General principles

When a drug is ingested in the body, what happens?

- The body acts on the drug :Pharmacokinetics
- The drug act on the body : Pharmacodymanics

- In these two complex processes, numerous factors interfere to give the final outcome.

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination

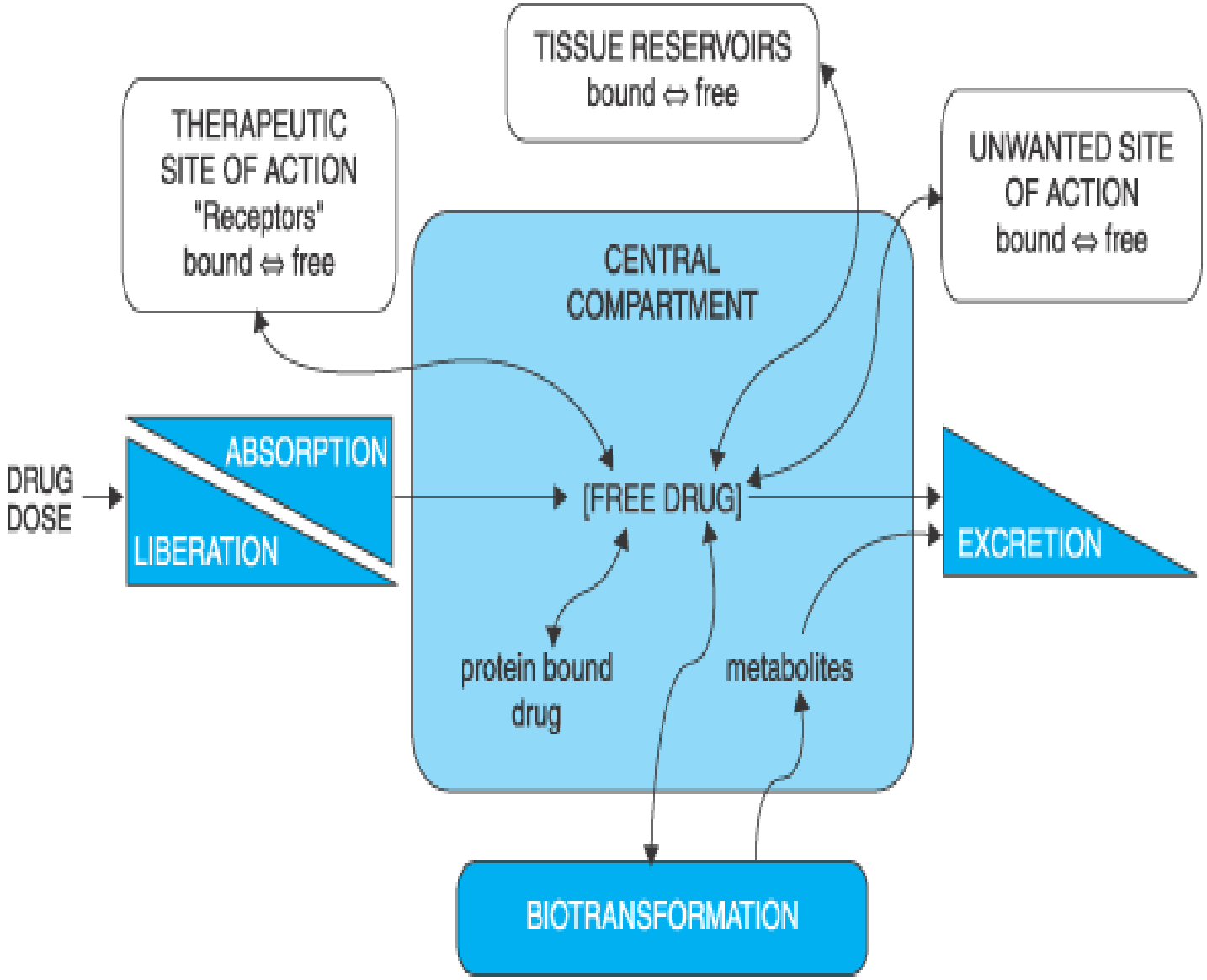


Figure 1-1. *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its conce*
sites of action.

