Introduction to Pharmacokinetics

Recommended books

1. Shargel L, Yu A: *Applied Biopharmaceutics & Pharmacokinetics*, 7th ed., McGraw-Hill Education / Medical, 2015
2. S. S. Jambhekar, P. J. Breen: *Basic Pharmacokinetics*, 2nd ed., Pharmaceutical Press, 2012

Contents

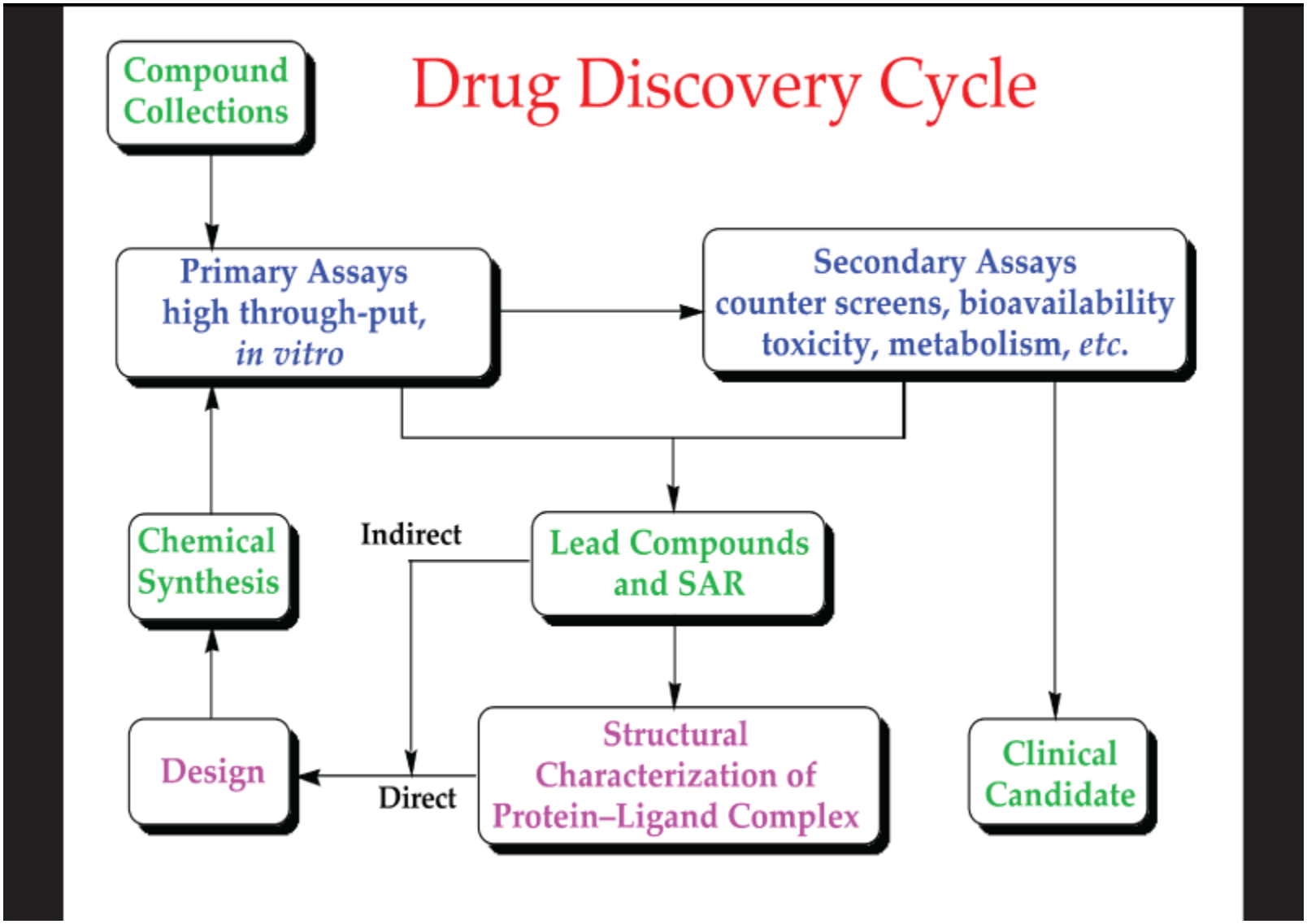
- Statistics about new drug approval
- Steps involved in the drug development process
- Drug Discovery Cycle

Statistics about new drug approval

- ✓ The average time for a new drug to be approved is between 7 and 9 years.
- ✓ The cost of introducing a new drug is approximately $700 million to $1 billion.

