General Pharmacology
(Pharmacokinetic II)
Principles of Pharmacology
(PP VI)

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- **<u>References:</u>**

- Basic & clinical pharmacology by Katzung

- Lippincott's illustrated reviews by Finkel, Cubeddu & Clark

- Clinical pharmacology by Laurence

Learning Objectives

At the end of pharmacokinetic lectures you should be able to

1. Describe the terms 'therapeutic window' and 'therapeutic range.'

2. Describe the relationship between plasma level and therapeutic response.

3. List three reasons why there may be no simple relationship between plasma level of parent drug and magnitude of the therapeutic response.

- 4. Define the terms 'clearance' (CL), half-life' (t½), volume of distribution' (V), and 'area under the curve' (AUC) as they relate to drug kinetic.

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5. State that: CL = Clrenal + Clhepatic, and be able to predict the consequence of change in either component on the plasma drug concentrations.

6. Predict the concentration of a drug immediately after i.v. administration, given an apparent V in litres from a text.

7. Draw a graph to depict the plasma level profile of a drug given by i.v. infusion, and identify the factors that determine the shape of this graph.

8. State that at steady state: Administration Rate = Elimination Rate

- 9. Define the term 'bioavailability' (F), state the use of AUC values to calculate F.

- 10. Explain the basis underlying zero-order and first-order kinetics of drug elimination from plasma. Give examples of drugs which are metabolized according to these kinetics.

- 11. Describe the relationship between pH, pKa, and degree of ionisation of acidic and basic drugs, and use this relationship to predict movements of drugs across membranes at various sites of the body.

- 12. List the factors that influence drug absorption from the skin, lungs, and muscle.

13.List the factors that determine the rate and extent of distribution of a

drug

14.Predict the distribution of a drug, given its volume of distribution

15.Describe the 1- and 2-compartment models of drug distribution

16. Describe the processes involved in reversible and irreversible binding of drugs to lipids, tissue proteins, and plasma proteins. Describe the effect of plasma and tissue binding of drugs on their distribution in the body

17.Describe the mechanisms underlying placental transfer of drugs

18. Describe the mechanisms underlying transfer of drugs across the .blood-brain barrier

19. Outline, with examples, the principal routes by which drugs may be metabolized.

20. Describe the physico-chemical consequences of drug metabolism

21. Describe the pharmacological consequences of drug metabolism

22. List, with examples, the factors that may modify the level of metabolism of a drug.

23. Describe the processes involved in biliary excretion of drugs, and give examples of drugs excreted principally by this route

24. Define the term 'enterohepatic recirculation' of drugs, and indicate its possible consequences on pharmacological action

Give examples of drugs eliminated in the expired air and milk

25. Describe the processes involved in the excretion of drugs in the urine$_2$

26. Indicate how knowledge of the renal clearance of a drug may help in elucidating the renal handling of that drug

27. Indicate the basis for determining modification of drug dosage in renal failure

List the possible causes for inter-individual variation in drug
28. response

29. Describe, with examples, the pharmacokinetic and pharmacodynamic bases underlying drug-drug interactions.

- 30. Describe the phenomenon of genetic polymorphism as it relates to drug treatment

- 31. Describe the mechanisms underlying the genetic polymorphism in the metabolism and effects of suxamethonium, isoniazid, and CYP2D6 substrates

- 32. Describe the mechanism underlying the genetic polymorphism in erythrocyte glucose-6-phosphate dehydrogenase activity as it relates to oxidant drugs

- 33. Describe the phenomenon of drug-induced malignant hyperthermia

- **<u>PHARMACOKINETIC PROCESSES:</u>**
- Are the processes whereby drugs are absorbed into, distributed around, metabolized by enzyme and excreted from the body (ADME).
- Common to all these processes is the necessity of drugs to pass across cell membrane.

- **<u>DRUGS PASSAGE ACROSS CELL MEMBRANES:</u>**
- It means the mechanisms by which drugs move across membrane barriers.
- The passage of drugs across membrane is determined by the natural processes of filtration, carrier mediated transport and diffusion.

