# Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations

**Sec. II**

**Chap 5**

- The biologic response to API is the result of an interaction between API and functionally important cell receptors or enzyme systems.
- The response is due to an alteration in the biologic processes that were present prior to the drug's administration.
- The magnitude of the response is related to the concentration of the drug achieved at the site of its action.
- The drug concentration depends on the **administered dosage**, the **extent of its absorption** and **distribution** to the site, and **the rate and extent of its elimination** from the body.
- ***Biopharmaceutics:*** The area of study that embracing the relationship between the physical, chemical, and biologic sciences as they apply to drugs, dosage forms, and drug action.
- ***Pharmacokinetics:*** is the study of the bodily absorption, distribution, metabolism, and excretion of drugs or the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.
- OR It is the study of the kinetics of absorption, distribution, metabolism, and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic effects in animals and man.

- Once a drug is administered and absorption begins, the drug does not remain in a single body location but rather is distributed throughout the body until its ultimate elimination.
- A number of drugs become bound to blood proteins (albumins) and only a small fraction of the drug administered may be found outside of the circulatory system.
- The transfer of drug from one compartment to another is mathematically associated with a specific rate constant describing that particular transfer.
- The rate of transfer of a drug from one compartment to another is proportional to the 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 bio-transformed into pharmacologically active (prodrug) or inactive metabolites, or both.
- This metabolism enhances the lipophilic character of the drug → increase drug penetration.
- ***Elimination:*** is both metabolism and excretion.

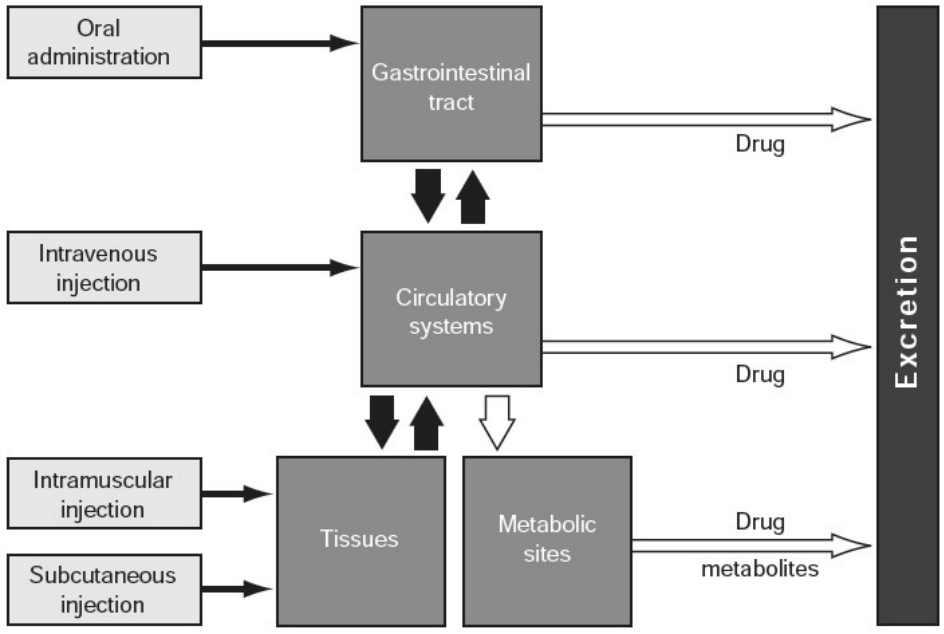



**FIGURE 5.1** Events of absorption, metabolism, and excretion of drugs after their administration by various routes.

## Principles of Drug Absorption

Body membranes classification:

a) Those composed of several layers of cells (skin).

b) Those composed of a single layer of cells (intestinal epithelium).

c) Those less than one cell thick (single cell membrane).

Drug → mouth → gastrointestinal membranes (stomach and intestines) → general circulation → organ or tissue → entrance to that tissue → individual cells.

Membranes are bimolecular lipoid (fat containing) layer attached on both sides to a protein layer.

Drugs are penetrate these biologic membranes in two general ways:

a) by passive diffusion.

b) by specialized transport mechanisms.

## Passive Diffusion

- *Passive diffusion:* the passage of (drug) molecules through a membrane that does not actively participate in the process (*Passively Absorbed Drugs*).
- The absorption process is driven by the concentration gradient across the membrane (High → Low conc.).
- Most drugs pass through biologic membranes by diffusion.
- Passive diffusion (*Fick first law):* the rate of diffusion or transport across a membrane (dc/dt) is proportional to the difference in drug concentration on both sides of the membrane:
- $C_1$ and $C_2$ are the drug concentrations on each side of the membrane (compartments) and P is a permeability coefficient.
- $C_1$ is the compartment with the greater concentration of drug (absorption site) and $C_2$ is the blood compartment.

$$-\frac{dc}{dt} = P(C_1 - C_2)$$

- $C_1$ usually >> $C_2$ because of the rapid dilution of the drug in the blood and its subsequent distribution to the tissues. So for practical purposes, $C_1 - C_2$ may ~ $C_1$. The first-order rate equation is written:

$$-\frac{dc}{dt} = PC_1$$

- The magnitude of the permeability constant depends on the **diffusion coefficient** of the drug, the **thickness and area** of the absorbing membrane, and the **permeability of the membrane** to the particular drug.
- The high permeability for lipid soluble substances is due to the lipoid nature of the cell membrane.
- The rate of diffusion of a drug across the membrane depends on its **concentration** and on the its **affinity for lipid** and rejection of water (a high lipid partition coefficient).
- The greater drug affinity for lipid and the more hydrophobic → the faster will be its rate of penetration into the lipid-rich membrane.

