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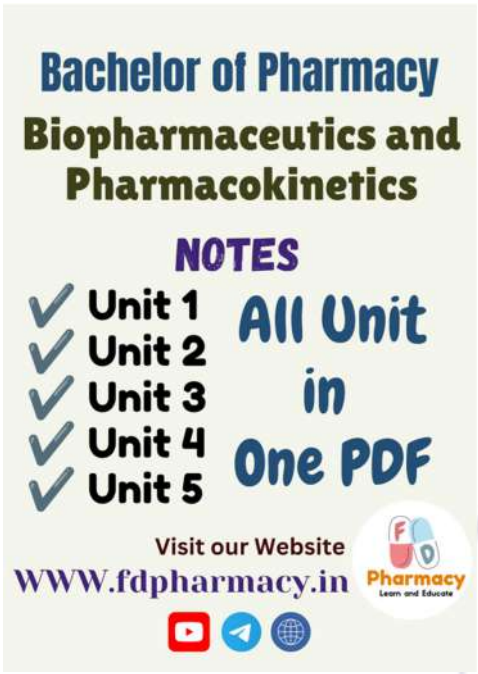
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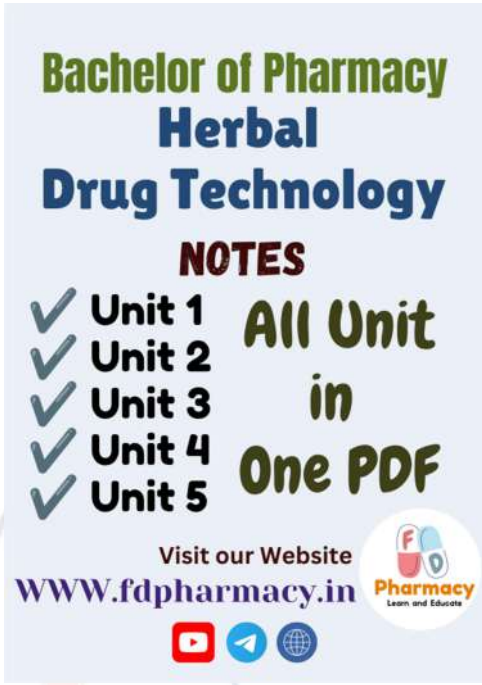
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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT 5

TOPIC :

- **Nonlinear Pharmacokinetics :**

  a. Introduction,

  b. Factors causing Non-linearity.

  c. Michaelis-menton method of estimating parameters, Explanation with example of drugs.

Nonlinear Pharmacokinetics

Nonlinear pharmacokinetics is a condition in which the relationship between the administered dose of a drug and the plasma drug concentration is not proportional.

In linear pharmacokinetics:

- If dose is doubled → plasma concentration also doubles.

But in nonlinear pharmacokinetics:

- If dose is doubled → plasma concentration may increase more or less than double.

This occurs because one or more pharmacokinetic processes become saturated at higher drug concentrations.

These processes include:

- Absorption
- Distribution
- Metabolism
- Excretion
- Protein binding

Nonlinear pharmacokinetics is also called:

- Dose dependent pharmacokinetics
- Capacity limited pharmacokinetics
- Saturable pharmacokinetics

Characteristics of Nonlinear Pharmacokinetics

1. Plasma concentration does not increase proportionally with dose.
2. Elimination half-life changes with dose.
3. Clearance is not constant.
4. Area under curve (AUC) is not proportional to dose.
5. Small increase in dose may produce toxic concentration.

Factors Causing Nonlinearity

1. Saturation of Drug Absorption

When transport proteins involved in absorption become saturated, absorption rate decreases.

Example:

- Riboflavin
- Gabapentin

2. Saturation of Plasma Protein Binding

At high drug concentrations, plasma protein binding sites become saturated, increasing free drug concentration.

Example:

- Salicylates, Valproic acid

3. Saturation of Hepatic Metabolism

Drug metabolizing enzymes become saturated at high concentrations.

Once enzymes are saturated:

- Metabolism rate becomes constant
- Elimination becomes slower
- Drug accumulates in body

Example:

- Phenytoin, Ethanol

4. Saturation of Renal Tubular Secretion

Active transport systems in kidneys become saturated.

Example:

- Penicillin

5. Saturation of Renal Tubular Reabsorption

Reabsorption carriers become saturated causing increased excretion.

Example:

- Vitamin C

6. Autoinduction or Enzyme Induction

Some drugs increase synthesis of metabolizing enzymes with repeated dosing.

Example:

- Carbamazepine, Rifampicin

Michaelis–Menten Theory

Nonlinear pharmacokinetics due to saturable metabolism is explained by Michaelis–Menten kinetics.

It describes the relationship between:

- Drug concentration
- Rate of metabolism

The metabolism process depends on enzyme capacity.

Michaelis–Menten Equation

$$v = \frac{V_{max} \cdot C}{K_m + C}$$

Where:

- v = rate of drug metabolism
- Vmax = maximum metabolic rate
- C = plasma drug concentration
- Km = Michaelis constant

Meaning of Km

- Km is the drug concentration at which metabolism rate becomes half of Vmax.

$$v = \frac{V_{max}}{2} \text{ when } C = K_m$$

Interpretation

- Low Km → high enzyme affinity
- High Km → low enzyme affinity

Conditions of Michaelis–Menten Kinetics

When C << Km

Drug concentration is much smaller than Km.

Then:

- First order kinetics occurs.
- Elimination rate depends on concentration.

$$v \approx \frac{V_{max}}{K_m} \cdot C$$

When C >> Km

Drug concentration is much greater than Km.

Then:

- Enzymes become saturated.
- Zero order kinetics occurs.
- Elimination rate becomes constant.

$$v \approx V_{max}$$

Estimation of Michaelis–Menten Parameters

The two important parameters are:

1. Vmax
2. Km

These are estimated using plasma concentration and elimination rate data.

Methods

1. Lineweaver–Burk Plot

Double reciprocal form of Michaelis–Menten equation:

$$\frac{1}{v} = \frac{K_m}{V_{max}} \cdot \frac{1}{C} + \frac{1}{V_{max}}$$

Plot:

- 1/v versus 1/C

From graph:

- Slope = Km/Vmax
- Intercept = 1/Vmax

2. Eadie–Hofstee Plot

Equation:

$$v = V_{max} - K_m \left(\frac{v}{C}\right)$$

Plot:

- v versus v/C

3. Nonlinear Regression Method

Computer software is used to directly estimate:

- Vmax
- Km

This is the most accurate method.

Example of Drugs Showing Nonlinear Pharmacokinetics

1. Phenytoin

Phenytoin

- Most common example.
- Hepatic metabolizing enzymes become saturated near therapeutic concentration.
- Small increase in dose may produce toxicity.
- Shows Michaelis–Menten kinetics.

Toxic effects:

- Nystagmus
- Ataxia
- CNS depression

2. Ethanol

Ethanol

- Alcohol dehydrogenase enzyme becomes saturated.
- Eliminated by zero order kinetics.

3. Aspirin

Aspirin

- Protein binding and metabolism become saturated at high doses.

4. Carbamazepine

Carbamazepine

- Shows autoinduction of metabolism.

Clinical Significance

1. Dose adjustment becomes difficult.
2. Risk of toxicity increases.
3. Therapeutic drug monitoring is important.
4. Small dose changes may produce large plasma concentration changes.
5. Individualized dosing is necessary.