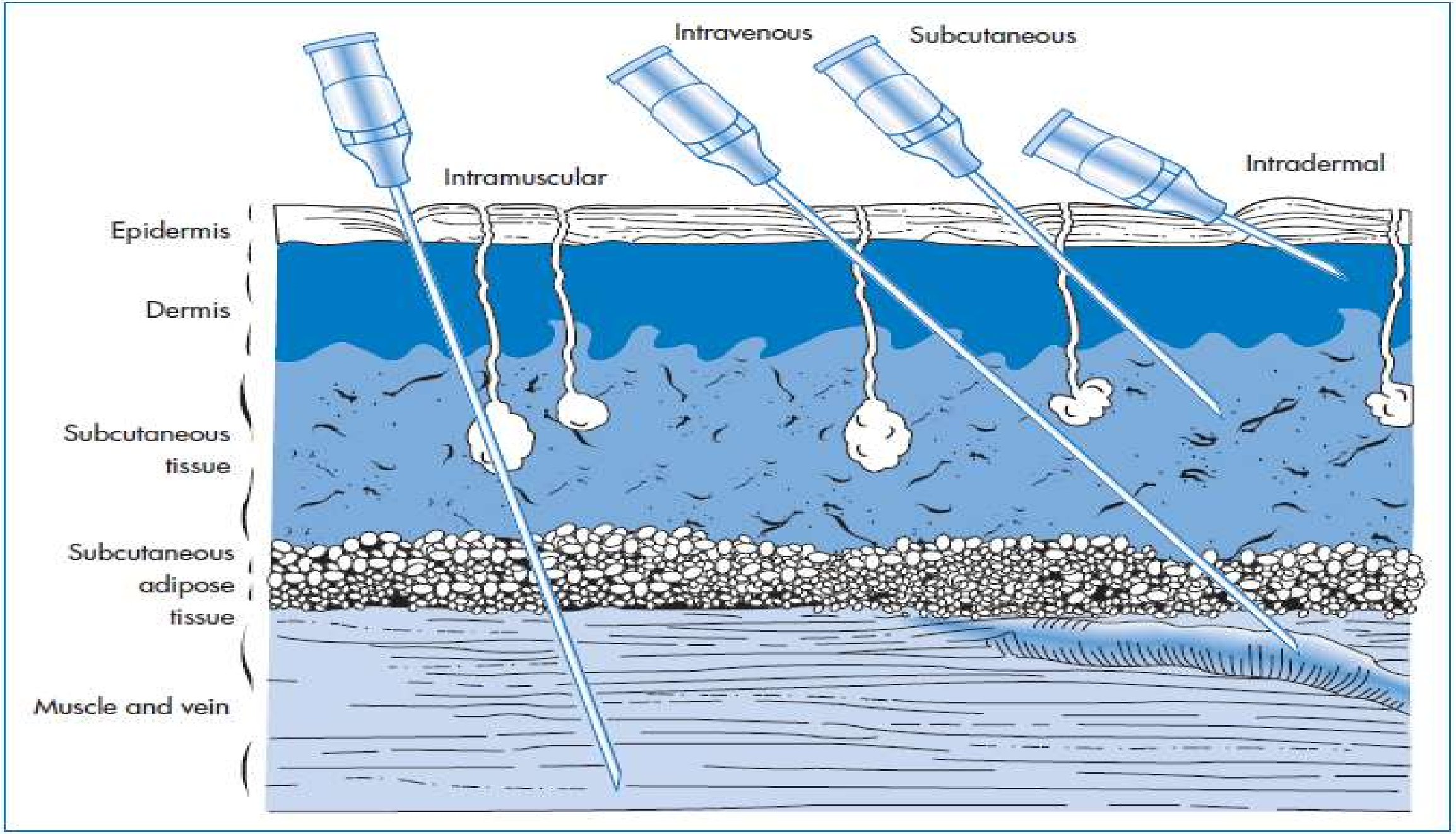
CHAPTER 6

➢ **The Parenteral Routes of Administration. Advantages and disadvantages. Routes for parenteral administration of drugs. (IV, IM and SC). (General study)**

- IV administration (Bolus & Infusion).

CHAPTER 7

- IM and SC administration Steps and kinetics of Absorption.
- Factors affecting the IM and SC Absorption.


Intravenous
Subcutaneous
Intramuscular
Intradermal
Epidermis
Dermis
Subcutaneous tissue
Subcutaneous adipose tissue
Muscle and vein

ADVANTAGES

1. An immediate physiological response can be achieved.
2. Suitable for uncooperative, nauseous or unconscious patients.
3. May inject large fluid volumes.
4. Suitable for irritating drugs.
5. Provides predictable blood concentration with 100% bioavailability. (**IV-Route of administration**).
6. Useful en emergency.
7. Accurate dose of drug can be given.
8. Completely avoidance of first-pass effect.

