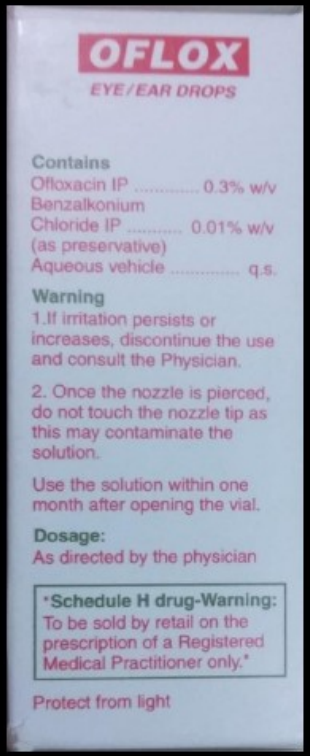
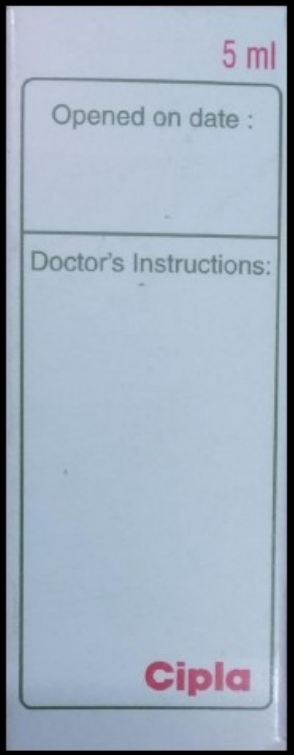
Unit 5:: Drug Stability

Physical Pharmaceutics

B.Pharm 4th semester


OFLOX
EYE/EAR DROPS
Contains
Ofloxacin IP ..... 0.3% w/v
Benzalkonium
Chloride IP ..... 0.01% w/v
(as preservative)
Aqueous vehicle ..... q.s.
Warning
1.If irritation persists or increases, discontinue the use and consult the Physician.
2. Once the nozzle is pierced, do not touch the nozzle tip as this may contaminate the solution.
Use the solution within one month after opening the vial.
Dosage:
As directed by the physician
*Schedule H drug-Warning:
To be sold by retail on the prescription of a Registered Medical Practitioner only.*
Protect from light


5 ml
Opened on date :
Doctor's Instructions:
Cipla


Rx
5 ml
Ofloxacin
Ophthalmic
Solution IP
OFLOX
EYE/EAR DROPS
Cipla


M. R. P. Rs.
(Incl. of all Taxes)
RS.28.00
B NO. IA70305
MFD. MAY 17
EXP. MAR. 20


Tablets of Vitamin B Complex with B12
NEUROBION
Forte
MERCK
30 tablets

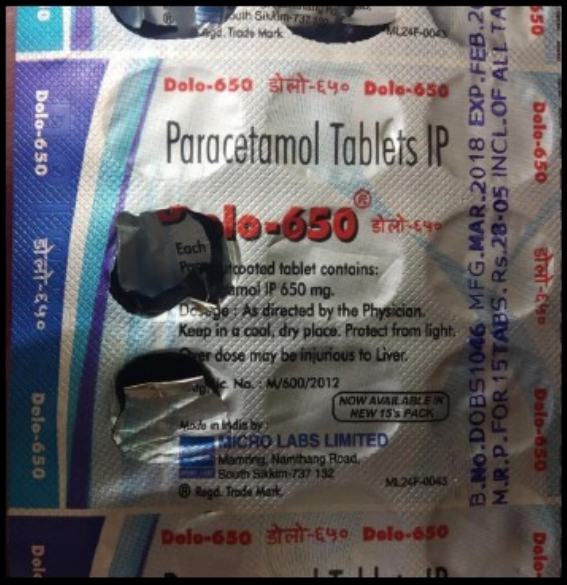

Tablets of Vitamin B Complex with B12
NEUROBION
Forte
Each film coated tablet contains:
Thiamine Mononitrate IP ..... 10 mg
Riboflavine IP ..... 10 mg
Pyridoxine Hydrochloride IP ..... 3 mg
Cyanocobalamin Triturate
in Gelatin equivalent to
Cyanocobalamin IP ..... 15 mcg
Nicotinamide IP ..... 45 mg
Calcium Pantothenate IP ..... 50 mg
excipients ..... q.s.
Colours used: Ponceau 4R Lake and
Titanium Dioxide IP
Appropriate overages added
Dosage: One tablet daily or
as directed by the Physician.
"For Therapeutic Use"
Store at or below 25°C in dry place
Keep out of reach of children.
M. L. : 718/L
Batch No. : M13FF10302
Mfg. Date : 07/2018
Expiry Date : 12/2019
26-13
Maximum Retail Price Rs.
per strip of 30 tablets
(inclusive of all taxes)
Manufactured by:
MERCK LIMITED,
At : L-40, Verna Industrial Estate,
Verna, Goa - 403 722.
® Registered Trade Mark.
For more information visit
www.neurobion.in
Toll free no.
1800 103 8888
Scan QR code
SMS Neurobion to
8861308888**
** Standard SMS charges will be
applicable as per tariff plan
adopted by user.
Write to us
myneurobion@merckgroup.com
P1418/4
8 901089 014181

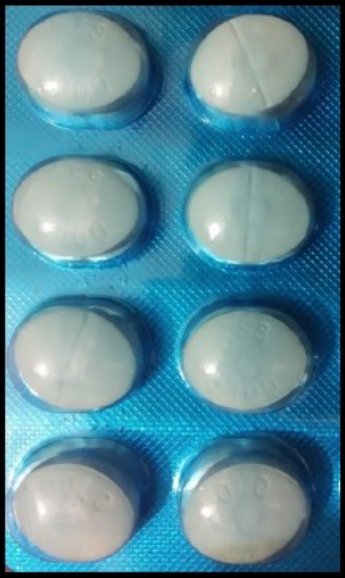

100 ml
Himalaya
SINCE 1930
Liv.52
SYRUP 200 ml
Protects the liver against various hepatotoxins.
Promotes appetite and
150 ml
INTAFRESH
INTAS


1g Sachet
Cholecalciferol Granules
Cipcal D3
Granules
Cipla


Each sachet of 1g contains:
Cholecalciferol IP 60, 000 IU
Excipients ..... q.s.
Appropriate overages of vitamin added to compensate loss on storage.
Dosage: ¼ to 1 sachet with milk or as directed by the Physician.
Store protected from light & moisture at a temperature not exceeding 30°C.
Keep out of reach of children. For oral administration only.
Cipcal D3
Granules
B. No.
MFD.
EXP.
M.R.P. Rs.
(Incl. of all Taxes)
GL7166
MAR. 17
FEB. 19
27.50
0.810696
Cipla
M.L. MB/07/553
Marketed by CIPLA LTD.
Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai - 400 013 INDIA.
Mfd. by Tirupati Medicare Limited
Nahan Road, Paonta Sahib,
Dist. Sirmour 173 025 (H.P.) INDIA.

e Tablets I.P.
Amoxyclav®625
Amoxyclav®625
Amoxyclav®625
B.No.1900111-1
MFG.FEB.2019
EXP.JAN.2021
M.R.P. ₹ 188.75
PER 10 TABS.
INCL.OF ALL TAXES
Abbott
e Tablets I.P.


