Kinetics and Drug Stability

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★ Kinetics

The means of kinetics is study the rate of chemical or biochemicals reaction. It is a branch of chemistry or biochemistry deals with measuring and study the rate of chemical reaction.

★ Drug:

It is a bunch of chemicals for the use by patients in people for the prevent or care or treatment of disease. and also both physical and chemical ability.

★ Stability:

It is a condition or stage that preserve or store capacity of dry substance or drug moiety.

- Chemical Kinetics is the study of the rate of chemical change takes place during chemical reaction, As applied to pharmaceutical formulation, this includes a study of physical and chemical reaction in drugs and dosage forms. Factor influencing the rate of these

chemical reaction, accelerated, stability testing and predication of shelf life of formulation.

★ Shelf life:

The time period from the product was manufactured to its expiry date. The time period of the product is expected to be safe, effective and fit for purpose to provided. It has been packaged and stored in recommended condition throughout this period.

All ~~dog~~ drug tend to degrade from the point of manufacture and the expiry date of a product is end point of its self life taking into account a tolerance of degradation (normally less than 10%).

★ Half life

This is usually a reference to the time taken for the body to eliminate 50% of the dosage of drug after the time of administration. It ~~varies with~~ varies with different drugs and between individual patients but average half life of drugs may

be found in the literature most penicillins - $\frac{1}{2}$ life around 20min.

✱ Factors affecting rate of reaction of kinetic and drug stability.

i). Light

Light energy may be absorbed by certain molecules which becomes sufficiently activated ~~for~~ to undergo reaction. Mostly visible and U.V. light cause photochemical reaction. Photochemical reaction don't depend on temperature for activation of the molecules. While, once a molecule has observed a quantum of radiant energy, it may collide with other molecules, raising their kinetic energy which results in the increase in temperature of the system.

Hence, Photochemical reaction are often followed by Thermal reaction, photochemical reaction are, in general, complex reaction and proceed by a series of steps :-

Example of pharmaceuticals compounds which undergo photochemical decomposition include riboflavin, phenothiazines, chlordiazepoxide, nifedipine etc.

2) Solvent :-

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

$$A + B \rightarrow (A \cdots B) \longrightarrow \text{Products.}$$

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

$$\log K = \log K_0 + \frac{V}{2.303} \cdot \frac{1}{T} (\Delta S_A + \Delta S_B - \Delta S^*)$$

Where,

K is the observed reaction rate constant.

K_0 is the reaction rate constant in infinity dilute solution

V is a molar volumes of the reactants.

A and B is activated complex form during reaction.

S_A, S_B and S^* is the solubility parameters of the reactants if the products formed are less polar than the reactants then the reaction proceeds better in solvent.

Commonly used non-aqueous solvents for drugs indude ethanol, Glycerol, propylene glycol, PEN and vegetable oils.

3.) Ionic Strength.

The effect of ionic strength of solution of the rate of degredation 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 is the degradation rate constant for the reaction.

K_0 is the reaction rate constant of infinite dilution.

Z_A and Z_B are the charge carried by the real A and B in solution respectively.

μ is the ionic strength of the solution.

According to the above equation, An increase in the ionic strength of the solution would tend to decrease the rate of reaction involving interaction b/w oppositely charge ions and increase the rate of reaction b/w similarly ions.

4) Temperature

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

The effect of temp. on reaction rate is given by Arrhenius equation is (as exponential form).

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

Where,

K is the specific reaction rate constant.

A is the frequency factor also K/a Arrhenius factor.

Ea is the energy of activation.

R is the gas constant as 1.987 Calories / deg · mole.

T is absolute temp.

The frequency factor A reffered to above is a measure of frequency of collisions.