DISADVANTAGES

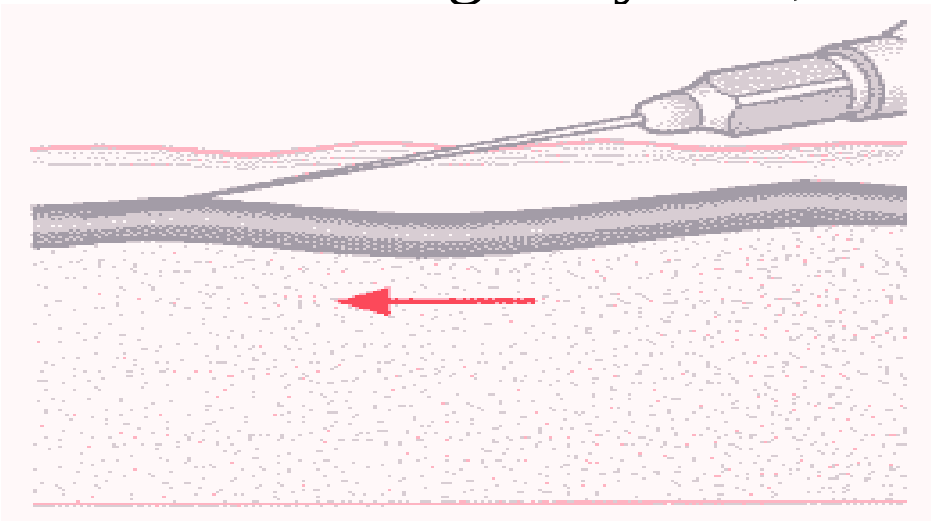
1. Requires trained personnel.
2. It is difficult to reverse its physiological effect.
3. It is more expensive than preparations of given by other routes.
4. Requires strict adherence to aseptic procedures and some pain on injection is inevitable. (**Pharmaceutics 3 and sterilization requirements**)
5. Chances of local tissue injury and injury to nerves.
6. Pain may be produced by injection.
7. More expensive.

Intravenous route of administration

✓ Drug is injected into a superficial vein → Directly reaches circulation → immediately available for action.

✓ Drugs can be given IV as:

- Bolus e.g. heparin
- Infusion e.g. Oxytocin, Dextrose, Saline



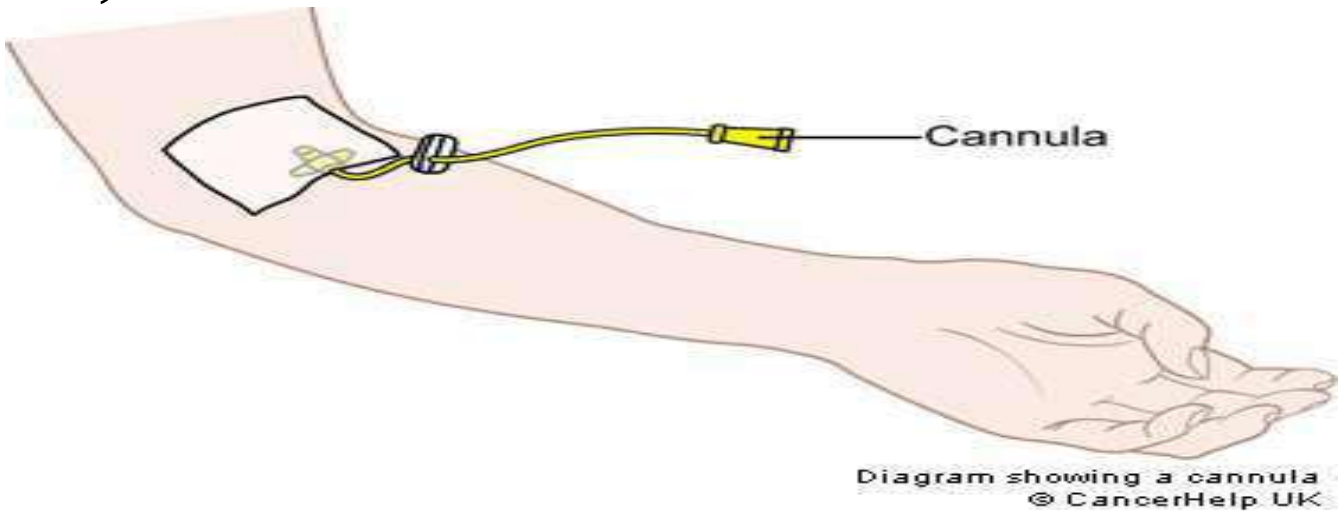


Diagram showing a cannula
© CancerHelp UK

Types of Parenteral Administrations

Parenteral R.O.A	Applications
IV	**Systemic effect**
IM	**Systemic effect**
SC	**Systemic effect**
Intra-cardiac	Local effect (Emergency)
Intra-arterial	Local effect (Tissues)
Thecael (Spinal)	Local effect (CNS)
Epidural (Arround spinal)	Local effect (CNS)
Intra-peritoneal	Systemic & Local effect
Intra-pleural	Local effect (Sepsis)
Intra-articular	Local effect (Synovia)
Intra-dermal	Local effect (Anesthetic, Vaccine)

❑ Intravenous Administration :

- A drug directly injected into a vein.

➢ Advantages:

1.The drug enters into circulation in an active form.

2.Desired blood concentration can be obtained.

3.Quick and immediate effect is produced.

4.It is useful in emergency.