Dolo-650 डोलो-६५० Dolo-650
Paracetamol Tablets IP
Dolo-650®
Each
coated tablet contains:
amol IP 650 mg.
Dosage : As directed by the Physician.
Keep in a cool, dry place. Protect from light.
Over dose may be injurious to Liver.
No. : M/600/2012
NOW AVAILABLE IN NEW 15's PACK
Made in India by :
MICRO LABS LIMITED
Mamring, Namthang Road,
South Sikkim-737 132
Regd. Trade Mark.
ML24F-0043
B.NO.DOBS1046 MFG.MAR.2018 EXP.FEB.2
M.R.P.FOR 15TABS. Rs.28-05 INCL.OF ALL TA



ipca

℞

Amoxycillin & Potassium Clavulanate Oral Suspension IP 457 mg

Rapiclav® forte

Dry Syrup

रेपीक्लेव फोर्ट

ड्राय सिरप्

(Combipack with Purified Water IP)

6.6g/30 ml

DIRECTIONS FOR PREPARING THE SUSPENSION

घोल बनाने के लिए निर्देश

Shake bottle to loosen powder.

चूरा (पाउडर) को ढीला करने के लिए बोतल को हिलाएं।

Twist and open the vial of purified water given with this pack.

पैक के साथ दी गई शुद्ध किया हुआ जल की शीशी को घुमा कर खोलें।

Slowly add purified water into the bottle upto the ring mark on the bottle.

बोतल में रिंग निशान तक धीरे-धीरे शुद्ध किया हुआ जल डालें।

Put the cap and shake the bottle vigorously.

ढक्कन लगाएं और बोतल को जोर से हिलाएं।

Adjust the volume upto the ring mark on the bottle by adding more purified water if necessary and shake again

यदि जरूरी हो तो ज्यादा शुद्ध किया हुआ जल मिलाकर बोतल की साइड की रिंग निशान तक समयोजित करें और फिर हिलाएं

Store the constituted suspension in the refrigerator at 2°C to 8°C. Content to be consumed within 7 days. Any extra portion left to be thrown away.

बनाए गए घोल को रेफ्रिजरेटर में २ डिग्री सेल्सियस से ८ डिग्री सेल्सियस पर रखें। माद्दा का सेवन ७ दिन के भीतर करें। बचा हुआ कोई भी अतिरिक्त भाग फेंक दें।

Each combipack contains:

A. Amoxycillin and Potassium Clavulanate Oral Suspension IP 457 mg

Each 5 ml of constituted suspension contains:

Amoxycillin Trihydrate IP equivalent to Amoxycillin	400 mg
Potassium Clavulanate Diluted IP equivalent to Clavulanic Acid	57 mg

B. One Vial of Purified Water IP

Each Vial contains :

Purified Water IP	30 ml

Dosage:

As directed by the Physician

Store protected from moisture, at a temperature not exceeding 25°C.

Schedule H Drug
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.

Drug Stability

The USP defines the stability of pharmaceutical product as “extent to which a product retains within specified limits” and throughout its period of storage and use (i.e its shelf life) the same properties and characteristics that it possessed at the time of its manufacturer

Why Stability?

Instability leads to-

- ü Loss of active drug or potency.
- ü Loss of content uniformity (e.g. creaming of emulsions, impaction of suspensions).
- ü Loss of elegance (e.g. fading of tablets and coloured solutions).
- ü Reduction in bioavailability (e.g. change in dissolution profile).
- ü Production of potential toxic materials (e.g. drug degradation products).
- ü Economic loss.

DRUG STABILITY

- The resistance of the drug to the various chemical, physical, and microbiological reactions that may change the original properties of the preparations during transport, storage and use.

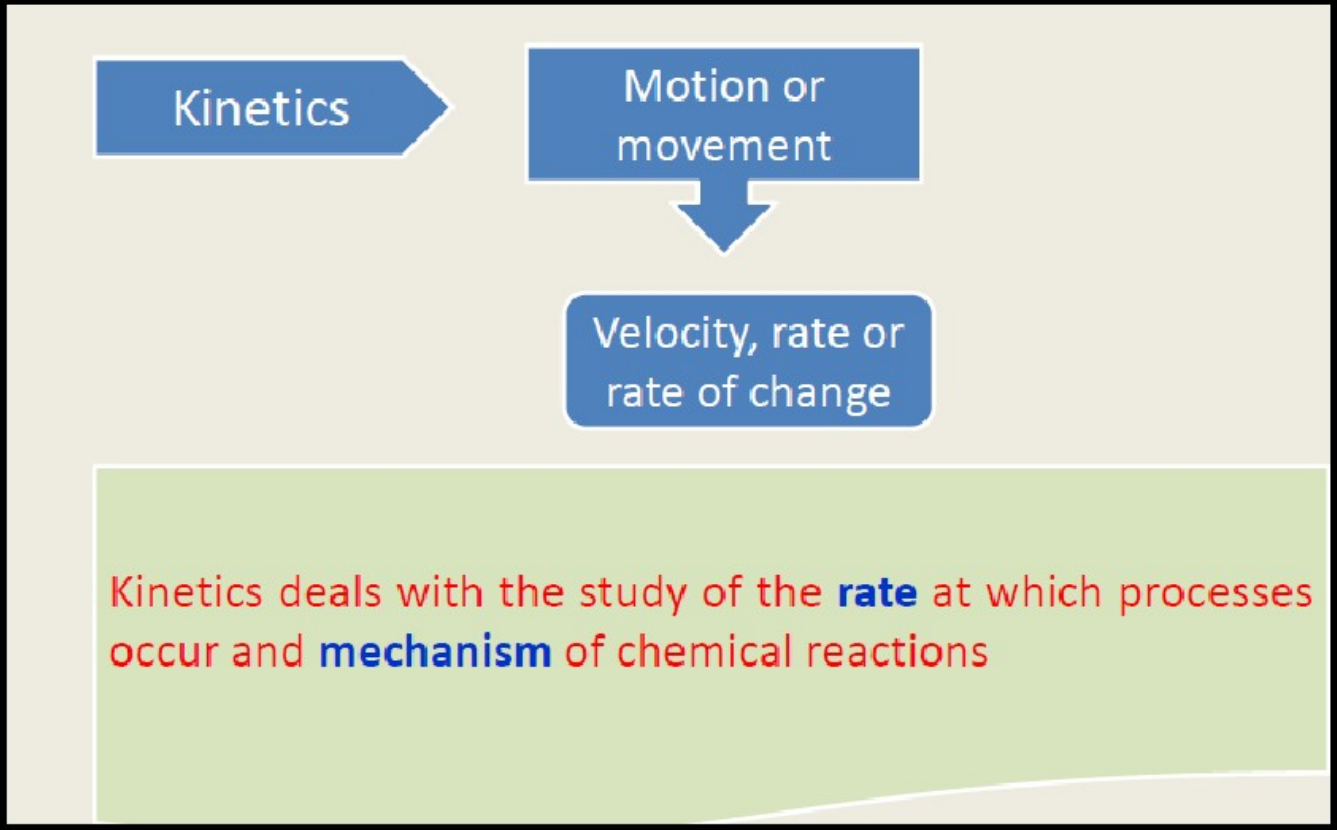
- Quantitatively it is expressed as shelf life.

Shelf Life

Shelf life

- ✓ is the time during which the medicinal product is predicted to remain fit for its intended use under specified conditions of storage.
- ✓ It is the time from manufacture or preparation until the original potency or content of the active ingredient has been reduced by 10% [t_{10} or t_{90}] which is the limit of chemical degradation

Kinetics


Kinetics
Motion or movement
Velocity, rate or rate of change
Kinetics deals with the study of the rate at which processes occur and mechanism of chemical reactions

RATES AND ORDERS OF REACTIONS

RATES

- the speed or velocity of a reaction with which a reactant or reactants undergoes a change.

- It is determined by the change in the concentration of the reactants or products as a function of time.

- The rate may be determined by the slowest or rate determining step.

$$\frac{dc}{dt} = Rate = kc^{n}$$

ORDERS OF REACTIONS

- the number of concentrations that determine rate.
- the way in which the concentration of the reactant influences the rate.

