

Drug stability is the ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within the specified limits throughout the shelf-life.

⇒ The principles of reaction kinetics are applied for predicting the stability of drugs.

⇒ Drug stability is officially defined as the time lapse during which a drug or dosage form retains the same properties and characteristics that are possessed at the time of manufacture.

Applications :-

① Improper medication -

Dosage form instability may lead to under-medication due to lowering the concentration of drug during storage and lowers the conc. of drug in during storage in blood after administration.

② Toxicity problems - drug degradation sometimes produce toxic products.

eg- p-aminosalicylic acid (PAS) is converted into p-aminophenol, which is toxic.

③ Marketing problems - Instability may be due to changes in physical appearance. Eg- mottling of tablets, creaming of emulsions, caking of solids in suspension.

④ Avoiding loss of drug in GIT.

⑤ Assurance to the patient.

Chemical kinetics

Chemical kinetics involve the study of the rate of a chemical reaction. The rate of a reaction can be understood by studying the time course of changes in the concentration.

⇒ The rate, velocity or speed of a reaction is given by $\pm \left(\frac{dx}{dt}\right)$. Here dx is the small change in the concentration within a given time interval dt .

Order of Reaction

Order of a reaction is defined as the number of concentration terms on which the rate of reaction depends when determined experimentally.

⇒ The orders that are common in pharmacy are -

- (i) zero order
- (ii) pseudo-zero order
- (iii) first order
- (iv) second order.

Zero Order Reaction:- It is defined as a reaction

in which the rate ~~of~~ does not depend on the concentration terms of the reactants.

This is mathematically expressed as:

$$-\frac{dx}{dt} = k_0$$

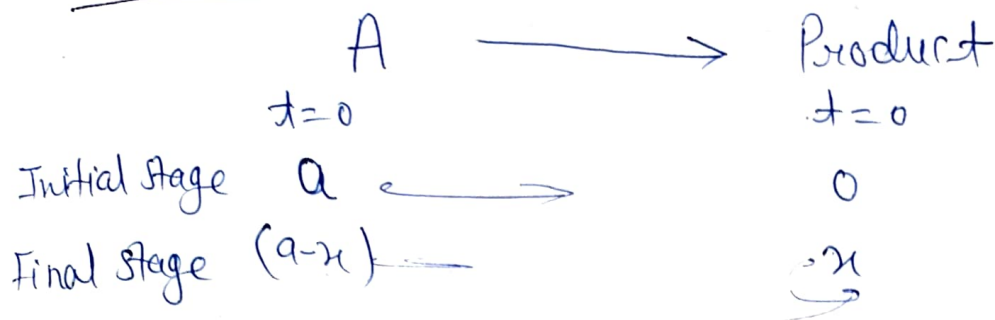
↳ specific constant for a zero order.

eg → Oxidation of vitamin A in an oily solution.

- Photochemical degradation of chlorpromazine in aqueous solution.

Derivation

(73)



\Rightarrow The rate equation for zero order can be written as:

$$-\frac{dx}{dt} = k_0 \quad \frac{d[A]}{dt} = k_0 [A]$$

$$\frac{d(a-x)}{dt} = k_0 (a-x)$$

taking integration \rightarrow

$$\int \frac{dx}{dt} = \int k_0$$

$$\Rightarrow \frac{x}{t} = k_0 \quad \text{or} \quad x = k_0 \cdot t$$

Half life :- It is the time required for the concentration of a reactant to decrease to half of its initial value.

$$k_0 = \frac{x}{t} \quad t = \frac{x}{k_0}$$

At $t = t_{1/2}$, $x = \frac{a}{2}$

$$t_{1/2} = \frac{x}{k_0} = \frac{a}{2k_0}$$

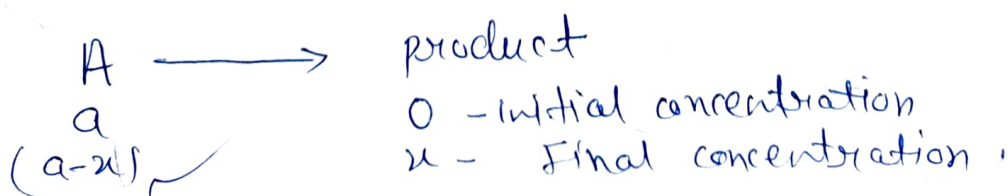
$$x = \frac{a}{2}$$

$$x = \frac{a}{2}$$

\Rightarrow First Order Reaction :-

First order reaction is defined as a reaction in which the rate of reaction depends on the concentration of one reactant.

