PHARMACOKINETICS/ BIOPHARMACEUTICS
PHAR533
Introduction

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Pharmacokinetics

- Pharmacokinetics is the science of the kinetics of drug
  - absorption,
  - distribution, and
  - elimination (ie, metabolism and excretion).

- The description of drug distribution and elimination is often termed drug disposition.

- Characterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for individuals and groups of patients.

The study of pharmacokinetics

Experimental approach

development of biologic sampling techniques,

analytical methods for the measurement of drugs and metabolites,

procedures that facilitate data collection and manipulation.

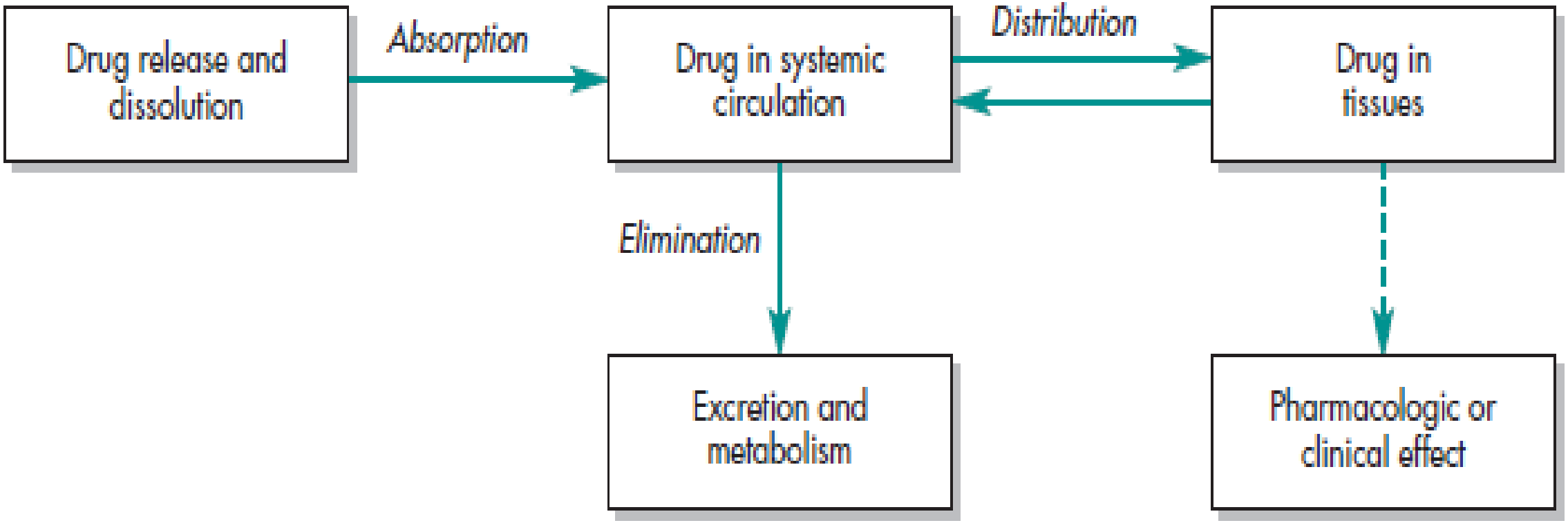
Theoretical approach

development of pharmacokinetic models that predict drug disposition after drug administration.

(Mathematics and computer Techniques are heavily utilized)

Biopharmaceutics

- Biopharmaceutics examines the interrelationship of the
  - physical/ chemical properties of the drug,
  - the dosage form (drug product) in which the drug is given, and
  - the route of administration
- on the rate and extent of systemic drug absorption.


Drug release and dissolution
Absorption
Drug in systemic circulation
Distribution
Drug in tissues
Elimination
Excretion and metabolism
Pharmacologic or clinical effect

- biopharmaceutics involves factors that influence:
  - (1) the design of the drug product,
  - (2) stability of the drug within the drug product,
  - (3) the manufacture of the drug product,
  - (4) the release of the drug from the drug product,
  - (5) the rate of dissolution/release of the drug at the absorption site,
  - (6) delivery of drug to the site of action,

- 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

Pharmacodynamics

- Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body; this includes the
  - mechanisms of drug action
  - relationship between drug concentration and effect.

