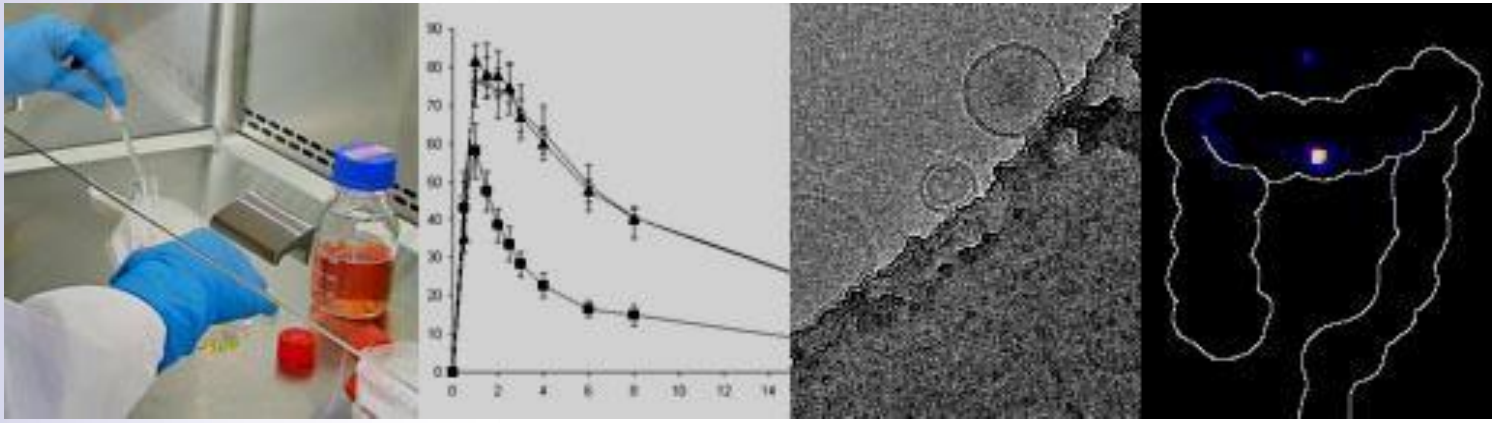
BIOPHARMACEUTICS



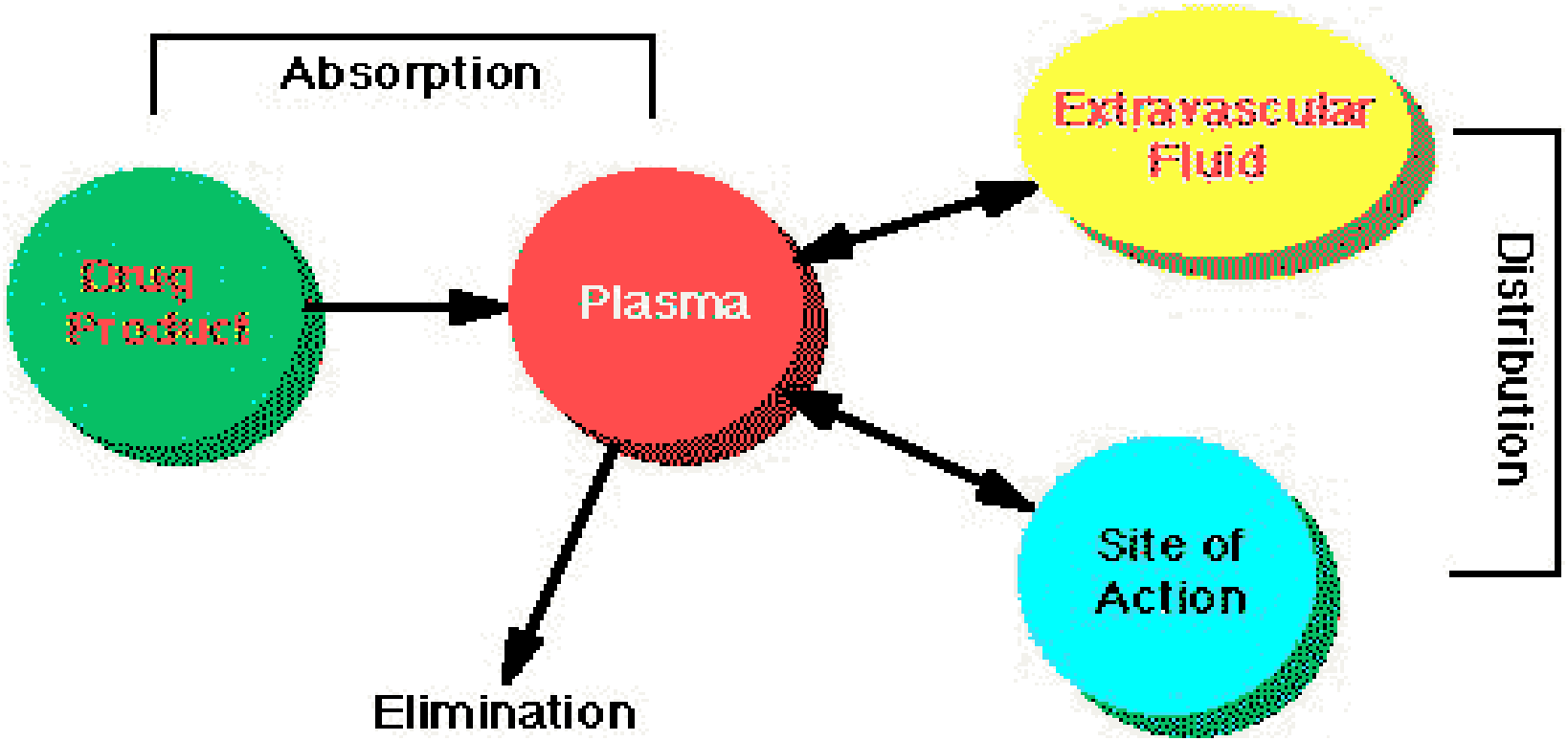
Introduction to bipharmaceutics:

- **Biopharmaceutics:** the study of how the physicochemical properties of drugs, dosage forms and routes of administeration affect the rate and extent of the drug absorption.
- Thus, biopharmaceutics involves factors that influence the:

1) protection and stability of the drug within the product;
2) the rate of drug release from the product;
3) the rate of dissolution of the drug at the absorption site; and
4) the availability of the drug at its site of action .

Introduction to bipharmaceutics (Cont.):

Scheme demonstrating the dynamic relationships among the drug, the product, and pharmacologic effect.



