Drug Stability

- **Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient**

- **It is measured by the rate of changes that take place in the pharmaceutical dosage forms.**

- **Stability is used to determine**
- **quality of a drug substance or drug product**
- **shelf life for the drug product**
- **Recommended storage conditions**

- **Why stability testing is necessary :**
- **Chemical degradation may lead lowering of concentration of drug in dosage form**
- **toxic product may form due to degradation of active ingredients**

Type of stability	Conditions to be maintained during the shelf life of the product.
Chemical	Retains its labelled chemical potency
Physical	Appearance, uniformity, dissolution etc are to be retained
Microbiological	Retain sterility, effectiveness of preservatives etc.
Therapeutic	Drug action remain unchanged
Toxicologic	No significant increase in toxicity

Factors affecting drug stability

***1. Temperature*:**

high temperature accelerate oxidation, reduction and hydrolysis reaction which lead to drug degradation

2. *Moisture*:

a. Water catalyses chemical reactions as oxidation, hydrolysis and reduction reaction

b. Water promotes microbial growth

***3. Light:* affects drug stability through its energy or thermal effect which lead to oxidation**

***4. Pharmaceutical dosage forms*: solid dosage forms are more stable than liquid dosage forms for presence of water.**

***5. Oxygen:* exposure of drug formulations to oxygen affects their stability**

Factors affecting drug stability

***6. Concentration*:**

rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution.

7. *Drug incompatibility*:

reactions between components of pharmaceutical dosage forms it self or between these components and cover of the container .

8. *pH*:

• Acidic and alkaline pH influence the rate of decomposition of most drugs. Many drugs are stable between pH 4 and 8.

• Weekly acidic and basic drugs show good solubility when they are ionized and they also decompose faster when they are ionized.

So if the pH of a drug solution has to be adjusted to improve solubility and the resultant pH leads to instability then to solve this tricky problem a water miscible solvent should be added into the product. It will increase stability by:

- suppressing ionization

- reducing the extreme pH required to achieve solubility

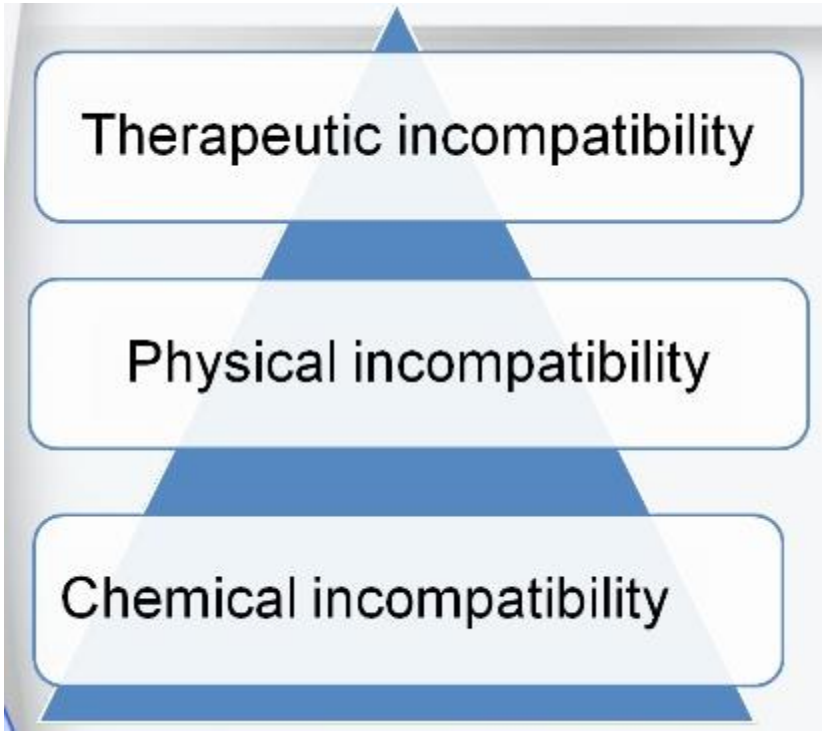
- enhancing solubility and

-reducing the water activity by reducing the polarity of the solvent.

For example, 20% propylene glycol is placed in chlordiazepoxide injection for this purpose.

- ***Three stabilities of drug must be considered:***

1. Physical stability
2. Chemical stability
3. Microbiological stability



PHYSICAL DEGRADATION:

Definition:
“Degradation, which results into the change of physical nature of the drug.”