- Biologic cells/membrane contains water-filled channels that permit the passage of water and lipid-insoluble substances (small molecules) by *filtration*.
- Aqueous channels vary in size from membrane to membrane → the permeability characteristics vary for certain drugs.
- Most drugs are weak organic acids or bases → ionization or dissociation characteristics affect their absorption (degrees of ionization).
- Cell membranes are more permeable to the un-ionized forms of drugs than to their ionized forms, due to the greater **lipid solubility** of the un-ionized forms and the **highly charged nature of the cell** membrane, which results in **binding** or **repelling** of the ionized drug and thereby decreases cell penetration.
- Hydrated Ions with water have larger particles than the un-dissociated molecule → decreased penetrating capability.
- The degree of API ionization depends both on the **pH of the solution** at the biologic membrane and on **the pKa (dissociation constant)** of the API.

**Henderson-Hasselbalch equation**

For an acid,

$$pH = pK_a + \log \frac{\text{ionized conc.(salt)}}{\text{un-ionized conc.(acid)}}$$

For a base,

$$pH = pK_a + \log \frac{\text{un-ionized conc.(base)}}{\text{ionized conc.(acid)}}$$

- Drug absorption from various body fluids will differ depending on fluid pH, the type of dosage form, the route of administration.

| Stomach pH 1 | lumen of the intestine pH 6.6 | blood plasma pH 7.4 |
|---|---|---|

- weak acid (pKa of 4) in stomach (pH of 1) → pKa – pH = 3 (the ratio of un-ionized to ionized API is 1,000:1 → gastric absorption is excellent.
- At the pH of plasma, the reverse is true, and in the blood, the drug is largely in the ionized form.

Rearranging the equation for an acid yields

$$pK_a - pH = \log \frac{\text{un-ionized concentration (acid)}}{\text{ionized concentration (acid)}}$$

Table 5.1 THE EFFECT OF pH ON THE IONIZATION OF WEAK ELECTROLYTES $pK_a$–pH % UN-IONIZED

| | IF WEAK ACID | IF WEAK BASE |
|---|---|---|
| – 3.0 | 0.10 | 99.90 |
| – 2.0 | 0.99 | 99.00 |
| – 1.0 | 9.09 | 90.90 |
| – 0.7 | 16.60 | 83.40 |
| – 0.5 | 24.00 | 76.00 |
| – 0.2 | 38.70 | 61.30 |
| 0.0 | 50.00 | 50.00 |
| + 0.2 | 61.30 | 38.70 |
| + 0.5 | 76.00 | 24.00 |
| + 0.7 | 83.40 | 16.60 |
| + 1.0 | 90.90 | 9.09 |
| + 2.0 | 99.00 | 0.99 |
| + 3.0 | 99.90 | 0.10 |

**Specialized Transport Mechanisms**

- Transport that involve membrane components e.g. enzymes or carriers capable of forming a complex with the drug at the surface membrane.
- The carrier moves across the membrane, where the drug is released, and carrier returning to the original surface.
- *Active transport* as a sub-classification of specialized transport process, the drug being moved across the membrane against a concentration gradient (from lower to higher conc.) or against an electrochemical potential gradient.
- *Facilitated diffusion* is a specialized transport mechanism, the drug is not transferred against a concentration gradient.
- Many body nutrients, sugars and amino acids, are transported across the membranes of the gastrointestinal tract by carrier processes.
- Certain vitamins, e.g. thiamine, niacin, riboflavin, pyridoxine, and APIs e.g. methyldopa and 5 fluorouracil, require active transport mechanisms for their absorption.

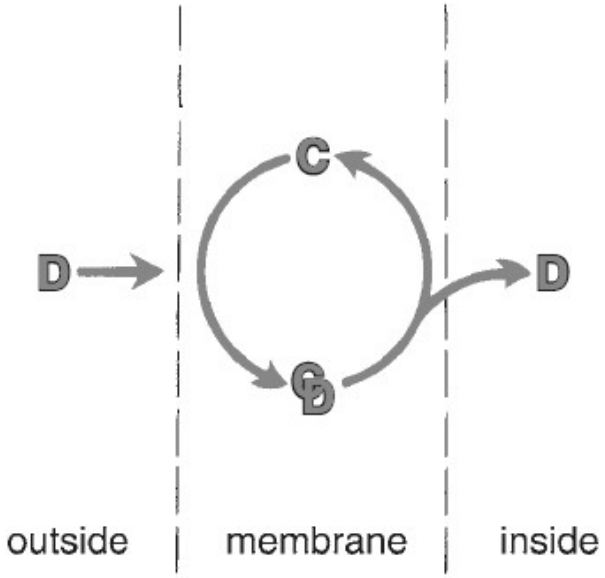



**FIGURE 5.2** Active transport mechanism. D, drug molecule; C, the carrier in the membrane.

**Dissolution and Drug Absorption**

- A drug need to be dissolved in the fluid at the absorption site in order to be absorbed.
- Tablet or capsule → *dissolution of* the drug particles by the fluids in the gastrointestinal tract.
- 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 which the drug molecules pass throughout the dissolving fluid and make contact with the biologic membranes, and absorption ensues.
- As the molecules of drug continue to leave the diffusion layer, the layer is replenished with dissolved drug from the surface of the drug particle, and the process of absorption continues.
- APIs with High Dissolution rate → Absorption depends drug membrane permeability.
- APIs with Low Dissolution Rate (Dosage/API solubility) → It will be rate-limiting step in absorption.
- Under normal circumstances, a drug may be expected to remain in the stomach for 2 to 4 hours (*gastric emptying time*) and in the small intestine for 4 to 10 hours.

