

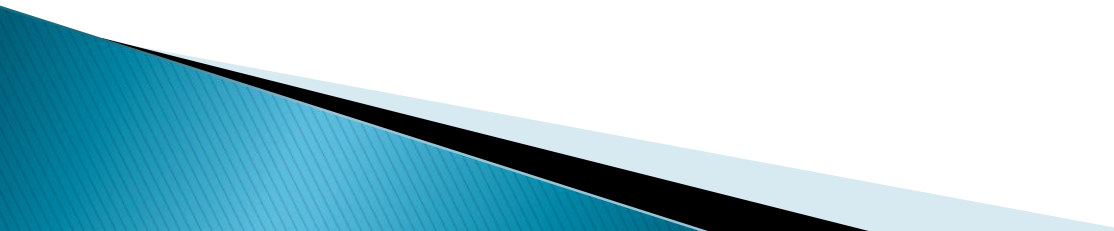
Biopharmaceutics

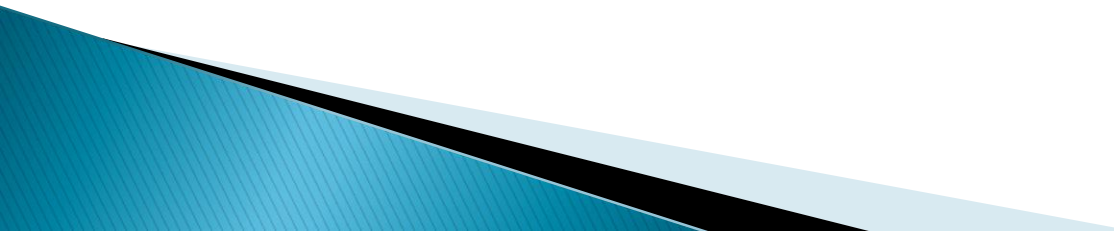
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Reference text

Shargel L., Yu AB

Applied Biopharmaceutics and
Pharmacokinetics

- ▶ To illustrate the importance of the drug substance and the drug formulation on absorption, and distribution of the drug to the site of action, one must first consider the sequence of events that precede elicitation of a drug's therapeutic effect.
 - ▶ First, the drug in its dosage form is taken by the patient either by an oral, intravenous, subcutaneous, transdermal, etc., route of administration.
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- ▶ Next, the drug is released from the dosage form in a predictable and characterizable manner.
 - ▶ Then, some fraction of the drug is absorbed from the site of administration into either the surrounding tissue, into the body (as with oral dosage forms), or both.
 - ▶ Finally, the drug reaches the site of action.
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- ▶ If the drug concentration at the site of action exceeds the *minimum effective concentration* (MEC), a pharmacologic response results. The actual dosing regimen (dose, dosage form, dosing interval) was carefully determined in clinical trials to provide the correct drug concentrations at the site of action.
- ▶ This sequence of events is profoundly affected—in fact, sometimes orchestrated—by the design of the dosage form, the drug itself, or both.

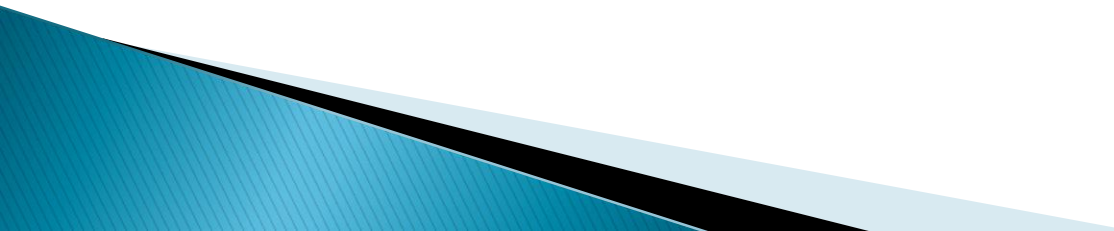
- ▶ Historically, pharmaceutical scientists have evaluated the relative drug availability to the body *in vivo* after giving a drug product to an animal or human, and then comparing specific pharmacologic, clinical, or possible toxic responses.
- ▶ For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level.

- ▶ In addition, the **bioavailability** (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug, even for the same route of administration.
- ▶ This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products.

In other words, the nature of the drug molecule, the route of delivery, and the formulation of the dosage form can determine whether an administered drug is therapeutically effective, toxic, or has no apparent effect at all.

Biopharmaceutics

- ▶ **Biopharmaceutics** is the science that examines this interrelationship of the physicochemical properties of the drug, the dosage form in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption

- ▶ Thus, biopharmaceutics involves factors that influence
 - (1) the stability of the drug within the drug product,
 - (2) the release of the drug from the drug product,
 - (3) the rate of dissolution/release of the drug at the absorption site, and
 - (4) the systemic absorption of the drug. A general scheme describing this dynamic relationship is described in Figure 1-1.
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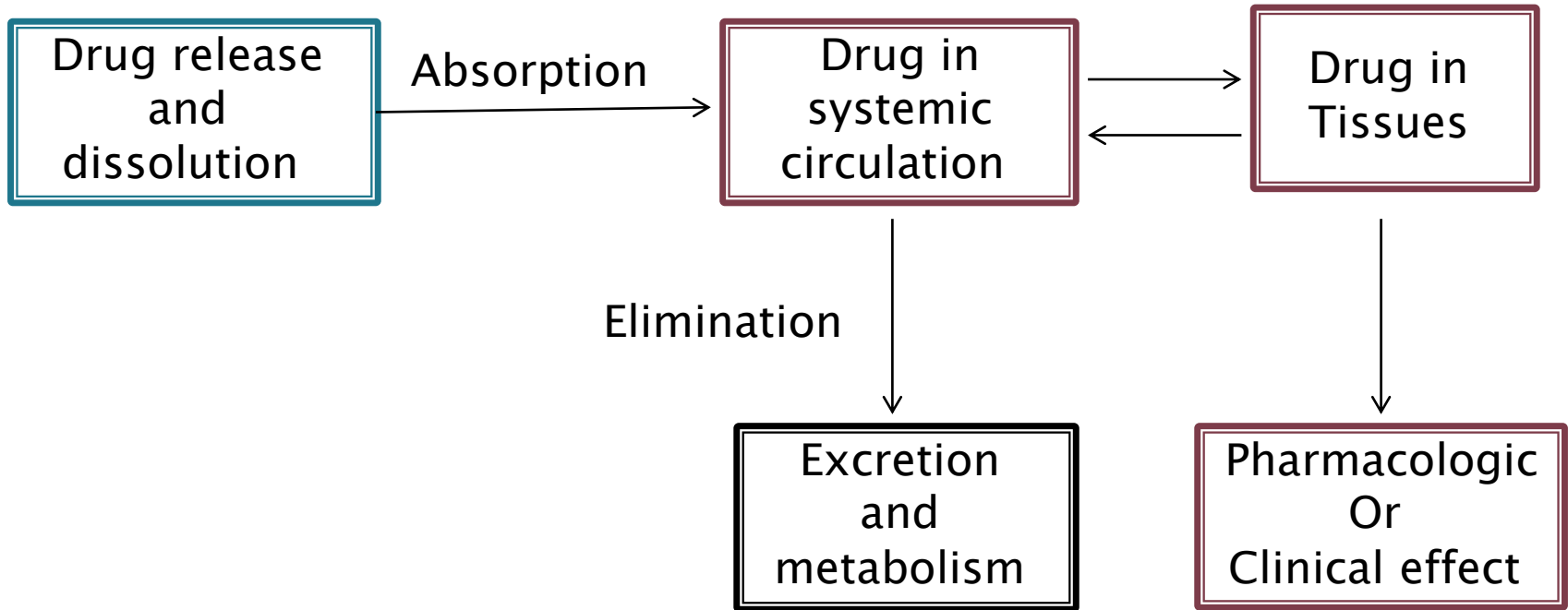
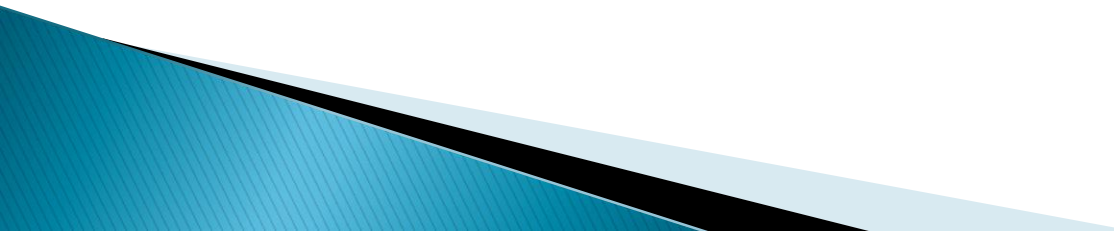
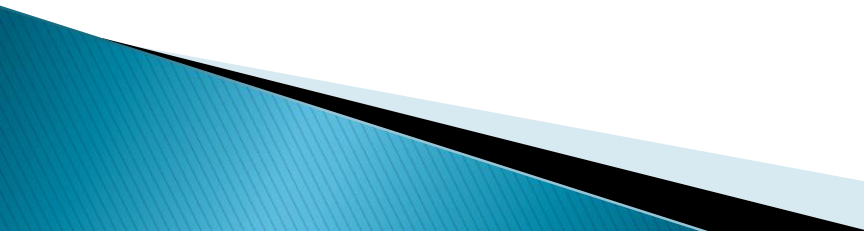
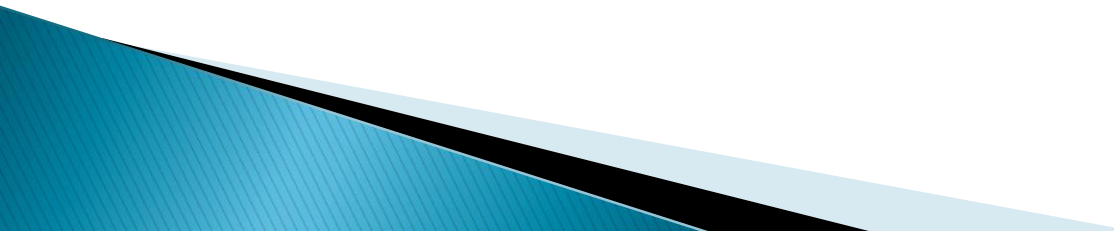


