Examples

① photochemical Reaction bet° H and Cl

$$H_2(g) + Cl_2(g) \xrightarrow{h\nu} 2HCl(g)$$

② Decomposition of N_2O on hot platinum surface

$$N_2O \longrightarrow N_2 + \tfrac{1}{2}O_2$$

$$\text{Rate} \propto [N_2O]^0 = K[N_2O]^0 = K$$

$$\frac{d[N_2O]}{dt} = K$$

③ Decomposition of NH_3 in the presence of molybdenum or tungsten

$$2NH_3 \xrightarrow{Mo} N_2 + 3H_2$$

Pseudo-Zero-Order-Reaction

Pseudo-zero-order reaction may be a first-order reaction, but behaves like a zero-order reaction, as per the experimental conditions.

Reactions taking place in pharmaceutical suspensions are generally of pseudo-zero-order type.

The solubility-limited degradation phenomenon can be explained as follows:

A part or the drug in suspension is present in the solution phase and undissolved solid. Degradation occurs only when the drug is in the solution-phase. When the drug in solution degrades the suspended particles become a reservoir and start releasing the drug into the solution, keeping the drug concentration in solution constant. Thus, the degradation rate follows a zero-order-reaction.

When there is no reservoir of solid and the drug is completely in the solution phase, First order reaction is followed.

The values of ... be determined ... temp.

(iii) (c) Ionic Strength

The effect of ionic strength of a solution on the degradation rate may be expressed in the form of the following equation.

$$\log k = \log k_0 + 1.02 Z_A Z_B \sqrt{\mu}$$

where,

k = Degradation rate constant for the reaction

k_0 = Reaction rate constant at infinite dilution

Z_A and Z_B = charges carried by the reaction A and B in solution.

μ = Ionic strength of the solution.

According to the above equation, an increase in the ionic strength of the solution would decrease the rate of reaction involving interaction between oppositely charged ions and increase the rate of reaction between similarly charged ions.

For example - The hydrogen ion-catalysed hydrolysis of sulphate ester would be inhibited by an increase in the electrolyte concentration.

$$ROSO_3^- + H_2O \xrightarrow{H^+} ROH + HSO_4^-$$

Reaction between ions and dipolar molecules and reaction between neutral molecules are not affected to a significant extent by change in ionic concentration. Reactions which results forms oppositely charged ions (as products) exhibit an increase in reaction rate on increasing ionic strength.

(iv) Dielectric constant of solvent

The dielectric constant of the solvent has a significant effect on the rate of reaction. For a reaction involving a charged reactant molecule and another ionic species (such as H^+ or OH^-), the effect of the dielectric constant on the reaction rate is given by the equation,

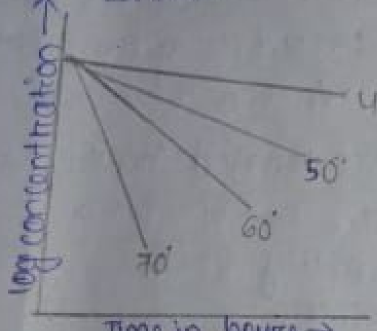
$$\ln k = \ln k_{\varepsilon=\infty} - \frac{N Z_A Z_B e^2}{RTr^*} \frac{1}{\varepsilon}$$

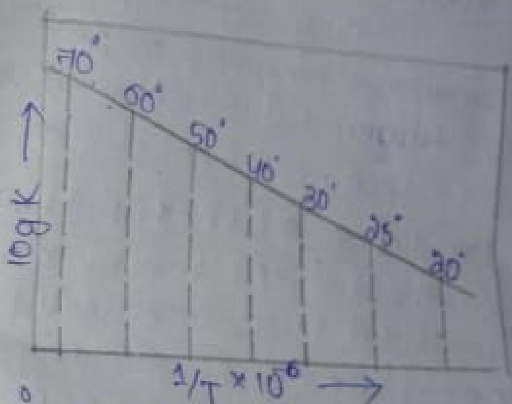
Accelerated ...

where K = Rate constant
R = Gas constant (1.987 cal / mole)
T = Absolute temp
A = Frequency Factor
E_a = Energy of Activation.
$T_{90\%} = (2.303/K) * (\log 100/90)$
$T_{90\%} = (2.303/K) * (\log 100/10)$

Methods

The steps involved in Garret and Carper method are.
(i) samples of the drug product are kept at 40°C, 50°C and 60°C
(ii) Drug content is determined at all the three storage points by taking a few samples and determining their mean drug content for a few weeks.
(iii) A graph between time and log concentration is plotted for each temp.
(iv) In the next step, a best fit line is drawn by taking $1/T \times 10^6$ on x-axis and the log K or log of reaction constant on Y-axis.





If the reaction is following zero-order:
expiration date at 25°C = Initial potency − minimum potency / reaction rate at 25°C

$t_x = Y_0 - Y_x / K_0$

If the reaction is following first order:
Expiration date at 25°C (t_x) = log Initial potency − log minimum potency / reaction rate at 25°C.

