UNIT- V DRUG STABILITY

Points to be covered in this topic

- REACTION KINETICS

- DETERMINATION OF ORDER

- DRUG STABILITY

- STABILIZATION OF MEDICINAL AGENTS AGAINST COMMON REACTIONS LIKE HYDROLYSIS AND OXIDATION

- ACCELERATED STABILITY TESTING IN EXPIRATION DATING OF PHARMACEUTICAL DOSAGE FORMS

REACTION KINETICS

- Reaction kinetics is also known as **chemical kinetics.**
- It includes the study of the **speed or rate** of chemical processes that occur during **chemical reactions.**
- Many properties such as the order of a **chemical reaction**, the rate of reaction or the **concentration of the components** can be easily calculated from the study of **chemical kinetics.**
- Rate of reaction is the speed at which **chemical reaction** takes place and it is measured by **change in concentration (dc)** with respect to time (dt).
- It is expressed as

$$\text{Rate of reaction} = \pm \frac{dc}{dt}$$

➢ APPLICATION IN PHARMACY

❖ DRUG STABILITY

- Chemical kinetics provide the basis to **predict drug stability.**
- The **extent of inactivation** of drug due to various **environmental adverse conditions** can be understood from the drug stability studies.

❖ DISSOLUTION

- Normally, the drug is expected to **release** from the **solid dosage forms** and immediately go into **molecular solution.**

❖ PHARMACOKINETICS

- It involves the study of the **transport of the drugs** from the site of application to blood, from **blood to tissue** spaces and **other body parts** and finally its **removal from the body.**

❖ DRUG ACTION

- The interactions of drugs with **biomembranes or receptors** are being interpreted using kinetic models.
- Such models **provide information** regarding the quantitative differences in the drug action of **different drugs** of the same **therapeutic category.**

➤ ZERO ORDER REACTION

- When **rate is independent** of the reactant concentration, then it is called **zero order reaction.**
- Suppose

  $A \Rightarrow B$

  Rate = k [A]^x

  As this is zero order reaction, **x = 0**

  Therefore **rate = k**

  Rate = $-\dfrac{dA}{dt}$

- Equate both above equations so

  $$-\dfrac{dA}{dt} = k$$

- Where $\dfrac{dA}{dt}$ = **change in concentration** with respect to time negative (-) sign indicates decrease in **concentration** k is specific rate **constant for zero order.**

✓ Derivation

- The rate of a **zero order reaction** is expressed by $-\dfrac{dA}{dt} = k$
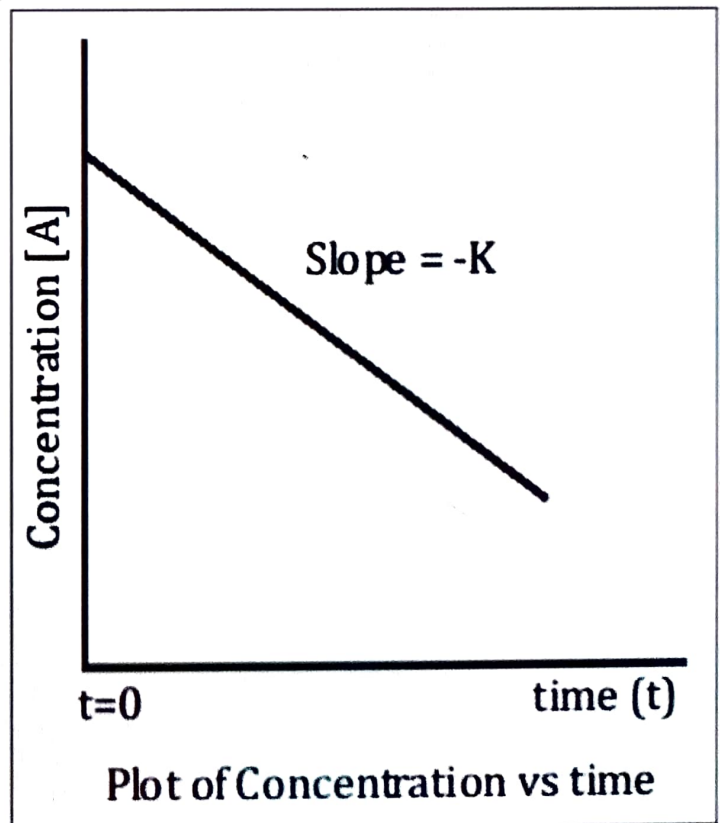- Or **– dA = kdt**
- On integrate the **equation**

$$= -\int_{A_0}^{A_T} dA = k\int_0^t dt$$

$$= -{}_{A_0}^{A_1}[A] = k\,{}_0^t[t]$$

$$= A0 - A1 = k\,(t - 0)$$

$$= A_0 - A_T = kt$$

$$\text{or } k\,\dfrac{A_0 - A_T}{t}$$

Slope = -K

Concentration [A]

t=0

time (t)