Introduction to bipharmaceutics (Cont.):

- **ADME:** is an acronym in pharmacokinetics and pharmacology for **a**bsorption, **d**istribution, **m**etabolism, and **e**xcretion, and describes the disposition of a pharmaceutical compound within an organism.

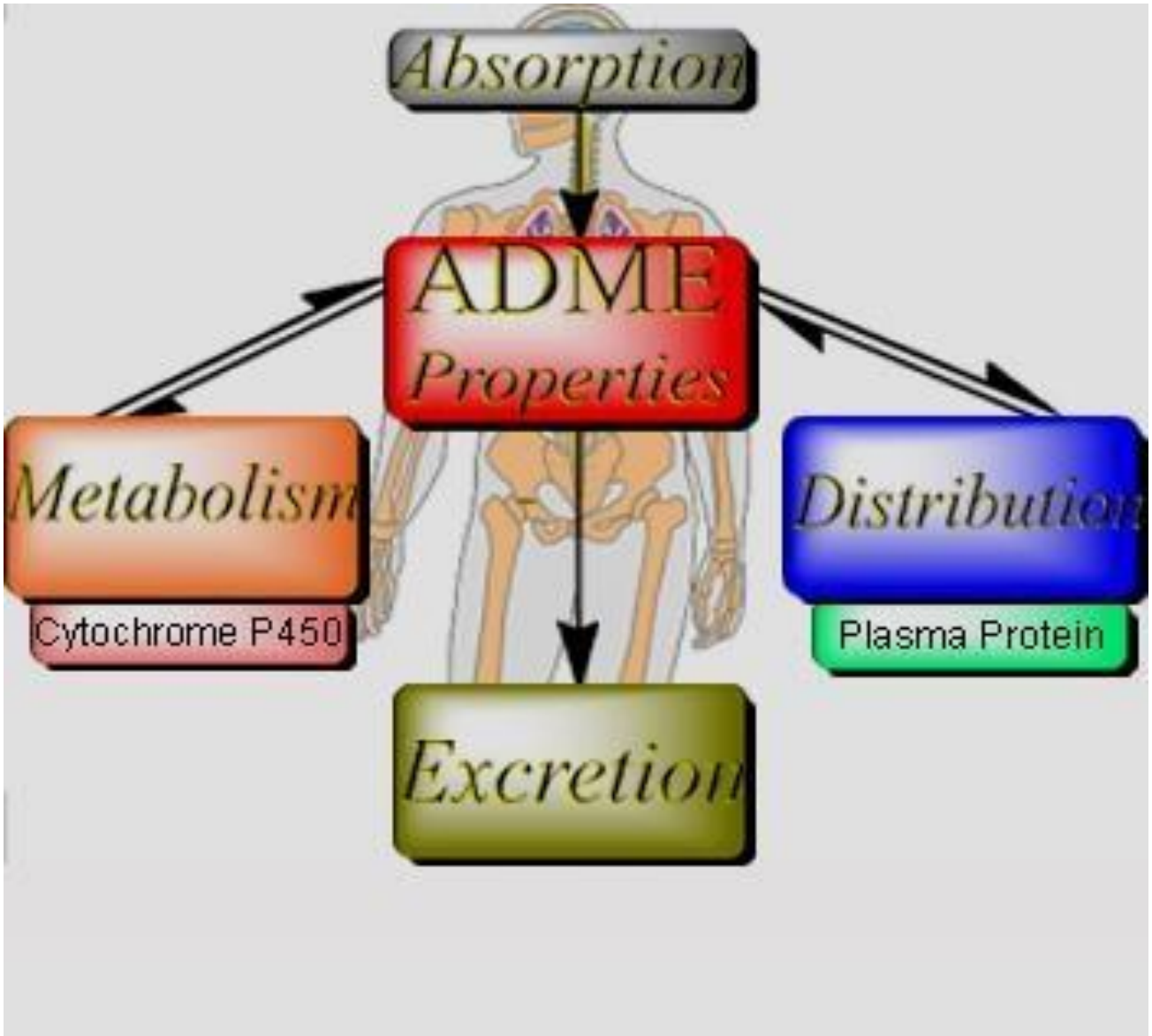
- **Pharmacokinetics:** The study and characterization of the time course (kinetics) of drug absorption, distribution, metabolism and elimination (ADME).

Introduction to bipharmaceutics (Cont.):

