solvates; and the trapped solvent molecules as solvent of crystallization.
        The solvates again can remain in different polymorphic states, called as pseudopolymorphs. The phenomenon is called as pesudopolymorphism.
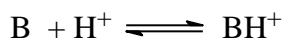   When the solvent with the drug is water, the solvate is known as hydrate.
Effect of absorption:
*   Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in equilibrium with water and therefore have less demand for water.
e.g. anhydrous form of theophyline and ampicillin have higher aqueous solubilities, dissolve at faster rate and show better bioavailability in comparison to their monohydrates and trihydrate forms respectively.
*   On the other hand nonaqueous solvates have greater aqueous solubility than the nonsolvates.
e.g. n-pentanol solvate of fludricortisone and succinyl sulfathiazole and the chloroform solvates of griseofulvin are more water soluble than their non-solvate forms.

5. Salt form of the drug
        Most drugs are either weak acids or weak bases. One of the easiest approach to enhance the solubility and dissolution rate of such drugs is to convert them into their salt forms.

- Weak acid HA is more soluble in basic pH and weak base B is more soluble in acidic pH by the formation of salt.
- Some time *in-situ* salt formation can be utilized, e.g. certain drugs like aspirin and penicillin are prepared as buffered alkaline tablets. When the tablets are put into water the pH of the microenvironment of the drug is increased which promotes the dissolution rate. So buffered aspirin tablets have two advantages

(i) the gastric irritation and ulcerogenic tendency of the drug is greatly reduced and,
(ii) in dry form the hydrolytic stability is better.
(iii) bioavailability is increased by increasing the dissolution.

- Size of counter ion
    Smaller the size of the counter ion (of the salt form of a drug) greater the solubility of the salt. e.g. bioavailability of novobiocin from its sodium salt, calcium salt and free acid forms are in the following ratio:

Novobiocin Na	Novobiocin Ca	Novobiocin free acid
50	20	1

- Ionic strength of the counter ion
    When the counter ion is very large in size and/or has poor ionic strength (as in the case of ester form of the drugs), the solubility may be much lower than the free drug itself.

e.g. pamoates, stearates and palmitates of weak bases having poor aqueous solubility:

prolong the duration of action	– e.g. steroidal salts
overcome bad taste	– e.g. chloramphenicol
overcome GI-instability	– e.g. erythromycin estolate

decrease the side effects, local or systemic.

6. pKa of the drug and pH

- Drug pKa and lipophilicity and GI pH (pH partition theory)
    The pH partition theory (Brodie et.al.) states that for drug compounds of molecular weight greater than 100, which are primarily transported across the biomembrane by passive diffusion:
    The process of absorption is governed by

1. dissociation constant (Ka) of the drug
2. lipid solubility of the unionized drug ($K_{o/w}$)
3. the pH at the absorption site

The above statement of the hypothesis was based on the assumptions that:

1. The GIT is simple lipoidal barrier to the transport of drug.
2. Larger the fraction of unionized drug, faster the absorption.
3. Greater the lipophilicity ($K_{o/w}$) of the unionized drug, better the absorption.

Handerson-Hasselbach equation
    The amount of drug that exists in unionized form is a function of dissolution constant (pKa) of the drug and pH of the fluid at the absorption site.

Handerson-Hasselbach equation

$$pH = pKa + \log \frac{[base]}{[acid]}$$

for weak acid:

$$HA \rightleftharpoons H^+ + A^-$$
acid   base

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

$$\% \, drug \, ionized = \frac{10^{(pH - pKa)}}{1 + 10^{(pH - pKa)}} \times 100$$

$$B + H^+ \rightleftharpoons BH^+$$

$$\% \,drug\,ionized = \frac{10^{(pKa-pH)}}{1+10^{(pKa-pH)}}\,x\,100$$

$$pH = pKa + \log\frac{[B]}{[BH^+]}$$

Drugs	pKa	pH at the site of absorption
Very weak bases	*(pKa < 5.0)*	
Theophyline	0.7	Unionized at all pH values: absorbed along the entire length of GIT.
Caffeine	0.8	
Oxazepam	1.7	
Diazepam	3.7	
Moderately weak bases	*(5 < pKa < 11)*	
Reserpine	6.6	Ionized at gastric pH, relatively unionized at intestinal pH better absorbed from intestine.
Heroin	7.8	
Codeine	8.2	
Amitriptyline	9.4	
Stronger base	*(pKa > 11.0)*	
Mecamylamine	11.2	Ionized at all pH values: poorly absorbed form GIT.
Guanethidine	11.7	

