1.5 ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF DRUGS (DRUG DISPOSITION AND PHARMACOKINETICS)

In order to achieve its effect, a drug must first be *administered* in a suitable dosage form at an appropriate site. It must then be *absorbed* effectively from the site of administration, and distributed in the body to reach its site of action. After its action, for the termination of its effect, the drug must be *metabolized*, and the metabolites *excreted* from the body **(Fig. 1.5.1)**

Absorption and distribution comprise the ***disposition*** of a drug, *i.e.*, its placement in the body. Metabolism and excretion comprise the ***fate*** of a drug.

Most commonly drugs are administered orally, and their pathway involves absorption, distribution, metabolism and excretion of both the unchanged drug and its metabolites (pathway a). A drug that is excreted in its unchanged form will bypass metabolism (pathway b). An intravenously administered drug undergoes no absorption (pathway c). An oral dose can be rapidly metabolized in the portal circulation and excreted in the bile before distribution in the body (pathway d). Lastly, excretion products in the intestine can be reabsorbed (pathway e).

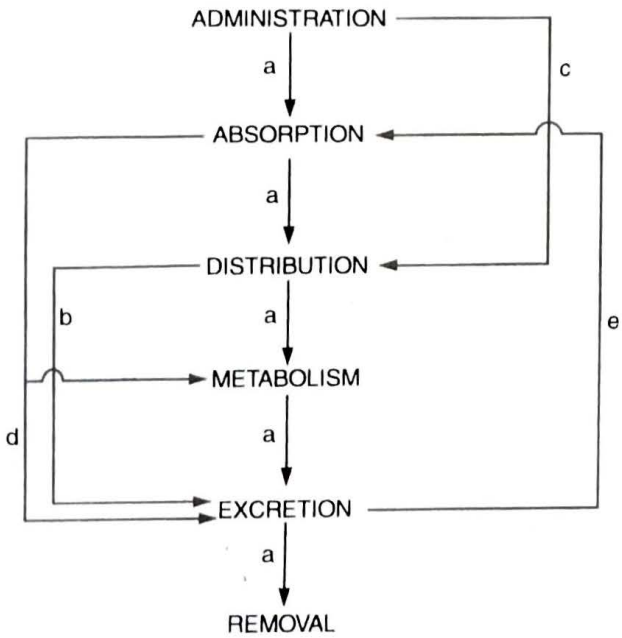

Fig. 1.5.1: Relationship between the various events involved in drug absorption, distribution, metabolism and excretion of drugs (see text).

Simply speaking, *absorption* is the entry of the drug molecules into the blood via the mucous membranes of the alimentary or respiratory tracts, or from the site of injection. *Distribution* is the movement of the drug molecules between the water, lipid and protein constituents of the body. ***Metabolism*** or ***biotransformation*** is the process of alteration in the structure of the drug molecule in the body, specially the liver, and excretion is the removal of the original drug molecule, or its metabolites from the body. Collectively, the term *elimination* is used for the process of metabolism and excretion of a drug.

The above mentioned four processes (absorption, distribution, metabolism, excretion) are studied quantitatively in the mathematical science of *pharmacokinetics*, and together they determine the concentration of drug molecules at the site of action.

Drugs and Cell Membranes

The processes of absorption, distribution, biotransformation and excretion require the *passage of the drug across cell membranes*. These membranes consist of a bimolecular layer of lipid molecules, coated with a protein layer on each surface **(Fig. 1.5.2)**. The cell membrane also has small "pores" and active transport systems. The ability of the drug to cross this membrane depends on its chemical and physical properties.

The chemical structure of a drug determines whether a drug will be more fat-soluble or water-soluble. In addition certain reactive portions of the molecule, or *functional groups* are responsible for the interaction of the drug with the tissue receptors.

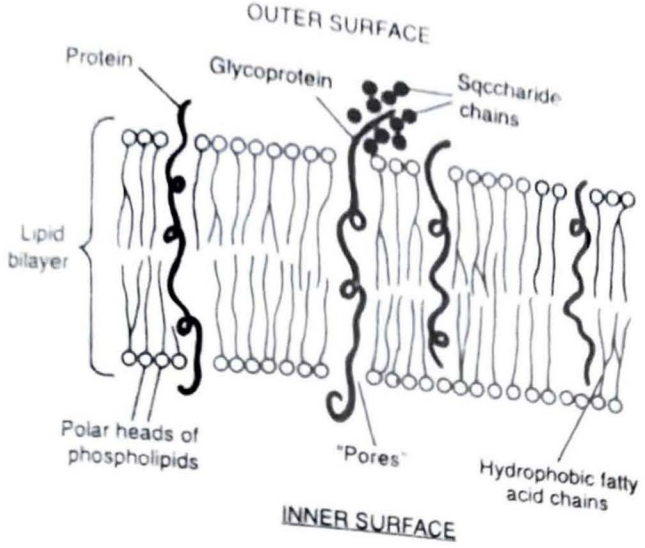

Fig. 1.5.2: Major features of a lipid bilayer cell membrane.

Drugs may cross body membranes by the following mechanisms:

1. **Passive Transfer**
   - Simple diffusion
   - Filtration
2. **Specialized Transport**
   - Active transport
   - Facilitated diffusion
   - Pinocytosis

Passive Transfer

The term *passive transfer* means that a drug or substance is taken up across a membrane without the need for energy. ***Simple diffusion*** requires no energy, and depends on the difference in concentration of the drug on either side of the membrane. Both fat-soluble and water-soluble molecules of small size may cross the membrane by simple diffusion. The term ***filtration*** is used when a porous membrane exists which allows the flow of substances of a certain size only, with the larger molecular sizes being blocked. The glomerular membrane of the kidney is an example of a filtering membrane.

Most drugs are weak *organic acids* or *bases*, and at the physiological pH of body fluids (7.35 to 7.45), drug molecules exist as a mixture of the *non-ionized* or uncharged molecular form, and the *ionized* or charged form. In general, it is observed that drugs are more lipid-soluble (fat-soluble) and less water-soluble when they are non-ionized; whereas, ionized molecules are less lipid-soluble and more water souble. The principle is that: *Cell membranes are more permeable to the non-ionized form of a drug than to an ionized form.* The basis of this is the greater lipid-solubility of the non-ionized form in the cell membrane. The *degree of ionization* of a given drug depends on two factors: the pKa of the drug, and the surrounding pH. The pKa value is defined as the pH at which the drug is half ionized and half non-ionized. For example, *acidic drugs* like *phenobarbital* (pK_a = 7.4) and *aspirin* (pK_a = 3.5) are present predominently in the un-ionized form in areas of low pH like the stomach (pH = 1-3). Hence, these drugs are significantly absorbed from this site. *Basic drugs*, in contrast, like *morphine* (pK_a = 7.9) and *amphetamine* (pK_a = 9.8) would be largely ionized at the pH of the stomach and not well absorbed. As these drugs move down the intestinal tract, the pH increases and acidic drugs become more ionized, whereas basic drugs are less ionized. Therefore, the absorption of basic drugs (morphine, amphetamine) increases as the molecules move through the intestines. The concept of pKa is derived from the Henderson- Hasselbalch equation:

$$pK_a = pH + \log \frac{(\text{conc. of non-ionized drug})}{(\text{conc. of ionized drug})} \quad \text{(acids)}$$

$$pK_a = pH + \log \frac{(\text{conc. of ionized drug})}{(\text{conc. of non-ionized drug})} \quad \text{(bases)}$$

It follows from these equations that, when a substance is half ionized and half non-ionized at a certain pH, its pK_a is equal to the pH. In other words, a substance is half ionized at a pH equal to its pK_a. The following examples would further substantiate the concept of pK_a, and the influence of the pH on the degree of ionization.