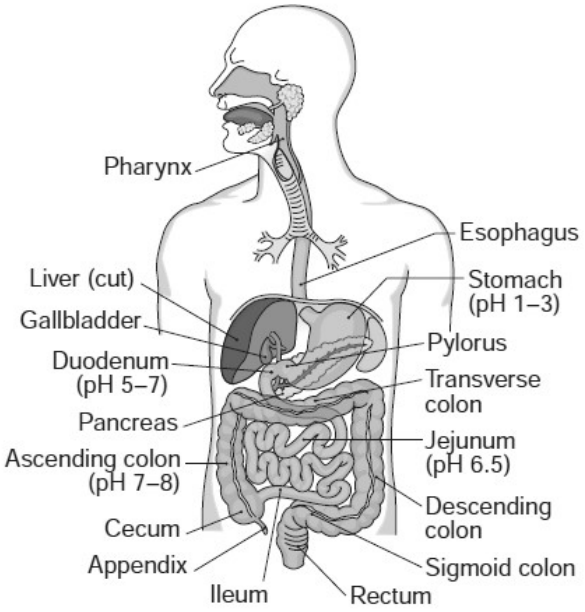
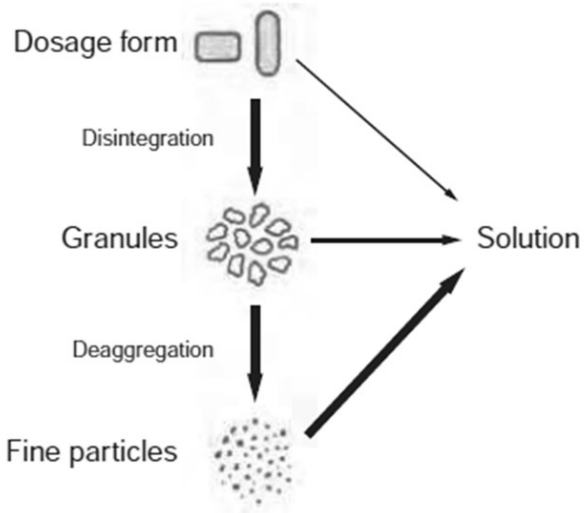



**FIGURE 5.3** The digestive system, including the locations of drug absorption and their respective pH values.

- The gastric emptying time for a drug is most rapid with a fasting state, slower at fed state.
- Changes in gastric emptying time and/or in intestinal motility can affect drug transit time and thus the opportunity for drug dissolution and absorption.



- Aging also influence gastrointestinal absorption (In elderly, gastric acidity, the number of absorptive cells, intestinal blood flow, the rate of gastric emptying, and intestinal motility are all decreased).
- The dissolution of a substance can be described by the modified Noyes-Whitney equation:

$$\frac{dc}{dt} = kS(c_s - c_t)$$

- dc/dt: dissolution rate.
- K: dissolution rate constant.
- S: surface area of the dissolving solid.
- $C_s$: the saturation concentration of drug in the diffusion layer.
- $C_t$: the concentration of the drug in the dissolution medium at time t.
- $(C_s - C_t)$: is the concentration gradient).

- For a given drug, the diffusion coefficient and usually the concentration of the drug in the diffusion layer will increase with increasing temperature.
- Also, increasing the rate of agitation of the dissolving medium will increase the rate of dissolution.
- A reduction in the viscosity of the solvent employed is another means to enhance the dissolution rate of a drug.
- Changes in the pH or the nature of the solvent that influence the solubility of the drug may be used to advantage in increasing dissolution rate.

**Surface Area**

- Decreasing API PSD particle → the total surface area is increased.
- Decreasing API PSD of poorly or slowly soluble APIs → increase in the *rate* of dissolution.
- Solid Dispersions: blending and melting of poorly water-soluble APIs with a water-soluble polymer e.g. (PEG, PVP) → increase in the *rate* of dissolution.
- Hot melt extrusion: API-Miscible Carrier → a molecular dispersion of the drug in the carrier → solid dispersion → increase in the *rate* of dissolution.

**Crystal or Amorphous Drug Form**

**Solid APIs:**

1. Pure crystalline substances (identifiable shape)
2. Amorphous particles (without definite structure).

- The amorphous or crystalline APIs vs. formulation and handling vs. chemical stability.
- The amorphous form of API is usually more soluble than the crystalline form → different drug absorption → different degree of pharmacologic activity.
- Some crystalline APIs are capable of forming different types of crystals (polymorphs) (temperature, solvent, time).
- The various polymorphic forms of the same API generally differ in many physical properties e.g. solubility and dissolution.

