Kinetics and drug stability

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Chapter outline

- Introduction
- Rate and order of reactions
- Chemical and physical degradation
- Factors affecting stability of drugs
- Stability study
- Prediction of shelf life

Introduction

Kinetics :

✓ Is study of the rate at which processes or changes occur.

- The changes may be
  - chemical such as decomposition of a drug, radiochemical decay
  - physical such as transfer across a boundary, such as the intestinal lining or skin

Introduction…

- The rate of chemical change is influenced :
  - ✓ concentration of reactants, products, and other chemical species that may be present and
  - ✓ By factors such as solvent, pressure, T^{O}

Introduction…

Importance of studying kinetics

- To determine half life
- To determine shelf life ($t_{0.9}$)
- Selection of proper storage condition
  - Temperature and humidity
  - advising patient on storage conditions

Introduction…

Importance of studying kinetics…

- Selection of proper container for dispensing
  - Glass vs. plastic
  - Clear vs. amber vs. opaque
- To determine incompatibilities
- Dissolution determinations
- To study ADME Processes in pharmacokinetics

Introduction…

Stability :

- ✓ Is the capacity of a drug product to remain within specifications established to ensure its identity, strength, quality, and purity

Stability study:

- ✓ Is the study of the extent to which the properties of a drug substance or drug product remain within specified limits at certain temperature and humidity
  - ➢ The properties may be physical, chemical, microbiological, or performance properties such as disintegration and dissolution.

Introduction…

Importance of Stability

- Extensive chemical degradation result in a substantial loss of quantity of therapeutic agent in the dosage form
- Degradation products may result in adverse events or be unsafe
- Instability may cause
  - ✓ Undesired change in performance, i.e. dissolution/bioavailability
  - ✓ Substantial changes in physical appearance of the dosage form causing product failures

Rate and order of reactions

Rate of reaction

Rate???

- Is the velocity or speed of a reaction with which a reactant(s) undergo a change.
- Can be measured by measuring the change in the conc. of a reactant or product in a particular period of time
- Given by; rate = $\pm dc/dt$

Rate and order of reactions…

Order of reaction??

- Refers to the way in which the concentration of the reactant (s) influence the rate of a chemical rxn.

i. Zero order rxn:

- the rate of rxn is independent of the concentration of the reactants and constant with respect to time

ii. First-order rxn:

- the rate of rxn is directly proportional to the concentration reactant remaining with respect to time

Rate and order of reactions…

- ✓ According to law of mass action, the rate of a reaction is proportional to the product of the molar concentration of reactants each raised to power equal to the number of molecules undergoing reaction.

$$a\,A + b\,B \longrightarrow \text{Product}$$

$$\text{Rate } \alpha\ [A]^a .[B]^b$$

$$\text{Rate} = K\,[A]^a .[B]^b \qquad (1)$$

Rate and order of reactions…

Order of reaction = sum of exponents

Order of A = a and B = b

Then overall order = a + b

K is the rate constant or specific rate constant

Rate and order of reactions…

Ex: The reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water

$$(CH_3\ CO)_2\ O + 2\ C_2H_5OH \longrightarrow 2\ CH_3\ CO_2\ C_2H_5 + H_2O$$

$$\text{Rate} = K\ [(CH_3\ CO)_2\ O]\ .\ [C_2H_5OH]^2$$

- Order for $(CH_3\ CO)_2\ O$ is 1st order
- Order for $[C_2H_5OH]^2$ is 2nd order
- Overall order of reaction is 3rd Order

Rate and order of reactions…

Molecularity

- Refers to the number of molecules, ions or atoms in elementary process to give the product

i. Unimolecular:

Only one type of molecule undergoes a change to yield the product

Eg. $Br_2 \longrightarrow 2Br$

ii. Bimolecular:

two molecule combine to give the product

Eg. $H_2 + I_2 \longrightarrow 2HI$

- Molecularity and order of a rxn are generally identical for elementary rxn

Rates and orders of reactions

zero order reaction

- The rate of a reaction is **not** dependent on the concentration of the reacting species
- Rate is constant

$$A \xrightarrow{k} \text{Product (P)}$$

$$\text{Rate} = -dC/dt = K[A]^0$$

$$-dc/dt = k$$

$$dc = -k\,dt$$

✓ where dC is the change in concentration wrt change in time t

minus sign indicates that the concentration is decreasing

Rates and orders of reactions...

- The rate equation may be integrated b/n the initial concentration (C_o) and concentration Ct after time t.

$$\int_{c=co}^{c=ct} dc = \int_{t=0}^{t=t} -k\,dt$$

$$[c]_{co}^{ct} = [kt]_{0}^{t}$$

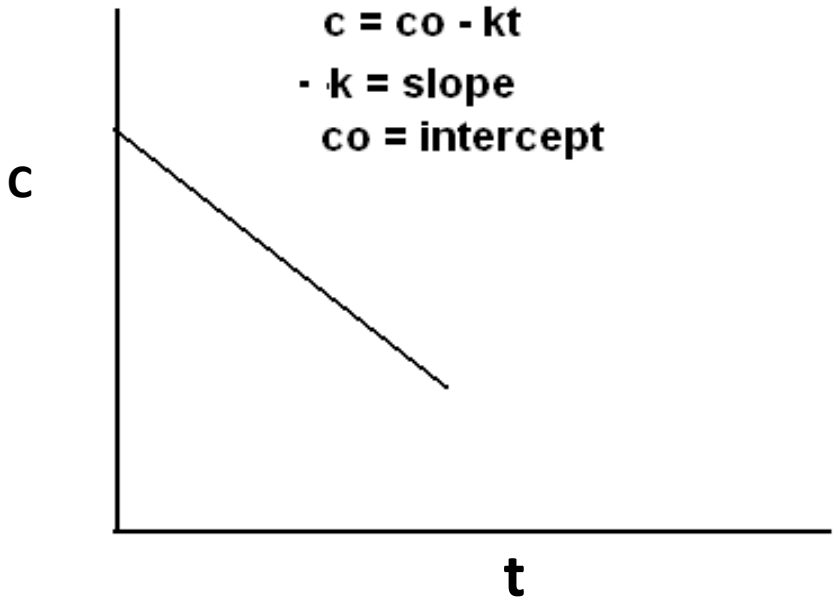
$$ct - co = -kt$$

$$c - co = -kt$$

$$C = Co - kt \qquad (2)$$

Rates and orders of reactions…

- When this linear equation is plotted with conc. on the vertical axis and time on the horizontal axis, the slop of the line give –K



- Unit of K for zero order rxn is moles Litre^{-1} second^{-1}

Rates and orders of reactions…

Half life of zero order reaction

- The half life is the time required for 50% of the material to disappear
- it is the time at which Co is decreased to 1/2Co