Salicylic acid (pK_a = 3)		*Quinine (base) (pKa = 8.4)*	
PH = 2	9% ionized	pH = 7.4	91% ionized
pH = 3	50% ionized	pH = 8.4	50% ionized
pH = 4	91% ionized	pH = 9.4	9% ionized

Specialized Transport

Active transport of a drug refers to a situation when the drug is moved against a concentration gradient, by the use of energy. ***Facilitated diffusion*** is a unique form of transport in which the drug attaches to a special "carrier" which facilitates the diffusion of the drug across the membrane, and then releases the drug. In this process the drug is not chemically altered, and the carrier is again free to facilitate further drug transfer. This process does not require energy as in the case of active transport. Further, facilitated diffusion differs from active transport in that *it can only work in the presence of an appropriate concentration gradient, i.e.*, it can only move drugs into the cell provided that their extracellular concentration is higher than their intracellular concentration. An example is the uptake of glucose by cells. ***Pinocytosis*** describes the ability of cells to surround and engulf small droplets. This process is of importance in the uptake of large molecules.

It is important to remember that the cell plasma membrane is not a fixed structure, but a *dynamic* one in which the various components are mobile. It contains membrane-bound water that interacts with ionized groups, and thus forms a barrier to the diffusion of water-soluble agents.The membrane is asymmetrical both structurally and electrically; it contains "pores" formed both within the membrane of a single cell and between the membranes of adjacent cells. Drugs with a molecular weight not exceeding 100 daltons are able to diffuse freely across the membrane through the polar pores. The pore size differs in the cell membrane of different tissues. The pores in the capillaries and the renal glomeruli are probably the largest (50–100 nm diameter) and offer greater ease of passage of substances compared to those in other tissues. The external surface of the membrane also contains pharmacological *receptors* (described later). These receptors are linked with intracellular mechanisms that can be switched on or off by the interaction of specific drug molecules with the membrane receptor.

A drug is unlikely to be absorbed unless it goes into solution, *e.g.*, barium ions are very poisonous but *barium sulphate* can be safely used in radiology as a contrast agent as it is *highly insoluble*.

Drug Absorption

Drugs may act at the site of drug administration, or more commonly at some distant part of the body. Most drugs are given *orally*, and they must pass through the gut wall to enter the blood stream. Whether a drug is applied locally, or is administered systemically, there are *five* main factors which determine its fate in the body: (*i*) *molecular weight*; (*ii*) *chemical stability*; (*iii*) *lipid solubility*; (*iv*) *degree of ionization*; and (*v*) *pharmaceutical formulation of the drug*. Each drug has its own characteristic *physico-chemical profile* which governs its fate in the body.

Molecular weight. Substances with a high molecular weight are not usually absorbed intact except in minute quantities. They may also be altered by enzymatic action, *e.g.*, on oral administration *proteins* will be broken down to their constituent amino acids. Thus, insulin undergoes enzymatic breakdown in the gut, and for practical purposes is not effectively absorbed.

Chemical stability. Unstable drugs are inactivated in the gastrointestinal tract. *Benzylpenicillin* is unstable in an acid medium, and cannot be relied upon to produce satisfactory results on oral administration, because a high proportion of the drug is inactivated by the acid in the stomach. In contrast, *phenoxymethylpenicillin* is more stable in an acid medium than benzylpenicillin, and adequate oral doses are therapeutically effective.

Lipid solubility. If a drug is to be absorbed from any part of the gastrointestinal tract, including the mouth, it is necessary for it to pass through cell membranes. Thus it must first pass through the cells of the mucous membrane of the gut, and then into the circulation either *directly* via the capillaries or *indirectly* via the lymphatic channels. As cell membranes are *lipid* in nature, the degree and rate of penetration of the drug through them is dependent to a large extent on the *lipid solubility of the drug*.

Degree of ionization. Under physiological conditions some substances, like *ethanol* (ethyl alcohol) are un-ionized, while others like *acetylcholine* are highly ionized. As also stressed earlier, majority of drugs are *weak bases* or *weak acids*, so that at a physiological pH (7.4) they exist partly in the *un-ionized* form and partly in the *ionized* form, the proportion of each varying with the environmental pH. The *absorption process is usually proportional to the lipid solubility of the drug*. The absorption of un-ionized molecules is favoured because they are more lipid-soluble than the ionized form which is surrounded by a "shell" of water molecules and is lipid-insoluble.

Pharmaceutical formulation. Various formulations of a drug can greatly influence the *amount* and *rate* at which it is absorbed, *e.g.*, effervescent aspirin (0.6 g orally) produced more than double the plasma level produced by an equivalent dose of ordinary aspirin (both measured after 30 minutes). However, when the same dose of ordinary aspirin was given in hot water it resulted in a plasma concentration almost as high as that attained with the effervescent preparation. Sometimes tablets or capsules may fail to disintegrate in the gut so that absorption does not take place. The absence of a therapeutic effect may be wrongly labelled to other factors such as too small a dose, or failure of the patient to take the medicine.

Absorption via Gastrointestinal Tract

Absorption of nearly all drugs from any site in the gastrointestinal tract is by passive diffusion. For most drugs, the proximal small intestine with its large surface area is the major site of absorption. Although ***acidic drugs*** such as aspirin and barbiturates can be absorbed from the stomach, they are usually absorbed faster when they reach the duodenum. ***Basic drugs*** including antipsychotics, anticholinergics, narcotics and sympathomimetics are usually absorbed only in the intestine. Their absorption is delayed if taken with food and trapped in the stomach until the pyloric sphincter opens.

First-pass metabolism refers to the biotransformation of drugs during absorption through the intestine and their transport through the liver in the portal circulation. It can significantly reduce the percentage of an oral dose that reaches systemic circulation. Drugs like *propranolol* are extensively metabolized as they pass through the liver–the "first-pass effect." ***Sublingual*** administration may be an alternative to the oral route if a drug is either *destroyed* in the gastrointestinal tract or *completely inactivated* as it passes through the liver for the first time, *e.g.*, *isoprenaline* and *nitroglycerin*, respectively. Nitrates, such as *nitroglycerin* and *isosorbide dinitrate* are more effective when given sublingually. Drugs may also be considered for sublingual administration, if the patient is vomiting. Sublingual *ergotamine* can be used to terminate migraine headaches in the nauseated and vomiting patient. Drugs administered sublingually must be non-irritating and absorbed quickly to avoid being swallowed in saliva. Few drugs fulfil both these criteria. Absorption of drugs through the buccal mucosa is limited by its *small surface area*, *palatibility* of the drug, and the extent to which it is ionized.

On ***oral*** administration three processes precede absorption: (*i*) ***Disintegration*** of the solid dosage form (tablet or capsule) into *granules*. The *disintegration rate* (in terms of time) is dependent on the dosage form. *Compressed tablets* take some time to break up in the stomach, and sometimes disintegration may be very slow, which delays absorption. Disintegration is deliberately delayed in *enteric coated tablets*, by a special acid-resistant coating material which is soluble only at a higher pH in the intestine. In general, both the *rate* and *extent* to which a drug is absorbed are greatest when the drug is administered in *solution* form and decreases in the mentioned sequence–solution, suspension, capsule, tablet, enteric coated tablet; (*ii*) ***Deaggregation*** of the granules forms fine particles; and (*iii*) ***Dissolution*** of the active material form fine particles into a *solution*. The dissolution rate depends on the particle size, the drug material, and the surrounding pH. On these three processes **(Fig. 1.5.3)** depends the ultimate absorption and *bioavailability* of the drug. With certain drugs none of the three processes is complete and thus their bioavailability is reduced. In contrast, with certain formulations the tablet or its granules may directly undergo dissolution to form a solution, thus increasing ***drug bioavailability***.