$t_x = \log Y_0 - \log Y_x / K_1$

where Y_0 = Initial potency
Y_x = Final potency
K_0 = zero-order constant
K_1 = First-order constant.

(5) Surfactants - These agents (polysorbate 80) enhance the oxidation rate of ascorbic acid at low ~~temp~~ concentration, but protect above its critical Micelle concentration (CMC), by entrapping the drugs in spherical micelles.

(6) Low temperature storage - The pharmaceutical products are stored in a cool place because high temperature enhances the rate of oxidation.

(7) Oxygen free environment - oxidative degradation is catalysed by oxygen. Therefore air is replaced with inert gases (N_2 and CO_2) or oxygen free solvents are used for manufacturing drugs.

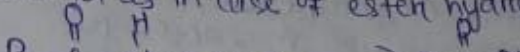
(A) Ester - Hydrolysis - procaine, tetracaine, aspirin, atropine (15)

The most common type of ester hydrolysis reactions involve acyl-oxygen cleavage. The ester hydrolysis whether acid or base catalysed can be represented as :

(Ester) Acid Alcohol.

(B) Amide hydrolysis - dibucaine, chloramphenicol, niacinamide

Amide hydrolysis usually involves the cleavage of the amide linkage to give an amine instead of an alcohol as in case of ester hydrolysis.



(Amide) (Amine)

(C) Ring - hydrolysis - benzodiazepines, nitrazepam, chlordiazepoxide, penicillines.

Hydrolytic reactions in certain drugs proceeds by ring cleavage with subsequent attack by hydrogen or hydroxyl ions.

Prevention :

(i) Buffer - Buffers are used for the stabilisation of drugs. By adjusting the pH of a solution, stability and therapeutic activity of a drug is maintained, In most cases, optimal pH remains 3.5 - 5

(ii) complexation = caffeine inhibits the hydrolysis of benzocaine in aqueous solution by forming a complex which decreases the attack of catalytic species on benzocaine, Thus, the hydrolysis rate is influenced by amount of the free-uncomplexed benzocaine in solution.

(iii) suppression of solubility : Drug concentration in the solution phase is linearly proposnal to drug solubility in the solution. Therefore on decreasing the solubility of a drug in the solution, its concentration in the solution also decreases.

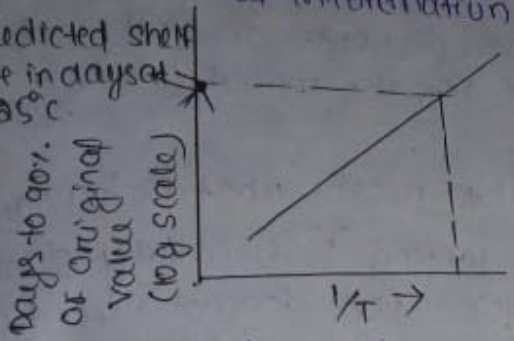
(iv) Removal of water - water content should be completely removed from the formulation because it causes hydrolysis.

... procaine, tetracaine, ... hydrolysis ...

Limitation Of Accelerated Stability Analysis (14)

(i) Stability predictions based on Arrhenius equation, are valid only when the energy of activation for the thermal decomposition lies within the range of 10 to 30 Kcal/mole.

(ii) Certain reactions which usually donot takeplace under normal conditions of storage may takeplace under accelerated or high stress conditions and hence actual information may not be obtained.



(iii) The order of the reaction may be different in real and accelerated conditions.

(iv) Accelerated testing cannot be used if the decomposition is due to freezing, contamination by micro-organisms (eg - breaking of tablets)

(v) Products such as emulsions may appear to be more stable at elevated temp. which may not be the case at normal storage conditions.

Stability Testing

A study of drug stability and of stability testing techniques is essential for following main reasons-

(A) Patient Safety - Pharmaceutical industry produces highly specific, chemically potent drugs. The patient should receive a uniform dose of the drug throughout the shelf life of the product.

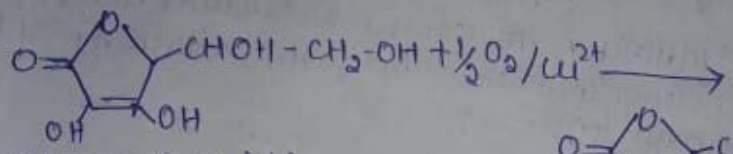
(B) Drug - Activity - In addition to the formation of toxic products, deterioration will also lead to a reduced activity of the compound or preparation and hence the therapeutic benifits of the preparation will be reduced.

(B) Oxidation ⇒

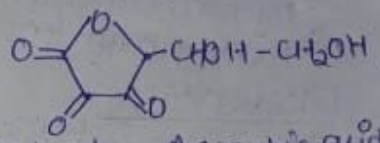
Oxidation involves either the addition of oxygen or removal of hydrogen. Autoxidation is a most common form of oxidative degradation that occurs in many pharmaceutical preparations and involves a free radial chain process.

In an oxidative degradation only a small amount of oxygen is required for initiating the reaction. Heavy metals such as copper, iron, cobalt and nickel have been known to catalyse the oxidative degradation.