Let $C = C_o / 2$ and $t_{1/2} = t$

substituting this in to eq. 2, yields

$$C = C_o - k\,t$$

$$t_{1/2} = C_o / 2K \qquad (3)$$

Rates and orders of reactions…

Shelf life of a zero order reaction

- The shelf life is the time required for 10% of the material to disappear
- it is the time at which Co has decreased to 90% of its original concentration

Let $c = 0.9C_o$ and $t = t_{0.9}$

substitute in eq. 2;

$$c = c_o - k\,t$$

$$t_{90\%} = t_{0.9} = 0.1\,c_o / k \qquad (4)$$

Rates and orders of reactions…

Q. 1. Drug X degrades by a zero-order process with a rate constant of 0.05 mg/ ml.year at room temperature. If a 1 mg/ml solution is prepared and stored at room temperature:

1. What concentration will remain after 18 months? Ans 0.925

2. What is the half-life and shelf-life of the drug? Ans 10 and 2 years

Q. 2. The conc of a drug preparation exposed at 40 °C decreased from 1.420 mg/ml to 1.400 mg/ml in 3 months. Determine the the rxn rate assuming that the rxn follows zero order rxn. Ans 0.00667 mg/ml . Mon

Rates and orders of reactions

First-order reaction

- The rate of the rxn is directly proportional to the first power of a concentration of single reactant.
- The reaction can be written as

$$A \xrightarrow{K} \text{products}$$

- The rate equation is given as

$$-\frac{dc}{dt} = kc \qquad (5)$$

Where C is the concentration of the reactant A remaining undecomposed at time t and K is the first-order rate constant

Rates and orders of reactions…

- Integrating this equation b/n the limits of concentaration Co at time t=0 and concentration C at t=t . we get

$$\int_{c_0}^{c} \frac{dc}{c} = -k \int_{0}^{t} dt$$

$$\ln c - \ln c_0 = -k(t - 0)$$

$$\ln c = \ln c_0 - kt \qquad (6)$$

- Converting to a logarithmic form, we get

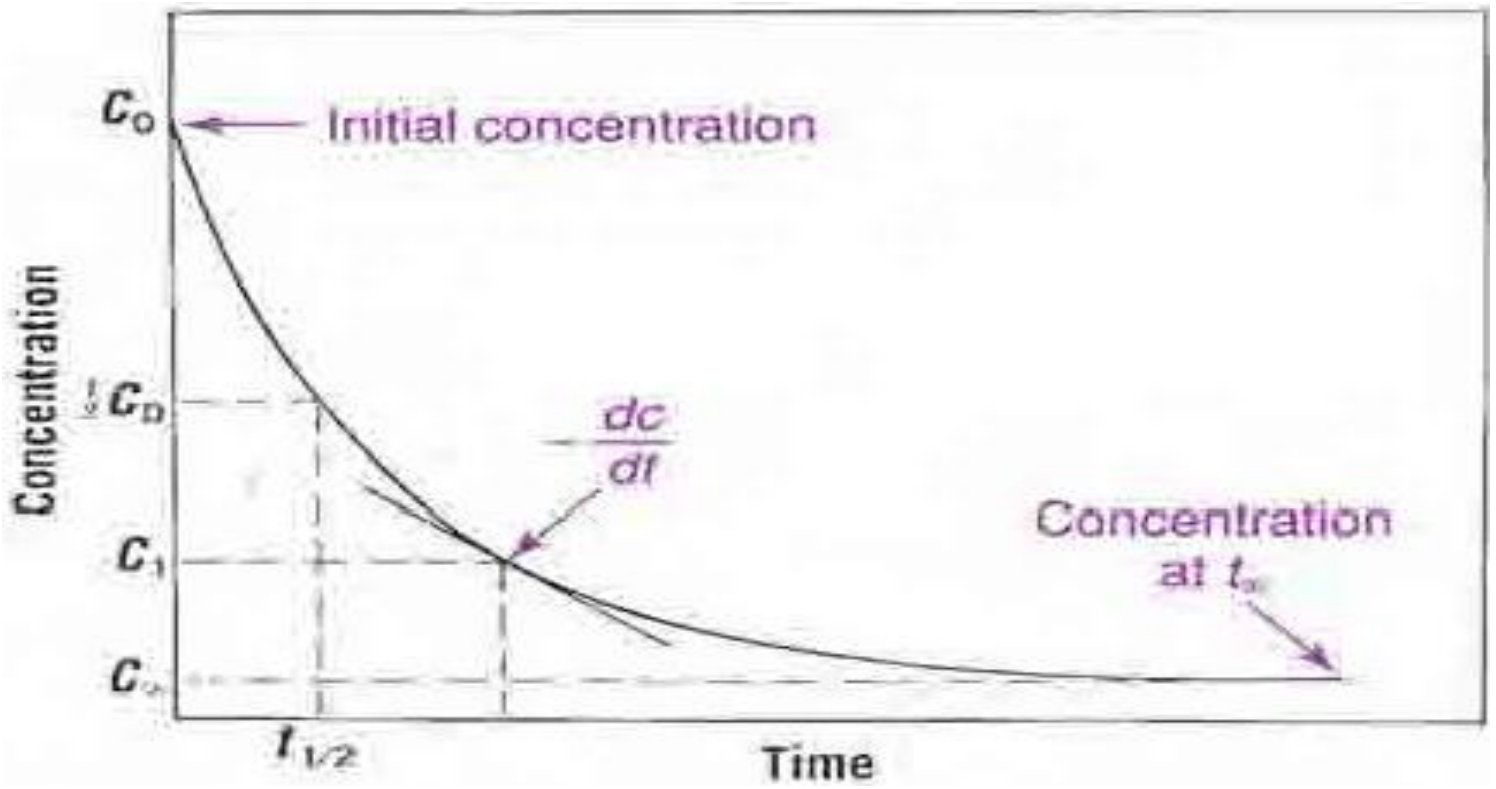
$$\log c = \log c_0 - kt/2.303 \qquad k = \frac{2.303}{t} \log \frac{c_0}{c} \qquad (7)$$