Plot of Concentration vs time

❖ 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**.
- Initial concentration = A_0
- Final concentration = $A_{0/2}$
- By putting these values in eq.

$$k\, t_{1/2} = A_0 - A_{0/2}$$

$$Kt_{1/2} = A_{0/2}$$

$$t_{1/2} = A_{0/2k}$$

- According to this equation, **half life** is **directly proportional** to the **initial concentration** of reactant.

❖ SHELF LIFE

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

$$At = 0.9A0$$

- By putting these values in eq.

$$t_{0.9} = \frac{A_0 - 0.9A_0}{k}$$

$$t_{0.9} = \frac{0.1A_0}{k}$$

➢ PSEUDO – ZERO ORDER REACTION

- Many drugs in certain dosage form such as **suspension**, decompose according to **pseudo zero order rate**.
- In **suspension drug** in **solution decompose** more of it from the **suspended particles** goes into the solution so that the concentration in **solution remain constant**.
- Once all **suspended particles** is goes into the solution, the system converts into **first order reaction**.
- In this situation the **rate equation** can be written as

$$-\frac{d[A]}{dt} = k_1[A]$$

- **Where**
  - [A] is concentration of **undecomposed drug** at **time t**
  - kt is **first order rate** constant
  - When **[A]** is maintained constant then rate equation changes to $-\frac{d[A]}{dt}=$ $k_1 \times$ **constant** = **k0**
  - The term constant is the solubility of drug.

➤ FIRST ORDER REACTION

- A **reaction** is to be considered as **first order reaction** when rate of reaction depends on the **first power of concentration** of single reactant.
- let us consider

  A ⇒ products

  Rate = k [A]¹

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

- Equate both above equations, we get

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

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

- Integrating the above equation

$$\Rightarrow k\int_{0}^{t} dt = -\int_{A0}^{A_t} \frac{dA}{A}$$

$$\Rightarrow k\,{}_{0}^{t}[t] = -{}_{A_0}^{A_0}[\log_e A]$$

$$\Rightarrow kt = [\log_e A_t - \log A_0]$$

$$\Rightarrow kt = -\left[\log \frac{A_t}{A_0}\right]$$

As we know

$$\log x^n = n \log x$$

$$\text{So, } kt = \log\left[\frac{A_0}{A_t}\right]$$

$$= kt = 2.303 \log_{10}\left[\frac{A_0}{A_t}\right]$$

Or

$$\boxed{\text{or } k = \frac{2.303}{t} \log\left[\frac{A_0}{A_t}\right]}$$
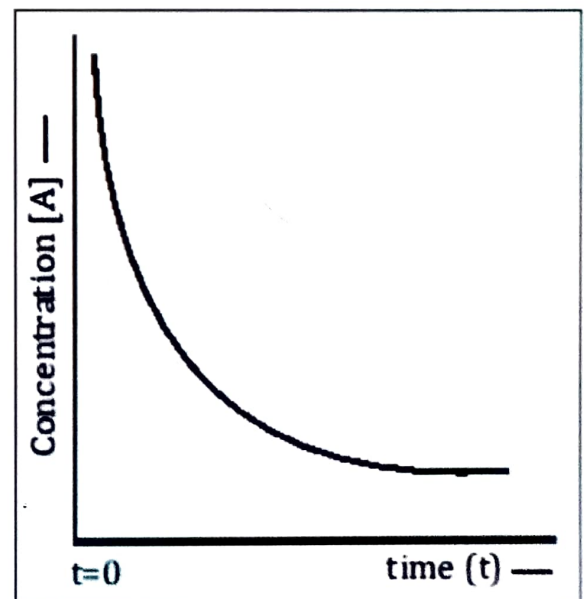
- This **equation** is integrated rate law equation in exponential form, the equation becomes
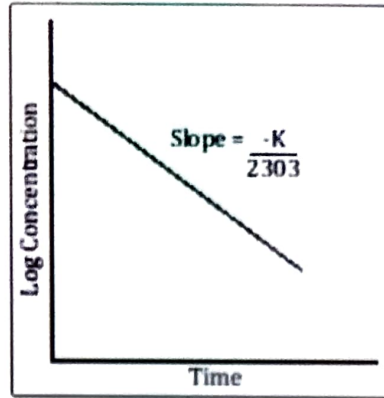
$$kt = \log_e \frac{A_0}{A_t}$$

$$\Rightarrow e^{kt} = \frac{A_0}{A_t}$$

$$\text{or } A_t = A_0 e^{-kt}$$

- For **first order equation**, when we **plot concentration** against time, a curve is obtained

