Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations

Chapter 5
Is the science that study relation of physicochemical properties of drug, dosage form, & route of administration on rate and extent of drug absorption.
pharmacokinetics

- It is the study of the kinetics of absorption, distribution, metabolism, and excretion (ADME) of drugs and their pharmacologic, therapeutic, or toxic effects in animals and man.

- Drugs given IV go directly into blood.
- Elimination refers to both metabolism and excretion.
- drug in blood exists in equilibrium with drug in tissues.

- In equilibrium concentration of the drug in blood different (greater or lesser) than the concentration of the drug in tissues. This is due to the physicochemical properties of the drug.

- the rate of transfer of a drug from one compartment to another is proportional to concentration of the drug in the compartment from which it exits; the greater the concentration, the greater is the amount of drug transfer.
During metabolism a drug substance may be biotransformed into:
1. pharmacologically active,
2. inactive metabolites,
3. or both.
For example, anticonvulsant drug carbamazepine is metabolized in the liver to active epoxide metabolite.

- **metabolism of drug to inactive products is irreversible process.**

- \( k_{el} \) : elimination rate constant for drug describe its rate of elimination from body.
PRINCIPLES OF DRUG ABSORPTION

Passive Diffusion:
1. From high to low concentration
2. depends on the molecule's lipid solubility, particle size, degree of ionization, and area of absorptive surface.
3. Primary mechanism for most drugs
4. No need for energy or carrier.
**Fick's law of Absorption**, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

\[
\frac{dQ}{dt} = \frac{DAK}{h} (C_{Gl} - C_p)
\]

- Where \( dQ/dt \) = rate of diffusion, \( D \) = diffusion coefficient,
- \( K \) = lipid water partition coefficient
- \( A \) = surface area of membrane;
- \( h \) = membrane thickness, and
- \( C_{Gl} - C_p \) = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.
Because $D$, $A$, $K$, and $h$ are constants under usual conditions for absorption, a combined constant $P$ or permeability coefficient may be defined.

$$P = \frac{DAK}{h} \quad (13.2)$$

drug concentration in plasma, $C_p$, is extremely small compared to the drug concentration in the gastrointestinal tract, $C_{GI}$. If $C_p$ is negligible and $P$ is substituted

$$\frac{dQ}{dt} = P(C_{GI}) \quad (13.3)$$
2-Facilitated Passive Diffusion:

1. From high to low concentration
2. Need **Carrier** in the membrane combines reversibly with the substrate molecule outside the cell membrane
3. No need for energy.
4. specific molecular configuration
5. Limited number of carrier
3-Active Transport:

1. Against concentration gradient.
2. selective,
3. requires energy
4. limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids).
5. These drugs are usually absorbed from specific sites in the small intestine.
The process by which a drug particle dissolves. For a drug to be absorbed, it must first dissolved in the fluid at absorption site.

As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution, creating a saturated layer of drug solution that envelops the surface of the solid drug particle. This layer of solution is the diffusion layer.

From diffusion layer the drug molecules pass throughout the dissolving fluid and make contact with biologic membranes, and absorption ensues.
If dissolution is rapid or if the drug is administered as a solution the rate at which the drug becomes absorbed depends mainly on its ability to traverse the membrane barrier.

If dissolution slow because of the physicochemical characteristics of the drug substance or dosage form, dissolution is a rate-limiting step in absorption.
Drug remain in stomach: 2 to 4 hours.
In small intestine: 4 to 10 hours.

Various techniques used to determine gastric emptying time like:

- **Gamma scintigraphy**: tracking dosage forms labeled with gamma-emitting radionuclides.
- The gastric emptying time for a drug is rapid with fasting stomach.
  1. slower as food content is increased.

