DRUG STABILITY

PHARMACEUTICAL TECHNOLOGY-IV

6TH WEEK

WHAT IS STABILITY?

- **Stability is defined as the distribution of the drug from the moment it is produced, its storage at the hospital or pharmacy, and its ability to remain within the pre-determined limits during the first production period.**

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Stability studies are carried out

- **to give the drug shelf life,**

- **to choose the packaging material,**

- **to determine the storage conditions of the drug.**

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Reaction Kinetics

- **The rate of change under the influence of various factors causing the change on the substance or the process that examines the factors affecting the rate of change of a substance is called «Reaction Kinetic».**

The areas of reaction kinetics are:

❖ For stability assessments,

❖ Formation of solid drug dissolution profiles,

❖ Determination of absorption, distribution, metabolism and elimination rates of drugs,

❖ Degredation of radioactive substances,

❖ Following of mixing, drying and sterilization processes.

Reaction Rate

The measurement of the progress of the reaction in a chemical reaction is called «Reaction Rate».

In other words; this is called time-dependent change observed in the concentrations of the reactants or reaction substances in unit time.

$$\text{Rate (V)} = \pm\, dC\, /\, dt \quad \text{or} \quad \text{Rate (V)} = \pm\, dA\, /\, dt$$

A = Amount of substance (mg, g..)
C = Concentration of substance (mg/ml)
t = Time (minute, hour..)
dA = Change in amount of the substance
dC = Change in concentration of the substance

V = Rate (mg/time; g/time)
(-) = Decrease in the amount of the reactant
(+) = Increase in the amount of substance formed at the end of the reaction

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For example:

a A + b B ⟶ c C + d D in a chemical reaction;

a, b, c, d ⟶ Mol numbers

Starting substances in a chemical reaction.

Substances formed at the end of the reaction

The rate of the reaction is proportional to the number of exponents and is expressed by the below equation.

$$V = -\frac{1}{a}\frac{d[A]}{dt} = -\frac{1}{b}\frac{d[B]}{dt} = +\frac{1}{c}\frac{d[C]}{dt} = +\frac{1}{d}\frac{d[D]}{dt}$$

or

$$V = k[A]^a[B]^b$$

k = Reaction rate constant

The unit varies depending on the degree of reaction. It is usually «concentration / time» or «time».

Orders of Reaction

The reaction order is changed by the concentration of the reactants and this is called as the «Reaction Order». It is equal to the sum of the exponential values of the reactants. It is defined as «n».

$$n = a + b$$

Reactants

A + 2B ⟶ Reaction products

Reaction Rate

$$V = k [A] [B] [B]$$

$$V = k [A]^1 [B]^2$$

$$n = 1 + 2 = 3 \text{ (Third Degree Reaction)}$$

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For example: When ethyl acetate and sodium hydroxide give a reaction, the equation of the reaction can be written as follows:

$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$

In this case, the rate of the reaction calculates through below equation;

$$V = -\frac{d\left[CH_3COOC_2H_5\right]}{dt} = -\frac{d\left[NaOH\right]}{dt}$$

$$= k\left[CH_3COOC_2H_5\right]^1\left[NaOH\right]^1$$

And finally, the order of reaction calculates as;

$n = 1 + 1 = \mathbf{2}$ (Second Degree Reaction)

Half life ($t_{1/2}$, $t_{50\%}$) is the time required for one-half of the material to disappear.

The term «half-life» is widely used to express:

❖ The rate of degradation of a radioactive isotope

❖ The rate at which the drug disappear from the blood (biological half-life).

Shelf life ($t_{\%10}$) is the time required for 10% of the material to disappear or the time taken to reduce the amount of active substance in the drug to 90%.

The term «shelf-life» is used to express the period of time during which the medicinal product is predicted to remain fit for its intended use under specified conditions of storage.

The other terms which are used in drug stability are

Expire Date:

This term means that drug can not be used after this date because the concentration of drug decreased and become lower than therapeutic blood concentration.

Instability:
This situation may cause undesired change in performance; such as dissolution, bioavailability... etc.

Kinetic reactions are divided into two sub-categories.

❖ **Simple reactions**

❖ **Complex reactions**

Simple reactions ⟶ are the reactions that move in one step. 0, 1, 2 and 3 order reactions are in this category.

Complex reactions ⟶ are the reactions that move in many steps.

Zero-Order Reactions

The reaction rate is independent of the concentrations of the reactants. The rate of reaction is related to the zero-order strength of the substance concentration.

The reactions usually run through a catalyst.

Examples of the zero-order reactions are
- ✓ Degrading of a substance by light effect
- ✓ Photolysis of a substance by light effect
- ✓ Solubility ability of a substance
- ✓ Hydrolysis of aqueous drug suspensions

A solid $\longrightarrow$ A solution $\xrightarrow{\ \ k\ \ }$ B

Reaction rate equation:

$$-\frac{dA}{dt} = k\left[A_{solution}\right] = k_0$$

$$A_t = A_0 - k_0 \cdot t$$

Concentration of substance at time t (quantity / volume)

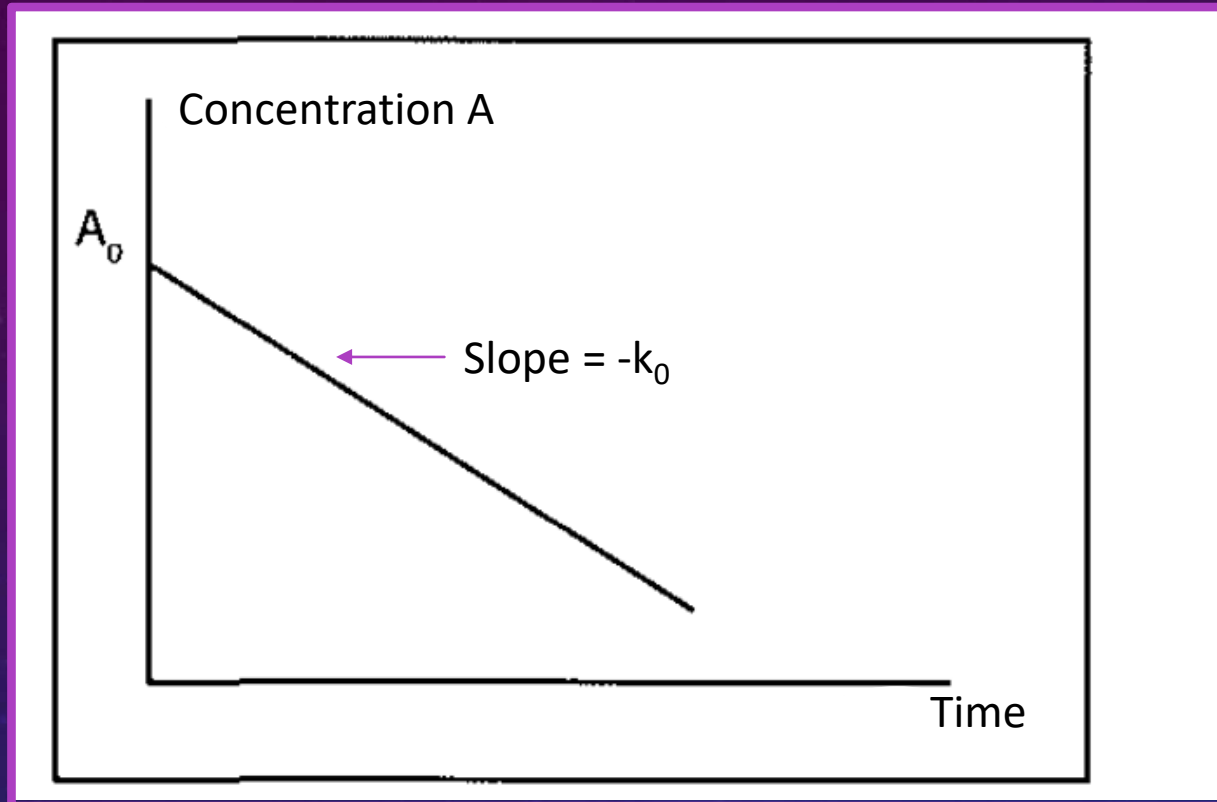**Concentration of substance at time t=0 (quantity / volume)**

$$k_0 = [A_0 - A_t] / t$$

Zero-order reaction rate constant (concentration / time)

Half life:

$$t = \frac{A_0 - A_t}{k_0}$$

$$t_{1/2} = \frac{(A_0 - 0.5A_0)}{k_0} = \frac{A_0}{2k_0}$$

Zero-Order Reaction Graphic

Concentration A

A_0

$\longleftarrow$ Slope = $-k_0$

Time

If a plot of concentration A versus time is linear with a slope of k_0, and an intercept of A_0, the reaction is degraded by zero-order reaction.

Shelf life:

$$t_{\%10} = \frac{(A_0 - 0.9A_0)}{k_0} = \frac{0.1A_0}{k_0} = \frac{A_0}{10k_0}$$

First-Order Reactions

The reaction rate depends on the concentration of only one of the reactants (a=1, b=0, c=0).

aA + bB + cC $\longrightarrow$ The substances formed at the end of the reaction

$V = k [A]^a [B]^b [C]^c$ } **Reaction Order**
n = a + b + c = 1 } $V = k [A]^1 [B]^0 [C]^0$
$V = k [A]$

If only 1 molecule substance reacts, the reaction rate is dependent solely A substance.

