

Pharmacokinetics.

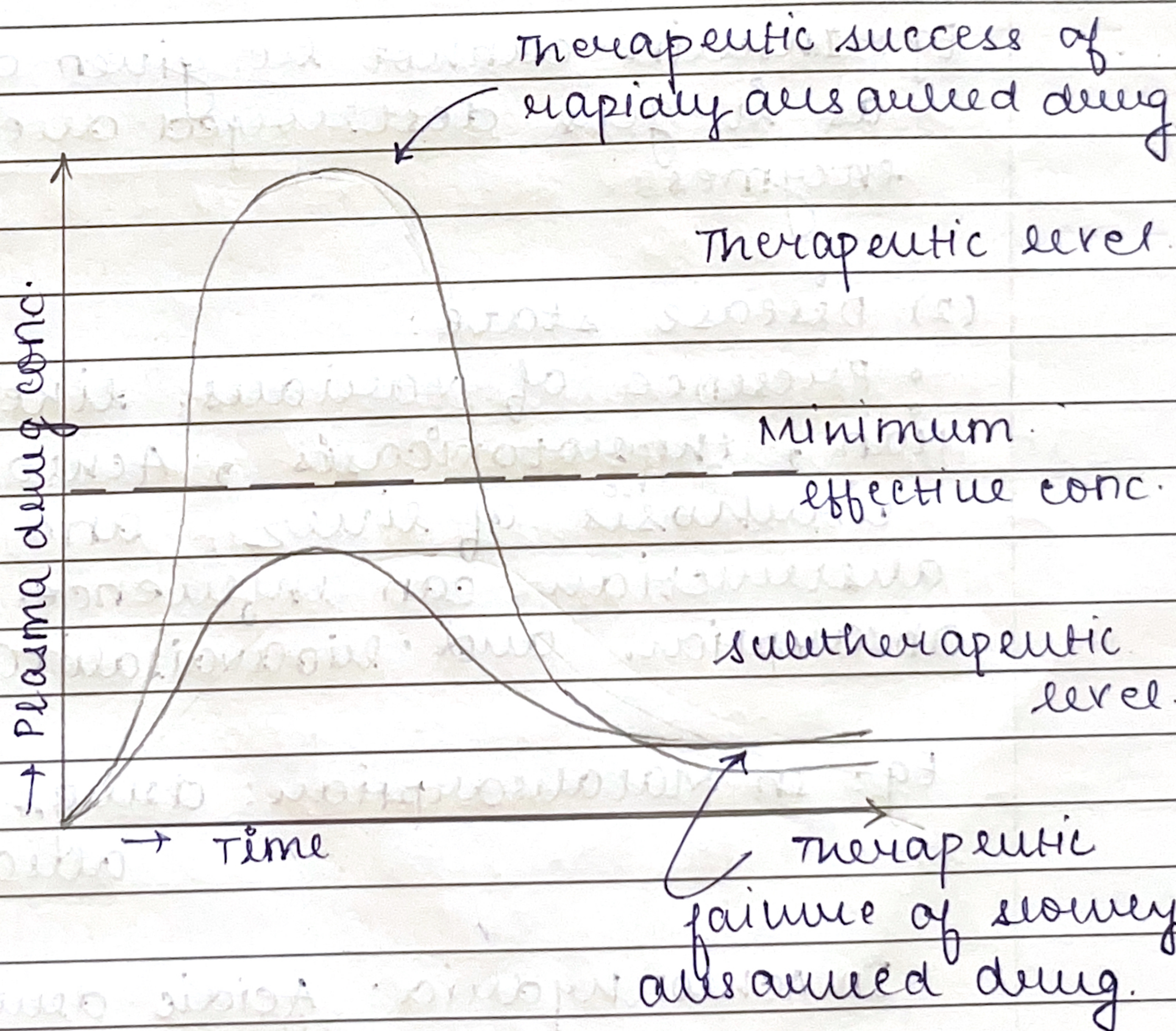
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ABSORPTION :

• The process of transporting the drug from gastrointestinal lumen to the systemic circulation is known as Absorption.

• If the drug is poorly soluble, it will affect the rate and extent of the absorption.

The rate and extent of the absorption of drug depends on the route of administration, formulation and chemical properties of the drug.



• Absorption of a drug is affected by 3 main factors.

They are:

- (I) Physiological
- (II) Physicochemical
- (III) Formulation

(1) Physiological: (RD, SE, GI, PPF)

(1) Route of administration

- The drug is absorbed faster when given parenterally than oral adm.
- Bioavailability of drugs through IV route is 100%.

Eg: Insulin cannot be given orally as it gets destroyed due to GIT enzymes.

(2) Disease state:

- Presence of various. like Malabsorption, thyrotoxicosis, Achlorhydria, cirrhosis of liver and biliary obstruction can influence the absorption and bioavailability of drugs.

Eg: In malabsorption: drugs can't be absorbed.

In Achlorhydria: Acidic drugs can't be absorbed.

In cirrhosis of liver, the drug is more

metabolized and produces toxic effects

(3) Splanchnic blood flow:

- The presence of food in the GI tract influence the bioavailability of the drug.