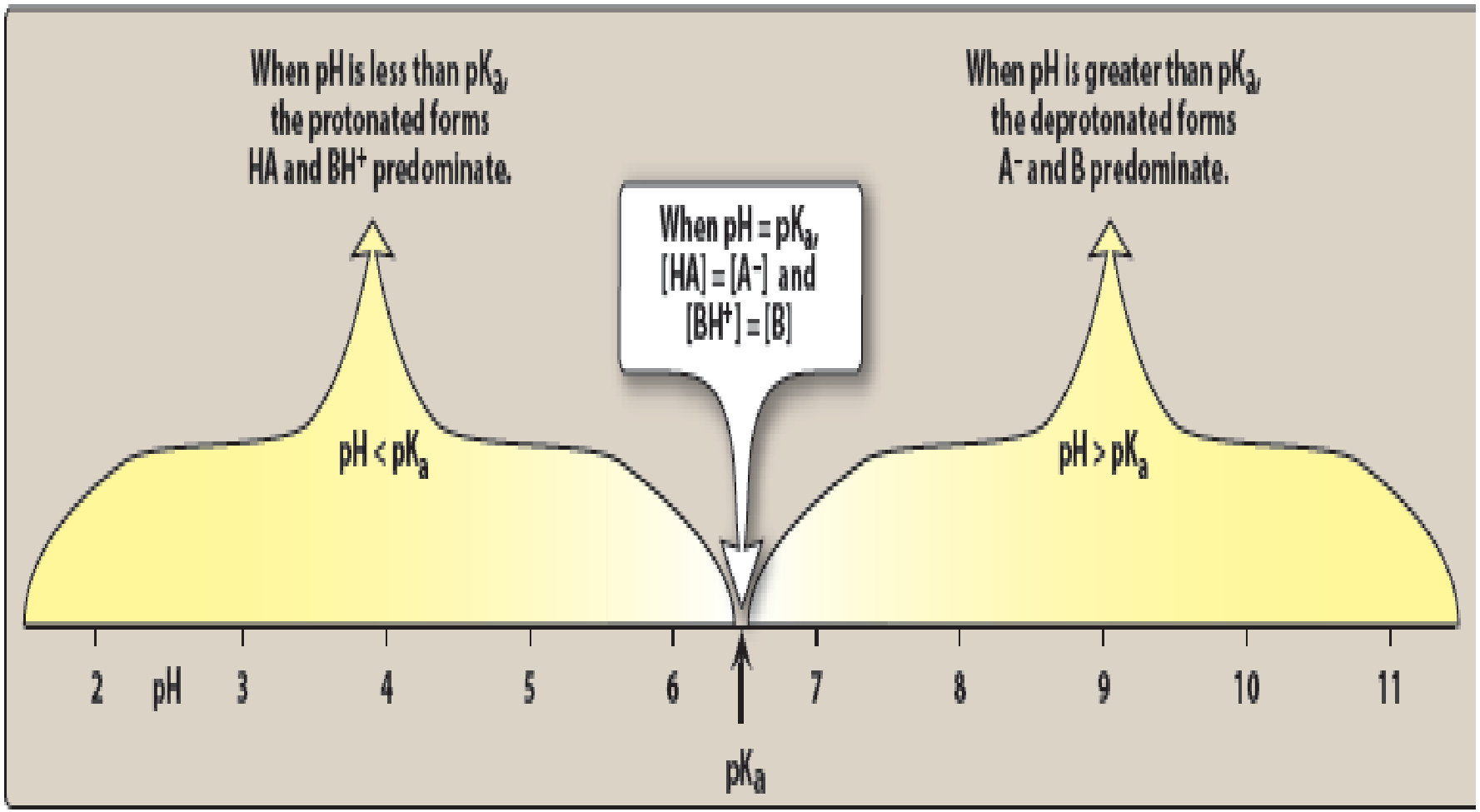
Absorption

- A drug should be absorbed from the site of adminstration into the plasma

- To produce its effect, a drug must reach its site of action at appropriate concentration.

