

Pharmacokinetics

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Areas of Pharmacology

Pharmacodynamics:

Is what the drug does to the body, which includes the biochemical and physiological effects of the drug, including the mechanism of action, interaction with receptors as well as the adverse effects.

Areas of Pharmacology

Pharmacokinetics:

- **Is what the body does to the drug.**
- **Deals with absorption, distribution, biotransformation and excretion of drugs:**
 1. **Absorption: Is the movement of drug molecules from the site of administration into the circulation.**
 2. **Distribution: Is the movement of drug molecules from the circulation to tissues and between different parts of the body.**

Areas of Pharmacology

- 3. Biotransformation: Is conversion of the drug from one chemical structure into another by the action of metabolic enzymes (metabolism).**
- 4. Excretion: Is the movement of drug molecules out of the body.**

Pharmacokinetics & Pharmacodynamics

Dosage form



Disintegration



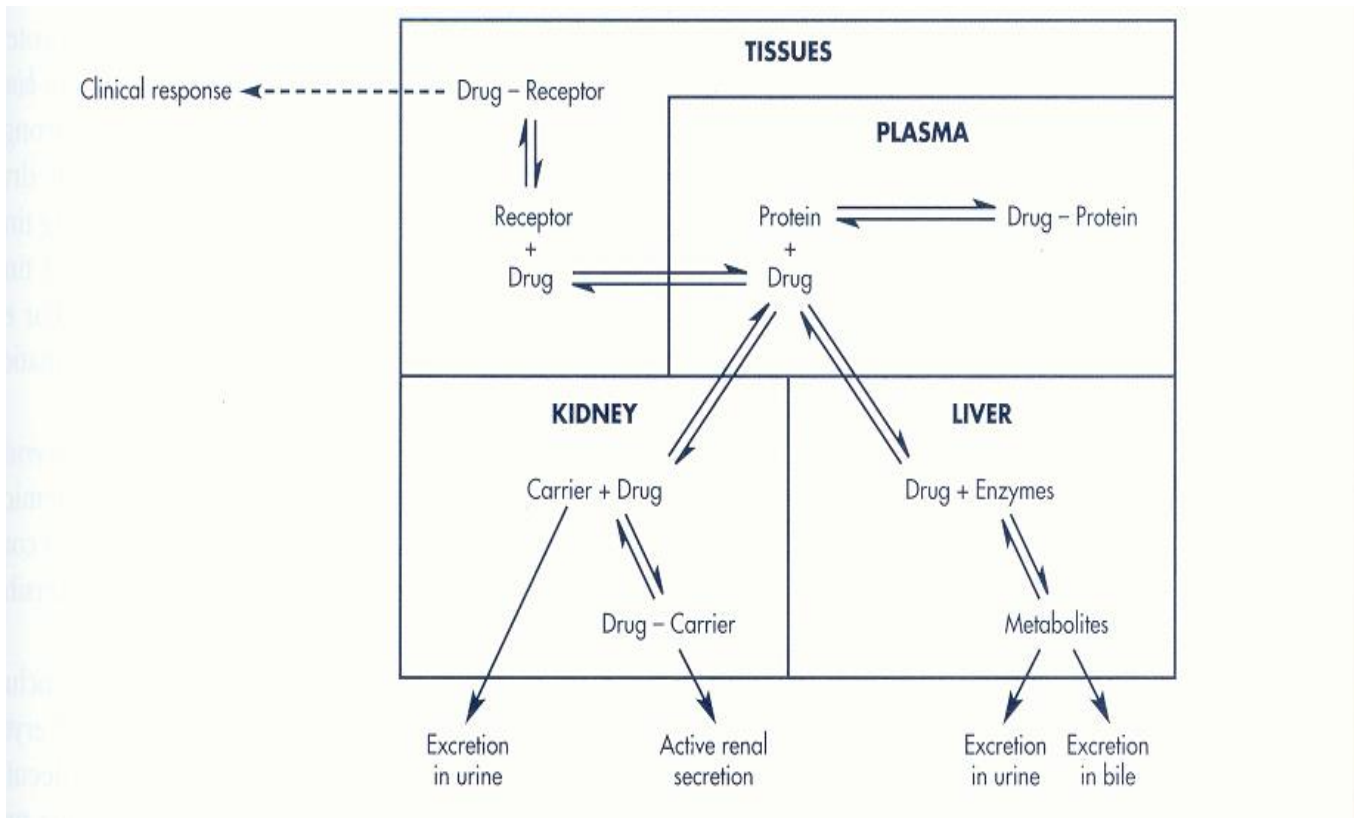
Dissolution



absorption

Drug in the systemic circulation

Drug Disposition



Primary Principles

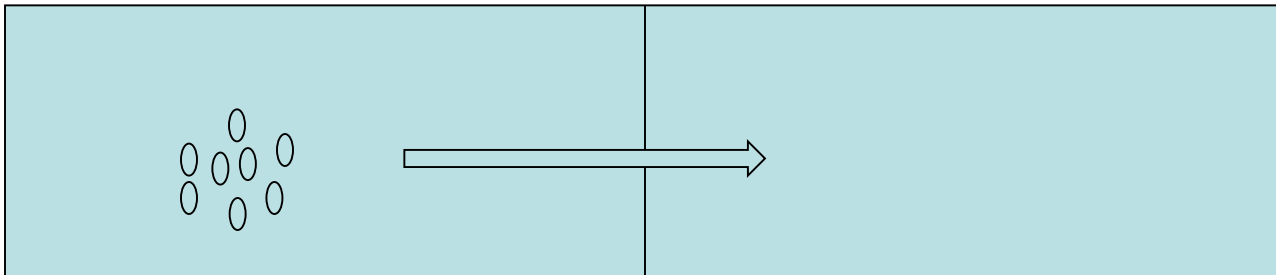
- **The goal of therapeutics is to achieve a desired beneficial effect with the minimal adverse effects possible.**
- **The clinician must determine the dose that most closely achieves this goal.**
- **A fundamental hypothesis of pharmacology is that a relationship exists between a beneficial or toxic effect of a drug and the concentration of the drug at the site of action (or in the blood).**

Mechanisms of Permeation of Drug Molecules

- The drug has to reach the site of action in order to be effective.
 - The movement of the drug between compartments requires passage through membranes.
- 1. Lipid diffusion (Passive diffusion):**
 - The most important mechanism.
 - The drug dissolves in the membrane.

Mechanisms of Permeation of Drug Molecules

- The more lipid soluble is a drug the more will be the passage across membranes, and vice versa.
- The drug has to be sufficiently water soluble to reach the membrane.
- The drug follows the concentration gradient.



Fick's Law of Diffusion

- **Governs passive flux of molecules across membranes.**
- **Flux (molecules/unit time) = $C_1 - C_2 \times [(Area \times Permeability \ coefficient) / Thickness]$**

C_1 is the higher concentration and C_2 is the lower concentration; area is the area across which diffusion occurs; permeability coefficient is a measure of the mobility of drug molecules in the medium of diffusion path; and thickness is the thickness or length of diffusion path.

Mechanisms of Permeation of Drug Molecules

- Most drugs are either weak acids or weak basis.**
- Therefore the pKa of the drug and the pH of the medium will affect lipid solubility of the drug and its passage across membranes.**
- Ionized drug molecules are polar and water soluble, whereas unionized drug molecules are nonpolar and lipid soluble.**

Mechanisms of Permeation of Drug Molecules

Ionization of weak acids and basis:

- **A weak acid** is a neutral molecule that can reversibly dissociate into an anion (negatively charged molecule) and a proton (a hydrogen ion).

R-COOH
Lipid soluble



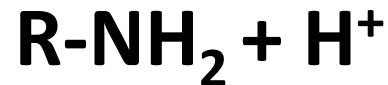
R-COO⁻ + H⁺
water soluble

Mechanisms of Permeation of Drug Molecules

- **A weak base** is a neutral molecule that can form a cation (positively charged molecule) by combining with a proton.



Water soluble



Lipid soluble

Mechanisms of Permeation of Drug Molecules

- These reactions move to the left in an acid environment and to the right in an alkaline environment.

Henderson-Hasselbalch Equation:

$$\text{Log} [\text{protonated}/\text{unprotonated}] = \text{pKa} - \text{pH}$$

- This equation applies to both acidic and basic drugs.

Mechanisms of Permeation of Drug Molecules

Examples:

1. **Pyrimethamine as a weak base drug with a pKa of 7.0.**

What is the proportion of ionized and unionized drug in blood (pH = 7.4) and urine (pH = 6)?

Mechanisms of Permeation of Drug Molecules

- **Blood:**

$$\text{Log (prot/unprot)} = \text{pKa} - \text{pH} = 7 - 7.4 = - 0.4$$

$$\text{Prot/unprot} = 10^{-0.4} = 0.4:1 = 0.4/1.4$$

- **Urine:**

$$\text{Log (prot/unprot)} = \text{pKa} - \text{pH} = 7 - 6 = 1$$

$$\text{Prot/unprot} = 10^1 = 10:1 = 10/11.$$

Mechanisms of Permeation of Drug Molecules

2. Phenobarbital is a weak acid with a pKa of 7.4.

What is the proportion of ionized and unionized drug in blood (pH = 7.4) and urine (pH = 6)?

Mechanisms of Permeation of Drug Molecules

- **Blood:**

$$\begin{aligned}\text{Log (prot/unprot)} &= \text{pKa} - \text{pH} \\ &= 7.4 - 7.4 = 0\end{aligned}$$

$$\text{Prot/Unprot} = 10^0 = 1:1 = 1/2$$

- **Urine:**

$$\begin{aligned}\text{Log (prot/unprot)} &= \text{pKa} - \text{pH} \\ &= 7.4 - 6 = 1.4\end{aligned}$$

$$\text{Prot/Unprot} = 10^{1.4} = 25:1 = 25/26$$

TABLE 1–3 Ionization constants of some common drugs.