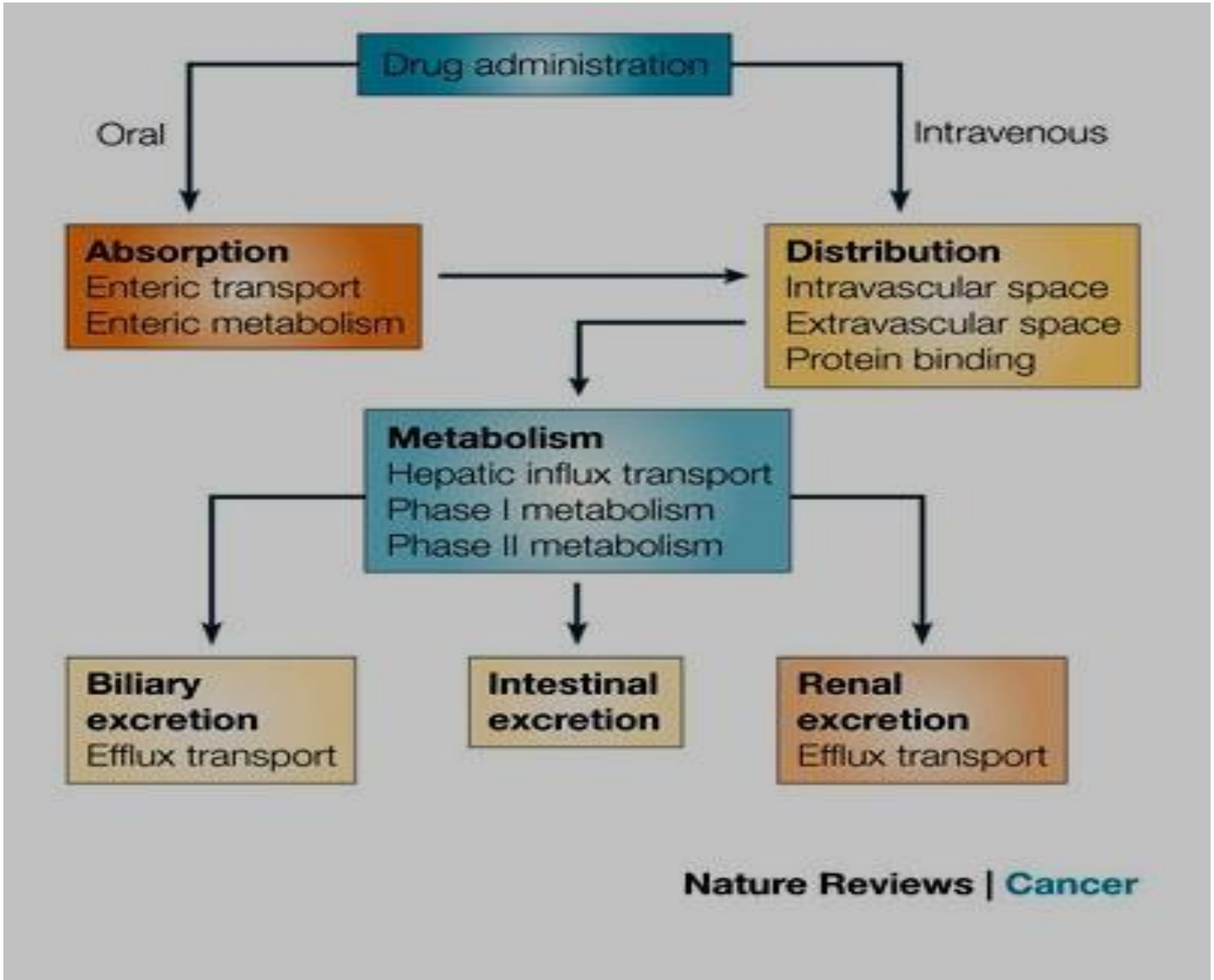


- **Absorption:** is the process of a substance entering the body.
- **Distribution:** is the dispersion of substances throughout the fluids and tissues of the body.
- **Metabolism:** is the irreversible transformation of parent compounds into daughter metabolites.
- **Excretion:** is the elimination of the substances from the body.

Introduction to bipharmaceutics (Cont.):

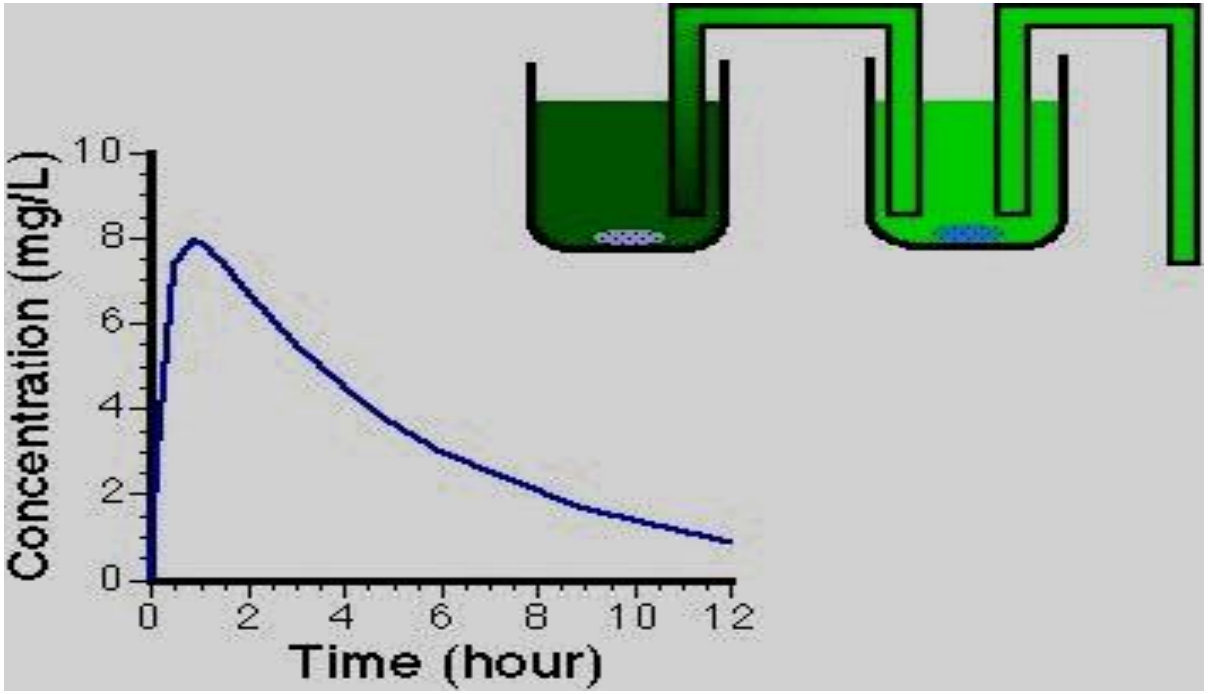


Introduction to bipharmaceutics (Cont.):



Introduction to bipharmaceutics (Cont.):

- **Bioavailability:** The rate and extent of drug absorption.
- **Bioavailable dose:** The fraction of an administered dose of a particular drug that reaches the systemic circulation intact.
- **Plasma level-time curve:**

