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1. Introduction

Drug research is a specific process toward the development of new therapeutic agents in this era to meet the current medical needs. Drug discovery and development are the two major stages in the development of new therapeutic drug substance. Drug discovery involves identification and characterization of new targets (enzymes or receptors), synthesis of new lead molecules, screening of new lead molecules for its in vitro and/or in vivo biological activities, and physicochemical characterization of leads. The drug discovery and development process requires close interaction among the different scientific discipline members for as many as 10–12 years. It is estimated that only 1 out of 5000 screened compounds is approved as a new drug. On an average, every new drug molecule requires 12±15 years to reach the patient and costs a staggering amount of US $ 400±650 million [1, 2].

**Active pharmaceutical ingredient (API):** Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form [3].

**Steps involved in developing a new drug are:**
1. Preclinical research
2. Investigational New Drug (IND) Application
3. Phase I trials
4. Phase II trials
5. Phase III trials
6. New Drug Application (NDA)
7. Approval [1]
2. Human body composition

Human body is composed of a series of membrane barriers divided by aqueous-filled compartments. These membrane barriers are principally composed of the phospholipid bilayers resulting from the orientation of the lipids (phospholipids, glycolipids, and cholesterol) in the aqueous medium, which surround the cells and also form intracellular barriers around the organelles present in cells (mitochondria, nucleus, etc.). The phospholipids are amphipathic in nature and have aligned polar head groups and lipid “tails,” so the polar head groups of phospholipid orientate toward the aqueous phases and the lipid tails form a highly hydrophobic inner core. Hence, the drug substance releases its hydration element and becomes hydrophobic. The drug disposition across the membrane depends on its lipophilicity and partition coefficient. Here, the protein binding plays an important role [4, 5].

The polar molecules will be dissociated in an aqueous environment; thereby, the hydrophilicity arises and vice versa in the case of nonpolar molecules in a lipophilic environment. Every component of an organic compound has a defined lipophilicity. Absorption and bile elimination rate are molecular weight dependent. Lower-molecular-weight compounds have better absorption and less bile excretion when compared to the higher-molecular-weight compounds. Drugs with higher lipophilicity can be better absorbed from the intestine [5, 6].

3. Biopharmaceutics

Biopharmaceutics is a major branch in pharmaceutical sciences which relates between the physicochemical properties of a drug in dosage form and the pharmacology, toxicology, or clinical response observed after its administration [7]. Drug efficacy and safety are dependent on the dosing regimen. The optimal dosage and dosing intervals can be quite different for different drugs. Moreover, for a single drug, the optimal dosage can be different widely between patients [8].

It is not sufficient to know what the drug does to the body; it is also crucial to know what the body does to the drug. The knowledge of the pharmacodynamic and pharmacokinetic properties of the drug and its metabolites in humans and animals is crucial to understand its different effects among species and for adjusting drug dosing [9, 10].

The plasma concentration of the drug is the basic concept of pharmacokinetics. Based on protein binding of the drug, the concentration of free drug available in the circulation influences greatly the dose calculations. The concentration of drug in the plasma is in equilibrium with some tissues in the body [11].

4. Bioanalytical method

Blood is the transporter of many vital substances and nutrients for the entire body and thus contains many endogenous and exogenous compounds in different concentrations. Biological
samples (tissue extracts, plasma, serum, or urine) are extremely complex matrices comprised of many components that can interfere in estimation/quantification; hence, biological samples cannot normally be injected directly into the analyzing system for the determination of active principle. Sample pretreatment is required for achieving sufficient sensitivity and selectivity to determine the active principle. Chemical assays of high quality which include adequate sensitivity, selectivity and reproducibility are essential for obtaining valuable data. Bioanalysis is a subdiscipline of analytical chemistry covering the quantitative measurement drugs and their metabolites in biological systems. Bioanalysis technique can provide a quantitative measure of the active drug and/or its metabolite(s) for the purpose of pharmacokinetics. Various analytical instrument methods such as high-performance liquid chromatography (HPLC) or gas chromatography (GC) or ultra performance liquid chromatography (UPLC) with variety of detectors such as UV, fluorescent, diode array, flame ionization, electron capture and mass spectrometry, and capillary electrophoresis–mass spectrometry may be used. For macromolecule, ELISA or RIA method can be used for quantification [1, 12].