## Salt Forms

- The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound.
- Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the respective free acids or bases.
- The result is a more rapid saturation of the diffusion layer surrounding the dissolving particle and the consequent more rapid diffusion of the drug to the absorption sites.

## Other Factors

- The *hydrated state* of an API → affect its solubility and pattern of absorption.
- Usually, the anhydrous form of an organic molecule is more readily soluble than the hydrated form.

## Bioavailability and Bioequivalence

- ***Bioavailability:*** the rate and extent to which an API is absorbed from a drug product and becomes available at the site of action.
- ***Bioequivalence:*** refers to the comparison of bioavailabilities of different formulations, drug products, or batches of the same drug product.

Bioavailability data are used to determine:

a) The amount or proportion of drug absorbed from a formulation or dosage form.

b) The rate at which the drug was absorbed.

c) The duration of the drug's presence in the biologic fluid or tissue correlated with the patient's response.

d) The relationship between drug blood levels and clinical efficacy and toxicity.

- ✓ During the product development stages of a drug product, pharmaceutical manufacturers employ bioavailability studies to compare different formulations of the drug substance to ascertain which one allows the most desirable absorption pattern.
- ✓ Bioavailability studies may be used to compare the availability of the drug substance in different production batches.
- ✓ Bioavailability studies may be used to compare the availability of the drug substance in different dosage forms (e.g., tablets, capsules, elixirs) or in the same dosage form produced by different (competing) manufacturers.

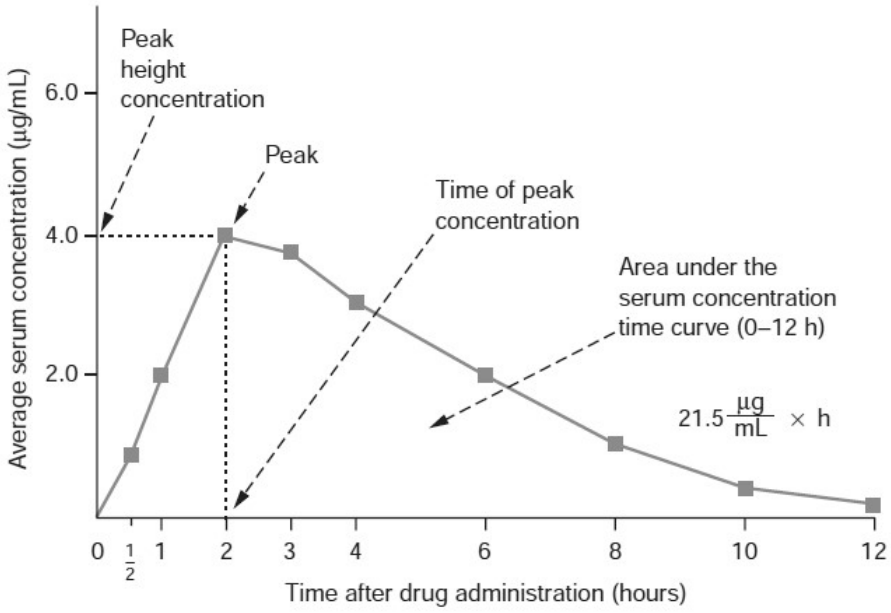



**FIGURE 5.4** Serum concentration–time curve showing peak height concentration, time of peak concentration, and AUC.

**Single-Dose and Multiple-Dose Bioavailability Studies**

- Single-dose bioavailability studies compare the drug product to be tested against the appropriate reference material.
- Studies are conducted in normal adults generally in the fasting state.
- A single-dose study is usually crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons.
- The sampling time for blood and/ or urine is usually at least three times the half life of the active drug ingredient or therapeutic moiety, its metabolite(s), or at least three times the half-life of the acute pharmacological effect.
- Measured are the peak concentration in the blood and the total area under the curve.
- Multiple-dose bioavailability studies compare the test product and the reference material after repeated administration to determine steady-state levels of the active drug ingredient or therapeutic moiety in the body.

- Studies are conducted in human subjects in the fasting or non fasting state, depending upon the conditions reflected in the proposed labeling of the test product.
- A multiple-dose study may be required for a test product if:
  a. there is a difference in the rate of absorption but not in the extent of absorption.
  b. there is excessive variability in bioavailability from subject to subject.
  c. the concentration of the active drug ingredient or therapeutic moiety, or its metabolites, in the blood resulting from a single dose is too low for accurate determination by the analytical method.
  d. the drug product is an extended- release dosage form.

**FDA Requires Bioavailability Data Submission In the Following Instances:**

1. *New Drug Applications* (*NDAs*).

2. *Abbreviated New Drug Applications* (*ANDAs*).

3. *Supplemental Applications*:

In vivo bioavailability data are required if there is a change in the following:

A. a. Manufacturing process, product formulation, or dosage strength beyond the variations provided for in the approved NDA.

B. Labeling to provide for a new indication for use of the drug product and if clinical studies are required, to support the new indication.

C. Labeling to provide for a new or additional dosage regimen for a special patient population (e.g., infants) if clinical studies are required to support the new or additional dosage regimen Conditions under which the FDA **may waive the in vivo bioavailability** requirement are as follows:

1) The drug product is a parenteral, ophthalmic, or otic solution and contains the same active agent in the same concentration and solvent as a product previously approved through a full NDA.