Optimal absorption of drugs from the gut cannot occur unless they are in solution by the time they reach the intestine. *Drug formulation* is one of the major factors determining the rate and extent of absorption. Variation between different "brands" of the same drug in their rate of dissolution produces major differences in the total amount of the drug reaching the site of action through systemic circulation (bioavailability). For drugs like *digoxin*, *phenytoin*, *tolbutamide* and *griseofulvin* the dissolution rate is an

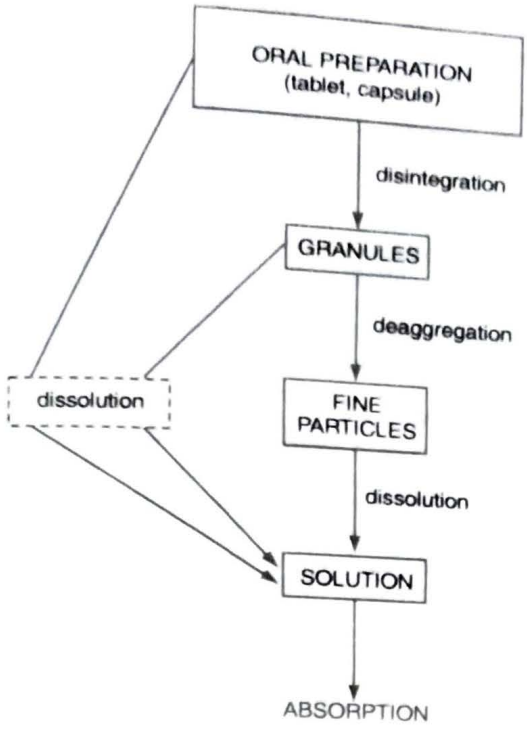

Fig. 1.5.3: Diagrammatic representation of the fate of oral preparations in the gut (see text).

important factor regulating their absorption. The binding of drugs in the gastrointestinal lumen also decreases the rate and extent of their absorption. One drug may decrease the absorption of another drug, *e.g.*, *tetracyclines* have *chelating* properties and form insoluble complexes with bivalent and trivalent cations in *antacids* and in iron salts. *Liquid paraffin* reduces the absorption of *lipid-soluble drugs and vitamins*.

Other factors which govern drug absorption from the gut are: (*i*) ***Surface area of absorption***; (*ii*) ***Gastric emptying speed***; (*iii*) ***Motility of the gut***; (*iv*) ***Splanchnic blood flow***; (*v*) ***Contents of the gut***, like food and other substances in the gut may delay absorption by binding or diluting drugs; (*vi*) **Certain disease states** involving the gut; and (*vii*) pH *within the gut*.

Briefly stated, the absorption of drugs from the gastrointestinal tract is mainly by *passive diffusion* through the lipid sheet, and few drugs are small enough to diffuse through the *pores* in the cell membrane. Uptake of sugar and other nutrients is by *active transport systems*. The gut membrane is more permeable to *non-ionized* lipid-soluble forms of drugs, and less permeable to the *ionized* form.

Absorption via Parenteral Sites

Drugs when injected intravenously (IV) are rapidly distributed, as they reach the blood stream directly without crossing any membranes. The factors which influence the rate of absorption from intramuscular (IM) and subcutaneous (SC) injection sites are: (*i*) *Drug concentration*; (*ii*) *Solubility of the drug*; and (*iii*) *Local blood flow*. Absorption following IM and SC injections usually occurs by *simple diffusion* in the direction of the concentration gradient from the injection site to the plasma or lymph. The most important factors controlling absorption from SC or IM sites are the *area of the absorbing capillary membranes*, and the *solubility of the drug in the interstitial fluid*. Filtration through channels in the endothelial capillary membrane is also very efficient, as these channels are relatively large and can allow passage of most lipid-insoluble drugs.

The dosage ***formulation*** can also affect absorption from parenteral sites, *e.g.*, drugs in aqueous ***solutions*** are usually absorbed more rapidly than drugs in ***suspension***, *e.g.*, benzathine penicillin with procaine penicillin G. Often drugs are suspended in certain vehicles, like oil, to reduce their rate of absorption and provide a prolonged action, *e.g.*, long-acting hormone preparations.

Absorption of drugs from IM sites is usually more rapid than from SC sites, because of the higher vascularity of the muscle compared to subcutaneous tissue. Decreased peripheral blood flow in conditions of "shock" significantly reduces the rate of absorption of injected drugs. Blood flow to an area can be increased and absorption enhanced by application of heat, local vasodilators and massage. In contrast, the absorption can be delayed by application of cold, a tourniquet, or vasoconstrictors. All the above mentioned factors have a profound effect on the *onset* and *duration* of action of a drug.

Absorption via Lungs (Inhalation)

Drugs presented in the correct form to the trachea and lungs are absorbed by *simple diffusion*. However, lipid-soluble compounds diffuse most readily. The correct form is a *vapour*, an *aqueous solution*, or a *suspension* of particles small enough to be evenly distributed over the mucous membrane. Examples of agents which diffuse rapidly through the respiratory mucosa include *nicotine*, *volatile anaesthetics* and *disodium cromoglycate*.

Absorption via Topical Sites

Drugs are usually applied to the skin for their topical (local) effects. Absorption of most drugs through the intact skin is poor, as the keratinized *epidermis* behaves like a barrier. However, the underlying *dermis* is quite permeable to many drugs, and significant absorption can occur if the skin is abraded or denuded. The extent of absorption through the skin is proportional to the lipid solubility of the drug and the surface area to which the drug is applied. Absorption can be enhanced by dissolving the drug in an *oily base*, *vigorous massaging of the area*, *occlusive dressing*, or simultaneously applying a keratin softening agent like *salicylic acid*.

Lately, drugs intended for systemic action are being formulated in a way that topical application is utilized as the route of administration. For example, the *nitroglycerin transdermal system patch* (Chap. **1.3**). This drug-impregnated patch is applied to the skin of the upper torso in patients of angina pectoris. Nitroglycerin is slowly absorbed through the skin to provide consistent and effective plasma levels for 12 to 24 hours. *Transdermal patches* of *scopolamine* and *clonidine* are now also available for control of motion sickness and hypertension respectively.

Absorption of most drugs through mucous membranes is usually very rapid, mainly due to the thin and highly vascular absorbing surface. However, drugs applied to mucous membranes are generally used for their local action, *e.g.*, nasal decongestants or vaginal anti-infectives. Rather their systemic absorption may result in unwanted side

effects. Some drugs like *ergotamine* and *vasopressin* may be applied to mucous membranes to facilitate their systemic absorption.

Bioavailability

The term *bioavailability* has been used to describe a number of concepts associated with the effect of administration of a drug preparation, namely, its *extent of absorption*, *its availat..ty at receptor sites*, and *its therapeutic effectiveness*. However, at a simplified level, it is used to describe the biological availability of a drug from a preparation, and is quantified in terms of the *amount* and the *rate* of appearance of the drug in the blood. There has been much interest currently in the observation that various preparations of the same drug administered orally may give different serum concentrations.

Bioavailability has been defined as the *relative absorption efficiency* of a test dosage form compared to a standard preparation. Thus, bioavailability of a drug is the percentage of a dose that reaches the systemic circulation after administration via a stated route. The application of this concept of bioavailability to the comparison of various formulations of the same drug is referred to as *bioequivalence*.

The bioavailability of any drug after IV administration is 100 percent, and is usually assumed to be close to this value when given IM or SC. However, some highly insoluble drugs like *phenytoin*, *digoxin* and *diazepam* partly precipitate at the site of injection, and then are slowly absorbed. The bioavailability of drugs after oral administration is frequently less than 100 per cent. In view of this, problems regarding drug bioavailability usually refer to the oral administration of drugs.

