
Basic Biopharmaceutics

Topic Outline

- How Drugs Work
 - Concentration & Effect
 - ADME Processes & Diffusion
 - Absorption
 - Distribution
 - Metabolism
 - Excretion
 - Bioequivalence
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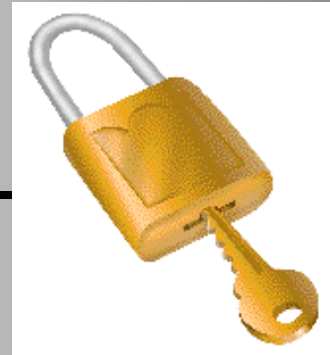
Objectives

- Explain how a drug produces a pharmacologic effect
 - Explain the terms in ADME
 - Explain why a blood concentration-time profile is an accepted means to describe drug concentration at the site of action
 - How does the FDA use bioequivalence information and why is it important to the technician
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Objectives

- Identify and explain the influence of three factors on the processes of absorption, distribution, metabolism and excretion
 - Define bioavailability and explain the difference between absolute and relative bioavailability
 - Explain at which points in the blood concentration-time curve each of the ADME processes happening
 - Explain how to determine a drug's half-life
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How Drugs Work



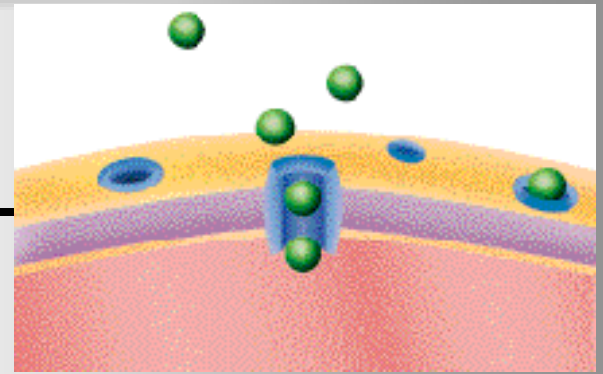
- **Receptor:**
 - The cellular material directly involved in the action of the drug. Receptors are located on the surface of cell membranes.
 - Described as a **lock** into which the drug molecule fits as a **key**.
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How Drugs Work



- **Receptor:**
 - Only those drugs able to bind chemically to the receptors in a particular **site of action** can produce effects at that site..
 - Specific cells only respond to certain drugs, even though their receptors are exposed to any drug molecules that are present in the body.
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How Drugs Work



- **Site of Action:**
 - The place where a drug causes an effect to occur.
 - The **objective of drug therapy** is to deliver the right drug, right concentration, right site of action, right time to produce the desired effect.
 - When a drug produces an **EFFECT**, it is interacting at a molecular level with cellular material or structure.
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How Drugs Work

- When drugs interact with the site of action, they can
 - Modify the metabolic activity of pathogens, as with antibiotics.
 - React chemically, as with antacids the reduced excess gastric acidity.
 - Act directly and change the physical action, as with the ointment upon topical application.
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Agonists vs. Antagonists

- When drug molecules bind with a receptor, they can cause a reaction that
 - stimulates (agonists) or
 - inhibits (antagonists) cellular functions.
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Agonists vs. Antagonists

- **Agonists** are substances that activate receptors and produce a higher response.
 - e.g. Epinephrine causing increased heart rate) or a slower response (acetylcholine like drugs to cause slow heart rate).
 - **Antagonists** are drugs that block the action of the receptor.
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Concentration & Effect Dose Response Curve