A $\xrightarrow{k}$ B } $V = \dfrac{dA}{dt} = -k[A]$ } **With the separation of variables in this equation** } $\displaystyle\int_{A_0}^{A_1} \dfrac{dA}{[A]} = -k \int_0^t dt$

The integrated rate equation is demonstrated as ➡️ $\ln A_t - \ln A_0 = -k(t-0)$

At the begining, when t=0; it will be A = A_0 and when any integral is taken at any time t (t = t, A = At);

$\ln A_t - \ln A_0 = -k(t-0)$ ➡️ $\ln A_t = \ln A_0 - k_1 \cdot t$

$\log A_t = \log A_0 - [k_1 / 2.303] \cdot t$

Lineer form

$A_t = A_0 \cdot e^{(-k_1 \cdot t)}$
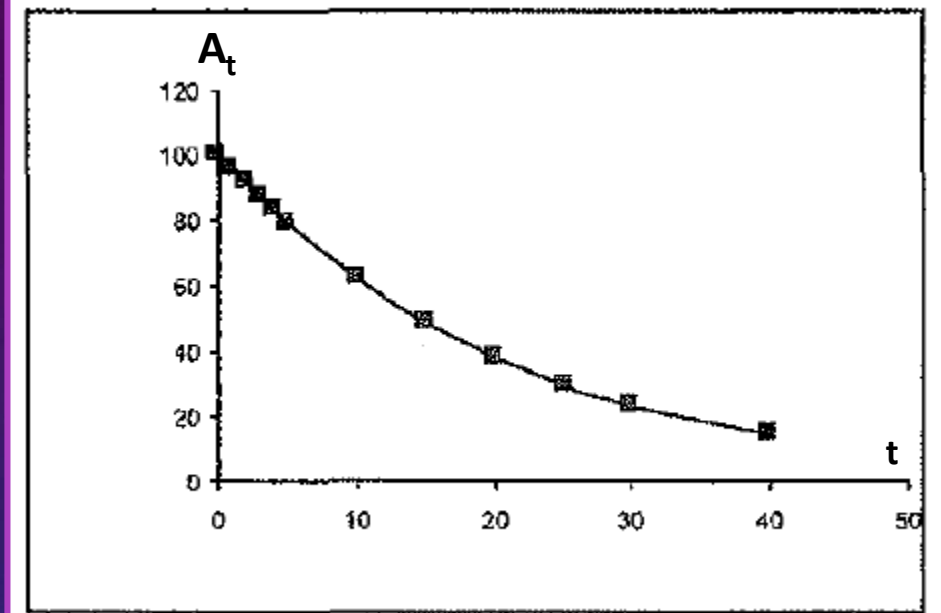
If it is shown exponentially; (Non-lineer form)

$k_1 = [\ln A_0 - \ln A_t] / t$

First-order reaction rate constant (time^{-1})

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Half life:

$$t_{1/2} = \frac{\ln\left[\dfrac{A_0}{A_t}\right]}{k} = \frac{\ln\left(\dfrac{A_0}{0.5A_0}\right)}{k} = \frac{\ln 2}{k}$$
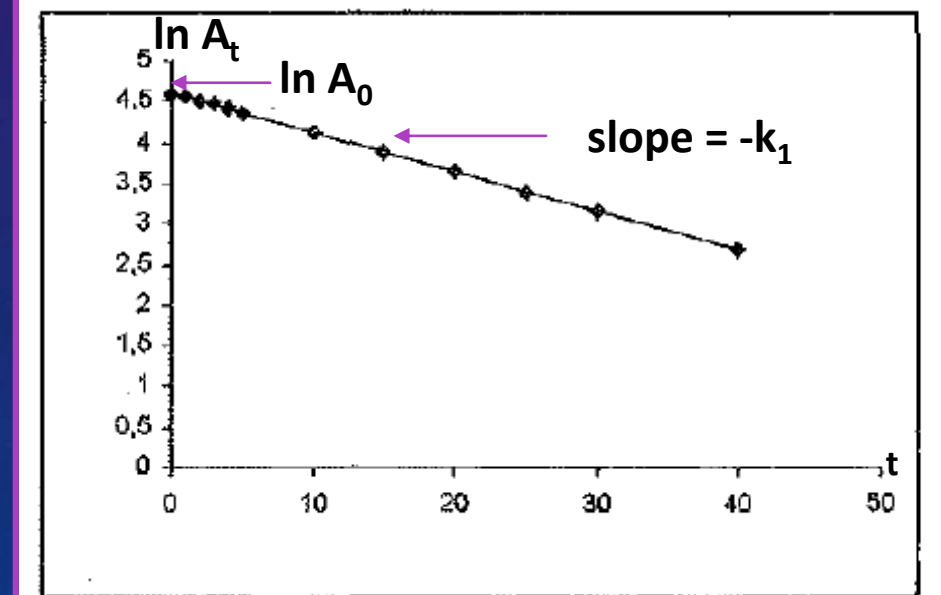
$$t_{1/2} = 0.693 / k_1$$

Shell life:

$$t_{\%10} = \frac{\ln\left(\dfrac{A_0}{0.9A_0}\right)}{k} = \frac{\ln(1.1111)}{k}$$

$$t_{\%10} = 0.105 / k_1$$

$\ln A_t$, $\ln A_0$, slope $= -k_1$

For example:

Glucosamine sulfate was found to be most stable at pH of 5 with the degradation constant of 5.39×10^{-6} hr^{-1} at 25°. Calculate the time taken (in years) for the concentration of the drug to fall to 75% of its original value.

$\ln A_t = \ln A_0 - k_1 t$

$\ln 0.75 = \ln 1 - [(5.39 \times 10^{-6})\ t]$

t = 53373 hr = 6.09 year

For example:

Aspirin has been found to be most stable at pH 2.5 where the first-order rate constant is 5 x 10^{-7} S^{-1} at 25°C. What is the half-life of the reaction?

$t_{50\%}$ = 0.693 / k_1

$t_{50\%}$ = 0.693 / 5 x 10^{-7}

$t_{50\%}$ = 1.39 x 10^6 S = 16 days

For example:

If $A_0 = 0.05$ M and $k_1 = 2 \times 10^{-2}$ min^{-1}, what is the A_t after 1 hour and what is the half-life for this reaction?

1 hour = 60 min

$\ln A_t = \ln A_0 - k_1 t$

$\ln A_t = \ln 0.05 - [(2 \times 10^{-2}) \times 60]$

$A_t = 6.4 \times 10^{-5}$ M

$t_{50\%} = 0.693 / k_1$

$t_{50\%} = [0.693 / 2 \times 10^{-7}]$

$t_{50\%} = 34.65$ min

Apparent Zero-Order Reactions

❖ **Many decomposition reactions in the solid phase or in suspensions «apparently» follow zero-order kinetics.**

❖ **In case of suspensions, as the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant.**

❖ **In case of solutions, the equation is for first-order expression:**

Rate = k_1 [A]

❖ **In case of suspension the concentration [A] is constant:**

k_0 = k_1 [A]

❖ **Where**

k_0: pseudo-zero-order rate constant

❖ **Thus, Rate = k_0**

For example:

If aspirin was formulated in a 6.5 g/100 ml suspension at pH 2.5 and 25°

where the first-order rate constant is $5 \times 10^{-7} S^{-1}$. It has a solubility of 0.33

g/100 ml. Calculate the half-life of 100 ml of this suspension:

$k_0 = k_1 [A]$

$k_0 = (5 \times 10^{-7}) \times 0.33 = 1.65 \times 10^{-7}$ g/(100ml) S^{-1}

$t_{50\%} = [A_0] / 2k_0$

$t_{50\%} = (6.5 / 2) \times (1.65 \times 10^{-7}) = 1.97 \times 10^{-7}$ S = 228 days.

Second Order Reactions

Second order reactions are biomolecular reactions. The rate of these reactions is dependent on the concentration of the two reacting substances, A and B, or two molecules of the same species, 2A. In this way, the rate of reactions in which the two molecules come together is usually defined by the second order reaction.

In these reactions; the concentrations of the reactants are equal or not.

If the initial concentrations of the reactants are equal; [A] = [B]

2A ⟶ The substances formed at the end of the reactions

$$V = -\frac{1}{2}\frac{dA}{dt} = -k[A]^2$$

If they are not equal; [A] ≠ [B]

A + B ⟶ The substances formed at the end of the reactions

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

When equality situation is to be examined;
[A] = [B]

2A ⟶ The substances formed at the end of the reactions

Reaction rate:

$$V = \frac{dA}{dt} = -k[A]^2$$

$$\int_{A_0}^{A_t} \frac{dA}{[A]^2} = -k \int_0^t dt$$

When t=0, A=A_0, and at any t moment, A=A_t.
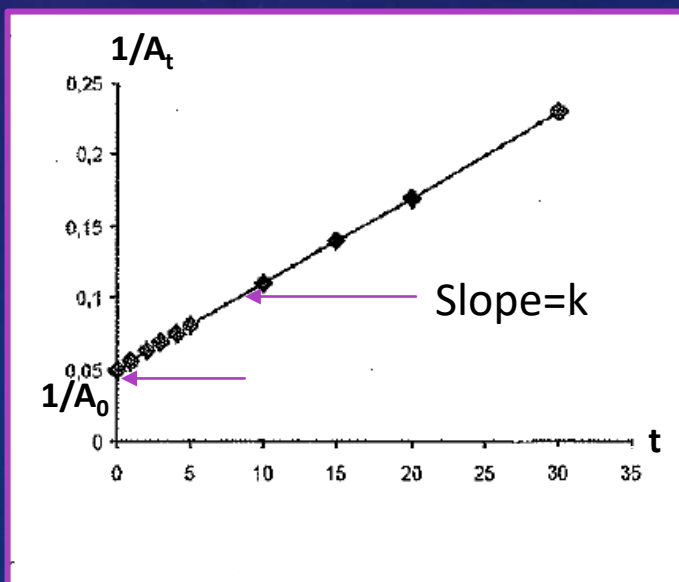When the integral of the both sides are taken;

$$\frac{1}{A_t} = \frac{1}{A_0} + kt$$

Constant of the Reaction
Rate (=k)
(concentration^{-1} . time^{-1})

$$k = \frac{A_0 - A_t}{t A_0 A_t}$$

Half life: $t_{1/2} = 1 / A_0 . k$

Shell life: $t_{\%10} = 1 / 9A_0 . k$

1/A_t
Slope=k
1/A_0

Apparent First-Order Reactions

❖ **If there are two reactants and one is in large excess, the reaction may still follow first-order kinetics because the change in concentration of the excess reactant is negligible.**