First order reaction be represented as -



Rate of Reaction = $\frac{dx}{dt} = k_1(a-x)$

$\Rightarrow \frac{dx}{(a-x)} = k_1 dt$

take the integration -

$\int \frac{dx}{a-x} = \int k_1 dt$

$\therefore I = \text{constant of integration}$

$\Rightarrow -\ln(a-x) = k_1 t + I$ (1)

If $t=0$, so, $x=0$

$I = -\ln a$

Put the equation (1)

$-\ln(a-x) = k_1 t + I$

put the value of I in equation (1)

$\Rightarrow -\ln(a-x) = k_1 t - \ln a$

$\Rightarrow -\ln(a-x) + \ln a = k_1 t$

$\Rightarrow k_1 t = -\ln(a-x) + \ln a$

$\Rightarrow k_1 t = \ln\left(\frac{a}{a-x}\right)$

$\log \frac{A}{B} = \log(A-B)$

$\Rightarrow k_1 = \ln \cdot \frac{a}{a-x} \cdot \frac{1}{t}$

changing into logarithm format

$k_1 = \frac{2.303}{t} \log \frac{a}{a-x}$

$t_{1/2} = \frac{0.693}{k}$ (with $x=a/2$ above)

$\frac{0.693}{k}$

$$k_2 t = \frac{a - (a-x)}{a(a-x)}$$

$$k_2 t = \frac{a - a + x}{a(a-x)}$$

$$k_2 t = \frac{x}{a(a-x)}$$

$$k_2 = \frac{1}{t} \cdot \frac{x}{a(a-x)}$$

Half life ←

$$k_2 = \frac{1}{t} \cdot \frac{x}{a(a-x)}$$

When $t = t_{1/2}$, $x = \frac{a}{2}$

$$t_{1/2} = \frac{1}{k_2} \cdot \frac{x}{a(a-x)}$$

$$t_{1/2} = \frac{1}{k_2} \cdot \frac{a/2}{a(a - a/2)}$$

$$t_{1/2} = \frac{1}{k_2} \cdot \frac{2a}{2a^2}$$

$$t_{1/2} = \frac{1}{k_2} \cdot \frac{1}{a} \text{ , hence } \Rightarrow$$

Self life

- 0 $\Rightarrow t_{90} = \frac{0.1A}{K_0}$
- I $\Rightarrow t_{90} = \frac{0.105}{K_1}$
- II $\Rightarrow t_{90} = \frac{0.11}{AK_2}$

$$t_{1/2} \propto \frac{1}{a}$$

eg- Hydrolysis of ester by NaOH.



⇒ Pseudo-Zero order Reaction:-

It is defined as a reaction which is originally a second order, but is made to behave like a first order reaction.

In second order reaction, the rate depends on the concentration terms of two reactants.

$$\text{So, } -\frac{dx}{dt} = K_2 [A][B].$$

But the conc. of B, does not change significantly during the course of the reaction,

$$\text{So, } -\frac{dx}{dt} = K_2 [A] = K_1 [A].$$

- Hydrolysis of ester catalyzed by H^+ ions.
- Acid catalyzed hydrolysis of digoxin.

⇒ Units of basic rate constants:-

$$\text{Standard formula} = \boxed{\text{mol}^{1-n} \cdot \text{litre}^{n-1} \cdot \text{sec}^{-1}}$$

n = order of Reaction.

⇒ For zero order -

$$\begin{aligned} n &= 0 & \text{unit} &= \text{mol}^{1-0} \cdot \text{litre}^{0-1} \cdot \text{sec}^{-1} \\ & & &= \text{mol} \cdot \text{litre}^{-1} \cdot \text{sec}^{-1} \Rightarrow \boxed{\text{mol} \cdot \text{litre}^{-1} \cdot \text{sec}^{-1}} \end{aligned}$$

⇒ First order -

$$\begin{aligned} n &= 1 & \text{unit} &= \text{mol}^{1-1} \cdot \text{litre}^{1-1} \cdot \text{sec}^{-1} \\ & & &= \text{mol}^0 \cdot \text{litre}^0 \cdot \text{sec}^{-1} \Rightarrow \boxed{\text{litre} \cdot \text{mol}^{-1} \cdot \text{sec}^{-1}} \end{aligned}$$