Rates and orders of reactions…

- In exponential form, the equation becomes

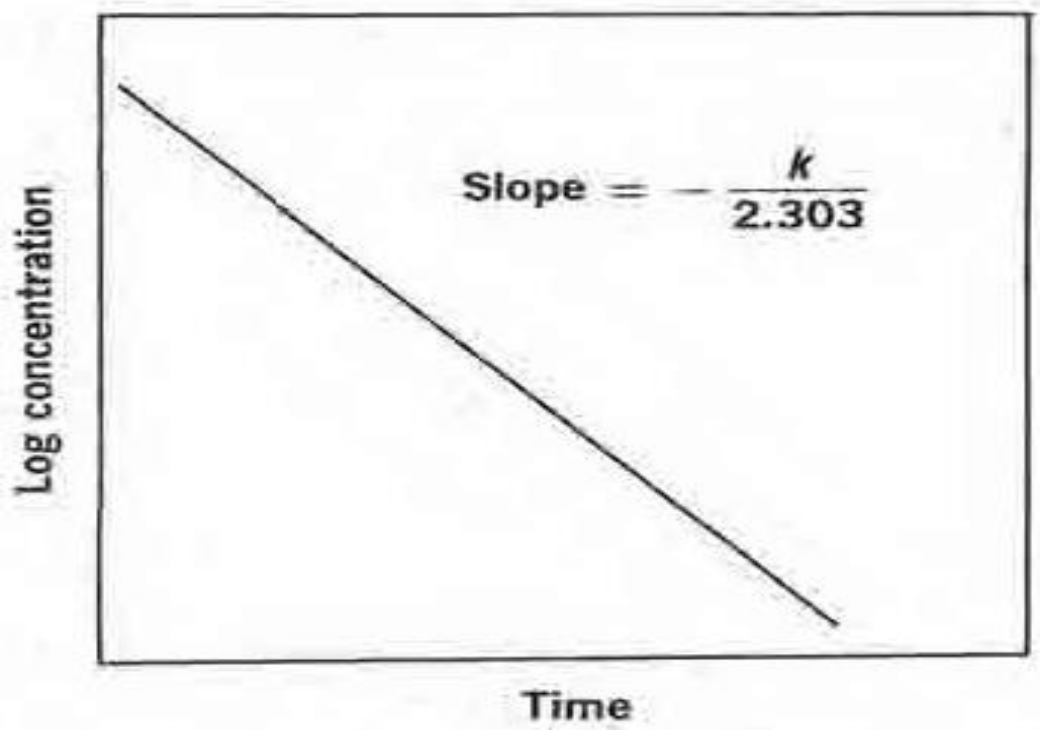
$$c = c_0 e^{-kt}$$

- The conc decrease exponentially with time



Rates and orders of reactions…

- If logc is plotted against time t, a straight line is obtained with slope equal to –k/2.303.
- The rate constant k can be obtained from the slope of the line and it has unit of Sec^{-1}



Rates and orders of reactions…

Half life of first order reaction

$C = 1/2 Co$

substituting in the equation

$$t = \frac{2.303}{k} \log C_o/C$$

$$t_{1/2} = 0.693/k \qquad (10)$$

Rates and orders of reactions…

Shelf life of first order reaction

$C = 0.9C_o$

substituting in equation

$$t = \frac{2.303}{k} \log C_o/C$$

$$\mathbf{t_{90\%}} = 0.105/k \qquad (11)$$

- the half life and shelf life of first order rxn is a constant independent of the concentration

Q. 1. A solution of drug contained 680 units/ml when prepared. It was analysed after a period of 60 days and was found to contain 400 units/ml. assuming the decomposition is first order, at what time the drug have decomposed to one half of its original concentration? Ans 78 days and 7 hrs

Q. 2. The initial concentration of a drug which decomposes according to 1st order kinetics, is 94 units/ml. the specific decomposition rate K obtained from an Arrhenius is 2.09 x 10-5 per sec at room T (25 oC). Previous experiments have shown that below 45 units/ml, the drug is not fit for use. What expiry date should assigned to the product? Ans 3.525×10^{4} sec

Q.3. Based on the Q 2 what the time taken for 5% of a drug to decompose?

Ans 2.45×10^{3} sec

Rates and orders of reactions...

Q. 4. What is the remaining concentration C in mg ml^{-1} of a drug (initial concentration Co = 7 mg ml^{-1}) after a time equivalent to 3 half-lives assuming that the decomposition follows first-order kinetics**?**

Q.5. The initial concentration of active principle in an aqueous preparation was 5.0 x 10^{-3} gcm^{-3}. After 20 months the concentration was shown by analysis to be 4.2 x10^{-3} gcm^{-3}. The drug is known to be ineffective after it has decomposed to 70% of its original concentration. Assuming that decomposition follows first order kinetics, calculate the expiry date of the drug preparation.

Q. 6. The rate of decomposition of a 0.056 M glucose at 140 °C in acidic solution was found to be as follows based on this data fined K, half life and shelf life.

Time (in hrs)	0.0	0.5	2.0	4.0	6.0	8.0	12.0
Glucose remaining (x10^{-2} mol.$liter^{-1}$)	5.65	5.52	5.31	5.02	4.80	4.52	4.09

Rates and orders of reactions…

Methods for determining the order of reaction:

- Substitution method
- Graphical method
- Half life method

Rates and orders of reactions…

Substitution method:

- The data obtained from a kinetic experiment is substituted in the relevant integrated equation.

- The equation that yields a fairly constant value of K with in the limits experimental variation indicates the order of the reaction

Rates and orders of reactions…

Graphical method

- The data obtained from a kinetic experiment is plotted in the relevant form to determine the order of a particular reaction

- Zero-order if straight line is obtained by plotting the concentration a against time t
- First-order if a plot of log c versus t yields a straight line, the reaction is first order.

Rates and orders of reactions…

Half life method

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

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

- If the two reactions are run at different initial concentrations, a_1 and a_2, the respective half-lives $t_{1/2(1)}$ and $t_{1/2(2)}$ are related as follows:

$$\frac{t_{1/2(1)}}{t_{1/2(2)}} = \frac{(a_2)^{n-1}}{(a_1)^{n-1}} = \left(\frac{a_2}{a_1}\right)^{n-1} \qquad (24)$$

Rates and orders of reactions…

Or in logarithmic form

$$\log \frac{t_{1/2(1)}}{t_{1/2(2)}} = (n-1)\log \frac{a_2}{a_1} \quad (25)$$

or

$$n = \log \frac{(t_{1/2(1)}/t_{1/2(2)})}{\log(a_2/a_1)} + 1 \quad (26)$$

- The half-lives are determined graphically by plotting c versus t at two different initial concentrations and reading the time at $1/2a_1$ and $1/2a_2$.
- The values for the half-lives and the initial concentrations are then substituted in to the above equation.

Rates and orders of reactions…

Q. 1. The kinetics of decomposition of a drug in aqueous solution were studied using a series of solutions of different initial drug concentrations, C_0 . For each solution the time taken for half the drug to decompose (that is, $t_{0.5}$) was determined with the following results:

C_0 (mol dm^{-3})	4.625	1.698	0.724	0.288
$t_{0.5}$(min)	87.17	240.1	563.0	1414.4

Determine the order of reaction.

