Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 2- Pharmacokinetics

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Pharmacokinetics

Mechanisms of Permeation of Drug Molecules

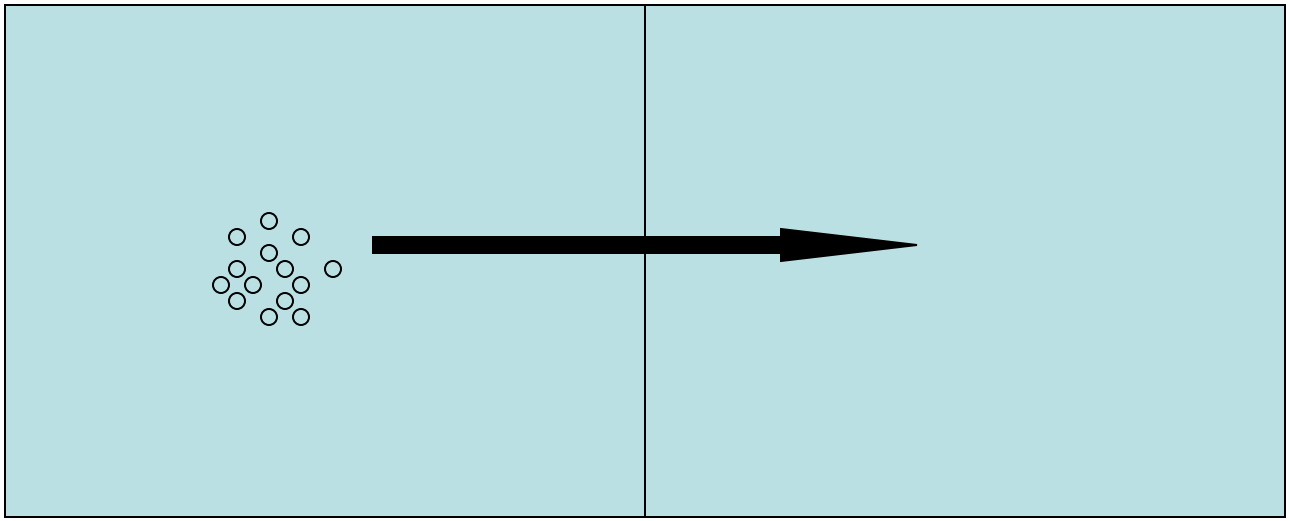
- **The movement of drug between compartments require passage through membranes.**

1. **Lipid diffusion (Passive diffusion):**

- **The most important mechanism.**
- **The drug dissolves in the membrane.**
- **The more lipid soluble is a drug the more will be the passage across membranes, and vice versa.**

Mechanisms of Permeation of Drug Molecules

- **The drug has to be sufficiently water soluble to reach the membrane.**
- **The drug follows the concentration gradient.**



Fick's Law of Diffusion

- **It governs passive flux of molecules across membranes.**
- **Flux (molecules/unit time) =**

  C_1-C_2 x [(Area x 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

- **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).**

$R\text{-}COOH$ ⟷ **$R\text{-}COO^- + H^+$**

Lipid soluble — **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.**

$R\text{-}NH_3^+$		$R\text{-}NH_2 + H^+$
Water soluble		**Lipid soluble**

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

Mechanisms of Permeation of Drug Molecules

Henderson-Hasselbalch Equation:

Log [protonated/unprotonated] = pKa – pH

- **This equation applies to both acidic and basic drugs.**

Mechanisms of Permeation of Drug Molecules

Examples:

1. **Pyrimethamine is 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:**

  Log (prot/unprot) = pKa – pH =7 – 7.4 = - o.4

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

- **Urine:**

  Log (prot/unprot) = pKa – pH =7 - 6 =1

  Prot/unprot = 10^{1} = 10:1

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:**

  Log (prot/unprot) = pKa – pH

  = 7.4-7.4 = 0

  Prot/Unprot = 10^0 = 1:1

- **Urine:**

  Log (prot/unprot) = pKa – pH

  = 7.4 – 6 = 1.4

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

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.**
- **More of a weak acid will be in a lipid soluble form at acidic pH; and more of a weak base will be lipid soluble at an alkaline pH.**

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 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.**

Mechanisms of Permeation of Drug Molecules

- **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.**

Mechanisms of Permeation of Drug Molecules

- **Also driven by the concentration gradient.**
- **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 though 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:**

Mechanisms of Permeation of Drug Molecules

a. **ATP-binding cassette (ABC) family, which includes P-glycoprotein or multidrug-resistance type 1 (MDR1) transporter found in the brain, intestine, testes, neoplastic cells, and other tissues.**

Mechanisms of Permeation of Drug Molecules

b. **Similar transporters from the ABC family, the multidrug-resistance associated protein (MRP) transporters, play a role in excretion of drugs and their metabolites into urine and bile; and resistance of some tumors to chemotherapeutic agents.**

Mechanisms of Permeation of Drug Molecules

c. Other transporter families do not bind ATP but use ion gradients for transport energy, the solute carrier family (SLC). They are important in the transport of neurotransmitters across nerve ending membranes.

Mechanisms of Permeation of Drug Molecules

4. **Endocytosis and exocytosis:**

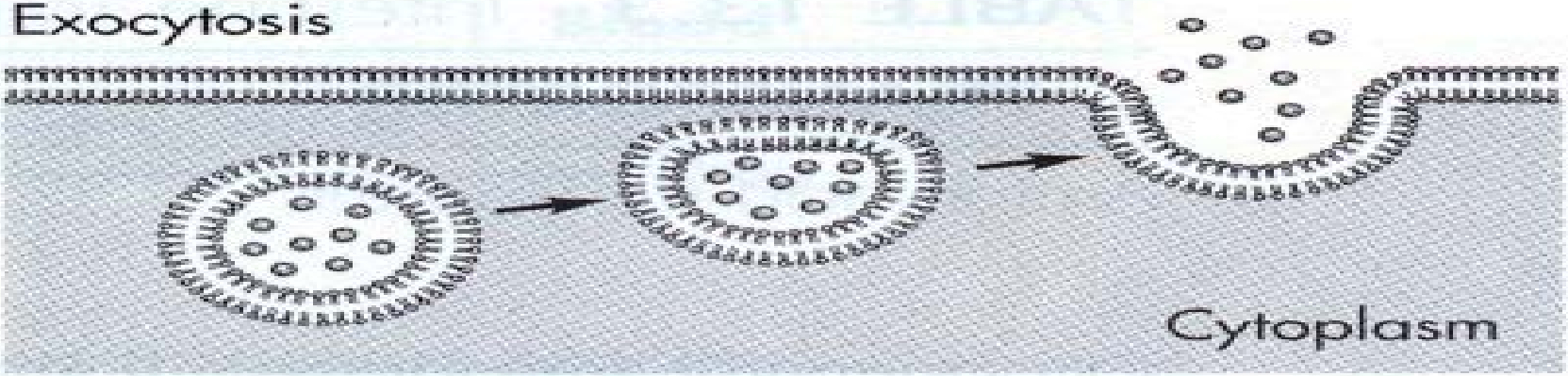
- **A few substances are so large or impermeant that they can enter cells by endocytosis (bind to cell surface receptor and are engulfed by cell membrane). This process is responsible for transport of vitamin B_{12} complexed with the intrinsic factor across the wall of the gut into the blood;**

Mechanisms of Permeation of Drug Molecules

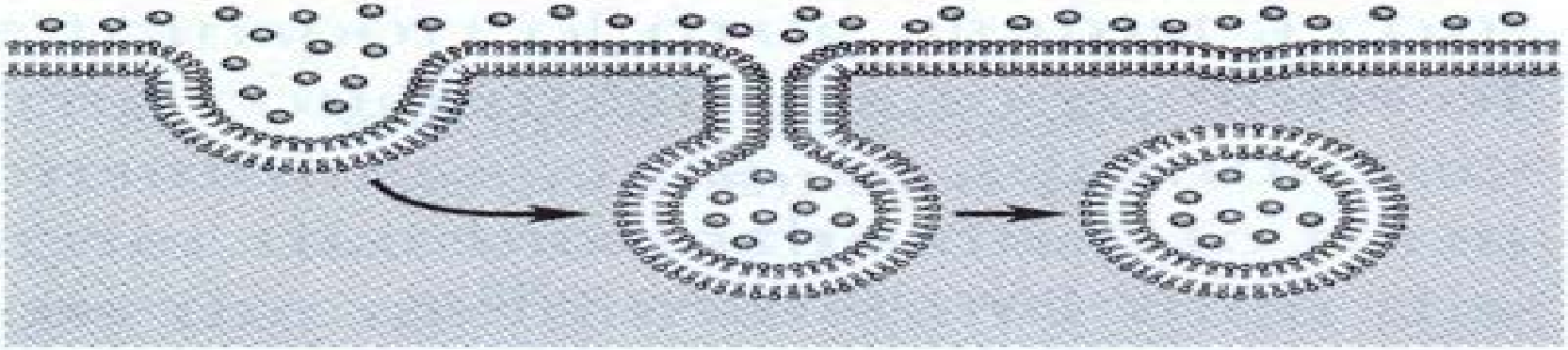
and iron associated with transferrin into RBCs.