Steps involved in the drug development process

1. The pharmacologically active molecule or drug entity must be synthesized, isolated or extracted from various possible sources.
2. The formulation of a dosage form (i.e., tablet, capsules, suspension, etc.) of this drug must be accomplished in a manner that will deliver a recommended dose to the “site of action” or a target tissue.
3. A dosage regimen (dose and dosing interval) must be established to provide an effective concentration of a drug in the body, as determined by physiological and therapeutic needs (utilizing pharmacokinetics and biopharmaceutics)


Drug Discovery Cycle
Compound Collections
Primary Assays high through-put, *in vitro*
Secondary Assays counter screens, bioavailability toxicity, metabolism, *etc.*
Chemical Synthesis
Indirect
Lead Compounds and SAR
Design
Direct
Structural Characterization of Protein–Ligand Complex
Clinical Candidate

Contents

- Drug Approvals
  - Preclinical Testing
  - Investigational New Drug Application (IND)
  - Phase I clinical trials
  - Phase II clinical trials
  - Phase III clinical trials
  - New Drug Application (NDA)
  - Phase IV studies

Drug Approvals - From Invention to Market

- In the United States, it takes an average of 12 years for an experimental drug to travel from the laboratory to your medicine cabinet.
- Only 5 in 5,000 drugs that enter preclinical testing progress to human testing. One of these 5 drugs that are tested in people is approved. The chance for a new drug to actually make it to market is thus only 1 in 5,000.

- **Preclinical Testing**: A pharmaceutical company conducts certain studies before the future drug is ever given to a human being. Laboratory and animal studies must be done to demonstrate the biological activity of the drug against the targeted disease. The drug must also be evaluated for safety. These tests take on the average 3.5 years.

- **Investigational New Drug Application (IND)**: The pharmaceutical company files an IND with the FDA to begin testing the drug in people. The IND becomes effective if the FDA does not disapprove it within 30 days. The IND must include the following information: the results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. The IND must also be reviewed and approved by the Institutional Review Board where the studies will be conducted.

- **Phase I Clinical Trials**: Phase I studies are usually the first tests of a drug under development in healthy volunteers. These studies involve about 20 to 80 volunteers. The tests determine a drug's safety profile, including the safe dosage range, plus how the drug is absorbed, distributed, metabolized and excreted, and the duration of its action. Phase I trials take on the average 1 year.

- **Phase II Clinical Trials**: These are slightly larger studies that are done in patients with the disease for which the drug is intended. This phase is usually designed to identify what are the minimum and maximum dosages. The trials generally involve 100 to 300 volunteer patients and are controlled in design. They are done to assess the drug's effectiveness. Phase II typically takes about 2 years.