- It is difficult to measure the amount of a drug at the site of action (inside a tissue or an organ) and therefore to predict an effect based upon the measurement.
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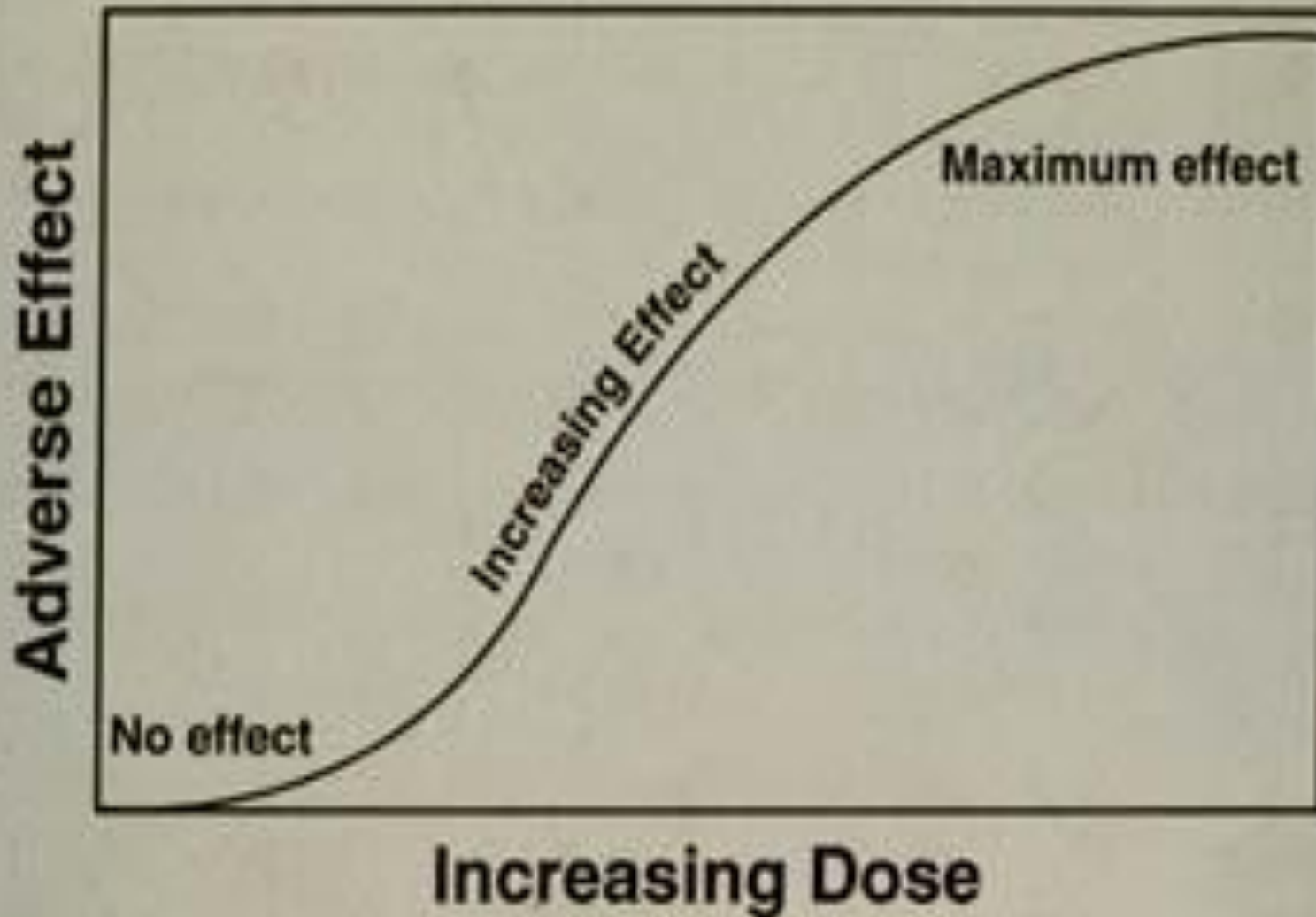
Concentration & Effect Dose Response Curve

- One way to monitor the amount of a drug in the body and its effect at the site of action is to use a dose-response curve.
 - By increasing the dose of Tylenol® you measure the degree of relief and you graph the results.
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Concentration & Effect Dose Response Curve