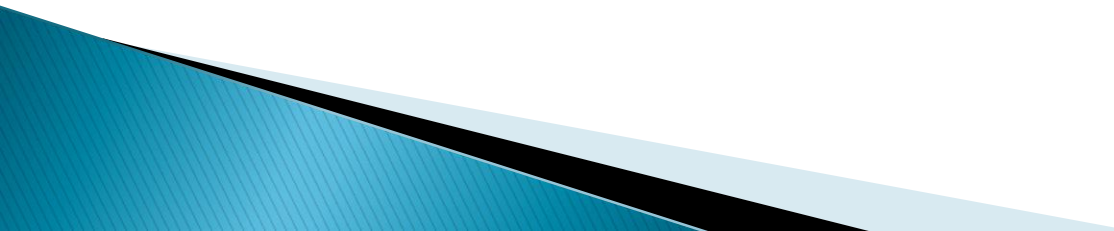
Figure 1-1 Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

- ▶ The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology.
 - ▶ Studies in biopharmaceutics use both *in-vitro* and *in-vivo* methods.
 - ▶ *In-vitro* methods are procedures employing test apparatus and equipment without involving laboratory animals or humans.
 - ▶ *In-vivo* methods are more complex studies involving human subjects or laboratory animals.
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- ▶ These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability, and large-scale production of the drug and drug product on the biologic performance of the drug.
 - ▶ Moreover, biopharmaceutics considers the properties of the drug and dosage form in a physiologic environment, the drug's intended therapeutic use, and the route of administration.
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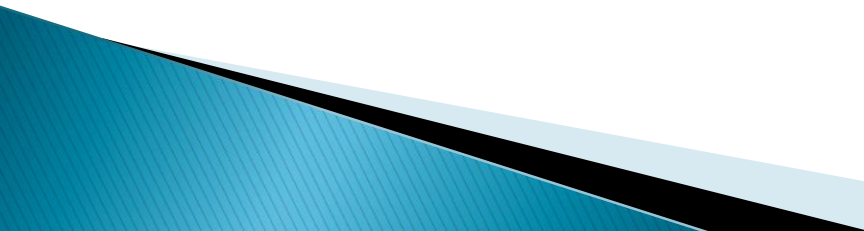
Pharmacokinetics

- ▶ After a drug is released from its dosage form, the drug is absorbed into the surrounding tissue, the body, or both.
 - ▶ The distribution through and elimination of the drug in the body varies for each patient but can be characterized using mathematical models and statistics.
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- ▶ Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (i.e., excretion and metabolism).
 - ▶ Characterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for individuals and groups of patients.
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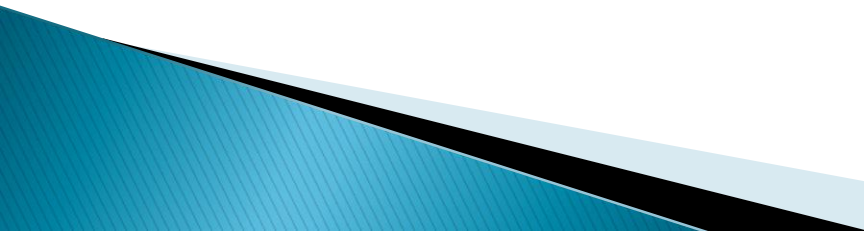
- ▶ Pharmacokinetics is also applied to therapeutic drug monitoring (TDM) for very potent drugs such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity.
- ▶ For these drugs, it is necessary to monitor the patient, either by monitoring plasma drug concentrations (e.g. Theophylline) or by monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (e.g. Warfarin)

Pharmacodynamics

- ▶ Pharmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with receptor.
 - ▶ The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacologic or toxic response.
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- ▶ Pharmacokinetic–pharmacodynamic models are constructed to relate plasma drug level to drug concentration in the site of action and establish the intensity and time course of the drug.

Measurement of drug concentrations

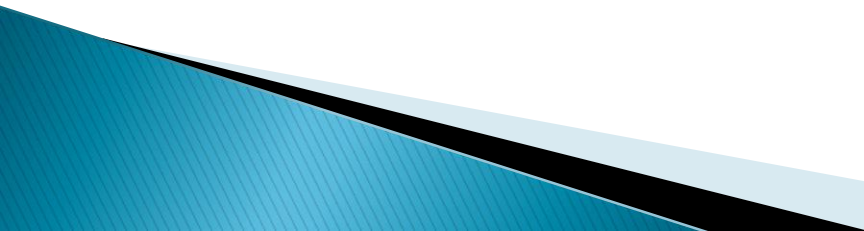
- ▶ because drug concentrations are an important element in determining individual or population pharmacokinetics, drug concentrations are measured in biologic samples, such as milk, saliva, plasma, and urine.
 - ▶ Sensitive, accurate, and precise analytical methods are available for the direct measurement of drugs in biologic matrices. Such measurements are generally validated so that accurate information is generated for pharmacokinetic and clinical monitoring.
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- ▶ In general, chromatographic methods are most frequently employed for drug concentration measurement, because chromatography separates the drug from other materials that may cause assay interference.