In short, bioavailability describes the *extent* and the *rate* of drug absorption from a dosage form as reflected by the ***serum concentration-time curve***. This curve is obtained by plotting serum concentration of the drug versus time **(Fig. 1.5.4)**.

Bioavaliability of an oral dosage form is determined by comparing the *Area Under the Curve* (AUC) after oral administration of a single dose with that obtained when the same dose is given IV (100 percent absorption):

$$\text{Drug bioavailability} = \frac{\text{AUC (oral)}}{\text{AUC (IV)}} \times 100$$

If all the drug that is absorbed is excreted unchanged in the *urine*, then a similar determination can be carried out using the *urine concentration versus time curve*. But if the drug is metabolized in the body, as usually happens, the metabolites as well as the parent drug must be measured. The bioavailability can also be determined after chronic administration of a drug, and there is usually good agreement between the results obtained by a single and multiple dose studies.

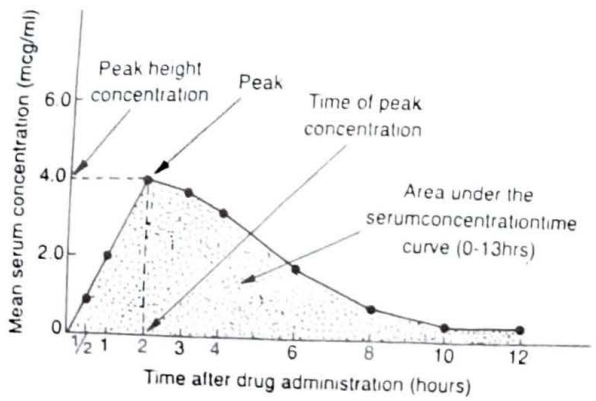

Fig. 1.5.4: Serum concentration-time curve for a hypothetical drug showing peak height concentration, time of peak concentration, and area under the curve (AUC).

The main factors determining bioavailability of an orally administered drug include: (i) Drug formulation; (ii) Inactivation in gut lumen, bowel wall and *liver; (iii) Interactions in gut lumen, (iv) pH within the gut; (v) Gastric emptying time and gut motility;* and *(vi) Certain disease states involving the gut*. The relevant details have already been discussed under the head—Absorption via gastrointestinal tract (refer back).

Bioequivalence

Bioequivalence is said to exist when the bioavailability of a drug from different formulations is the same. But manufacturers do not always use identical processes and formulae in tablet production of a drug, so that *disintegration* and *dissolution* rates may very. Such variations often lead to differences in drug bioavailability from tablets of identical stated potency prepared by different manufacturers. Such *bio-inequivalence* has been found to exist in different preparations of a number of drugs like *digoxin, tetracyclines, aspirin, phenytoin, theophylline* and *warfarin*. The clinical significance of bio-inequivalence of some dosage forms is greatest for drugs with a low therapeutic index, where the drug effect is closely related to their plasma concentration, and the margin of safety is narrow, *e.g., warfarin, digoxin, phenytoin, oral hypoglycaemics* and *cytotoxic drugs*. Bio-inequivalence of different formulations of the same drug has been widely publicised by the pharmaceutical industry as a rational argument in favour of prescribing drugs by their *proprietary or brand names* rather than their *generic names*.

Prodrugs

An approach to improve bioavailability is to modify the drug molecule chemically to form a better absorbed compound, which liberates the active drug after absorption. Such modified drugs are known as *prodrugs*. For example, *dipivalyladrenaline* is a prodrug of adrenaline, and is enzymatically converted to adrenaline after instillation in the eye. As dipivalyladrenaline is better absorbed, less drug is required and side effects are minimized. Similarly, carbenicillin is poorly absorbed from the gut, but its ester *indanyl carbenicillin* is much better absorbed, and on absorption is hydrolysed to carbenicillin (Table 1.5-1).

Table 1.5-1. *Prodrugs and their active metabolites*

Prodrug	*Active metabolite*
Dipivalyladrenaline	Adrenaline
Ibuterol	Terbutaline
Indanyl Carbenicillin	Carbenicillin
Pivampicillin	Ampicillin
Talampicillin	Ampicillin
Prazepam	Desmethyldiazepam
Clorazepate	Desmethyldiazepam

Drug Distribution

After a drug has been absorbed into the circulatory system, its distribution in the dody is governed by a number of factors. Drug distribution describes the process which

transports a drug to its site of action, to other storage sites in the body, and to organs of metabolism and excretion (Fig. 1.5.5). The movement of drug molecules in these areas determines its *effectiveness, its duration of action*, its mode of

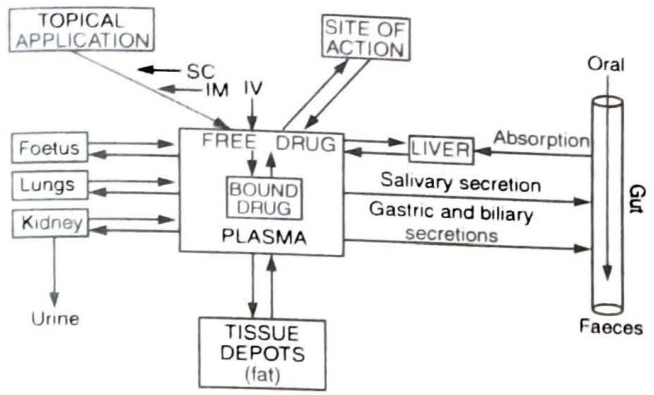

Fig. 1.5.5: Basic model of pathways of drug movement (pharmacokinetics) in the body. Bidirectional arrows denote that a drug and/or its metabolites move in both directions between the indicated points. (SC = Subcutaneous; IM = Intramuscular; IV = Intravenous).

metabolism, and its rate of excretion. As the distribution pattern of a drug is ultimately dependent on its ability to cross cellular membranes, the principles governing membrane transport of drugs, discussed earlier in this Chapter, also apply here. Thus, *lipid-soluble* drugs tend to distribute more widely in the body compared to lipid insoluble drugs, as they cross cellular membranes more readily. Considering the highly permeable nature of the capillary endothelium (except brain capillaries), almost all organs (except CNS) can be affected by any given drug. Initial distribution of a drug is primarily dependent on the cardiac output and the local blood flow in various body organs. Thus, highly perfused organs like the heart, liver, kideny and brain receive the largest amount of drug immediately after absorption. Subsequently, other factors come into play that govern the final distribution pattern of a drug.

The main factors which govern distribution are:

1. Physicochemical characteristics of the drug.
2. Route of drug administration.
3. Binding to plasma proteins.
4. Regional blood flow.
5. The availability of active transport systems.
6. Special compartments and barriers.

All these factors are interdependent, and are considered briefly below :

Physicochemical characteristics. Drugs reach the extracellular space by *passive diffusion* through junctions or "pores" between the endothelial cells, except in the brain which has tight junctions between these cells. Only lipid soluble drugs cross cell membranes effectively to an extent which depends on their pK_a and the pH of the surrounding medium as discussed earlier. Lipid-soluble compounds like *lignocaine, propranolol*, and *tricyclic antidepressants* are widely distributed in tissues like the brain, liver and lung. In contrast, heparin is confined to the plasma because of its high molecular weight and ionization.

Route of administration. Drugs given intravenously are preferentially distributed in organs with a high regional blood flow. In contrast, drugs which are well absorbed from the gut are extracted and concentrated in the liver during their "first-pass", *e.g., propranolol* and *tricyclic antidepressants*. Their distribution pattern and metabolic fate is different when administered orally and intravenously.