5. Pharmacodynamics
Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and its adverse effects. Studies are designed to investigate all primary and secondary effects related to the desired therapeutic effects, extensions of the therapeutic effect that might produce toxicity at higher doses, and effects related to interactions with other drugs.

6. Pharmacokinetics
Pharmacokinetics refers to the study of the time course of a drug within the body (extent and duration of systemic exposure to the drug) and also incorporates the process about the drug’s absorption, distribution, metabolism, and excretion (ADME) pattern. In general, pharmacokinetic parameters are derived from the measurement of drug concentrations in blood or plasma [1].

7. Absorption
Absorption studies generally involve serial determinations of drug concentration in blood and urine after dosing to indicate the rate and extent of absorption.

Drug absorption refers to the passage of drug molecules from the site of administration into the circulation. Drug absorption requires that drugs cross one or more layers of cells and cell membranes.

Solubility is manipulated mainly by the structure of the drug. In general, solubility is inversely proportional to the number and type of lipophilic functions within the molecule and tightness
of the crystal packing of the molecule. Solubility decreases when there is increase in crystal packing or lipophilicity.

The concentration of drug in solution is the driving force of the membrane transfer of drug into the body, and low aqueous solubility often continues to present itself as a problem even after formulation improvements.

Factors that influence drug absorption through oral route are:

i. Biological factors: Permeation of the drug across the membrane, GI transit, site specificity, first-pass metabolism, metabolism in the liver, excretion as bile, excretion through bladder, and protein binding of drugs

ii. Pharmaceutical factors: Excipients, type of dosage forms, process of preparation, stability testing, and storage directions

iii. Other factors: Solubility of the drug; partitioning properties; dissociation characteristics; salt formation; particle size, shape, volume, and its distribution; crystallinity; polymorphism; prodrugs; and stereotype and its formation [8, 13, 14]

8. Drug absorption

Drugs may be either weak acids or bases that exist in both ionized and non-ionized forms in the body. Drug in the non-ionized form is sufficiently soluble in membrane lipids and can cross cell membranes. The rate of absorption depends upon the ratio of the two forms at a particular site and is also a factor in distribution and elimination. The protonated form of a weak acid is non-ionized, whereas the protonated form of a weak base is ionized. The pKa is the negative log of the ionization constant, particular for each acidic or basic drug. Protonated form predominates when the pH is less than the pKa, whereas nonprotonated form predominates when pH is greater than the pKa. In the stomach, with a pH of 1, weak acids and bases are highly protonated. At this site, the non-ionized form of weak acids (pKa = 4 ± 1) and the ionized form of weak bases (pKa = 9 ± 1) will prevail upon. Weak acids are absorbed without dissociation than weak base from the stomach and exactly opposite in the intestine where weak bases are absorbed readily than weakly acidic drugs. In intestine, weakly acidic drugs are also found to be absorbed even though they are ionized due to the large surface area [15].

Absorption takes place across the biological membrane by two methods. Lipid drugs are absorbed by transcellular mechanism where the drug distributes into the lipid core of the membrane which diffuses into the other side of the membrane. The solute may also diffuse across the cell membrane and enter into the circulation. Another mechanism is the paracellular absorption. The aqueous-filled pores in between the cells aid absorption of the drugs. Water-soluble drugs are readily absorbed, but the molecule size of the particle plays an important role [5, 12].

Drug absorption through transcellular and paracellular pathways is shown in Figure 1.
9. Transport across cell membranes

9.1. Passive diffusion

The concentration gradient provides energy for the transportation of the drug across the membrane, and also partitioning of the drug in favor of the lipid membrane decides the quantity of the drug absorbed. The unionized drug is absorbed markedly higher than the ionized form. Passive diffusion could be explained with Fick’s first law which relates the diffusive flux to the concentration under the assumption of steady state. It postulates that the flux goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the concentration gradient, or in simplistic terms, the concept that a solute will move from a region of high concentration to a region of low concentration across a concentration gradient.