- **Exocytosis is responsible for secretion of many substances from cells such as neurotransmitters and some hormones.**

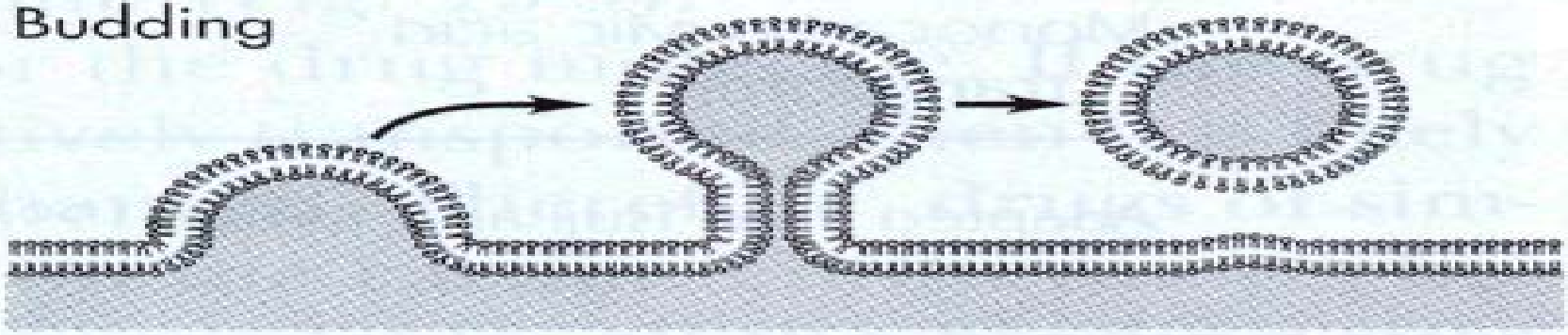
Exocytosis



Endocytosis



Budding



Mechanisms of Permeation of Drug Molecules

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

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:**

  1. gut wall

  2. portal vein

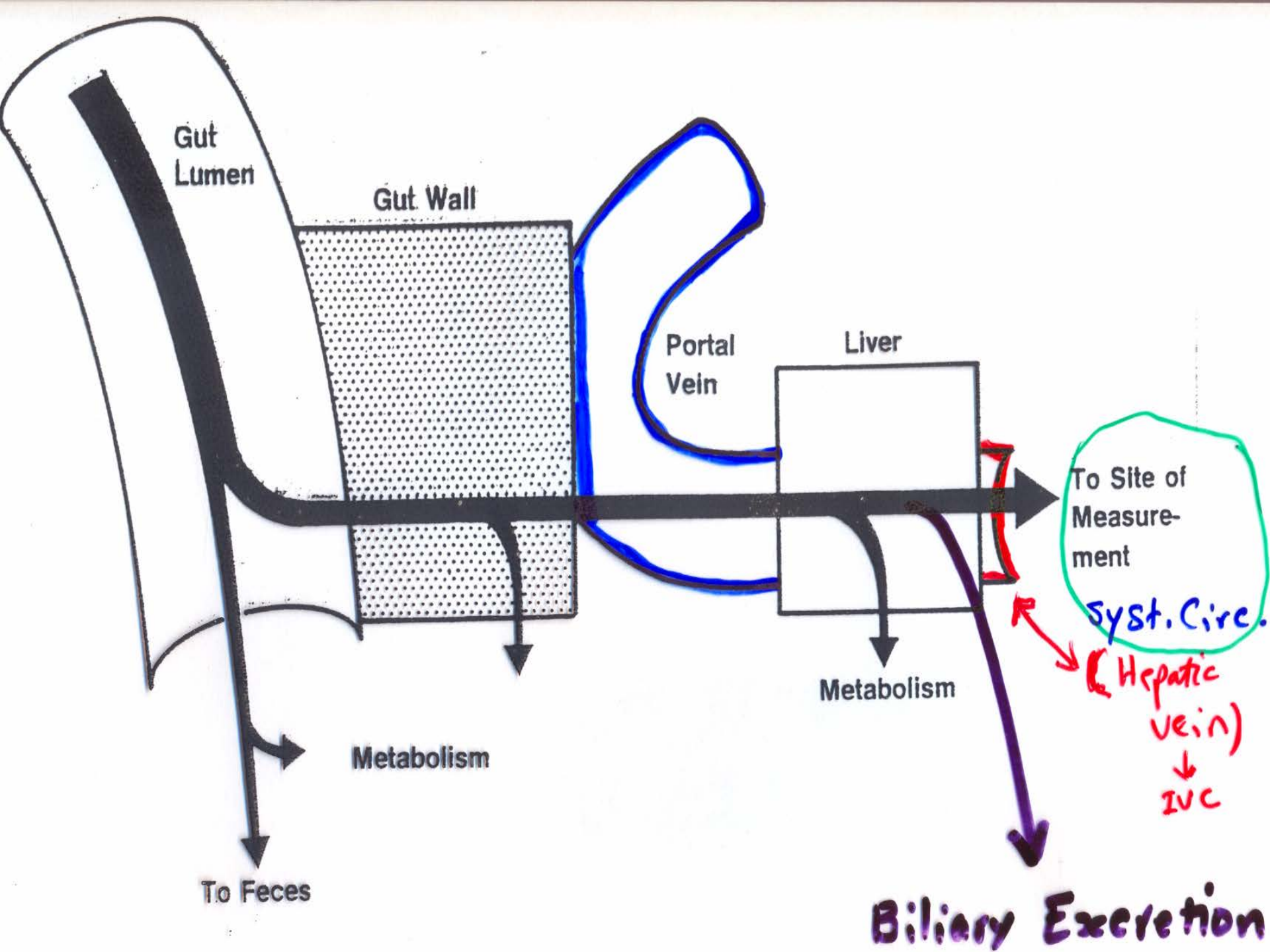
  3. liver

  prior to entry into the systemic

First-Pass Effect

circulation

- **Or, get excreted by the liver through bile.**
- **This will lead to incomplete delivery of the dose given to the systemic circulation → low bioavailability.**


Gut Lumen
Gut Wall
Portal Vein
Liver
To Site of Measure-ment
Syst. Circ.
(Hepatic vein)
IVC
Metabolism
Metabolism
To Feces
Biliary Excretion

First-Pass Effect

- **This process is called “first-pass effect” or ‘first-pass metabolism” or “pre-systemic elimination”.**
- **Therapeutic blood concentration may still be reached by using larger dose. Therefore, the oral dose is usually higher than intravenous dose for such drugs.**

First-Pass Effect

- **Also the concentration of drug metabolites after oral administration will be higher than after intravenous administration.**
- **If the patient is having liver cirrhosis and there is shunting of blood by-passing the portal circulation, giving the same dose orally will lead to substantial increases in concentration of the drug and drug toxicity.**

First-Pass Effect

- **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.**

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.**
- **For 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:**

1. **The drug may be too hydrophilic (atenolol), or too lipophilic (acyclovir), to be absorbed easily.**

