LECTURE NOTES
ON

BIOPHARMACEUTICS AND PHARMACOKINETICS

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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT-1

Gastrointestinal Absorption of Drugs - Biologic considerations

What is absorption?

Absorption is defined as the process by which a drug proceeds from the site of administration to the site of measurement (usually blood, plasma or serum).The first stage for the drugs to reach to their target organs is known as “absorption”.

Introduction The systemic absorption of a drug is dependent on
the physicochemical properties of the drug,the dosage form used, andthe anatomy and physiology of the drug absorption site.This chapter will focus on the anatomic and physiologic considerations for the systemic absorption of a drug.

Introduction contd.Many drugs are not administered orally because of drug instability in the gastrointestinal tract or drug degradation by the digestive enzymes in the intestine.For example, erythropoietin and human growth hormone (somatrophin) are administered intramuscularly, and insulin is administered subcutaneously or intramuscularly, because of the potential for degradation of these drugs in the stomach or intestine.

Introduction contd.Biotechnology products are often too labile to be administered orally and therefore are usually given parenterally.Drug absorption after subcutaneous injection is slower than intravenous injection.Pathophysiologic conditions such as burns will increase the permeability of drugs across the skin compared with normal intact skin.When a drug is administered by an extravascular route of administration (eg, oral, topical, intranasal, inhalation, rectal), the drug must first be absorbed into the systemic circulation and then diffuse or be transported to the site of action before eliciting biological and therapeutic activity.

Nature of Cell Membranes

Many drugs administered by extravascular routes are intended for local effect.Other drugs are designed to be absorbed from the site of administration into the systemic circulation.For systemic drug absorption, the drug must cross cellular membranes.After oral administration, drug

molecules must cross the intestinal epithelium by going either through or between the epithelial cells to reach the systemic circulation.

Nature of Cell Membranes

The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure of the drug and to the physical and biochemical properties of the cell membranes.Once in the plasma, the drug may have to cross biological membranes to reach the site of action. Therefore, biological membranes potentially pose a significant barrier to drug delivery.

Nature of Cell Membranes

Transcellular absorption is the process of drug movement across a cell.Some polar molecules may not be able to traverse the cell membrane but, instead, go through gaps or tight junctions between cells, a process known as paracellular drug absorption.The following figure shows the difference between the two processes.Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

Nature of Cell Membranes

Membranes are major structures in cells, surrounding the entire cell (plasma membrane) and acting as a boundary between the cell and the interstitial fluid.In addition, membranes enclose most of the cell organelles (eg, the mitochondrion membrane).Functionally, cell membranes are semipermeable partitions that act as selective barriers to the passage of molecules.Water, some selected small molecules, and lipid-soluble molecules pass through such membranes, whereas highly charged molecules and large molecules, such as proteins and protein-bound drugs, do not.

Nature of Cell Membranes

The transmembrane movement of drugs is influenced by the composition and structure of the plasma membranes.Cell membranes are generally thin, approximately 70 to 100 Å in thickness.Cell membranes are composed primarily of phospholipids in the form of a bilayer interdispersed with carbohydrates and protein groups.There are several theories as to the structure of the cell membrane.

Nature of Cell Membranes

The lipid bilayer or unit membrane theory, considers the plasma membrane to be composed of

two layers of phospholipid between two surface layers of proteins, with the hydrophilic "head" groups of the phospholipids facing the protein layers and the hydrophobic "tail" groups of the phospholipids aligned in the interior.The lipid bilayer theory explains the observation that lipid-soluble drugs tend to penetrate cell membranes more easily than polar molecules. However, the bilayer cell membrane structure does not account for the diffusion of water, small-molecular-weight molecules such as urea, and certain charged ions.

Nature of Cell Membranes

The fluid mosaic model explains the transcellular diffusion of polar molecules.According to this model, the cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix.These proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier.

Nature of Cell Membranes

The transmembrane proteins are interdispersed throughout the membrane.Two types of pores of about 10 nm and 50 to 70 nm were inferred to be present in membranes based on capillary membrane transport studies.These small pores provide a channel through which water, ions, and dissolved solutes such as urea may move across the membrane.

Model of the plasma membrane including proteins and carbohydrates as well as lipids.

Nature of Cell Membranes

As shown in the figure-Integral proteins are embedded in the lipid bilayer;peripheral proteins are merely associated with the membrane surface.The carbohydrate consists of monosaccharides, or simple sugars, strung together in chains attached to proteins (forming glycoproteins) or to lipids (forming glycolipids).

Nature of Cell Membranes

The asymmetry of the membrane is manifested in several ways.Carbohydrates are always on the exterior surface and peripheral proteins are almost always on the cytoplasmic, or inner, surface.The two lipid monolayers include different proportions of the various kinds of lipid molecule.Most important, each species of integral protein has a definite orientation, which is the same for every molecule of that species.

Passage of Drugs Across Cell Membranes

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

Passage of Drugs Across Cell Membranes

In the Fig, drug molecules move forward and back across a membrane.If the two sides have the same drug concentration, forward-moving drug molecules are balanced by molecules moving back, resulting in no net transfer of drug.When one side is higher in drug concentration, at any given time, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules; the net result will be a transfer of molecules to the alternate side, as indicated in the figure by the big arrow.

Passage of Drugs Across Cell Membranes

The rate of transfer is called flux, and is represented by a vector to show its direction in space.The tendency of molecules to move in all directions is natural, because molecules possess kinetic energy and constantly collide with one another in space.

Passive diffusion of molecules

Fig.13-3: drug molecules move forward and back across a membrane.

Passive diffusion of molecules

Passive diffusion is the major absorption process for most drugs.The driving force for passive diffusion is higher drug concentrations on the mucosal side compared to the blood.According to Fick's law of diffusion, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

Passive diffusion of molecules equation :1

Passive diffusion of molecules

where dQ/dt = rate of diffusion, D = diffusion coefficient, K = lipid water partition coefficient of drug in the biologic membrane that controls drug permeation, A = surface area of membrane; h = membrane thickness, and CGI – Cp = difference between the concentrations of drug in the

gastrointestinal tract and in the plasma.Because the drug distributes rapidly into a large volume after entering the blood, the concentration of drug in the blood initially will be quite low with respect to the concentration at the site of drug absorption.

Passive diffusion of molecules

For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the µg/mL or ng/mL. If the drug is given orally, then a large concentration gradient is maintained, thus driving drug molecules into the plasma from the gastrointestinal tract.

Passive diffusion of molecules

Given Fick's law of diffusion, several other factors can be seen to influence the rate of passive diffusion of drugs. For example, the degree of lipid solubility of the drug influences the rate of drug absorption.The partition coefficient, K, represents the lipid–water partitioning of a drug across the hypothetical membrane in the mucosa. Drugs that are more lipid soluble have a larger value of K.The surface area, A, of the membrane also influences the rate of absorption.Drugs may be absorbed from most areas of the gastrointestinal tract. However, the duodenal area of the small intestine shows the most rapid drug absorption, due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.

Passive diffusion of molecules

The thickness of the hypothetical model membrane, h, is a constant for any particular absorption site.Drugs usually diffuse very rapidly through capillary plasma membranes in the vascular compartments, in contrast to diffusion through plasma membranes of capillaries in the brain.In the brain, the capillaries are densely lined with glial cells, so a drug diffuses slowly into the brain as if a thick lipid membrane existed.

Passive diffusion of molecules

The term blood–brain barrier is used to describe the poor diffusion of water-soluble molecules across capillary plasma membranes into the brain.However, in certain disease states such as meningitis these membranes may be disrupted or become more permeable to drug diffusion.

Passive diffusion of molecules

The diffusion coefficient, D, is a constant for each drug and is defined as the amount of a drug that diffuses across a membrane of a given unit area per unit time when the concentration

gradient is unity. The dimensions of D are area per unit time—for example, cm2/sec.Because D, A, K, and h are constants under usual conditions for absorption, a combined constant P or permeability coefficient may be defined.

Passive diffusion of molecules

Furthermore, in Equation 1 the drug concentration in the plasma, Cp, is extremely small compared to the drug concentration in the gastrointestinal tract, CGI. If Cp is negligible and P is substituted into Equation, the following relationship for Fick's law is obtained:

Passive diffusion of molecules

The above equation is an expression for a first-order process.In practice, the extravascular absorption of most drugs tends to be a first-order absorption process.Moreover, because of the large concentration gradient between CGI and Cp, the rate of drug absorption is usually more rapid than the rate of drug elimination.

Passive diffusion of molecules

Many drugs have both lipophilic and hydrophilic chemical substituents.

Those drugs that are more lipid soluble tend to traverse cell membranes more easily than less lipid-soluble or more water-soluble molecules.For drugs that act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the rate of drug transport.The ionized species of the drug contains a charge and is more water soluble than the nonionized species of the drug, which is more lipid soluble.

Passive diffusion of molecules

The extent of ionization of a weak electrolyte will depend on both the pKa of the drug and the pH of the medium in which the drug is dissolved. Henderson and Hasselbalch used the following expressions pertaining to weak acids and weak bases to describe the relationship between pKa and pH:

Henderson and Hasselbalch equations

Henderson and Hasselbalch equations

With Equations 13.4 and 13.5, the proportion of free acid or free base existing as the nonionized species may be determined at any given pH, assuming the pKa for the drug is known. For

example, at a plasma pH of 7.4, salicylic acid (pKa = 3.0) exists mostly in its ionized or water-soluble form, as shown below:

Henderson and Hasselbalch equations

Passive DiffusionIn a simple system, the total drug concentration on either side of a membrane should be the same at equilibrium, assuming Fick's law of diffusion is the only distribution factor involved.For diffusible drugs, such as nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium.However, for electrolyte drugs or drugs that ionize, the total drug concentrations on either side of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane.

Passive DiffusionAccording to the pH–partition hypothesis, if the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then(1) the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane;(2) the total drug concentrations (ionized plus nonionized drug) on either side of the membrane will be unequal; and(3) the compartment in which the drug is more highly ionized will contain the greater total drug concentration. For these reasons, a weak acid (such as salicylic acid) will be rapidly absorbed from the stomach (pH 1.2), whereas a weak base (such as quinidine) will be poorly absorbed from the stomach.

Passive DiffusionAnother factor that can influence drug concentrations on either side of a membrane is a particular affinity of the drug for a tissue component, which prevents the drug from moving freely back across the cell membrane.For example, a drug such as dicumarol binds to plasma protein, and digoxin binds to tissue protein. In each case, the protein-bound drug does not move freely across the cell membrane.

Passive DiffusionDrugs such as chlordane are very lipid soluble and will partition into adipose (fat) tissue.In addition, a drug such as tetracycline might form a complex with calcium in the bones and teeth.Such drugs may have a higher total drug concentration on the side where binding occurs, yet the free drug concentration that diffuses across cell membranes will be the same on both sides of the membrane.

Membrane transport Mechanism of Drug Passage across Cell Membranes:

1. Passive diffusion2. Carrier-mediated transport

Carrier-mediated transport

MechanismsPassive diffusionCarrier-mediated transportActive TransportFacilitated DiffusionCarrier mediated intestinal transportVesicular transportPore (Convective) transportIon-Pair Formation

Carrier-Mediated Transport

Theoretically, a lipophilic drug may pass through the cell or go around it.If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.In the intestine, drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism.Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body. Active TransportActive transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites.A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are absorbed from the gastrointestinal tract by this process.

Active TransportActive transport is characterized by the transport of drug against a concentration gradient—that is, from regions of low drug concentrations to regions of high concentrations. Therefore, this is an energy-consuming system.In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane.

Hypothetical carrier-mediated transport process

Active TransportThe carrier molecule may be highly selective for the drug molecule.If the drug structurally resembles a natural substrate that is actively transported, then it is likely to be actively transported by the same carrier mechanism.

Active TransportTherefore, drugs of similar structure may compete for sites of adsorption on the carrier.Furthermore, because only a fixed number of carrier molecules are available, all the binding sites on the carrier may become saturated if the drug concentration gets very high.

Active TransportA comparison between the rate of drug absorption and the concentration of drug at the absorption site is shown in the following figure-

In case of a drug absorbed by passive diffusion, the rate of absorption increases in a linear relationship to drug concentration.

In contrast, when a drug is absorbed by a carrier-mediated process, the rate of drug absorption increases with drug concentration until the carrier molecules are completely saturated.At higher drug concentrations, the rate of drug absorption remains constant, or zero order.

Comparison of the rates of drug absorption of a drug absorbed by passive diffusion (line A) and a drug absorbed by a carrier-mediated system (line B).

Facilitated Diffusion

Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (ie, moves from a region of high drug concentration to a region of low drug concentration).Therefore, this system does not require energy input. However, because this system is carrier mediated, it is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure.In terms of drug absorption, facilitated diffusion seems to play a very minor role.

Carrier-Mediated Intestinal Transport

Various carrier-mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body.Both influx and efflux transporters are present in the brush border and basolateral membrane that will increase drug absorption (influx transporter) or decrease drug absorption (efflux transporter).

Vesicular TransportVesicular transport is the process of engulfing particles or dissolved materials by the cell.Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.Pinocytosis refers to the engulfment of small solutes or fluid, whereas phagocytosis refers to the engulfment of larger particles or macromolecules, generally

by macrophages.Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.

Vesicular TransportDuring pinocytosis or phagocytosis, the cell membrane invaginates to surround the material and then engulfs the material, incorporating it into the cell.Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell.

Vesicular TransportVesicular transport is the proposed process for the absorption of orally administered Sabin polio vaccine and various large proteins.

Diagram showing exocytosis and endo-cytosis.

Phagocytosis

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

Pore (Convective) Transport

Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores.The model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell. Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.

Ion-Pair FormationStrong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pKa values.Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membranes poorly.When the ionized drug is linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral.This neutral drug complex diffuses more easily across the membrane. For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid (increased the permeability through excised porcine buccal membrane)and quinine, which forms ion pair with hexylsalicylate

Gastrointestinal Physiology

Reference : Biopharmaceutics and Clinical Pharmacokinetics by Milo GibaldiGastrointestinal Blood FlowGastrointestinal pH

Class workWhat are the differences between Passive and Active transport?Draw the curve of Passive diffusion and Carrier-mediated transport.What are the differences between pinocytosis and phagocytosis?What are the differences between endocytosis and exocytosis?How does ion pair formation affect the transport of drug through membrane?

GI Tract

Major physiologic process In GI tract

1. Secretion2. Digestion3. Absorption

Gastrointestinal Motility

GI motility tends to move the drug through the alimentary canal, so the drug may not stay at the absorption site.For drugs given orally, an anatomic absorption window may exist within the GI tract in which the drug is efficiently absorbed.Drugs contained in a nonbiodegradable controlled-release dosage form must be completely released into this absorption window to be absorbed before the movement of the dosage form into the large bowel.The transit time of the drug in the GI tract depends on the physiochemical and pharmacologic properties of the drug, the type of dosage form, and various physiologic factors.

Gastrointestinal Motility

Physiologic movement of the drug within the GI tract depends on whether the alimentary canal contains recently ingested food (digestive or fed state) or is in the fasted or interdigestive state.During the fasted or interdigestive state, alternating cycles of activity known as the migrating motor complex (MMC) act as a propulsive movement that empties the upper GI tract to the cecum. Initially, the alimentary canal is quiescent (at rest).

Gastrointestinal Motility

Then, irregular contractions followed by regular contractions with high amplitude (housekeeper waves) push any residual contents distally or farther down the alimentary canal.In the fed state, the migrating motor complex is replaced by irregular contractions, which have the effect of

mixing intestinal contents and advancing the intestinal stream toward the colon in short segments.

Gastric Emptying Time

Anatomically, a swallowed drug rapidly reaches the stomach.Eventually, the stomach empties its contents into the small intestine.Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time for the drug to reach the duodenum will slow the rate and possibly the extent of drug absorption, thereby prolonging the onset time for the drug.Some drugs, such as penicillin, are unstable in acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact.

Gastric Emptying TimeA number of factors affect gastric emptying time.Some factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs.Liquids and small particles less than 1 mm are generally not retained in the stomach. These small particles are believed to be emptied due to a slightly higher basal pressure in the stomach over the duodenum.Different constituents of a meal empty from the stomach at different rates.Thus, liquids are generally emptied faster than digested solids from the stomach

Gastric Emptying TimeTherefore the factors that promote gastric emptying tend to increase the absorption rate of all drugs.Slow gastric emptying can delay the onset of effect of drugs such as analgesics or sedatives in situations requiring prompt clinical response.Prompt gastric emptying is important for drugs that are unstable in stomach fluids because of low pH or enzyme activity. For e.g the extent of degradation of penicillin G after oral administration depends on its residence time in the stomach and on the pH of the stomach fluids.

Gastric Emptying Time Factors Influencing Gastric Emptying –

Gastric empyting is reduced by :1. by fats and fatty acids in the diet,2. High concentrations of electrolytes or hydrogen ion3. high viscosity or bulk,4. Mental depression5. Lying on the left side6. Diseases such as gastroenteritis, pyloric stenosis, gastroesophageal reflux, hypothyroidism and luteal phase of menstrual cycle.

Gastric Emptying Time7. Drugs such as atropine, propantheline, amitriptyline, chlorpromazine, aluminium hydroxide.Gastric empyting is increased by :Fasting or hungerAlkaline buffer

solutionAnxietyLying on the right sideDiseases such as hyperthyroidismDrugs such as metoclopromide (a dopaminergic blocker used in nausea and vomitting associated with cancer chemotherapy).

Gastric Emptying TimeGastric empyting of liquids is much faster than that of food or solid dosage forms.Intact tablets have been observed in the stomach as long as 6 hours after ingestion of an enteric coated product with a meal.Tablets and capsules are commonly swallowed with little or no water and many patients in bed swallow them.Under these conditions a solid dosage form may lodge in the esophagus and stay there until it disintegrates. This may cause damage to the esophageal mucosa leading to ulceration and later perforation.

Gastric Emptying TimeDrugs causing esophageal ulceration includes aspirin, other NSAIDS, tetracycline, doxycycline, clindamycine, quinidine , iron salts.Slow esophageal transit also delays drug absorption.Patients should be advised that tablets and capsules must be taken with several swallows (at least 2 ounces) of water or other beverages, while standing or sitting upright.Migraine causes a significant delay in gastric emptying.

Gastric Emptying TimeThe motility of the small intestine as indicated by small bowel transit time also plays a role in drug absorption.The mean transit time of unabsorbed food residues or insoluble granules through the human small intestine is estimated to be about 4 hours.Intestinal transit of pharmaceutical dosage forms – solutions, small pellets and several unit forms such as nondisintegrating capsules and tablets – ranged from 3 to 4 hour, independent of the dosage form and whether the subjects were fed or fasted.

Gastric Emptying Time

The gastrointestinal transit is the time to reach the cecum after oral administration.Short residence in the small intestine has implications for the design of prolonged release dosage forms.A product designed to release drug over a 6 –hour period may demonstrate poor availability if it is rapidly emptied from the stomach and the drug is poorly absorbed in the large bowel.Propantheline and similar drugs increase small bowel transit time and metoclopromide accelerated transit through the small intestine.

Effects of food on Drug Absorption

Gastrointestinal absorption is favored by an empty stomach.One should not give all the drugs on

an empty stomach, some are irritating and should be administered with or after a meal.Food tends to decrease the rate of stomach emptying due to feedback mechanisms from receptors in the proximal small intestine and delays the rate of drug absorption.

