

# ORDER OF REACTION AND ITS APPLICATION IN PREDICTION OF HALF LIFE AND SHELF LIFE

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# CONTENTS

- DEFINITION
- KINETIC OF REACTION
  - ZERO ORDER OF REACTION
  - FIRST ORDER OF REACTION
  - SECOND ORDER OF REACTION
  - DETERMINATION OF ORDER OF REACTION
  - COMPARISON OF REACTION
  - COMPLEX REACTIONS
- PREDICTION OF SHELF LIFE AND OVERAGES
- QUESTIONS BANK & REFERENCES

# INTRODUCTION

## KINETICS

- Kinetics is the study of the rate at which processes occur. It is useful in providing information that:
  - √ Gives an insight into the mechanisms of changes involved, and
  - √ Allows a prediction of the degree of the change that will occur after a given time has elapsed.

## RATE CONSTANT

- A rate constant is a proportionality constant that appears in a rate law. **For example**,  $k$  is the rate constant in the rate law  $d[A]/dt = k[A]$ .
- Rate constants are independent of concentration but depend on other factors, most notably temperature.

## ORDER OF REACTION

- This is the number of concentration terms that determine the rate.
- Consider the reaction:  
 $A + B \longrightarrow C + D$
- The rate of the reaction is proportional to the concentration of A to the power of  $x$ ,  $[A]^x$
- and also the rate may be proportional to the concentration of B to the power of  $y$ ,  $[B]^y$ .
- The overall equation is,  
$$\text{Rate} = k [A]^x [B]^y$$
- The overall order of reaction is  $x+y$

# Reaction Rate and Order

- Reaction rate is the velocity of reaction to convert the reactants into its product.
- Reactions may be classified according to the order of reaction, which is the number of reacting species whose concentration determines the rate at which the reaction occurs.
- **The most important orders of reaction are;**  
**zero-order** (breakdown rate is independent of the concentration of any of the reactants),  
**first-order** (reaction rate is determined by one concentration term) and **second-order** (rate is determined by the concentrations of two reacting species).
- The decomposition of many drugs can occur simultaneously by two or more pathways, which complicates the determination of rate constants.

# TYPES OF ORDER OF REACTION

- 1. Zero order reaction**
- 2. First order reaction**
- 3. Second order reaction**
- 4. Third order reaction & Higher**
- 5. Pseudo order reaction**
- 6. Complex reactions**

# 1. ZERO ORDER REACTION

- “When the reaction rate is **independent of concentration** of the reacting substance, it depends on the zero power of the reactant and therefore is zero order reaction.”
- In this type of reaction, the limiting factor is something other than concentration, for example, solubility or absorption of light in certain photochemical reactions.

## **Example:**

- Loss of colour of multi-sulfa drug.
- Rate of The rate of decomposition can be described mathematically as:

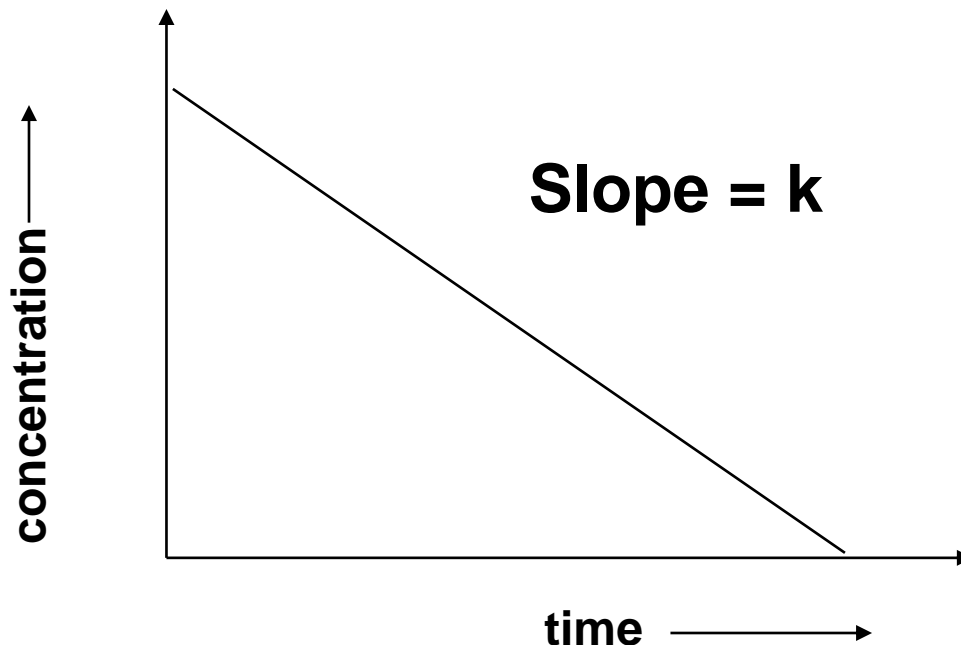
**Rate of concentration decrease;**

$$-\frac{dC_x}{dt} = K \dots \dots \dots (1)$$

- Integrating the equation respect to time from  $t=0$  to  $t=t$ , we get;

$$X = Kt + \text{constant} \dots \dots \dots (2)$$

- Comparing this equation with  $y=mx + c$ , and
- A plot of **X Vs time** results in **straight line** with **slope** equal to **K**. The value of K indicate the amount of drug that is degraded per unit time, and intercept of line at time zero is equal to constant in equation (2).