❖ **For example; MeAc + H_2O ⟶ HAc + MeOH**

1 M

❖ **Concentration of water is very high (55.5 M), compared to the concentration of the ester (1 M); therefore, the change in water concentration is negligible compared to that of ester.**
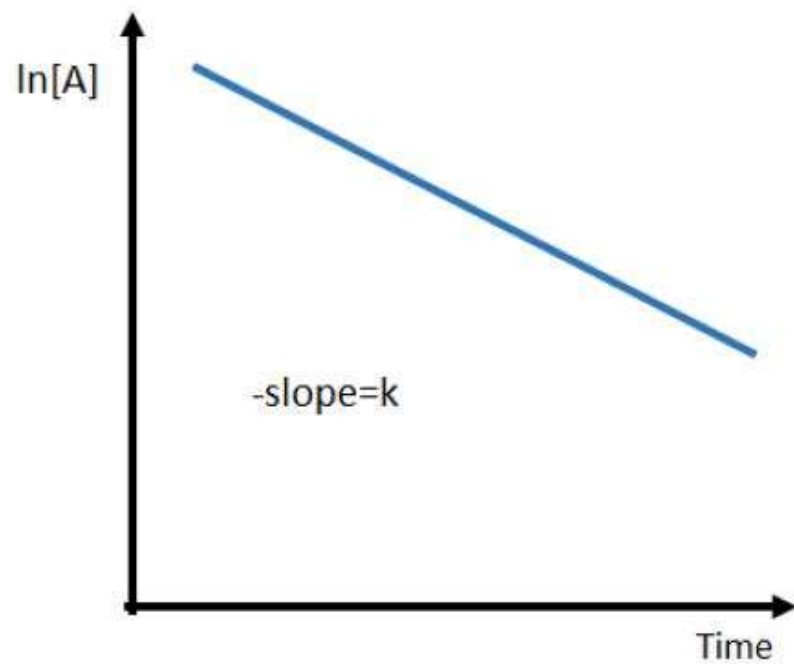
❖ **Rate = k [MeAc] [H_2O] = k_1 [MeAc]**

❖ **So, k_1 = k [H_2O] is the observed pseudo first-order rate constant. This type of reaction is called as a pseudo first-order rate reaction**
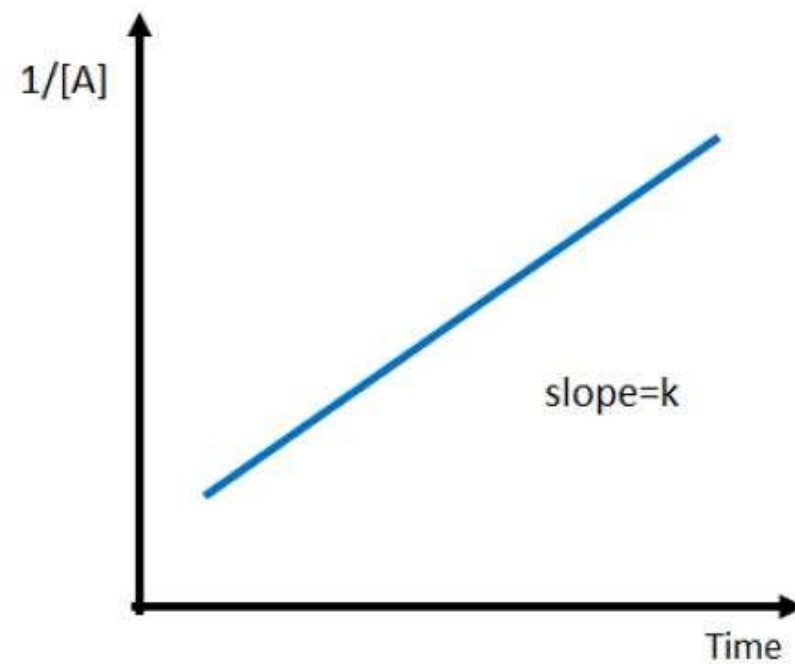
	Zero Order	First Order	Second Order
Rate Equation	$-\dfrac{dA}{dt} = k\left[A_{solution}\right] = k_0$	$V = \dfrac{dA}{dt} = -k[A]$	$V = -\dfrac{1}{2}\dfrac{dA}{dt} = -k[A]^2$
Integrated Rate Equation	$A_t = A_0 - k_0 \cdot t$	$A_t = A_0 \cdot e^{(-k1 \cdot t)}$	$(1/A_t) = (1/A_0) + k_0 \cdot t$
Rate Constant and Unit	$k_0 = [A_0 - A_t] / t$ (concentration/time)	$k_1 = [\ln A_0 - \ln A_t] / t$ (1 / time)	$k = [A_0 - A_t] / t\,[A_0 . A_t]$ (concentration^{-1} . time^{-1})
Half Life [t ½]	$t_{1/2} = A_0 / 2k_0$	$t_{1/2} = 0.693 / k_1$	$t_{1/2} = 1 / A_0 \cdot k$
Shell Life [t %10]	$t_{\%10} = A_0 / 10k_0$	$t_{\%10} = 0.105 / k_1$	$t_{\%10} = 1 / 9A_0 \cdot k$
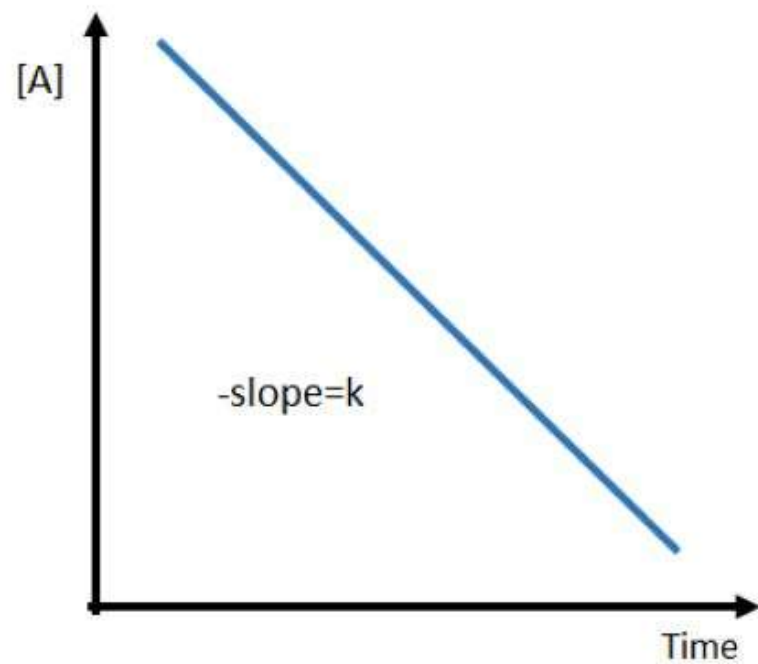
Zeroth-order Reaction — First-order Reaction — Second-order Reaction

[A] vs Time, -slope=k

ln[A] vs Time, -slope=k

1/[A] vs Time, slope=k

Determination of Reaction Order

The order of a reaction is determined using the test results.

Methods used for this purpose;

❖ Differential method

❖ Graphical method

❖ Substitution method

❖ Change in reaction rate versus change in concentration

❖ Half-life method

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Differential Method:

It is an indicator of the rate of change of reactant concentration. **The change in the concentration of the previously monitored substance is plotted. The** slope of the tangent drawn from one point of the drawn curve ($- d [A] / d [t]$) gives the rate at which the concentration changes over time. **The rate of change is determined in two different time and then, the rate of the constant and the degree of the reaction are found by using the differential rate law equation.**

Graphical method:

The data obtained in a kinetic study can be plotted according to each reaction order equation until linear plot is obtained.

Time versus concentration data are plotted and kinetic equations for each degree are obtained.

Concentration (A)

2.degree

1.degree

0.degree

Time (t)
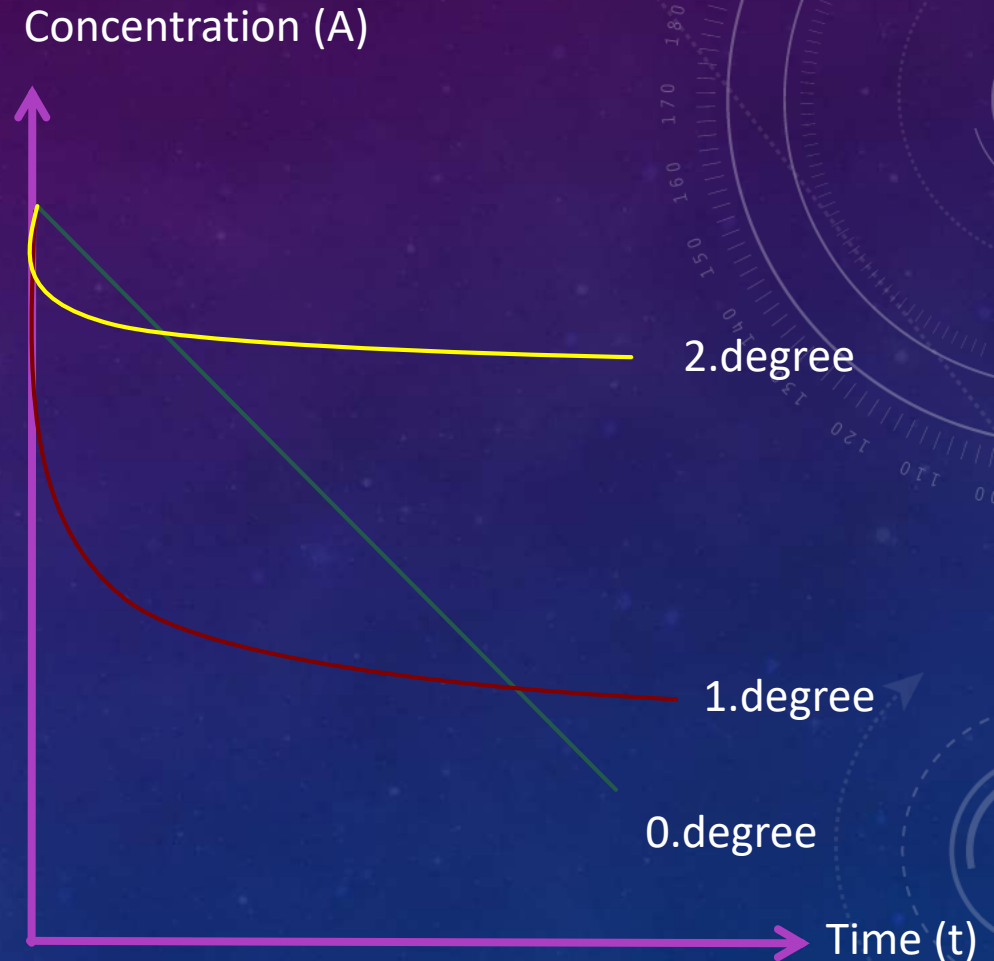
| Order	Zero	First	Second
Graphical plot	$[A]_t$ vs t	$ln[A]_t$ vs t	$1/[A]_t$ vs t

The reaction is zero order if $[A]_t$ vs t gives a straight line.