Types of physical degradation are as :

1. Loss of volatile components
2. Loss of H2O
3. Absorption of H2O
4. Crystal growth
5. Polymorphic changes
6. Color changes

A. Physical instability:

1. Crystal formation in pharmaceutical preparations:

Causes:

a. Polymorphism phenomena: i.e. Chloramphenicol (change of amorphous to crystalline form.

b. Saturated solution: by different temperature precipitation of solute may occur.

c. In suspension: when very fine powder is used a part of suspending agent will dissolve then precipitate as crystal.

2. Loss of volatile substances from pharmaceutical dosage forms: *Examples:*

a. Aromatic waters

b. Elixirs

c. Spirits

d. Some types of tablets which contain aromatic water (Nitroglycerin tablets)

3. Loss of water:

This can be seen in the following dosage forms:

a. Saturated solution: by loss of water they become supersaturated and precipitate as crystals is formed

b. Emulsions: Loss of water lead to separation of the two phases and change to other type

c. Creams: especially oil/water, they become dry by loss of water

d. Pastes

e. Ointments: especially aqueous base ointments

Humectants **is added to the previous dosage forms which defined as hydrophilic substances added to aqueous phase to absorb water from atmosphere and prevent its loss from the dosage forms.**
Examples: Glycerin

4. Absorption of water:

This phenomena can be seen in the following pharmaceutical forms:

a. Powders: Liquification and degradation may occur as a result of absorption of water

b. Suppositories which base made from hydrophilic substances as Glycerin, Gelatin, poly ethylene glycol.

The consistency of these forms becomes jelly-like appearance Depends on temp and humidity of surrounding material

e.g.

- **Glycerin suppositories may become opaque**
- **Gelatin capsule may soften**
- **Some deliquescent salts calcium chloride, potassium citrate.**

5. Change in crystalline form:

In polymorphic changes crystal forms are changed. A stable crystal form loosens.

This may cause alteration in solubility and possibly crystalline growth in aqueous suspensions

- **Example: Cocoa butter which is capable of existing in four polymorphic forms.**

6. Colour Changes:

Colour changes are of two types.

1. Loss of color
- **PH change**
- **Presence of reducing agent**

2. Development of color
- **Exposure to light**

Preventive measures:

1. Loss of volatile components:
Such product should be placed in well closed container

2. Loss of water:
Products should be placed in well-closed container.

3. Absorption of water:
Product should be placed in well-closed container.

4. Crystal growth:
For solutions
· Stabilizers are added

For suspensions
· Minimum temp. flocculation should be managed
· Incorporation of surface active agent
· By increasing viscosity of suspending material

5. Polymorphic changes:
Formulated products should contain a stable crystalline form of the drug.

6. Colour changes:
· PH should not be changed
· Exposure to light should be avoided
. An attempt has been made to prevent the fading by incorporating UV light absorbing material.

B. Chemical instability:

- **CHEMICAL DEGRADATION:**

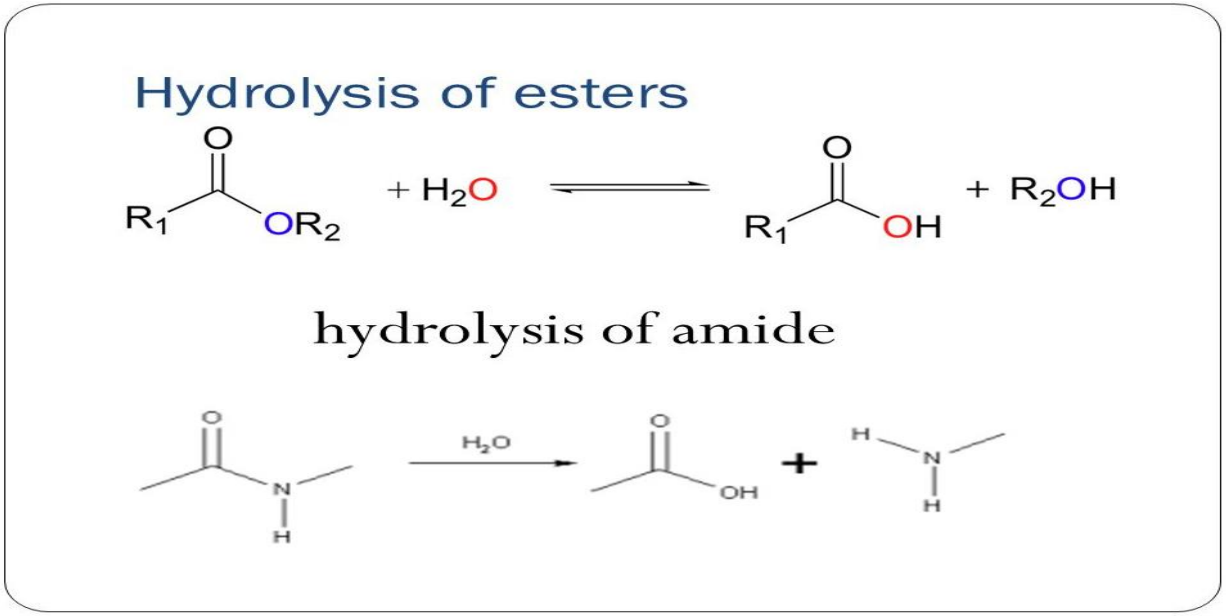
- **Definition:**
  “Change in the physical nature of the drug is called as chemical degradation.”