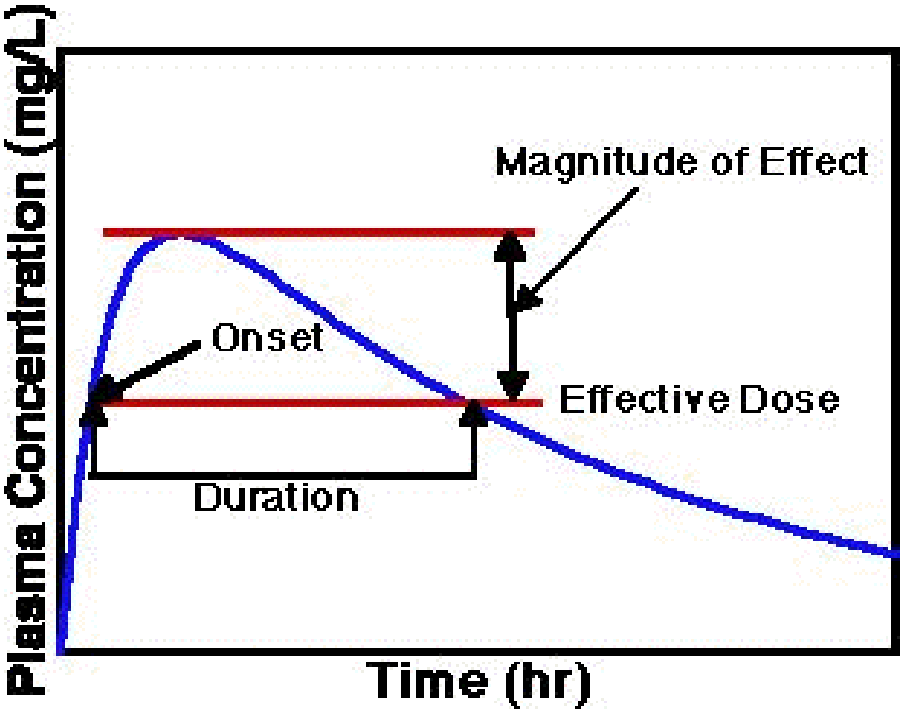


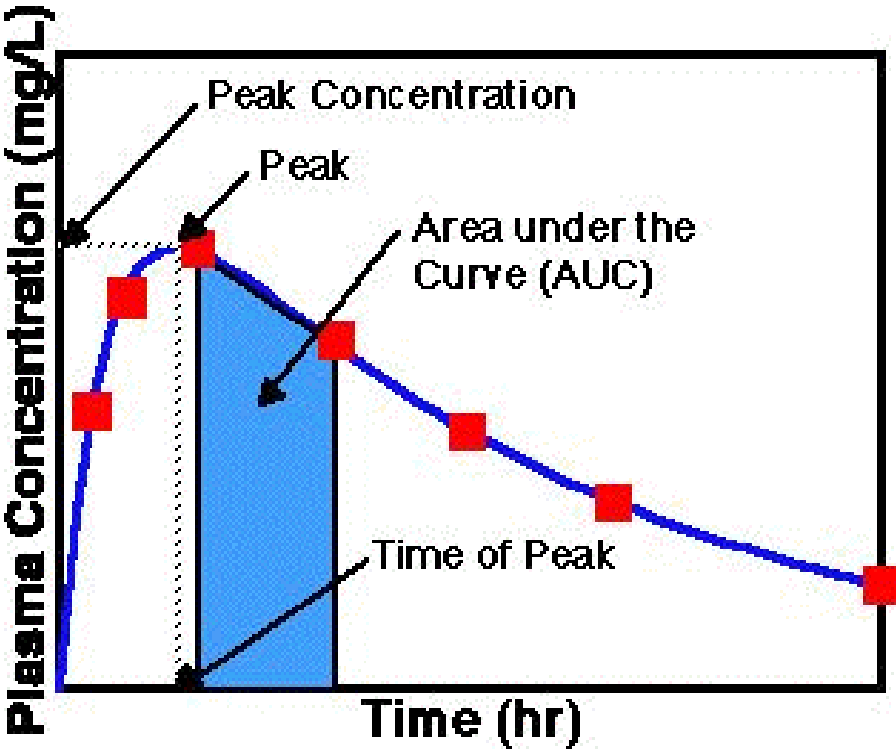
Introduction to bipharmaceutics (Cont.):

- The plasma level-time curve is generated by measuring 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 against the corresponding time at which the plasma sample was removed.

Introduction to bipharmaceutics (Cont.):





Introduction to bipharmaceutics (Cont.):

- **Drug Product Performance Parameters:**

1. **Minimum effective concentration (MEC):** The minimum concentration of drug needed at the receptors to produce the desired pharmacologic effect.

2. **Minimum toxic concentration (MTC):** The drug concentration needed to just produce a toxic effect.

3. **Onset time:** The time required for the drug to reach the MEC.

4. **Duration of action:** The difference between the onset time and the time for the drug to decline back to the MEC.

Introduction to bipharmaceutics (Cont.):

5. **The time of peak plasma level:** The time of maximum drug concentration in the plasma and is proportional to the rate of drug absorption.

6. **The peak plasma level:** The maximum drug concentration, usually related to the dose and the rate constants for absorption and elimination of the drug.

7. **Area under the curve:** It is related to the amount of drug absorbed systemically.

Absorption

Main factors affecting oral absorption:

I.Physiological factors.
II.Physical-chemical factors.
III Formulation factors.

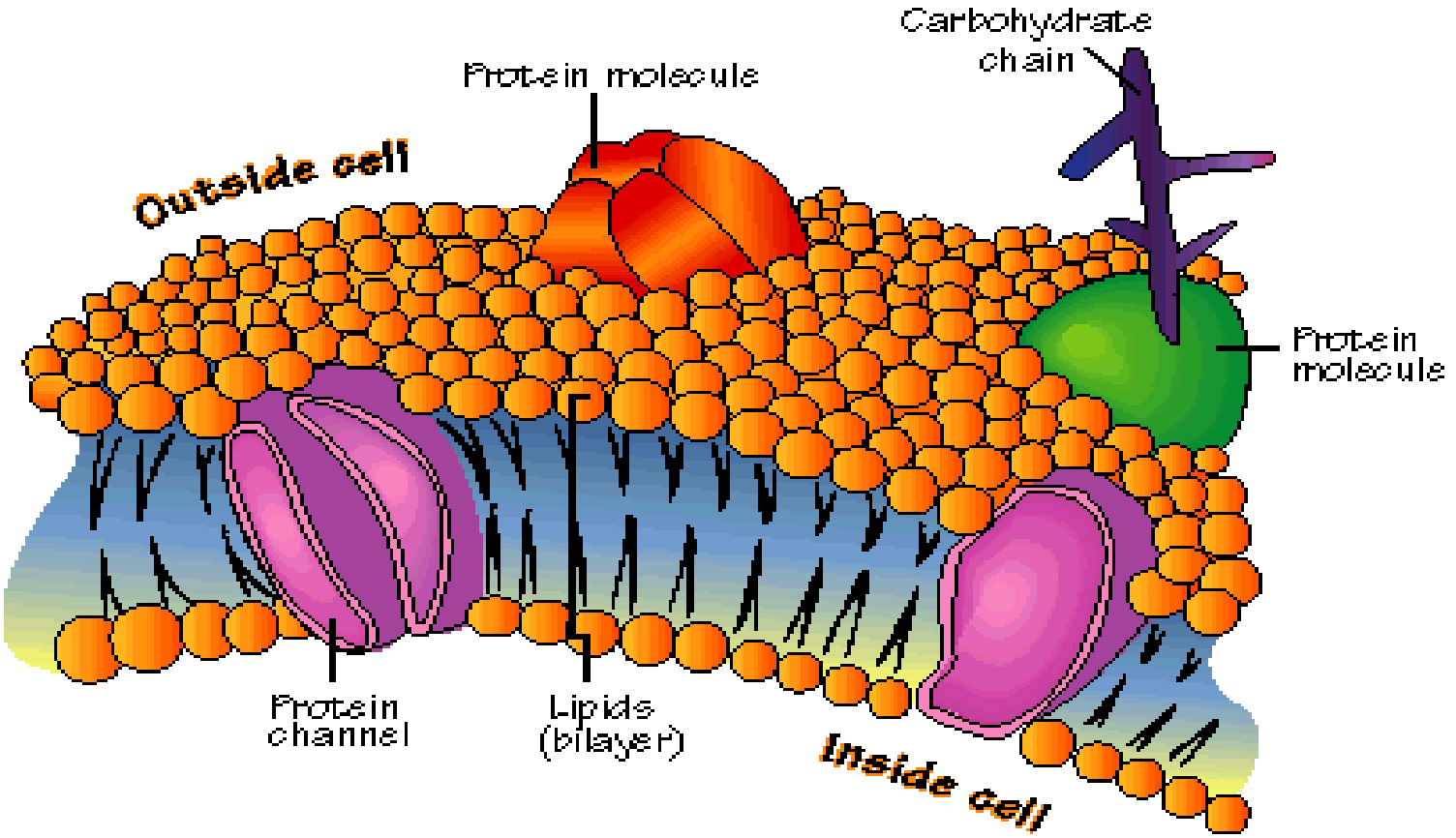
I Physiological factors affecting oral absorption:

1 Membrane physiology.
2 Passage of drugs across membranes.
3 Gastrointestinal physiology.

I. Characteristics of GIT physiology and drug absorption
II. Gastric emptying time and motility
III. Effect of food on drug absorption

Physiological factors influencing bioavailability:

1- Membrane physiology:



1- Membrane physiology (Cont.):

- The cell membrane is the barrier that separates the inside of the cell from the outside.
- The cell membrane is made up of phospholipids, proteins, and other macromolecules.

- The phosopholipids make up a bilayer. It contains hydrophilic and hydrophobic molecules.

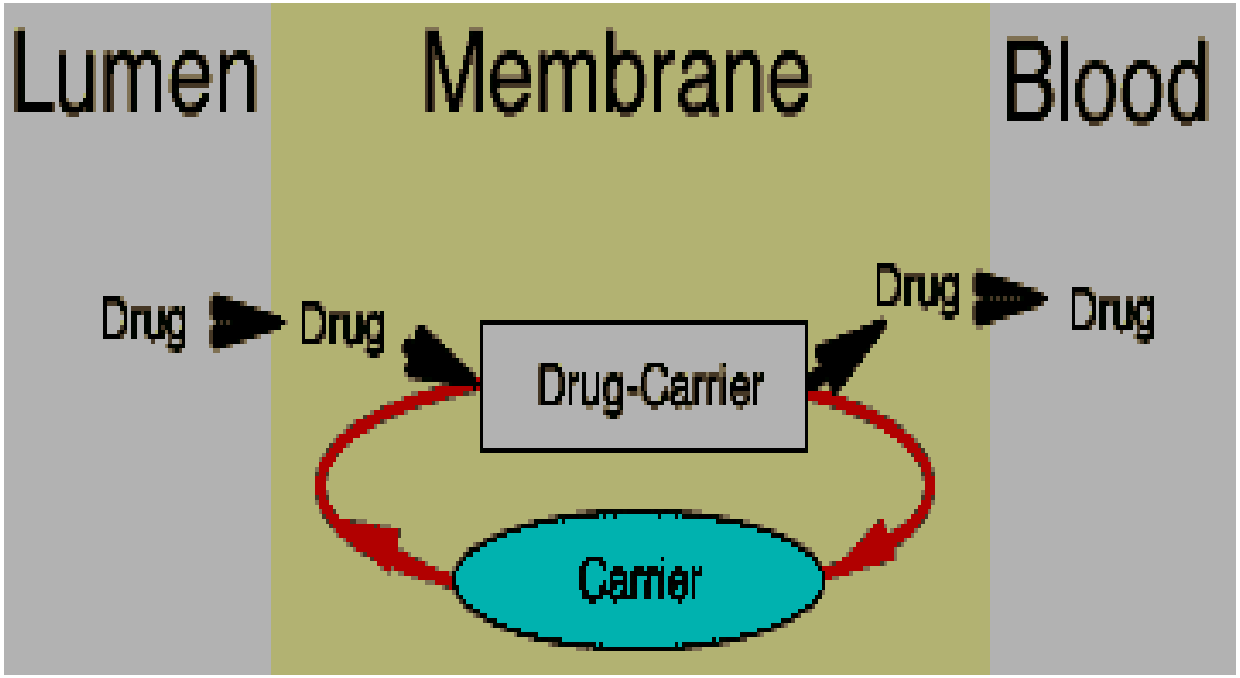
- The proteins in the cell membrane are located within the phospholipid bilayer.

- So, the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.

2-Passage of drugs across membranes:

•••Transport across the membranes:

1- Carrier mediated:

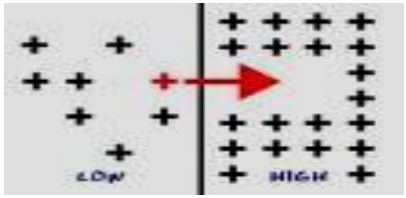


2-Transport across the membranes (Cont.):

A- Active transport:

- A few lipid-insoluble drugs (e.g.5-flurouracil) that resemble natural physiologic metabolites (e.g. glucose, amino acids) are absorbed from the GIT by this process.

- Transport of a drug against concentration gradient (from regions of low drug concentrations to regions of high concentrations).