⇒ Second order -

$$n = 2 \Rightarrow \text{mol}^{1-2} \cdot \text{litre}^{2-1} \cdot \text{sec}^{-1} \Rightarrow \boxed{\text{litre}^2 \cdot \text{mol}^{-2} \cdot \text{sec}^{-1}}$$

Determination of Reaction Order

Physical and chemical factors influencing the chemical degradation of pharmaceutical product

① Temperature :-

Arrhenius was the first developer, who studied the effect of temperature on decomposition of drug.
⇒ The rate of a reaction doubles with every 10°C rise in temperature

Arrhenius equation -

$$K = A e^{-E_a/RT}, \quad [K \propto T] \quad \text{Temp} \uparrow = \text{Rate of reaction} \uparrow$$

where,

K = Specific rate constant

A = Frequency factor or Arrhenius factor.

E_a = Activation energy.

R = Ideal gas constant (1.987 cal/mol-deg.)

T = Absolute temperature.

Log-form -

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

② Solvent - The nature of the solvent also affects the rate of decomposition of drug. The relation between reaction rate constant and solubility of reactant and product is given by -

$$\log k = \log k_0 + \frac{V}{2.303 RT} (\Delta S_a - \Delta S_b - \Delta S^*)$$

where,

k = observed reaction rate constant

k₀ = rate constant in infinitely dilute solution

v = molar volume of solute

ΔS_a, ΔS_b and ΔS* = difference in solubility parameter of solvent and reactant 'a', reactant 'b' and activated complex respectively.

So,

⇒ If polarity of product > polarity of reactant then, reaction rate increases if the solvent is more polar.

⇒ If polarity of product < polarity of reactant, then reaction rate increases if the solvent is less polar.

③ Ionic Strength:-

The effect of ionic strength on rate of decomposition of drug is explained by following equation:-

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

where, Z_A & Z_B are the charges on reactant A and B respectively.

μ is the ionic strength.

k = is rate constant of degradation.

k₀ = is the rate constant at infinite dilution in which μ = 0

④ Dielectric constant:-

The dielectric constant is used to measure polarity of the solvent. Dielectric constant shows significant effect on the rate of reaction.

⇒ The effect of the dielectric constant on the rate constant of an ionic reaction,
charge ↑ = rate of reaction ↑ = degradation ↑.

$$\ln k = \ln k_{\epsilon=\infty} - \frac{N_A Z_A Z_B e^2}{RT \epsilon^*} \frac{1}{\epsilon}$$

Where,

$k_{\epsilon=\infty}$ is the rate constant in a medium of infinite dielectric constant.

k = constant.

N = Avogadro's number

Z_A & Z_B = charges on two ions, e is the

e = unit of electric charge.

ϵ = dielectric constant of solution.

⑤ Specific Acid Base Catalysis:-

A reaction that change due to change in pH.

⇒ In specific catalyst not added any acid or base but change in pH.

⇒ This catalyst chemical reaction based on the pH change.

⇒ pH change occurs due to H^+ or OH^- concentration.

Conclusion-

In any drug solution buffer is added then there is no change in acidic and basic nature but change in the pH due to change in H^+/OH^- ion concentration inside the solution.

- This type of reaction called as specific acid base reaction.

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

General Acid Base Catalysts:-

In general catalyst, change in the nature of solution occurs due to added of acid or base.

→ If added acid then increase the acidity and if added base then increase basicity of solution.

→ ~~It~~ The evaluation of a general acid or general base catalysis can be done by determining the degradation rates of a drug in a series of buffers having the same pH but they should be prepared with increasing concentration of buffer species.

Stabilization of medicinal Agents against

Common reactions - (Hydrolysis & Oxidation)

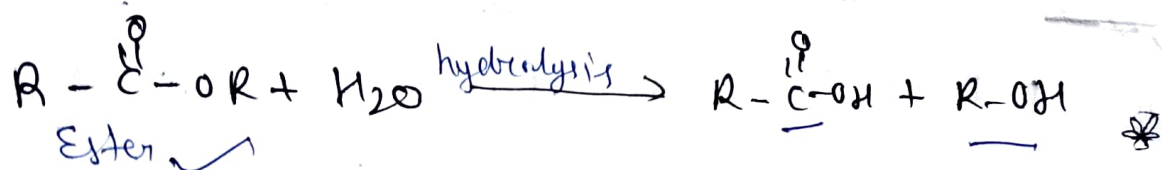
Pharmaceutical product like tablets, elixirs, syrup, emulsion & suspension etc. their stability depend on various factor but most important factor reaction with environment - if oxidation & hydrolysis occur with medicinal

product, they are affected directly on their stability. (82)

Hydrolysis:-

Breakdown the reactant due to presence of water.

