Application of Colloids

1) Electrical precipitation of Smoke

* Smoke released from Industries causes air pollution
* Smoke is a colloidal solution of carbon particles, Arsenic Compounds, dust etc in air
* Now Smoke is passed through a chamber containing plates having a charge opposite to that of Smoke particles
* when the particles in Smoke comes in contact with plate results in neutralized and gets precipitated leads to settling of particles on the floor of the chamber
* ∴ This is how the dust particles are removed & release the pure air into atmosphere.

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colloidal in nature (2)

Ex :- Fyc bhion

Milk of Magnesia

* Medicines are more effective in colloidal dispersions because of its increased surface area.

* As the surface area increases the effectiveness of the medicine also Increases.

(2) Purification of water:

* The water obtained from natural sources often contain suspended impurities.

* with the addition of Alum into water results in Coagulate the suspended impurities and make the water fit for drinking.

(3) Medicines

* Most of the Medicines are in

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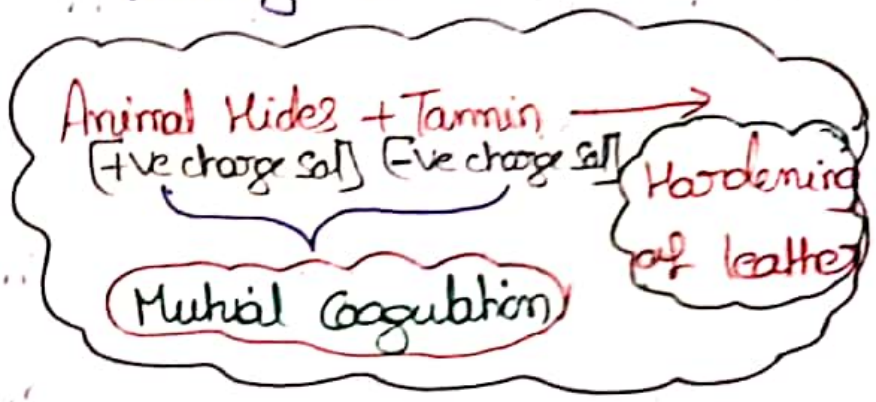
4) Tanning of leather

* Leather is made up of Animal hides.
* Animal hides are Colloidal in nature
* Animal hide is having positive charge when it is soaked in Tannin having Negative charge.
* Because of opposite charge mutual Coagulation takes place results in Hardening of leather.

* This process is called.

Tanning of leather.



5) Rubber Industry

* Rubber is getting from rubber tress which gives latex
* This latex is Colloidal solution of Rubber particles

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which are negatively charged.

Ex :- Paint
Ink
Cement
Graphite.

* The Hardening of rubber particles in latex is done by Coagulation of rubber particles with the addition of oppositely charged Coagulant.

* These hardened rubber is used in preparation of tyres

(6) Industrial products

* A large number of Industrial products are Colloids.

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COARSE DISPERSION

SUSPENSION:

Types and theories of suspensions, effect of Brownian motion, interfacial properties of suspended particles, settling in suspensions. Sedimentation parameters, wetting of particles, controlled flocculation, flocculation in structured vehicles, rheological considerations.

Definition: Pharmaceutical suspension may be defined as a dispersion in which insoluble solids are suspended in a liquid medium. Suspensions are also called as heterogeneous system, or more precisely biphasic systems. A good pharmaceutical suspension is one in which the particle size distribution lies between 1 and 50 µm.

Advantages:

Suspensions offer distinct advantages they are as follows:

1. **Stability**: Some drugs are not stable in solution form. In such cases it is necessary to prepare an insoluble form of that drug. Therefore drugs are administered in the form of suspension. e.g. Procaine Penicillin G.
2. **Choice of solvent**: If the drug is not soluble in water and solvents other than water are not acceptable, suspension is the only choice. e.g. Parenteral corticosteroid.
3. **Mask the taste;** In some cases, drugs are made insoluble and dispensed in the form of suspension to mask the objectionable taste. e.g. Chloramphenicol base is very bitter in taste, hence the insoluble chloramphenicol palmitate is used which does not have the bitter taste
4. **Prolonged action:** Suspension has a sustaining effect, because, before absorption the solid particles should be dissolved. This takes some time. e.g. Protamine Zinc Insulin and procaine penicillin G.
5. **Bioavailability:** Drugs in suspension exhibit a higher bioavailability compared to other dosage forms (except solution) due to its large surface area, higher dissolution rate. e.g. Antacid suspensions provides immediate relief from hyperacidity than its tablet chewable tablet form.

Disadvantages:

1. In the formulation, the sediment of solids occasionally gives false alarm about the suitably of the product.
2. Physical stability, sedimentation and compaction of sediment causes problems that are by no means an easy task to solve.
3. The product is liable to undergo oxidation and hydrolysis. Therefore, chemical stability is a problem, which needs attention.

Classification of suspension:

Deflocculated System	Flocculated System
i) Pleasant appearance, because of uniform dispersion of particles.	i) Somewhat unsightly sediment.
ii) Supernatant remains cloudy.	ii) Supernatant is clear
iii) Particles exist as separate entities	iii) Particles form loose aggregates.
iv) Rate of sedimentation is slow, as the size of particles are small	iv) Rate is high, as flocs are the collection of smaller particles having a larger size.
v) Particles settle independently and separately	v) Particles settle as flocs.
vi) The sedimentation is closely packed and form a hard cake.	vi) Sediment is a loosely packed network and hard cake cannot form.
vii) The hard cake cannot be redispersed.	vii) The sediment is easy to redisperse.
viii) Bioavailability is higher due to large specific surface area.	viii) Bioavailability is comparatively less due to small specific surface area.

Interfacial properties of suspended particles:

An acceptable suspension should not exhibit settling of dispersed solids. This can be achieved by reducing the particle size to a level of 5µm so that they exhibit Brownian motion. Since size reduction implies that work has to be done to divide large particles, this process can be written as:

$$W = \Delta G = \gamma_{SL}. \Delta A$$

Where ΔG = increase in surface free energy, J/m^2

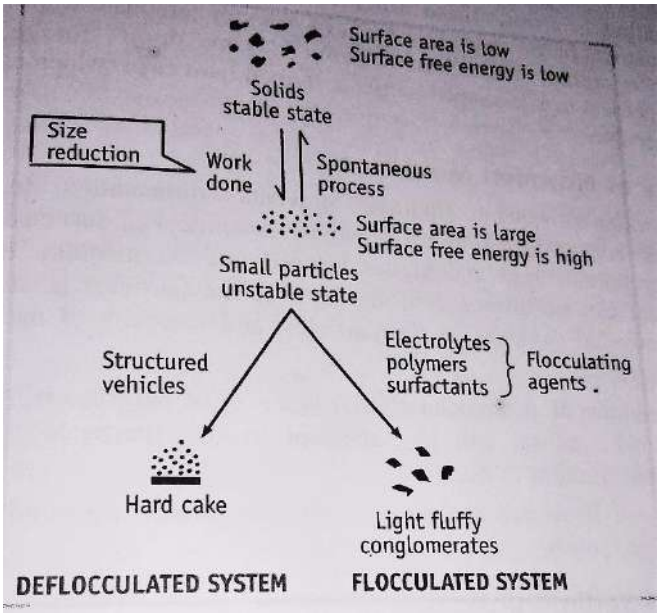
γ_{SL} = interfacial tension between liquid medium and solid particles, mN/m

ΔA = increase in surface area of the interface due to size reduction, m^2

During size reduction, the surface area of the solids increases enormously leading to an enhanced surface free energy (ΔG), a state in which the system is thermodynamically unstable. Now, the system spontaneously reacts and tends to return to a stable state, in order to reduce its surface free energy ($\Delta G = 0$). Two approaches are possible to regain stability.

A. In above equation, the ΔA may be reduced to zero, so that ΔG will become zero. This is possible by regrouping the particles to form aggregates or flocs. From the point of physical stability, such a change is undesirable. The pharmacist should strike a balance between the particle size and stability of the system. Regrouping of particles with strong interactions can be prevented by paying attention to the following points.
   i. Charge on the insoluble solid surface and the formation of electrical double layer.
   ii. Zeta potential of the solid surface.
   iii. Particle to particle distance and their influence on the potential energy barrier.

In order to achieve stability substances, such as electrolytes and polymers are added. Dilute suspensions are relatively stable based on the interparticle distance. High viscosity restricts the movement of particles and prevents the aggregation and sedimentation.



B. In above equation, the interfacial tension, γ_{SL} may be reduced, so that the system can be stabilized. But it cannot be made zero, because dispersed particles have certain positive interfacial tension. Hence, the term 'ΔG' in above equation cannot zero. The manufacturing pharmacist adds surface active agents to reduce γ_{SL} value to a minimum. Thus, the system can be stabilized to a certain extent.

Settling in suspension (Theory of suspension):

The rate of sedimentation of particles can be expressed by the Stoke's law, using the following formula:

$$\text{Se dimentation rate} = \frac{d^2 (\rho_s - \rho_l) g}{18\eta}$$

Where d is the particle diameter

ρ_s, ρ_l are densities of a particle and liquid respectively.

g is the acceleration of gravity.

η is the viscosity of the medium.

Stock's law is applicable if:

i) particles are spherical; but particles in the suspension are largely irregular.

ii) Particles settle freely and independently.

In suspensions containing 0.5 - 2 % (w/v) solid, the particles do not interfere with each other during sedimentation - hence free settling occurs.

Most pharmaceutical suspensions contain 5 - 10 % or higher percentages of solid. in this cases particles interfere with one another as they fall - hence hindered settling occurs and Stoke's law no longer applies.

Stoke's law is applicable to deflocculated systems, because particles settle independently. However, this law is useful in a qualitative manner in fixing factors which can be utilized in formulation of suspensions.

1. Particle size

Rate of sedimentation $\propto$ (diameter of particle)^2

So smaller the particle size more stable the suspension. The particle-particle interaction results in the formation of floccules or coagules where the sedimentation rate increases. The particles are made fine either by **dry milling** prior to suspension or **wet-milling** of the final suspension in a colloid mill or a homogenizer.

2. Viscosity of the medium

According to Stoke's law:

Rate of sedimentation $\propto$ 1 / (viscosity of the medium)

The viscosity of suspension should be optimum. Viscosity can be increased by adding suspending agents or thickening agents. selection of high viscosity have both advantages and disadvantages.

Advantages

i) Sedimentation rate is retarded, hence enhances the physical stability of the suspension.
ii) Inhibits crystal growth, because movement of particles is diminished.

Disadvantages

i) Redispersibility of the suspension on shaking is difficult.
ii) Pouring out of the suspension from the container may be difficult.
iii) Creates problems in the handling of materials during manufacture.
iv) May retard absorption of drugs from the suspension.

3. Density of the medium:

Rate of sedimentation $\propto$ (density of solid – density of liquid medium)

Lesser the difference between the densities of solid particles and liquid medium slower is the rate of sedimentation. Since it is very difficult to change the absolute density of the solid particles so the density of the liquid medium can be manipulated by changing the composition of the medium. The addition of nonionic substances such as sorbitol, polyvinylpyrrolidone (PVP), glycerin, sugar, or one of the polyethylene glycols or combination of these may be helpful in the manipulation.

If the density of the particles is greater than the continuous medium the particles will settle downwards, the phenomenon is known as sedimentation. If the density of particle is lesser than that of the liquid medium then the particles will move upward - the phenomenon is known as creaming.

Sedimentation volume

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since the sediment formed should be easily dispersed by moderate shaking to yield a homogeneous system, measurement of the sedimentation volume and its ease of redispersion are the two common evaluative procedures.

Definition: The sedimentation volume, F, is defined as the ratio of the final, or ultimate volume of the sediment (Vu), to the original volume of the suspension (Vo), before settling. Thus

$$F = Vu / Vo$$

The sedimentation volume can have values less than 1 to greater than 1. If the volume of sediment in a flocculated system equals the original volume of suspension, then F = 1. Such a product is said to be in 'flocculation equilibrium'.

Procedure: The suspension is taken in a measuring cylinder upto a certain height and left undisturbed. The particles will settle gradually. The value of F is determined from the ratio of the volume of the sediment at that instant of time (Vu) and the original volume of the suspension (Vo). The value of F is plotted against time (t). The plot will, will start at 1.0. at time zero. The curve will either run horizontally or gradually sloping downward to the right as time goes on.

One can compare different formulations and choose the best by observing the line, the better formulation obviously producing lines that are more horizontal and/or less steep.

If the suspension is highly concentrated then the suspension is diluted with the continuous medium (liquid phase) and then the sedimentation volume is determined.

Degree of flocculation

A more useful parameter is the degree of flocculation, β.

