PHARMACEUTICS VII (4th Sem)
(MID SEM PAPER)

1.

a) RDS.

→ In a series of kinetic or rate process the rate at which the drug reaches the systemic circulation is determined by the slowest of the various steps involved in the sequence. Such a step is called as the rate determining or rate limiting step (RDS).

b) Example of diluent

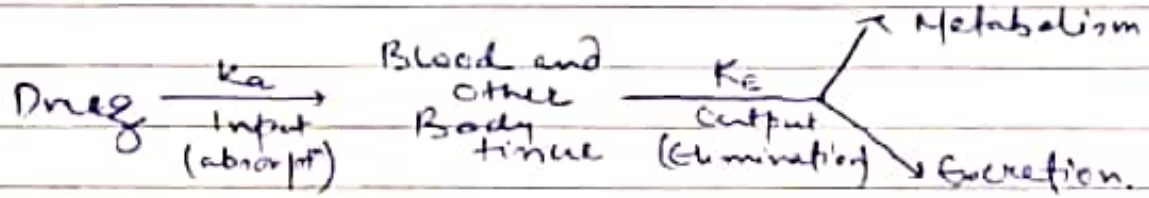
→ • Lactose (most widely used diluent)
- Inorganic calcium salt
↳ Dicalcium phosphate

⇨ C_{max} ⟶

The point of maximum concentration of drug in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration (C_{max}).

2.

⇨ One compartment model



One-compartment Open Model

- Intravenous Bolus Administration

When a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection (i.e. i.v. bolus), it takes about 1-3 min for complete circulation and therefore the rate of absorption is neglected in calculation

Blood & other Body tissue $\xrightarrow{K_E}$

Rate of drug presentation

dx/dt = Rate in − Rate out

dx/dt = − Rate out

$$dx/dt = -K_E X$$

Estimation of pharmacokinetic parameter - IV Bolus Administration

Elimination phase can be char. by 3 parameter-

i) Elimination Rate constant

$$\ln X = \ln X_0 - K_E t.$$

$$X = X_0 e^{-K_E t} \quad \text{(monoexponential)}$$

$$\log X = \log X_0 - K_E t / 2.303$$

As. $X = V_d C$

$$\log C = \log C_0 - K_E t / 2.303$$

2) Elimination half life.

→ time taken for the amt. of drug in the body as well as plasma conc. to decline by one-half or 50% its initial value.

$$t_{1/2} = 0.693 / K_E$$

or $t_{1/2} = 0.693 V_d / Cl_T$

3) Clearance → important parameter in clinical drug applications and is useful in evaluating the mechanism by which a drug is eliminated by the whole organism.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma drug conc.}}$$

$$Cl = \frac{dx/dt}{C}$$

by Michaelis Menten Constant

$$-dC/dt = V_{max}C/K_m + C$$

where $-dC/dt$ - rate of decline of drug conc.
V_{max} = theoretical max^m rate of the process
K_m = Michaelis constant.

1) When $K_m = C$

$$-dC/dt = V_{max}/2$$

i.e. rate of process is equal to one-half its max^m rate (mixed order rate)

2) when $K_m >> C$

$$-dC/dt = V_{max}C/K_m \quad \text{(first order)}$$

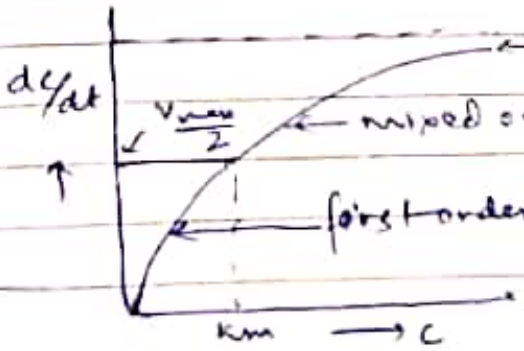
$V_{max}/K_m = K_e$.

means that the drug conc. in the body that results from usual dosage regimen of most drugs is well below the K_m.