9.2. Active transport

Active transport is the movement of molecules across the lipid cell membrane against concentration gradient, i.e., moving from an area of lower concentration in the GIT to an area of higher concentration in the plasma. The absorption sites are at a specific place in the GIT. Active transport is usually associated with accumulating high concentrations of molecules that the cell needs, such as ions, glucose, and amino acids. This active transport process uses chemical energy, such as from adenosine triphosphate (ATP). These energy molecules are site specific – the drugs are transported at a particular site in the GIT, they are limited in number, and they act like a ferry service: it picks a molecule from the GIT, ferries across, leaves in the cytoplasm, and comes back to pick another molecule. The concentration of the drug in the plasma is maintained constant because of this “ferry” service, and the energy/carrier molecules are nothing but ATP-dependent proteins.

9.3. Endocytosis

Endocytosis is an energy-using process by which cells absorb molecules (such as proteins) by engulfing them. It is used by large polar molecules that cannot pass through the hydrophobic
plasma or cell membrane. The opposite process is exocytosis. Phagocytosis is a specific form of endocytosis involving the vascular internalization of solids such as bacteria by an organism and is therefore distinct from other forms of endocytosis such as the vesicular internalization of various liquids (pinocytosis). Phagocytosis is involved in the acquisition of nutrients for some cells. Pinocytosis, otherwise known as cell drinking, fluid endocytosis, and bulk-phase pinocytosis, is a mode of endocytosis in which small particles are brought into the cell, forming an invagination and then suspended within small vesicles [14, 16-21]. Various types of endocytosis are shown in Figure 2.

Figure 2. Various pathways of endocytosis

10. Models for drug absorption

Various in vitro, in situ, and in vivo tools and techniques are used to characterize the absorption of drug substance to determine the rate and extent of absorption.

Various models from low-throughput (in situ rat model) to high-throughput (in silico) models are used. Screening models for absorption such as human colon adenocarcinoma cell lines Caco-2 and HT-29 are widely used; recently, MDCK cell line is used as an alternative one.

Other in vitro methods are:

1. Cell culture models

In vitro cell culture models have been utilized to assess the permeability and metabolism of drugs, to elucidate molecular mechanism of drug transport to provide information on pathways of drug degradation, and to explore the influence of structure in the absorption of new chemical entities.

Several human colon carcinoma cells lines, such as the Caco-2, HT-29, SW116, LS174T, and SW480, are investigated for absorption. The cultured epithelial cells undergo enterocyte-like differentiation in culture and spontaneously differentiate into polarized columnar cells that are representative of the small intestine, with developed microvilli and polarized distribution of brush border enzymes. When grown on plastic membrane, epithelial cells result in a confluent monolayer and therefore serve as a model to study drug absorption.
2.  *Isolated mucosal cells*

Isolated mucosal cell suspensions have been used to study enzyme activity, drug transport, and cellular metabolism. The use of mucosal cells in drug absorption and transport studies is limited due to rapid autolysis.

3.  *Brush border membrane vesicles*

Isolation of brush border membrane vesicles has been used extensively to study mucosal uptake process especially to investigate factors that influence mucosal uptake without interference of intracellular metabolism.

4.  *Everted tissue approach*

   a.  Everted sac technique: To prepare everted sac, a small length of the intestine is excised, turned inside out, filled, and ligated at both ends. The sac is immersed in an oxygenated solution that contains a drug. The fluid inside the sac is assayed for the drug, and the rate of drug transfer across the membrane provides an estimate of drug permeability.

   b.  Intestinal rings: Prepared by excising a portion of the intestine, everting it over a glass road, and cutting it into rings approximately 30–50 mg. The rings are then incubated in an oxygenated culture media that contain a drug. At the end of the incubation, the tissues are extracted and the unchanged drug is measured. Intestinal ring preparation can be used to measure the rate of uptake and accumulation of a drug from the intestines.

5.  *Isolated tissue technique*

In this technique, the epithelium is mounted as a flat sheet between two chambers. The solution on each side of the chamber is oxygenated and maintained at physiological temperature. The test drug and markers for volume fluctuation or tissue viability are placed in the chambers. The chambers can be stirred using a gas lift of O/CO₂ (95 %/5 %) at a flow rate of 15–2 ml/min. Samples can be obtained from the serosal and mucosal chambers to study diffusion and permeability.

**In situ methods**

1.  Closed-loop studies

2.  Perfused-loop studies

3.  Perfused intestine–liver preparations [12, 22-25]

11. **Distribution**

Distribution provides information on the extent and time course of tissue accumulation and the elimination of drug and/or its metabolites.