Changes in gastric **emptying time** or intestinal **motility** can affect drug transit time and thus opportunity for drug dissolution and absorption.
a. **anticholinergic drug, slows gastric emptying.** Which increases drugs absorption from stomach and reduce drugs absorption from small intestine.

b. drugs that **enhance gastric motility**, for example, laxatives, **reduce** amount of drug absorbed.

c. **Aging** decrease absorption (geriatrics)

- **decrease in gastric emptying time** is advantageous for **drugs absorbed** from stomach but disadvantage for **drugs prone to acid degradation**, like penicillins and erythromycin, or **inactivated by stomach enzymes**, like L-dopa.
The rate of dissolution

- Rate of dissolution described by **Noyes-Whitney equation**:

\[
\frac{dW}{dt} = \frac{DA(C_s - C)}{L}
\]
where

\( \frac{dw}{dt} \) is the rate of dissolution,

\( D \) is the dissolution rate constant,

\( A \) is the surface area of dissolving solid,

\( c_s \) is saturation concentration of drug in diffusion layer (which may be approximated by the maximum solubility of the drug in the solvent, because the diffusion layer is considered saturated), and

\( c_t \) is the concentration of the drug in dissolution medium at time \( t \) (\( c_s - c_t \) is concentration gradient).

\( L \): length of diffusion layer.
rate of dissolution governed by rate of diffusion of solute through diffusion layer.

dissolution rate increased by:

1. **increasing surface area** (reducing the particle size),
2. by increasing the solubility of drug in diffusion layer, by factors embodied in dissolution rate constant, $D$, including the **intensity of agitation of the solvent** and **diffusion coefficient of dissolving drug**. For a given drug, the diffusion coefficient and usually concentration of the drug in diffusion layer will increase with **increasing temperature**.
3. Increasing rate of agitation of the dissolving medium will increase the rate of dissolution.
4. **reduction in the viscosity** of solvent enhance dissolution rate of a drug.
5. **Changes in pH** or nature of solvent that influence the solubility of the drug may be used to increase dissolution rate.
Henderson–Hasselbalch equation:

\[ \text{pH} = \text{pK}_a + \log \frac{[A^-]}{[HA]} \quad \text{for acidic drugs} \]

\[ \text{pH} = \text{pK}_a + \log \frac{\text{ionized}}{\text{unionized}} \quad \text{for basic drugs} \]

\[ \text{pK}_a = -\log(K_a) = -\log \left( \frac{[H_3O^+][A^-]}{[HA]} \right) \]
Drug movement **not always affected by** pH.

Very weak acids and bases completely **non ionized** at physiological pH, their transfer rapid and independent of pH.

Strong acids and bases are completely ionized and so their transfer is usually slow and pH-independent.
drugs include acids within the pK range 3 to 7.5 and bases in the pK range 7 to 11

- Stomach pH: 1–2
- Duodenum pH: 2–4
- Small intestine pH: 4–6
- Large intestine 6–7.8
Surface area

- When a drug particle is broken up, surface area increased. For drug substances that are poorly or slowly soluble, this generally results in increase in the rate of dissolution.

- To increase surface area, use micronized powders in their solid products. Micronized powders consist of drug particles reduced in size to about 5 µm and smaller.
Solid drug materials may occur as crystalline or amorphous. Amorphous usually more soluble than crystalline form, different extents of drug absorption:

- antibiotic chloramphenicol palmitate, are inactive when administered in crystalline, but when administered amorphous, absorption from GIT rapidly, with good therapeutic response.

- In other instances: crystalline forms of drugs may be used because of greater stability than amorphous forms.

For example, the crystalline forms of penicillin G as potassium salt or sodium salt are more stable than amorphous forms. Thus, in formulation work on penicillin G, the crystalline forms are preferred and result in excellent therapeutic response.
The *amorphous*, or **Prompt Insulin Zinc Suspension**, USP, is *rapidly absorbed* upon intramuscular. The larger *crystalline* material, called **ultralente insulin** or Extended Insulin Zinc Suspension, USP, is more *slowly absorbed* and has a resultant longer duration of action.

By combining the two types in various proportions, a physician can provide patients with intermediate-acting insulin of varying degrees of onset and duration of action. A physical mixture of *70% of the crystalline form* and *30% of the amorphous form*, called **lente insulin** or Insulin Zinc Suspension, USP, is *intermediate acting* and meets the requirements of many diabetics.
Polymorphism:

Only one form of a pure drug is stable, the other is metastable forms, converting in time to the stable crystalline form. It is therefore fairly common for a metastable form of a medicinal agent to change form even in a completed pharmaceutical preparation.

Time required for a complete change may exceed the normal shelf life of the product.

Any change in crystal structure of agent affect the stability and therapeutic efficacy of the product.
Salt forms

The dissolution rate of a salt of a drug is different from that of the parent compound.

Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve more than free acids or bases.