3) when $K_m << C$.

$$-dC/dt = V_{max} \quad \text{(zero order)}$$

(rate process occurs at a constant rate V_{max})



factors affecting drug absorption

- Physico - chemical factors -
  1) Drug solubility & Dissolution rate
  2) Particle size & effective surface area
  3) Polymorphism & Amorphism.
  4) Pseudo polymorphism.
  5) Salt form of the drug.
  6) Drug stability.
  7) Stereochemical nature of the drug.
  8) Lipophilicity and pKa of the drug

- Pharmacotechnical factors.
  - Disintegration time
  - Dissolution time.
  - Manufacturing variable
  - Pharmaceutical ingredients
  - Nature and type of dosage form
  - Product age and storage condition

- Patient related factors -
  - Age
  - Gastric emptying time
  - Intestinal transit time
  - Gastro intestinal content
  - Contact time with GIT mucosa
  - disease state.

a) Drug solubility & dissolution rate

Solid dosage form → (disintegration) → Solid drug particles → (Dissolution) → Drug in solution at the absorption site → (permeation across the membrane) → Drug in the body

Dissolution → RDS for lipophilic drug

Permeation across the membrane → RDS for hydrophilic drugs.

Noyes & Whitney Equation

$$dc/dt = k(C_s - C_b)$$

b) Particle size and effective surface Area

- Absolute S Area – Total surface area of solid particles of any particle
- Effective S. Area → Area exposed to the dissolution medium

P. size ∝ 1/S. Area

4. by adding hydrophilic diluents such as PEG

c) Amorphous > Metastable > Stable] on basis of stability

d) Salt form of the drug

- Convenient reason for increased solubility of salt of weak acids in the precipitation of the drug as very fine particle

- Drug stability

– Drug from oral use may destabilize either during its self life or in the GIT. To measure stability of an orally administered drug – degration of the drug into inactive form.

- Stereochemical Nature

→ Appox 60-1. drugs are chiral drugs, majority of them are marketed as racemic mixture.

a) Bioequivalence

- It is a relative term which denotes that the drug substance in two or more identical dosage forms reaches the systemic circulation at the same relative rate and to the same relative extent i.e. their plasma concentration time profile will be identical without significant statistical differences.

When statistically significant differences are observed in the bioavailibility of 2 or more drug products, bio-inequivalence is indicated

Types — in vivo
in vitro

1) In vivo bioequivalence studies.

1) Oral immediate-release products with systemic action-

- Indicated for serious conditions requiring assured response
- Narrow therapeutic margain
- Pharmacokinetics complicated by absorption <70% or absorption window > 70%.
- Unfavourable physicochemical properties e.g low solubility, metastable modifications, instability etc.
- Documented evidence for bioavailibility problem
- Not relevant data available, unless justification by applicant that in vivo study is not necessary

2) Non-oral immediate-release product.

3) Modified-release products with systemic action

5) The drug product differs only in strength of the active substance it contains, provided all the following condition—

- Pharmakinetics are linear
- The qualitative composition is the same.
- The ratio between active substance and the excipients in the same, or the ration between the excipients in the same.
- Both products are produced by the same manufacturer at the same production site.
- A bioavailability or bioequivalence study has been performed with the original product.

↳ Distribution

⟶ which involves reversible transfer of a drug between compartments

Distribution is defined as the reversible transfer of a drug between one compartment and another. Since the process is carried out by the circulation of blood, one of the compartment is always the blood or the plasma, and the other represents extravascular fluids and other body tissues. In other word distribution is reversible transfer of a drug between the blood and the extravascular fluids and tissues.

Steps in drug distribution.

Distribution of drug present in systemic circulation to extravascular tissues involves following steps-

- Permeation of free or unbound drug present in the blood through the capillary wall and entry into the interstitial / (ECF)
- Permeation of drug in the ECF through the membrane of tissue cells and into the intracellular fluid. This step is rate-limiting & depends upon two major factors -
  - Rate of perfusion to the extracellular tissue
  - Membrane permeability of the drug