- A specific dose is administered to many subjects and the effect is measured.
 - Some people respond to low doses and others require a higher dose to get an equal response. This is called **human variation**.
 - Not ideal for relating the amount of drug in the body to its effect.
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Concentration & Effect Dose Response Curve



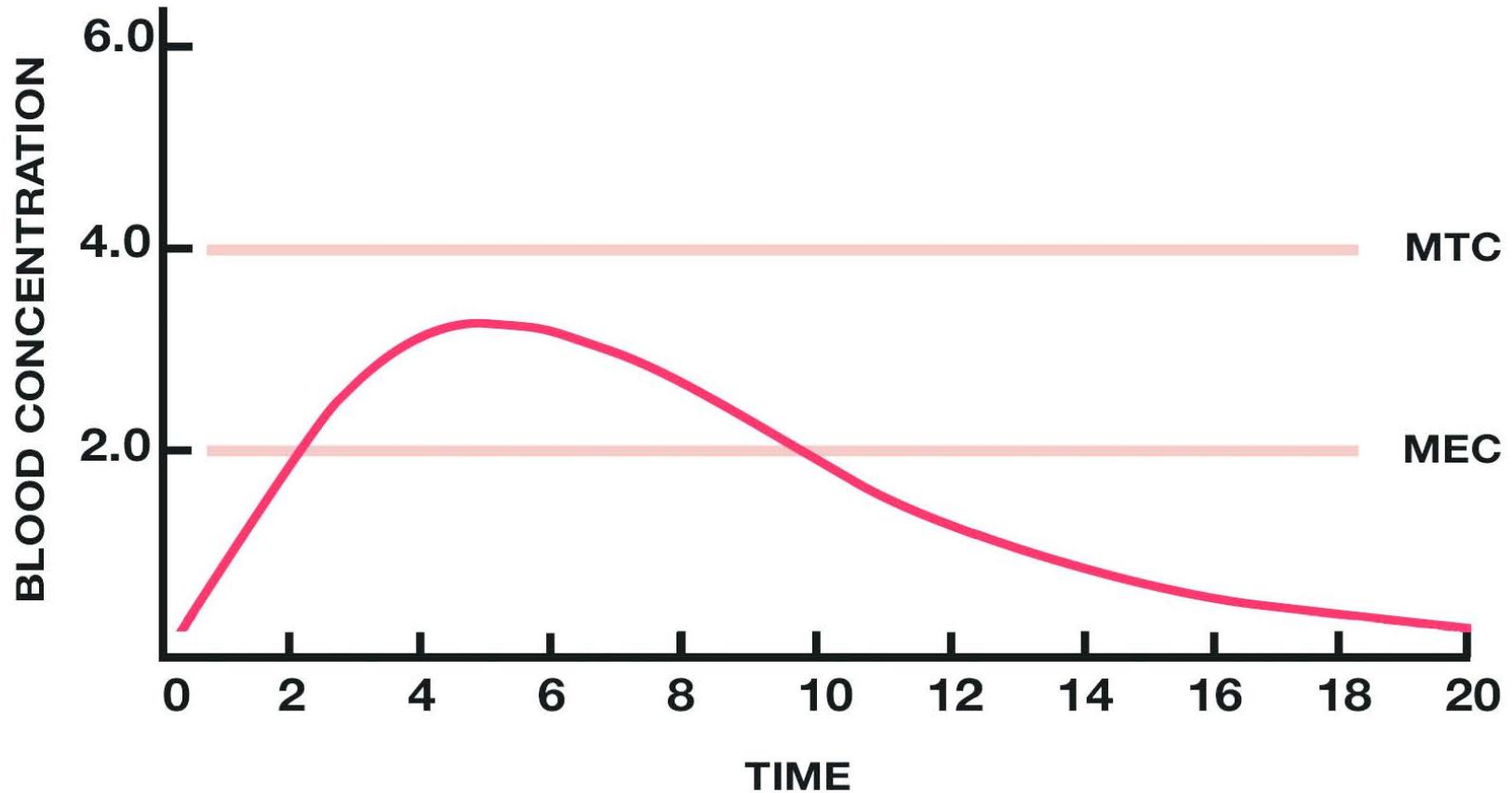
Concentration and Drug Effect

- A better way is to relate the effect to the amount of drug in the body.
 - Its effect is to determine drug concentrations in the body's fluids.
 - **Blood is generally used** because of its rapid equilibrium between the site of administration and the site of action.
 - Knowing a drug's concentration in the blood can be directly related to its effect.
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Blood Concentration-Time Profiles

