Chapter 2

Pharmacokinetics: Membrane Transport, Absorption and Distribution of Drugs

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. The overall scheme of pharmacokinetic processes is depicted in **Fig. 2.1**. The intensity of response is related to concentration of the drug at the site of action, which in turn is dependent on its pharmacokinetic properties. **Pharmacokinetic considerations, therefore, determine the route(s) of administration, dose, and latency of onset, time of peak action, duration of action and frequency of administration of a drug.**

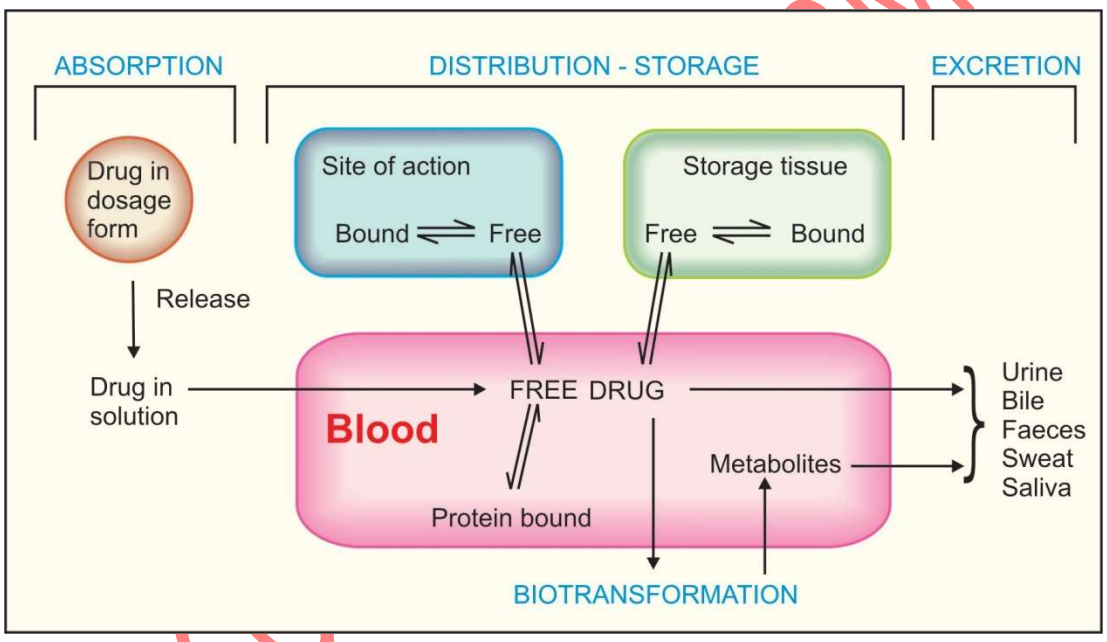

Fig. 2.1: Schematic depiction of pharmacokinetic processes

All pharmacokinetic processes involve transport of the drug across biological membranes.

Biological membrane

This is a bilayer (about 100 Å thick) of phospholipid and cholesterol molecules, the polar groups (glyceryl phosphate attached to ethanolamine/choline or hydroxyl group of cholesterol) of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix to form a continuous sheet. This imparts high electrical resistance and relative impermeability to the membrane. Extrinsic and intrinsic protein molecules are adsorbed on the lipid bilayer (**Fig. 2.2**).

Glyco- proteins or glycolipids are formed on the surface by attachment to polymeric sugars, aminosugars or sialic acids. The specific lipid and protein composition of different membranes differs according to the cell or the organelle type. The proteins are able to freely float through the membrane: associate and organize or vice versa. Some of the intrinsic ones, which extend through the full thickness of the membrane, surround fine aqueous pores.