It is the pKa of the drug that determines the degree of ionization at a particular pH and that only the unionized drug, if sufficiently lipid soluble, is absorbed into the systemic circulation.

Ideally, for optimum absorption, a drug should have sufficient aqueous solubility to dissolve in the fluids at the absorption site and lipid solubility ($K_{o/w}$) in the lipoidal biomembrane and into the systemic circulation. In other words, a perfect hydrophilic-lipophilic balance (HLB) should be there in the structure of the drug for optimum bioavailability.

DOSAGE FORM FACTORS AFFECTING DRUG ABSORPTION

1. Disintegration time

Disintegration time (DT) is of particular importance in case of solid dosage forms like tablets and capsules. After disintegration of a solid dosage form into granules, the granules must deaggregate into finer particles and then dissolution takes place. If DT is long the bioavailability will be less. Rapid disintegration is thus important in the therapeutic success of a solid dosage form.

DT increases with increase in the amount of binder and hardness of a tablet.

Disintegration can be aided by incorporating disintegrants in suitable amounts during formulation.

2. Manufacturing / process variables

Dissolution from a solid dosage form depends on:

(A) excipients and (B) manufacturing process.

(A) **Excipients**

A drug is rarely administered in its original form. All dosage forms contains a number of suitable excipients (non-drug components of a formulation).

(a) *Vehicle*

Vehicle or solvent system that carries a drug is the major component of liquid orals and parenterals. The three categories of vehicles generally used are:

(i) aqueous vehicles e.g. water, syrup etc.

(ii) nonaqueous but water miscible e.g. propylene glycol, glycerol, sorbitol.

(iii) nonaqueous and water immiscible vehicle e.g. vegetable oils.

Bioavailability of a drug from vehicle depends, to a large extent, on its miscibility with biological fluids.

- Aqueous and water miscible vehicles are rapidly miscible with body fluids (e.g. G.I.-fluid, tissue fluid, blood etc.) and drugs are rapidly absorbed from them.
- Propylene glycol, glycerol etc. are used as co-solvent to increase the solubility of a drug in water. Sometimes solubilisers, such as Tween 80 are used to promote solubility of a drug in aqueous vehicle.
- In case of water immiscible vehicles, the rate of drug absorption depends upon its partitioning from the oil phase to the aqueous body fluids, which could be a rate limiting step.

b) Diluents (Fillers)
    Diluents are commonly added to tablet (and capsules) formulations.
- Hydrophilic powders used as diluent are starch, lactose, microcrystalline cellulose etc. These hydrophilic powders forms a coating over the hydrophobic drugs particles (e.g. spironolactone and triamterene) and rendering them hydrophilic.
- Inorganic diluents like dicalcium phosphate (DCP) forms divalent calcium-tetracycline complex which is poorly soluble in water and thus unabsorbable.

c) Binders and granulating agents
    These materials are used to hold powders together to form granules or promote cohesive compacts for directly compressible materials and ensure that the tablet remains intact after compression.
- Large amount of binders increase hardness and thus decrease disintegration / dissolution rates of tablets.
- Non-aqueous binders like ethyl cellulose also retard dissolution.

d) Disintegrants
    These agents overcome the cohesive strength of tablet and break them up on contact with water.
- Almost all the disintegrants are hydrophilic in nature.
- A decrease in the amount of disintegrant can significantly lower the bioavailability.