- The **unit of K** is **conc time<sup>-1</sup>**, with typical units of **mole L<sup>-1</sup> s<sup>-1</sup>**.
- **Half-life is given by equation;**

$$t_{1/2} = C_0/2k$$

## Examples: -

- Vitamin A acetate to anhydrous vitamin A.
- Photolysis of cefotaxime.
- Loss in color of multi sulfa product.
- Intravenous infusion, Drug released from TDDS.

## 2. FIRST ORDER REACTION

- “When the reaction rate depends on the first power of concentration of a single reactant,” it is considered to be **first order**.

### **Example are**

- Absorption, distribution, elimination rates.
- Microbial death kinetics.
- Thus the rate of reaction is directly proportional to the concentration of reacting substance and can be expressed as follows:

**Rate of concentration decrease;**

$$- \frac{dC_x}{dt} = KCx \dots \dots \dots (1)$$

- When the reaction rate depends on the **first power of concentration** of a single reactant, it is considered to be **first order**.
- If concentration of reactant X is 'a' at beginning of reaction **when t = 0**, & if amount that has reacted after time t is denoted by x then amount of X remaining at time t will be (a-x).

• Therefore,

$$-\frac{dC_x}{dt} = K(a-x) \dots\dots\dots(2)$$

$$\frac{dC_x}{(a-x)} = -K dt \dots\dots\dots(3)$$

• Integrating equation between time limit 0 to t

$$\int_a^{a-x} \frac{dC_x}{dt} = -K \int_0^t dt$$

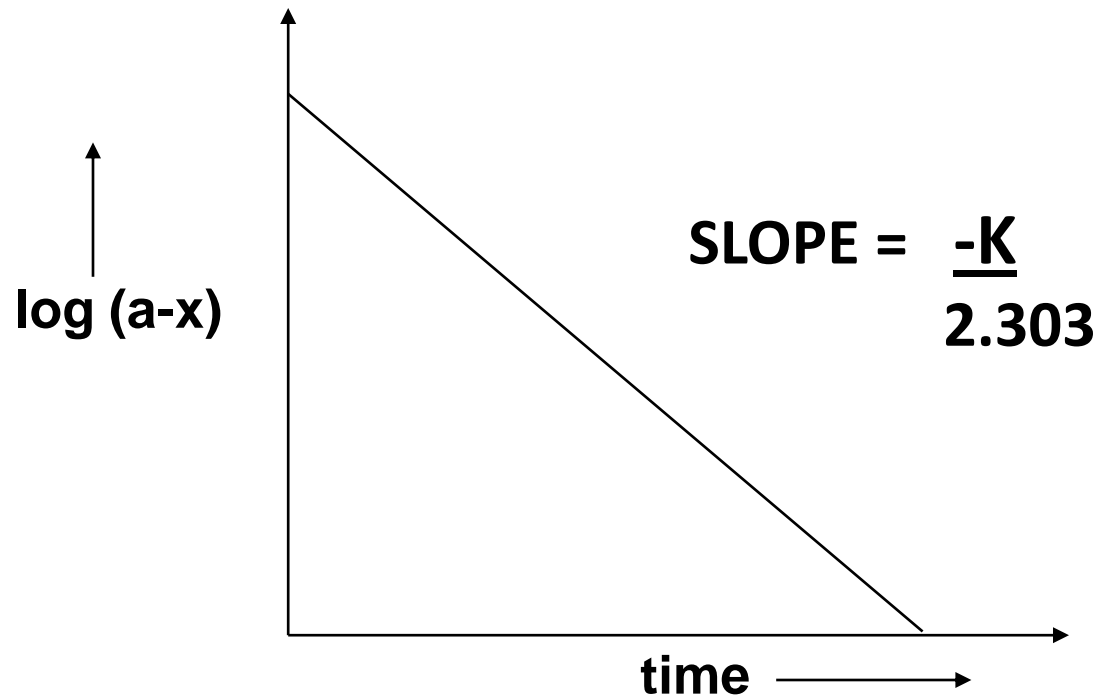
$$\ln(a-x) - \ln a = -Kt$$

$$\log(a-x) - \log a = -Kt/2.303$$

$$\log(a-x) = \log a - Kt/2.303 \dots\dots\dots(4)$$

• Equation (4) is like **y = mx + c** (linear relationship)

- If first order law is obeyed then a graph of  $\log (a-x)$  v/s time  $t$  will give straight line with **slope of  $-\frac{K}{2.303}$**  and an intercept of  $\log a$  at  $t = 0$ .