2) The drug product is administered by inhalation as a gas or vapor and contains the same active agent in the same dosage form as a product previously approved through a full NDA.

3) The drug product is an oral solution, elixir, syrup, tincture, or similar other solubilized form and contains the same active agent in the same concentration as a previously approved drug product through a full NDA and contains no inactive ingredient known to significantly affect absorption of the active drug ingredient.

4) The drug product is a topically applied preparation (e.g., ointment) intended for local therapeutic effect.

5) The drug product is an oral form that is not intended to be absorbed (e.g., antacid or radiopaque medium).

6) The drug product is a solid oral form that has been demonstrated to be identical or sufficiently similar to a drug product that has met the in vivo bioavailability requirement.

## Blood, Serum, or Plasma Concentration–Time Curve

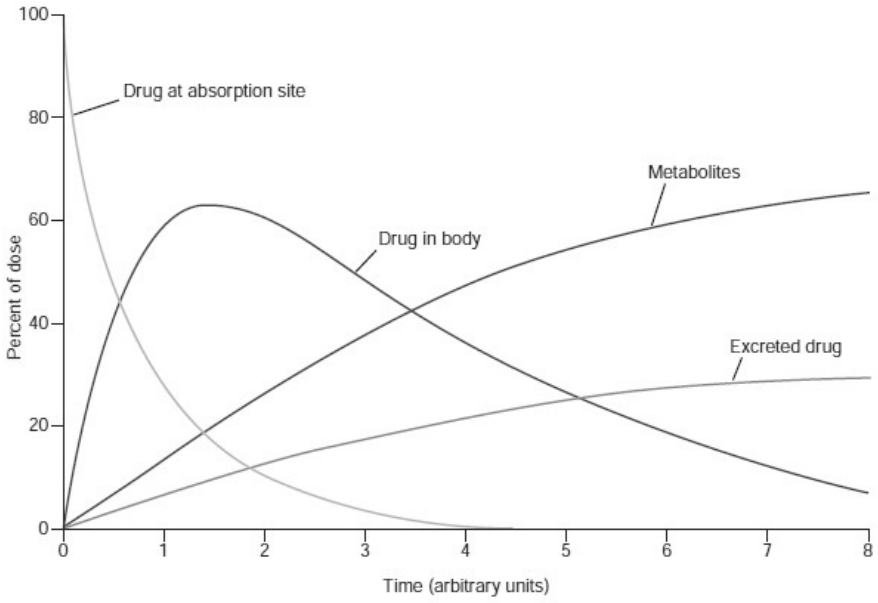



FIGURE 5.5 Time course of drug in the body.

## Parameters for Assessment and Comparison of Bioavailability

- The peak height concentration ($C_{max}$).
- The time of the peak concentration ($T_{max}$).
- The area under the blood (or serum or plasma) concentration–time curve (AUC).

***Peak Height***

- Peak height concentration is the $C_{max}$ observed in the blood plasma or serum following a dose of the drug, indicating a slope of zero, meaning the rates of absorption and elimination are equal.
- For conventional dosage forms, such as tablets and capsules, the $C_{max}$ will usually occur at only a single time, $T_{max}$.
- The amount of drug is usually expressed in terms of its concentration in relation to a specific volume of blood, serum, or plasma.

***Time of Peak***

- The second important parameter in assessing the comparative bioavailability of two formulations is $T_{max}$.
- This parameter reflects the *rate* of absorption from a formulation, which determines the time needed for the MEC to be reached and thus for initiation of the desired effect.
- In Figure 5.6, $T_{max}$ is 1 hour for formulation A and 4 hours for formulation B.