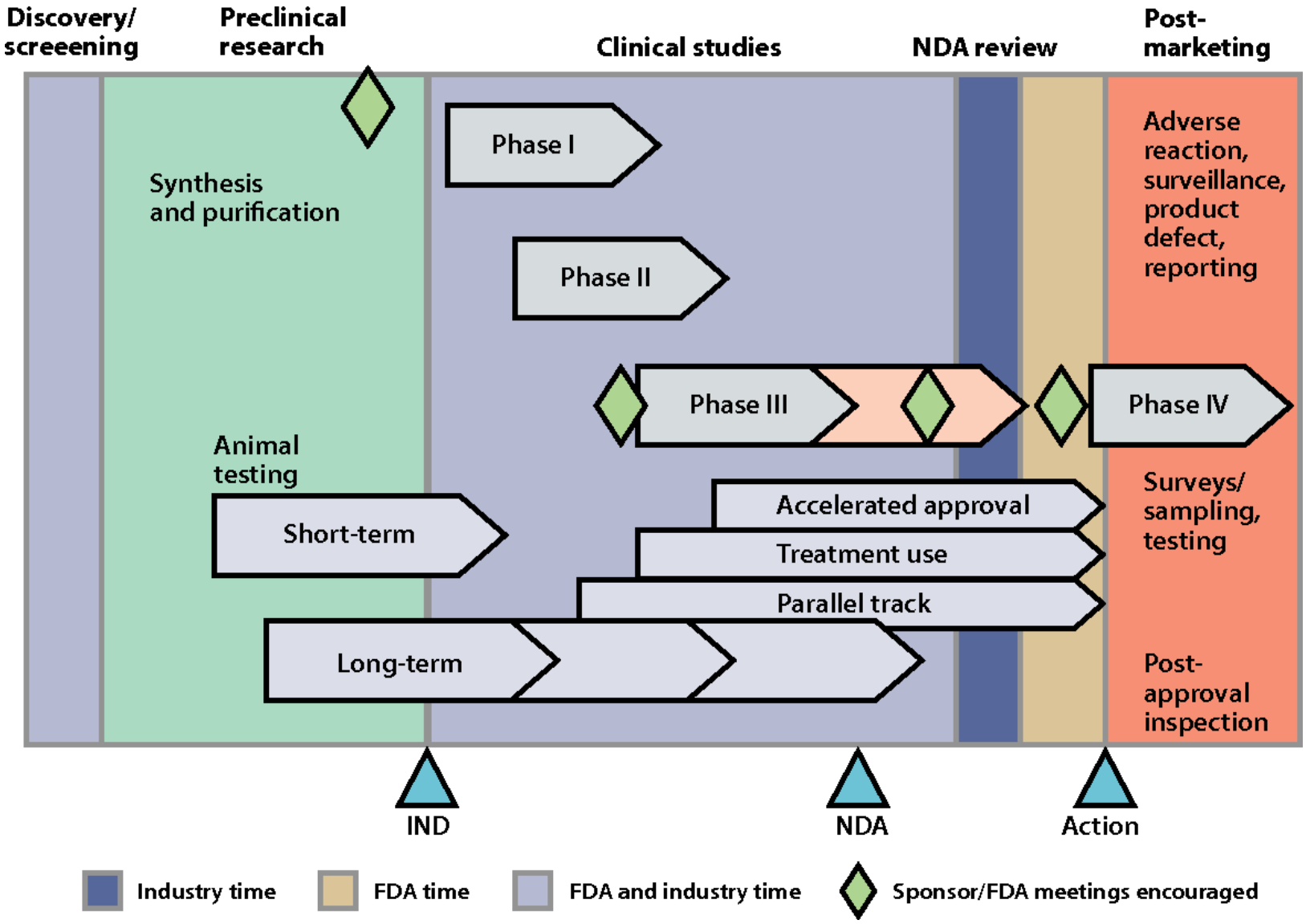
- **Phase III Clinical Trials**: These are the definitive, large randomized trials that are submitted to the FDA in order to obtain approval of a drug. This phase examines the effectiveness as well as the safety (adverse events) of the new drug. Phase III trials usually involve 1,000 to 3,000 patients in clinics and hospitals. Patients are usually asked a list of possible side effects, often derived from what was observed in phase II studies. Patients are also free to report any other side effects that occur while they are on the new drug. Phase III takes on the average 3 years.

- **New Drug Application (NDA):** Following the Phase III Clinical Trials, the drug manufacturer analyzes all the data from the studies and files an NDA with the FDA (provided the data appear to demonstrate the safety and effectiveness of the drug). The NDA contains all of the data gathered to date about the drug. (An NDA typically consists of at least 100,000 pages.) The average NDA review time for new drugs approved in 1992 was close to 30 months (2 1/2 years).

- **Phase IV Studies**: Phase IV is any organized collection of data from patients who are taking a drug that has already received approval from the FDA. In Phase IV studies, patients may check boxes on a list (as in phase III studies) or they may just report other symptoms. Phase IV studies are commonly called "post-marketing studies."

Although there are other routes that can expedite the process (referred to as fast-tracking), this is the usual journey for a drug from invention to market in the U.S.