Binding to proteins. Drugs may bind either to plasma proteins, usually albumin, or to proteins of cells (nucleoproteins). Drugs bound to plasma protein are in equilibrium with free drug in the plasma water, but only the *free drug* exerts a pharmacological effect. Plasma protein binding of a drug slows the disappearance of the drug from the plasma, limits its access to its site of action, and prolongs the time the drug remains in the body by slowing its renal filtration. Most of the drugs bind to plasma albumin because of its high concentration providing a large total surface area. Only a few drugs are appreciably bound to other proteins, *e.g.*, steroid hormones and thyroxine to alpha-globulins; fat soluble vitamins to alpha- and beta-globulins. The importance of protein binding is illustrated in the use of *diazoxide*, an antihypertensive drug used to treat acute hypertensive crisis. The speed of intravenous injection is critical to its intensity and duration of action. If it is injected slowly over minutes, its antihypertensive effect is not pronounced. When it is injected rapidly (10 seconds), its intensity of action and duration of effect is pronounced, as the drug in this case exists in much greater quantity in the "free" or unbound form. Therefore its access to its site of action in the blood vessels is enhanced. On slower injection, nearly all the drug becomes protein bound, and its effectiveness is reduced. Thus, diazoxide is administered intravenously as a rapid "bolus" injection for its optimal effect.

The total amount of drug bound in the plasma depends on: (*i*) its *plasma concentration*; (*ii*) *affinity for binding sites on albumin*; and (*iii*) *the total number of available protein binding sites*. The binding is usually reversible and an equilibrium exists between the *free* and *bound* forms of a drug, expressed as:

$$\text{Free Drug} + \underset{\text{(albumin)}}{\text{Plasma protein}} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Drug:Protein complex}$$

here k_1 reflects the rate at which the drug binds to plasma proteins, and k_2 is the rate of *dissociation* of drug from plasma proteins. The processes of *association* and *dissociation* are very rapid and are measured in milliseconds only. Since it is only the *free drug* that is capable of crossing membranes, protein binding interferes with the access of a drug to its site of action. In addition, as binding slows excretion, a "reservoir" of the drug develops in the plasma. As free drug leaves the plasma by excretion, metabolism, or diffusion into other tissues, the drug-protein complex dissociates to supply more free drug. Conversely, as the drug concentration increases in the plasma, more free drug becomes bound. As the binding capacity of plasma proteins is limited, a point of saturation can be reached. Once the protein-binding sites are completely occupied, further administration of the drug results in toxic reactions due to the large amount of the drug remaining non-protein-bound. Many different kinds of drugs are protein bound, and simultaneous administration of two or more of these drugs can result in competition for available sites on the binding proteins, and displacement of active drug may result in enhanced or toxic drug effects. This aspect is further discussed in **Chapter. 1.8.** There are a large number of

drugs which are more than 90 per cent bound to plasma albumin at therapeutic blood concentrations, *e.g., doxycycline, nalidixic acid, warfarin, sulphinpyrazone, indomethacin, chlorothiazide, propranolol, diazoxide, chlorpropamide, imipramine, amitriptyline,* and *phenytoin*. The distribution and efficacy of drugs which are highly bound to plasma proteins can be influenced by disease, *e.g.*, in *hypoalbuminaemia* due to hepatic cirrhosis or nephrotic syndrome.

Regional blood flow. Blood flow markedly varies from tissue to tissue. The brain, endocrine glands, the heart, kidneys, liver and the lung are well perfused. Muscle and skin are moderately perfused, whereas adipose tissue (fat) is poorly perfused, and the bones and teeth receive the least blood supply. Tissues with a good regional flow equilibrate rapidly with the drug present in the blood, *i.e.*, the skeletal muscle equilibrates more slowly than the heart and brain, but faster than adipose tissue. Drug distribution is grossly altered when tissue perfusion is reduced like in *heart failure, cardiogenic shock* or *hypothyroidism*.

Availability of active transport systems. Some drugs are concentrated in certain tissues as a result of uptake by selective active transport systems, *e.g.*, the adrenergic neurone blocker (guanethidine) into the adrenergic nerve terminal; iodine is actively concentrated into the thyroid cells. In contrast, the blood-brain barrier prevents many drugs from entering the central nervous system (CNS).

Special Compartments and Barriers

The plasma space. Drugs leave the plasma by diffusing across the capillary membrane which has the characteristics of a lipid membrane. In contrast to other membranes there are relatively large "pores" in capillary membrances that allow unrestricted diffusion of water-soluble drugs of molecular weight (MW) upto 5000, and relatively unrestricted diffusion upto MW 69000. Thus all drugs other than those that are proteins can readily diffuse into the extracellular space. The protein bound fraction of drugs cannot diffuse out of the plasma, hence cannot reach receptor sites. The capillaries of the hepatic sinusoids, and those of the gut have larger "pores" than elsewhere, and this accounts for the fact that some highly protein-bound drugs can be taken up rapidly by the liver.

Blood-brain barrier. Anatomically there is a dual barrier in the CNS—the blood-brain barrier and the blood-CSF (cerebrospinal fluid) barrier. The dye *trypan blue* given IV does not stain the brain, but the brain is stained after its intrathecal administration. It is established that some drugs enter the CNS with relative ease, while others do not enter at all. This is because the endothelial cells of brain capillaries differ from most other capillaries, as they are very tightly joined together and lack intercellular "pores" and pinocytotic vesicles. In addition, brain capillary cells are enveloped by less permeable cells, known as the *pericapillary glial cells*. Thus, drug molecules have not only to diffuse across the tightly packed endothelial cells, but also must cross the poorly permeable glial cells to enter the CNS. It must be stressed that this is *not an absolute barrier*, but there is a measurable difference in the permeability of CNS capillaries to various drugs compared to other capillaries. To cross the blood-brain barrier more easily, a drug should possess the following qualities:

(*i*) Low ionization at plasma pH;

(*ii*) High lipid-solubility of the non-ionized form of the drug; and

(*iii*) Minimal plasma protein binding.

Thus, a highly lipid-soluble barbiturate like thiopentone readily enters the CNS and exerts almost an immediate depressive effect on the CNS. Whereas, drugs which are highly ionized like most *penicillins* and *gentamicin* penetrate very slowly. On inflammation of the meninges (meningitis or encephalitis) the permeability of the blood-brain barrier is greatly increased, and many drugs previously excluded from the CNS are able to cross the barrier.

Placental barrier. The structure of the placenta is well suited for exchange of materials. The passage of most drugs from the maternal to foetal circulation occurs quite easily. Thus the term barrier is inappropriate as applied to the placenta. The placental membrane is lipid in nature, and readily allows the transfer of *non-ionized, lipid-soluble* drugs by simple diffusion down a concentration gradient. Thus, most drugs that are well absorbed orally can easily enter the foetal circulation. Only other drugs that are highly ionized or have a molecular weight above 1000 find it difficult to cross the placental membrane. Lipid-soluble drugs like *paraldehyde, chlorpromazine, gaseous anaesthetics, sulphonamides, barbiturates, morphine, pethidine, heroin* and *alcohol* readily cross the placental membrane.

Placental transfer of drugs is responsible for many untoward effects on the foetus that result from use of drugs by the mother. Moreover, many drugs have the potential to cause physical defects in the growing foetus, specially if given during the first trimester of pregnancy. These are labelled as *teratogenic effects*, and have been found to be associated with the use of *phenytoin, cortisone, streptomycin* and many *antineoplastic drugs*.