Drug	pK _a ¹	Drug	pK _a ¹	Drug	pK _a ¹
Weak acids		Weak bases		Weak bases (cont'd)	
Acetaminophen	9.5	Albuterol (salbutamol)	9.3	Isoproterenol	8.6
Acetazolamide	7.2	Allopurinol	9.4, 12.3 ²	Lidocaine	7.9
Ampicillin	2.5	Alprenolol	9.6	Metaraminol	8.6
Aspirin	3.5	Amiloride	8.7	Methadone	8.4
Chlorothiazide	6.8, 9.4 ²	Amiodarone	6.6	Methamphetamine	10.0
Chlorpropamide	5.0	Amphetamine	9.8	Methyldopa	10.6
Ciprofloxacin	6.1, 8.7 ²	Atropine	9.7	Metoprolol	9.8
Cromolyn	2.0	Bupivacaine	8.1	Morphine	7.9
Ethacrynic acid	2.5	Chlordiazepoxide	4.6	Nicotine	7.9, 3.1 ²
Furosemide	3.9	Chloroquine	10.8, 8.4	Norepinephrine	8.6
Ibuprofen	4.4, 5.2 ²	Chlorpheniramine	9.2	Pentazocine	7.9
Levodopa	2.3	Chlorpromazine	9.3	Phenylephrine	9.8
Methotrexate	4.8	Clonidine	8.3	Physostigmine	7.9, 1.8 ²
Methyldopa	2.2, 9.2 ²	Cocaine	8.5	Pilocarpine	6.9, 1.4 ²
Penicillamine	1.8	Codeine	8.2	Pindolol	8.6
Pentobarbital	8.1	Cyclizine	8.2	Procainamide	9.2
Phenobarbital	7.4	Desipramine	10.2	Procaine	9.0
Phenytoin	8.3	Diazepam	3.0	Promethazine	9.1
Propylthiouracil	8.3	Diphenhydramine	8.8	Propranolol	9.4
Salicylic acid	3.0	Diphenoxylate	7.1	Pseudoephedrine	9.8
Sulfadiazine	6.5	Ephedrine	9.6	Pyrimethamine	7.0–7.3 ³
Sulfapyridine	8.4	Epinephrine	8.7	Quinidine	8.5, 4.4 ²
Theophylline	8.8	Ergotamine	6.3	Scopolamine	8.1
Tolbutamide	5.3	Fluphenazine	8.0, 3.9 ²	Strychnine	8.0, 2.3 ²
Warfarin	5.0	Hydralazine	7.1	Terbutaline	10.1
		Imipramine	9.5	Thioridazine	9.5

¹The pK_a is that pH at which the concentrations of the ionized and nonionized forms are equal.²More than one ionizable group.³Isoelectric point.

Mechanisms of Permeation of Drug Molecules

- The lower the pH relative to the pKa, the greater will be the fraction of the drug in the protonated form.
- Acids in an acid environment are unionized (non-polar).
- Bases in an alkaline environment are unionized (non-polar).

Mechanisms of Permeation of Drug Molecules

- The protonated weak acid is neutral and more lipid soluble.**
- The unprotonated weak base is neutral and more lipid soluble.**
- In an acid environment, the acidic drug is neutral while the basic drug is ionized.**
- In an alkaline environment, the acidic drug is ionized while the basic drug is neutral.**

Mechanisms of Permeation of Drug Molecules

Application:

Manipulation of drug excretion by the kidney:

- If the drug is filtered in urine in unionized form, it will be reabsorbed by renal tubules.
- If we want to accelerate excretion of drug from the body (in case of overdose), it is important to ionize the drug within the renal tubules to reduce reabsorption.

Mechanisms of Permeation of Drug Molecules

- This can be accomplished by changing urine pH.
- Weak acids are excreted faster in alkaline urine. Urine can be alkalinized by sodium bicarbonate (NaHCO_3) given orally or intravenously.
- Weak basis are excreted faster in acidic urine. Urine can be acidified by ascorbic acid (vitamin C) or ammonium chloride (NH_4Cl).

Mechanisms of Permeation of Drug Molecules

2. **Aqueous diffusion:**

- Through aqueous pores in membranes.
- Occurs within the larger aqueous compartments of the body (Interstitial space, cytosol, etc), across epithelial membranes tight junctions, and the endothelial lining of blood vessels.
- Also driven by the concentration gradient.

Mechanisms of Permeation of Drug Molecules

- **Drugs bound to plasma proteins do not permeate aqueous pores.**
- **If the drug is charged, its flux is influenced by electrical fields (membrane potentials).**

Mechanisms of Permeation of Drug Molecules

3. Special carriers:

- **Exist for substances that are important for cell function and are too large or too insoluble in lipids to diffuse passively through membranes (peptides, amino acids, glucose, etc).**
- **They bring about drug movement by active transport or facilitated diffusion.**

Mechanisms of Permeation of Drug Molecules

- They are selective, saturable and inhibitable.
- Many cells contain less selective membrane carriers that are specialized in expelling foreign molecules including drugs:

A.ATP-binding cassette (ABC) family:

- It includes **P-glycoprotein** or the multidrug-resistance type 1 (MDR1) transporter found in the brain, intestine, testes, neoplastic cells, and other tissues.

Mechanisms of Permeation of Drug Molecules

B. The multidrug-resistance associated protein (MRP) transporters (also from the ABC family):

- They play a role in excretion of drugs and their metabolites into urine and bile.
- They mediate the resistance of some tumors to chemotherapeutic agents.

Mechanisms of Permeation of Drug Molecules

C. The solute carrier families (SLC):

- They **do not bind ATP** but **use ion gradients for transport energy.**
- They are important in the transport or the uptake of neurotransmitters across nerve ending membranes.

Mechanisms of Permeation of Drug Molecules

4. Endocytosis and exocytosis:

- Endocytosis is responsible for transport of vitamin B₁₂ complexed with the intrinsic factor across the wall of the gut into the blood, and iron associated with transferrin into RBCs.
- Exocytosis is responsible for secretion of many substances from cells such as neurotransmitters and some hormones.

Mechanisms of Permeation of Drug Molecules

- *These principles of permeation of drug molecules apply to drug absorption, distribution and elimination.*
- *These processes determine how rapidly and for how long the drug will appear in the target organ, the site of action, and organs of elimination.*

Barriers Against Drug Permeation & Transport

- 1. Tight junctions between endothelial cells and absence of pores.**
- 2. The presence of thick basement membrane at which endothelial cells lie.**
- 3. The presence of connective tissue cells around endothelial cells (such as astrocytes in the brain).**
- 4. The presence of drug export pumps.**

Barriers Against Drug Permeation & Transport

- 4. The presence of intracellular and extracellular enzymes that metabolize drugs.**
 - This occurs in endothelial cells of brain (blood-brain-barrier).**
 - It is present in other tissues such as testis.**

Placental Barrier

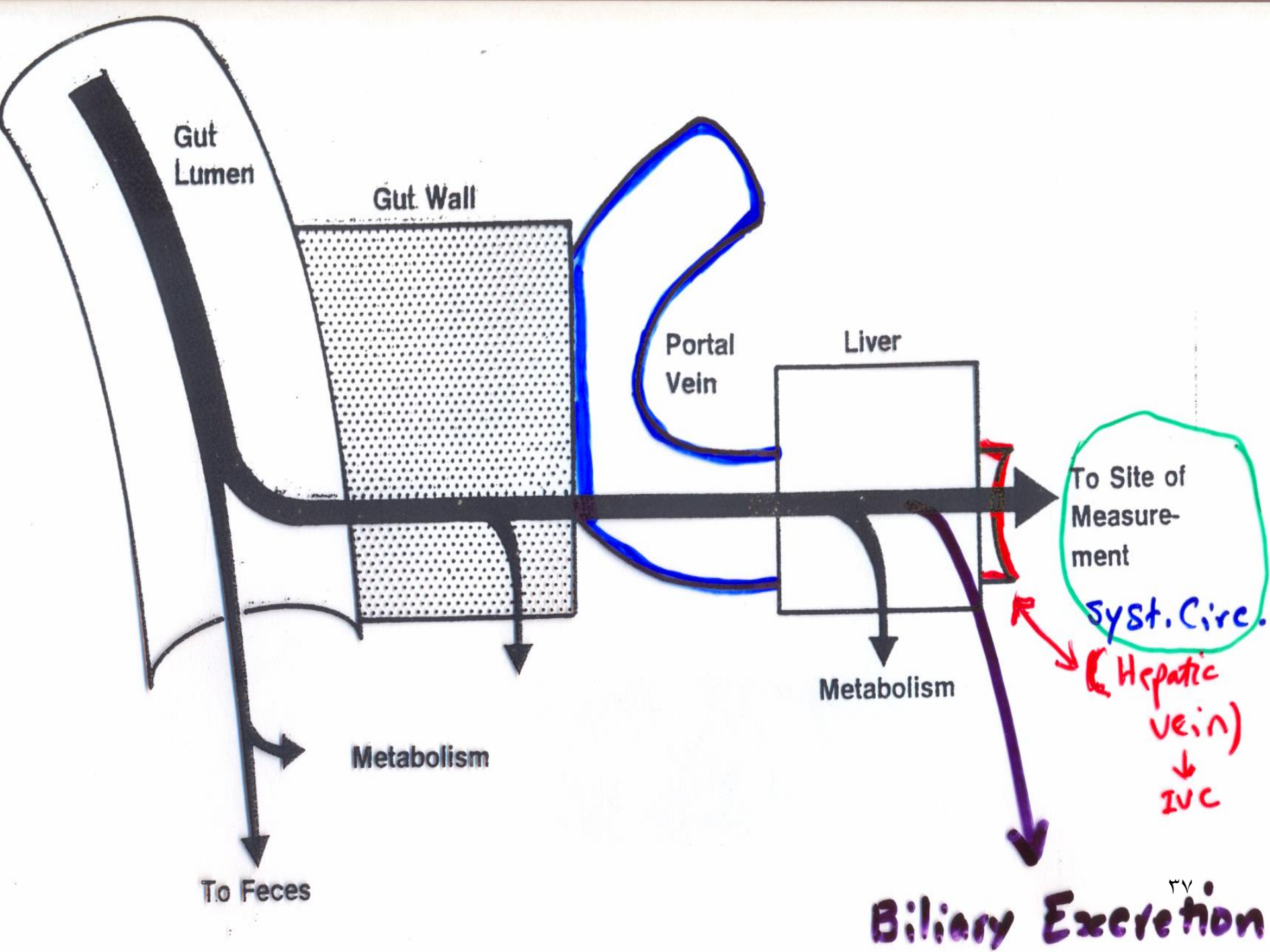
- **A semipermeable membrane made up of placental tissues, where the maternal and fetal circulations remain completely separated.**
- **Between cells, there are tight junctions that allow slow passage of ions and small molecules but restrict movement of larger molecules and certain drugs.**

First-Pass Effect

- **Drugs absorbed from the GIT must pass through the gut wall and portal vein to the liver before reaching the systemic circulation.**
- **The drug **may be** metabolized in the gut wall, portal vein, and the liver prior to entry to the systemic circulation.**
- **Or, it may get excreted by the liver through bile.**

First-Pass Effect

- This will lead to incomplete delivery of the dose given to the systemic circulation.
- This process is called “**first-pass effect**” or “**first-pass metabolism**” or “**pre-systemic elimination**”.