Definition: degree of flocculation is the ratio of ultimate sediment volume of *flocculated* suspension to that of *a deflocculated* suspension.

$$\beta = \frac{\text{sedimentation volume of } \textit{flocculated} \text{ suspension (F)}}{\text{sedimentation volume of } \textit{deflocculated} \text{ suspension (F}\infty\text{)}}$$

$F\infty = V\infty / Vo$ $F\infty$ = sedimentation volume of *deflocculated* suspension

$V\infty$ = ultimate sediment volume of *deflocculated* suspension

Vo = original volume of suspension

$F = Vu / Vo$ F = sedimentation volume of *flocculated* suspension

Vu = ultimate sediment volume of *flocculated* suspension

Therefore, $\beta = F / F\infty$

$= (V\infty / Vo) / (Vu / Vo)$

$= (V\infty / Vu)$

$$\beta = \frac{\text{ultimate sediment volume of } \textit{flocculated} \text{ suspension (Vu)}}{\text{ultimate sediment volume of } \textit{deflocculated} \text{ suspension (V}\infty\text{)}}$$

Theory Brownian movement

Brownian movement counteracts sedimentation by keeping the dispersed material in random motion. Brownian movement of particles prevents sedimentation. In general, particles are not in a state of Brownian motion in pharmaceutical suspensions, due to

i) larger particle size (Brownian movement is seen in particles having diameter of about 2 to 5 μm)

ii) and higher viscosity of the medium.

No sedimentation diameter (NSD) is a size of particles below which the Brownian motion will be sufficient to keep particle suspended. Hence sedimentation is nil. Theory of Brownian movement proposes particle size and viscosity as the major factors.

Particle shape:

Particle shape determines the packing arrangements and influences the settling behavior. These also affect the resuspendability and stability. Symmetrical barrel shaped particles of calcium carbonate were found to produce stable suspension without caking upon storage, while asymmetrical needle-shaped particles formed hard cake, which cannot be redispersible.

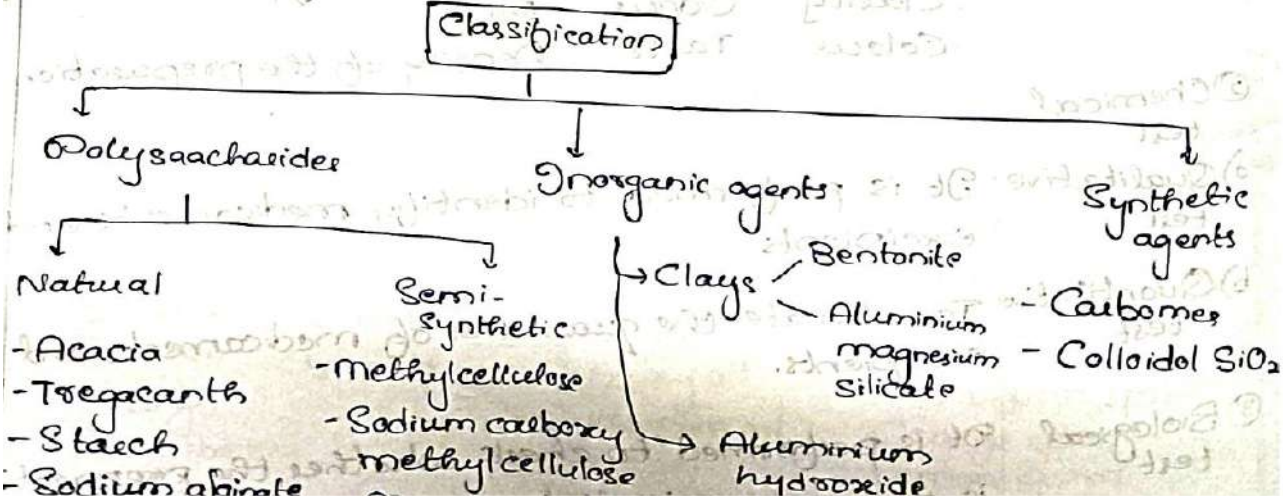
Formulation of suspension:

Formulation of Suspension:

* Suspending agent
* Wetting agent
* Flocculating agent
* Vehicle
* Preservatives (Stabilizers)
* Antioxidants (Stabilizers)
* Colouring agents
* Sweetening agents
* Flavouring agents

Suspending agents:

These are the agents used to disperse the particles uniformly throughout the medium for sufficient period of time after mild agitation by increasing the viscosity of dispersion medium.



Polysaccharides (Natural Polysaccharides)

Suspending agent	Properties
① Acacia	• It is a good suspending agent • It is effective in combination than individually, therefore acacia is used as compound Tragacanth Powder. Composition of Acacia compound Tragacanth Powder: • Acacia – 20% • Tragacanth – 15% • Starch – 20% - It is used in the conc of 2% - It is used only if vehicle is other than water or chloroform water. - Acacia consists of oxidase enzyme which detonates readily & oxidase medicaments & excipients - Therefore suitable anti-oxidants should be added to make the preparation stable.
② Tragacanth	- It is effective over acacia as a suspending agent. - It is available as either compound tragacanth powder or tragacanth mucilage. - Tragacanth mucilage is used if the vehicle is water or chloroform water. - It is used in concentration of 2%.
③ Starch	- It is rarely used as suspending agent because of its high viscous nature - Therefore, it is used in combination of suspending agent. - It is one of the ingredient in preparation of compound tragacanth powder.
④ Sodium alginate	- It is used in concentration of 1%. - Suspending property of 1% sodium alginate is equivalent to that of suspending property of 2% of tragacanth mucilage

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Semi-synthetic Polysaccharides

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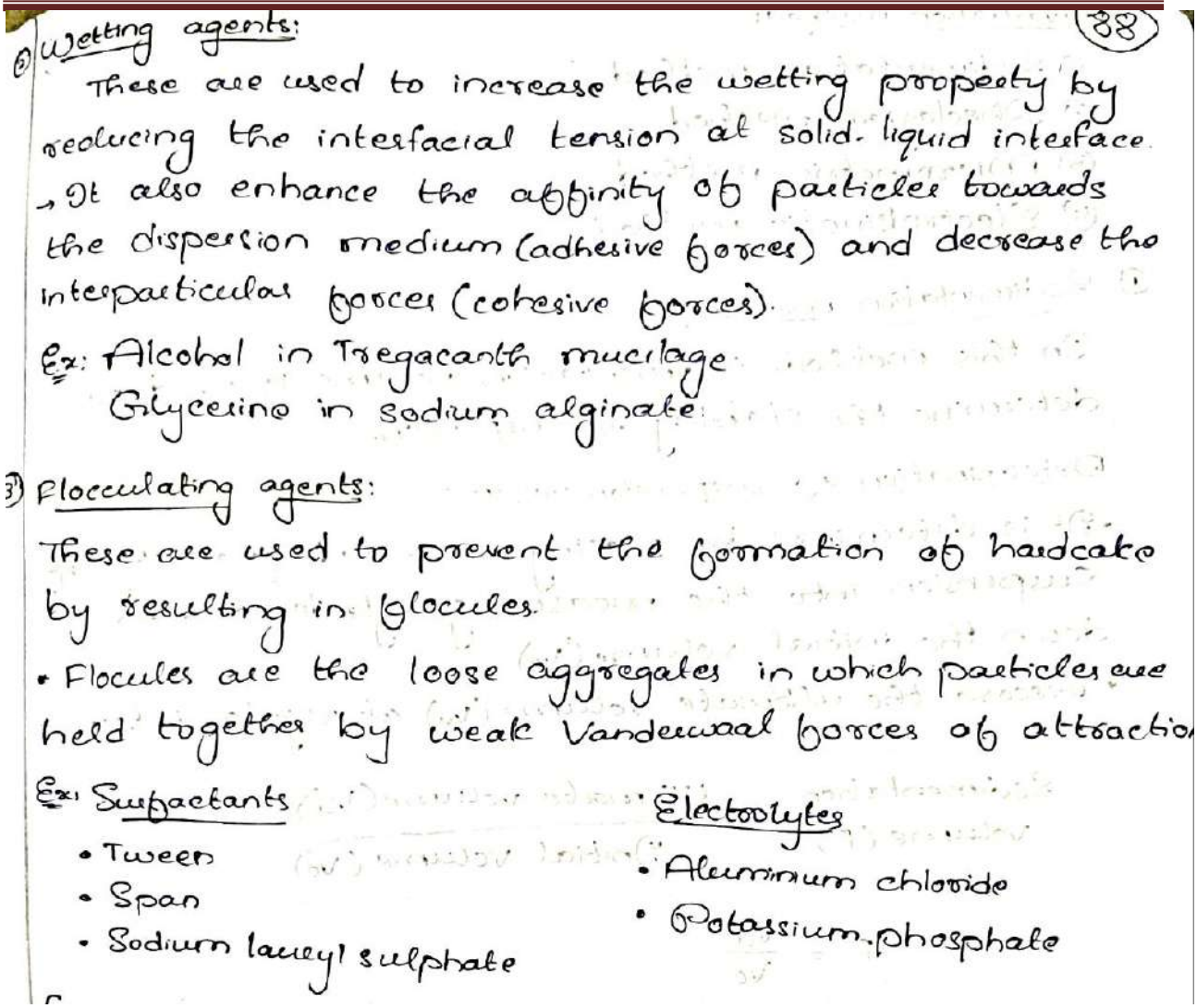
Suspending agent	Properties
① Methyl cellulose	• It is used in concentration of 0.5-2%. • Used in both external & internal preparation.
② Sodium Carboxy methyl cellulose	• Used in concentration of 0.25-1%. • Used in both external and internal preparation.
③ Microcrystalline cellulose	• It is prepared by acid-hydrolysis of wood • It is slightly yellowish to colourless, odourless, tasteless in nature.

Inorganic agents

Suspending agent	Properties
a) Clays:	
① Bentonite	• It is used in concentration of 2%. • Used only in external preparation.
② Aluminium magnesium silicate.	• Used in concentration of 1%. • Used in both external & internal preparation
b) Aluminium hydroxide	It is used only in suspensions containing medicaments such as Barium sulphate, Sulphur, Calamine, Sulphanamite.

Synthetic agents

Suspending agent	Properties	
① Carbomer	• It is used in 0.1-0.4%	Both are used in internal and external preparations.
② Colloidal Silicondioxide	• It is used in 1.5-4%	



2) Wetting agents:

These are used to increase the wetting property by reducing the interfacial tension at solid-liquid interface. It also enhance the affinity of particles towards the dispersion medium (adhesive forces) and decrease the interparticular forces (cohesive forces).

Ex: Alcohol in Tragacanth mucilage
Glycerine in sodium alginate

3) Flocculating agents:

These are used to prevent the formation of hardcake by resulting in flocules.

- Flocules are the loose aggregates in which particles are held together by weak Vandeewaal forces of attractio

Ex: Surfactants
- Tween
- Span
- Sodium lauryl sulphate

Electrolytes
- Aluminium chloride
- Potassium phosphate

Rheologic consideration:

Rheologic behavior can also be used to help determine the settling behavior and the arrangement of the vehicle and particle structural features for purposes of comparison. The structure of the suspension changes during storage period. These structural changes can be evaluated by rheologic method.

The flow properties, such as pseudoplastic and thixotropy (gel-sol-gel behavior), are important for physical stability. During storage, the suspension exhibits gel like structure and lowers the rate of settling. On moderate shaking, the product from the bottle. The sol like behavior also helps in uniform spreading of dermatological preparations.

A practical rheologic method involves the use of a Brookfield viscometer mounted on a helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various level in the sediment. In this technique, the T-bar is continually changing position and measures undisturbed samples as it advances down in the suspension

EMULSIONS

Definitions:

Emulsions are the bi phasic systems in which the dispersed phase is also a liquid. These are coarse dispersions having the globule diameter in the range from about 0.1 to 100 µm. emulsions are also called heterogeneous systems or more precisely bi phasic systems.

Advantages:

1. Medicines having an unpleasant taste and odour can be made more palatable for oral administration in the form of an emulsion. E.g., castor oil, cod-liver oil etc.
2. Emulsion provides protection against drugs which are prone to oxidation or hydrolysis.
3. Various external preparations such as, creams, lotions and foam aerosols are formulated in emulsion.
4. The sterile stable intravenous emulsions containing fats, carbohydrates and vitamins can be administered to the patients who are unable to take them orally.
5. Emulsion improves the absorption of oils when takes internally.
6. Radio opaque emulsions are used as diagnostic agent in X-ray examination.

Types of Emulsions:

(I) Ordinary emulsion systems / Primary emulsion systems / Simple emulsion systems

(i) o/w type – oil dispersed in water

oil → dispersed phase

water → continuous phase

(ii) w/o type – water dispersed in oil

water → dispersed phase

oil → continuous phase

(II) Special emulsion systems

(i) Multiple emulsions → w/o/w – type

o/w/o – type

(ii) Micro emulsion

Simple emulsion type:

o/w- type of emulsion is a system in which the oil is dispersed as droplet throughout the aqueous phase. Most pharmaceutical emulsions designed for oral administration are of the o/w type; emulsified lotions and creams either of o/w or w/o type depending on their use.