Eye. The conjunctiva, sclera, iris and the ciliary muscle receive moderate blood supply (cornea and lens are avascular). Lipid-soluble drugs can penetrate and reach these structures and the aqueous humour from the conjunctival sac, *e.g., prednisolone sodium phosphate, atropine, chloramphenicol* and *cocaine*. The choroid and retina are moderately vascular but the vitreous humour is avascular. These structures are not reached by medication via the conjunctival sac, but only from systemic circulation.

To sum up, after absorption drugs are distributed like nutrients by the blood stream. A variable amount of the drug is bound to plasma proteins and tissues, and is rendered temporarily inactive. Because of special characteristics of the capillaries in the brain, placenta, eye, intestinal mucosa and kidneys there is a differential distribution of drugs which is dependent on their physicochemical properties **(Fig. 1.5.6).**

Drug Metabolism (Biotransformation)

Termination of drug effect, also termed as drug elimination, involves two processes: (*i*) metabolism, mainly in the liver and kidney; and (*ii*) excretion of the unchanged drug and/or its metabolites by the kidneys, gut, lungs, sweat glands, breasts and salivary glands. Some drugs (general anaesthetics) are excreted from the body unchanged, but the majority of them are metabolized in the body. The metabolic conversions, *firstly*, render the compound more suitable for excretion by the liver and kidney, and *secondly*, play a role in determining the effective concentration of the

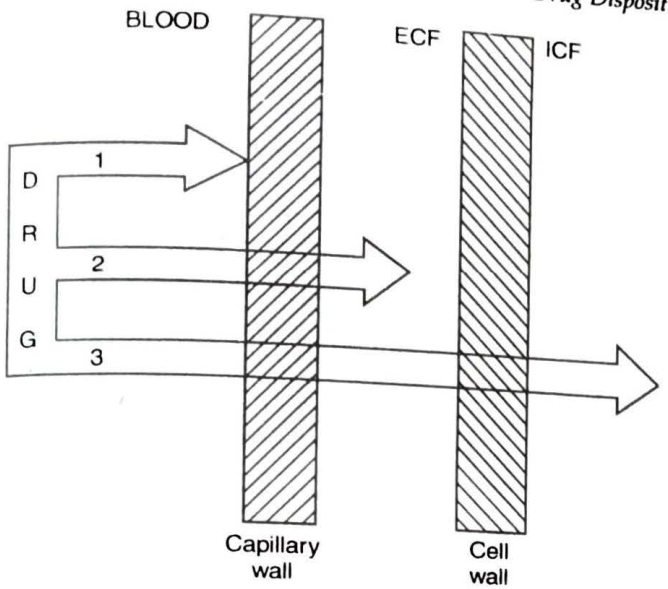

Fig. 1.5.6: Differential drug distribution: After absorption drug is bound to plasma protein (1); water soluble drugs may either penetrate fully (3) or be confined to the ECF (2); lipid-soluble drugs readily penetrate into the ICF (3). Important membrane barriers are the blood-brain barrier, placenta, eye, intestinal mucosa and the kidney. ECF = extracellular fluid; ICF = intracellular fluid.

drug in the body. The term *biotransformation* may be used interchangeably with *metabolism* of drugs.

Drug metabolism occurs predominently in the liver by way of ***hepatic microsomal enzyme systems***. These consist of a group of enzymes located on the *smooth endoplasmic reticulum* of liver cells. The endoplasmic reticulum resembles a series of canals that are continuous with the cell membrane and the membrane of the nucleus. Lipid-soluble drugs easily gain access to these metabolizing enzymes in liver cells. The microsomal enzymes catalyze several important reactions involved in drug metabolism, notably ***oxidation*** and **conjugation.** Other reactions like *hydrolysis* and *reduction* may be catalyzed both by microsomal and non-microsomal enzymes (see later).

Biotransformation generally results in the conversion of a drug to a metabolite that is less *active,* less lipid-soluble, and hence easily excreted. Some drugs are converted by liver enzymes into metabolites that are *equally active, e.g., imipramine* and *amitriptyline* are N-methylated (a methyl group is removed from a nitrogen) to form *desipramine* and *nortriptyline,* respectively. All four of these compounds are effective antidepressants. Whereas, some drugs are administered in the form of an inactive *prodrug,* which is then converted to an active metabolite in the body. This aspect is discussed earlier in this Chapter as a means to improve bioavailability.

The activity of **hepatic microsomal enzymes** can be altered by a number of factors. Enzymatic function is reduced in the presence of *liver diseases* or *impaired circulation.* Drugs like monoamine oxidase inhibitors (MAOIs) and organophosphorus insecticides also adversely affect the liver microsomal enzyme system. Decreased enzymatic activity results in slowed metabolism of drugs, leading to *cumulation* and *toxicity.*

Microsomal enzyme function can also be increased by a number of drugs, and is termed as enzyme induction. Prolonged administration of *barbiturates, phenytoin, carbamazepine, ethanol* and a number of other drugs results in an accelerated metabolism of drugs by the hepatic microsomal system. This effect is responsible for the development of tolerance to the action of those drugs which are metabolized in the liver because of the presence of an enzyme inducer.

In the liver biatransformation of drugs usually occurs in two phases : (*i*) *Phase I reactions;* and (*ii*) *Phase II reactions* (**Table 1.5-2**).

Phase I reactions. These preconjugation reactions produce a chemical change in the drug molecule. Such reactions include *oxidation* (*e.g.,* hydroxylation; dealkylation; deamination; sulfoxide formation); *reduction* (*e.g.,* azo dye reduction; nitro-reduction; dehalogenation); and *hydrolysis* (*e.g.,* cleavage of ester and amide bonds). The concerned enzymes require the presence of cytochrome P450, NADPH (reduced nicotinamide adenine dinucleotide phosphate) and molecular oxygen, which are localized mainly in the microsomal fraction of the liver cell. Phase I reactions are non-synthetic in nature, and generally produce a more water soluble and less active metabolite. The majority of phase I metabolites are generated by a ccmmon hydroxylating enzyme system known as cytochrome P450.

Phase II reactions. These *conjugation* or *synthetic* reactions inivolve the coupling of the drug or its metabolites formed in phase I to another chemical group (*e.g.,* sulphate, acetate), or substrate (carbohydrate, amino acid). The end products formed are more water soluble and can be eliminated in bile or urine. Phase II reactions can also occur without prior phase I reactions (oxidation, reduction or hydrolysis) if suitable groupings pre-exist on the molecule. The outline of processes involved in biotransformation is given in **Fig. 1.5.7.**

Hepatic non-microsomal drug metabolism. Apart from the hepatic celllular microsomes, the *cell sap* is another site in the liver where phase II reactions can take place. An important enzyme located in the cell sap is N-acetyltransferase which is responsible for *acetylation* of *isoniazid, hydralazine, sulphonamides* and *procainamide.*

Table 1.5-2. *Phase I and Phase II reactions involved in drug metabolism.*

Phase	*Reaction*	*Enzyme*	*Typical Examples*
I	*Oxidation* of aliphatic and aromatic groups	Cytochrome P450	Meprobamate, Barbiturates, Phenytoin, Phenothiazines, Antihistamines, Steroids, Chlordiazepoxide, Diazoxide Chloramphenicol
I	*Reduction* of azo and nitro groups	Flavin enzymes	Chloral hydrate Procaine
I	*Hydrolysis*	Esterases Amidases	Lignocaine, Indomethacin Paracetamol, Chloramphenicol
II	*Glucuronide synthesis*	Glucuronyl transferase	Isoprenaline
II	*Methylation*	Catechol-O-methyl transferase	Isoniazid, Sulphonamides
II	*Acetylation*	N-acetyl transferase	

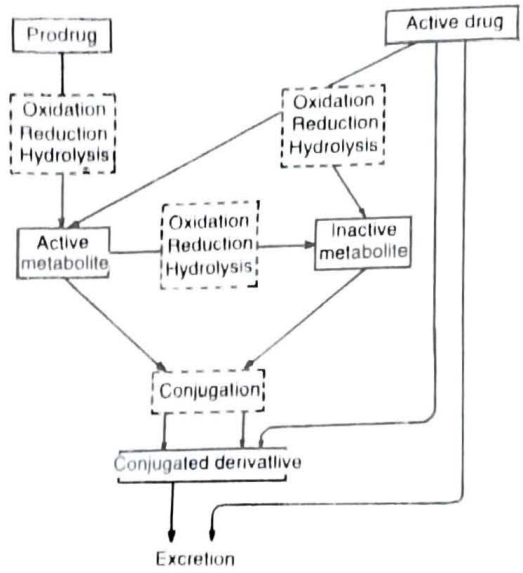

Fig. 1.5.7. Flow chart of reactions involved in biotransformation of drugs. Active drugs may be conjugated or excreted without undergoing metabolism (right).