The reaction is first order if $ln[A]_t$ vs t gives a straight line.

The reaction is second order if $1/[A]_t$ vs t gives a straight line.

If data are plotted according to the linear equations of each kinetics:

◆ **When the concentration of A reactant versus time is graphed, and aslo if the relationship is linear, the degradation reaction takes place as the zero order reaction.**

Concentration

A_0
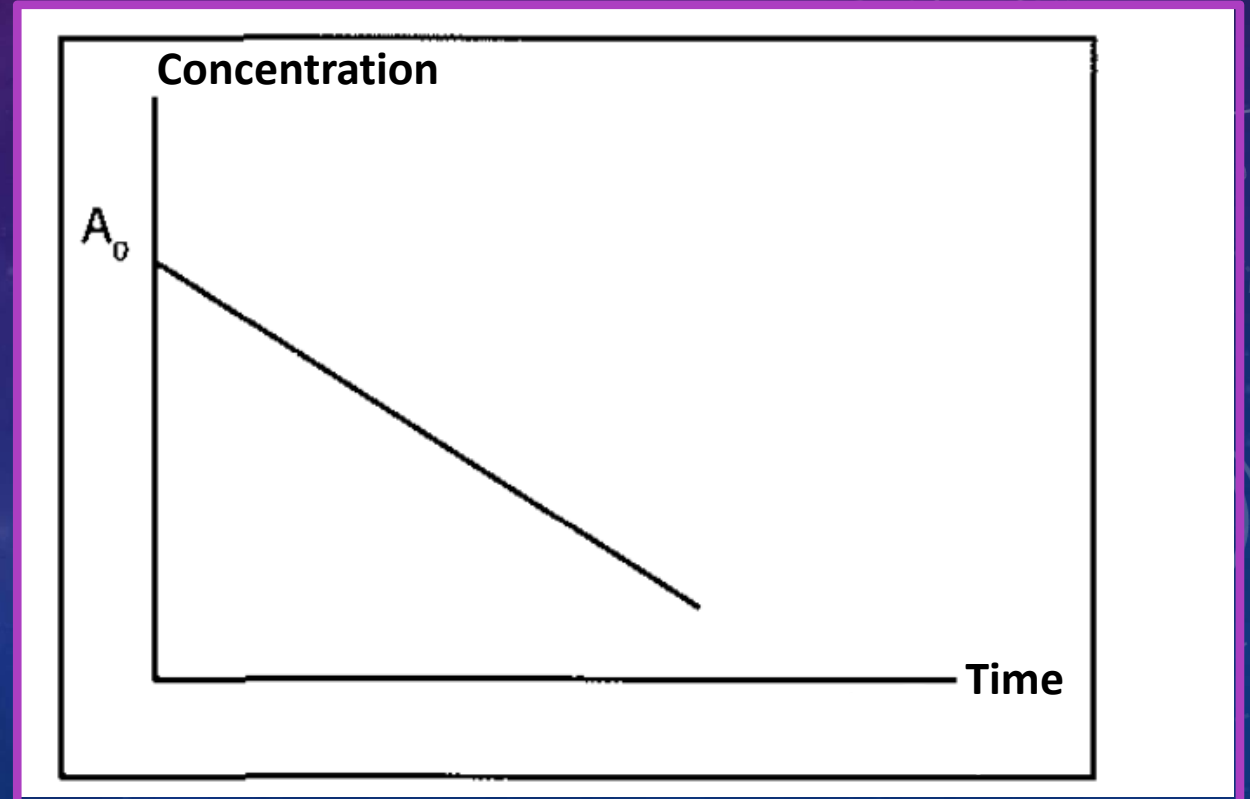
Time

◆ **When the logarithm (lnA) of the concentration of A substance against time (t) is plotted, and also, if the relationship is linear, the degredation reaction takes place as the first order reaction.**
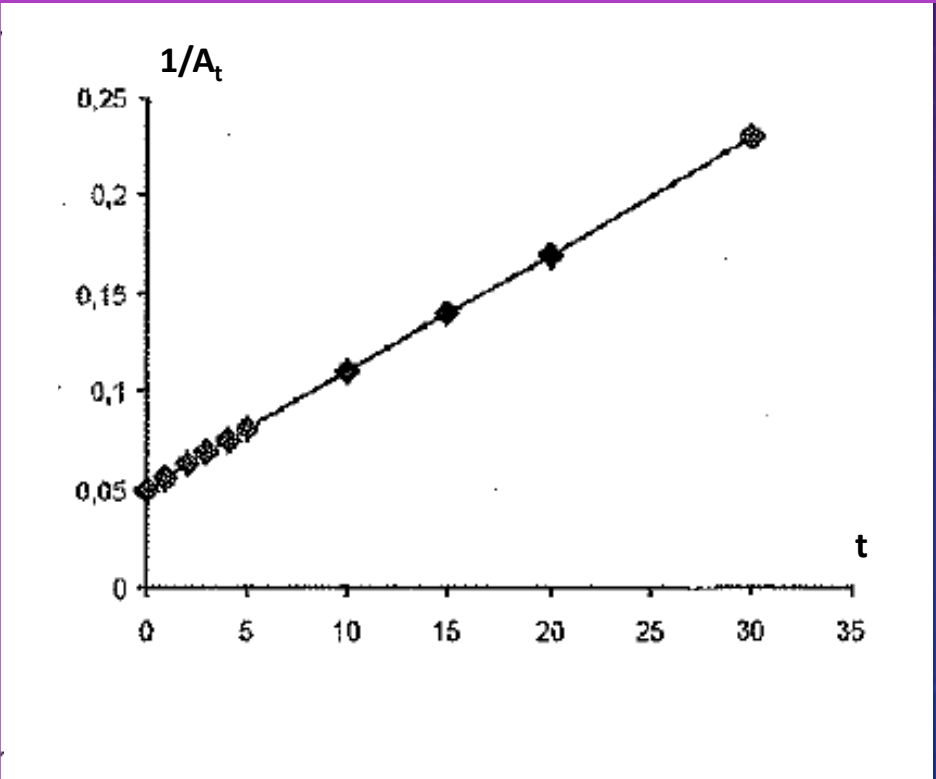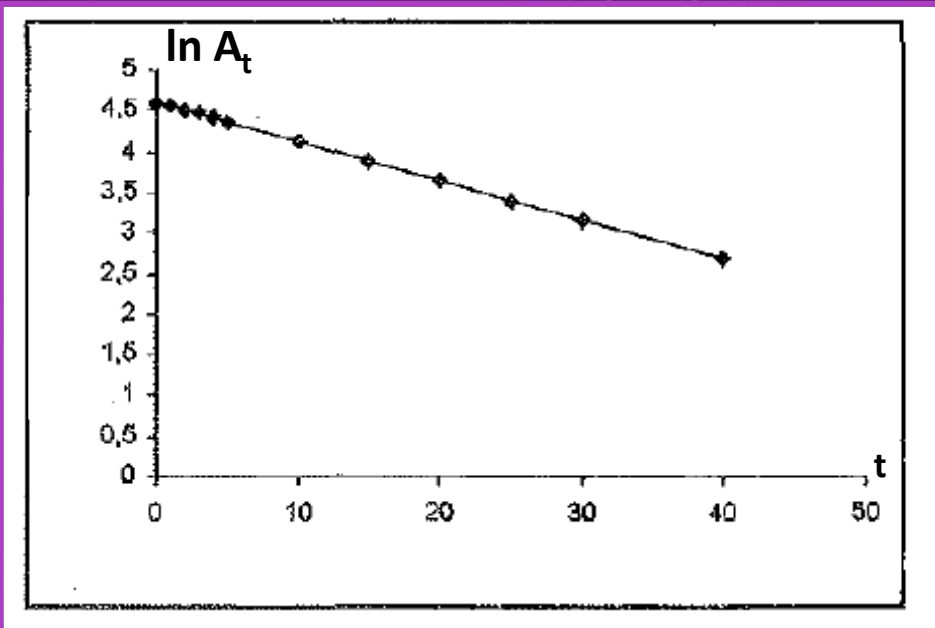
◆ **When the inverse of the concentration of substance A (1 / A) versus time (t) is plotted, and also, if the relationship is linear, the degradation reaction takes place as second order reaction**

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◆**The data is plotted in 3 ways. The degree of reaction is determined by the graph that gives the linear form.**

For example:

The chemical kinetics of a reaction was investigated. It was found that the initial reactant concentration, which was 0.5 M, reduced to 0.125 M after 180 seconds. Given this information and the graphs provided, determine the rate constant.