- The **curve shows** that concentration **decrease exponentially** with time.
- If **log concentration** is plotted against time, the **straight line** with slop equal to $-\dfrac{K}{2.303}$ is obtained.

- The equation can be written as

$$k = \frac{2.303}{t} \log \frac{a}{a-x}$$

✓ **Where**
  - **a** is **initial concentration** and equals to A_0
  - X is **decrease in concentration** with time
  - **a - x** is the concentration remained at **time t and equals to A_t**
  - The unit of **k for first order reaction** is time^{-1} i.e. sec^{-1}, minutes^{-1}, hours^{-1}

❖ **HALF LIFE**
  - $A_t = A_{0/2}$
  - As we know rate equation for **first order reaction** is

$$kt = 2.303 \log\left[\frac{A_0}{A_t}\right]$$

- By putting value of **At** into **above equation**, we get

$$kt_{1/2} = 2.303 \log\left[\frac{A_0}{A_t}\right]$$

$$kt_{1/2} = 2.303 \log 2$$

$$t_{1/2} = \frac{0.693}{k}$$

- This equation shows that in first order reaction the half life is independent of the initial concentration

❖ SHELF LIFE

- $A_t = 0.9 A_0$

- By putting these values in we get

$$t_{90} = \frac{2.303}{k} \log \frac{A_0}{0.9 A_0}$$

$$t_{90} = \frac{2.303}{k} \log \frac{10}{9}$$

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

➤ SECOND ORDER REACTION

- **Second order reaction** is defined as a reaction in which the rate depends on the **concentration terms** of **two reactants** each raised to the power one.

- The **following reaction** is considered

    $$A + B \rightarrow products$$

- The rate equation can be **written as**

    $$-\frac{dA}{dt} = -\frac{dB}{dt} = k_2 [A]^1 [B]^1$$

- Where **[A] and [B]** are the **concentration of A and B**, respectively, and K_2 is the **specific rate constant** for second order.

- In other words , the **rate of reaction** is **first order** with respect to B.

- So the overall order of this **reaction is second order.**

✓ Derivation

- As per the definition, the **rate equation** for second order in

$$-\frac{dA}{dt} = -\frac{dB}{dt} = k_2[A][B] \quad \text{.......} 1$$

- let **a and b** be the initial concentrations of **A and B**, respectively, and x be the concentration of each species reacting in time t, substituting these terms in equation gives

$$\frac{dX}{dt} = k_2 (a - x)(b - x) \quad \text{..........} 2$$

- Now consider a case where **a = b** (both A and B have the same concentration).

- Then the above equation changes to equation

$$\frac{dX}{dt} = k_2(a-x)2 \quad \text{.............} 3$$

- Integration equation 3 employing the conditions **x = 0** at **t = 0** and **x = x** at **t = t** gives

$$\left[\frac{1}{-1(a-x)} \right]_0^x \cdot 1 = k_2 [t]_0^t$$

$$\frac{1}{(a-x)} - \frac{1}{(a-0)} = k_2(t-0)$$

$$\frac{a-a+x}{a(a-x)} = k_2 t$$

$$\frac{x}{a(a-x)} = k_2 t$$

Or

$$\boxed{k_2 = \frac{1}{at} \cdot \frac{x}{(a-x)}}$$

- Equation is the integral equation for second order reaction, where **a = b**.
- If **x/a (a-x)** is plotted against time, **t(on x axis)**, a straight line with a positive slope is obtained.
- Intercept will **not be zero**
- This graph permits the **estimation of k_2.**
- Since a is defined as the **initial concentration** of the reactant which is normally a constant , a plot of **x/(a - x)** vs. time also gives a straight line with a **positive slope.**
- The slope is equal to k_2/a.
- The units for k_2 are **concentration time.**
- When the **concentration of reactants** is expressed as **moles/liter**, then k_2 has **units liter/mol**. time (min).
- When **a ≠ b** the integral equation is