Expressing the eqn in logarithmic form.

$$\boxed{\ln k = \frac{-E_a}{RT} + \ln A}$$

Converting to common logarithmic form

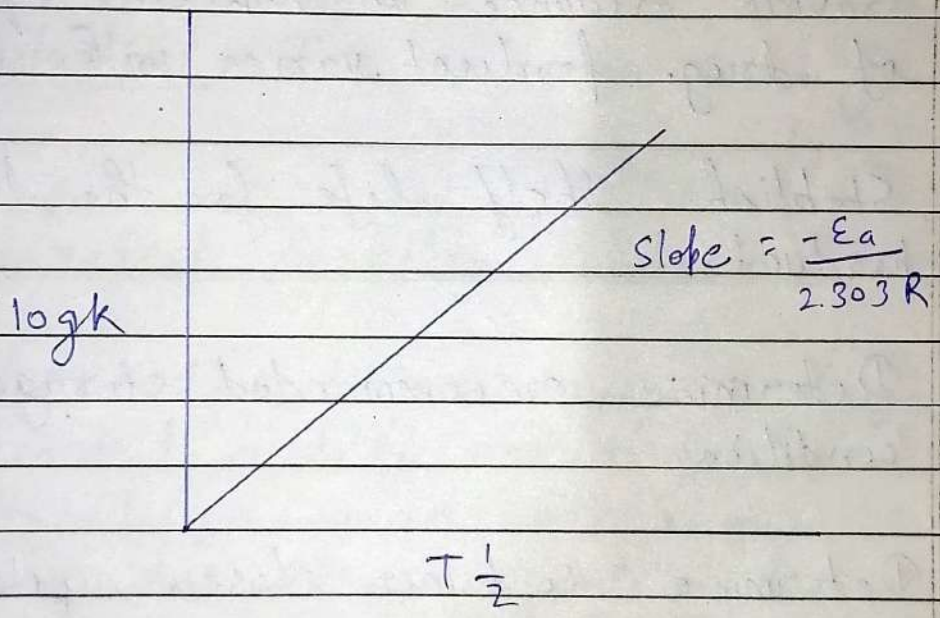
$$\boxed{\log k = \frac{-E_a}{2.303RT} + \log A}$$

Where,

$\log A$ is constant.

The value of constant A and E_a can be determined by determining K at various temp.

Plot a graph of $\log k$ versus $T\frac{1}{2}$ gives a straight line with slope equal to $-E_a/2.303R$ and Y-axis intercept is equal to $\log A$.



Arrhenius plot.

☆ Stability

Stability of pharmaceutical product may be defined as the capability of particular formulation in a specific container or closer system to remain its physical, chemical, microbiological, therapeutic, toxicological specification.

Need for Stability Testing :-

i) Provide evidence as how the equality of drug product varies with time.

ii) Stablish shelf life for the drug product.

iii) Determine recommended storage condition.

iv) Determine container closer system suitability.

v) Safety point of view of Patients.

vi) Prevention of economical refresion.

vii) Essential quality attributes.

According to USP types of stability.

Types.

1. Chemical :- Chemical integrity and labelled potency.
2. Physical. - Appearance, uniformity.
3. Microbiological :- Sterility
4. Therapeutic - Drug action remains unchanged.
5. Toxicological - Increase in toxicity.

★ Accelerated Stability Analysis.

Accelerated stability analysis is designed to predict stability and shelf life of formulation under normal or recommended storage condition by carrying out the study under accelerated condition of temp., moisture and light.

Objective of accelerated Stability Analysis

* Acc. stability testing is generally undertaken with the following objectives.

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

ii) To predict the shelf life of the product.

iii) To serve as a rapid means of quality control.

(iv) Determine recommended storage condition.

★ Common High Stresses during Stability Testing :-

⇒ Preparation are generally subjected to the following high stresses during stability testing.

1. Temperature.

Increase in the temp., increase degradation. Hence, preparation are subjected to different elevated temp. At various time ~~to~~ intervals, samples are ~~withd~~ withdrawn, extent and nature of degradation is determined.

2. Humidity:

High humidity condition accelerates decomposition that results from Hydrolysis. Product without container are exposed to high humidity condition 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 light source should be however emit similar radiation as the sunlight.

* Limitation of Accelerated stability Analysis.

1) Stability Predication based on Arrhenius equation are valid only when energy of activation for the thermal decomposition lies within the range of 10-30 kcal/mole.

2 Certain reactions which usually don't take place under normal conditions of storage may take place under accelerated or high stress conditions and hence actual information may

not be obtained.

3) The order of reaction may be different in real and acc. conditions

4) Accelerated testing can't be used if the decomposition is due to freezing, contamination by micro-organisms, excessive agitation during transport.