The reaction is first order since a plot of logarithm of the concentration of substance A ($\ln[A]$) vs time is linear:

$$\ln A_t = \ln A_0 - k_1 t$$

$$\ln 0.125 = \ln 0.5 - [k_1 \times 180]$$

$$k_1 = 7.7 \times 10^{-4} \text{ M/S}$$
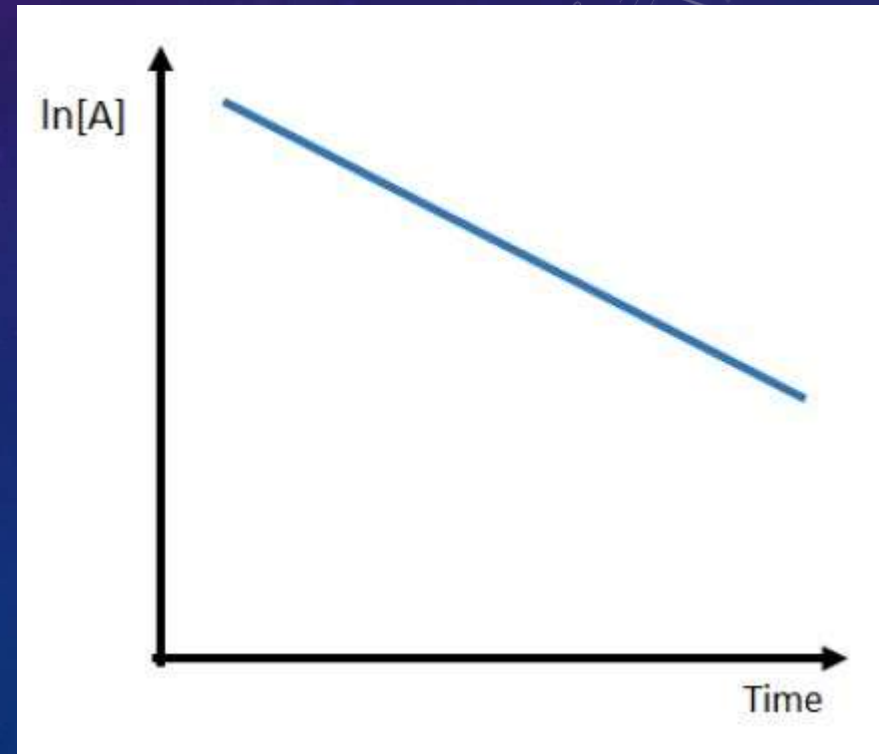
Substitution Method:

- ✓ **From the time and concentration data, the reaction rate constant (k) is calculated for each order.**

- ✓ **The order of reaction (t) for each time, the value of reaction rate constant (k) gives the same result if the reaction is that order.**

- ✓ **If a clear decision is not reached, linear regression is performed.**

- ✓ **The reaction order with the greatest r^2 value is the order of reaction kinetics in which the reaction also takes place.**

Change in reaction rate versus change in concentration:

The aim of this method is based on the following principles:

- ✓ **The reaction speed is constant in zero order reactions.**
- ✓ **The reaction rate in the first order reactions is directly proportional to the concentration.**
- ✓ **The reaction rate in the second order reactions is proportional to the square of the concentration, as you seen in the figure.**

Reaction Rate (V)

2.degree

1.degree

0.degree
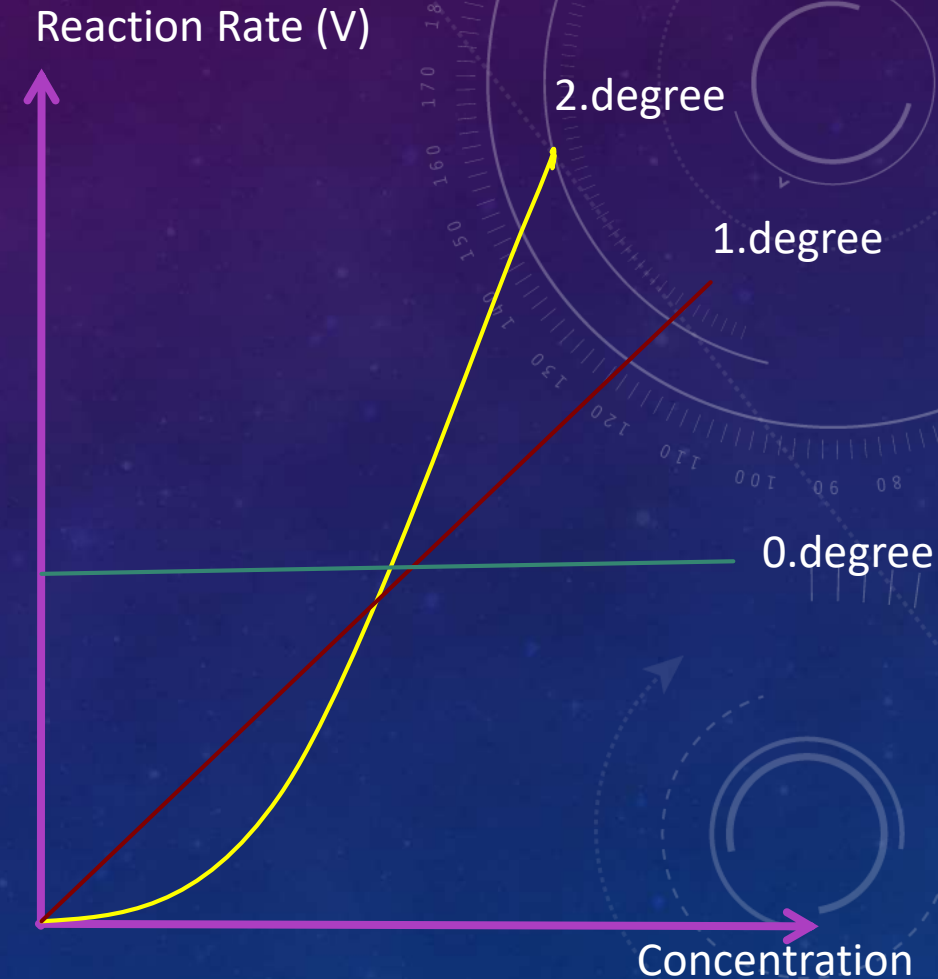
Concentration

Half-life method:

The half-lives for various initial concentrations are measured:

Reaction Order	Half Life Equation
Zero Order	$t_{1/2} = A_0 / 2k_0$
First Order	$t_{1/2} = 0.693 / k_1$
Second Order	$t_{1/2} = 1 / A_0 . k$

❖ **If half-life is directly proportional to the initial concentration, the degredation occurs with a zero-order reaction.**

❖ **If the half-life is independent of the initial concentration, the degradation takes place with a first order reaction.**

❖ **If the half-life is proportional to the inverse of the initial concentration, the degradation is takes place with a second order reaction.**

Reaction Order	Half Life Equation
Zero Order	$t_{1/2} = A_0 / 2k_0$
First Order	$t_{1/2} = 0.693 / k_1$
Second Order	$t_{1/2} = 1 / A_0 \cdot k$

in other words;

❖ **The reaction is zero-order if half-life increase when initial concentration increase.**

❖ **The reaction is first-order if half-life is not affected by initial concentration.**

❖ **The reaction is second-order if half-life decrease when initial concentration increase.**

In general, the half-life of an active agent is proportional to the $(n-1)^{th}$ force of the inverse of the initial concentration.

A = Initial concentration
n = Reaction order

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

If the two reactions go through two different initial concentrations such as A1 and A2, the relationship between the half-lives is calculated with this equation:

$$n = \frac{\ln\left(t_{1/2(1)} / t_{1/2(2)}\right)}{\ln\left(A_2 / A_1\right)} + 1$$

Concentration-Time plots are used to determine when concentrations are halved. These two half-life values are put in the corresponding equation and the reaction order is calculated.

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Example: The degradation data of an active substance is as follows. Calculate the order of kinetics of degradation reaction by using graphical method?

t (hour)	0	10	20	30	40	50	60
A (mg.L^{-1})	10	6.2	3.6	2.2	1.3	0.8	0.6
ln A	2.30	1.83	1.27	0.79	0.26	-0.22	-0.51
1/A	0.10	0.161	0.278	0.455	0.769	1.250	1.667

