Biopharmaceutics

4th Stage

College of Pharmacy

Lecture 1: - Introduction to biopharmaceutics
- Drug absorption

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Ph.D in Pharmaceutics

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Semester: 1st

Department	**Pharmaceutics**			
Course Title	**Biopharmaceutics**			
Couse Level	**Year**	**5**	**Semester**	**1**
Total Credits	**4**			
Theory credits	**3**		**Practical Credits**	**2**

Reference(s):

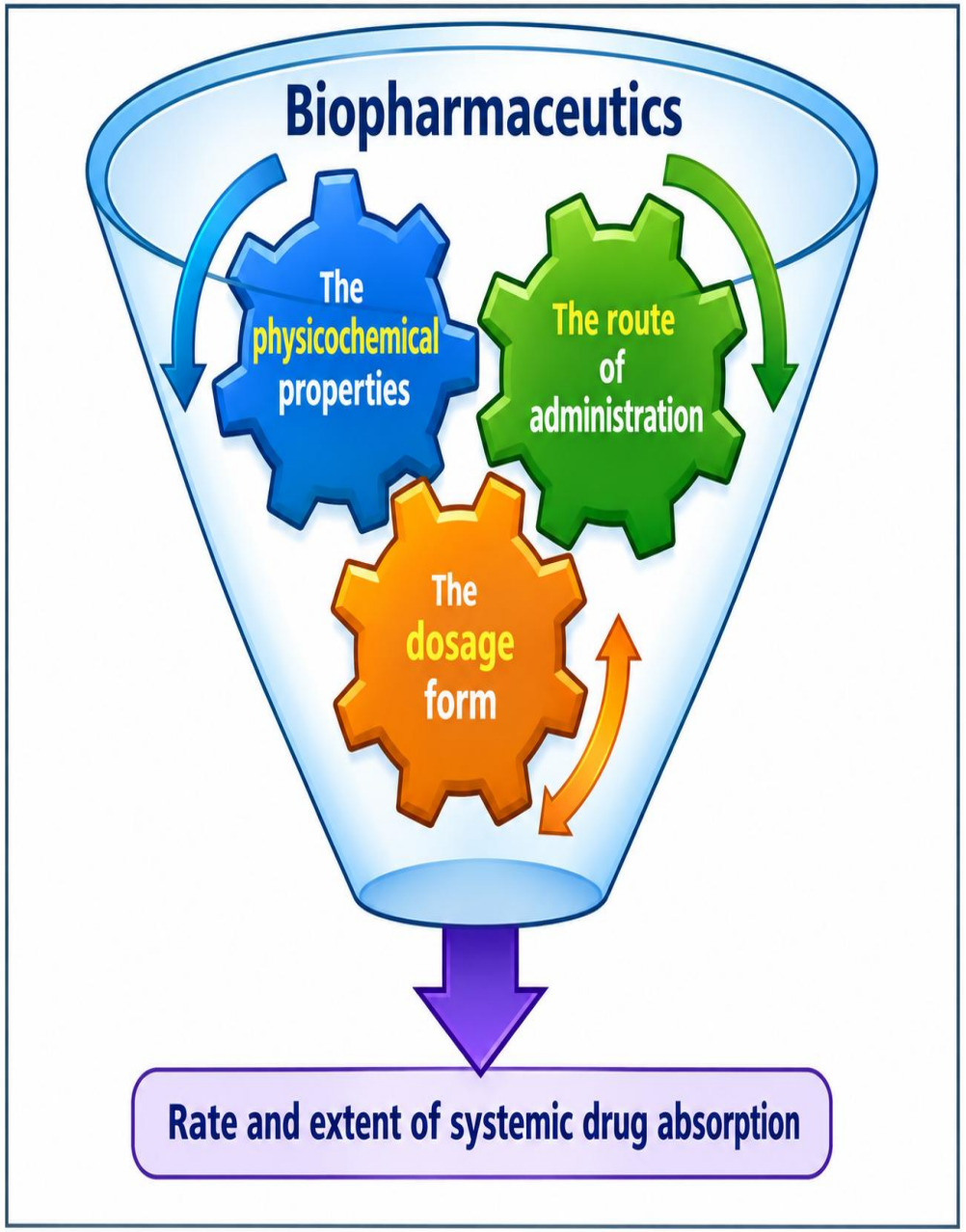
1) Shargel L., Yu AB., (Eds). Applied Biopharmaceutics and Pharmacokinetics, 7th edition, International Edition 2016.
2) Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 6th Edition, Michael E. Aulton (Author) Churchill, Livingstone-Elsevier

Introduction to biopharmaceutics

- Drugs are substances intended for use in the diagnosis, cure, treatment, or prevention of disease.
- Drugs are given in a variety of dosage forms or *drug products* such as solids (tablets, capsules), semisolids (ointments, creams), liquids, suspensions, emulsions, etc, for **systemic or local** therapeutic activity.
- **Drug products** can be considered drug delivery systems designed to release and deliver a drug to its site of action in an appropriate manner, thereby achieving the desired therapeutic effect.
- They are also specifically formulated and designed to meet the individual needs of patients, including efficacy, safety, convenience, and ease of administration.

Biopharmaceutics: The study of how the **physicochemical properties** of the drug, **dosage form**, and **route of administration** influence the **rate and extent of drug absorption**.

- **Therapeutic Effect Sequence:**
  - Drug taken via a route (oral, IV, transdermal, etc.).
  - Drug released from the dosage form.
  - Drug absorbed into circulation or local tissue.
  - Drug reaches site of action.
  - Pharmacologic/clinical effect occurs.