- **Minimum effective concentration (MEC)**
 - Smallest concentration of the drug that is sufficient to cause an effect.
 - **Minimum Toxic Concentration (MTC):**
 - Smallest concentration beyond which there are undesirable or toxic effects.
 - **Therapeutic window**
 - Range between MEC and MTC.
 - **Duration of action**
 - Time the drug should be above the MEC.
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Blood Concentration-Time Profiles



A blood concentration-time profile

ADME Processes & Diffusion

- The blood concentrations are the result of four simultaneously occurring processes.
 - **ADME** are aspects of elements of a drug disposition.
 - * **A**bsorption
 - * **D**istribution
 - * **M**etabolism
 - * **E**xcretion
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How Drugs Move Through the Body

- **Absorption**

- Process by which a drug is transferred from the dosage form to the blood.

- **Distribution**

- Drug travels through the blood and into various cells or tissues.
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How Drugs Move Through the Body

Metabolism

- Chemical changes made to the drug by the body, often by the liver but sometimes by the gastrointestinal tract wall, kidneys lungs or blood.

Excretion

- Most drugs and their metabolites are excreted by the kidneys through urine.
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Half-life

- Amount of time it takes for the blood concentration of a drug to decline to **one-half an initial value**.
- **Example** – Estimate the half-life.

Time	Concentration
at 6 hrs	30 mcg/ml
at 15 hrs	15 mcg/ml

Answer: 15 hours minus 6 hours = 9 hours

Half-life

Five times the half-life is used to estimate how long it takes to essentially remove the drug from the body.

- This would be 5 x the half-life of 9 hours or 45 hours.
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Initial dose/ []

Half-Life	New []	Amt Eliminated	
1st	5 mg	5 mg	
2nd	2.5 mg	2.5 mg	
3rd	1.25 mg	1.25 mg	
4th	0.625 mg	0.625 mg	
5th	0.3125 mg	0.3125 mg	9.6875
6th	0.15625 mg	0.15625 mg	
7th	0.078125 mg	0.078125 mg	
8th	0.039063 mg	0.039063 mg	
9th	0.019531 mg	0.019531 mg	
10th	0.004883 mg	0.004883 mg	0.297852