$$K_2 = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

- When log [{b(a – x)}/{a(b - x)}] is plotted against t, a straight line with a positive slope can be obtained.
- The slope is equal to $k_2 \frac{(a-b)}{2.303}$
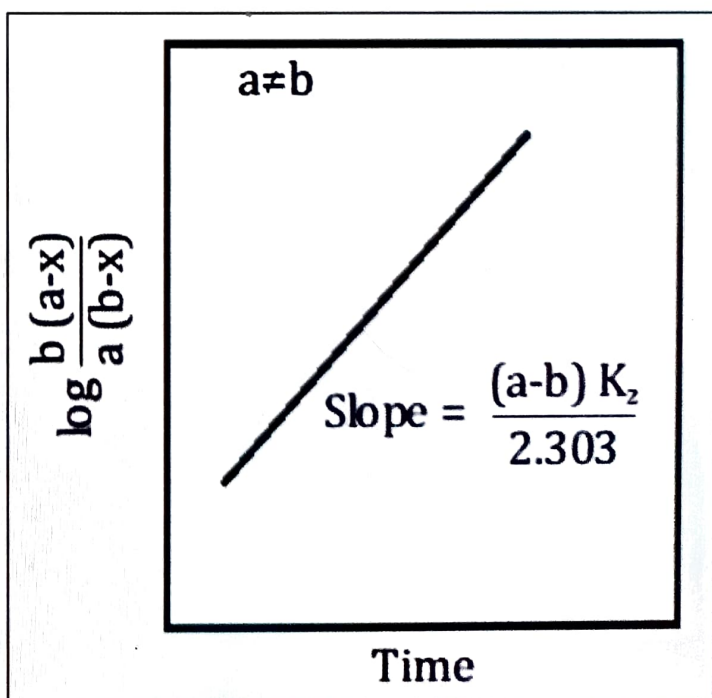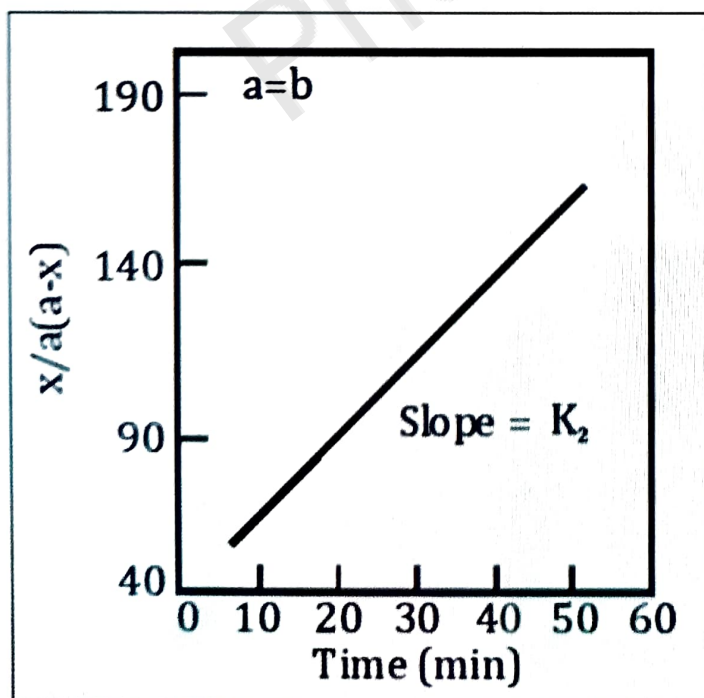
❖ HALF LIFE

- It is the **time required** to reduce the concentration of the **reactant to half** of its **initial concentration.**
- As per the definition

$$(a - x) = a/2 \; ; \; t = t_{1/2} \; ; \; x = a/2$$

$$K_2 = \frac{1}{at} \cdot \frac{x}{(a - x)} = \frac{1}{at_{1/2}} \cdot \frac{a/2}{a/2}$$

$$K_2 = \frac{1}{at_{1/2}}$$

$$K_2 = \frac{1}{ak_2}$$

❖ SHELF LIFE

- It is the **time required** for the **concentration of the reactant** to reduce to 90 % of its **initial concentration.**
- The calculating shelf life, equation can be used , when **a = b**

$$t_{90\%} = \frac{0.11}{ak_2}$$

DETERMINATION OF ORDER

➤ GRAPHIC METHOD

- In this method data is collected by **conducting experiment** and **graph is plotted.**
- The plot of data in form of graph is used to **determine order of reaction.**
- A straight line between **concentration against** time indicates **zero order reaction** while a straight line between log concentration against time shows **first order reaction.**
- If relation between **1/concentration** against time is linear, then reaction is considered to be **second order.**

❖ SUBSTITUTION METHOD

- In this method **data is collected** by **conducting experiment.**
- The data is substituted in the **integral equations** of **zero, first and second order reaction** to get k values.
- The equation which gives a **fairly constant** value of k indicates order of reaction.