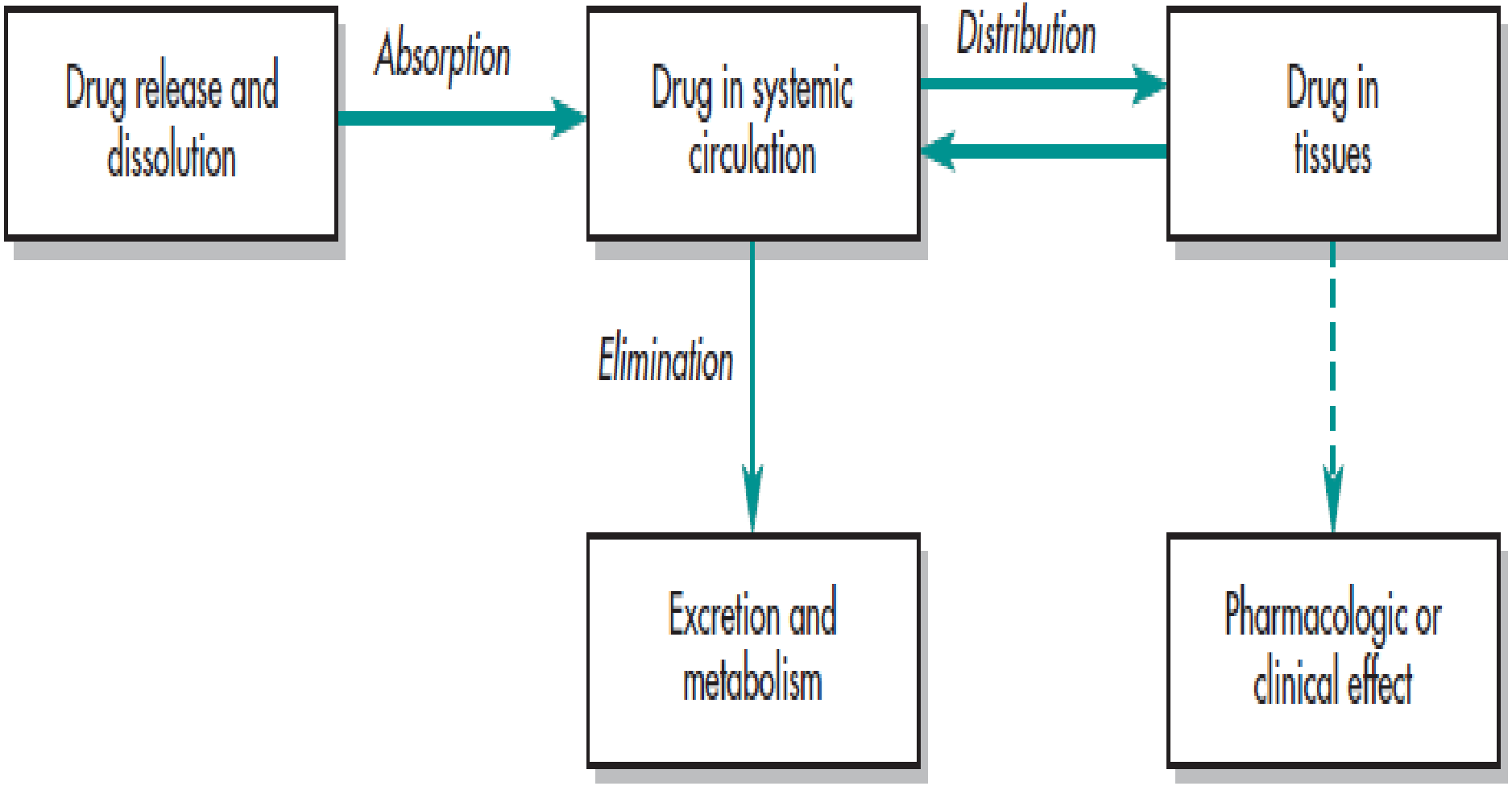


FIGURE 1-1 Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

- **Bioavailability (F)** is the **fraction of an administered drug dose that reaches the systemic circulation in an unchanged form**.
- Bioavailability may **vary between different drug products containing the same active ingredient**, even when administered by the same route.
- Differences in bioavailability can lead to **differences in drug exposure and, consequently, therapeutic response**.
  - Therefore, **pharmacists and pharmaceutical scientists evaluate bioavailability** to assess and select the most appropriate drug product.

- **Study Approaches:**
  - **In vitro studies: Laboratory studies** conducted **outside living organisms** to evaluate drug properties, formulation characteristics, dissolution, stability, and manufacturing-related factors.
  - **In vivo studies:** Studies conducted in **humans or animals** to evaluate drug absorption, distribution, metabolism, and elimination, and to determine how formulation and manufacturing factors affect drug exposure and performance.

- **Bioequivalence** refers to the **absence** of a significant difference in the **rate and extent of drug absorption** between **two** pharmaceutical products when administered at the **same molar dose under similar conditions**.
- In simple terms:
  - **Two drug products are bioequivalent when they deliver the same amount of active drug into the body at a similar rate, producing comparable drug exposure.**
- **Example:** A generic drug is considered bioequivalent to its reference (brand-name) drug when it shows **comparable** systemic drug exposure and absorption characteristics

PHARMACOKINETICS

- **Pharmacokinetics is the science of the kinetics of drug , include :**
  - **absorption**
  - **distribution, and**
  - **elimination (i.e, metabolism and excretion).**
- **The description of drug distribution and elimination is often termed drug disposition.**
- The study of **pharmacokinetics** involves two complementary approaches:
  - **Experimental approach:** Involves the development of **biological sampling techniques**, **analytical methods** for measuring drugs and their metabolites, and **procedures for collecting, processing, and analyzing pharmacokinetic data**.
  - **Theoretical approach:** Involves the development of **pharmacokinetic models** that describe and predict the **absorption, distribution, metabolism, and excretion (ADME)** of drugs after administration
    - **Mathematical and computational techniques** are extensively used to develop and analyse these models.

PHARMACODYNAMICS

- Studies what a drug does to the body (mechanism, effects, dose–response).
- Example: drug binding to receptor → response.
  - Effects can be:
    - **Therapeutic** (desired).
    - **Toxic/adverse** (side effects).
- Relationship is often **dose/concentration-dependent**:
  - 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 pharmacodynamic effect up to a maximum effect.
  - Side effects often increase with higher concentrations

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.

