PHYSICAL PHARMACEUTICS-II

UNIT 5 NOTES

DRUG STABILITY

- ORDER OF REACTION
- DEGRADATION OF PHARMACEUTICAL PRODUCTS
- TEMPERATURE, SOLVENT, IONIC STRENGTH
- DIELECTRIC CONSTANT
- SPECIFIC AND GENERAL ACID BASE CATALYSIS
- STABILIZATION OF MEDICINAL AGENTS
- ACCELERATED STABILITY TESTING
- PHOTOLYTIC DEGRADATION

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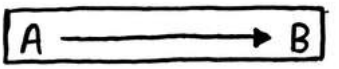
Reaction Kinetics

- Reaction kinetics is defined as "The study of the rate at which chemical reactions occur and the factors that influence this rate.
- It helps us to describe order of reaction
  - Zero Order reaction
  - First Order reaction
  - Second Order reaction

Zero Order Kinetics

- Zero order Reaction is a type of chemical reaction where rate of reaction is independent of concentration of reactant.
- Lets suppose



Now rate = $K\,[A]^x$

As this is a zero order reaction, $x = 0$

Hence rate = K

Now we know Rate of Reaction can also be expressed as :

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

Here we can write above equation as :

$$\Rightarrow \quad \frac{-d[A]}{dt} = K$$

$$[A] = -K\,dt$$

On integrating both side, we get :

$$\int_{A_0}^{A} d[A] = -\int_{0}^{t} K\,dt$$

$$A - A_0 = -K(t - 0)$$

$$A - A_0 = -Kt$$

$$A = A_0 - Kt$$

$$\boxed{A = A_0 - kt}$$

Here, A_0 = Initial concentration of A

A = Concentration of A at any time 't'

K = rate constant

t = time in which concentration changes from $A_0 \rightarrow A$

Concentration v/s Time Plot

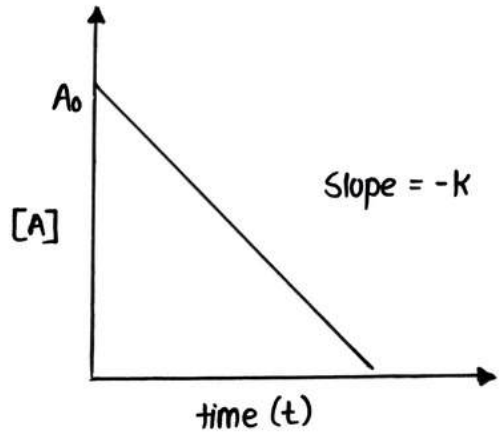
Comparing $A = -kt$ at A_0 with $y = mx + c$, we get:

$y = A$

$m = -K$

$x = t$

$c = A_0$



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

It is the time required to reduce initial concentration of the reactant to become half of its value during the progress of the reaction.

Time = $t_{1/2}$

Concentration = $\frac{A_0}{2}$

We have : $A_0 - Kt = A$

Putting above values, we get:

$$\frac{A_0}{2} = A_0 - Kt_{1/2} \Rightarrow Kt_{1/2} = A_0 - \frac{A_0}{2}$$

$$Kt_{1/2} = \frac{A_0}{2} \Rightarrow t_{1/2} = \frac{A_0}{2K}$$

$$\boxed{t_{1/2} = A_0/2K}$$

SHELF LIFE (t_{90})

It is the time required for reactant concentration to decrease to 90% of its initial concentration.

$$\text{time} = t_{90}$$
$$\text{Concentration} = 0.9\,A_0$$

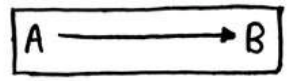
Putting above values in $A = A_0 - kt$, we get

$$0.9\,A_0 = A_0 - kt_{90}$$
$$kt_{90} = A_0 - 0.9\,A_0$$
$$t_{90} = \frac{A_0 - 0.9A_0}{K}$$

$$\boxed{t_{90} = \frac{0.1\,A_0}{K}}$$

First Order Reaction

- A first order reaction is a chemical reaction where the rate of reaction is directly proportional to the concentration of the reactant.
- Let's consider:



Now rate = $k[A]^x$

As this is a first order reaction $x = 1$

Hence rate = $k[A]$

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

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

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

Integrating both side, we get:

$$\int_{A_0}^{A} \frac{d[A]}{[A]} = \int_{0}^{t} -k\,dt$$

$$[\log A]_{A_0}^{A} = -k\,[t]_0^t$$

$$\log_e A - \log_e A_0 = -k(t-0)$$

$$\log_e A - \log_e A_0 = -kt$$

$$\log_e A = \log_e A_0 - kt$$

continued.....