Gut Lumen

Gut Wall

Portal Vein

Liver

To Site of Measurement

Syst. Circ.

(Hepatic vein)
↓
IVC

Metabolism

Metabolism

To Feces

Biliary Excretion

rv

First-Pass Effect

- **Therapeutic blood concentration may still be reached by using larger dose. Therefore, the oral dose is usually higher than intravenous dose for such drugs.**
- **Also the concentration of drug metabolites after oral administration will be higher than after intravenous administration.**

First-Pass Effect

- **If the patient is having liver cirrhosis and there is shunting of blood by-passing the portal circulation, giving a larger dose orally will lead to substantial increases in concentration of the drug and drug toxicity.**

Bioavailability

- It is the fraction of the unchanged active drug reaching the systemic circulation, following drug administration; irrespective of the route.
- It is equal to “1” or 100% following intravenous drug administration.
- After oral administration, bioavailability may be less than 1, because of:

Bioavailability

- 1. First-pass effect.**
- 2. Incomplete absorption.**
- 3. Incomplete disintegration and dissolution.**
- 4. Destruction of drug within GIT lumen by gastric acid, bacteria, ..etc.**
- 5. Faulty manufacturing of the dosage form.**
- 6. Enterhepatic cycling.**

Bioavailability

- **The area under the blood concentration *versus* time curve (AUC) is a common measure of the extent of bioavailability.**
- **Causes of reduction of the extent of absorption:**

Bioavailability

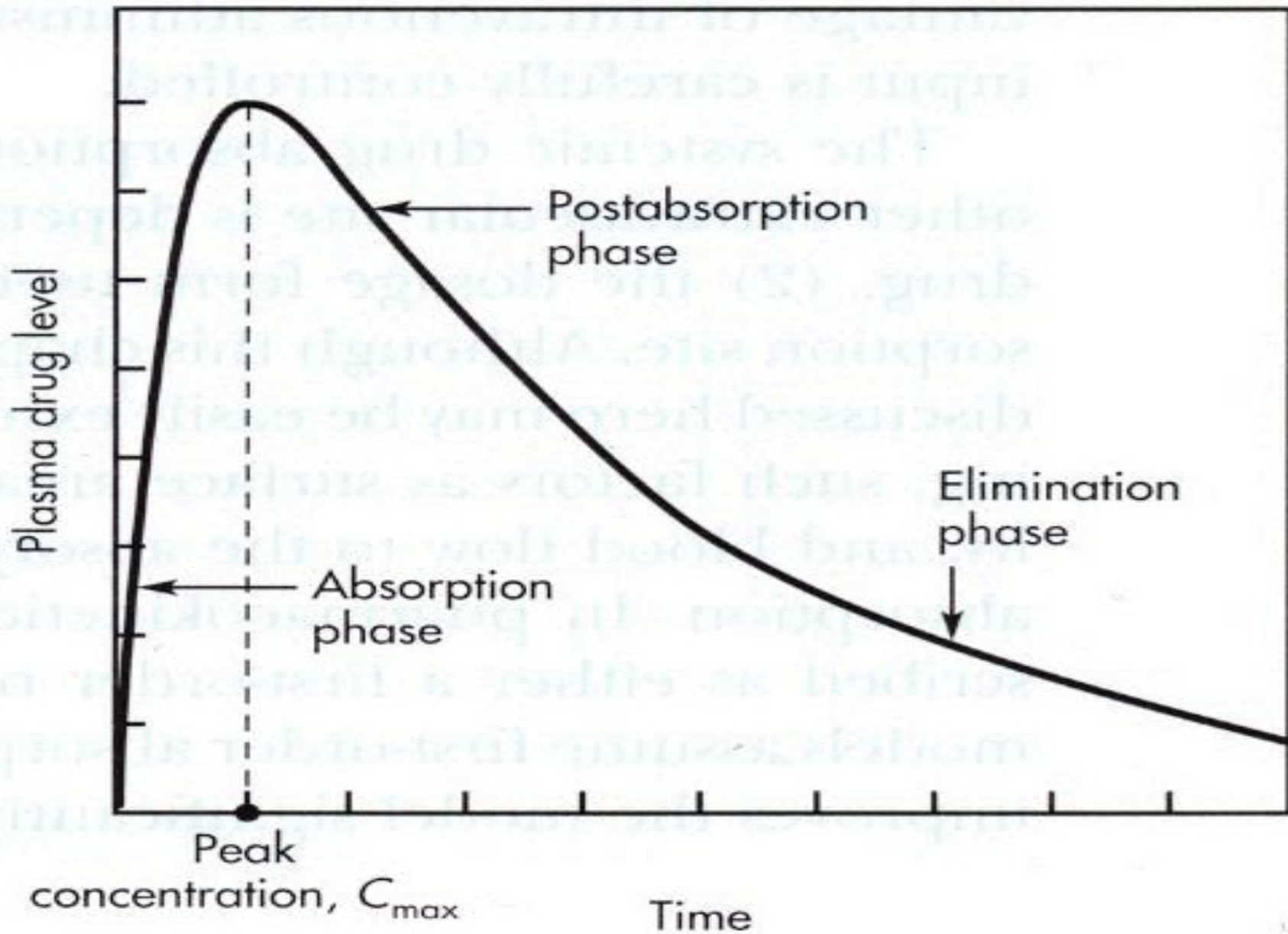
- 1. The drug may be too hydrophilic (atenolol), or too lipophilic (acyclovir), to be absorbed easily.**
 - Too hydrophilic drugs can NOT cross lipid membranes easily.**
 - Too lipophilic drugs are NOT water soluble enough to reach the membrane (to cross the water layer adjacent to the cell).**

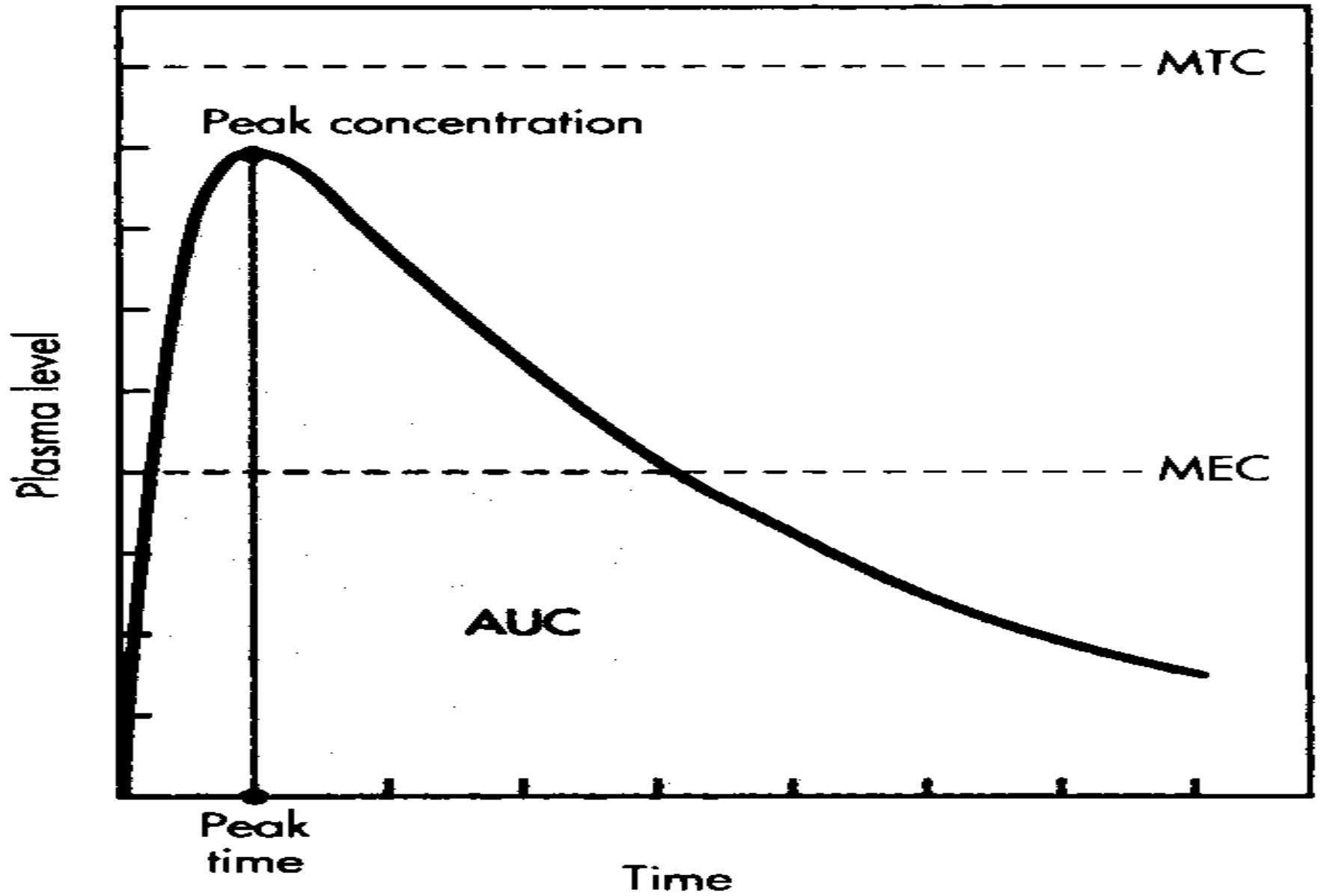
Bioavailability

- 2. Drugs may NOT be absorbed because of the presence of a reverse transporter (P-glycoprotein) that pumps the drug out of the gut wall cells back into the gut lumen.**