Sampling of Biologic Specimens

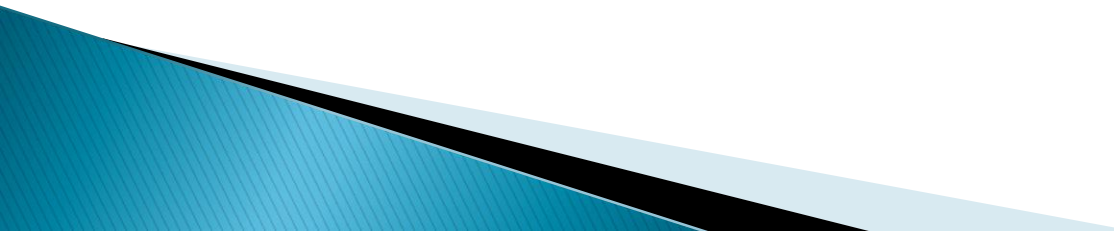
- ▶ Only a few biologic specimens may be obtained safely from the patient to gain information as to the drug concentration in the body.
- ▶ *Invasive methods* include sampling blood, spinal fluid, synovial fluid, tissue biopsy, or any biologic material that requires parenteral or surgical intervention in the patient.
- ▶ In contrast, *noninvasive methods* include sampling of urine, saliva, feces, expired air, or any biologic material that can be obtained without parenteral or surgical intervention.
- ▶ The measurement of drug and metabolite concentration in each of these biologic materials yields important information, such as the amount of drug retained in, or transported into, that region of the tissue or fluid, the likely pharmacologic or toxicologic outcome of drug dosing, and drug metabolite formation or transport.

Drug Concentrations in Blood, Plasma, or Serum

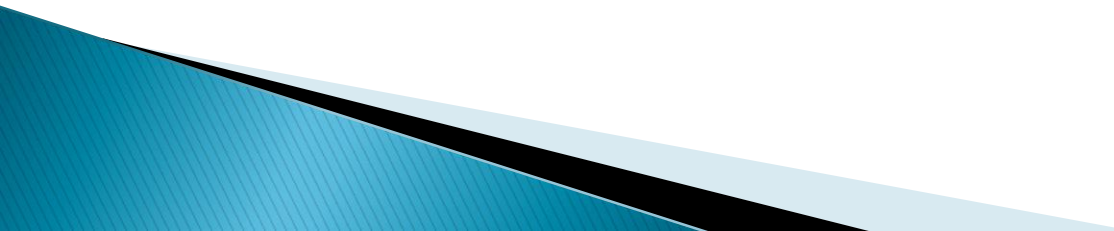
- ▶ Measurement of drug concentration (levels) in the blood, serum, or plasma is the most direct approach to assessing the pharmacokinetics of the drug in the body. Whole blood contains cellular elements including red blood cells, white blood cells, platelets, and various other proteins, such as albumin and globulins.
 - ▶ In general, serum or plasma is most commonly used for drug measurement. To obtain serum, whole blood is allowed to clot and the serum is collected from the supernatant after centrifugation.
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- ▶ Plasma is obtained from the supernatant of centrifuged whole blood to which an anticoagulant, such as heparin, has been added. Therefore, the protein content of serum and plasma is not the same.
- ▶ Plasma perfuses all the tissues of the body, including the cellular elements in the blood. Assuming that a drug in the plasma is in dynamic equilibrium with the tissues, then
- ▶ changes in the drug concentration in plasma will reflect changes in tissue drug concentrations.

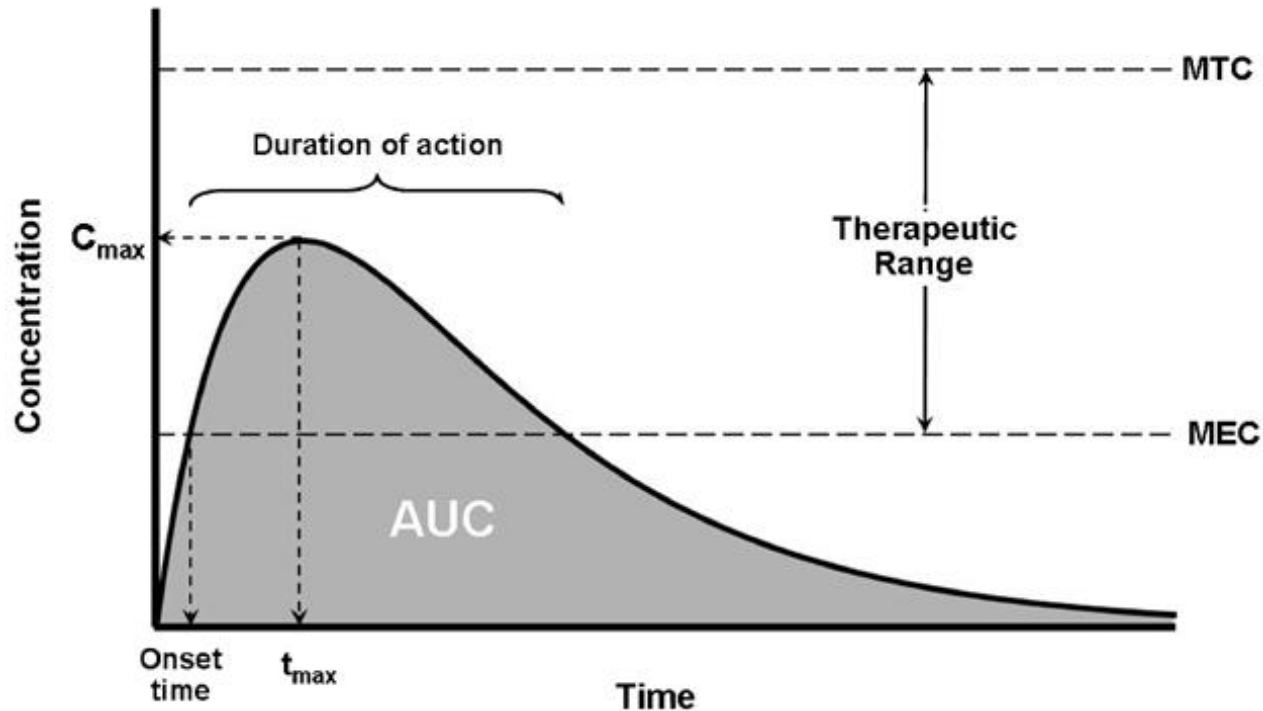
Differences between plasma and serum

1. Plasma is the part of the blood that contains both the serum and clotting factors.
 2. Serum is the part of the blood that remains once the clotting factors like fibrin have been removed.
 3. Plasma contains the clotting factors and water, while serum contains proteins like albumin and globulins.
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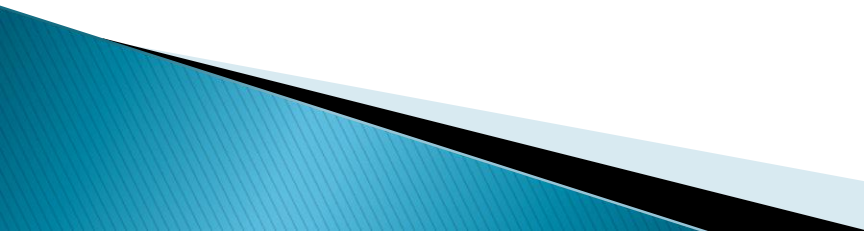
Plasma Level–Time Curve

