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PHYSICAL PHARMACEUTICS - II

UNIT 5

TOPIC :

- **Drug stability :** Reaction kinetics: zero, pseudo-zero, first & second order, units of basic rate constants, determination of reaction order. Physical and chemical factors influencing the chemical degradation of pharmaceutical product: temperature, solvent, ionic strength, dielectric constant, specific & general acid base catalysis, Simple numerical problems. Stabilization of medicinal agents against common reactions like hydrolysis & oxidation. Accelerated stability testing in expiration dating of pharmaceutical dosage forms. Photolytic degradation and its prevention

Reaction Kinetics

Reaction kinetics is the study of the rate at which chemical reactions occur and the factors affecting this rate.

Importance:

- Helps determine the order of reaction (Zero, First, Second).
- Important in pharmaceutical stability studies and predicting drug shelf life.

ZERO-ORDER KINETICS

A zero-order reaction is a reaction in which the rate of reaction is independent of the concentration of reactants.

Rate Expression:

$$\text{Rate} = k[A]^0 = k$$

- k = zero-order rate constant
- $[A]$ = concentration of reactant

Differential Form:

$$-\frac{d[A]}{dt} = k$$

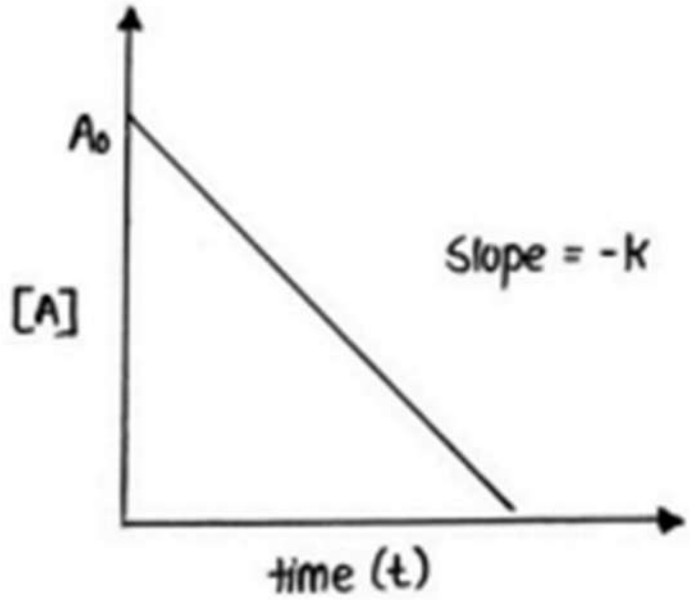
Integrated Form:

$$[A] = [A]_0 - kt$$

- $[A]_0$ = initial concentration
- $[A]$ = concentration at time t

Graphical Representation:

- Plot of $[A]$ vs. t is **linear** with:
  - Slope = $-k$
  - Y-intercept = $[A]_0$



HALF-LIFE ($t_{1/2}$)

Time required for the reactant concentration to reduce to half of its initial value.

For zero-order reaction:

$$t_{1/2} = \frac{[A]_0}{2k}$$

SHELF LIFE (t_{90})

Time required for the reactant concentration to decrease to 90% of its initial concentration.

For zero-order reaction:

$$[A] = [A]_0 - kt_{90}$$

$$0.9[A]_0 = [A]_0 - kt_{90} \implies t_{90} = \frac{0.1[A]_0}{k}$$

FIRST-ORDER REACTION

A first-order reaction is a chemical reaction where the rate of reaction is directly proportional to the concentration of a single reactant.

$$\text{Rate} = k[A]^1 = k[A]$$

- k = first-order rate constant
- $[A]$ = concentration of reactant

Differential Form:

$$-\frac{d[A]}{dt} = k[A]$$

Integrated Form:

$$\ln[A] = \ln[A]_0 - kt$$

or in base 10 logarithm:

$$\log_{10}[A] = \log_{10}[A]_0 - \frac{kt}{2.303}$$

- $[A]_0$ = initial concentration
- $[A]$ = concentration at time t

Graphical Representation:

- Plot of $\log_{10}[A]$ vs. t is linear
  - Slope = $-k/2.303$
  - Y-intercept = $\log_{10}[A]_0$

HALF-LIFE (t1/2)

Time required for the reactant concentration to reduce to half of its initial value.

For first-order reaction:

$$[A] = \frac{[A]_0}{2} \implies t_{1/2} = \frac{0.693}{k}$$

- Note: Half-life is **independent of initial concentration** in first-order reactions.

SHELF-LIFE (t90)

Time required for the reactant concentration to decrease to 90% of its initial concentration.

For first-order reaction:

$$[A] = 0.9[A]_0 \implies t_{90} = \frac{0.105}{k}$$

Degradation of Pharmaceutical Products

- Degradation of a pharmaceutical product is the process by which a drug substance or product undergoes undesirable physical, chemical, or microbiological changes, leading to loss of potency, reduced safety, and formation of inactive or harmful by-products.

Factors Affecting Drug Degradation

1. Temperature

- **Effect:** Increased temperature accelerates molecular motion, leading to more frequent and energetic collisions and faster degradation.
- **Principle:** Follows Arrhenius Equation:

$$k = Ae^{-E_a/RT}$$

Where:

- k = rate constant
- A = frequency factor
- E_a = activation energy
- R = gas constant
- T = absolute temperature (K)

- **Examples:**
  - Penicillin G degrades rapidly at high temperatures.
  - Aspirin hydrolyzes at elevated temperatures forming salicylic acid and acetic acid.
- **Prevention:** Store temperature-sensitive drugs in cool or refrigerated conditions (2–8°C); avoid high temperatures during storage and transport.