Examples of drugs which undergo oxidative decomposition are- ascorbic acid, morphine, epinephrine, heparin, vitamin A, D & K



(Ascorbic acid)



(Dehydro-Ascorbic acid)

PREVENTION

(1) Anti-oxidant - Many natural (ascorbic acid, tocopherols etc..) and synthetic anti-oxidants. (e.g- butylated hydroxyl anisole, propyl gallate etc.) are widely used in food, cosmetics and drugs to inhibit oxidation reaction.

(2) chelating Agents - These agents are used in heavy metal-catalysed oxidation reaction. chelating Agents (EDTA, citric acid, and tartaric acid) form complexes with heavy metal ions.

(3) vehicles - For most of the pharmaceutical preparations, water is used as a solvent or vehicle to dispense the drug.

(4) Butteres - The oxidation reactions catalysed by H^+ or OH^- ions can be controlled by using a buffer solution of appropriate pH. Thus buffer solution is helpful in improving maximum stability to the product.

(5) Surfactants enhance the o
at low temp
its critical
entrapping

(6) Low tempe
products are
temperature

(7) Oxygen
degrada
air is rep
or oxyge
manufac

where K = Observed reaction rate in a solvent of dielectric constant ε.

$K_{\varepsilon=\infty}$ = Reaction rate constant in a solvent of infinite dielectric constant

N = Avogadro's Number

Z_A and Z_B = charges on the reacting ionic species

e = unit of electric charges

r^* = Distance between the ionic species in the activated complex

ε = The dielectric constant of the solution.

According to the above equation, reactions involving ions of opposite charge are accelerated by solvents of low dielectric constant. For example, the rate of H^+ ion catalysed hydrolysis of sulphate esters is much greater in low dielectric solvents such as methylene chloride than in water, on the otherhand, in reactions involving similarly charged species, the rate of reaction is accelerated on increasing the dielectric constant of the solvent. Reaction between neutral molecules which produce a highly polar transition state are also enhanced by high dielectric constant solvents.

(V) catalysis

S.P. Agarwal, Rajesh Khanna - Book

page no - 240.

(iii) Legal requirement: Preparations formulated according to official compounds must comply with requirement for identity strength, purity and quality of drug.

(iv) Bad image for manufacturer.

A poorly formulated or unstable product may show problems like fading or darkening of colour, caking of suspensions or breaking of emulsion. This will result in non-acceptance by the user community i.e doctors, pharmacists, patients etc. and it will be a poor-advertisement for the manufacturer.

(v) patient Economy-

A patient is entitled to receive what he is paying for.

Stability testing is generally done to ensure that the deterioration doesnot exceed an acceptable level and the activity of the drug and safety of the patient is ensured.

Stabilisation Of medicinal Agents Against Common Reactions

Two most common causes of instability or decomposition of drugs are hydrolysis and oxidation. Photochemical decompositions and isomerisation also lead to instability of some drugs.

(A) Hydrolysis

This problem is most important in system containing water such as emulsions, suspensions, solutions etc. Also for drugs which are affected by traces of moisture in the form of water vapour from atmosphere. The main classes of drugs that undergo hydrolysis are the esters, amides and lactams

Hydrolysis is usually catalysed by hydrogen ion (specific acid hydrolysis) or hydroxyl ions (specific base catalysis) and also by and also by other acidic or basic species commonly encountered as components of buffers.

Accelerated Stability Testing in Expiration Dating of pharmaceutical Dosage Forms

Accelerated stability analysis is designed to predict stability and shelf life of formulations under normal or recommended storage conditions by carrying out the study under accelerated conditions of temperature, moisture and light. In accelerated stability testing, a product is stored at elevated stress conditions.

Temp is probably the most common acceleration factor used for chemicals, pharmaceuticals, and biological products since its relationship with the degradation rate is well characterised by the Arrhenius equation. This equation describes a relationship between temperature and the degradation rate =

$$k = A\exp\left(\frac{-Ea}{RT}\right)$$

This relationship can be used in accelerated stability studies when the following conditions are met-

① A zero- or first-order kinetic reaction takes place at each elevated temperature, as well as at the recommended storage temperature

② The same model is used to fit the degradation patterns at each temperature.

Objectives of Accelerated Stability Studies =

Accelerated stability testing is generally undertaken with the following objectives.

(1) To serve as a rapid means of selecting the best formulation from amongst a series of similar formulations of the product.

(2) To predict the shelf-life of product

(3) To serve as a rapid means of quality control.

Common High Stresses during Stability Testing (11)

preparations are generally subjected to the following high stresses during stability testing -

1. Temperature - Increase in temp, ↑ degradation. Hence, preparations are subjected to different elevated temperature.
2. Humidity - High humidity condition accelerated decomposition that results from hydrolysis. products without containers are exposed to high humidity conditions, usually in humidity chambers and analysed at regular intervals.
3. Light - Artificial light of varying intensity can be used to accelerate the effect of sunlight. The lightsource should however emit similar radiation as the sunlight.

Accelerated Stability Study profile.