Certain foods such as butter and some salad creams are w/o type emulsions.

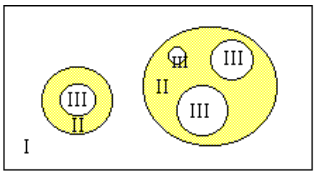
Multiple emulsion type

These multiple emulsions have been developed with a view to delay the release of an active ingredient. In this type of emulsions three phases are present, i.e. the emulsion has the form w/o/w or o/w/o. In these "emulsions within emulsions", any drug present in the innermost phase now has to cross two phase-boundaries to reach the external continuous phase.

I : Continuous phase (External aqueous phase)

II: Middle oil phase

III: Inner aqueous phase



Photomicrograph of w/o/w emulsion system

Advantages of multiple emulsions

(i) Prolongation of drug action

(ii) Location of drug in the body.

Micro emulsions

Microemulsions are liquid dispersion of water and oil that are made homogeneous, transparent and stable by the addition of relatively large amount of a surfactant and a co-surfactant. They appear to represent a state intermediate between thermodynamically unstable emulsions and solubolised systems.

Unlike emulsions, they appear as clear transparent solution, but unlike solubilised systems micro-emulsions may not be thermodynamically stable.

Microemulsions containing droplets (w/o or o/w types) with the globule size 10 to 200nm and the volume fraction of the dispersed phase varies from 0.2 to 0.8.

Theories of emulsifications:

There is no universal theory which explains the theory of emulsification. But there are some primitive theories. In general, they are classified as follows.

Theory of emulsification which explains

a. Stability:

1. Surface tension
2. Electrical repulsion
3. Orientation theory
4. Surface film theory

b. Types:

1. Bancroft's rule
2. Hawkins oriented wedge theory
3. Davis theory

Stability:

1. **Surface tension theory:**
   This is also called as interfacial tension theory. The water-water molecules and the oil-oil molecules always attract each other due to cohesive forces. At the same time oil and water molecule can attract each other. This force involved is called as adhesion forces. If the adhesive force is more than the cohesive force, then the stability will be more due to reduction in surface tension or interfacial tension.
2. **Electrical repulsion theory:**
   This theory is applicable to ionizing type of emulgents.
   Example: If sodium stearate ionizes into anions and cations. The positives Na^+ is more soluble in water and will be present at the interface. The stearate ions are more soluble in oil and that will also be present at the interface. Because of these charges an electrical double layer will be forms at the interface and that will be contributing towards the stability of the system. The like charges will be repelling where as the unlike charges will be attracted and therefore results in stability.
3. **Orientation theory:**
   This theory is based on the preferential wetting of the hydrophilic group and the lipophilic group. To have a stable system the hydrophilic and lipophilic group must be oriented in a proper amount.
4. **Surface film theory:**
   For a stable emulsion, there should be film formation at the interface. All natural emulgents except cholesterol and lecithin forms a multi-molecular layer. In a mixture of emulgents mixed interfacial effect is seen.

Types:

1. **Bancroft's rule:**
   a. According to Bancroft's rule the phase in which the emulgents is soluble becomes the external phase.
      Example: all monovalent soaps are soluble in water and therefore gives in O/W type emulsion and all divalent and trivalent soaps are soluble in oil and therefore gives W/O type of emulsion.
   b. If the poly oxy ethylene group is less than 5 then it gives W/O emulsion. More than 5 it gives O/W type of emulsion.
2. **Hawkin's oriented wedge theory:**
   In this the type of emulsion formed is based on the curvature of the bulk at the interface.
   If the hydrophilic portion is more-bulkier then it gives O/W type of emulsion.
   Example: Monovalent soaps like sodium stearate.
   If the lipophilic portion is more-bulkier than it gives W/O type of emulsion.
   Example: Divalent and trivalent soaps.
   In this case the lipophilic portion is bulkier because of the unsaturation present.

3. Davis theory of emulsification:

This theory explains the kinetics coalescence. This theory gives two rate equations:

$$\text{Rate 1} = C_1 \times e^{-w1/RT}$$

$$\text{Rate 2} = C_2 \times e^{-w2/RT}$$

Rate 1 and Rate 2 are rate of coalescence oil droplets r water droplets.

C_1 and C_2 are the proportionality constant.

W_1 and W_2 are energy barriers which have to overcome before the oil droplets coalesce or the water droplet coalesce. This is inversely proportional to viscosity and the depends on energy of hydration.

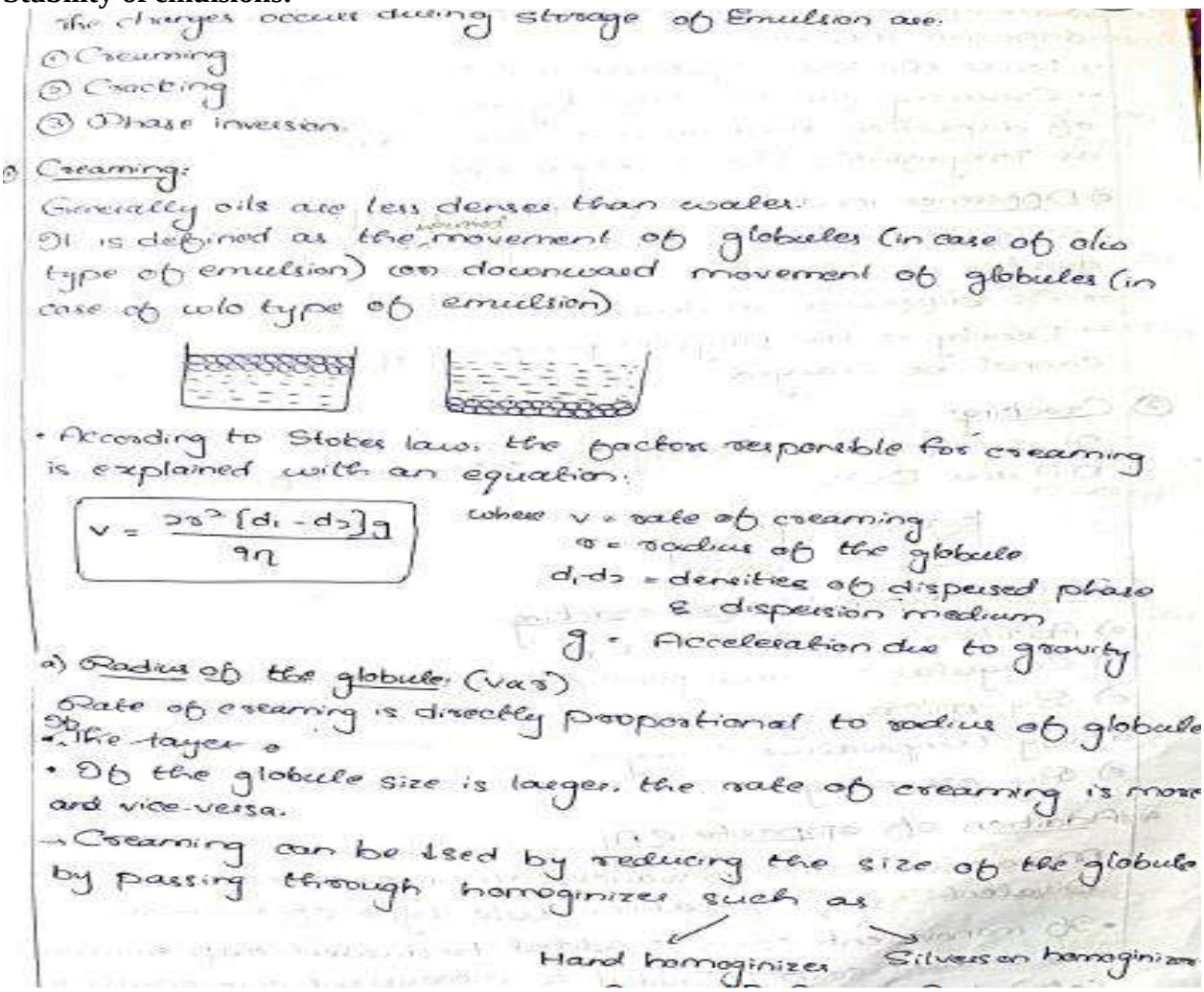
R is the molar gas constant

T is the absolute temperature

Initially both the type of emulsions are forms but the final type depends on the rate equation. If Rate 1 is greater than Rate 2 than W/O emulsion is formed. If Rate 2 is greater than Rate 1 then O/W type is formed.

Example: In case of tweens Rate 2 is faster, therefore it gives O/W type of emulsions.

Stability of emulsions:



b) Viscosity of dispersion medium: $[v \alpha \frac{1}{\eta}]$

→ Rate of creaming is inversely proportional to viscosity of dispersion medium.

→ Lower the viscosity, more will be creaming & vice-versa

→ Creaming can be lead by increasing the viscosity of dispersion medium with the addition of E.A such as Tragacanth, Starch, Agar etc.

c) Difference in densities of DP & DM: $[v \alpha d_1 - d_2]$

→ Rate of creaming is directly proportional to difference in densities of DP & DM

→ As difference in densities ↑es, rate of creaming ↑es.

→ Density is the physical property of DP & DM and cannot be changed.

② Cracking:

It is defined as complete seperation of two phases i.e, DP and D.M.

Factors responsible for cracking:

a) Addition of opposite E.A

b) Coagulation and precipitation of E.A

c) By micro-organisms

d) By temperature changes

e) By creaming

a) Addition of opposite E.A:

Monovalent soap produces o/w type of emulsion.

Divalent soap produces w/o type of emulsion.

• If monovalent soap is added to divalent soap emulsion (w/o) and divalent soap is added to monovalent soap emulsion (o/w) leads to cracking.

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b) Coagulation and Precipitation of E.A:

By coagulation: If small quantities of acid is added to alkali soap emulsion leads to coagulation of E.A results in cracking.

By precipitation: If NaCl is added to sodium soap emulsion or potassium soap emulsion leads to ppt of E.A that results in cracking.

c) By micro-organisms:

If emulsion is not preserved properly, especially if E.A is obtained from plant source leads to microbial growth which results in destruction of E.A that results in cracking.

d) By temperature change:

At high temperature:

If emulsion placed at high temperature for sufficient period of time

↓

Leads to use in viscosity of dispersion medium

↓

results in creaming

↓ prolonged creaming

Cracking

At low temperature:

If emulsion placed at low temperature for prolonged period of time

↓

Leads to freezing of aqueous phase

↓

results in cracking.

e) By creaming:

* Creamy emulsions are more liable to cracking than the stable emulsions.

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③ Phase Inversion:

It is defined as conversion of one type of emulsion to another type of emulsion i.e. o/w type to w/o type of emulsion & vice-versa

Factors responsible for phase inversion:

a) By changes in dispersed phase volume.
b) By addition of opposite E.A
c) By temperature change

Phase Inversion can be minimized by keeping the concentration of dispersed phase in between 30-60%
→ Store in a cool place with the addition of suitable EA in adequate concentration.

EVALUATION OF EMULSIONS:

① Phase seperation method
② Rheological method
③ Microscopic method
④ Electrokinetic method.

① Phase seperation method:

In this method, rate of phase seperation is used to determine the stability of emulsion.

- In this, a measured quality of emulsion is placed in centrifuge & operated at a rate of 2000 - 3000rpm.

If rate of phase seperation is high
↓
It leads to creaming
↓
Results in un-uniform dose
↓
Said to be unstable

If rate of phase seperation is low
↓
Uniform distribution of globule takes place
↓
Results in uniform dose
↓

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② Rheological method:

In this method, viscosity of the D.M is used to determine the stability of emulsion.

- Viscosity is measured by using Brook field Viscometer.

If viscosity ↓ → leads to creaming → Results in un-uniform dose → Said to be unstable

If viscosity ↑ → Difficult to pour the preparation from the container & difficult to re-disperse the globules uniformly → Said to unstable

If viscosity remains same → Globules dispersed uniformly with mild agitation → Results in uniform dose → Said to be stable.

③ Micrometric method:

- In this method, globule size is used to determine the stability of emulsion.
- Globule size is measured by / Microscopic method / Coulter counter method

If globule size ↑ → Leads to creaming → Result in un-uniform dose → Said to be unstable.

If globule size remains same → Globules dispersed uniformly with mild agitation → Results in uniform dose → Said to be stable.

④ Electrokinetic method:

In this method, zeta potential and Electrical conductivity is used to determine the stability of emulsion.