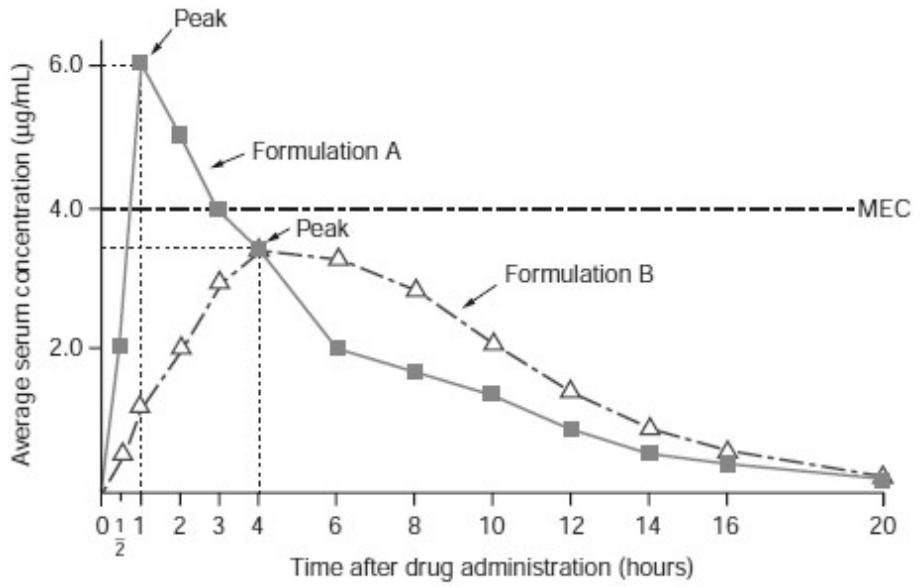



**FIGURE 5.6** Serum concentration–time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration.

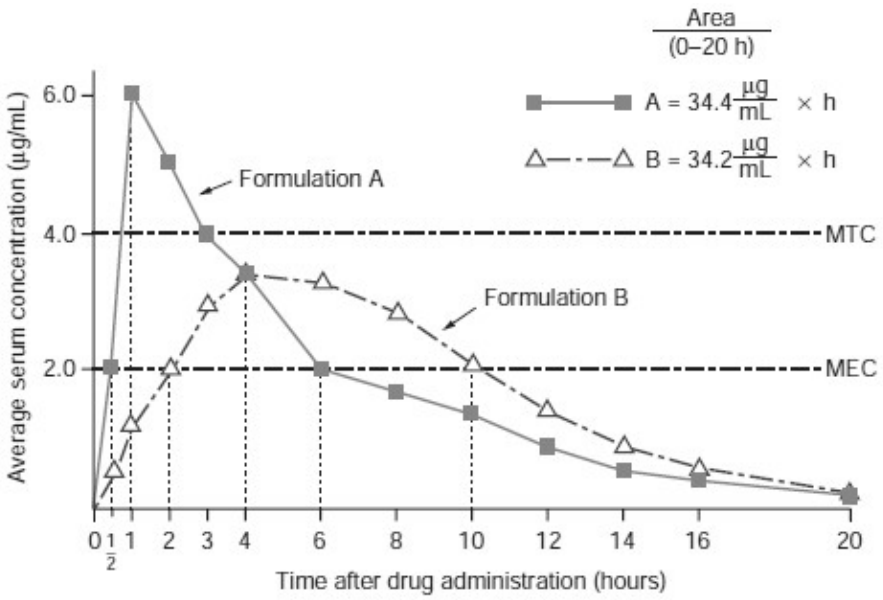



**FIGURE 5.7** Serum concentration–time curve showing peak height concentrations, peak height times, times to reach MEC, and areas under the curves for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration.

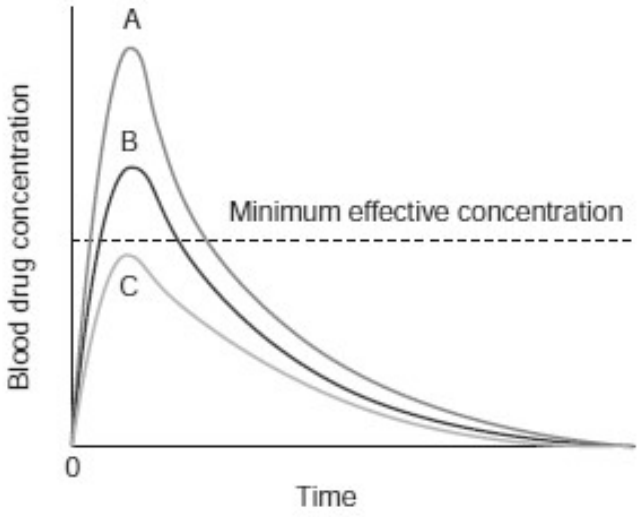



**FIGURE 5.8** The influence of dose size on the blood drug concentration–time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A, 100 mg; B, 80 mg; C, 50 mg.

***Area Under the Serum Concentration -Time Curve*** $F = (AUC)_{oral}/(AUC)_{intravenous}$

- The AUC of a concentration-time plot is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug.
- Equivalent doses of a drug, when fully absorbed, produce the same AUC. Thus, two curves dissimilar in terms of peak height and time of peak (Figure 5.7) may be similar in terms of AUC and thus in the amount of drug absorbed.
- If equivalent doses of drug in different formulations produce *different* AUC values, differences exist in the *extent* of absorption between the formulations (Figure 5.9) In general, the smaller the AUC, the lesser drug absorbed.
- The fraction (F) (or bioavailability) of an orally administered drug may be calculated by comparison of the AUC after oral administration with that obtained after intravenous administration.
- It is rare for a drug to be completely absorbed into the circulation following oral administration (first-pass effect, formulation, dissolution, chemical and physical interactions with the gastrointestinal contents, gastric emptying time, intestinal motility).
- The absolute bioavailability following oral dosing is generally compared to intravenous dosing.

**Bioequivalence of Drug Products**

- The rate and extent to which a drug in a dosage form becomes available for biologic absorption or use depend in great measure on the materials in the formulation and on the method of manufacture.
- Thus, the same drug when formulated in *different* dosage forms may be found to possess different bioavailability characteristics and hence exhibit different clinical effectiveness.
- Furthermore, two seemingly identical or equivalent products of the 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.
- According to the USP, significant bioavailability and bioinequivalence problems that may be revealed through dissolution testing are generally the result of one or more of the following factors: the drug's **particle size**, excessive amounts of a **lubricant** such as magnesium stearate in the formulation, **coating materials**, and inadequate amounts of tablet or capsule **disintegrants**.

- ***Pharmaceutical equivalents:*** drug products that contain identical amounts of the identical active drug 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, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable content uniformity, disintegration times, and/or dissolution rates (e.g., chlordiazepoxide hydrochloride, 5-mg capsules).
- ***Pharmaceutical alternatives:*** 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. Each such drug product individually meets either the identical or its own compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times, and/or dissolution rates (tetracycline phosphate or tetracycline hydrochloride equivalent to 250 mg tetracycline base).
- ***Bioequivalent drug products:*** pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose.
- ***Therapeutic equivalents:*** pharmaceutical equivalents that provide essentially the same therapeutic effect when administered to the same individuals in the same dosage regimens.