US Food and Drug Administration drug approval process



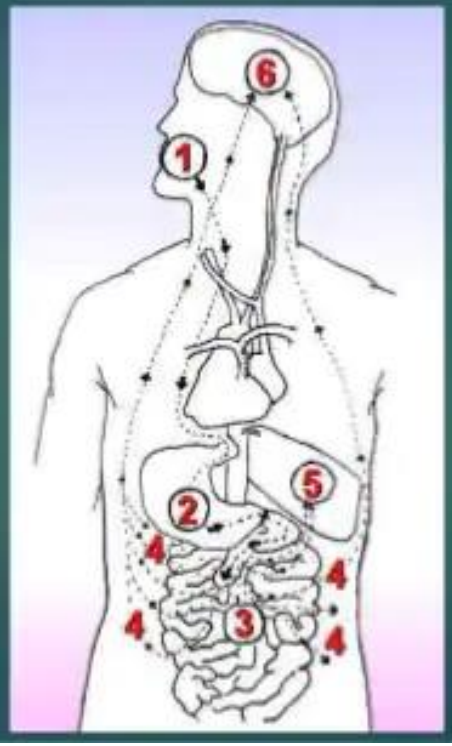
Lecture-3

Contents

- Journey of medicine in the body
- Biopharmaceutics
- Some factors affecting bioavailability
- Pharmacokinetics
- Applications of pharmacokinetics studies
- Plasma level- time curve

JOURNEY OF MEDICINE IN THE BODY

1. Mouth
2. Stomach
3. Small Intestine
4. Bloodstream
5. Liver
6. Brain



DRUG OR MEDICINE (TABLET, CAPSULE, SYRUP)

↓

ENTERS INTO HUMAN BODY THROUGH MOUTH

↓

ENTERS INTO BLOOD

↓

CIRCULATES THROUGHOUT THE BODY

↓

PRODUCES DESIRED EFFECTS (USEFUL) AND UNDESIRED (HARMFUL) EFFECTS

↓

DRUG GOES TO LIVER AND DETOXIFIED
FINALLY REACHES TO KIDNEY AND ELIMINATED FROM THE BODY

Biopharmaceutics

Biopharmaceutics is the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacological and therapeutic activity of drug products.

Some factors affecting bioavailability

- Chemical nature of a drug (weak acid or weak base)
- Inert excipients used in the formulation of a dosage form (e.G. Diluents, binding agents, disintegrating agents, coloring agents, etc.)
- Method of manufacture (dry granulation and/or wet granulation)
- Physicochemical properties of drugs (pka, particle size and size distribution, partition coefficient, polymorphism, etc.).

Goal of biopharmaceutical studies

Generally, the goal of biopharmaceutical studies is to develop a dosage form that will provide consistent bioavailability at a desirable rate. The importance of a consistent bioavailability can be very well appreciated if a drug has a narrow therapeutic range (e.g. digoxin) where small variations in blood concentrations may result in toxic or subtherapeutic concentrations.

Bioavailability :The relative amount of an administered dose that reaches the general circulation and the rate at which this occurs.