Factors affecting Drug Absorption

- Drug physicochemical properties
- Route of drug administration
- Effect of pH on drug absorption
- Blood flow to the absorption site
- Total surface area available for absorption
- Contact time at the absorption surface
- Expression of drug carriers such as “ P-glycoprotein”


When pH is less than pK_a, the protonated forms HA and BH^+ predominate.
When pH = pK_a, [HA] = $[A^-]$ and $[BH^+]$ = [B]
When pH is greater than pK_a, the deprotonated forms A^- and B predominate.
$pH < pK_a$
$pH > pK_a$
2
pH
3
4
5
6
7
8
9
10
11
pK_a

P-glycoprotein

- Multidrug transmembrane transporter protein
- Transports various drugs and causes drug resistance!

Liver	transporting drugs into bile for elimination
Kidney	pumping drugs into urine for excretion
Placenta	transporting drugs back into maternal blood,
Intestine	transporting drugs into the intestinal lumen and reducing drug absorption into the blood
Brain Capillaries	pumping drugs back into blood, limiting drug access to the brain

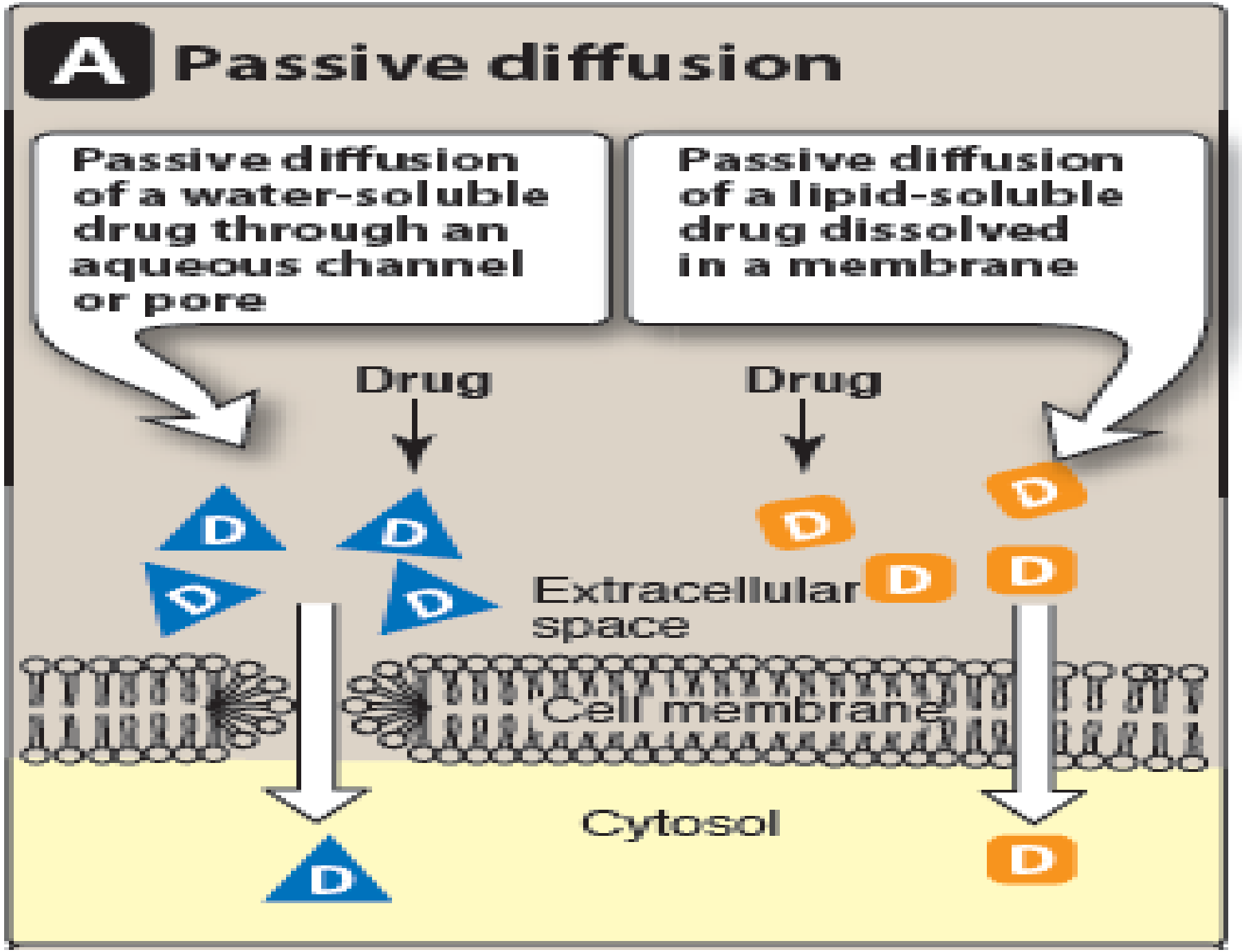
Mechanisms of absorption of drugs from the GI tract