- **1)	Filtration**: Aqueous channels in the tight junctions between adjacent epithelial cells allow the passage of some water-soluble (hydrophilic) substances.

- Neutral or uncharged molecules (non-polar) pass most readily since the pores are believed to be electrically charged.

  **2)	Carrier-Mediated transport:** (needs energy): some drugs move into or out of the cells against concentration gradient. (Active Transport).

- **3)	Diffusion:** it's the most important mean by which a drug enters tissues and distributed throughout them.

- simply is a movement of particles according to concentration gradient from high to low concentrations (natural tendency).

- **PHYSIOCHEMICAL CLASSIFICATION OF DRUGS:**
- Electrolytes (ionized)
- Drugs that are incapable of becoming ionized.
- Permanently ionized.

- **ELECTROLYTES:** They are drugs that are "variably" ionized, according to environmental pH.
- Many drugs are weak electrolytes which mean that their structural groups ionize to a greater or lesser extent according to environmental pH.
- i.e. drugs are present partly in the ionized form and partly in the no ionized form.

- **THE EFFECT OF INONIZATION OF DRUGS ON THEIR DIFFUSIABILITY**

- Non-ionized = non-polar = lipid soluble = diffusible

- Ionized = polar = lipid insoluble = non diffusible

- **<u>PH VARIATION AND DRUG KINETICS:</u>**
- There is a wide range of pH values in the gut - 7stomach= 1.5, upper intestine= 6.8, lower intestine= 7.6

- But pH inside the body (away from the gut) is maintained within a limited pH range of 7.4 $\pm$ 0.04·

- So, only drugs which are non-ionized at this pH will be "lipid soluble" and so are diffusible across tissue barriers and membranes. So, they're widely distributed into far areas like CNS.

- **For example** Aspirin (acetyl salicylic acid) with pKa of 3.5 (the lower the pKa, the more the acidity and vice versa) So, Aspirin in the stomach (acidic medium) is unionized and becomes lipid soluble and diffusible.

- pKa: measure of strength of interaction of compounds with proton.

- Then after diffusion it will enter the gastric epithelial cells where pH is 7.4 (slightly Alkaline), so it will become IONIZED and become LIPID INSOLUBLE thus becomes LESS DIFFUSIBLE.

- Then it will be localized there (in the gut epithelial cells) and become harmful for mucosa and it will remain in the ECF until elimination.

- Eventually, the molecules of Salicylic Acid (Aspirin) in the plasma will be filtered by glomeruli into the tubular fluid which is more acidic than plasma.

- Then a portion of Aspirin becomes UNIONIZED (LIPID SOLUBLE), so it will diffuse back into the tubular cells.

- **Note:** Urine Alkalization will prevent reabsorption and facilitate its elimination in the urine and this could be used in case of Aspirin poisoning.

- **2)DRUGS THAT ARE INCAPABLE OF BECOMING IONIZED:**
- This type of drugs includes Digoxin, Chloramphenicol (antibiotic).
- They have no ionized group " so they are unaffected by environmental pH and they are permanently LIPID SOLUBLE.
- So, they can cross tissue barriers easily and they are NON-POLAR at all values of pH.

- **3)PERMANENTLY IONIZED DRUGS:**
- They remain ionized at all values of pH. They are POLAR (either -ve or +ve charged).

- **For example:**
- Heparin (-ve)
- Tubocurarine (muscle relaxant) (+ve)
- Suxamethonium (+ve)
- These drugs have limited capacity to cross membranes or barriers.

- **BARRIERS:**

1) **<u>BLOOD-BRAIN BARRIER (BBB):</u>** represents constraints of the passage of drugs from blood to brain and CSF, so lipid insoluble compounds do not cross this barrier readily like (Atenolol) (antihypertensive) so it has no side effects on CNS.

   While lipid insoluble drugs like (Propanalol) (antihypertensive) can cross this barrier, so it has CNS side effects.

Also, (Methotrexate) (anti-cancer) is lipid insoluble so it has no effect on leukemia deposit in CNS, while (Diazepam) is lipid soluble so enters brain easily. When is given IV it's effective in cases of Epilepsy

2) PLACENTA: Fetal and maternal blood streams are separated by a lipid barrier that readily allows only lipid soluble drugs to pass, while excludes water soluble drugs especially when their molecular weight is over 600.