Ionization and Unionization

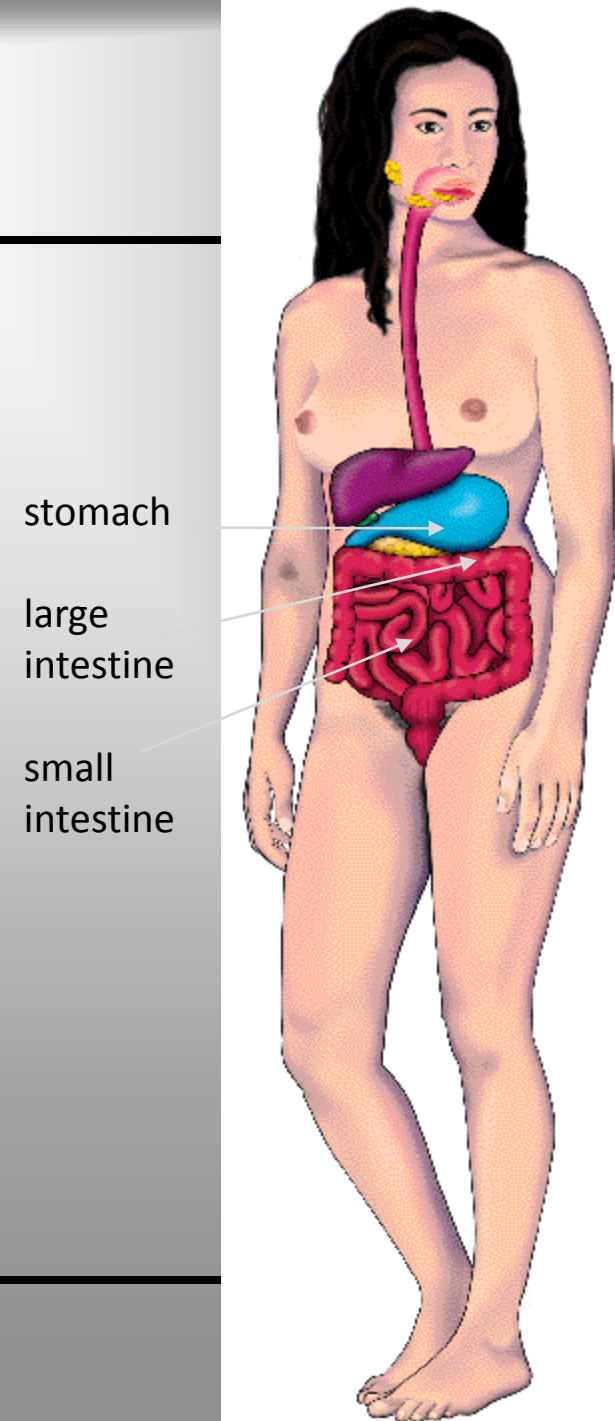
- Most drugs are **weak acids or bases**.
 - They **dissociate** (come apart) and **associate** (reattach to other chemicals) in solutions.
 - When **acids** dissociate, they become **ionized**.
 - When **bases** dissociate, they become **unionized**.
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Ionization and Unionization

- **Unionized drugs penetrate biological membranes more EASILY than ionized drugs.**
 - Unionized drugs are more lipid soluble.
 - Charges on biological membranes bind or repel ionized drugs.
 - Ionized drugs associate with water molecules, creating larger particles with reduced penetrating capability.
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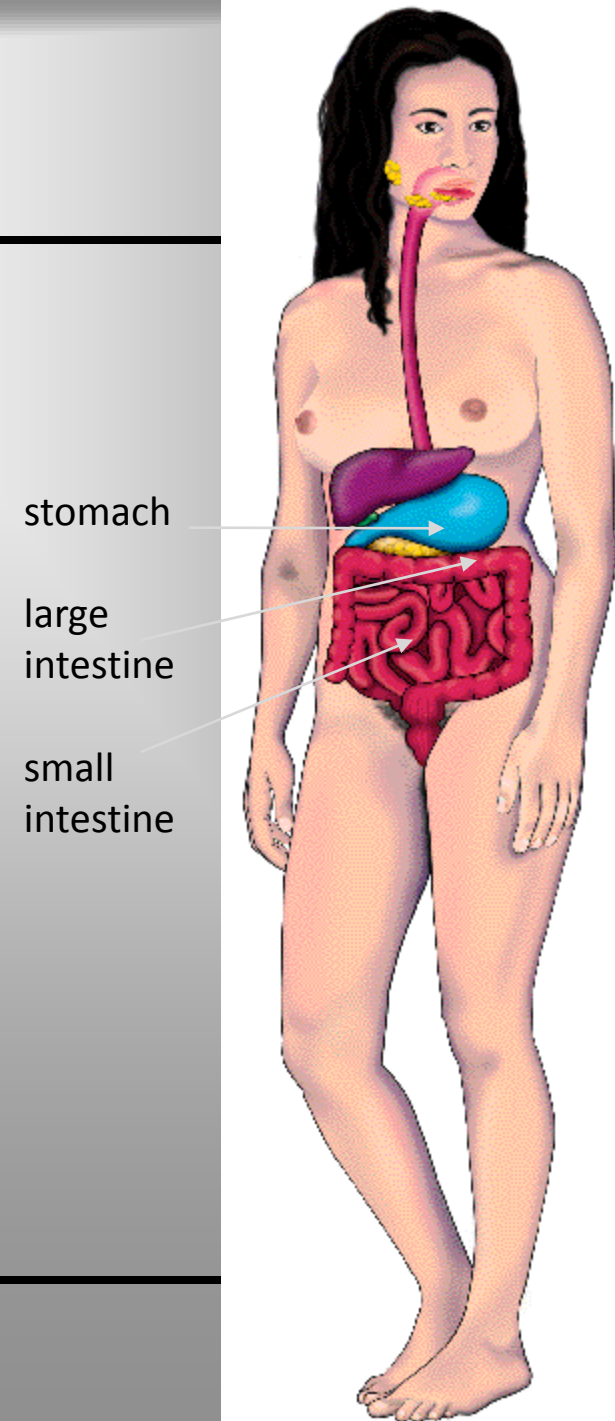
Absorption