- ✓ **Passive diffusion :**

  Along concentration gradient

  Semi permeable membrane

  Major mechanism of absorption of drugs


A Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
D
Extracellular space
Cell membrane
Cytosol

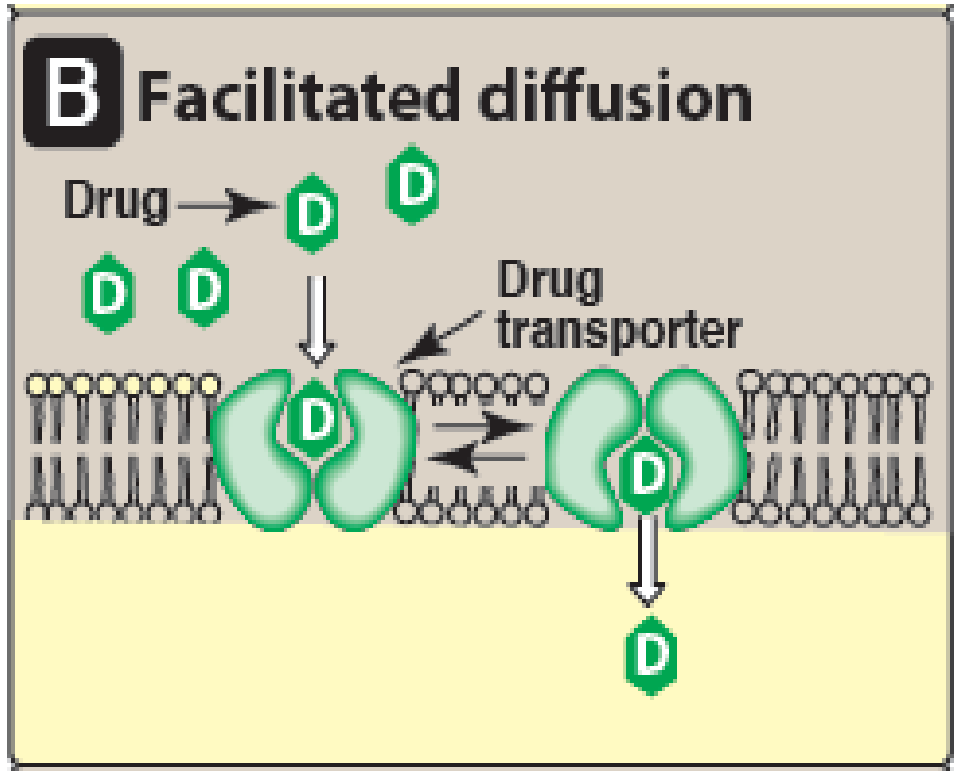
Mechanisms of absorption of drugs from the GI tract

