Physical Pharmacy II
2nd stage
College of Pharmacy

lec: 5
Chemical kinetics and stability (part I)

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Ph.D in Pharmaceutics

2025 -2026

Semester: 2nd

CHEMICAL KINETICS AND STABILITY

- The stability of drug product with time is important in determination of **shelf life** and **expired date**.
- The stability affected by **factors**, such as temperature, humidity, and light.
  - For example, **thiamine hydrochloride** is most stable at a pH of 2 to 3 and is unstable above pH 6, so in preparation, the pharmacist should select the buffered vehicle that prevents the degradation.
- Applications of chemical kinetics in pharmacy result in the production of **more-stable drug preparations.**

FUNDAMENTALS AND CONCENTRATION EFFECTS

Rates, Order, and Molecularity of Reactions

- **Molecularity** is the number of particles (molecules, atoms, or ions) that collide and react **in a single elementary step**.
- It only applies to **elementary reactions** (one-step reactions).
- **Types of Molecularity**
  1. **Unimolecular reaction:** Only **one molecule** reacts.
     - Example: $Br_2 \rightarrow 2Br$ Molecularity = 1 Here, one Br_2 molecule breaks apart
  2. **Bimolecular reaction:** Two particles collide and react.
     - Example: $H_2 + I_2 \rightarrow 2HI$ Molecularity = 2 Two molecules collide to form products.
  3. **Termolecular reaction:** Three particles collide at the same time (rare in reality).
     - Example: $2NO + O_2 \rightarrow 2NO_2$ Molecularity = 3 Three molecules interact together.
- **Molecularity**:
  - Describes **only one elementary step**
  - Is always a **whole number (1, 2, or 3)** (Cannot be zero or fractional)
- **Multi-Step Reactions (Reaction Mechanism)**
  - Many reactions occur in **several steps**, not one.
    - Example mechanism:

      Step 1 (Fast): $2NO \rightleftharpoons N_2O_2$

      Step 2 (Slow): $N_2O_2 + O_2 \rightarrow 2NO_2$
    - **The Slow Step Determines the Rate**
    - The **slowest step** is called the: **Rate-determining step** -The rate of reaction depends mainly on the slow step.

Rate

- The **reaction rate** tells us **how fast a chemical reaction occurs**.



- Mathematically:

$$\text{Rate} = \frac{dc}{dt}$$

dc = change in concentration
dt = small change in time

Rate Law Expression

- For many reactions:

$$\text{Rate} = k[\text{Reactant}]^a$$

Where:

- **k** = rate constant
- **[Reactant]** = concentration
- **a** = order of reaction

- The exponent **a** shows how strongly concentration affects the rate.

Rate

Specific Rate Constant

- **The constant, k**, appearing in the rate law associated with a single-step (elementary) reaction is called the **specific rate constant** for that reaction.
  - Any **change** in the conditions of the reaction, for example, in temperature or solvent, or a slight change in one of the reacting species, will lead to a rate law having a different value for the specific rate constant
- **The half-life** is the time required for one-half of the material to disappear; the time at which C has decreased to 1/2 C.
- **The shelf-life** is the time required for 10% of the material to disappear; it is the time at which C has decreased to 90% of its original concentration (i.e., 0.9C).

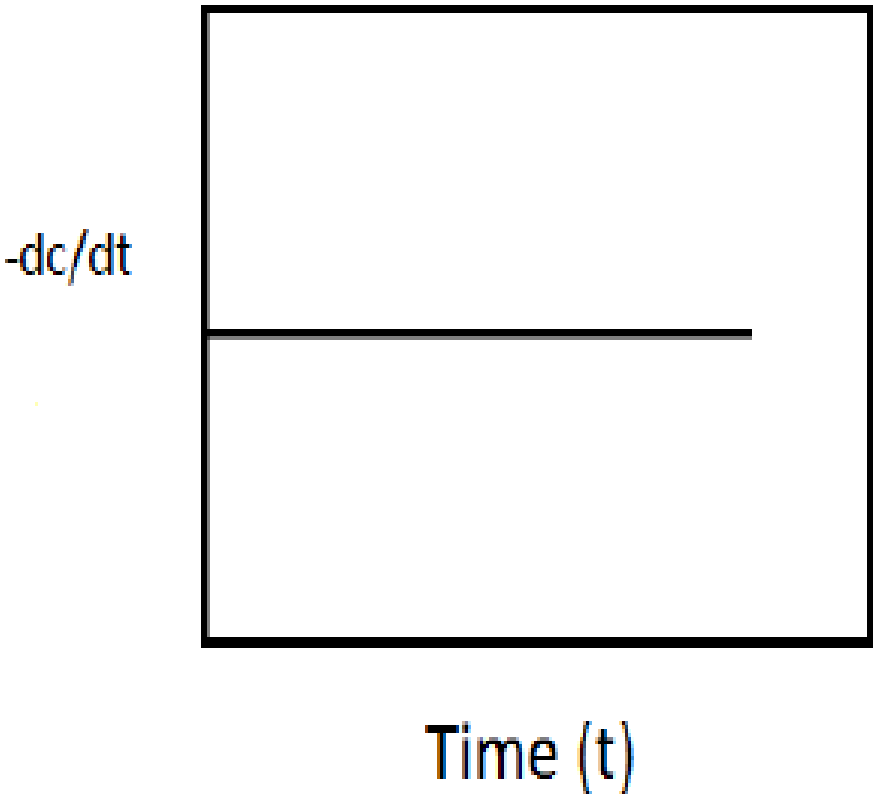
Kinetic study

Zero-Order Reactions

- *Garrett* found that the loss in color of a multisulfa product followed a zero order rate.
- The rate expression for the change of concentration, C, with time is therefore

$$-\frac{dC}{dt} = k_0$$

- It means that the **rate of reaction** not depend on **concentration of reactant**, it is **constant with time**.



where the **minus** sign signifies that the concentration of a substance is decreasing

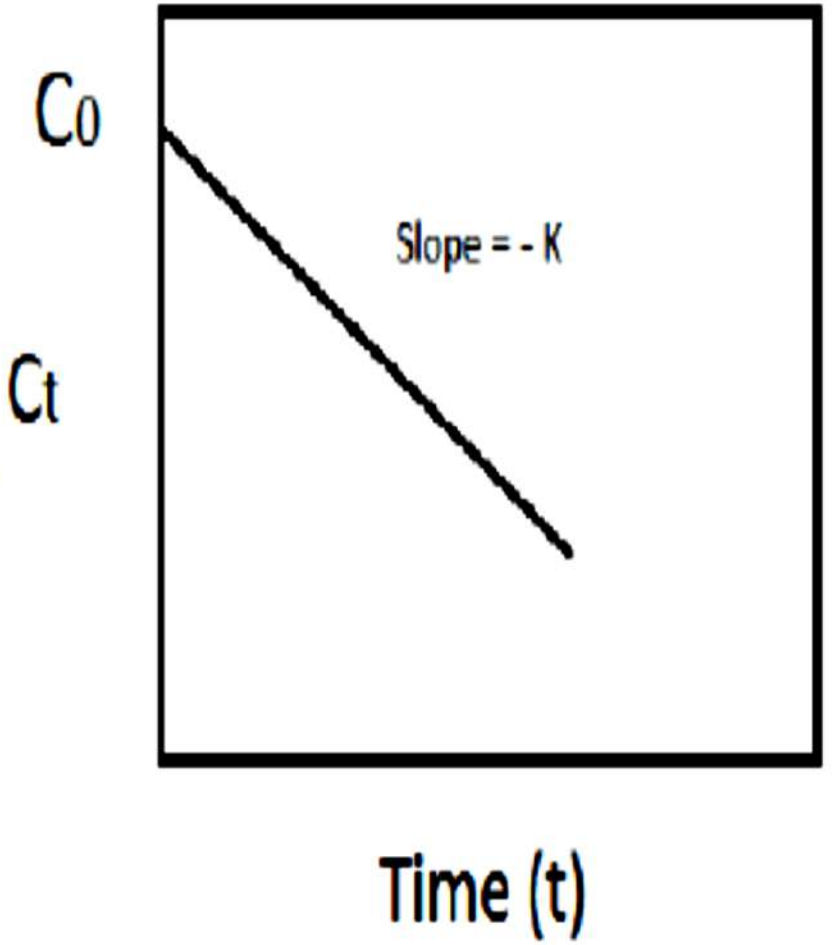
Zero-Order Reactions

- The rate equation can be integrated between the initial concentration, C_0, at t = 0, and C_t, after time (t):

$$C_t = C_o - k_o t$$

$$t = \frac{Co - Ct}{ko}$$

$$ko = \frac{C0 - Ct}{t}$$



Zero-Order Reactions

- Because the **half-life** is the time required for one-half of the material to disappear, in the present case, after one half, the concentration C becomes 1/2Co.