This exclusion is very important with short-term use of drugs as: Tubocurarine (water soluble) which is used as muscle relaxant during CS so it's not harmful for the fetus as it doesn't cross the placenta.

ABSORPTION:

It's the process by which a drug is made available for the fluids distribution.

The rate of absorption depends on :

1)The method of administration

2)Drug solubility and chemical properties:

The use of drugs almost always involves the transfer of these agents into blood stream EXCEPT in case of local applications on skin or mucous membranes or in case of Oral administration of drugs that act within the gut lumen as (Antacids) and (Laxatives), But even in these cases still there is some absorption into blood While IV routes BYPASS the absorption process.

PHYSICAL FACTORS INFLUENCING ABSORPTION:

1) <u>Blood flow to the absorption site</u>: as the blood flow to intestines is much more than that to the stomach, the intestine has much faster rate of absorption than that of the stomach.

2) <u>Total surface are at absorption surface</u>: because intestines have a surface rich in microvilli, they have a surface area 1000 times greater than that of the stomach, thus absorption across intestine is more efficient.

3) <u>Contact time at absorption site</u>: if a drug moves through GIT quickly (diarrhea), it's not well absorbed, conversely anything that delays the transport of drug from stomach to intestine delays the rate of absorption of the drug.

   Also, delayed gastric emptying of drugs taken with food will also slow down absorption.

SYSTEMIC AVAILIBILITY AND BIOAVAILABILITY:

BIOAVAILABILITY: is the fraction of UNCHANGED drug (non metabolized) reaching the systemic circulation following administration by any route.

When a drug injected IV, it will enter systemic circulation and then gain access to the tissues and receptors which means it's 100% available to exert its therapeutic effect so its Bioavailability is 100%.

If the same drug was taken orally, it will reach the portal circulation first, then systemic circulation. This means that its therapeutic effect (Bioavailability) will be less than 100%, BECAUSE OF:

1) Incomplete absorption.

2) Metabolism in the gut wall, portal blood or liver before reaching systemic blood causing some of the drug in systemic blood to be changed.

The Main site of metabolism is the LIVER.

- **FACTORS INFLUENCING BIOAVAILABILITY:**

- 1)first-pass hepatic metabolism:
  If the drug is readily metabolized in the liver, the amount of unchanged drug gains access to systemic blood is DECREASED for example: Propanalol and Lidocaine (anesthetic).

- 2)Chemical instability:
  Drugs such as (Penicillin-G) are unstable in the pH of gastric contents. Others as (Insulin) may be destroyed in the GIT by enzymes.

3)Solubility of Drugs:

VERY HYDROPHILIC drugs are poorly absorbed (cannot cross lipid membranes), EXTREMEL Y HYDROPHOBIC drugs are also poorly absorbed totally in aqueous body fluid.

For a drug to be readily absorbed, it must be LARGELY HYDROPHOBIC yet have some solubility in aqueous solution.

4)Nature of drug formulation:

Absorption may be altered or changed by factors that are not related to the chemistry of the drug but rather due to particle size, salt form, presence of Excipients, binders and dispersing