Bioavailability

- **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).**

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

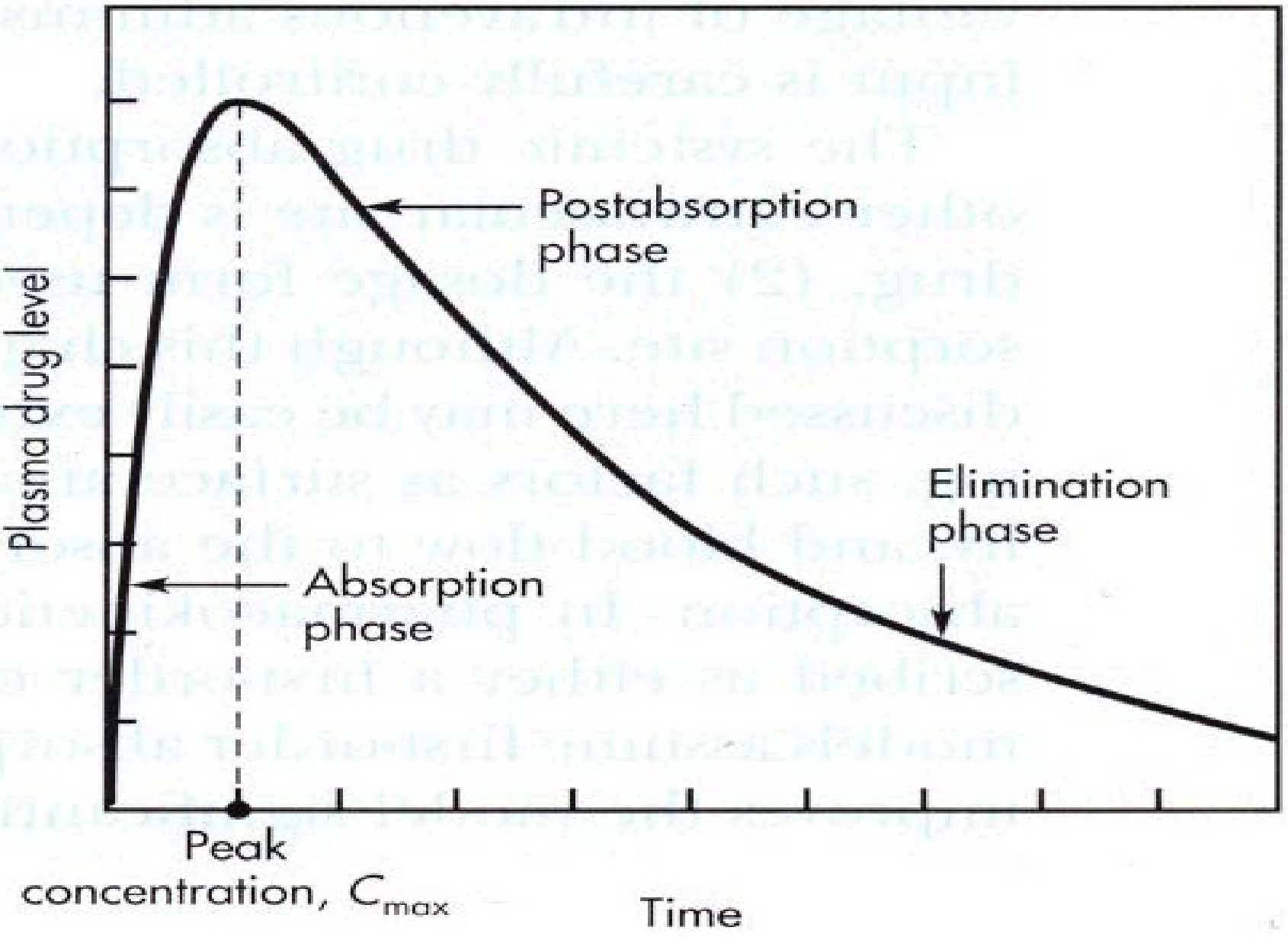
Bioavailability

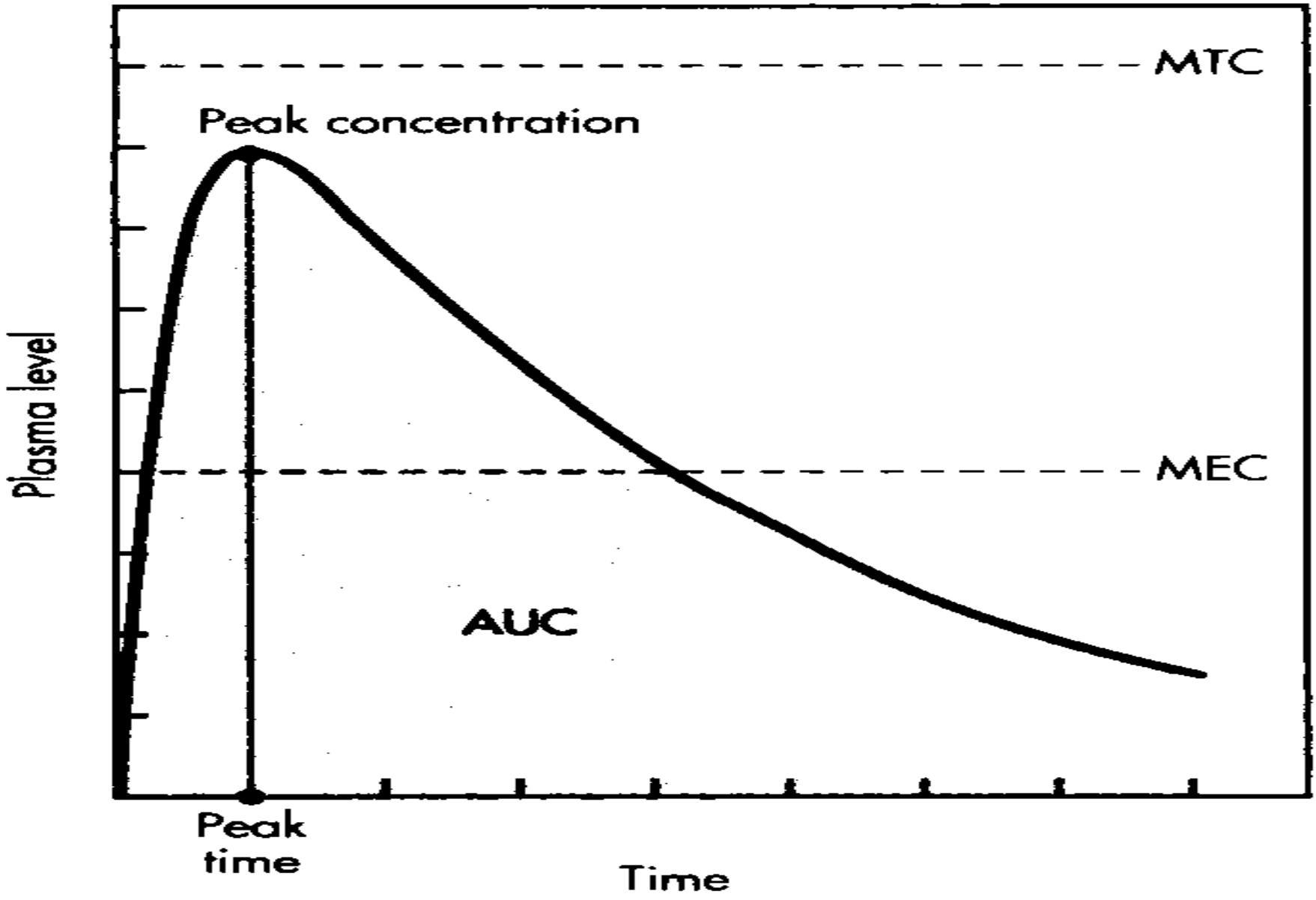
gut lumen. Inhibition of the reverse transporter by the use of some drugs and grapefruit juice, may be associated with substantial increase in drug absorption and thus bioavailability.

- Grapefruit juice also inhibits presystemic elimination of some drugs, and thus, increases their bioavailability.

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).**


Plasma drug level
Postabsorption phase
Elimination phase
Absorption phase
Peak concentration, C_{max}
Time