Rates and orders of reactions…

- Drug substances and expients have diverse molecular structures
  - susceptible to many degradation pathways.
- **chemical degradation pathways**
  - hydrolysis, dehydration, isomerization, oxidation, decarboxylation and elimination and photodegradation
- **physical change**
  - Vaporization, Crystallization of Amorphous Drugs, Transitions in Crystalline States, and Moisture Adsorption

Rates and orders of reactions…

Chemical degradation

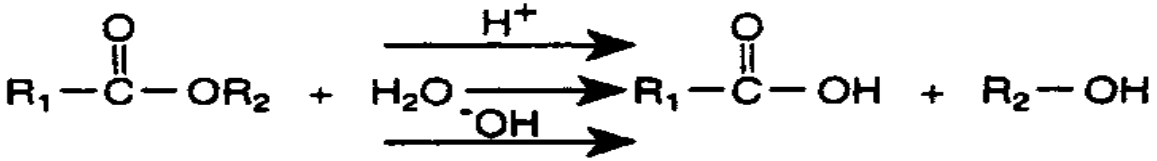
Hydrolysis (solvolysis)

- interaction of drug molecules with water molecule to yield breakdown product
- Most important
  - in system containing water such as emulsion, suspensions, solutions
  - for drug which are affected by trace of moisture in the form of water vapour from the atmosphere

Chemical and physical degradation…

❑Esters hydrolysis

- Involves acyl-oxygen cleavage
- procaine, atropine, aspirin, tetracycline and physostigimine

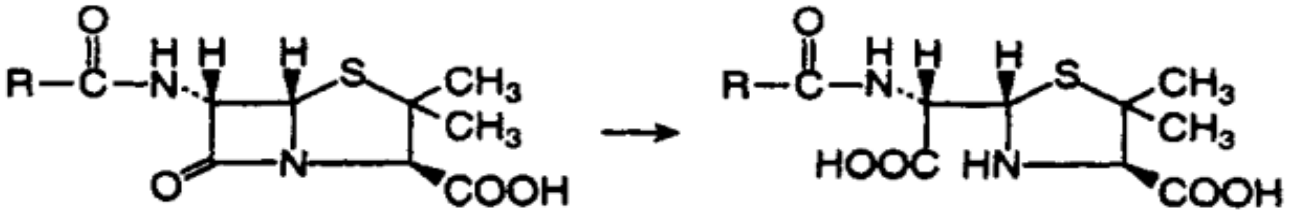


❑Amides hydrolysis

- Involves the cleavage of the amide linkage to give an amine
- chloramphenicol, penicillin, cephalosporins, niacinamide, and barbiturates

Chemical and physical degradation…

- Ring hydrolysis
  - Proceed by ring cleavage with subsequent attack by hydrogen or hydroxyl ions
  - penicillins, cephalosporins, nitrazepam and chlordiazepoxide



Chemical and physical degradation…

Protection against hydrolysis

- Solid dosage form may be prevented by
  - avoiding their contact with moisture at the time of manufacture,
  - packaging in suitable moisture resistant packs
  - storage in controlled humidity and temperature
  - incorporating a suitable desiccant in the pack such as silica gel bags

Chemical and physical degradation…

- Liquid dosage form can be prevented by
  - Selecting an optimum pH for maximum stability and the formulation should be stabilized at this pH by inclusion of proper buffering agent
  - General acid-base catalyzed hydrolytic decomposition due to components of buffers can be minimized by keeping buffer concentration to the minimum required for maintaining the pH
  - By altering the dielectric constant of the system by partial or complete replacement of water with non-aqueous solvents such as alcohol, glycerin and propylene glycol.

Chemical and physical degradation…

- Addition of specific complexing agent like caffeine to the drug solutions
- By preparing insoluble derivatives of the drug which can then be formulated in the form of suspension.
- Formulating susceptible drugs such as penicillin and its derivative in the form of dry powder for reconstitution

Chemical and physical degradation…

Oxidation

- In pharmaceutical dosage forms, oxidation is usually mediated through reaction with atmospheric oxygen under ambient conditions
- Autoxidation is the most common of oxidative degradation that occur in many of the pharmaceutical preparation
  - Only small amount of oxygen is required for initiating the rxn
  - involves multiple pathways: initiation, propagation and termination.

Chemical and physical degradation…

Initiation : $RH \longrightarrow R^{\bullet} + H$

Propagation : $R^{\bullet} + O_2 \longrightarrow ROO^{\bullet}$

$ROO^{\bullet} + RH \longrightarrow ROOH + R^{\bullet}$

Termination:

$ROO^{\bullet} + ROO^{\bullet} \rightarrow$ stable product

$ROO^{\bullet} + R^{\bullet} \rightarrow$ stable product

$R^{\bullet} + R^{\bullet} \rightarrow$ stable product

Chemical and physical degradation…

- Many oxidation reactions are catalyzed by acids and bases
- Heavy metals like copper, iron, cobalt and nickel catalyse the oxidation rxn
- Heat and light further influence the kinetics of oxidative degradation process

Chemical and physical degradation...

Protection against oxidation

- Use of Antioxidants

- True antioxidants
  - Block chain reaction by reacting with free radicals
  - Inhibit autoxidations but not effective in redox reactions.
  - Eg. Tocopherol, ascorbyl palmitate, propyl gallate
- Reducing agents
  - are more readily oxidized than the drug or adjuvant,
  - are effective in the redox rxn.
  - Eg sodium metabisulphite, sodiumthiosulphate

Routes by which pharmaceuticals degrade…

- Antioxidant synergists
  - Enhance effect of antioxidants
  - Complexing metal by using specialized agents such as chelating agents e.g., EDTA, citric acid and tartaric acid.

Chemical and physical degradation...

- Replacing oxygen in pharmaceutical containers with nitrogen or carbon dioxide.
- Storage at reduced temperatures
- Oxidation of fats and oils may be retarded by hydrogenation
- If oxidation is catalyzed by hydrogen or hydroxyl ion , the pH of optimum stability must be ensured

Chemical and physical degradation…

Photodegradation

- sunlight or room light may cause substantial degradation of drug molecules.
- The energy from light radiation must be absorbed by the molecules to cause a photolytic reaction.
  - If this energy is sufficient to achieve activation, degradation of the molecule is possible

Chemical and physical degradation…

- Photolysis reactions often are associated with oxidation
  - because the oxidation reactions frequently can be initiated by light.
  - But photolysis reactions are not restricted to oxidation
- E.g. phenothiazines, hydrocortisone, prednisolone, riboflavin, nifedipine, colchicine and chlorpromazine

Chemical and physical degradation...

Protection against Photolysis

- use of coloured glass containers (amber glass excludes light of wavelength < 470 nm)
- storage in the dark place
- Packaging in cartons (physical barrier to light)
- opaque shells for capsules
- Coating tablets with a polymer film containing ultraviolet absorbers

Chemical and physical degradation…

Dehydration

- The elimination of a water molecule from structure of the cpd.
- In covalent (chemical) dehydration process, there is the formation of a double bond that can then participate in electronic resonance with neighboring functional groups

Eg. prostaglandin E2 and tetracycline

Sugars (glucose and lactose) are known to undergo dehydration to form 5-(hydroxymethyl) furfural.