- A typical example of pharmacodynamics is how a drug interacts quantitatively with a drug receptor to produce a response (effect).

pharmacodynamic effect

- The pharmacodynamic effect, (the pharmacologic effect), can be therapeutic and/or cause toxicity.
- For many drugs, the pharmacodynamic effect is dose/drug concentration related; the higher the dose, the higher drug concentrations in the body and the more intense the pharmacodynamics effect up to a maximum effect.
- It is desirable that side effects and/or toxicity of drugs occurs at higher drug concentrations than the drug concentrations needed for the therapeutic effect.
- Unfortunately, unwanted side effects often occur concurrently with the therapeutic doses.

Clinical pharmacokinetics

- Clinical pharmacokinetics is the application of pharmacokinetic methods to drug therapy in patient care.

- It involves a multidisciplinary approach to individually optimized dosing strategies based on
  - the patient's disease state (e.g. renal, hepatic….)
  - and patient-specific considerations (e.g. genetics)

- The study of pharmacokinetic differences of drugs in various population groups is termed *population pharmacokinetics* (Sheiner and Ludden, 1992)

TDM

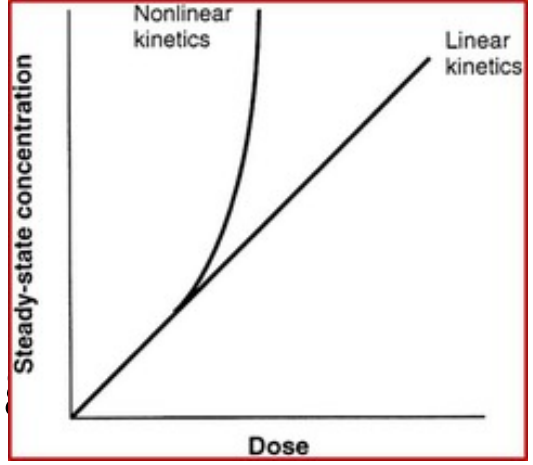
- Clinical pharmacokinetics is also applied to therapeutic drug monitoring (TDM) for very potent drugs, such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity.
  - monitoring plasma drug concentrations (e.g., theophylline) or by
  - monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (e.g., warfarin).

- Pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the clinical pharmacokinetic service (CPKS). Some drugs frequently monitored are the aminoglycosides and anticonvulsants. Other drugs closely monitored are those used in cancer chemotherapy, in order to minimize adverse side effects

TOXICOKINETICS AND CLINICAL TOXICOLOGY

- Toxicokinetics is the application of pharmacokinetic principles to the design, conduct, and interpretation of drug safety evaluation studies (Leal et al, 1993) and in validating dose-related exposure in animals.

- Toxicokinetic data aid in the interpretation of toxicologic findings in animals and extrapolation of the resulting data to humans. Toxicokinetic studies are performed in animals during preclinical drug development and may continue after the drug has been tested in clinical trials.



- Clinical toxicology is the study of adverse effects of dru substances (poisons) in the body.

- The pharmacokinetics of a drug in an overmedicated (intoxicated) patient may be very different from the pharmacokinetics of the same drug given in lower therapeutic doses.

- At very high doses, the drug concentration in the body may saturate enzymes involved in the absorption, biotransformation, or active renal secretion mechanisms, thereby changing the pharmacokinetics from linear to nonlinear pharmacokinetics.

MEASUREMENT OF DRUG CONCENTRATIONS

- Drug concentrations are an important element in determining individual or population pharmacokinetics.

- drug concentrations are measured in biologic samples, such as
  - milk,
  - saliva,
  - plasma,
  - urine.
  - others

- Sensitive, accurate, and precise analytical methods are available for the direct measurement of drugs in biologic matrices.

- chromatographic and mass spectrometric methods are most frequently employed for drug concentration measurement,

- chromatography separates the drug from other related materials that may cause assay interference and mass spectrometry allows detection of molecules or molecule fragments based on their mass-to-charge ratio.

Sampling of Biologic Specimens

- Invasive methods include sampling
  - blood,
  - spinal fluid,
  - synovial fluid,
  - tissue biopsy, or any biologic material that requires parenteral or surgical intervention in the patient.

- noninvasive methods include sampling of
  - urine,
  - saliva,
  - feces,
  - expired air,
  - or any biologic material that can be obtained without parenteral or surgical intervention.

Drug Concentrations in Blood, Plasma, or Serum

- Measurement of drug and metabolite concentrations (levels) in the
  - blood,
  - serum, or
  - plasma
- is the most direct approach to assessing the pharmacokinetics of the drug in the body.