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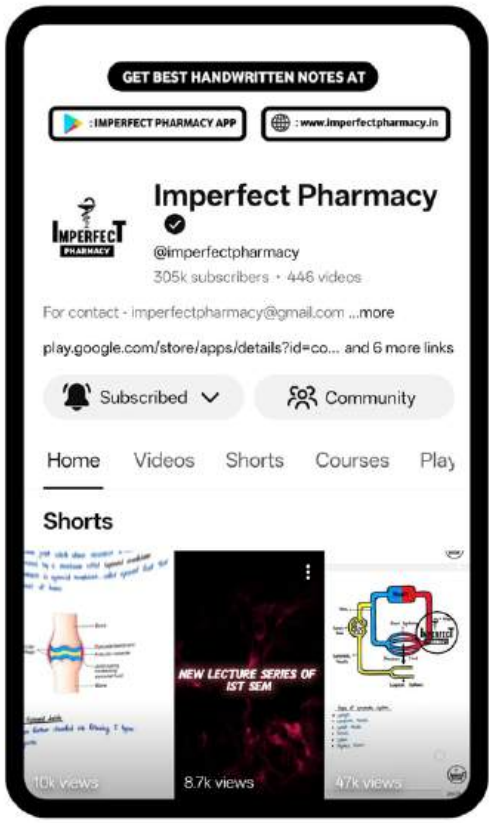

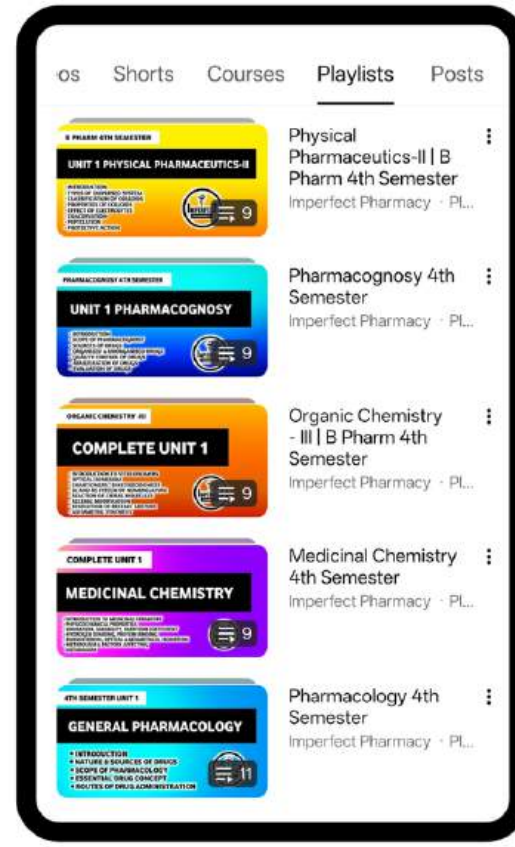

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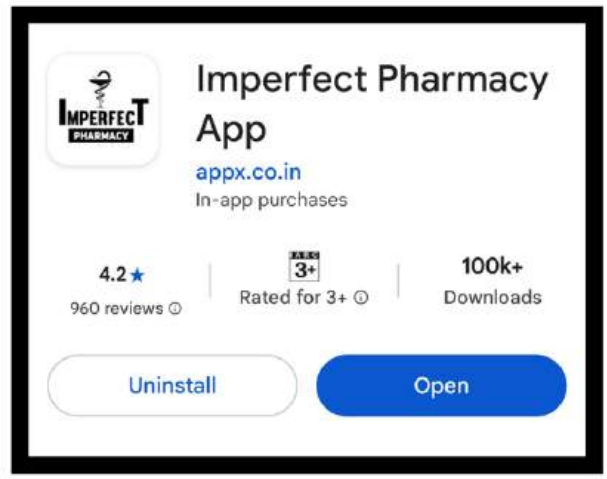