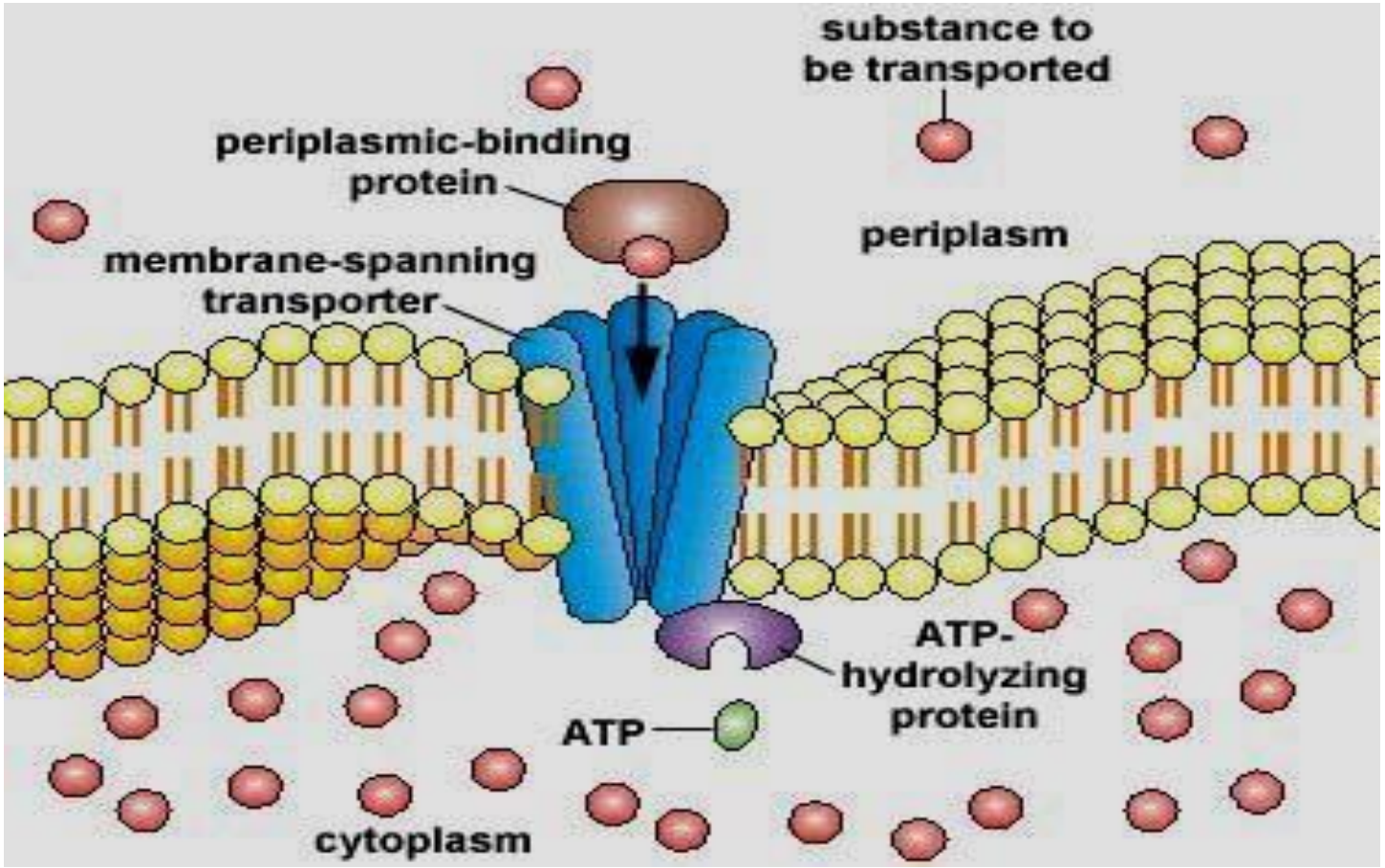


- It is an energy-consuming system.

- The carrier molecule may be highly selective for the drug molecule, therefore, drugs of similar structure may compete for sites of adsorption on the carrier (competitive inhibition is possible)

- Because only a certain amount of carrier is available, all the adsorption sites on the carrier may become saturated if the drug concentration gets very high.

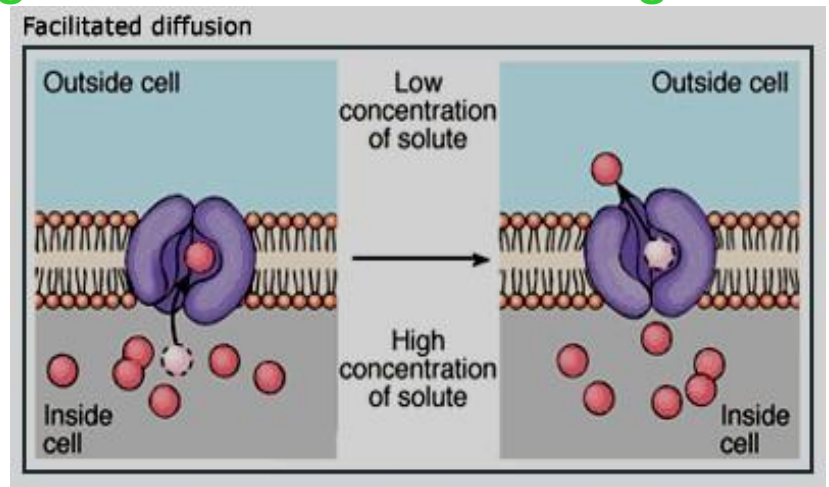
2-Transport across the membranes (Cont.):



2-Transport across the membranes (Cont.):

B- Facilitated diffusion:

- Play a very minor role in absorption.
- A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport.
- Saturable if not enough carrier and structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- No transport against a concentration gradient only downhill but faster.



2-Transport across the membranes (Cont.):

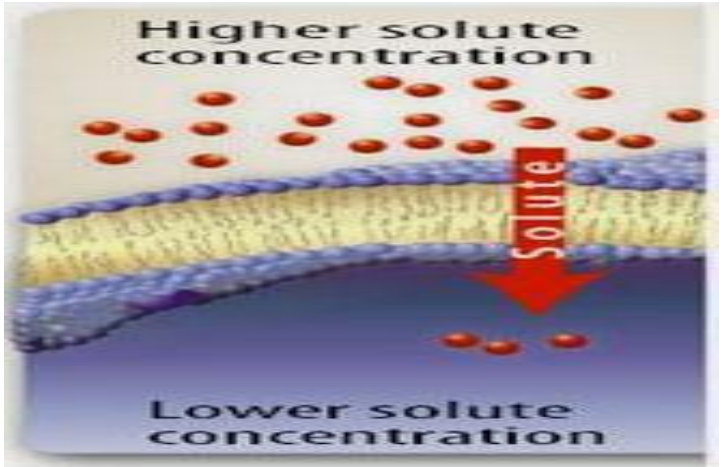
C- P-glycoprotein:

- P-glycoprotein transporters (PGP) are present throughout the body including liver, brain, kidney and the intestinal tract epithelia.
- Act as reverse pump generally inhibiting absorption.
- This is an active, ATP-dependent process.

2-Transport across the membranes (Cont.):

2- Passive diffusion:

- Most drugs cross biologic membranes by passive diffusion.
- Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side.
- The process is passive because no external energy is expended.
- The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane.