  Types of chemical degradation are as under

  1. Hydrolysis
  2. Oxidation
  3. De-carboxilation
  4. Isomerization
  5. Polymerization
  6- Combination
  7- Complexation or chelation

1. Hydrolysis:

- **“It is defined as the reaction of a compound with water.” ,**
- **Major cause of degradation of drug**
- **Factors Effecting Hydrolysis:**
  - **Moisture**
  - **PH**
  - **Temp.**
  - **Type of the solvent**



Some Functional Groups Subject to Hydrolysis

Drug type	Examples
Esters	Aspirin, alkaloids Dexmethasne sodium phosphate Nitroglycerin
Lactones	Pilocarpine Spironolactone
Amides	Chloramphenicol
Lactams	Penicillins Cephalosporins
Malonic urea	barbiturates

Hydrolysis Preventive Measures:

Adjustment of pH:

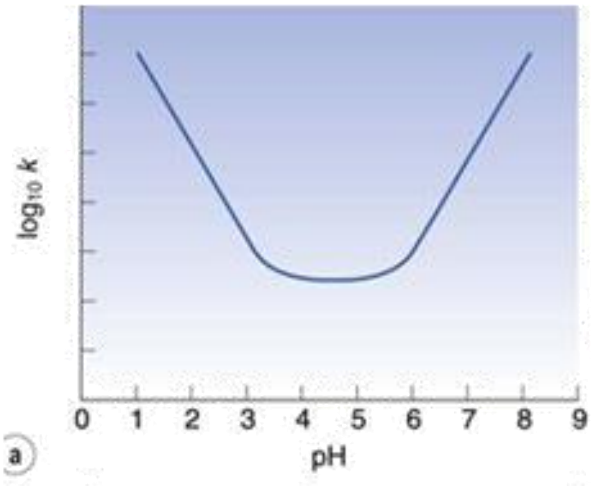
Rate of decomposition is critically dependent Upon pH.

In the case of acid-base catalyzed hydrolysis at minimum pH The drug stability is maximum

This can be shown by plotting a relationship between log of the reaction velocity constant for decomposition (Log K) and pH

Maximum stability for different drugs at different pH

e.g. Atropine sulphate 3.8, Procaine 3.6, Benzocaine 4.9



Choice of solvent:

using solvent rather than water if possible .Aspirin is unstable in aqeous Solution , So it is formulated in alcohol i.e. propylene glycol.

In some cases non-aqeus Solvent increases the instability of product e.g. Cyclamic acid in aq. sol. Hydrolyze in slow rate while in alcohol high rate.

Production of insoluble form of drug:

· By making suspensions
· By pH adjustment of the aqeouse Vehicle.
· By preparing insoluble salt of the drug.
    -e.g. insoluble procaine salt of benzyl penicillin.
· By preparing “transient derivatives” of the drug.

Addition of surfactants:

Addition of surface-active agents results into significant improvement of drug stability. This occurs due to the micelles formation , Anionic micelles are more effective.

Modification of chemical structure:

Change of chemical structure of a chemical drug may prevent the hydrolysis

e.g. Alkyl to alkyl chain.

Presence of complexing agent:

By the presence of a compound, which would form water, soluble complex with drug the rate of decomposition may be decreased.

e.g. caffeine decrease the rate of decomposition of local anesthetics such as benzocaine, procaine & amethocaine.

2. Oxidation

- is defined as loss of electrons or gain of oxygen.
- Auto-oxidation: It is a reaction with oxygen of air which occur spontaneously without other factors.
- Pre-oxidants: Are substances catalyze oxidation process i.e. metals, some impurities.