The disposition of drug into the organs and tissues via circulation depends upon the nature of the drug. The more lipophilic the drug is, the better will be the distribution into the organs.
and tissues. Hydrophilic drugs are normally concentrated in cells and they are referred to as **ion trapping**.

When a drug is introduced into the body, the rate of distribution is dependent upon the following:

1. **Tissues with the highest blood flow receive the drug**: The rate at which a drug is distributed to various organs after a drug dose is administered depends largely on the proportion of **cardiac output** received by the organs.

2. **Protein binding**: Binding to proteins is inevitable in the case of drugs particularly lipoproteins, glycoproteins, and β-globulins. The extent of binding depends on the affinity of the drug molecule with the protein, and the maximum affinity could be 99% also. Unbound drug diffuses in the liquids surrounding the cells.

3. **Lipid solubility**: Lipid solubility is a major factor affecting the extent of drug distribution, particularly to the brain, where the **blood–brain barrier** restricts the penetration of polar and ionized molecules. Highly lipid-soluble drug can enter the tissues.

4. **Molecular size**: Molecular size is a factor affecting the distribution of extremely large molecules.

5. **Distribution depends upon the ionization of drug**, whereas unionized drugs can go anywhere into the body.

**Reasons for the variation in concentration of drug distribution are:**

1. **Tissue differences in rates of uptake of drugs**: Blood flow and capillary permeability

2. **Differences in tissue/blood ratios at equilibrium**: Dissolution of lipid-soluble drugs in adipose tissue, binding of drugs to intracellular sites, and plasma protein binding

3. **Apparent volume of distribution (V_d)**

**11.1. Volume of distribution**

The volume of distribution (V_d), also known as apparent volume of distribution, is a pharmacological, theoretical volume that the total amount of administered drug would have to provide the same concentration as it is in blood plasma.

If the amount of drug (X) and the resulting concentration (C) are known, then the volume of distribution (V_d) can be calculated using the simplified equations:

\[ X = V_d C, \text{ where } X = \text{amount of drug in body}, \ V_d = \text{volume of distribution}, \text{ and } C = \text{concentration in the plasma}. \]

Lipid-insoluble drugs are mainly confined to the plasma and interstitial fluid; most do not enter the brain following acute dosing. Lipid soluble drugs reach all compartments and may accumulate in fat. For drugs that accumulate outside the plasma compartment, V_d may exceed the total body volume.
Factors involved in drug distribution and diffusion across blood tissue barrier are:

1. Blood flow
2. Permeability across blood tissue barrier
3. Tissue solubility
4. pH partition
5. Protein binding within compartment

In our body, various structures are acting as reservoir for storage of drug substance. They are plasma proteins, erythrocytes, and cellular reservoir like muscles, fat tissue, bone, and transcellular compartments.

Multiple paths of drug distribution in the blood stream are shown in Figure 3.

**Figure 3.** Multiple paths of drug distribution in the blood stream

11.2. Compartment models in kinetics of drug distribution

Compartment models are hypothetical structures used to describe the fate of a drug in a biological system after its administration into the body. Various compartment models in pharmacokinetic are:

*One-compartment model:* Following drug administration, the body is depicted as a kinetically homogeneous unit.

*Two-compartment model:* The two-compartment model resolves the body into a central compartment and a peripheral compartment.

*Multicompartment model:* In this model, the drug distributes into more than one compartment and the concentration–time profile shows more than one exponential [9, 15, 26-29].
Various body compartments and the drug distribution is shown in Table 1.

<table>
<thead>
<tr>
<th>Body compartments (L/kg body weight)</th>
<th>Drug distribution in the body compartments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body water = 0.6</td>
<td>Small water-soluble drugs</td>
</tr>
<tr>
<td>(extracellular and intracellular)</td>
<td></td>
</tr>
<tr>
<td>Extracellular water = 0.2</td>
<td>Larger water-soluble drugs</td>
</tr>
<tr>
<td>Blood = 0.08</td>
<td>Plasma protein-bound large drugs</td>
</tr>
<tr>
<td>Plasma = 0.04</td>
<td></td>
</tr>
<tr>
<td>Fat = 0.2 – 0.35</td>
<td>Lipid-soluble drugs</td>
</tr>
<tr>
<td>Bone = 0.07</td>
<td>Certain ions</td>
</tr>
</tbody>
</table>