Blood Component	How Obtained	Components
Whole blood	Whole blood is generally obtained by venous puncture and contains an anticoagulant such as heparin or EDTA	Whole blood contains all the cellular and protein elements of blood
Serum	Serum is the liquid obtained from whole blood after the blood is allowed to clot and the clot is removed	Serum does not contain the cellular elements, fibrinogen, or the other clotting factors from the blood
Plasma	Plasma is the liquid supernatant obtained after centrifugation of non-clotted whole blood that contains an anticoagulant	Plasma is the noncellular liquid fraction of whole blood and contains all the proteins including albumin

Plasma Drug Concentration–Time Curve

- As the drug reaches the systemic circulation, plasma drug concentrations will rise up to a maximum if the drug was given by an extravascular route.

- 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.

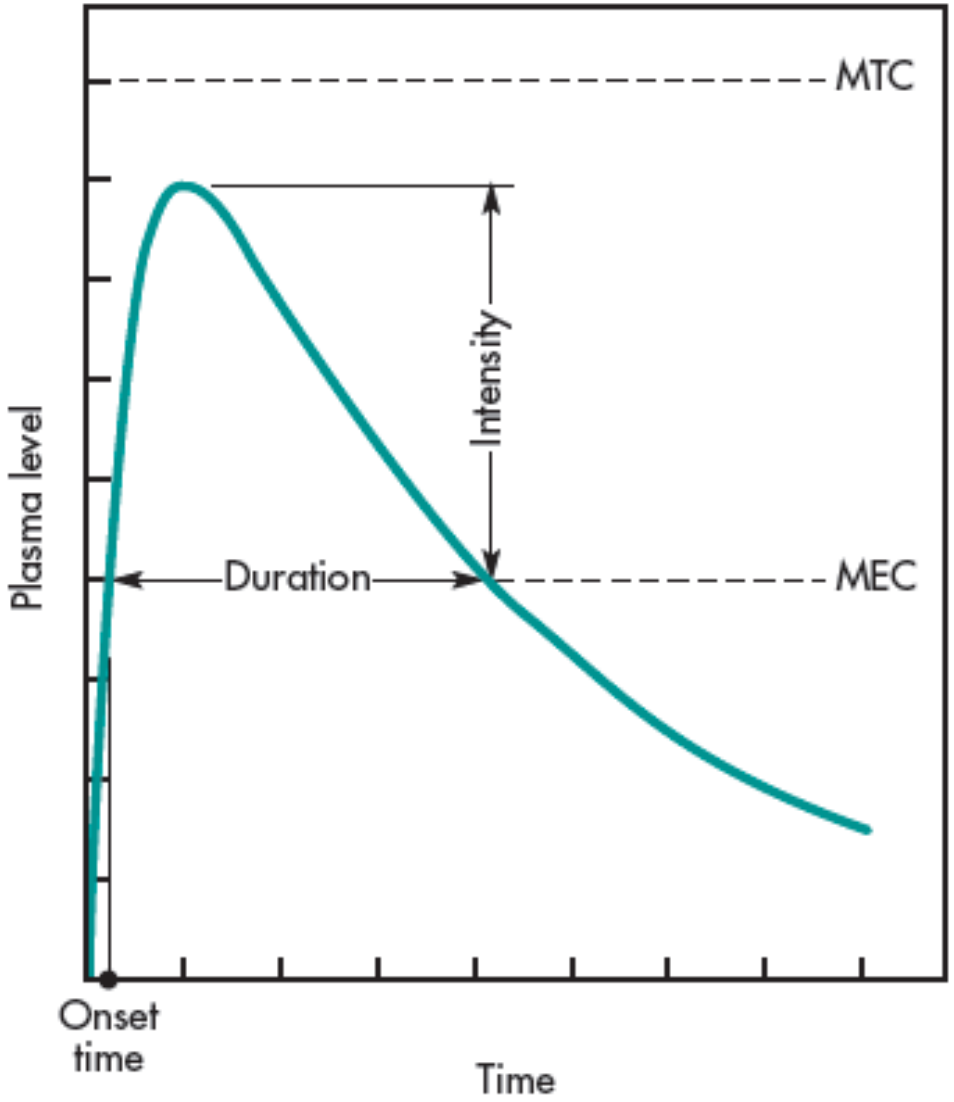


FIGURE 1-3 Generalized plasma level–time curve after oral administration of a drug.