Bioavailability

- **Inhibition of the reverse transporter by the use of some drugs and grapefruit juice, may be associated with substantial increase in drug absorption and thus bioavailability.**
- **Grapefruit juice also inhibits presystemic elimination of some drugs, and thus, increases their bioavailability.**





Effect of First-Pass Effect on bioavailability

- The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):

- $ER = \text{Clearance}_{\text{liver}} / \text{Blood flow to the liver}$ (90 L/hour in a healthy 70 Kg man).

$$ER = Cl_{\text{liver}} / Q$$

- Bioavailability (F) can be predicted from the extent of absorption (f) and ER.

$$F = (f) \cdot (1 - ER)$$

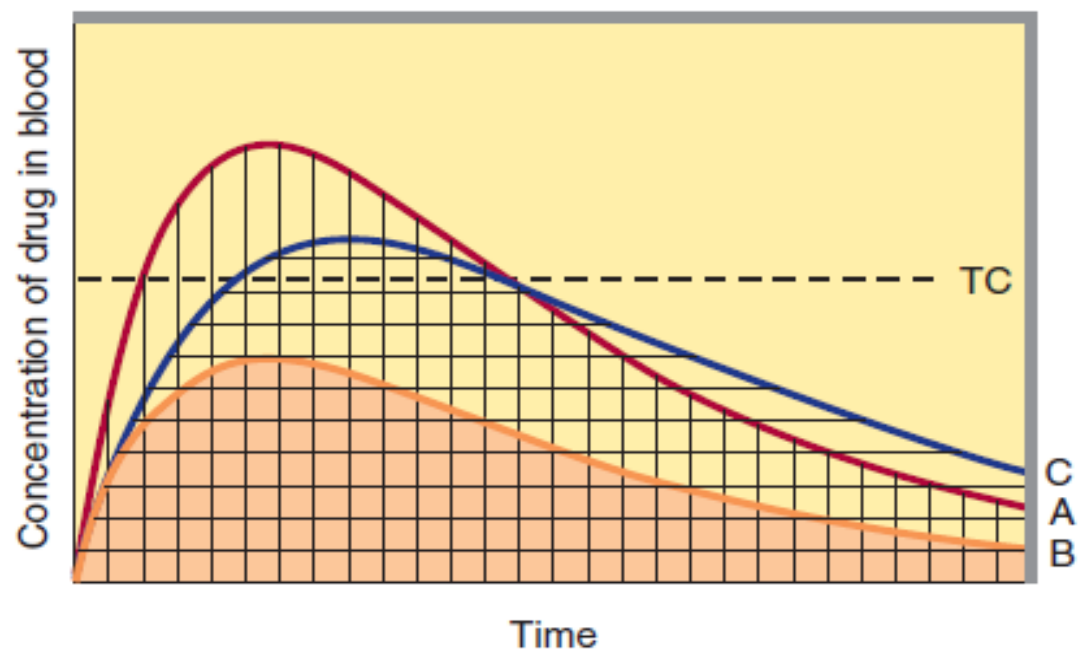
Effect of First-Pass Effect on bioavailability

- A drug like morphine is completely absorbed but its ER is 0.67, so its bioavailability is 33%.**
- Drugs with high extraction ratio exhibit interindividual differences in bioavailability and drug concentration, because of differences among individuals in hepatic blood flow and hepatic drug metabolism.**

Bioequivalence

- This term is used to compare the rate and extent of absorption of different formulations of the same active drug.
- The extent of absorption is measured by AUC, and the rate is assessed by C_{\max} (peak concentration) and T_{\max} (time to peak concentration).

Rate of B is also less than that of A





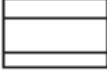
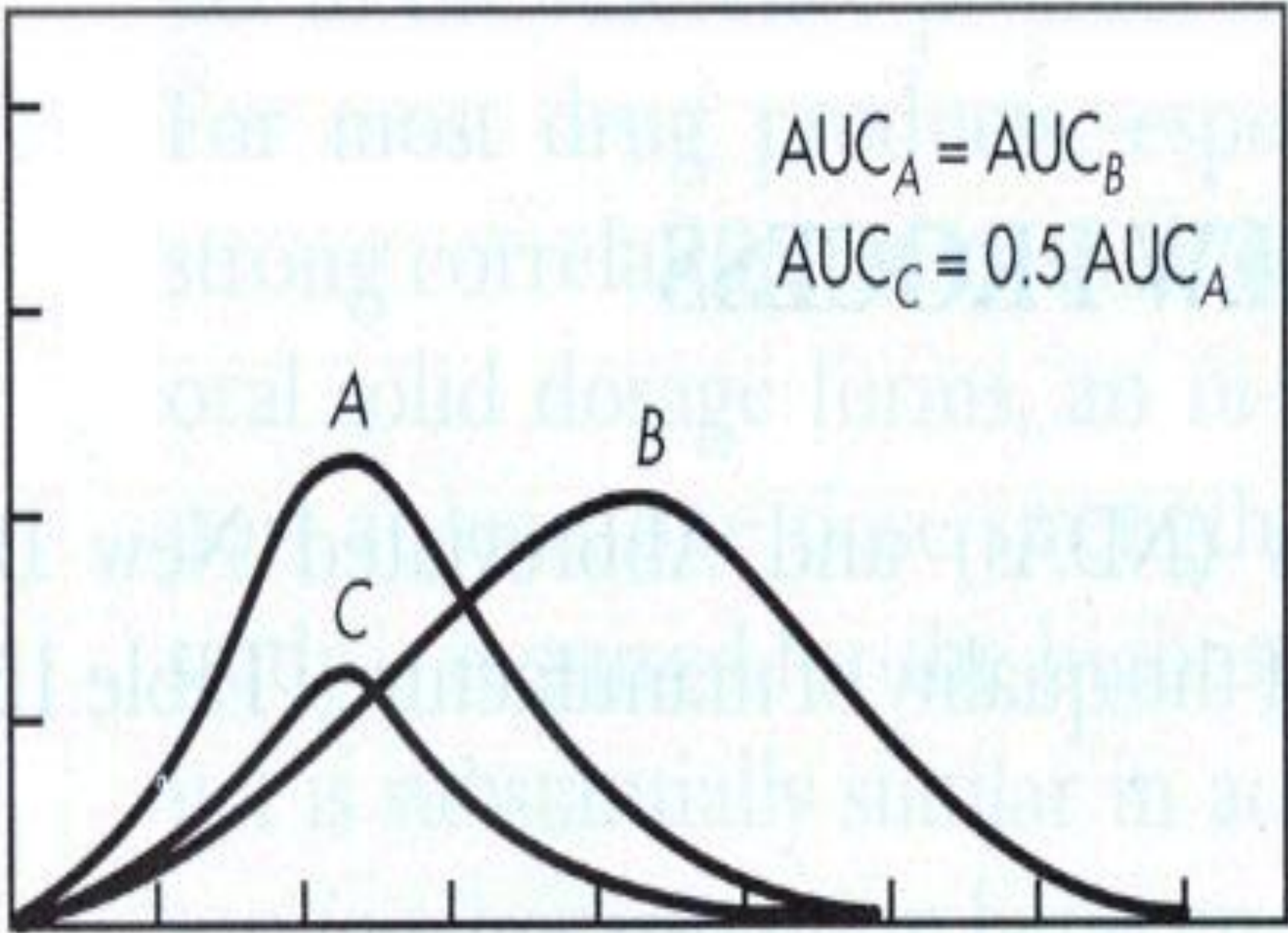
-  A: Drug rapidly and completely available
-  B: Only half of availability of A but rate equal to A
-  C: Drug completely available but rate only half of A

FIGURE 3-4 Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.