e) Lubricants
    These agents are added to tablet formulations to aid flow granules, to reduce interparticular friction and to reduce sticking or adhesion of particles to dies and punches.
- The commonly used lubricants are hydrophobic in nature (several metallic stearates and waxes). They reduce the wettability of particle surface, penetration of water into tablet.
- The best alternative is to use soluble lubricants like sodium lauryl sulphate and carbowax which promotes drug dissolution.

f) Suspending agents /Viscosity building agents
    Agents like vegetable gums (acacia, tragacanth etc.), semisynthyetic gums (carboxy methyl cellulose, methyl cellulose) and synthetic gums which reduces the sedimentation rate of a suspension
- The macromolecular gums often form unabsorbable complex with amphetamine.
- An increase in viscosity by these agents acts as a mechanical barrier to the diffusion of drug from the dosage form into the bulk of GI fluids.

h) Surfactants
    Surfactants are widely used in formulations as wetting agents, solubilizers, emulsifiers, etc. Surfactants increase the absorption of a drug by the following ways:
    1. Promotion of wetting (through increase in effective surface area) and dissolution of drugs e.g. Tween80 with phenacetin.
    2. Better membrane contact of the drug for absorption
    3. Enhanced membrane permeability of the drug .
Decreased absorption of drug in the presence of surfactants has been suggested to be due to :

1. Formation of unabsorbable drug-micelle complex at surfactant concentrations above critical micelle concentration.
2. Laxative action induced by a large surfactant concentration.

i) *Complexing agents*

Several examples where complexation has been used to enhance drug bioavailability are:
1. Enhanced dissolution through formation of a soluble complex
   e.g. ergotamine-caffeine complex
   hydroquinone-digoxin complex.
2. Enhanced lipophilicity for better membrane permeability e.g. caffeine-PABA complex (PABA = para amino benzoic acid) and
3. Enhanced membrane permeability e.g. enhanced GI absorption (normally not absorbed from the GIT) in presence of EDTA (ethylene diamine tetraacetic acid) which chelates Ca^{++} and Mg^{++} ions of the membrane.

Disadvantages of complexation:-
1. complexation may produce poorly absorbable drugs complexes e.g. tetracycline with divalent and trivalent cations e.g.. tetracycline with divalent and trivalent cations like calcium (milk, antacids), iron (hematinics), magnesium (antacids) and aluminium (antacids).
2. large molecular size of drug-protein cannot diffuse through the cell membrane.

j) *Colorants*

Even a very low concentration of water-soluble dye can have an inhibitory effect on dissolution rate of several
- crystalline drugs. The dye molecules get adsorbed onto the crystal faces and inhibit drug dissolution – e.g. brilliant blue retards dissolution of sulphathiazole.
- Dyes have also been found to inhibit <u>micellar solubilizaion effect of bile acids</u> which may impair the absorption of hydrophobic drugs like steroids.

(B) Manufacturing process
   (i) method of granulation and
   (ii) Compression force
   (iii) Intensity of packing of capsules

i) *Method of granulation*

The wet granulation process is the most conventional technique of manufacturing tablet granules. The limitation of this method include –
(i) formation of crystal bridge due to the presence of solvent,
(ii) the liquid may act as medium or affecting chemical reactions such as hydrolysis, and
(iii) the drying step may harm the thermolabile drugs.
Wet granulation includes greater number of steps than dry granulation or direct compression which can adversely affect the dissolution.

ii) *Compression force*

The compression force employed in tableting process influence density, porosity, hardness, disintegration time and dissolution of tablets.

The curve obtained by plotting compression force versus rate of dissolution can take one of the 4 possible shapes shown in the figures:

Rate of dissolution ↑   A   B   C   D
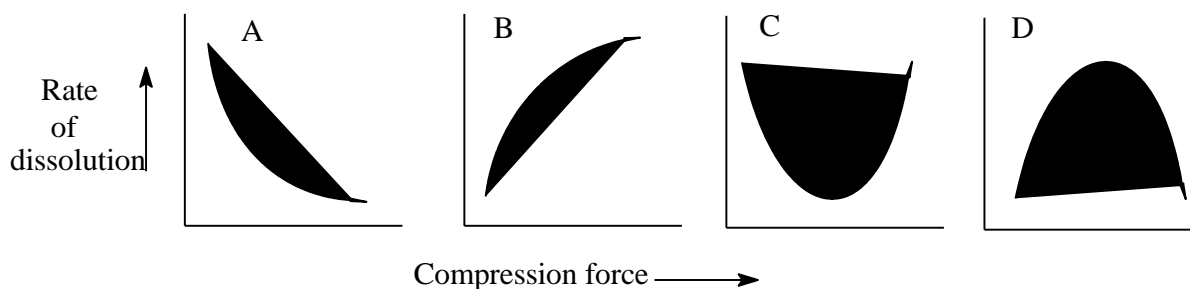
Compression force ⟶

A. Higher compression force → ↑ density and hardness of tablet

                               ↓ porosity, hence penetrability of the solvent into the tablet

                               ↓ wettability by forming a firmer and more effective sealing layer by the lubricant

B. Higher compression force

         → causes deformation, crushing or fracture of drug particles into smaller ones or, convert a spherical granules into a disc shaped particle with large increase in effective surface area

         → ↑ in dissolution rate

C and D are combination of both the causes of A and B.

In short, the influence of compression force on the dissolution is difficult to predict.

(iii) Intensity of packing of capsule contents

         Packing density in case of capsule can either inhibit or promote dissolution.

• Diffusion of GI fluids into the tightly filled capsules creates a high pressure within the capsule results in rapid bursting and dissolution of contents.

• In some cases capsules with tight packing

         → pore size of the compact mass is decreased

         → poor penetrability of GI - fluid

         → poor rate of drug release

NATURE AND TYPES OF DOSAGE FORM

Cause of events that occur following oral administration of various dosage forms:
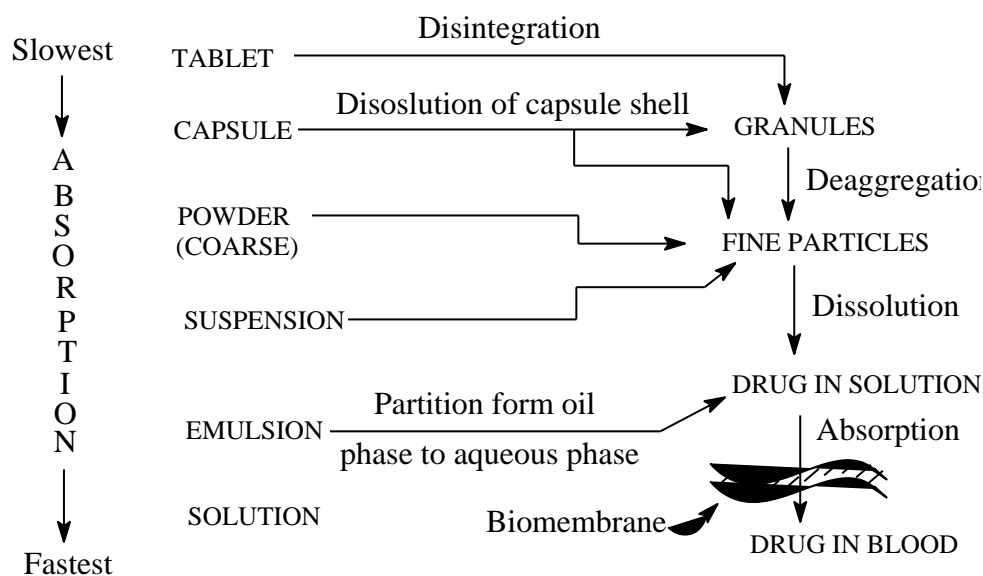
As a general rule, the bioavailability of a drug from various dosage forms decreases in the following order:

Solution > Emulsions > Suspensions > Capsules > Tablets > Coated tablets > Enteric coated tablets > Sustained release tablets.

Thus, absorption of a drug from solution is fastest with least potential for bioavailability problems whereas absorption from sustained release product is lowest with greatest bioavailability.