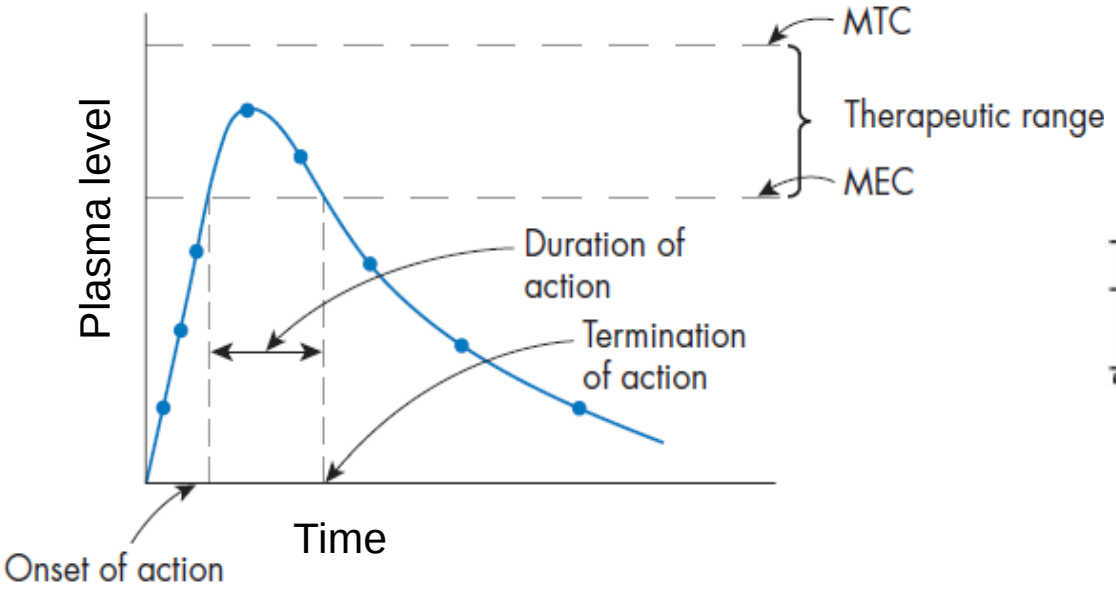
Pharmacokinetics

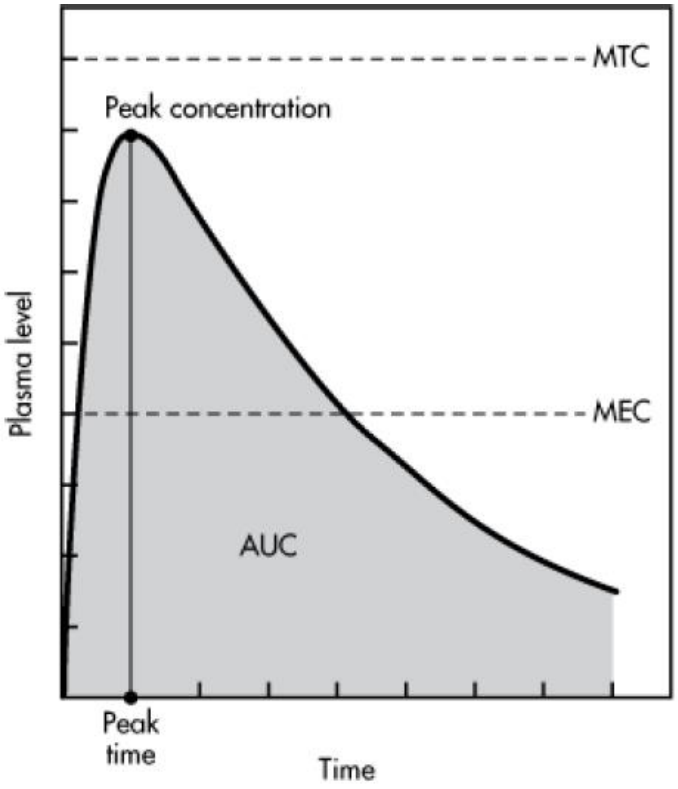
Pharmacokinetics is the study of kinetics of absorption, distribution, metabolism and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic responses in man and animals.

Applications of pharmacokinetics studies

- Bioavailability measurements
- Effects of physiological and pathological conditions on drug disposition and absorption
- Dosage adjustment of drugs in disease states, if and when necessary
- Correlation of pharmacological responses with administered doses
- Evaluation of drug interactions
- Clinical prediction: using pharmacokinetic parameters to individualize the drug dosing regimen and thus provide the most effective drug therapy.

Plasma level-time Curve





MTC = minimum toxic concentration
MEC = minimum effective concentration
AUC = area under curve

Plasma level-time Curve

Onset of action

The time at which the administered drug reaches the therapeutic range and begins to produce the effect.

Duration of action

The time span from the beginning of the onset of action up to the termination of action.

Termination of action

The time at which the drug concentration in the plasma falls below the minimum effective concentration (MEC).

Plasma level-time Curve

Therapeutic range

The plasma or serum concentration (e.g., μg mL^{-1}) range within which the drug is likely to produce the therapeutic activity or effect.

Amount of drug in the urine

One can monitor the drug in the urine in order to obtain selected pharmacokinetic parameters of a drug as well as other useful information such as the bioavailability of a drug.

Lecture-4

Contents

- Sites of drug administration
- Intravascular routes
- Important features of the intravascular route of drug administration
- Extravascular Routes of Drug Administration
- Important features of extravascular routes of drug administration
- Review of ADME processes

Sites of Drug Administration

Sites of drug administration are classified into two categories:

- intravascular routes
- extravascular routes

Sites of Drug Administration

Intravascular routes

Intravascular administration can be:

- intravenous
- intra-arterial.

Important features of the intravascular route of drug administration

✓1. There is no absorption phase.