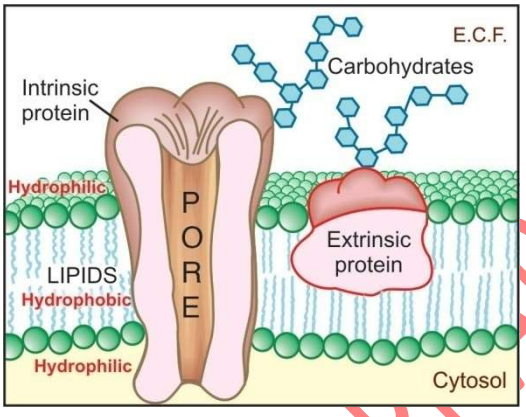

Fig. 2.2: Illustration of the organization of biological membrane

Paracellular spaces or channels also exist between certain epithelial/endothelial cells. Other adsorbed proteins have enzymatic, carrier, receptor or signal transduction properties. Lipid molecules also are capable of lateral movement. Thus, biological membranes are highly dynamic structures.

Drugs are transported across the membranes by:

(a) **Passive diffusion and filtration**

(b) **Specialized transport**

a. Passive diffusion

The drug diffuses across the membrane in the direction of its concentration gradient, the membrane playing no active role in the process. This is the most important mechanism for majority of drugs; drugs are foreign substances (xenobiotics), and specialized mechanisms are developed by the body primarily for normal metabolites.

Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane (**Fig. 2.3**), the rate of transport being proportional to the lipid: water partition coefficient of the drug. A more lipid-soluble drug attains higher concentration in the membrane and diffuses quickly. Also, greater the difference in the concentration of the drug on the two sides of the membrane, faster is its diffusion.

Influence of pH Most drugs are weak electro- lytes, i.e. their ionization is pH dependent (contrast strong electrolytes that are nearly completely ionized at acidic as well as alkaline pH). The ionization of a weak acid HA is given by the equation:

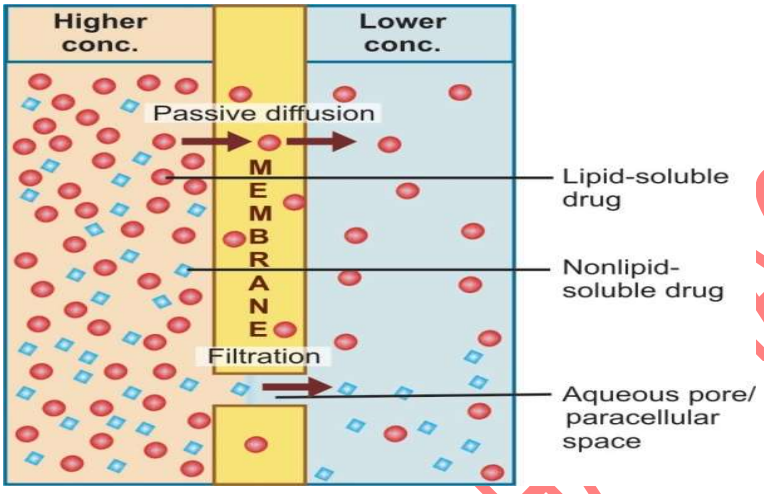

Fig. 2.3: Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

$$pH = pKa + \log \frac{[A^-]}{[HA]} \quad ...(1)$$

pKa is the negative logarithm of acidic disso- ciation constant of the weak electrolyte. If the concentration of ionized drug [A^-] is equal to concentration of unionized drug [HA], then

$$\frac{[A^-]}{} = 1\,[HA]$$

since log 1 is 0, under this condition

$$pH = pKa \quad ...(2)$$

Thus, *pKa* is numerically equal to the pH at which the drug is 50% ionized.

If pH is increased by 1 scale, then—

$\log [A^-]/[HA] = 1$ or $[A^-]/[HA] = 10$ Similarly, if pH is reduced by 1 scale, then—

$$[A^-]/[HA] = 1/10$$

Thus, weakly acidic drugs, which form salts with cations, e.g. *sod*. phenobarbitone, *sod.* sulfadiazine, *pot.* penicillin-V, etc. ionize more at

alkaline pH and 1 scale change in pH causes 10 fold change in ionization.

Weakly basic drugs, which form salts with anions, e.g. atropine *sulfate*, ephedrine *HCl*, chloroquine *phosphate,* etc. conversely ionize more at acidic pH. Ions being lipid insoluble, do not diffuse and a pH difference across a membrane can cause differential distribution of weakly acidic and weakly basic drugs on the two sides (Fig. 2.4).