ORDER OF REACTION	RATE EQUATION
Zero	$k_0 = \dfrac{A_0 - A_1}{t}$
First	$k = \dfrac{2.303}{t} \log\left[\dfrac{A_0}{A_1}\right]$
Second	$K = \dfrac{1}{at} \cdot \dfrac{x}{(a-x)}$

❖ HALF LIFE METHODS

- By **calculating value** of k by above **methods**, $t_{1/2}$ value can be estimated for each time period in **kinetic study.**

ORDER OF REACTION	$t_{1/2}$
Zero	$t_{1/2} = A_0/2k$
First	$t_{1/2} = 0.693/k$
Second	$t_{1/2} = 1/ak$

- In case of **zero order reaction**, half life is directly proportional to **initial concentration** of reactants while in case of **first order reactions**, half life is independent on **initial concentration** of reactants.

- For **second order,** half life is **inversely proportional** to initial concentration of reactants. But in general

$$t_{1/2} \; \alpha \; \frac{1}{\alpha^{n-1}}$$

- Where n is the **order of reaction**

- When **two reactions** are conducted with different **initial concentration** , **a1 and a2**, respectively , then

$$t_{1/2} \, (1) \; \alpha \; 1/a_1^{n-1}$$

$$t_{1/2} \, (2) \; \alpha \; 1/a_2^{n-1}$$

- Divide both equations we get

$$\frac{t_{1/2} \, (1)}{t_{1/2} \, (2)} = \frac{1/a_1^{n-1}}{1/a_2^{n-1}}$$

- On applying log and by simplified the equation, we get

$$n = \frac{\log t_{1/2}(1)/t_{1/2}(2)}{\log(a_2/a_1)} + 1$$

- By **plotting a graph** between **'a'** vs **'t'** for two different **initial concentrations.**

- The **half life** can be calculated from the **graph** by taking reading **of ½ a₁ and a₂**

- By substituting the value of **half life** and **initial concentration** (a_1 and a_2) in above equation, we can determine the **order of reaction.**

DRUG STABILITY

- **Drug stability** is the ability of a **pharmaceutical product** to retain its chemical, physical, microbiological and biopharmaceutical properties within the specified limits throughout the **shelf life.**

➤ PHYSICAL DEGRADATION OF DRUG

❖ LOSS OF VOLATILE COMPONENTS

- **Volatile components** such as alcohol, ether , iodine volatile oils camphor menthol etc. Escape from the **formulation.**
- E.G. **Nitroglycerine** from drugs evaporates.
- Preventive measures : keeping the product in well **closed container** and storing in a **cool place.**

❖ LOSS OF WATER

- Loss of **water from o/w emulsions** thus its stability changes.
- Water evaporates causing the **crystalline growth.**
- This will result into **increase in potency** and **decrease in weight.**
- This tendency depends on **temperature and humidity** of surrounding environment.

❖ ABSORPTION OF H_2O

- **Hygroscopic drugs absorb** the water from **external atmosphere** causing the **physical degradation.**
- Depends on **temperature and humidity** of surrounding material.
- E.g. **glycerine suppositories** may become opaque

❖ CRYSTAL GROWTH

- In solutions after **super saturation crystal growth** occurs.
- Reason may be the **fall in temperature** and a **consequent decrease** in solubility of solute.
- E.g. injection of **calcium glucconate.**
- In **suspension crystals** settle down and caking occurs and suspension becomes unstable.

❖ POLYMORPHIC CHANGES

- In **polymorphic changes** crystal forms are changed.
- A **stable crystal** form loosens.
- This may **cause alteration** in solubility and **possibly crystalline growth** in aqueous suspensions.