Answer: In order to find out which kinetics is suitable for a substance, the given data is plotted and if the graph is linear, the reaction takes place through that reaction order. If not, linear regression is performed. Whichever r^2 is greater, the reaction is appropriate to that order.
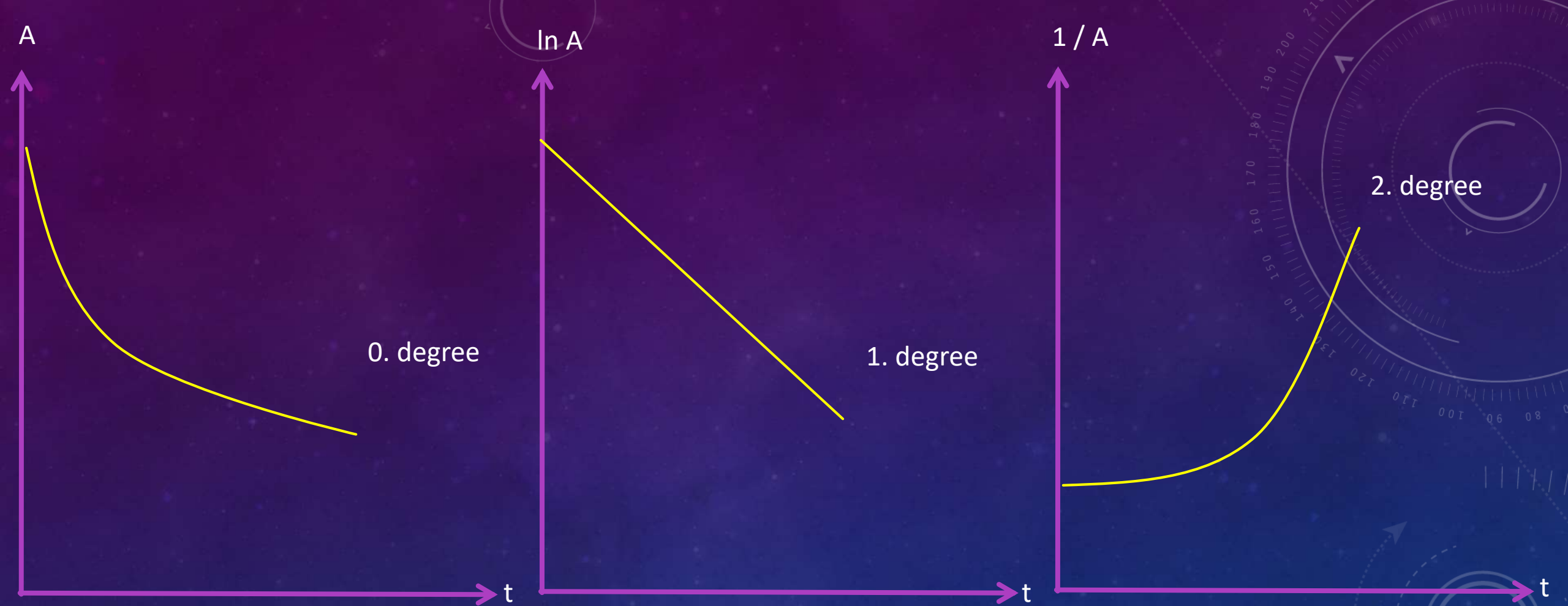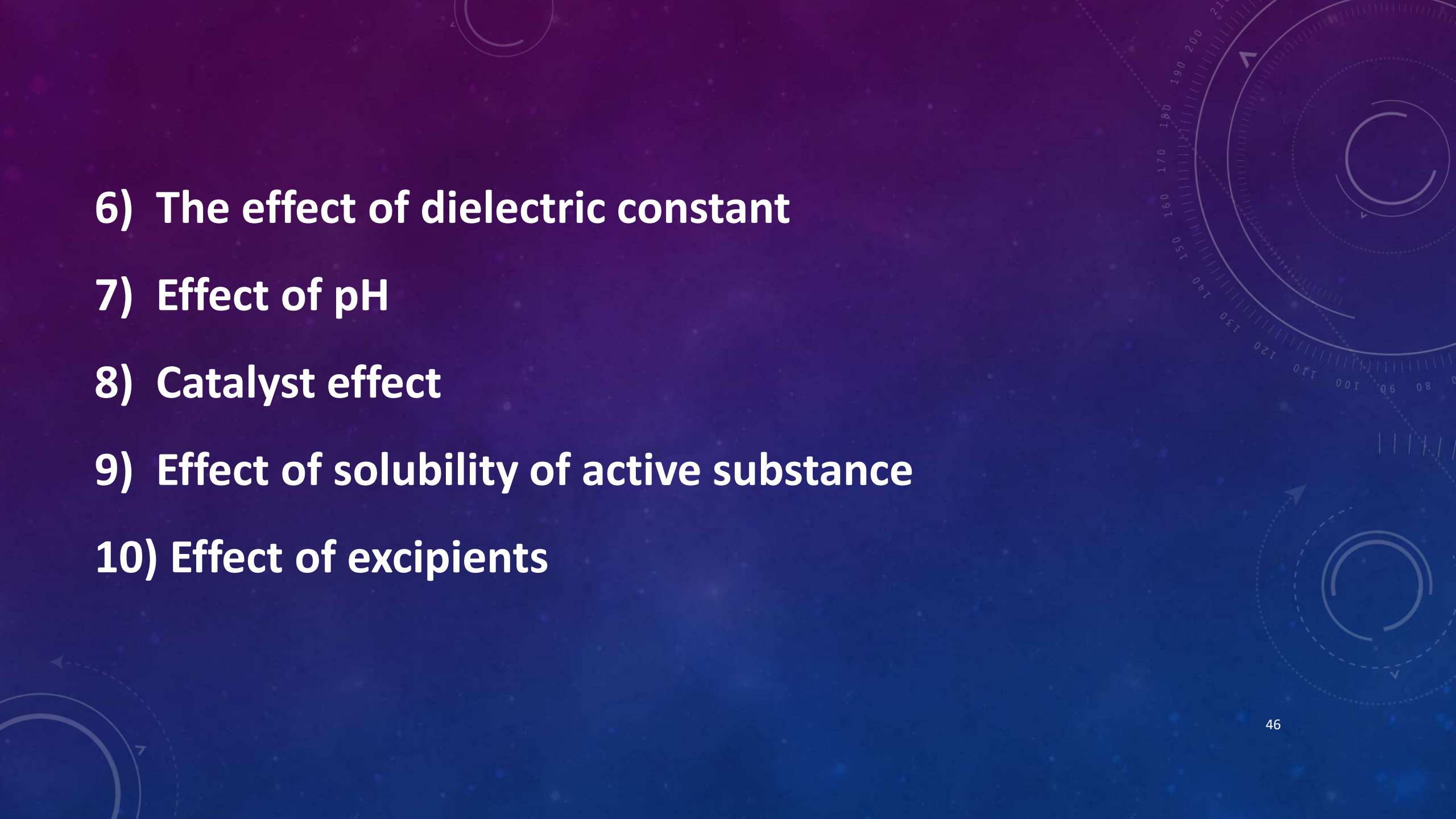
When the data in the table are plotted, it is determined that the reaction takes place with 1st order because the straight line is observed in the 1st order degredation kinetic graph.

Factors Affecting Reaction Rate

The reaction rate varies depending on many factors. These factors can be listed as follows;

1) Temperature effect

2) Moisture effect

3) Light effect

4) Solvent effect

5) Effect of ionic strenght

6) The effect of dielectric constant

7) Effect of pH

8) Catalyst effect

9) Effect of solubility of active substance

10) Effect of excipients

1) Temperature Effect:

- ✓ **Temperature is one of the most important factors affecting the reaction rate. The higher the temperature, the greater the number of exponents of the molecules and therefore the rate of reaction.**

- ✓ **Increase in temperature usually causes a very pronounced increase in the hydrolysis rate of drugs in solution.**

- ✓ **When the temperature of the reactions increased to $10°C$, the reaction rate increased by 2-4 fold.**

The equation which describes the effect of temperature on the reaction rate and decomposition is the «Arrhenius Equation».

Based on experimental results, Arrhenius determined that the reaction rate constant changes exponentially with absolute temperature. Using this equation, the researchers gain an idea about the stability of drugs.

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

$$\ln k = \ln A - \frac{E_a}{R} \cdot \frac{1}{T}$$

$$\log k = \log A - \frac{E_a}{(2.303 \cdot R)} \cdot \frac{1}{T}$$

k = Reaction rate constant
A = Frequency of collision of molecules (frequency factor or Arrhenius constant)
E_a = Activation energy (cal / mol)
R = Gas constant (1.987 cal / degree / mol)
T = Absolute temperature (ºK) (ºC + 273.15ºC)

Arrhenius plot is used to theoretically estimate the rate constant at room temperature (where reaction occurs at a rate too slow to measure)

This method is used for the measurements of drug stability during preformulation studies.

Dependence of reaction rate on temperature (Arrhenius plot)