Blood Components for Measurement

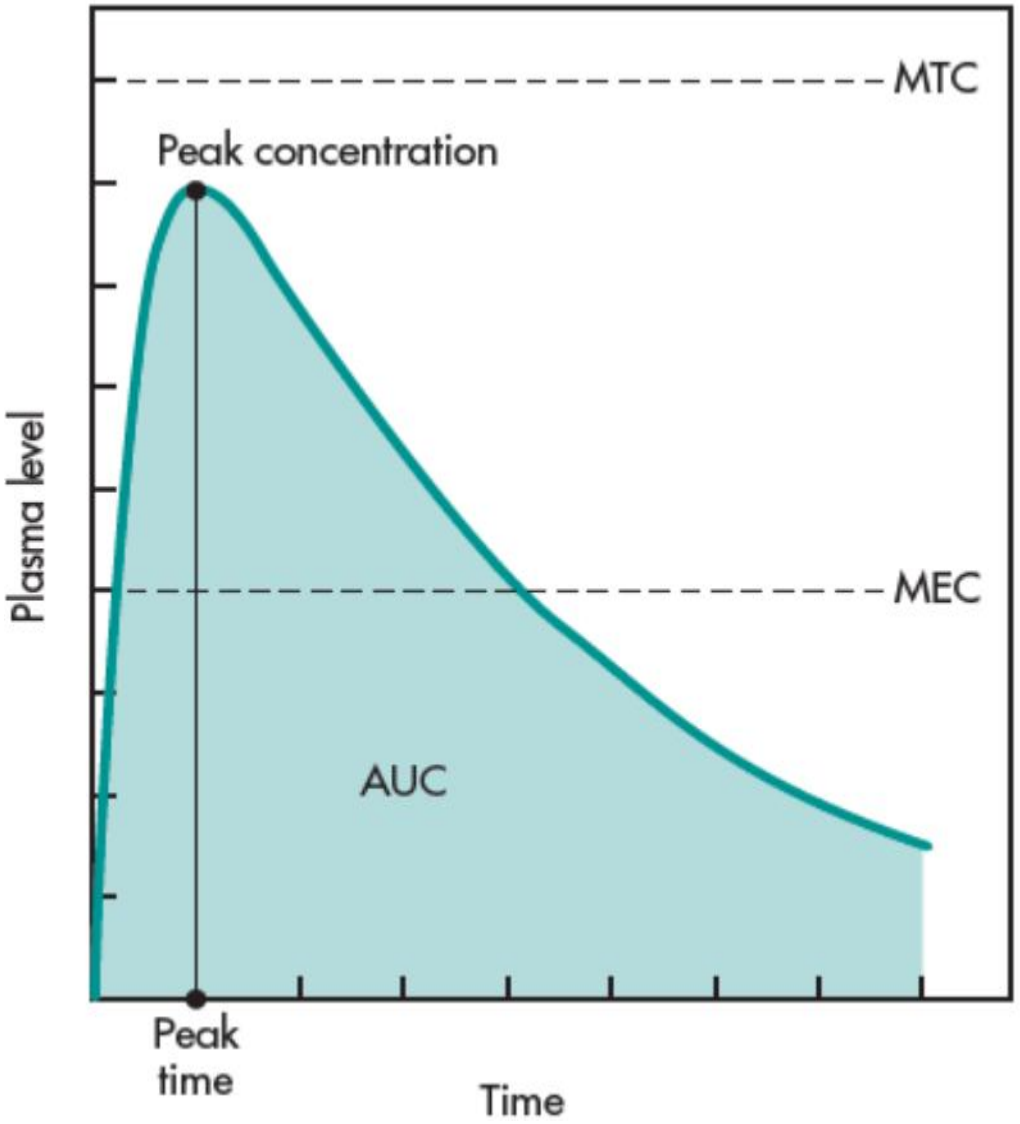
TABLE 1-4 Blood Components

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

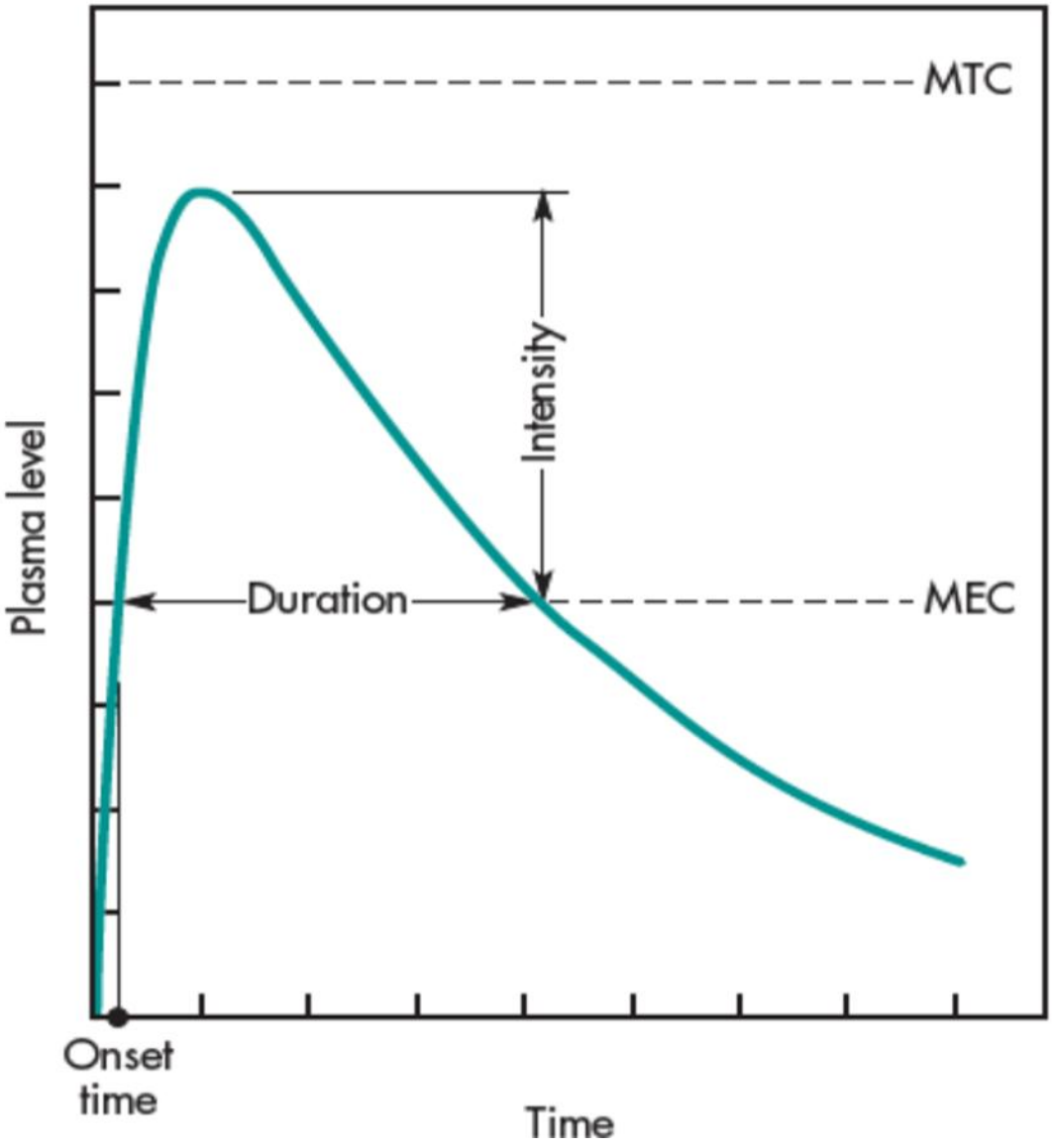
- **The plasma drug concentration (level)–time curve is generated by obtaining the drug concentration in plasma samples taken at various time intervals after a drug product is administered**

- **Key parameters**:
  - **Cmax** = **Maximum plasma drug concentration =** peak plasma level — the highest concentration of a drug reached in the plasma after administration.
  - **Tmax**: Time to reach maximum plasma drug concentration (Cmax) - *the time required for the drug to reach its highest concentration in plasma after administration.*
  - **MEC**: **minimum effective concentration** which the concentration of drug that will just barely produce a pharmacologic effect
  - **MTC** = **Minimum Toxic Concentration** — the lowest plasma drug concentration at which **toxic effects may begin to occur**.
  - **AUC**: overall exposure. is related to the amount of drug absorbed systemically