The addition of the ethylenediamine moiety to theophylline increases the water solubility of theophylline fivefold.

The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline.
Other factors

- A drug's solubility in GIT can be affected by pH also by food.
- A drug may interact with agents present to form a chemical complex that result in reduced drug solubility and decreased absorption.
- The classic example of this complexation: between tetracycline and calcium, magnesium, and aluminum, resulting in decreased absorption of the tetracycline.
bioavailability is the rate and extent of drug absorption from site of administration to the general circulation.

The term bioequivalence refers to a comparison of bioavailabilities of different formulations, drug products, or batches of the same drug product.
Bioavailability used to determine

1. **amount of drug absorbed** from a formulation or dosage form,
2. **rate** at which the drug was absorbed,
3. **duration** of the drug's presence in biologic fluid or tissue correlated with the patient's response, and
4. **relationship between drug blood levels and clinical efficacy and toxicity**.
During product development stage:

1. **studies bioavailability** to compare different formulations of the drug substance to ascertain which one allows the most desirable absorption pattern.

2. Later **bioavailability studies** used to compare the availability of the drug substance in different production batches.

3. They may also be used to compare **the availability of the drug substance in different dosage forms** (e.g., tablets, capsules, elixirs),

4. or in the same dosage form produced by different (companies) manufacturers.
Blood, Serum, or Plasma Concentration time curve

- Following oral administration of drug, blood samples are withdrawn at specific time intervals and analyzed for drug content.
- The vertical presents the concentration of drug in blood, and horizontal axis presents time the samples were obtained following drug administration.
- **time zero the blood concentration of drug should be zero.**
- As the drug passes into the stomach and/or intestine, dissolves, and absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug until maximum (peak) concentration ($C_{\text{max}}$) is reached. Then the blood level of the drug decreases.
- Absorption does not terminate after the peak blood level is reached; it may continue for some time.
- **process of drug elimination is continuous.** It begins as soon as the drug first appears in the blood stream and continues until all the drug has been eliminated.
- The positive or negative slope of the curve indicates which process is faster.
Parameters for assessment and comparison of bioavailability

- Following oral administration of single doses of two formulations of the same drug:
  - The peak height concentration ($C_{\text{max}}$)
  - The time to peak concentration ($T_{\text{max}}$)
  - The area under the blood (or serum or plasma) concentration time curve (AUC)
  - $C_{\text{max}}$ observed in blood following a dose of the drug, indicating a slope of zero, meaning the rates of absorption and elimination are equal.
FIGURE 5.7 Serum concentration-time curve showing peak height concentrations, peak height times, times to reach MEC and areas under the curves for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)
When the rate of absorption is decreased, the $C_{\text{max}}$ is lowered and $T_{\text{max}}$ occurs at a later time.
The AUC of concentration-time curve) represent **total amount of drug absorbed following administration of a single dose of that drug.**

If similar doses of drug in **different formulas produce different AUC values**, differences exist in **extent of absorption** between formulations.

In general, the smaller AUC, the lesser drug absorbed.
F: bioavailability of orally administered drug calculated by comparison of AUC after oral administration with that obtained after intravenous administration:

\[ F = \frac{(AUC)_{\text{oral}}}{(AUC)_{\text{IV}}} \times \frac{\text{DOSE IV}}{\text{DOSE oral}} \]

The absolute bioavailability following oral dosing is generally compared to intravenous dosing.
Bioavailability: rate and extent to which a drug in a dosage form becomes available for biologic absorption.

the same drug when formulated in different dosage forms have different bioavailability and exhibit different clinical effectiveness.

Furthermore, two identical or equivalent products of same drug in the same dosage strength and in the same dosage form but differing in formulative materials or method of manufacture may vary widely in bioavailability and thus, in clinical effectiveness.
FDA uses the following terms to define type or level of equivalency between drug products.

- **Pharmaceutical equivalents**: are drug products that contain identical amounts of identical active ingredient, that is, the same salt or ester of the same therapeutic moiety, in identical dosage forms but not necessarily containing the same inactive ingredients.

- **Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety or its precursor but not necessarily in the same amount or dosage form or as the same salt or ester.
bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption are similar.