- **Absorption**
 - The process where a drug is taken up from the site of administration and is transported to the blood stream.
- Absorption occurs **orally, topically, rectally, and by inhalation.**



Absorption

- **Gastric emptying time**
 - The time a drug will stay in the stomach before it is emptied into the small intestine.
- Most drugs are given orally and absorbed into the blood **from the small intestine.**



Distribution

- **Distribution**

- Movement of a drug within the body once it reaches the blood to exert its pharmacological effects.

- **The first pass effect**

- Occurs with drugs given orally and a portion of the drug is eliminated before distribution throughout the body.

Distribution

- **Protein Binding**
 - Many drugs bind to proteins in blood plasma to form a complex that is too large to penetrate cellular openings.
 - The drug remains inactive.
 - Rapidly administered **intravenous solutions** (i.e., bolus) do not have an absorption site.
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Metabolism

- **Metabolism**

- Breakdown of a drug or the disappearance of a drug from the body.
 - Takes place in many body organs primarily in the **liver**.
 - The breakdown of drugs into metabolites is caused by **Enzymes**.
 - The transformed drug is called **metabolite**.
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Metabolism

- **Enzymes**

- Complex proteins that catalyze (facilitate) chemical reactions into other substances.

- **Enterohepatic Cycling**

- The transfer of drugs and their metabolites from the liver to the bile in the gall bladder, then into the intestine, and then back into circulation.
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Metabolism

- **First-Pass Metabolism**

- With oral administration, before it reaches the circulatory system, the drug has to go through the liver. During this process it can be substantially degraded or destroyed by the liver's enzymes. This is called “first-pass metabolism”.
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Metabolism

- **Enzyme induction**
 - the increase in hepatic enzyme activity that results in greater metabolism of drugs.
 - **Enzyme inhibition**
 - the decrease in hepatic enzyme activity that results in reduced metabolism of drugs.
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Excretion