Chemical and physical degradation…

- In physical dehydration processes water removal does not create new bonds but often changes the crystalline structure of the drug.
- Anhydrous compounds may have different dissolution rates compared to their hydrates
  - dehydration reactions involving water of crystallization may potentially affect the absorption rate of the dosage form.

  Eg theophylline hydrate and ampicillin trihydrate

Chemical and physical degradation…

Isomerization

- The process of conversion of a drug in to its optical or geometric isomers.
- may be regarded as a form of degradation resulting in serious loss of therapeutic activity
- Racemization and epimerization, which are reversible conversions between optical isomers, are common

Chemical and physical degradation…

- Examples of isomerization of drug substance
  - *Trans-cis* isomerization of amphotericin B and vitamin A
  - Pilocarpine undergoes epimerization by base catalysis, tetracyclines and ergotamine exhibit epimerization by acid catalysis.
  - Epinephrine undergoes racemization under strongly acidic conditions
  - adrenaline at low pH undergoes racemisation – the conversion of the therapeutically active form (levorotary form) into its less active isomer.

Chemical and physical degradation…

Elimination

- Drug substances having a carboxylic acid group are sometimes susceptible to decarboxylation
  - E.g. 4-Aminosalicylic acid under strongly acidic conditions
- Other elimination reactions have been reported for various drug substances
  - E.g. levothyroxine eliminates iodine

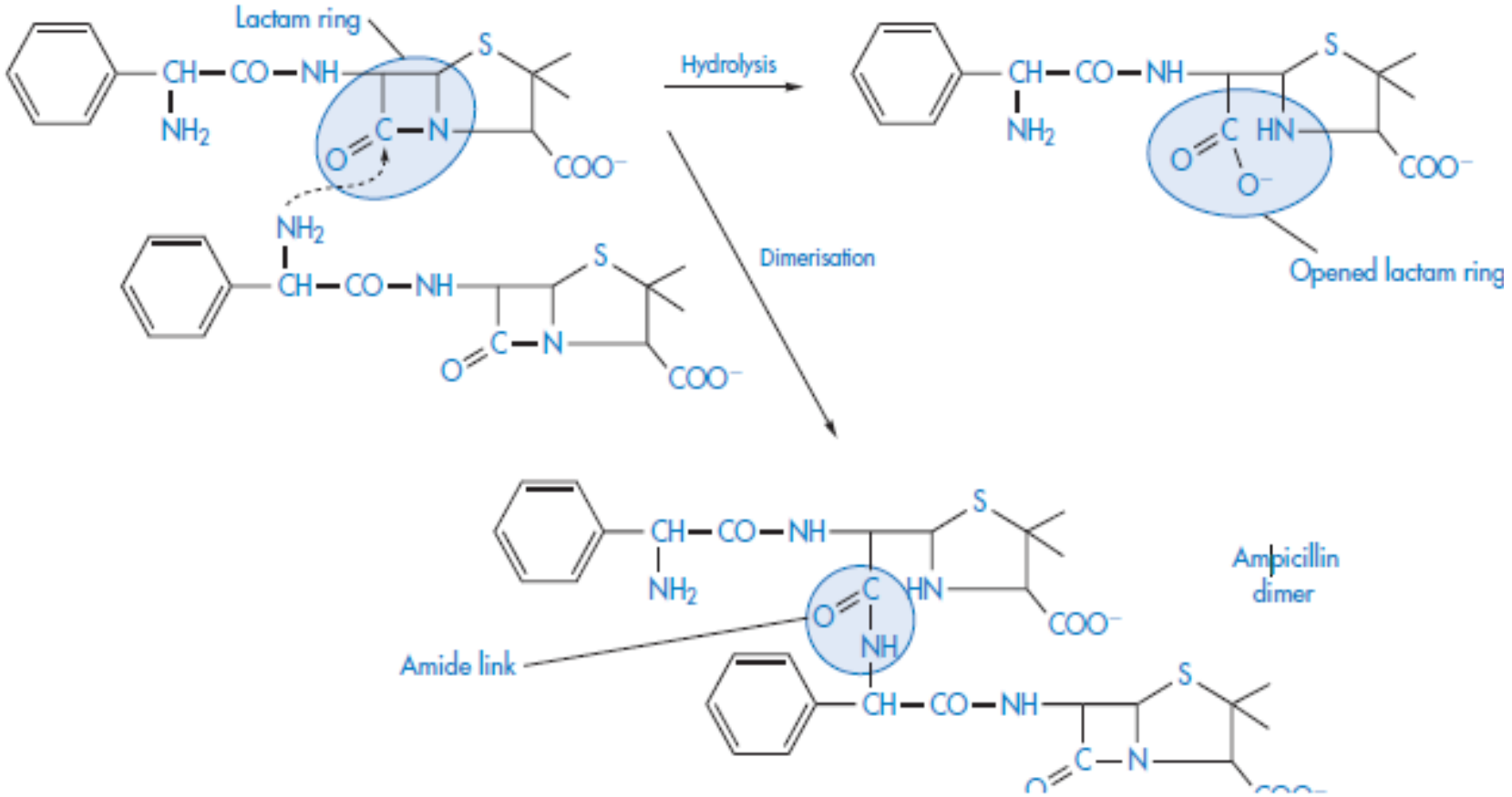
Chemical and physical degradation…

Polymerisation

- is the process by which two or more identical drug molecules combine together to form a complex molecule.
- a polymerisation process occurs during the storage of concentrated aqueous solutions of aminopenicillins, such as ampicillin sodium.
  - The reactive β- lactam bond of the ampicillin molecule is opened by reaction with the side-chain of a second ampicillin molecule and a dimer is formed. The process can continue to form higher polymers.
  - elicit pencilloylspecific allergic reactions

Routes by which pharmaceuticals degrade...

- Dimerisation and hydrolysis of ampicillin.



Chemical and physical degradation…

Physical Degradative Routes

Vaporization

- Some drugs and excipients possess sufficiently high vapor pressures at room temperature that their volatilization constitutes a major route of drug loss.
- Flavors, solvents and cosolvents (LMW alcohols) may be lost from the formulation
  - Volatility of solvents could leads to
    - potentially hazardous concentration of dugs.
    - Crystallization of drug and excipients.

Chemical and physical degradation...