❖ COLOUR CHANGES

- **Colour change** are of two types
  1. **Loss of colour**
  2. **Development of colour**
- **Loss of colour** is due to **pH change** and presence of reducing agent.
- Development of colour is due to **exposure to light.**

➤ CHEMICAL DEGRADATION

❖ TEMPERATURE

- **High temperature** accelerate oxidation, reduction and hydrolysis reaction which lead to drug degradation.
- With **every 10°C** rise in temperature, the rate of reaction also rises two or three times.
- The effect of temperature on **rate of reaction** is explained by **Arrhenius equation.**
- Svante Arrhenius developed a **mathematical relationship** between **k and Ea**

$$K = Ae^{-Ea/RT}$$

✓ **Where**
- K is **specific rate constant**
- A is frequency factor or **Arrhenius factor**
- Ea is **activation energy**
- T is **kelvin temperature**
- R is universal **gas constant**

❖ SOLVENT

- The **nature of the solvent** can also affect the **rate of decomposition** of drugs.
- The relation between **reaction rate constant** and **solubility of reactant** and products is given by

$$\text{Log } k = \log k0 + \frac{v}{2.303RT}(\Delta S_a - \Delta S_b - \Delta S^*)$$

✓ **Where**

- **K** = observed reaction rate constant
- **K_0** = rate constant in infinitely dilute solution
- **V** = molar volume of solute
- **ΔS_a, ΔS_b and ΔS^*** = difference in solubility parameter of solvent and reactant 'a' reactant 'b' and activated complex respectively.

❖ IONIC STRENGTH

- The effect of **ionic strength** on **rate of decomposition** of drug is explained by the following equation :

$$\log k = \log k0 + 1.02\, Z_A\, Z_B\, \sqrt{\mu}$$

✓ **Where**

- **ZA and ZB** are the charges on reactant **A and B** respectively.
- Is the **ionic strength**
- K is rate **constant of degradation**
- K_0 is rate constant at infinite dilution in which $\mu = 0$

❖ DIELECTRIC CONSTANT

- The **dielectric constant** is used to **measure polarity** of the solvent.
- **Dielectric constant** shows significant effect on the **rate of reaction.**
- The effect of the **dielectric constant** on the rate constant of an ionic reaction, extrapolated to infinite dilution where the **ionic strength** effect is zero is determined by the following equation

$$\text{In } k = \text{In } k\,\varepsilon = \infty - \frac{NzA\,zBe^2}{RTr}\frac{1}{\varepsilon}$$

✓ Where

- $k_{\varepsilon = \infty}$ is the **rate constant** in a medium of infinite dielectric constant
- **K** is observed **rate constant** in medium of dielectric constant ε
- **N is Avogadro's number**
- **ZA and ZB** are the charges on the two ions, e is the unit of electric charge , r* is the distance between ions in the activated complex
- ε is **dielectric constant** of the solution.

❖ CATALYSIS

- The **rate of a reaction** is also influenced by the **presence of a catalyst.**
- A catalyst is a substance that either **increase or decrease** the rate of a reaction but itself remain **unchanged chemically.**
- The catalyst only makes the **reaction faster**, it does not affect the yield of product. **A catalyst** that reduces the rate of reaction is called **Negative catalyst.**

✓ Specific acid base catalysis

- The **number of drugs** decomposed on the addition of **acids or bases.**
- When the **rate law** for an **accelerated decomposition** reaction contains a term involving the concentration of the **hydrogen ion** or the concentration of the **hydroxyl ion**, the reaction is called **specific acid base catalysis.**

✓ General acid base catalysis

- Buffers are used to **maintain pH** of the solution.
- Buffer salts (i.e acetates, phosphates, borates etc shows catalytic effects on **drug degradation** rate in solution.
- The reaction is said to be **general acid catalysis** if catalytic component is **acidic while reaction** is said to be general base catalysis if **catalytic component is basic.**

STABILIZATION OF MEDICINAL AGENTS AGAINST COMMON REACTIONS LIKE HYDROLYSIS AND OXIDATION

➢ HYDROLYSIS

- The principles that generally **govern hydrolysis reactions** may be listed as follows

- Drugs with **ester an amide groups** react with one molecule of water and **undergo hydrolysis**. Ester groups break faster than amide groups.

- Drug are either **weak acids or bases**. Therefore, these may be available as **ionic forms** or neutral molecules. **Hydrolysis reaction** between **ionic species proceeds** faster than with neutral molecules

- **Hydrolysis reactions** are catalyzed by H^+ and $(OH)^-$ ions. Hydroxyl ions catalyse hydrolysis by about **100 to 1000 times** more actively than hydrogen ions.

- These **principles** help in **rationalizing** the design of formulations from stability point of view.

- A **few drugs** which decompose by hydrolytic pathway are given below :

Esters	Amides
Aspirin	Chloramphenicol
Procaine	Ampicillin
Atropine	Cephalosporins, barbituric acid

➢ OXIDATION

- **Oxidation involves** the **removal of electrons** from a molecule.