Storage conditions	Testing conditions.
Controlled room temp. 20-25°C.	40°C and 75% RH for 6 months
Refrigerated condition - 2-8°C	25°C and 60% RH for 6 months
Freezer condition - 3-10°C	5°C for 6 months.

Prediction of Shelflife from Accelerated Stability Data

On the basis of chemical kinetics, shelf life can be predicted from accelerated stability studies performed by following methods -

① Shelf-Life Determination Based On Arrhenius's plot (Correct and Carpet method)

The shelf-life can be mathematically predicted by applying Arrhenius equation. On plotting the effect of temperature on rate constant (K) of a chemical reaction & thermodynamic temperature (1/T), a straight line is obtained.

The value of K is obtained, if the slope of this line is determined from the results of temperature by extrapolation. Therefore, for the determination of this order some preliminary experiments are necessary:

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

$$\log K = \log A - Ea/2.303RT$$

(11) Solvent

The effect of solvents on the degradation rate of drugs is generally related to the relative solubility of the reactants and the products in the given solvents.

For a reaction:

$$A + B \longrightarrow (A \cdots B) \longrightarrow \text{product}$$

The quantitative relationship between the reaction rate constant and the solubility of the reactants and products is given by the equation -

$$\log K = \log K_0 + \frac{V}{2.303RT}(\Delta\delta_A + \Delta\delta_B - \Delta\delta^*)$$

where K = observed reaction rate constant

K_0 = Reaction rate constant in an infinitely dilution solution exhibiting ideal-behaviour.

V = Approximation for the molar volumes of the reactants (A and B) and the activated complex formed during the reaction and prior to the formation of the products.

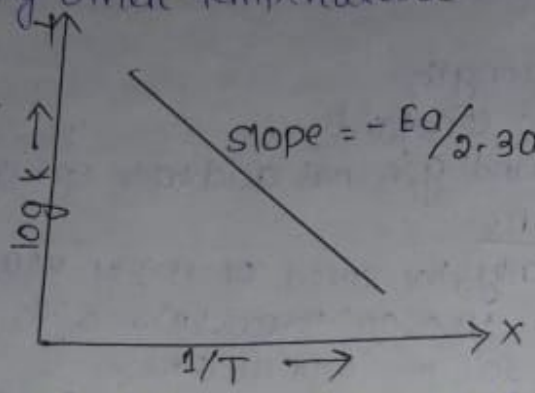
δ_A, δ_B and δ^* = solubility parameters of the reactants A, B and the activated complex respectively.

On the basis of the above equation, it can be said that polar solvents tend to accelerate reactions in which the products formed are more polar than the reactants. On the otherhand, if the products formed are less polar than the reactants, the reaction proceeds better in solvent of relatively low polarity.

Commonly used non-aqueous solvents for drugs include ethanol, glycerol, propylene glycol, polyethylene glycols and vegetable oils.

The values of constants A and Ea can be determined by determining K at various temperatures. Plot of log K versus 1/T gives a straight line with slope equals to $-Ea/2.303R$ and intercept at Y-axis equals to log A.

The graph can also be used to determine K at any other temperature



Ea can also be determined by plotting log $t_{1/2}$ against 1/T which yields a straight line with slope equals to $Ea/2.303R$.

Ea can also be obtained by determining K_1 at t_1 and K_2 at t_2 and using the following equation.

$$\log \frac{K_2}{K_1} = \frac{Ea}{2.303R} \cdot \frac{(T_2 - T_1)}{T_1 T_2}$$

The arrhenious equation is useful when the energy of activation is in the range of 10 - 30 Kcal/mole. If Ea is only 2-3 Kcal/mole as in case of photolytic reactions, little advantage is gained from the equation. Similarly if the energy of activation is more as in case of pyrolysis, the rate of degradation is so fast that it becomes difficult to make use of this relationship.

Methods for determination of order of the Reaction

The order of a reaction can be determined by any one of the following methods.

① Substitution - Method -

In this method, the data obtained from a kinetic experiment is substituted in the appropriate rate equation. The equation gives a fairly constant value of K and indicates the order of a reaction. The rate of half life equation for different order reactions are given by a table -

Order of Reaction	Rate Equation	Half - Life equation
0	$K = \frac{A_0 - A_t}{t}$	$t_{1/2} = \frac{A_0}{2K}$
1	$K = \frac{2.303}{t} \log \frac{a}{a-x}$	$t_{1/2} = \frac{0.693}{K}$
2	$K = \frac{1}{at} \cdot \frac{x}{(a-x)}$	$t_{1/2} = \frac{1}{aK}$

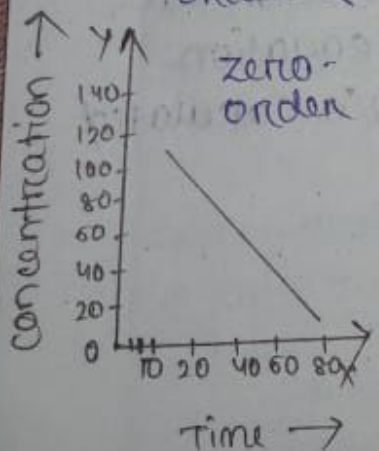
② Graphical Method

In this method, the data uptained from a kinetic experiment is plotted in the appropriate form for determining the order of reaction.