Some pharmaceutical equivalents or pharmaceutical alternatives equivalent in extent absorption but not in rate of absorption and yet may be considered bioequivalent. because such differences in rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the drug product studied.

therapeutic equivalents: used to indicate pharmaceutical equivalents that provide same therapeutic effect when administered to same individuals in same dosage regimens.
The most common experimental plan to compare the bioavailability of two drug products is **simple crossover design study**.

- 12 to 24 individuals carefully matched subjects (usually healthy men aged 18 to 40 years and having similar height and weight) is administered both products under fasting conditions.
- Each test subject is randomly assigned one of the two products for the first phase of the study.
- Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time.
- The same procedure is then repeated (crossover) with the second product after an appropriate interval, that is, a washout period to ensure that there is no residual drug from the first administered product that would artificially inflate the test results of the second product. Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability; that is, \( C_{\text{max}} \), \( T_{\text{max}} \), and AUC are analyzed with statistical procedures. Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcomes.
- The value in the crossover experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences between individuals are minimized.
Absolute bioequivalency between drug products rarely occurs. Such absolute equivalency would yield serum concentration-time curves for the products that would be exactly superimposable. This simply is not expected of products that are made at different times, in different batches, or indeed by different manufacturers.

In most studies of bioavailability, the originally marketed product (brand name drug product) is recognized as the established product of the drug and is used as the standard for the bioavailability comparative studies.
According to the FDA: generic drug is considered bioequivalent if the rate and extent of absorption do not show a significant difference from that of standard drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions.

Because in the case of a systemically absorbed drug blood levels even if from identical product may vary in different subjects, in bioequivalence studies each subject receives both the standard and the test drug and thus serves as his own control.
Under the **1984** act, to gain FDA **approval a generic drug product** must have these characteristics:

1. **The same active ingredients** as the standard drug.
2. **Identical strength, dosage form, and route of administration**
3. **The same indications and precautions** for use.

- **Bioequivalency**
- The same batch-to-batch requirements for **identity, strength, purity, and quality**
- If a standard manufacturer reformulates an FDA-approved product, the subsequent formulation must meet the same bioequivalency standards that are required of generic manufacturers of that product.
The difference in absorption between dosage forms is a function of the formulation and the route of administration.

The bioavailable fraction is determined by the fraction of drug that is absorbed from the gastrointestinal tract and the fraction that escapes metabolism during its first pass through the liver.
most drug absorbed from various surfaces along GIT.

oral route is considered natural, uncomplicated, convenient, and safe means of administering drugs.

Disadvantages of the oral route include:

1. slow response.

2. chance of irregular absorption of drugs, depending on factors: amount or type of food in GIT and destruction of certain drugs by the acid of stomach or by enzymes.
Dosage Forms Applicable

- tablets, capsules, suspensions, and various pharmaceutical solutions. Briefly, tablets contain medicinal substances with or without suitable diluents, disintegrants, coatings, colorants, and other pharmaceutical adjuncts.

- **Diluents** are fillers used to prepare tablets of the proper size and consistency.

- **Disintegrants** are used for the breakup or separation of the tablet's compressed ingredients. This ensures prompt exposure of drug particles to the dissolution process, enhancing drug absorption.

- **Tablet coatings** are of several types and for several purposes. Some, called enteric coatings, are employed to permit safe passage of a tablet through the acid environment of the stomach, where certain drugs may be destroyed, to the more suitable juices of the intestines, where tablet dissolution safely takes place.

  Other coatings protect the drug substance from the destructive influences of moisture, light, and air during storage or to conceal a bad or bitter taste from the taste buds of a patient.
- **Capsules** are solid dosage forms contain, fillers, are enclosed in either a hard or a soft shell.

- Drug materials are released from capsules *faster* than from tablets.

- Capsules of gelatin rapidly disfigured within GIT permitting the gastric juices to permeate and reach the contents.

- Also, *capsule-shaped and coated tablets*, called *caplets*, are increasingly used. These are easily swallowed, but their contents are sealed and protected from tampering like tablets.
Suspensions aqueous vehicle, whereas those employed for other purposes may use a different vehicle. Suspensions of certain drugs to be used for intramuscular injection, for instance, may be maintained in a suitable oil.

To be suspended, the drug particles must be insoluble in the vehicle. Nearly all suspensions must be shaken before use because they tend to settle.