PATIENT RELATED FACTORS AFFECTING DRUG ABSORPTION
Physiology of GIT
- The major components of the GIT are stomach, small intestine (duodenum, jejunum and ileum) and large intestine (colon) which differ from each other in terms of anatomy, function, secretions and pH.
- The mean length of the entire GIT is 450 cm.
- The entire inner surface of GIT from stomach to large intestine is lined by a thin layer of muco-polysaccharides (mucous membrane) which normally acts as a barrier to bacteria, cells or food particles.

1. <u>Mouth</u>	pH 6 – 8	small surface area	lipophilic, neutral and basic drugs are absorbed directly
2. <u>Stomach</u>	pH 1 – 3	not too large a surface area	lipophilic, neutral and acidic drugs absorbed but lesser than that from intestine
3. <u>Small intestine</u>	pH 5 – 7.5	very large surface area	major site for absorption of all types of drugs (lipophilic, neutral, acidic or basic)
4. <u>Large intestine</u>	pH7.9–8.0	small surface area	all types of drugs are absorbed but to a lesser extent
5. <u>Rectum</u>	pH 7.5–8.0	much smaller surface area	all types of drugs are absorbed, about half of the absorbed drug goes directly into the systemic circulation and the other half to the liver

Stomach
The stomach is a bag like structure having a smooth mucosa and thus small surface area. Its acidic pH, due to its secretion of HCl, favors absorption of weakly acidic drugs like aspirin.
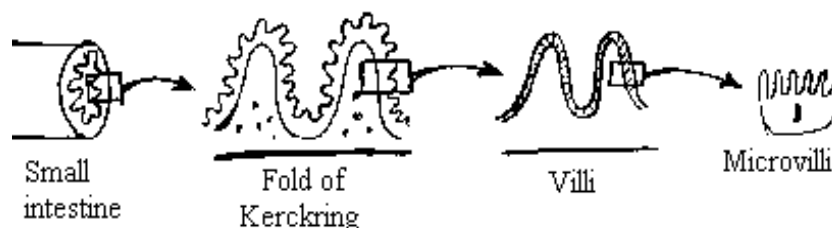
Small intestine

Fig. Components of intestinal epithelium

The folds in intestinal mucosa, called as *fold of Kerckring* result in 3 fold increase in surface area. The surface of this folds possess finger like projections as *villi* which increases the surface area by 30 times.
- From the surface of villi protrude several microvilli resulting in 600 times increase in the surface area. All these combined to impart a large surface area of more than 200 sq.m.
- The blood flow is 6 – 10 times more than stomach.
- pH range is 5 to 7.5 which is more favorable for most drugs to remain unionized.
- The peristaltic movement of intestine is slow, transit time is long, and penetrability is high. All this factors make intestine the best site for absorption of most drugs.

Large intestine
Its length and mucosal surface area is very small (villi and microvilli are absent) compared to small intestine and thus absorption of drug from this region is very small.

However, because of the long residence time (6 to 12 hrs), colonic transit may be important in the absorption of some poorly soluble drugs and sustained release dosage forms.

PATIENT RELATED FACTORS

1. **Age**

In infants gastric:	pH is high
	intestinal surface is small
	blood flow is less.
In elderly persons:	altered gastric emptying
	decreased intestinal surface area
	decreased GI blood flow
	achlorhydria
	bacterial overgrowth in small intestine.

In both of these age drug absorption is impaired.

2. **Gastric emptying**

Passage of gastric content from stomach to small intestine is called gastric emptying.

- Rapid gastric emptying is required where:
    (i) a rapid onset of action is required e.g. sedatives.
    (ii) dissolution of drug occurs in the intestine e.g. enteric coated dosage forms.
    (iii) the drugs are not stable in gastric fluid e.g. penicillin-G and erythromycin.
    (iv) the drug is best absorbed from the distal part of the small intestine e.g. vitamin B_{12}.

- Delay in gastric emptying is required where:
    (i) the food promotes drug dissolution and absorption e.g. griseofulvin
    (ii) disintegration and dissolution of dosage form is promoted by gastric fluid
    (iii) the drugs are absorbed from the proximal part of the small intestine e.g. vitamin B_2 and vitamin C.