Zeta-potential:

It is measured by the migration velocity of particles with application of electric [illegible] pair of

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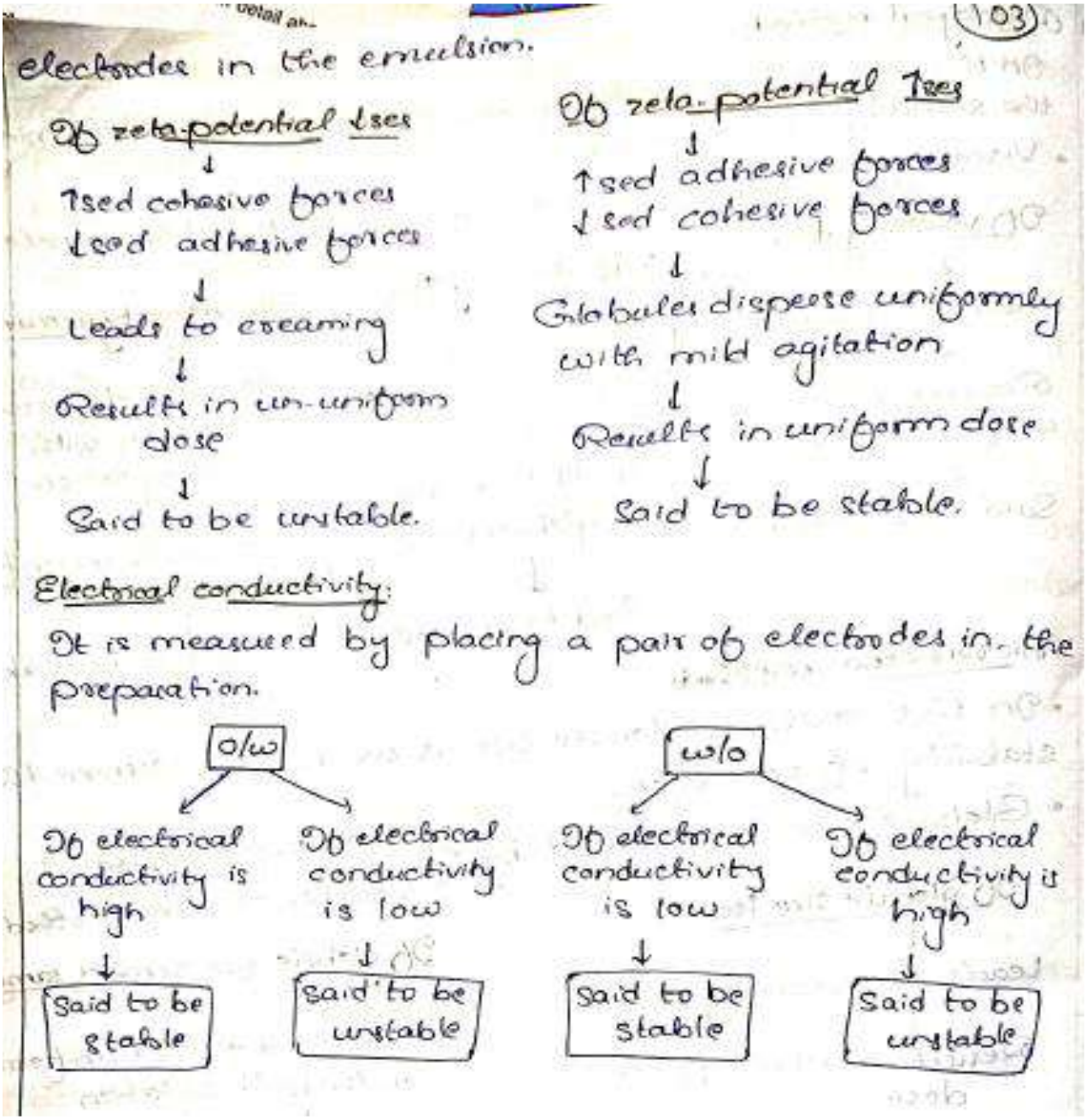


Determination of type of Emulsion:

Several methods are commonly used to determine the type of emulsion. The types of emulsion determined by one method should always be confirmed by means of second method.

(1) Dye solubility test

A small amount of a water-soluble dye (e.g. methylene blue or brilliant blue) may be dusted on the surface of the emulsion.

If water is the external phase (i.e. o/w type) then the dye will be dissolved uniformly throughout the media.

If the emulsion is of the w/o -type then particles of dye will lie in clumps on the surface.

(2) Dilution test

This method involves dilution of the emulsion with water. If the emulsion mixes freely with the water, it is of o/w -type. Generally, addition of disperse phase will crack an emulsion.

(3) Conductivity test

This test employs a pair of electrodes connected to an external electric source and immersed in the emulsion. If the external phase is water, a current will pass through the emulsion and can be made to deflect a volt-meter needle or cause a light in the circuit to glow. if the oil is the continuous phase then the emulsion will fail to carry the current.

(4) Fluorescence test:

In this the emulsion is exposed to UV radiations. If the continuous fluorescence is observed under microscope, then it is w/o type. If only spotty fluorescence is observed, then it is o/w type emulsion.

Preservation of emulsions:

Preservation from microorganism:

Emulsions are free from microbial contamination and growth. Microorganisms, such as fungi, bacteria ad yeast, use some of the ingredients (carbohydrates, proteins, sterols and gums) of the emulsion for their growth. As a result, these ingredients get digested leading to instability of the product. In case of parenteral emulsions, however, sterility of the product is essential. Preservatives, such as benzoic acid, sodium benzoate, methyl paraben and propyl paraben, are

employed in the preparation of emulsions for nonparental use. Adequate concentration of these preservatives has to be established.

The optimum concentration of a preservative is decided by considering the following features.

a. **Aqueous phase:** Bacteria are generally grown in the aqueous phase, and at the oil-water interphase. Therefore, the preservatives should partition in favour of the aqueous phase. Special care should be taken on the use of preservatives in o/w emulsions.
b. **The volume fraction of the aqueous phase:** The higher the volume fraction of the aqueous phase, the higher is the concentration of the preservative required**.**
c. **pH of the aqueous phase:** The preservatives should be in an undissociated form for its transport across the membranes of the organism. The undissociated form is effective as a bacteriostatic agent. The pH of an aqueous phase should favour the formation of the undissociated form.

   The following equation is used to calculate the concentration of preservatives

$$[HA]_w = \frac{C}{kq+1\frac{k_a}{H_3O^+}}$$

   Where C = total concentration of acid, g/ml

   $[HA]_w$ = concetration of undissociated acid in aqueous phase, g/ml

   K_a = dissociation constant of the acid

   $[H_3O^+]$= concentration of H^+ ions in the aqueous phase, mol/L

   k = partition coefficient of acid between o/w

   q = volume ratio of oil to aqueous phase.

Preservation from oxidation:

The oxygen present in atmosphere cause oxidative changes such as rancidity and spoilage. Antioxidants are used to prevent the changes occurs due to atmospheric oxygen. The ideal antioxidant should be nontoxic, nonirritant, effective at low concentration, soluble in the medium and stable. Antioxidants for use in oral preparation should also be odorless and tasteless. Some of the commonly used antioxidants for emulsified systems include alkyl gallate such as ethyl, propyl or dodecyl gallate , butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA).

Rheological Properties of Emulsions

Emulsions are evaluated for its flow behavior. The following flow related attributes are desirable for the overall performance of an emulsion:

a. Removal of an emulsion from a bottle or tube.
b. Flow of an emulsion through a hypodermic needle.
c. Spreadability of an emulsion on the skin.
d. Stress induced flow changes during manufacture.

In general, dilute emulsion exhibit Newtonian flow and the comparison of flow curves among different batches is easy. Analysis becomes complicated in case of concentrated emulsions owing to their non-Newtonian flow. Multipoint viscometers such as cone and plate or cup and bob type can be employed for evaluation.

An optimum level of viscosity is to be identified for maximum physical stability. The factors mentioned earlier, which are related to dispersed phase, continuous phase and the emulsifying agent should be considered.

Formulation of emulsions:

The formulation of emulsions are related to the selection of the aqueous phase, oil phases and type of emulgents and their relative proportions.

Selection of lipid phase:

The ingredients used for oil phase emulsions are: mineral oils, petrolatum, polyethylene waxes, vegetable oils, animal facts, lanolin, plant waxes and animal waxes.

Selection of aqueous phase:

Mostly water is used as aqueous phase. The optimum ratio of aqueous phase should be selected.

Selection of emulsifying agents/emulsifiers/emulgents:

The selection of emulsifying agents are based on the site of application i.e. either for internal or external use. The emulsifying agents are synthetic emulsifying agent/surfactants, hydrophilic colloid and finely divided solids. Non ionic and water-soluble emulsifying agents are selected for internal use while ionic and non-ionic emulsifying agents are selected for external use.

1. **Dry gum method (continental method):**
   This method is used to prepare primary emulsion from oil, water and a gum type emulsifier (gum acacia) in 4:2:1 ratio (4parts oil, 2 parts water, and 1 part emulsifier). Mortar and pestle are used to prepare emulsion.

Steps involved in preparation of emulsion are:

- 1 part gum is triturated with the 4 parts oil in a dry mortar
- Now add 2 parts water all at once
- Triturate it continuously until "crackling" sound is produced.
- At this time the primary emulsion will be creamy white.
- Then add more quantity of water to the primary emulsion
- Solid substance, if any, are added as a solution to the primary emulsion
- Oil soluble substance, in small amounts, may be incorporated directly into the primary emulsion.
- Any substance such as alcohol should be added near to the end of the process to avoid breaking the emulsion
- Transfer the primary emulsion to a calibrated vessel
- Make the final volume with water.

2. Wet gum method (English method):

In this method oil, water and a gum type emulsifier in 4:2:1 ratio (4parts oil, 2 parts water, and 1 part emulsifier), but the steps and techniques of mixing are not same. This method produces more stable emulsion

Steps involved in preparation of emulsion are:

- 1 part gum is triturated with 2 parts water to form a mucilage
- Add 4 parts oil slowly during trituration
- Continuously triturate to form the primary emulsion
- Add other ingredients, if any
- Transfer the primary emulsion to graduated cylinder
- Make the final volume with water

3. Bottle method (Forbes method):

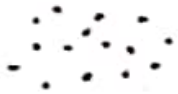
This method is used to prepare emulsions of volatile oils or substances having very low viscosities. It is not suitable for very viscous oils.

Steps involved in preparation of emulsion are:

- 1 part gum or powdered acacia is placed in a dry bottle
- 2 parts of oil are added
- Shake the mixture thoroughly after capping
- A volume of water (approximately equal to that of the oil) is added in portions
- Again, shake the mixture thoroughly until the primary emulsion is formed.
- Dilute it with proper volume of water.

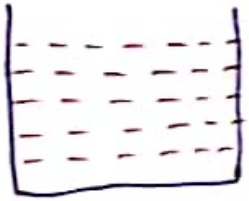
UNIT - I

Solution



Solute

↓



Monophasic

Homogerous

→ [only liquid phase]

Suspension

Solute

↓

Biphasic → [Both Solid & Liquid phase]

Non - Homogerous [Heterogenous]

Solute Size is

More than 1 μm

i.e >1000 nm

Colloidal Dispersion

Colloidal Dispersion

↓

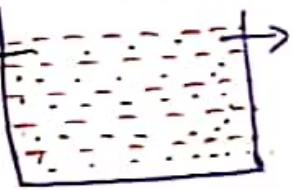
It is in between Solution & Suspension.

Solute →  → The particle size is very small.

i.e It ranges from 1 nm - 1000 nm

↓

Because of Such a small size it is not visible



→ The particles dispersed uniformly.

↓

Monophasic

↓

Homogenous

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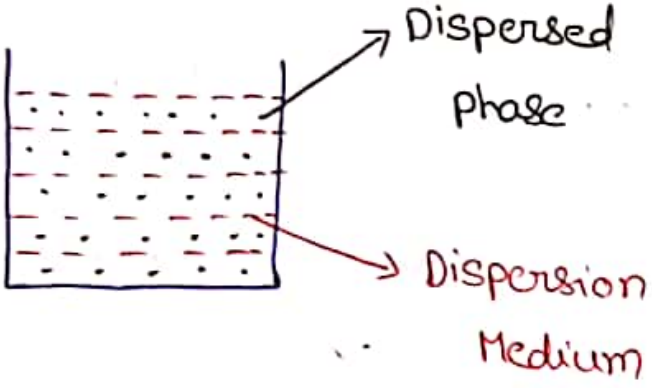
Components in Colloidal Dispersion

There are two Components They are



* Dispersed phase & Dispersion Medium Can be

Solid
(or)
Liquid
(or)
Gas.