Table 1. Body compartment and the drug distribution

12. Biotransformation/Metabolism

Biotransformation or drug metabolism is the enzyme-catalyzed conversion of drugs to their metabolites. Metabolism makes the drug less polar; lipid-soluble substance makes it more polar as well as water soluble, thus facilitating their excretion by the kidney. If a drug is already highly polar and water soluble, then it may not get metabolized and may get excreted as such. Liver is the chief organ for biotransformation of most drugs, but drug-metabolizing enzymes are found in many other tissues, including the gut, kidneys, brain, lungs, and skin. Lipophilic drug is converted to a hydrophilic one by extensive metabolism in the liver.

Drug metabolism is traditionally carried out by phase I and phase II processes.

Cytochrome P450 system has an important role and occupies a pivotal role in drug clearance in phase I.

Phase I: First step in biotransformation is the formation of product susceptible to phase II conjugative reaction. The phase I also involves unmasking a functional group like OH, NH₂, and SH and conversion to more polar products which may be mostly inactive, less active, and modified activity.

Phase II: Coupling of drug or its oxidized metabolite to endogenous conjugating agent derived from carbohydrate, protein, or sulfur sources; generally products are more water-soluble and more readily excreted in urine or bile. Phase II involves conjugation reactions with glucuronic acid, sulfuric acid, acetic acid, and amino acid.

Biotransformation occurs somewhere between absorption and excretion; some may occur in the gut (digestion, decomposition in gastric acidity).

Role of enzymes in the biotransformation are drug metabolism; conversion of prodrug to active forms; synthesis of steroidal hormones, cholesterol, and bile acids; and finally formation and excretion of bilirubin.
Biotransformation is mediated by cellular enzymes in the sarcoplasmic reticulum, mitochondria, cytoplasm, lysosomes, and nucleus.

Drug-metabolizing enzymes are classified into:

1. Microsomal (inducible)
2. Nonmicrosomal (non-inducible)

12.1. Microsomal enzymes (inducible)

Microsomes are artificial spheres obtained from the endoplasmic reticulum by homogenization and fractionation, and they possess various drug-metabolizing enzymes.

1. Mixed-function oxidases (monooxygenases) cytochrome P-450, cytochrome P-450 reductase, and NADPH

Reactions catalyzed by monooxygenase are N-dealkylation, O-dealkylation, aromatic ring oxidation, side-chain oxidation, sulfoxide formation, N-oxidation, N-hydroxylation, deamination of primary and secondary amines, and desulfuration (S replacement by O2).

2. Glucuronyl transferase for conjugation

The drugs containing phenols, alcohols, and carboxylic acids are metabolized by conjugation method. The conjugates are mostly inactive and excreted in the bile and urine by anion carrier mechanism and enter into enterohepatic cycling (β-glucuronidase and sulfatase in the gut).

3. Some enzymes are involved in reduction and hydrolysis

The modification of enzyme activity such as enzyme induction and enzyme inhibition was observed.

Majority of the drugs however are metabolized by the nonmicrosomal enzymes resulting in their activation, inactivation, or modification. The reactions are:

1. Inactivation by conjugation: Synthetic process by which a drug or its metabolite is combined with an endogenous substance.
2. Inactivation by oxidation: Involves introduction of a hydroxyl group into the drug molecule.
3. Inactivation by reduction: Many halogenated compounds and nitrated compounds are reduced by microsomal enzymes.
4. Inactivation by hydrolysis: Carried out by enzyme esterase; this hydrolyses the esters.

Drug metabolism is affected by various factors. The diseases that are categorized as acute and chronic liver diseases (reduces metabolism), liver cancer, cardiac diseases limiting blood flow to the liver, pulmonary diseases reducing hydrolysis of procainamide, and hyperthyroidism where metabolism are affected. And also metabolism increases t1/2 and hypothyroidism reduces metabolism t1/2 [14, 30-36].
12.2. Metabolism methodologies

12.2.1. In vitro methods

In vitro techniques are well suited for the study of biochemical toxicology, cytotoxicity, irreversible drug protein binding, drug metabolism, and enzyme regulation. Induction of drug-metabolizing enzymes can have a dramatic impact on the disposition, toxicology, and metabolic profile of the agent under study.