- 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.

therapeutic window

therapeutic index

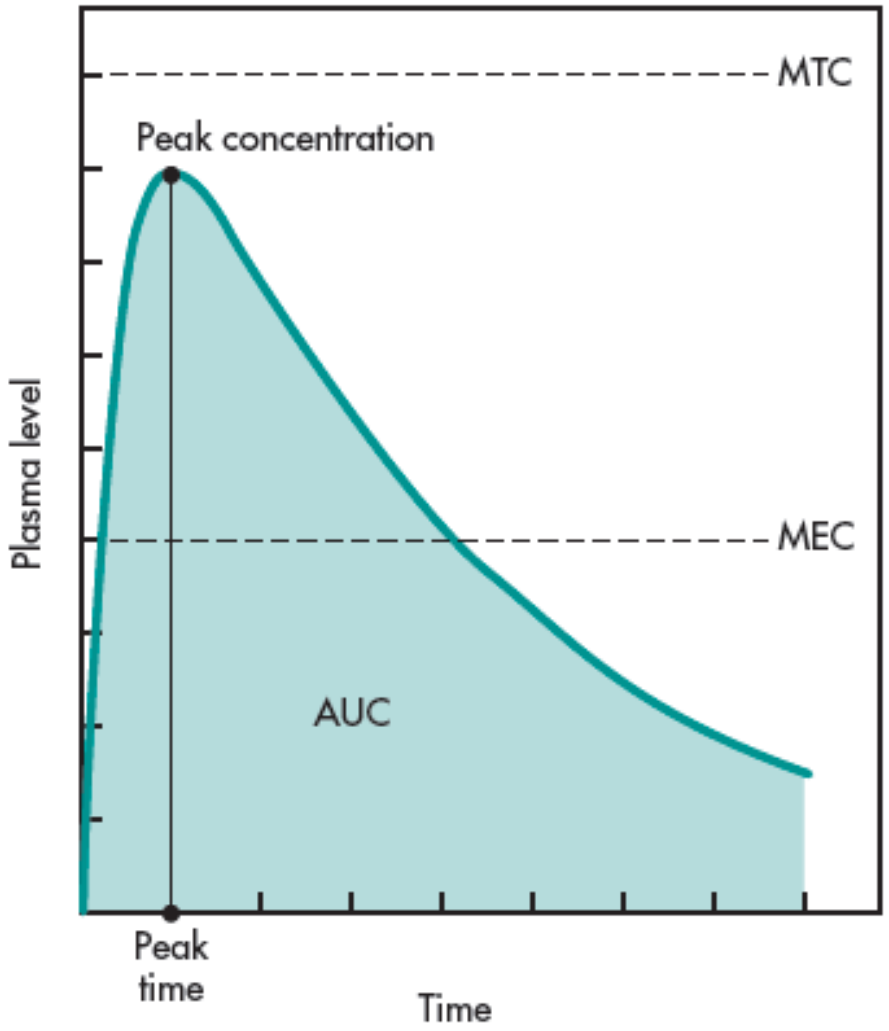


FIGURE 1-4 Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

- *peak plasma level* (C_{max}), is related to the dose, the rate constant for absorption, and the elimination constant of the drug

- *time for peak plasma level* (T_{max}) is the time of maximum drug concentration in the plasma and is a rough marker of average rate of drug absorption

- *area under the curve,* or AUC The AUC is related to the amount of drug absorbed systemically.

PHARMACOKINETIC MODELS

- Drugs are in a dynamic state within the body as they
  - move between tissues and fluids,
  - bind with plasma or cellular components, or
  - are metabolized.

- The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously.

- Such factors must be considered when designing drug therapy regimens.

- The inherent and infinite complexity of these events requires the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

PHARMACOKINETIC MODELS

- A *model* is a hypothesis using mathematical terms to describe quantitative relationships concisely.

- The model predicts (estimates) certain kinetic parameters by the proper selection and development of mathematical function(s) that fit kinetic variables (experimental data).

- A pharmacokinetic function relates an ***independent variable*** to a **dependent variable.**

- For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose.
- The independent variable is **time** and the dependent variable is the **drug concentration** in the liver.

- Such mathematical models can be devised to *simulate* the rate processes of drug absorption, distribution, and elimination to describe and *predict* drug concentrations in the body as a function of time.