MTC
Peak concentration
MEC
AUC
Plasma level
Peak time
Time

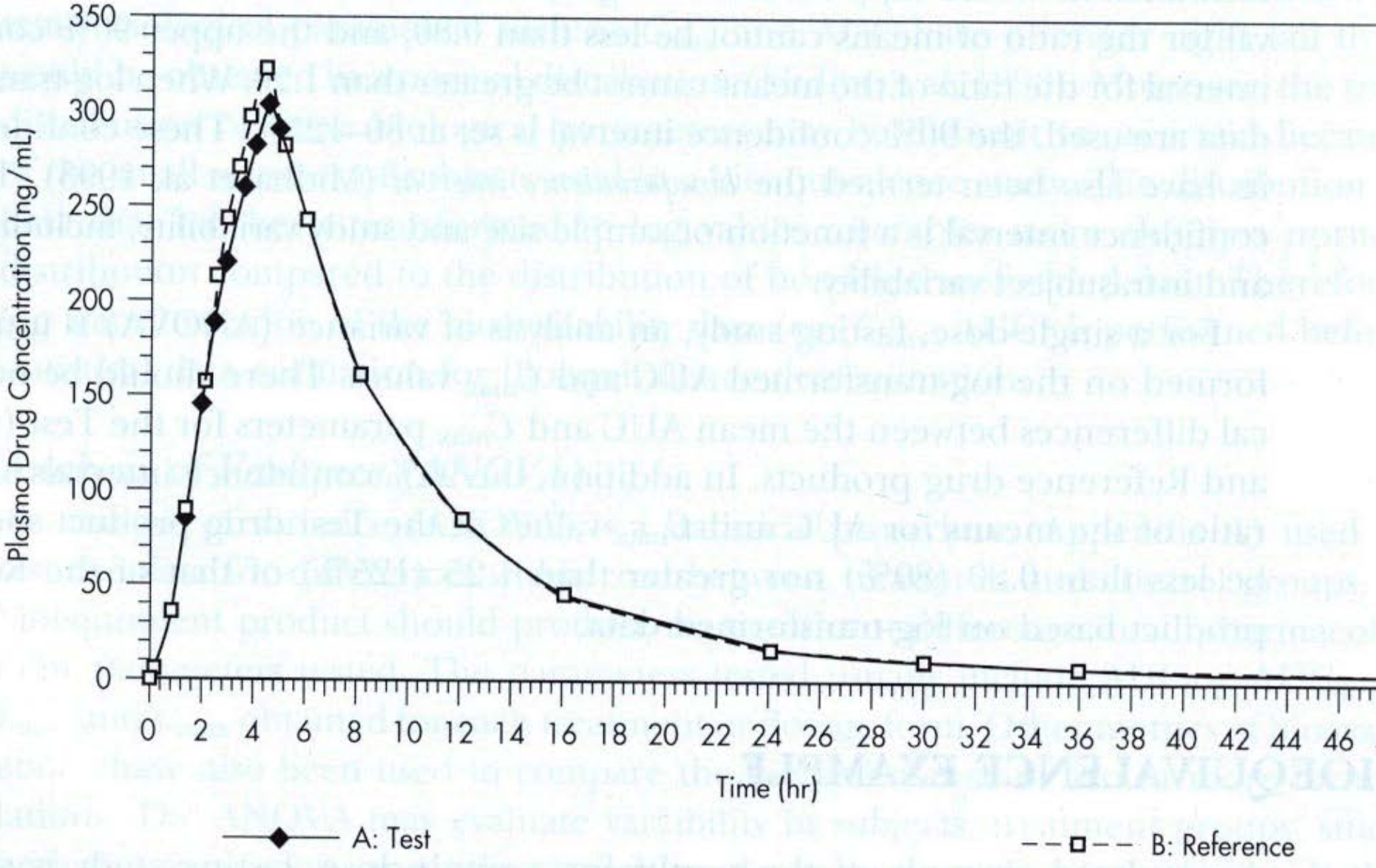


Figure 15-8. Bioequivalence of Test and Reference drug products: mean plasma drug concentration

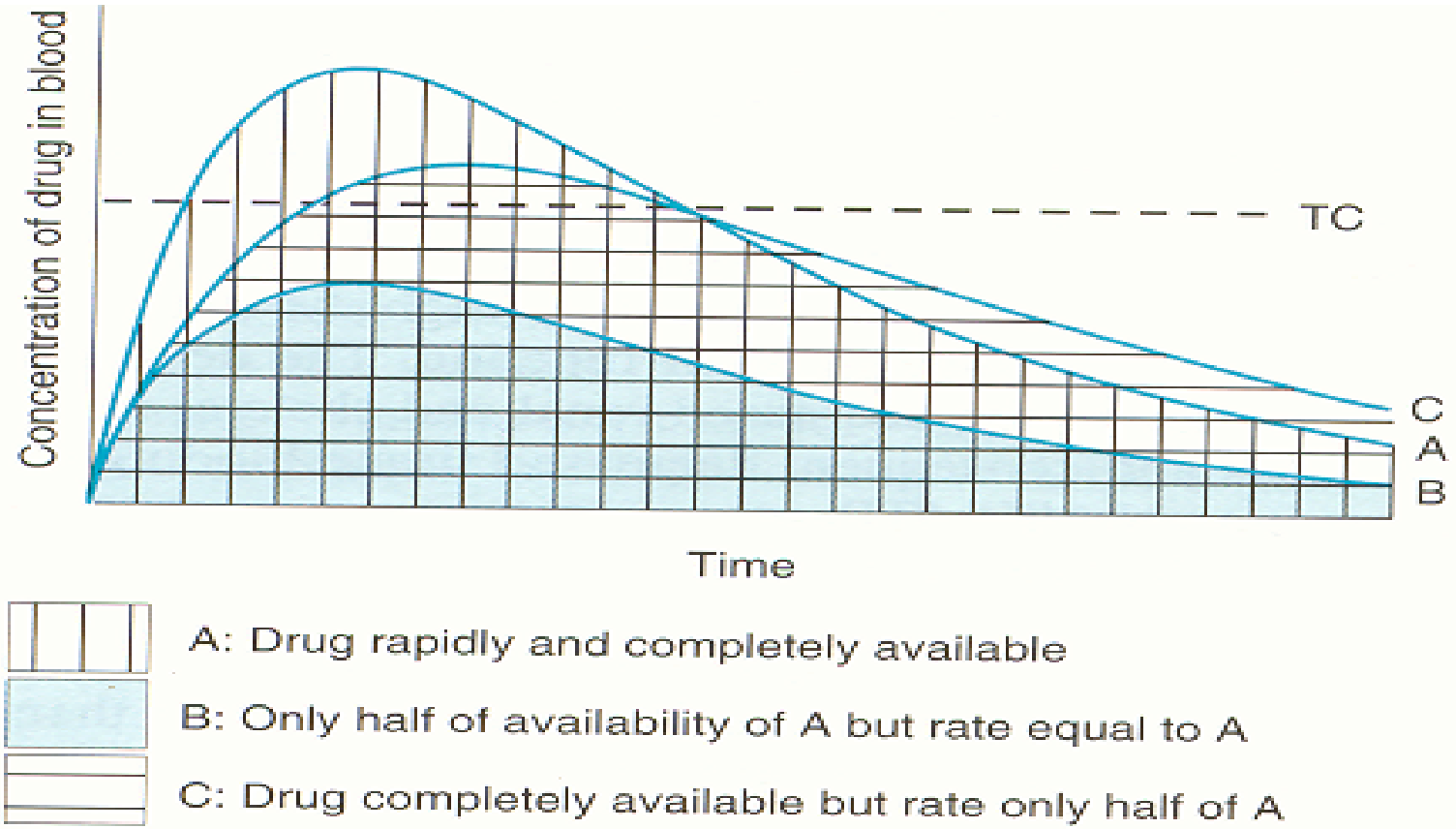
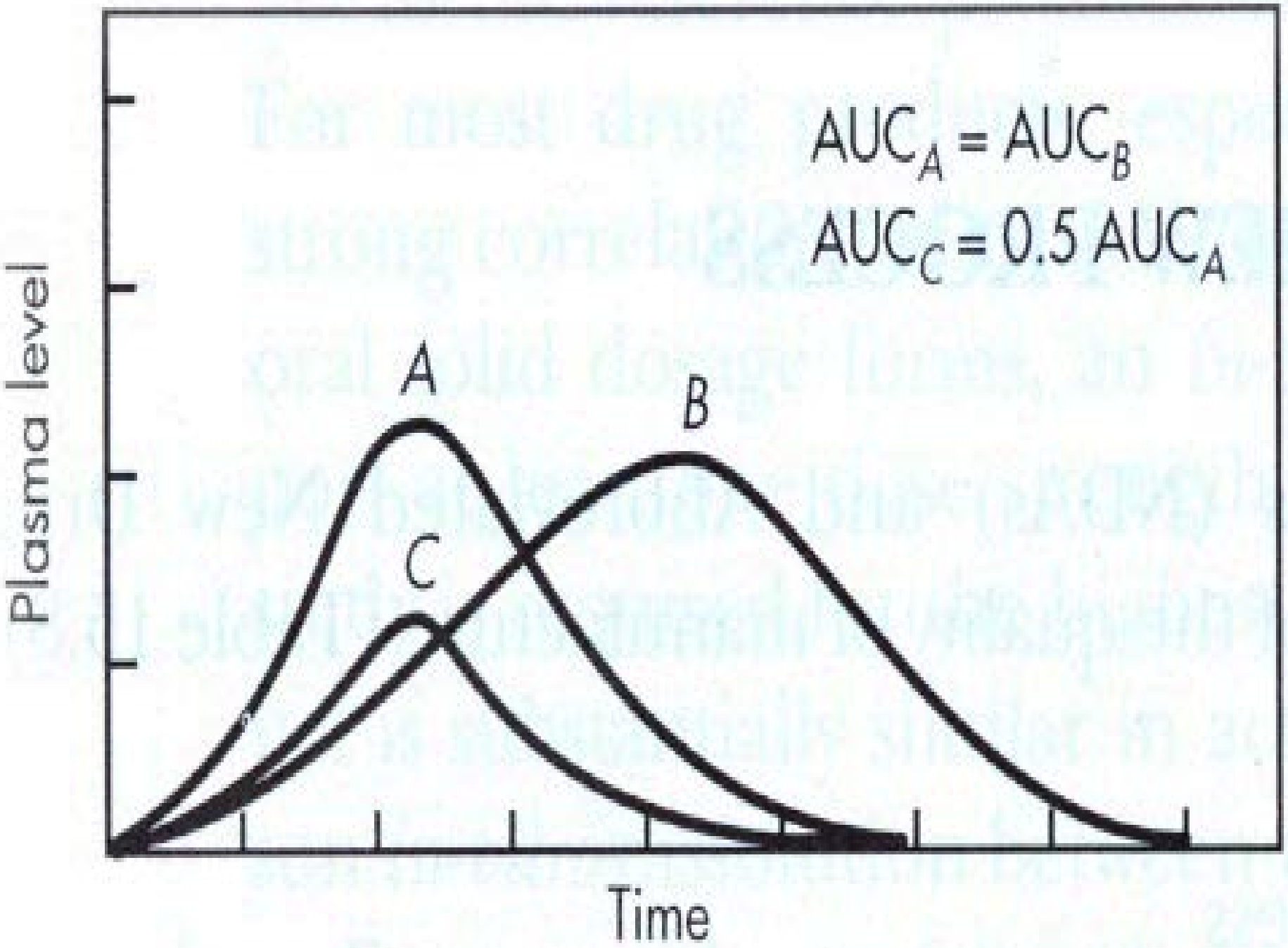