- Rearranging equation (4) we have

$$K = \frac{2.303}{t} \log (a/a-x) \dots\dots\dots (5)$$

- **Unit of K** for first order is **time<sup>-1</sup>** i.e. **SI unit is (sec)<sup>-1</sup>** because K is inversely proportional to t.
- The **half-life  $t_{1/2}$**  of a drug is the time required for 50% of drug to degrade and can be calculated as follows:

$$\begin{aligned}
 t_{1/2} &= \frac{2.303 \log C_0}{k} = \frac{2.303 \log 100}{k} \\
 &= \frac{2.303 \log 2}{k} = \frac{0.693}{k}
 \end{aligned}$$

therefore,

$$t_{1/2} = \frac{0.693}{k} \dots\dots\dots (7)$$

- **In pharmaceutical field** , the time required for 10% of the drug to degrade is an important value to know, since it represents a reasonable limit of degradation of active ingredients.  
The  $t_{10\%}$  value can be calculated as

$$t_{10\%} = \frac{0.104}{k}$$

*or*

$$t_{10\%} = 0.152 t_{1/2}$$

### **Example :**

- Decomposition rate of hydrogen peroxide, catalyzed by 0.02 molar KI.

# 3. SECOND ORDER REACTION

- “Rate of change in conc. of product and reactant is dependent on **second power of conc. of single reactant or to first powers of the conc. of two reactants.**”

$$\text{i.e. } -\frac{dC_X}{dt} = K [X] [Y] \text{-----(1)}$$

$$\text{or } -\frac{dC_X}{dt} = K [X]^2 \text{-----(2)}$$

Let us discuss;  $-\frac{dC_X}{dt} = K [X] [Y]$  in detail

- Here decrease in conc. of Y is similar to X. If conc. of X and Y at time  $t = 0$  are  $a$  and  $b$  respectively, and conc. of each substance that has reacted after time  $t$  is equal to  $x$  then conc. of X and Y remaining will be  $(a-x)$  &  $(b-x)$  respectively.

## a) In case when $(a \neq b)$

$$-\frac{dx}{dt} = K (a-x) (b-x) \text{-----(3)}$$

Where  $-\frac{dx}{dt}$  = rate of decrease in conc. of X or Y

Integrating equation (3) we get

$$Kt = \frac{2.303}{(a-b)} \log \frac{b(a-x)}{a(b-x)} \text{-----(4)}$$

Rearranging equation (4) we get

$$\log \frac{(a-x)}{(b-x)} = \frac{(a-b)Kt}{2.303} + \log \frac{a}{b} \text{-----(5)}$$

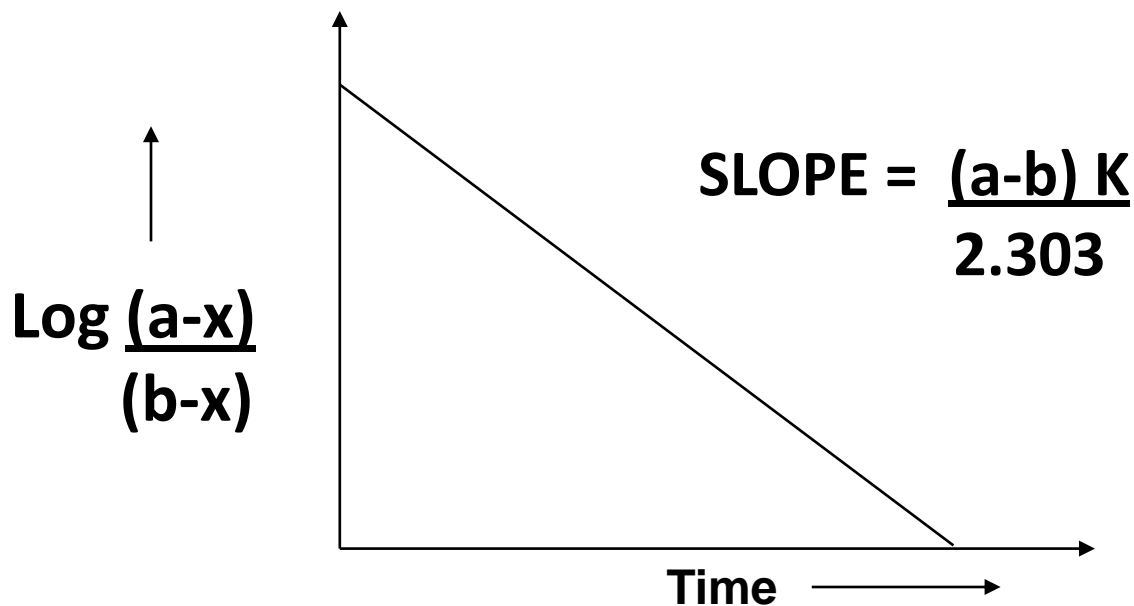


So, if second order reaction is observed then graph of

$$\log \frac{(a-x)}{(b-x)} \text{ V}_s \text{ t}$$

gives **straight line** with slope  $\frac{(a-b)K}{2.303}$  and

intercept  $\log a/b$  at  $t = 0$ .