- Simplifying assumptions are made in pharmacokinetic models to describe a complex biologic system concerning the movement of drugs within the body.

- For example, most pharmacokinetic models assume that the plasma drug concentration reflects drug concentrations globally within the body.

- Pharmacokinetic models are used to:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicologic activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug
7. Explain drug interactions

PHARMACOKINETIC MODELS

A model may be:

1. **Empirically based:**

- Simply interpolates the data and allows an empirical formula to estimate drug level over time (justified when limited information is available).

- *Empirical models* are practical but not very useful in explaining the mechanism of the actual process by which the drug is absorbed, distributed, and eliminated in the body.

2. Physiologically based models:

- Requires tissue sampling.
- Requires monitoring organ blood flow.
- Used in describing drug distribution in animals (tissue samples are easily available for assay)
- Has limitations to its use in humans.

3. Compartmentally based models:

- Very simple and useful tool in pharmaco-kinetics.

- For example, assume a drug is given by intravenous injection and that the drug dissolves (distributes) rapidly in the body fluids.

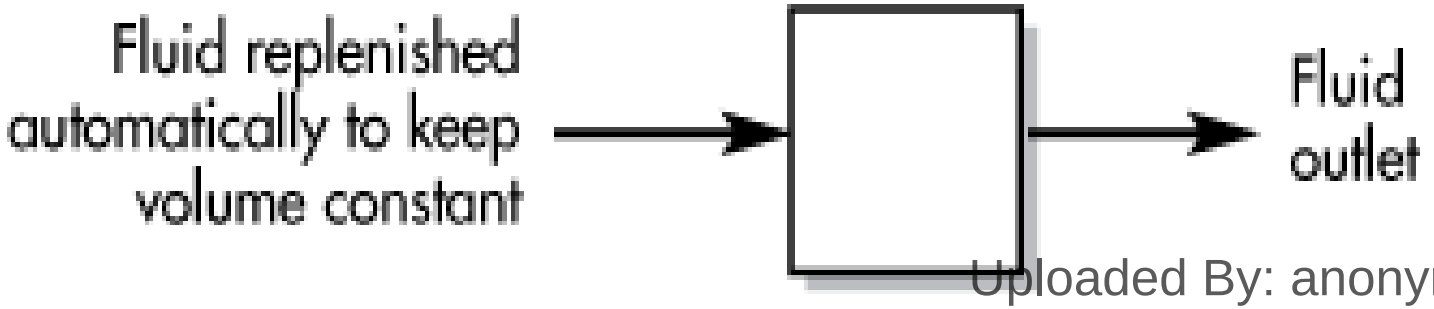
Compartmentally based models:

- A model that can describe this situation is a tank containing a volume of fluid that is rapidly equilibrated with the drug.

- The concentration of the drug in the tank after a given dose is governed by two parameters:

  (1) the fluid volume of the tank that will dilute the drug.

  (2) the elimination rate of drug per unit of time.



Compartmentally based models:

- Because a model is based on a hypothesis, a certain degree of caution is necessary when relying totally on the pharmacokinetic model to predict drug action.
- For some drugs, plasma drug concentrations are not useful in predicting drug activity.
- For other drugs, an individual's genetic differences, disease state, and the compensatory response of the body may modify the response of a drug.

- A compartment is not a real physiologic or anatomic region but is considered as a tissue or group of tissues that have similar blood flow and drug affinity.
- Within each compartment, the drug is considered to be uniformly distributed.
- Mixing of the drug within a compartment is rapid and homogeneous and is considered to be "well stirred,"
- so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment.

- Rate constants are used to represent the overall rate processes of drug entry into and exit from the compartment.

- The model is an *open system* because drug can be eliminated from the system.

- A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment.

Mammillary Model

- A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment.

  - The *mammillary model* is the most common compartment model used in pharmacokinetics.

  - The mammillary model is a strongly connected system, because one can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment.

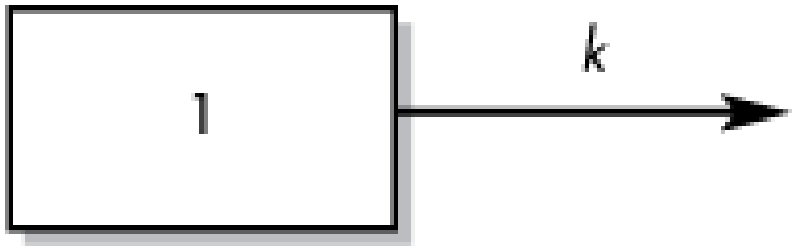
  - The mammillary model consist of one or more compartments around a central compartment like satellites.

