General pharmacology (*Pharmacokinetics)*

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Pharmacology Department

Pharmacokinetics

By the end of this lecture, the student should be able to

- **Discuss the different routes of drug administration**
- **Identify the advantages and disadvantages of various routes of drug administration**
- **Know the various mechanisms of drug absorption**
- **List different factors affecting drug absorption**
- **Define bioavailability**

Recommended books

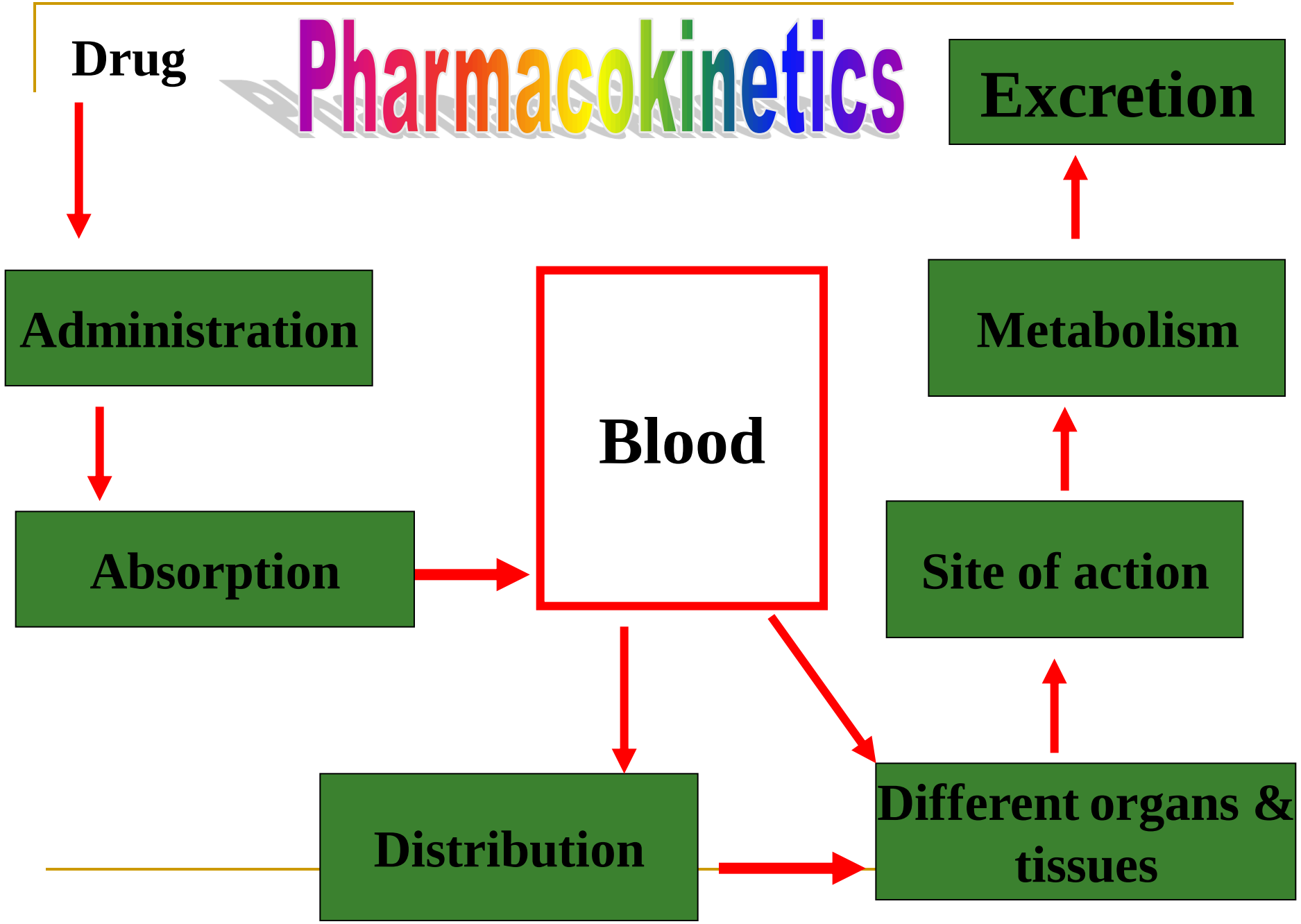
- **Lippincott's illustrated reviews (Pharmacology)** ***by Howland and Mycek***

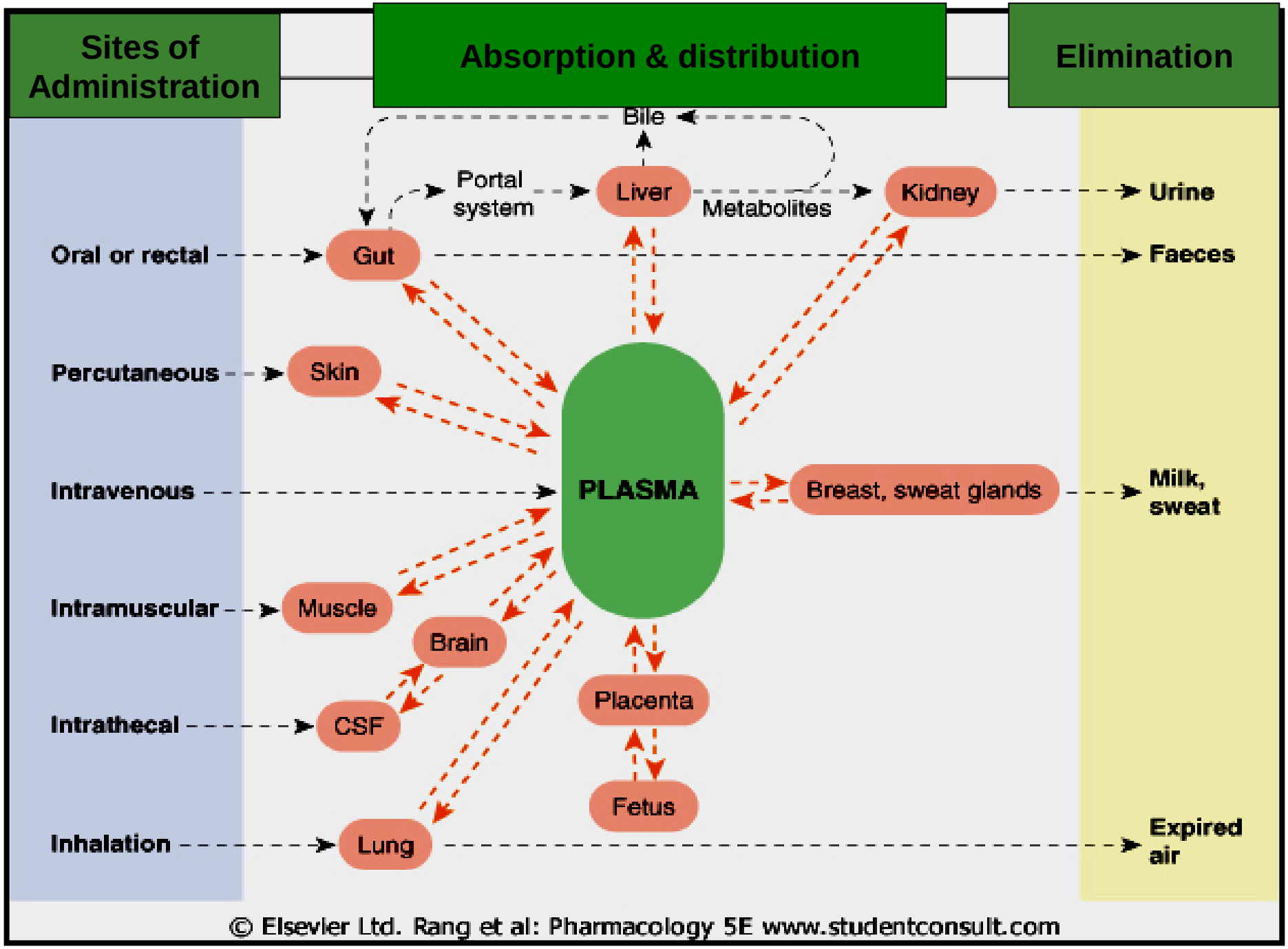
- **Basic and Clinical Pharmacology** ***by by Katzung***

Pharmacokinetics of drugs (ADME)

Are studies of

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion of drugs


Drug
Pharmacokinetics
Excretion
Administration
Metabolism
Blood
Absorption
Site of action
Distribution
Different organs & tissues


Sites of Administration
Absorption & distribution
Elimination
Bile
Portal system
Liver
Kidney
Urine
Metabolites
Oral or rectal
Gut
Faeces
Percutaneous
Skin
PLASMA
Intravenous
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air
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Routes of drug administration

- **Enteral via gastrointestinal tract (GIT).**
  - ***Oral***
  - ***Sublingual***
  - ***Rectal***
- **Parenteral administration = injections.**
- **Topical application**
- **Inhalation**

Oral administration

Advantages	Disadvantages
- Easy - Self use - Safe - Convenient - cheap - No need for sterilization	- Slow effect - No complete absorption - Destruction by pH and enzymes - GIT irritation - Food - Drug interactions - Drug-Drug interactions - First pass effect - (Erratic& low bioavailability). ***Not suitable*** for ❑ vomiting & unconscious patient ❑ emergency ❑ bad taste drugs