Effects of food on Drug Absorption

Foods tend to increase gastric pH which may increase or decrease the dissolution or chemical degradation of some drugs.Food appears to interact directly with certain drugs either to enhance or to reduce the extent of absorption.Food stimulates hepatic blood flow which may have implications for the bioavailability of drugs subject to first-pass hepatic metabolism.

Effects of food on Drug Absorption

In general, the absorption of drugs taken 30 minutes or more before a meal is not affected by food.Food appears to have little effect on drug absorption when the drug is given 2 hours or more after a meal.Food have little effect on drug absorption or may decrease the rate but not the extent of drug absorption. Example of such drugs are digoxin, acetaminophen .

Effects of food on Drug Absorption

Enteric coated tablets pass intact from the stomach to the small intestine and do not release the drug until reaching the intestine so delay in drug absorption is observed.Less important effects are observed with well-dispersed dosage forms (e.g. solutions, suspensions, rapidly disintegrating tablets and capsules) and drugs that are water soluble.

Effects of food on Drug Absorption

Effect of food on drug absorption may depend on the dosage form used. For example , food delays the absorption of enteric coated aspirin tablets and digoxin tablets but has no effect on the absorption of enteric coated aspirin granules and digoxin elixir.Absorption of tetracycline is reduced when these drugs are taken with milk or milk products because of an interaction with calcium resulting in a poorly soluble complex.

Double-Peak Phenomenon

Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks.This double-peak phenomenon is generally observed after the administration of a single dose to fasted patients.The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form.

Double-Peak Phenomenon

The double-peak phenomenon observed for cimetidine may be due to variability in stomach emptying and intestinal flow rates during the entire absorption process after a single dose.For many drugs, very little absorption occurs in the stomach.For a drug with high water solubility, dissolution of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak.A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

Double-Peak Phenomenon

In contrast, ranitidine produces a double peak after both oral or parenteral (IV bolus) administration.Ranitidine is apparently concentrated in the bile within the gallbladder from the general circulation after IV administration.When stimulated by food, the gallbladder contracts and bile containing drug is released into the small intestine.The drug is then reabsorbed and recycled (enterohepatic recycling).

Double-Peak Phenomenon

Tablet integrity may also be a factor in the production of a double-peak phenomenon. compared a whole tablet or a crushed tablet of dipyridamole in volunteers and showed that a tablet that does not disintegrate or incompletely disintegrates may have delayed gastric emptying, resulting in a second absorption peak.

Double-Peak Phenomenon

ReferencesApplied Biopharmaceutics and Pharmacokinetics – Leon Shargel, Sussana Wu-Pong, Andrew B.C. Yu, 6th Edition, Mc Graw Hill Inc.Chapter -13Biopharmaceutics and Clinical Pharmacokinetics by Milo Gibaldi – Fourth Edition. Chapter -2

Factors affecting drug absorption

Physicochemical factorsRate-Limiting Steps in Drug Absorption:Systemic drug absorption from a drug product consists of a succession of rate processes.For solid oral drug products (eg, tablets, capsules), the rate processes include-(1) Disintegration of the drug product and subsequent release of the drug,(2) Dissolution of the drug in an aqueous environment, and(3) Absorption across cell membranes into the systemic circulation.

Rate Limiting StepIn the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence. The slowest step in a series of kinetic processes is called the rate-limiting step.

Disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption.For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exerts a rate-limiting effect on drug bioavailability.In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid, and the rate at which the drug crosses or permeates cell membranes (Absorption) is the slowest or rate-limiting step.

Figure: Systemic Drug Absorption from Solid Dosage Form

Figure -Some of the steps involved in the absorption of drugs administered orally from solid dosage forms. GI=gastrointestinal.Figure: Systemic Drug Absorption from Solid Dosage Form

DissolutionDissolution is the process by which a solid drug substance becomes dissolved in a solvent.Solubility is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in mL of water at 25°C).

Solubility is a static property; wheareas dissolution is a dynamic property.

Noyes--Whitney Equation

The Noyes–Whitney equation tells us that the dissolution rate (dC/dt) of a drug in the GI tract depend on-Diffusion coefficient (D) of a drugSurface area (S) of the undissolved solid drugSaturation, or equilibrium, solubility (Cs) of the drug in the GI fluidThickness of the diffusion layer (h).

Factors affecting the dissolution rate

Surface area and particle sizeSolubility of drug in the diffusion layerThe crystal form of a drugThe state of hydrationComplexationChemical modification.

Appearance or physical existence or polymorphism

Amorphous FormVery fine and smaller the particle size. So the greater the surface area. More soluble than crystalline forms. Because the energy required for a drug molecule to transfer from the amorphous form is less than the crystals.e.g. The amorphous form of the antibiotic,

novobiocin (Albamycin) is 10 times more soluble than the crystalline form and has similar differences in dissolution rate.

Crystal forms Many drugs exist in more than one crystalline form, a property known as polymorphism. Drug molecules exhibit different space–lattice arrangement in crystal form in each polymorph. Though chemically the same, polymorphs differ substantially with regards to physicochemical properties.These properties include solubility, dissolution rate, density and melting point, among others. Solubility and dissolution rate, in turn, will likely influence the rate of absorption.

Solvates and HydratesMany drugs can associate with solvents to produce crystalline forms called solvates. When the solvent is water then the crystal is termed as hydrate.Several reports suggest that solvates forms of a drug with organic solvents may dissolve faster than the non-solvated form.

Particle size of the drugs

The effective surface area of the drugs is increased enormously by a reduction of particle size.Because dissolution takes place at the surface of the solute (drugs), the greater the surface area, the more rapid is the rate of drug dissolution.For example, griseofulvin, nitroglycerin and many other steroids are drugs with low aqueous solubility;reduction of the particle size by milling to micronized form has improved the oral absorption of these drugs.

ComplexationFormation of a complex of drugs in the GI fluid may alter the rate and, in some cases, the extent of absorption.The complexing agent may be a substance normal to the GI tract, a dietary component or a component (excipient) of a dosage form.

Complexing with a substance in the gastrointestinal tract

Intestinal mucus, which contains the polysaccharide mucin, can avidly bind streptomycin and dihydrostreptomycin. This binding may contribute to the poor absorption of these antibiotics.Bile salts in the small intestine interact with certain drugs, including neomycin and kanamycin, to form insoluble and non-absorbable complexes.

Complexing with a dietary component

Tetracycline forms insoluble complexes with calcium ions.Absorption of these antibiotics is substantially reduced if they are taken with milk, certain food or other sources of calcium such as

some antacids. In the past, the incorporation of dicalcium phosphate as a filler in tetracycline dosage forms also reduced its bioavailability.

Complexing with excipients

The most frequently observed complex formation is between various drugs and macromolecules such as gums, cellulose derivatives, high- molecular-weight polyols and non-ionic surfactants.Mostly, however, these complexes are reversible with little effect on the bioavailability of drugs.

Dosage Form Consideration

Role of different dosage form like solution, suspension, emulsion, tablet, capsule etc on gastrointestinal absorption

Oral RouteThe oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs.DisadvantagesSlow drug responseChance of irregular absorption of drugsThe amount or type of food present within the gastrointestinal tract

The destruction of certain drugs by the acid reaction of the stomach or by gastrointestinal enzymes.

Dosage forms applicable

Drugs are administered by the oral route in a variety of pharmaceutical forms.The most popular are tablets, capsules, suspensions and various pharmaceutical solutions.

The Tablet is the most commonly used oral dosage form

The Tablet is the most commonly used oral dosage form. Tablets need to break down into granules/small particles which is called disintegration before dissolution. After disintegration, small particles go into solution termed as dissolution. Thus, drug from tablet dosage form becomes available for absorption after dissolution followed by disintegration.Tablet → Disintegration → Dissolution → GI Absorption

Tablet ingredients include materials to break up the tablet formulation.

Drug - may be poorly soluble, hydrophobicLubricant - usually quite hydrophobicGranulating agent (binder/adhesive)- tends to stick the ingredients togetherFiller - may interact with the drug, etc., should be water solubleWetting agent - helps the penetration of water into the tabletDisintegrating agent - helps to break the tablet apart

Coated TabletsCoated tablets are used to mask an unpleasant taste, to protect the tablet ingredients during storage, or to improve the tablets appearance.This coating can add another barrier between the solid drug and drug in solution. This barrier must break down quickly or it may hinder a drug's bioavailability.

Capsules are solid dosage forms in which the drug substance and appropriate pharmaceutical adjuncts as fillers are enclosed in either a hard or a soft “shell”, generally composed of a form of gelatin.Drug material are released from capsules faster than from tablets.

118 Suspensions are preparations of finely divided drugs held in suspension throughout a suitable vehicle.Suspensions are taken orally generally employ an aqueous vehicle.Nearly all suspensions must be shaken before use because they tend to settle.Suspension are a useful means to administer large amounts of solid drugs that would be inconveniently taken in tablet or capsule form.

119 Drugs administered in aqueous solution are absorbed much more rapidly than those administered in solid form, because the processes of disintegration and dissolution are not required.Among the solutions frequently administered orally are elixirs, syrups and solutions.

2.Pharmacokinetics

Introduction to Pharmacokinetics.

Contents;

a. Mathematical model

b. Drug levels in blood.

c. Pharmacokinetic model

d. Compartment models

e. Pharmacokinetic study

Pharmacokinetics is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an

individual patient. Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations. A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practical. For example, the receptor sites for digoxin are thought to be within the myocardium. Obviously we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids . Kinetic homogeneity describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect .Changes in the plasma drug concentration reflect changes in drug concentrations at the receptor site, as well as in other tissues. As the concentration of drug in plasma increases, the concentration of drug in most tissues will increase proportionally. Similarly, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. Figure 1-3 is a simplified plot of the drug concentration versus time profile after an intravenous drug dose and illustrates this concept.

The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics. It is the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

BASIC PHARMACODYNAMIC CONCEPTS;

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 adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. Receptors may be present on neurons in the central nervous system (i.e., opiate receptors) to depress pain sensation, on cardiac muscle to affect the intensity of contraction, or even within bacteria to disrupt maintenance of the bacterial cell wall. For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect . However,

other factors affect drug response as well. Density of receptors on the cell surface, the mechanism by which a signal is transmitted into the cell by second messengers (substances within the cell), or regulatory factors that control gene translation and protein production may influence drug effect. This multilevel regulation results in variation of sensitivity to drug effect from one individual to another and also determines enhancement of or tolerance to drug effects. In the simplest examples of drug effect, there is a relationship between the concentration of drug at the receptor site and the pharmacologic effect. If enough concentrations are tested, a maximum effect (Emax) can be determined .When the logarithm of concentration is plotted versus effect , one can see that there is a concentration below which no effect is observed and a concentration above which no greater effect is achieved. One way of comparing drug potency is by the concentration at which 50% of the maximum effect is achieved. This is referred to as the 50% effective concentration or EC50. When two drugs are tested in the same individual, the drug with a lower EC50 would be considered more potent. This means that a lesser amount of a more potent drug is needed to achieve the same effect as a less potent drug. The EC50 does not, however, indicate other important determinants of drug response, such as the duration of effect. Duration of effect is determined by a complex set of factors, including the time that a drug is engaged on the receptor as well as intracellular signaling and gene regulation.

For some drugs, the effectiveness can decrease with continued use. This is referred to as tolerance. Tolerance may be caused by pharmacokinetic factors, such as increased drug metabolism, that decrease the concentrations achieved with a given dose. There can also be pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure. An example of drug tolerance is the use of opiates in the management of chronic pain. It is not uncommon to find these patients requiring increased doses of the opiate over time. Tolerance can be described in terms of the dose–response curve, as shown in Figure 1-6. To assess the effect that a drug regimen is likely to have, the clinician should consider pharmacokinetic and pharmacodynamic factors. Both are important in determining a drug’s effect.

THERAPEUTIC DRUG MONITORING ;

Therapeutic drug monitoring is defined as the use of assay procedures for determination of drug concentrations in plasma, and the interpretation and application of the resulting concentration data to develop safe and effective drug regimens. If performed properly, this

process allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes. Together with observations of the drug's clinical effects, it should provide the safest approach to optimal drug therapy. The usefulness of plasma drug concentration data is based on the concept that pharmacologic response is closely related to drug concentration at the site of action. For certain drugs, studies in patients have provided information on the plasma concentration range that is safe and effective in treating specific diseases—the therapeutic range. Within this therapeutic range, the desired effects of the drug are observed. Below it, there is greater probability that the therapeutic benefits are not realized; above it, toxic effects may occur. No absolute boundaries divide subtherapeutic, therapeutic, and toxic drug concentrations. A gray area usually exists for most drugs in which these concentrations overlap due to variability in individual patient response. Numerous pharmacokinetic characteristics of a drug may result in variability in the plasma concentration achieved with a given dose when administered to various patients. This interpatient variability is primarily attributed to one or more of the following:

• Variations in drug absorption

- Variations in drug distribution
- Differences in an individual's ability to metabolize and eliminate the drug (e.g., genetics)

•Disease states (renal or hepatic insufficiency) or physiologic states (e.g., extremes of age, obesity) that alter drug absorption, distribution, or elimination

• Drug interactions Therapeutic monitoring using drug concentration data is valuable when: 1. A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. This relationship allows us to predict pharmacologic effects with changing plasma drug concentrations .2. Wide intersubject variation in plasma drug concentrations results from a given dose.

3. The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration). 4. The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensives). The value of therapeutic drug monitoring is limited in situations in which: 1. There is no well-defined

therapeutic plasma concentration range. 2. The formation of pharmacologically active metabolites of a drug complicates the application of plasma drug concentration data to clinical effect unless metabolite concentrations are also considered. 3. Toxic effects may occur at unexpectedly low drug concentrations as well as at high concentrations. 4. There are no significant consequences associated with too high or too low levels. Theophylline is an excellent example of a drug in which significant interpatient variability in pharmacokinetic properties exists. This is important from a clinical standpoint as subtle changes in serum concentrations may result in marked changes in drug response. Figure 1-10 shows the relationship between theophylline concentration (x-axis, on a logarithmic scale) and its pharmacologic effect, (changes in pulmonary function [y-axis]). This figure illustrates that as the concentration of theophylline increases, so does the intensity of the response for some patients. Wide interpatient variability is also shown. Figure 1-11 outlines the process clinicians may choose to follow in making drug dosing decisions by using therapeutic drug monitoring. Figure 1-12 shows the relationship of pharmacokinetic and pharmacodynamic factors. Examples of therapeutic ranges for commonly used drugs are shown in Table 1-1. As can be seen in this table, most drug concentrations are expressed as a unit of mass per volume.

PHARMACOKINETIC MODELS ;

The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Simplifications of body processes are necessary to predict a drug's behavior in the body. One way to make these simplifications is to apply mathematical principles to the various processes. To apply mathematical principles, a model of the body must be selected. A basic type of model used in pharmacokinetics is the compartmental model. Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body. There are one-compartment, two-compartment, and multicompartment models. The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids. These models can be used to predict the time course of drug concentrations in the body (Figure 1-13). Compartmental models are termed deterministic because the observed drug concentrations determine the type of compartmental model required to describe the pharmacokinetics of the drug. This concept will become evident when we examine one- and two-compartment models. To construct a compartmental model as a representation of the body,

simplifications of body structures are made. Organs and tissues in which drug distribution is similar are grouped into one compartment. For example, distribution into adipose tissue differs from distribution into renal tissue for most drugs. Therefore, these tissues may be in different compartments. The highly perfused organs (e.g., heart, liver, and kidneys) often have similar drug distribution patterns, so these areas may be considered as one compartment. The compartment that includes blood (plasma), heart, lungs, liver, and kidneys is usually referred to as the central compartment or the highly blood-perfused compartment (Figure 1-14). The other compartment that includes fat tissue, muscle tissue, and cerebrospinal fluid is the peripheral compartment, which is less well perfused than the central compartment. Another simplification of body processes concerns the expression of changes in the amount of drug in the body over time. These changes with time are known as rates. The elimination rate describes the change in the amount of drug in the body due to drug elimination over time. Most pharmacokinetic models assume that elimination does not change over time. The value of any model is determined by how well it predicts drug concentrations in fluids and tissues. Generally, it is best to use the simplest model that accurately predicts changes in drug concentrations over time. If a one-compartment model is sufficient to predict plasma drug concentrations (and those concentrations are of most interest to us), then a more complex (two-compartment or more) model is not needed. However, more complex models are often required to predict tissue drug concentrations.

COMPARTMENTAL MODELS

The one-compartment model is the most frequently used model in clinical practice. In structuring the model, a visual representation is helpful. The compartment is represented by an enclosed square or rectangle, and rates of drug transfer are represented by straight arrows .The arrow pointing into the box simply indicates that drug is put into that compartment. And the arrow pointing out of the box indicates that drug is leaving the compartment. This model is the simplest because there is only one compartment. All body tissues and fluids are considered a part of this compartment. Furthermore, it is assumed that after a dose of drug is administered, it distributes instantaneously to all body areas. Common abbreviations are shown in . Some drugs do not distribute instantaneously to all parts of the body, however, even after intravenous bolus administration. Intravenous bolus dosing means administering a dose of drug over a very short time period. A common distribution pattern is for the drug to distribute rapidly in the bloodstream and to the highly perfused organs, such as the liver and kidneys. Then, at a slower

rate, the drug distributes to other body tissues. This pattern of drug distribution may be represented by a two-compartment model. Drug moves back and forth between these compartments to maintain equilibrium .simplifies the difference between oneand two-compartment models. Again, the one-compartment model assumes that the drug is distributed to tissues very rapidly after intravenous administration.

Volume of Distribution ;

Until now, we have spoken of the amount of drug (X) in a compartment. If we also consider the volume of the compartment, we can describe the concept of drug concentration. Drug concentration in the compartment is defined as the amount of drug in a given volume, such as mg/L

concentration = amount of drug in body/ volume in which drug is distributed

= X/ V

Volume of distribution (V) is an important indicator of the extent of drug distribution into body fluids and tissues. V relates the amount of drug in the body (X) to the measured concentration in the plasma (C). Thus, V is the volume required to account for all of the drug in the body if the concentrations in all tissues are the same as the plasma concentration:

volume of distribution = amount of drug /concentration

A large volume of distribution usually indicates that the drug distributes extensively into body tissues and fluids. Conversely, a small volume of distribution often indicates limited drug distribution. Volume of distribution indicates the extent of distribution but not the tissues or fluids into which the drug distributes. Two drugs can have the same volume of distribution, but one may distribute primarily into muscle tissues, whereas the other may concentrate in adipose tissues. Approximate volumes of distribution for some commonly used drugs are shown in Table 1-2. When V is many times the volume of the body, the drug concentrations in some tissues should be much greater than those in plasma. The smallest volume in which a drug may distribute is the plasma volume. To illustrate the concept of volume of distribution, let us first imagine the body as a tank filled with fluid, as the body is primarily composed of water. To calculate the volume of the tank, we can place a known quantity of substance into it and then measure its concentration in the fluid (Figure 1-20). If the amount of substance (X) and the

resulting concentration (C) is known, then the volume of distribution (V) can be calculated using the simplified equations:

$X = VC$ or $C = X/V$ or $V = X/C$

X = amount of drug in body

V = volume of distribution

C = concentration in the plasma

As with other pharmacokinetic parameters, volume of distribution can vary considerably from one person to another because of differences in physiology or disease states. Something to note: The dose of a drug (X0) and the amount of drug in the body (X) are essentially the same thing because all of the dose goes into the body. In this example, important assumptions have been made: that instantaneous distribution occurs and that it occurs equally throughout the tank. In the closed tank, there is no elimination. This example is analogous to a one-compartment model of the body after intravenous bolus administration. However, there is one complicating factor—during the entire time that the drug is in the body, elimination is taking place. So, if we consider the body as a tank with an open outlet valve, the concentration used to calculate the volume of the tank would be constantly changing. We can use the relationship given in Equation 1-1 for volume, amount of drug administered, and resulting concentration to estimate a drug's volume of distribution in a patient. If we give a known dose of a drug and determine the concentration of that drug achieved in the plasma, we can calculate a volume of distribution.