Plasma level



$$AUC_A = AUC_B$$

$$AUC_C = 0.5 AUC_A$$

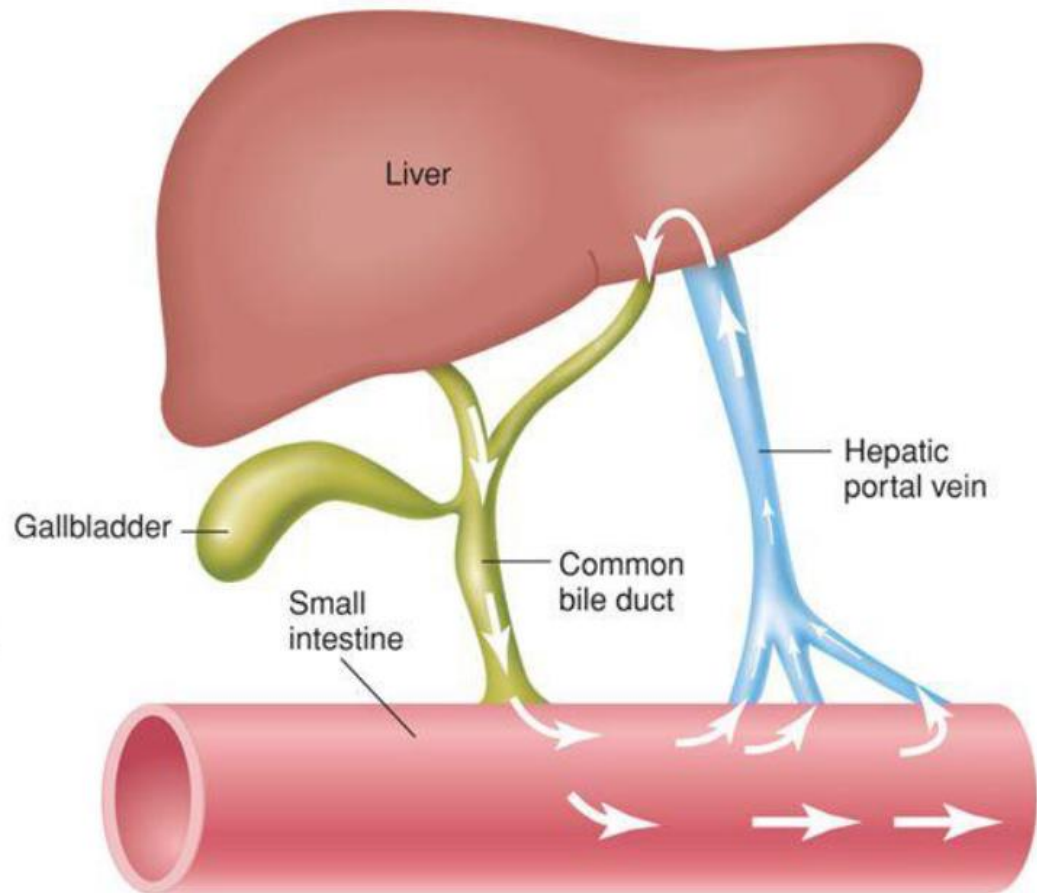
Time

Enterohepatic Cycling of Drugs

- **After oral administration and absorption, a drug can be excreted in bile before reaching the systemic circulation, go back to gut lumen, and then reabsorbed again.**
- **This is called enterohepatic cycling of the drug.**
- **It reduces drug bioavailability and prolongs its half-life of elimination.**

Enterohepatic Circulation

- ▶ Is recirculation of compounds between liver and intestine
- ▶ Many compounds are released in bile, reabsorbed in SI, and returned to liver to be recycled
- ▶ Liver excretes drug metabolites into bile to pass out in feces



Enterohepatic Cycling of Drugs

Application:

- This phenomenon can be taken advantage of in cases of drug overdose.
- Activated charcoal can adsorb many drugs and chemicals (except ionized ones) into its surface.
- If we give activated charcoal in cases of drug overdose, and the drug undergoes enterohepatic cycling, then the portion of the drug that is excreted into the gut through bile can be trapped and prevented from reabsorption back into the systemic circulation.

Enterohepatic Cycling of Drugs

- **This will accelerate drug elimination from the body and reduces its half-life of elimination.**

Volume of Distribution (V_D)

- It is the **size of body fluid** that would be required if the **drug molecules were to be homogeneously distributed through all parts of the body.**
- It reflects the **apparent space available for the drug in the tissues of distribution.**
- It does **NOT** represent a real volume.

Volume of Distribution (V_D)

- In a normal 70 Kg man, the volume of:
- But the volume of distribution for:

Plasma = 2.8 L
Blood = 5.6 L
ECF = 14 L
TBW = 42 L
Fat = 14 - 25 L

Aspirin = 11 L
Ampicillin = 20 L
Phenobarbital = 40 L
Digoxin = 640 L
Imipramine = 1600 L
Chloroquine = 13000 L

Volume of Distribution (V_D)

- The apparent volume of distribution **will be small** if the drug is **restricted to plasma**:
 1. due to binding to plasma proteins
 2. when it is highly ionized at plasma pH.
- The apparent volume of distribution **will be large** when the drug **distributes into tissues**.
- It relates the amount of the drug in the body (A_b), with its plasma concentration (C_p), such that: $V_D = A_b/C_p$

Drug Binding in Plasma

- **Albumin** is the most important drug-binding protein.
- **α_1 -Acid-glycoprotein** is also important for binding certain **basic** drugs.
- Binding to plasma proteins is mostly **reversible**.

Drug + Protein \rightleftharpoons Drug-Protein complex

D + P \rightleftharpoons DP

Drug Binding in Plasma

- The free unbound drug fraction (D) is **responsible for** the **pharmacological action** and is also available for **elimination**.
- The bound drug fraction (DP) is not so available, and it represents a reservoir for the drug.
- **One clinical importance of plasma protein binding of drugs is to help interpretation of measured plasma drug concentration of such drugs.**

Drug Binding in Plasma

- When plasma protein concentrations are lower than normal, then the total drug concentration will be lower than expected, but the free concentration may not be affected (**why?**).
- Plasma protein binding is also a **site for drug-drug interactions**.
- If a drug is displaced from plasma proteins it would increase the unbound drug concentration and **increase the drug effect** and, perhaps, **produce toxicity**.

Drug Binding in Plasma

- Drug displaced from plasma protein will of course distribute throughout the volume of distribution, and its rate of elimination will also increase, **thus, its plasma concentration will NOT increase dramatically.**

Drug Clearance (CL)

- It is the volume of blood or plasma that is completely cleared of drug per unit time.
- It is a measure of the ability of the body to **eliminate** (and **distribute**) the drug.
- Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration:

$$CL = \text{rate of elimination} / C_p$$

Drug Clearance (CL)

- Assume that the rate of elimination of a drug is 10 mg/hour, and the plasma concentration is 1 mg/L. What is drug clearance?
- $CL = [10 \text{ mg/hour}] / [1 \text{ mg/L}]$
= 10 L/hour

Drug Clearance (CL)

- There may be more than one method of elimination, and thus the rate of elimination will be the sum of all these methods.
- **Renal clearance (CL_R) = $C_u \cdot V / C_p$,**

where C_u is concentration of drug in urine, V is urine flow rate, and C_p is the plasma concentration of the drug.

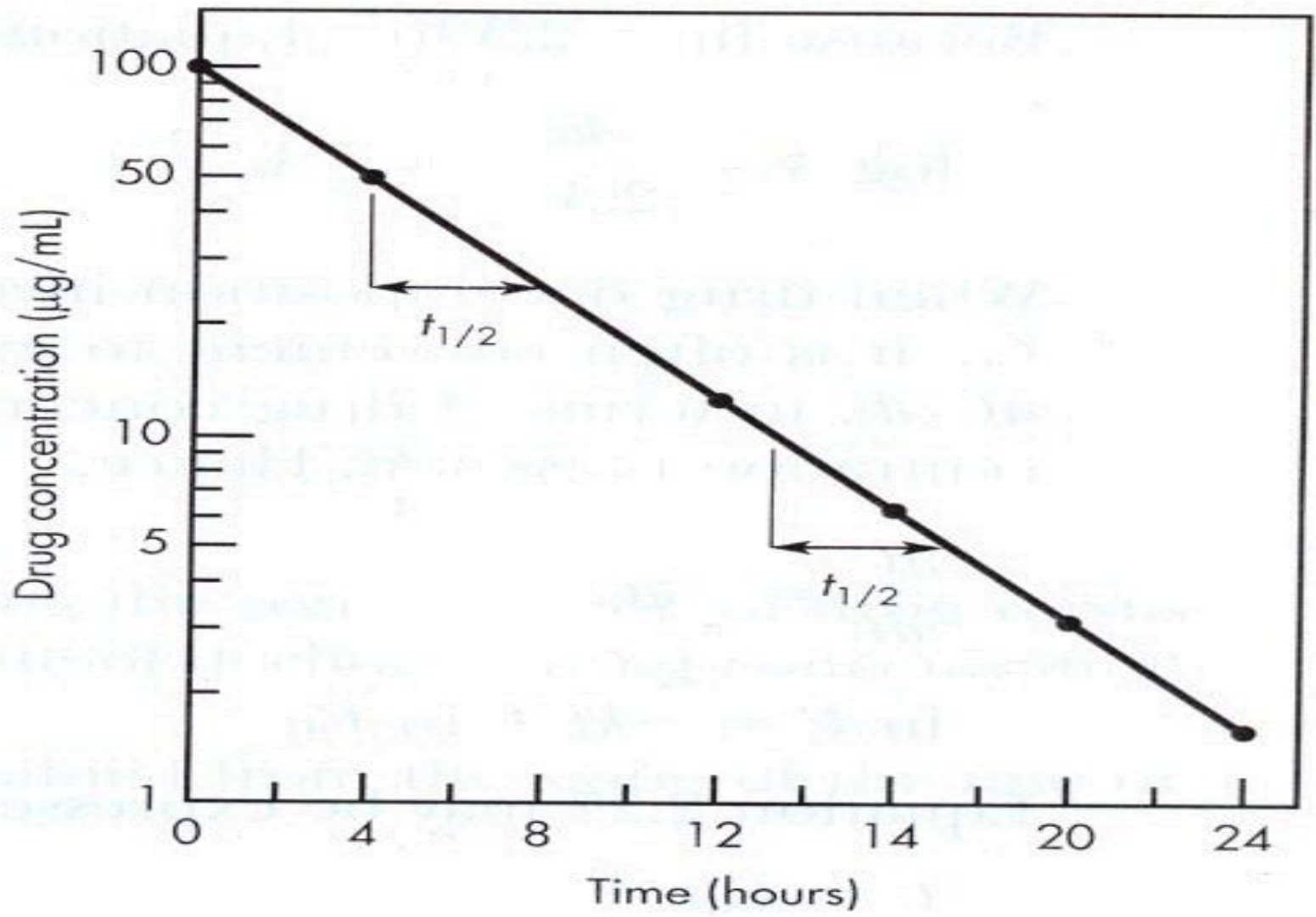
Drug Clearance (CL)

- **Hepatic clearance (CL_H) =**
 $[(\text{blood flow} \cdot C_i) - (\text{blood flow} \cdot C_o)] / C_i$
 $CL_H = \text{blood flow} (C_i - C_o) / C_i$
 $CL_H = Q \cdot ER$

C_i is drug concentration in blood going to the liver, C_o is drug concentration in blood leaving the liver, Q is blood flow, ER is the extraction ratio of the drug.