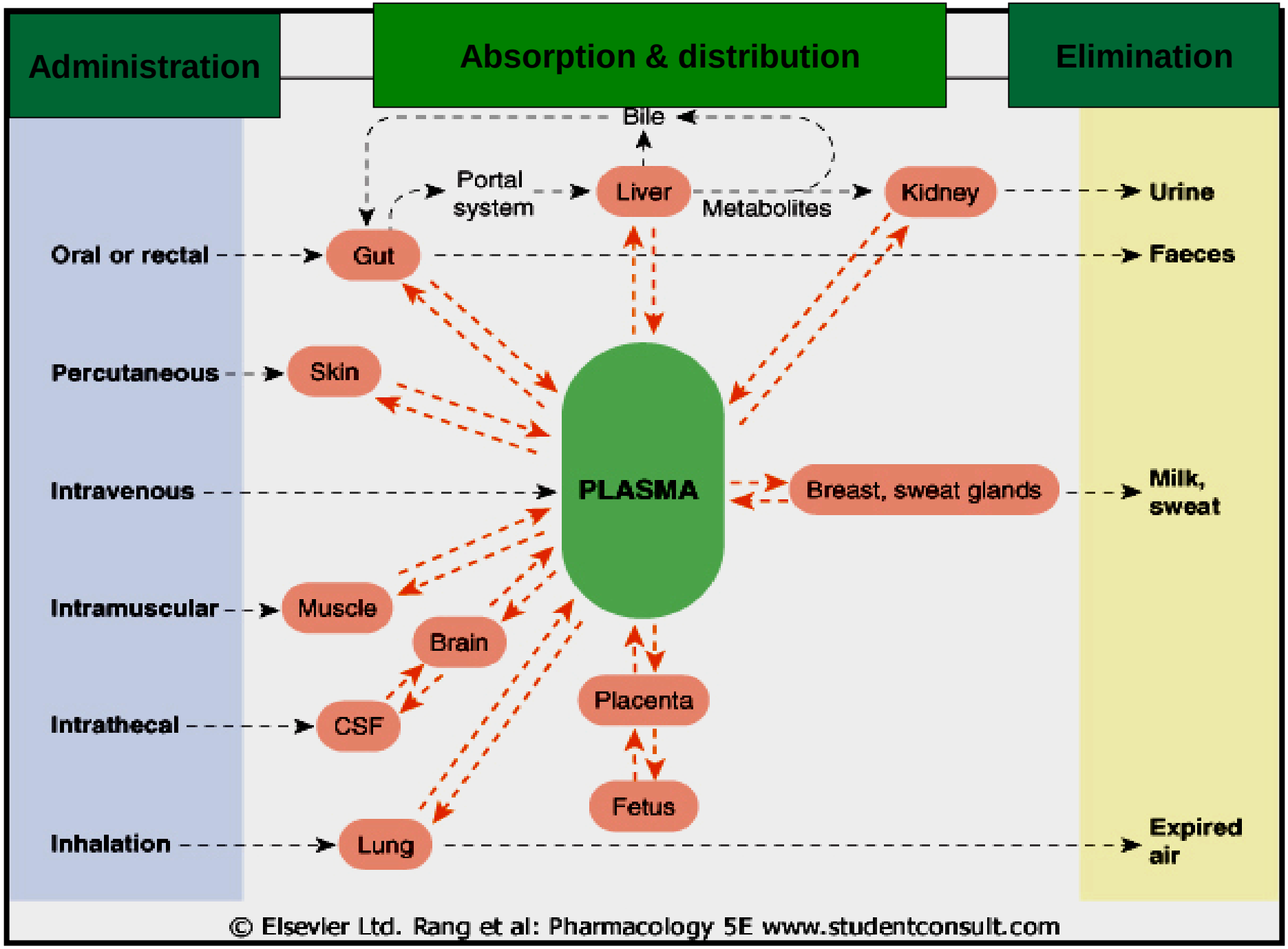
First pass Metabolism

Drugs taken orally are first taken to liver (via portal circulation) where they are metabolized before reaching to rest of body.

so the amount reaching system circulation is less than the amount absorbed

Results ?

Low bioavailability = low serum level of active drug that can produce action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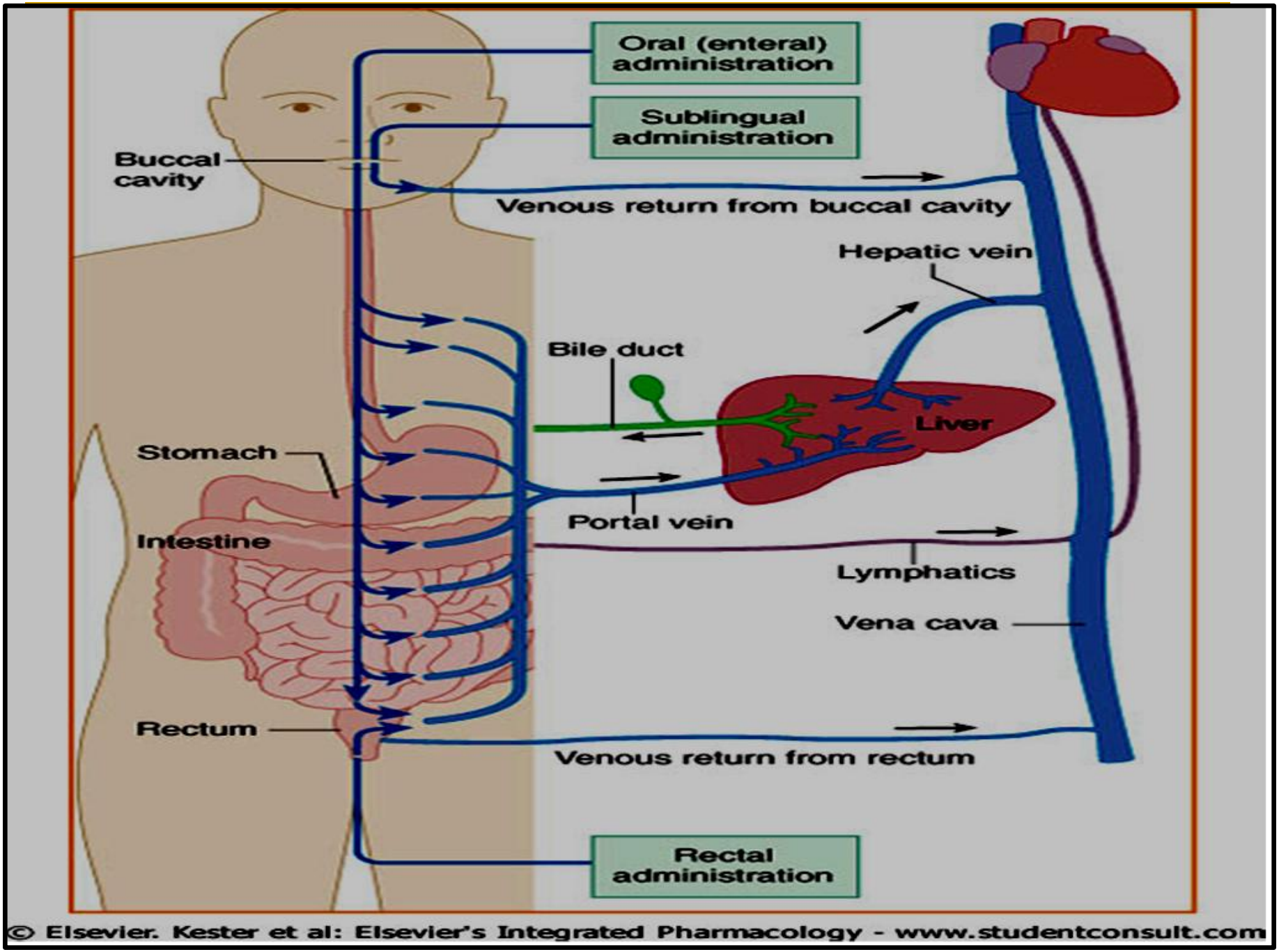
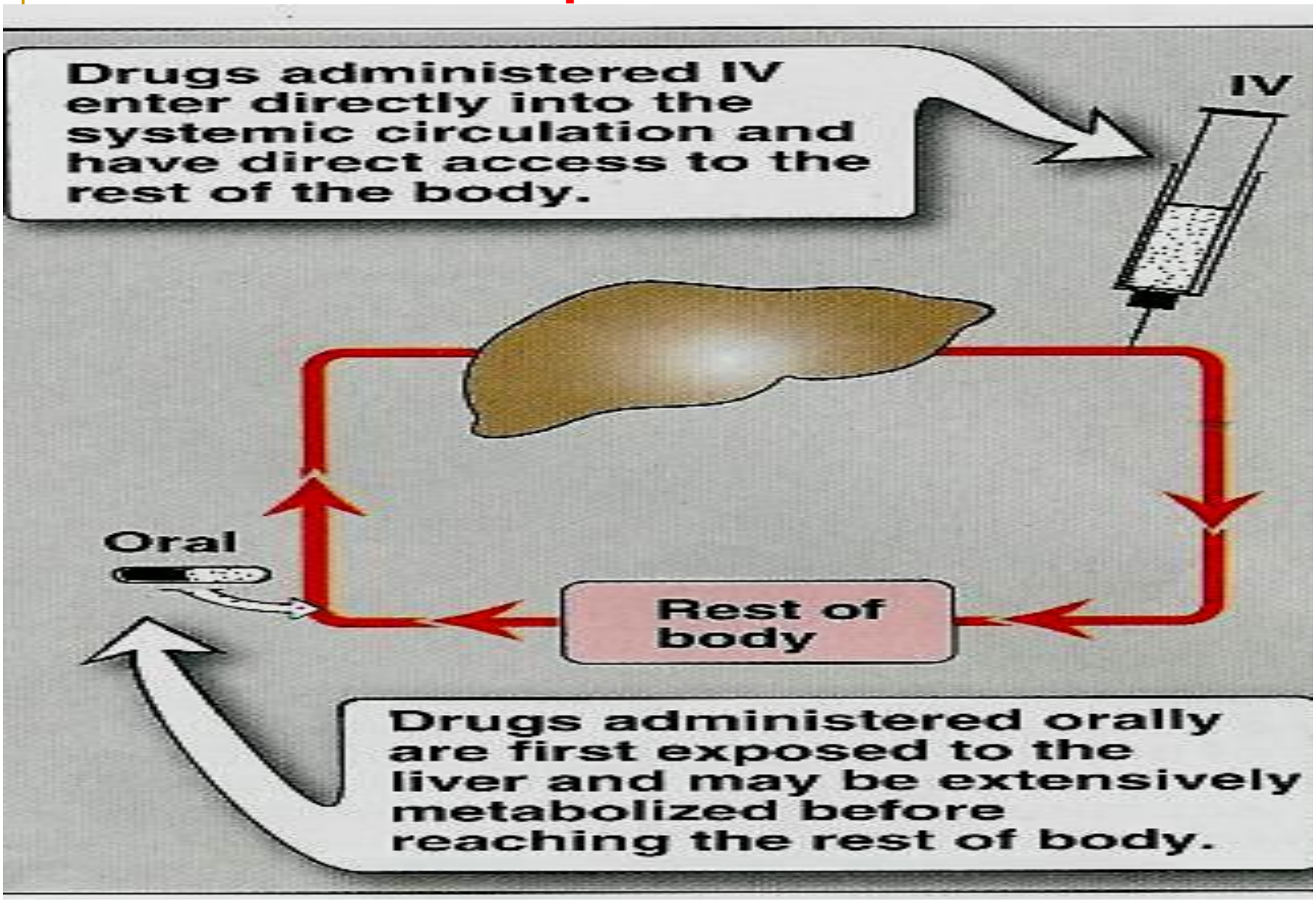


First pass effect



Oral Dosage Forms (oral formulations)

- **Tablets (enteric coated tablets)**
- **Capsules (hard and soft gelatin capsules)**
- **Syrup**
- **Suspension**
- **Emulsion**

Tablets

Spansule

Suspension

Hard- gelatin capsule

Soft- gelatin capsule

Emulsion

Sublingual

Advantages	Disadvantages
▫ Rapid effect ▫ can be used in emergency ▫ High bioavailability ▫ No first pass effect. ▫ No GIT irritation ▫ No food drug - interaction ***Dosage form:*** friable tablet	***Not for*** - irritant drugs - Frequent use

Rectal administration

Advantages	Disadvantages
Suitable for ▪ children ▪ Vomiting or unconscious patients ▪ Irritant & Bad taste drugs. ▪ less first pass metabolism (50%) ***Dosage form:*** suppository or enema	▪ Irregular absorption & bioavailability. ▪ Irritation of rectal mucosa.