$$\ln k = \ln A - E_a/RT$$

intercept $= \ln A$

$\ln k$

$\text{slope} = - E_a/R$

$1/T \ (K^{-1})$

ln k

log k

$m = - [E_a / R]$

$m = - [E_a / 2.303 . R]$

1 / T

1 / T
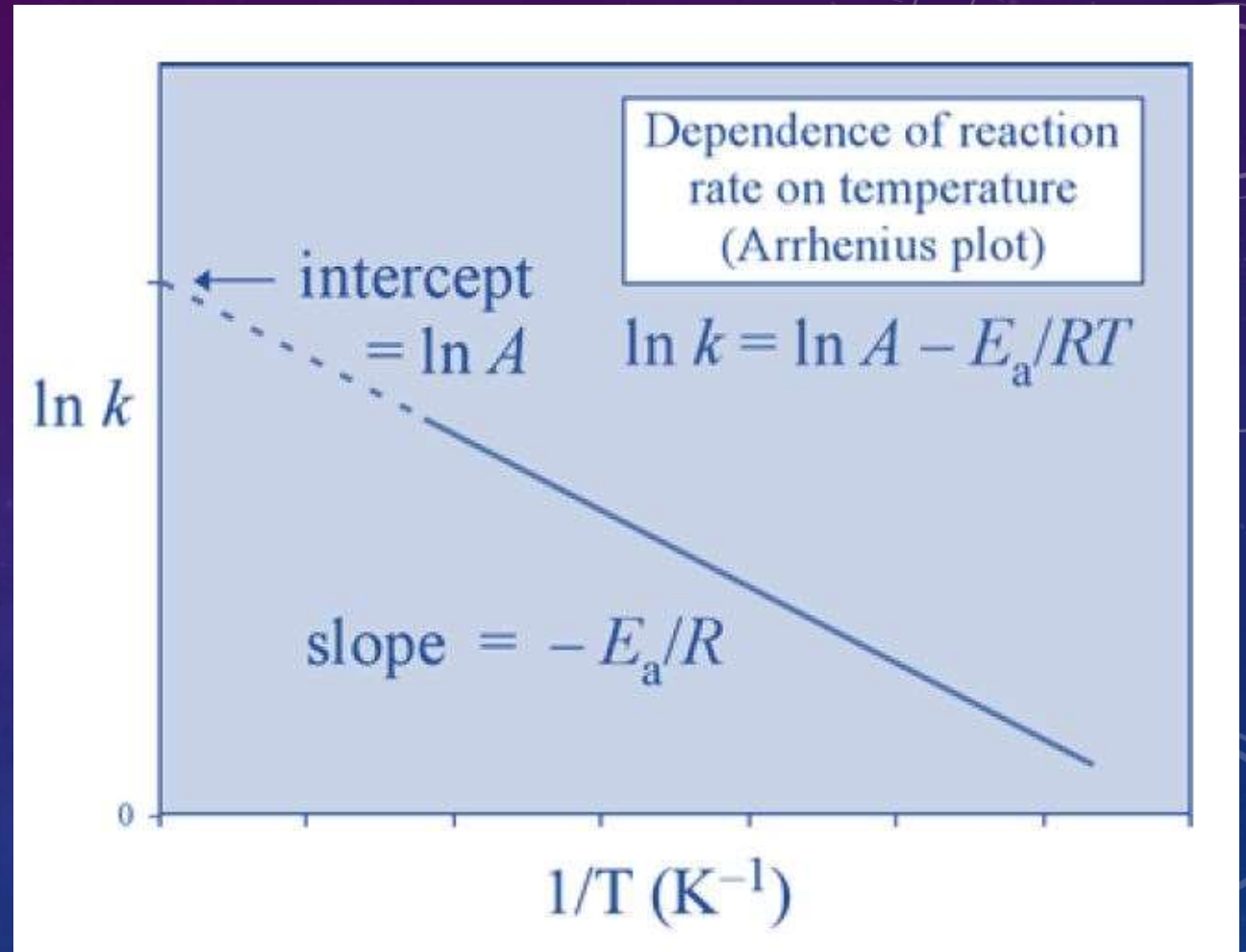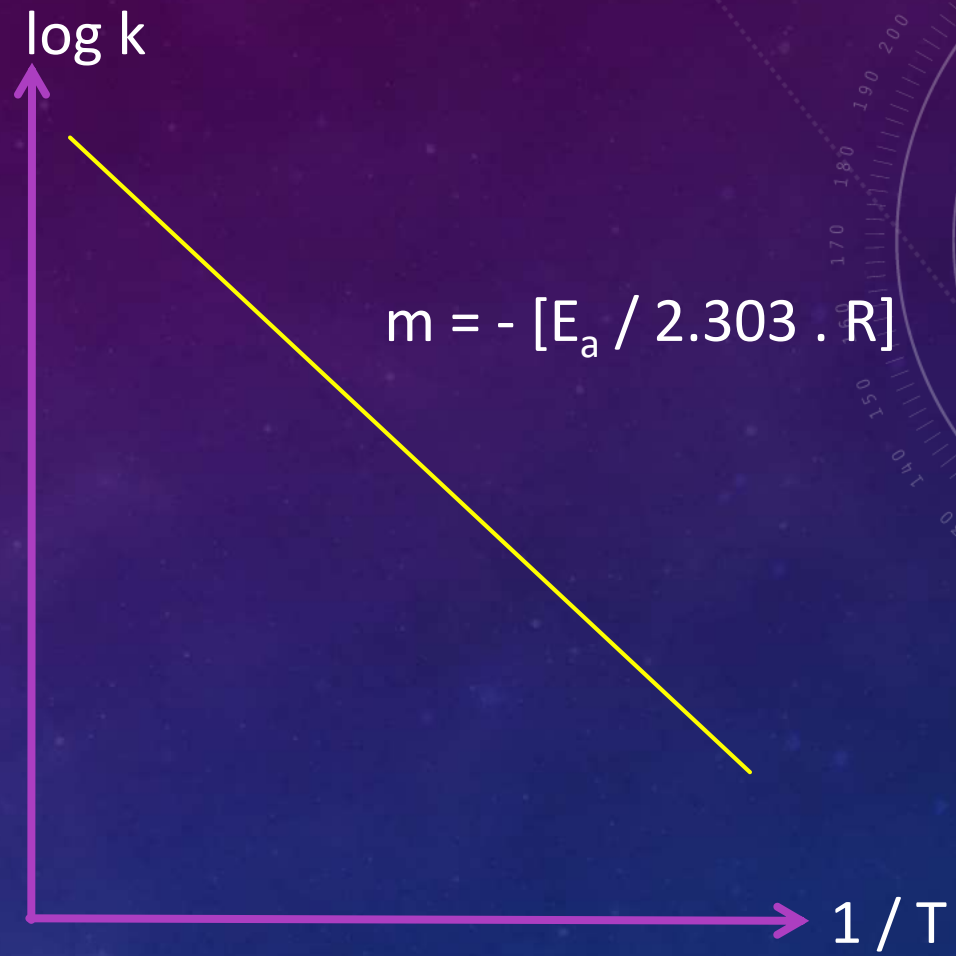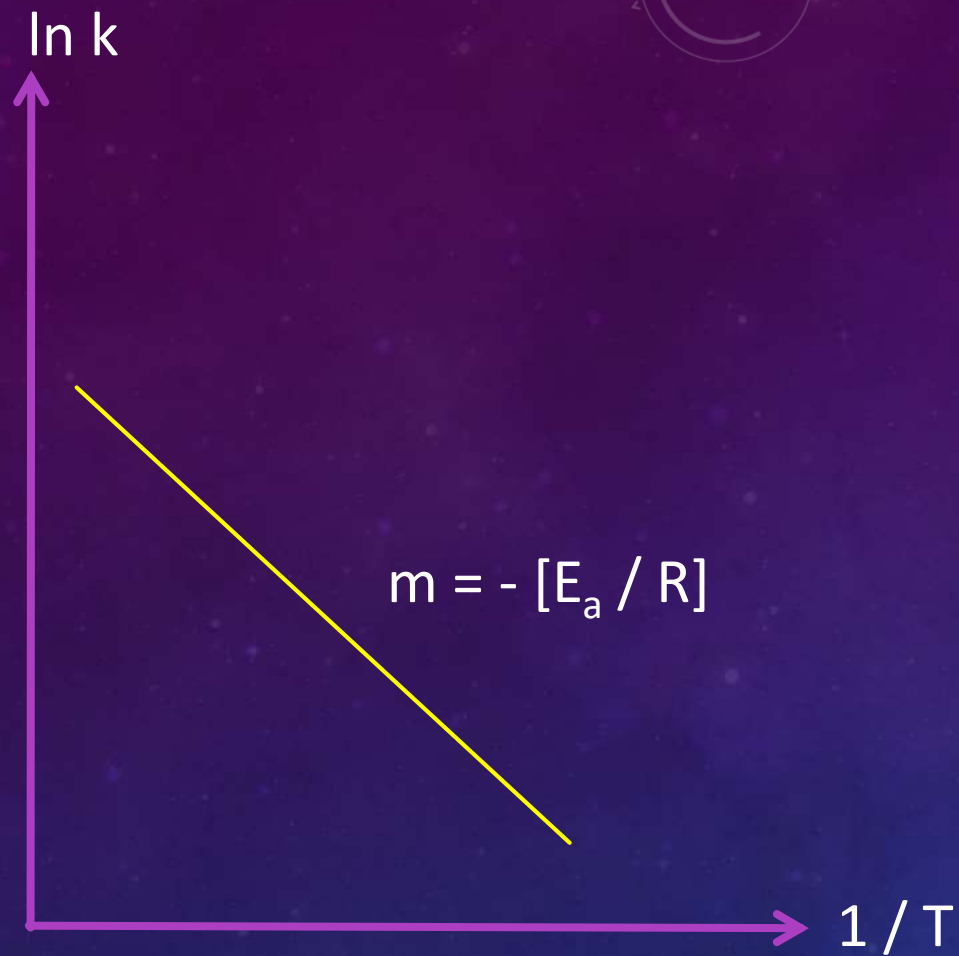
The lowest energy required for the components to start a reaction is called as «Activation energy (Ea)» .

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In cases where the activation energy (Ea) is less than 10 kcal / mol, decomposition reactions will occur more easily and therefore the drug solution will be more easily hydrolyzed so that it is decomposed at room temperature more quickly.

In cases where the Ea value is greater than 30 kcal / mol, decomposition reactions will be very difficult and therefore the drug solution is resistant to room temperature.

If the Ea value is between 10 and 30 kcal / mol values, the condition of temperature tests is required.

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To determine the stability depending on the temperature of the drug at temperatures of 40°C - 50°C - 60°C is held for a period of time specified previously. Depending on time, the concentration of the active substance is determined.

From these values «k» the speed constant is calculated. «1 / T» versus «log k» is graphed to extrapolate the line obtained by the desired point «k» value is calculated. From this, the «shelf life» of the active substance is determined.

Example : The initial concentration and the specific decomposition rate constant of an active substance which is decomposed by first-order kinetics is Ao = 94 u/ml, and k = 2.09×10^{-5} hours^{-1}, respectively. Preliminary trials have shown that when the concentration of the active substance decreases to 45 u/ml, the potency of the active substance will disappeared and the active substance is ineffective. What is the expire date of this drug?

Answer:

$$logA_t = logA_0 - [k_1 / 2.303] \cdot t$$ $\longrightarrow$

$t = (2.303 / k_1) \cdot log (A_0 / A_t)$

$t = [2.303 / (2.09 \times 10^{-5})] \cdot log (94 / 45)$

$t = 3.5 \times 10^{-5}$ hour $\cong$ 4 years

Isothermal Tests:

The tests carried out by holding the drug for a certain period of time at each temperature to be examined.

The equation used to calculate the activation energy from the experimental data made at only two temperatures is as follows:

$$\ln \frac{k_2}{k_1} = \frac{E_a}{R} \cdot \left\{ \frac{T_2 - T_1}{T_2 \cdot T_1} \right\}$$

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303 \cdot R} \cdot \left\{ \frac{T_2 - T_1}{T_2 \cdot T_1} \right\}$$

90% residual concentration

$m = k$

Non-Isothermal Tests:

Instead of keeping the drug separately at each temperature, it depends on the time of the experiment to change the temperature according to a specific program such as hyperbolic temperature change, linear temperature rise, logarithmic increasing or decreasing temperature program.