Some Functional Groups Subject to Autoxidation

Functional group	Examples
Catechols	Catecholamines (dopamine)
Ethers	Diethylether
Thiols	Dimercaprol (BAL)
Thioethers	Chlorpromazine
Carboxylic acids	Fatty acids

Factors lead to oxidation

- **Presence of oxygen**
- **Light: It can cause photo-chemical reactions: chemical reaction occur in presence of light.**
- **Temperature: Elevated temperature accelerate oxidation reaction**
- **PH : each drug has its ideal pH for stability. Any change in pH affect drug stability and may accelerate oxidation reaction.**
- **Pharmaceutical dosage form Oxidation reaction occur in solutions faster than in solid dosage forms.**
- **Presence of pre-oxidants as metals & peroxides**
- **Type of solvent used Oxidation reaction occur faster in aqueous solution than others.**
- **Presence of unsaturated bonds : as double and triple bonds (oils) which undergo easier than saturated bonds for oxidation.**

Protection of drugs from oxidation

- **Addition of Antioxidants and inorganic sulfur compounds: Vitamin E, Vitamin C, thio sulfate and polysulfide**

- **Addition of chemicals which form complexes with metals: EDTA, Benzalkonium chloride**

- **Protection from light: Using of dark container , Storage in dark places , Packaging with substances which absorbed light i.e. Oxybenzene**

- **Choice of suitable pharmaceutical dosage forms which reduce the possibility of oxidation process (solid dosage)**

- **Maintenance of pH by using buffer solution**

- **choice of suitable solvent(rather than water)**

- **Storage in low temperature**

- **protection from air by: using good closed containers and Replacement of oxygen by nitrogen**

Polymerization

- **In polymerization, small repeating units called monomers are bonded to form a long chain polymer.**

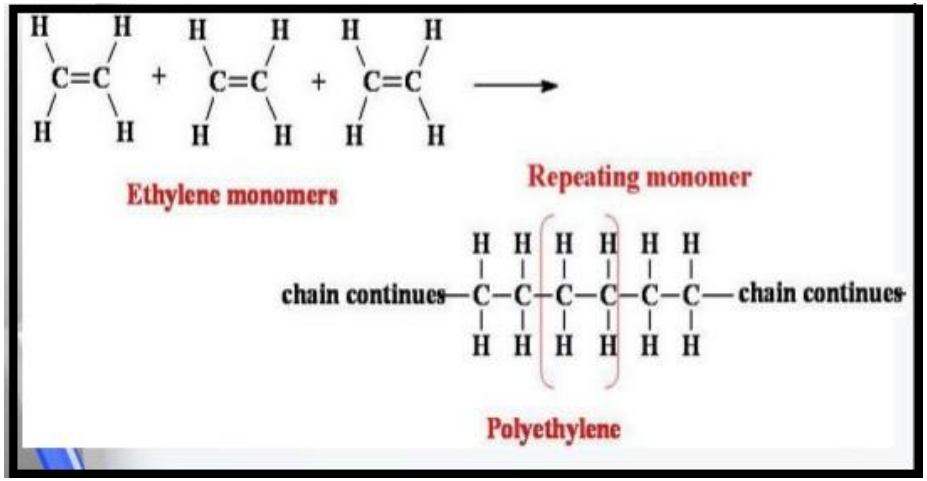
Ex:

Formaldehyde $\xrightarrow{\text{Heat}}$ Para formaldehyde

- **To avoid this formaldehyde must be stored in suitable temperature and addition of methanol 15%.**
- **Ampicillin in high temperature forms polymers which cause allergy**

Factors induce Polymerization

1. **Temperature**
2. **Light**
3. **Solvent**
4. **pH**
5. **Impurities**



Isomerization

- **It means conversion of drug to its isomer**
- **Isomers have Identical molecular formulas but posses a different arrangement of atoms.**

Types of Isomerization

1.Optical isomerization

2.Geometric isomerization

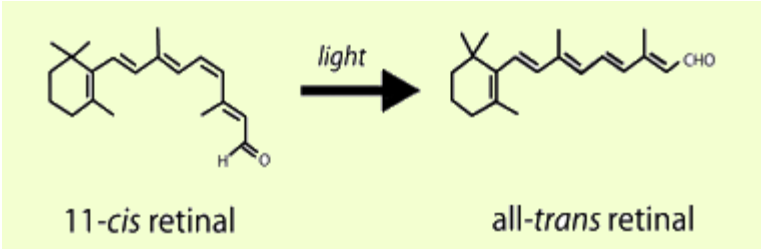
Optical Isomerization – Conversion of optical active drug into less active