Parenteral administration

Intradermal (I.D.) (into skin)

Subcutaneous (S.C.) (under skin)

Intramuscular (I.M.) (into muscles)

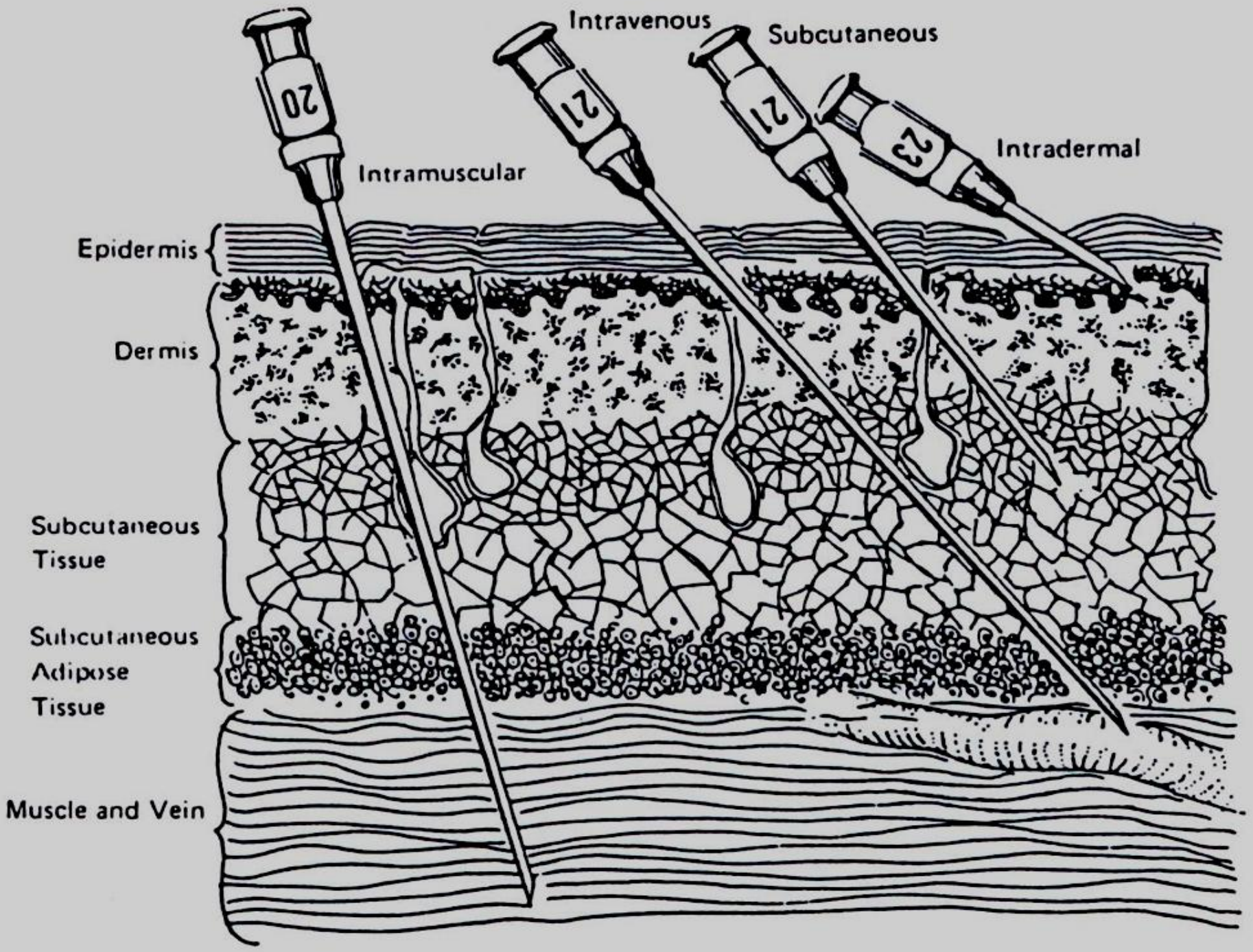
Intravenous (I.V.) (into veins)

Intra-arterial (I.A.) (into arteries)

Intrathecal (I.T.) (cerebrospinal fluids)

Intraperitoneal (I.P.) (peritoneal cavity)

Intra - articular (Synovial fluids)


Intravenous
Subcutaneous
20
21
21
23
Intramuscular
Intradermal
Epidermis
Dermis
Subcutaneous Tissue
Subcutaneous Adipose Tissue
Muscle and Vein

Intravenous administration

Advantages	Disadvantages
❑ Rapid action (emergency) ❑ High bioavailability ❑ No food-drug interaction ❑ No first pass metabolism ❑ No gastric irritation *Suitable for* ❑ Vomiting &unconscious ❑ Irritant & Bad taste drugs. *Dosage form:* Vial or ampoule	❑ Only for water soluble drugs ❑ Infection ❑ Sterilization. ❑ Pain ❑ Needs skill ❑ Anaphylaxis ❑ Expensive *Not suitable* for oily solutions or poorly soluble substance

Ampoule

Single use

Vial

Repeated use

Injection	Special Utility	Limitations
I.D.	Minute volume (0.1 ml) Suitable for vaccinations & sensitivity test	Not suitable for large volumes
S.C.	0.1 ml – 1 ml Suitable for poorly soluble suspensions and for instillation of slow-release implants e.g. insulin zinc preparation	Not suitable for large volumes
I.M.	larger volume 3-5 ml Suitable for moderate volumes, for oily solutions or poorly soluble substances	Not suitable for irritant drugs Abscess- necrosis may happen
I.V.	Suitable for large volumes and for irritating substances	Not suitable for oily solutions or poorly soluble substances Must inject solutions slowly as a rule

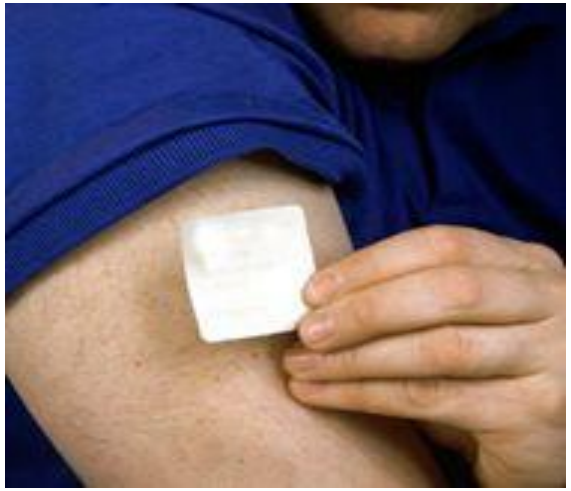
Topical application

- **Drugs are applied to skin, ear, eye, nose, vagina, respiratory tract**
- **Usually used to provide local action.**
- **No first pass metabolism.**
- **Used for lipid soluble drugs**

Transdermal patch

a medicated adhesive patch applied to skin to provide systemic effect (prolonged drug action)

e.g. the nicotine patches

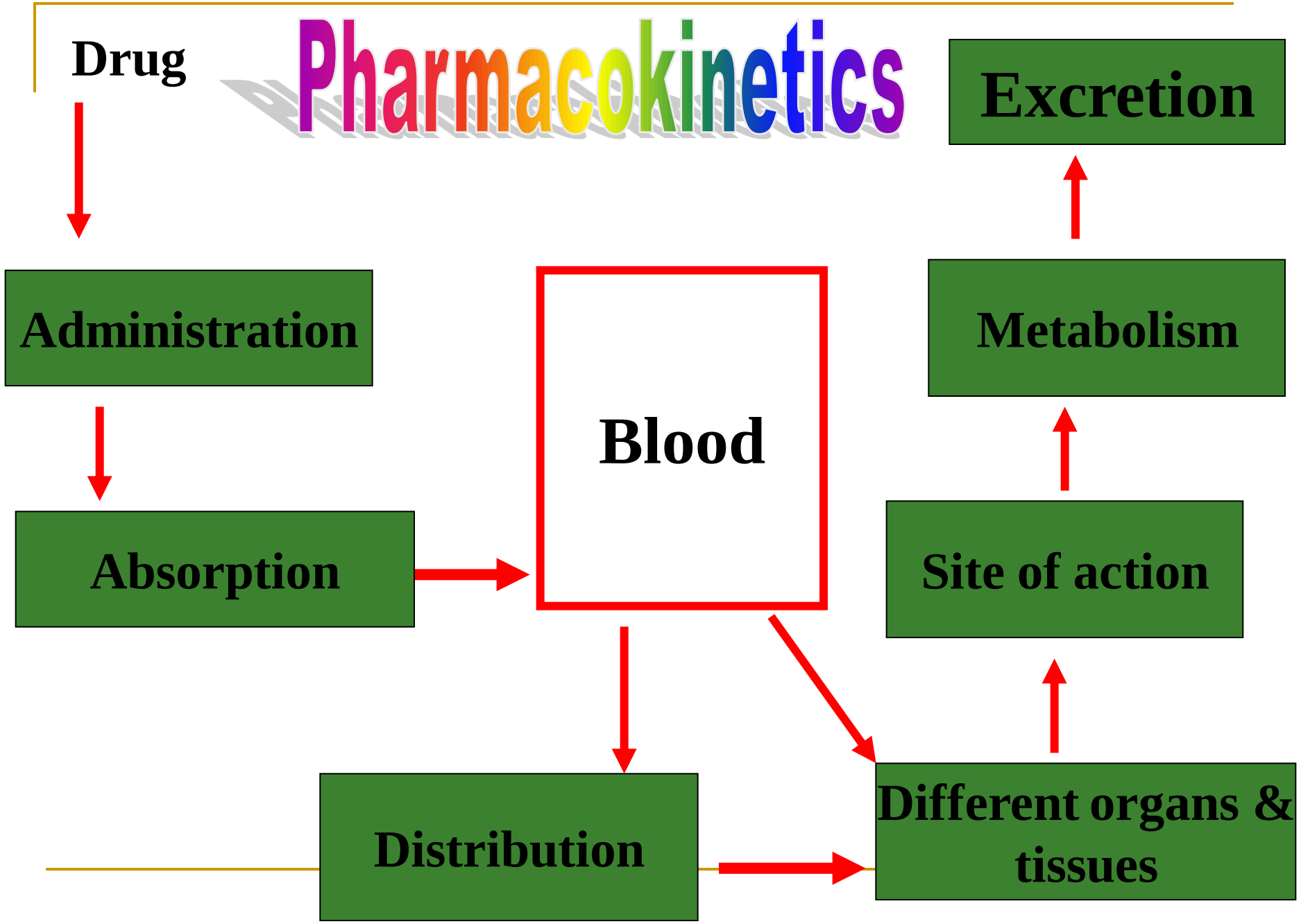


Inhalation

Advantages	Disadvantages
▫ Mucous membrane of respiratory system ▫ Rapid absorption *(large surface area)* ▫ Provide local action in ▫ Limited systemic effect ▫ Less side effects. ▫ No first pass effect *Dosage form:* aerosol, nebulizer	Not suitable for irritant drugs Only for some drugs as inhalation anesthetics & bronchodilators