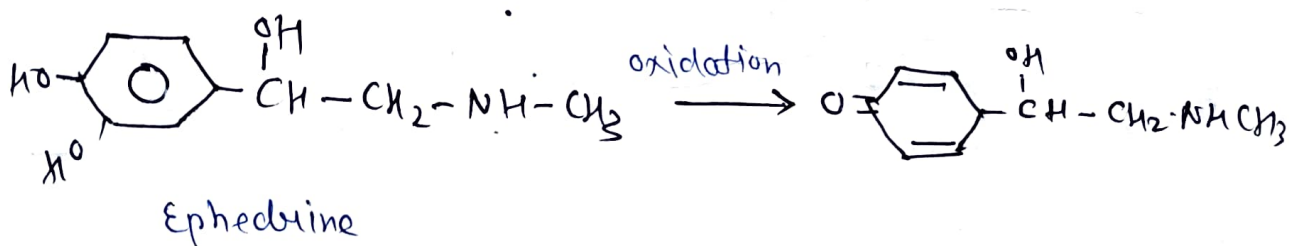
⇒ Drugs with ester and amide group react with one molecule of water and undergo hydrolysis. Ester groups break faster than amide groups.



⇒ Oxidation:-

Oxidation involves the removal of electrons from a molecule. ✓

⇒ The reaction b/w the compound and molecular oxygen is called autooxidation.



Accelerated stability testing in Expiration dating of Pharmaceutical dosage forms? (83)

⇒ This method is designed to
predict stability and hence shelf life of
formulations.

under normal or recommended storage conditions
by carrying out the study under accelerated
conditions of temperature, moisture and light.

⇒ The stability testing is done to predict
the time period upon which
the quality of product remain satisfactory
under prescribed storage condition.

ICH and WHO Guidelines for stability studies -

Q1A (R2) - Stability testing of New Drug Substance
and products.

Q1B - Photo stability testing of New Drug Substance
and products.

Q1C - Stability Testing of New Dosage form.

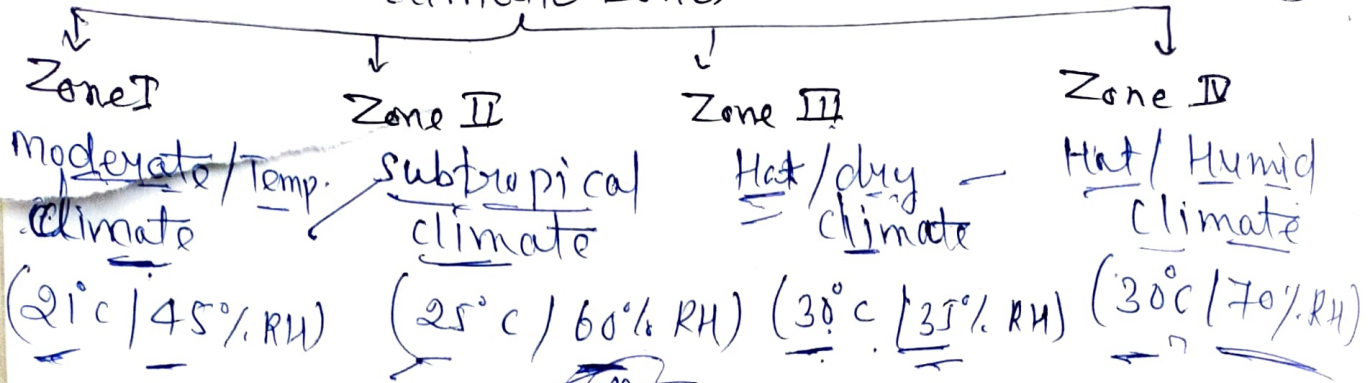
Q1D - Bracketing and Matrixing Designs for
Stability Testing of Drug Substance and
products.

Q1E - Evaluation of Stability Data

Q1F - Stability Data for climatic Zone III & IV.