PLASMA DRUG CONCENTRATION VERSUS TIME CURVES

With the one-compartment model if we continuously measure the concentration of a drug in the plasma after an intravenous bolus dose and then plot these plasma drug concentrations against the times they are obtained, the curve shown in would result. Note that this plot is a curve and that the plasma concentration is highest just after the dose is administered, at time zero (t0). Because of cost limitations and patient convenience in clinical situations, only a small number of plasma samples can usually be obtained for measuring drug concentrations From these known values, we are able to predict the plasma drug concentrations for the times when we have no samples In clinical situations, it is rare to collect more than two samples after a dose.

The prediction of drug concentrations based on known concentrations can be subject to multiple sources of error. However, if we realize the assumptions used to make the predictions, some errors can be avoided. These assumptions are pointed out as we review the one-compartment system. From a mathematical standpoint, the prediction of plasma concentrations is easier if we know that the concentrations are all on a straight line rather than a curve. This conversion can be accomplished for most drugs by plotting the natural logarithm (ln) of the plasma drug concentration versus time. The plot of a curve is, in effect, converted to a straight line by using the natural log of the plasma drug concentration .A straight line is obtained from the natural log of plasma drug concentration versus time plot only for drugs that follow first-order elimination processes and exhibit one-compartment distribution. First-order elimination occurs when the amount of drug eliminated from the body in a specific time is dependent on the amount of drug in the body at that time. This concept is explained further in Lesson 2. An alternative to calculating the natural log values is to plot the actual concentration and time values on semilogarithmic (or semilog) paper a special graph paper that automatically adjusts for the logarithmic relationship by altering the distance between lines on the y-axis. The lines on the y-axis are not evenly spaced but rather are logarithmically related within each log cycle (or multiple of 10). So when the actual values of plasma drug concentrations are plotted against the time values, a straight line results. The x-axis has evenly spaced lines; there is no logarithmic conversion of those values. (The term semilogarithmic indicates that only one axis is converted.) The numbers on the yaxis may be used to represent 0.1 through 1, 1 through 10, 10 through 100, or any series with a 10-fold difference in the range of values.

CHAPTER 3

COMPARTMENT MODELING

INTRODUCTION

One compartment open model.

a. Intravenous Injection (Bolus)

b. Intravenous infusion.

The time course of drug concentration determined after its administration can be statisfactorily explained by assuming the body as a single, well mixed compartment with first –

order desposition processes. In case of other drugs, two or more body compartments may be postulated to decscribe mathematically the data colloected.

ONE-COMPARTMENT OPEN MODEL

(Instantaneous Distribution Model) The one-compartment open model is the simplest model which depicts the body as a single, kinetically homogenous unit that has no barriers to the movement of drug and final distribution equilibrium between the drug the plasma and other body fluids is attained instantaneously and maintained at all times. This model thus applies only to those drugs that distribute rapidly throughout the body. The anatomical reference compartment is the plasma and concentration of drug in plasma is representative of drug concentration in all body tissues. i.e. any change in plasma drug concentration reflects a proportional change in drug concentration thorught out the body. However, the model does not assume that the drug concentration in plasma is equal to that in other body tissue. The term openindicates that the input (availability) and output (elimination) are unidirectional and that the drug can be eliminated from the body.

One-compartment open model is generally used to describe plasma levels following administration of a single dose of a drug. Depending upon the input, several one-compartment open models can be defined. One – compartment open model, intravenous bolus administration One –Compartment open model, continuous intravenous infusion One-compatmtment open model, extravascular administration, zero-order absorption, and One-Compartment open model, extravascular administration, first-order absorption.

One – Compartment Open Model; Intravenous Bolus Administration when a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection (i.e. i.v. bolus or slug), it takes about one to three minutes for complete circulation and therefore the rate of absorption is neglected in calculations. The model can be depicted as follows:

Blood and other Body Tissues---------- KE

The general expression for rate of drug presentation to the body is :

dx/dt = Rate in (availability) – Rate out (elimination)

Since rate in or absorption is absent, the equation b ecomes;

$dx/dt = -\text{Rate out}$

If the rate out or elimination follows first-order kinetics, then:

$dx/dt = -KEX$

Where KE = first-order elimination rate constant, and X = amount of drug in the body at any time t remaining to be eliminated. Negative sign indicates that the drug is being lost from the body. The various releted pharmacokinetic parameters can now be estimated.

Elimination Rate Constant: For a drug that follows one-compartment kinetics and administered as rapid. i.v. injection, the decline in plasma drug concentration is only due to elimination of drug from the body (and not due to distribution), the phase being called as elimination phase. Elimination phase can be characterized by 3 parameters – elimination rate constant, elimination half-life and clearance.

Integration of equation 5.3 yields:

$\text{Ln } X = \ln X0 – Ket$

Where Xo = amount of drug at time t = zero i.e. the initial amount of drug injected.

Equation 5.4 can also be written in the exponential form as :

$X = Xoe - K E t$

The above equation shows that disposition of a drug that follows one-compartment kinetics is monoexponential.

Transforming equation 4.4 into common logarithms (log base 10), we get:

Since is difficult to determine directly the amount of drug in the body X, advantage is taken of the fact that a constant relationship exists between drug concentration in plasma C (easily measurable) and X; thus:

$X = Vd C$

Where Vd = proportionality constant popularly known as the apparent volume of distribution. It is a pharmacokinetic parameter that permits the use of drug concentration in place of amount of drug in the body. The equation 5.6 therefore becomes:

Where Co = plasma drug concentration immediately after i.v. injection Equation 5.8 is that of a straight line and indicates that a semilogarithmic plot of log C versus t will be linear with Y-intercept logCo . The elimination rate constant is directly obtained from the slope of the line (Fig. 5.3). It has units of min-1. Thus, a linear plot is easier to handle mathematically than a curve which in this case will be obtained from a plot of C versus t on regular (Certesian) graph paper (Fig. 5.2). Thus, Co, KE (and 1/2) can be readily obtained from log C versus t graph. The elimination or removal of the drug from the body is the sum or urinary excretion, metabolism, biliary excretion, pulmonary excretion, and other mechanisms involved therein. Thus KE is an additive property of rate constants for each of these processes and better called as overall elimination rate constant. KE = Ke + Km + Kb + Kl+ …….

The fraction of drug eliminated by a particular route can be evaluated if the number of rate constants involved by and their values are known. For example, if a drug is eliminated by urinary excretion and metabolism only, them, the fraction of drug excreted unchanged in urine Fe and fraction of drug metabolized Fm can be given as

Elimination Half-Life : Also called as biological half-life. It is the oldest and the best known of all pharmacokinetic parameters and was once considered as the most important characteristic of drug. It is defined as the time taken for the amount of drug in the body as well as plasma concentration to decline by one-half or 50% its initial value. It is expressed in hours or minutes.

elimination half-life can be readily obtained from the graph of log C versus t as shown in Fig. 5.2 Today , increased physiologic understanding of pharmacokinetics shows that half-life is a secondary parameter that depends upon the primary parameters clearance and apprent volume of distribution according to following equation :

Apparent volume of distribution : Clearance and apparent volume of distribution are two separate and independent pharmacokinetic characteristics of a drug. Since they are closely related with the physiologic mechyanisms in the body. They are called as primary parameters. Modification of equation 5.7 defines apparent volume of distribution:

Vd =X/C

Vd is a measure of the extent of distribution of drug and is expressed in liters. The best and the simplest way of estimating Vd of a drug is administering it by rapid i.v. injection and using the following equation: X0 i.v. bolus dose

Vd =X0/C0

Equation 5.15 can only be used for drugs that obey one-compartment kinetics. This is because the Vd can only be estiamted when distribution equilibrium is achieved between drug in plasma and that in tissues and such an equilibrium is established instantaneosuly for a drug that follows one-comapartment kinetics. A more general, more useful non-compartmental method that can be applied to many compartment models for estimating the Vd is:

Clearance:

Difficulties arise when one applies elimination rate constant and half-life as pharmacokinetic parameters in an anatomical /physiological context and as a measure of drug elimination mechanisms. A much more valuable alternative appraoch for such applications is use of clearance parameters to characterize drug disposition. Clearance is the most important parameter in clinical drug applications and is useful in evaluating the mechanism by which a drug is eliminated by the whole organism or by a particular organ.

Clearance is defined as the theoretical volume of body fluid containing drug. (i.e. that fraction of apparent volume of distribution) from which the drug is completely removed in a given period of time.

Total Body Clearance : Elimination of a drug from the body involves processes occuring in kidney, liver, lungs, and other eliminating organs. Clearance at an individual organ level is called as organ clearacne.

One-Compartment

Open Model -Intravenous Infusion Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintainance of a stable concentration or amount of drug in the body is desired. In such a situation, the drug (for example, several antibiotics, theophyline, procainmide, etc.) is administered at a constant rate (zero-order) by i.v. infusion. In contrast to

the short duration of infusion of an i.v. bolus (few seconds), the duration of constant rate infusion is usually much longer than the half-life of the drug.

Advantages of such a zero-order infusion of such a zero order infusion of drugss include –

1. Ease of control of rate of infusion to fit individual patient needs.

2. Prevents fluctuating maxima and minima (peak and valley) plasma level, desired especially when the drug has a narrow therapeutic index.

3. Other drugs, electrolytes and nutrients can be conveniently administered simultaneously by the same infusion line in critically ill patients.

The model can be represented as follows:

At any time during infusion, the rate of change in the amount of drug in the body. dX/dt is the difference between the zero-order rate of drug infusion Ro and first-order rate of elimination, – KEX:

Integration and rearrangement of above equation yields:

Since X = Vd C, the equation 5.37 can be transformed into concentration terms as follows:

At the start of constant rate infusion, the amount of drug in the body is zero and hence, there is no elimination. As time passes, the amount of drug in the body rises gradually (elimination rate less than the rate of infusion) until a point after which the rate of elimination equals the rate of infusion i.e. the concentration of drug in plama appraches a constant value called as steady-state, plateau or equilibrium.

One-Compartment Open Model --Extravascular Asministration The rate of absorption may be described mathematically as a zeroorder or first-order process. A large number of plasma concentration-time profiles can be described by a one-compartment model with first-order absorption and elimination. However, under certain conditions, the absorption of some drugs may be better described by assuming zero-order(constant rate) kinetics. Differences between zero-order and first-order kinetics are illustrated in Fig. 5.7. Zero-order absorption is characterized by a constant rate of absorption. It is independent of amount remaining to be absorbed (ARA), and its regular ARA versus t plot is linear with slope equal to tate of absorption

while the semilog plot is described by an ever-increasing gradient with time. In contrast, the first –order absorption process is distinguished by a decline in the rate with ARA i.e. absorption rate is dependent upon ARA ; its regular plot is curvilinear and semilog plot a straight line with absorption rate as its slope.

Besides the method of residuals, Ka can also be estimated by Loo-Riegelman method for a drug that follows two-compartment characteristics. This method is in contrast to the Wagner-Nelson method for determination of Ka of a drug with one-compartment characteristic. The Loo Riegelman method requires plasma drug concentration-time data after oral and i.v. administration of the drug to the same subject at different times in order to obtain all the necessary kinetic constants. Despite its complexity the method can be applied to drugs that distribute in any number of compartments.

UNIT-4

Multicompartment Pharmacokinetic Models

a. Two compartment open model.

b. IV bolus, IV infusion and oral administration

OBJECTIVES

After completing this chapter you should be able to

• Describe the differences between the one-compartment and the two-compartment pharmacokinetic models

• Define all the parameters of the two-compartment pharmacokinetic model

• Describe the plasma concentration–time profile after a single IV and oral administration, during constant rate IV infusion, and multiple drug administration of drugs that follow two-compartment pharmacokinetic model

• Estimate all the pharmacokinetic parameters of the two-compartment pharmacokinetic model from plasma concentrations obtained after a single IV administration

• Analyze the effect of changing one or more of the pharmacokinetic parameters on the plasma concentration–time profile and the drug distribution between the central and the peripheral

compartments after administration of drugs that follow the two-compartment pharmacokinetic model

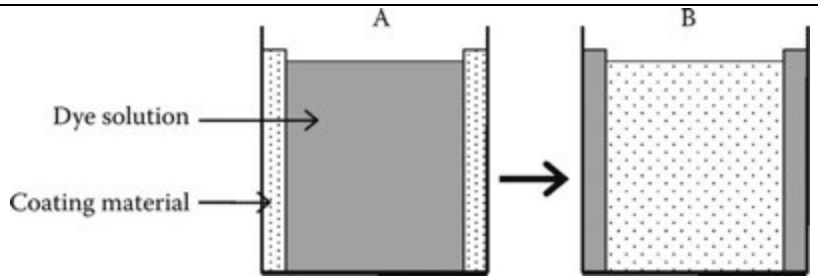
• Describe the general steps for compartmental modeling and discuss the general approaches used to evaluate the goodness of model fit

INTRODUCTION

In the previous discussions, it was assumed that the drug is rapidly distributed to all parts of the body once it enters the systemic circulation. An immediate equilibrium is established between the drug in the systemic circulation and the drug in all parts of the body. The drug concentration in different parts of the body is different because of the differences in drug affinity to the different tissues. However, any change in the plasma drug concentration due to drug absorption or drug elimination is accompanied by a proportional change in the drug concentration in the different tissues. So the drug concentration–time profiles in the different parts of the body are parallel to each other. The rapid distribution equilibrium achieved between the different tissues makes the body act as one homogenous compartment.

The process of drug distribution to the different parts of the body can be demonstrated by a beaker that has a coating material covering its inner wall and is filled with a liquid as in Figure 17.1 In this example, the liquid in the center of the beaker represents the systemic circulation and the beaker wall coating materials represents the tissues. If a drop of dye is added to the liquid, the dye is distributed in the liquid in the center of the beaker first and then to the coating material of the beaker wall. If the dye is rapidly distributed from the liquid to the coating material, the dye distribution equilibrium is achieved rapidly. The dye concentration in the liquid in the center of the beaker becomes constant immediately after addition of the dye. In this case, the beaker behaves as a single compartment despite the difference in dye concentration in the liquid and in the beaker wall covering. For drugs that are rapidly distributed from the systemic circulation to the tissues, rapid distribution equilibrium between the drug in the systemic circulation and tissues is achieved. When the drug is eliminated, the drug concentrations in the systemic circulation and in all tissues decline at the same rate because of the rapid distribution equilibrium. Drugs that follow this behavior follow the one-compartment pharmacokinetic model. When these drugs are administered by a rapid IV bolus dose, the plasma drug concentration declines monoexponentially and the plasma drug concentration–time profile is linear on the semilog scale.

FIGURE 17.1 Diagrammatic presentation of the distribution of the dye from the solution in the center of the beaker to the beaker wall coating material. The distribution process causes decrease in the dye concentration in solution and increase in the dye concentration in the coating material. When the dye distribution to the beaker wall coating material (A → B) is fast, the beaker behaves as a single compartment, while when the dye distribution to the beaker wall coating material (A → B) is slow, the beaker behaves as if it consists of two different compartments.

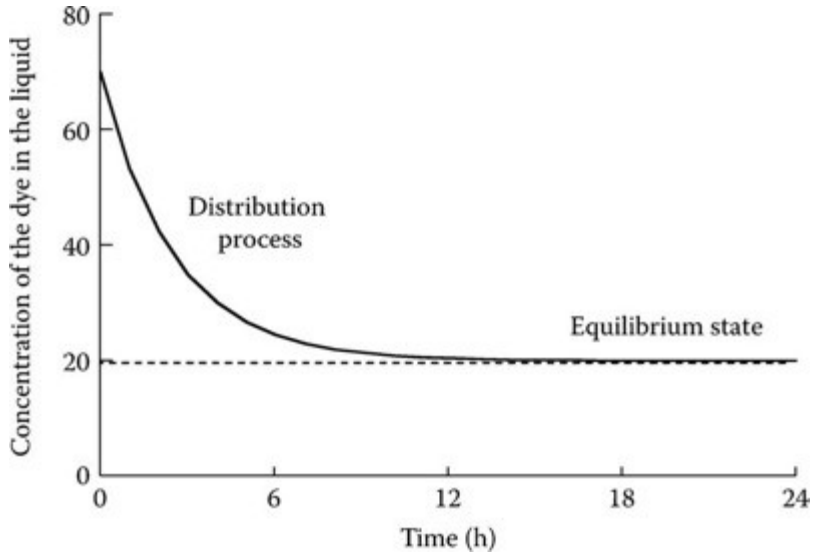


For some drugs, the distribution from the systemic circulation to the different tissues is slow. The beaker example mentioned earlier can be used to explain this condition. After addition of the dye to the beaker, it distributes in the liquid in the center of the beaker initially. Then the dye starts to distribute slowly to the beaker wall coating material. The distribution of the dye from the liquid in the center of the beaker to the beaker wall coating material causes gradual decrease in the dye concentration in the liquid and gradual increase in the dye concentration in the beaker coating material as illustrated in Figure 17.1. The dye concentration in the liquid reaches a constant value when equilibrium is achieved between the dye in the liquid and the beaker wall coating material as illustrated in Figure 17.2.

After IV administration of a drug that is slowly distributed to the tissues, the drug is immediately distributed in the systemic circulation and other highly perfused tissues. The drug concentration in the systemic circulation decreases initially at a fast rate due to drug distribution to the tissues and also due to drug elimination from the body. When equilibrium is established between the drug in the systemic circulation and all tissues, the drug concentration in the systemic circulation and tissues declines at a rate dependent on the rate of elimination, which is slower than 1the initial rate of decline. After IV bolus administration of the drugs that follow this behavior, the plasma drug concentration–time profile is curvilinear on the semilog scale. These drugs follow

the two-compartment, three-compartment, or any other multi-compartment pharmacokinetic model. This model consists of a central compartment that includes the vascular space and highly perfused tissues and one or more peripheral compartments that include the other organs of the body.

FIGURE 17.2 Dye concentration–time profile in the liquid with the decrease in the dye concentration representing the distribution of the dye from the liquid in the central of the beaker to the beaker wall coating material.