Suspensions are a useful to administer large amounts of solid drugs that would be inconvenient to take in tablet or capsule form. In addition, suspensions have the advantage over solid dosage forms in that they are presented to body in fine particle size, ready for dissolution immediately upon administration.
Drugs administered in aqueous solution are absorbed much more rapidly than those administered in solid form.

Pharmaceutical solutions may differ in type of solvent employed and fluidity characteristics.

Among the solutions frequently administered orally are elixirs, which are solutions in a sweetened hydroalcoholic vehicle and are more mobile than water; syrups, which generally use a sucrose solution as the sweet vehicle, resulting in a viscous preparation; and solutions themselves, which officially are preparations in which the drug substance is dissolved predominantly in an aqueous vehicle and do not for reasons of their method of preparation (e.g., injections, which must be sterilized).
Absorption

Absorption of drugs after oral administration may occur at various body sites between mouth and rectum.

In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. Because of the differences in chemical and physical nature among drug substances, a given drug may be better absorbed from one site than from another in the alimentary tract.
Sometimes the oral cavity is the absorption site. Physically, oral absorption of drugs is managed by allowing the drug substance to dissolve within the oral cavity with little or no swallowing until the taste of the drug has dissipated. This process is accommodated by providing the drug as extremely soluble and rapidly dissolving uncoated tablets.

Drugs capable of being absorbed in the mouth present themselves to the absorbing surface in a much more concentrated form than when swallowed, because drugs become progressively more diluted with gastrointestinal secretions and contents as they pass along the alimentary tract.
Nitroglycerin, a coronary vasodilator used in the prophylaxis and treatment of angina pectoris, is available in the form of tiny tablets that are allowed to dissolve under the tongue, producing therapeutic effects a few minutes after administration. The dose of nitroglycerin is so small (usually 400 µg) that if it were swallowed, nitroglycerin is rapidly destroyed by the liver through the first-pass effect.

Retaining drug substances in the mouth is unattractive because of the bitter taste of most drugs.
Drugs altered within the gastrointestinal tract to render them less available for absorption. This may result from the drug's interaction with or binding to some normal constituent of the gastrointestinal tract or a food stuff or even another drug.

For instance, the absorption of the tetracycline group of antibiotics is greatly interfered with by the simultaneous presence of calcium. Because of this, tetracycline drugs must not be taken with milk or other calcium-containing foods or drugs.
Gastric emptying time increased by presence of fatty foods or lying on the back when bedridden (lying on the right side facilitates passage in many instances), or decreased, as by the presence of drugs (e.g., morphine).

If a drug is administered in the form of a solution, it may be expected to pass into the intestines more rapidly than drugs administered in solid form.

As a rule, large volumes of water facilitate gastric emptying and passage into the intestines.
pH 1 in stomach, pH 8 at the far end of the intestines.

**pH affect degree of ionization** of most drugs, and this in turn affects **lipid solubility, membrane permeability, and absorption**.

**lipid-water partition coefficient and the pKₐ** of the drugs are of prime importance to both the **degree and the site of absorption**.

As a general rule, **weak acids** are largely un-ionized in the **stomach** and are absorbed fairly well from this site.

**weak bases** are highly ionized in the stomach and are not significantly absorbed from the gastric surface.

**Alkalinization of the gastric environment** by artificial means (simultaneous administration of alkaline or **antacid drugs**) would be expected to **decrease the gastric absorption of weak acids** and to **increase that of weak bases**. Strong acids and bases are generally poorly absorbed because of their high degree of ionization.
The **small intestine** is the **major absorption pathway** for drugs because:

1. **suitable pH**.
2. **great surface area available** for drug absorption along its approximately 20-foot length.

The pH of intestine lumen is 6.5 and both **weakly acidic and weakly basic drugs are well absorbed** from intestinal surface, which behaves in the ionization and distribution of drugs between it and the plasma on the other side of the membrane as though its pH were 5.3.
drugs are administered rectally for their **local** effects or **systemic** effects.

The composition of the **suppository base**, can influence the degree and **rate of drug release** and should be selected on an individual basis for each drug.

The use of **rectal ointments** is generally limited to treat of **local conditions**.

Rectal solutions are usually employed as **enemas** or cleansing solutions.
The rectum and colon can absorb many soluble drugs.