Primarily hepatic enzymes from animals and humans are used for drug metabolism studies. Other enzymes from the intestine and brain are also being used in the metabolism studies. In human, cytochrome P450 is used primarily, whereas its subfamilies such as CYP1A, CYP2C, CYP2D, CYP2E, CYP3A, and CYP4A are also being used.

Enzyme systems: Single or isolated enzyme systems are a powerful technique for the study of enzymatic process due to easy maintenance and manipulation in the substrate, enzyme, and cofactor concentrations. Interested enzyme from animal or human tissue can be isolated by extraction and purification and reconstituted to study the drug metabolisms. Single-enzyme system is useful in the study of enzyme kinetics, specificity, and mechanism. Other enzymes such as cytochromes CYP450, flavin-containing monoxygenases, glucuronyltransferases, sulfotransferases, epoxide hydrolases, glutathione S-transferases, and N-acetyltransferases are also used in the drug metabolism studies.

Subcellular fractions: Microsomes as subcellular fraction is frequently utilized as in vitro model. These subcellular components, composed of endoplasmic reticulum, contain most of the oxidative drug-metabolizing enzymes, such as the cytochromes P450 and flavin monoxygenases, glucuronyltransferase, epoxide hydrolases, alcohol dehydrogenases, esterases, and methyltransferases, that can be separated by cell disruption and differential centrifugation.

Cellular systems: Cell culture system is utilized to study both drug metabolism and toxicology within a physiological environment due to manipulation of its enzyme concentrations and cofactors under appropriate conditions. These systems can be used to evaluate multiple aspects of drug metabolism, drug transport across cell membranes, enzyme induction, and cytotoxicity from such organs as the kidney, intestinal mucosa, and liver.

Liver slices: Organ slices were extensively used to study a variety of biochemical process because of the ability to produce uniform-cut organ slices by commercial tissue slicers and improved organ culture conditions. The slices have been isolated from many different species including human, and several organs such as the liver, brain, heart, and kidney are used.

Organ perfusion: Organ perfusion is used to measure the toxicological and pharmacokinetic events and parameters because of its close approximation to the tissues. This perfusion method offers several advantages over other in vitro methods such as preservation of organ architecture and ability to regulate perfused flow rate; two sampling sites are available for determination of substrate and metabolite concentrations.

But the limitation is that only one experiment can be performed per animal.
12.2.2. In vivo methods

Radionuclides: Formation and excretion of metabolites can be easily monitored by attaching radiotracer tag on a drug candidate. Radiotracer tag is placed at chemically and metabolically stable site. Tritium ($^3$H) and carbon14 ($^{14}$C) are the most commonly used radionuclides used as tracer tag in drug metabolism studies [37].

13. Clearance (Elimination)

Drug clearance (CL) is defined as the volume of plasma in the vascular compartment cleared of drug (only free, i.e., not protein bound) per unit time by the processes of metabolism and excretion. Clearance is related to the concentrations of the drug present in blood after administration. Clearance of drug occurs by the perfusion of blood to the organs of extraction. Extraction is the ratio of the clearance process ($E$) referring to the proportion of drug presented to the organ which is removed irreversibly (excreted) or altered to a different chemical form (metabolism) from the organ.

Hepatic clearance ($Cl_H$) and renal excretion ($Cl_R$) are generally involved in the extraction of the drug from the body. The overall value for systemic clearance ($Cl_S$) can be calculated by

$$\text{Cl}_S = \text{Cl}_H + \text{Cl}_R$$

The amount of drug in the circulation is related to the volume of distribution, and therefore elimination rate constant ($k_{el}$) can be calculated by

$$k_{el} = \frac{\text{Cl}}{V_d}$$

Clearance for a drug is constant if the drug is eliminated by first-order kinetics.

Half-life: The time required to reduce the plasma concentration to one half its initial value is defined as the half-life ($t_{1/2}$).

Zero-order reaction: The reaction proceeds at a constant rate and is independent of the concentration of drug present in the body.

First-order reaction: The reaction proceeds at a rate that is dependent on the concentration of drug present in the body.

Excretory organs:

Major routes: kidneys, liver, and lungs.