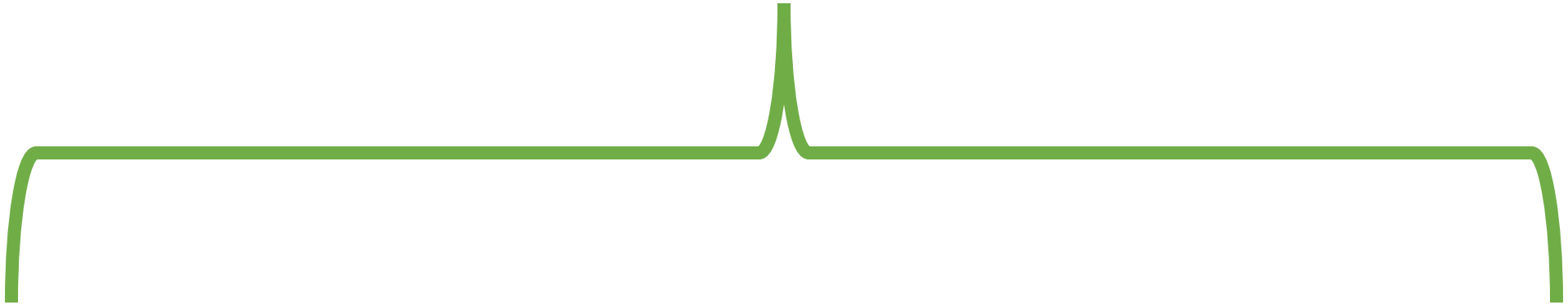
5.It is useful in an unconscious patient.

➢ Disadvantages:

1. Drug which precipitates blood constituents can not be administered.
2. Unwanted reactions, if occurred are immediate.
3. Withdrawal of the drug is not possible.
4. Risk of toxicity.
5. Special person.
6. Administration rate. (Slow) **??**
7. Expensive→ Sterility, pyrogen testing ,larger volume of solvent means greater cost for preparation and transport and storage conditions.

Manners of administration

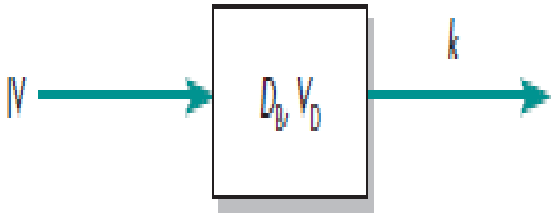
Will be discussed in details in the Biopharmaceutics and Pharmacokinetics 2