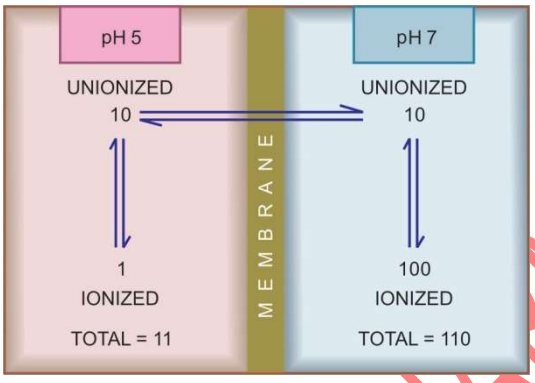

Fig. 2.4: Influence of pH difference on two sides of a biological membrane on the steady-state distribution of a weakly acidic drug with *pKa* = 6

Implications of this consideration are:

Acidic drugs, e.g. aspirin (*pKa* 3.5) are largely unionized at acid gastric pH and are absorbed from stomach, while bases, e.g. atropine (*pKa* 10) are largely ionized and are absorbed only when they reach the intestines.

The unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell, reverts to the ionized form within the cell (pH 7.0) and then only slowly passes to the extracellular fluid. This is called *ion trapping*, i.e. a weak electrolyte crossing a membrane to encounter a pH from which it is not able to escape easily. This may contribute to gastric mucosal cell damage caused by aspirin.

Basic drugs attain higher concentration intracellularly (pH 7.0 *vs* 7.4 of plasma).

Acidic drugs are ionized more in alkaline urine—do not back diffuse in the kidney tubules and are excreted faster. Accordingly, basic drugs are excreted faster if urine is acidified.

Lipid-soluble nonelectrolytes (e.g. ethanol, diethyl-ether) readily cross biological membranes and their transport is pH independent.

Filtration

Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces. This can be accelerated if hydrodynamic flow of the solvent is occurring under hydrostatic or osmotic pressure gradient, e.g. across most capillaries including glomeruli. Lipid-insoluble drugs cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores (Fig. 2.3). Majority of cells (intestinal mucosa, RBC, etc.) have very small pores (4 Å) and drugs with MW > 100 or 200 are not able to penetrate. However, capillaries (except those in brain) have large paracellular spaces (40 Å) and most drugs (even albumin) can filter through these (Fig. 2.8). As such, diffusion of drugs across capillaries is dependent on rate of blood flow through them rather than on lipid solubility of the drug or pH of the medium.

b. Specialized transport

This can be carrier mediated or by pinocytosis.

Carrier transport

All cell membranes express a host of transmem- brane proteins which serve as carriers or transporters for physiologically important ions, nutrients, metabolites, transmitters, etc. across the membrane. At some sites, certain transporters also translocate xenobiotics, including drugs and their metabolites. In contrast to channels, which open for a finite time and allow passage of specific ions, transporters combine transiently with their substrate (ion or organic compound)—undergo a conformational change carrying the substrate to the other side of the membrane where the substrate dissociates and the transporter returns back to its original state (Fig. 2.5). Carrier transport is specific for the substrate (or the type of substrate, e.g. an organic anion), saturable, competitively inhibited by analogues which utilize the same transporter, and is much slower than