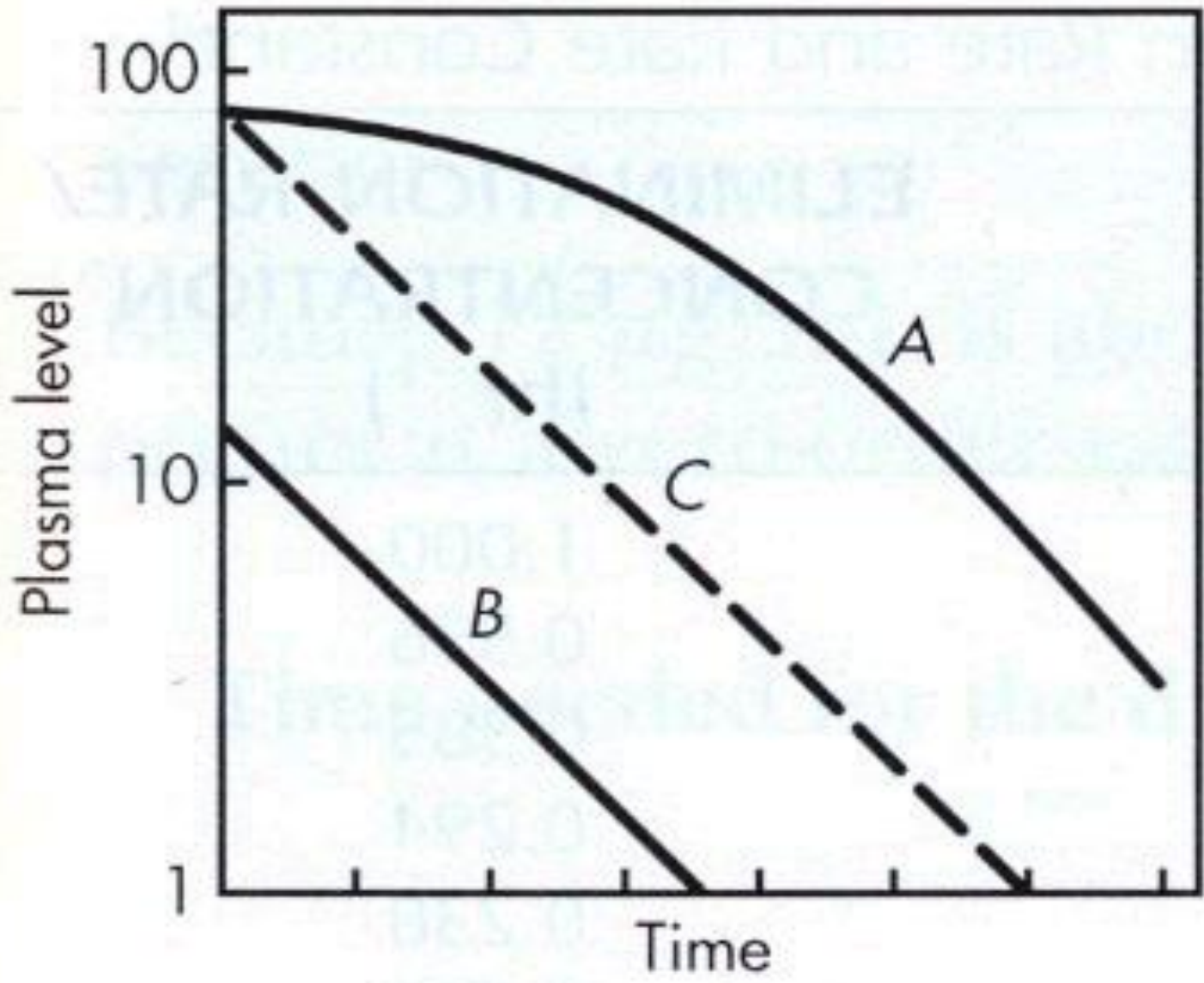
First-Order Drug Elimination

- It occurs when the rate of drug elimination is directly proportional to the amount of drug in the body.
- Occurs with many drugs at therapeutic concentrations.
- A constant fraction of the drug is eliminated per unit time.
- The elimination rate constant is designated as k , and its units are reciprocal time (1/time) meaning fraction per unit time.



Zero-Order Drug Elimination

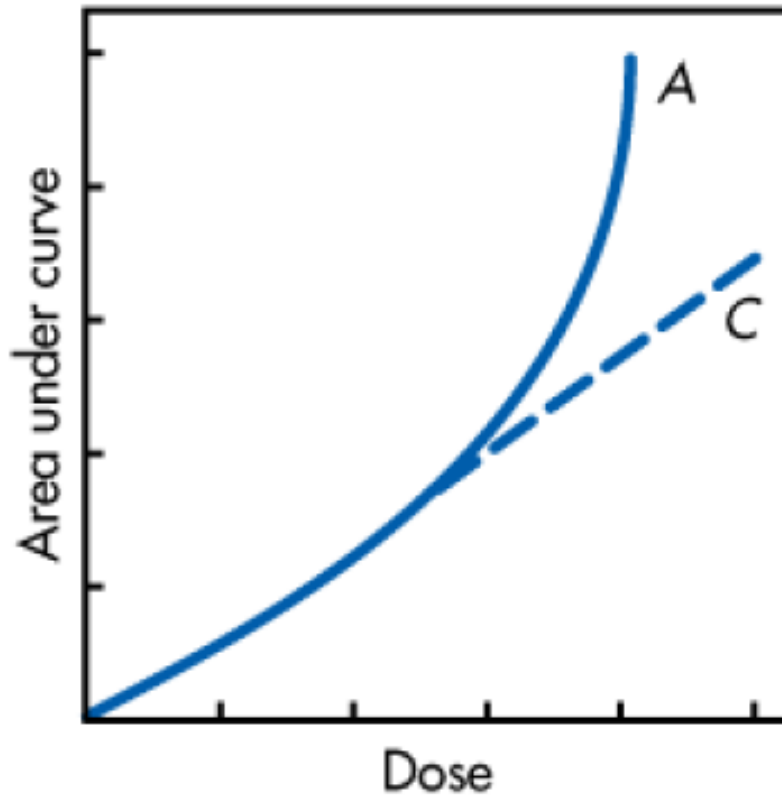
- Also called **Saturable elimination**.
- Occurs with few drugs (aspirin, phenytoin, ethanol, ..).
- Elimination rate is **NOT** proportional to the amount of drug in the body, but a **constant amount is removed per unit time**, because of saturation of the elimination process.



Zero-Order Drug Elimination

- Rate of elimination = $V_{\max} \cdot C / K_m + C$

Where V_{\max} is the maximal elimination capacity, and K_m is the drug concentration at which rate of elimination is 50% of V_{\max} .



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 6th Edition: www.accesspharmacy.com

Curve C represent first-order kinetics

Flow-Dependent Drug Elimination

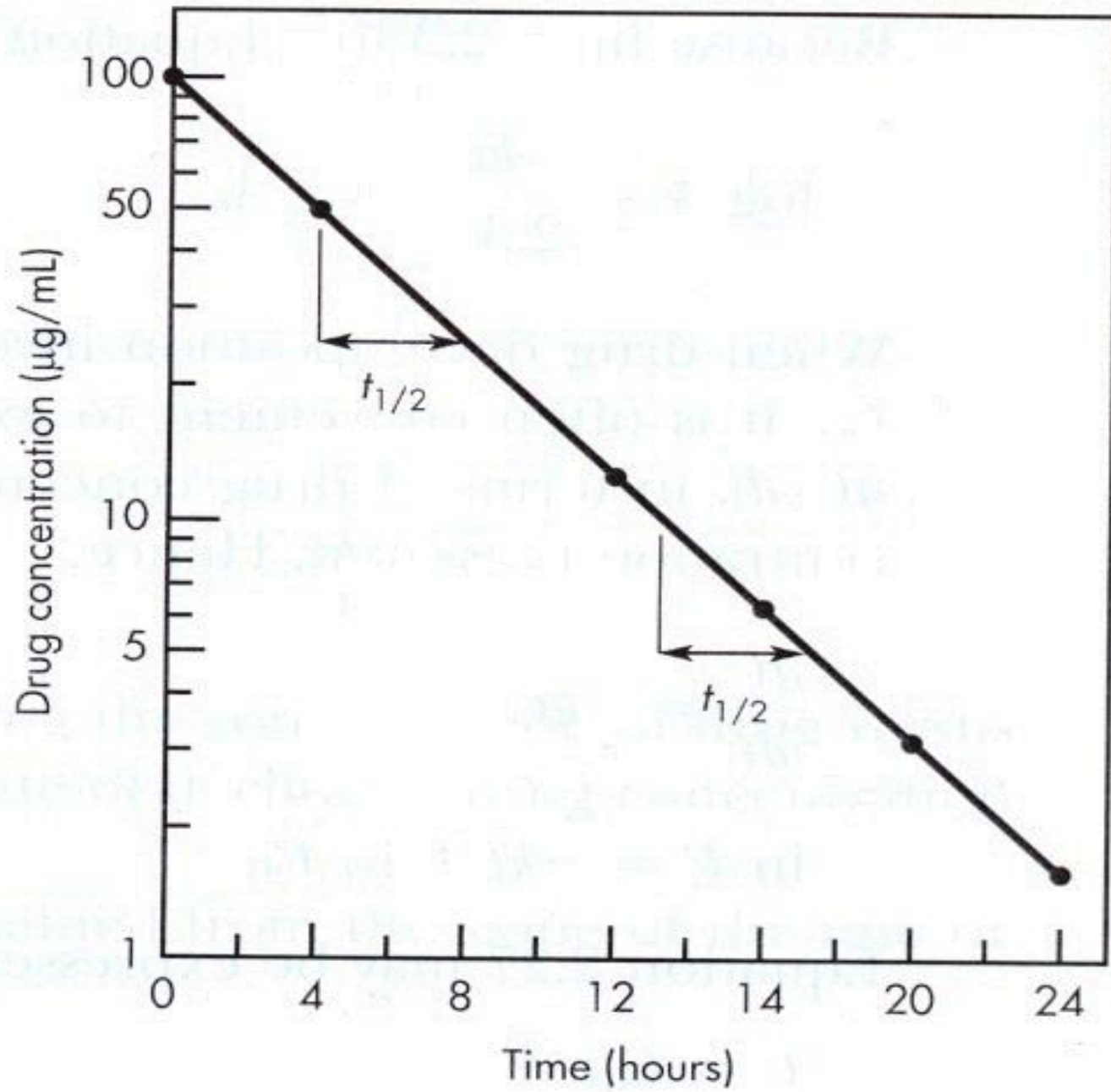
- Some drugs are **cleared very rapidly by the organ of elimination (liver)**, so that at clinical concentrations of the drug, **most of the drug perfusing the organ is eliminated on first pass** of the drug through the organ.
- **Rate of elimination is determined by the rate of hepatic blood flow.**
- Drugs that have this property are called **“high extraction ratio”** drugs.
- Include morphine, lidocaine, propranolol, verapamil, and others.