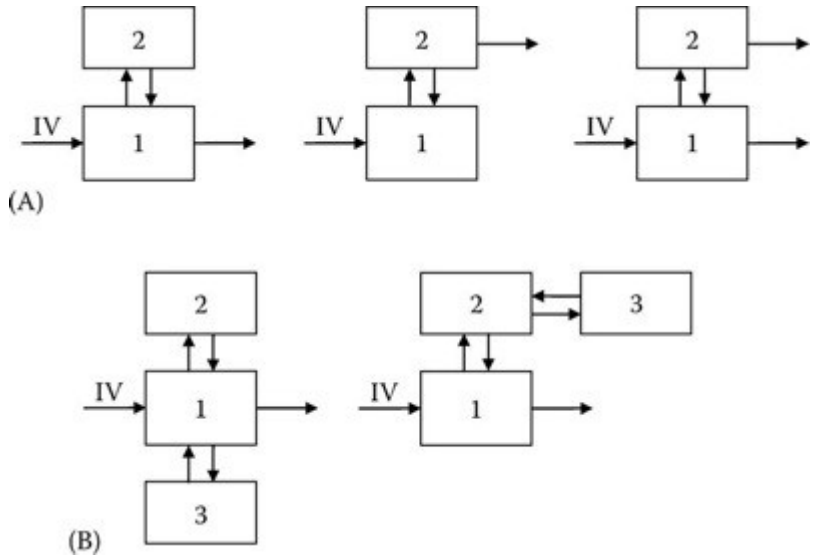
17.2 COMPARTMENTAL PHARMACOKINETIC MODELS

Pharmacokinetic modeling in general involves the development of a model that can quantitatively describe the pharmacokinetic behavior of the drug in the body. In compartmental modeling, the body is described by one or more interconnected compartments depending on the rate of drug distribution to the different parts of the body. The number of compartments in the model depends on the rate of drug distribution to the different parts of the body. Each of the compartments has its own volume of distribution and the intercompartmental clearances that govern the drug distribution and transfer between these compartments. The model includes an input function that describes the drug entry to the systemic circulation. The order of the elimination process and the compartment where the elimination process takes place are included in the model [1].

Compartmental pharmacokinetic models differ in the number of compartments, the compartment(s) where drug elimination occurs, and the arrangement of these compartments. The number of compartments in the model depends on the rate of drug distribution to the different parts of the body. If the drug in the systemic circulation is distributed rapidly to all parts of the

body, the body behaves as a single compartment and the drug pharmacokinetic behavior can be described by one-compartment pharmacokinetic model, while if the drug is distributed rapidly to some tissues and organs and slowly to other tissues and organs, the two-compartment pharmacokinetic model can be used to describe the pharmacokinetic behavior of the drug in this case. On the contrary, when the drug is distributed to the different parts of the body at three distinguished rates, for example, rapid, slow, and very slow, the three-compartment pharmacokinetic model can be used to describe this pharmacokinetic behavior. The pharmacokinetic behavior of most drugs can be described by one-, two-, or three-compartment pharmacokinetic models; however, models with more compartments can be used if the obtained data can support these complicated models.

FIGURE 17.3 Diagram represents different compartmental pharmacokinetic models. (A) Examples of two-compartment pharmacokinetic models with elimination from compartment 1, compartment 2, or both compartments. (B) Examples of the many possible three-compartment pharmacokinetic models that differ in the arrangement of the compartments and in the compartment(s) where drug elimination takes place.



Pharmacokinetic models that have the same number of compartments can be different when drug elimination occurs from different compartments [2]. The different two-compartment pharmacokinetic models presented in Figure 17.3A differ in the compartment where drug elimination takes place. One of the models has drug elimination from compartment 1, the second model has drug elimination from compartment 2, and the third model has drug elimination from both compartments. For the three-compartment pharmacokinetic model, there are seven different possibilities for the compartment(s) where drug elimination takes place. Also, pharmacokinetic

compartment models can differ in the way the compartments are arranged. For example, the models presented in Figure 17.3B are examples of the three-compartment pharmacokinetic models.

17.3 TWO-COMPARTMENT PHARMACOKINETIC MODEL

The two-compartment pharmacokinetic model with elimination from the central compartment is the most common model used to describe the pharmacokinetic behavior of drugs that follow two-compartment model. So this model will be used in the following discussion. After IV bolus dose, the drug is distributed rapidly to the body spaces and tissues that represent the central compartment. Then the drug is distributed by a first-order process from the central compartment to the other body spaces and tissues that represent the peripheral compartment. Because the blood is usually part of the central compartment, the drug can be delivered to the eliminating organ(s) once the drug is in the central compartment. So distribution and elimination occur simultaneously after drug administration, which causes rapid decline in the drug concentration in the central compartment. After the distribution process is completed and equilibrium is established between the drug in the central compartment and the drug in the peripheral compartment, the drug concentration in the central compartment declines at a rate dependent on drug elimination. The rate of decline in the drug concentration in the central compartment due to drug elimination is slower than the initial rate of decline due to distribution and elimination. So the plasma drug concentration–time profile that represents the drug profile in the central compartment consists of two phases on the semilog scale. An initial distribution phase characterized by rapid decline in drug concentration, followed by a terminal elimination phase with slower rate of decline in drug concentration. The drug concentration–time profile during the terminal elimination phase is linear on the semilog scale since it declines depending on the rate of drug elimination [3]. A typical plasma concentration–time profile after IV bolus administration of drugs that follow two-compartment pharmacokinetic model is presented in Figure 17.4.

The two-compartment pharmacokinetic model assumes that at time zero there is no drug in the tissues representing the peripheral compartment. After an IV dose, the drug is rapidly distributed in the central compartment. The amount of drug in the central compartment declines rapidly due to the transfer of drug out of the central compartment to the peripheral compartment and also due to drug elimination that occurs simultaneously. The drug in the central compartment is transferred to the peripheral compartment by a first-order process, and can return back to the

central compartment also by a first-order process. Initially the amount of the drug in the central compartment is larger than the amount of the drug in the peripheral compartment, so the net drug transfer is from the central compartment to the peripheral compartment. This means that initially the amount of drug in the peripheral compartment increases with time.

FIGURE 17.4 Plasma concentration–time profile of a drug that follows the two-compartment pharmacokinetic model after single IV bolus dose.

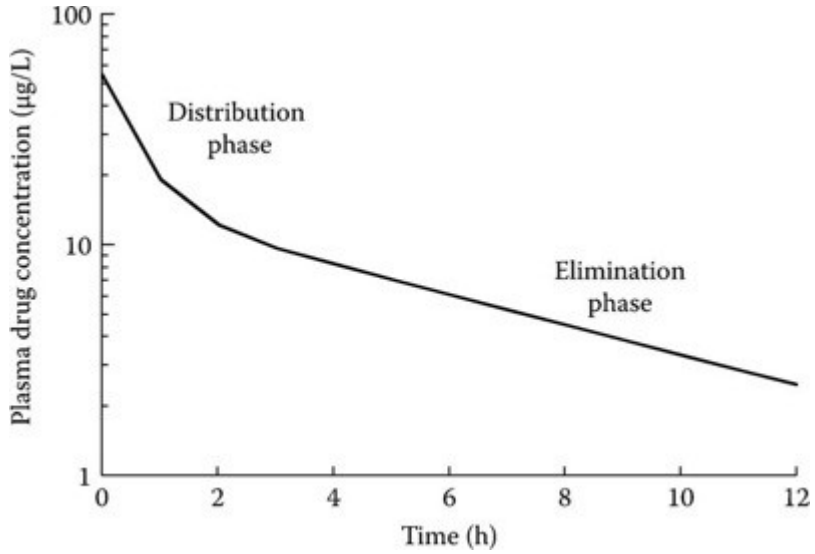
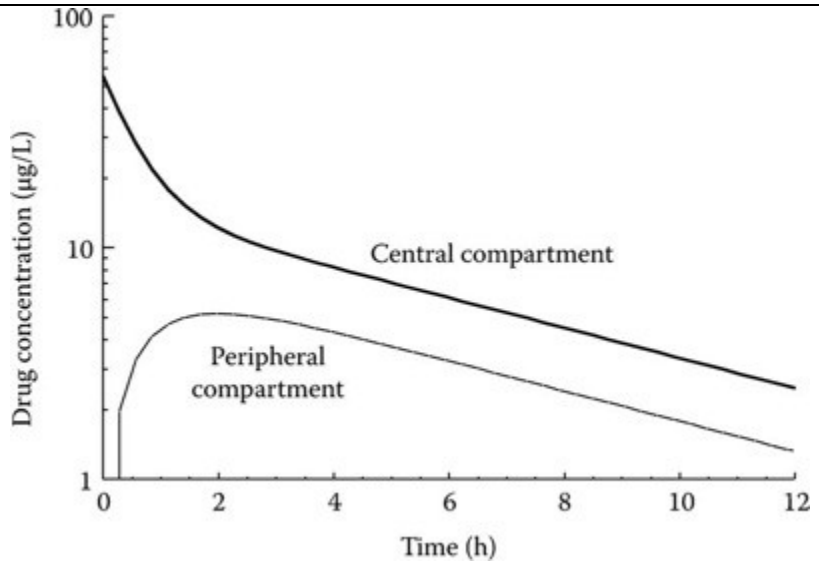


FIGURE 17.5 Drug concentration–time profile in the central and peripheral compartments after administration of a single IV bolus dose of a drug that follows two-compartment pharmacokinetic model.



s the amount of drug in the peripheral compartment increases, the rate of drug transfer from the peripheral to the central compartment approaches that from the central to the peripheral compartment. When these two rates become equal, the amount of drug in the peripheral compartment reaches a maximum value. Because the drug is continually eliminated from the central compartment, the amount of drug in the central compartment decreases and the rate of drug transfer from the peripheral to the central compartment becomes larger than that from the central to peripheral compartment. The net drug transfer is from the peripheral to the central compartment, and the amount of drug in the peripheral compartment starts to decline parallel to the decline in the amount of the drug in the central compartment. Figure 17.5 shows the drug concentration–time profile in the central and peripheral compartments after administration of a single IV bolus dose. The concentration of drug in the central compartment is determined by dividing the amount of drug in the central compartment by the volume of the central compartment. Likewise, the concentration of drug in the peripheral compartment is determined by dividing the amount of drug in the peripheral compartment by the volume of the peripheral compartment. So, the drug concentration in the peripheral compartment can be higher or lower than the drug concentration in the central compartment depending on the drug affinity to the tissues.

17.4 PARAMETERS OF THE TWO-COMPARTMENT PHARMACOKINETIC MODEL

The two-compartment pharmacokinetic model presented by the block diagram in Figure 17.6 assumes that the drug transport between the central and peripheral compartments follows first-order kinetics and that the drug is eliminated from the central compartment by a first-order process.

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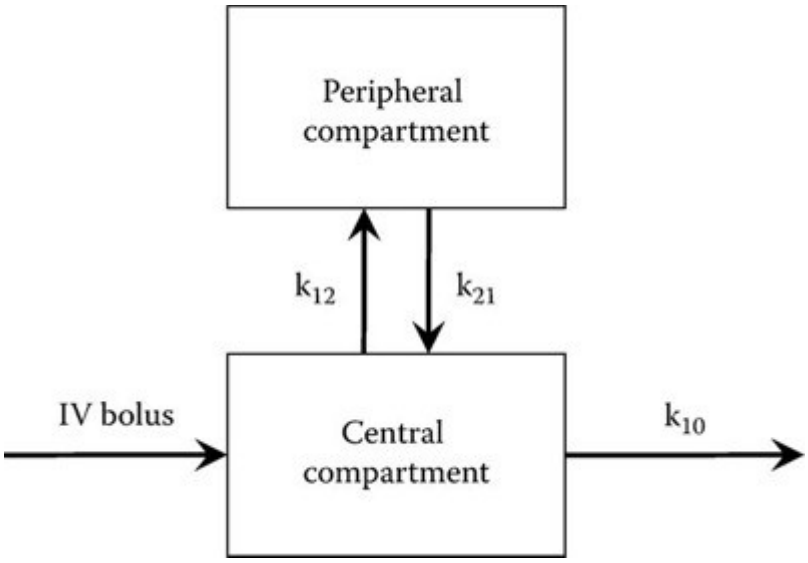
FIGURE 17.6 Block diagram that represents the two-compartment pharmacokinetic model with first-order transport between the central and peripheral compartments and first-order drug elimination from the central compartment.



17.4.1 DEFINITION OF THE PHARMACOKINETIC PARAMETERS

The following are the definitions of the pharmacokinetic parameters used in deriving the equations for the two-compartment pharmacokinetic model:

X is the amount of drug in the central compartment and has units of mass.
Y is the amount of drug in the peripheral compartment and has units of mass.
k_{12} is the first-order transfer rate constant from the central compartment to the peripheral compartment and has units of $time^{-1}$.
k_{21} is the first-order transfer rate constant from the peripheral compartment to the central compartment and has units of $time^{-1}$.
k_{10} is the first-order elimination rate constant from the central compartment and has units of $time^{-1}$.
A and B are the hybrid coefficients and have units of concentrations.
α is the hybrid first-order rate constant for the distribution process and has units of $time^{-1}$.
β is the hybrid first-order rate constant for the elimination process and has units of $time^{-1}$.
$t_{1/2\alpha}$ is the half-life for the distribution phase and has units of time.
$t_{1/2\beta}$ is the half-life for the elimination phase and has units of time.
V_c is the volume of the central compartment and has units of volume. This term relates the administered dose to the initial plasma drug concentration (central compartment concentration) after administration of a single IV dose:

Vd_{ss} is the volume of distribution of the drug at steady state and has units of volume. This term relates the amount of the drug in the body and the plasma drug concentration at steady state:

Vd_β or Vd_{area} is the volume of distribution during the elimination phase and has units of volume. This term relates the amount of the drug in the body and the plasma drug concentration during the elimination phase (β-phase):

Amount of the drug in the body during the elimination phase = $Vd_\beta Cp_{\beta\text{-phase}}$ (17.3)

17.4.2 MATHEMATICAL EQUATION THAT DESCRIBES THE PLASMA CONCENTRATION–TIME PROFILE

The rate of change of the amount of the drug in any compartment is equal to the sum of the rates of drug transfer into the compartment minus the sum of the rates of drug transfer out of the compartment. After a single IV bolus dose and based on the pharmacokinetic model in Figure 17.6, the rate of change of the amount of the drug in the central compartment (X) at any time is equal to the rate of drug transfer from the peripheral compartment to the central compartment minus the rate of drug transfer from the central compartment to the peripheral compartment, minus the rate of drug elimination. Similarly, the rate of change of the amount of drug in the peripheral compartment (Y) is equal to the rate of drug transfer from the central compartment to the peripheral compartment minus the rate of drug transfer from the peripheral compartment to the central compartment. The differential equations that describe these two rates are

$$\frac{dX}{dt} = k_{21}Y - k_{12}X - k_{10}X \qquad (17.4)$$

and

$$\frac{dY}{dt} = k_{12}X - k_{21}Y \qquad (17.5)$$

Integrating the first differential equation yields the integrated equation for the amount of drug in the central compartment (X) as a function of time after a single IV bolus dose (D):

$$X = \frac{D(\alpha - k_{21})}{(\alpha - \beta)}e^{-\alpha t} + \frac{D(k_{21} - \beta)}{(\alpha - \beta)}e^{-\beta t} \qquad (17.6)$$

This equation contains two exponents, one exponent describes the distribution process and the other describes the elimination process. These exponents contain the hybrid rate constants for the distribution and elimination processes, α and β. As a result of the integration process to get the integrated equation for the amount of the drug in the central compartment, the following two relationships were obtained:

$$\alpha + \beta = k_{12} + k_{21} + k_{10} \qquad (17.7)$$

$$\alpha\beta = k_{21}k_{10} \qquad (17.8)$$

where

$$\alpha = \frac{1}{2}\left[(k_{12} + k_{21} + k_{10}) + \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}}\right] \quad (17.9)$$

$$\beta = \frac{1}{2}\left[(k_{12} + k_{21} + k_{10}) - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}}\right] \quad (17.10)$$

Since the distribution process is usually faster than the elimination process, the larger hybrid rate constant α is the rate constant for the distribution process and the smaller hybrid rate constant β is the rate constant for the elimination process as in Equations 17.9 and 17.10. During the distribution phase, the drug distribution rate does not depend only on k_{12}, the transfer rate constant from the central to peripheral compartment. This is because while the drug is distributing from the central to the peripheral compartment, there is drug returning back to the central compartment at a rate dependent on the rate constant k_{21}, and also there is elimination from the peripheral compartment affected by the rate constant k_{10}. So the observed rate of the distribution process is described by the hybrid rate constant α, which is dependent on the three rate constants k_{12}, k_{21}, and k_{10} as inEquation 17.9. Similarly, the drug elimination rate does not depend only on k_{10}, the elimination rate constant from the central compartment. This is because during the elimination of the drug from the central compartment, there is drug transfer from the central to the peripheral compartment at a rate dependent on the rate constant k_{12}, and drug returning back to the central compartment at a rate dependent on the rate constant k_{21}. So the observed rate for the elimination process is described by the hybrid rate constant β, which is dependent on the three rate constants k_{12}, k_{21}, and k_{10}as in Equation 17.10. The first-order rate constants k_{12}, k_{21}, and k_{10} are usually termed the micro rate constants, while α and β are termed the macro rate constants.

Dividing Equation 17.6 by the volume of the central compartment, V_c, gives the equation for the drug concentration in the central compartment, and hence the plasma drug concentration, at any time after a single IV bolus dose:

$$Cp = \frac{D(\alpha - k_{21})}{V_c(\alpha - \beta)}e^{-\alpha t} + \frac{D(k_{21} - \beta)}{V_c(\alpha - \beta)}e^{-\beta t} \quad (17.11)$$

which can be simplified to

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \quad (17.12)$$

where

$$A = \frac{D(\alpha - k_{21})}{V_c(\alpha - \beta)} \qquad (17.13)$$

and

$$B = \frac{D(k_{21} - \beta)}{V_c(\alpha - \beta)} \qquad (17.14)$$

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Equation 17.11 and its simplified form Equation 17.12 are the equations that describe the plasma drug concentration at any time after a single IV bolus dose of a drug that follows the two-compartment pharmacokinetic model [4]. These equations include two exponents: one describes the distribution process and includes the larger hybrid rate constant, α, and the other describes the elimination process and includes the smaller hybrid rate constant, β. As time elapses after IV drug administration, the exponential term that has the distribution (larger) hybrid rate constant approaches zero and the plasma concentration declines at a rate dependent on the hybrid elimination rate constant, β. So the plasma drug concentration–time profile after a single IV bolus dose on the semilog scale has a rapidly declining distribution phase and a linear terminal elimination phase.

17.5 DETERMINATION OF THE TWO-COMPARTMENT PHARMACOKINETIC MODEL PARAMETERS

The pharmacokinetic parameters k_{21}, V_c, α, and β, in Equation 17.11, or the parameters A, B, α, and β, in Equation 17.12, can be estimated from the plasma drug concentrations obtained after a single IV dose (D) of the drug by nonlinear regression analysis utilizing specialized statistical programs. The estimated parameters in both equations can be used to calculate all the other parameters of the model. The pharmacokinetic parameters allow prediction of the drug steady-state plasma concentration during repeated drug administration and determination of the dose required to achieve certain drug concentration at steady state. The pharmacokinetic parameters in Equation 17.12, A, B, α, and β, can be estimated graphically utilizing the method of residuals.