Mammillary Models

One-compartment model:

- Drug is both added to and eliminated from a central compartment.
- The central compartment is assigned to represent plasma and highly perfused tissues that rapidly equilibrate with drug.
- When an intravenous dose of drug is given, the drug enters directly into the central compartment.
- Elimination of drug occurs from the central compartment because the organs involved in drug elimination, primarily kidney and liver, are well-perfused tissues.

MODEL 1. One-compartment open model, IV injection.



MODEL 2. One-compartment open model with first-order absorption.

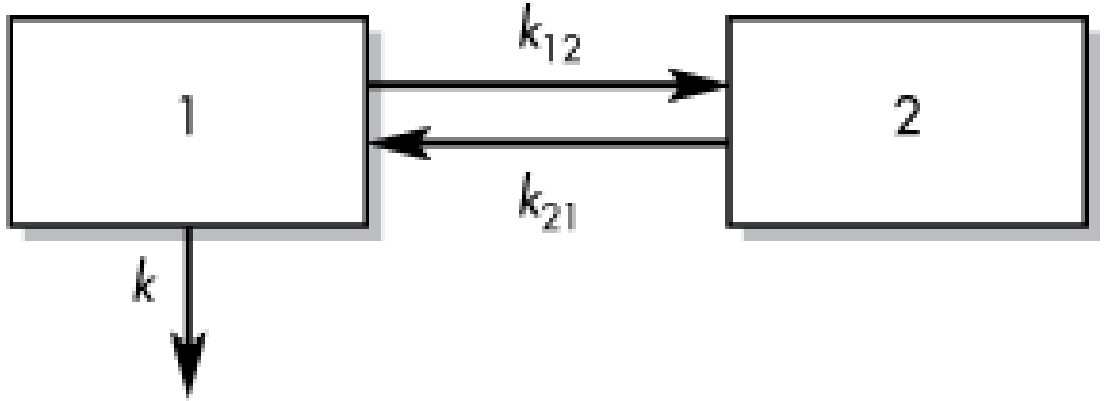
Mammillary Models

Two-compartment model:

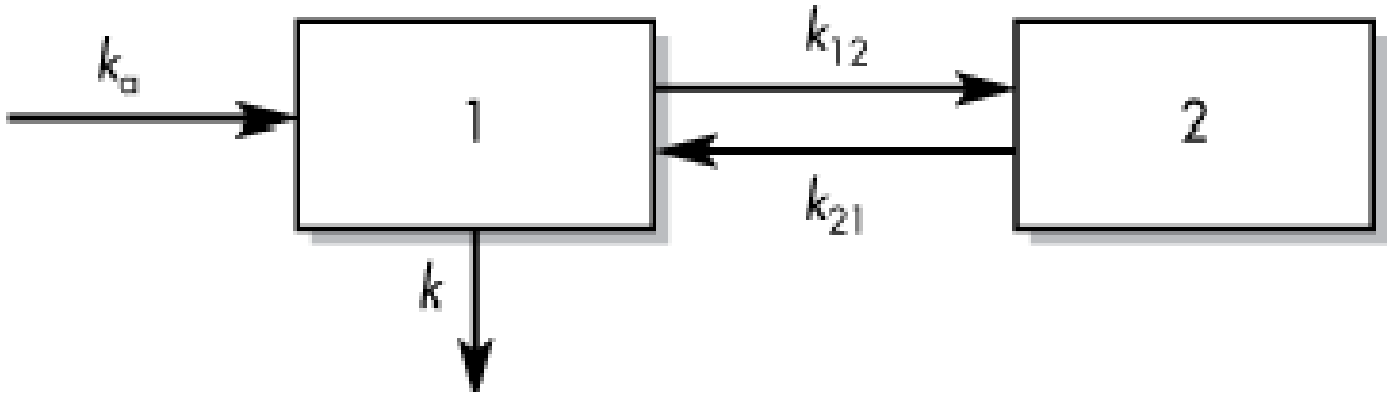
- drug can move between the central or plasma compartment to and from the tissue compartment.