## b) In case when (a=b)

$$-\frac{dC_x}{dt} = K [X]^2$$

Integration gives,

$$Kt = \frac{x}{a(a-x)} \text{-----(6)}$$

- Rearrangement of equation (6) gives us

$$Kt = \frac{1}{a-x} - \frac{1}{a} \text{-----(7)}$$

- So if second order reaction is observed then **graph of  $1/a-x$  vs  $t$**  gives straight line with **slope  $K$**  and **intercept  $1/a$  at  $t = 0$** .
- **Unit of second order** reaction is **conc.<sup>-1</sup> time<sup>-1</sup>** and unit is **mol<sup>-1</sup> sec<sup>-1</sup>**
- Half-life in this case is  **$t_{1/2} = 1/ak$** .

SI

# 4. THIRD ORDER REACTION & HIGHER

- Rate of change in conc. is proportional to **three concentration terms**. However such reactions are rare and their analysis is complex. Reaction of even higher order is unlikely to occur.
- Rate equation for third order reaction is as follows

$$K = 1/2t [1/(a-x)^2 - 1/a^2]$$

- Half-life equation is

$$t_{1/2} = \frac{3}{2} \frac{1}{a^2k}$$

# **5. PSEUDO ORDER REACTION**

## **A) PSEUDO - ZERO ORDER REACTION**

- In solid state, many drugs decompose by pseudo zero order i.e. reaction between drug and moisture in solid dosage form. The system behaves like suspensions and because of the presence of excess solid drug; the first order rate actually becomes pseudo zero order.

Equation for it is similar to zero order except  $K$  is replaced by  $K'$ .

### **How suspension degradation follows pseudo zero order reaction?**

- Suspension is the 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.

- This concentration is of course the drug's equilibrium solubility in a particular solvent at a particular temperature. The important point is that the amount of the drug in the solution remains constant despite its decomposition with time.
- The reservoir of solid drug in suspension is responsible for this constancy. It follows zero order kinetics because the suspended drug reservoir that ensures constant concentration.
- Once all the suspended particles have been converted into drug in solution the system changes to a first – order reaction.

## **B) PSEUDO-FIRST ORDER REACTION**

- Here a second order or bimolecular reaction is made to behave like first order. This is found in the case in which one reacting material is present in great excess or is maintained at constant concentration as compared with other substance. Here reaction rate is determined by one reactant even though two are present.

### **EXAMPLES:**

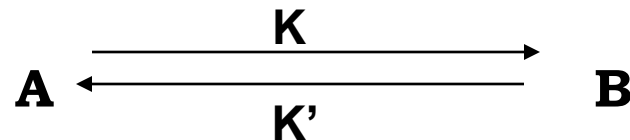
- Decomposition of ascorbic acid tablet.
- Aspirin hydrolysis.

# 6. COMPLEX REACTION

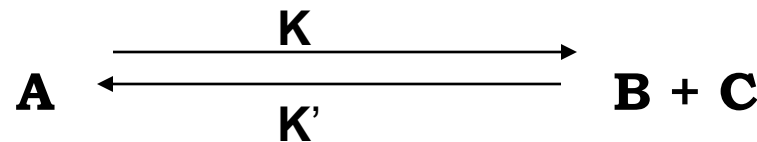
- These are reactions involving simultaneous breakdown by more than one route or by a sequence of reaction steps.
- Although most degradative reactions in pharmaceutical systems can be treated by simple zero order, first order and pseudo-first order kinetics, there are certain pharmaceutical formulations that exhibit more complicated reactions.
- **Three types of reaction;**
  - a) OPPOSING REACTION (REVERSIBLE)**
  - b) SIDE REACTIONS (PARALLEL)**
  - c) CONSECUTIVE REACTIONS**

# a) OPPOSING REACTION (REVERSIBLE)

- The simplest case is, in which both reactions are of first order



- A somewhat more complicated reaction is when forward is first order type and reverse reaction is second order type.



**Example:**

Epimerization of tetracycline.



## b) CONSECUTIVE REACTIONS

- Simplest is one where both the reaction is of first order.
- If  $k_2 > k_1$  then B can be considered as unstable intermediate and rate determining step for overall reaction would be conversion of A to B.

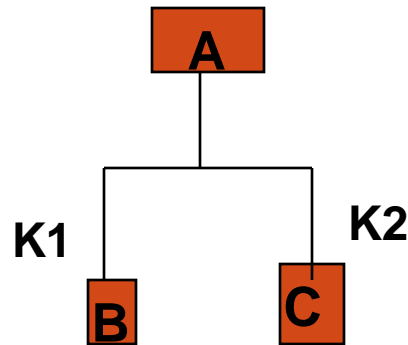


### Examples: -

- Radioactive series \ Isotopic decay that follows first order, but it is a consecutive reaction.
- Degradation of chlorbenzodiazepine by hydrolysis to lactam form and further to benzophenone.

## c) SIDE REACTIONS (PARALLEL)

- Here the reacting substance can be removed by two or more reactions occurring simultaneously, as depicted



### EXAMPLE:

- Purified insulin degrades by two mechanisms- deamidation and polymerization.
- The relative rates of deamidation and polymerization are pH and temperature dependent.