Now $\log_e x = 2.303 \log_{10} x$

Hence we can write above equation as :

$$2.303 \log_{10} A = 2.303 \log_{10} A_0 - kt$$

dividing the above equation by 2.303, we get :

$$\log_{10} A = \log_{10} A_0 - \frac{kt}{2.303}$$

$$\boxed{\log_{10} A = \log_{10} A_0 - \frac{kt}{2.303}}$$

GRAPHICAL REPRESENTATION

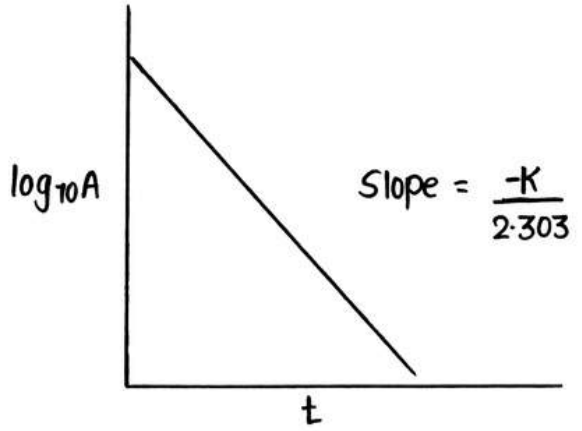
Comparing above equation with $y = mx + c$, we get:

$y = \log_{10} A$

$m = \frac{-k}{2.303}$

$x = t$

$C = \log_{10} A_0$



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

Time in which reaction completes 50%

Time = $t_{1/2}$

$A = \frac{A_0}{2}$

Now, we have $\log_{10} A = \log_{10} A_0 - \frac{Kt}{2.303}$

We can write it like:

$$\log_{10} A_0 - \log_{10} A = \frac{Kt}{2.303}$$

$$\log_{10} \frac{A_0}{A} = \frac{Kt}{2.303}$$

$$t = \frac{2.303}{K} \log_{10} \frac{A_0}{A}$$

Now, If we put the value of $t = t_{1/2}$ & $A = A_0/2$ in above equation, we get:

$$t_{1/2} = \frac{2.303}{K} \log_{10} \frac{A_0}{A_0/2}$$

$$Kt_{1/2} = 2.303 \log_{10} 2$$

$$= 2.303 \times 0.3010$$

$$= 0.693$$

$$\boxed{t_{1/2} = \frac{0.693}{K}}$$

SHELF LIFE

Time = t_{90}

$A = 0.9A_0$

we have $t = \frac{2.303}{K} \log_{10} \frac{A_0}{A}$

Putting above values, we get:

$$t_{90} = \frac{2.303}{K} \log_{10} \frac{A_0}{0.9A_0}$$

$$= \frac{2.303}{K} \log_{10} \frac{10}{9}$$

$$= \frac{2.303}{K} (\log_{10} 10 - \log_{10} 9)$$

$$= \frac{2.303}{K} (1 - 0.95)$$

$$t_{90} = \frac{0.105}{K}$$

Degradation Of Pharmaceutical Product

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

Factors Affecting Degradation of Pharmaceutical Products

There are following factors which mainly affects the degradation of pharmaceutical products:

1. Temperature
2. Solvent
3. Ionic strength
4. Dielectric constant
5. Specific & General Acid-Base catalyst.

1. Temperature

- As temperature increases, molecular motion and energy increase.
- This leads to more frequent and energetic collisions between molecules.
- More molecules cross the activation energy barrier, speeding up the reaction → faster degradation.

Follows Arhenius Equation :

$$k = A \cdot e^{-Ea/RT}$$

Ea : Activation energy
R : Gas constant
T : Absolute Temperature (kelvin)

Higher temperature = higher k = faster degradation

Examples

- Penicillin G degrades quickly at high temperature.
- Aspirin undergoes hydrolysis at elevated temperature to form salicyclic acid + acetic acid.

Prevention

- Store temperature-sensitive drugs in cool or refrigerated conditions (2-8°C).
- Avoid exposure to high temperatures during storage and transport.

② SOLVENT

- Solvent polarity and composition influence:
  - Drug solubility
  - Reaction Pathway (e.g. hydrolysis, oxidation)
- Aqueous solvents (water) can cause hydrolysis.
- Organic solvents (e.g. Alcohol, PEG) can reduce degradation by limiting water activity.

Examples

- Esters degrade via hydrolysis in water.
- Nitroglycerin is more stable in alcoholic solvents.

Prevention

- Use mixed solvents (e.g. water + ethanol) to reduce hydrolysis.
- Replace water with anhydrous or non-aqueous solvents when stability is a concern.
- Choose solvent systems based on drug compatibility and stability data.

③ Ionic Strength

It's measures of the total concentration of charged particles (ions) in a solution.