✓ **Facilitated diffusion :**

More specific mechanism

Specific transmembrane protein carriers

Along concentration gradient, No energy needed



Mechanisms of absorption of drugs from the GI tract

✓ **Active transport :**

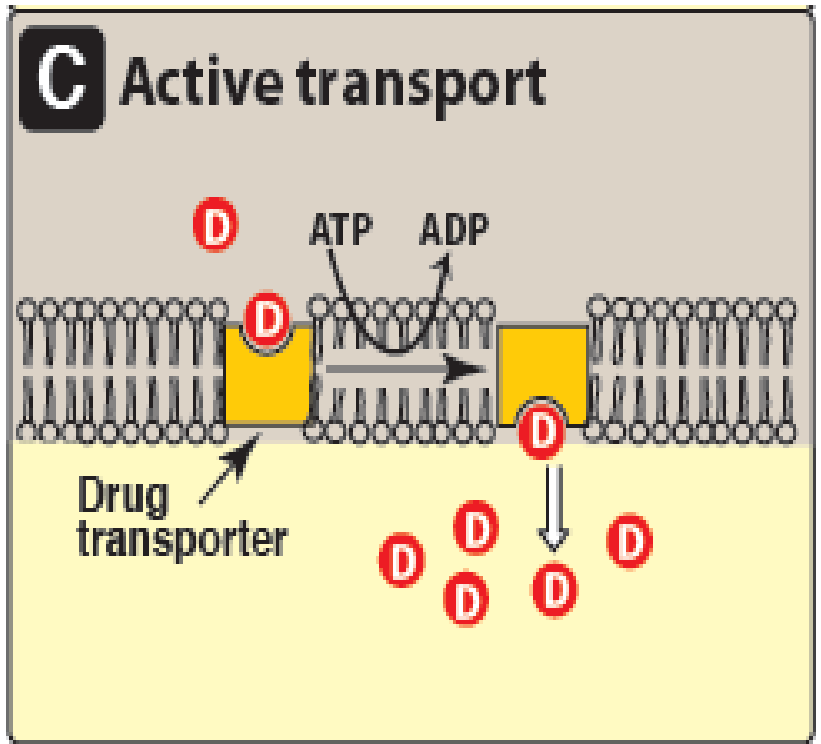
Involves specific carrier proteins

More specific to drug structure

Against concentration gradient

Needs energy

Shows saturation kinetics

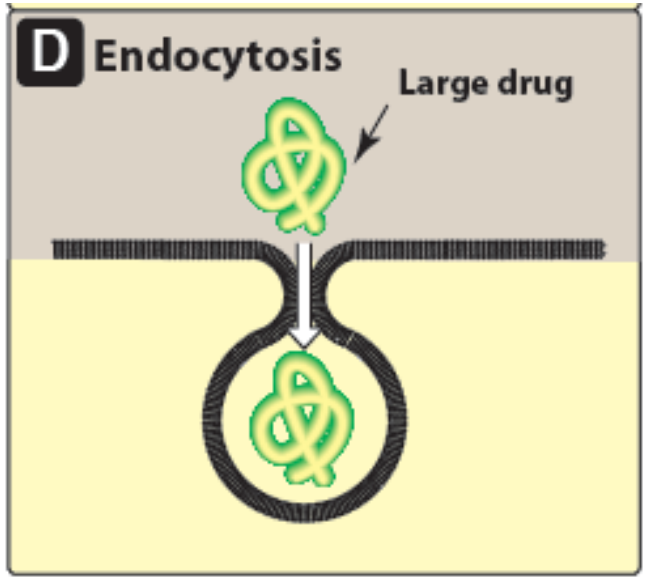


Mechanisms of absorption of drugs from the GI tract

- ✓ **Endocytosis and exocytosis :**

  Large sized drugs

  Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug filled vesicle



Bioavailability

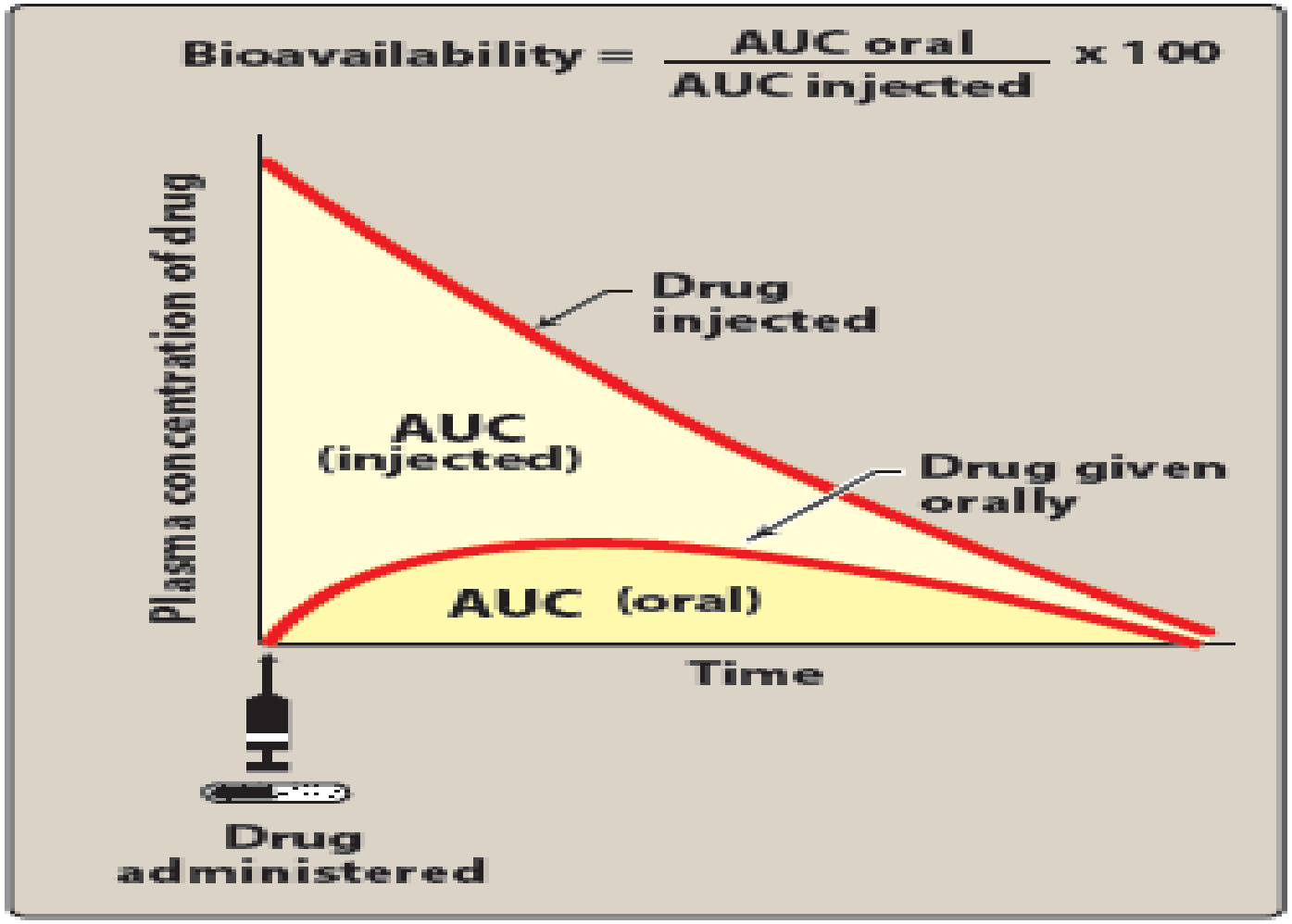
- The fraction of administered drug that reaches the systemic circulation.
- **Determination of bioavailability :**

  (1) Absolute B.A: Drug plasma levels of a given route (PO)**/**Drug plasma levels of the IV route(100%).

  (referred to the I.V route)

  Absolute Bioavailability is used when the drug is approved for IV adminstration

Absolute Bioavailability



Relative Bioavailability:

Many drugs are not approved for intravenous administration.

In such cases, the bioavailability of the test drug is compared to a reference standard , both being given by the same route (other than intravenous) and in the same dose. This is known as relative bioavailability

Relative bioavailability=AUC(test)/AUC(std)

Bioavailability is NOT Absorption !!