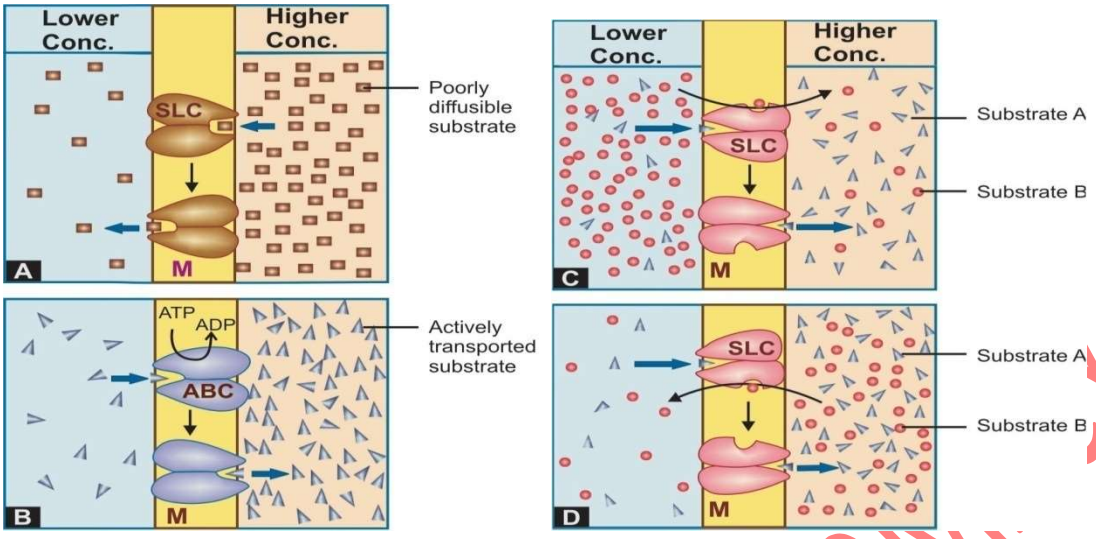

Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane ABC—ATP-binding cassettee transporter; SLC—Solute carrier transporter; M—Membrane

Facilitated diffusion*:* the carrier (SLC) binds and moves the poorly diffusible substrate along its concentration gradient (high to low) and does not require energy

Primary active transport*:* the carrier (ABC) derives energy directly by hydrolysing ATP and moves the substrate against its concentration gradient (low to high)

Symport*:* the carrier moves the substrate 'A' against its concentration gradient by utilizing energy from downhill movement of another substrate 'B' in the same direction

Antiport*:* the carrier moves the substrate 'A' against its concentration gradient and is energized by the downhill movement of another substrate 'B' in the opposite direction the flux through channels. Depending on requirement of energy, carrier transport is of two types:

Facilitated diffusion The transporter, belonging to the super-family of *solute carrier* (SLC) transporters, operates passively without needing energy and translocates the substrate in the direction of its electrochemical gradient, i.e. from higher to lower concentration (Fig. 2.5A). It mearly facilitates permeation of a poorly diffusible substrate, e.g. the entry of glucose into muscle and fat cells by the glucose transporter GLUT 4.

Active transport It requires energy, is inhibited by metabolic poisons, and transports the solute against its electrochemical gradient (low to high), resulting in selective accumulation of the substance on one side of the membrane. Drugs related to normal metabolites can utilize the transport processes meant for these, e.g. levodopa and methyl dopa are actively absorbed from the gut by the aromatic amino acid transporter. In addition, the body has developed some relatively nonselective transporters, like *P-glycoprotein* (P-gp), to deal with xenobiotics. Active transport can be primary or secondary depending on the source of the driving force.

Primary active transport Energy is obtained directly by the hydrolysis of ATP (Fig. 2.5B). The transporters belong to the superfamily of *ATP binding cassettee* (ABC) transporters whose intracellular loops have ATPase activity. They mediate only efflux of the solute from the cytoplasm, either to extracellular fluid or into an intracellular organelli (endoplasmic reticulum, mitochondria, etc.)

Secondary active transport In this type of active transport effected by another set of SLC transporters, the energy to pump one solute is derived from the downhill movement of another solute (mostly Na+). When the concentration gradients are such that both the solutes move in the same direction (Fig. 2.5C), it is called *symport* or *cotransport*, but when they move in opposite directions (Fig. 2.5D), it is termed *antiport* or *exchange transport*. Metabolic energy (from hydrolysis of ATP) is spent in maintaining high transmembrane electrochemical gradient of the second solute (generally Na+). The SLC transporters mediate both uptake and efflux of drugs and metabolites.

As indicated earlier, carrier transport (both facilitated diffusion and active transport) is saturable and follows the Michaelis-Menten kinetics. The maximal rate of transport is dependent on the density of the transporter in a particular membrane, and its rate constant (Km), the substrate concentration at which rate of transport is half maximal, is governed by its affinity for the substrate. Genetic polymorphism can alter both the density and affinity of the transporter protein for different substrates and thus affect the pharmacokinetics of drugs. Moreover, tissue specific drug distribution can occur due to the presence of specific transporters in certain cells.