# KNOWN FACTS: -

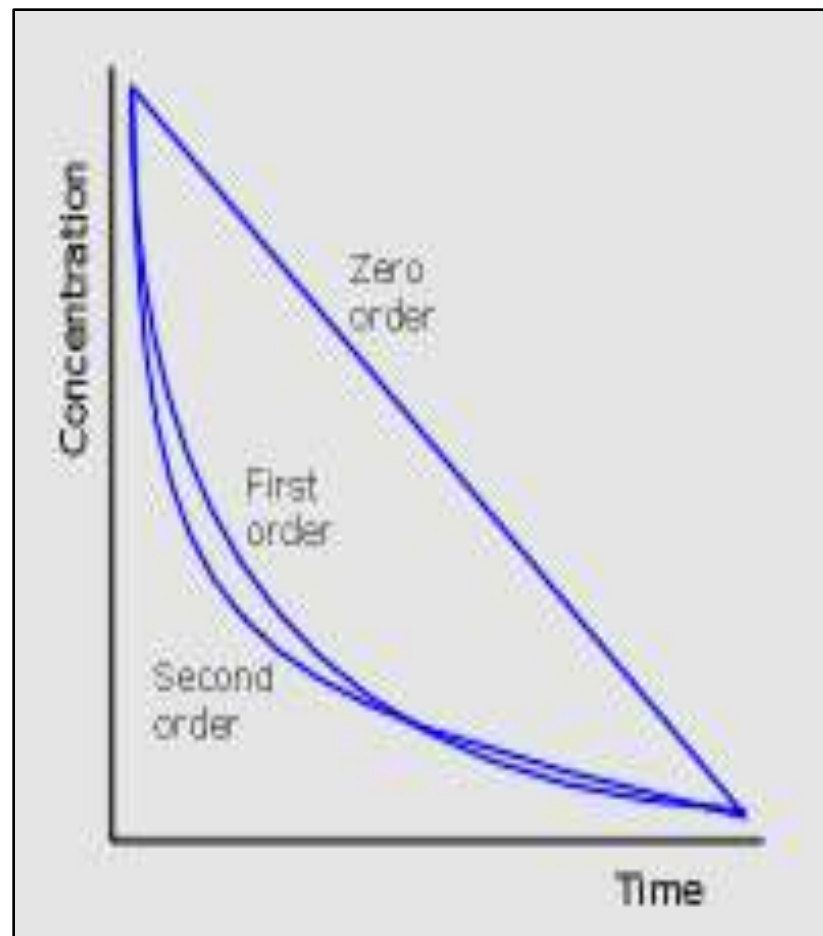
- There is no detectable difference between first order and zero order at less than **15%** decomposition.
- Many companies take the attitude of plotting by **first order** in situation where the order is unknown.
- Establishing the true order of reaction can often be difficult, due to the fact that strength changes at **25°C** are small and that unit-to-unit and assay variation make such a distinction difficult.

# SUMMARY OF PARAMETERS

Order	Integrate rate equation	$t_{1/2}$	Linear Graph			
			Ordinate	Abscissa	Slope	Intercept
0	$X = Kt$	$= a/2K$	X	t	K	0
1	$\log (a/a-x) = Kt/2.303$	$= 0.693/K$	$\log(a-x)$	t	$-K/2.303$	$\log a$
2 (a = b)	$X/a(a-x) = Kt$	$= 1/aK$	$1/a-x$	t	K	$1/a$

# Cont...

Order of reaction	Unit of K
Zero	$M L^{-1}Sec^{-1}$
First	$Sec^{-1}$
Second	$M^{-1}Sec^{-1}$



# COMPARISON OF FIRST, SECOND & ZERO ORDER REACTION

- Suppose a tablet decomposes after one year to 75% of its initial concentration.
- In the following table the data of rate constant and half-life is given for particular order.

PARAMETER	1 <sup>ST</sup> ORDER	2 <sup>ND</sup> ORDER	ZERO ORDER
K(PER YEAR)	1.38%	0.03%	75%
HALF LIFE	0.50	0.33	0.66

Initially speed of reaction:

**2 order > 1 order > 0 order**

- Because in 2nd order reaction, two molecules of reactants collide faster than one. Ideally if every collision between molecules led to product, a second order reaction would be twice as fast as first order. But in our case this is not true as half-life of first order is not twice as that of second order. This indicates that not every collision between molecules lead to reaction. **After two years,**

<b>Order of reaction</b>	<b>Zero</b>	<b>First</b>	<b>second</b>
<b>Drug remaining</b>	<b>- 50 %</b>	<b>6.76%</b>	<b>20%</b>

- This shows that in 2nd year the speed of reaction reverses and 2nd order reaction becomes slowest as it is dependent upon the concentration of reactants and the concentration of reactants gets depleted as the reaction progresses so the % of drug remaining is more in case of 2nd order reaction while in zero order all the drug got decomposed before two years.