- Gastric emptying is a *first order rate process*. Several parameters are used to quantify gastric emptying:
(i) *Gastric emptying rate* is the rate at which the stomach content empty into the intestine.
(ii) *Gastric emptying time* is the time required for the gastric content to empty completely into the small intestine.
(iii) *Gastric emptying $t_{1/2}$* is the time taken for half the stomach contents to empty.

N.B.   In vivo gastric emptying can be studied by using radio-opaque contrast materials (e.g. $BaSO_4$) or tagging the drug with a radio-isotope and scanning the stomach at regular intervals of time.

- *Factors influencing gastric emptying rate:-*
1. Volume of meal:
    Larger the volume of meal longer the gastric emptying time.
2. Composition of meal
    The rate of gastric emptying for various food materials is in the following order:
        carbohydrates > protein > fats
3. Physical state and viscosity of meal
    Liquid meals take less than an hour to empty solid meals take as long as 6 – 7 hours to empty.
    Viscous material empty at a slow rate in comparison to less viscous materials.
4. Temperature of the meal
    High or low temperature of the ingested fluid (compared to body temperature) reduce gastric emptying rate.
5. Gastrointestinal pH

Gastric emptying is retarded at low stomach pH and
is promoted at higher or alkaline pH.

6. Electrolyte and osmotic pressure

Water, isotonic, and solutions of low salt concentration empty the stomach rapidly whereas higher electrolyte concentration decreases gastric emptying rate.

7. Body posture

Gastric emptying is favoured while standing and while lying on the right side; while lying on the left side or in supine position retards it.

8. Emotional state

Stress and anxiety promote gastric motility whereas depression retards it.

9. Exercise

Vigorous physical exercise retards gastric emptying.

10 Disease states

Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying.

11. Drugs

Drugs that retard gastric emptying includes

(i) poorly soluble antacids e.g. aluminium hydroxide,
(ii) anticholinergics e.g. atropine, propantheline
(iii) narcotic analgesics e.g. morphine and
(iv) tricyclic antidepressants e.g. imipramine, amytriptyline.

Drug that stimulate gastric emptying are:

(i) metoclopramide
(ii) domperidone
(iii) cisapride

3. Effect of GI pH on drug absorption

GI fluid pH influence drug absorption in several ways:

1. *Disintegration*

The disintegration of some dosage forms is pH sensitive. With enteric coated formulations, the coat dissolves only in the intestinal pH, followed by disintegration of the tablet.

2. *Dissolution*

A large number of drugs are either weakly acidic or weakly basic whose solubility is greatly affected by pH. A pH that favours the formation of salt of the drug enhances the dissolution rate. e.g. Weakly acidic drugs dissolve rapidly in the alkaline pH of the intestine whereas basic drugs dissolves in the acidic pH of the stomach.

3. *Absorption*

Depending upon the pKa of the drug and the pH of the GI fluid some amount of the drug remain in ionized state and some in unionized state. The unionized form will be absorbed through GIT quickly than the ionized form.

4. *Stability*

GI pH influences the chemical stability of drugs. e.g. The acidic stomach pH is known to affect degradation of Penicillin-G and erythromycin.

4. Effect of GI content

A number of GI contents can influence drug absorption.

1. Food-drug interaction

Presence of food may either delay, reduce, increase or may not affect drug absorption.

Delayed	Decreased	Increased	Unaffected
Aspirin	Penicillins	Griseofulvin	Methyldopa
Paracetamol	Erythromycin	Diazepam	Sulfasomidine
Diclofenac	Ethanol		
	Tetracyclines		

Levodopa, Iron

As a general rule, drugs are better absorbed under <u>fasting</u> conditions and presence of food retards or prevents it.

Food does not significantly influence absorption of a drug taken half an hour or more before meals and two hours or more after meals.

- Delayed or decrease drug absorption by food can be due to one or more of the following reasons:
(a) Delayed gastric emptying, affecting the drugs unstable in the stomach e.g. penicillin, erythromycin.
(b) Preventing the transit of enteric tablets into the intestine which may be as long as 6 – 8 hrs.
(c) Formation of poorly soluble, unabsorbable complex e.g. tetracycline-calcium complex.
(d) Increased viscosity due to food thereby preventing drug dissolution and/or diffusion towards the absorption site.