Nebulizer

Atomizer


Drug
Pharmacokinetics
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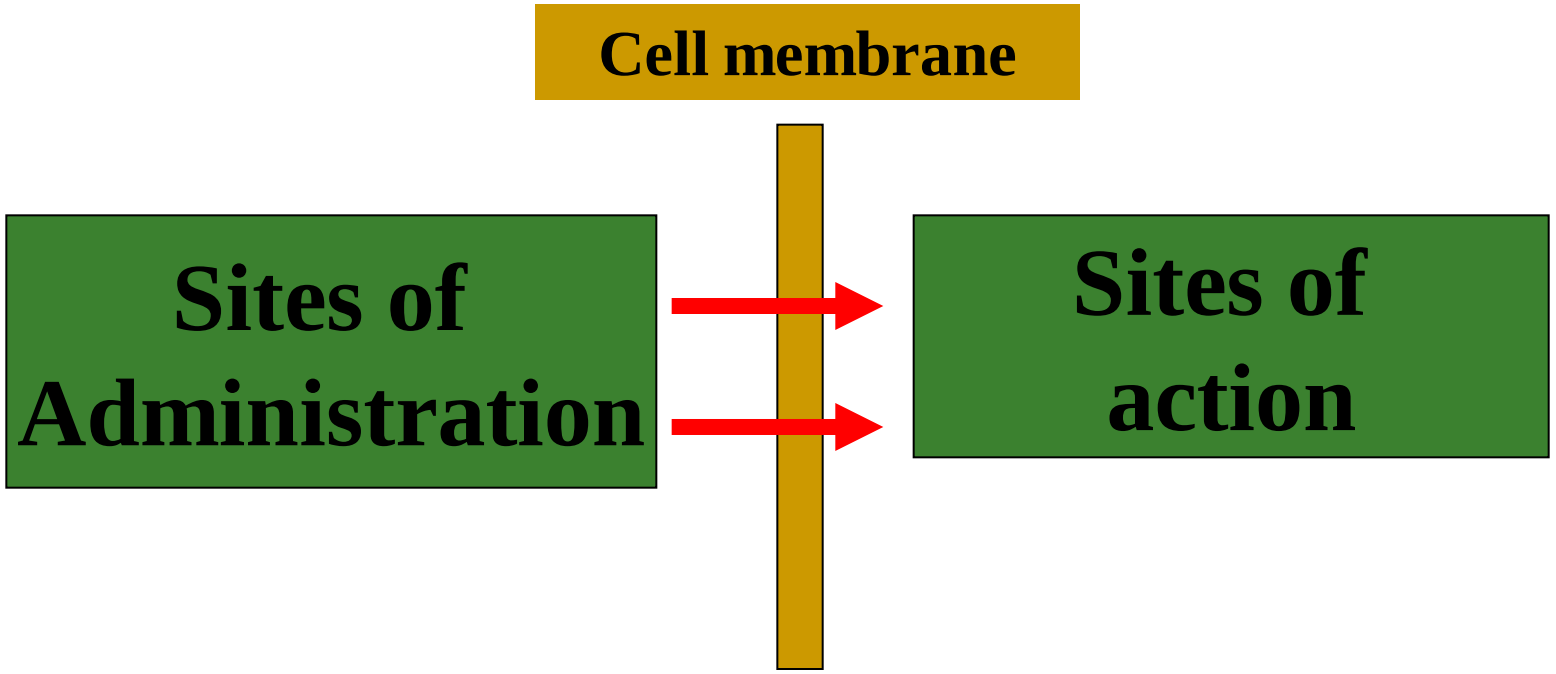
Absorption
Site of action
Distribution
Different organs & tissues

Drug absorption

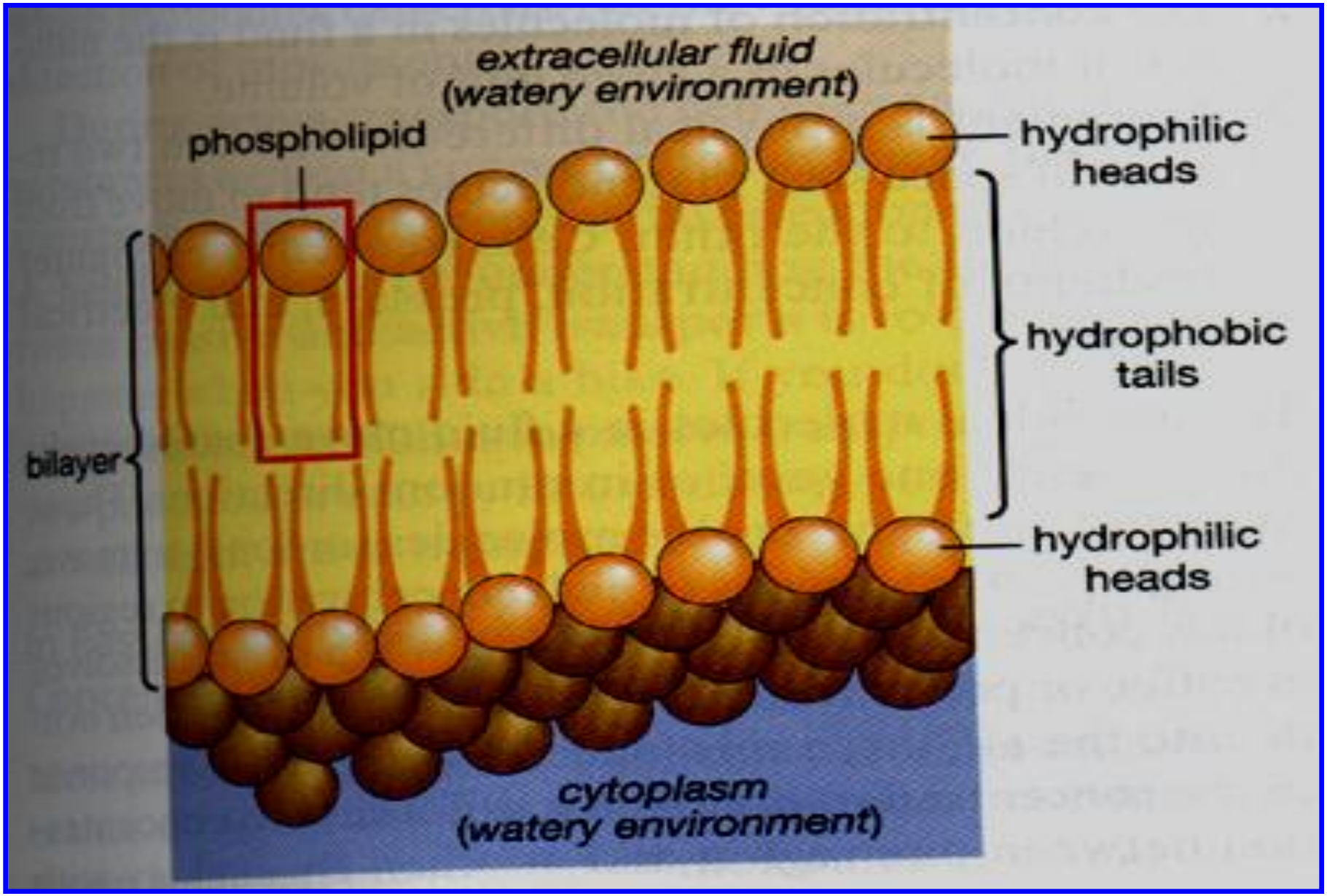
Is the passage of drug from its site of administration to its site of action through cell membranes.



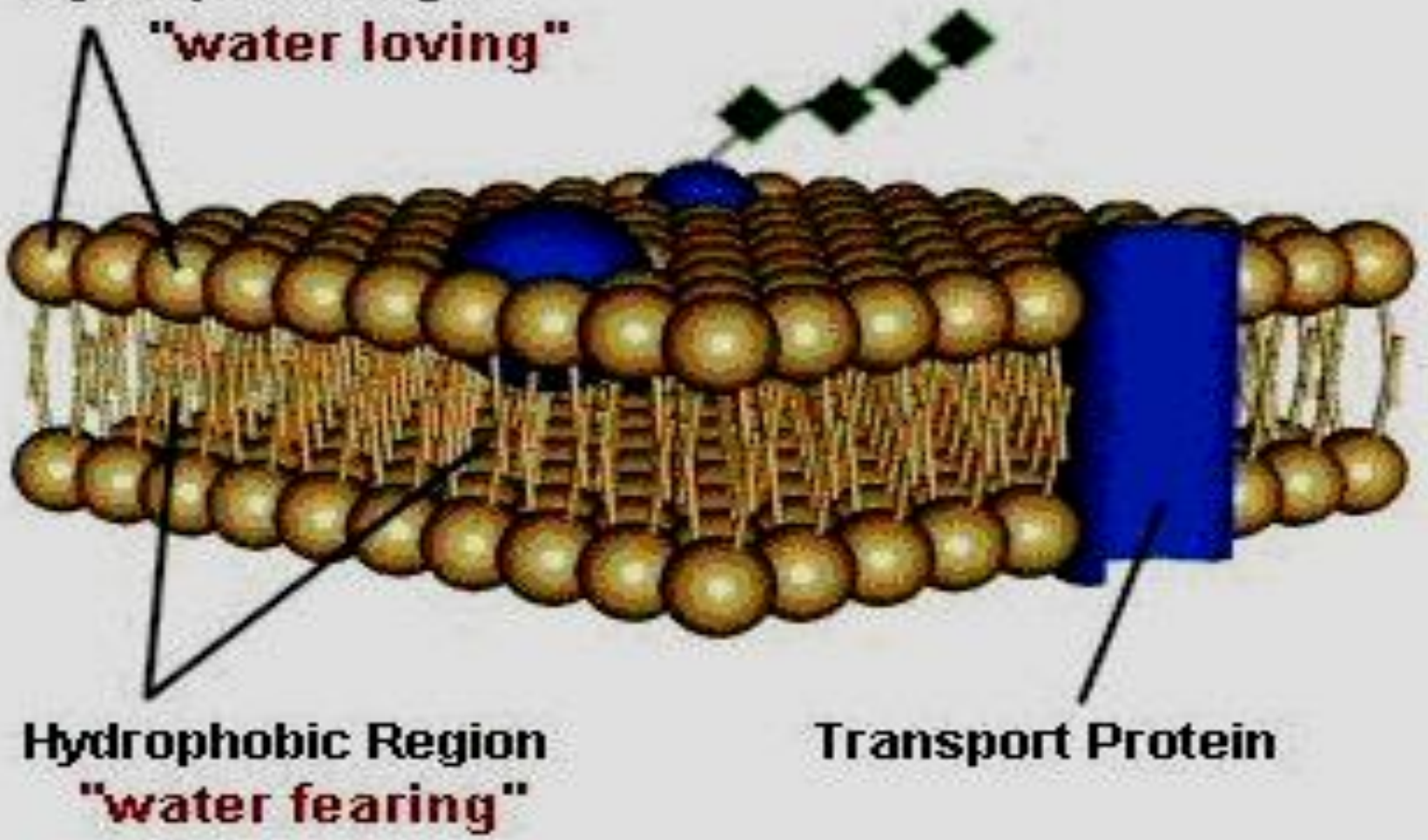
Mechanisms of drug absorption

1. **Simple diffusion = passive diffusion.**
2. **Active transport.**
3. **Facilitated diffusion.**
4. **Pinocytosis (Endocytosis).**