Plasma Drug Concentration–Time Curve

- **The onset** time corresponds to the time required for the drug to reach the MEC
- **The duration** of drug action is the difference between the onset time and the time for the drug to decline back to the MEC
- The therapeutic window is the concentrations between the MEC and the MTC
- The **intensity** of drug is mainly related to the **concentration of the drug at its site of action**.
  - **Higher drug concentration at the receptor → greater intensity of effect** (up to the drug's maximum effect).
  - **Lower concentration → weaker effect.**
- **Orally administered dosage forms in decreasing order of bioavailability : Solution > Emulsion > Suspension > Powder > Capsule > Tablet > Coated table**



Drug Concentrations in Other Biological Fluids

- **Tissues**: Biopsies can be analyzed, but blood flow varies between tissues, so not always representative.
- **Urine**: reflects extent of drug absorption (bioavailability).
- **Feces**: may indicate unabsorbed drug or biliary excretion.
- **Saliva**: reflects free (unbound) drug but not always reliable (depends on drug pKa and saliva pH).
- **Forensic samples:** Biological specimens collected for the **detection and identification of drugs, drugs of abuse, or poisons**, especially in cases of poisoning, overdose, or suspected drug abuse.
  - **Examples:** blood, urine, saliva, and hair.

Pharmacokinetic (PK) model:

A mathematical representation used to describe and predict how a drug **moves through the body over time**.

Main purposes:

- Describe drug concentration–time relationships.
- Estimate pharmacokinetic parameters.
- Predict drug concentrations after different doses.
- Help design appropriate **dosage regimens**.

The major types of PK models are:

1. **Compartmental models**
2. **Physiological (PBPK) models**
3. **Non-compartmental analysis (NCA)**

Compartmental Models

The body is represented as one or more **compartments** in which the drug is assumed to distribute.

1. One-compartment model

- The body is considered as a **single homogeneous compartment**.
- Drug concentration changes according to drug input and elimination.
- Simple and commonly used for introductory PK.

Example:

Drug → [Body] → Elimination

After IV bolus administration, concentration often follows: $C = C_0 e^{-kt}$

2. Two-compartment model

- The body is divided into:
  - **Central compartment:** blood and highly perfused tissues.
  - **Peripheral compartment:** tissues where drug distribution is slower.

Drug → Central ⇄ Peripheral

Central → Elimination

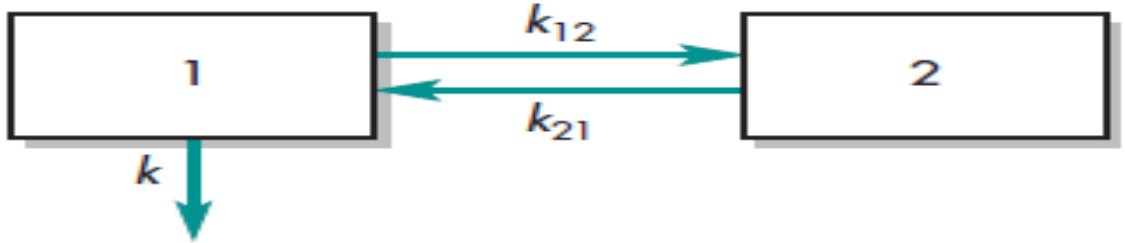
MODEL 1. One-compartment open model, IV injection.



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



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



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

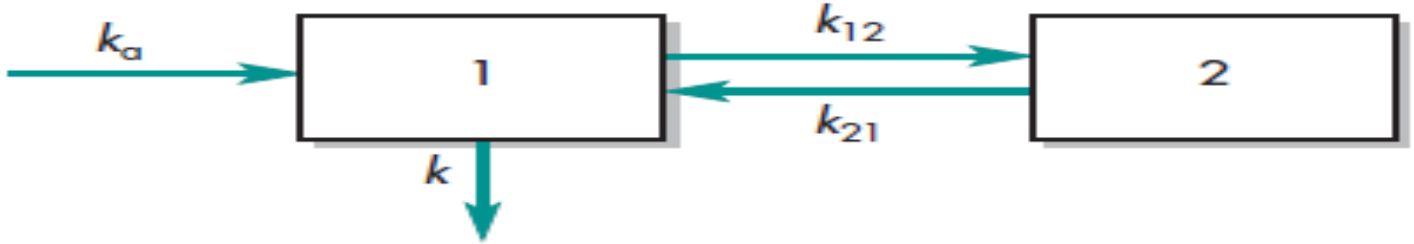


FIGURE 1-6 Various compartment models.

Physiologically Based Pharmacokinetic (PBPK) model

- PBPK models represent the body using **actual physiological organs and tissues**.

Example:

GI tract → Blood → Liver → Kidney → Muscle → Fat → other tissues

- Each organ is described using parameters such as:
  - Organ **volume**
  - Blood flow
  - Tissue partition coefficient
  - Drug metabolism
  - Renal clearance

Advantages:

- More physiologically realistic.
- Can describe drug distribution among specific organs.
- Useful for predicting drug behavior in different populations.

Limitation:

- More complex and requires a large amount of physiological and drug-specific information.

Non-Compartmental Analysis (NCA)

- **NCA does not assume a specific compartment structure.**
- Instead, it uses the **observed concentration–time data** to calculate important PK parameters.

➢ **Important parameters:**

Parameter	Meaning
AUC	Total systemic drug exposure
Cmax	Maximum observed concentration
Tmax	Time to reach Cmax
t½	Drug elimination half-life
CL	Clearance
Vd	Volume of distribution