Law of mass action

- ***The rate of a reaction is proportional to the molar concentrations of the reactants each raised to power equal to the number of molecules undergoing reaction.***

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

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

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

Order of reaction = sum of exponents

Order of A = a and B = b

Then Overall order = a + b

Example:

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

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

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

Order for $(CH_3\,CO)_2\,O$ is 1^{st} order

Order for $[C_2H_5OH]^2$ is 2^{nd} order

Overall order of reaction is 3^{rd} Order

ZERO Order Reactions

Rate is constant and independent of the concentration of any reactants.

a [A] $\xrightarrow{k}$ Product (P)

Rate = - dc/dt = K $[c]^0$

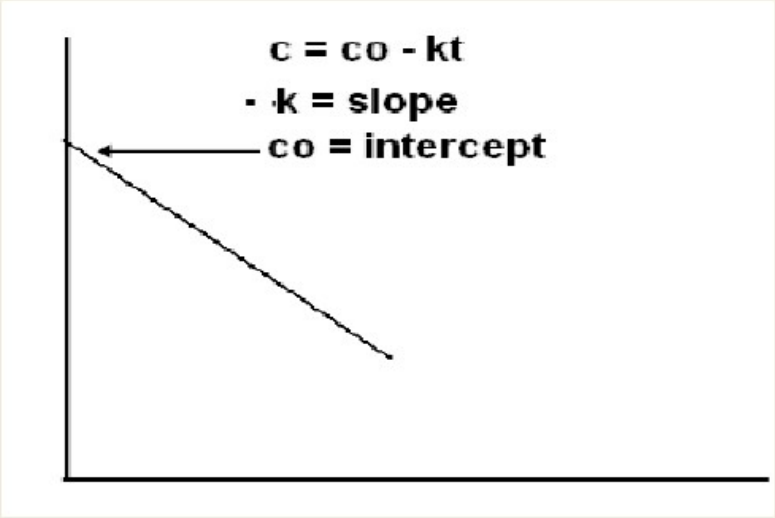
- dc/dt = k dc = - k dt

$$\int_{c_0}^{c_t} dc = \int_{t_0}^{t} -k\,dt$$

c_o = Initial concentration

c_t = Concentration at time t

$C - C_0 = -kt$



Units of the rate constant K K = Concentration / time = mole / liter . second = M. sec^{-1}

ZERO Order Reactions

Determination of $t_{1/2}$

Let $c = c_o / 2$ and $t_{1/2} = t$

substitute in equation;

$c = c_o - k\,t$

$t_{1/2} = c_o / 2K$

Determination of $t_{0.9}$

Let $c = 0.9\ c_o$ and $t = t_{0.9}$

substitute in equation;

$c = c_o - k\,t$

$t_{90\%} = t_{0.9} = 0.1\ c_o / k$

First Order Reaction

Rate of the reaction or change is directly proportional to the concentration of the reactant.

Units of Rate Constant K= time^{-1}

$-dc/dt = kc^1 = kc$

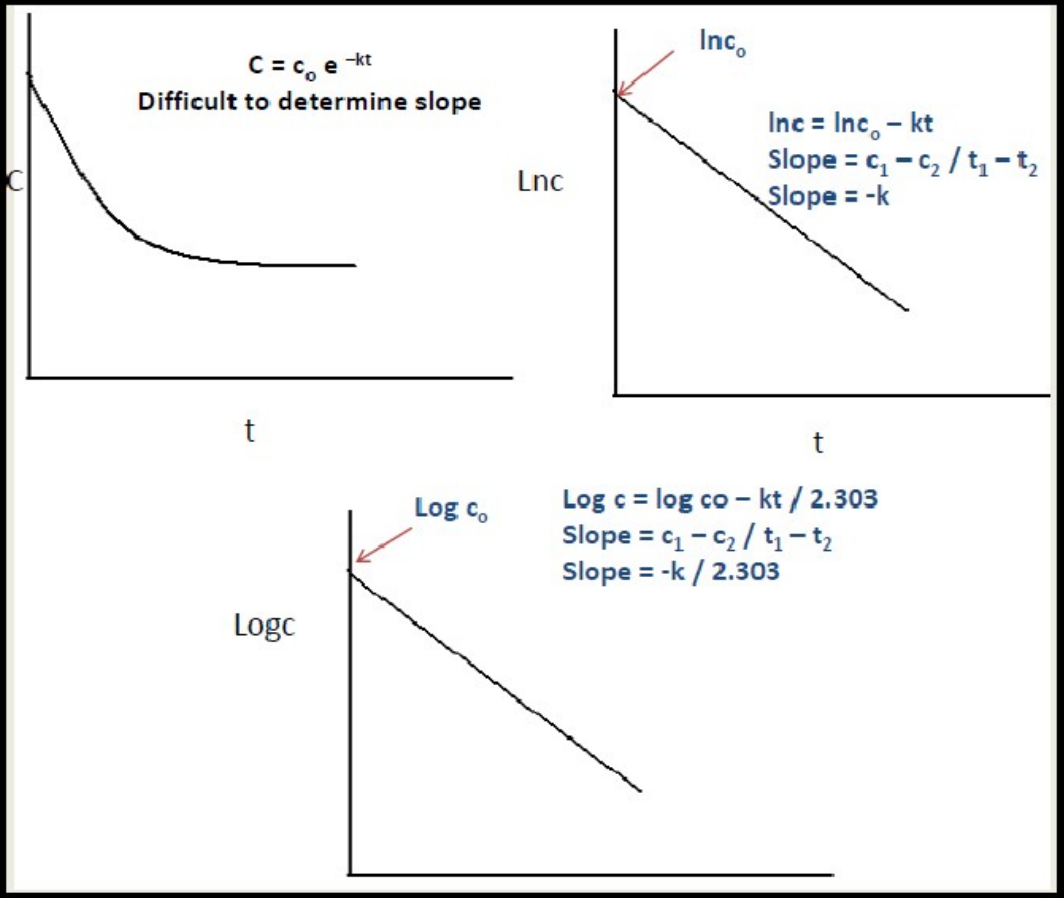
$-dc/c = kdt$

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

$$\ln c - \ln c_o = -kt$$

$$\log c = \log c_0 - \frac{kt}{2.303}$$

First Order Reaction



First Order Reaction

Determination of $t_{1/2}$	Determination of $t_{0.9}$
Let $t = t_{1/2}$ and $C = C_0/2$ substitute in $\ln C = \ln C_0 - Kt$ $t_{1/2} = \ln 2/K = \mathbf{0.693 / K}$ K units = $0.693 / t_{1/2}$ = $time^{-1}$	Let $t = t_{0.9}$ $c = 0.9$ Co substitute in $\ln c = \ln co - Kt$ $t_{0.9} = \mathbf{0.105 / K}$ and $K = 0.105/ t_{0.9}$

Second Order Reaction

Rate of the reaction depends upon the product of the two concentration terms i.e.when two component reacting with each other or one component reacting with itself.