Cell membrane



Cell Membrane

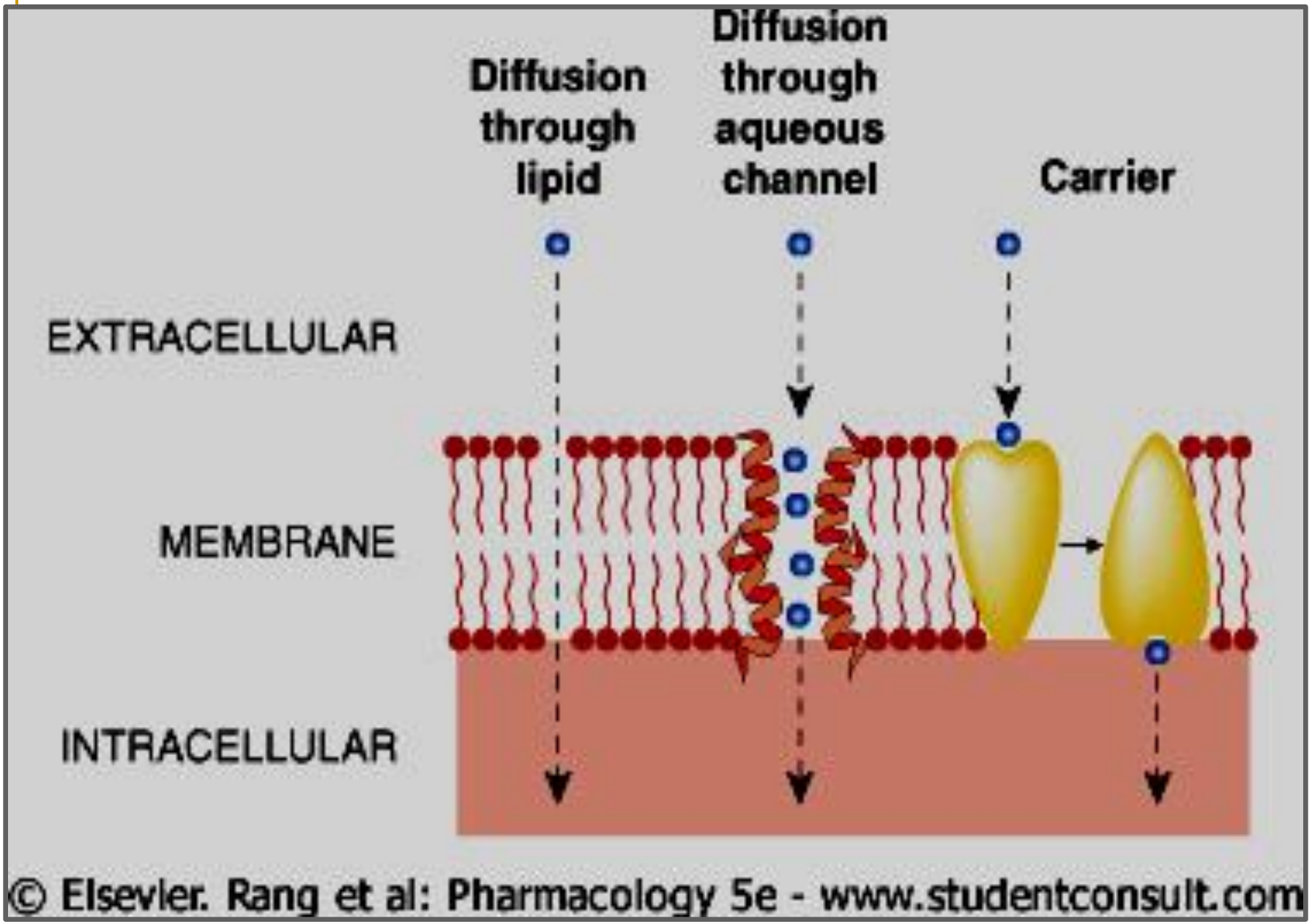


Simple or passive diffusion

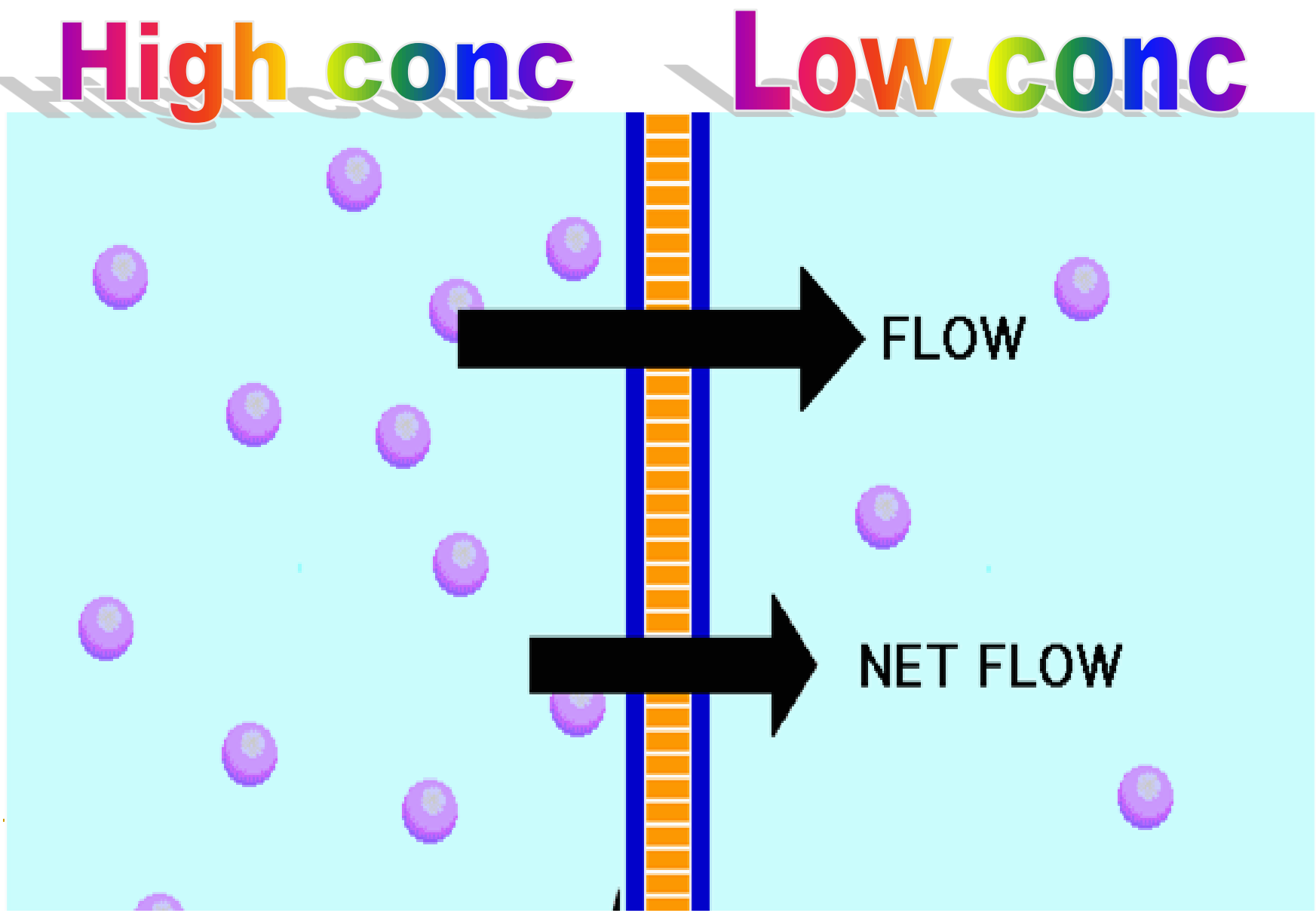
- **water soluble drug *(ionized or polar)* is readily absorbed via diffusion through aqueous channels or pores in cell membrane.**

- **Lipid soluble drug *(nonionized or non polar)* is readily absorbed via diffusion through lipid cell membrane itself.**