$$t_{1/2} = \frac{Co - 1/2Co}{ko} \longrightarrow t_{1/2} = \frac{½Co}{ko}$$

For shelf life

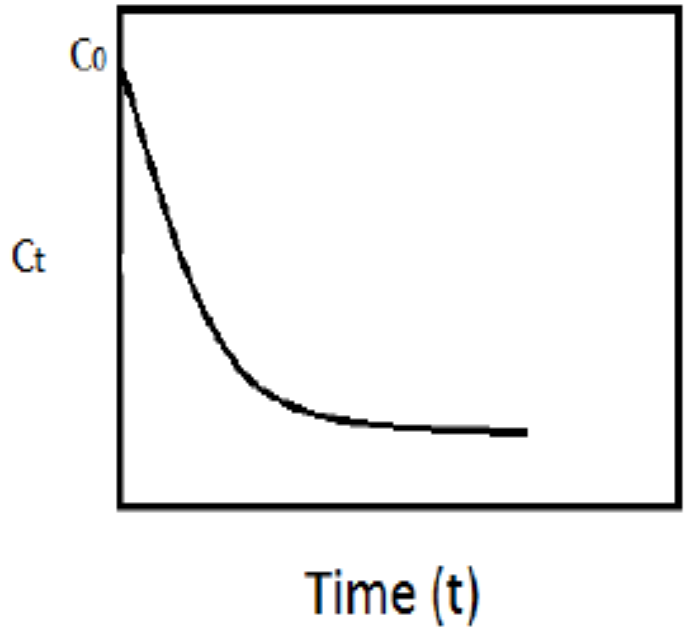
$$t_{90\%} = \frac{Co - 0.9Co}{ko} = \frac{0.1C0}{K0}$$

- The unit of zero order rate constant is:

$$k_0 = -\frac{dC}{dt} = \frac{mole/liter}{second} = \frac{mole}{liter\ second} = \text{mole liter}^{-1}\text{second}^{-1}$$

First-Order Reactions

- **A first-order** reaction is one where the **rate** of reaction is **directly proportional** to the **concentration of one of the reactants**
- *Harried* showed that the decomposition rate of hydrogen peroxide catalysed by 0.02 M KI was **proportional to the concentration** of hydrogen peroxide **remaining in the reaction mixture at any time**.
- The data for the reaction
  - $2H_2O_2 = 2H_2O + O_2$
- Although two molecules of hydrogen peroxide appear in the equation, the reaction was found to be **first order**.



The rate equation is written

$$-\frac{dC}{dt} = kC$$

- where **c** is the concentration of hydrogen peroxide remaining undecomposed at time t and **k** is the first-order rate constant.

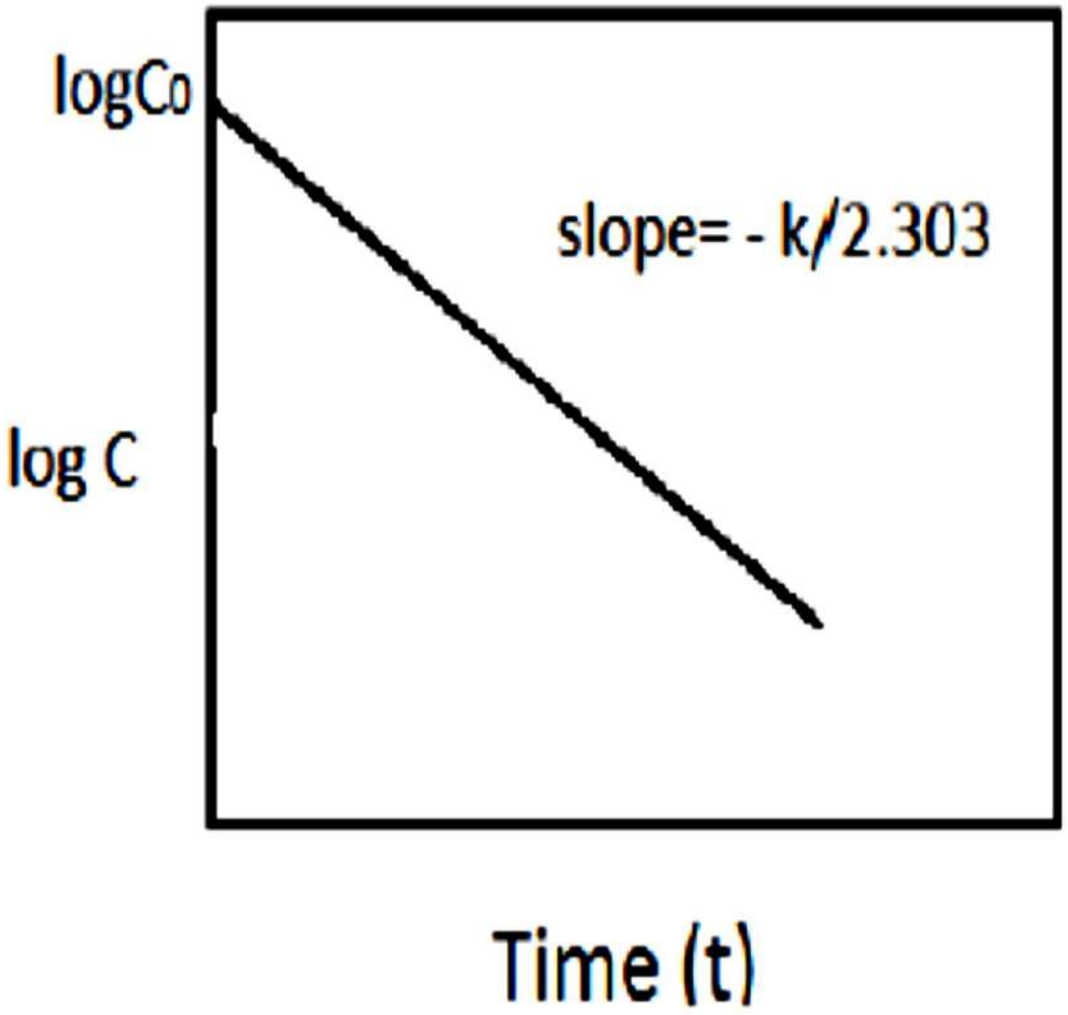
First-Order Reactions

Integrating above equation, we have

$$\ln C = \ln C_0 - Kt$$

(Common logarithm)

$$\log C = \log C_0 - \frac{k}{2.303}t$$



First-Order Reactions

$$\log C = \log C_0 - \frac{k}{2.303} t$$

For calculation of half life of reaction follows first order:

$$\log \frac{C_0}{C_t} = \frac{Kt}{2.303}$$

At half life; t= t1/2, Ct= ½ C_0

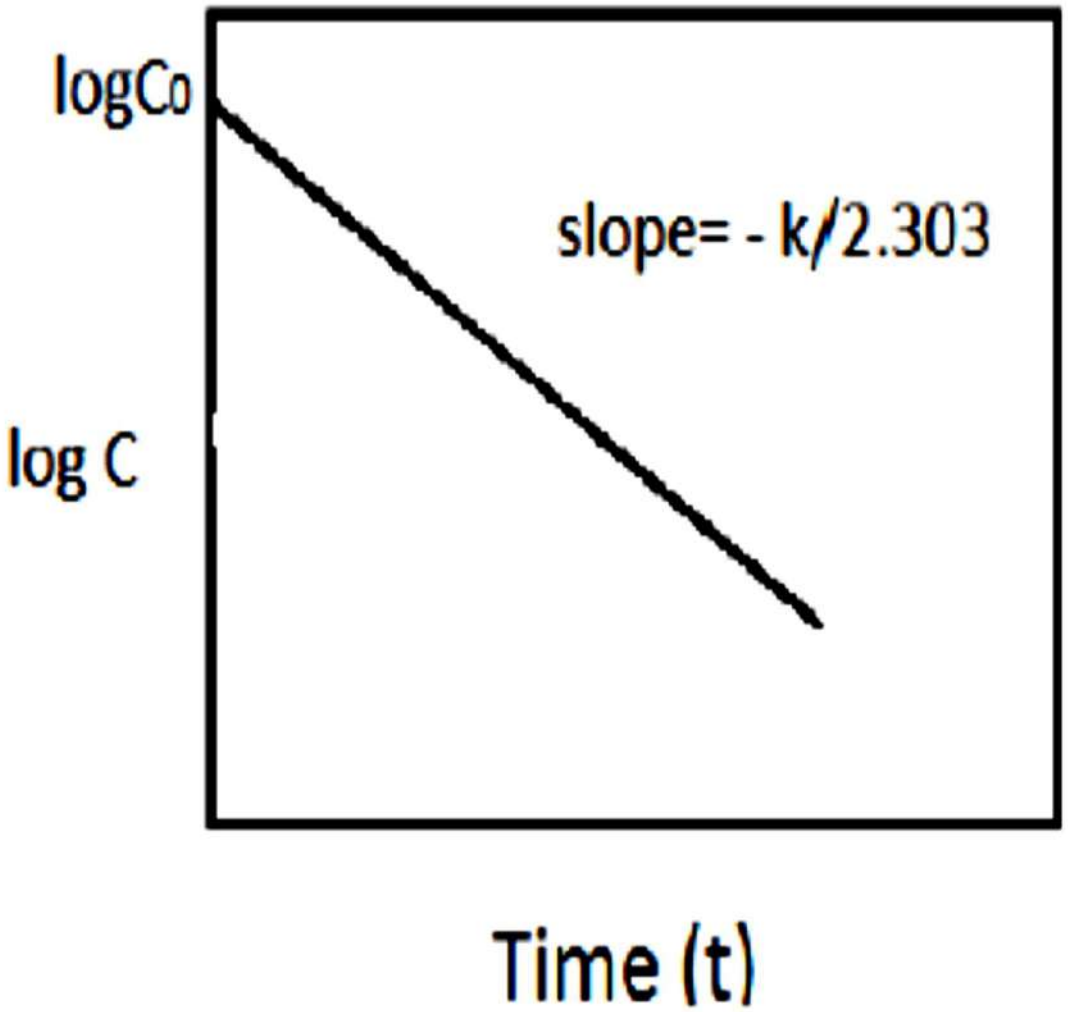
$$\log \frac{C0}{½\ C0} = \frac{K\ t1/2}{2.303}$$

$$\log 2 = \frac{K\ t\ 1/2}{2.303}$$

$$0.3 = \frac{K\ t\ 1/2}{2.303}$$

$$t_{1/2} = \frac{0.3\ x\ 2.303}{K}$$

$$t\ ½ = \frac{0.693}{K}$$



First-Order Reactions

For shelf life t_{90} :

For shelf life t_{90}:

$$\log \frac{C0}{0.9\,C0} = \frac{K\,t90\%}{2.303}$$

$$\log 1.11 = \frac{K\ t\ 90\%}{2.303}$$

$$0.045 = \frac{K\ t\ 90\%}{2.303}$$

$$t_{90\%} = \frac{0.045\ x\ 2.303}{K}$$

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

- The unit of first order rate constant is:

$$-\frac{dC}{dt} = K\,C$$ ....RE- Arrangement

$$k = -\frac{dC}{dt}\frac{1}{C} = \frac{mole/liter}{second.mole/liter} = \frac{1}{second} = second^{-1}$$

EXAMPLE .

Decomposition of Hydrogen Peroxide

- The catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after **65 min**, expressed as the volume in milliliters of gas evolved, was **9.60** from an initial concentration of **57.90**.

(a) Calculate k

$$k = \frac{2.303}{t} \log \frac{C0}{C}$$

$$k = \frac{2.303}{t} \log \frac{57.90}{9.60} = 0.0277 \text{ min}^{-1}$$

OR

$$\log Ct = \log C0 - \frac{K\,t}{2.303}$$

$$\log 9.6 = \log 57.9 - \frac{K\ 65}{2.303}$$

$$0.982 = 1.763 - \frac{K\ 65}{2.303}$$

$$K = 0.0277 \text{ min}^{-1}$$

EXAMPLE .

Decomposition of Hydrogen Peroxide

- The catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 min, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.

(b) How much hydrogen peroxide remained undecomposed after 25 min?

$$0.0277 = \frac{2.303}{25} \log \frac{57.90}{c}$$

$$c = 29.01$$

OR

$$\log Ct = \log C0 - \frac{Kt}{2.303}$$

$$\log Ct = \log 57.9 - \frac{0.0277 \; x \; 25}{2.303}$$

$$= 1.462$$

$$Ct = 28.97$$

EXAMPLE

First-Order Half-Life

- A solution of a drug contained 500 units/mL when prepared. It was analysed after 40 days and was found to contain 300 units/mL. Assuming the decomposition is first order, at what time will the drug have decomposed to **one-half** of its original concentration?

$$\left(k = \frac{2.303}{t} \log \frac{C_0}{C}\right)$$

$$\log Ct = \log Co - \frac{K\,t}{2.303}$$

OR

$$k = \frac{2.303}{40} \log \frac{500}{300} = 0.0128 \text{ day}^{-1}$$

$$\log 300 = \log 500 - \frac{K \times 40}{2.303}$$

$$2.477 = 2.699 - \frac{K\,40}{2.303}$$

$$K = 0.01278 \text{ day}^{-1}$$

$$t = \frac{2.303}{0.0128} \log \frac{500}{250} = 54.3 \text{ days}$$

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

$$= \frac{0.693}{0.0128} = 54.22 \text{ day}$$

Suspensions, Apparent Zero-Order Kinetics

- Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility.
- As the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant.
- The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

$$-d[C]/dt = k_f [C]$$

where **C** = concentration of drug in solution = solubility

$\mathbf{K_f}$ = first-order rate constant of solution

- When the concentration [C] is rendered constant, as in the case of a suspension, we can write

$K_f [C] = K_0$ where **K_0= zero order rate constant of suspension**

Thus, $K_0 = K_f$ x Solubility

$$-d[C]/dt = K_0$$ (Apparent zero – order equation)

Example

Shelf Life of an Aspirin Suspension-

- A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25°C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is 4.5×10^{-6} sec^{-1}. **Calculate the zero-order rate constant**. **Determine the shelf life, t_{90}, for the liquid prescription**, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25°C.

Answer: $k_0 = k \times [\text{Aspirin in solution}]$, from equation $(k[A] = k_0)$. Thus,

$$k_0 = (4.5 \times 10^{-6}\ \text{sec}^{-1}) \times (0.33\ \text{g}/100\ \text{mL})$$

$$k_0 = 1.5 \times 10^{-6}\ \text{g}/100\ \text{mL sec}^{-1}$$

$$t_{90} = 0.10[A]_0/k_o =$$

$$\frac{(0.10 \times 6.5\ \text{g}/100\ \text{mL})}{(1.5 \times 10^{-6}\ \text{g}/100\ \text{mL sec}^{-1})}$$

$$= 4.3 \times 10^5\ \text{sec} = 5.0\ \text{days}$$

Example

Increased Shelf Life of Aspirin

- Aspirin is most stable at pH 2.5. At this pH the apparent **first-order rate** constant is 5×10^{-7} sec^{-1} at 25°C. The **shelf life of aspirin** in solution under these conditions can be calculated as follows:

  $t_{90} = 0.105/(5 \times 10^{-7}) = 2.1 \times 10^{5}$ sec = 2 days

- As one can see, aspirin is **very unstable** in aqueous solution.
- Would making a **suspension increase** the shelf life of aspirin? The solubility of aspirin is 0.33g/100mL.
- At pH 2.5, the apparent zero-order rate constant for an aspirin suspension **is $k_o = K_f$ * solubility**

  $= 5 \times 10^{-7}$ sec^{-1} x 0.33 g/100 mL

  $= 1.65 \times 10^{-7}$ g/100mL • sec

- If one dose of aspirin at 650 mg per teaspoonful is administered, then one has **650 mg/5 mL** = 13 g/100 mL. For this aspirin suspension, **$t_{90} = 0.1 A_o / K_o$**

  $= [(0.1) (13)]/ [1.65 \times 10^{-7}]$

  $= 7.9 \times 10^{6}$ sec = **91 days**

Example

Increased Shelf Life of Aspirin

- The increase in the shelf-life of suspensions as compared to solutions is a result of the interplay between the **solubility and the stability** of the drug.
- In the case of aspirin, the **solid form of the drug is stable**, whereas when aspirin is in solution, it is unstable.
- As aspirin in solution decomposes, the solution concentration is maintained as additional aspirin dissolves up to the limit of its aqueous solubility.