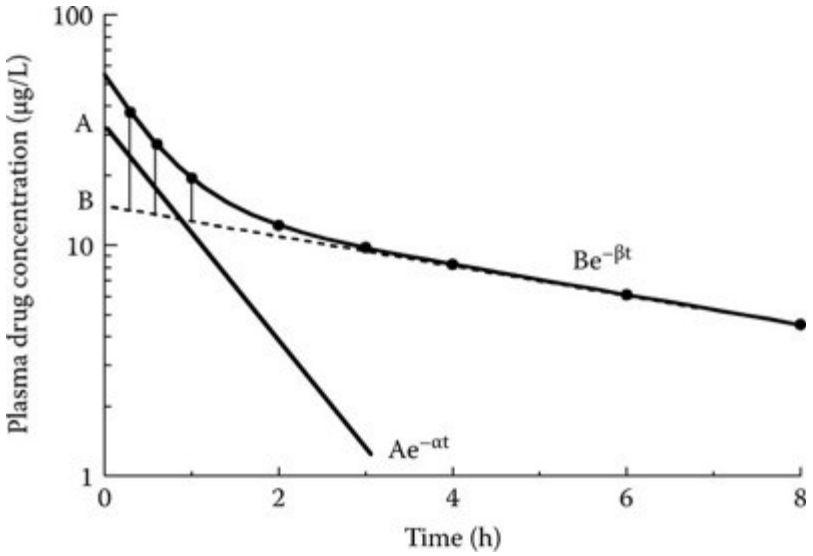
17.5.1 METHOD OF RESIDUALS

The method of residuals is a graphical method used to estimate the two-compartment pharmacokinetic model parameters after a single IV dose. The basic principle of the method of residuals is to separate the two exponential terms in Equation 17.12 as illustrated in Figure 17.7. The method of residuals can be summarized by the following steps:

- • The experimentally obtained plasma concentrations are plotted against their corresponding time values on the semilog scale.
- • The plasma drug concentrations that decline linearly during the elimination phase are identified. The best line that passes through these points is drawn and the line is back extrapolated to meet the y-axis.
- • This line is corresponding to the ($Be^{-\beta t}$) term in the biexponential equation. The y-intercept of the extrapolated line is equal to the coefficient B in the equation. The hybrid rate constant β can be determined from the slope of the line (slope = −β/2.303). Also, the $t_{1/2\beta}$ can be determined directly from the line by calculating the time required for any concentration on the line to decrease by 50%. Then β is calculated as
-

$$\beta = \frac{0.693}{t_{1/2\beta}} \qquad (17.15)$$

FIGURE 17.7 Method of residuals applied to separate the two exponential terms of the equation that describes the plasma concentration–time profile of drugs that follow the two-compartment pharmacokinetic model after a single IV dose.



- • The residuals are calculated from the difference between the observed plasma concentration–time data and the corresponding values on the extrapolated line representing the elimination phase. The residuals are plotted versus their corresponding time values.
- • The residual versus time plot is linear on the semilog scale and this line is corresponding to the ($Ae^{-\alpha t}$) term in the biexponential equation. The y-intercept of this line is equal to the coefficient A in the equation. The hybrid rate constant α can be determined from

the slope of the line (slope = −α/2.303). Also, the $t_{1/2\alpha}$ can be determined directly from the line by calculating the time required for any point on the line representing the α-phase to decrease by 50%. Then the hybrid rate constant α is calculated as

$$\alpha = \frac{0.693}{t_{1/2\alpha}} \qquad (17.16)$$

- • A is always the y-intercept of the faster process (the process with shorter $t_{1/2}$, the distribution process), and B is always the intercept of the slower process (the process with longer $t_{1/2}$, the elimination process).

17.5.2 DETERMINATION OF THE MODEL PARAMETERS

Once the parameters A, B, α, and β are determined from the method of residuals, the other model parameters can be calculated [1].

17.5.2.1 Volume of the Central Compartment, V_c

After IV bolus administration, the drug is distributed initially in the central compartment. So the volume of the central compartment can be determined from the dose and the initial drug concentration in the central compartment, which is same as the initial plasma drug concentration. The plasma concentration at time zero is determined from Equation 17.12 by substituting the time by zero, and it is equal to (A + B):

$$V_c = \frac{\text{Dose}}{Cp_o} = \frac{\text{Dose}}{A + B} \qquad (17.17)$$

17.5.2.2 Area under the Plasma Concentration–Time Curve, AUC

The area under the plasma concentration–time curve is determined by integrating Equation 17.12, which describes the plasma concentration–time profile from time 0 to ∞:

$$AUC\Big|_{t=0}^{t=\infty} = \frac{A}{\alpha} + \frac{B}{\beta} \qquad (17.18)$$

17.5.2.3 Total Body Clearance, CL_T

The CL_T is determined from the dose and the AUC similar to the one-compartment pharmacokinetic model:

$$CL_T = \frac{\text{Dose}}{AUC\Big|_{t=0}^{t=\infty}} \qquad (17.19)$$

17.5.2.4 First-Order Elimination Rate Constant from the Central Compartment, k_{10}

The CL_T is the product of the first-order elimination rate constant k_{10} and V_c. When V_c and CL_T are known, k_{10} can be calculated:

$$CL_T = k_{10} V_c \qquad (17.20)$$

.

$$k_{10} = \frac{CL_T}{V_c} \qquad (17.21)$$

17.5.2.5 First-Order Transfer Rate Constant from the Peripheral Compartment to the Central Compartment, k_{21}

As a result of integrating the differential equation to obtain the integrated equation for the amount of the drug in the central compartment, the relationship in Equation 17.8 has been obtained ($\alpha\beta = k_{21}k_{10}$). Based on this relationship, k_{21} can be calculated:

$$k_{21} = \frac{\alpha\beta}{k_{10}} \qquad (17.22)$$

17.5.2.6 First-Order Transfer Rate Constant from the Central Compartment to the Peripheral Compartment, k_{12}

Also, while integrating the differential equation to obtain the integrated equation for the amount of the drug in the central compartment, the relationship in 320321Equation 17.7 has been obtained ($\alpha + \beta = k_{12} + k_{21} + k_{10}$). Based on this relationship, k_{12} can be calculated:

$$k_{12} = (\alpha + \beta) - (k_{21} + k_{10}) \qquad (17.23)$$

17.5.3 DETERMINATION OF THE VOLUMES OF DISTRIBUTION FOR THE TWO-COMPARTMENT PHARMACOKINETIC MODEL

In the one-compartment pharmacokinetic model the drug is distributed rapidly to all parts of the body and the distribution equilibrium is established immediately after drug administration. So the drugs that follow one-compartment pharmacokinetic model are distributed in the same tissues once they enter the systemic circulation and they have only one volume of distribution. However, in the two-compartment pharmacokinetic model there is more than one volume of distribution. Initially, after IV drug administration the drug is distributed in the central compartment only. Then the drug distributes from the central compartment to the peripheral compartments. During the elimination phase the drug volume of distribution is equal to Vd_β and during steady state the drug volume of distribution is equal to Vd_{ss}. The volume of the central compartment is the smallest, while Vd_β is the largest of the three volumes in the two-compartment pharmacokinetic

model. Vd_{ss} is larger than V_c and smaller than Vd_β. V_c can be calculated from the dose of the initial drug concentration as in Equation 17.17.

17.5.3.1 Volume of Distribution at Steady State, Vd_{ss}

Vd_{ss} is the factor that relates the amount of the drug in the body and the plasma drug concentration during steady state when the drug is administered by constant rate IV infusion and the drug concentration in the body is constant. When the drug concentration is constant, the rate of drug transfer from the central to the peripheral compartment is equal to the rate of drug transfer from the peripheral to the central compartment. Also, a transient steady state is achieved for brief moment after a single IV administration when the drug concentration in the peripheral compartment reaches its maximum value, and the net rate of drug transfer between the central and peripheral compartments is equal to zero. The rate of drug transfer can be expressed by the drug transfer rate constant and the amount of the drug in each compartment. At steady state,

$$k_{12}X = k_{21}Y \qquad (17.24)$$

$$Y = \frac{Xk_{12}}{k_{21}} = \frac{Cp_{ss}V_ck_{12}}{k_{21}} \qquad (17.25)$$

Since the amount of the drug in the central compartment is the product of the plasma drug concentration and V_c. At steady state, Vd_{ss} relates the amount of the drug in the body to the drug concentration in plasma:

$$Vd_{ss} = \frac{X+Y}{Cp_{ss}} = \frac{Cp_{ss}V_c + Cp_{ss}V_c(k_{12}/k_{21})}{Cp_{ss}} \qquad (17.26)$$

$$Vd_{ss} = V_c + V_c\frac{k_{12}}{k_{21}} \qquad (17.27)$$

$$Vd_{ss} = V_c\left(1+\frac{k_{12}}{k_{21}}\right) \qquad (17.28)$$

17.5.3.2 Volume of Distribution in the Elimination Phase, Vd_β

During the elimination phase, distribution equilibrium is established between the drug in the central and peripheral compartments, which makes the drug concentration in the central and peripheral compartments decline at the same rate. However, there is more drug transfer from the peripheral compartment to the central compartment to compensate for the drug elimination that occurs from the central compartment. The volume of distribution during the elimination phase can be calculated from the CL_T and the first-order hybrid elimination rate constant:

$$Vd_\beta = \frac{CL_T}{\beta} = \frac{V_c k_{10}}{\beta} \qquad (17.29)$$

EXAMPLE

After a single IV bolus dose of 1000 mg of an antiarrhythmic drug, the following concentrations were obtained:

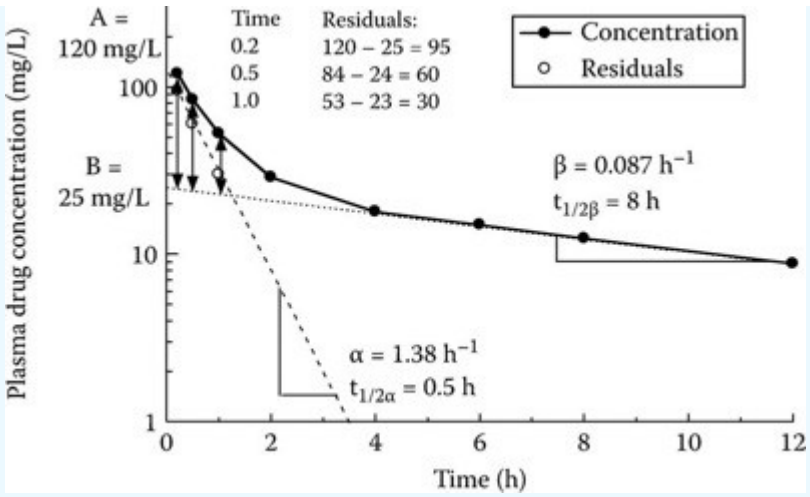
Time (h)	Concentration (mg/L)
0.2	120
0.5	84
1.0	53
2.0	29
4.0	18
6.0	15
8.0	12.5
12.0	8.8

- a. Using the method of residuals, calculate the following parameters: $t_{1/2\alpha}$, $t_{1/2\beta}$, k_{12}, k_{21}, k_{10}, V_c, Vd_β, Vd_{ss}, AUC, and CL_T
- b. What will be the amount of drug remaining in the body after 15 h?

Answer

- a. The method of residuals used to solve the problem and presented in Figure 17.8 can be performed by the following steps:
  - • Plot the concentration versus time on a semilog scale.
  - • Identify the best line that represents the drug elimination process.322323

FIGURE 17.8 Application of the method of residuals in solving the example.



  - • The y-intercept is equal to B. The hybrid elimination rate constant (β) and β-half-life can be determined from the line.
  - • Calculate the residuals from the difference between the plasma drug concentration and the values on the extrapolated line during the distribution phase.
  - • Plot the residuals versus time, and draw the best line that goes through the points.
  - • The y-intercept of this line is equal to A. The hybrid distribution rate constant α and α-half-life can be determined from this line.

A 120 mg/LB 25 mg/L

$$\alpha = 1.38\,h^{-1} \quad t_{1/2\alpha} = 0.5\,h$$

$$\beta = 0.087\,h^{-1} \quad t_{1/2\beta} = 8\,h$$

$$V_c = \frac{\text{Dose}}{A+B} = \frac{1000}{120+25\,mg/L} = 6.9\,L$$

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} = \frac{120\,mg/L}{1.38\,h^{-1}} + \frac{25\,mg/L}{0.087\,h^{-1}} = 374.4\,mg\,h/L$$

$$CL_T = \frac{\text{Dose}}{AUC} = \frac{1000\,mg}{374.4\,mg\,h/L} = 2.67\,L/h$$

$$k_{10} = \frac{CL_T}{V_c} = \frac{2.67\,L/h}{6.9\,L} = 0.387\,h^{-1}$$

$$k_{21} = \frac{\alpha\beta}{k_{10}} = \frac{1.38\,h^{-1} \times 0.087\,h^{-1}}{0.387\,h^{-1}} = 0.310\,h^{-1}$$

$$k_{12} = (\alpha+\beta) - (k_{21}+k_{10}) = (1.38 + 0.087\,h^{-1}) - (0.310 + 0.387\,h^{-1}) = 0.77\,h^{-1}$$

$$Vd_\beta = \frac{CL_T}{\beta} = \frac{2.67\,L/h}{0.087\,h^{-1}} = 30.7\,L$$

$$Vd_{ss} = V_c\left(1+\frac{k_{21}}{k_{21}}\right) = 6.7\,L\left(1+\frac{0.77\,h^{-1}}{0.310\,h^{-1}}\right) = 23.3\,L$$

- b. $Cp = Ae^{-\alpha t} + Be^{-\beta t}$ Amount of the drug in the body during the elimination phase = $Cp \times Vd_\beta Amount_{15\,h} = Cp_{15\,h} \times Vd_\beta = 6.78\ mg/L \times 30.7\ L = 208\ mg$

- **17.6 ORAL ADMINISTRATION OF DRUGS THAT FOLLOW THE TWO-COMPARTMENT PHARMACOKINETIC MODEL**

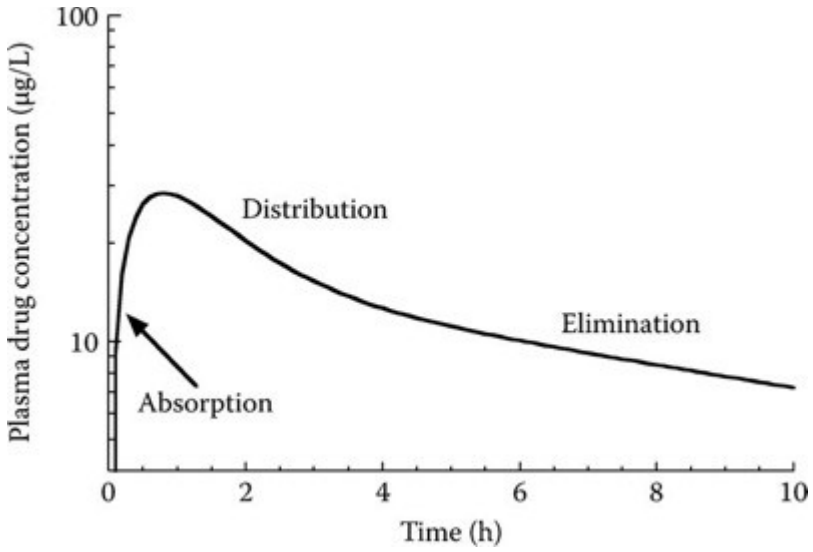
- After oral administration of a drug that follows two-compartment pharmacokinetic model, the drug is absorbed to the systemic circulation, which is part of the central compartment. Once in the central compartment, the drug can be eliminated from the body or distributed to the peripheral compartment. If the drug is rapidly absorbed, the decline

in the plasma concentration–time profile after the end of the absorption phase will be biexponential, reflecting the distribution and the elimination phases. The biexponential decline in the drug plasma concentration after drug absorption will be clear only if the absorption, distribution, and elimination processes proceed at three distinctive rates. However, if the drug absorption is slow, the biexponential decline in the plasma concentration after the end of drug absorption may not be evident. Figure 17.9 represents the plasma concentration–time profile after a single oral dose of a drug that follows the two-compartment pharmacokinetic model. The decline of the drug concentration in the post-absorption phase is biexponential. The plasma drug concentration–time profile after oral administration of drugs that follow two-compartment pharmacokinetic model can be described by a triexponential equation that represents the absorption, distribution, and elimination processes as in Equation 17.30 [2]. The plasma drug concentrations obtained after single oral administration of drugs that follow two-compartment pharmacokinetic model can be fitted to Equation 17.30 to estimate the model parameters. Specialized computer programs are usually utilized in this fitting process.

- $$Cp = \left(\frac{k_a FD}{V_c}\right)\left[\frac{(k_{21}-\alpha)e^{-\alpha t}}{(\beta-\alpha)(k_a-\alpha)} + \frac{(k_{21}-\beta)e^{-\beta t}}{(k_a-\beta)(\alpha-\beta)} + \frac{(k_{21}-k_a)e^{-k_a t}}{(\alpha-k_a)(\beta-k_a)}\right] \quad (17.30)$$

- 324325

- **FIGURE 17.9 Plasma concentration–time profile for a drug that follows two-compartment pharmacokinetic model after administration of a single oral dose.**

- 

- **17.6.1 LOO–RIEGELMAN METHOD FOR DETERMINATION OF K_a AFTER ORAL ADMINISTRATION OF DRUGS THAT FOLLOW THE TWO-COMPARTMENT PHARMACOKINETIC MODEL**

- This method is similar in principle to the Wagner–Nelson method that is used for the determination of the absorption rate constant as discussed inChapter 9. The Loo–Riegelman method can be applied to determine the absorption rate constant for drugs that follow linear kinetics, with zero-order or first-order absorption, and follow two-compartment pharmacokinetic model [5]. The method depends on calculation of the fraction of the dose remaining to be absorbed at different time points [1-(fraction of dose absorbed)] to determine the order of drug absorption process and to calculate the absorption rate constant. The amount of the drug absorbed up to any time is the sum of the amount of the drug in the body and the amount of the drug excreted, while the total amount of the drug absorbed is equal to the total amount of the drug excreted. The fraction of the dose absorbed at any time is the ratio of the amount of drug absorbed up to this time to the total amount of the drug absorbed. If the absorption process is first order, a plot of the fraction remaining to be absorbed versus time should give a straight line on the semilog scale. The slope of this line is equal to $-k_a/2.303$. On the contrary, if the absorption process is zero order, a plot of the fraction remaining to be absorbed versus time should give a straight line on the Cartesian scale. The slope of this line is equal to $-k_a$.
- he only difference is that for the drugs that follow the two-compartment pharmacokinetic model, the amount of the drug in the body is the sum of the amount of the drug in the central compartment and the amount of the drug in the peripheral compartment. The drug amounts in the two compartments have to be calculated separately from the concentration and volume of each compartment because the drug in the two compartments is not at equilibrium all the time after a single drug administration. Calculation of the amount of the drug in each compartment requires the pharmacokinetic parameters for the two-compartment model that can 325326only be obtained after IV administration of the drug. So IV administration of the drug is necessary to obtain these parameters before the absorption rate constant can be determined after oral administration. This limits the application of this method to drugs that can be administered intravenously.