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

★ Stability of semi-solid Dosage forms:-

→ Stability of active ingredients incorporated into ointments or creams often depends upon the nature of ointments and creams base used in formation. Cream bases containing water are more active to decomposition of drugs which proceeds via hydrolysis [The chemical breakdown of a compound due to reaction with water].

Dilution of ointment and creams by the user with untested diluents can further lead to instability problems. Diluents containing oxidizing agents could cause chemical degradation. Incorporation of drugs into gel structure lead to change in their stability. Penicillin G sodium has been shown to undergo increased degredation in hydrogels of various natural and semi-synthetic polymer.

Stability of solid Dosage forms:-

The effect of various factors on the stability in solid dosage forms are following.

1) Temperature :

The kinetic of decomposition in the solid state is different from that in solution. The temperature dependence of the rate constant usually follows the Arrhenius equation. Exception to this rules are those solids in which decomposition exhibits an approach to equilibrium as in case of vitamin A in gelatin beadlets and vitamin E in lactose base tablets.

In this case, the effect of temperature is ~~desired~~ described by ~~vast~~ Vant Hoff equation:-

$$\ln K = \frac{-\Delta H}{RT} + \text{constant}$$

2. Moisture.

Moisture has a significant effect on the kinetics of decomposition of solid dosage forms. When the moisture content is quiet high, the decomposition of drug in solid dosage form becomes similar to that in a saturated solution i.e. Zero under kinetic.

3. Chemical interaction :-

Chemical interaction between components in solid dosage form may often lead to increased decomposition. In APC tablets [Aspirin, Phenacetin and caffeine], Phenacetin was replaced by paracetamol but this led to an unexpected decrease in stability. A number of tablet excipient have also found to decrease the stability of the Active ingredient.

International Regulatory Guideline for Stability studies.

Stability testing of drug substance and dry products has long been a concern area for both the pharmaceutical industry as well as the regulatory agencies world wide.

The first effort of technical requirements for pharmaceutical stability, ICH (International council ~~Conference~~ for Harmonization of Technical Requirements for Pharmaceuticals for Human Use)(ICH). stated in 1990 at brussels. The ICH steering committee has since been meeting regularly and atleast twice a year. Harmonization of stability requirement guideline in stability testing of new ~~drug~~ substance and products in 1993. This guideline describe ~~in~~ the stability testing requirements for registration of pharmaceutical products in Europe, Japan and USA.

The world Health Organization (WHO) being the observer of the ICH process felt that the ICH parent guideline Q1A was not to address the requirements in

my country having extreme climatic condition to existing drug product.

◎ Q1A → guideline is a stability testing of New drug substance and products.

It published a separate guideline on stability testing of pharmaceutical product containing well established drug substances in conventional dosage forms; updated in the report of 37th meeting of WHO in october 2001.

(4.) ICH and WHO guideline for stability Studies

The ICH released six guideline for stability studies. The parent guideline Q1A has been raised twice and the current version Q1A (R_2) lays down the requirements pertaining to registration application within the three regions of the Europe, Japan and USA.

The Q1B guideline gives the recommendation for photostability testing of new drug substance and drug products.

The Q1C guideline for stability testing of New dosage forms.

The Q1D guidelines explain the bracketing and matrixing designs for stability testing of drug substances and products.

The Q1E guideline explain the principle of the parent guideline and gives specific stability requirement for other regions of the world.

	ICH guideline	Title
1	Q1A (R_2)	Stability testing of new drug substance and products.
2	Q1B	Stability testing - photostability of new drug substances and products.
3.	Q1C	Stability testing for new dosage forms.
4.	Q1D	Bracketing and matrixing design for stability testing of drug substances and products.

5. Q1E Evaluation of stability data.

6. Q1F Stability data package for registration application in climatic zone.

Bracketing:

It assumes that the stability of the intermediate is represented by the stability of the estrems tested. The ~~uses~~ uses of this design is in appropriate if the selected sample are not the estrems.

Matrixing:

It is use to confirm a prediction of the stability information.

ICH guideline on stability studies

Climatic zones:-

As per the ICH and WHO guideline on stability studies. The world has been divided into four zones as per annual climatic condition of temp. and humidity.