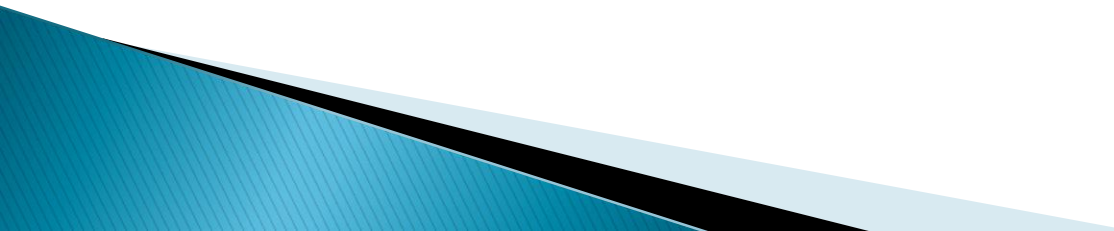
- ▶ The plasma level–time curve is generated by obtaining the drug concentration in plasma samples taken at various time intervals after a drug product is administered.
 - ▶ The concentration of drug in each plasma sample is plotted on rectangular–coordinate graph paper against the corresponding time at which the plasma sample was removed.
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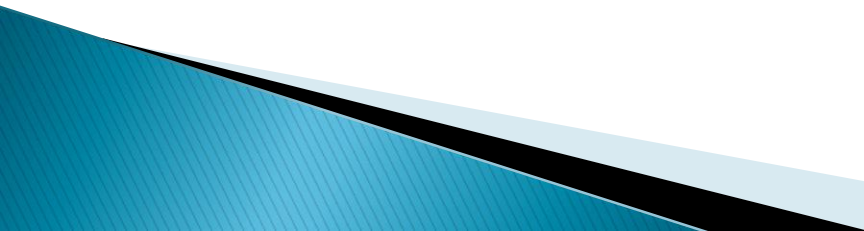
Generalized plasma level–time curve after oral administration of a drug




- ▶ As the drug reaches the general (systemic) circulation, plasma drug concentrations will rise up to a maximum. Usually, absorption of a drug is more rapid than elimination. As the drug is being absorbed into the systemic circulation, the drug is distributed to all the tissues in the body and is also *simultaneously* being eliminated. Elimination of a drug can proceed by excretion, biotransformation, or a combination of both.

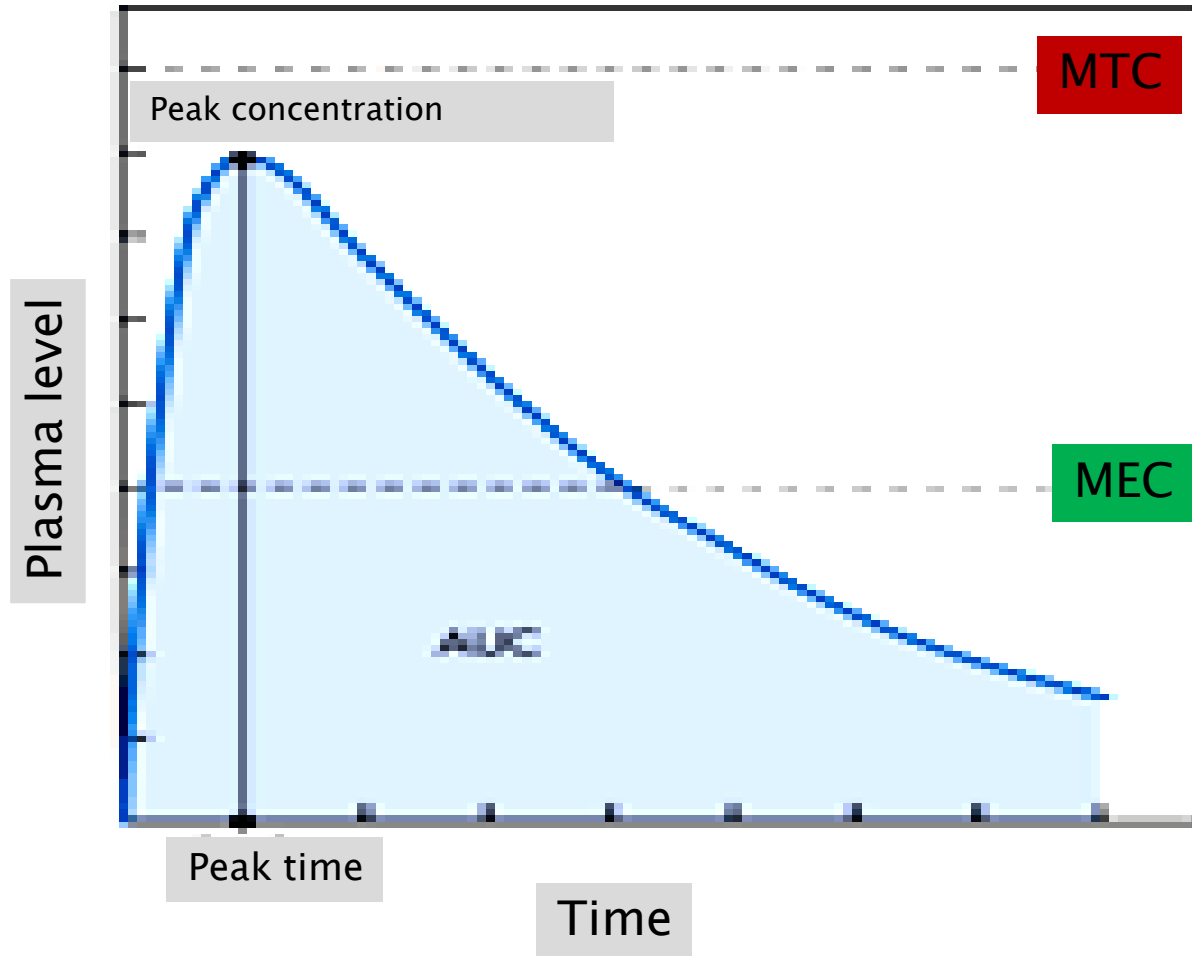
- ▶ The relationship of the drug level–time curve and various pharmacologic parameters for the drug is shown in.
 - ▶ MEC and MTC represent the minimum effective concentration and minimum toxic concentration of drug, respectively.
 - ▶ For some drugs, such as those acting on the autonomic nervous system, it is useful to know the concentration of drug that will just barely produce a pharmacologic effect (i.e., MEC).
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- ▶ Assuming the drug concentration in the plasma is in equilibrium with the tissues, the MEC reflects the minimum concentration of drug needed at the receptors to produce the desired pharmacologic effect.
 - ▶ Similarly, the MTC represents the drug concentration needed to just barely produce a toxic effect.
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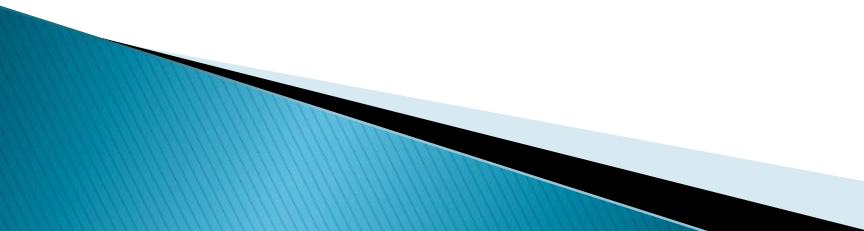
- ▶ The onset time corresponds to the time required for the drug to reach the MEC. The intensity of the pharmacologic effect is proportional to the number of drug receptors occupied, which is reflected in the observation that higher plasma drug concentrations produce a greater pharmacologic response, up to a maximum.
 - ▶ The duration of drug action is the difference between the onset time and the time for the drug to decline back to the MEC.
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- ▶ In contrast, the pharmacokineticist can also describe the plasma level–time curve in terms of such pharmacokinetic terms as peak plasma level, time for peak plasma level , and area under the curve , or (AUC).
 - ▶ The time of peak plasma level is the time of maximum drug concentration in the plasma and is a rough marker of average rate of drug absorption.
 - ▶ The peak plasma level or maximum drug concentration is related to the dose, the rate constant for absorption, and the elimination constant of the drug.
 - ▶ The AUC is related to the amount of drug absorbed systemically.
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Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