Second-Order Reactions

- The rates of bimolecular reactions, which occur when two molecules come together, are frequently described by the **second-order equation**.

$$A + B \longrightarrow \text{Products}$$

- When the speed of the reaction depends on the concentrations of A and B with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B, and **both are proportional to the product of the concentrations of the reactants**:

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

Second-Order Reactions

- If **a** and **b** are the initial concentrations of **A** and **B** respectively, and **x** is the concentration of each species reacting in time t, the rate law can be integrated and written as

$$\frac{dx}{dt} = K(a - x)(b - x)$$

where :

dx/dt is the rate of reaction

a - x and b - x are the concentrations of A and B, respectively, **remaining** at time t

Second-Order Reactions

- Integrating and write the second order equation according to 3 possibilities:

1. When, in the simplest case, both A and B are present in the same concentration so that **a = b**,

$$\frac{dx}{dt} = k(a-x)^2$$

$$\int_0^x \frac{dx}{(a-x)^2} = k\int_0^t dt$$

$$\left(\frac{1}{a-x}\right) - \left(\frac{1}{a-0}\right) = kt$$

$$\frac{x}{a(a-x)} = kt$$

$$k = \frac{1}{at}\left(\frac{x}{a-x}\right)$$

- The rate constant, k, in a second-order reaction therefore has the dimensions liter/ (mole sec) or liter $mole^{-1}$ sec^{-1}.
- The half-life of a second-order reaction is $t_2^1 = \frac{1}{ak}$

Second-Order Reactions

2. When, in the general case, A and B are not present in equal concentrations but the difference in concentration is not big, integration of equation :

$$\frac{dx}{dt} = K(a-x)(b-x)$$

yields:

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

Second-Order Reactions

3. When **A and B are not present in equal concentrations** and the difference in concentration is very big **(*Pseudo-first-order reaction):***

- Suppose that in this reaction, **A** was in *great excess* and **B** was in a *relatively low concentration.*
- As the reaction proceeded, B would change appreciably from its original concentration, whereas the concentrations of A would remain essentially unchanged because they are present in great excess. In this case the contribution of A to the rate expression is considered constant, and the reaction rate can be written as:

A + B = Products

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

K is constant and [A] is constant

$$-\frac{d[B]}{dt} = K'\,[B]$$

Where **K'= K [A]**

K'= Pseudo-first-order constant

Example .5

Saponification of Ethyl Acetate

- Walker investigated the saponification of ethyl acetate at 25°C:

  $CH_3COOC_2H_5 + NaOH \rightarrow CH_3COONa + C_2H_5OH$

- The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 *M*. The change in concentration, *x*, of alkali during 20 min was 0.000566 mole/liter, therefore, (a - x) = 0.01000 - 0.00566 = 0.00434.
- Compute (a) the rate constant and (b) the half-life of the reaction.

(a) Using equation

$$\frac{x}{a(a-x)} = Kt$$

$$a = 0.01$$

$$x = 0.000566$$

$$a - x = 0.009434$$

$$k = \frac{1}{at}\left(\frac{x}{a-x}\right)$$

$$K = \frac{1}{0.01 \times 20}\left(\frac{0.000566}{0.009434}\right) = 0.299 \text{ liter mole}^{-1} \text{ min}^{-1}$$

(b) The half-life of a second-order reaction is:

$$t_{1/2} = \frac{1}{ak}$$

- It can be computed for the reaction only when the initial concentrations of the reactants are identical. In the present example,

$$t_{1/2} = \frac{1}{0.01 \times 0.299} = 334.44 \text{ min}$$

Example : In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$$(CH_3CO)_2O + 2C_2H_5OH = 2CH_3CO_2C_2H_5 + H_2O$$

The rate of reaction is

$$\text{Rate} = -\frac{d[(CH3CO)2O]}{dt}$$

$$= k\,[(CH_3CO)_2O]\,[C_2H_5OH]^2$$

- **What is the order** of the reaction with respect to acetic anhydride? With respect to ethyl alcohol? What is the overall order of the reaction?
- If the **alcohol**, which serves here as the solvent for acetic anhydride, is in large excess such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

Answer:

- The reaction appears to be first order with respect to acetic anhydride, second order with respect to ethyl alcohol, and overall third order.
- However, because **alcohol** is the solvent, its concentration remains essentially constant, and the rate expression can be written $\mathbf{-d\,[(CH_3C0)_2O]/dt = k'[(CH_3CO)_2O]}$
- Kinetically the reaction is therefore **a pseudo-first-order reaction**.

Order	Integrated equation	Units of K	Half- life	Shelf -life	Straight line obtained by drawing
Zero	$Ct = Co - kt$	mole liter $^{-1}$ sec^{-1}	$t_{1/2} = \frac{\frac{1}{2}Co}{K}$	$t_{90\%} = \frac{0.1Co}{K}$	Ct Vs time
First	$\log Ct = \log Co - \frac{Kt}{2.303}$	time^{-1}	$t\ ½ = \frac{0.693}{K}$	$t_{90\%} = \frac{0.105}{K}$	log Ct vs. time
Second	$\frac{1}{a-x} = \frac{1}{a} + Kt$	liter mole^{-1} sec^{-1}	$t_{1/2} = \frac{1}{aK}$		$\frac{1}{Conc.}$.vs time

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Determination of Order

- The order of a reaction can be determined by several methods.

1. Substitution Method:

- The data from kinetic study can be substituted in the equations for each order.
- If the **calculated k values remain constant at different times**, the reaction follows that order.
- **Example idea**
  - If we assume a reaction is **first order**, we use the first-order equation.
    - If the calculated **k values are the same for all time points**, our assumption is correct.
    - If k changes, the reaction is not of that order.
    - So we test different orders until k becomes constant.

2. Graphic Method:

- We plot experimental data in different ways and see which graph becomes a straight line.
  - **a straight line results when concentration is plotted against t, the reaction is zero order.**
  - The reaction is first order if log (concentration) versus t yields a straight line.
  - second-order if 1/(concentration) versus t gives a straight line.

3. Half-Life Method:

- Different reaction orders show different relationships between half-life and initial concentration.
  - In a **zero-order reaction**, the half-life is *proportional to the initial concentration*
  - The half-life of a **first order rea**ction is *independent of initial concentration*
  - $t_{1/2}$ for a **second-order** reaction, in which a = b, is *proportional to 1 /a*.

Factors effects on stability

- A number of factors other than concentration may affect the reaction velocity.
    - Among these are temperature, solvents, catalysts, and light.

1. Temperature effect

Collision Theory

- Reaction rates are expected to be proportional to the number of collisions per unit time.
- Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.

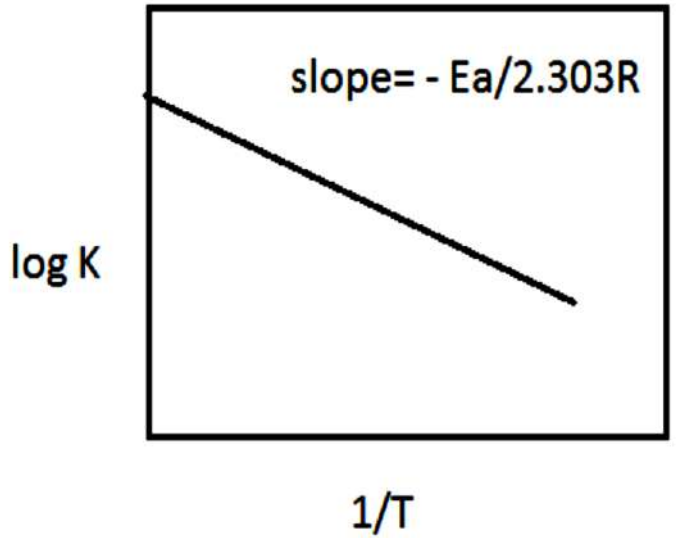
Factors effects on stability

1. Temperature effect

- The effect of temperature on reaction rate is given by the equation, first suggested by Arrhenius,

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

$$\log K = \log A - \frac{Ea}{2.303R}\frac{1}{T}$$



where

- **k** is the specific reaction rate
- **A** is a constant known as the Arrhenius factor or the frequency factor
- ***Ea*** is the energy of activation.
- **R** is the gas constant, 1.987 calories/deg mole
- **T** is the absolute temperature.