Zone I - temperature.
Zone II - Subtropical with possible high humidity

Zone III - hot, dry
Zone IV - hot, humid.

Types of stability studies.

1) Long term stability studies.

ICH guideline Q1A (R2) defines long term studies as stability studies under recommended storage condition for the ratest period or shelf life proposed for labeling.

This study is generally performed at 25°C/60% or 30°C/65% RH. Ideally 12 months data is to be generated. 5x month data is also acceptable.

For drug substances recommended to be stored in a refrigerator, the long term stability study is carried out 5 ± 3°C and for freezer stored carried out at -20 ± 5°C.

Climatic zones	Recommended Conditions for long term stability studies in general case	
	Temperature (°C)	Humidity (%)
I and II	25 ± 2°C	60 ± 5%
III and IV	30 ± 2°C	65 ± 5%

Table : Recommended Conditions for long term stability studies.

(2) Accelerated Stability Studies :-

For accelerated stability studies; A storage condition of 40°C ± 2°C and RH of 75 ± 5% has been recommended for all the four zones for drug substances and drug products at 25°-30°C. The studies carried out for 6 month storage. At intermediate storage conditions additional testing where significant change occurs at any time during 6 month storage at 30°C ± 2°C and 65% ± 5% RH (Relative humidity) should be conducted.

For drug substances and drug products intended to be stored in a refrigerator, studies carried out at 25 ± 2°C and 60 ± 5% RH.

3) Testing Frequency

The frequency of testing at the long term storage condition should normally be every 3 month over the first year, every 6 month over the 2nd year and annually through the proposed shelf life.

At the accelerated storage condition, A minimum of three time points, including the initial and final time point eg. (0, 3 and 6 months) from a 6 months study is recommended.

4) Packaging container.

Stability studies should be carried out in the final packaging proposed for marketing. Additional testing of unprotected finished product can form a useful part of the stress testing and pack evaluation.

5. Stability Testing.

A study of drug stability and of stability testing technique is essential for the following main reasons.

i) Patient Safety:

Pharmaceutical Industry produces highly specific, chemically complex, Potent drugs. The patient should reciere a uniform dosage of the drug throughout the shelf life of the product. The drug may have shown to be safe but the decomposition product may not be safe.

ii) Drug activity:-

In addition to the formation of toxic products, ~~determination~~ deterioration will also lead to reduce activity of the compound or preparation. And hence the therapeutic benefits of the preparation will be reduced. Microbial contamination may ~~be~~ also cause degredation and be otherwise harmful.

iii) Legal requirement.

Preparation formulated according to official compendia must comply with requirement for identify, strength, purity and quality of the drug. This is true of the product not only when it is manufactured but throughout

its shelf life..

iv) Bad image for the manufacturers:-

A poorly formulated or unstable product may show problems like fading or darkening of colour, caking of suspension or breaking of emulsions This will result in not acceptence by the user community that is doctor, pharmacists etc. And it will be a poor advertisement for the manufacturers. From economic point of view it will result in financial loss resulting from non-sale, withdrawal, reformulation etc.

v) Patients Economy.

A patients is entitled to reciene what he is paying for. Stability testing is generally done to ensure that the ~~determination~~ deterioration does not exceed and acceptable level and the activity of the drug and safety of the patients is ensured.

✱3). Cause of instability and prevention

The most common cause of instability and decomposition of drug are :- Hydrolysis and oxidation.

Photochemical decomposition and isomerization lead to instability of ~~sod~~ some drug.

1) Hydrolysis :

This problem is most important in system containing water such as emulsion, suspension, solution etc. Also for drug which are affected by traces of moisture in the form of water vapour from the atmosphere. The main class of drugs that undergo hydrolysis are the esters, amides and lactems.

* Any insoluble substance present in liquid form ~~is~~ is called suspension.

eg. Antacids (oral).

Protection against hydrolysis.