2-Transport across the membranes (Cont.):

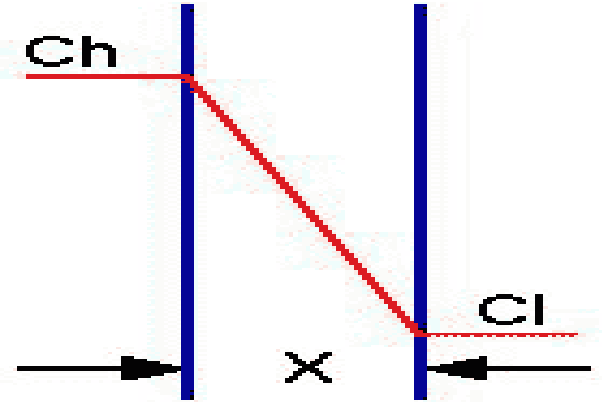


Diagram of Passive Transport with a Concentration Gradient

-The rate of transport of drug across the membrane can be described by Fick's first law of diffusion:-

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{D \bullet A \bullet (Ch - Cl)}{x}$$

Fick's First Law, Rate of Diffusion

2-Transport across the membranes (Cont.):

- The parameters of this equation are:-

D: diffusion coefficient. This parameter is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium.

As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

A: surface area. As the surface area increases the rate of diffusion also increase.

The surface of the intestinal lining (with villae and microvillae) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

2-Transport across the membranes (Cont.):

x: membrane thickness. The smaller the membrane thickness the quicker the diffusion process. As one example, the membrane in the lung is quite thin thus inhalation absorption can be quite rapid.

(Ch -Cl): concentration difference.

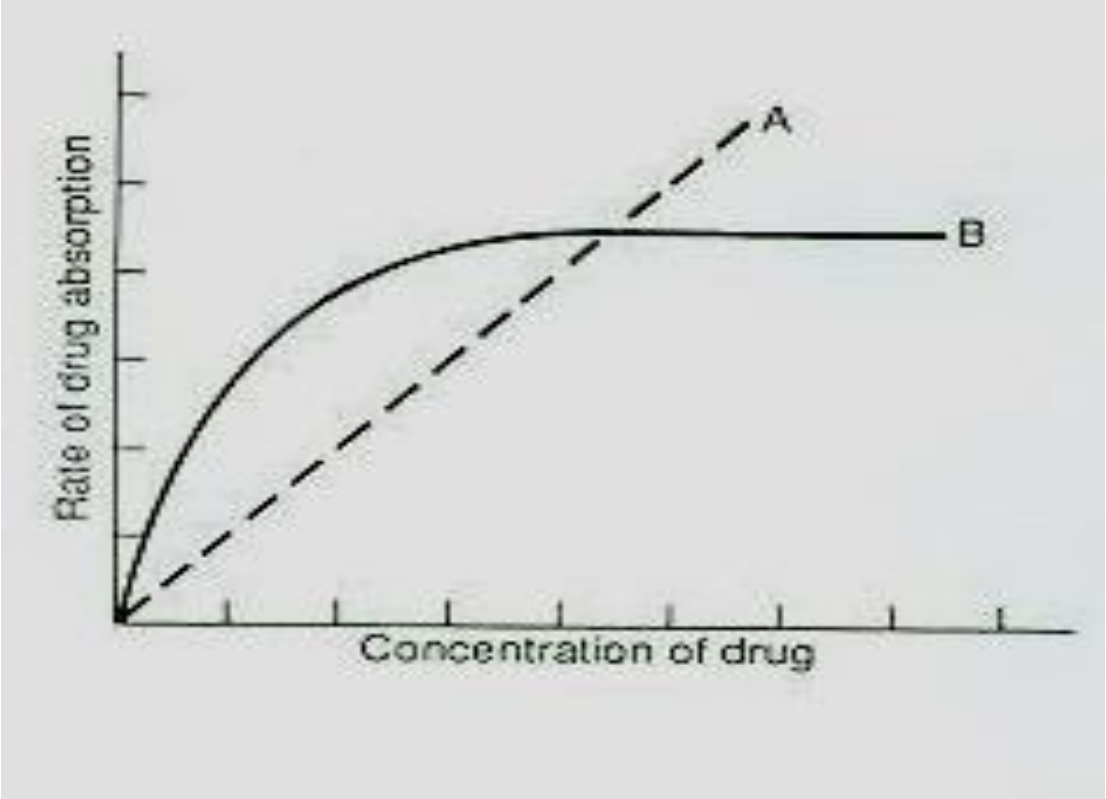
The drug concentration in blood or plasma will be quite low compared with the concentration in the GI tract. It is this concentration gradient which allows the rapid complete absorption of many drug substances.

- Normally Cl << Ch then:-

$$\frac{dM}{dt} = -\frac{D \bullet A \bullet Ch}{x}$$

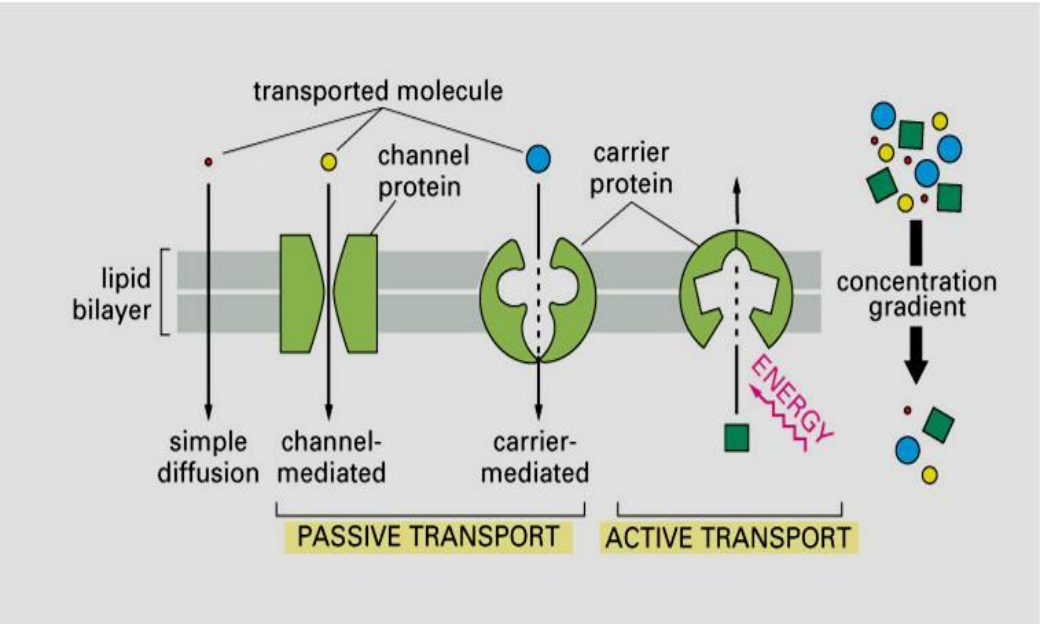
constant, ka

2-Transport across the membranes (Cont.):



Relationship between drug concentration and absorption rate For a passive process (Curve A) and for a carrier-mediated Process (Curve B).