- *Absorption*

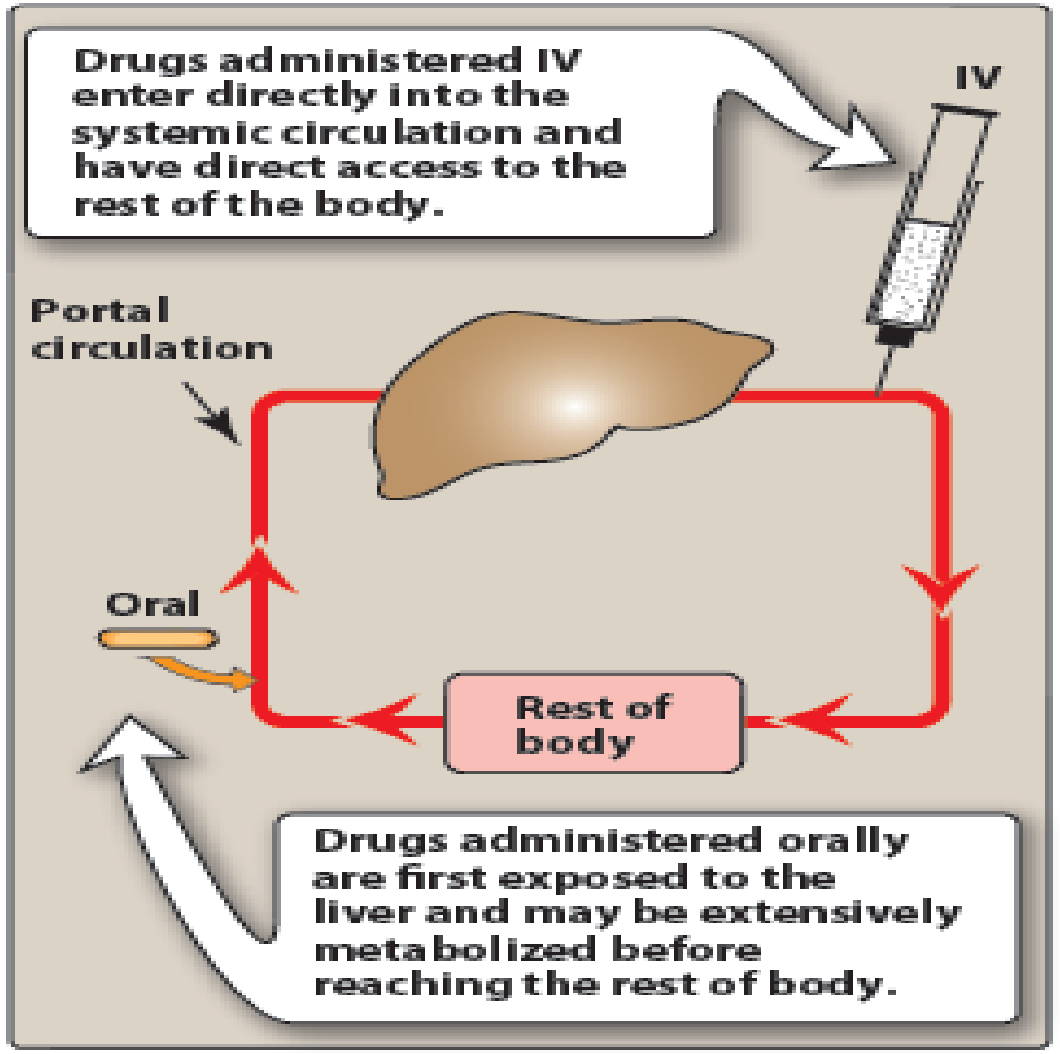
  It is only one of the steps separating drug administration from its delivery to the site of action.

  e.g. a drug can be 100% absorbed from a given formulation but have nevertheless a low bioavailability due to breakdown after absorption

Factors that influence bioavailability

- **First-pass hepatic metabolism**
- **Solubility of the drug**
- **Chemical instability**
- **Nature of the drug formulation**

First-pass hepatic metabolism



Bioequivalence:

- Two related drug preparations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.
- Used to compare generic products with original brands

✓ Differences of **less than 25%** in bioavailability among several formulations of one drug will usually have *no significant effect on clinical outcome* , hence such formulations can be called as bioequivalent.