- In case at 2 temperatures t_1 and t_2, the equation becomes:

$$\log \frac{K2}{K1} = \frac{Ea}{2.303R}\left(\frac{T2-T1}{T2T1}\right)$$

2. Medium Effects: Solvent, Ionic Strength, Dielectric Constant

A. Effect of the Solvent

- In summary, it can be said that the polarity of solvents affects the rate of reactions depending on the polarity of reactant.
  - ❑ Depending on the specific reaction and the polarity of the reactants, the choice of **solvent** can either accelerate or decelerate the reaction rate.
  - ❑ Selecting a solvent with an appropriate polarity that complements the polarity of the reactants can **optimize reaction conditions and improve reaction efficiency**

B. Effect of the ionic strength

- **Ionic strength** refers to the **total concentration of ions present in the solution**.
  - **Ionic reactions** → affected by ionic strength
  - **Neutral molecule reactions** → mostly **not affected**
- When many ions are present in solution, they **interact electrostatically** with the reacting ions.
  - These interactions can **either help or hinder the reaction** depending on the charges involved.
  - So the **rate constant of ionic reactions can change** when ionic strength changes.

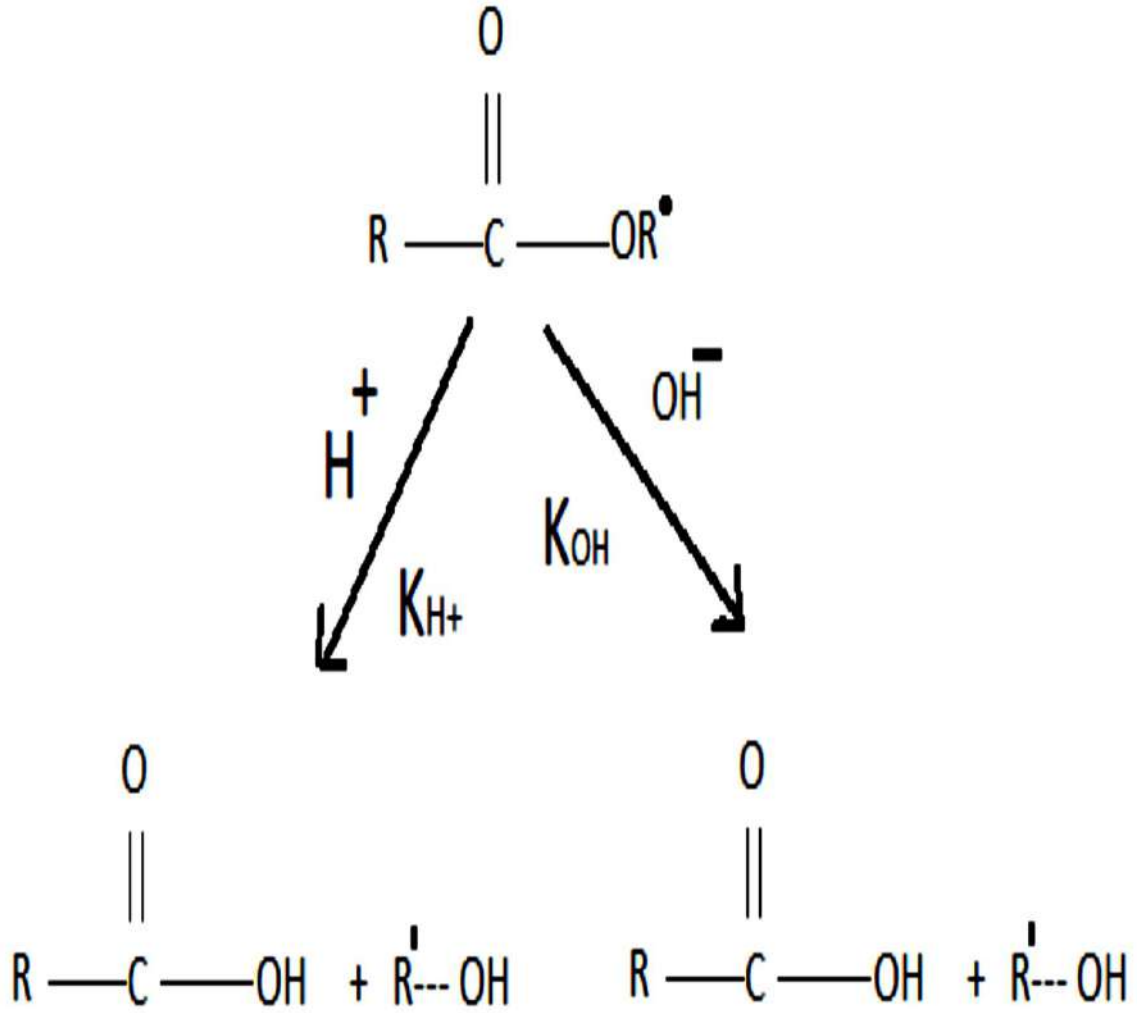
2. Medium Effects: Solvent, Ionic Strength, Dielectric Constant

C. Effect of the Dielectric Constant

- The **dielectric constant (ε)** is a property of a solvent that measures **its ability to reduce electrostatic forces between charged particles**.
- The dielectric constant affects the rate constant of an ionic reaction.
- For a reaction between **ions of opposite sign**, an **increase** in dielectric constant of the solvent results in a **decrease** in the rate constant.
- For **ions of like charge**, on the other hand, an **increase** in dielectric constant results in an **increase** in the rate of the reaction.
    - For reactions between **ions of opposite sign**, increasing the dielectric constant **decreases** the rate constant by reducing the electrostatic attraction between the ions.
    - Conversely, for reactions between **ions of like charge**, increasing the dielectric constant **increases** the rate constant by improving the solvation of the ions and reducing their mutual repulsion

3. Catalysis effect: *Specific Acid-Base Catalysis Effects*

- **A catalyst** is defined as a *substance that influences the speed of a reaction without itself being altered chemically.*
- Solutions of several drugs undergo accelerated decomposition on the addition of acids or bases.
- If the drug solution is buffered, the decomposition may not be accompanied by an appreciable change in the concentration of acid or base, so that the reaction can be considered to be catalyzed by hydrogen or hydroxyl ions.
- The best example of specific acid-base catalysis , is the hydrolysis of esters.