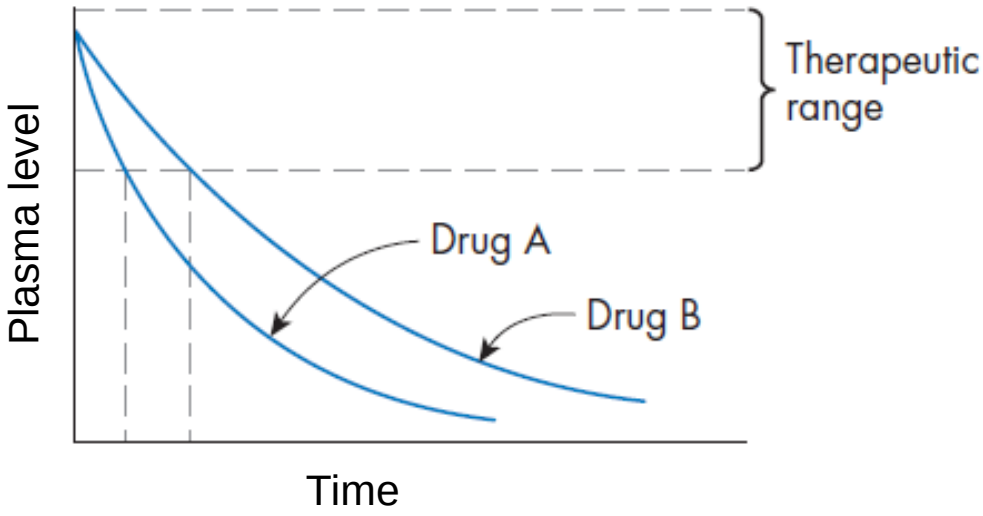
✓2. There is immediate onset of action.

✓3. The entire administered dose is available to produce pharmacological effects.

✓This route is used more often in life-threatening situations.

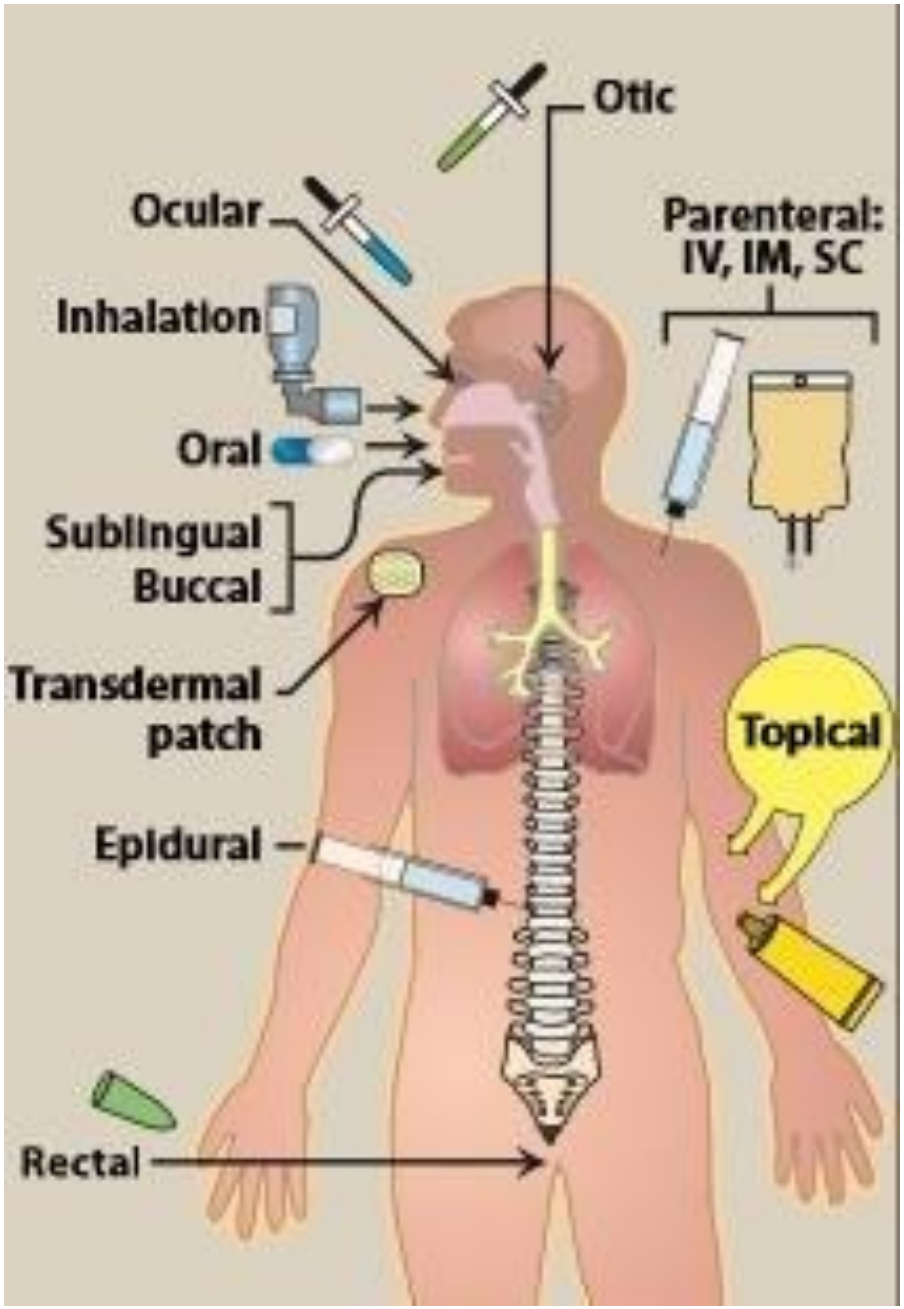
✓5. Adverse reactions are difficult to reverse or control; accuracy in calculations and administration of drug dose, therefore, are very critical.