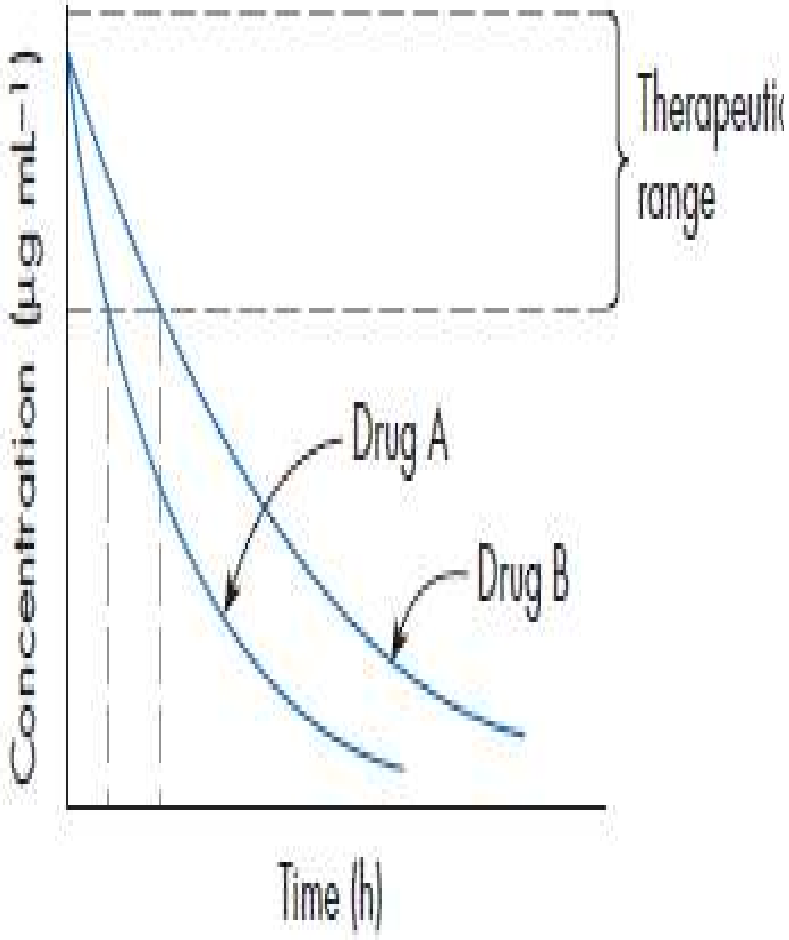
IV- Bolus

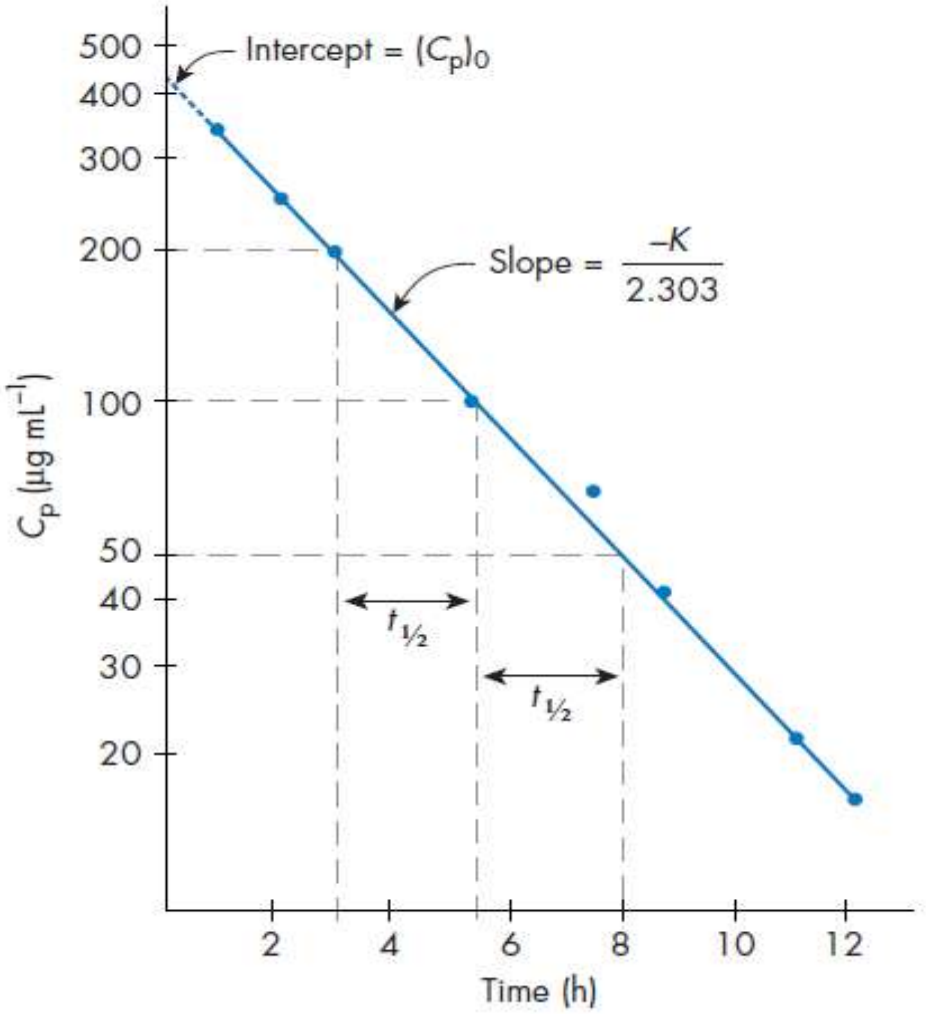
IV- Infusion

❖ IV -Bolus



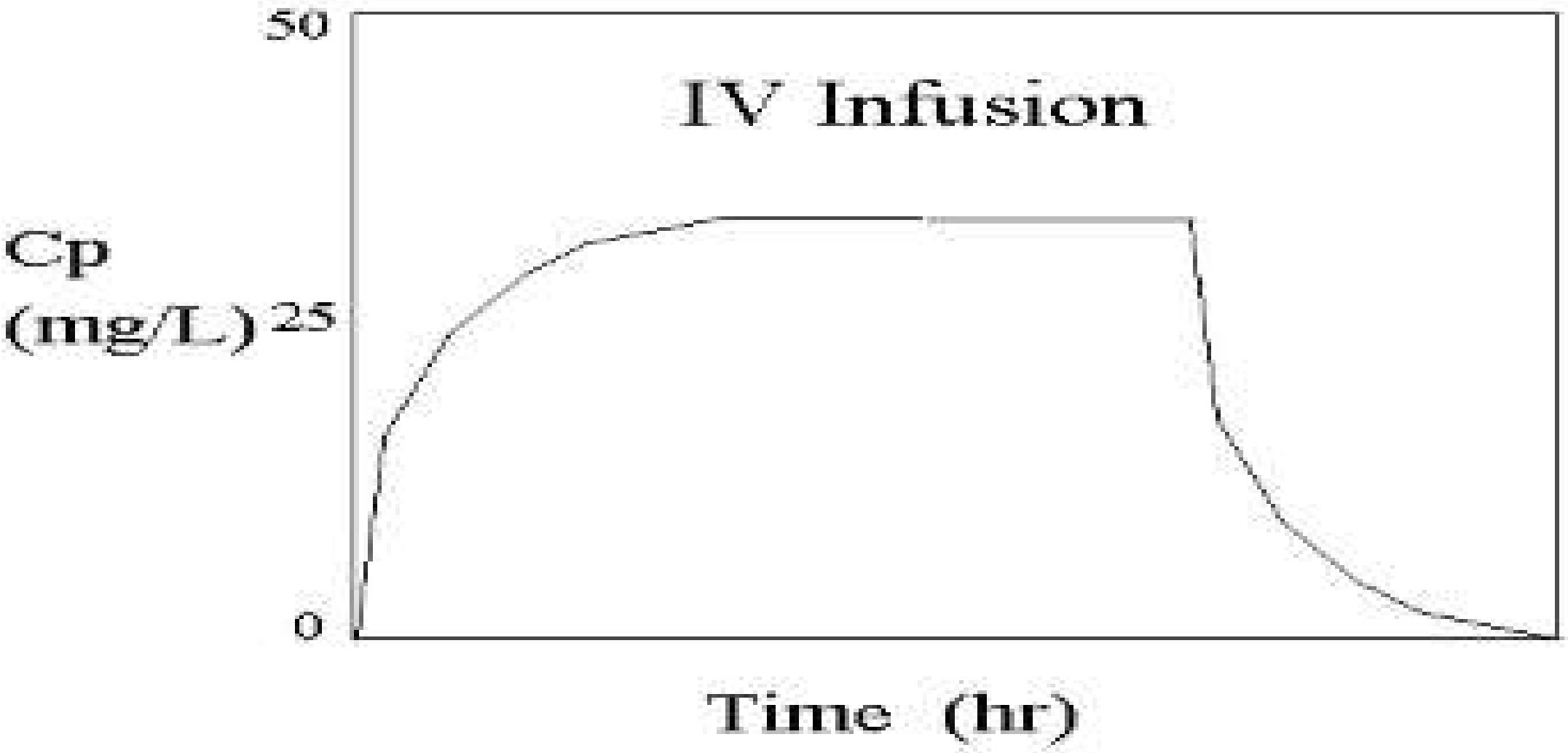
$$Cp = (Cp)_o \cdot e^{-kt}$$