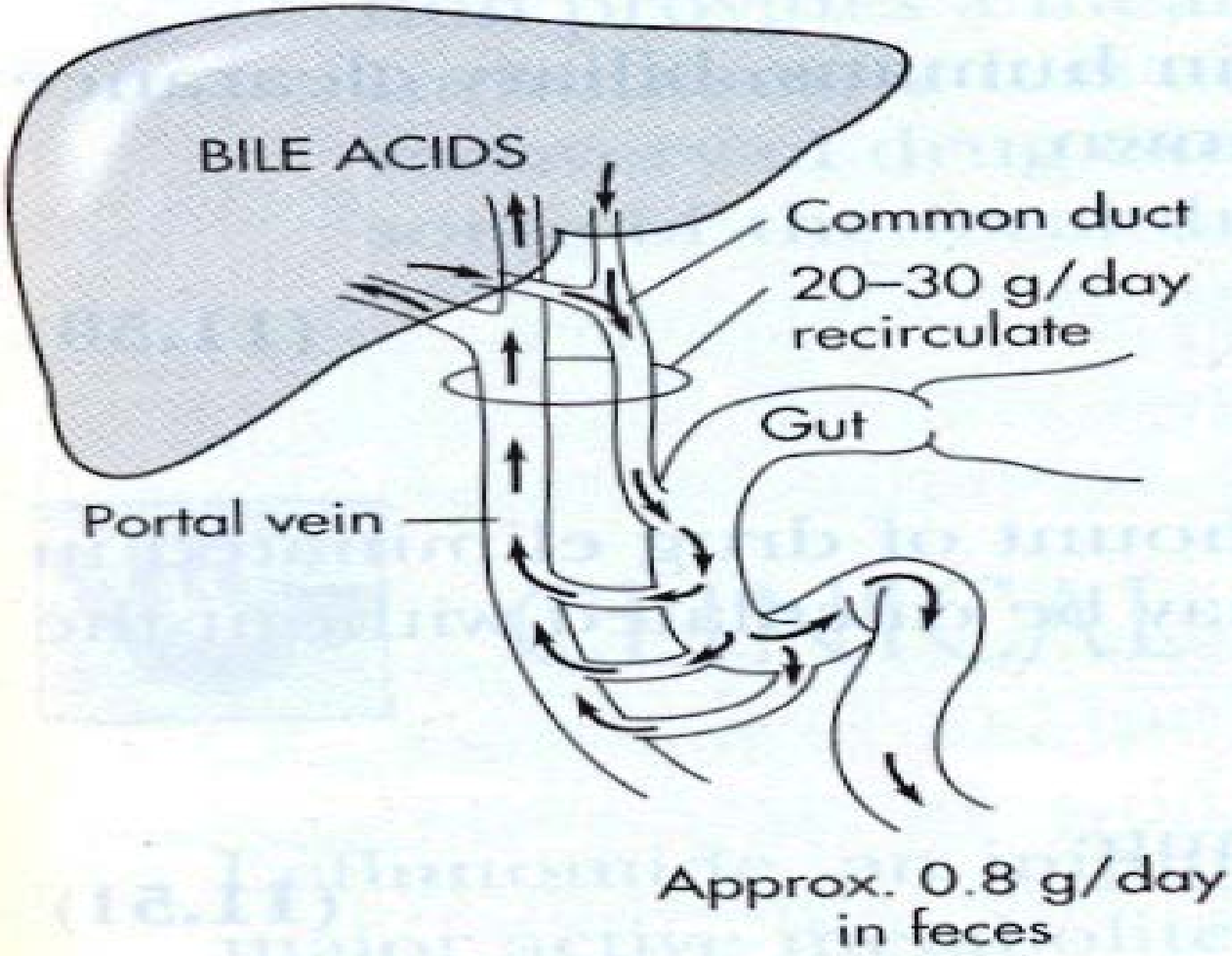
Figure 3–5. Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.

*Rate of B is also less than that of A


$AUC_A = AUC_B$
$AUC_C = 0.5\ AUC_A$
A
B
C
Plasma level
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 the reabsorbed again.**
- **This is called enterohepatic cycling of the drug.**
- **It reduces drug bioavailability and prolongs its half-life of elimination.**


BILE ACIDS
Common duct
20–30 g/day
recirculate
Gut
Portal vein
Approx. 0.8 g/day
in feces

Enterohepatic Cycling of Drugs

Application:

- **This phenomenon can be taken advantage of in cases of drug overdose.**
- **Activated charcoal can adsorb may drugs and chemicals (except ionized ones) into its surface.**
- **If we give activated charcoal in cases of**

Enterohepatic Cycling of Drugs

drug overdose, and the drug undergoes enterhepatic 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.**
- **Some call this process “gastrointestinal dialysis”.**

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:**

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

- **But the volume of distribution for:**

  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, due to binding to plasma proteins, or when it is highly ionized at plasma pH.**
- **The apparent volume of distribution will be large when the drug distributes in tissues.**

Volume of Distribution (V_D)

- **It relates the amount of the drug in the body (Ab), with drug plasma concentration (Cp) such that:**

- **V_D = Ab/Cp ..... (1)**

Drug Binding in Plasma

- **Albumin is the most important drug binding protein.**
- **α_1- Acid-glycoprotin, an acute phase reactant, is also important for binding certain basic drugs.**
- **Binding to plasma proteins is reversible and follows the law of mass action.**

Drug Binding in Plasma

- **Drug + Protein ⟷ Drug-Protein complex**

  D + P ⟷ DP

- **The free unbound drug fraction (D) is responsible for the pharmacological action and is also available for elimination.**
- **The bound drug fraction (DP) it is not so available, and it represents a resevoir for the drug.**

Drug Binding in Plasma

- **The clinical importance of plasma protein binding of drugs is to help interpretation of measured plasma drug concentration. 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 (?).**
- **Plasma protein binding is also a site for drug-drug interactions.**

The Effect of 5% Displacement from Binding of Two Drugs

	Before displacement	After Displacement	% Increase of free drug
Drug A			
% Bound	95	90	
% Free	5	10	+ 100
Drug B			
% Bound	50	45	
% Free	50	55	+ 10

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.**
- **It is equal to rate of elimination of the drug divided by its plasma concentration.**
- **CL = rate of elimination/Cp**

Drug Clearance (CL)

- **Renal clearance (CL_R) = Cu.V/Cp , where Cu is concentration of drug in urine, V is urine flow rate, and Cp is the plasma concentration of the drug.**
- **Hepatic clearance (CL_H) =**

  (blood flow.Ci - blood flow.Co)/Ci

  CL_H = blood flow (Ci-Co)/Ci

  CL_H = Q.ER

Drug Clearance (CL)

- **Ci is drug concentration in blood going to the liver.**
- **Co is drug concentration in blood leaving the liver.**
- **Q is blood flow**
- **ER is the extraction ratio of the drug**

Drug Clearance (CL)

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

  ER = Cl_{liver}/Q

- **Bioavailability (F) can be predicted from the extent of absorption (f) and ER.**
- **F = (f) . (1 - ER)**

Drug Clearance (CL)

- **If a drug is 80% absorbed from the GIT (f), and its extraction ratio is 0.67, then its bioavailability (F) would be =**

  0.8 (1 - 0.67) = 0.26

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.**
- **$- dAb/dt \sim Ab$**
- **$- dAb/dt = k.Ab$**