Hydrolysis or solvolytic reactions may be retarded by the following approaches.

i) Hydrolytic reaction in solid drug products such as tablets, capsules, powders and granules may be prevented by avoiding their contact with moisture at the time of manufactures, packaging in suitable moisture resistant packs such as strip packs and storage in controlled humidity and temp. cond.. Extra protection can be achieved by incorporating a suitable desiccant in the pack such as silica gel bags.

ii) Hydrolysis of certain drugs such as benzocaine and procaine (local anasthesia) can be decreased by addition of specific complexing agent like caffeine to the drug solution..

iii) In case of liquid dosage form such as solution, suspension and emulsion. The main emphasis is on reducing the rate of hydrolysis.

iv) Refrigeration of drug solution and drugs also retards hydrolytic reaction,

2) Oxidation

Instabilities in a number of pharmacentical preparation are due to ~~oxidation~~ oxidative ~~degregat~~ degredation of the active ingredient of this preparation when exposed to atmospheric oxygen.

Oxidation ~~two~~ involves either the addition of oxygen or removal of hydrogen. ~~Oxyg~~ oxidation and reduction reaction generally occurs simultaneously. Oxidation is the lose of electrons while reduction is the gain of electron.

Auto-oxidation is a most common foom of oxidative degredation that occurs in many pharmaceutical preparation and involves a free radical chain process. In an auto-oxidative degredation, only a small quantity or amount of oxygen is required for initiating the reaction and ~~their a~~ thereafter oxygen concentration ~~is~~ is relatively important.

Protection against oxidation.

i) The most common approach to prevent oxidation in pharmaceutical preparation is to ~~ind~~ include antioxidants in the preparation. An antioxidant is an agent that has lower oxidation potential than the drug.

eg. vit-E, C or Hydrogen peroxide, Halogen etc.

ii) The effectiveness of antioxidant can be increase through the use of ~~synergists~~ synergists such as chelating agent like EDTA, Citric acid and tartaric acid which react with impurities such as those of heavy metals which may catalyst the oxidation reaction.

EDTA = Ethylene diamine tetraacetic acid.

[Examples of drug which undergo oxidation decomposition are - Ascorbic acid, Morphine, Heparin, Paraldehyde, Tetracycline, Vitamin - A, D and K.]

iii) When oxidation is catalysed by hydrogen and hydroxyl ion the pH of optimum stability must be ensure.

iv) Replacement of air from the container of the drug preparation by an inert gas such as - Nitrogen can also prevent oxidation.

v) Oxidation of fat and oils may be retarded by hydrogenation.

vi) Protection from light.

eg:- Packeging in amber coloured bottle or container and storage at low temp. can also minimize oxidation-reduction in certain preparation.

Ascorbic acid is also an antioxidant agent.

3) Photolysis.

Many pharmacentical compounds including ascorbic acid, ~~Nitrogen~~ riboflenin, ~~hydrocardisat~~ Hydrocortisone, Prednisolone Nifedipine etc undergo degradation when it posses to light. Its posses of light may produce oxidation-reduction, ring arrangement or modification and polymerisation. The shorter the wavelength of light the greater is the effect of light in initiating the chemical reaction because of higher energy

4) Isomerisation.

Isomerisation is the process of conversion of a drug into optical or geometric isomer. Since different isomers of a drug have different activities, such a conversion from one form to another may be regarded as a form of degration. Resulting in serious loss of therapeutic activity. "For example, there is an appreciable loss of activity of adrenaline solution at low pH due to the conversion of its therapeutidy active laevo-rotatory form to the less active dextro-rotatory form, the process often known as racemisation".

* PH :-

Acidic and alkaline pH influence the rate of decomposition of most drugs. Many drugs are stable between pH 4 and 8. Weakly acidic and basic drugs show good solubility when they are ionized and they also decompose faster when they are ionised.

✱ Drug Kinetics

* Drug follows two kind of kinetics:

i) First order
ii) Zero order.

i) First order:

→ In first order, fraction is constant. It means in same time, some fraction will be eliminated. That is in same time, some parcentage of drug will be eliminated. Suppose initial plasma concentration of drug is 100.

ii) Zero order.

→ Amount ~~of~~ is constant. It means in same time, same amount will be remove not percentage.

~~First order~~:

Zero Order

Plasma conc.: 100

1 hr ↓ 20

80

1 hr ↓ 20

60

1 hr ↓ 20

40

1 hr ↓ 20

20

1 hr ↓ 20

0

First order.