E.g.:

- **L-Adrenaline is converted to d-adrenaline by change of pH or temperature**
- **L-adrenaline is more therapeutically active than d-adrenaline, a although they have the same physical properties but different arrangement of atoms.**
- **Factors affect optical isomerization:**

Temperature , pH , Solvent and Impurities

Geometric Isomerization



- **Expressed by cis or trans**
- **Cis: Means the groups in the same direction: , Trans: Means the groups in opposite direction**
- **Cis is more therapeutically active than trans , E.g.:Vitamine A**

C. Microbiological stability:

1. Contamination from microorganisms is a big problem for all formulations containing moisture but it can be a bother in solid dosage forms also if some natural polymers are used because many natural polymers are fertile sources of microorganisms.

2. In the type of hygienic manufacture carried out today where "Quality Assurance" is a prerequisite as per the GMP procedures, there are definite procedures to prevent microbial contamination in all formulations.

- ***Sources of Microbial Contamination:***

1. Water

2. Air

3. Raw materials, containers and closures

4. Personnel

5. Instruments and apparatus

Packaging And Stability

- Packaging of the drug product is very important when its stability is being considered.

- Glass, plastic, rubber (natural and synthetic) and metal are the four types of containers commonly utilized for packing drug products.

1. Glass

• Glass is resistant to chemical and physical change and is the most commonly used material, but it has the limitations which are overcome by the technologists in the following way:

Limitations	Overcome
1. Its alkaline surface	use of Borosilicate glass
2. Ions may precipitate insoluble crystals from the glass	the use of buffers
3- Permits the transmission of light which may accelerate decomposition.	Amber coloured glass

2. Plastics

• Plastics include a wide range of polymers of varying density and molecular weight, each possessing different physicochemical characteristics.

The problems with plastic are:

1. Migration of the drug through the plastic into the environment.

2. Transfer of environmental moisture, oxygen, and other elements into the pharmaceutical

product.

3. Leaching of container ingredients into the drug.

4. Adsorption or absorption of the active drug or excipients by the plastic.

Stability testing

Stability testing is used to:

- **Provide evidence as to how the quality of the drug product varies with time.**
- **Establish shelf life for the drug product and Determine recommended storage conditions.**
- **Determine container closure system suitability**

Why Stability studies are necessary ?

- **Chemical degradation of the product leads to lowering of the concentration of the drug in the dosage form.**
- **Toxic products may be formed , due to chemical degradation of the active ingredient.**

Advantages of Stability studies

- **Assurance to the patient**
- **Economic considerations**
- **Legal requirement**

Stability protocol

Study	Storage condition	Minimum time period covered by data at submission
Long Term (Ambient)	25º C ± 2º C 60%RH ± 5%	12 months
Intermediate (controlled)	30º C ± 2º C 60%RH ± 5%	6 months
Accelerated	40º C ± 2º C 75%RH ± 5%	6 months

Testing Frequency

- **For Long term testing, during first year sampling should be done every three months, during second year, sampling should be done every six months and after two years, sampling should be done once a year.**

- **Accelerated testing should be done at least six months and it suggests sampling points of 0, 3, 6 months.**

Accelerated Stability Studies

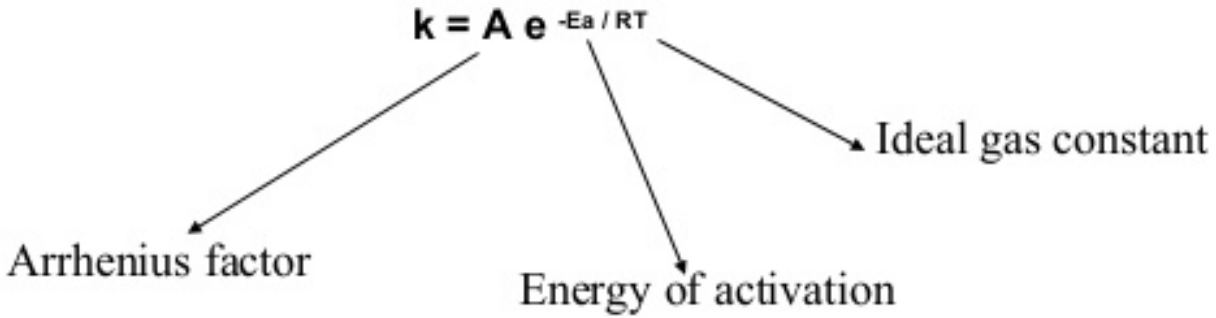
- **study to predict the shelf life of the product, by accelerating the rate of decomposition, preferably by increasing the temperature of reaction conditions.**