Plasma level-time curve



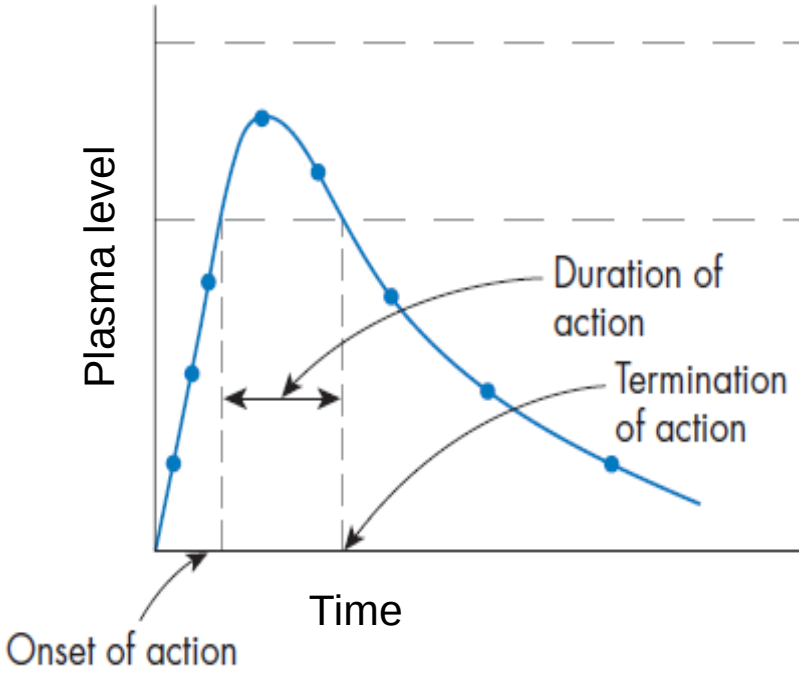
Extravascular Routes of Drug Administration

- oral administration (tablet, capsule, suspension,etc.)
- intramuscular administration (solution and suspension)
- subcutaneous administration (solution and suspension)
- sublingual or buccal administration (tablet)
- rectal administration (suppository and enema)
- transdermal drug delivery systems (patch)
- inhalation (metered dose inhaler).


Otic
Ocular
Parenteral:
IV, IM, SC
Inhalation
Oral
Sublingual
Buccal
Transdermal
patch
Topical
Epidural
Rectal

Important features of extravascular routes of drug administration

- An absorption phase is present.
- The onset of action is determined by factors such as formulation and type of dosage form, route of administration, physicochemical properties of drugs and other physiological variables.
- The entire administered dose of a drug may not always reach the general circulation (i.e. incomplete absorption).



Review of ADME processes

Absorption: Absorption is defined as the process by which a drug proceeds from the site of administration to the site of measurement (usually blood, plasma or serum).

Distribution: Distribution is the process of reversible transfer of drug to and from the site of measurement (usually blood or plasma).

Metabolism: Metabolism is the process of a conversion of one chemical species to another chemical species

Elimination: Elimination is the irreversible loss of drug from the site of measurement (blood, serum, plasma). Elimination of drugs occur by one or both of metabolism and excretion.

Review of ADME processes