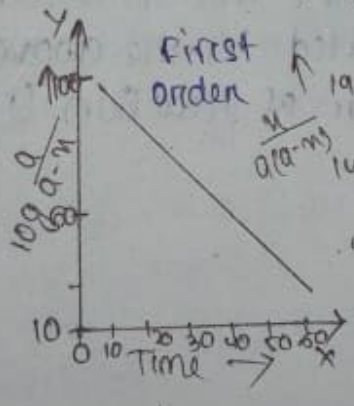
If a plot of conc. versus t gives straight line → zero order Reaction.

If a plot of $\log \frac{a}{a-x}$ versus t gives St. line → First order Reaction

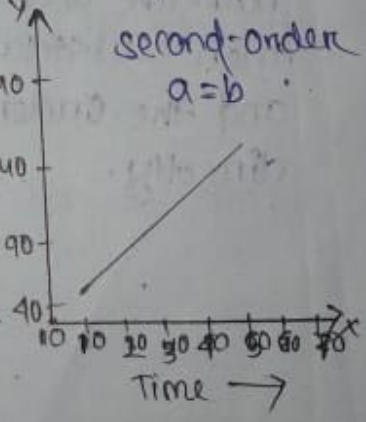
If a plot of $\frac{x}{a(a-x)}$ versus t gives St. line → second order Reaction



zero - order



First order



second - order
a = b

physical and chemical Factors influencing The chemical Degradation of pharmaceutical Products

The different physical and chemical factors which affects the chemical degradation of pharmaceutical products are -

i) Temperature
ii) solvent
iii) Ionic strength
iv) Dielectric constant
v) specific and general acid base catalysis.

① Temperature

Generally, the speed of many reactions can be increased two or three times with each increase of 10°C in temperature.

The effect of temperature on reactions. rate is given by the Arrhenius Equation which in the exponential Form is -

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

where K = specific reaction rate constant
A = Arrhenius factor
Ea = Energy of activation
R = Gas constant (1.987 calories/deg mole)
T = absolute Temperature

The Arrhenius factor (A) is a measure of the Frequency of collision between the reacting molecules. The energy of activation (Ea) is the energy required for effective collisions to cause a reaction between the molecules.

on expressing the Arrhenius Equation to logarithmic Form, we get $\ln K = \frac{Ea}{RT} + \ln A$

On converting the above Equation to common logarithmic Form, we get

$$\log K = \frac{-Ea}{2.303RT} + \log A$$

where $\log A$ = constant

Let's consider a reaction.

(iii) Half-Life-Method

A general expression for the determination of the half-life of a reaction can be given as

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

where,

n = order of the Reaction.

If two reactions are initiated with two different initial concentration (a_1 and a_2, respectively), the half-lives are determined as -

$$t_{1/2}(1) \propto \frac{1}{a_1^{n-1}}$$

And $$t_{1/2}(2) \propto \frac{1}{a_2^{n-1}}$$

on deviding $t_{1/2}(1)$ with $t_{1/2}(2)$

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

on taking log:

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

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

where n = order of the Reaction.

Half-Lives are calculated by plotting a graph bet^n 'a' and 't' at two diff initial conc. (a_1 and a_2). The half life times are then read at $t_{1/2}a_1$ and $t_{1/2}a_2$ respectively from the graph. The values of half-life and the initial concentration are then substituted in the above equation and the order of reaction (n) is calculated directly.

Order
Zero
First
Second
Third
nth

unit of Rate constant for second order reaction has $= Lit\ mol^{-1}\ sec^{-1}$

Half-Life of second-Order-Reaction

The half life for a second-order-Reaction (only when a=b) is given by

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

Examples

(i) Hydrolysis of ester by an alkali (saponification)

$$CH_3COOC_2H_5 + NaOH \longrightarrow CH_3COONa + C_2H_5OH$$

(ii) Decomposition of NO_2 into NO and O_2

$$2NO_2 \longrightarrow 2NO + O_2$$

(iii) conversion of ozone into oxygen at 100°c

$$2O_3 \longrightarrow 3O_2$$

(iv) Thermal decomposition of chlorine-Monoxide

$$2Cl_2O \longrightarrow 2Cl_2 + O_2$$

Rate-Constant

Lets consider a reaction:

$$A \longrightarrow B$$

If C_A is the active mass or molar concentration of A at a time t:

$$\frac{dx}{dt} \propto C_A$$

$$\frac{dx}{dt} = KC_A$$

where K = proportionality constant / velocity constant / Rate constant / specific Reaction Rate

If the value of C_A is 1 at a fixed temperature

$$\frac{dx}{dt} = K$$

Thus, velocity constant is the rate of a reaction if the molar concentration is unity at a fixed temperature.

Let's consider a reaction:

$aA + bB + cC \dots \rightarrow$ products

The rate of the reaction $\frac{dx}{dt} = K[A]^a[B]^b = KC_A^a C_B^b$

If $C_A = C_B = 1$

$\frac{dx}{dt} = 1$

Rate constant depends upon the following factors:

(i) Nature of the reactants

(ii) Temperature at which reaction occurs..