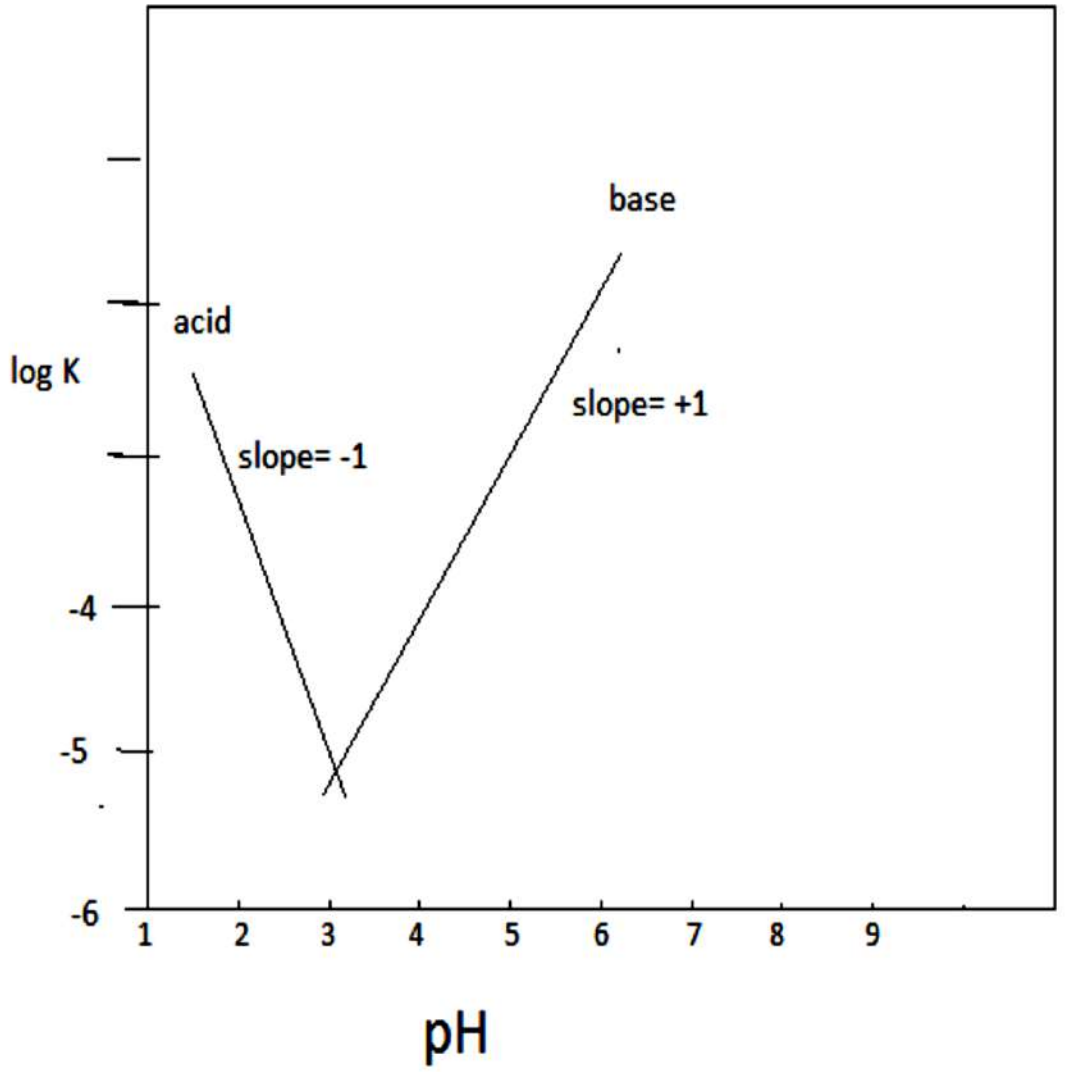


- The general formula for **hydrolysis of ester** which affected by both H+ and OH^- is

$$-\frac{dc}{dt} = K_{observed}[ester]$$

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

$K_{observed}$ = total rate constant of the system
K_{H^+} = rate constant for acid catalysis reaction
K_{OH^-} = rate constant for base catalysis reaction
[H+] = hydrogen ion concentration
[OH^-] = hydroxide ion concentration
Note: K_{H^+} **and** K_{OH^-} are second order rate constants.
The pH^- Rate profile for the specific acid-base-catalyzed hydrolysis of ester as shown in this figure:

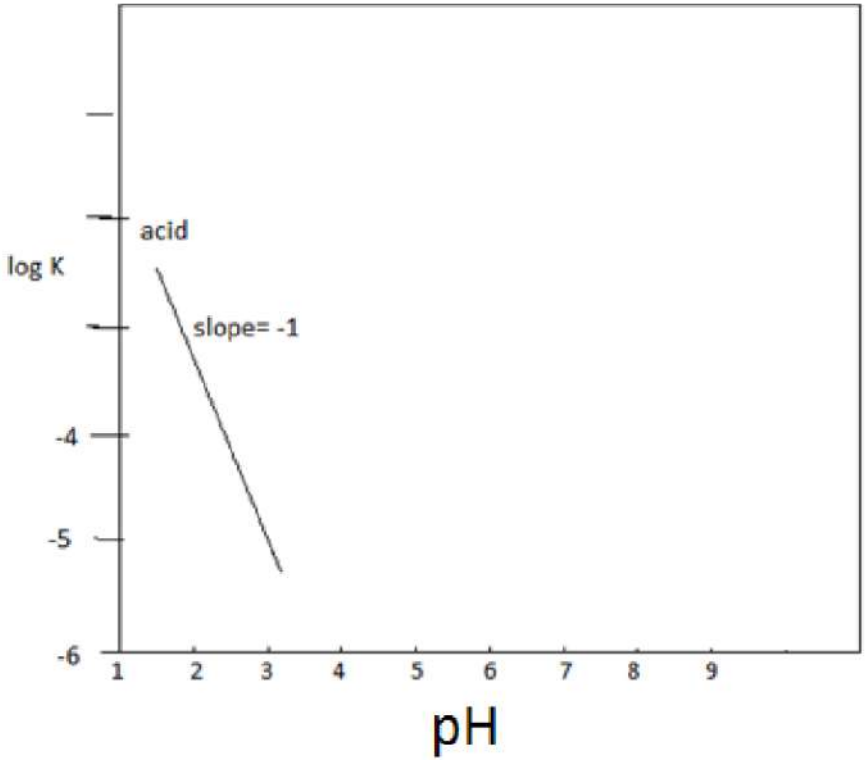


Explanation of pH- Rate profile

1. at low PH

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

- Since [OH-] concentration value is very low, thus the part (K_{OH^-} **[OH$^-$])** is **neglected** from equation at low pH.



So, $K_{observed} = K_{H}\ [H^+]$

$\log K_{observed} = \log K_{H+} + \log [H^+]$

$\log K_{observed} = \log K_{H^+} - (-\log [H^+])$

$\log K_{observed} = \log K_{H^+} - pH$

$\log K_{observed} = \log K_{H^+}$ **-1**x pH

2. at high PH

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

- **Since $[H^+]$ concentration value is very low, thus the part**

$(K_{H^+}[H^+])$ is neglected from equation at high pH.

So, $K_{observed} = K_{OH^-}[OH^-]$

$Kw = [H^+][OH^-] \longrightarrow [OH^-] = Kw/[H^+]$

$K_{observed} = K_{OH^-}[OH^-]$

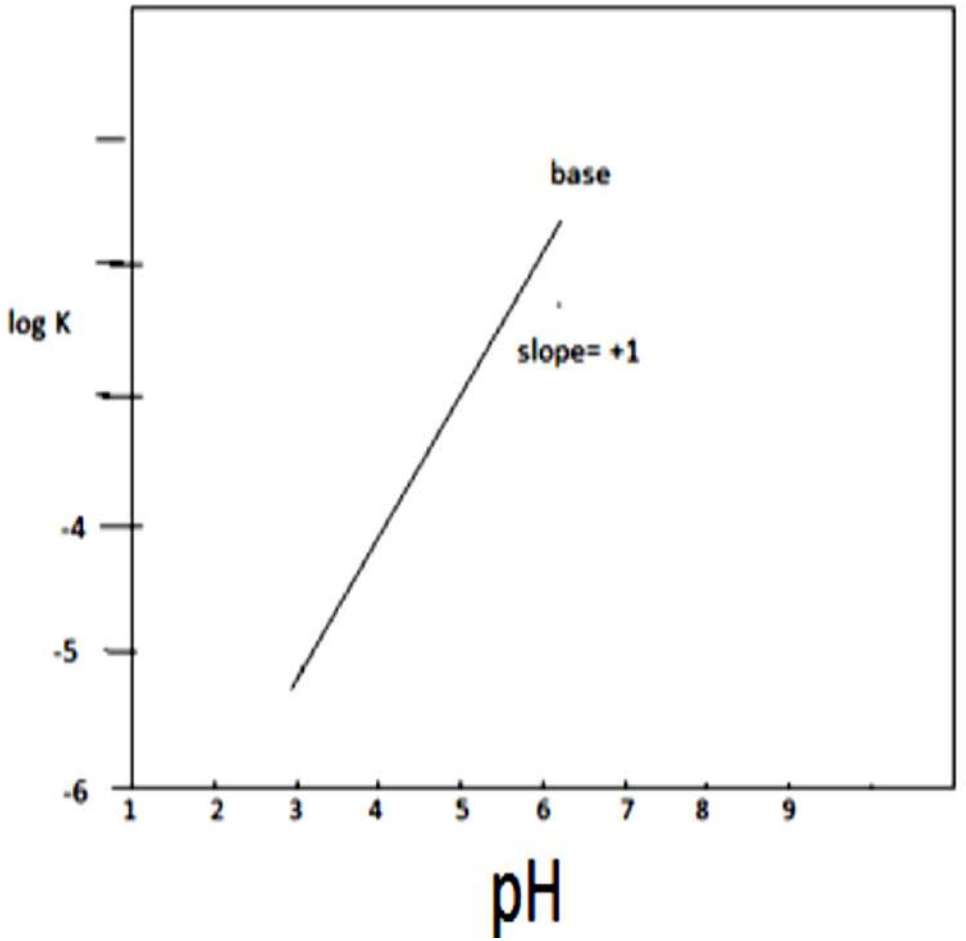
$$K_{observed} = K_{OH^-} \frac{kw}{[H+]}$$

$$\log K_{observed} = \log K_{OH^-} + \log kw - \log [H^+]$$

$$\log K_{observed} = \log K_{OH^-} + \log kw + (-\log [H^+])$$

$$\log K_{observed} = \log K_{OH^-} + \log kw + pH$$

$$\log K_{observed} = (\log K_{OH^-} + \log kw) + 1x\ pH$$



STABILITY OF PHARMACEUTICALS

Decomposition and Stabilization of Medicinal Agents

- Pharmaceutical decomposition can be classified as
  - *hydrolysis*
  - *Oxidation*
  - *isomerization*
  - *Epimerization*
  - *Photolysis*
- These processes may affect the stability of drugs in liquid, solid, and semisolid products.