- E.g. Nitroglycerin
- Reduction of vapor pressure can be achieved through dispersion of the volatile drug in macromolecules that can provide physicochemical interactions
  - The addition of macromolecules such as PEG, PVP, and MCC allows for preparation of ``stabilized'' nitroglycerin sublingual tablets
  - A β-cyclodextrin-nitroglycerin tablet is currently being marketed

Chemical and physical degradation…

Adsorption (Sorption)

- Drug-plastic interaction is a major potential problem when intravenous solutions are stored in bags or infused via administration sets that are made from polyvinyl chloride (PVC)
  - up to 50% drug loss can occur after nitroglycerin is stored in PVC infusion bags for 7 days at room temperature.
  - more than 40% of a dose of quinidine gluconate was lost when the drug was administered with a conventional PVC intravenous administration set
- A diverse array of drugs, including diazepam, insulin, isosorbide dinitrate, and others, has shown substantial adsorption to PVC.

Chemical and physical degradation…

Crystallization of Amorphous Drugs

- Poorly water-soluble drugs formulated in their amorphous state to improve the solubility
  - because of the lower free energy of the crystalline state, amorphous substances tend to change to their more thermodynamically stable crystalline state with time.
- Therefore, crystallization of amorphous drug substances may occur during long-term storage and may lead to drastic changes in the release characteristics of the drug and, hence, the absorption

Chemical and physical degradation…

Transitions in Crystalline States

- Polymorphs are different crystalline forms of the same drug.
- have different free energy
  - transitions between polymorphs
- may alter critical properties of drugs because the solubility and dissolution rate of drug substances generally vary with changes in their crystalline form
- Temperature and humidity affect polymorphic transitions

Examples:- Nitrofurantoin, Theophylline

Chemical and physical degradation…

physical changes in emulsion

- such as cracking, creaming …

physical changes in suspension

- which depends on the magnitude of opposing forces of attraction and repulsion.
  - caking

Changes in semisolids

- Gels, ointments and pastes may soften, harden or become granular or gritty during storage.

Factors affecting stability of drugs

Temperature

- According to classic collision theory reaction rates are proportional to the number of collisions per unit time.

- Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.

- The speed of many reactions increases about 2 to 3 x with each 10 degree rise in T.

Factors affecting stability of drugs …

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

$$k = Ae^{-E_a/RT} \tag{42}$$

or

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT} \tag{43}$$

Factors affecting stability of drugs …

Where

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

- Ea and A can be obtained by determining K at several temperatures and plotting 1/T against log K
- The slope of the line obtained is –Ea/2.303R and the intercept on the vertical axis is log A

Factors affecting stability of drugs …

- Ea can also be obtained by writing eq. 43 for a temperature T1 as

$$\log k_1 = \log A - \frac{E_a}{2.303R}\frac{1}{T_1} \quad (44)$$

- And for another temperature T2 as

$$\log k_2 = \log A - \frac{E_a}{2.303R}\frac{1}{T_2} \quad (45)$$

- Subtracting the eq. 44 from the eq. 45 yields

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2 T_1}\right) \quad (46)$$

Factors affecting stability of drugs …

Q. 1. The first-order rate constant for the hydrolysis of sulfacetamide at 120°C is $9x10^{-6}$ S^{-1} and the activation energy is 94 kJ mol^{-1}. Calculate the rate constant at 25°C.

Factors affecting stability of drugs …

Solvent

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

For a bimolecular rxn

$$A + B \rightleftharpoons [A \cdots B]^{\ddagger} \rightarrow \text{Products}$$

- The quantitative r/ship b/n the rxn rate constant and solubility of the reactants and products is given by

$$\log k = \log k_0 + \frac{V}{2.303RT}(\Delta\delta_A + \Delta\delta_B - \Delta\delta_s^{\ddagger}) \qquad (47)$$

where δ_A, δ_B, and $\delta^{\ddagger}$ are solubility parameters of reactants A, B and activated complex respectively

V is an approximation for the molar volumes of the reactants A and B the activated complex

Factors affecting stability of drugs …

- It is assumed that the properties of the activated complex are quite similar to those of the products so that $\Delta\delta^{\ddagger}$ can be taken as a square term expressing the internal pressure difference b/n the solvents and the products
- Based on the above equation,
  - Polar solvents tend to accelerate rxns in which the products formed are more polar than the reactants
  - If the products formed are less polar than the reactants then the rxn proceeds better in the solvents of relatively low polarity

Factors affecting stability of drugs …

Light

- Mostly visible light and UV light causes photo degradation rxn
- Photochemical rxn do not depend on Temperature for activation of molecules.
- Are complex rxns and proceed by a serious of steps

Factors affecting stability of drugs …

Ionic strength

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

$$\log k = \log k_0 + 1.02 z_A z_B \sqrt{\mu} \qquad (48)$$

where

- z_A *and* z_B *are the charge* numbers of the two interacting ions
- K is the degradation rate constant for the reaction
- K_o is the rxn rate constant at infinite dilution
- μ is the ionic strength of the solution

Factors affecting stability of drugs …

- According to eq. 48 , increase in the ionic strength of the solution
  - decrease the rate of rxn b/n oppositely charged ions and
  - Increase the rate of rxn b/n similarly charged ions
- Rxn b/n ions and neutral molecules are generally not affected by to significant extent by change in ionic concentration

Factors affecting stability of drugs …

Dielectric constant

- Has a significant effect on rate of rxn
- For rxn involving ionic species , the effect of the dielectric constant on the rxn rate is given by the equation

$$\ln k = \ln k_{\epsilon=\infty} - \frac{N z_A z_B e^2}{RT r^{\ddagger}} \frac{1}{\epsilon} \qquad (49)$$

Where

- z_A and z_B are the charge on two ionic species
- K is the observed rxn rate constant in a solvent of dielectric constant ε
- kε=∞ is the rxn rate constant in a solvent of infinite dielectric constant

Factors affecting stability of drugs …

-  is the distance b/n the ionic species in the activated complex
- ε is the dielectric constant of the solution
- e is the unit of electric charge

- According to the above eq 49, rxn involving ions of opposite charge accelerated by solvents of low dielectric constant
- Rxn involving similarly charged species, the rate of rxn is accelerated on increasing the dielectric constant of the solvent

Factors affecting stability of drugs …

- If a rxn occurs b/n a dipole or neutral molecule and an ion the equation is

(50)

$$\ln k = \ln k_{\epsilon=\infty} + \frac{N z_A^2 e^2}{2RT}\left(\frac{1}{r_A} - \frac{1}{r^{\ddagger}}\right)\frac{1}{\epsilon}$$

- Where z_A is the charge on the ion A , r_A is the radius of ion and the radius of the activated complex $r^{\ddagger}$
- According to eq 50 the rate of rxn b/n an ion and a neutral molecule will increase with decreasing dielectric constant of the medium

Factors affecting stability of drugs …

Catalysis

- Catalyst is defined as a substance that influences the speed of a reaction with out itself being altered chemically

- It cannot change the position of the equilibrium of a reversible reaction

- catalyst combines with the reactant known as the substrate and forms intermediate known as a complex, which decomposes to generate the catalyst and yield the products

Factors affecting stability of drugs …

- In this way, the catalyst decreases the energy of activation by changing the mechanism of the process, and the rate is accordingly increased
- Alternatively, a catalyst may act by producing free radical such as CH3, which bring about fast chain rxns

Specific Acid-Base Catalysis

- Solutions of a number of drugs undergo accelerated decomposition on the addition of acids or bases.
- If the drug solution is buffered, the decomposition may not be accompanied by appreciable change in the concentration of of acid or base so that the reaction can be considered to be catalyzed by hydrogen or hydroxyl ions.
- When the rate law for such an accelerated decomposition is found to contain a term involving the concentration of hydrogen ion or the concentration of hydroxyl ion, the rxn is said to be subject to specific acid-base catalysis.