Rate constant doesnot depends on the concentration of reactants.

Units of Basic - Rate Constant

For different order reactions, the rate constant has different units. Rate of Reaction can be given by

$$\text{Unit of Rate constant} = \left[\frac{1}{\text{unit of concentration}}\right]^{n-1} \times \text{time}^{-1}$$

$$= \left[\frac{1}{\text{mol/lit}}\right]^{n-1} \times \text{sec}^{-1}$$

$$= \left[\frac{\text{lit}}{\text{mol}}\right]^{n-1} \times \text{sec}^{-1}$$

where n = order of Reⁿ

Order ↓	Rate	M/t	units of K
zero	$K[A]^0$	K	m/s, m/min, m/hrs
First	$K[A]^1$	KM	s^{-1}, min^{-1}, hr^{-1}
second	$K[A]^2$ / $K[A][B]$	KM^2	$m^{-1}s^{-1}$, $m^{-1}min^{-1}$, $m^{-1}hr^{-1}$
Third	$K[A]^3$ / $K[A]^2B$ / $K[A][B][C]$	$m^{-2}s^{-1}$, $m^{-2}min^{-1}$, $m^{-2}hr^{-1}$	KM^3
nth	$K[A]^n$	KM^n	$m^{-(n-1)}s^{-1}$ etc.

Half-Life of First Order Reaction

$$t_{1/2} = \frac{2.303}{K} \log \frac{a}{a-x} \quad (\text{eq}^n - (IV))$$

at $t = t_{1/2}$, $x = a/2$

Hence, $K = \frac{1}{t_{1/2}} \ln \frac{a}{a-(a/2)}$

$= \frac{1}{t_{1/2}} \ln \frac{a}{a/2} = \frac{1}{t_{1/2}} \ln 2 =$

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

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

Shelf-Life (t_{90})

$$t_{90} = \frac{2.303}{K} \log \frac{a}{a-x} \quad (\text{eq}^n - (IV))$$

at $t = t_{90}$, $(a-x) = \left(\frac{90}{100}a\right) = 0.9a$.

putting these values on eq^n (IV)

$$t_{90} = \frac{2.303}{K} \log \frac{a}{0.9a} = \frac{2.303}{K} \log \frac{10}{9}$$

$$= \frac{2.303 \times 0.04575}{K_1} = \frac{0.105}{K}$$

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

(example of 1st order Rac^n) ⇒

Pseudo-First Order-Reaction

In pseudo-first-order reaction, one reactant is present in excess amount and the reactions shows diff order of the reaction from the actual order, that experimental order which differs from the actual order is pseudo order.

Pseudo-order reactions are also known as pseudo-molecular reactions, because for elementary reactions the molecularity and order are same.

On putting the value of 'c' in eqⁿ (iii), we get (A)

$$-\log_e(a-x) = kt - \log_e a$$

$$\log_e a - \log(a-x) = kt$$

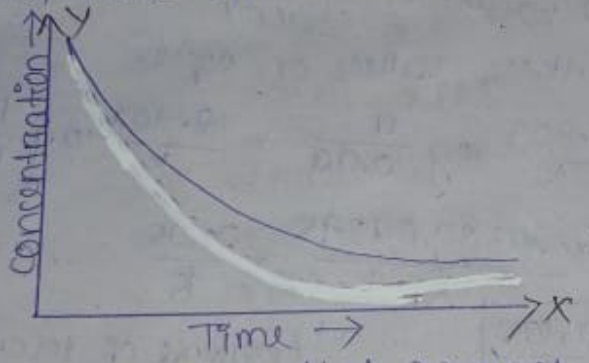
$$\log_e \frac{a}{(a-x)} = kt$$

$$\boxed{k = \frac{2.303}{t} \log_{10} \frac{a}{a-x}}$$ (Rate constant for first order reaction) ——— (iv)

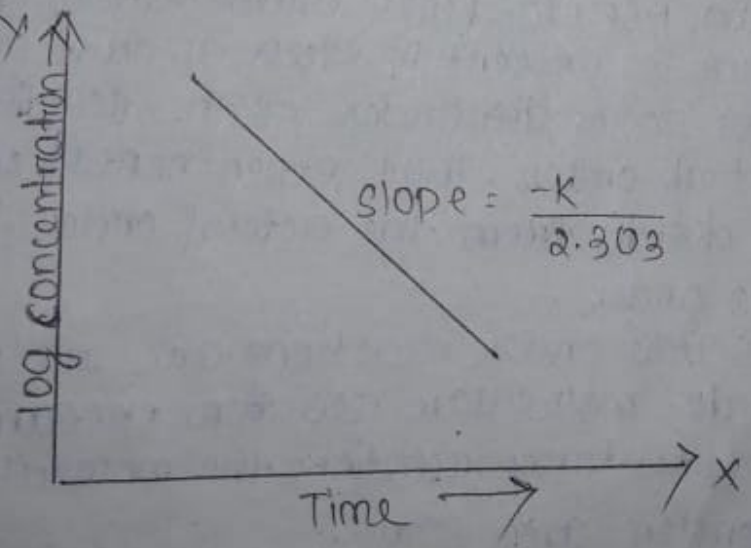
* unit = sec^{-1}

($\log_e$ = ln, while converting $\log_e$/ln into log we have to multiply it with 2.303)

In eqⁿ (iv), concentration decreases exponentially with time and this may be shown by plotting concentration on y axis against time on x-axis.