Accelerated Stability and Stress Testing

- Stability testing means **studying how stable a drug is during storage** over time.
  - The purpose is to ensure that the drug:
    - Remains **safe**
    - Maintains its **quality**
    - Keeps its **therapeutic effectiveness**
- During stability testing, several properties of the drug product are monitored:
  - **Physical properties** (Color, Appearance, Viscosity, Precipitation)
  - **Chemical properties** :Degradation of the active pharmaceutical ingredient (API)
  - **Biological properties**
  - **Microbiological properties** :Effectiveness of preservatives such as **antioxidants** and **antimicrobial preservatives**
  - **Functionality**: Whether the product still performs its intended function.

Accelerated Stability and Stress Testing

Accelerated Stability Studies

- Normally, drugs are stored for **months or years** to observe their stability.
  However, this process is very slow.
- So scientists use **accelerated stability studies**, where the drug is stored under **exaggerated conditions**, such as:
  - Higher **temperature**
  - Higher **humidity**
  - Sometimes **light exposure**
- These conditions **speed up the degradation process**, allowing us to predict the **shelf life** of the drug more quickly.

Accelerated Stability and Stress Testing

Principle Behind Accelerated Testing

- Accelerated stability testing is based on **chemical kinetics**. The procedure involves:
  1. Measuring the **rate constant of degradation (k)** at several elevated temperatures.
  2. Taking the **logarithm of the rate constants (log k)**.
  3. Plotting **log k versus the reciprocal of the absolute temperature (1/T)**.
- This relationship follows the **Arrhenius equation**.
- From this plot, scientists can **extrapolate the line to room temperature**.

What is K25 ?

- From the Arrhenius plot, we can calculate **$K_{(25)}$**, which is:The **rate constant of drug degradation at 25°C**.
- This value helps estimate **how stable the drug will be under normal storage conditions**.

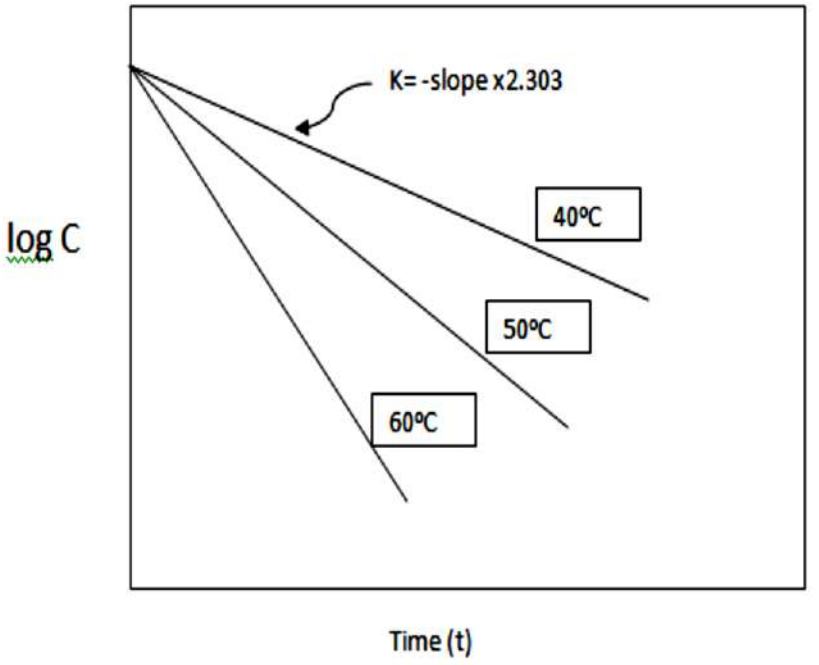
Accelerated Stability and Stress Testing

Stress Testing

- **Stress testing** is different from accelerated stability testing.
- In stress testing, the drug is exposed to **extreme conditions**, such as:
  - Very high temperature
  - Strong light
  - Oxidizing agents
  - Extreme pH
- The purpose is to:
  - Identify **degradation products** and Understand the **degradation pathway**
  - Determine the **intrinsic stability of the drug molecule**
  - Validate **stability-indicating analytical methods**
- The **type of stress testing performed depends on:**
  - The **drug substance**
  - The **type of dosage form** (tablet, cream, solution, etc.)
- Different products may require different stress conditions.

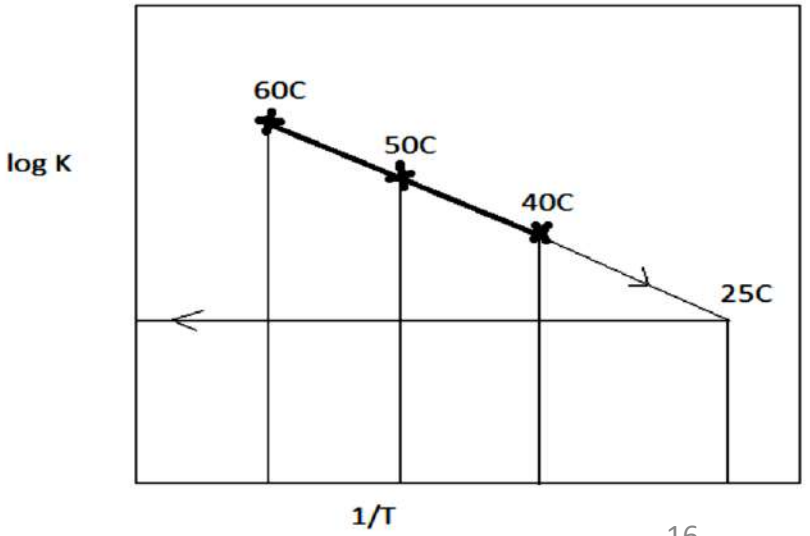
Accelerated stability testing

- The k values for the decomposition of drug at various elevated temperatures are obtained by **plotting** log of concentration against time as shown in this figure
- Then the logarithm of rate constants (k) at various temperatures are plotted against reciprocal of absolute temperature and the resulting line extrapolated to the room temperature to get $K_{25°C}$ as shown in this figure:



- **The shelf life $t_{90\%}$ can be calculated from the equation:**

$$t_{90\%} = 0.105 / K_{25°C}$$



- **Stress testing** to elucidate the intrinsic stability of the drug substance is part of the development strategy and is normally carried out under more severe conditions than those used for **accelerated testing**.
- The testing typically includes the effects of temperature [in 10◦C increments (e.g., 50◦C–60◦C) above that for accelerated testing], humidity (e.g., 75% relative humidity or greater) where appropriate, oxidation, and photolysis on the drug substance.

Example

- The rate constant k_1 for the decomposition of 5-HMF (5-hydroxymethylfurfural) at 120°C (393 K) is 1.173 hr^{-1} or 3.258 x 10^{-4} sec^{-1}, and k_2 at 140°C (413 K) is 4.860 hr^{-1}. What is the activation energy, Ea, in kcal/mole and the frequency factor, A, in sec^{-1} for the breakdown of 5-HMF within this temperature range?