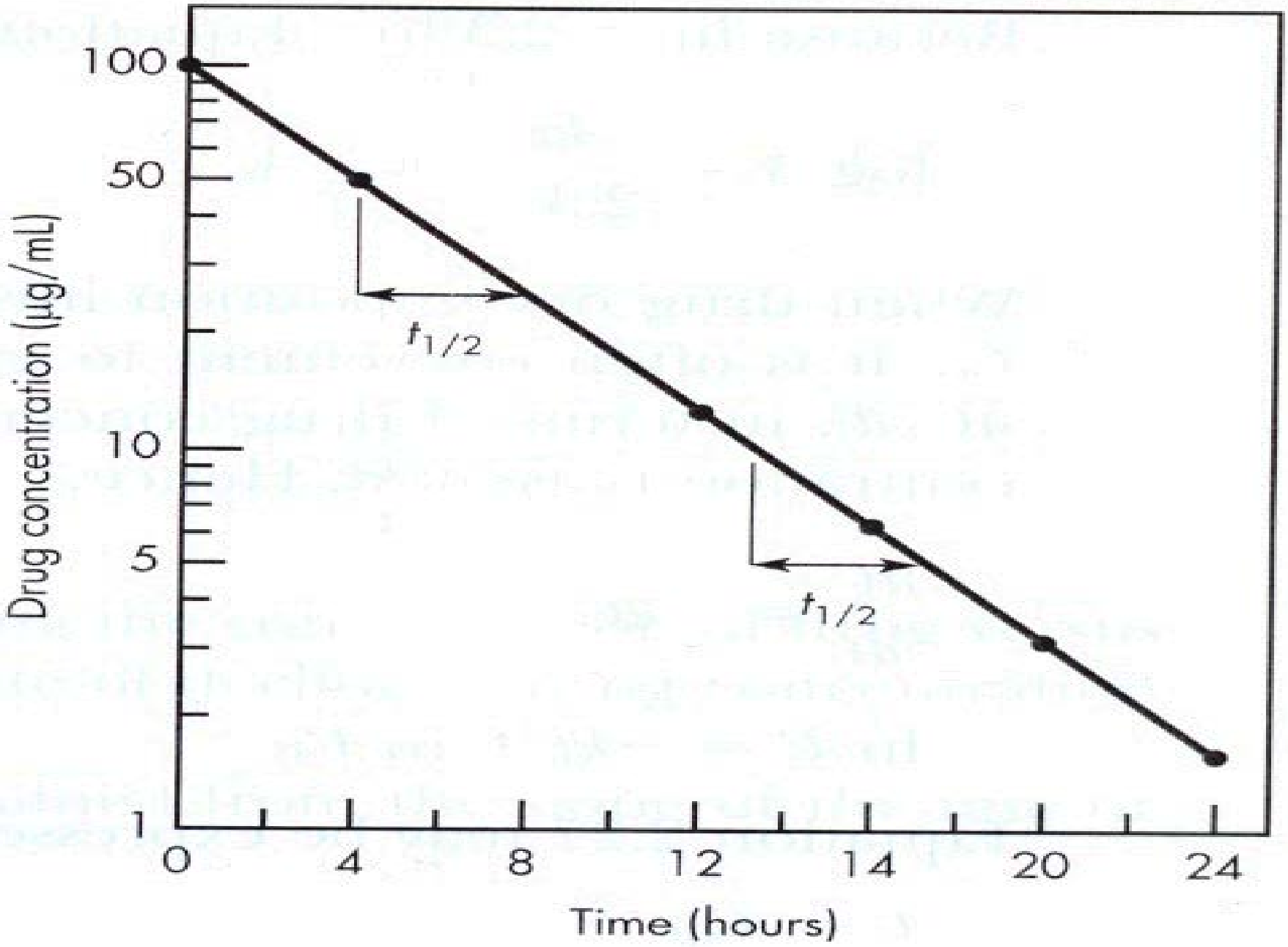
First-Order Drug Elimination

- **Where k is the first-order elimination rate constant (unit is per time).**
- **Integration of this equation from time 0 to time t gives:**

  $Ab^t = Ab^0 \cdot e^{-kt}$

  When divided by V_D , the equation becomes:

  $Cp^t = Cp^0 \cdot e^{-kt}$ …….. (2)


100
50
10
5
1
Drug concentration (µg/mL)
$t_{1/2}$
$t_{1/2}$
0
4
8
12
14
20
24
Time (hours)

CL and V_D

- **Rate of elimination = CL.Cp**
- **- dAb/dt = k.Ab**
- **Therefore:**

  k.Ab = CL.Cp

  CL = k.Ab/Cp

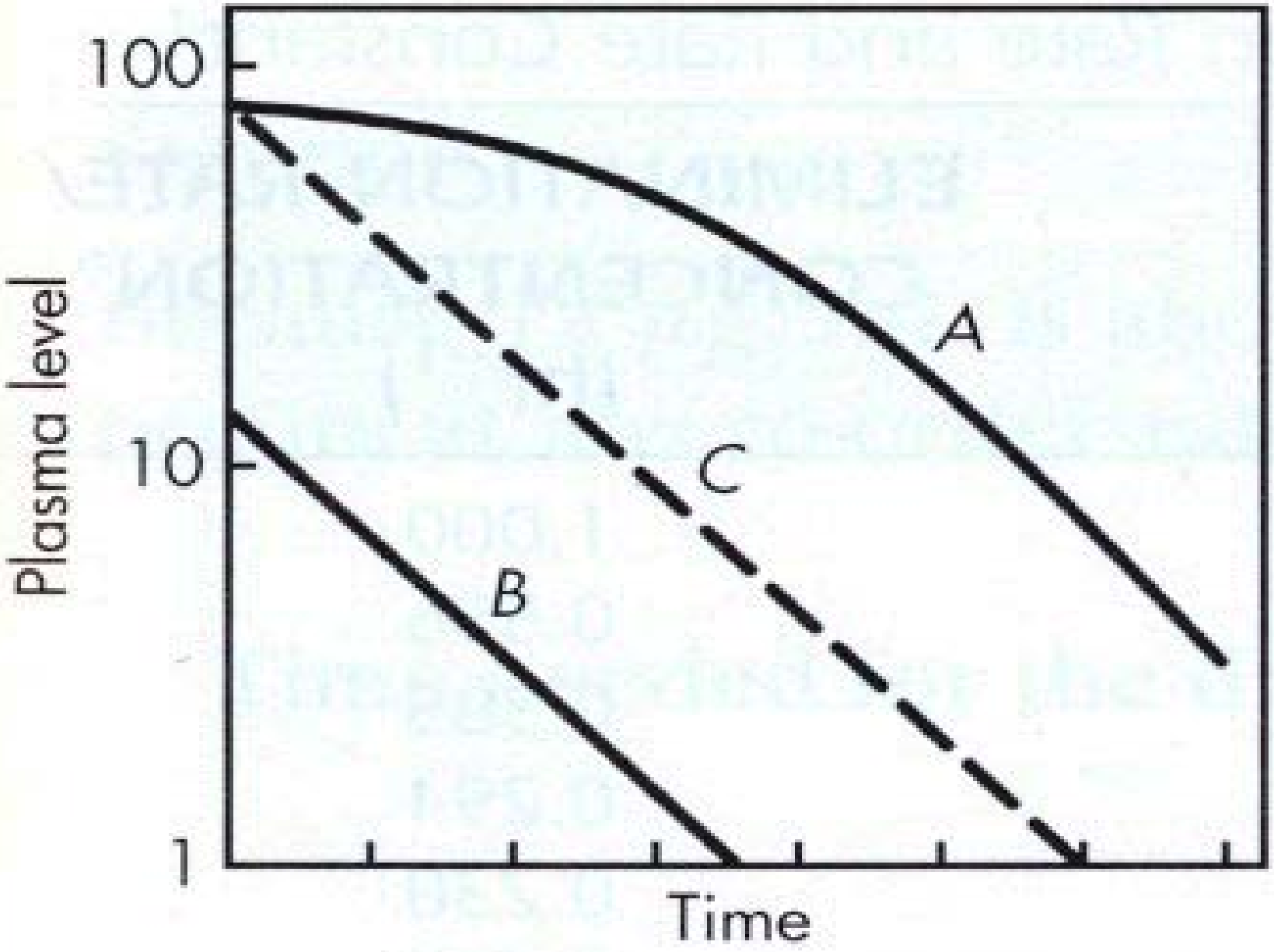
  CL = k. V_D ..... (3)

Capacity-Limited Elimination

- **Also called:**

1. **Zero-order elimination**
2. **Saturable elimination**
3. **Dose- or concentration-dependent elimination**
4. **Non-linear elimination**
5. **Michaelis-Menten elimination**