100

1 hr ↓ 50%/100

50 50%

1 hr ↓ 25/100

25 50%

1 hr ↓ 12.5/100

12.5 50%

1 hr ↓ 6.25/100.

6.25 50%

It means 50% per hr.

50% → Rate of elimination.

i) Rate of elimination

ii) Clearance .: = Rate of elimination / plasma concentration

iii) Half life ($t_{\frac{1}{2}}$) :- It is the time ~~at~~ at which plasma concentration become half.

First order	Zero Order
i) Rate of elimination is directly proportional to plasma conc.	i) Constant
ii) Clearance is constant.	ii) Clearance is inversely proportional to plasma conc. $CL \propto \frac{1}{PC}$
iii) Half life is constant	iii) Half life is directly proportional to plasma conc. $(T\frac{1}{2})$ Half life $\propto$ PC

Zero order eg.

W - Warfarin
A - Alcohol, Aspirin
T - Theophylline
T - Tolbutamide
Power - Zero Phenytoin.

* If enzymes is the limiting factor then it follow zero order kinetics.

Rates and order of Reactions

Rate of Reaction

⇒ The rate of a chemical reaction is defined as the velocity with which a reactant or reactants undergo chemical change. The rate of a reaction can therefore be measured by measuring the change in the concentration of a reactant or product in a particular period of time.

The rate of a reaction is given by.

$$\boxed{\pm \frac{dc}{dt}}$$

The + or - sign indicates an increase or decrease respectively in concentration dc within a time interval dt

④ Rate constant and order of Reaction.

⇒ According to the law of mass action, the rate of a chemical reaction is proportional to the product of the molar concentration of the reactants each raised to a power usually equal to the number of molecules, a and b

of the substance A and B undergoing reaction.

Thus, in the reaction

$$aA + bB \rightarrow \text{Products}$$

the rate of the reaction is given by:

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

OR

$$\boxed{\text{Rate} = \frac{-1}{b}\frac{d[B]}{dt} = k[A]^a[B]^b}$$

in which k is the rate constant also known as specific rate constant.

The order of reaction is the ~~term~~ sum of the powers of the concentration terms involved in the eq.

Thus the order of the above reaction is $(a+b)$. The order of a reaction determines the way in which the conc. of a reactant or reactants influences the rate of a chemical reaction.

Zero Order Reaction

If the rate of a reaction is independent of the concentration of the reacting species, the reaction is said to be a zero-order reaction.

The rate of a zero-order reaction is given by:

$$\frac{-dA}{dt} = k.$$

Where,

dA is the change in concentration with respect to change in time t.

'-' signs indicates that the concentration is decreasing.

This rate equation may be integrated between initial concentration A_0 (original concentration) and A_t, the concentration after time interval t.

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

$$A_t - A_0 = -kt$$

$$A_t = A_0 - kt$$

This being the equation of a straight line, the plot between A_t on y-axis against on x-axis gives a straight line with slope equal to -k.

Unit of k for a zero order reaction is moles/litre/second.

The above equation can also be written as :

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

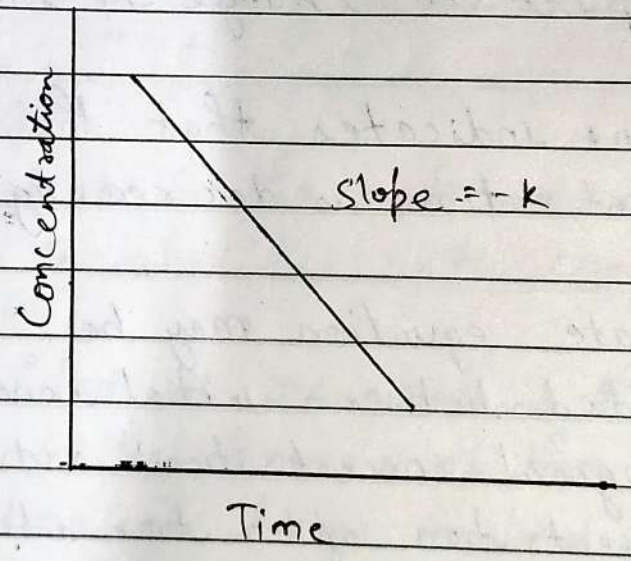


Fig:→ 6.1: Plot of concentration versus time for a zero order reaction.