$$2HI = H_2 + I_2$$

$$\text{Rate} = dc/dt = k[HI][HI] = k[HI]^2$$

$$dc/dt = -kc^2$$

$$dc/c^2 = -kdt$$

$$\int_{c_0}^{c} \frac{dc}{c^2} = -k \int_{t=0}^{t} dt$$

$$\frac{1}{c} = \frac{1}{c_0} + kt$$

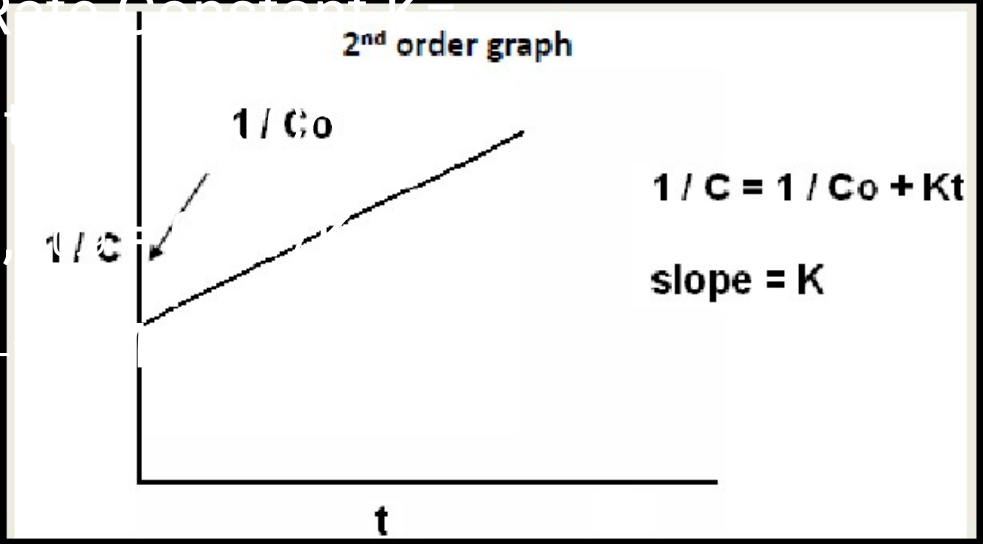
Second Order Reaction

Units of R

Half Life,

Shelf Life,

-1 Time-



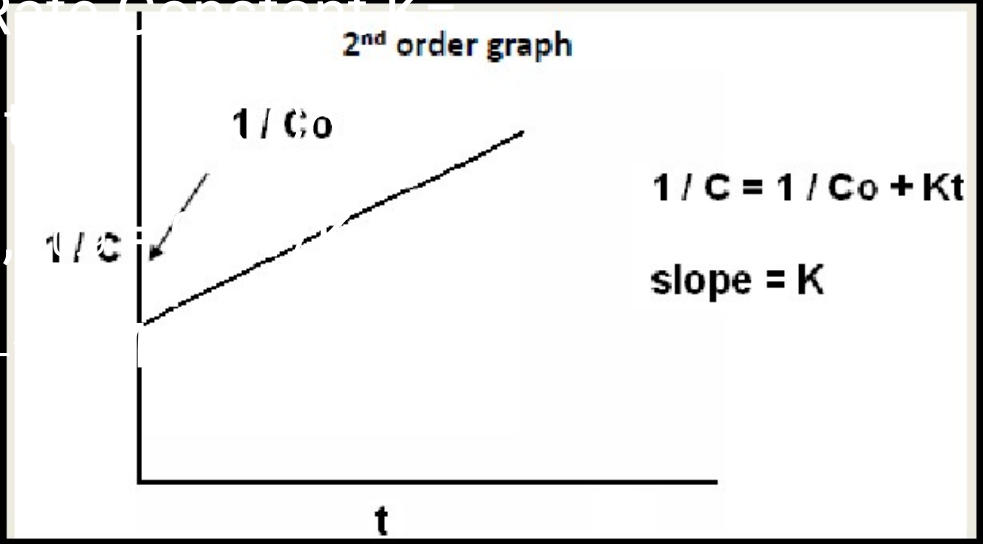
Second Order Reaction

Units of R

Half Life,

Shelf Life,

-1 Time-



Pseudo Order Reaction

The rate of the reaction may be independent of the concentration of one or more of the reacting species over a wide range of reactions.

These may occur under the following conditions:

- ü One or more of the reactants enters into the rate equation in great excess compared to others;
- ü One of the reactant is catalyst;
- ü One or more of the reactants is constantly replenished during the course of reaction
- ü Example: Decomposition of a drug from saturated suspension

Determination of reaction order

Substitution Method

Graphic Method

Half life Method

Ostwald Isolation Method

Determination of reaction order

Substitution Method

Data accumulated in experimental kinetic study may be substituted in the integrated form of the zero, first and second order equation. The equation which gives constant value of K, indicates the order of the reaction

Order of Reaction	Rate equation
Zero	$k_0 = \frac{A_0 - A_t}{t}$
First	$k = \frac{2.303}{t} \log \left[\frac{A_0}{A_t} \right]$
Second	$k = \frac{1}{at} \cdot \frac{x}{(a-x)}$

Determination of reaction order

Graphic Method

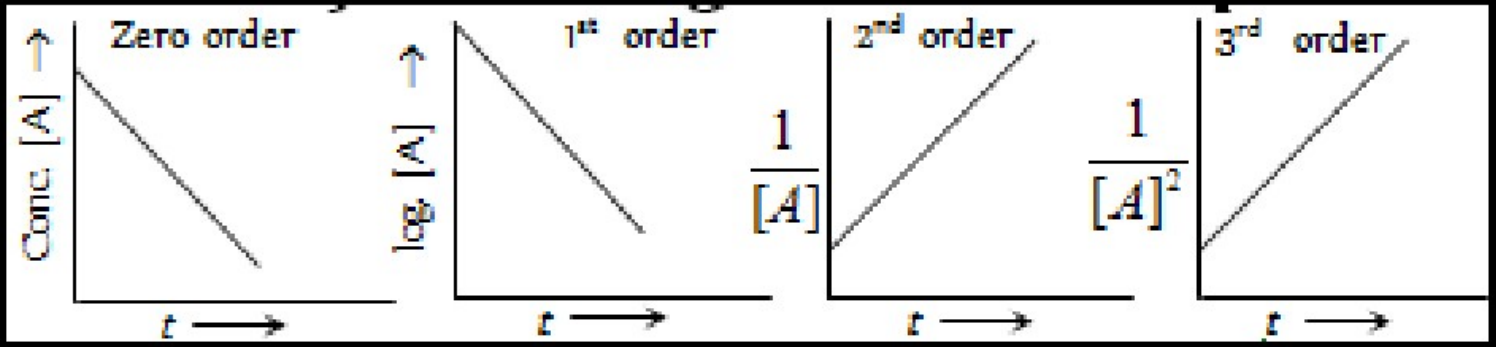
A plot of:

Concentration against time …….. zero order reaction [if straight line]

log concentration against time ……. First order reaction [if straight line]

1/[concentration] against time …….. second order reaction [if straight line].

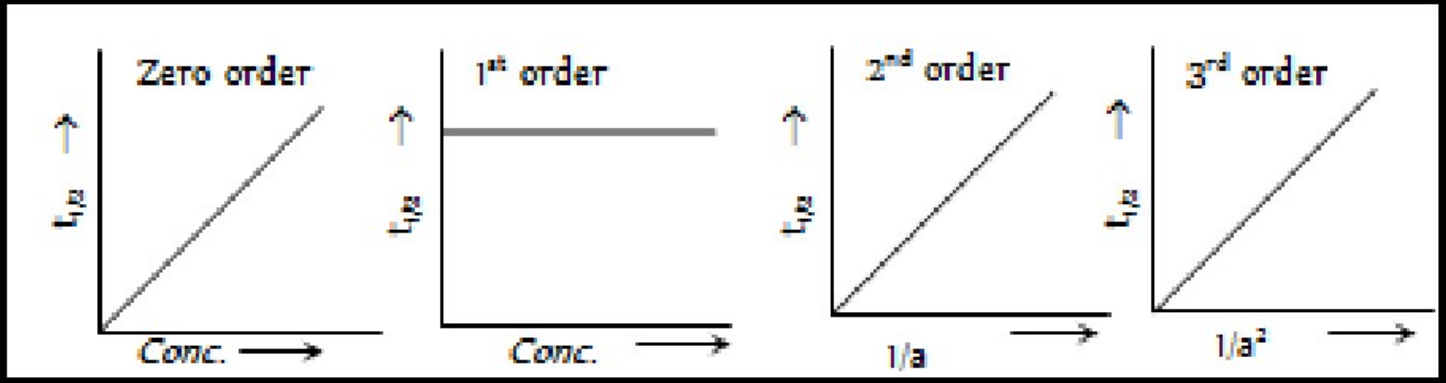
1/[concentration]$_2$ against time …….. second order reaction [if straight line].