Half-Life ($t_{1/2}$) of Elimination

- It is the time required for the amount of drug in the body or the plasma concentration of the drug (assuming first-order elimination) to drop by 50%.
- In this case it is constant, and not related to dose.
- After ~ 4 half-lives, most of the drug will be eliminated from the body.
- It is related to first-order elimination rate constant such that:

$$k \times t_{1/2} = 0.693$$

Half-lives	% of drug removed
1	50
2	75
3	87.5
4	93.75



Half-Life ($t_{1/2}$) of Elimination

- The half-life is related to volume of distribution and clearance for drugs that follow first-order kinetics by the following equation:

$$CL = k \cdot V_d$$

$$t_{1/2} = 0.693 \cdot V_d / CL$$

Half-Life ($t_{1/2}$) of Elimination

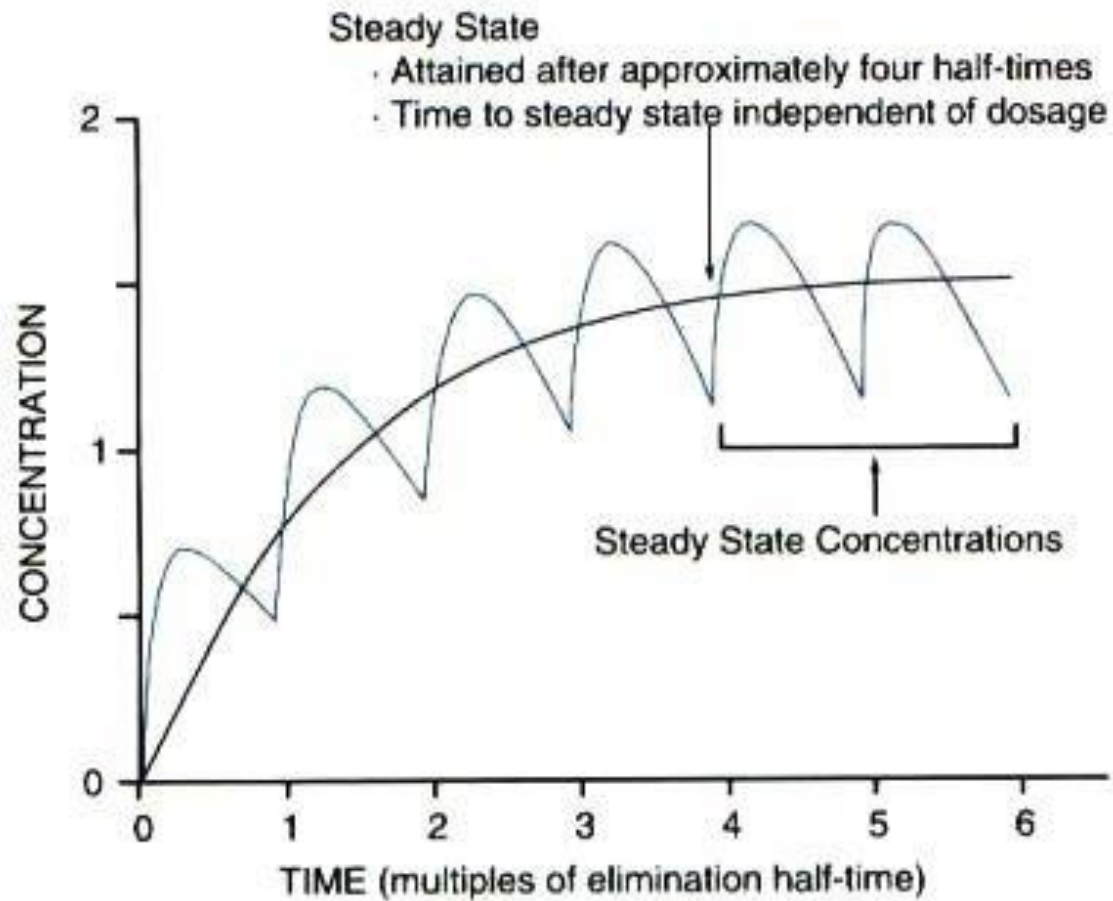
- It is related to dose and plasma concentration for drugs undergoing zero-order kinetics, and is **NOT constant**.
- The higher the concentration, the longer the half-life of elimination and vice versa.