Although the liver is the main site for metabolism of the majority of drugs, several other organs also contain drug-metabolizing enzymes and biotransform drugs.These important sites are the *kidney, lung, intestinal mucosa, plasma,* and *nerve endings.*

There may be considerable variation in the *rate* at which different individuals metabolize drugs. Some of the important factors are: (*i*) *Associated liver diseases;* (*ii*) *Age;* (*iii*) Presence of other drugs like barbiturates; pesticides and dyes which cause *microsomal enzyme induction;* and (*iv*) Genetically determined differences in metabolic activity, which may explain hypersensitivity, drug resistance or tolerance in certain subjects.

Drug Excretion

Drugs can be excreted in their *unchanged* form or as metabolites by several routes including the *kidney, lungs* and *intestine,* and to a *lesser* extent by the *sweat, salivary* and *mammary glands.* Among these, the most important excretion channel for the majority of drugs is the kidney. In general, the more water-soluble a drug or a metabolite, the more efficiently it is eliminated from the body.

Renal Excretion

Three major processes are involved in the excretion of drugs by the kidneys: (*i*) *Glomerular filtration;* (*ii*) *Tubular secretion;* and (*iii*) *Tubular reabsorption.*The first two processes remove drugs from the plasma, whereas the third process retains drugs in the body by returning them to the plasma **(Fig. 1.5.8)**. The *net excretion* of a drug therefore, depends on the sum total of the three processes.

Glomerular filtration. By this process drug molecules diffuse out of the blood perfusing the glomeruli of the nephron, and pass into the tubules of the kidney. The capillaries of the glomerulus are similar to those elsewhere allowing unimpeded diffusion of drugs with a molecular weight (MW) 5000 or less, and partially impeded diffusion of drugs between 5000–69000 MW. Thus, all drugs that are not protein bound appear in the glomerular filtrate. The glomerular filtrate is about 120 litres/day, but the daily urine

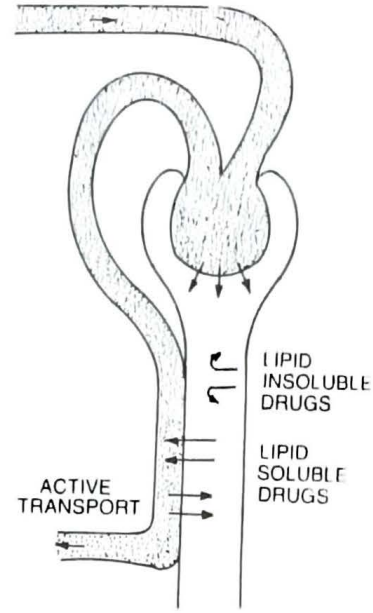

Fig. 1.5.8: Excretion of drugs by the kidney (diagrammatic)

volume is only 1-2 per cent of this volume. Drugs which are highly protein bound (phenobarbitone, warfarin, diazepam, digoxin) are excreted slowly, as the amount of free drug available for filtration is low. The drug which is passed into the glomerular filtrate may either be reabosorbed into the blood at various segments of the tubule, or excreted into the urine. Thus, several factors influence renal excretion by glomerular filtration: (*i*) Molecular size, as smaller molecules are more readily filtered; (*ii*) *Plasma protein binding,* as only free drug can be filtered by the kidney, and protein binding decreases renal excretion; and (*iii*) *Renal* flow and *volume of filtrate,* as greater the glomerular perfusion, larger is the volume of fluid filtered leading to faster drug removal from the plasma.

Tubular secretion. The proximal renal tubule can actively secrete certain drugs, transporting them from the blood stream into the tubular fluid. This is an energy requiring or carrier-mediated process, and is not significantly affected by protein-binding as long as the binding is reversible. Active secretory mechanisms exist for both acidic (*e.g.,* salicylates, sulphonamides, thiazide diuretics, penicillins, cephalosporins) and basic (*e.g.,* adrenaline, noradrenaline, dopamine, neostigmine, hydralazine, morphine, procaine, quinine) drugs. Many drugs that are secreted by the tubule are also filtered by the glomeruli, and thus have a very short duration of action, *e.g., penicillin.* Since the tubular secretion process requires energy, it can be inhibuted by certain drugs. For example, *probenecid* is often combined with *penicillin* to inhibit the active tubular secretion of penicillin by competing for the saturable transport system, thus prolonging the duration of action of penicillin in the body. There are no drugs available for use in clinical practice that block the active secretion of bases.

Tubular reabsorption. Almost throughout the renal tubules, reabsorption of drugs, back into the capillary network occurs, and a portion of the filtered fraction of a drug is retained back. The renal tubule behaves like a typical lipid barrier, specially in the distal region. Thus, renal tubular reabosorption is quite similar to absorption from the gut, *i.e.,* drug molecules are *passively* transported through the tubular epithelial cells. Hence, a drug existing in the non-ionized,

lipid-soluble state in the tubular fluid is more rapidly and more completely reabsorbed than a drug which is highly ionized in tubular fluid. Therefore, weak acids like *salicylates, barbiturates* and *sulphonamides* are excreted more readily as the pH of the tubular fluid increases, as weak acids ionize more as the urine is made more basic. In contrast, weak bases like *amphetamines, ephedrine* and *pethidine* are best excreted in an acid urine, as they are largely ionized at low pH. Acidification or alkalization of urine with drugs like ascorbic acid or sodium bicarbonate, respectively, may be employed to hasten excretion of certain drugs in cases of overdosage or poisoning. For example, phenobarbital or salicylate intoxication may be managed in part by administration of sodium bicarbonate (forced alkaline diuresis) to raise the urine pH, thus promoting ionization of the drug. Less frequently forced acid diuresis may be used to enhance the excretion of amphetamines, strychnine and quinidine.

Biliary Excretion

Excretion in the bile is a relatively minor route of elimination of unmetabolized drugs, but it is a *major* route of elimination of drug metabolities, particularly water-soluble conjugates like glucuronides. Drugs like *ampicillin, tetracycline* and *rifampicin* are actively secreted in the bile, and passed into the intestines, from where they may be either reabsorbed or lost in the faeces. Drugs that are unabsorbed from the gut, or secreted into the gastrointestinal tract by the bile, salivary glands and digestive glands are excreted in the faeces.

Pulmonary Excretion

This route of excretion is important primarily for *gaseous* and *volatile liquid general anaesthetics*, which can be excreted from the blood stream across the alveolar membrane into the expired air. Many other volatile substances like *ethyl alcohol, paraldehyde* and *oils* can appear in the expired air in small amounts. Enough ethyl alcohol can be eliminated unchanged by the lungs to be detected and measured. This procedure (breathometer) is often used to estimate the blood level of alcohol which correlates with the degree of intoxication.