• 17.7 CONSTANT RATE IV ADMINISTRATION OF DRUGS THAT FOLLOW THE TWO-COMPARTMENT PHARMACOKINETIC MODEL

- The plasma concentration–time profile of drugs that follow two-compartment pharmacokinetic model during constant rate IV infusion increases gradually until it reaches the steady state. At steady state, the rate of drug administration is equal to the rate of drug elimination. The steady-state plasma concentration is dependent on the rate of the IV infusion and the CL_T of the drug as in Equation 17.31. This is similar to the drugs that follow one-compartment pharmacokinetic model.

$$Cp_{ss} = \frac{\text{Infusion rate}}{CL_T} = \frac{K_o}{CL_T} \qquad (17.31)$$

- The time to reach steady state during constant rate IV infusion of drugs that follow two-compartment pharmacokinetic model is dependent on the drug elimination half-life ($t_{1/2\beta}$). It takes five to six times the elimination half-life of continuous IV infusion to reach the steady state. Termination of the IV infusion results in biexponential decline in the drug plasma concentration, a rapid distribution phase and a slow elimination phase.
- Administration of a loading dose may be necessary to achieve faster approach to steady state especially in emergency situations. In this case, simultaneous administration of an IV loading dose and the constant rate IV infusion is necessary. Calculation of the loading dose based on V_c and the desired steady-state concentration ($Cp_{ss} \times V_c$) should achieve the desired concentration initially. However, due to drug distribution to the peripheral compartment the drug concentration declines transiently, possibly to subtherapeutic concentration, and then increases gradually to the desired steady-state concentration. Calculation of the loading dose based on Vd_β and the desired steady-state concentration ($Cp_{ss} \times Vd_\beta$) can avoid this transient decline in plasma drug concentration. However, this loading dose should produce very high drug concentration initially, which may be toxic for drugs with narrow therapeutic range. The loading dose should be calculated based on an average value for V_c and Vd_β. Another approach that can be used is to give a loading dose calculated based on V_c initially followed by smaller IV doses to compensate for the transient decline in drug concentration after the loading dose.

17.8 MULTIPLE DRUG ADMINISTRATION

Drugs that follow two-compartment pharmacokinetic model accumulate during repeated administration until steady state is achieved. At steady state, the plasma concentration will be changing during each dosing interval; however, 326327the maximum and minimum plasma concentrations will be similar if the drug is administered as a fixed dose at equally spaced intervals. The average steady-state concentration is directly proportional to the dosing rate and inversely proportional to the CL_T:

$$Cp_{average\ ss} = \frac{F\,Dose}{CL_T \tau} \qquad (17.32)$$

where

- τ is the dosing interval
- F is the bioavailability

This relationship is similar for one- and two-compartment pharmacokinetic models. It takes five to six elimination half-lives ($t_{1/2\beta}$) to reach the steady state during multiple administration of drugs that follow two-compartment pharmacokinetic model. Administration of a loading dose may be necessary to achieve faster approach to steady state.

17.9 RENAL EXCRETION OF DRUGS THAT FOLLOW THE TWO-COMPARTMENT PHARMACOKINETIC MODEL

For a drug that follows two-compartment pharmacokinetic model, the amount of the drug in the central compartment declines biexponentially. So the renal excretion rate (dA_e/dt) versus time profile will also decline biexponentially:

$$\frac{dA_e}{dt} = A'e^{-\alpha t} + B'e^{-\beta t} \qquad (17.33)$$

where A′ and B′ are the hybrid coefficients and have units of amount/time. The renal clearance can be determined from the renal excretion rate and the average plasma concentration during the urine collection interval. This is similar to the drugs that follow one-compartment pharmacokinetic model.

$$CL_R = \frac{\Delta A_e/\Delta t}{Cp_{t\text{-}mid}} \qquad (17.34)$$

The renal clearance can also be determined from the total amount of the drug excreted in urine and the drug AUC. This is similar to the drugs that follow one-compartment pharmacokinetic model.

$$CL_R = \frac{A_{e\infty}}{AUC\big|_{t=0}^{t=\infty}} \qquad (17.35)$$

The fraction of the drug dose excreted in urine is determined from the ratio of the renal clearance to the total body clearance.

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17.10 EFFECT OF CHANGING THE PHARMACOKINETIC PARAMETERS ON THE DRUG CONCENTRATION–TIME PROFILE FOR DRUGS THAT FOLLOW THE TWO-COMPARTMENT PHARMACOKINETIC MODEL

After a single IV dose, the rate of drug distribution depends on the hybrid distribution rate constant, while the rate of elimination depends on the hybrid elimination rate constant. During multiple drug administration, the steady state is directly proportional to the administration rate and inversely proportional to the CL_T, and the time to reach the steady state is dependent on the hybrid elimination rate constant [6].

17.10.1 PHARMACOKINETIC SIMULATION EXERCISE

Pharmacokinetic simulations can be used to examine how the pharmacokinetic parameters affect the plasma concentration–time profile and the steady state drug concentration achieved after single and multiple drug administration. The drug plasma concentration–time profile is simulated using an average value of each of the pharmacokinetic parameters. The pharmacokinetic parameters are changed one parameter at a time, while keeping all the other parameters constant, and simulation of the drug concentration–time profile is repeated. The resulting profiles are examined to see how the changes affect the drug concentration–time profile. The plotting exercise of the two multicompartment pharmacokinetics modules in the basic pharmacokinetic concept section and the pharmacokinetic simulations section of the companion CD to this textbook can be used to run these simulations.

17.10.1.1 Dose

Administration of increasing doses results in proportional increase in the plasma concentrations. The plasma concentration–time profiles after administration of increasing doses will be parallel, while during multiple drug administration the average steady-state concentration 328329is directly proportional to the administered dose, if the CL_T is constant.

17.10.1.2 Total Body Clearance

The change in CL_T will result in different elimination rate of the drug if the volume is kept constant. If the same dose is administered and the volume of distribution is kept constant, the decrease in clearance produces larger AUC and longer elimination half-life. During multiple drug administration of the same dose, the decrease in drug clearance will result in higher steady-

state concentration and longer time to achieve the steady state, if the volume fd distribution is constant.

17.10.1.3 Volume of the Central Compartment

The change in the volume of the central compartment is accompanied by a proportional change in Vd_{ss} and Vd_{β}. Larger volume of distribution results in lower initial drug plasma concentration after administration of the same dose and similar AUC if the CL_T does not change. When the volume of distribution changes while CL_T remains constant, the elimination rate constant will be different. Multiple administration of the same dose should achieve the same average steady-state concentration if the clearance is similar, but the time to achieve steady state will be different if the volume is different because the elimination half-life will be different.

17.10.1.4 Hybrid Distribution Rate Constant

Larger hybrid distribution rate constant results in faster completion of the distribution process without affecting the rate of drug elimination. This is assuming that the three micro rate constants k_{12}, k_{21}, and k_{10} change in a way that will change the rate of the distribution process without affecting the elimination process.

17.10.1.5 Hybrid Elimination Rate Constant

Larger hybrid elimination rate constant results in faster drug elimination without affecting the rate of drug distribution. This is assuming that the three micro rate constants k_{12}, k_{21}, and k_{10} change in a way that will change the rate of the elimination process without affecting the distribution process.

17.11 EFFECT OF CHANGING THE PHARMACOKINETIC PARAMETERS ON THE DRUG DISTRIBUTION BETWEEN THE CENTRAL AND PERIPHERAL COMPARTMENTS

Drugs that follow the two-compartment pharmacokinetic model have different concentration–time profiles in the central and peripheral compartments after a single IV administration. During the elimination phase, distribution equilibrium is established and the ratio of the drug concentration in the central and peripheral compartments is dependent on the transfer rate constants.

17.11.1 DOSE

The change in dose results in proportional change in the amount and concentration of the drug in the central and peripheral compartments. However, the distribution ratio between the central and peripheral compartments does not change. Changing the dose does not affect the ratio of the

amount of the drug in the peripheral compartment to the amount of the drug in the central compartment when the distribution equilibrium is established.

7.11.2 FIRST-ORDER TRANSFER RATE CONSTANT FROM THE CENTRAL TO THE PERIPHERAL COMPARTMENT

The change in k_{12} affects the drug distribution rate, elimination rate, and the tissue distribution. Larger k_{12} results in higher amount of the drug distributing to the 329330peripheral compartment, faster distribution rate, and slower elimination rate. The ratio of the amount of the drug in the peripheral compartment to the amount of the drug in the central compartment at steady state increases due to the increase in k_{12}/k_{21} ratio.

17.11.3 FIRST-ORDER TRANSFER RATE CONSTANT FROM THE PERIPHERAL TO THE CENTRAL COMPARTMENT

The change in k_{21} affects the drug distribution rate, elimination rate, and the tissue distribution. Larger k_{21} results in lower amount of the drug distributing to the peripheral compartment, faster distribution rate, and faster elimination rate. The ratio of the amount of the drug in the peripheral compartment to the amount of the drug in the central compartment at steady state decreases due to the decrease in k_{12}/k_{21} ratio.

17.11.4 FIRST-ORDER ELIMINATION RATE CONSTANT FROM THE CENTRAL COMPARTMENT

The change in k_{10} affects the drug distribution rate and elimination rate. Larger k_{10} results in faster distribution rate and faster elimination rate. However, the drug distribution ratio between the central and the peripheral compartments does not change. The ratio of the amount of the drug in the peripheral compartment to the amount of the drug in the central compartment at steady state does not change due to the change in k_{10} because the ratio k_{12}/k_{21} does not change.

17.12 THREE-COMPARTMENT PHARMACOKINETIC MODEL

With the development of accurate sampling methods and sensitive analytical techniques it has been shown that some drugs follow three-compartment pharmacokinetic model. After drug administration into the central compartment, the drug is distributed slowly to the tissues. However, the distribution of the drug to some tissues is much slower than its distribution to other tissues. This results in two distinct rates of distribution and a biexponential distribution phase followed by a terminal elimination phase. Figure 17.10 is an example of the plasma concentration–time profile for a drug that follows three-compartment pharmacokinetic model. The diagram presented in Figure 17.11 is an example of a three-compartment pharmacokinetic

model in which the elimination of the drug is from the central compartment, and the two peripheral compartments are connected to the central compartment.

FIGURE 17.10 Plasma concentration–time profile for a drug that follows three-compartment pharmacokinetic model after administration of a single IV bolus dose.

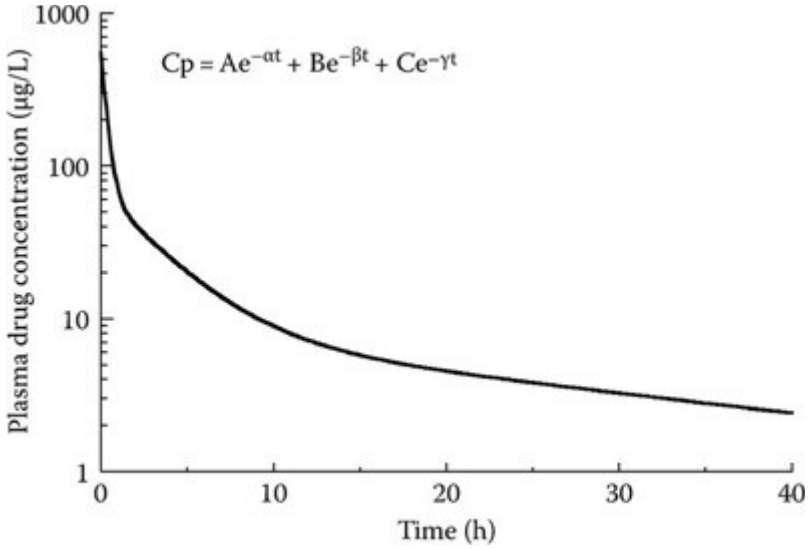
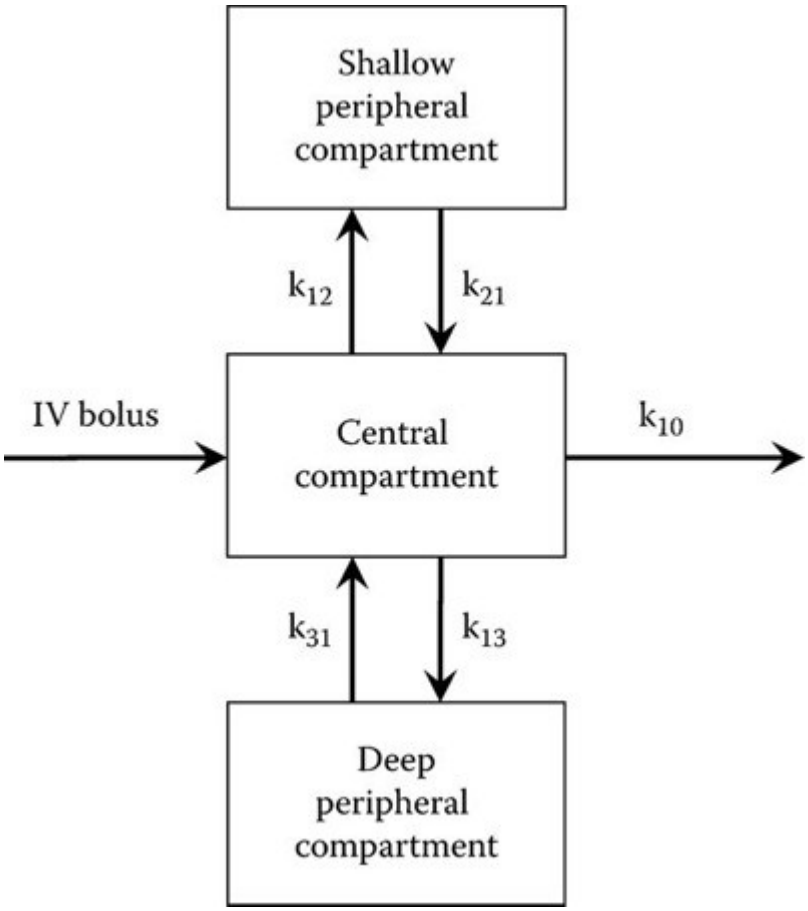


FIGURE 17.11 Block diagram representing the three-compartment pharmacokinetic model with the two peripheral compartments connected to the central compartment and drug elimination from the central compartment.



The equation that describes the plasma concentration–time profile after a single IV bolus dose is triexponential with the three exponential terms describing the rapid and slow distribution processes and the elimination process. Equation 17.36 is the mathematical expression that describes the plasma concentration–time profile for a drug that follows three-compartment pharmacokinetic model after administration of a single IV bolus dose [2]:

$$Cp = \left(\frac{D}{V_c}\right)\left[\frac{(k_{21}-\alpha)(k_{31}-\alpha)}{(\beta-\alpha)(\gamma-\alpha)}e^{-\alpha t} + \frac{(k_{21}-\beta)(k_{31}-\beta)}{(\alpha-\beta)(\gamma-\beta)}e^{-\beta t} + \frac{(k_{21}-\gamma)(k_{31}-\gamma)}{(\alpha-\gamma)(\beta-\gamma)}e^{-\gamma t}\right] \quad (17.36)$$

This equation can be simplified to

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \quad (17.37)$$

The pharmacokinetic parameters for three-compartment pharmacokinetic models are usually obtained by nonlinear regression analysis utilizing specialized data analysis software.

17.13 COMPARTMENTAL PHARMACOKINETIC DATA ANALYSIS

The first step in compartmental pharmacokinetic data analysis is to construct the model that can describe the pharmacokinetic behavior of the drug. The choice of the compartmental pharmacokinetic model is usually based on the observed 331332drug concentrations after drug

administration. So compartmental modeling is considered data-based modeling. For example, when the plasma drug concentrations observed after a single IV bolus dose of the drug decline as a straight line on the semilog scale, this suggests that the one-compartment model is the appropriate model to describe the drug pharmacokinetic behavior, while if the decline in the drug concentrations is curvilinear on the semilog scale, the two-compartment pharmacokinetic model will be appropriate in this case. On the contrary, if the drug concentrations after a single IV bolus dose on the semilog scale decline at three distinct rates, this pharmacokinetic behavior may be described by the three-compartment pharmacokinetic model.

In addition to the number of the compartments, other model components such as the input function that depends on the route of drug administration and the output function that describes the drug elimination process should be included. Drug input into the systemic circulation, which is usually part of the central compartment, can be instantaneous such as in the case of IV bolus administration, first order as in oral administration, or zero order as in constant rate IV infusion and drugs absorbed by zero-order process, while drug elimination can follow first-order process, Michaelis-Menten process, or a combination of the two. The compartment where drug elimination occurs is usually the central compartment because most of the eliminating organs are highly perfused organs, unless there are evidences that drug elimination takes place in organs that are part of the peripheral compartments. Once all the model components are included, the model is defined mathematically.

17.13.1 MATHEMATICAL DESCRIPTION OF THE MODEL AND ESTIMATION OF THE MODEL PARAMETERS

Based on the constructed compartmental model, a set of differential equations are usually utilized to describe the rate of change of the dependent variable that is usually the drug amount or concentration with respect to time, which is the independent variable. These equations usually include the pharmacokinetic parameters that control the drug pharmacokinetic behavior in addition to constants like the administered dose. For each compartment, the rate of change of the dependent variable is the difference between the rate of drug entering the compartment and the rate of drug leaving the compartment. The differential equations describe the rate of change of the dependent variable with time at a finite period of time. Integration of these differential equations gives the integrated equations which can be used to calculate the dependent variable at any time. The integrated equations contain the pharmacokinetic model parameters that have to be

estimated to allow prediction of the drug concentration at any time. The pharmacokinetic parameters are estimated from the drug concentration data obtained from pharmacokinetic studies. Since most pharmacokinetic studies involve determination of the plasma drug concentrations, the observed plasma drug concentrations and their corresponding time values are fitted to the integrated equation that describes the drug concentration–time profile in the central compartment to estimate the pharmacokinetic model parameters.

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17.13.2 FITTING THE EXPERIMENTAL DATA TO THE MODEL EQUATION

Fitting of the experimentally observed data to the model equation to estimate the pharmacokinetic parameters utilizes nonlinear regression analysis, which is usually performed with the aid of specialized statistical software. The basic principle for estimation of the pharmacokinetic parameters involves selecting the best values for the pharmacokinetic parameters, which will minimize the sum of the squared differences between the experimentally observed drug concentrations and the model predicted drug concentrations [7]. The model predicted concentrations are determined by substituting the estimated pharmacokinetic parameters to the model equation and calculating the drug concentration at different time points. The process is not simple because the data analysis program has to check all possible combinations of the parameter values to find the combination of the parameter values that will minimize the sum of the squared error for all data points. So most programs require the input of an initial estimate for each parameter to be used as the starting point for the parameter estimation process. Different programs utilize different algorithms to search for the best estimates for the pharmacokinetic parameters.