Semilogarithmic plot of plasma concentration (Cp) versus time following administration of the drug by intravenous bolus

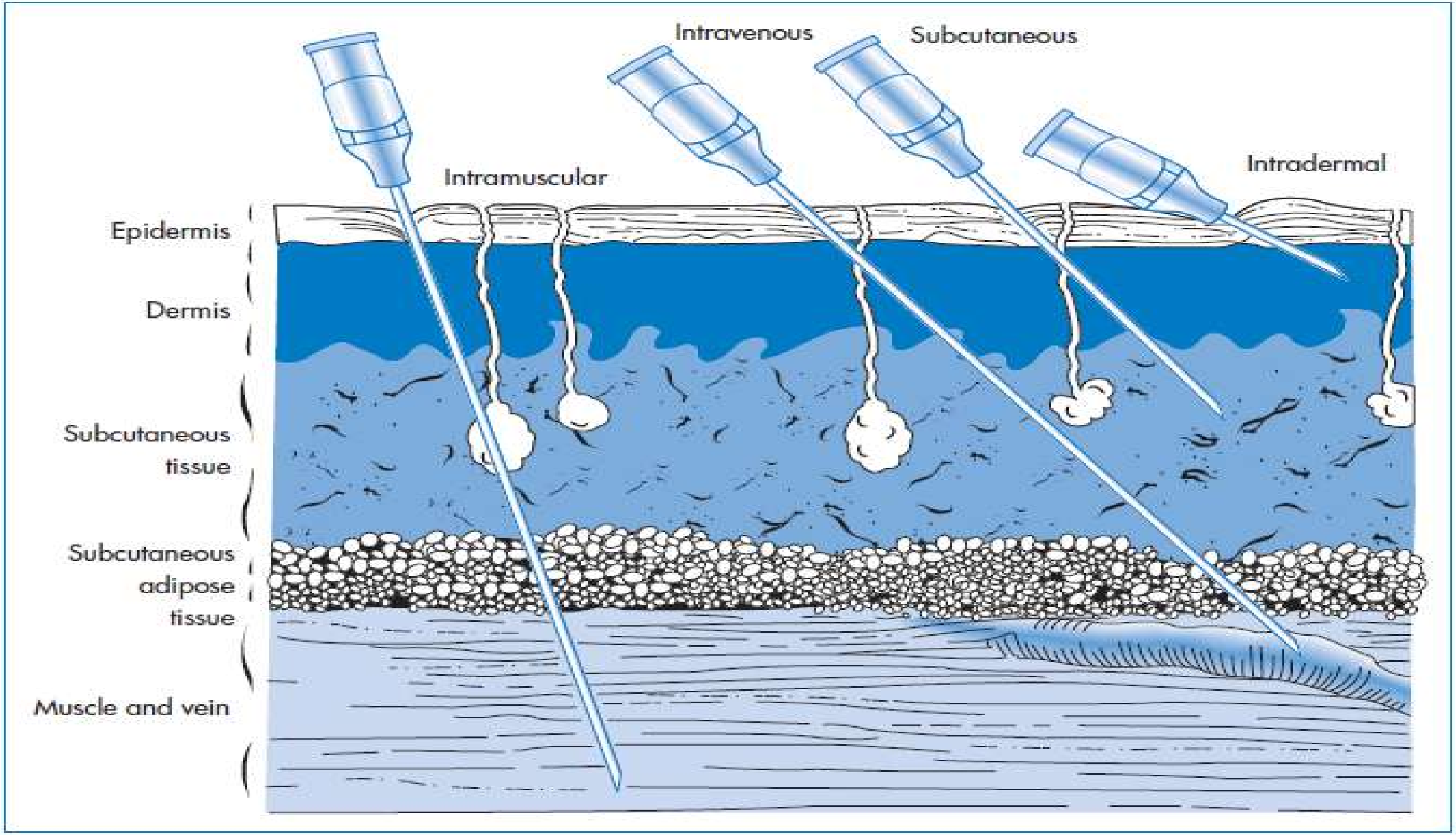
❖ IV- Infusion



CHAPTER 7

- IM and SC administration Steps and kinetics of Absorption.