# METHODS TO DETERMINE ORDER OF REACTION

- 1. SUBSTITUTION METHOD**
- 2. INITIAL RATE METHOD**
- 3. DATA PLOTTING METHOD**
- 4. HALF-LIFE DETERMINATION METHOD**
- 5. SOFTWARE TOOLS FOR SECOND ORDER REACTION**



# SUBSTITUTION METHOD

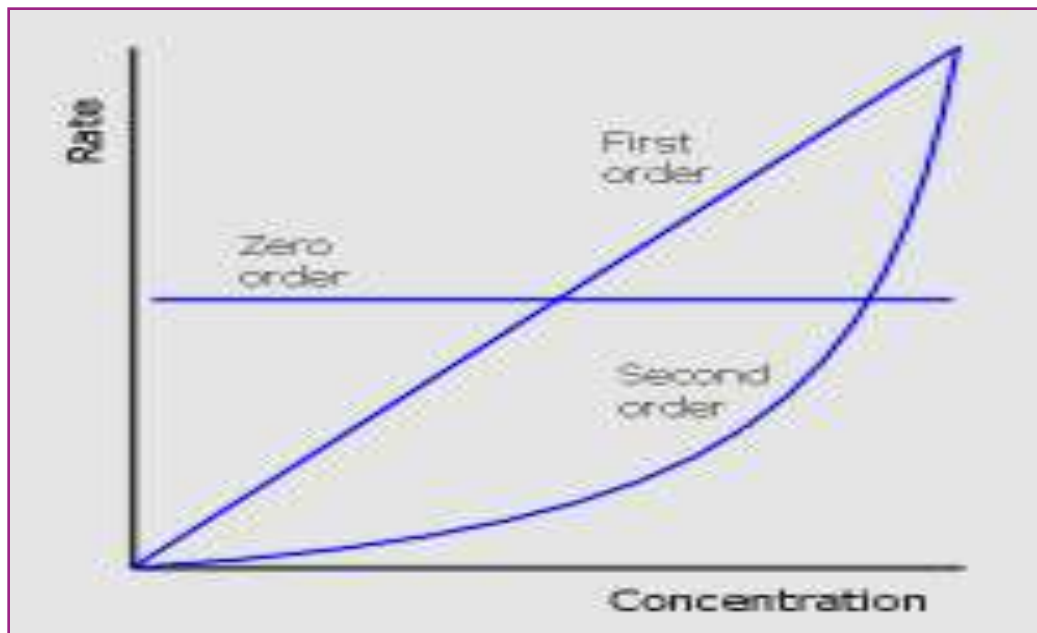
- The data accumulated in a kinetic study may be substituted in the integrated form of the equations which describes the various orders. When the equation is found in which the calculated  $k$  values remain constant the reaction is considered to be of that order.

## GRAPHICAL (DATA PLOTTING) METHOD

- If a straight line results when concentration is plotted against time the reaction is zero order.
- If plot of  $1/c$  against time is linear then it is second order.
- If plot of  $\log c$  against time is linear then it is first order reaction.

# INITIAL RATE METHOD

- Graphs are plotted of rate of reaction against concentration and the initial rate determined from the gradient at time = 0.
- If it is a straight line the reaction is first order.
- A line which is independent of concentration is zero order.
- If a curve is obtained then it is second order.



**Fig. Curves for different types of order**

# HALF-LIFE DETERMINATION METHOD:

- In general the half-life of a reaction in which the concentration of all reactants are identical, the relationship is;

$$t_{1/2} \propto 1/a^{n-1}$$

where  $n$  is the order of reaction.

- Thus if two reactions are run at different initial concentrations,  $a_1$  &  $a_2$  with their respective half-lives and putting them in above equation in logarithmic form we finally get

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

# Determination of $t_{10\%}$ by Arrhenius equation

- Temperature influences rate and order of reaction. So shelf life of product can be obtained under exaggerated condition.
- It is said that for every  $10^{\circ}\text{C}$  rise, rate of reaction increases by 2-3 times.
- For this **Arrhenius equation** is used

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

where ; A= frequency factor,  
R= gas constant,  
K = rate constant,  
E<sub>a</sub> = energy of activation

- Therefore,  $\text{Log } K = \log A - \frac{E_a}{2.303RT}$
- Graph of  $\log K$  vs  $1/T$  gives **straight line** with slope  $\frac{E_a}{2.303R}$   
& intercept at  $t=0$

- $E_a$  represents energy required by molecule to react and undergo reaction. Higher is value of  $E_a$  higher is dependency on temperature.
  - $E_a = 2-3$  k-cal/mole -----Photolysis
  - $E_a = 10-30$  k-cal/mole ---Hydrolysis- Solvolysis
  - $E_a =$  very high abt 50-70 k-cal/mole--Pyrolysis
- Rate constant at different temperature can be obtained by

$$\log (K_2/K_1) = \frac{E_a (T_2 - T_1)}{R (T_2 * T_1)}$$

- With help of  $K$  at different temperature we can predict  $T_{10\%}$

$$t_{10\%} = 0.105 / k$$

(For first order only)