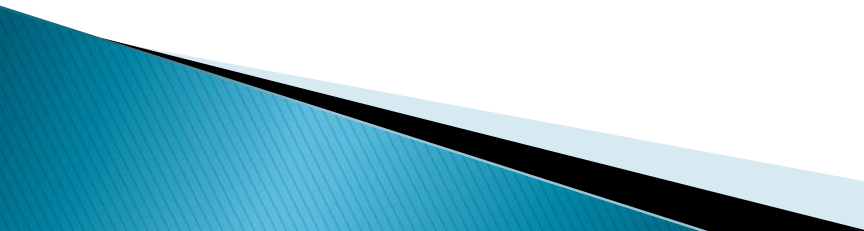


Drug Concentrations in Tissues

- ▶ tissue biopsies are occasionally removed for diagnostic purposes, such as the verification of a malignancy.
 - ▶ Usually, only a small sample of tissue is removed, making drug concentration measurement difficult.
 - ▶ Drug concentration in tissue biopsies may not reflect drug concentrations in other tissues nor the drug concentration in all parts of the tissue from which the biopsy material was removed.
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- ▶ For example, if the tissue biopsy was for diagnosis of a tumor within the tissue, the blood flow to the tumor cells may not be the same as the blood flow to other cells in this tissue.
- ▶ In fact, for many tissues, blood flow to one part of the tissues need not be the same as the blood flow to another part of the same tissue.
- ▶ The measurement of the drug concentration in tissue biopsy material may be used to ascertain if the drug reached the tissues and reached the proper concentration within the tissue.

Drug concentration in urine and feces

- ▶ Measurement of the drug in urine is an indirect method to ascertain the bioavailability of a drug.
 - ▶ The rate and extent of drug excreted in the urine reflects the rate and extent of systemic drug absorption.
 - ▶ Measurement of drug in feces may reflect drug that has not been absorbed after an oral dose or may reflect drug that has been expelled by biliary secretion after systemic absorption.
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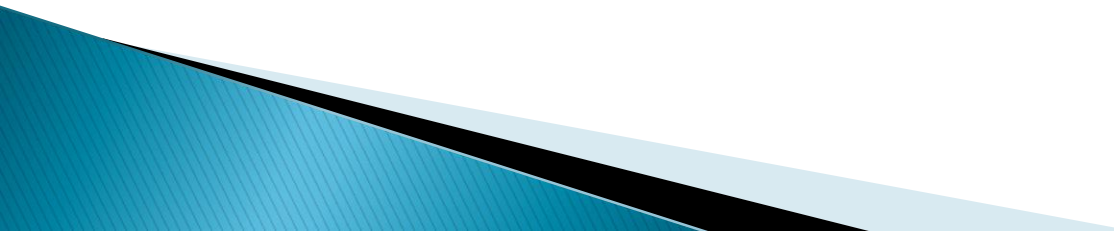
- ▶ Fecal drug excretion is often performed in mass balance studies, in which the investigator attempts to account for the entire dose given to the patient.
- ▶ for a mass balance study, both urine and feces are collected and their drug content measured.
- ▶ For certain solid oral dosage forms that do not dissolve in the gastrointestinal tract but slowly leach out drug, fecal collection is performed to recover the dosage form. The undissolved dosage form is then assayed for residual drug.

Drug concentration in saliva

- ▶ Saliva drug concentrations have been reviewed for many drugs for therapeutic drug monitoring.
- ▶ Because only free drug diffuses into the saliva, saliva drug levels tend to approximate free drug rather than total plasma drug concentration.
- ▶ The saliva/plasma drug concentration ratio is less than 1 for many drugs. The saliva/plasma drug concentration ratio is mostly influenced by the pKa of the drug and the pH of the saliva.

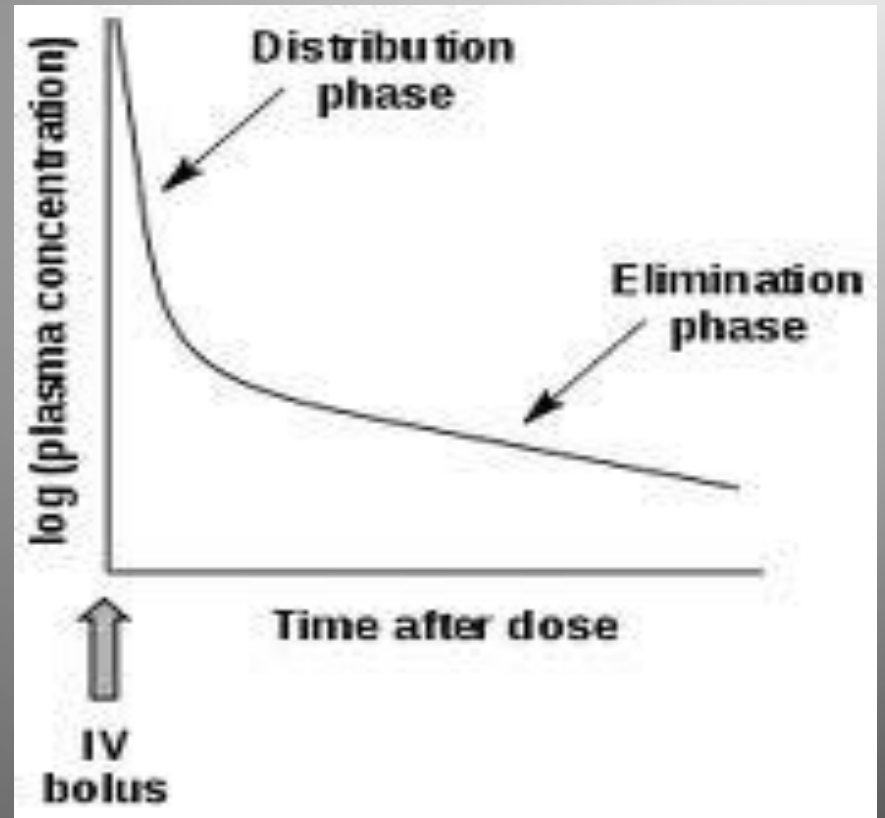
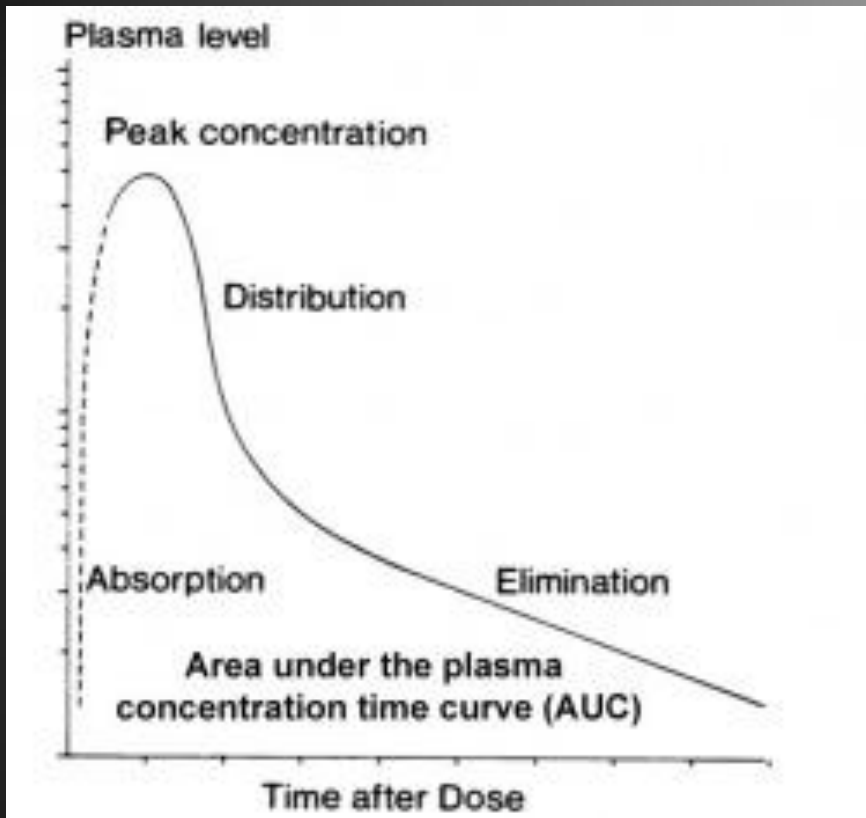
- ▶ Weak acid drugs and weak base drugs with pKa significantly different than pH 7.4 (plasma pH) generally have better correlation to plasma drug levels.
- ▶ The saliva drug concentration generally provide more stable indication of drug levels in the body.
- ▶ The use of salivary drug concentrations as a therapeutic indicator should be used with caution and preferably as a secondary indicator.