Types of Colloidal Dispersion

Dispersed phase	Dispersion Medium	Example
Solid Colloidal Dispersion — Solid	Solid	Colloidal Gold
Solid Colloidal Dispersion — Liquid	Solid	Mineral oil in Wax
Solid Colloidal Dispersion — Gas	Solid	Solid Foam
Liquid Colloidal Dispersion — Solid	Liquid	Colloidal Gold in water
Liquid Colloidal Dispersion — Liquid	Liquid	oil Globules
Liquid Colloidal Dispersion — Gas	Liquid	Foam
Gas Colloidal Dispersion — Solid	Gas	Smoke
Gas Colloidal Dispersion — Liquid	Gas	Fog

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* Type of Colloidal Dispersion

Solid Colloidal Dispersion
Liquid Colloidal Dispersion
Gaseous Colloidal Dispersion

Depends on the type of Dispersed Medium but not Dispersed phase.

* If Dispersion Medium is Solid Then the Colloidal dispersion is Called.

Solid Colloidal Dispersion

* If the Dispersion medium is Liquid. Then the type of Colloidal Dispersion is Called.

Liquid Colloidal Dispersion

* If the Dispersion medium is Gas. Then the type of Colloidal Dispersion is Called.

Gaseous Colloidal Dispersion

∴ The type of Colloidal Dispersion depends on Dispersion Medium but not Dispersed phase.

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Colloidal Dispersion Consists of

① Dispersed phase ② Dispersion medium

↓ [Solute] ↓ [Solvent]

Classification of Colloidal Dispersion

→ Based on relationship b/n Dispersed phase & Dispersion Medium.

Lyophilic Colloids

* Lyo → means Solvent

  Solvent → Dispersion Medium

* philic → Loving.

* Lyophilic Means

  Solvent loving

  ↓

  It means Dispersion Medium loving.

Lyophobic Colloids

* Lyo → Means Solvent

  Solvent → Dispersion Medium

* phobic → Hating

* Lyophobic Means

  Solvent Hating

  ↓

  It means Dispersion Medium Hating.

Association Colloids

* In these Colloids the Dispersed phase act Smartly based on the Dispersion Medium.

* For example if the Dispersion Medium is polar Solvent.

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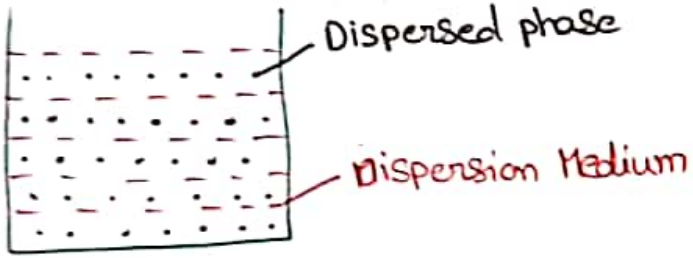
Lyophilic Colloid

* Dispersion Medium loving means
↓
Dispersed phase has Affinity [love] towards Dispersion Medium

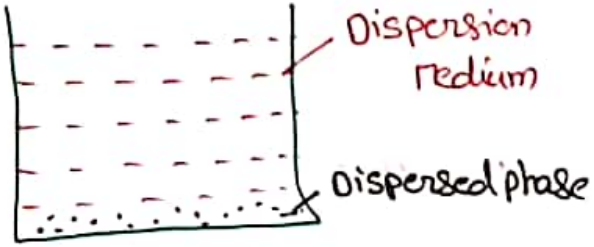


↓
It is said to be Stable Colloid.

Ex: Hydrophilic → Solvent [water]
Lipophilic → Solvent [oil].

Lyophobic Colloid

* Dispersion Medium Hating means
↓
Dispersed phase has no Affinity [Heat] towards Dispersion Medium



* It is said to be unstable.

Association Colloid

* The Dispersed Phase will become polar and dispersed uniformly.

* If the Dispersion Medium is non-polar the Dispersed phase will act Smartly as Non polar & dispersed uniformly.

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Properties of Colloids

1) optical properties
2) Kinetic properties
3) Electrical properties

optical Colloids Properties

* optical properties of Colloids Includes

1) ultramicroscopy
2) Electron Microscopy
3) Tyndall effect — ***Very Important***
4) light Scattering

Kinetic properties

* Kinetic properties of Colloid Include

Very Important

1) Brownian Motion
2) Diffusion
3) Sedimentation
4) Viscosity

Electrical properties

* Electrical properties of Colloid include

1) Effect of Viscosity
2) Electrical Double Layer
3) protective Colloid
4) Gold Number

Very Important

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1) Optical properties of Colloids

These properties helps to Known about Size, Shape, Structure & Molecular weight of Colloids.

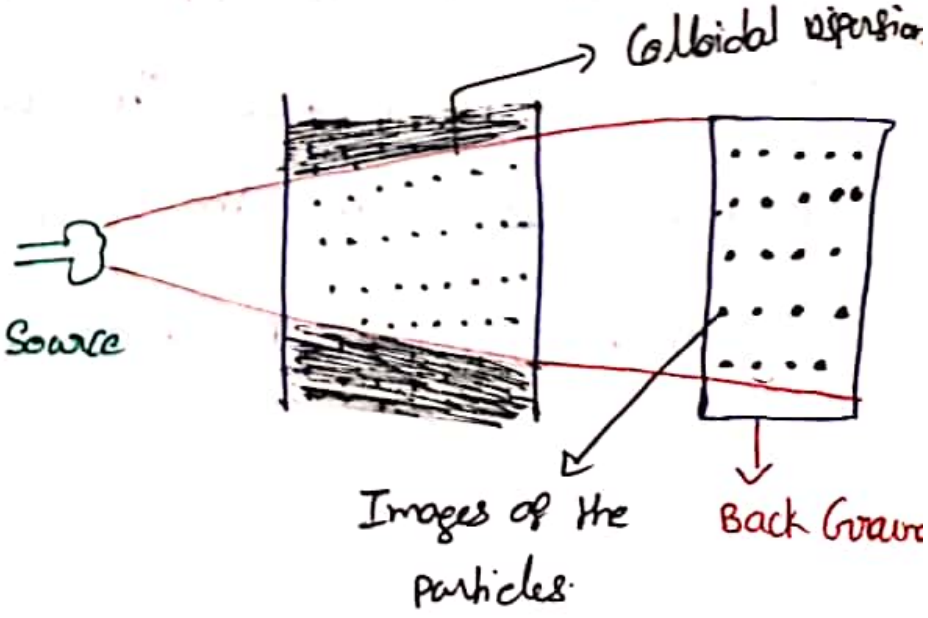
1) Tyndall effect

* When a beam of light is passed though a Colloidal dispersion, the path of the beam gets illumirated with the particles dispersed.

* A Background was placed next to the beaker Containing Colloidal dispersion in which beam of light passed.

* The images of the particles in the Colloidal dispersion was reflected on the Background.

* The images gives the information regarding Size, Shape, Structure of the particles



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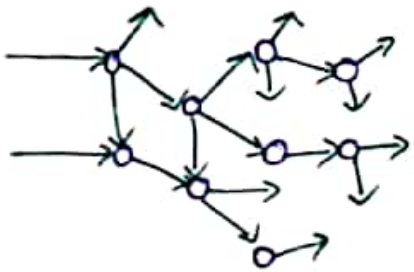
Light Scattering



In this process the light ray falls on one particle absorb the energy & start scatter the light in different directions on surrounding particles. The surrounding particles also scatter the light in different directions by absorbing the energy.

ultramicroscopy

* when a intense light beam is passed through the Colloidal dispersion through the Condensed lens.
* The Intense light beam was passed perpendicular to the optical axis of the microscope
* ultramicroscope can capture only the particles scatter light & their movements as flash agaist Black Background but structure of the particle is not resolved.

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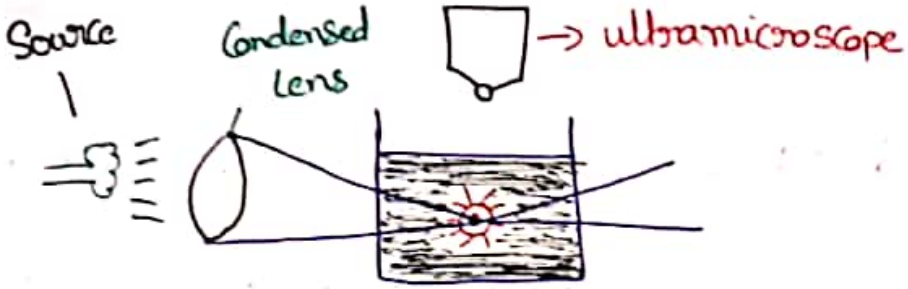


Electron Microscopy

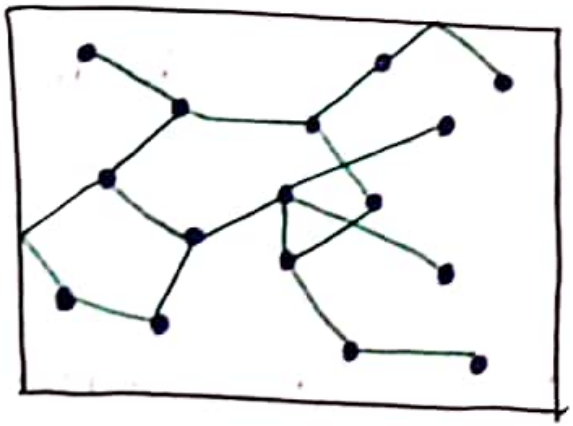
* It gives the actual picture of the Colloidal particles.
* High energy electron beam was passed.
* It is used to observe the Size, Shape & Structure of Colloidal particle.

Kinetic properties of Colloid

* These properties helps to Known about the motion of Colloidal partides in Colloidal Dispersion.

Brownian movement

* This theory was given by Scientist Robert Brown.



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* Each particle Strike with Each other and also with the walls of the Containers.

* If this happens the particles are in Continous motion and won't result in Sedimentation.

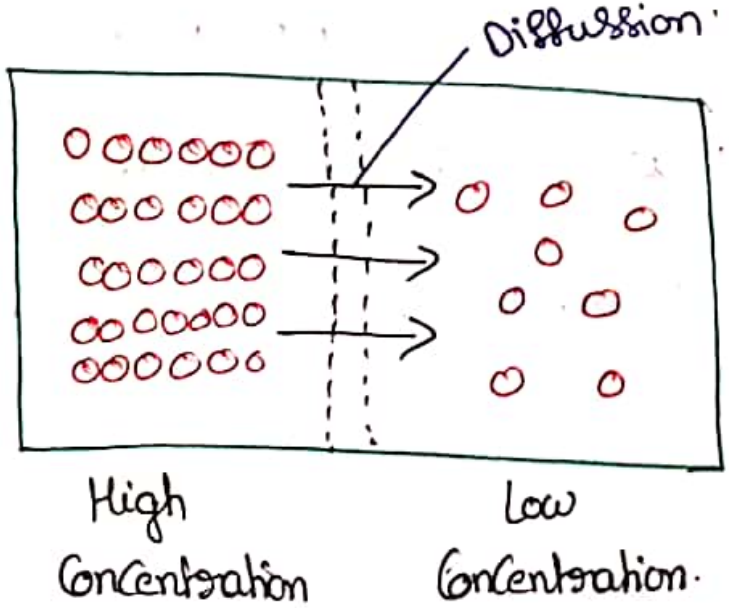
* If the Sedimentation doesn't occur then it was Said to be stable Colloid.

* If Brownian Movement ↑ — Stability of Colloid ↑

Diffusion

* It is the movement of particles from an area of higher Concentration to the area of lower Concentration.

* It is based on Ficks law that particles diffuses Continously unhill equilibrium is reached.



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Sedimentation

* It is the process of Settling down of Dispersed phase particles in Dispersion Medium due to gravity.

* Sedimentation of Colloidal particles depends on

1) Molecular weight of particles
2) Difference in the densities of Dispersed phase & Dispersed Medium

1) Molecular weight of particles

Sedimentation rate $\propto$ Molecular weight of particles

* If Molecular weight of particle Increases the Sedimentation rate also Increases and vice versa.

2) Difference in Densities of Dispersed phase & Dispersion Medium

Sedimentation rate $\propto$ Difference in Densities of Dispersed phase & Dispersion Medium

* If Brownian Motion ↑ the Sedimentation rate ↓ then the Stability of Colloid ↑.

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Viscosity

* It is the resistance to fluid to flow under an applied stress.

* It depends on

1) Size, Shape + Molecular weight

2) Interaction b/w Dispersed phase + Dispersion Medium.

* Molecular weight $\propto$ Viscosity.