Climatic Zones

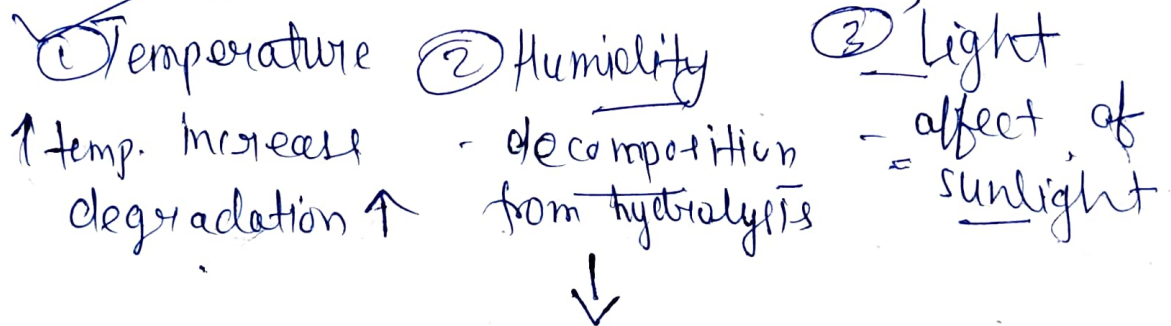
RH = Relative Humidity (RH)



Objective of Accelerated Stability Analysis:-

- (i) To serve as a rapid means for selection of best formulation from a series of similar formulations.
- (ii) To predict the shelf life of the product.
- (iii) To serve as a rapid means of quality control.

Common High stresses during Stability Testing



Stability Study type

Storage Condition

⇒ Long term stability studies -

→ Duration - 5 years
Temp → $25 \pm 2^\circ\text{C}$
RH → $60 \pm 5\%$

⇒ Intermediate stability studies -

- Duration - 6 months
Temp → $30 \pm 2^\circ\text{C}$
RH = $65 \pm 5\%$

⇒ Accelerated stability studies -

Duration = 6 months
Temp = $40 \pm 2^\circ\text{C}$
RH - $75 \pm 5\%$

Prediction of shelf life:-

⇒ Arrhenius equation explains the effect of temperature on rate of a reaction.

⇒ According to Arrhenius equation -

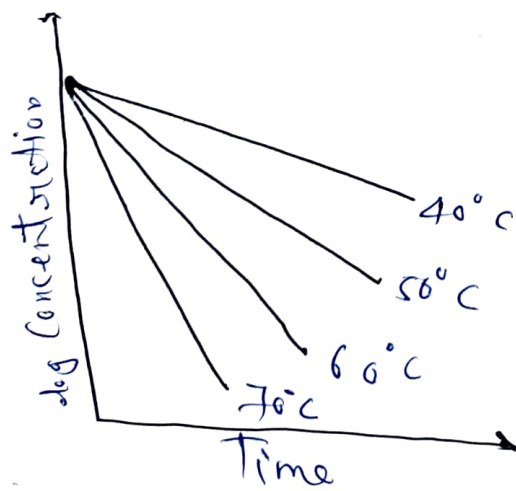
↓
for every 10°C rise, the speed of reaction increase about 2-3 times

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

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

Steps involved in Accelerated Stability Testing - (86)

- ① The preparation is stored at different elevated temperature ($40, 50, 60$ & 70°C)
- ② Concentration of reactant at each elevated temperature is also determined.
- ③ Sample is withdrawn at different time intervals.
- ④ The rate of reaction is determined by plotting the conc. against time and linear relationship is determined.
- ⑤ Straight line in a graph permits the estimation of k value from the slope.
- ⑥ From the slopes of the lines, the reaction rate constant k for the degradation at each elevated temp. is calculated.
- ⑦ The reaction rate constant k for degradation at room temp. (25°C) is determined.
- ⑧ The k value obtained for 25°C is substituted in already determined order of reaction and an estimate is obtained for shelf life of the product.



Limitation of Accelerated Stability Analysis

(i) Stability predictions based on Arrhenius equation

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valid only when energy of activation for thermal decomposition lies b/w 10 to 30 Kcal/mole.

(ii) This method is not used in case of complex reactions because Arrhenius equation consist of only one rate constant.

(iii) This method is not applicable in degradation is due to

↓
Freezing, microbial contamination, excess agitation

(iv) This method is not valid when order changes at higher temp.

Photolytic degradation

By the effect of light degrade the drug \Rightarrow radiation fall in a molecules and molecules goes to breakdown.

Prevention.

(i) Use dark or grey coloured container.

(ii) Store it in dark place.

(iii) Coating the tablet tablet with polymer film.