There are three factors must be considered in order to get reliable pharmacokinetics study including:

- ▶ Time of sampling
 - ▶ Frequency of sampling
 - ▶ How long we keep sampling
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➤ *Time of sampling*

We must try sampling as early as possible after drug administration in order to notice the absorption phase in case of extra vascular (any route other than i.v. i.e., oral, i.m., rectal) drug administration and to notice the distribution phase in case of i.v. Drug administration as presented by the following figures:



➤ *Frequency of sampling*

- ▶ We try sample as frequent as possible in order to notice any fluctuation on the plasma concentration of a drug because of enterohepatic circulation and redistribution of drug as in the following figures

➤ *How long we keep sampling*

- ▶ Keep sampling for at least 6–8 $t_{1/2}$
- ▶ For example atenolol $t_{1/2} = 1$ day so keep sample for 7 days

Dose	time (day)
100	0
50	1
25	2
12.5	3
6.25	4
3.125	5
1.6	6
0.8	7

▶ *Drug distribution can be studied by two approaches*

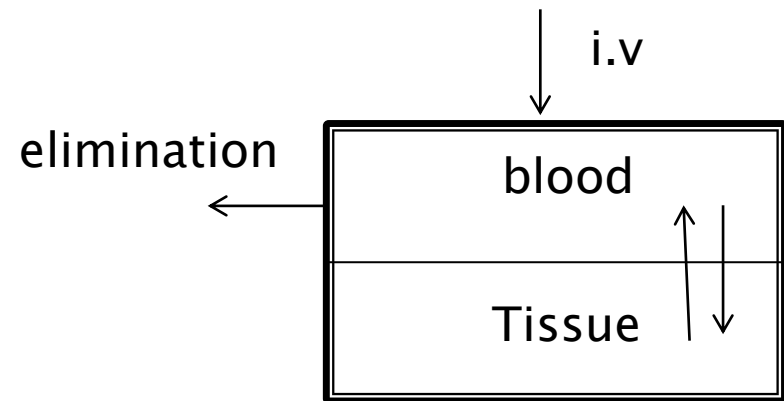
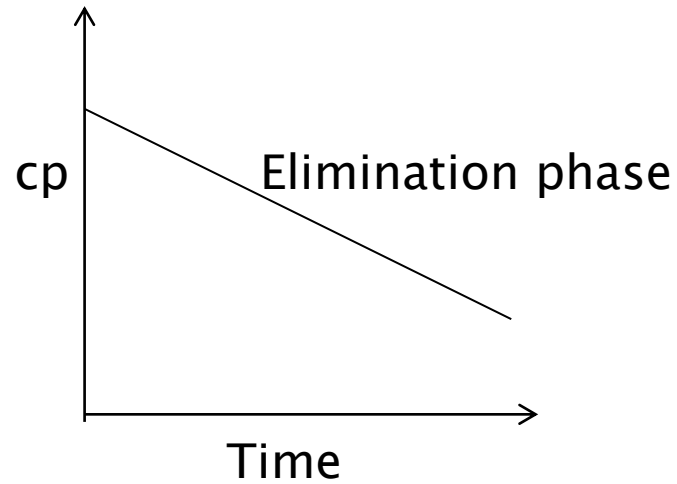
1. Compartmental approach
2. Physiological approach

The generally applied method to study drug distribution in human is compartmental approach while the physiological approach is used to study drug distribution mainly in animals.

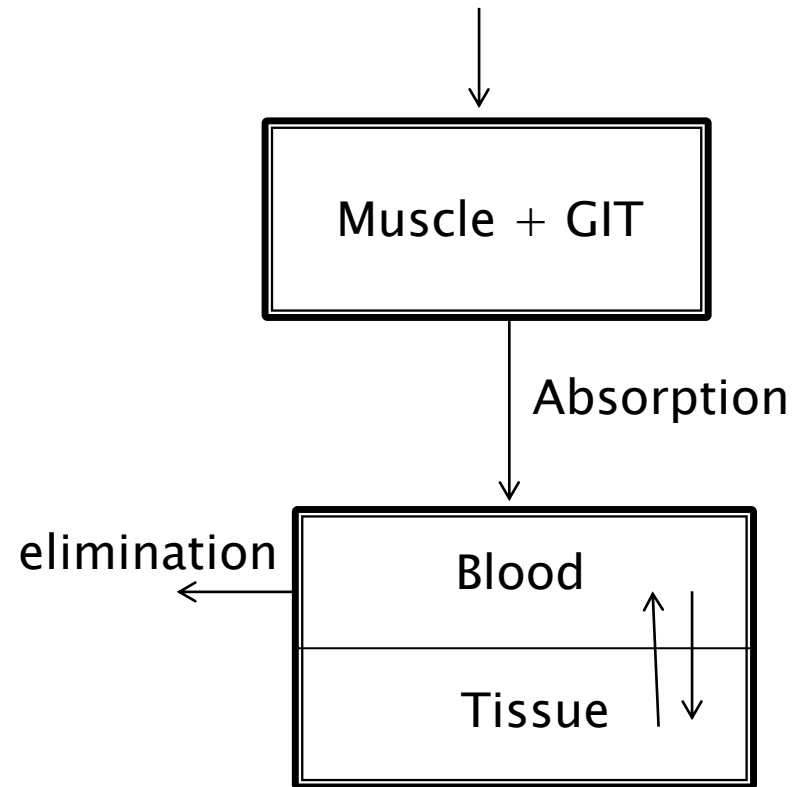
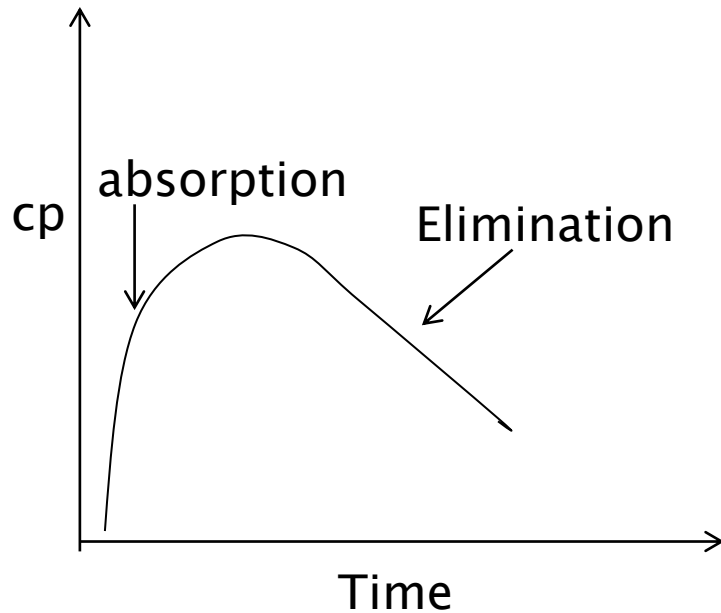
Compartmental approach

- ▶ The drug distribution may follow three models
 1. one compartment open model
 2. Two compartment open model
 3. Three compartment open model
- in one compartment open model it seems that the drug distribution is very rapid and we can't notice the distribution phase