Simple diffusion



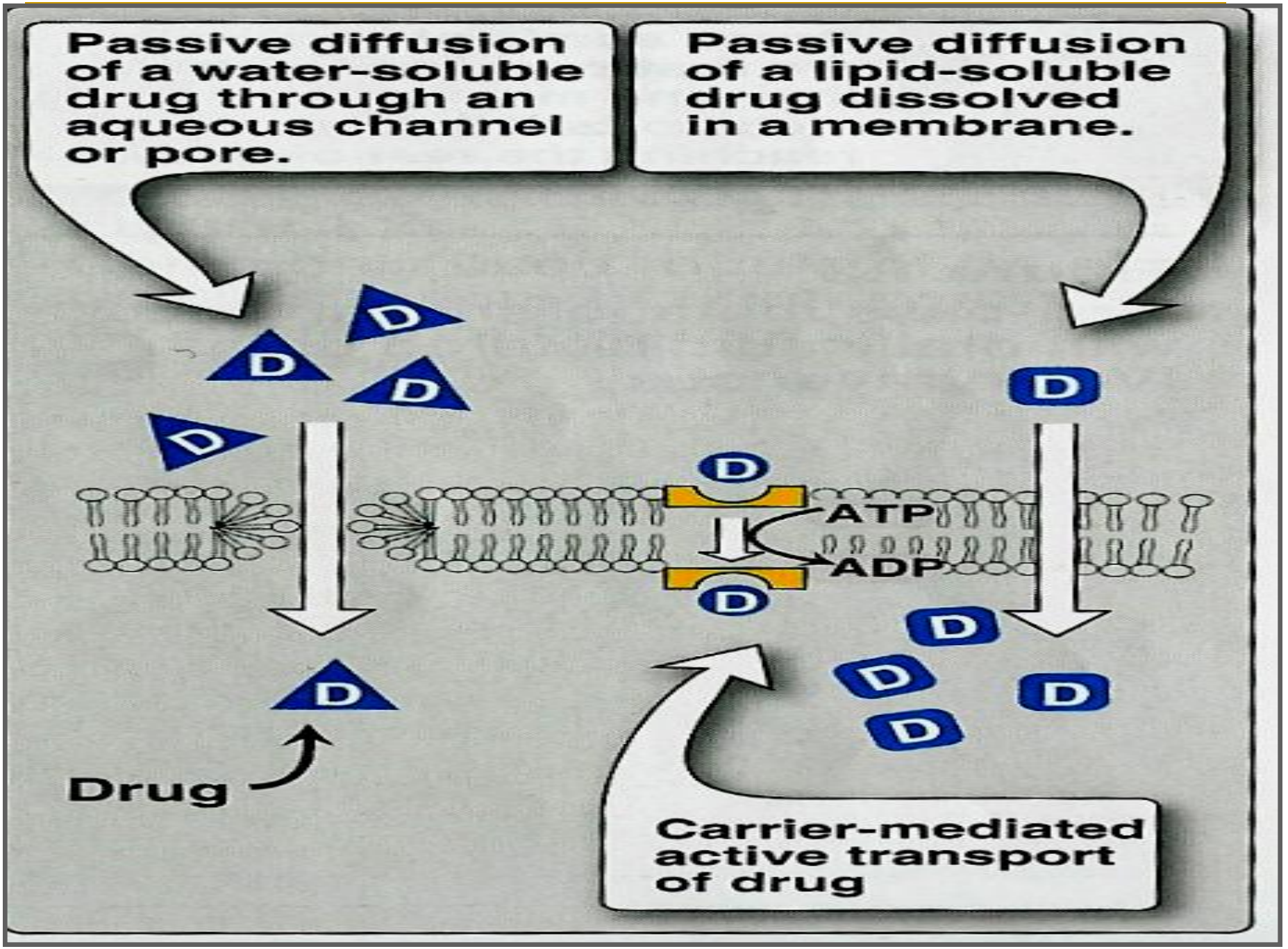
Simple diffusion



Simple diffusion

Characters

- common.
- Occurs along concentration gradient.
- Non selective
- Not saturable
- Requires no energy
- No carrier is needed
- Depends on lipid solubility.
- Depends on pka of drug - pH of medium.


Passive diffusion of a water-soluble drug through an aqueous channel or pore.
Passive diffusion of a lipid-soluble drug dissolved in a membrane.
D
ATP
ADP
Drug
Carrier-mediated active transport of drug

Simple diffusion

Drugs exist in two forms ionized (water soluble) nonionized forms (lipid soluble) in equilibrium.

Drug  **ionized form + nonionized form**

- **Only nonionized form is absorbable.**
- **Nonionized / ionized fraction is determined by pH and pKa**

PKa of the drug

(Dissociation or ionization constant):

pH at which half of the substance is ionized & half is unionized.

pH of the medium

Affects ionization of drugs.

- **Weak acids → best absorbed in stomach.**
- **Weak bases → best absorbed in intestine.**

Which one of the following drugs will be best absorbed in stomach (pH=3)?

Aspirin pka=3.0

warfarin pka=5.0

Arrange the following drugs in ascending order from least to greatest in rate of absorption in small intestine (pH=7.8)?

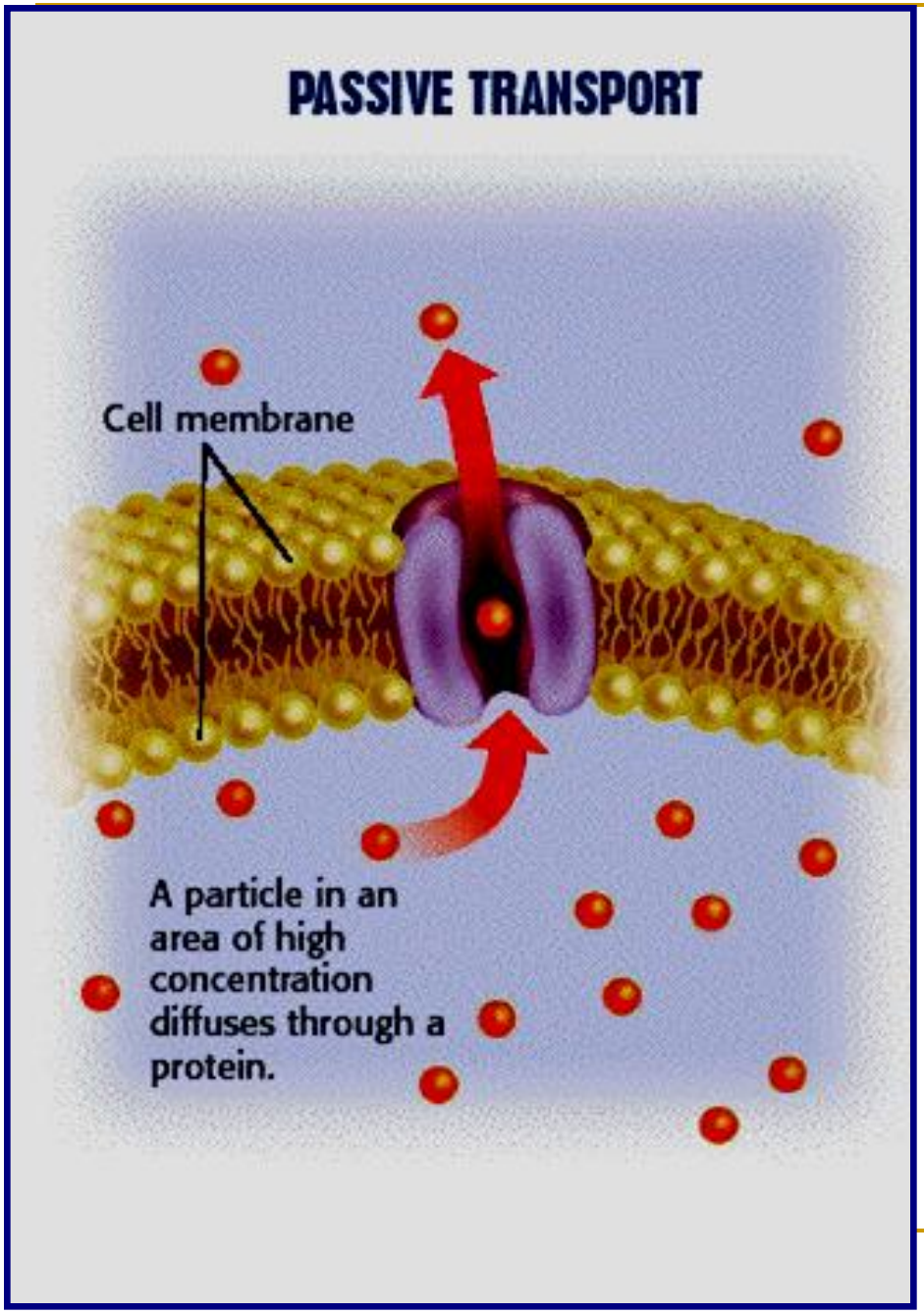
Propranolol pka= 9.4

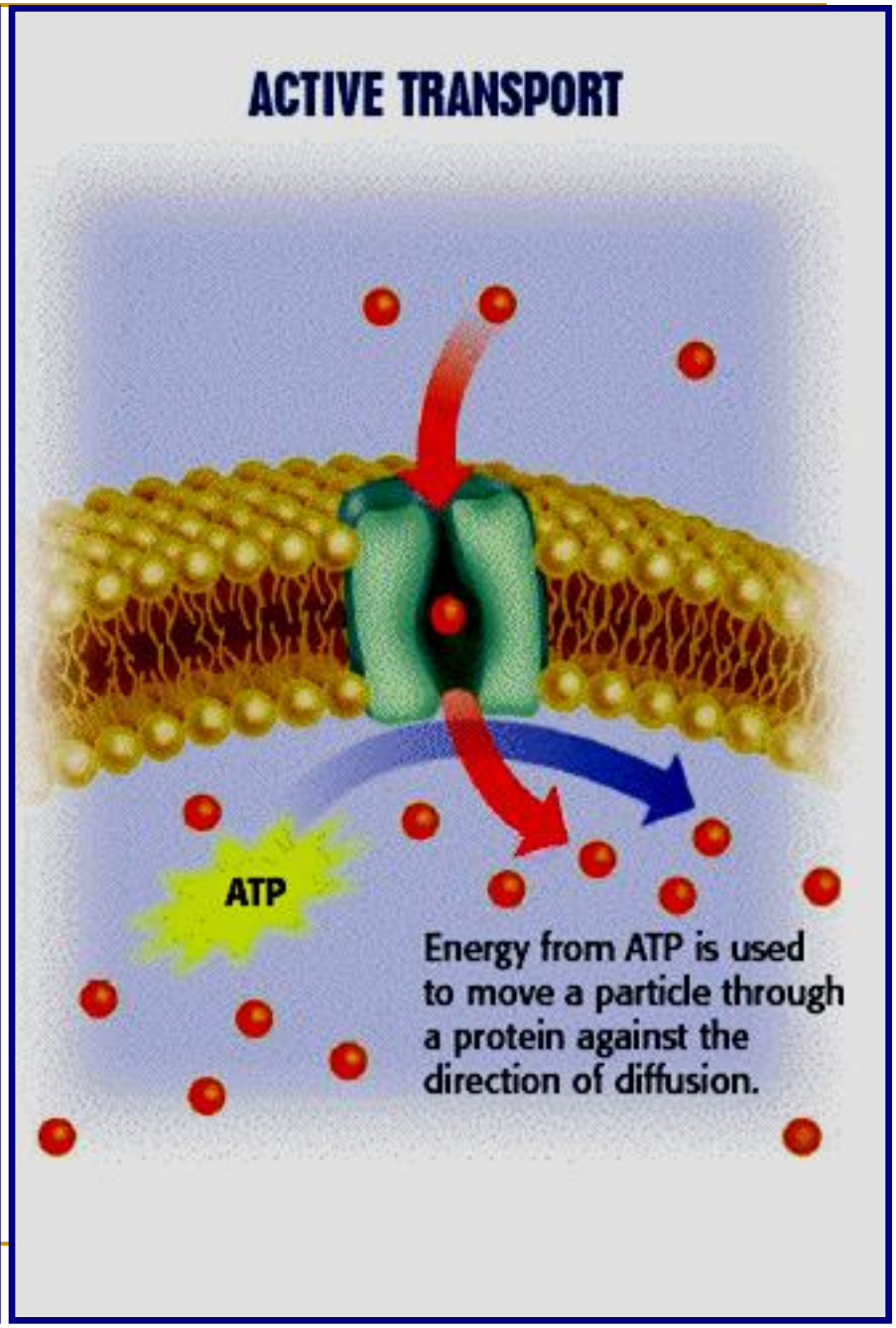
Aspirin pka=3.0

warfarin pka=5.0

Active Transport

- Relatively unusual.
- Occurs against concentration gradient.
- Requires carrier and energy.
- Specific
- Saturable.
- Iron absorption.
- Uptake of levodopa by brain.