**Table 5.3 SOME FACTORS THAT INFLUENCE BIOAVAILABILITY OF ORAL DRUGS**

*DRUG SUBSTANCE PHYSIOCHEMICAL PROPERTIES*

- Particle size
- Crystalline or amorphous form
- Salt form
- Hydration
- Lipid or water solubility
- pH and $pK_a$

*PHARMACEUTICAL INGREDIENTS*

- Fillers
- Binders
- Coatings
- Disintegrating agents
- Lubricants
- Suspending agents
- Surface active agents
- Flavoring agents
- Coloring agents
- Preservative agents
- Stabilizing agents

*DOSAGE FORM CHARACTERISTICS*

- Disintegration rate (tablets)
- Dissolution time of drug in dosage form
- Product age and storage conditions

*PHYSIOLOGIC FACTORS AND PATIENT CHARACTERISTICS*

- Gastric emptying time
- Intestinal Transit Time
- Gastrointestinal abnormality or pathologic condition
- Gastric contents
- Other drugs
- Food
- Fluids
- Gastrointestinal pH

DRUG METABOLISM (GUT AND DURING FIRST PASSAGE THROUGH LIVER)

**Table 5.4 ROUTES OF DRUG ADMINISTRATION**

| TERM | SITE |
|---|---|
| Oral | Mouth |
| Peroral (per os[a]) | Gastrointestinal tract via mouth |
| Sublingual | Under the tongue |
| Parenteral | Other than the gastrointestinal tract (by injection) |
| Intravenous | Vein |
| Intra-arterial | Artery |
| Intracardiac | Heart |
| Intraspinal or intrathecal | Spine |
| Intraosseous | Bone |
| Intra-articular | Joint |
| Intrasynovial | Joint fluid area |
| Intracutaneous, intradermal | Skin |
| Subcutaneous | Beneath the skin |
| Intramuscular | Muscle |
| Epicutaneous (topical) | Skin surface |
| Transdermal | Skin surface |
| Conjunctival | Conjunctiva |
| Intraocular | Eye |
| Intranasal | Nose |
| Aural | Ear |
| Intrarespiratory | Lung |
| Rectal | Rectum |
| Vaginal | Vagina |

**Table 5.5 ROUTE OF ADMINISTRATION AND DELIVERY SYSTEM OF PRIMARY DOSAGE FORMS**

| | |
|---|---|
| ORAL | Tablets |
| | Capsules |
| | Solutions |
| | Syrups |
| | Elixirs |
| | Suspensions |
| | Magmas |
| | Gels |
| | Powders |
| SUBLINGUAL | Tablets |
| | Troches, lozenges |
| | Drops (solutions) |
| PARENTERAL | Solutions |
| | Suspensions |
| EPICUTANEOUS, TRANSDERMAL | Ointments, gels |
| | Creams |
| | Infusion pumps |
| | Pastes |
| | Plasters |
| | Powders |
| | Aerosols |
| | Lotions |
| | Transdermal patches, disks, solutions |
| CONJUNCTIVAL | Contact lens inserts |
| | Ointments |
| INTRAOCULAR, INTRAAURAL | Solutions |
| | Suspensions |
| INTRANASAL | Solutions |
| | Sprays |
| | Inhalants |
| | Ointments |
| INTRARESPIRATORY | Aerosols |
| RECTAL | Solutions |
| | Ointments |
| | Suppositories |
| | Gels |
| VAGINAL | Solutions |
| | Ointments |
| | Emulsion foams |
| | Gels |
| | Tablets |
| | Inserts, suppositories, sponge |
| URETHRAL | Solutions |
| | Suppositories |

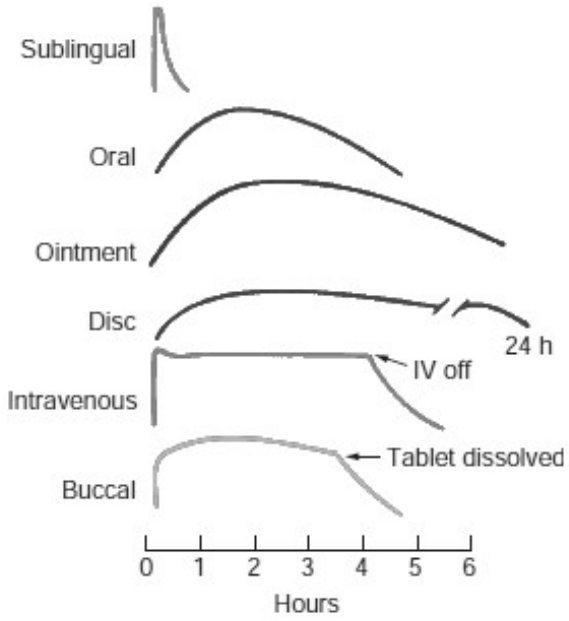



**FIGURE 5.10** Blood level curves of nitroglycerin following administration of dosage forms by various routes.

**Table 5.6 DOSAGE AND KINETICS OF NITROGLYCERIN IN VARIOUS DOSAGE FORMS**

| NITROGLYCERIN, DOSAGE FORM | USUAL DOSE (MG) | ONSET OF ACTION (MIN) | PEAK ACTION (MIN) | DURATION |
|---|---|---|---|---|
| Sublingual | 0.3–0.8 | 2–5 | 4–8 | 10–30 min |
| Buccal | 1–3 | 2–5 | 4–10 | 30–300 min[a] |
| Oral | 6.5–19.5 | 20–45 | 45–120 | 2–6 h[b] |
| Ointment (2%) | 0.5–2 in. | 15–60 | 30–120 | 3–8 h |
| Transdermal Infusion System | 20–160 | 30–60 | 60–180 | 12–14 h |