- **Excretion:** the process by which the drug is eliminated from the body primarily by the **kidney**
 - Drugs can be excreted **through urine, feces, lungs, skin, etc.**
 - The kidneys filter the blood and remove waste materials including drugs and metabolites.
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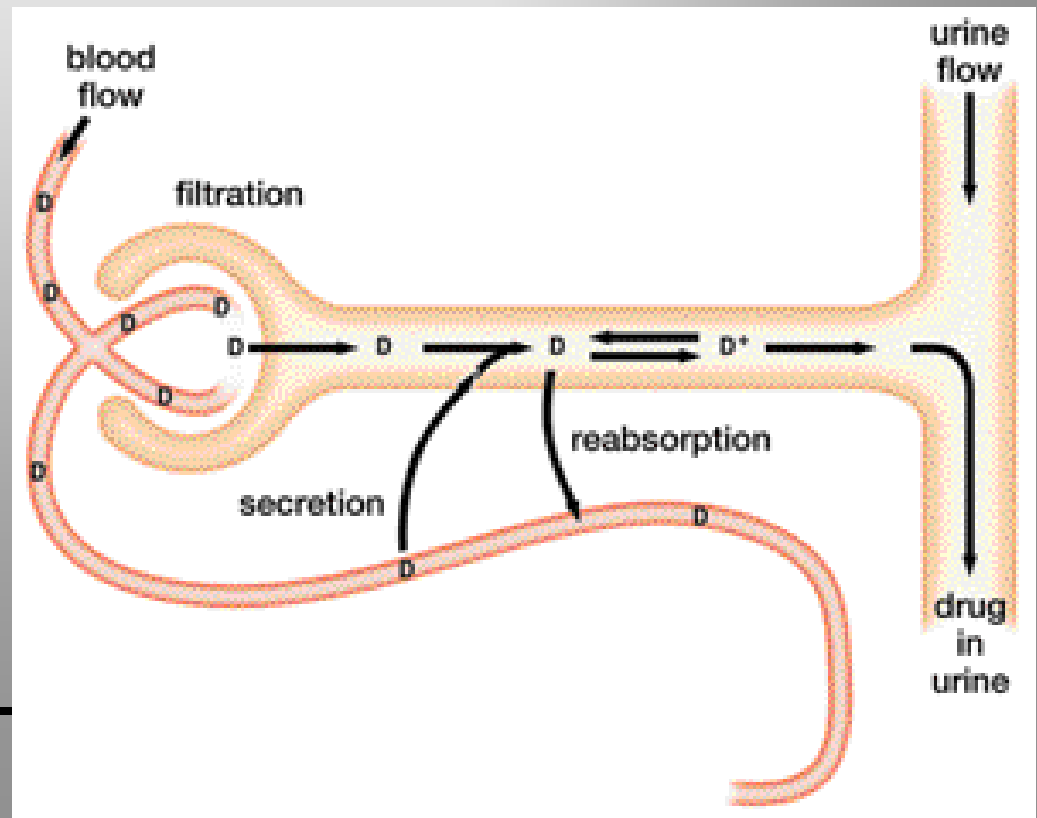
Excretion

- **Nephron** is the functional unit of the kidney involved in filtration of waste products from the body.
 - Most drugs and their metabolites are eliminated in the urine by the kidneys by the process called **glomerular filtration**.
 - **Elimination** is the term used for **metabolism and excretion**.
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Excretion

The three processes of nephrons:

- Glomerular filtration
- Secretion
- Reabsorption



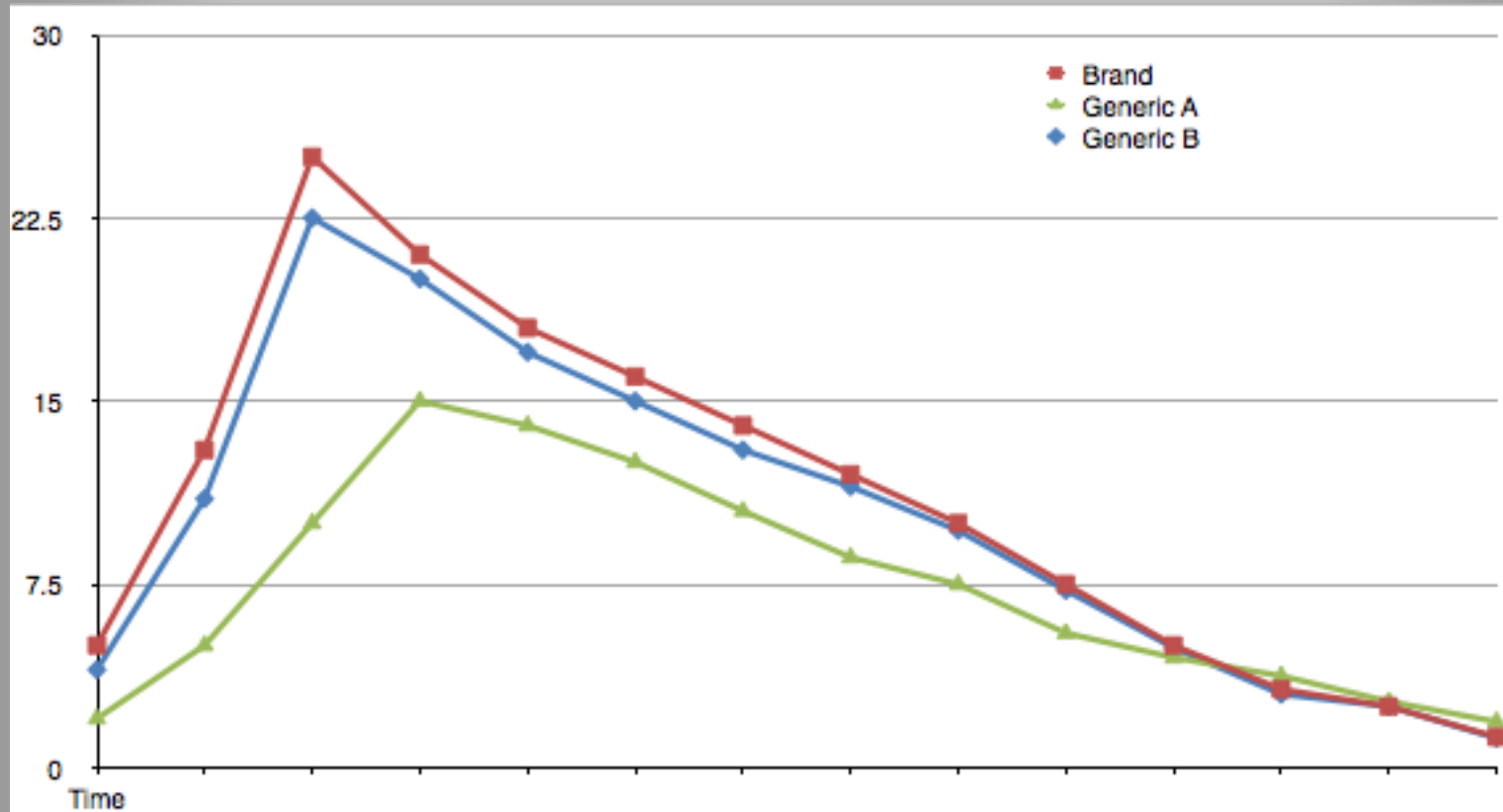
Bioequivalence

- **Bioavailability**
 - The amount of a drug that is delivered to the site of action.
 - The rate at which it becomes available.
 - **Bioequivalent**
 - Drugs that have the same bioavailability
 - **Absolute Bioavailability**
 - **Relative bioavailability**
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Bioequivalence

- **Pharmaceutical Equivalent**
 - Similar bioavailability and include
 - active ingredients
 - drug amounts
 - dosage form
 - They may **NOT** have the same **Inactive ingredients**.
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Pharmaceutical Equivalents



Bioequivalence

- **Pharmaceutical Alternative**

- Drug products that have

- same active ingredients (different salt)
- amounts can be different
- dosage form can be different
- inactive ingredients can be different

- **Therapeutic Equivalents**

- Drug products that produce the same effects in patients.

Orange Book

- The FDA annually publishes *Approved Drug Products With Therapeutic Equivalence Evaluations*.
- It is available online at:

www.fda.gov/cder/ob/default.htm

Terms to Remember

1. Metabolite
 2. Minimum effective concentration
 3. Minimum toxic concentration
 4. ADME
 5. Onset of action
 6. Passive diffusion
 7. Pharmaceutical alternative
 8. Pharmaceutical equivalent
 9. Protein binding
 10. Receptor
 11. Selective (action)
 12. Site of action
 13. Therapeutic equivalent
 14. Therapeutic window
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