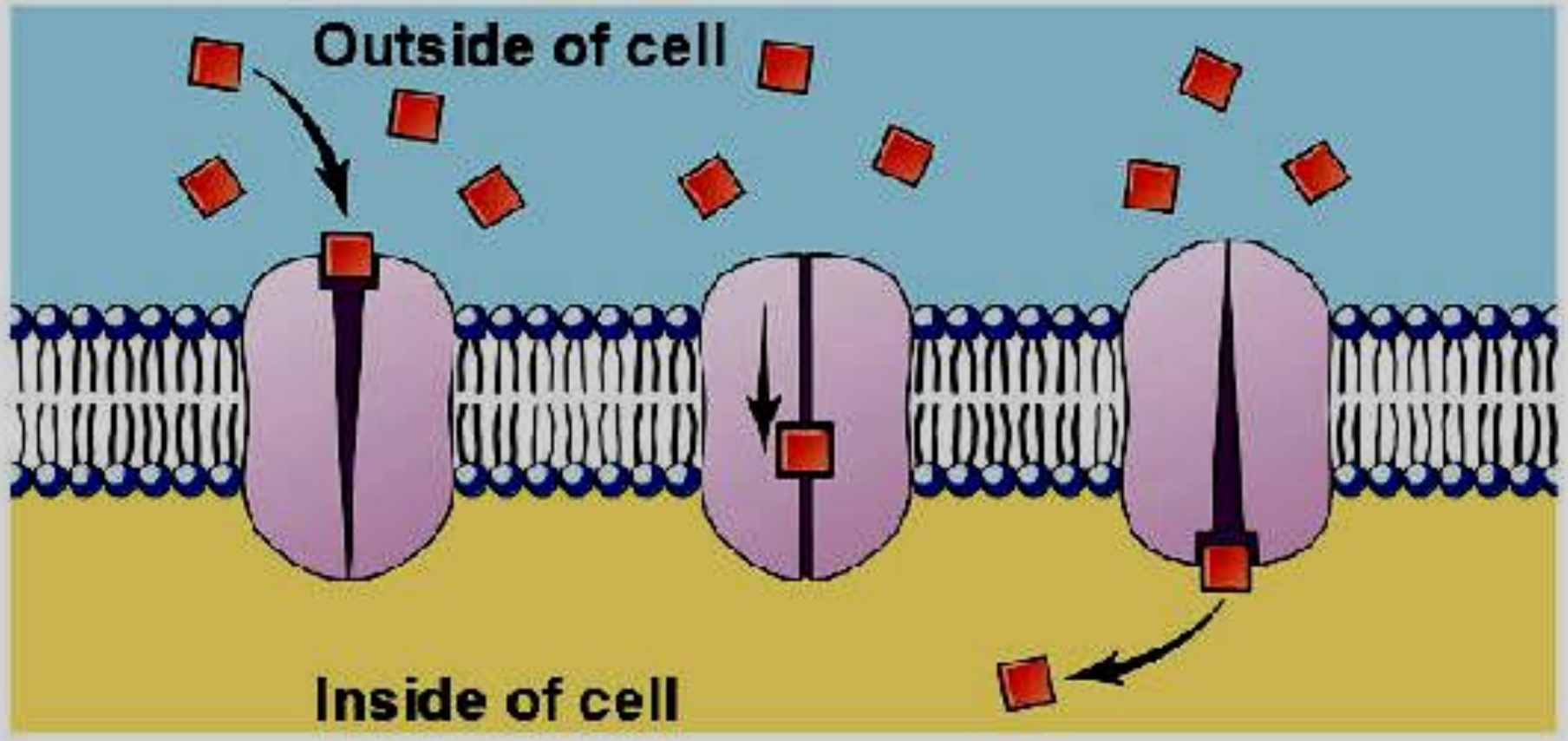

PASSIVE TRANSPORT
Cell membrane
A particle in an area of high concentration diffuses through a protein.


ACTIVE TRANSPORT
ATP
Energy from ATP is used to move a particle through a protein against the direction of diffusion.

Carrier-mediated Facilitated Diffusion

- **Occurs along concentration gradient.**
- **Requires carriers**
- **Selective.**
- **Saturable.**
- **No energy is required.**

Facilitated Diffusion



Passive transport	Active transport
along concentration gradient (From high to low)	against concentration gradient (From low to high)
No carriers	Needs carriers
Not saturable	saturable
Not selective	Selective
No energy	energy is required

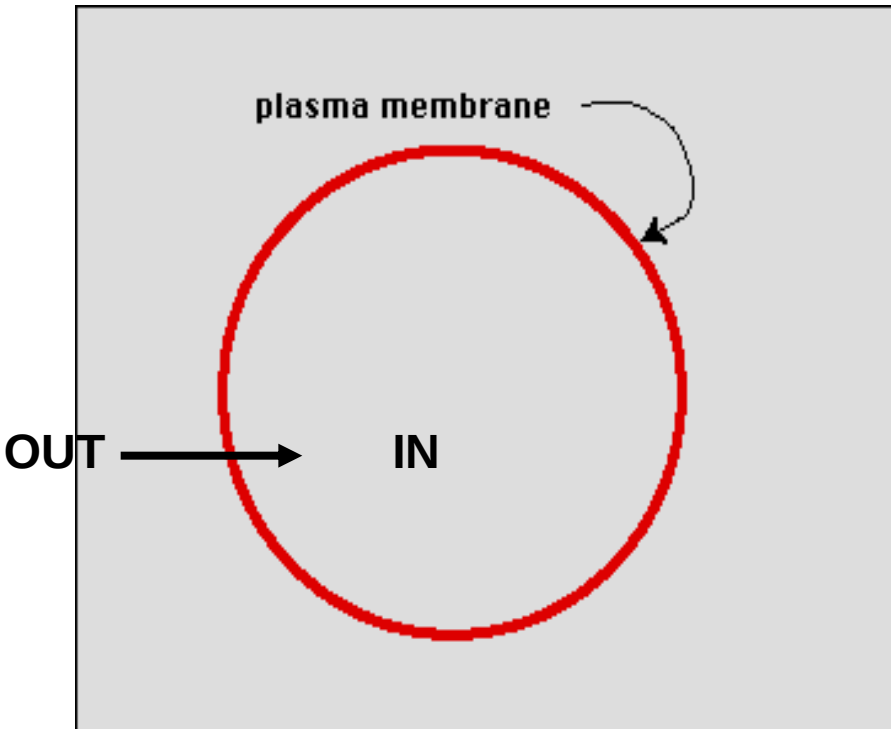
Active transport	Carrier-mediated facilitated diffusion
Against concentration gradient (From low to high)	along concentration gradient (From high to low)
Needs carriers	Needs carriers
saturable	saturable
Selective	Selective
Energy is required	No energy is required

Phagocytosis (Endocytosis & Exocytosis)

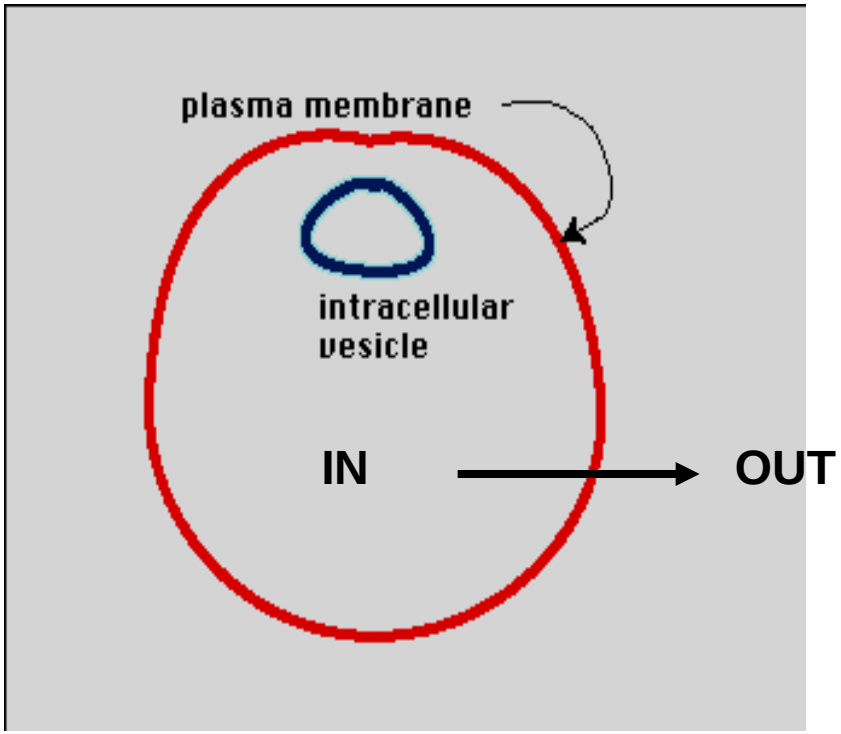
Endocytosis: uptake of membrane-bound particles.
Exocytosis: expulsion of membrane-bound particles.

Phagocytosis occurs for high molecular weight Drugs or highly lipid insoluble drugs.

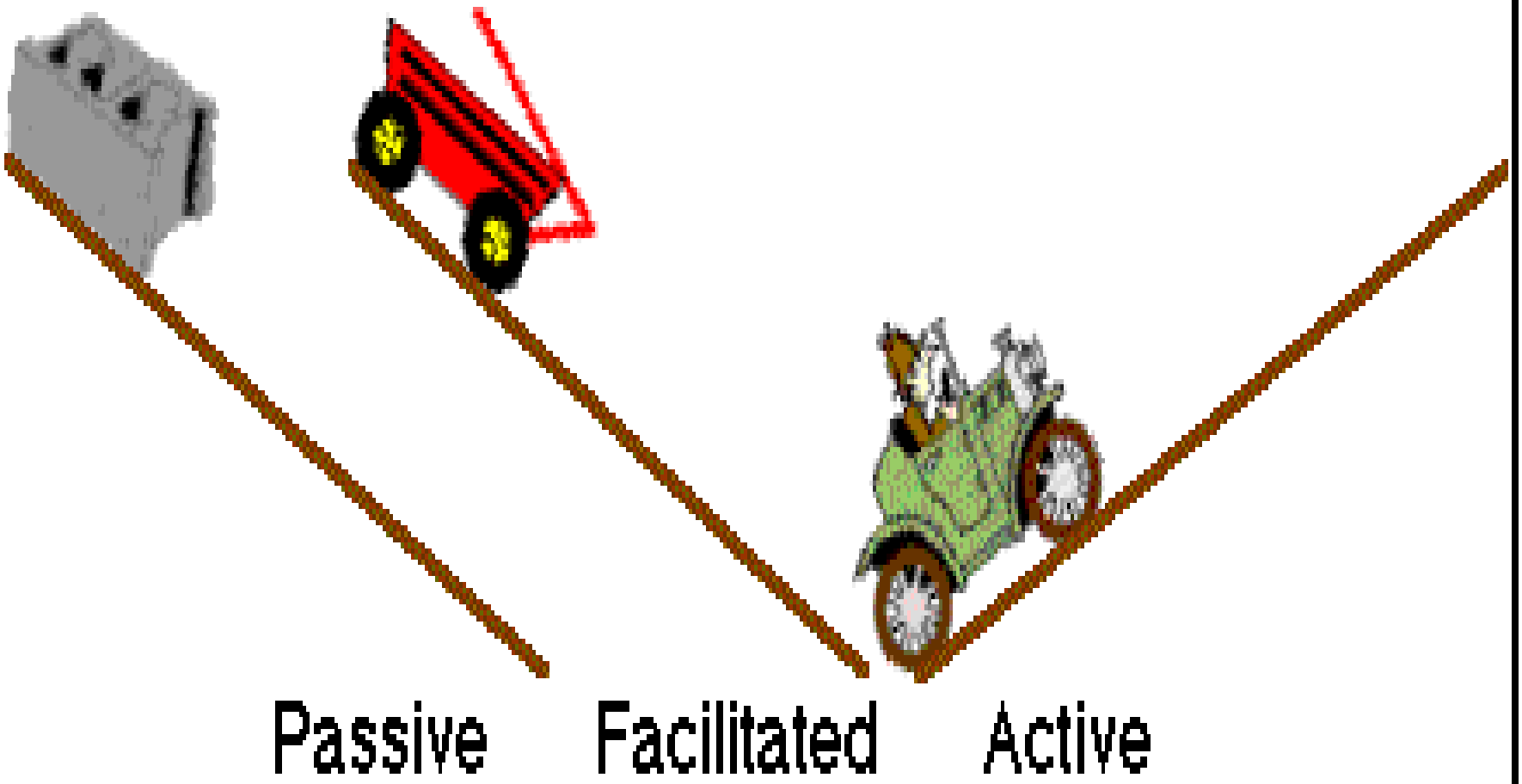
(Endocytosis)