Determination of reaction order

Half Life Method

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



Isolation Method

Determination of reaction order

This method can be used irrespective of the number of reactants involved e.g., consider the reaction

(i) Concentrations of B and C constant, while A is doubled, the rate of the reaction becomes four times.i.e., order with respect to A is 2

(ii) Concentrations of A and C constant, while B is doubled, the rate of reaction is also doubled i.e., order with respect to B is 1

(iii) Concentrations of A and B constant, while C is doubled, the rate of reaction remains without any affect. This means that rate is independent of the concentration of C i.e., order with respect to C is zero. Hence the overall rate law expression will be, Rate = $k [A]_2 [B] [C]_0$

For any reaction to occur -

Molecules must collide with each other

Collision Theory

– once molecules collide they may react together

Molecules must have sufficient energy

Molecules must have correct geometry

$O_3(g) + NO(g) \rightarrow O_2(g) + NO_2(g)$

$O=O-O + NO[O=O-O....NO] \rightarrow O=O(g) + ONO(g)$

$O=O-O + ON[O=O-O....ON] \rightarrow O=O(g) + OON(g)$ XX

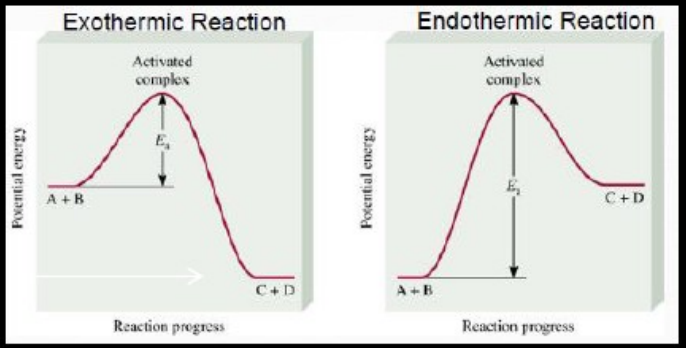
Activation Energy

A+B

C+D ⟶

Energy barrier to the reaction

Activation energy



– amount of energy needed to convert reactants into the activated complex

Activated Complex

– activated complex is a chemical species with partially broken and partially

formed bonds

– always very high in energy because of partial bonds

Factors affecting drug degradation

Temperature

Solvent

Ionic Strength

Dielectric constant

Catalyst

Factors affecting drug degradation

Solvent

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

k is observed reaction rate constant

k_0 is rate constant in infinitely dilute solution

V is molar volume of solute

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

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.

Factors affecting drug degradation

Ionic Strength

Ionic strength can be calculated from:

$$\mu = \tfrac{1}{2} \Sigma(mz^2)$$
$$= \tfrac{1}{2} (m_A z_A^2 + m_B z_B^2 + \ldots)$$

So, for example, if we have a monovalent drug ion of concentration 0.01 mol kg^{-1} in the presence of 0.001 mol kg^{-1} of Ca^{2+} ions, then the ionic strength of the solution will be $\mu = \tfrac{1}{2}[(0.01 \times 1^2) + (0.001 \times 2^2)] = 0.007$ mol kg^{-1}. Note that if the drug ion and the electrolyte ion are both monovalent, then the ionic strength will be equal to the total molality of the solution.

Factors affecting drug degradation

Ionic Strength

$$\log k = \log k_0 + 1.02\, z_A\, z_B \sqrt{\mu}$$

where

z_A and z_B are the charges on reactant A and B respectively.

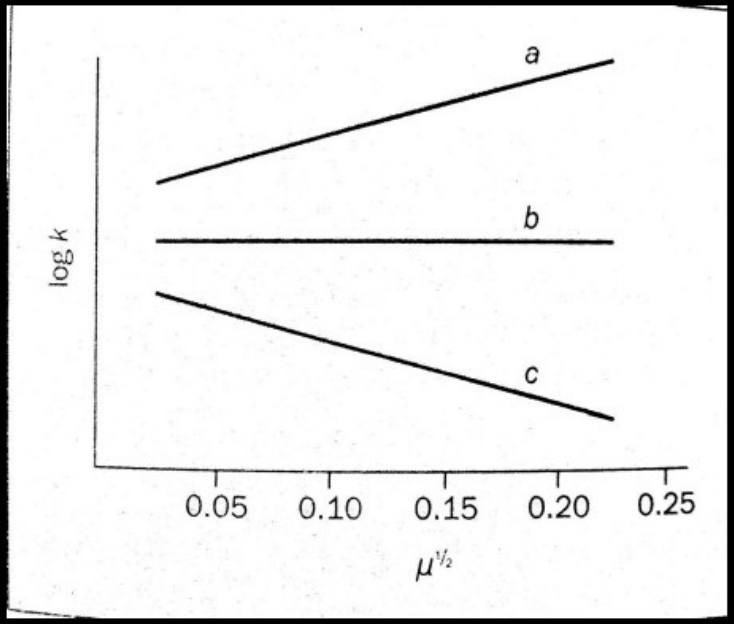
μ is the ionic strength

k is rate constant of degradation

k_0 is rate constant at infinite dilution in which $\mu=0$

Factors affecting drug degradation

Ionic Strength



Factors affecting drug degradation

Dielectric constant

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

Where

$k\varepsilon = \infty$ is the rate constant in a medium of infinite dielectric constant

k is observed rate constant in medium of dielectric constant ε

N is Avogadro's number,

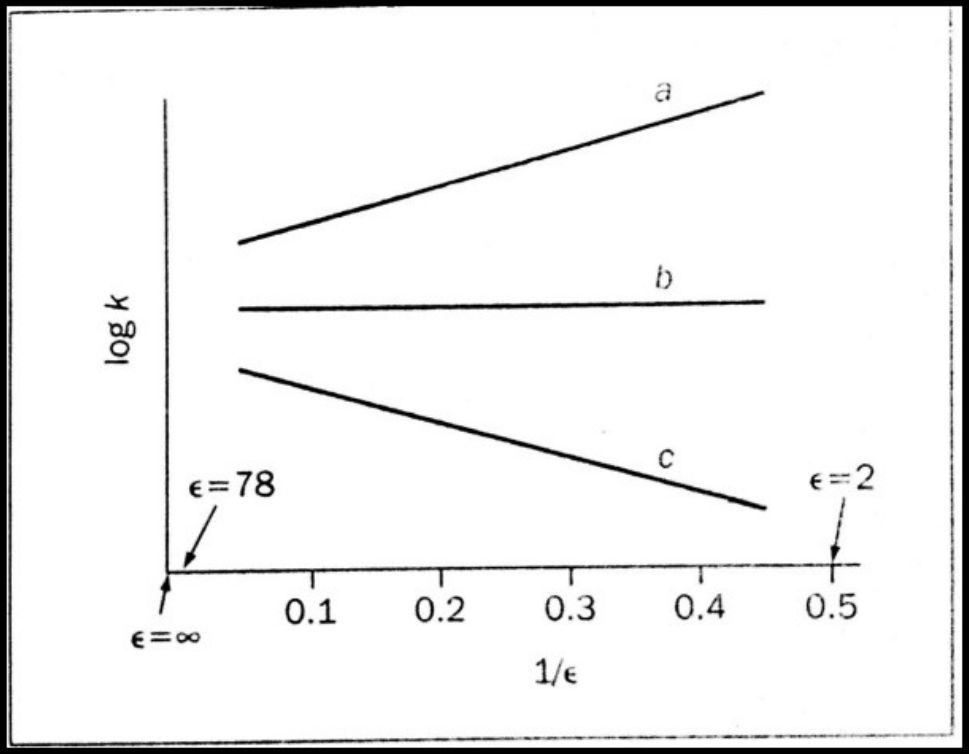
z_A and z_B are the charges on the two ions, e is the unit of electric charge,