Factors affecting stability of drugs …

- The effect of H and OH ion concentration on specific acid base catalyzed rxns can be expressed as

$$\frac{dP}{dt} = (k_0 + k_1[H^+] + k_2[OH^-])[S] \qquad (45)$$

- For which the observed rate constant is given by

$$k_{obs} = k_0 + k_1[H^+] + k_2[OH^-] \qquad (46)$$

- At low pH, the observed rxn rate constant becomes

$$k_{obs} = k_1[H^+] \qquad (47)$$

  - The rxn specific hydrogen ion or acid catalysed

Factors affecting stability of drugs ...

- At higher pH, the observed rxn rate constant becomes

$$k_{obs} = k_2[OH^-] \quad (48)$$

  - The rxn specific hydroxyl ion or base catalysed

- At an intermediate pH, when the concentration of hydrogen and hdroxyl ions are low, the observed rxn rate constant becomes

(49)

  - The rxn is solvent cat $k_{obs} = k_0$

- If the pH of the rxn medium is slightly acidic
  - both solvent and specific acid catalysis are involved
- If the pH of the rxn medium is slightly alkaline
  - both solvent and specific base catalysis are involved

Factors affecting stability of drugs …

- The effect of pH on the degradation may be determined by obtaining the pH profile for specific acid-base catalysed rxn

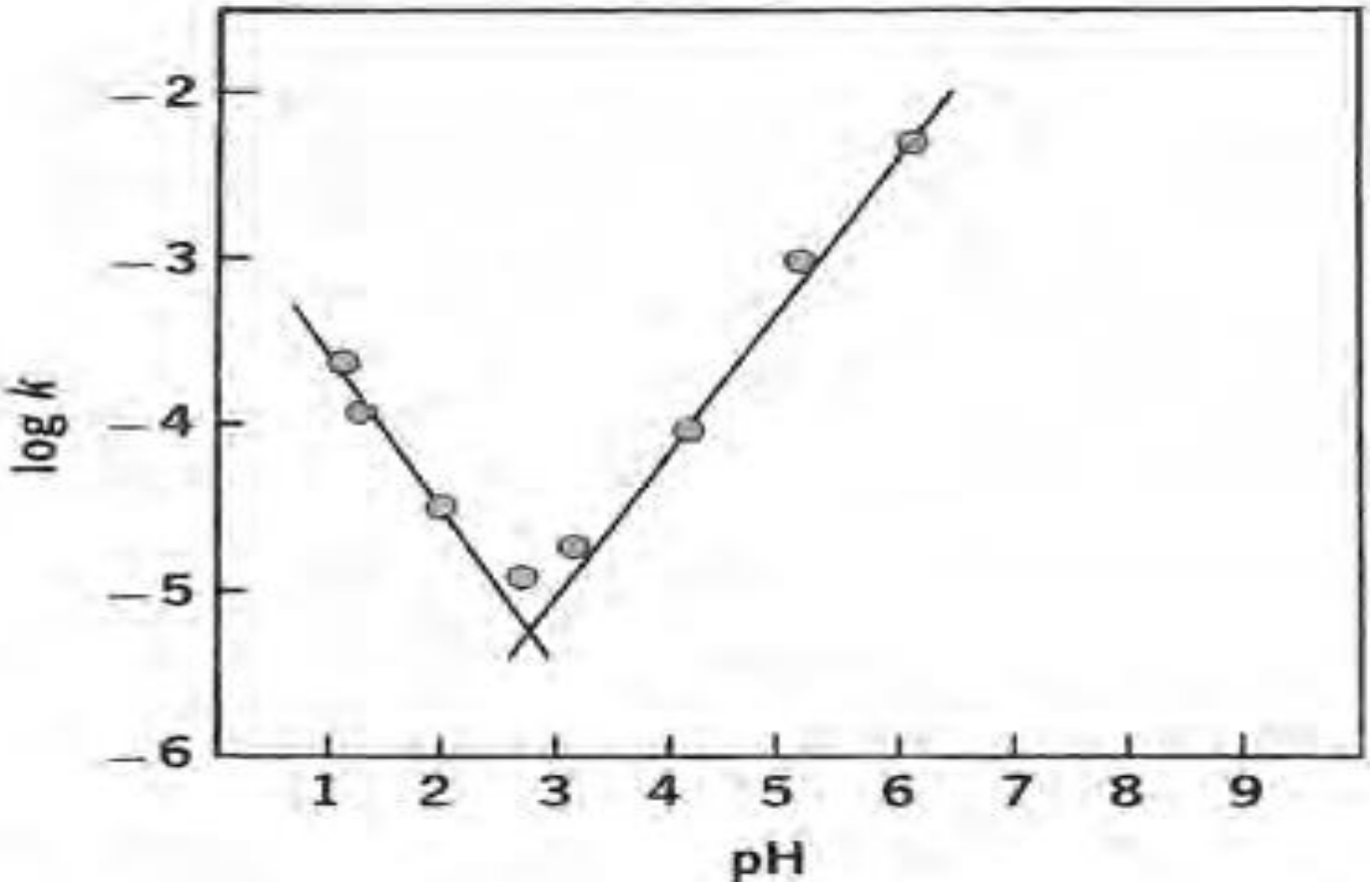


Figure. Log rate–pH profile for the specific acid-base-catalyzed hydrolysis of methyl-dl-o-phenyl-2-piperidylacetate.

Factors affecting stability of drugs …

General acid-base catalysis

- acid-base catalysis in solution is not restricted to hydrogen ions an hydroxyl ion only but often undissociated acids or bases also produce a catalytic effect on the rxn
  - This is general acid catalyzed or general base catalyzed reaction
- These two types of acid–base catalysis can be combined together in a general expression as follows:

$$K_{obs} = K_o + K_1 [H^+] + K_2 [oH^-] + K_{HX} [HX] + K_x[X^-]$$

Stability study

- The purpose of stability testing is to provide evidence on how the quality of a drug substance (active ingredient) or drug product (formulation) varies with time under the influence of a variety of environmental factors
  - temperature, humidity, and light.
- Permits the establishment of recommended storage conditions, retest periods, and shelf lives
- Stability studies should include testing of those attributes of the drug substance or drug product that are susceptible to change during storage and are likely to influence quality, safety, and efficacy

Stability study...