- The reaction between the **compounds** and **molecular oxygen** is called **auto-oxidation.**

- The **general principles** that govern an **oxidation reaction** may be listed as follows

- The presence of **atmospheric oxygen** (also air) promotes the rate of oxidation.

- Since **oxidation frequently** involves **free radicals, chain reactions** occur.
- The **presence of trace metals** also accelerate the **rate of oxidation.**
- **Organic peroxides** promote the **chain initiation** and **propagate** the oxidation reaction.
- Drugs are either **weak acids or bases.** Therefore these may be available as **ionic forms** or neutral molecules. Oxidation reaction between **ionic species proceeds** faster than with **neutral molecules.**
- **Oxidation reactions** are catalyzed by H^+ and OH^- **ions.** Hydroxyl ions **catalyze oxidation** faster than hydrogen ions. Alkaline solutions are known to react with **atmospheric oxygen** and form oxides.
- Drugs which **decompose by oxidation pathways** are given below.

Arachis oil	vitamin A
Ethyl Oleate	riboflavin
Clove oil	vitamin B12
Cinnamon oil	ascorbic acid
Promethazine	morphine
Epinephrine	prednisolone

ACCELERATED STABILITY TESTING IN EXPIRATION DATING OF PHARMACEUTICAL DOSAGE FORMS

## ➤ ACCELERATED STABILITY TESTING

- Stability is defined as the **time during** which the drug product regions the **same properties** existing at the **time of manufacture.**
- **Accelerated stability** test is designed to **test stability** and **set self life as formulations** under normal as recommended **storage condition.**
- The study is carried out **under accelerated** condition at **temperature moisture and light.**
- The product which are to be **stored 25°C and 45%** Rh should be **stored at 40° C and 60% Rh**
- Similarly test is carried out for product to be **stored cool and cold temperature.**

❖ COMMON HIGH STRESS CONDITION ARE

- **Temperature** :- Increase in temperature increase degradation.

- **Humidity** :- High humidity results in hydrolysis

- **Light** :- Artificial light can be used accelerate the effect of sun light.

❖ SELF LIFE

- It is defined as the time required for the concentration of the reactant to reduce 90% of its original/initial concentration.

- The various steps for self life are as follows

- Each portion is stored at different temperature such as 40°C , 50 °C, 60°C, 70°C.

- Samples from each portion are withdrawal at various interval of time.

- The order of reaction is determine by plotting concentration verses time graph.