r^* is the distance between ions in the activated complex

ε is dielectric constant of the solution

Factors affecting drug degradation

Dielectric constant



Factors affecting drug degradation

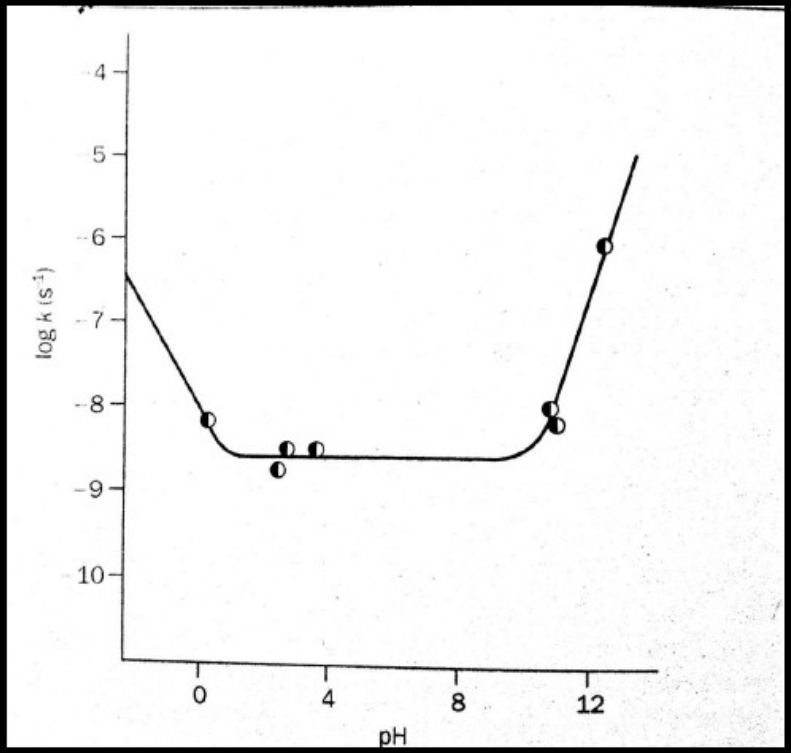
Catalyst

$$k_{obs} = k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{HX}[HX] + k_{X^-}[X^-]$$

where k_{obs} is the experimentally determined hydrolytic rate constant, k_0 is the uncatalysed or solvent-catalysed rate constant, k_{H^+} and k_{OH^-} are the specific acid and base catalysis rate constants respectively, k_{HX} and k_{X^-} are the general acid and base catalysis rate constants respectively and [HX] and [X^-] denote the concentrations of protonated and unprotonated forms of the buffer.