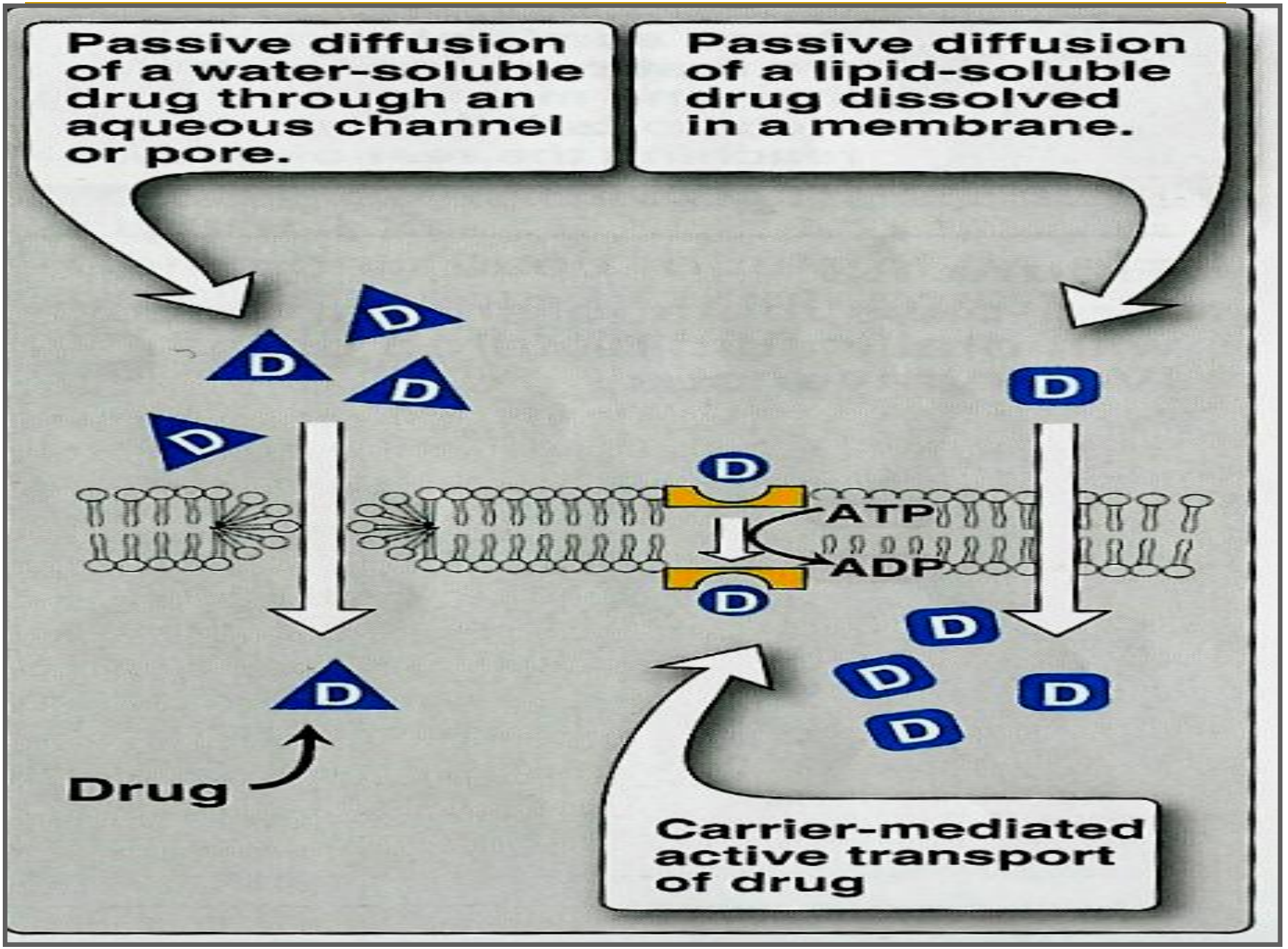


(Exocytosis)



Mechanisms of drug absorption

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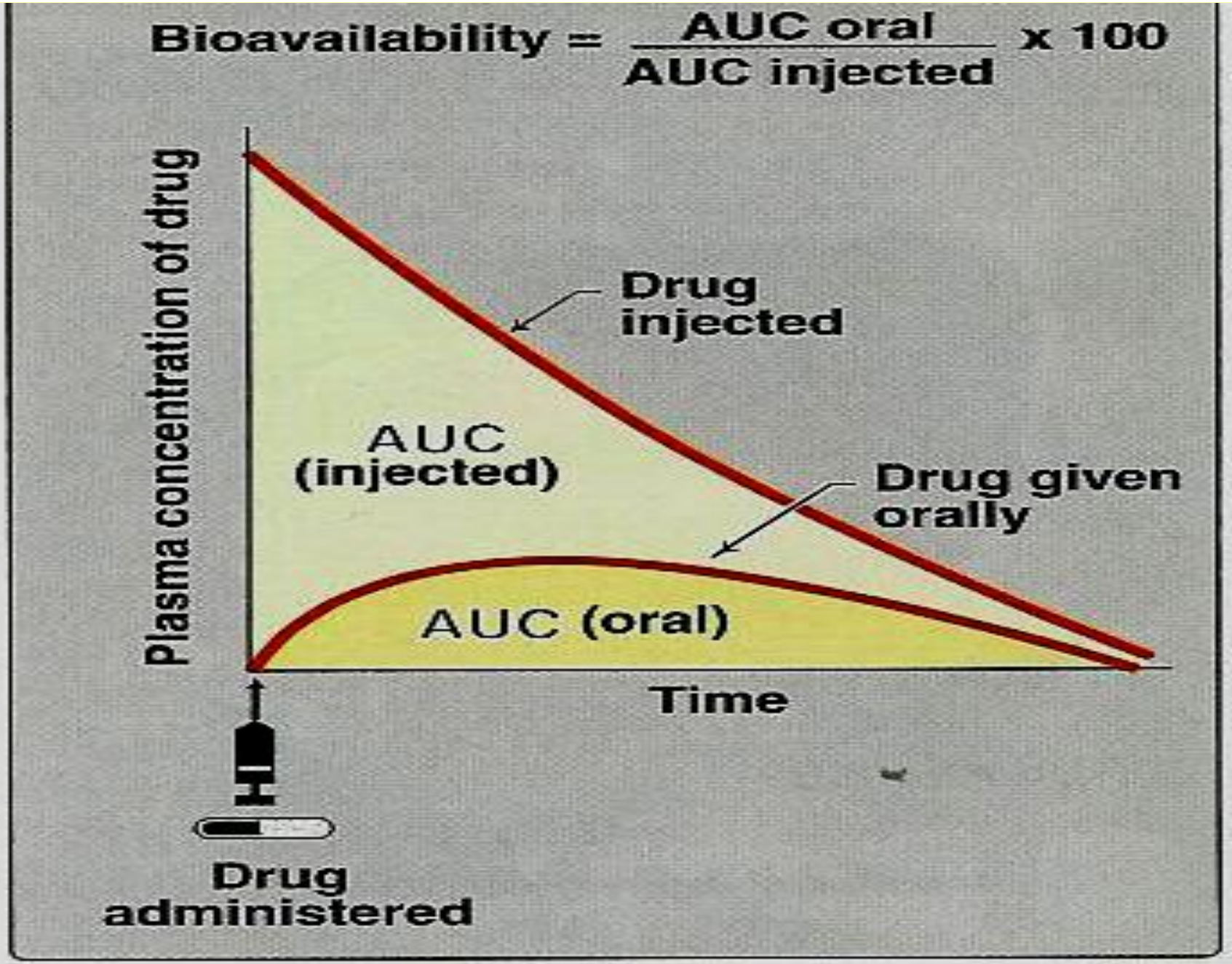
Bioavailability

- **Is the fraction of unchanged drug that enters systemic circulation after administration and becomes available to produce an action**
- **I.V. provides 100% bioavailability.**
- **Oral usually has less than I.V.**

- **Bioavailability = $\frac{\text{AUC oral}}{\text{AUC IV}} \times 100$**


Bioavailability = AUC oral / AUC injected x 100
Plasma concentration of drug
Drug injected
AUC (injected)
Drug given orally
AUC (oral)
Time
Drug administered

Factors Affecting Bioavailability:

1. Drugs

- **Molecular weight**
- **Lipid solubility**
- **Drug Formulation (rate of dissolution).**

  (solution > suspension > capsule > tablet)
- **Chemical instability in gastric pH**

  (Penicillin & insulin)

2. Patient

- **pH of gut.**
- **Rate of gastric emptying**
  - rapid gastric emptying ⟶ fast transit to intestine
- **Intestinal motility (Transit Time).**
  - Diarrhea reduce absorption
- **Surface area available for absorption.**
- **Presence of food in gut.**
  - **slow gastric emptying**
  - **generally slow absorption**
- **Drug interactions**

Summary

- **Different routes of administration are available**
- **Parenteral administration is the suitable route to provide rapid effect**
- **IV is used in emergency and provide high availability**
- **Oral administration is best avoided during emergency or when severe first pass metabolism may occur**
- **Drugs may cross any cell membrane by simple diffusion, active transport, facilitated diffusion, Pinocytosis**

Questions?