Pinocytosis

It is the process of transport across the cell in particulate form by formation of vesicles. This is applicable to proteins and other big molecules, and contributes little to transport of most drugs, barring few like vit B12 which is absorbed from the gut after binding to intrinsic factor (a protein).

ABSORPTION

Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given i.v., the drug has to cross biological membranes; absorption is governed by the above described principles. Other factors affecting absorption are:

Aqueous solubility Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed. For poorly water soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption. Ketoconazole dissolves at low pH: gastric acid is needed for its absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

Concentration Passive diffusion depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

Area of absorbing surface Larger is the surface area, faster is the absorption.

Vascularity of the absorbing surface Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow hastens drug absorption just as wind hastens drying of clothes.

Route of administration This affects drug absorption, because each route has its own peculiarities.

Oral

The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal. Nonionized lipid soluble drugs, e.g. ethanol are readily absorbed from stomach as well as intestine at rates proportional to their lipid : water partition coefficient. Acidic drugs, e.g. salicylates, barbiturates, etc. are predominantly unionized in the acid gastric juice and are absorbed from stomach, while basic drugs, e.g. morphine, quinine, etc. are largely ionized and are absorbed only on reaching the duodenum. However, even for acidic drugs absorption from stomach is slower, because the mucosa is thick, covered with mucus and the surface area is small. Absorbing surface area is much larger in the small intestine due to villi. Thus, faster gastric emptying accelerates drug absorption in general. Dissolution is a surface phenomenon, therefore, *particle size* of the drug in solid dosage form governs rate of dissolution and in turn rate of absorption.

Presence of food dilutes the drug and retards absorption. Further, certain drugs form poorly absorbed complexes with food constituents, e.g. tetracyclines with calcium present in milk; moreover food delays gastric emptying. Thus, most drugs are absorbed better if taken in empty

stomach. However, there are some exceptions, e.g. fatty food greatly enhances lumefantrine absorption. Highly ionized drugs, e.g. gentamicin, neostigmine are poorly absorbed when given orally.

Certain drugs are degraded in the gastrointes- tinal tract, e.g. penicillin G by acid, insulin by peptidases, and are ineffective orally. Enteric coated tablets (having acid resistant coating) and sustained release preparations (drug particles coated with slowly dissolving material) can be used to overcome acid lability, gastric irritancy and brief duration of action.

The oral absorption of certain drugs is low because a fraction of the absorbed drug is extru- ded back into the intestinal lumen by the efflux transporter P-gp located in the gut epithelium. The low oral bioavailability of digoxin and cyclo- sporine is partly accounted by this mechanism. Inhibitors of P-gp like quinidine, verapamil, erythromycin, etc. enhance, while P-gp inducers like rifampin and phenobarbitone reduce the oral bioavailability of these drugs.

Absorption of a drug can be affected by other concurrently ingested drugs. This may be a *luminal effect*: formation of insoluble complexes, e.g. tetracyclines and iron preparations with calcium salts and antacids, phenytoin with sucralfate. Such interaction can be minimized by administering the two drugs at 2–3 hr intervals. Alteration of gut flora by antibiotics may disrupt the enterohepatic cycling of oral contraceptives and digoxin. Drugs can also alter absorption by *gut wall effects*: altering motility (anticholinergics, tricyclic antidepressants, opioids, metoclopramide) or causing mucosal damage (neomycin, methotrexate, vinblastine).

Subcutaneous and Intramuscular

By these routes the drug is deposited directly in the vicinity of the capillaries. Lipid soluble drugs pass readily across the whole surface of the capillary endothelium. Capillaries having large paracellular spaces do not obstruct absorption of even large lipid insoluble molecules or ions (Fig. 2.8A). Very large molecules are absorbed through lymphatics. Thus, many drugs not absorbed orally are absorbed parenterally. Absorption from s.c. site is slower than that from i.m. site, but both are generally faster and more consistent/ predictable than oral absorption. Application of heat and muscular exercise accelerate drug absorption by increasing blood flow, while vasoconstrictors, e.g. adrenaline injected with the drug (local anaesthetic) retard absorption. Incorporation of hyaluronidase facilitates drug absorption from s.c. injection by romoting spread. Many depot preparations, e.g. benzathine penicillin, protamine zinc insulin, depot progestins, etc. can be given by these routes.