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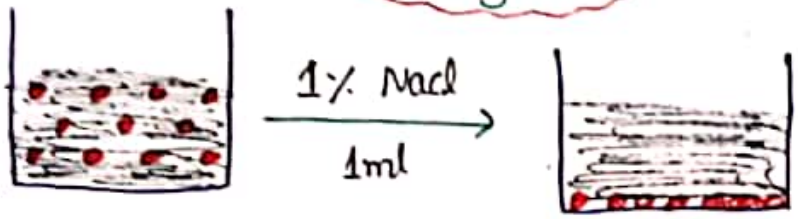
Electrical Properties

Effect of Electrolyte

Pephization

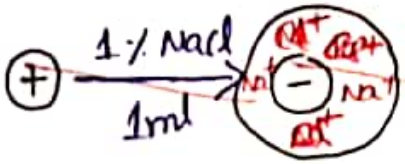


Stable Colloid → Unstable Colloid

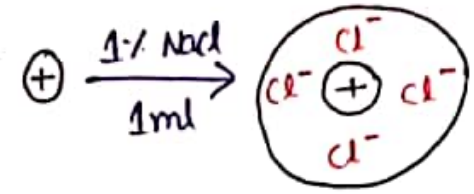
If 1% NaCl of 1ml was added to the stable colloidal dispersion where particles are dispersed uniformly leads to Sedimentation of Dispersed phase i.e particles 4 become unstable colloidal Dispersion.

Mechanism Involved

* If the charge on the Dispersed phase i.e Colloidal particle is +ve, then the -ve charge ions of electrolyte binds to the Dispersed phase.



→ leads to Increase in particle size.

* 

→ leads to Increase in particle size.

* Surround the -ve charge of the particle +ve charge electrolyte ions will binds which further increase in particle size.

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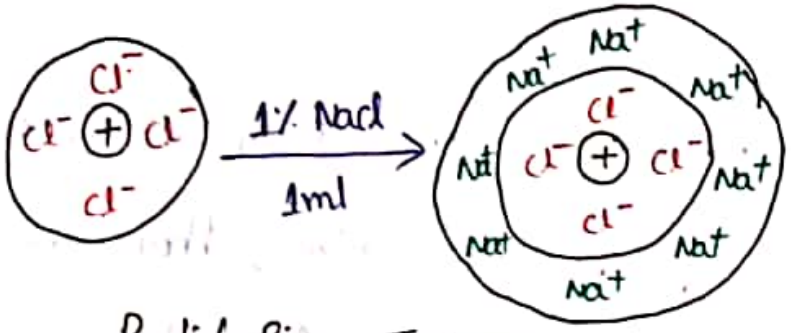
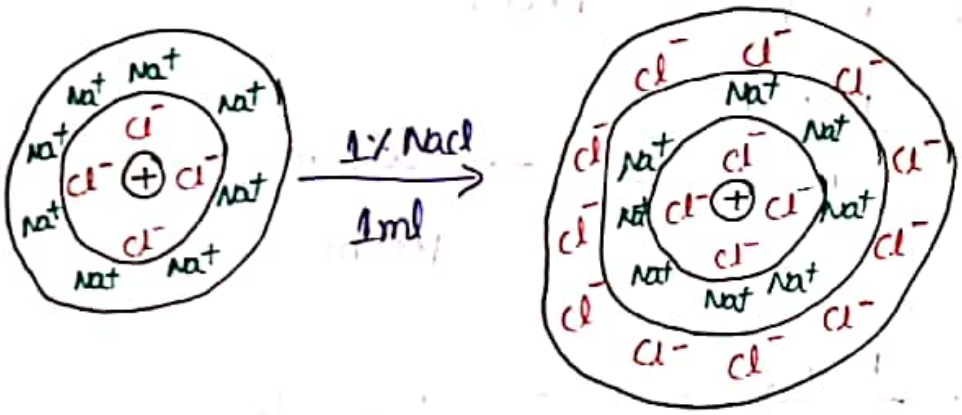


Particle Size Increases



Further Increase in particle size

* This process continues unhill the complete electrolyte added binds to the Colloidal particle.

* In this process the very important point to be observed is gradually the particle size increases which results in increase in mass of the particles.

* As we know the concept that increase in particle size & mass Results in increase in sedimentation rate

* ∴ With the addition of electrolyte the Stable Colloidal Dispersion become unstable Colloidal Dispersion.

↓

Pephization

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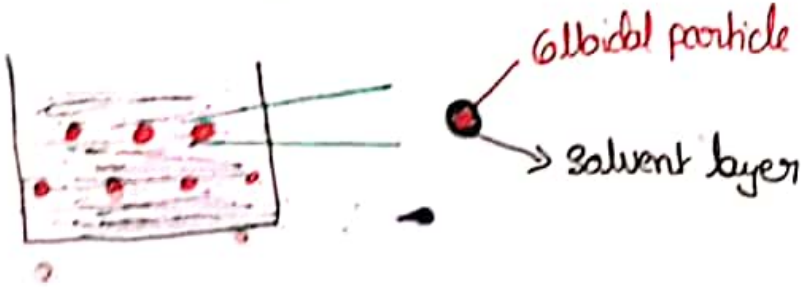
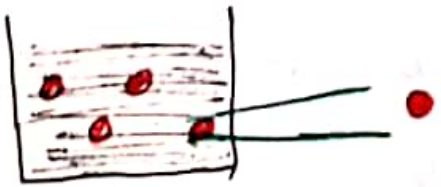
Protective Colloid

* In Case of Lyophilic Colloid which is said to be Stable Colloid where the Colloidal particle [Dispersed phase] Surrounded by Solvent molecules because the Colloidal particles are Solvent loving & forms a layer.



* In Such Case the Solvent layer which forms a layer over the Colloidal particle protects from the addition of electrolyte by increase in size leads to sedimentation & become unstable which we discussed in peptization.

* where as in Case of Lyophobic Colloid where which is said to be unstable. Colloid where the Colloidal particles [Dispersed phase] not Surrounded by the Solvent molecules because the Colloidal particles are Solvent hating



Solvent doesn't form a layer.

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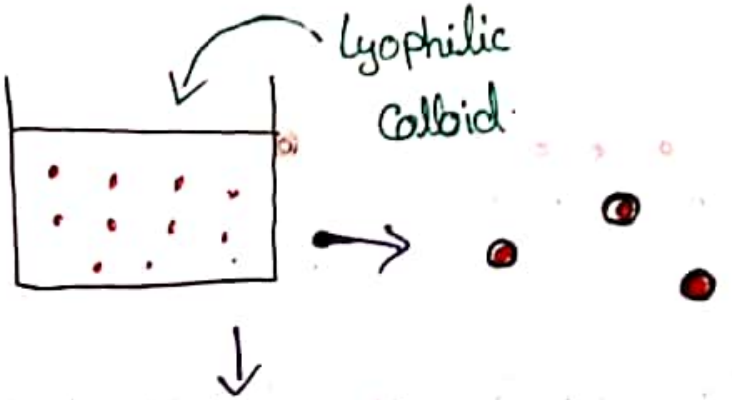
* It Says that the Colloidal particle is not protected by Solvent layer.

* In Such Case if the electrolyte is added it easily gets bind to the free Colloidal particle results in increase in size of the particle and gets Coagulated.

* Therefore in Current Concept the challange is How to protect the lyophobic Colloid from the action of electrolyte.

* It was found to be very Simple Solution that addition of lyophilic Solution to the lyophobic Colloid Colloid
where the lyophilic Colloid forms a protective layer over the Colloidal particle and protects from the electrolyte added.



↓

Not resulted in Coagulation of Colloidal particles.

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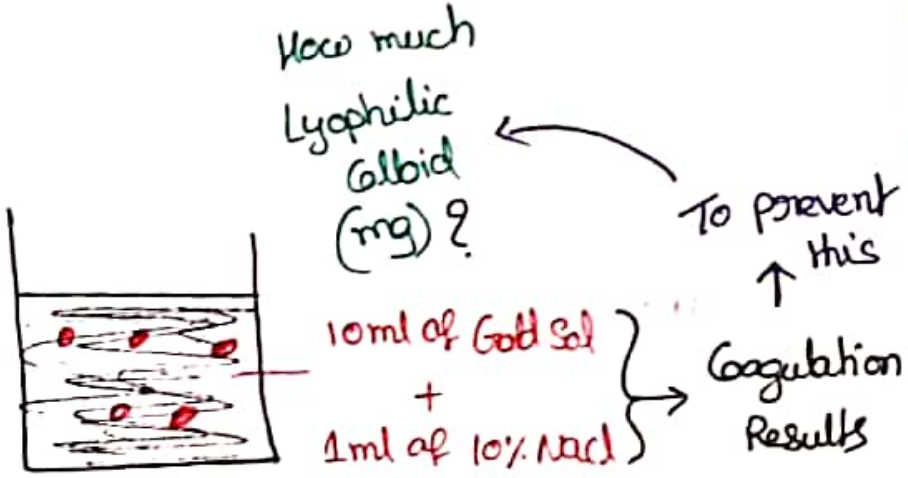
Gold Number

* The Gold number of protective Colloid is its minimum amount of in mg which is Just Sufficient to prevent the Coagulation of 10 ml of Gold Sol on the addition of 1ml of 10% NaCl Solution.

(or)

* The minimum amount of protective Colloid in mg required to Just prevent the Coagulation of 10 ml of Gold Sol on addition of 1ml of 10% NaCl Solution.



* Gold number of a protective Colloids explains the protective power of the protective Colloid.

* If Gold number is Low it means Small amount of protective Colloid is Sufficient to prevent Coagulation and Vice Versa.

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Protective Colloid [Lyophilic Colloid]

Gold Number

Gelatin	0.005 – 0.01
Casein	0.01 – 0.02
Haemoglobin	0.03 – 0.07
Egg Albumin	0.08 – 0.1
Starch	20 – 25

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Application of Colloids

1) Electrical precipitation of Smoke

* Smoke released from Industries causes air pollution
* Smoke is a colloidal solution of carbon particles, Arsenic Compounds, dust etc in air
* Now Smoke is passed through a chamber containing plates having a charge opposite to that of Smoke particles
* when the particles in Smoke comes in contact with plate results in neutralized and gets precipitated leads to settling of particles on the floor of the chamber
* ∴ This is how the dust particles are removed & release the pure air into atmosphere.

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② Purification of water:

* The water obtained from natural sources often contain suspended impurities.
* With the addition of Alum into water results in Coagulate the suspended impurities and make the water fit for drinking.

③ Medicines

* Most of the Medicines are in colloidal in nature ②

Ex: Eye lotion
Milk of Magnesia

* Medicines are more effective in colloidal dispersions because of its increased surface area.
* As the surface area increases the effectiveness of the medicine also increases.

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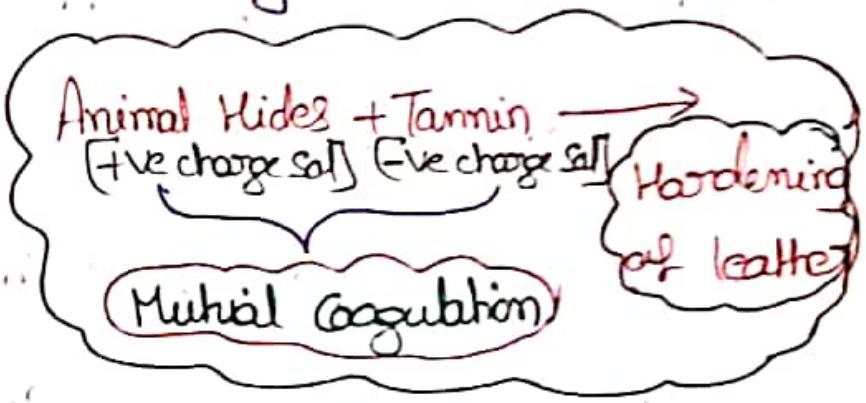
4) Tanning of leather

* leather is made up of Animal hides.
* Animal hides are Colloidal in nature
* Animal hide is having positive charge when it is soaked in Tannin having Negative charge.
* Because of opposite charge mutual Coagulation takes place results in Hardening of leather.
* This process is called. Tanning of leather.



5) Rubber Industry

* Rubber is getting from rubber tress which gives latex
* This latex is Colloidal solution of Rubber particles

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which are negatively charged.

Ex :- Paint
Ink
Cement
Graphite

* The Hardening of rubber particles in latex is done by Coagulation of rubber particles with the addition of oppositely charged Coagulant.

* These hardened rubber is used in preparation of tyres

(6) Industrial products

* A large number of Industrial products are Colloids.

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DEFORMATION OF SOLIDS

Definition: It is defined as change in the size and shape of an object. When loads are applied to a body, some deformation will occur resulting to a change in dimension.

Stress:

Stress (σ) is the force per unit area that applies to an object to deform it.