$$\ln k_t = \ln k_0 - \frac{E_a}{R} \cdot \left\{ \frac{1}{T_t} - \frac{1}{T_c} \right\}$$

t
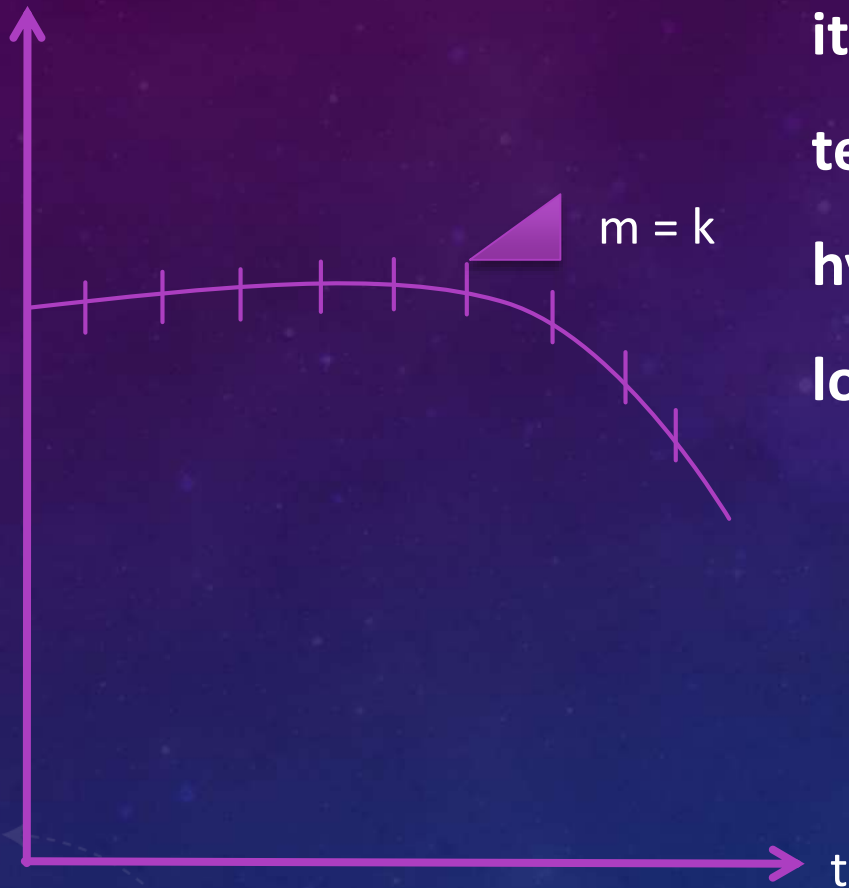
at

$$1 / T_t = 1 / T_0 + at$$

T_t = Temperature value at time t
T_0 = Inıtial temperature
a = Inverse of heating rate constant
t = Time

Non-isothermal tests are short-term tests, especially in formulation studies. It has less sensitivity than isothermal tests. They are promising tests. They are not accepted testes as isothermal tests.

Shelf life is determined by using Arrhenius equation for room temperature. However, in the experiments with very high temperatures, errors may occur in the shelf life determination due to the evaporation of the solvents.

The Arrhenius equation is not applied for each reaction. Solvatic processes which occur in degredation reactions in the solutions, are applied when Ea is 10-30 kcal/mol.

The Conditions When the Arrhenius Equation is Unused

1. Diffusion and photochemical reactions in which the activation energy is between 2-3 kcal / mol

2. Pyrolysis reactions of polyhydroxylic substances in which the activation energy is between 50-70 kcal / mol

3. Freezing process, decomposition by microorganisms and decomposition during transportation

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4. Products containing suspending agents such as microcellulose which are coagulated at high temperature or proteins that are denatured at high temperature

5. Dosage forms in the form of ointments, suppositories and emulsions

6. The order of reaction can change during operation

7. Multiple decomposition mechanisms

8. Autocatalysis reactions, in other words, increase the rate of degradation of substances formed in the reaction

Example: A drug that degraded by a first-order reaction loses 30% of its effectiveness at 100°C in 1 hour. The same drug loses 23.7% of its efficacy in 20 minutes at 110ºC. How long does this drug lose 10% of its activity at 25°C?

Answer:

$k = [2.303 / t] . \log (A_0 / A)$

$k_{100} = [2.303 / 60] . \log (100 / 70) = 5.9 \times 10^{-3} \, dk^{-1}$

$k_{110} = [2.303 / 20] . \log (100 / 76.3) = 0.014 \, dk^{-1}$

So the activation energy :

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303 . R} . \left\{ \frac{T_2 - T_1}{T_2 . T_1} \right\}$$

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303 \cdot R} \cdot \left\{ \frac{T_2 - T_1}{T_2 \cdot T_1} \right\}$$

$T_1 = 273 + 100 = 373°K$

$T_2 = 273 + 110 = 383°K$

$$\log \frac{k_{110}}{k_{100}} = \frac{E_a}{2.303 \cdot R} \cdot \left\{ \frac{383 - 373}{373 \cdot 383} \right\}$$

$$\log \frac{0.014}{5.9 \times 10^{-3}} = \frac{E_a}{2.303 \cdot 1.987} \cdot \left\{ \frac{383 - 373}{373 \cdot 383} \right\}$$

$E_a = 24533$ cal / mol

$= 24.533$ kcal / mol

$$\log \frac{k_{110}}{k_{25}} = \frac{E_a}{2.303 \cdot R} \cdot \left\{ \frac{T_2 - T_1}{T_2 \cdot T_1} \right\}$$

$$\log \frac{0.014}{k_{25}} = \frac{24553}{2.303 \cdot 1.987} \cdot \left\{ \frac{383 - 298}{298 \cdot 383} \right\}$$

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$$\log \frac{0.014}{k_{25}} = 3.99 \longrightarrow k_{25} = 1.43 \times 10^{-6}$$

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

$$T_{\%10} = 0.105 / 1.43 \times 10^{-6}$$

$$T_{\%10} = 73426 \text{ minutes} \cong 51 \text{ days}$$

Example: It was determined that a drug which had A_0 = 400 units / ml and decomposed by a first order reaction decreased to 336 units / ml at room temperature when it was checked after 24 months. Find the shelf life of this drug.

1. order $\longrightarrow$ $\ln A_t = \ln A_0 - (k_1 \cdot t)$

$\ln 336 = \ln 400 - (k_1 \cdot 24)$

$k = 7.26 \times 10^{-3} \ month^{-1}$

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

$t_{\%10} = 0.105 \ / \ 7.26 \times 10^{-3}$

$t_{\%10} = 14.46 \ months$

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Example: The decomposition amount and time data of 0.056 M glucose at 140°C in an aqueous solution containing 0.35 N HCl are as follows;

t (hour)	Remaining Glucose (mol / L x 10^{-2})
0.5	5.52
2	5.31
3	5.18
4	5.02
8	4.78
10	4.31
12	4.11

Calculate the order of reaction and the half-life of the glucose.

Answer: Linear regression analysis is performed for all three reaction degrees and the degree of degradation with the highest r^2 is determined.

t (hour)	Remaining Glucose (mol / L x 10^{-2})	At	lnAt	1 / At
0.5	5.52	5.52 x 10^{-2}	-2.896	18.115
2	5.31	5.31 x 10^{-2}	-2.935	18.832
3	5.18	5.18 x 10^{-2}	-2.960	19.305
4	5.02	5.02 x 10^{-2}	-2.991	19.920
8	4.78	4.78 x 10^{-2}	-3.040	20.920
10	4.31	4.31 x 10^{-2}	-3.144	23.201
12	4.11	4.11 x 10^{-2}	-3.191	24.330

0. order $\longrightarrow$ $A_t = A_0 - (k_0 . t)$

1. order $\longrightarrow$ $\ln A_t = \ln A_0 - (k_1 . t)$

2. order $\longrightarrow$ $1 / A_t = 1 / A_0 + (k_2 . t)$

Because this is the highest r^2 value, the reaction is zero degrees.

0. order $\longrightarrow$ y = -0.001180x + 0.055,   r = -0.9880, r^2 = 0.976*

1. order $\longrightarrow$ y = -0.024x − 2.882,   r = -0.9854, r^2 = 0.971

2. order $\longrightarrow$ y = 0.520x +17.721,   r = 0.9815, r^2 = 0.963

Zero order degradation kinetic;

$k_0 = -0.001180$

$t_{1/2} = A_0 / 2k_0$

$t_{1/2} = 0.056 / 2 \times 0.001180$

$t_{1/2} = 23.72$ hour $\cong 24$ hour $= 1$ day

2) Moisture effect:

In solids and semi-solids, the degradation of the active substance is affected by the moisture content and humidity of the environment. Role of moisture as a catalyst can be summarized as;

a) Reactive (biomolecular reactions),

b) Adsorption,

c) Hydrate formation.

Moisture Content of Excipients

Some substances contain crystal water in their structure. As a result of the applied processes, crystal water is got out and degredation occurs. If substances are stored below critical moisture content, crystal water is again got out and degredation occurs.

For example; ampicillin trihydrate contains 3 molecules crystal water. As a result of the grinding process, cystal water is got out and degredated.

If the excipient is able to adsorb the moisture in the medium, the degradation of the active substance decreases and the stability increases.

For example; Colloidal silicon, reduces the rate of aspirin degradation.

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The excipients may also catalyze the degradation of the active substance.

For example; when Mg-stearate is used as a lubricant in vitamin B1 (Thiamine) tablets and there is moisture in the environment, Mg-stearate plays the role of catalyst and increases the degradation of the active substance.

Hygroscopic substances; are the substances that get moisture from the environment. They directly dehumidify and cause degradation of the active substance.

For example; Starch, sorbitol, propylene glycol, polyethylene glycol ..

3) Light effect :

Normal sunlight or room lights can also lead to degredation of drug molecules. **Light energy, like as heat, also provides the activation energy required to start a reaction.** For this, the light must be at a certain frequency and a certain amount of energy. **The light energy must be absorbed by the molecule in order to initiate the degradation reaction.** As light energy is absorbed by the molecule, electrons emerge from low to high energy levels and cause various chemical reactions.

Major reactions caused by this energy (photon) are;

➤ **Decomposition,**

➤ **Immersion or transfer to other molecules,**

➤ **Heat energy conversion,**

➤ **Propagation of light at a different wavelength (fluorescence or phosphorescence agents)**

The degradation reactions that occur with light are called PHOTOLIS REACTIONS. In photolysis reactions, the wavelength is small and the high energy rays are effective. In other words, there is an inverse relationship between wavelength and energy.

Wavelengths and energies of UV, Visible and IR rays.

Light Type	Wavelength (nm)	Energy (Kcal/mol)
UV	50-400	286-72
Visible	400-750	72-36
IR	750-10000	36-1

- In general, drugs absorbing light at wavelengths below 280 nm are susceptible to sunlight degradation.

- Molecules absorbing light above 400 nm are susceptible to degradation in both sun and room temperature.

In order to examine the effects of photolysis reactions, «Photostability» studies are performed.

In this context, photostability tests are carried out on the active substance and in the primary packaging material. If the results are not suitable, the test must be carried out in secondary packaging material too.

To perform the photostability test;

- Fluorescent lamp (visible + UV) are used to reflect artificial daylight.
- Fluorescent lamps (UV-A) are used to give a cool white light.