$$t_{10\%} = C_0 / 10 * k$$

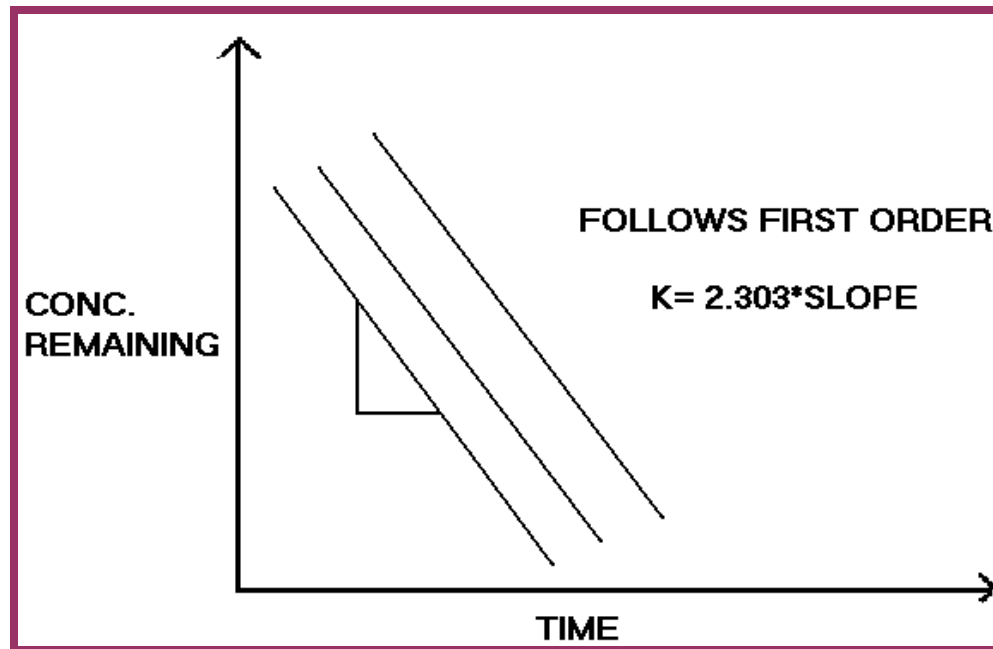
(for zero order only)

# Disadvantages of Arrhenius equation:

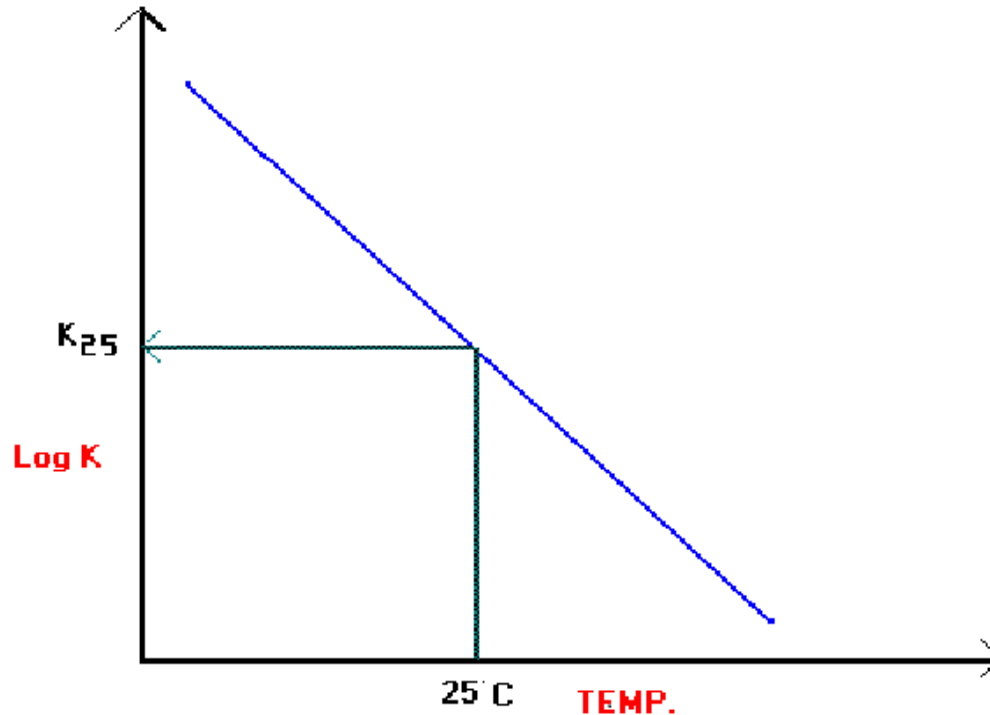
- At higher temperature evaporation of solvent takes place and thus changes in concentration.
- At higher temperature change in solubility and humidity (decreases) which cannot be correlated with room temperature.
- For disperse systems at higher temperature viscosity decreases which can change physical characteristics resulting in potentially large errors in prediction of stability.
- Different degradation mechanisms may predominate at different temperatures thus making stability prediction difficult.

# METHOD TO DETERMINE OVERAGES

- **STEP I:** - Perform the experiment and find out concentration of drug remaining at different time intervals at different temperature including room temperature.
- Plot the graph of **concentration vs time for different temp.**
- As shown in the figure **measure the slope** and from that get rate Constant **K**.