How it affects drug degradations:

i) Faster Reactions: Higher ionic strength can speed up chemical reactions, including drug breakdown, because ions increase interactions b/w molecules.

ii) Stability changes: Some drugs degrade quicker in salty (high ionic) solutions, while others may stay stable longer.

iii) pH Influence: Ion can alter pH, indirectly affecting drug stability.

Examples

A liquid medicine stored in a saline solution (high ionic strength) might degrade faster than in pure water.

Prevention

- Formulate with controlled ionic strength using appropriate buffers or salts forms.
- Avoid excessive addition of salts unless required for isotonicity.

④ Dielectric Constant

- The dielectric constant (ε) measures solvent polarity.
- High dielectric constant (e.g. water) promotes ionization of drugs and reagents ⟶ may enhance ionic degradation.
- Low dielectric constant (e.g., oils, alcohols) suppresses ionization ⟶ slows degradation reaction like hydrolysis.

Examples

- Drugs stable in non-polar solvents (low ε) degrade faster in water.
- Nitrofurantoin is more stable solvents with low dielectric constant.

Prevention

Use non-polar or moderately polar solvents for ion-sensitive drugs.

⑤ Acid - Base Catalysis

- Many degradation reactions (e.g., hydrolysis) are catalyzed by H^+ (acid) or OH^- (Base).
- Two types:
  - Specific acid / base catalysis: Only involves H^+ or OH^-.
  - General acid/ base catalysis: Involves buffer species in addition to H^+ or OH^-.

Examples

- Aspirin: Hydrolyzed faster under alkaline conditions (base-catalyzed).
- Penicillin-G: Degraded in acidic conditions due to β-lactam ring opening.
- Buffers (like acetate, phosphate) may catalyze degradation even at stable pH.

Prevention

- Select optimum pH for stability of each drug.
- Use buffer systems 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 various strategies and techniques to prevent or minimize physical, chemical, microbiological and therapeutic degradation of drugs, thereby maintaining their efficacy and safety during storage and use.

① Hydrolysis

- Hydrolysis a chemical reaction in which a drug molecule reacts with water, causing bond breakdown and leading to drug degradation.
- Common in esters, amides and lactams.

Example

Aspirin ⟶ Salicyclic acid + acetic acid (on hydrolysis)

Stabilization against Hydrolysis

- Use anhydrous (dry) formulations.
- Store - in moisture-proof containers.
- Add desiccants (silica gel).
- pH adjustments to reduce hydrolytic rate.
- Use non-aqeous solvents like oils or alcohols.
- Prepare as dry powders for reconstitution.

② Oxidation

- Oxidation is the loss of electrons or addition of oxygen to a drug molecule, often leading to color changes, potency loss or toxicity.
- Common in Phenols, aldehydes, alcohols and unsaturated compounds.

Examples

Adrenaline gets oxidized and turns brown.

Stabilization against Oxidation

- Add antioxidants (e.g. ascobic acid, sodium bisulfite)
- Use airtight and light-resistant containers (amber bottles).
- Replace air with nitrogen or carbon dioxide (in ampoules).
- Add chelating agents (e.g. EDTA) to bind metal ions.
- 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 (such as high temperature and humidity) to speed up degradation.

Purpose

- To determine expiration date quickly.
- To study the degradation pattern of the drug.
- To guide formulation improvements and packaging selection.
- To ensure regulatory compliance (e.g. ICH guidelines).

Principle

- Chemical reactions (like degradation) are temperature-dependent and follow the Arrhenius equation.
- By storing drugs at higher temperatures and humidity, reaction rates increase, and degradation occur faster, allowing shelf-life prediction in a short time.

Common Stress Condition Used

Condition Type	Typical Setting
Temperature	40 ± 2°C
Humidity	75 ± 5% RH
Duration	6 months

- These are based on ICH Q1A (R2) guidelines for accelerated testing.

PROCEDURE

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

ADVANTAGES

- Fast estimation of shelf life.
- Useful in early formulation stage.
- Reduces time and cost of long-term studies.

PHOTOLYTIC DEGRADATION

- Photolytic Degradation refers to the breakdown of pharmaceutical substances when exposed to light, especially ultraviolet (UV) or visible light.
- The reaction can cause changes in the drug's structure, potency, and safety.

Example

Nifedipine, Riboflavin and Vit A are light-sensitive drugs.

Prevention Methods

- Use of amber coloured or opaque containers.
- Storage in dark or light-protected containers.
- Addition of light stabilizers or UV absorbers in formulations.
- Proper packaging (e.g. blisters packs, aluminium foils).
- This helps maintain drug stability and extends shelf-life.

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