Excretion of drugs in *sweat, saliva, milk* and *gastric juice* is mainly by passive diffusion of the non-ionized form. Some drugs are reported to be transferred to the suckling infant in breast milk in significant amounts. Hence, drug use by a *breast feeding* mother should be restricted to the minimum.

Pharmacokinetics

In a broad sense pharmacokinetics is the study of drug absorption, distribution, metabolism and excretion. All these factors interact to produce a definite pattern for the time course of *absorption, distribution* and *excretion* of each drug and its metabolites. Strictly speaking pharmacokinetics is the science which uses mathematical models to describe and quantify processes which determine the time course of drug action. It is a complex science, hence only basic considerations are included in this text.

Drug plasma concentration. The speed of onset, intensity and duration of drug effects are determined by the drug concentration at its site or sites of action. In most cases, it is impossible to obtain this measurement. Thus, an assumption is made that the time course of drug concentration at its site of action is determined by that in the plasma.

If a drug is administered intravenously, it enters the blood and is rapidly distributed to the tissues. By taking repeated blood samples, the fall in *plasma concentration* of the drug as related to time can be measured, *i.e.* the *rate of drug elimination*. Often the concentration falls rapidly at first, and then the rate of fall progressively decreases. If this fall is plotted against time, the resultant curve is *exponential, i.e.* at any given time a *constant fraction* of the drug is eliminated in unit time. This is called ***first-order kinetics*** of drug elimination **(Fig. 1.5.9)** Most drugs follow the first-order kinetics. If any enzyme system responsible for drug metabolism becomes saturated then the elimination kinetics changes to ***zero-order kinetics***, *i.e.*, the rate of elimination proceeds at a *constant rate* and is unaffected by the level of concentration of the drug (*e.g.*, ethanol, phenytoin).

Volume of distribution (Vd). This is the apparent volume into which the drug is distributed on intravenous administration. Vd can be calculated by the following equation:

$$\text{Vd (in litres)} = \frac{\textit{Amount of drug in the body (dose in mg)}}{\textit{Concentration of drug in plasma (mg/l)}}$$

A value of Vd < 5 litres implies that the drug is retained within the vascular compartment. A value of < 15 litres suggests that the drug is restricted to the extracellular fluid, while large volumes of distribution (Vd > 15 litres) indicates distribution throughout the total body water or concentration in certain tissues. The Vd can be used to calculate the clearance of the drug.

Clearance. This represents another estimate of the body's efficiency to remove a drug. Clearance is analogous to renal clearance, *i.e.*, the total volume of plasma from which the drug has been removed per unit time. It can be calculated from the equation:

$$\text{Clearance (Clp)} = \frac{\text{Vd} \times 0.693}{\text{half-life}(t_{1/2})}$$

The whole body clearance of a drug is the volume of plasma "cleared" of the drug per minute, regardless of the means by which it is cleared or removed from the plasma. Thus, Clp = Clm (metabolic clearance) + Clr (renal excretion). In fact, it is clearance and not half-life ($t_{1/2}$) which provides an indication of the ability of the liver and kidney to dispose of drugs.

Half-life ($t_{1/2}$). It is the time taken for the concentration

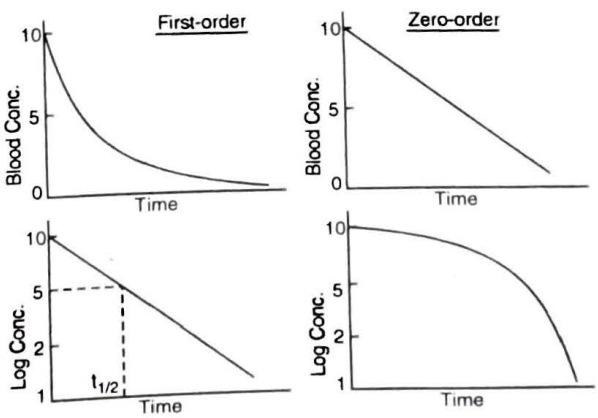

Fig. 1.5.9: The relationship between drug concentration and time with first order and zero-order elimination processes (see text).

of a drug in the plasma to fall by half of its original value. The ***plasma half-life*** is the most used measure, and is closely related to the concentration of the drug at the site of action. It is comparatively easily measured, and is influenced by the route of administration, diffusion into tissues, plasma protein and tissue binding, metabolism and renal excretion. Further, plasma $t_{1/2}$ determines the time taken to achieve a steady-state or an equilibrium condition with any constant dose rate. In practice a useful estimate of time required to reach a steady-state is obtained by the equation:

Time to 95% steady-state = $4.3 \times t_{1/2}$

As a working rule it is followed that it will take five half-lives to reach a steady-state on regular dosing. A caution is that if a *loading dose* is given the time taken to reach a steady-state is reduced.

Drug dosage. The clearance values of drugs can be used to plan dosage regimens. Ideally, in drug treatment, a ***steady-state plasma concentration*** is required within a known *safe and effective therapeutic range*. It is important to maintain the blood concentration of a drug within the therapeutic range for an optimal effect, as at a lower level it would be ineffective, and higher levels would lead to overdosage toxicity **(Fig. 1.5.10)**. This steady-state will be achieved when the rate of drug entering the systemic circulation (dosage rate) equals the rate of elimination.

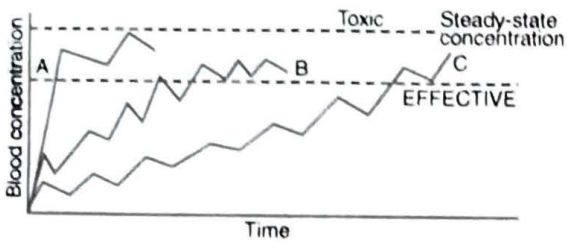

Fig. 1.5.10: Drug concentration profiles on repetitive dosing. A: drug with a long plasma $t_{1/2}$ given in an initial loading dose followed by constant maintenance doses; B: drug with a short plasma $t_{1/2}$ given in constant repetitive dosage; and C; drug with a long plasma $t_{1/2}$ given in constant repetitive dosage. Steady-state concentrations can be maintained on repetitive dosing in all three cases.

Therapeutic Drug Monitoring (TDM)

There is at times marked variability between patients in their pharmacokinetic parameters and in drug responsiveness. This renders the concept of generally accepted 'therapeutic dose' rather inaccurate and invalid. An alternative would be to monitor and maintain drug plasma concentrations at a level which is necessary to produce a therapeutic effect. Such a procedure is designated as *therapeutic drug monitoring (TDM)*. Some commonly monitored drugs are *carbamazepine, digoxin, lithium, phenytoin, sodium valproate* and *theophylline*.

Situations in which monitoring of drug plasma concentration is useful are as under:

1. Drugs which have a *narrow therapeutic index, e.g., digoxin, gentamicin, lithium* and *procainamide* should be desirably monitored by determination of their plasma concentrations. This reduces the liability of overdose effects.
2. In *renal failure*, when it is necessary to use drugs mostly excreted in the urine, *e.g. gentamicin, rifampicin, digoxin, doxycycline, tetracycline* and others. The half-lives of these drugs are appreciably prolonged in renal failure, and the dosage has to be accordingly reduced.
3. To establish *patient compliance, i.e.*, whether the patient is following the doctors' instructions or not. Poor patient compliance is the single most important factor accounting for treatment failure and/or a high incidence of *adverse drug reactions* (ADRs).
4. In the management of *drug overdose poisoning* repeated estimations of drug levels are helpful in determining the severity of poisoning and response to therapy.

Basic knowledge about *drug disposition* and *pharmacokinetics* is essential for rational and safe drug therapy.

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