For example, the pharmacokinetic parameters in the equation for the two-compartment pharmacokinetic model for drugs administered by IV bolus dose are A, B, α, and β, Equation 17.12. The dose and the experimentally determined drug concentrations at different time points are used to estimate the pharmacokinetic parameters. The best estimates for these parameters are the values that should minimize the sum of the squared differences between all the observed and predicted concentrations, whereas the pharmacokinetic parameters in the equation for the three-compartment pharmacokinetic model for drugs administered by a single IV bolus dose are A, B, C, α, β, and γ, Equation 17.37. These parameters are estimated by selecting the best values for the six parameters that when used together minimizes the sum of the squared differences between all the observed and predicted concentrations. When the pharmacokinetic experiment is

repeated several times, the data for each individual experiment are fitted to the model equation to estimate the parameters for that particular experiment. The fitting is repeated for each data set and the parameters for the different experiments can be summarized using descriptive statistics. Estimation of the pharmacokinetic parameters depends primarily on the drug concentrations in the experimentally obtained samples. So the quality of the obtained data is important in improving the accuracy in pharmacokinetic parameter estimation. The quality of data is dependent on the number of samples, the period of time over which the samples were obtained, and the accuracy of the analytical method used for determination of the drug concentration in the samples. Accurate estimation of the three-compartment pharmacokinetic parameters cannot be obtained if only few samples were obtained after a single IV drug administration. In general, complicated models have more parameters that require larger number of samples for their accurate estimation. Also, samples obtained over a short period of time cannot be used to accurately estimate the parameters of a drug that follows two-compartment pharmacokinetic model with long elimination half-life even if large number of samples were obtained after drug administration. Enough samples should be obtained 333334during each phase of the plasma drug concentration–time profile to obtain accurate estimation of all model parameters. There is no strict rule for the number and the timing of samples that should be obtained in pharmacokinetic experiments because frequent sampling can be obtained in some experimental settings, while samples can be very limited in other settings. However, the minimum number of samples required to obtain reasonable estimates for the pharmacokinetic parameters should not be less than three samples for each phase of the drug profile, and samples should be spread over the entire drug concentration–time profile. In addition to the number and the timing of the obtained samples, the analytical procedures used for the determination of the drug concentration in the obtained samples have to be accurate and precise to minimize the error in the experimental data. So, fewer number of samples obtained at the proper time and analyzed using accurate analytical method can be used to obtain estimates for the pharmacokinetic parameters that are better than the parameter estimates obtained from larger number of samples obtained at inappropriate time schedule and analyzed using inaccurate method.

After drug administration, the drug concentration declines exponentially and usually there is big difference in the concentrations measured shortly after drug administration and during the terminal elimination phase specially after IV bolus doses. Since the objective of the fitting procedures is to obtain the parameter estimates that will minimize the sum of the squared errors,

the samples with the high concentrations usually have larger influence in the estimation of the parameters. This is because absolute error of 1 mg/L represents 2% relative error if the drug concentration is 50 mg/L and represents 200% relative error if the drug concentration is 0.5 mg/L. So the fitting program will usually fit the high concentration values better than the low concentration values when all the data points are treated equally, that is, weighted equally. In this case, fitting of the measured concentrations to the model equation during the distribution phase will be much better compared to fitting the concentrations during the elimination phase. Weighting of the pharmacokinetic data is used during the fitting procedures to give the different data points different weights to compensate for the difference in their magnitude [7]. Different weighting schemes can be used for weighting the pharmacokinetic data. The reciprocal of the variance at each data point has been used as a weighting function to make all the data points have approximately the same influence while estimating the pharmacokinetic parameters. So if the pharmacokinetic experiment is repeated several times, the drug concentrations measured at specific time point in all of these experiments are used to calculate the variance for the concentrations obtained at this time. The value for 1/variance is used as the weight for the drug concentrations at this particular time. The same is done for each time point to determine the weight for each data point. When the variance for each data point cannot be determined, other weighting functions can be used such as $1/(\text{predicted concentration})^2$, $1/(\text{observed concentration})^2$, or 1/(observed concentration), that is, $1/\hat{y}^2$, $1/y^2$, or 1/y, respectively. These weighting functions give less weight to the high drug concentration and higher weight to the lower drug concentrations, which compensate for the difference in the absolute values of the concentrations. So when the appropriate weighting function is used, all the drug concentrations should have similar influence in the estimation of the pharmacokinetic parameters.

17.13.3 EVALUATION OF THE PHARMACOKINETIC MODEL

The primary goal of modeling in pharmacokinetics is to choose the best model that can describe the drug pharmacokinetic behavior in the body and to estimate the model parameters with acceptable accuracy. For example, in the previous discussion of the two-compartment pharmacokinetic model, it was mentioned that after IV bolus administration the drug is distributed rapidly to the tissues of the central compartment and slowly to the tissues of the peripheral compartment. This does not mean that the drug distribution to the different tissues is either rapid or slow. In reality, the drug may be distributed to the different tissues at different rates but the drug distribution can be approximated by two rates and the two-compartment model

can approximate the overall behavior of the drug in the body. So the observed plasma drug concentrations should fit with reasonable accuracy to the equation for the two-compartment pharmacokinetic model. Using the three-compartment pharmacokinetic model may improve fitting the observed data to the model equation and usually decreases the sum of the squared deviations between the observed and the predicted concentrations. However, the use of more complicated models is not necessarily better because increasing the number of compartments increases the number of pharmacokinetic parameters as in Equations 17.12 and 17.32. When the same number of data points is used to estimate larger number of pharmacokinetic parameters, the accuracy of the parameter estimates is compromised. So it is necessary to evaluate the goodness of fit of the experimental data to the pharmacokinetic model.

There is no single diagnostic procedure or statistical test that can be used to determine the validity of the model to describe the observed data. However, there are several statistical and graphical methods that are generally used to evaluate how well the model fits the data set [7]. Most data analysis programs provide information regarding the variability for each of the estimated parameters such as the standard error or the coefficient of variation. Coefficient of variation >20% for any parameter indicates uncertainty of this parameter estimate, which usually results from overparameterization of the model or insufficient data. Also, the Akaike information criteria are used to determine if going to more complex model improves the fit without compromising the accuracy in model parameter estimation.

Several graphical methods can be used to evaluate the goodness of fit including a scattered plot of the observed concentrations around the model predicted drug concentration–time curve to determine how well the model fit the data. Small differences between the observed and model predicted values and random distribution of the observed values around the predicted values indicate good fit, as in Figure 17.12A. The existence of trend in the data points that is presented by a series of consecutive data points above or below the predicted profile is an indication of inappropriate fit as inFigure 17.12B. Also, the observed versus the model predicted drug concentration values is a very useful diagnostic plot to evaluate the goodness of fit. A good model fit can be concluded when the values are gathered uniformly and closely around the line with slope equal to one as in Figure 17.12C, while the presence of trend in the data points is an indication of inappropriate fit as in Figure 17.12D. Also, several residuals plots can be utilized in the model evaluation. The residuals are the difference between the observed drug concentration and the model predicted drug concentration, which 335336is a measure of the error at each data

point. For example, the residual versus predicted concentration plot to examine the error value at different drug concentrations and determine if the model fit one end of the curve better than the other. Also, the residual versus time plot to evaluate if the model accurately accounts for all the different phases in the drug concentration–time profile. Furthermore, the plot of the weighed residuals versus predicted values and weighed residuals versus time are useful to evaluate the model fit as in Figure 17.13A–D. When the model fits the observed data properly, the magnitude of the weighted residuals in the weighted residuals versus predicted value plot and the weighted residuals versus time plot, should be small with approximately uniform magnitude, and randomly distributed around the zero residual line, as in Figure 17.13Aand C. While the existence of trend or inconsistent weighted residual magnitude indicates improper fit, as in Figure 17.12B and D.

FIGURE 17.12 Examples of the diagnostic graphs for compartmental pharmacokinetic data analysis. The scattered plot of the observed concentration and the model predicted drug plasma profile. Random distribution of the data around the predicted profile indicates good data fitting (A), while the presence of a trend that appears as series of observations above or below the model predicted values indicates inappropriate data fitting (B). The observed versus predicted plasma drug concentration. Uniform and random distribution of data around the line with slope of 1 indicates good data fitting (C), while the presence of trend indicates unacceptable data fitting (D).

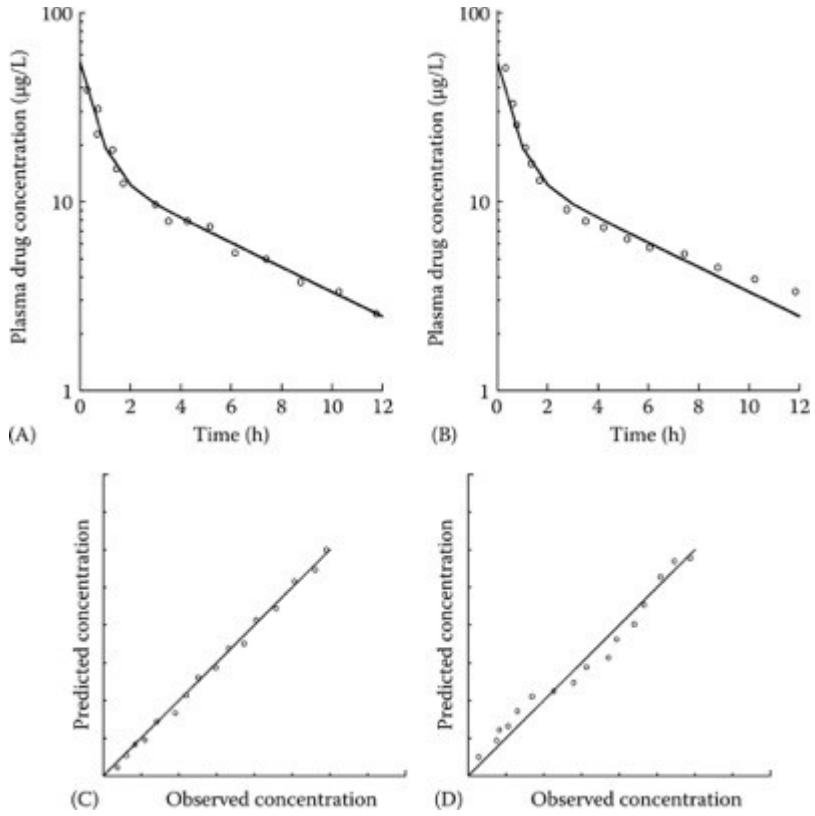

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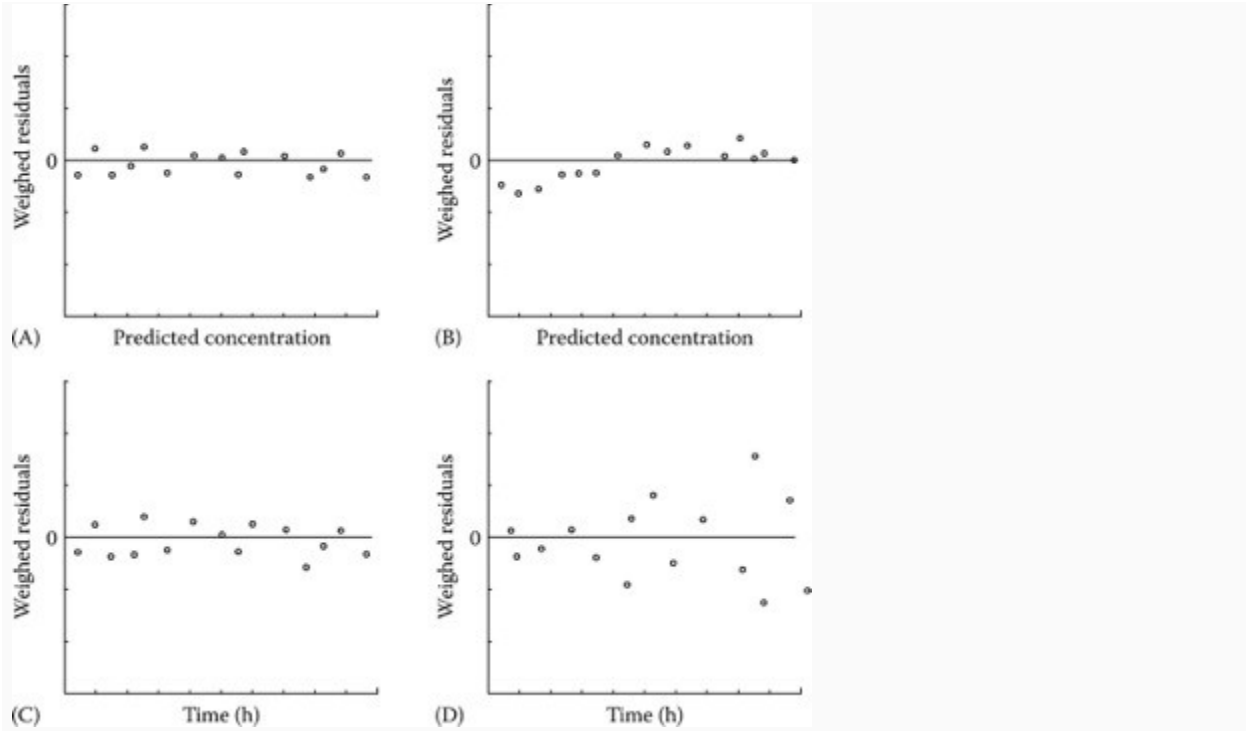
FIGURE 17.13 Examples of the residual plot used as a diagnostic test for evaluating curve fitting. (A and B) is the weighted residuals versus predicted concentrations, and (C and D) is the weighted residuals versus time. Small, uniform, and randomly distributed weighted residuals indicate good fitting of data (A and C), while the presence of trend or unequal weighed residuals suggest improper data fitting (B and D).



PRACTICE PROBLEMS

- **17.1** A drug that follows a two-compartment pharmacokinetic model is given to a patient by rapid IV injection. Would the drug concentration in each tissue be the same after the drug equilibrates between the plasma and all the tissues in the body? Explain.
- **17.2** A drug follows two-compartment pharmacokinetic model. If a single IV bolus dose is given, what is the cause of the initial rapid decline in the plasma concentration (α-phase)? What is the cause of the slower decline in the plasma concentration (β-phase)?
- **17.3** A drug that follows two-compartment pharmacokinetic model was given as a single IV bolus dose of 5.6 mg/kg. The equation
- that describes the plasma concentration–time data is

$$CP\ (mg/L) = 18e^{-2.8t} + 6e^{-0.11t}$$

  - a. Calculate the plasma concentration after 0.5, 3, and 12 h of drug administration.
  - b. What will be the equation that describes the plasma concentration–time profile if the dose given was 11.2 mg/kg?
- **17.4** After administration of a single IV bolus dose of 75 mg of a drug to a healthy volunteer, the pharmacokinetics of this drug followed the two-compartment model. The following parameters were obtained

$$A = 4.62\,\text{mg/L} \quad B = 0.64\,\text{mg/L}$$

- : $\alpha = 8.94\,h^{-1} \quad \beta = 0.19\,h^{-1}$
  - a. Calculate the following parameters: $t_{1/2\alpha}$, $t_{1/2\beta}$, k_{12}, k_{21}, k_{10}, V_c, Vd_β, Vd_{ss}, AUC, and CL_T.
  - b. What will be the amount of drug remaining in the body after 8 h?
- **17.5** A single dose of 500 mg of a drug was administered by a rapid IV injection into a 70 kg patient. Plasma samples were obtained over a 7 h period and assayed for the drug. The results are tabulated as follows:

Time (h)	Concentration (mg/L)
0.00	70.0
0.25	53.8
0.5	43.3
0.75	35.0
1.0	29.1
1.5	21.2
2.0	17.0
2.5	14.3
3.0	12.6
4.0	10.5
5.0	9.0
6.0	8.0
7.0	7.0

- a. Calculate the following parameters: $t_{1/2\alpha}$, $t_{1/2\beta}$, k_{12}, k_{21}, k_{10}, V_c, Vd_β, Vd_{ss}, AUC, and CL_T.
- b. What will be the plasma concentration 12 h after drug administration?
- c. What will be the initial plasma concentration if a dose of 1500 mg is administered as an IV bolus?
- d. Which of the aforementioned pharmacokinetic parameters will change with the increase in the dose to 1500 mg?
- e. Calculate the new values for these parameters.
- f. What will be the IV infusion rate required to achieve a steady-state plasma concentration of 10 mg/L?

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- **17.6** The plasma concentration time data following a 50 mg IV bolus dose of lidocaine is tabulated as follows:

Time (min)	Concentration (mg/L)
2.0	1.51
4.0	1.20
10	0.796
15	0.639
20	0.462
40	0.329
60	0.271
90	0.242
120	0.179
180	0.112
240	0.081

- a. Using the method of residuals, calculate the following parameters: $t_{1/2\alpha}$, $t_{1/2\beta}$, k_{12}, k_{21}, k_{10}, V_c, Vd_β, Vd_{ss}, AUC, and CL_T
- b. Calculate the plasma concentration at the time of each sample from the equation that describes the plasma concentration–time profile, and comment on the differences between the measured and the calculated concentrations.
- c. What will be the amount of lidocaine remaining in the body after 240 min?
- d. What will be the plasma concentration when 90% of the administered dose is eliminated?

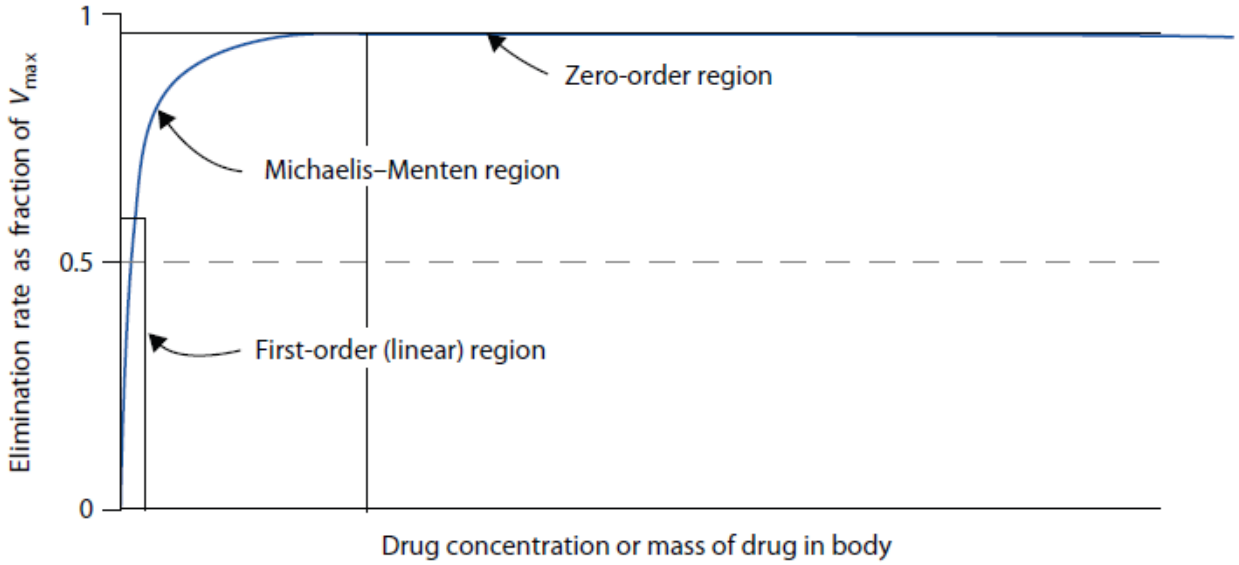
UNIT-5

Non-linear pharmacokinetics

- Introduction:
- Linear Pharmacokinetic parameters, such as elimination half life (t1/2), the elimination rate constant (K), the apparent volume of distribution (V), and the systemic clearance (Cl) of most drugs are not expected to change when different doses are administered and/or when the drug is administered via different routes as a single dose or multiple doses
- The kinetics of these drugs is described as linear, or dose-independent, pharmacokinetics and is characterized by the first-order process
- The term linear simply means that plasma concentration at a given time at steady state and the area under the plasma concentration versus time curve (AUC) will both be directly proportional to the dose administered
- Introduction: NonlineaFor some drugs, however, the above situation may not apply
- For example, when the daily dose of phenytoin is increased by 50% in a patient from 300 mg to 450 mg, the average steady-state plasma concentration, (Cp)ss, may increase by as much as 10-fold
- This dramatic increase in the concentration (greater than directly proportional) is attributed to the nonlinear kinetics of phenytoin
- Introduction: NonlinearNonlinearity may arise at any one of the pharmacokinetic steps, such as absorption, distribution and/or elimination
- For example, the extent of absorption of amoxicillin decreases with an increase in dose
- For distribution, plasma protein binding of disopyramide is saturable at the therapeutic concentration, resulting in an increase in the volume of distribution with an increase in dose of the drug
- As for nonlinearity in renal excretion, it has been shown that the antibacterial agent dicloxacillin has saturable active secretion in the kidneys, resulting in a decrease in renal clearance as dose is increased
- Both phenytoin and ethanol have saturable metabolism, which means that an increase in dose results in a decrease in hepatic clearance and a more than proportional increase Nonlinearity in Nonlinearity in metabolism

Capacity-limited metabolismThe rate of metabolism, or the rate of elimination if metabolism is the only pathway of elimination, is defined by the Michaelis–Menten equation:

- metabolismrCapacity-limited metabolism is also called saturable metabolism, Michaelis–Menten kinetics
- Nonlinearity in metabolism, is one of the most common sources of nonlinearity
- where Vmax is the maximum rate (unit: amount/time) of metabolism; Km is the Michaelis–Menten constant (unit: same as the concentration [amount/volume]), and C is the drug concentration
- metabNonlinearity in metabolism
  Capacity-limited olismTwo cases:
- Km>>C
- Km<<cc
  Nonlinearity in metabolism
  Capacity-limited metabol
- Estimation of Michaelis–Menten parameters from administration of a single doseEstimation


1
0.5
0
Elimination rate as fraction of V_{max}
Zero-order region
Michaelis–Menten region
First-order (linear) region
Drug concentration or mass of drug in body

UNIT-6

Non-compartmental Models

The noncompartmental approach for data analysis does not require any specific compartmental model for the system (body) and can be applied to virtually any pharmacokinetic data.