If log c is plotted against t, a straight line is obtained with slope equals to $-k/2.303$



In this condition, the rate equation is written as

$$-\frac{d[A]}{dt} = K_1[A]$$

where [A] = conc. of nondegradable drug at t
K_1 = First-order rate constant

The value of [A] constant, when the solid in the suspension acts as reservoir. Here zero-order-reaction is followed and equation becomes $-\frac{d[A]}{dt} = K_1 \times \text{constant} = K_0$

First-Order-Reaction

In first-order reaction, the rate of a reaction depends on the alternation of only one concentration (unimolecular reaction)

Lets us consider a reaction:

A ⟶ products

Let 'a' be the concentration of A at initial point which becomes (a-x) after time t i.e. 'x' has been changed into products. Thus, after time 't' the rate of a reaction can be expressed as:

$$\frac{dx}{dt} = K(a-x) \quad \text{——— (I)}$$

$$\frac{dx}{(a-x)} = Kdt \quad \text{——— (II)}$$

On Integrating eq (II), we get

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

$$-\log_e(a-x) = Kt + C \quad \text{——— (III)}$$

(C = Integration constant)

when $t = 0$, $x = 0$

Then eq^n (III) becomes.

$$C = -\log_e a \quad \text{——— (IV)}$$

Half-life of First

(I) If the initial concentrations of A and B are equal, i.e $a=b$, the above equation can be written as:

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

on integrating between the limits $x=0$ at $t=0$ and $x=dx$ at $t=t$, we get.

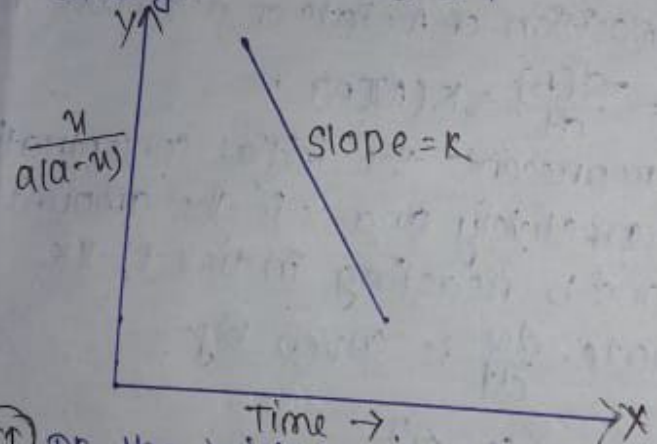
$$\int_0^x \frac{dx}{(a-x)^2} = k\int_0^t dt$$

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

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

or $$\boxed{k = \frac{1}{at}\frac{x}{(a-x)}}$$

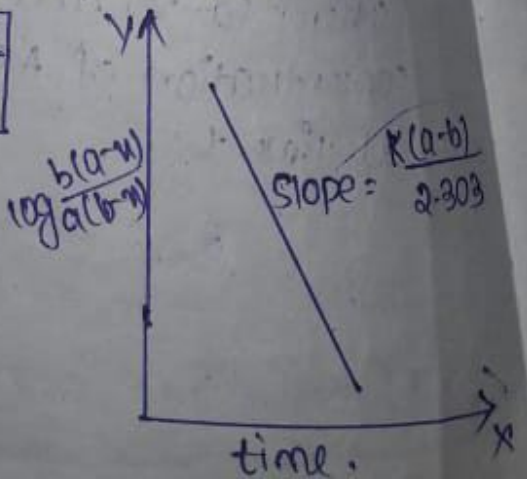
If we plot of $\frac{x}{a(a-x)}$ against t gives a straight line with slope equal to k.



(II) If the initial concentrations of A and B are not equal, i.e $a \neq b$, integration of equation (1) gives

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

In such a case, plot of $\log \frac{b(a-x)}{a(b-x)}$ against t yields a straight line with slope equals to $\frac{(a-b)k}{2.303}$.



Half life of a zero-order-Reaction

Half life is the time required for the concentration of the reactant to reduce to half of it's initial concentration.