- **With the advancement in branch of kinetics, shelf life of a dosage form can be predicted within months based on accelerated stability reports Preparations are subjected to high stresses during stability testing.**
- **Common high stresses include Temperature , Humidity and Light**

Arrhenius equation

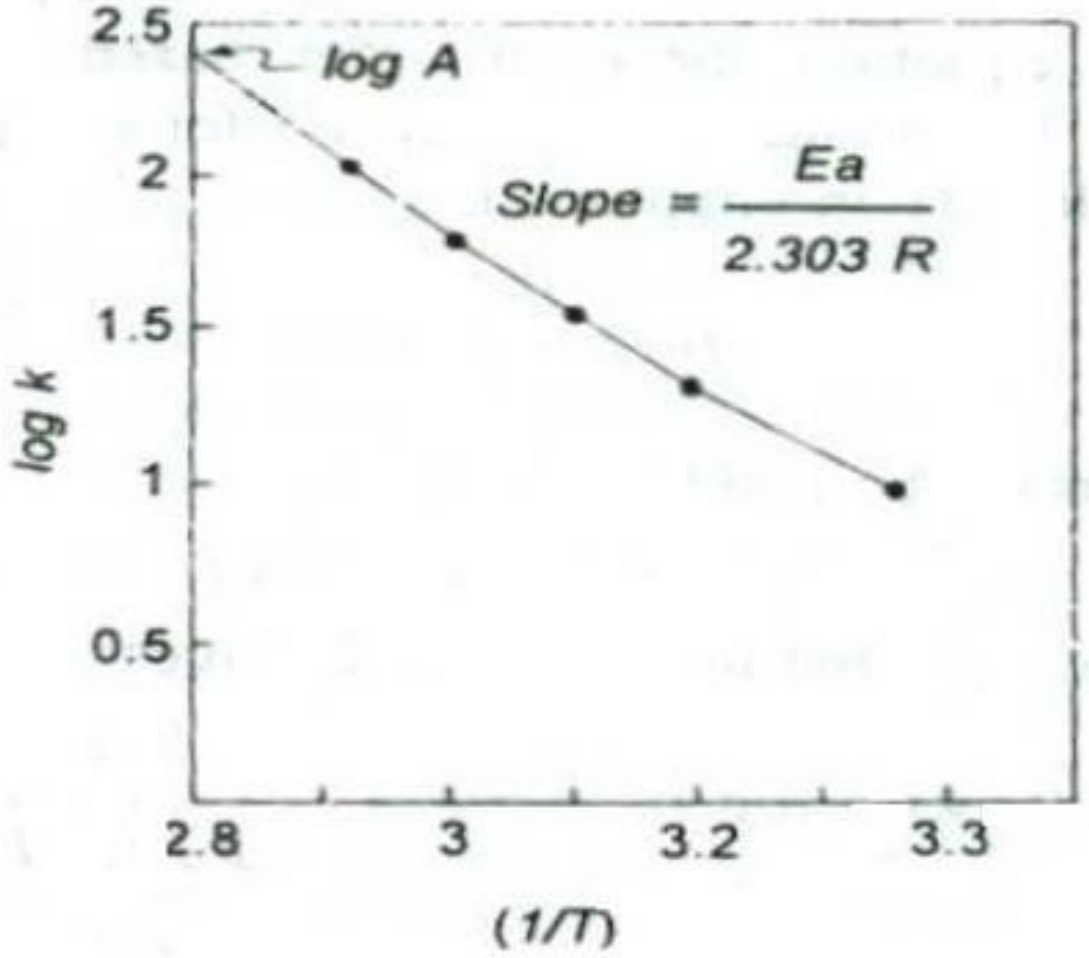
It explains the effect of temperature on rate of a reaction.

According to Arrhenius, for every 10° rise in temperature, the speed of reaction increases about 2-3 times.



Arrhenius factor is the frequency of molecular collisions occuring between the molecules.

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


2.5
2
1.5
1
0.5
log k
log A
Slope = Ea / 2.303 R
2.8
3
3.2
3.3
(1/T)