2-Transport across the membranes (Cont.):



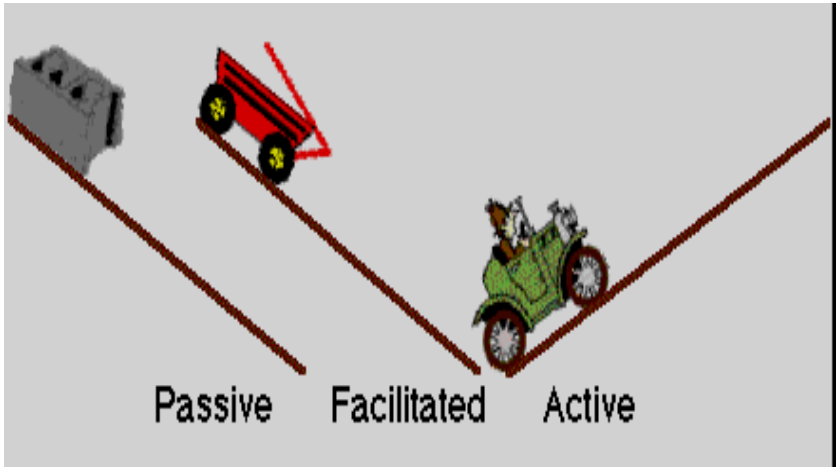


Illustration of Different Transport Mechanisms

2-Transport across the membranes (Cont.):

3- Vesicular transport:

- It is the process of engulfing particles or dissolved materials by the cell.

- Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.

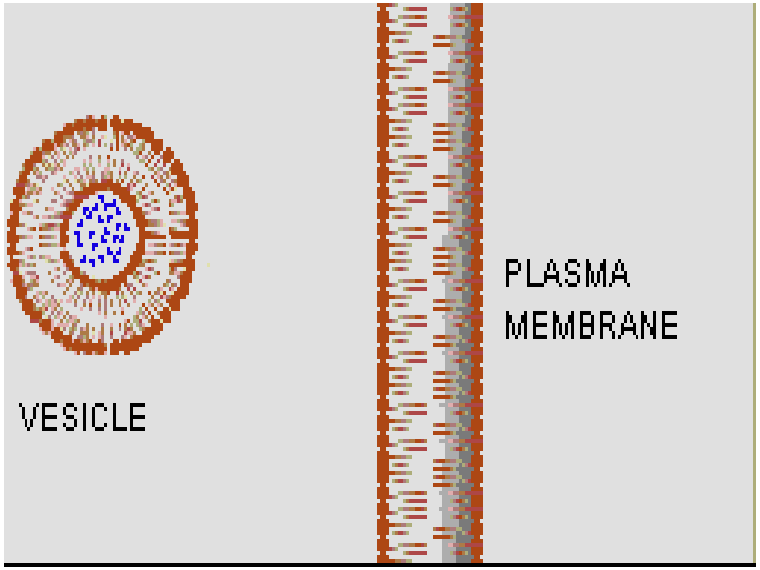
Pinocytosis: refers to the engulfment of small molecules or fluid.

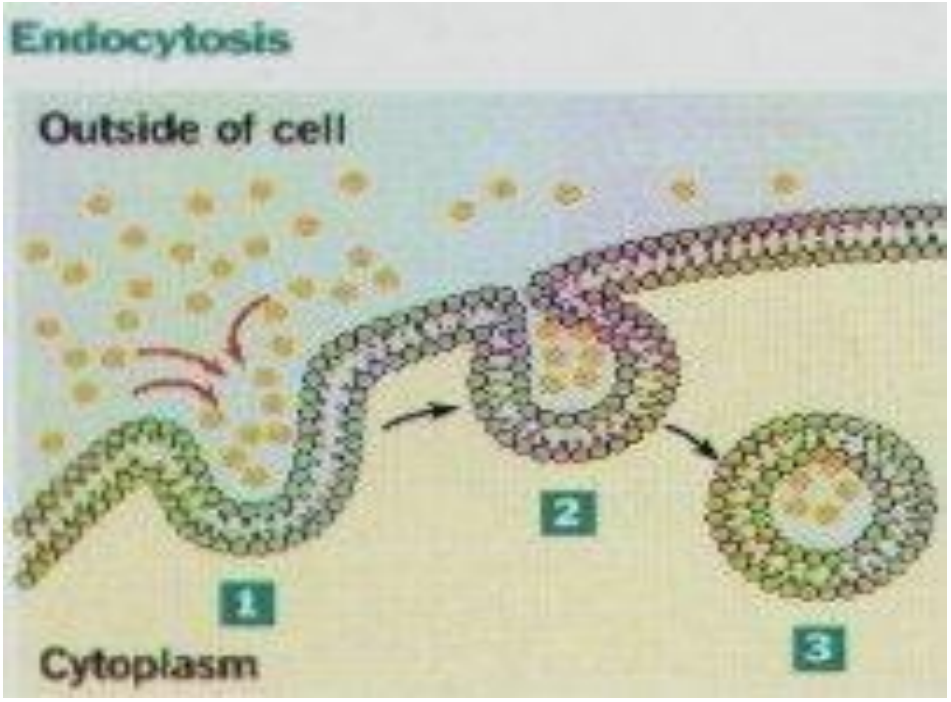
Phagocytosis: refers to the engulfment of larger particles or macromolecules.

- During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into the cell. Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell.

- Vesicular transport is the proposed process for the absorption of Vitamin A, D, E, and K, peptides in new born.

2-Transport across the membranes (Cont.):





2-Transport across the membranes (Cont.):

4- Pore (convective) transport:

- A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell.
- Very small molecules, such as urea, water and sugars are able to rapidly cross the cell membrane through these pores.

5- Ion pair formation:

- Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds.
- These drugs penetrate membranes poorly. When linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral complex diffuses more easily across the membrane.
- e.g. the formation of an ion pair for propranolol (basic drug) with oleic acid.

Transport of Substances Across a Membrane by Channel Proteins