**Rectal** administration for **systemic action** preferred for drugs destroyed or inactivated by the environments of the stomach and intestines.

rectal route also indicated when oral route is precluded because of **vomiting** or when the patient is **unconscious** or incapable of swallowing.

Colon Protect from first pass effect
1. disadvantage of parenteral is that once the drug is injected, there is no retreat.
2. Drugs in solution act more rapidly than drugs in suspension,
3. with an aqueous vehicle providing faster action in each instance than an oleaginous vehicle.
4. suspension of a drug in a vegetable oil slowly absorbed than an aqueous solution of the same drug.

- Slow absorption means prolonged drug action is referred to as a depot or repository injection, because it provides a storage reservoir of the drug substance within the body from which it is slowly removed into the systemic circulation.
- the use of subcutaneous implantation of compressed tablets, termed pellets, slowly dissolved, releasing their medication at a fairly constant rate over several weeks to many months.
Subcutaneous Injections

1. prepared as aqueous solutions or suspensions administered small volumes, 2 mL or less.
2. blood supply to the site of injection is an important.
3. the more the capillaries, the more surface area for absorption and the faster the rate of absorption.
4. The addition of a vasoconstrictor to the injection formulation (or its prior injection) will diminish drug absorption by causing constriction of the blood and reducing blood flow and the capacity for absorption.

This principle is used in the administration of local anesthetics by use of the vasoconstrictor epinephrine.

- Conversely, vasodilators may be used to enhance subcutaneous absorption by increasing blood flow to the area.

Physical exercise can also influence the absorption of drug from an injection site.
Intramuscular Injections

1. volumes (2 to 5 mL)
2. When a volume greater than 5 mL is to be injected, it is frequently administered in divided doses to two injection sites.
3. Injection sites are best rotated when a patient is receiving repeated injections over time.
• **Bound drug** is neither exposed to metabolism nor filtered through the renal glomeruli.

• Bound drug is inactive portion in the blood.

• Unbound drug, with its ability to penetrate cells, is active blood portion.

• The bound portion of drug serves as a reservoir or depot from which the drug is released as the free form when the level of free drug in the blood no longer is adequate to ensure protein saturation.
PHARMACOKINETIC PRINCIPLES

- Simplest pharmacokinetic model is one compartment open-model system.
- This model depicts the body as one compartment characterized by **volume of distribution** \((V_d)\) that remains constant. Each drug has its own distinct volume of distribution, and this influenced by **age** and **disease**.
- the drug is absorbed at a certain rate and is characterized by **absorption rate constant** \(K_a\).
- Finally, the drug is eliminated from the compartment at a certain rate that is characterized by an **elimination rate constant**, \(K_{el}\).
volume of distribution, $V_d$, a proportionality constant that refers to the volume into which the total amount of drug in the body must be uniformly distributed to provide the concentration of drug actually measured in plasma or blood.

Where:
- $C_p$ is the drug concentration in plasma
- $V_d$ is the volume of the compartment or volume of distribution

**FIGURE 5.12** A one-compartment system.
- It is influenced by the **plasma protein binding** and **tissue binding** of a drug.
- the total amount of drug in the body \((Q_b)\) can be calculated from the following equation:

\[
Q_b = [C_p^0] [V_d]
\]

\[
\log C_p = \log C_p^0 - \frac{K_d}{2.303(t)}
\]
two-compartment model

FIGURE 5.14 A semilogarithmic plot of plasma concentration versus time of an intravenous drug that follows first-order two-compartment
Where:

- $Q_c = \text{Quantity of drug in central compartment}$
- $V_c = \text{Volume of the central compartment}$
- $Q_p = \text{Quantity of drug in peripheral compartment}$
- $V_p = \text{Volume of the peripheral compartment}$

**FIGURE 5.15** A two-compartment system.
In two-compartment system: a drug enters and distributed throughout the central compartment. Its subsequent distribution into second or peripheral compartment is slower.

The central compartment is usually blood, the extracellular space, and organs with good blood perfusion, such as lungs, liver, kidneys, and heart.

The peripheral compartment usually comprises tissues and organs that are poorly perfused by blood, such as skin, bone, and fat.
HALF-LIFE

- The half-life ($T_{1/2}$) of a drug is the time required for a drug's blood or plasma concentration to decrease by half.

- $T_{1/2} = 0.693/k$

- Clearance: $Cl = Vd \times k$