- Factors affecting the IM and SC Absorption.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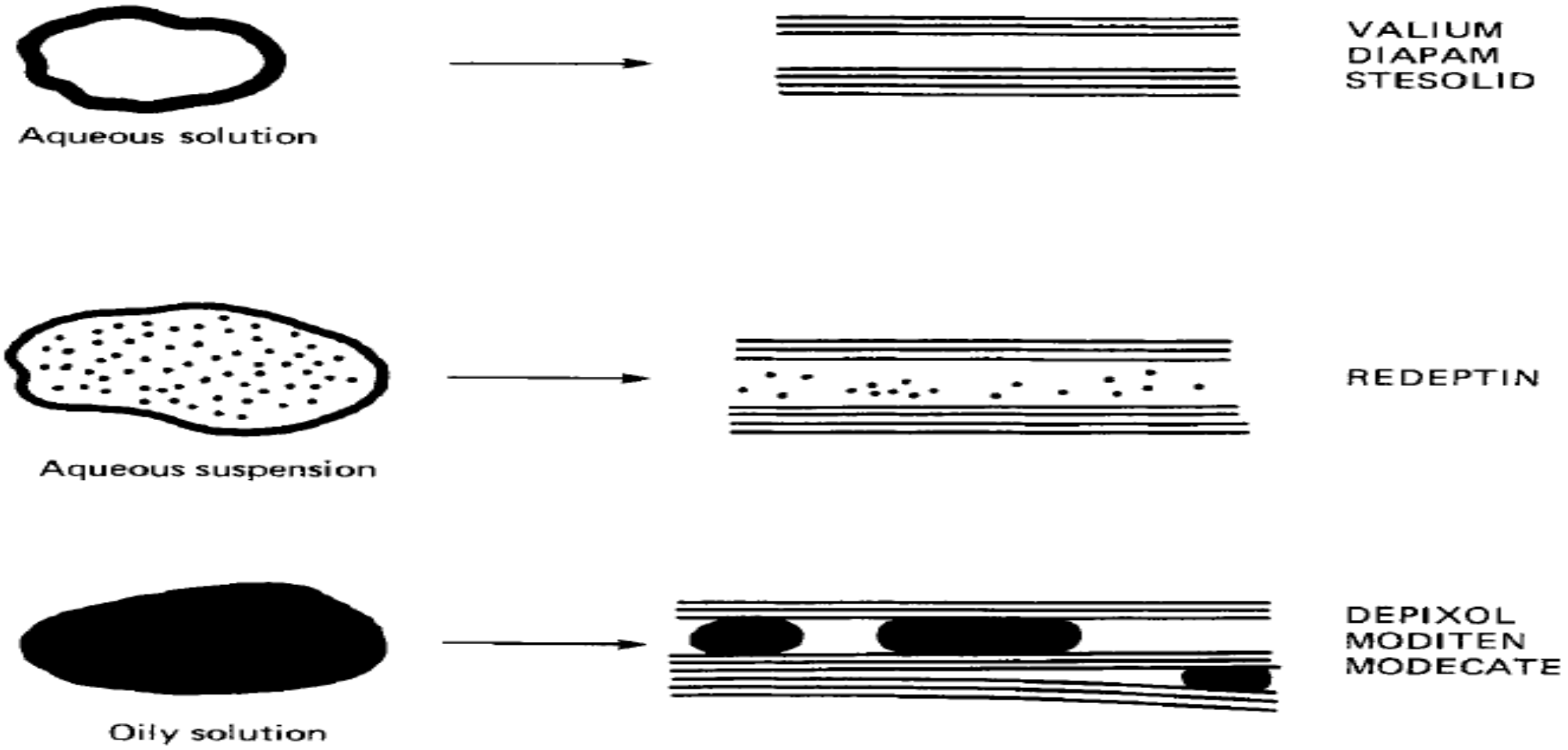
➢ Intramuscular injection (IM)

- Drug injected deep into muscles.
- Absorption into plasma occurs by simple diffusion.
- Rapid & uniform absorption!!!!
- Volume should not exceed 10 ml.



Diagrammatic representation of three types of intramuscular formulation, and mode of dispersal. Examples of commercial formulations of drugs used in psychiatric medicine are shown

- **Steps of IM Absorption:**

1. Release of drug from the formulation (Molecular size).
2. Absorption through the capillary walls.

- The transport through the capillary wall is the rate limiting step.
- It is assumed that the drug absorption proceed by passive diffusion of the drug, the absorption can be a 1st- order kinetic process. Thus the rate of absorption is proportional to the concentration of drug remaining at the injection site.

$$\mathbf{Ct = C_0 \,.\, e^{-ka.t}}$$

- where ka is the first-order rate constant. The half-life of the absorption process is

$$t_{1/2} = 0.693/\ ka$$

- Drug absorption is 90% completed when a time equivalent to three times the half-life has elapsed.