Stress (σ) = Force / Area (F/A)

Its unit is N/m or Pa

Type of Stress

There are three type of stress

1. Direct stress
2. Indirect stress
3. Combined stress

1. Direct stress: These stresses produced under direct loading condition i.e force will be in line with the axis of member. Based on the type of force acting on the body, it may be tensile or compressive or shear stresses.

a. Tensile stress: It is defined as tensile force acting per unit area of the body. It is that type of force which produce extension or elongate the dimension of the body. These forces will be in line with the axis of member. The tensile stress is the ratio of change in length to the original length.

b. Compressive stress: It is defined as compressive force acting per unit area of the body. In this the forces applied is opposite to each other. It is that type of force which compress the dimension of the body.

c. Shear stress: It is defined as shear force acting per unit area of the body. When we applied load on the surface of the 'body. Due to this body develop some resistive force which is parallel to each surface but opposite to direction of force applied.

2. Indirect stress: These stress occur due to torque produced in the body.

3. Combined stress: These stress are the combination of above type of stress.

Strain:

Strain (Ɛ) is the measure of the amount of deformation- If the bar has original length (L) and when the load is applied on a bar the length of bar will change which is indicated as (AL)

$$\text{Strain } (Ɛ) = \Delta L / L$$

It has no unit.

Type of Strain:

1. Tensile strain: It is defined as ratio of increase in length to original length of bar.

2. Compressive strain: It is defined as ratio of decrease in length to original length of bar.

3. Shear strain: The strain produced by shear force is called shear strain.

Elastic modulus:

It is the ratio of stress to strain. It is expressed as

Elastic modulus = stress / strain

The constant of proportionality depends on the material being deformed and the nature of the deformation. This constant is called the elastic modulus. The elastic modulus determined the amount of force required per unit deformation. A material with large elastic modulus is difficult to deform, while one with small elastic modulus is easier to deform.

Hooke's law:

This law states that, "in an elastic member stress is directly proportional to the strain within elastic limit".

$$\sigma \alpha \varepsilon$$

$$\sigma = E.\varepsilon \text{ or } E = \sigma / \varepsilon$$

Where,

E is constant known as modulus of elasticity or Young's modulus (Its unit is N/m^2)

σ is stress

ε is strain

Young's modulus will help to identify how much the material is elastic.

The elastic limit of a substance is defined as the maximum stress that can be applied to the substance before it deforms permanently.

Initially, a stress—strain curve is a straight line. As the stress increases, the curve is no longer straight. When the stress exceeds the elastic limit, the object is permanently distorted and does not return to its original shape after the stress is removed. Hence, the shape of the object is permanently changed. As the stress is increased even further, the material ultimately breaks.

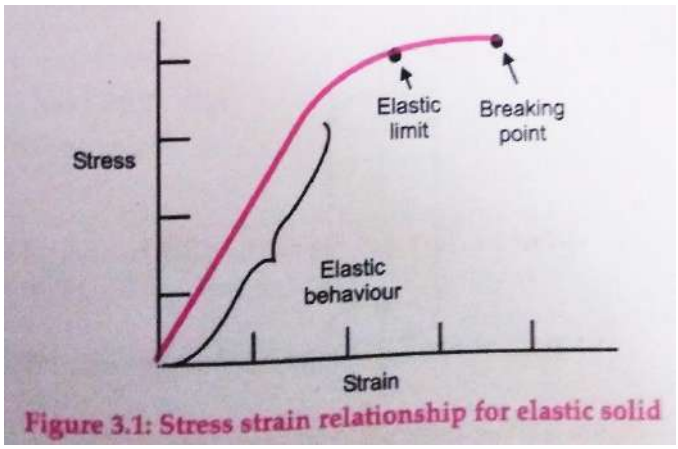


Figure 3.1: Stress strain relationship for elastic solid

Stress strain relationship for elastic solid

Poisson's Ratio

When a material is loaded within elastic limit, the ratio of lateral strain to linear strain remain constant. This phenomenon is called Poisson's ratio. It is denoted by μ.

Mathematically,

μ = lateral strain / linear strain

$\mu = e_L / e$

Its value ranges from 0.1 to 0.5.

If we have a rod having diameter d and length l. When we apply pull type of load on both side of rod. Due to this length will increase but diameter will decrease. This is called linear strain. In linear strain the load is parallel to length while lateral strain is perpendicular to linear strain. Therefore, linear strain will be positive due to increase in length while lateral strain will be negative due to decrease in diameter.

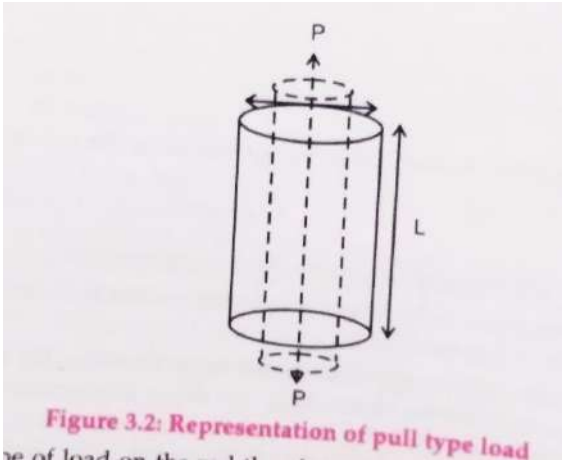


Figure 3.2: Representation of pull type load

Representation of pull type load

If we apply push type of load on the rod then length decrease and diameter increase. So, in this case linear strain will be negative while lateral strain will be positive,

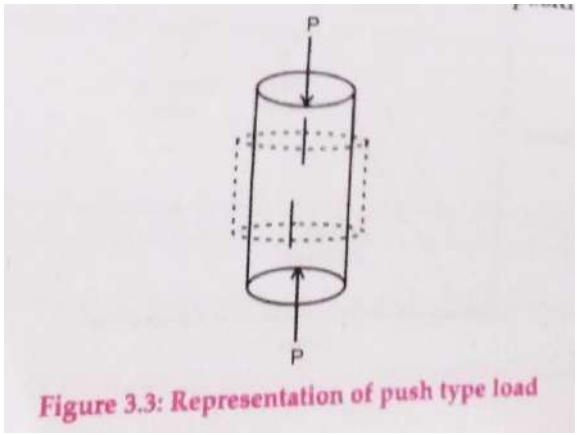
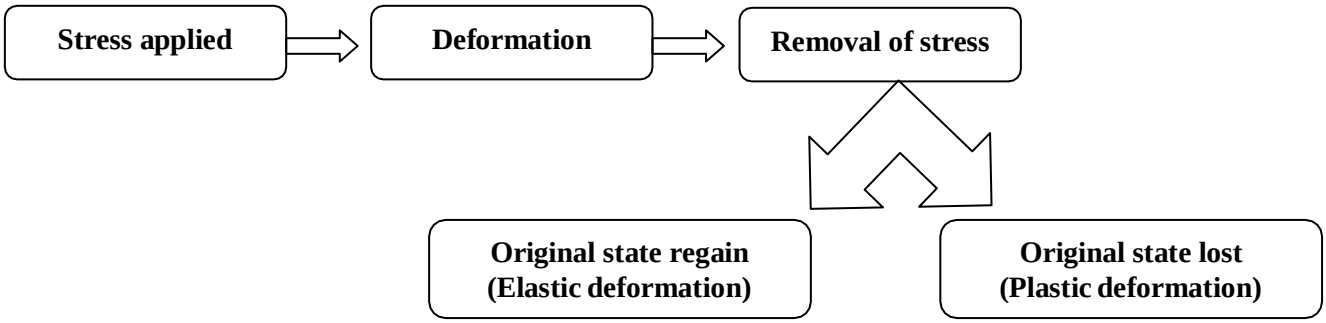


Figure 3.3: Representation of push type load

Representation of push type load

Types of deformation:



Elastic Deformation

When a load is applied and removed, no permanent deformation has occurred. It is a reversible process. The material return to its original shape when force is removed. Such type of behaviour is seen metals, ceramics, rubbers and polymers.

Elastic deformation in a solid can take place due to change in pressure, or by an application of force or load. Elasticity depends on depends on both the chemical bonding and the structure of solid.

The deformation is said to be an ideal deformation which takes place instantaneously upon application of or load and disappears completely on removal of the force or load. Such deformations in a solid materials obey Hooke's law. Ideal deformation occurs with comparatively smaller deformation forces.

Plastic Deformation

The material does not return to its original shape when force is removed. It is irreversible phenomenon. In this permanent deformation occurred. Plastic deformations in a sold materials do not obey Hooke's law. Progressive, permanent deformation under constant load is called creep.

For visco-elastic materials, both recoverable and permanent deformations occur together which are dependent on time. When force is applied to a material, it experiences elastic deformation followed by plastic deformation. The transition from elastic state to plastic state is characterized by the yield strength of the material.

Plastic deformation mechanism is different for crystalline and amorphous materials. For crystalline materials, deformation is accomplished through a process called slip that involves motion of dislocations. In amorphous materials, plastic deformation takes place by viscous flow mechanism in which atoms or ions slide past one another under applied stress without any directionality.

The ability of metals to undergo plastic deformation is called ductility.

Difference between Elastic and Plastic deformation

Elastic deformation	Plastic deformation
The material return to its original shape when force is removed.	The material does not return to its original shape when force is removed.
It is reversible	It is Irreversible
In this, no permanent deformation occurred	In this, permanent deformation occurred
In elastic deformation the chemical bonds of substance undergo stretching and bending	In elastic deformation some of the chemical bonds of substance undergo breakage
It is time dependent	It is time in-dependent
It occurs in metals within elastic limits	It occurs beyond plastic limits

Heckel Equation:

The Heckel equation is mostly useful for estimating the volume reduction under the compressional pressure.

As tablets are the most common dosage platform understanding the deformation behaviour of the individual components. The Heckel analysis is a most useful method for estimating the volume reduction under the compression pressure in pharmacy.

Heckel plots can be affected by the time of compression, the degree of lubrication and size of the die. The effects of these variables should be taken into consideration.

The basic assumption of Heckel equation is that the densification of the bulk powder on applying force obeys first-order kinetics. The Heckel equation is expressed as;

$$\ln [1/1-D] = KP + A$$

Where

D is the relative density of the tablet which is the ratio of tablet density to true density of powder, P is pressure, and K is the slope of straight-line portion of the Heckel plot.

A is the constant representing the rearrangement of particles.

Significance of Heckel Plot

1. The crushing strength of tablets is also correlated with the values of k of the Heckel plot.
2. Larger k values indicate harder tablets.
3. The knowledge of this can be used to select binder during designing of tablet.

KINETICS

The rate, velocity or speed of a reaction is given by ± (dc/dt). Here dc is the small change in the concentration within a given time interval dt.

Pharmacokinetics is the mathematical analysis of process of ADME. The movement of drug molecules from the site of application to the systemic circulation, through various barriers, their conversion into and other chemical from and finally their exist out of the body can be expressed mathematically by the rate at which they proceed, the order of such processes and the rate constants.

The velocity with which a reaction or a process occurs is called as its rate. Consider the following chemical reaction:

Drug A $\longrightarrow$ drug B

The rate of forward reaction is expressed as;

$$\frac{-dA}{dt}$$

Negative sign indicates that the concentration of drug A decreases with time t. As the reaction proceeds, the concentration of drug B increases and the rate of reaction can also be expressed as:

$$\frac{dB}{dt}$$

Experimentally, the rate of reaction is determined by measuring the decreases in concentration of drug A with time t.

The manner in which the concentration of drug influences the rate of reaction or process is called as the order of reaction or order of process. If C is the concentration of drug A, the rate of decreases in C of drug A as it is changed to B can be decreased by a generally expression as a function of time t.

$$dc/dt = - KC^n$$

where, k = Rate constant

n = order of reaction

If n= 0, it's a zero – order process, if n= 1, it is a first-order process and so on.

***Molecularity*:** It is the number of atoms, molecules or ions colliding simultaneously to give the products. Unlike the order of reaction, it has only integral values.

Unimolecular Reaction: This reaction involves only one molecule.

Eg : Cis - Lactic acid $\longrightarrow$ Trans - Lactic acid.

Bimolecular Reaction: This involves reaction between two molecules

Eg : $H_2 + I_2 \longrightarrow 2HI$

Trimolecular Reaction: These reactions which involve more than two molecules and are rarely occur.

Zero Order Reaction:

Zero order reaction is defined as a reaction in which the rate does not depend on the concentration terms of the reactants. i.e. the rate of reaction cannot be increased further by increasing further by increasing the concentration of reaction.

Examples:

1. Colour-less of liquid multisulfonamide preparation. Colour-loss is proportional to decreases in the concentration.
2. Oxidation of vitamin A in an oily solution.
3. Photochemical degradation of chlorpromazine in aqueous solution.
4. Administration of a drug as a constant rate i.v. infusion.
5. Controlled drug delivery such as that from i.m. implants or osmotic pumps.

$$dc/dt = - K. C^n$$

$$dc/dt = - K_0 C^0 = -K_0$$

Rearranging the above equation

$$dc = - K_0 \, dt$$

Integrating on both sides

$$C - C_0 = - K_0 t$$

Or

$$C = C_0 - K_0 \, t$$

C_0 = Concentration of drug at t = 0,

C = Concentration of drug to undergo reaction at time t

Half life:

It is the time required for the concentration of the reactant to reduce to half of its initial concentration.