One compartment open model, i.v. Bolus injection

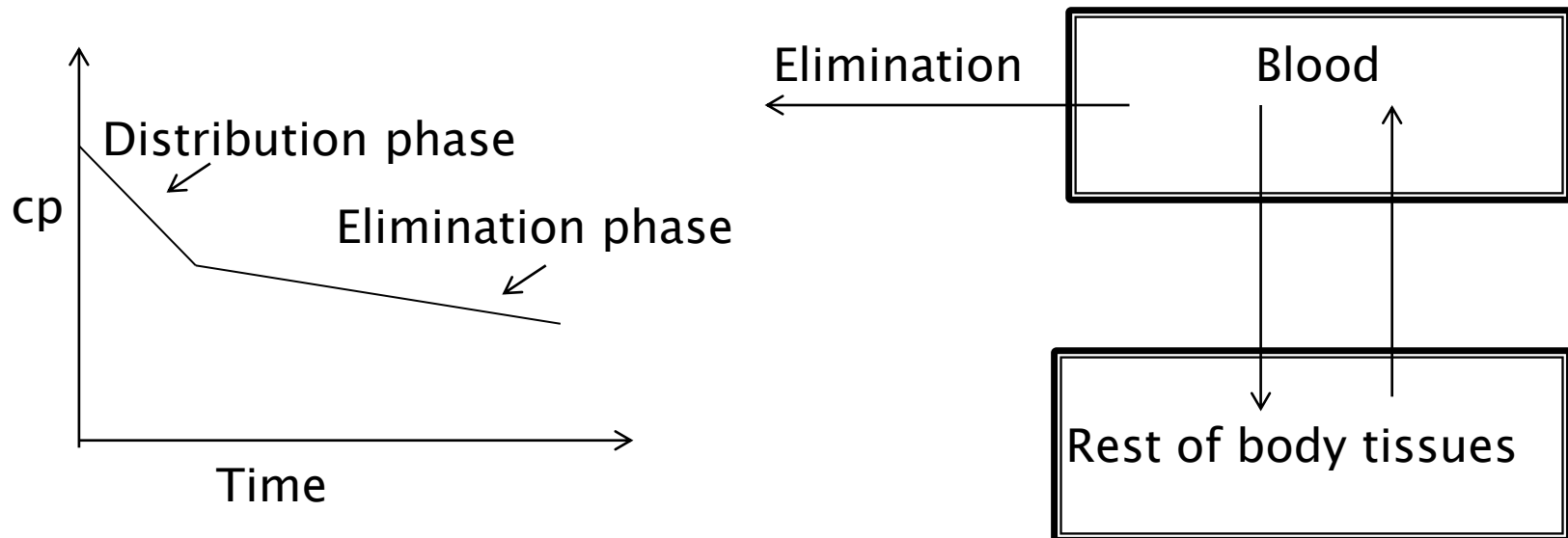


One compartment open model with first order absorption (extra vascular)

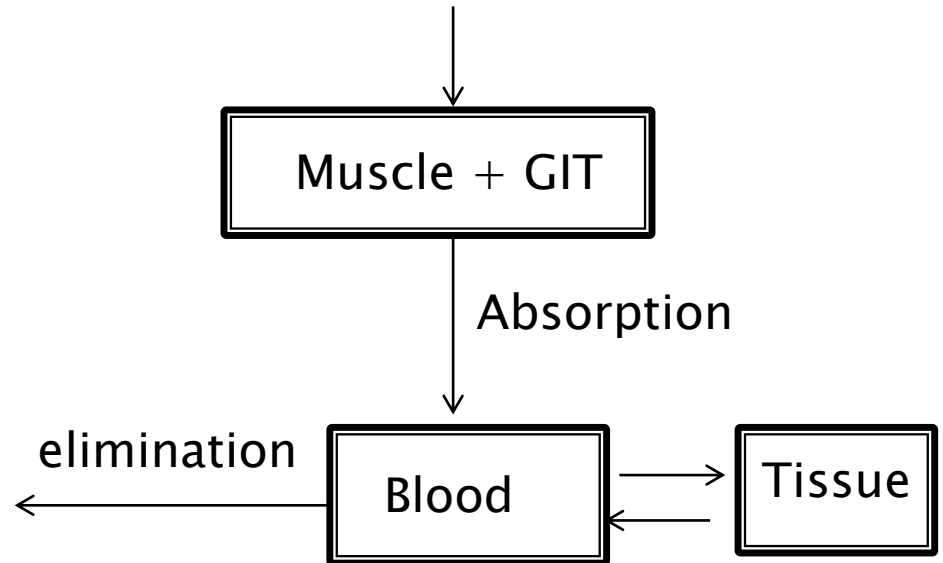
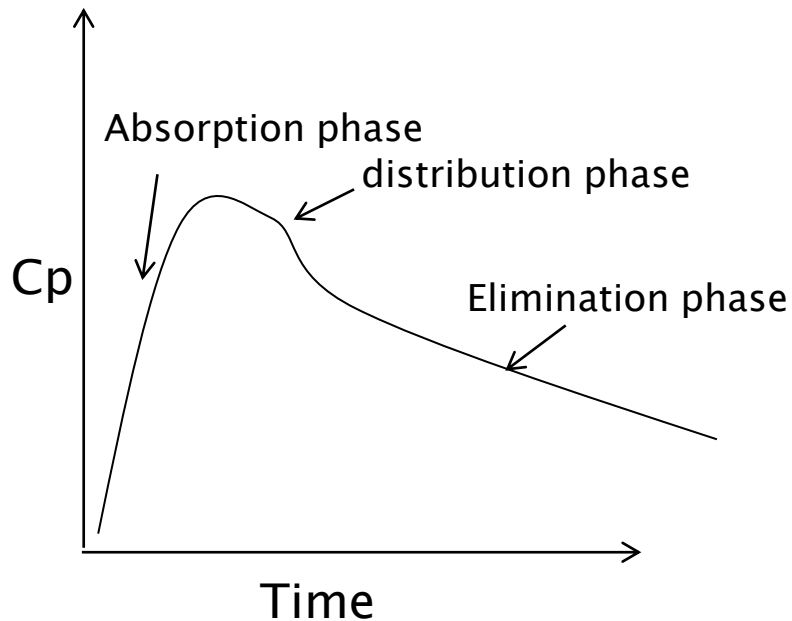


Two compartment open model

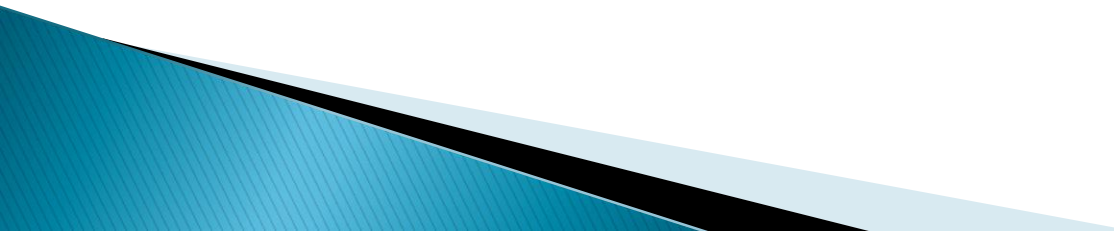
- ▶ In this case there will be a clear distribution phase
- 1. Two compartment open model, iv bolus injection