➢ **NCA → data-based, model-independent approach**

- **Main limitation:**

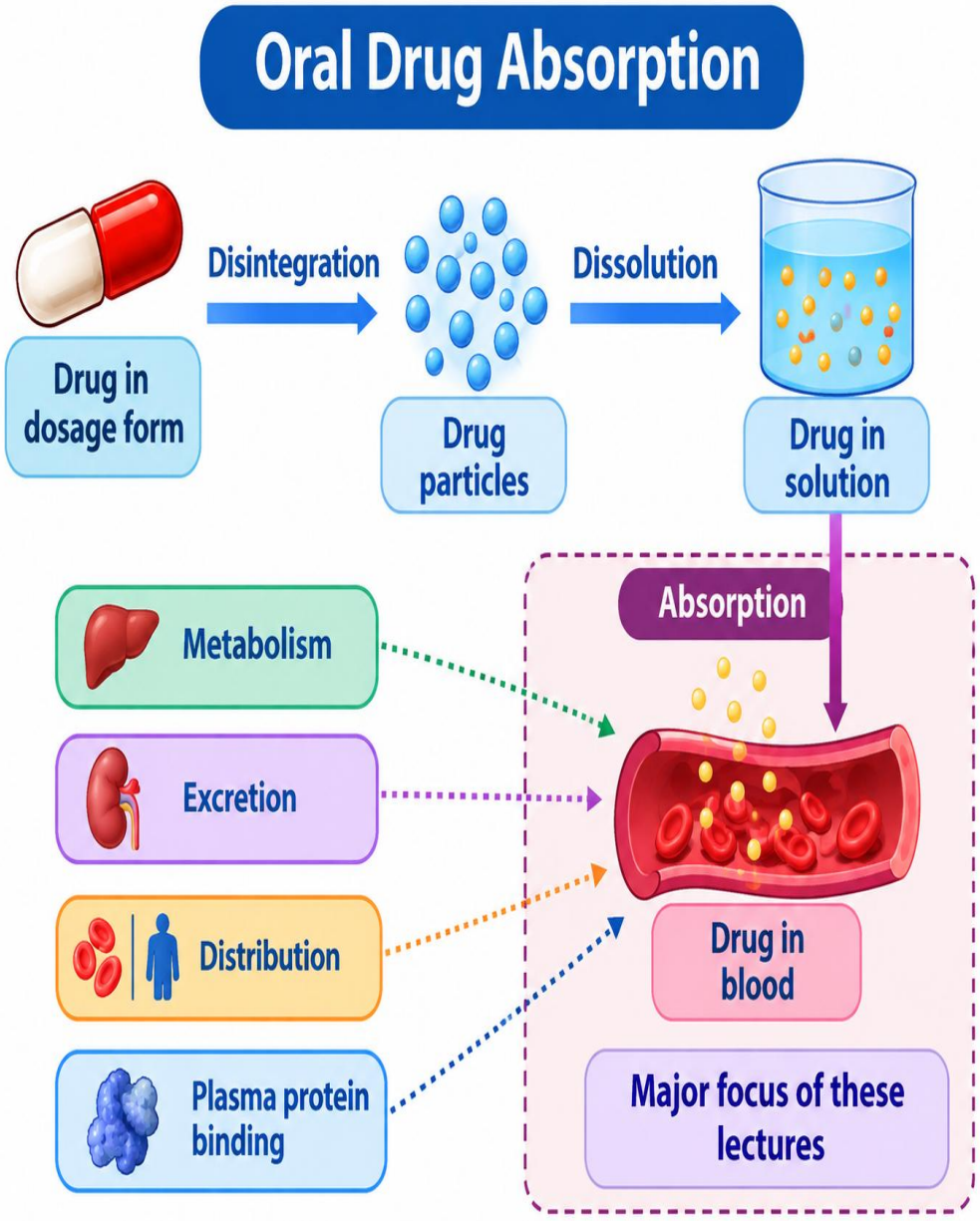
  ✗ Provides less mechanistic information about **where the drug goes in the body**.

Drug absorption

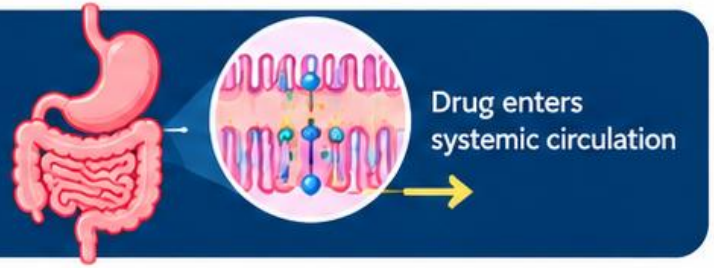
- **Drug absorption** is the movement of the drug from its site of administration into the bloodstream.
- intravenous therapy, absorption and bioavailability is 100%.

Oral drug absorption

- In order for a drug to reach its site of action, it must pass from the lumen of the small intestine into the bloodstream
- To reach the bloodstream, a drug must permeate the small intestinal epithelium (outer membrane)
- Overcoming this epithelial barrier is one of the most important considerations for drug delivery
- Intestinal epithelial transporters: Various carriers (e.g., PEPT1, GLUT5, P-glycoprotein) facilitate or restrict drug absorption.
- duodenal area of small intestine shows most rapid drug absorption, due to villi and microvilli, which provide a large surface area.

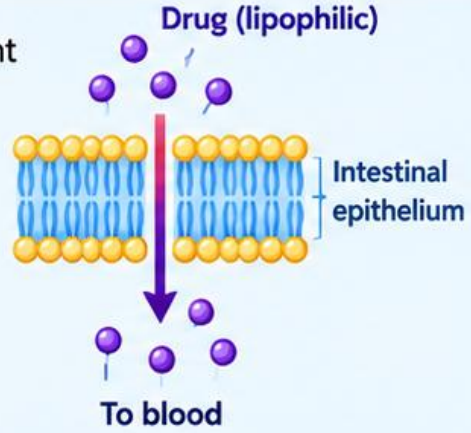


Mechanisms of Drug Absorption after Oral Administration



1 Passive Diffusion

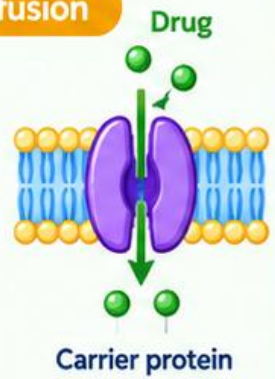
- Down the concentration gradient (high → low).
- No energy required.
- Occurs mainly for small, non-polar, lipophilic drugs (e.g., benzodiazepines, steroids).



2 Carrier mediated transport

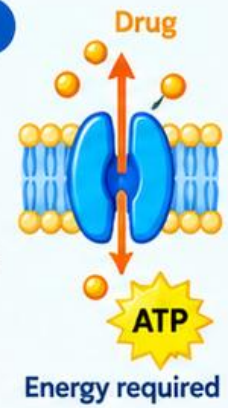
a Facilitated Passive Diffusion

- Uses carrier proteins (no energy).
- Moves down the gradient.
- e.g., Glucose, amino acids, some drugs (e.g., levodopa).



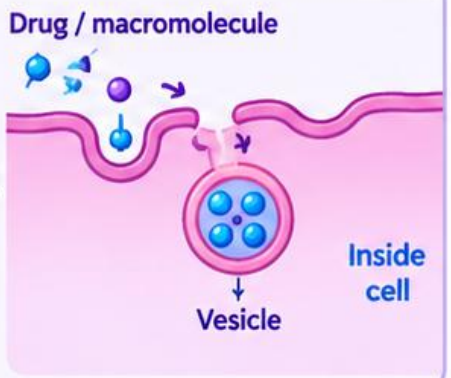
b Active Transport

- Uses carrier proteins and energy (ATP).
- Can move against the concentration gradient.
- e.g., Vitamin B12, certain antibiotics (e.g., penicillin G).