agents.
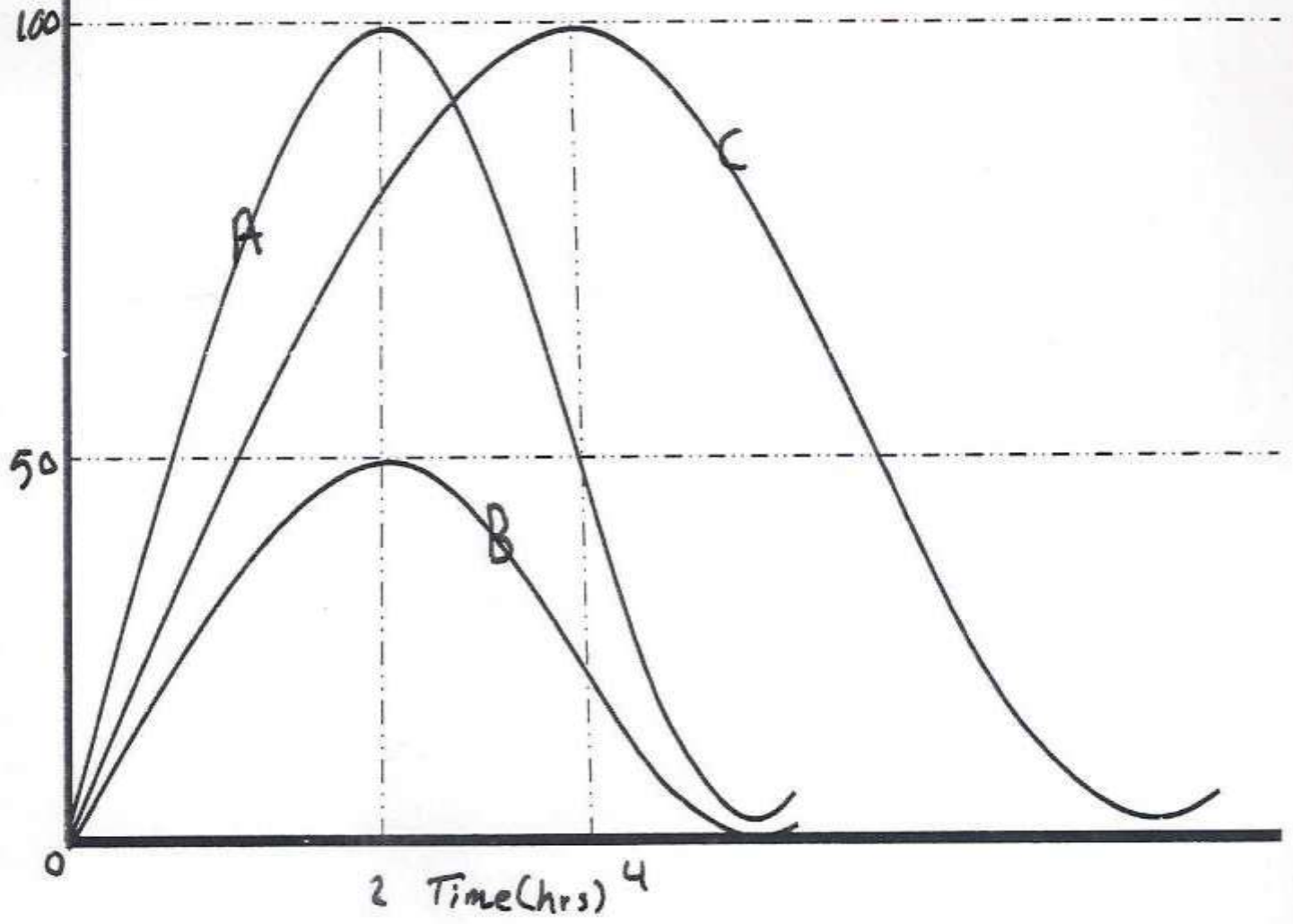
- **A:** a drug RAPIDLY and COMPLETELY available.
- **B**: a drug RAPIDLY but INCOMPLETELY available.
- **C:** a drug COMPLETELY available but NOT RAPIDLY, its rate is only 1/2 that of A.

- In the figure above, we have 3 dosages A, B and C.
- A and B are absorbed into the blood at the same rate but twice as fast as the dose C.
- This means, the time at which peak concentration is identical for A and B and occurs earlier than peak time of C.
- The order of peak times following drug administration corresponds to the rate of availability of the drug of various dosages forms.

- **THE RATE OF AVAILABILITY MAY BE MEASURED BY USING:**

- Drug concentration in blood, or
- Amount of drug in urine.
- Drugs A and B are identical in the rate of availability but differ in drug concentration in blood (100% or 50%)
- The area under curve of a drug (AUC):
- It's a common measure of the availability.
- AVC for A and C are the same, but they are twice as that AUC of B.