2. Solvent

- **Effect:** Solvent polarity and composition affect solubility and reaction pathways (e.g., hydrolysis, oxidation).
  - **Aqueous solvents:** Can cause hydrolysis.
  - **Organic solvents (alcohols, PEG):** Reduce degradation by limiting water activity.
- **Examples:**
  - Esters hydrolyze in water.
  - Nitroglycerin is more stable in alcoholic solvents.
- **Prevention:**
  - Use mixed solvents (water + ethanol) to reduce hydrolysis.
  - Replace water with non-aqueous solvents if stability is a concern.
  - Choose solvent systems based on drug compatibility and stability data.

3. Ionic Strength

- Total concentration of charged particles (ions) in a solution.
- **Effect:**
  1. High ionic strength may accelerate degradation**.**
  2. Alters stability of some drugs.
  3. Can affect pH, indirectly influencing stability.
- **Example:** Liquid medicines in saline degrade faster than in pure water.
- **Prevention:**
  - Control ionic strength with appropriate buffers or salt forms.
  - Avoid excessive salts unless required for isotonicity.

4. Dielectric Constant

- **Definition:** Measures solvent polarity.
- **Effect:**
  - High dielectric constant (water) promotes ionization → faster ionic degradation.
  - Low dielectric constant (oils, alcohols) suppresses ionization → slower degradation.
- **Examples:**
  - Nitrofurantoin is more stable in solvents with low dielectric constant.
  - Drugs stable in non-polar solvents degrade faster in water.
- **Prevention:** Use non-polar or moderately polar solvents for ion-sensitive drugs.

5. Acid-Base Catalysis

- **Effect:** Many degradation reactions (e.g., hydrolysis) are catalyzed by **H^+ (acid)** or **OH^- (base)**.
- **Types:**
  1. **Specific acid/base catalysis:** Only involves H^+ or OH^-.
  2. **General acid/base catalysis:** Involves buffer species in addition to H^+ or OH^-.
- **Examples:**
  - Aspirin: Hydrolyzed faster under alkaline conditions (base-catalyzed).
  - Penicillin G: Degrades in acidic conditions (β-lactam ring opening).
- **Prevention:**
  - Select optimum pH for stability.
  - Use buffers that do not catalyze degradation.
  - Avoid strongly acidic or basic environments unless necessary for solubility.

Stabilization of Medicinal Products

- Stabilization of medicinal products is the application of strategies and techniques to prevent or minimize physical, chemical, microbiological, and therapeutic degradation of drugs, thereby maintaining efficacy and safety during storage and use.

1. Hydrolysis

Hydrolysis is a chemical reaction in which a drug molecule reacts with water, causing bond breakdown and leading to drug degradation.

- **Commonly affected drugs:** Esters, amides, lactams.
- **Example:** Aspirin → Salicylic acid + Acetic acid (on hydrolysis).

Stabilization Strategies Against Hydrolysis:

1. Use anhydrous (dry) formulations.
2. Store in moisture-proof containers.
3. Add desiccants (e.g., silica gel).
4. Adjust pH to reduce hydrolytic rate.
5. Use non-aqueous solvents like oils or alcohols.
6. Prepare as dry powders for reconstitution.

2. Oxidation

Oxidation is the loss of electrons or addition of oxygen to a drug molecule, often causing color changes, potency loss, or toxicity.

- **Commonly affected drugs:** Phenols, aldehydes, alkaloids, and unsaturated compounds.
- **Example:** Adrenaline oxidizes and turns brown.

Stabilization Strategies Against Oxidation:

1. Add antioxidants (e.g., ascorbic acid, sodium bisulfite).
2. Use airtight and light-resistant containers (amber bottles).
3. Replace air with inert gases like nitrogen or carbon dioxide (especially in ampoules).
4. Add chelating agents (e.g., EDTA) to bind metal ions.
5. Store in cool conditions to slow oxidation.

Accelerated Stability Testing

- Accelerated stability testing is a method used to predict the shelf life or expiration date of pharmaceutical products by storing them under elevated stress conditions (e.g., high temperature, high humidity) to speed up degradation.

Purpose

1. To determine the expiration date quickly.
2. To study the degradation pattern of the drug.
3. To guide formulation improvements and packaging selection.

Principle

- Drug degradation is temperature-dependent and often follows the Arrhenius equation.
- By storing drugs at higher temperatures and humidity, degradation occurs faster, allowing prediction of shelf life in a shorter time.

Common Stress Conditions

Condition Type	Typical Setting
Temperature	Elevated (e.g., 40°C ± 2°C)
Humidity	High (e.g., 75% RH ± 5%)
Duration	Usually 6 months (per ICH guidelines)

Procedure

1. Select minimum 3 batches of the drug product.
2. Store samples under accelerated conditions.
3. Take samples at intervals (e.g., 0, 1, 2, 3, 6 months).
4. Analyze for:
    - Physical appearance
    - Assay (potency)
    - Degradation products
    - Dissolution

Advantages

1. Provides fast estimation of shelf life.
2. Useful during early formulation development.

Photolytic Degradation

- Photolytic degradation is the breakdown of pharmaceutical substances when exposed to light, especially ultraviolet (UV) or visible light.
- This reaction can lead to changes in the drug's chemical structure, potency, and safety.

Examples of Light-Sensitive Drugs

- Nifedipine
- Riboflavin
- Vitamin A

Prevention Methods

- Use light-protective containers: Amber-colored or opaque bottles.
- Store in dark conditions: Avoid exposure to sunlight or bright light.
- Incorporate light stabilizers or UV absorbers in formulations.
- Proper packaging: Blister packs, aluminum foils, or multilayer containers.

Significance:

- Preventing photolytic degradation maintains drug stability, preserves potency, and extends shelf life.