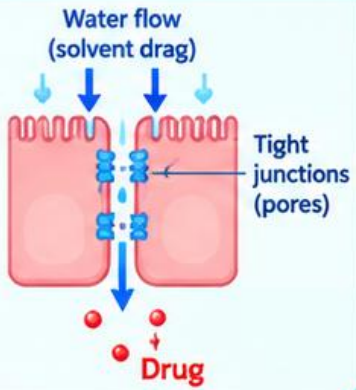
3 Pinocytosis

- Uptake of larger molecules or particles.
- Involves invagination of the cell membrane forming vesicles.
- e.g., proteins, nanoparticles, some macromolecules.



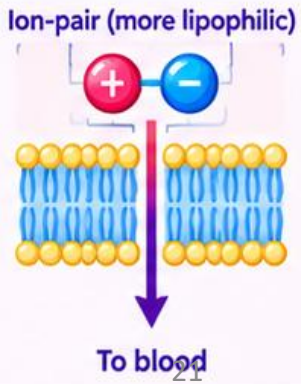
4 Pore Convective Mechanism

- Through aqueous pores (e.g., tight junctions or pores).
- Driven by solvent flow (water movement).
- Important for hydrophilic and small molecules.



5 Ion-Pair Formation

- Improves lipophilicity of ionized drugs.
- Allows passive diffusion through the lipid membrane.
- e.g., weak acids/bases forming ion pairs with counter-ions.



1-Passive Diffusion:

- depends on the molecule's **lipid solubility**, **size**, **degree of ionization**, and the **area** of absorptive surface.
- **Primary mechanism for most drugs**
- Small molecules tend to penetrate membranes more rapidly than larger ones.

Passive diffusion is best express by ficks first law of diffusion :

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_{Cl} - C_p) \quad (1)$$

$$\frac{dQ}{dt} = P(C_{Gl}) \quad (13.3)$$

- Drugs that can passively diffuse through cell membrane must be
  - *Lipid soluble*
  - *Unionized form*

dQ/dt = rate of diffusion.
D = diffusion coefficient.
K = lipid water partition coefficient of drug in biologic membrane that controls drug permeation.
A = surface area of membrane
h = membrane thickness
$C_{GI} - C_p$ = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.
C p is extremely small
Because D, A, K, and h are constants under usual conditions for absorption, a combined constant P or permeability coefficient

2-Carrier mediated transport

- Some **polar drugs** cross the membrane more readily than can be predicted from *their concentration gradient and partition coefficient values*.
- The mechanism involves **a carrier** which binds reversibly with the solute molecules to be transported to yield the carrier solute complex which transverses across the membrane to the other side where it dissociates to yield the solute molecule
- The carrier then returns to its original site to accept a fresh molecule of solute.
- The carrier may be enzyme or other component of cell membrane.
- There are two types of carrier mediated transport system:
    a) Facilitated diffusion
    b) Active transport

Characteristics of Carrier-Mediated Transport:

1.Structure Specificity: Carriers recognize and transport only substances with a particular chemical structure, typically essential nutrients.

2.Transport of Similar Structures (False Nutrients): Because the system is structure-specific, drugs that resemble essential nutrients—called *false nutrients*—can also be transported by the same carriers. This is especially important for certain anticancer drugs like 5-fluorouracil and 5-bromouracil, which mimic natural nutrients to gain cellular entry.

3.Limited Carrier Availability and Competition: Since the number of carriers is limited, substances with similar structures must compete for transport.

4. Carrier-Mediated Absorption and Absorption Window: This type of absorption typically takes place at specific regions of the intestinal tract where there is a **high concentration of carrier proteins**.

- A region in the intestine where the **carrier system is most densely located** is referred to as the *absorption window*.
- Drugs that depend on carrier-mediated absorption and are absorbed primarily in these windows **may not be suitable for controlled release formulations**, because once the drug passes that specific region, further absorption is significantly reduced.