- **<u>DETERMINATION OF BIOAVAILABILITY:</u>**
- It's determined by comparing plasma levels of a drug after a particular
- route of administration.
- Example: oral administration with plasma levels of I/V inj.
- Bioavailability = (AUC oral/AUC injection) x 100

cone (plasma)

drug injected

drug given orally

AUC injected

AUC oral

time
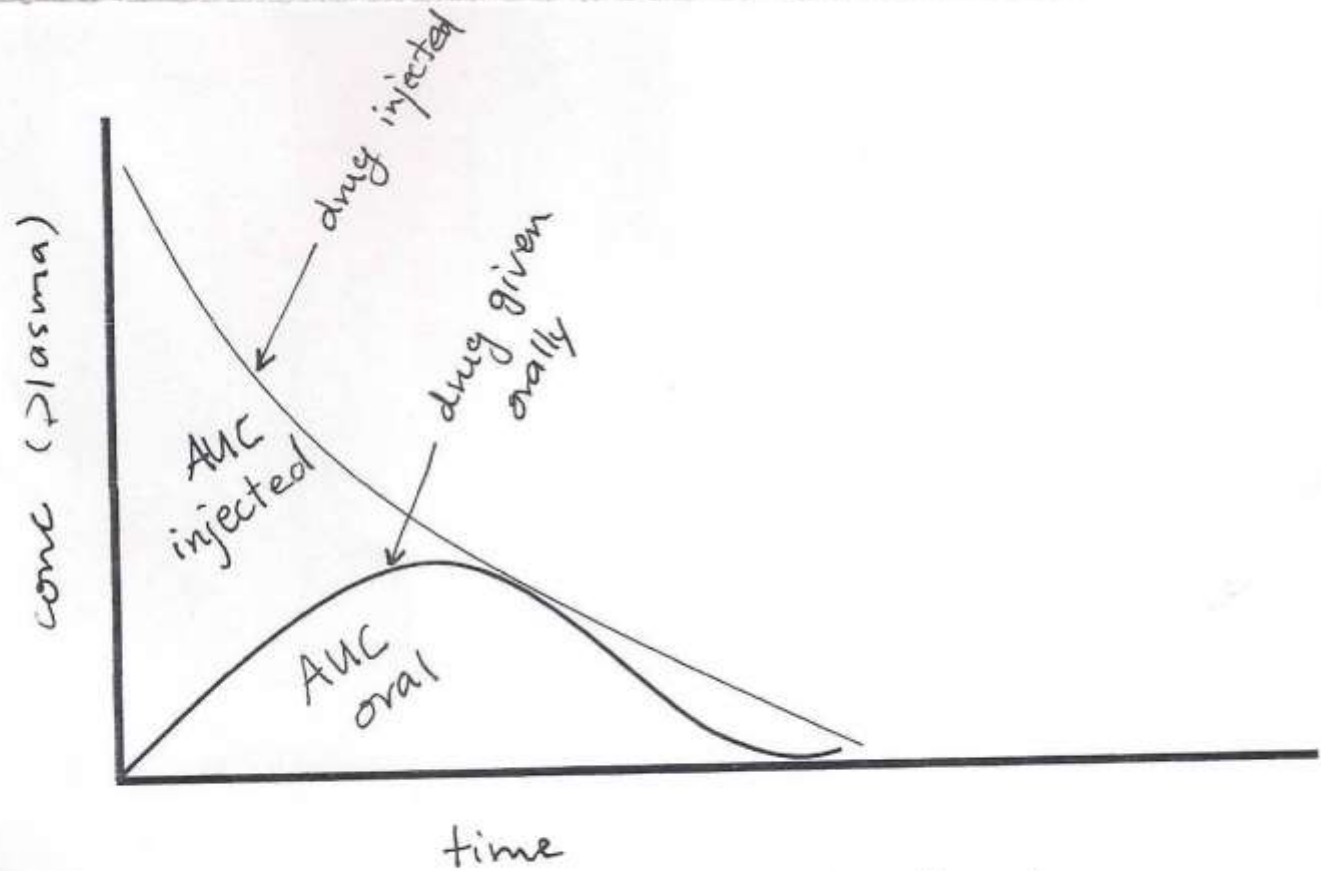
* Determination of Bioavailability of a drug.