- **STEP II:** - After measuring the K at different temperature find **value of  $K_{25}$**  from the graph as shown in the figure.



- **STEP III:** - The value of  $K_{25}$  is substituted into eq.

$$K = 2.303/t * \log (a / a-x)$$

And get the value of **t10 %**, **t20%... t 90%**.

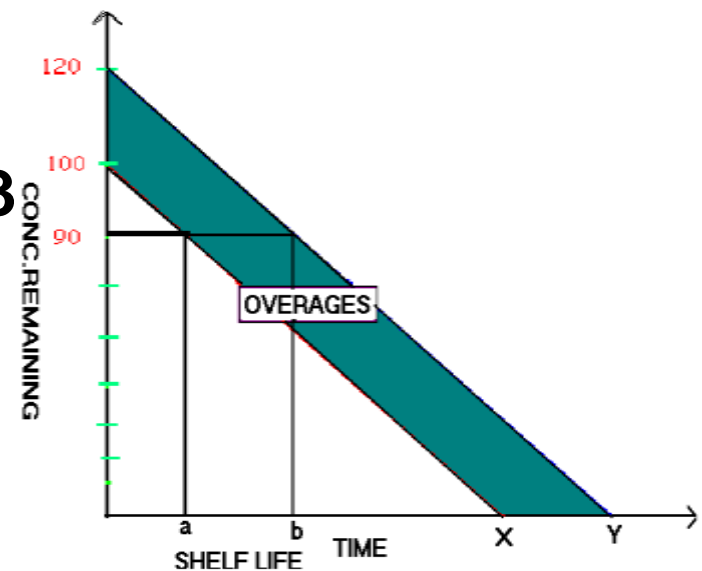


## ➤ STEP IV: - Calculation for overages

- Plot the graph of **time (Days) Vs conc. remaining**.
- Extrapolate line from Y- axis, **at 90%** to the X- axis. The intersect point will give **shelf life**.
- To maintain or increase the shelf life as per need (from a to b as shown in fig.) draw a parallel line from Y to that of X, the intersect point at Y- axis will give the value of overages per 100 unit.

As shown in the figure,

- The value of overages is **20%**. So need to add 20 unit drug more to preexisting formulation
- As per **European guidelines the maximum amount of overages is 3**



## ➤ **STEP V: - Expiration period**

- Prime goal of stability testing is to establish an Expiry Date.
- The terms defined in lines 82-90 of guidelines as  
**“The date placed on the immediate container label of a drug product that designates the date through which the product is expected to remain within specification.”**
- If the expiration date includes only a month and year, it is expected that the product meet specification through the last day of the month.

# Estimation of the Shelf Life (Expiration Period) of Drug Products

- **Shelf life is best defined** as the time span over which the quality of a product remains within specifications. That is, it is the time period over which the efficacy, safety, and esthetics of the product can be assured. When the degradation of the essential components cannot be adequately described by a rate expression, shelf life cannot be easily estimated or projected.
- When a quality-indicating parameter changes with time via complex kinetics that cannot be adequately explained or predicted, one must determine stability solely from experimental observations. Many physical degradation processes exhibit this kind of behavior. In contrast, estimation of shelf life is often possible when the shelf life is governed by a degradation process that can be adequately described by a rate expression (like many chemical degradation processes).

- Estimation of product shelf life is done by two methods— estimation from data obtained under the same conditions as those that the final product is expected to withstand and estimation from tests conducted under accelerated conditions. This section describes these two methods for estimating the shelf life of pharmaceuticals when chemical degradation is the major contributor to the degradation process and the degradation can be adequately described by a rate expression.

### **DIFFERENT METHODS:**

- A. Extrapolation from Real-Time Data**
- B. Shelf-Life Estimation from Temperature-Accelerated Studies**
- C. Estimation of Shelf Life under Temperature-Fluctuating Conditions**

# QUESTION BANK

- What is kinetics?
- What is order of reaction? Describe different methods to determine order of reaction.
- Discuss first order drug degradation in detail.
- How one can predict shelf life of suspension and ascorbic acid tablet?
- Compare first, zero, second order of degradation.
- Discuss complex reactions.....(2005)
- Short note on order of reaction and its utility in stability studies.....(2006)

# REFERENCES

- Remington's pharmaceutical Science, Mack Publishing Company, 15th edition 1975, **275-283**.
- Physical; pharmacy by Alfred martin, second edition , **355-377**.
- The theory and practice of industrial pharmacy by Lachman, **760**.
- Pharmaceutics the science of dosage form design by AULTON, **119-128**
- Drug stability by Carstensen, dekker series vol: 49
- [www.rsc.org](http://www.rsc.org).
- [Entrez pubmed.html](http://Entrez.pubmed.html)
- Biopharmaceutics and Pharmacokinetics A treatise by D. M. Brahmankar Sunil B. Jaiswal. **Page no. 215-220**.
- Stability of drugs and dosage forms by Yoshioka and Stella (2002)

Thank You