Minor routes: sweat, saliva, tears, and breast milk.
Urine: It helps to quantitate the amount of drug excreted and is the most important excretory route for nonvolatile drugs and their metabolites (drug not bound to plasma proteins), proximal tubular active secretion, and passive tubular reabsorption.

Renal excretion: Small molecules with low molecular weight will appear in urine through glomerular filtration. Through tubular carrier systems (tubular secretion), a drug can be transported against the concentration gradient from the blood capillaries to the nephron lumen to be excreted in the urine.

Lipophilicity in drug clearance: Reduction in lipophilicity is observed when compared to the parent molecule during administration. For hydrophilic drugs (log $D_{7.4}$ below 0), renal clearance is the predominant mechanism, whereas the drugs with log $D_{7.4}$ values are above 0, renal clearance decreases with lipophilicity. Metabolic clearance increases with increasing log $D$, and this becomes the major clearance route of lipophilic compounds. The lowest clearance (negligible) is observed below log $D_{7.4}$ values of 0 by combined renal and metabolic processes (log $D_{7.4}$, Logarithm of the distribution coefficient ($D$) at pH 7.4).

Lipophilicity and reabsorption by the kidney: The degree of reabsorption (all along the nephron) depends on the physicochemical properties (degree of ionization and intrinsic lipophilicity) of the drug. After absorption, the equilibrium is reestablished in the kidney where the unbound drug in the urine and unbound drug in plasma are present on both sides of the membrane. The water-soluble drugs are absorbed easily, but lipophilic drugs will be reabsorbed by diffusion due to concentration gradient.

Effect of charge on renal clearance: Tubular pH is often more acidic (pH 6.5) than plasma; hence, acidic drugs are reabsorbed more extensively than basic. Greater rates of excretion/clearance can occur for these charged moieties due to the tubular active transport proteins.

Renal clearance: The unbound drug will be cleared by filtration, and the protein-bound drug will be cleared slowly as it dissociates after a long time. Drugs with increasing plasma protein binding have increased lipophilicity, which decreases the renal clearance.

Renal clearance in drug design: Small molecules with relatively simple structures (molecular weights below 350) can successfully combine paracellular absorption and renal clearance.

Liver and biliary excretion: Liver is the organ where maximum metabolism takes place. The unabsorbed drugs and the metabolized drugs are excreted through fecal matter. Enzyme cytochrome is having a pivotal role in drug clearance by various oxidation reactions such as aromatic hydroxylation, aliphatic hydroxylation, $N$-dealkylation, $O$-dealkylation, $S$-dealkylation, $N$-oxidation, $S$-oxidation, and alcohol oxidation. Hepatic and renal clearance process is shown in Figure 4.

Lungs: The lungs are an important route for the excretion of gaseous anesthetics, alcohol, iodine, and iodates.

Other excretion routes are sweat, saliva, and tears which are generally pH dependent that mediate drug excretion by passive diffusion of lipophilic drugs.
Milk: Milk is more acidic than plasma; hence, basic drugs tend to accumulate due to ionic trapping, whereas concentration of acidic drugs is lesser than in the plasma. Nonelectrolytes (ethanol, urea) enter milk in a pH-independent manner.

Hair and skin: Toxic metal may be excreted (murder, suicide) [8, 14, 29, 38-42].

14. Conclusion

Pharmacokinetics is the study of the time course of a drug within the body and incorporates the processes of absorption, distribution, metabolism, and excretion (ADME). The simplest pharmacokinetic concept is that based on concentration of drug in the biological matrix. Selective and sensitive bioanalytical method is required to quantify the concentration of the drug in the biological matrix. Most of the drugs are absorbed by passive diffusion process. The rate of drug diffusion by passive process depends upon the lipid solubility and the surface area available for absorption. The drug distribution is based on the plasma protein binding, molecular size, and lipid solubility. After distribution, the drug is metabolized into a metabolite as either a pharmacologically active or inactive one. The liver plays a vital role in the drug metabolism. Metabolized drugs are cleared mainly by the liver and kidney. The drug discovery and development process required a large amount of clinical data for rapid screening, selection, and development of new compounds. Various mathematical models are developed to assess the pharmacokinetic parameters. Preliminary pharmacokinetic study results are very much useful to characterize the absorption, disposition profile, and drug metabolism, which are very much essential and important in the discovery and development of new therapeutic agents in areas of currently unmet medical needs.
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