We have

$$\log \frac{K_2}{K_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2 T_1}\right)$$

$$\log \frac{4.860}{1.173} = \frac{E_a}{2.303 \times 1.987}\left(\frac{413 - 393}{413 \times 393}\right)$$

Ea = 23000 cal/mole

Ea = 23 kcal/mole

At 120°C, using equation

$$\log K = \log A - \frac{E_a}{2.303R}\left(\frac{1}{T}\right)$$

we obtain

$$\log(3.258 \times 10^{-4}\,\text{sec}^{-1}) = \log A - \frac{23000\,\text{cal}}{2.303 \times 1.987}\left(\frac{1}{393}\right)$$

$$A = 2 \times 10^{9}\ \text{sec}^{-1}$$

اسئله وزاریه

Regarding hydrolysis of ester. If an ester drug is affected by [H+], which statement is correct :

a. **K observed = K H+ [H+] + KOH- [OH-]**
b. **K observed = KOH- x kw/([H+])**
c. **Slope = +1**
d. **Slope = -1**
e. **K observed = K_{H+} [H+]**

The concentration of the reactant in the first-order kinetics affects:

a. **Rate of the reaction**
b. **Half-life**
c. **Shelf-life**
d. **Both a and b**
e. **All a, b, and c**

Regarding second-order reaction:

a. **The rate of decomposition is independent of concentration of reactant .**
b. **The rate of decomposition is dependent of concentration of one of the reactants .**
c. **A plot of amount remaining against time is linear with a slope of 1/k .**
d. **Unimolecular reactions**
e. **t1/2 = 1/ak**

If you know that the rate of decomposition of new drug product follow zero order reaction, then its shelf life can be calculated using the following equation:

a. **0.105/K**
b. **0.1C0/K**
c. **C0/K**
d. **0.693/K**
e. **1/2 C0/K**

Pseudo first order reaction is used to describe the kinetic of reaction when:

a. **The reaction is independent on the concentration**
b. **The reaction depends on the concentration of one reactant**
c. **The reaction proceeds with A and B reactants, and there is a big difference in their concentration**
d. **The reaction proceeds with A and B reactants, and there is a small difference in their concentration**
e. **The reaction proceeds with A and B reactants, and their concentrations are similar**

A new drug product was prepared with original concentration of 10 mg/ml, after 20 months its concentration was found to be 8.4 mg/ml. Assuming that the decomposition is first order so the half-life of the product is:

a. **5 months**
b. **110 months**
c. **12.07 months**
d. **79.2 months**
e. **10 months**

Regarding rate of reaction. Suspension always follows:

a. **Apparent Zero-Order**
b. **Apparent First-Order**
c. **Zero-Order**
d. **First-Order**
e. **Second-Order**

The rate constant, k, in a second-order reaction has the dimensions:

a. **l / (sec)**
b. **liter/ (sec)**
c. **liter/ (mole sec)**
d. **liter/ mole**
e. **mole/ liter sec**

Regarding chemical Kinetics and Stability. How is the half-life of a second-order reaction related to the rate constant?

a. **Half-life is inversely proportional to the rate constant**
b. **Half-life is directly proportional to the rate constant**
c. **Half-life is not related to the rate constant**
d. **Half-life is equal to the rate constant**
e. **Half-life is squared of the rate constant**

Regarding chemical Kinetics and Stability. What is the primary purpose of accelerated stability testing?

a. To determine the reaction rate at room temperature
b. To determine the rate constant at different temperatures
c. To predict the shelf life of a product under normal storage conditions
d. To determine the decomposition process of a pharmaceutical product
e. To calculate the activation energy of a reaction.

A drug decomposes as a second-order reaction and the rate constant was found to be 0.000139 L/(mole sec). If the initial concentration in an aqueous solution is 2 M, the half-life (in hours) is approx.

a. 0.5
b. 1
c. 2
d. 4
e. 10

Degradation of aspirin containing products. Which of the following is CORRECT?

a- The shelf-life of aspirin in solution is long
b- Formulation of aspirin as suspension decreases its shelf life
c- The degradation of aspirin solution follows second order kinetic
d- The degradation of aspirin suspension is apparent zero order
e- The degradation of aspirin suspension becomes second order kinetic upon depletion of all aspirin from suspended particles

Regarding drugs kinetics. The method used to determine the order of a reaction by using data from kinetic study replaced in the equations for each order is called:

a- Substitution method
b- Graphic method
c- Half-life method
d- Accelerated method
e- kinetic method

Regarding drugs kinetics. The units of first order rate kinetics is

a- Mole/liter
b- 1/Time
c- Mole/liter.sec
d- Second
e- Liter/mole.sec

Assuming the reaction is second order. The half-life of a reaction with initial drug concentration equal to 0.01 mole/liter and reaction rate constant equal to 0.3 liter/mole. min is

a- 33 min
b- 133 min
c- 233 min
d- 333 min
e- 433 min

The half-life of a first order reaction is 4 years. What is its shelf life (in years)?

a- 0.18
b- 0.09
c- 0.015
d- 0.88
e- 0.61

How does the half-life of a second-order reaction change with increasing initial reactant concentration?

a- The half-life is constant regardless of initial concentration.
b- The half-life increases in proportion to the initial concentration.
c- The half-life increases with the square of the initial concentration.
d- The half-life decreases with increasing initial concentration.
e- The relationship between half-life and initial concentration is indeterminate.

A pharmaceutical dosage form was prepared at room temperature. If the initial drug concentration, C_o, was 200 mg/mL, and k_o was determined to be 0.380 (mg/mL)·days^{-1}. What will be its half life

a- 263 days
b- 100 d
c- 526 days
d- 2 days
e- 5 days

Regarding chemical Kinetics and Stability. What is the unit of the zero-order rate constant?
a- Mole liter^{2} second^{-2}
b- Mole liter^{-1} second^{-1} **(**
c- Mole liter second
d- Mole^{-1} liter^{2} second
e- Mole liter^{-2} second^{-1}

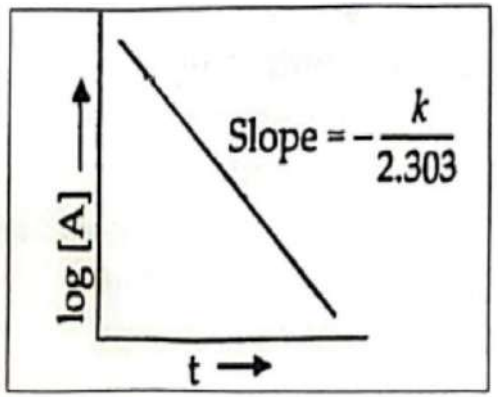
A solution of a drug contained **600 units/mL** when prepared. It was analyzed after **40 days** and was found to contain **400 units/mL**. Assuming the decomposition is first order, at what time will the drug have decomposed to **one-half of its original concentration**
a- 96.3 days
b- 157.5 days
c- **69.3 days**
d- 12 days
e- 54.3 days

In graphic Method. Following plot of the data in the form of a graph, select the best answer from in below.
a- The reaction is first order if concentration versus t yields a straight line,
b- The reaction is Zero order if concentration versus t yields a curve line,
c- it is second order if 1/(concentration) versus t gives a straight line.
d- The reaction is Zero order if ln C versus t yields a straight line,
e- If a straight-line results when concentration is plotted against t, the reaction is second order.

The main difference between half and shelf life is percent of material to disappear. Choose the correct answer:
a- Fifty percent for half-life and ten percent for shelf life
b- Ten percent for half-life and Fifty percent for shelf life
c- Ninety percent for half-life and ten percent for shelf life
d- Fifty percent for half-life and Ninety percent for shelf life
e- Fifty five percent for half-life and Ninety five percent for shelf life

When the initial concentration of two reactants is equal, the half-life for a second-order reaction is
a- proportional to reciprocal of initial concentration
b- Not proportional to reciprocal of initial concentration
c- proportional to the initial concentration
d- proportional to the logarithm of initial concentration
e- proportional to the logarithm of reciprocal initial concentration

According to the concentration vs time profile of the antibiotic (A) shown in the following figure, the pharmacist may expect that the kinetics of the antibiotic follows Figure
a- Zero-order
b- Pseudo-first order
c- First-order
d- Second-order
e- Third-order



A suspension dosage form of drug has low solubility of **3 mg/L** in water, the first order rate constant of drug in solution is **0.2 hr^{-1}**, calculate zero order rate constant??
a- 5 mg/L/h
b- 0.6 mg/L/h
c- 1.4 mg/L/day
d- 2.5 mg/L/h
e- 3.7 mg/L/h

A linear plot of **log C versus time** indicates order of reaction
a- Zero-order
b- First order
c- Second order
d- Third order
e- None of the above

If straight line is obtained between **log Ct and time**. All are True **EXCEPT**
a- the reaction is first order
b- the slope equals − K / 2.303
c- the slope equals K / 2.303
d- t½ = 0.693 / K
e- t90% = 0.105 / K