There are various noncompartmental approaches, including statistical moment analysis, system analysis, or the noncompartmental recirculatory model

The main purpose of the noncompartmental approach is to estimate various pharmacokinetic parameters, such as systemic clearance, volume of distribution at steady state,

mean residence time, and bioavailability without assuming or understanding any structural or mechanistic properties of the pharmacokinetic behavior of a drug in the body

Introduction In addition, many noncompartmental methods allow the estimation of those pharmacokinetic parameters from drug concentration profiles without the complicated, and often subjective, nonlinear regression processes required for the compartmentOwing to this versatility and ruggedness, the noncompartmental approach is a primary pharmacokinetic data analysis method for the pharmaceutical industry

Statistical moment theorySuppose one could observe a single molecule, from the time it is administered into the body ($t = 0$) until it is eventually eliminated ($t = t_{el}$ Clearlyt_{el} is not predictable.

This individual molecule could be eliminated during the first minute or could reside in the body for weeks. If, however, one looks at a large number of molecules collectively, their behavior appears much more regular

The collective, or mean time of residence, of all the molecules in the dose, is called the mean residence time (MRT).

Mean Residence Time (MRT) A mean time interval during which a drug molecule resides in the body before being excreted

A mean time interval during which a drug molecule resides in the body before being excrEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysiEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment Analysis.

Estimating AUC and AUMC

Linear trapezoidal methodFor the last observed sample and infinity ($t_2 = \infty$)

Estimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisvvEstimating

Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisvvEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Estimating Pharmacokinetic Parameters with Moment AnalysisParameters with Moment AnalysisClearance: The systemic clearance (Cl) of a drug can be estimated as the intravenous dose (D_{iv}) divided by the AUC after intravenous bolus administration (AUC_{iv}): Estimating Pharmacokinetic Parameters with Moment AnalysisVolume of Distribution at Steady State: The volume of drug distribution at steady state (Vdss) can be estimated as the product of MRT after intravenous bolus injection (MRTiv) and CI:

- Estimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with MomentEstimating Pharmacokinetic Parameters with MomentEstimating Pharmacokinetic Parameters with MomentEstimating Pharmacokinetic Parameters with Moment AnalysisEstimating Pharmacokinetic Parameters with Moment Analysismean absorption time (MAT) mean absorption time (MAT) The difference between MRT after oral administration (MRT_{oral}) and MRT_{iv} is the mean absorption time (MAT), representing the average time required for the drug to reach the systemic circulation from the gastrointestinal tract after oral administration intravenous infusionIf the dose of drug is administered by intravenous infusion, the MRT_{iv} may be calculated as:

$$MRT_{iv} = MRT_{\text{infusion}} - \frac{(Infusion\ time)}{2}$$

a. Statistical Moment Theory.

b. MRT for various compartment models.

c. Physiological Pharmacokinetic model.

Non-compartmental Analysis

When analyzing pharmacokinetic data, one generally employs either model fitting using nonlinear regression analysis or non-compartmental analysis techniques (NCA). The method one actually employs depends on what is required from the analysis. If the primary requirement is to

determine the degree of exposure following administration of a drug (such as AUC), and perhaps the drug's associated pharmacokinetic parameters, such as clearance, elimination half-life, Tmax, Cmax, etc., then NCA is generally the preferred methodology to use in that it requires fewer assumptions than model-based approaches. In this chapter we cover NCA methodologies, which utilize application of the trapezoidal rule for measurements of the area under the plasma concentration–time curve. This method, which generally applies to first-order (linear) models (although it is often used to assess if a drug's pharmacokinetics are nonlinear when several dose levels are administered), has few underlying assumptions and can readily be automated. In addition, because sparse data sampling methods are often utilized in toxicokinetic (TK) studies, NCA methodology appropriate for sparse data is also discussed.

INTRODUCTION

Bioequivalence studies are designed to examine whether the systemic bioavailability of a test product and those of the reference product differ significantly. In the classical approach, a "test" formulation is compared with the standard/innovator "reference" formulation in a group of normal, healthy subjects. Each of the subjects receives both treatments alternately in a crossover fashion (two-period, two-treatment crossover design), with a "washout period" of at least 5 half-lives between them. The sequence is assigned to each subject randomly, but an equal number of subjects receive each treatment in each phase. Following the relevant FDA and EMEA Guidelines, the statistical analysis should be based on the noncompartmental parameters AUCinf and Cmax, derived from the drug concentration-time curve (although plasma is the preferred matrix, sometimes whole blood or free concentration are used). These parameters are compared by means of an ANOVA in which the variance is partitioned into components due to subjects, periods and treatments. To conclude bioequivalence between the test and reference formulations, the 90% confidence intervals for the mean difference of the parameters after

INPUT DATASET ;

The input data file is a text file with the following variables separated by spaces: Subject, Period, Treatment, (1 Test, 2 Reference), Time, Concentration and Dose. Sequence of treatment is derived by the program in the ANOVA step. Sequence 1 is assigned if the subject receives the test formulation during period 1 and after the washout period the reference formulation and

sequence 2 if the order of administration is the opposite. An example of input data is given below.

Subject Period Treatment Time Concentration Dose

1 2 1 0 0 40

1 2 1 0.5 11.31 40

1 2 1 1 22.29 40

1 2 1 2 11.91 40

1 2 1 3 8.19 40

1 2 1 4 3.03 40

1 2 1 6 0 40

1 1 2 0 0 40

1 1 2 0.5 0 40

1 1 2 1 8.88 40

1 1 2 2 11.14 40

1 1 2 3 8.67 40

1 1 2 4 2.25 40

1 1 2 6 0 40

NONCOMPARTMENTAL ANALYSIS

Noncompartmental analysis is preferred over compartmental analysis in bioequivalence evaluation due to several reasons. The main reason is that noncompartmental analysis is less prone to data manipulation. Calculation of pharmacokinetic parameters should be made with a minimum of intervention by the investigator and the rules of calculus should be defined prior to the analysis. Two steps are crucial in the process: calculation of AUC from time 0 to the last point with quantifiable concentration and calculation of terminal elimination constant. Both

quantities will be used to compute one of the parameters to evaluate bioequivalence: AUCinf. Cmax is obtained directly from the data. Prior to the calculations, individual profiles and its total number are extracted from input data. There are several ways to do this. The proposed in this paper is to create a variable named order with an ascendent value for each profile as follows:

```
proc sort data = inputdata out = temp nodupkey ; by subject period;run; data temp;
```

TERMINAL ELIMINATION CONSTANT

The next macro calculates the first order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. The rules are that a minimum of three points is needed to define the terminal (log-linear) portion of the curve and the selection is based on the best adjusted square coefficient of regression (r2). Additionally, if the adjusted r2 does not improve, but is within 0.0001 of the largest adjusted R2 value, the regression with the larger number of points is used.

INDIVIDUAL PLOTS AND TABLES

Finally, results have to be reported in tables and graphs. The following figures and tables show the result of implementing the advanced tools available is SAS for these purposes. Graphs have been created using PROC GPLOT, then grouped with PROC GREPLAY and exported to cgm (Computer Graphics Metafile) format, that can be directly imported to Microsoft® Word. Again, the last process can be made at once via DDE (Dynamic Data Exchange).

CONCLUSION

The program described in this paper was proved to be a useful tool to obtain pharmacokinetic parameters using noncompartmental analysis. In the scenario of bioequivalence studies, the integration of all parts can automatize the whole process, from raw data to final report. Although the program was developed for the common 2x2 crossover design, it can be easily adapted for other bioequivalence designs.

Unit-VIII

Bio-avilability and bio-equivalence

Contents

- Bio-avilability
- Assessment of bio-avilability
- Bio-avilability study protocal

BIOAVAILABILITY ;

INTRODUCTION ;

The bioavailability or systemic availability of an orally administered drug depends largely on the absorption and the extent of hepatic metabolism ¾The bioavailability of an oral dosage form is determined by comparing the Area Under Curve (AUC) after oral administration of a single dose with that obtained when given IV.

Drug bioavailability = AUC (oral)/ AUC (IV)

= Bioavailable dose/Administered dose

DEFINITION;

- Bioavailability is defined as the rate and the absorption of drug that reaches the biological system in an active form, capable of exerting the desired pharmacological effect, including its onset, intensity and duration of its action.
- **Relative bioavailability –**
- Relative bioavailability is a measure of the fraction of the given drug that is absorbed in the systemic circulation from a particular dose compared to a clinically proven standard dose of the same drug.
- Relative bioavailability = (AUC) test /(AUC) STD
- Relative bioavailability = (AUC) test x Dstd /(AUC) std x Dtest
- **ASSESSMENT OF BIOAVAILABILITY**
- **ASSESSMENT OF BIOAVAILABILITY;**

- For assessing the bioavailability or clinical availability of a drug, its rate and extent of absorption and its first-pass metabolism must be evaluated.
- These criteria are difficult or even impossible to quantify.
- The method used to assess bioavailability depend upon the assumption that measurement of the drug concentration in a suitable body fluid, such as blood, plasma, serum, urine or sometime saliva, can be correlated with its clinical availability.
- **Bio-availability is determined by following methods ;**
- Pharmacokinetics method
- Pharmacodynamic method
- Pharmacokinetics method –
    - This method is more practical and discriminative.
    - Pharmacokinetic methods are of two types.
- a)Determination of whole blood, plasma or serum concentration
- b)Urinary excretion method
- Pharmacodynamic method –
- Acute pharmacological studies
- Therapeutic response studies
- Pharmacokinetics method;
- **a)Determination of whole blood, plasma or serum concentration**
- Cmax
- tmax
- AUC
- **b)Urinary excretion method**
- (dXu/dt)max
- (tu)max
- Xuα

- Pharmacokinetics ---‘’what the body does to the drug”
    - The blood (or serum or plasma) concentration-time curve –
        - Absorption
        - Distribution
        - Metabolism
            - Based on the plasma concentration-time curve, the following measurements are important for bioavailability studies.

- MINIMUM EFFECTIVE PLASMA CONCENTRATION-
- The minimum plasma concentration of the drug required to achieve a given pharmacological or therapeutic response. This value varies from drug to drug and from individual to individual as well as with the type and severity of the disease.
- MAXIMUM SAFE CONCENTRATION-
- The plasma concentration of the drug beyond which adverse effects are likely to happen.
- THERAPEUTIC RANGE-
- The range of plasma drug concentration in which the desired response is achieved yet avoiding adverse effect. The aim is clinical practice is to maintain plasma drug concentration within the therapeutic range.
- ONSET OF ACTION-
- On set of action is the time required to achieve the minimum effective plasma concentration following administration of drug formulation.
- DURATION OF ACTION-
- Duration of action of the therapeutic effect of the drug is defined as the time period during which the plasma concentration of the drug exceeds the minimum effective level.
- INTENSITY OF ACTION-

- In general, the difference between the peak plasma concentration and the minimum effective plasma concentration provides a relative measure of the intensity of the therapeutic response of the drug.
- Peak Plasma concentration ;
    - Peak concentration (Cmax) represents the highest concentration attained by the drug in the plasma. At this concentration, rate of drug input becomes equal to rate of drug output.
    - It is clear that formulation A should produce pain relief than formulation B, even though it seemed well absorbed, would not produce the desired pharmacological effect and would be ineffective in producing analgesia.
-

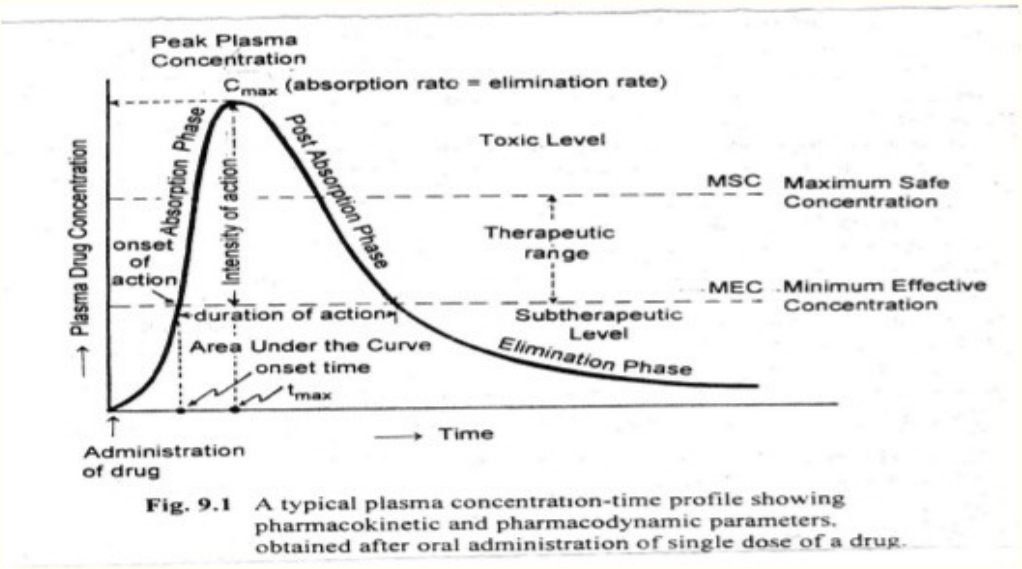


Fig. 9.1 A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters, obtained after oral administration of single dose of a drug.

b) URINARY EXCRETION-

- This method can be based if urinary excretion of unchanged drug is the main mechanism of elimination of the drug.

- Bioavailability can be calculated as follows, F = (Du∞)/ f
    - F = Fraction of the dose absorbed

- Du∞ = cumulative amount of drug excreted in the urine
- f = fraction of unchanged drug excreted in the urine

- FROM DISSOLUTION STUDIES
- In vitro dissolution studies are used to asses the product quality.
- In vitro dissolution rate should correlate with in vivo bioavailability.
- Bioavailability is not dependent on the dissolution of the drug product, but also the permeability and solubility of the drug substance .
- A dosage form with a rapid dissolution rate is likely to have a rapid rate of drug bioavailability in vivo.
- FACTORS AFFECTING BIOAVAILABILITY ;
- There are three major absorption factors
- 1. The dose of drug administered, i.e. the blood level will rise and fall in Proportion to the dose administered.
- 2) The same as the first but brought about by a different process, of drug absorbed from a given dosage form. The effect of only one half of the drug absorbed from a dosage form is equivalent to lowering the dose.
- 3) The rate of absorption of the drug, if absorption from the dosage form is more rapid than the rate of absorption then toxic level can be exceeded. If absorption from the dosage form is sufficiently slow minimum effective level cannot be attained.
- BIO-EQUIVALENCE STUDIES;
- Both bioavailability and bioequivalence focus on measuring the absorption of the drug into systemic circulation.
- Bioavailability is a comparison of the drug product to an IV formulation, a solution or a suspension, where as bioequivalence is a comparison with predetermined bioequivalence limits.
- The bioequivalence is said to exist when the bioavailability of a drug with different formulation is same
- **DEFINITION**
- **Equivalence –**

- Equivalence is more relative term that compares one drug product with another or with a set of established standards.
- Equivalence may be defined in several ways:
- Chemical equivalence indicates that two or more dosage forms contain the labelled quantities of drug.
- Clinical equivalence occurs when the same drug from two or more dosage forms gives identical in vivo effects as measured by a pharmacological response or by control of a symptom or a disease.
- Therapeutic equivalence implies that one structurally different chemical can yield the same clinical result as another chemical. Bioequivalence indicates that drug in two or more similar dosage forms reaches the general circulation at the same relative rate and the same relative extent.
- **NEED FOR BIOEQUIVALENCE ;**
- •Bioequivalence studies pr o vide a link between the pi v otal and ear l y clinical trial formulation.
- •Bioequivalence studies are for determination o f the therapeutic equivalence between the pharmaceutical equivalence generic drug product and a corresponding reference listed drug.

•Bioequivalence studies pr o vide information on prod u quality and performance when there are changes in components, composition and method o f manufacture after approval of the drug product.

- **LIMITATION OF BIOAVAILABILITY AND BIOEQUIVALENCE;**
- A cross over design may be difficult for drugs with a long elimination half life.
- Highly variable drugs may require a far greater number of subjects to meet the FDA bioequivalence characteristics.
- Certain characteristics in the biotransformation of drugs make it difficult to evaluate the bioequivalence of such drugs.
- For e.g. for drugs that are stereoisomer with a different rate of biotransformation and a different pharmacodynamic response, the measurement of individual isomers may be difficult for analytical reasons.

- Drugs that are administered by routes other than the oral route drugs/dosage forms that are intended for local effects have minimal systemic bioavailability. E.g. ophthalmic, dermal, intranasal and inhalation drug products.
- Bio-avilability study protocal
- **COMPONENTS OF A BIOAVAILABILITY STUDY PROTOCOL;**
- • Title
- Principle investigator (study director)
- Project/protocol number and date
- • Study objective
- • Study design
- Design
- Drug products
- Test product(s)
- Reference product
- • Dosage regimen
- • Sample collection schedule
- • Housing/confinement
- • Fasting/meals schedule
- • Analytical methods
- • Study population
- • Subjects
- • Subject selection
- Medical history
- • Physical examination
- • Laboratory tests

- • Inclusion/exclusion criteria
- • Restrictions/prohibitions
- • Clinical procedures
- • Dosage and drug administration
- • Biological sampling schedule and handling
- procedures
- • Activity of subjects
- • Ethical considerations
- • Basic principles
- • Institutional review board
- • Informed consent
- • Indications for subject withdrawal
- • Adverse reactions and emergency procedures
- • Facilities
- • Data analysis
- • Analytical validation procedure
- • Statistical treatment of data
- • Appendix