- Increased drug absorption following a meal can be due to the following reasons:
(a) Increased time for dissolution of poorly soluble drug.
(b) Enhanced solubility due to GI secretions like bile.
(c) Prolonged residence time and absorption site contact of the drug e.g. water-soluble vitamins.

- **Types of meal**
(i) Meals high in fat aid solubilisation of poorly aqueous soluble drugs like griseofulvin.
(ii) Food high in proteins increases oral availability of propranolol because
    a) such a meal promotes blood flow to the GIT helping in drug absorption.
    b) increases hepatic blood flow due to which the drug can bypass first-pass hepatic metabolism (propranolol is a drug with high hepatic metabolism)

5. <u>Drug-drug interaction</u>

Drug-drug interactions can be either physicochemical or physiological.
(a) <u>Physicochemical drug-drug interactions</u> can be due to –

Adsorption: Antidiarrheal preparations containing adsorbents like *attapulgite* or *kaolin-pectin* retard / inhibit absorption of *promazine* and *lincomycin* when co-administered with them.

Complexation: Antacids containing heavy metals such as aluminium, calcium, iron, magnesium or zinc retard absorption of tetracyclines due to the formation of unabsorbable complexes.

pH change: Basic drugs dissolve in gastric pH. Co-administration of sodium bicarbonate with tetracycline results in evaluation of stomach pH and hence decreases dissolution rate or cause precipitation of drug.

(b) <u>Physiologic drug-drug interaction</u> can be due to following reasons:

Decreased GI transit: Anticholinergic drugs such as propantheline retard GI motility and promote absorption of drugs like ranitidine and digoxin.

Increased gastric emptying: Metoclopramide promotes GI motility and enhances absorption of tetracycline, pivampicillin and levodopa.

Altered GI metabolism: Antibiotics inhibit bacterial metabolism of drugs e.g. erythromycin enhances efficacy of digoxin by this mechanism.

6. <u>Presystemic metabolism / First pass effects</u>

The loss of drug through biotransformation by GIT and liver during the passage to systemic circulation in called *First pass* or *presystemic metabolism*.
The 4 primary systems which affect presystemic metabolism of drugs are:
1. Lumenal enzymes
2. Gut wall enzymes /mucosal enzymes

3. Bacterial enzymes, and
4. Hepatic enzymes

1. <u>Lumenal enzymes</u>

These are enzymes present in the gut fluids and include enzymes from intestinal and pancreatic secretions.

- Pancreatic enzymes contains *hydrolases* which hydrolyze ester drugs like *chloramphenicol palmitate* into active chloramphenicol.
- *Peptidases* split amide (–CONH) linkages and inactivate protein / polypeptide drugs. Thus one of the approaches is to deliver them to colon which lacks peptidases.

2. <u>Gut-wall enzymes</u> (also called mucosal enzymes)

They are present in stomach, intestine and colon.

- Stomach mucosa contains *alcohol dehydrogenase* (ADH) inactivates ethanol.

3. <u>Bacterial enzymes</u>

The GI microorganisms are scantily present in stomach and small intestine and is rich in colon. Hence, most orally administered drugs remain unaffected by them.

- The colonic microbes generally render a drug more active or toxic on biotransformation:

e.g. sulfasalazine (used in ulcerative colitis) is hydrolyzed to sulfapyridine and 5-amino salicylic acid by the microbial enzymes of the colon.

- Digoxin, oral contraceptive drugs are absorbed in the upper intestine; exerted through bile as glucuronide conjugates. This conjugates of drugs are hydrolyzed by microbial enzymes. The free drugs are reabsorbed into the systemic circulation.

4. <u>Hepatic enzymes</u>

e.g. isoprenaline, propranolol, alprenolol, pentoxyfylline, nitroglycerin, diltiazem, nifedipine, lidocaine, morphine etc.