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

5 Half Life of a zero-order Reaction.

Half life ($t_{\frac{1}{2}}$) of a chemical reaction is the time required for the initial concentration of a reactant to get reduced to half, i.e.,

$$A_t = \frac{1}{2} A_0$$

Substituting this in the above equation, we get,

$$\frac{A_0}{2} = A_0 - k t_{\frac{1}{2}}$$

$$\frac{A_0}{2} - A_0 = -k t_{\frac{1}{2}}$$

$$-\frac{A_0}{2} = -k t_{\frac{1}{2}}$$

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

Shelf life of a zero-order Reaction

An expression of importance in the pharmaceutical field is $t_{0.9}$, i.e., the time required for the drug to decompose by 10% (i.e. to 90% of its original conc.)

Thus,

$$A_t = 0.9A.$$

Substituting this in the above equation we get,

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

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

First Order Reaction

When the rate of a reaction is directly proportional to the first power of the concentration of a single reactant, the reaction is said to be of first order with respect to the single reactant.

In this type of reaction of a first order reaction is given by.

$$-dc/dt = kC$$

$$dc/c = -k\,dt$$

Integrating the equation between the limits of concentration c_0 at time $t = 0$ and conc. c at time $t = t$, we get,

$$\int_{C_0}^{C} dc/c = -k \int_{0}^{t} dt$$

$$\ln c - \ln C_0 = -k(t-0)$$

$$-\ln c = \ln C_0 - kt.$$

Converting to common logarithmic form, we get,

$$\log c = \log C_0 - kt/2.303.$$

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

In exponential form, the equation becomes:

$$C = C_0 e^{-kt}$$

$$C = C_0 10^{-kt/2.303}$$

These equation indicate a first order reaction since the concentration decreases exponentialy with time and this may be shown by plotting concentration against time. when a curve similar to fig. below.

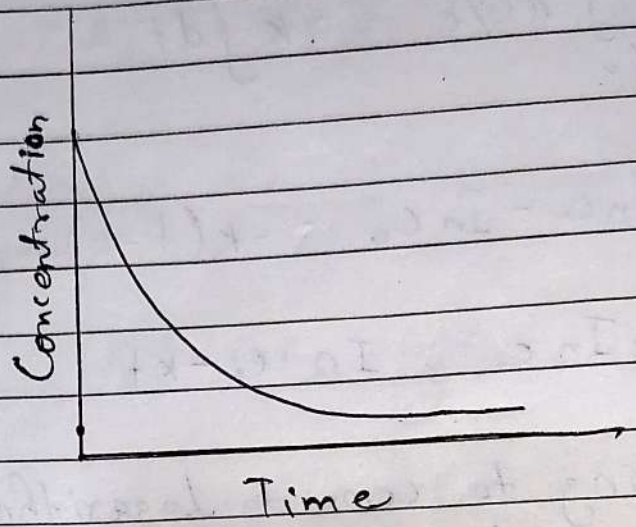


Fig :-6.2 : Plot of concentration versus time for a first order equation.

If log c is plotted against t, a straight line is obtained with slope equal to $-k/2.303$. The rate constant k can then be obtained from the slope of the line (fig. 6.3)

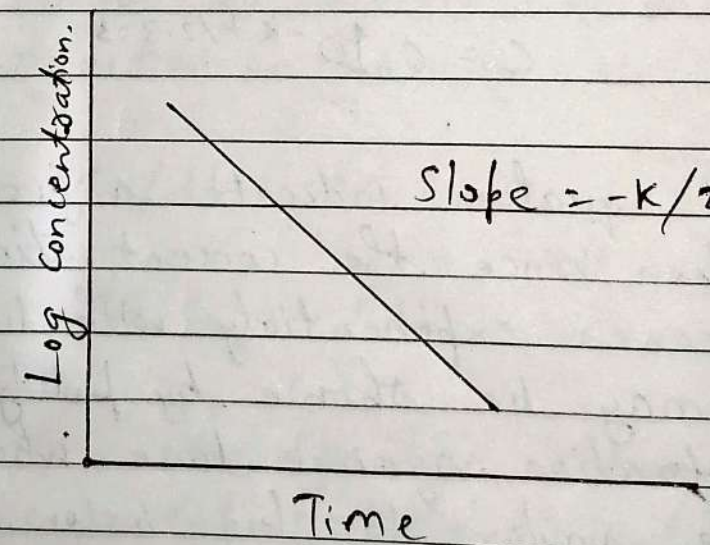


Fig 6.3 : Plot of log concentration versus time for a first order reaction.