- Food increases splanchnic blood flow.

- Some drugs attain peak plasma concentration after food.

Eg: Propranolol, chloramphenicol, lithium carbonate

- Absorption of some drugs is reduced by the presence of food.

Eg: Ampicillin

Aspirin

L-dopa

(4) Enterohepatic circulation:

- It enhances the bioavailability of drugs.

Eg: Morphine is less potent when given orally.

(5) Gastric motility:

- The rapid movement of the GIT impairs the absorption because the drug has a very brief residence time and less opportunity for adequate absorption.

- Some disorders like diabetic neuropathy decreases the drug absorption as it causes gastric stasis.

(6) Ionization and gastric emptying:

- Acidic drugs are absorbed faster in acidic pH because they remain unionized in acidic medium.

- Basic drugs remain unionized in basic medium and get absorbed faster.

- For Acidic drug, gastric emptying time should be more. While for basic drugs, it should be faster.

(7) Pharmacogenomic factors:

- The difference in action of drug on different human beings is known as Pharmacogenomics.

Eg: Alcohol dehydrogenase enzyme, \uparrow ent in gastric mucosa, converts alcohol into acetaldehyde, which is not intoxicating.

Females have less quantity of this enzyme. So, there are more chances of adverse effects in females than male.

- (8) Presence of other substances:
Vitamin C favours absorption of iron from GIT while phytates retard it.

(II) Physico-chemical factors: (ss, D, 3P)

(1) Salt form of drug-

It is assumed that the salt form of drugs dissolve more rapidly than their corresponding free acids.

Eg: Sodium & Potassium salts of Penicillin-G, sulfonamides, phenytoin etc.

(2) Salts and hydrates:

The salts have greater solubility and gets readily absorbed than the non-salts.

(3) Dissolution rate:

If the drug is lipophilic in nature, it will be more readily absorbed.

(4) Particle size and surface area:

It is assumed that

Smaller particle size \rightarrow Larger surface area.



Higher absorption.

(5) pH and pKa:

- The solubility of weak acid drugs or weak basic drugs are influenced by the pH of the fluid.

pKa can be calculated by the Henderson-Hasselbalch equation:

⇒ For acidic drugs-

$$pH = pKa + \log \frac{[\text{unionized drug}]}{[\text{ionized drug}]}$$

⇒ For basic drug-

$$pH = pKa + \log \frac{[\text{unionized drug}]}{[\text{ionized drug}]}$$

(6) Polymorphism:

- When a substance exists in more than one crystalline form, it is called Polymorphism.

- Stable polymorphs → low energy state



least aqueous solubility

- Metastable polymorphs → higher energy state



Higher aqueous solubility.

(III)

Formulation factors

- (1) Disintegration time
- (2) Manufacturing variables
- (3) Nature and type of dosage form
- (4) Pharmaceutical ingredients.

→ Disintegrants

→ Binders

→ Lubricants

→ Surfactants

→ Viscosity agent

Mechanisms of drug absorption:

- There are 6 ways by which the drug can be migrated.
- They are:

- (i) Passive diffusion
- (ii) Pure transport
- (iii) Active transport
- (iv) Endocytosis
- (v) Ion pair transport
- (vi) Facilitated diffusion

(i) Passive diffusion:

- The process in which molecules diffuse from a region of higher concentration to a region of lower concentration.

- No external energy used.
- Here, Fick's law is applied:

$$\text{Rate of diffusion} \propto \frac{\text{surface area} \times \text{concentration difference}}{\text{thickness of membrane}}$$

OR

$$\frac{dQ}{dt} = \frac{DAK}{h} (C_{GIT} - C)$$

(ii) Pure transport:

- It is also called convective transport, bulk flow or filtration.

- This mechanism is responsible for the transport of molecules into the cell through the protein channels in the cell membrane.

- Low molecular weight (< 100 dalton)
- Low molecular size
- Hydrophilic drugs

- Eg: urea, water and sugars.

(iii) Ion-pair transport:

- Here, the drugs penetrate the membrane by forming reversible neutral complexes with endogenous ions of GIT.

- Eg: Quaternary ammonium compounds
- Sulphonic acid

(iv) Active transport:

- The drug transports from a region of low concentrations to high concentrations, which is against the concentration gradient.

- Here, it requires energy for the push.

• Eg: 5-Fluorouracil

- Therefore, it is a specialized process that requires a carrier that binds to the drug to form a carrier-drug complex to transfer the drug across the membrane and then dissociates the drug on the other side.

(v) Endocytosis:

- The capturing of substance by engulfing with the cell membrane and bringing it into the cell.

- It involves both

Pinoctosis

Phagocytosis

- cell drinking

- cell eating

(usually liquid droplets)

(usually solid particles).

- The transport is facilitated by the formation of vesicles.
- It is an active process and hence requires energy.

Eg: complex proteins
Antibodies

(vi) Facilitated diffusion:

- A passive transport mechanism. Hence, involves a special carrier molecule for the movement of

drugs across the membrane.

- It does not require any energy.

Eg: Vitamin B₁₂.