Topical sites (skin, cornea, mucous membranes)

Systemic absorption after topical application depends primarily on lipid solubility of drugs. However, only few drugs significantly penetrate intact skin. Hyoscine, fentanyl, GTN, nicotine, testosterone, and estradiol have been used in this manner. Corticosteroids applied over extensive areas can produce systemic effects and pituitary-adrenal suppression.

Absorption can be promoted by rubbing the drug incorporated in an olegenous base or by use of occlusive dressing which increases hydration of the skin. Organo- phosphate insecticides coming in contact with skin can produce systemic toxicity. Abraded surfaces readily absorb drugs, e.g. tannic acid applied over burnt skin has produced hepatic necrosis.

Cornea is permeable to lipid soluble, unioni- zed physostigmine but not to highly ionized neostigmine. Drugs applied as eye drops may get absorbed through the nasolacrimal duct, e.g. timolol eye drops may produce bradycardia and precipitate asthma. Mucous membranes of mouth, rectum, vagina absorb lipophilic drugs: estrogen cream applied vaginally has produced gynaeco- mastia in the male partner.

BIOAVAILABILITY

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form as determined by its concentration-time curve in blood or by its excretion in urine (Fig. 2.6). It is a measure of the fraction (*F*) of administered dose of a drug that reaches the systemic circulation in the unchanged form. Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because—the drug may be incompletely absorbed. The absorbed drug may undergo first pass metabolism in the intestinal wall/liver or be excreted in bile.

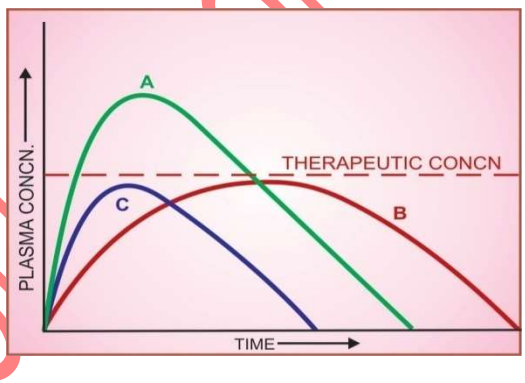

Fig. 2.6: Plasma concentration-time curves depicting bioavailability differences between three preparations of a drug containing the same amount

Note that formulation *B* is more slowly absorbed than *A*, and though ultimately both are absorbed to the same extent (area under the curve same), *B* may not produce therapeutic effect; *C* is absorbed to a lesser extent— lower bioavailability

Incomplete bioavailability after s.c. or i.m. injection is less common, but may occur due to local binding of the drug.

Bioequivalence Oral formulations of a drug from different manufacturers or different batches from the same manufacturer may have the same amount of the drug (chemically equivalent) but may not yield the same blood levels—***biologically inequivalent***. Two preparations of a

drug are considered ***bioequivalent*** when the rate and extent of bioavailability of the active drug from them is not significantly different under suitable test conditions. Before a drug administered orally in solid dosage form can be absorbed, it must break into individual particles of the active drug (disintegration). Tablets and capsules contain a number of other materials—diluents, stabilizing agents, binders, lubricants, etc. The nature of these as well as details of the manufacture process, e.g. force used in compressing the tablet, may affect ***disintegration***. The released drug must then *dissolve* in the aqueous gastrointestinal contents. The rate of dissolution is governed by the inherent solubility, particle size, crystal form and other physical properties of the drug. Differences in bioavailability may arise due to variations in disintegration and dissolution rates.

Differences in bioavailability are seen mostly with poorly soluble and slowly absorbed drugs. Reduction in particle size increases the rate of absorption of aspirin (microfine tablets). The amount of griseofulvin and spironolactone in the tablet can be reduced to half if the drug particle is microfined. There is no need to reduce the particle size of freely water soluble drugs, e.g. paracetamol.

Bioavailability variation assumes practical significance for drugs with low safety margin (digoxin) or where dosage needs precise control (oral hypoglycaemics, oral anticoagulants). It may also be responsible for success or failure of an antimicrobial regimen. However, in the case of a large number of drugs bioavailability differences are negligible and the risks of changing from branded to generic product or to another brand of the same drug have often been exaggerated.