The above equation is also written as:

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

Where,

a is the initial conc. equal to C_0

x is the decrease in conc. in time t

(a-x) is the concentration remaining at time t and is equal to C in the above reaction.

Unit of K for a first order reaction is sec^{-1} (or $time^{-1}$).

Half life of a first order reaction

$$t_{\frac{1}{2}} = \frac{2.303}{K} \log \frac{C_0}{C}$$

$$= \frac{2.303}{K} \log \frac{C_0}{\frac{1}{2} C_0}$$

$$= 2.303 / K \log 2$$

$$= 0.693 / K.$$

Thus, half life of a first order reaction is a constant independent of the concentration.

Shelf life of a first order reaction

$$t_{0.9} = \frac{2.303}{K} \log \frac{C_0}{0.9C_0}$$

$$= 2.303/K \times 0.0457$$

$$= 0.1052/K$$

Second Order Reaction

A reaction is said to be of second order if the experimentally determined rate of reaction is proportional either to the second power of the concentration of a single reactant or to the first power of the concentration of the two reactants.

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

If the reaction is one mole per basis of A and B rate of decomposition of A = rate of decomposition of B.

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

If a and b represents the initial concentrations of A and B respectively and x in the amount of each of A and B reacting in time t, the reaction rate dx/dt is given by:

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

Where (a-x) and (b-x) represent the concentration of A and B remaining unreacted at time t.

1. If the initial concentration 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:

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

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

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

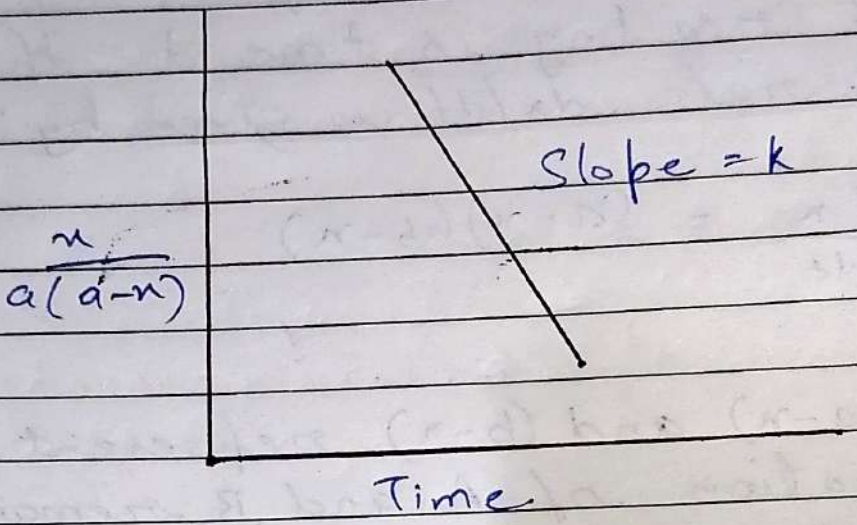


Fig: 6.4. Plot of $x/a(a-x)$ versus time for a second order reaction.

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

Plot of $x/a(a-x)$ against t gives a straight line with slope equal to K (fig. 6.4.).

2. If the concentration of A and B are not equal, i.e. $a \neq b$., integration of equation (i) gives:

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

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

The rate ~~of~~ constant k for a second order reaction has the units, $litre \cdot mole^{-1} sec^{-1}$.

Half life of a Second order Rxn

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

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

PSUEDO FIRST ORDER REACTION

In a second order rxn if the conc. of one reactant is in such large excess that is virtually remain constant, when the rate of change of concentration follows first order. Hydrolysis reaction are common example of pseudo first order reaction. Also if a buffer is use to maintain the pH, the reaction proceeding of an addition of an acid or a base is pseudo first order.