Factors affecting drug degradation

Catalyst



Factors affecting drug degradation

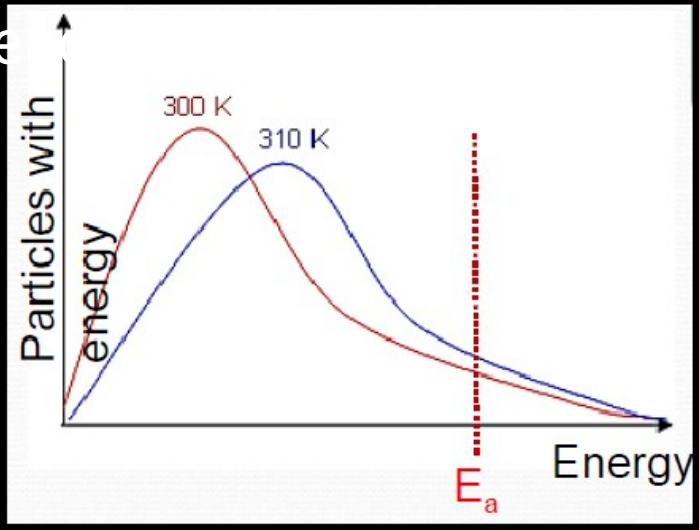
Temperature

Measure of average kinetic energy

^{o}C rise doubles the rate of reaction Every 10

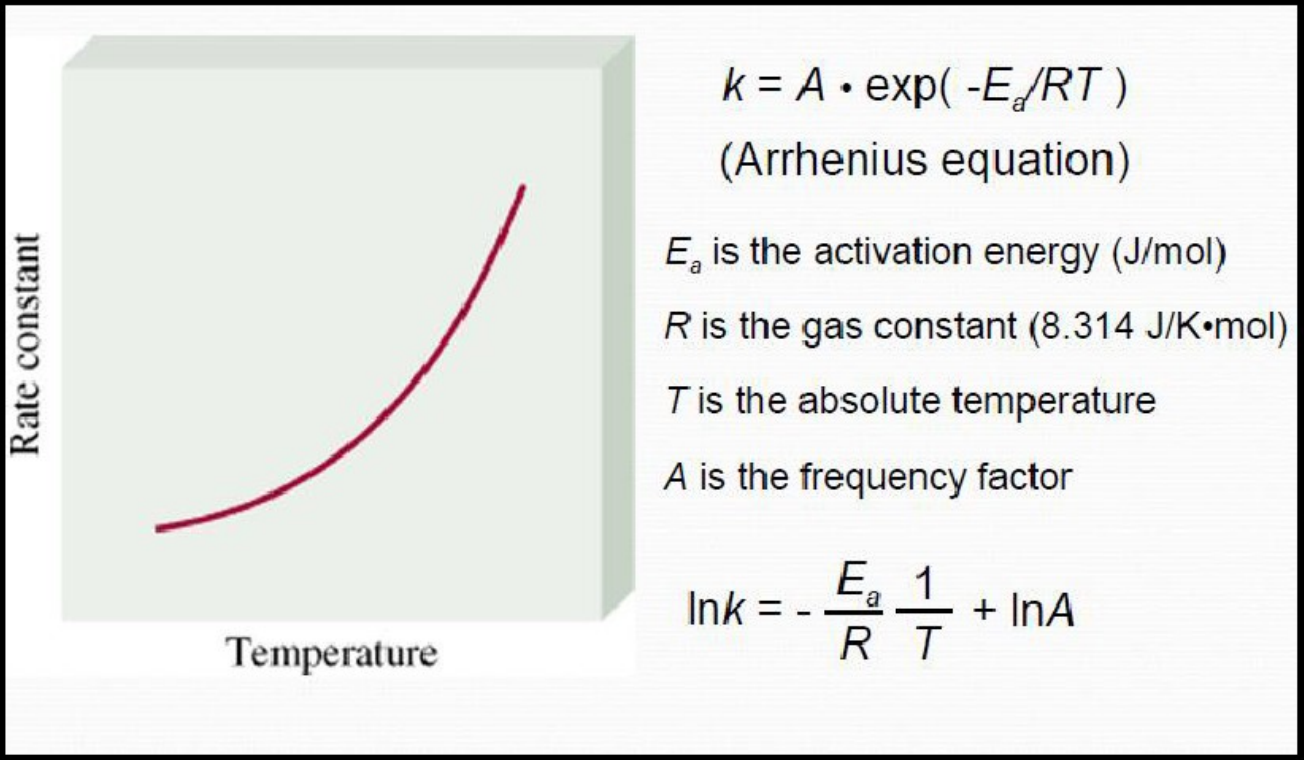
Particles above Ea will

re



Factors affecting drug degradation

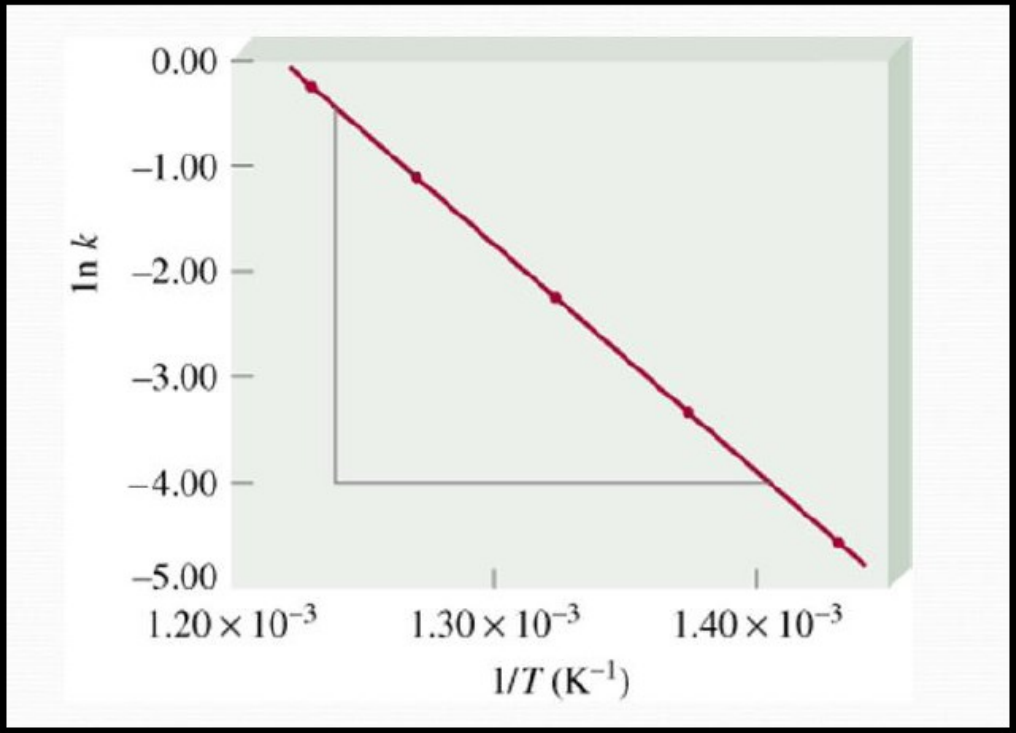
Temperature



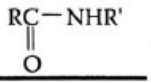
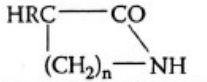
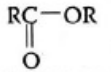
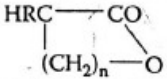
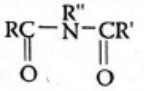
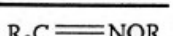
Factors affecting drug degradation

Temperature

Slope=Ea/R



Hydrolysis of drugs

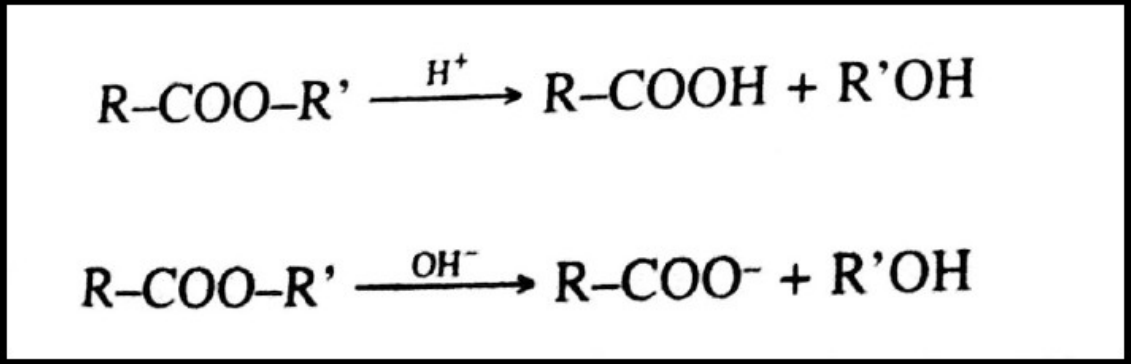
CHEMICAL CLASS	STRUCTURES
Amide	
Lactam, cyclic amide	
Ester	
Lactone, cyclic ester	
Imide	
Oximes	

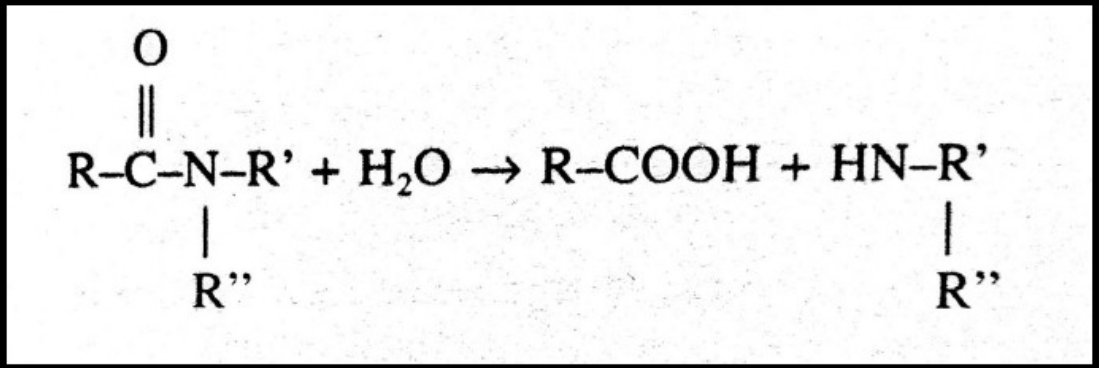
Chemical groups susceptible to hydrolysis.

Hydrolysis of drugs

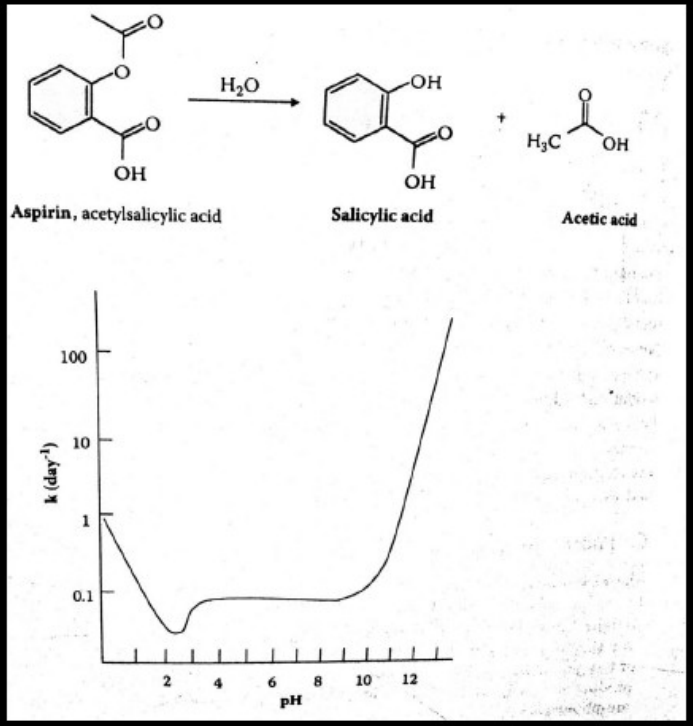
Drug type	Examples
Esters	Aspirin, alkaloids Dexmethasne sodium phosphate Nitroglycerin
Lactones	Pilocarpine Spironolactone
Amides	Chloramphenicol
Imides	Glutethimide
Malonic ureas	Barbiturates