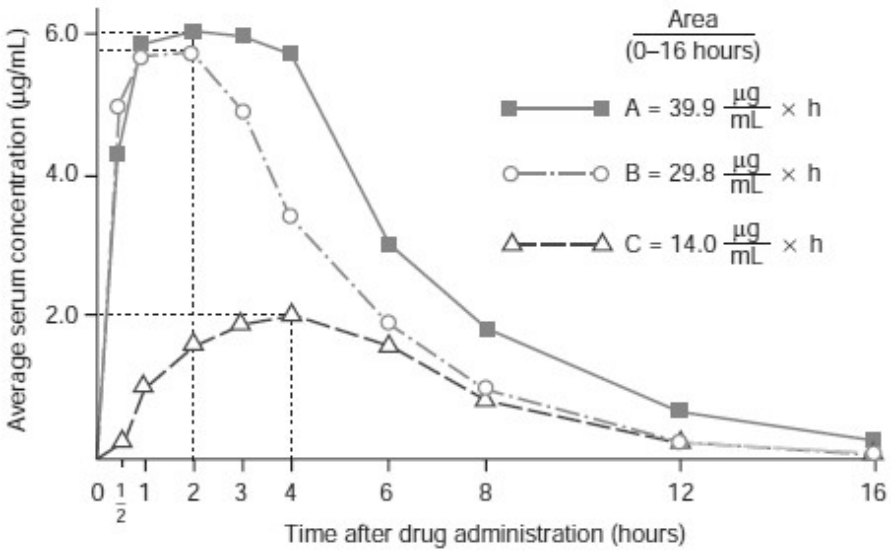



**FIGURE 5.9** Serum concentration–time curve showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration.

## Fate of Drug After Absorption

- After absorption into the general circulation from any route of administration, a drug may become bound to blood proteins and delayed in its passage into the surrounding tissues.
- The degree of drug binding to plasma proteins is usually expressed as a percentage or as a fraction (termed *alpha*) of the bound concentration ($C_b$) to the total concentration ($C_t$), bound plus unbound ($C_u$) drug:

$$\alpha = \frac{C_b}{C_u + C_b} = \frac{C_b}{C_t}$$

- The binding of drugs to biologic materials by the formation of relatively weak bonds (van der Waals, hydrogen, and ionic bonds).
- Bound drug is neither exposed to the body's detoxification (metabolism) processes nor is it filtered through the renal glomeruli.
- Bound drug is therefore referred to as the *inactive* portion in the blood, and unbound drug, with its ability to penetrate cells, is termed the *active* blood portion.
- A drug's binding to blood proteins may be affected by the simultaneous presence of another drug or drugs.
- Many drugs, because of their affinity for and solubility in lipids, are deposited in fatty body.

**Drug Metabolism or Biotransformation**

- Some drugs are excreted from the body in their original form.
- Many drugs undergo biotransformation prior to excretion.
- Biotransformation → chemical changes to drugs within the body → metabolized (altered by various biochemical mechanisms).
- The biotransformation of a drug results in its conversion to one or more compounds that are more water soluble, more ionized.
- Principal chemical reactions in the metabolism of drugs: **oxidation, reduction, hydrolysis, and conjugation**.
- Most oxidation reactions are catalyzed by enzymes (oxidases) in liver cells.
- Small fraction of drugs are metabolized by reduction, through the action of reductases in the gut and liver.

- Esterases in the liver participate in the hydrolytic breakdown of drugs containing ester groups and amides.
- Glucuronide conjugation is the most common pathway for drug metabolism, through combination of the drug with glucuronic acid, forming ionized compounds that are easily eliminated via the urine.
- Other metabolic processes, including methylation and acylation conjugation reactions, occur with certain drugs to foster elimination.

**Excretion of Drugs**

- The excretion of drugs and their metabolites terminates their activity and presence in the body.
- Drugs be eliminated by various routes, kidney via the urine (most important).
- Drug excretion in the feces, especially for drugs that are poorly absorbed and remain in the gastrointestinal tract after oral administration (bile).
- The lungs provide the exit for many volatile drugs through the expired breath.
- The sweat glands, saliva, and milk play only minor roles in drug elimination.
- Some drugs may be reabsorbed from the renal tubule even having been sent there for excretion. By acidifying the urine, as with the oral administration of ammonium chloride, or by alkalinizing it, as with the administration of sodium bicarbonate, one can increase or decrease the ionization of the drug and thereby alter its prospect of being reabsorbed.
- Alkalinization of the urine has been demonstrated to enhance the urinary excretion of weak acids such as salicylates.