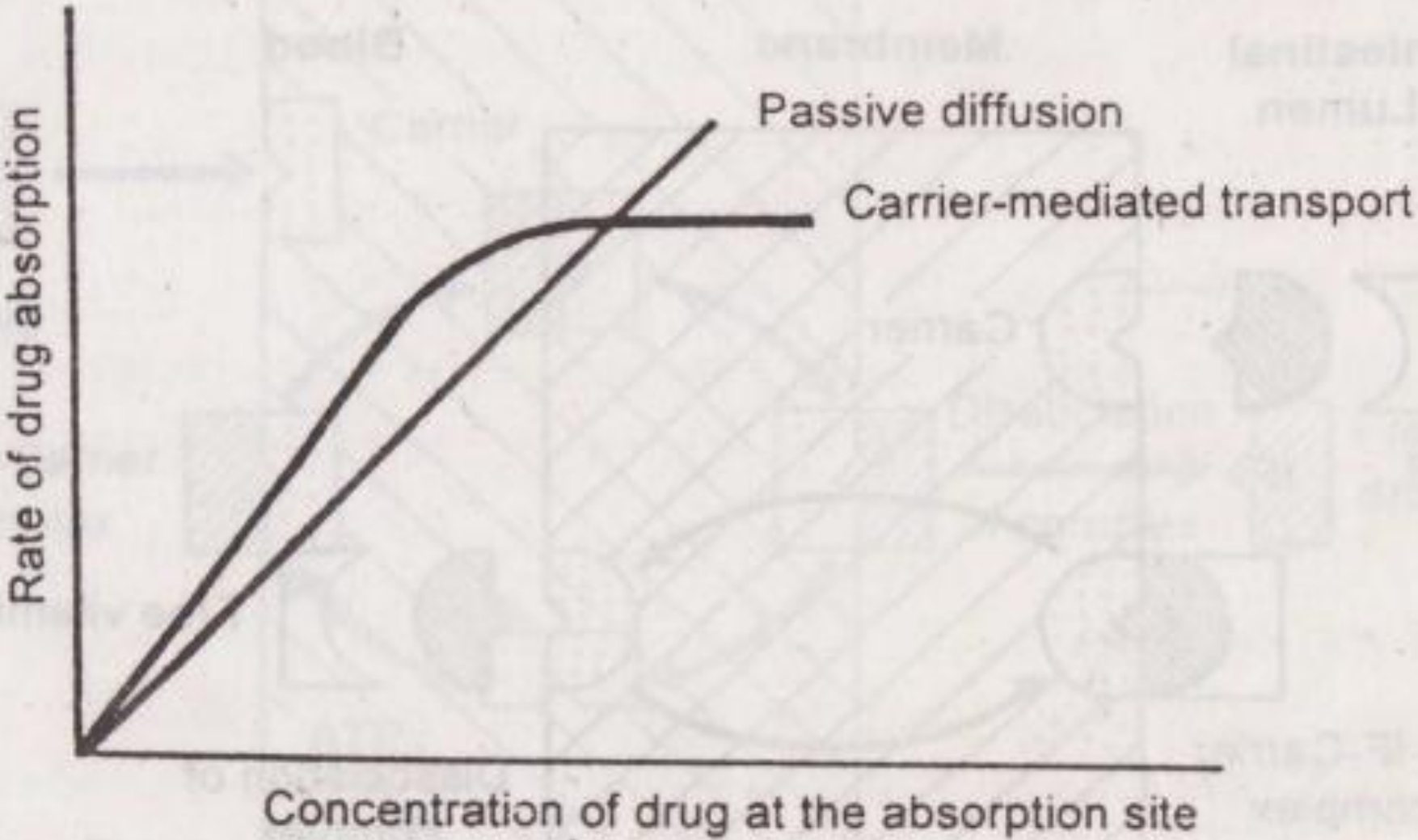


Fig. 2.3 Comparison of rate of absorption versus drug concentration plots for passive and carrier-mediated transport processes

Carrier mediated transport

A-Facilitated Passive Diffusion:

- Facilitated diffusion is a type of carrier-mediated transport in which molecules move from an area of high concentration to an area of low concentration, facilitated by specific transport proteins.
- This process **does not require energy** (no ATP is used).
- Carrier in the membrane combines reversibly with the substrate molecule outside the cell membrane
- It is **not a major mechanism** for most drug absorption and Limit carrier
- An example of a substance absorbed through facilitated diffusion is **cyanocobalamin** (vitamin B12).

Carrier mediated transport

B- Active Transport

- Active transport plays a more significant role than facilitated diffusion in the absorption of nutrients and drugs.
- It differs from facilitated diffusion in the following ways:

  1.Movement Against the Gradient: The drug is moved *against the concentration gradient*, also known as *uphill transport*.

  2.Energy Requirement: Because the transport is against the gradient, **energy is needed**, which is supplied by the carrier during the process.

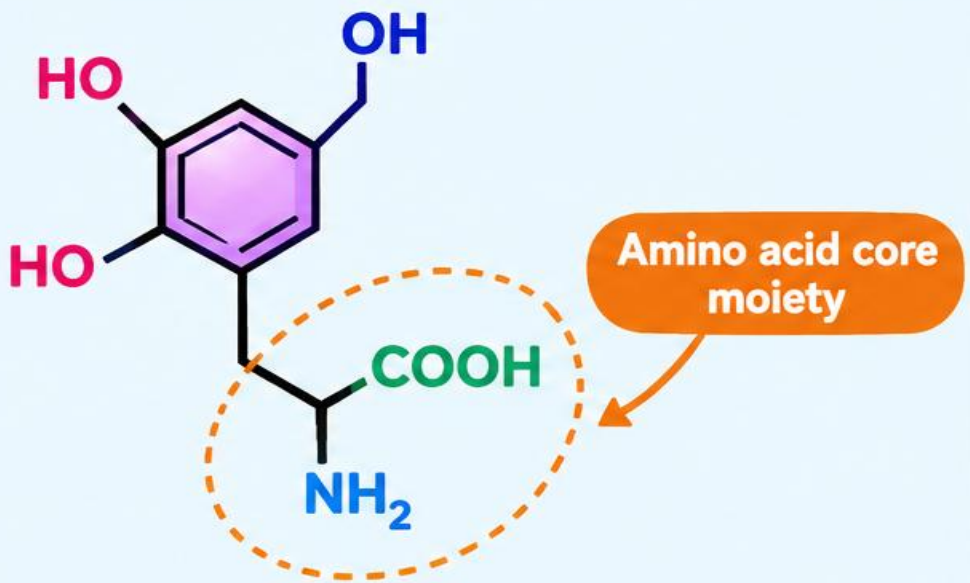
  3.Sensitivity to Inhibitors: Since the process consumes energy, it can be **inhibited by metabolic poisons** that interfere with energy production, such as **fluorides, cyanide, dinitrophenol**, or **lack of oxygen**.

  4.Saturation of the carrier : Due to a limited number of active sites on the carrier protein, there can be saturation at higher substrate concentrations

Examples of drugs absorbed by active transport

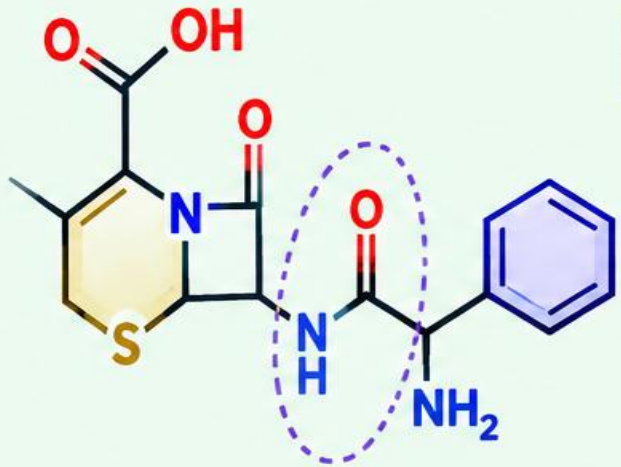
- Many active transport proteins exist in the small intestine for absorption of important molecules (vitamins, amino acids, peptides, monosaccharides, nucleosides)
- Drugs with similar structures may be substrates for such transporters
- Drugs may be designed with functional groups to allow interaction with carrier proteins and therefore improved absorption

Levodopa

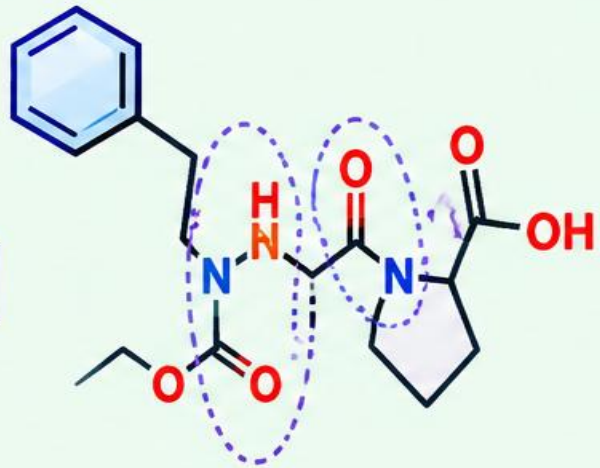


- Actively transported by intestinal amino acid transporter.
- Foods, especially high in protein, can alter levodopa absorption due to competitive inhibition by food-derived amino acids.