- The slope of line give the rate constant 'k' for degradation at each temperature.
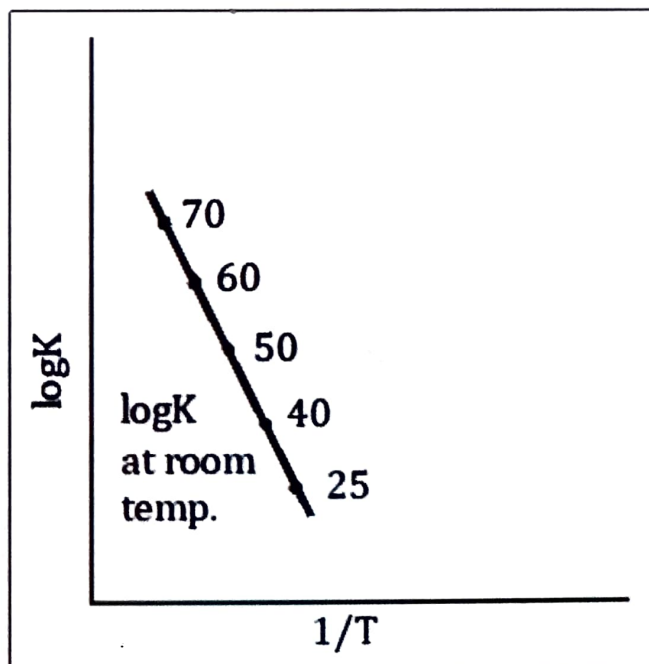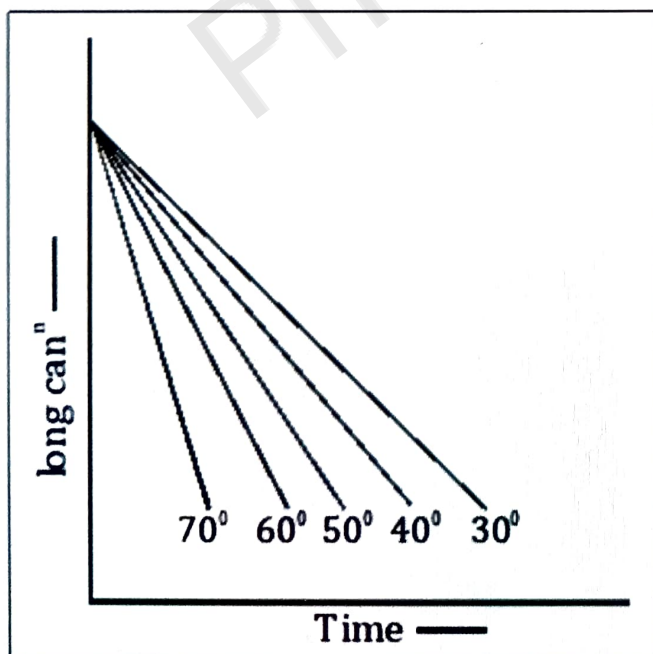
- From **Arrhenious equations**, the **rate constant 'k'** for degradation at room **temperature (25°C)** is determined
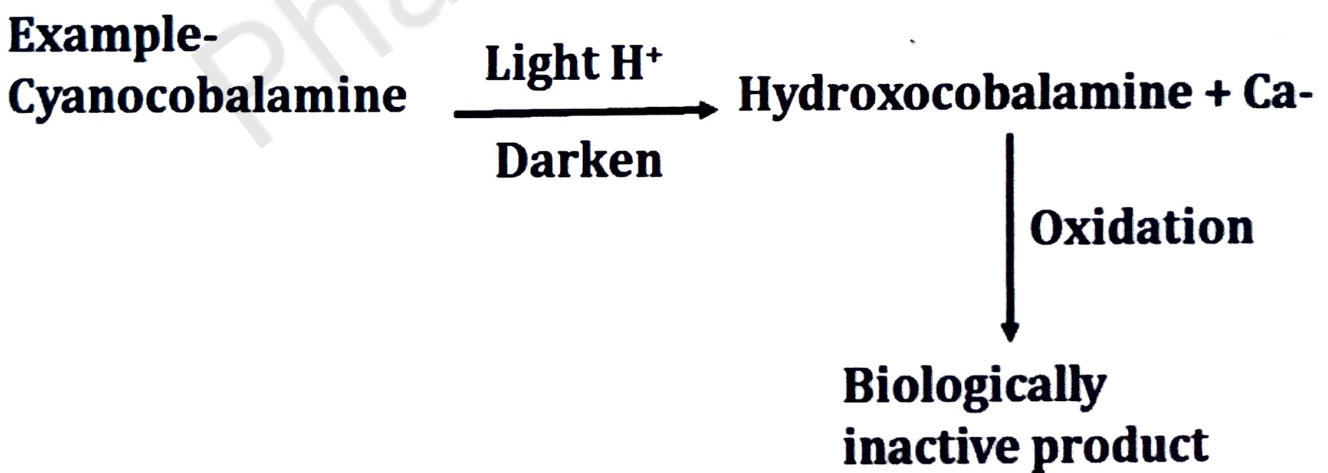
$$K = Ae^{-Ea/RT}$$

- The values of k at **25°C is substituted** in appropriate rate equation and estimate for **self life** of the product is obtained.

$$k = \frac{2.303}{\alpha} \log \left(\frac{c.}{c} \right)^{1/T}$$

$$k = \frac{At - A_0}{\alpha}$$

➤ PHOTOLYTIC DEGRADATION

- Many **pharmaceutical compounds** including ascorbic acid, cyanocobalamine, riboflavin, folic acid, hydrocortisone, prednisolone etc. undergo degradation when it **exposure to light.**
- Exposure to light.
- Exposure to light may **produce oxidation** and **reduction, ring arrangement, malification and polymerization.**

Example-
Cyanocobalamine $\xrightarrow[\text{Darken}]{\text{Light H}^+}$ Hydroxocobalamine + Ca-

$$\downarrow \text{Oxidation}$$

Biologically inactive product

- **Photochemical reaction** may be accompanied by **thermal reaction.**
- The thermal reaction once induced by light may continue after the **light source** has been withdrawn.

❖ PREVENTION

- It can be reduced by **using amber coloured glass container.**
- By **using black plastic** it can also be reduced.
- By **storing product** in dark place or by **packing in cartoons** also act as varrier to light.
- **Coating of tablet** with polymer film containing **ultraviolet absorbes** also protect from light.
- **Ordinary containers** can be wrapped with black paper also provide protection against light.