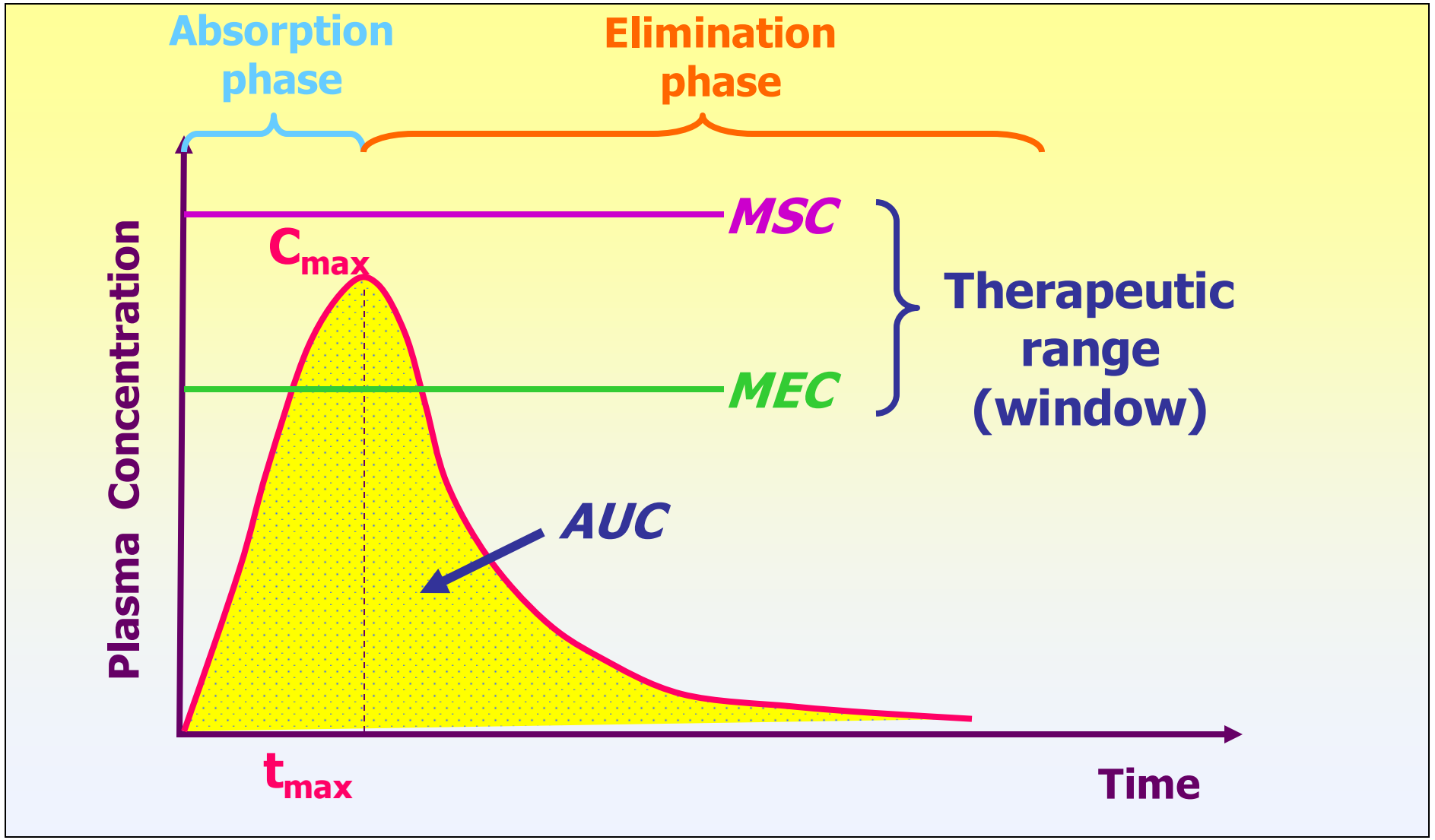


Figure: A typical blood plasma concentration-time curve obtained following the IM administration.

- **Drug Product Performance Parameters:**

1) Minimum effective concentration (MEC): Minimum conc. of drug needed at the receptor site to produce the desired pharmacologic effect.

2) Minimum toxic concentration (MTC): Minimum drug conc. needed to produce a toxic effect.

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

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

5) Tmax: The time at which maximum drug conc. observed in plasma. It is proportional to the rate of drug absorption.

6) Cmax: The maximum drug conc. observed in plasma at a particular time.

7) AUC: It is related to the amount of drug absorbed systemically.

8) Therapeutic range or window: A range of plasma drug concentrations over which the desired response is obtained and toxic effects are avoided.

9)The intensity of pharmacological effect is proportional to the number of drug receptors occupied, which is reflected in the observation that higher plasma drug concentrations produce a greater pharmacologic response.

➢**Factors affecting the IM absorption:**

1. **Blood supply** → muscle activity.
2. **Solution and dissolution of drug**. (factors)
3. **pKa of a drug and pH of a medium (more acidic)** → 6.4
4. **Injected volume** (2mL-4mL) and diffuision.
5. **Tonicity.**
6. **Sex**: female have more fatty tissues.
7. **Binding of drug to the muscle protein**→ decreases free drug conc.→Prolongation of action.

Dicloxacillin is 95% bound to protein.
Ampicillin is 20%.

8. Addition of hyaluronidase with the drug →decreases viscosity→ increases absorption.

9. Pathological state: Patients with circulatory shock, hypotension, congestive heart failure and myxedema, blood flow to skeletal muscle is decreased.

10. Pharmaceutical forms(Technological process)

- Aqueous dissolution.
- Oily dissolution.
- Aqueous suspension
- Addition of PEG 300 or 400 or propyleneglycol.