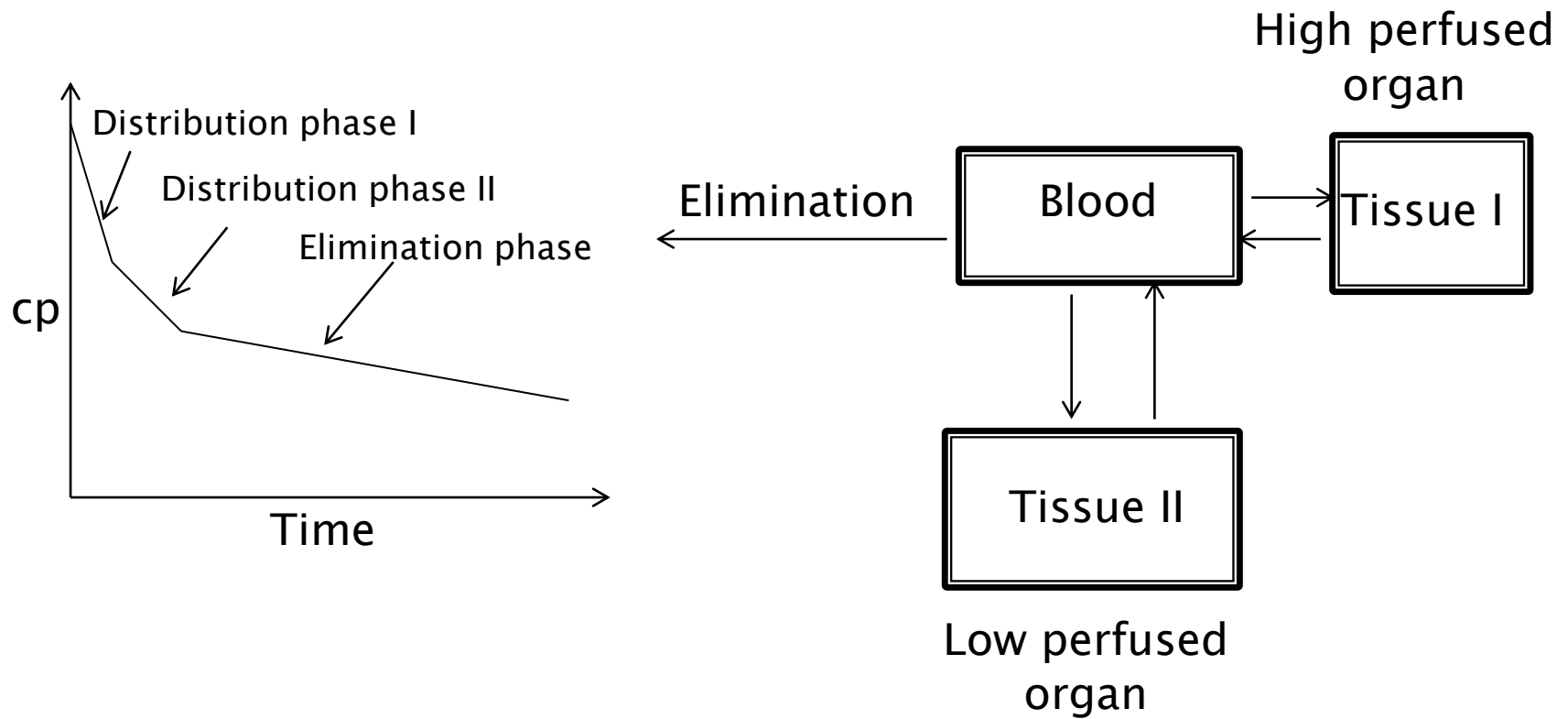
2. Two compartment open model with first order absorption



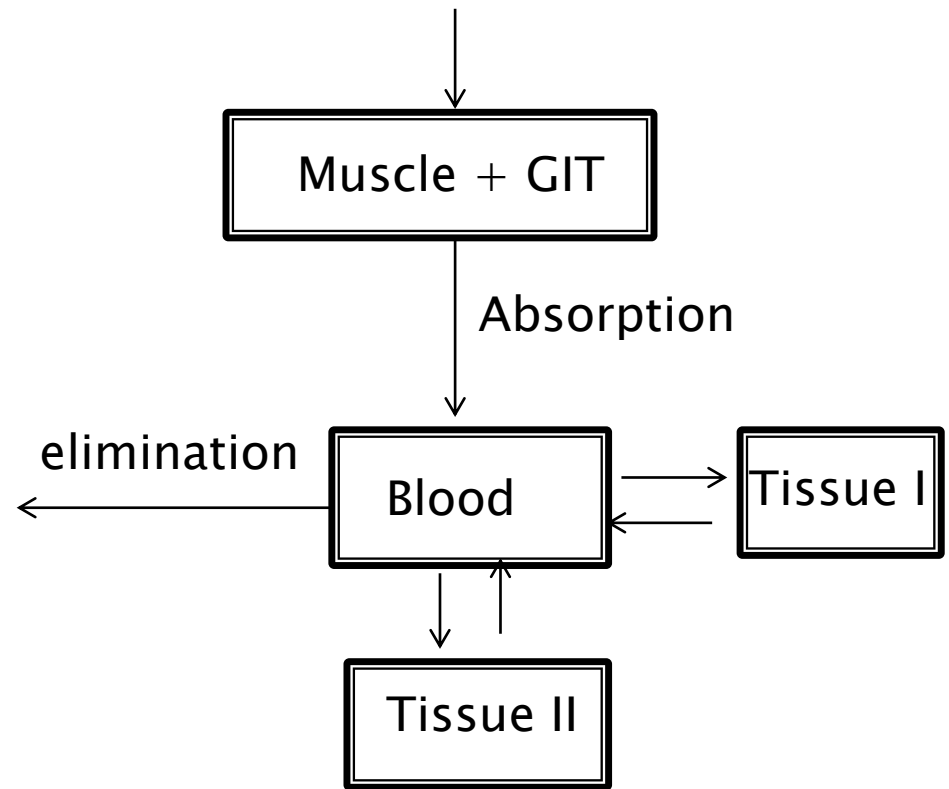
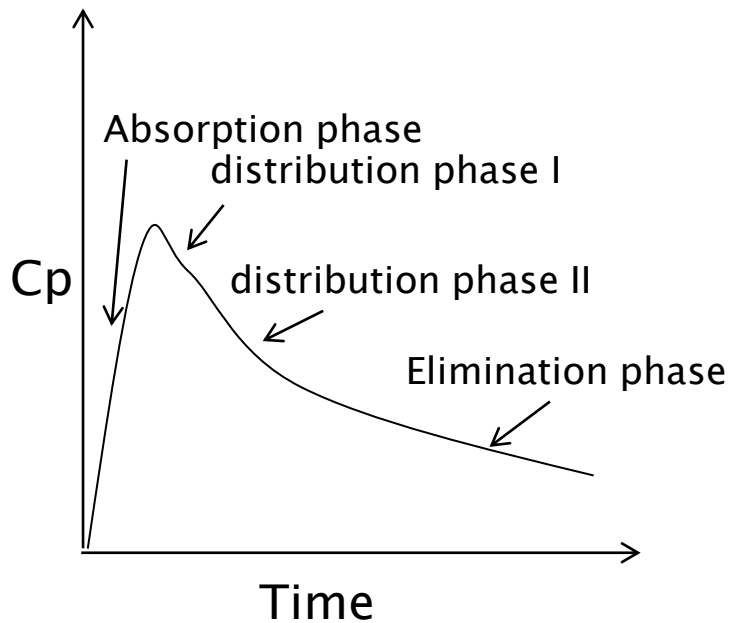
Three compartment open model

- ▶ In this case we notice
 1. a rapid decline in the concentration–time curve which represent a rapid distribution phase and then
 2. it followed by a slower decline in the concentration–time curve which represent a slower distribution phase and then
 3. finally we notice a terminal phase which represent the elimination phase.
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1. Three compartment open model, iv bolus injection



2. Three compartment open model with first order absorption



Physiological approach

- ▶ This study is usually performed in animals since we have to administer the drug and then separate each organ and tissue and measure the concentration of drug in each organ and tissue rather than in blood alone as in case of compartmental approach.