Hydrolysis of drugs

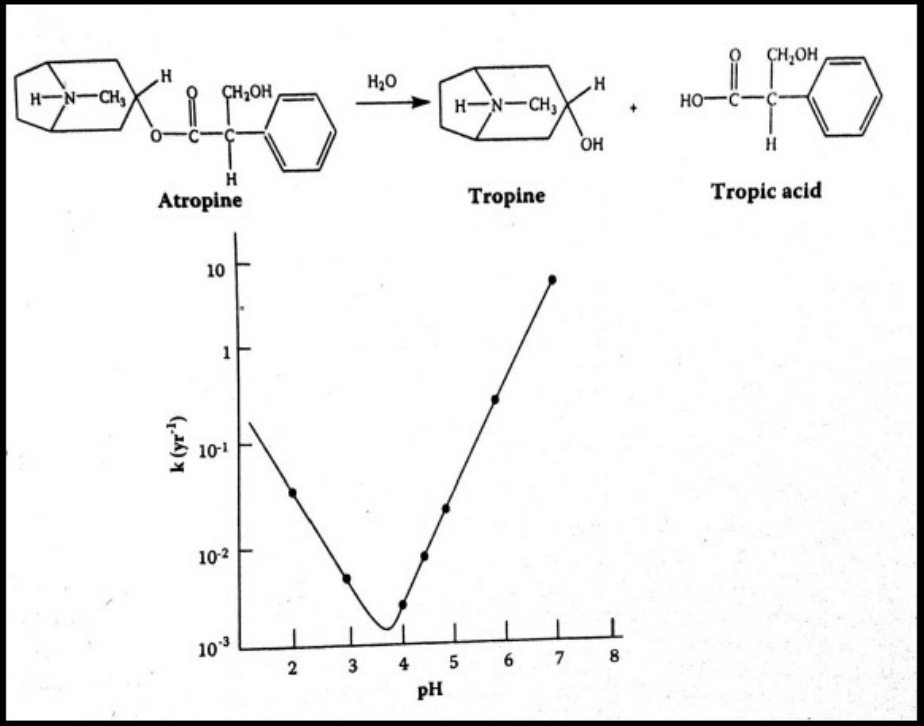




Hydrolysis of drugs



Hydrolysis of drugs



Hydrolysis of drugs

Good packaging practices like moisture resistant packs. Eg- strip packs stored in controlled humidity and temperature conditions, even using desiccant such as silica gel.

Buffering agents for pH control

Alteration of dielectric constant

Addition of complexing agents like caffeine

Use of Surfactants ,Good Refrigeration

Oxidation of drugs

$$RO^* + O_2 \rightarrow ROOO^*$$

$$ROOO^* + RH \rightarrow ROOOH + RO^*$$

$$Fe^{2+} + ROOH \rightarrow Fe^{3+} + OH + RO^*$$

Oxidation of drugs

Oils, Polyunsaturated fatty acids

Steroids and Sterols

Phenothiazines

Statins-Simvastatin, Atorvastatin

Polyene antibiotics

Oxidation of drugs

ü✋■♍□❒□□□❒♋♦♓□■ of antioxidants such as BHA, BHT, Propyl

gallate, Tocopherol, Ascorbic acid, Sodium sulfate

ü👍♒♏●♋♦♓□■ using EDTA, Citric acid, Tartaric acid

ü☥♦♏ of inert gas like Nitrogen

ü🏳❒□♦♏♍♦♓□■ from light by use of amber colored container

ü🔥♦□❒♋♑♏ at low temperature

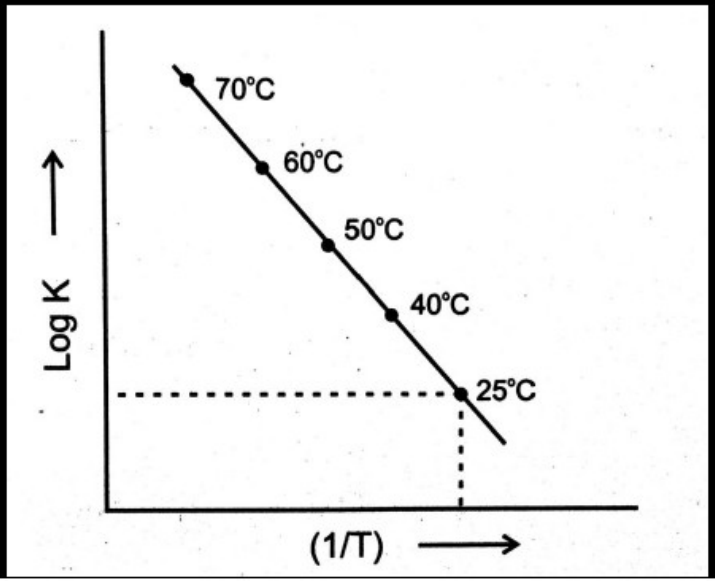
Photolysis of drugs

Vitamins, Steroids, Phenothiazines, Doxorubicin, Nifedipine, Metronidazole, Soruvidine, Molsimidine etc.

Prevention

- Light actinic amber glass containers (exclude radiation of < 470nm)
- Storage in dark
- Aluminium wraps, Cardboard outers
- Photostabilizing agents, coating
- Complexation

Accelerated Stability Studies



Limitation of Accelerated stability study

1. This method is not used in case of complex reactions because Arrhenius equation consist of only one rate constant therefore it is applicable to simple decomposition mechanism.
2. This method is not applicable if degradation is due to freezing, microbial contamination, excess agitation etc.
3. This method is valid only if energy of activation lies between 10 to 30 kcal/mole.
4. The products which loose their physical integrity at elevated temperature is not suitable for accelerated testing.
5. This method is not valid when order changes at higher temperature.

ICH

ICH stands for International Conference on Harmonization of Technical

Requirements for Registration of Pharmaceuticals for Human use

Objectives of ICH

Harmonization of registration applications within the three regions of

the EU, Japan and the United States.

ICH is a joint initiative involving both regulators and industry as equal

partners in the scientific and technical discussions of the testing

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	Humidity % RH	Temp °C	Humidity % RH
Climatic Zone I "Temperate" Japan, United Kingdom, Northern Europe, Canada, Russia, United States	20	20	42	21	45
Climatic Zone II "Mediterranean, Subtropical" Japan, United States, Southern Europe	26.4	22	52	25	60

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	Humidity % RH	Temp °C	Humidity % RH
Climatic Zone III "Hot, dry" Iran, Iraq, Sudan	26,4	27,9	35	30	35
Climatic Zone IV "Hot, humid" Brazil, Ghana, Indonesia, Nicaragua, Philippines	26,7	27,4	76	30	70

Stability Studies

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C / 60% ± 5% r.h or 30°C ± 2°C / 65% ± 5% r.h.	12 months
Intermediate	30°C ± 2°C / 65% ± 5% r.h.	6 months
Accelerated	40°C ± 2°C / 75% ± 5% r.h.	6 months

Drug substances - intended for storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C / 60% ± 5% r.h.	6 months

Stability Studies

Drug substances/Product- intended for storage in Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	-20°C ± 5°C	12 months

Drug products - General case

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C / 60% ± 5% r.h. or 30°C ± 2°C / 65% ± 5% r.h.	12 months
Intermediate	30°C ± 2°C / 65% ± 5% r.h.	6 months
Accelerated	40°C ± 2°C / 75% ± 5% r.h.	6 months

Stability Studies

Drug products - packaged in Semi-permeable containers

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C / 40% ± 5% r.h. or 30°C ± 2°C / 35% ± 5% r.h.	12 months
Intermediate	30°C ± 2°C / 65% ± 5% r.h.	6 months
Accelerated	30°C ± 2°C / 65% ± 5% r.h.	6 months

• THANK YOU...