Cephalosporin antibiotics and ACE inhibitors



Cephalexin

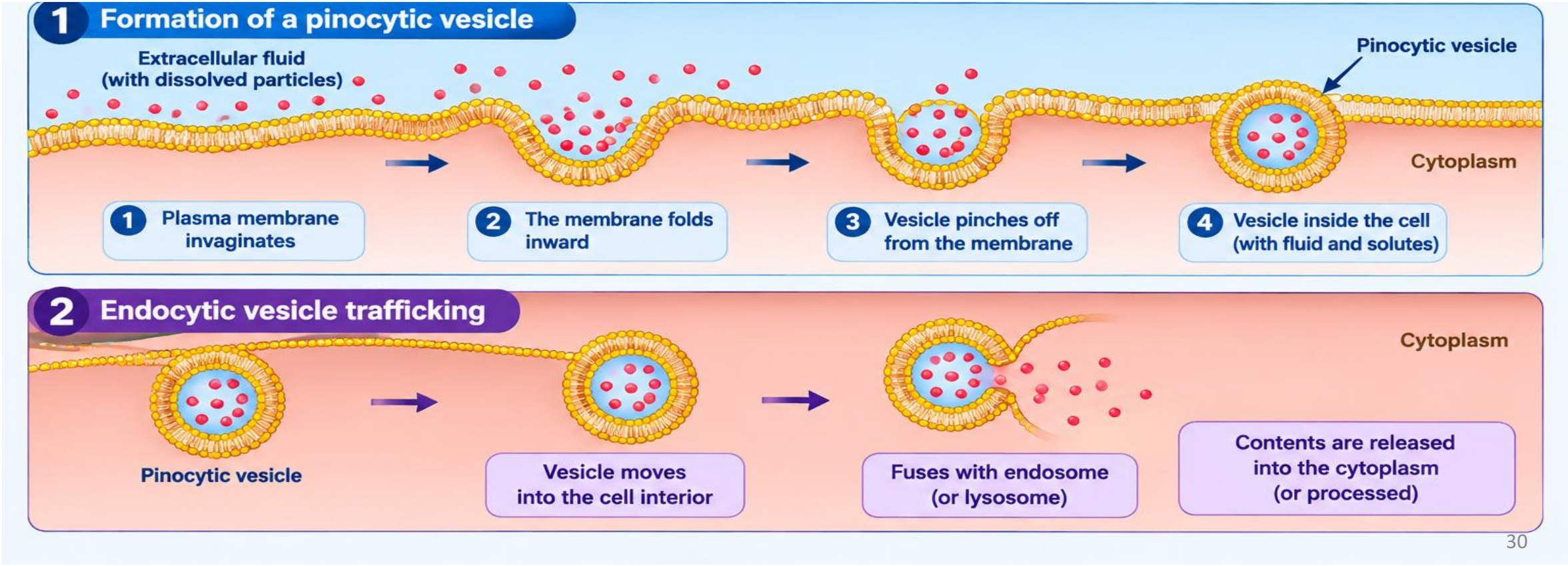


Enalapril

- Actively transported by intestinal oligopeptide transporter.

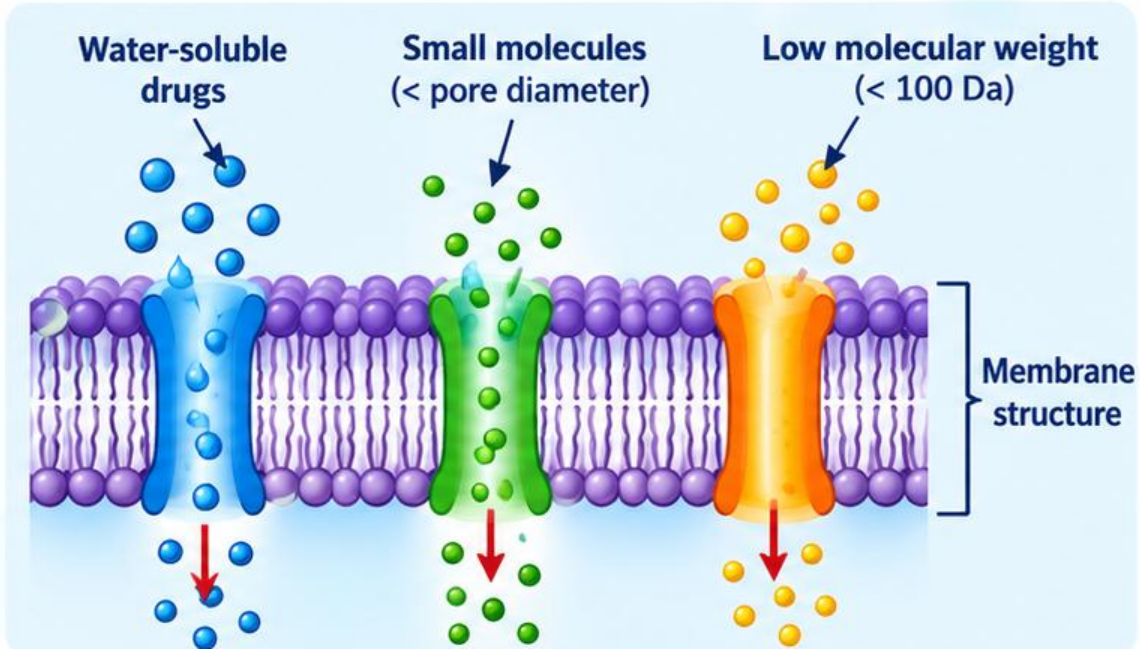
3-Pinocytosis:

- The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later moves to the cell interior.
- Energy required.
- Pinocytosis probably plays a small role in drug transport, except for **protein drugs**.



4- Pore Transport

- Pore transport is also known as: **Convective transport, Bulk flow or Filtration**
- This process is important for the absorption of **low molecular weight** (less than 100 Da), **low molecular size** (smaller than the pore diameter), and generally **water-soluble drugs**.
- Transport occurs through narrow, aqueous-filled channels or pores in the membrane structure.



Examples of substances absorbed this way:


Urea


Water


Sugars

Chain-like or linear compounds with molecular weights up to **400 Daltons** can be absorbed by filtration.

The driving force for this transport is:

- **Hydrostatic pressure, or**
- **Osmotic differences across the membrane**

5-Ion-Pair Formation

- **Strong electrolyte** maintain their charge at physiologic pH and penetrate membranes poorly.
- Transport of charged molecules due to the formation of a neutral complex with **another** charged molecule carrying an opposite charge.
- Drugs have **low** o/w partition coefficient values, yet these penetrate the membrane by forming reversible neutral complexes with endogenous ions. e.g. mucin of GIT.
- Such neutral complexes have both the required lipophilicity as well as aqueous solubility for passive diffusion.

Examples:

- **propranolol**, basic with oleic acid.