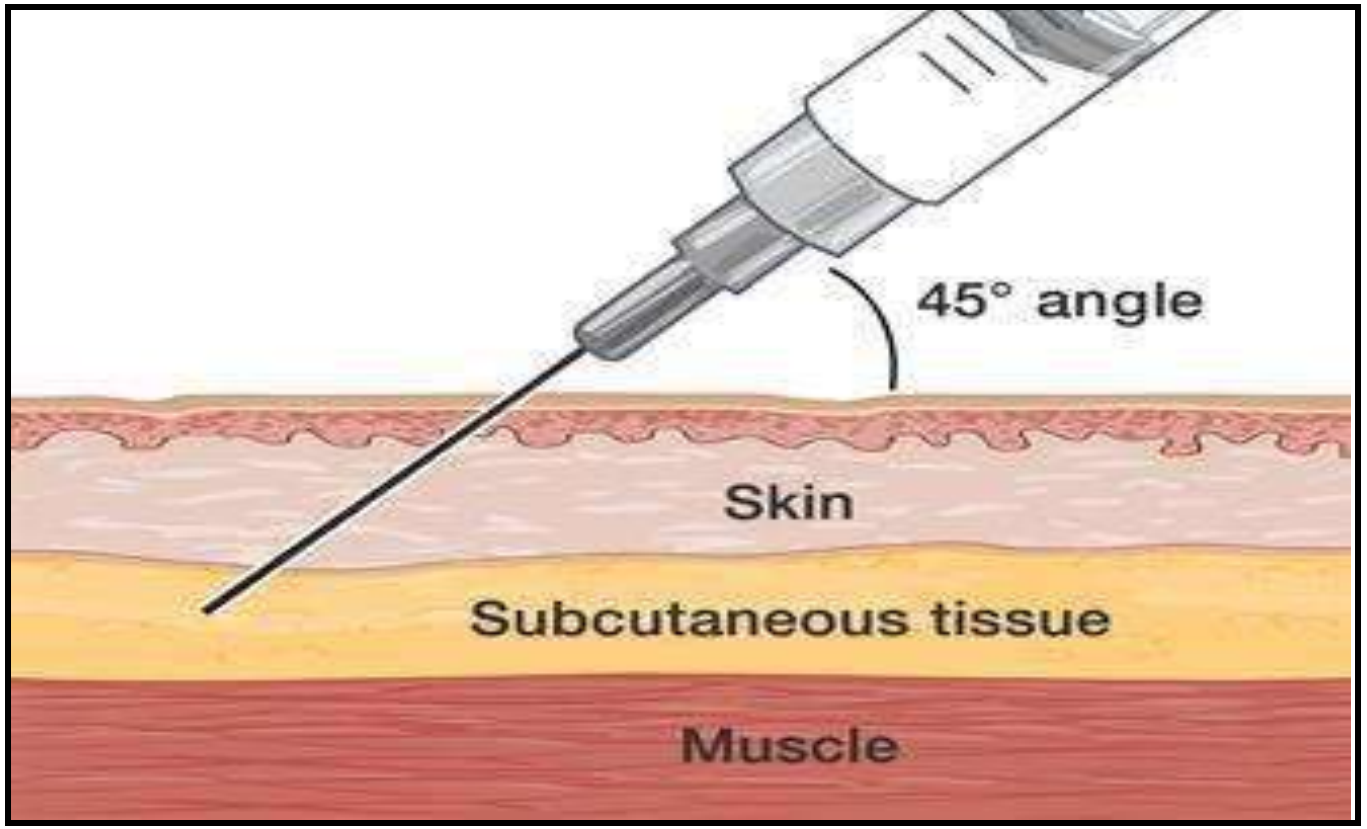
➢Subcutaneous Administration

- Drug administered as a bolus into the sub-cutis.
- The layer of skin directly below the dermis and epidermis.
- The SC region has a good supply of capillaries and lymph vessels
- e.g.: insulin & morphine.
- Non irritant substances can be injected by this route.
- The rate of absorption is even and slow→ Prolonged effect.

- **Steps of SC Absorption:**

1.Release of drug from the formulation (Molecular size).

2.Absorption through the capillary walls.



➢Factors affecting the SC absorption:

1. **Blood supply** → Vasodilation.
2. **Solution and dissolution of drug**. (Factors)
3. **pH of a medium and pKa of a drug.**
4. **Concentration of drug.**
5. **Viscosity of medium** viscosity increases → absorption decreases.

Addition of hyaluronidase with the drug →decreases viscosity→ increases absorption.

The enzyme →breaking down the hyaluronic acid in intercellular spaces → a decrease in viscosity →easing the passage of small molecules in the matrix.

6. **Liquid dosage form**
   - **Homogenous drug system**
   - **Heterogeneous drug system**

   Example: Insulin

Pharmaceutical injections of insulin BP

Preparation	pH	Buffer	Description	Onset (h)	Duration of effect (h)
Insulin injection	3.0–3.5	–	Solution	~0.5–1	6–8
Neutral injection	6.6–7.7	Acetate	Solution	~0.5–1	6–9
Protamine zinc	6.9–7.4	Phosphate	Amorphous particles; rod-shaped crystals	~5–7	36
Globin zinc	3.0–3.5	–	Solution	~2	18–24
Isophane	7.1–7.4	Phosphate	Rod-shaped crystals (about 20 µm long)	~2	28
Zinc suspension (amorphous) 'Semilente'	7.0–7.5	Acetate	Amorphous particles (2 µm diameter)	~1	12–16
Zinc suspension 'Lente'	7.0–7.5	Acetate	Amorphous particles (30%) Rhombohedral crystals (70%)	~2	24
Zinc suspension (crystalline) 'Ultralente'	7.0–7.5	Acetate	Rhombohedral crystals (about 20 µm across)	~5–7	36
Biphasic	6.6–7.2	Acetate	Insulin in solution (25%) Rhombohedral crystals (75%)	~1	18–22