- The total amount of drug in the body is simply the sum of drug present in the central compartment plus the drug present in the tissue compartment.

MODEL 3. Two-compartment open model, IV injection.



MODEL 4. Two-compartment open model with first-order absorption.

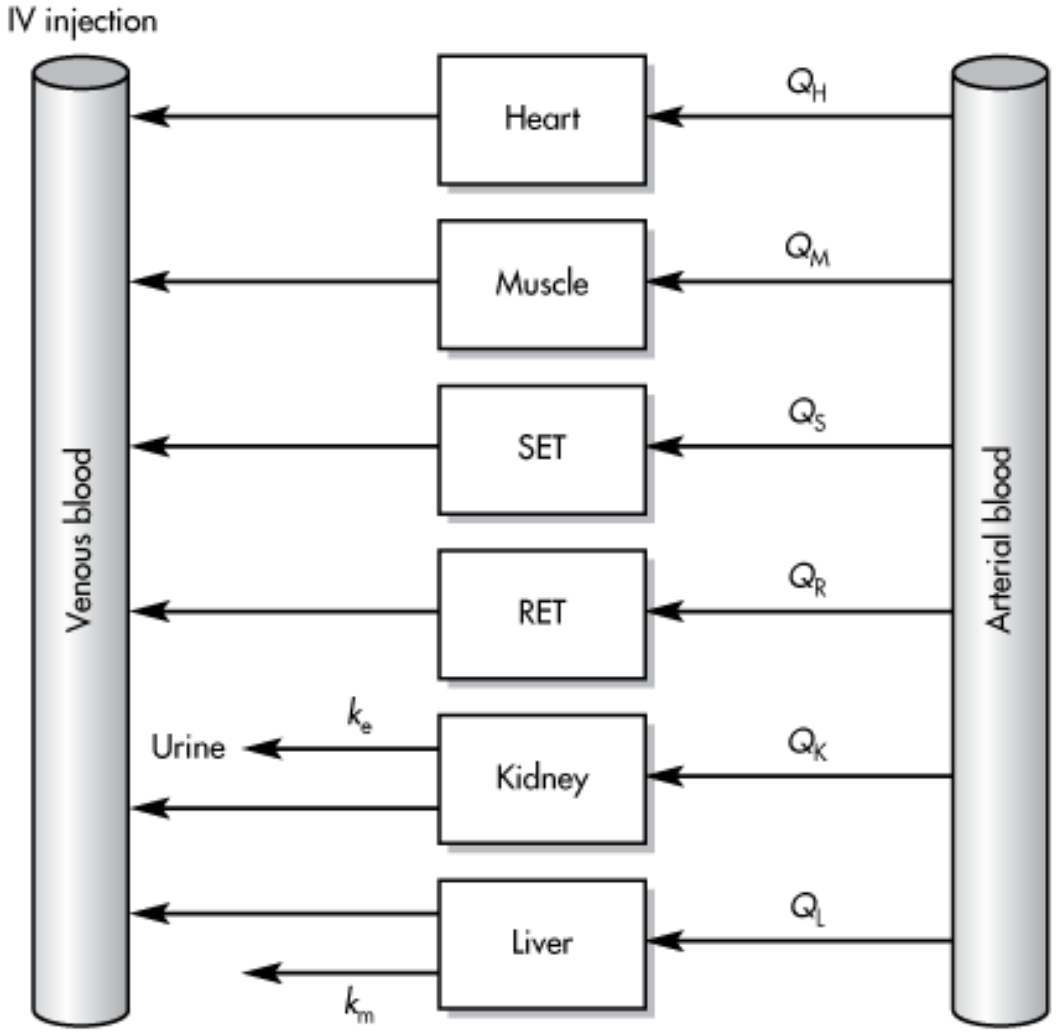


Physiologic Pharmacokinetic Model (Flow Model)

- The model would potentially predict realistic tissue drug concentrations, which the two-compartment model fails to do.

- Much of the information required for adequately describing a physiologic pharmacokinetic model are experimentally difficult to obtain.

- In spite of this limitation, the physiologic pharmacokinetic model does provide much better insight into how physiologic factors may change drug distribution from one animal species to another.


IV injection
Venous blood
Heart
Muscle
SET
RET
Kidney
Liver
Urine
k_e
k_m
Q_H
Q_M
Q_S
Q_R
Q_K
Q_L
Arterial blood