- The testing should cover, as appropriate, the physical, chemical, and microbiological attributes, preservative content and functionality test
- Tests on chemical , physical and microbiological stability of drug substances and excipients involve application of a suitable stress or challenge such as temperature, light, RH, and microorganism, over a period of time and assess its effects.

Stability study...

Climatic zone

- According to ICH (international conference on harmonization) and WHO guideline on stability studies, the world has been divided in to four zones taking in to account the prevalent annual climatic conditions of temperature and humidity
  - Zone I- temperate (**21°C/45% RH**)
  - Zone II – subtropical with possible high humidity (**25°C/60% RH)**
  - Zone III- hot, dry (**30°C/35% RH**)
  - Zone IV
    - **Zone IVA: 30°C/65% RH (hot/ humid)**
    - **Zone IVB: 30°C/75% RH (hot/very humid)**

Stability study...

Stability testing protocols

- Stability testing requires the careful design of protocols which must define clearly the following:
  - The temperature and humidity for storage
  - Storage time before sampling
  - The number of batches to be sampled
  - The number of replicates within each batch
  - A suitable light challenge
  - Details of assay
  - container

Stability studies…

Type of stability study

- Major types of stability testes are
  - Long term stability test
  - Field stability test
  - Accelerated stability test

Stability study…

Long term stability (Real time studies)

- ICH guideline Q1A(R2) define long term studies as stability studies under the recommended storage conditions for the retest period or shelf life proposed or approved for labeling.

- WHO guideline defines long term testing as the stability testing during and beyond expected shelf life under storage conditions in the intended market.

Stability study...

- Conducted in the laboratory under controlled stresses similar to those likely to be encountered during storage.
- Minimum of 12 months data
- For product stored at room temperature : 25 ± 2°C and RH of 60 ± 5% (zone I and II) and 30 ± 2 °C and RH 65 ± 5 % (zone III and IV)
- For drug substances and drug products recommended to be stored in a refrigerator: 5± 3 ° C
- For drug substances and drug product to be stored in a freezer: -20 ± 5 ° C

Stability study…

Accelerated stability study

- Use of exaggerated conditions of temperature, humidity, light & others.
- Accelerated stability tests are done:
  - To detect the deterioration of the product rapidly, in order to select the best formulation;
  - To predict shelf life;
  - To provide rapid means of quality control.

Stability study...

Accelerated storage condition

- For drug substance and drug products stored at room temperature: 40 ± 2 °C with 75 ± 5 % RH (for all zone)
- For drug substance and drug products intended to be stored in a refrigerator : 25 ± 2 °C and RH of 60 ± 5 %

Field stability test

- Done at manufacturers laboratory after the packaged drug product has transported to a typical pharmacy level and stored at different levels.

Stability study...

Testing frequency

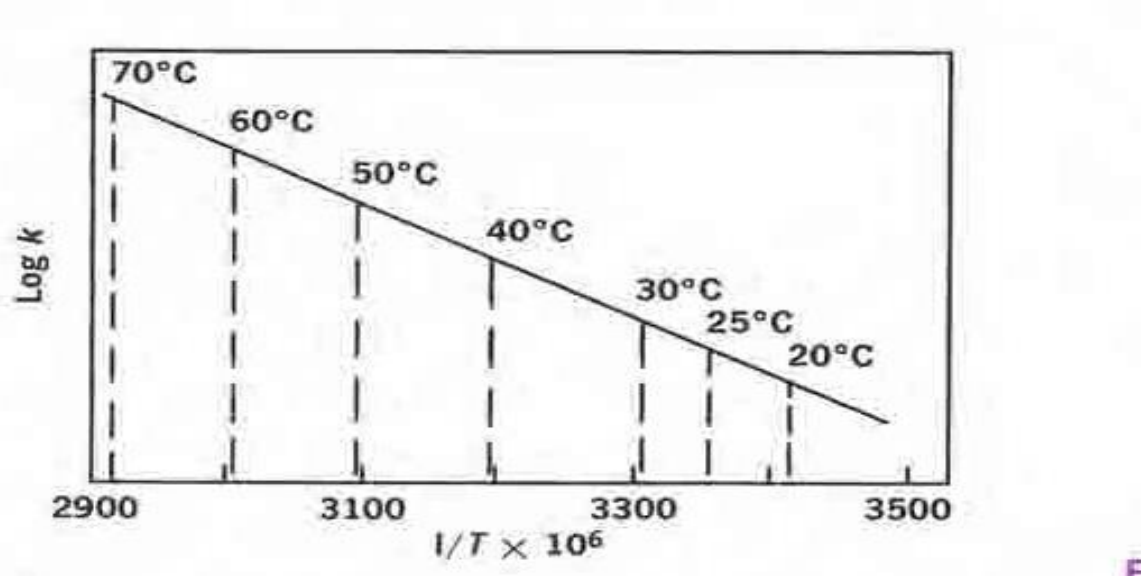
- For long term storage condition should be every 3 months over the first year, every 6 month over the second year and annually thereafter through the proposed shelf life
- At the accelerated storage condition, a minimum of three points, including the initial and final time points (0, 3 and 6 months)
  - When expectation exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted by including a fourth time point in the study design.

Prediction of shelf life

- The time period during which the dosage form is supposed to retains its original qualities
- Steps involved in prediction of shelf life
  - The preparation is divided in to d/f portions and each portion is stored at different elevated T such as 40, 50, 60 and 70 °c
  - Samples from each portion are withdrawn at various intervals of time and the remaining concentration of the active ingredients is measured
  - The order of rxn is determined by a suitable methods such as graphic, half-life or substitution method
  - From the slopes of the lines, the reaction rate constant K for the degradation at each of the elevated temperatures is calculated.

Prediction of shelf life...

- K for the degradation at room temperature is determined by applying Arrhenius r/ship. It may also be obtained from the plot of log k values against the reciprocal of absolute T and extrapolating the curve to 25 °c
- The k value is then substituted in the appropriate rate equation and an estimate is obtained for shelf life of the product
- Calculation are then carried out to determine the amount of drug to be added in access to compensate for the loss in concentration



Prediction of shelf life...

- A similar method with some modifications has also been suggested for the determination of shelf life
  - Log % of drug remaining is plotted against time (in days)
  - From the graph, the time required for the concentration to fall to 90% of the original value at different T is obtained
  - Then the log time to 90% is plotted against the reciprocal of T (either Celsius or Kelvin)
  - The straight line obtained is extrapolated to lower T (25 °c) and from this the number of days required for the concentration to fall to 90% of its original value is read directly at 25 °c

Prediction of shelf life...