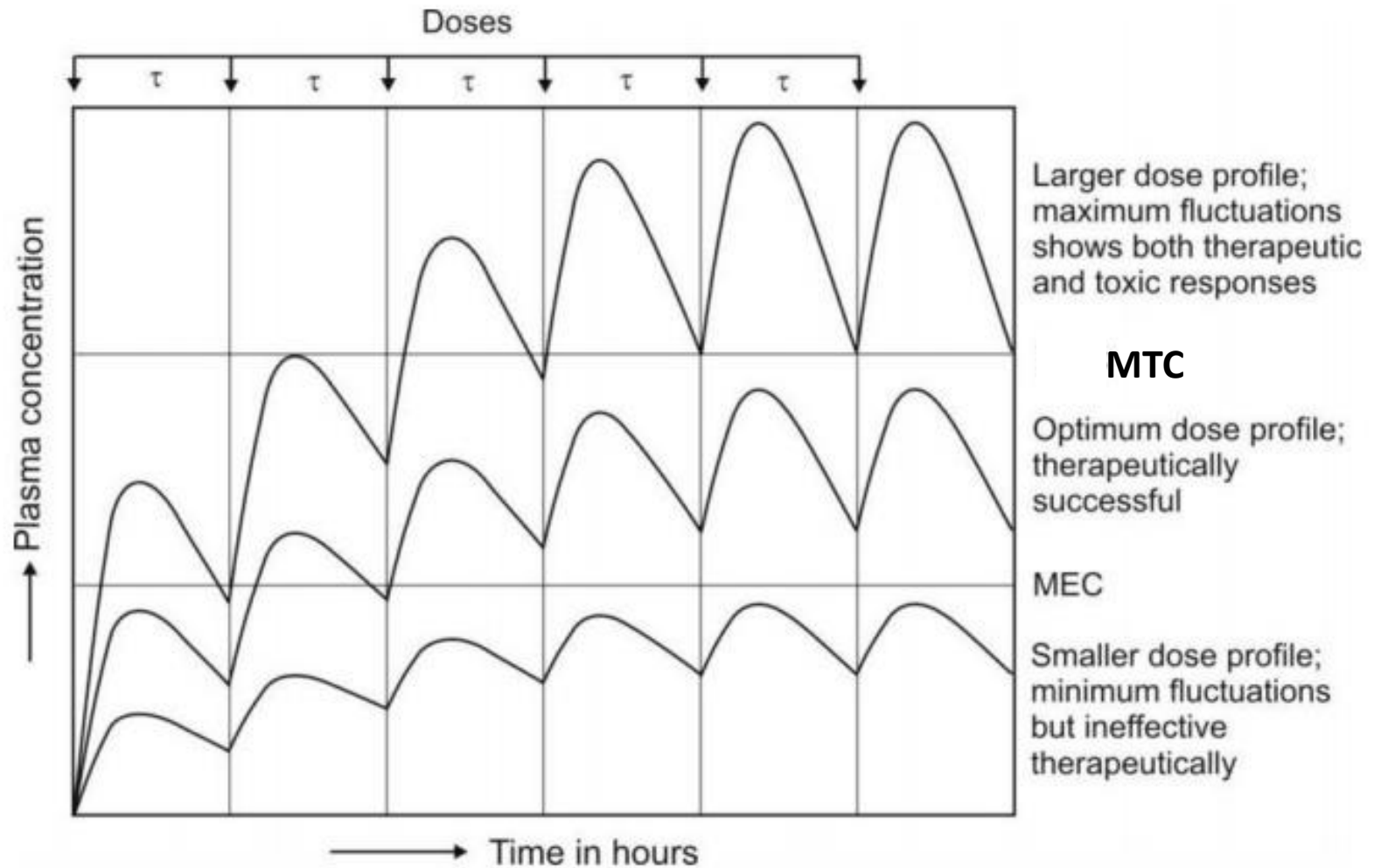
Steady-State

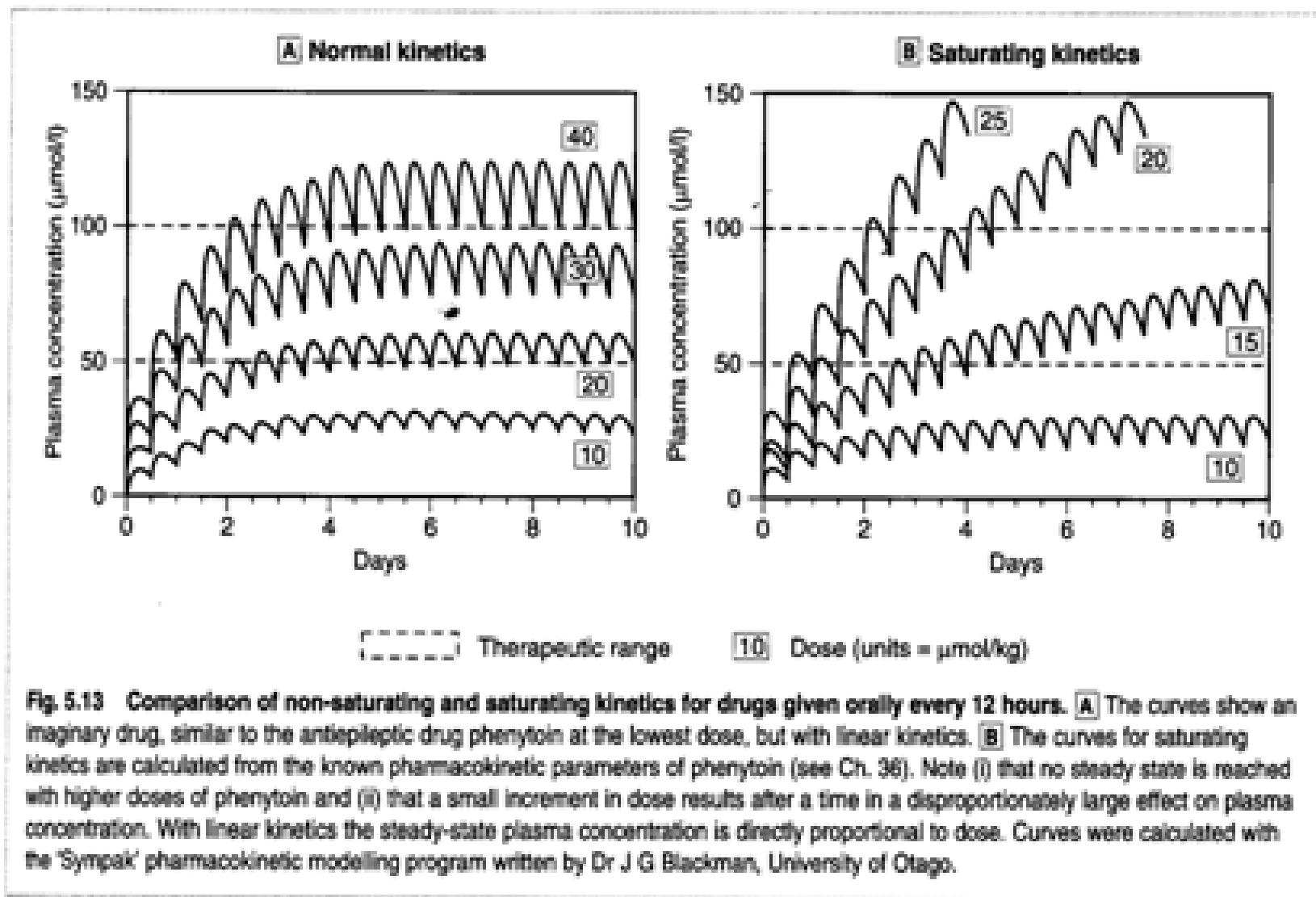
- **Steady-state** is a condition achieved following **repeated drug administration** as occurs in clinical practice.
- It occurs when **the rate of drug administration** (dosing rate) **is equal to the rate of drug elimination**.
- At steady-state, **a constant peak, trough, and average drug concentrations** are achieved.

Steady-State

- **Steady-state is achieved after approximately 4 half-lives of repeated drug administration. 50% of SS is achieved after one half-life of administration.**
- **Our aim during drug therapy is to attain a steady-state drug concentration (C_{ss}) within the therapeutic range, but NOT subtherapeutic or toxic.**







Loading Dose (LD)

- When the half-life is too long, steady-state will take a long time to be achieved.
- Therefore, we may need to give a loading dose to achieve drug concentration within the therapeutic range sooner (target concentration).

$$LD = V_D \cdot C_{SS_{\text{desired}}}$$

Maintenance Dose (MD)

- To attain and maintain a desired C_{ss} of a drug, we need to adjust the dose so that, the rate of drug administration is equal to the rate of drug elimination.
- Elimination is a function of clearance.

$$MD = CL \cdot C_{ss_{\text{desired}}}$$

$C_{ss_{\text{desired}}}$ is also called the target concentration.

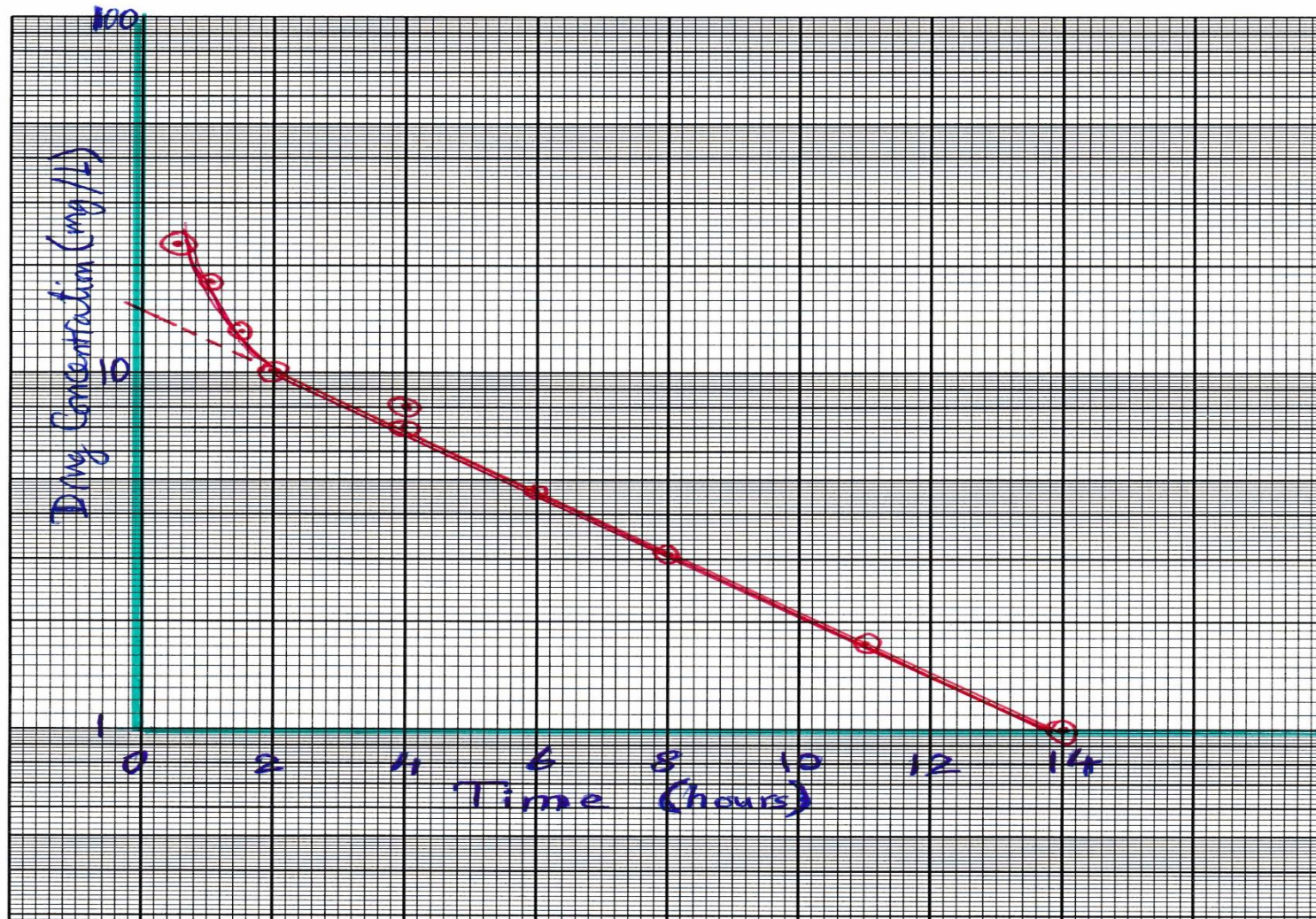
Case Scenario

- **A volunteer was given a single 400 mg of a drug by IV injection. Serial blood samples were taken to analyze for drug level and construct a plasma concentration-versus-time curve.**

Results

Time (hours)	Drug concentration (mg/L)
0.5	23
1	18
1.5	13
2	10
4	7
6	4.7
8	3.1
11	1.75
14	1

The following semi-log plot of plasma concentration-versus-time was obtained



Q1

Which of the following is the **approximate** apparent volume of distribution of the drug?

- A. 5 L
- B. 10 L
- C. 25 L
- D. 50 L
- E. 100 L

Q2

What is the half-life of elimination of the drug?

- A. 1.5 hours**
- B. 3.5 hours**
- C. 5.5 hours**
- D. 7.5 hours**
- E. 9.5 hours**

Q3

Which of the following is the first-order elimination rate constant of the drug?

- A. 0.0385 / hour**
- B. 0.0770 / hour**
- C. 0.1155 / hour**
- D. 0.1540 / hour**
- E. 0.1925 / hour**

Q4

Which of the following is the clearance of this drug?

- A. 1 L/hour**
- B. 2 L/hour**
- C. 3 L/hour**
- D. 5 L/hour**
- E. 10 L/hour**

Q5

What is the maintenance dose every 24 hours if the steady-state therapeutic concentration of the drug is 10 mg/L?

- A. 100 mg**
- B. 500 mg**
- C. 750 mg**
- D. 1000 mg**
- E. 1200 mg**

Q6

Does this drug require a loading dose?

- A. Yes**
- B. No**
- C. I do not know**

If the answer is yes, calculate the loading dose.