In a reaction $A \xrightarrow{t} \text{product}$

$t_{1/2} = A/2$

where $t_{1/2}$ = half life period

A = Initial concentration of reactant.

consider a reaction

$A_0 \longrightarrow A_t$

A_0 = Initial concentration

A_t = conc. at time t

$$A_t = A_0/2$$

Substituting this in above equation (iv), we get

$$A_0/2 = A_0 - Kt_{1/2}$$

$$A_0/2 - A_0 = -Kt_{1/2}$$

$$-A_0/2 = -Kt_{1/2}$$

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

Shelf-Life

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

$$A_t = \frac{90}{100} A_0 = 0.9 A_0$$

Substituting this in the above equation (iv), we get

$$\boxed{t_{0.9} = \frac{A_0 - 0.9A_0}{K} = \frac{0.1 A_0}{K}}$$

Examples

① photo

H_2

② D

Hydrolysis reactions (acid or base catalysed) are common examples of pseudo-first-order reactions. ⑤

examples of First-order reaction

① Decomposition of H_2O_2 in aqueous medium / solution

$$H_2O_2 \longrightarrow H_2O + \frac{1}{2}O_2$$

② Hydrolysis of methylacetate

$$CH_3COOCH_3 + H_2O \xrightarrow{Acid} CH_3COOH + CH_3OH$$

③ Inversion of cane sugar in the presence of mineral acids

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow{Acid} C_6H_{12}O_6 + C_6H_{12}O_6$$

Second-Order Reaction

In second-order-Reaction, the rate of a reaction depends on the variation of two concentration terms:

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

If the reaction is on mole per mole basis of A and B,

Rate of decomposition of A = Rate of decomposition B

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

If a and b represents the initial concentration of A and B respectively and x is the amount of each of A and B reacting in time t, the reactantion rate. $\frac{dx}{dt}$ is given by

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

where $(a-x)$ and $(b-x)$ represents the concentration of A and B remaining unreacted at time t.

For this reaction, the order will be zero (2)

$$-\frac{dA}{dt} = K[A]^0 = K \quad \text{——— (1)}$$

where dA = change in conc. with respect to change in time t.

'$-$' sign indicates the decrease in concentration.

$$-\frac{dA}{dt} = K \text{ (equation - 1)}$$

$$-dA = K\,dt$$

On Integrating both the sides.

$$\int_{A_0}^{A_t} dA = -K \int_0^t dt$$

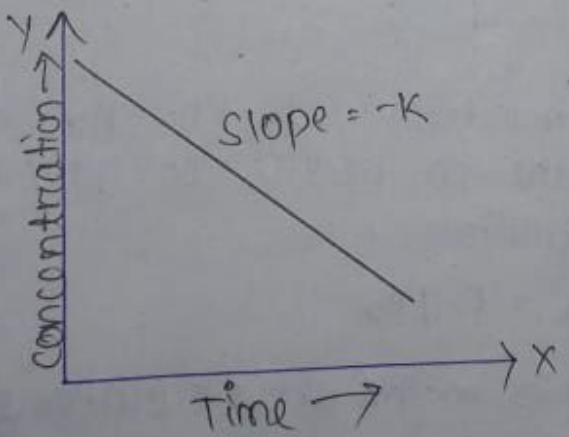
$$A_t - A_0 = -Kt \quad \text{——— (II)}$$

$$A_t = A_0 - Kt \quad \text{——— (III)}$$

From eqn (II), $\boxed{K = \frac{A_0 - A_t}{t}}$

Unit of K = mol lit^{-1} $time^{-1}$

If we plot a graph plooting A_t or concentration on y-axis against time (t) on x axis, the slope will be $-K$, which is a straight line.



or $\boxed{t = \frac{A_0 - A_t}{K}}$ ——— (IV)

The rate of the reaction is given by

$$\text{Rate} = -\frac{1}{a}\frac{d[A]}{dt}$$

$$\text{Rate} = -\frac{1}{b}\frac{d[B]}{dt}$$

$$\text{Rate} = K[A]^{a}[B]^{b}$$

where K = rate constant / specific rate constan

order of Reaction

The sum of the powers of concentrations in the rate law is determined as the order of a reaction.

Let's consider a rate law reaction

$$\text{Rate} = K[A]^{m}[B]^{n}$$

$$\text{order} = (m+n)$$

on the basis of order, Reactions can be classified as -

(i) First order Reaction, $m+n = 1$
(ii) Second Order Reaction, $m+n = 2$
(iii) Third order Reaction, $m+n = 3$

Zero-Order-Reaction

In zero order reaction, the rate of a reaction is independent upon the concentration of the reactant.

Let's consider a reaction

$$A \longrightarrow \text{product}$$

Chemical Kinetics -

Chemical kinetics is the study of the rate of chemical changes taking place during chemical reactions. It is the branch of physical chemistry dealing with the rate of reactions or chemical processes.

In pharmaceutical formulations, this includes study of physical and chemical reaction in drugs and dosage forms, factors influencing the rate of these chemical reaction, stability testing and prediction of shelf-life of drug

Rate of the reaction

The rate of a chemical reaction is defined as the velocity with which a reactant undergo chemical changes.

The rate of a reaction can be measured by measuring the change in the concentration of a reactant in a perticular period of time.

Therefore,

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

where c = concentration change

t = time interval

Rate constant

According to the law of mass action, the rate of a chemical reaction is proposed to the product of molar conc. of the reactant each raised to a power equals to the numbers of molecules a and b, of the substances A and B undergoing reaction.

Thus, in the reaction

$$aA + bB \longrightarrow \text{products}$$