- **Occurs with few drugs (aspirin, phenytoin, ethanol, ..)**


100
10
1
Plasma level
Time
A
B
C

Capacity-Limited Elimination

- **$- dAb/dt = k_0$, where k_0 is the zero-order elimination rate constant (units are amount per time).**
- **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.**

Capacity-Limited Elimination

- **Rate of elimination = V_{max}. 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}.**
- **Capacity-limited elimination can not be explained by clearance, which has NO real meaning for drugs following this type of elimination.**

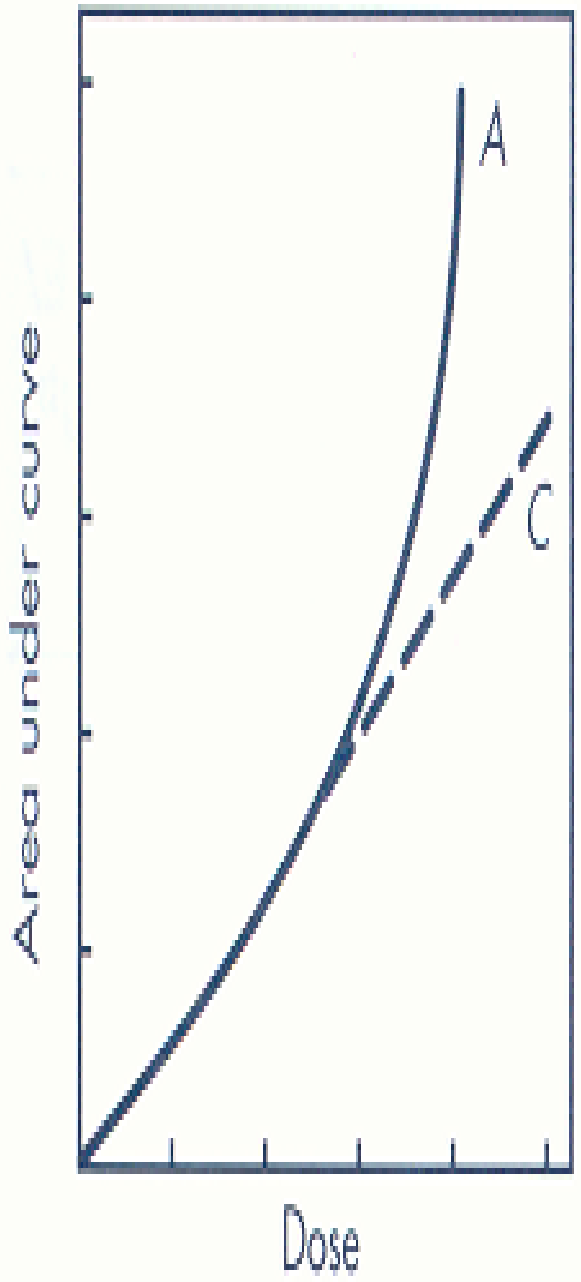


Figure 16-2. Area under the plasma level–time curve versus dose for a drug that exhibits a saturable elimination process. Curve *A* represents dose-dependent or saturable elimination kinetics. Curve *C* represents dose-independent kinetics.

Curve C represent first-order kinetics

Flow-Dependent 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.**

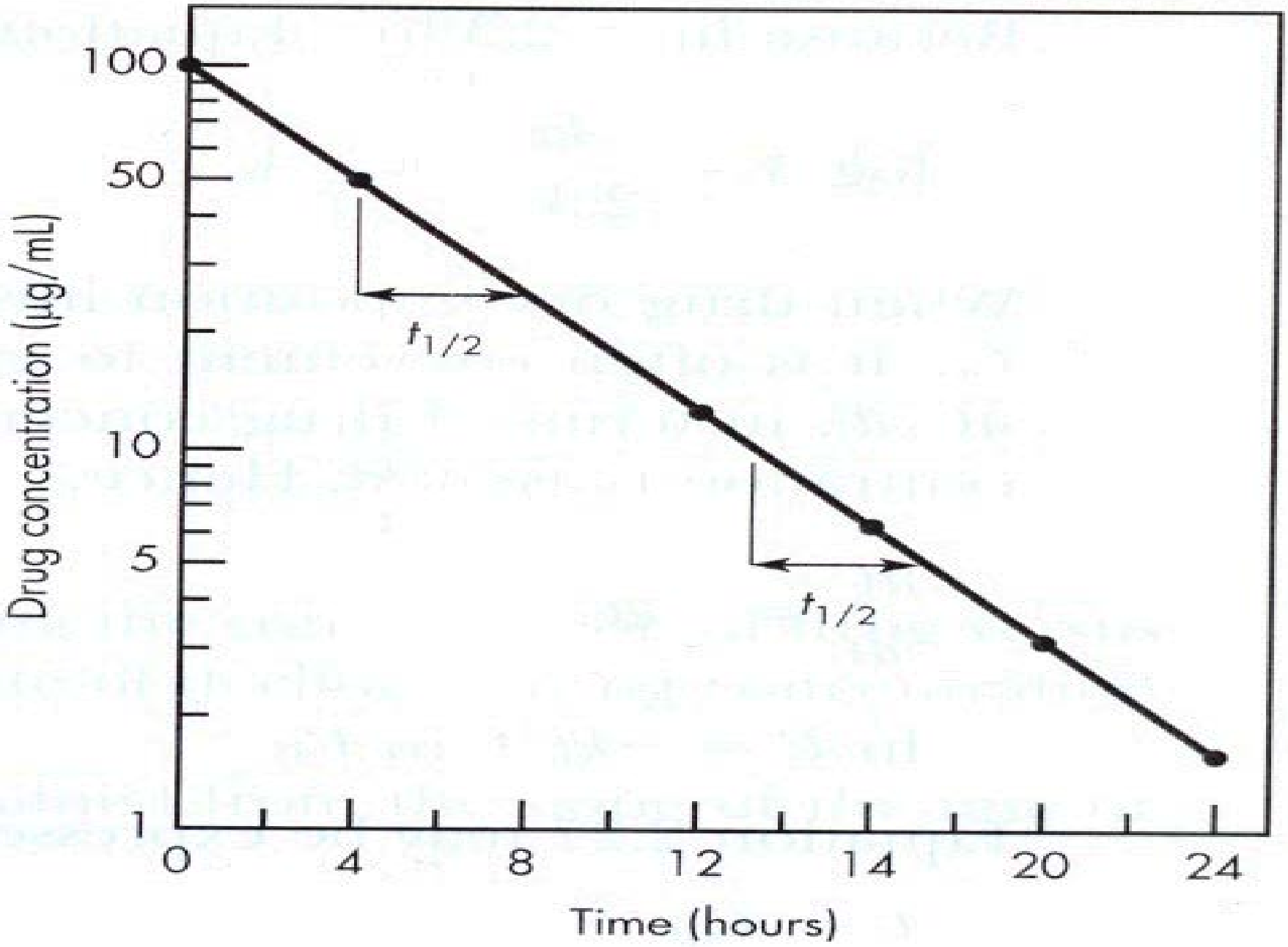
Flow-Dependent Elimination

- **Drugs that have this property are called “high extration ratio” drugs.**
- **Include morphine, lidocaine, propranolol, verapamil, ..**

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

- **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%.**
- **After 4 half-lives, most of the drug will be eliminated from the body.**

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


100
50
10
5
1
Drug concentration (µg/mL)
$t_{1/2}$
$t_{1/2}$
0
4
8
12
14
20
24
Time (hours)

Half-Life ($t_{½}$)

- **It is constant for drugs that undergo first-order kinetics.**
- **If we substitute $t_{½}$ for t in equation 2:**

$$Cp^{t_{½}} = Cp^{0} \cdot e^{-k.\, t_{½}}$$

$$Cp^{0}/2 = Cp^{0} \cdot e^{-k.\, t_{½}}$$

$$e^{-k.\, t_{½}} = 0.5$$

$$k.\, t_{½} = 0.693 \quad \ldots\ldots\ldots (4)$$

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

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

Drug Accumulation

- **When drug dosing is repeated, drug will accumulate in the body if the dosing interval is shorter than 4 half-lives.**
- **Accumulation is inversely proportional to the fraction of the dose lost in each dosing interval.**
- **Accumulation factor = 1/fraction lost, or 1/1-fraction remaining, in one dosing interval.**