- **LOADING DOSE :**
- It is the amount of drug required to achieve a given steady state concentration in the plasma and this is used in case of drugs with long half-life as (digoxin and warfarin).

- **Maintenance dose:** the amount of drug required to maintain a steady state of drug in the body(just enough drug is given in each dose to replace the drug eliminated since the previously dose)

- **<u>Distribution:</u>** It is the process by which a drug is reversibly leaves blood stream and enters the interstitium (ECF) and/or the cells of the tissues. In other words , for drugs required to reach an organ inaccessible to topical application, it must go into the blood and then be distributed into the body compartments.

- **<u>Distribution depends on:</u>**

- Blood flow.
- Capillary permeability.
- The degree of drug binding to tissue proteins and plasma.
- Relative hydrophobocity of drug.
- So, most drugs are distributed widely to body water (dissolved)
- In part are bound to tissue and plasma proteins. if the drug is bound to plasma protein,it may remain in the vascular compartment until elimination.

- Water soluble drugs(drugs of small molecular weight) may be freely distributed in total body water.

- Lipid soluble drugs ultimately distributed to fat.

- Heavy ions or metals(e.g.fluoride) slowly squestrated into bone and localized there.

- The above are the real volumes (compartments) of potential drug distribution.

Factors contributing to the unequal distribution of drugs:

1) Binding to plasma protein: it causes a higher concentration of the drug in blood than in ECF (decrease distribution). it provides a depot, since the bound portion of drug is in equilibrium with the free form

- As the bound fraction is excreted or metabolized, additional amount are dissociated from the protein.
- Protein binding prolongs the half-life of the drug, since the bound fraction is not filtrated and not exposed to metabolism until freed.

- **2)Cellular binding** :it's usually a result of an affinity of some molecular structures ,the high concentration of antimalarial drugs (quinocrine) in liver cells or muscles is probably caused by the affinity of the nucleo-proteins.

- **3) Blood brain barrier(BBB)**: a unique example of unequal distribution of drugs

- Even when given IV, many drugs failed to penetrate the CNS,CSF or aqueous humour as rapidly as do other tissues.

- **<u>VOLUME OF DISTRIBUTION (VD):</u>**

- It is a hypothetical volume of fluid into which the drug is disseminated, in other words .it's the measure of the apparent space in the body available to contain the drug.

- Sometimes .it's useful to compare the distribution of a drug with the volumes of water compartments in the body.

Water compartments in the body:

- **Plasma compartment:** it's about 6% of body weight in a 70 kg individual (about 4.2 liters)of body fluids.

- **Extracellular fluid**: it's about 20% of body weight in a 70 kg individual (about 14 liters)of body fluid.

- **Total body fluid:** it's about 60% of body weight in a 70 kg individual (about 42 liters)of body fluid.

- **Other site:** in pregnancy, the volume of distribution increase. drugs that are lipid soluble may show unusually high volume of distribution e.g. thiopental.

- The volume of distribution relates the amount of drug in the body to the concentration (c) of drug in the blood or plasma.

- VD = amount of drug in the body / (C)
- C: is the concentration of drug in the blood or plasma.
- It's defined in terms of blood or plasma concentration depending upon fluid measured.
- VD is sometimes useful to compare distribution of drug with the volumes of water compartment in the body.
- total body water (plasma) interstitial volume,intracellular volume= 42 liters.
- plasma volume of a 70 kg man = 4.2 liters.
- blood volume = 5.5 liters.
- ECF outside plasma = 12.0 liters.
- many drugs exhibit volume of distribution .far in excess of the above body fluid volume.

- e.g. 500 mg of digoxin in the body of a healthy 70 kg male will show a plasma concentration of O. 78 ng/ml of blood.

  By dividing 500 mg/O.78 ng/ml in the body➡Vd for digoxin is 645 L and this value is about 9 times the body volume of a 70kg man.

- The above result means Vd does not represent a real volume, but it must be considered as the size of the pool of the body fluids, required if the drug is distributed equally throughout all portions of the body.

- Digoxin distributes mostly into muscles and adipose tissue leaving a small concentration (0.78) in plasma because it's a hydrophobic drug.

Thank you