Drug Accumulation

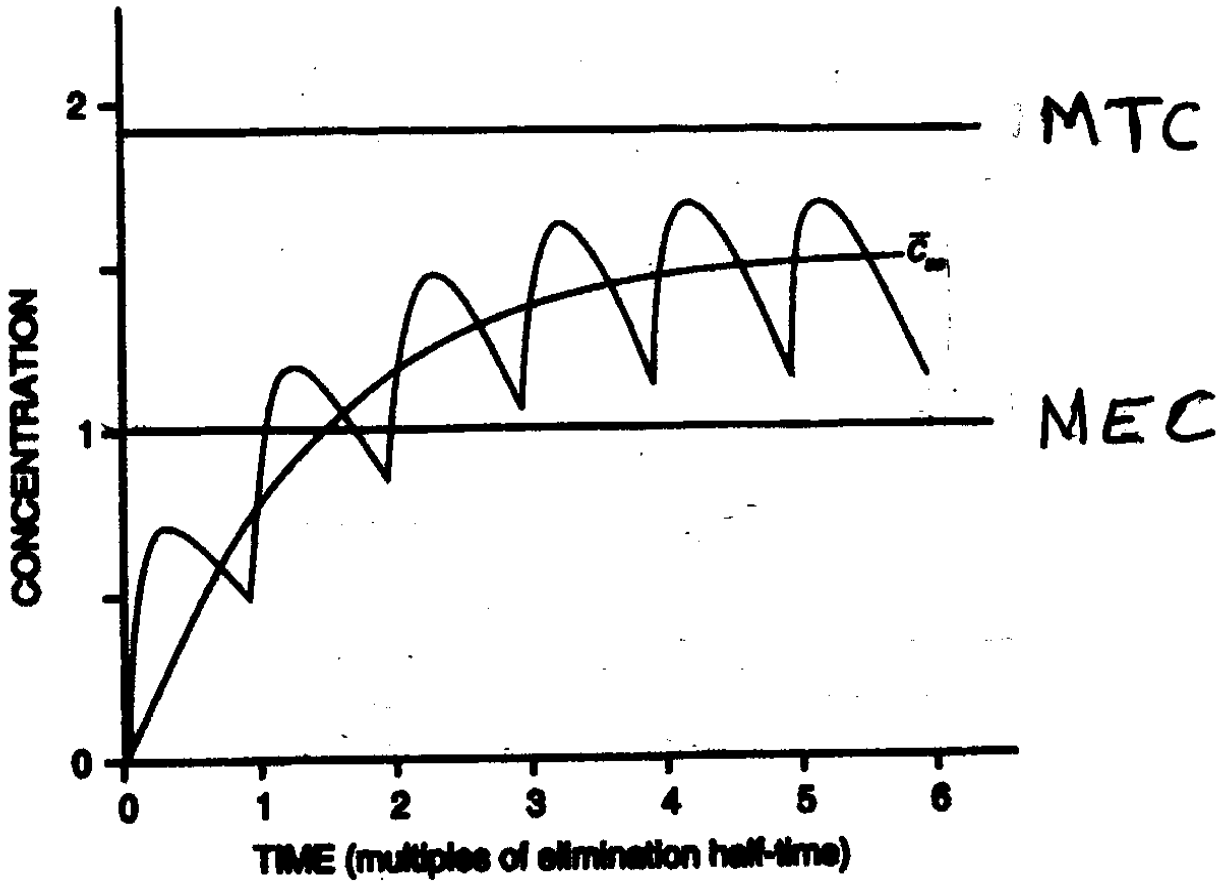
- **For a drug given every half-life, the accumulation factor is 1/0.5 = 2**
- **Accumulation factor predicts the ratio of plasma drug concentration at steady-state to that seen at the same time following the first dose.**
- **Peak concentration at steady-state is equal to peak concentration after first dose multiplied by the accumulation factor.**

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 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 a subtherapeutic or toxic C_{ss}.**


MTC
MEC
$\bar{c}_{ss}$
CONCENTRATION
2
1
0
0
1
2
3
4
5
6
TIME (multiples of elimination half-time)

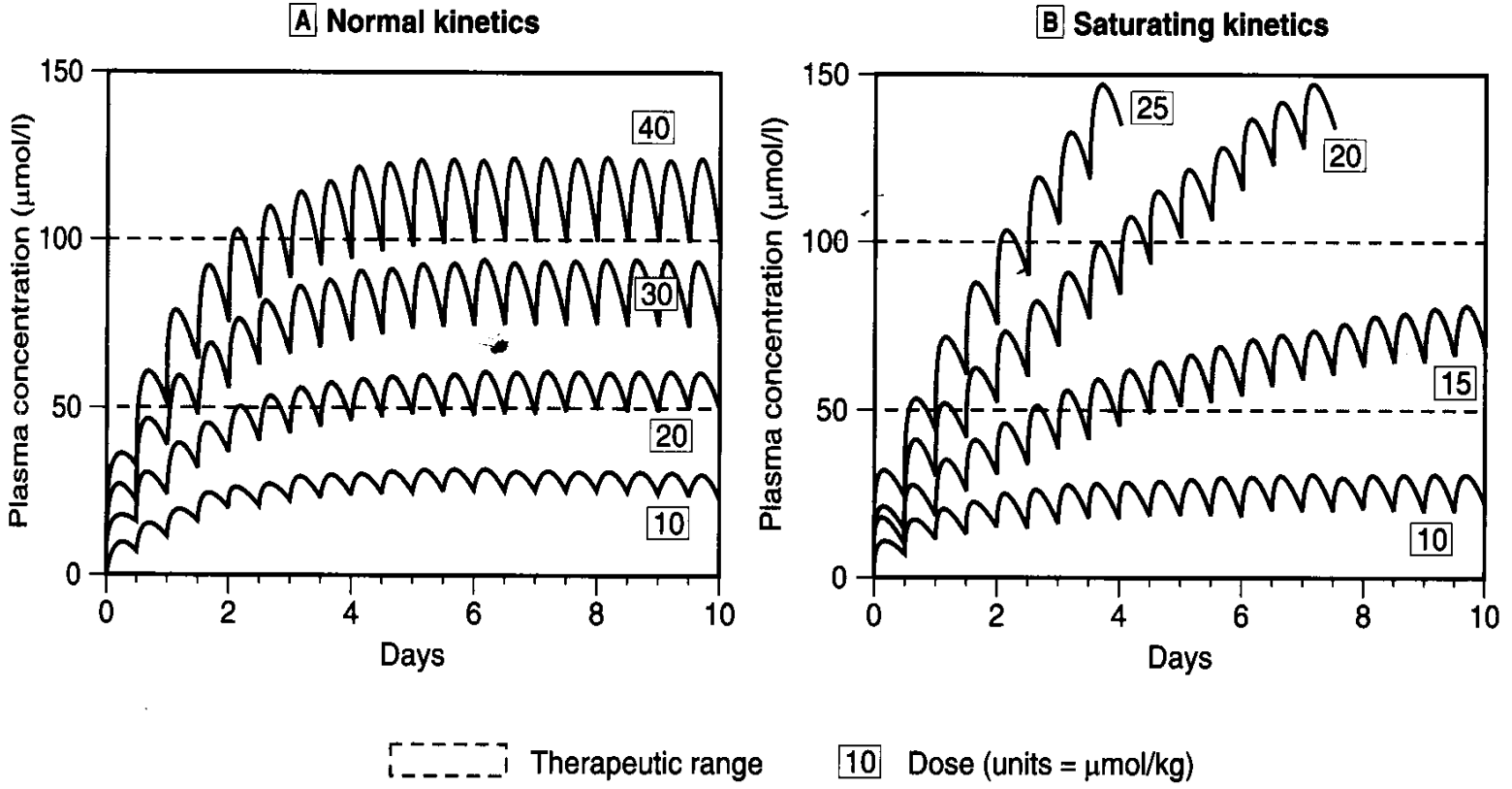


Fig. 5.13 Comparison of non-saturating and saturating kinetics for drugs given orally every 12 hours. A The curves show an imaginary drug, similar to the antiepileptic drug phenytoin at the lowest dose, but with linear kinetics. B The curves for saturating kinetics are calculated from the known pharmacokinetic parameters of phenytoin (see Ch. 36). Note (i) that no steady state is reached with higher doses of phenytoin and (ii) that a small increment in dose results after a time in a disproportionately large effect on plasma concentration. With linear kinetics the steady-state plasma concentration is directly proportional to dose. Curves were calculated with the 'Sympak' pharmacokinetic modelling program written by Dr J G Blackman, University of Otago.

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).**
- **$LD = V_D \,.\, Css_{desired}$ …….. (5)**

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 clearnce.**
- **MD = CL. $Css_{desired}$ …….. (6)**
- **$Css_{desired}$ is also called the target concentration.**

Problem

- **A drug has a volume of distribution of 7 L/Kg, and a half-life of 40 hours is to be given for a 70 Kg male patient. Its therapeutic concentration is 1 µg/mL. Find:**

1. **First-order elimination rate constant.**
2. **Clearance**
3. **Loading dose**
4. **Maintenance dose**
5. **Time needed to reach steady-state.**