The half-life equation can be derived as follows.

When $t = t1/2$, $C = C_0/2$

$$C_0/2 = C_0 - K_0 . t1/2$$

$$C_0/2 - C_0 = -K_0 . t1/2$$

$$-K_0 . t1/2 = \frac{C_0 - 2C_0}{2}$$

$$K_0 . t1/2 = C_0/2$$

$$t1/2 = C_0/2K_0$$

Shelf life:

It is defined as the time required for the concentration of the reactant to reduce to 90% of its initial concentration.

Shelf life is represented as t_{90} and the units of time/conc. the shelf life equation can be derived as follows.

$$C = 90C_0/100 = 0.9 \, C_0 \qquad \boxed{t = t_{90}}$$

Substitute the above values in

$$K_0 = \left[\frac{C_0 - C}{t}\right]$$

$$K_0 = \frac{C_0 - 0.9\,C_0}{t_{90}}$$

$$t_{90} = \frac{0.1\,C_0}{K_0}$$

First order kinetics:

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

$$dc/dt = -K_1C \quad \ldots\ldots\ldots\ldots 1$$

By rearranging the above equation

$$dc/c = -K_1dt$$

Integrating on both sides at concentration C_0 at time t = 0 and concentration C_t time t = t

$$\int_{Co}^{Ct} dc/c = -K \int_{0}^{t} dt$$

$$[\ln C]_{C0}^{Ct} = -K_1[t]_0^t$$

$$\ln C_t - \ln C_0 = -K_1\,[t - 0]$$

$$\ln C_t = \ln C_0 - K_1t \ldots\ldots\ldots\ldots 2$$

Converting eq 2 into logarithm to the base 10

$$\text{Log } C_t = \log C_0 - K_1t/2.303 \ldots\ldots\ldots\ldots 3$$

By rearranging eq 3

$$K_1 = 2.303/t \log C_0/Ct$$

Half life:

It is the time required for the concentration of the reactant to reduce to half of its initial concentration.

The half life equation can be derived as follows.

$$\log C = \log C_0 - K_1t/2.303$$

Substituting $C = C_0/2$, $t = t\,½$

$$K_1 = \frac{2.303}{t1/2} \log \frac{C_0}{C_0/2}$$

$$t1/2 = \frac{2.303}{K_1} \log 2$$

$$\frac{2.303 \text{ X } 0.3010}{K_1}$$

$$\frac{0.693}{K_1}$$

Shelf life:

It is defined as the time required for the concentration of the reactant to reduce to 90% of its initial concentration.

Shelf life is represented as t_{90} and the units of time/conc. the shelf life equation can be derived as follows.

$$C_t = \frac{90}{100} C_0$$

By substituting this in $K = \frac{2.303}{t} \log \frac{C_0}{C_t}$

$$t_{90} = \frac{2.303}{K_1} \log \frac{C_0}{0.9\, C_0}$$

$$t_{90} = \frac{2.303}{K_1} \log \frac{10}{9}$$

$$\frac{2.303 \times 0.04575}{K_1}$$

$$\frac{0.105}{K_1}$$

Second order:

Second order reaction is defined as a reaction in which the rate depends on the concentration terms of two reactants each raised to the power one.

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

$$- \frac{dA}{dt} = - \frac{dB}{dt} = K_2 [A]^1 [B]^1$$

Let a and b are the initial concentrations of A and B and x be the concentration of each species reacting in time t

$$\frac{dx}{dt} = K_2 (a-x) (b-x) \ldots\ldots\ldots\ldots\ldots 1$$

If a = b then

$$\frac{dx}{dt} = K_2 (a-x) (a-x)$$

$$\frac{dx}{dt} = K_2 (a-x)^2 \ldots 2$$

Integrate of eq 2 x= 0, t= 0 and x = x at t= t

$$\int_0^x \frac{dx}{(a-x)^2} = K_2 \int_0^x dt$$

$$\frac{1}{-(a-x)}_0^x - 1 = K_2 [t]_0^t$$

$$\left(\qquad \right)$$

$$\frac{1}{(a-x)} - \frac{1}{a-0} = K_2 (t-0)$$

$$\frac{a-a+x}{a\,(a-x)} = K_2 t$$

$$\frac{x}{a(a-x)} = K_2 t$$

$$K_2 = \frac{x}{a-x} \cdot \frac{1}{at}$$

If $a \neq b$

$$K_2 = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

Half life:

$K_2 = \frac{1}{at} \cdot \frac{x}{a-x}$

Put $(a - x) = a/2$, $t = t1/2$ and $x = a/2$ in above equation

$K_2 = \frac{1}{a.t1/2} \cdot \frac{a/2}{a/2}$

$K_2 = \frac{1}{a.t1/2}$ 3

$t1/2 = 1/ak$

Order of reaction	Equation	Half life	Shelf-life
Zero order	$C = C_0 - K_0 t$ Or $C - C_0 = - K_0 t$	$t1/2 = C_0/2K_0$	$t_{90} = \frac{0.1\ C_0}{K_0}$
First order	$K_1 = \frac{2.303}{t} \log \frac{C_o}{Ct}$	$t1/2 = \frac{0.693}{K_1}$	$t_{90} = \frac{0.693}{K_1}$
Second order	$K_2 = \frac{x}{a-x} \cdot \frac{1}{at}$ if $a \neq b$ $K_2 = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$	$t1/2 = \frac{1}{ak}$	----

Apparent or Pseudo zero order reaction:

Pseudo zero order is a reaction, which may be a first order, but behaves like a zero order, depending on the experimental conditions.

In suspensions, drug degradation is a chemical reaction and follows an apparent (or pseudo) zero order reaction. Here, the rate of degradation depends on solubility. The phenomenon of solubility-limited degradation can be explained as follows:

In suspensions, a part of the drug is in solution-phase and remaining part is present as undissolved solid. Degradation is possible only when the drug is available in solution-phase. As soon as the drug in solution degrades, suspended particles act as a reservoir and continuously release the drug into solution. Thus, the concentration of the drug in solution will remain constant during this process. Therefore, the degradation rate follows a zero-order reaction.

When there is no reservoir of solid, the drug is in solution form and follows a first order pattern. In this situation, rate equation can be written as:

$$\frac{-d[A]}{dt} = K_1[A]$$

Where [A] is the concentration of undecomposed drug at time t, and K_1 is the first order rate constant. When [A] is maintained constant due to reservoir of solids in the suspension, the rate equation changes

$$\frac{-d[A]}{dt} = K_1 \text{ X constant } = K_0$$

In above equation the term constant is is equal to intrinsic solubility of the drug.

Pseudo first order reaction:

Pseudo first order reaction 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. Therefore the rate equation would be

$$\frac{-dc}{dt} = K_2 [A][B]$$

Where A and B reactants in the reaction and K_2 is the second order rate constant. The reaction conditions are maintained in such a manner that one reactant (say B) is present in large excess compared to the concentration of the other substance (say A). Therefore, the concentration of 'B' does not change significantly during the course of the reaction. Then above equation changes to

$$\frac{-dc}{dt} = K_2 [A][\text{constant}] = K_1 [A]$$

Thus rate depends on the concentration of one reactant (on A), i.e., first order reaction. This type of reaction is also termed as apparent first order.

Examples:

1. Base-catalyzed oxidative degradation of prednisolone in aq. solution.
2. Hydrolysis (inversion) of sucrose to glucose and fructose in aq. Solution catalysed by acid. (water is in large excess).
3. Acid catalysed hydrolysis of erythromycin oxime.
4. Acid catalysed hydrolysis of digoxin.

Differences between order and molecularity

Order of a reaction	Molecularity of a reaction
It is the sum of powers of the concentration terms in the rate law expression	It is the number of reacting species undergoing simultaneous collision in the elementary or simple reaction
It is an experimentally determined value	It is a theoretical concept
It can have fractional value	It is always a whole number
It can assume zero value	It cannot have zero value
Order of reaction can change with the conditions such as pressure, temperature, concentration.	Molecularity is invariant for a chemical equation

Determination of Order:

1. ***Substitution Method:*** In this method different initial concentrations of the reactant (a) are taken. The values of concentration (a - x) at regular intervals of time (t) were noted. These values a, (a - x) and t thus obtained from the experiment are substituted into the integrated rate equations for the first, second and third order. The equation that yields a constant value of K corresponds to the order of the reaction.
2. ***Half-life Method:*** In this method half-life is determined as a function of concentration. The order is considered as unity if the half-life is independent of concentration. The Half-life of a reaction is inversely proportional to the concentration term raised to the power (n - 1), where n = order of reaction.

So, half-life $\alpha \frac{1}{[A]}$ (for 2nd order reaction)

half-life $\alpha \frac{1}{[A]^2}$ (for 3rd order reaction)

For a η^{th} order reaction.

half-life $\alpha \frac{1}{[A]^{n-1}}$

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

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

or in logarithmic form finally we will get

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

The rate and half life equations are given in Table 8.1.

(c) ***Graphical Method :*** As seen earlier for first order reaction the rate reaction is

$$\ln \frac{C_o}{C_1} = k_1 t$$

(or)

$$\ln (C_t) = \ln (C_o) - kt$$

$$y = C - mx.$$

So for the values of two variables $\ln \frac{C_o}{C_1}$ (vs) t if, we obtain a straight line then the corresponding reaction is said to be first order. If a curve is obtained then the reaction is not a first order reaction.

For second order similarly we plot for values of $\frac{1}{(a-x)}$ versus t.

The line obtained has equation

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

$$y = mx + c.$$

In case if we get a curve for values of $\frac{1}{(a-x)}$ versus t then it is not a second order reaction.

If straight line obtained then it is second order reaction. When a plot of $\frac{1}{(a-x)^2}$ aganist t produces a straight line, with all reactants at the same initial concentration, the reaction is third order.

(d) ***Ostwald's Isolation Method :*** This method is generally useful for determining the order of complex reaction whose rate is influenced by more than two ingredients.

Lets consider the reaction

$$A + B + C \rightarrow \text{products}$$

The order of reaction with respect to three reactants is given by

$$n = n_A + n_B + n_C$$

n_A is determined by taking B and C in excess concentration. Similarly n_B is determined by taking A and C in excess and so can be determined n_C.

(e) ***Van't Hoff's Differential Method :*** The rate of a reaction of n^{th} order is directly proportional to the concentration term raised to n^{th} power.

$$\frac{-dc}{dt} = KC^n$$

For two experiments with different initial concentration we can write the rate of reactions as

$$\frac{-dc_1}{dt} = KC_1^n \qquad .....(8.12)$$

$$\frac{-dc_2}{dt} = KC_2^n \qquad .....(8.13)$$

Applying log to both equations

$$\log\left(\frac{-dc_1}{dt}\right) = \log K + n \log C_1 \qquad .....(8.14)$$

$$\log\left(\frac{-dc_2}{dt}\right) = \log K + n \log C_2 \qquad .....(8.15)$$

Subtracting Eq. (8.15) from Eq. (8.14) we get,

$$n = \frac{\log\left(\frac{-dc_1}{dt}\right) - \log\left(\frac{-dc_2}{dt}\right)}{\log C_1 - \log C_2}$$

So, in order to calculate the value of n, one should plot the values of concentration and time on y-axis and x-axis respectively.

The slope $\frac{-dc}{dt}$ is found by drawing tangent at a given time internal.

DRUG STABILITY:

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

Expiry date: means that drug can not be used after this date because the concentration of drug is decreased and become lower than therapeutic concentration. In addition, some products of drug degradation is toxic and harmful to patients.

Physical Degradation:

Definition:

Degradation, which results into the change of physical nature of the drug."

Types:

Types of physical degradation are as under

- Loss of volatile components
- Loss of H_2O
- Absorption of H_2O
- Crystal growth
- Polymorphic changes
- Colour changes

1. Loss of volatile components:

Volatile components such as Alcohol ether Iodine volatile oils Camphor menthol etc. escape from the formulations.

e.g.

Nitroglycerine from drugs evaporates.

Preventive measures: keeping the product in well closed containers and storing in a cool place.

2. Loss of water:

Loss of water from o/w emulsions thus its stability changes.

· Water evaporates causing the crystalline growth.

· This will result into increase in potency & decrease in weight.

This tendency depends on temp. and humidity of surrounding environment.

e.g. water evaporates from efflorescent salts such as Na_2SO_4, borax

Preventive measures: keeping the product in well closed containers and storing in a cool place.

3. Absorption of H_2O:

Hygroscopic drugs absorb the water from external atmosphere causing the physical degradation.

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.

Preventive measures: products stored in air tight containers amd keeping in a cool place.

4. Crytsal growth:

In solutions after super saturation crystal growth occurs. Reason may be the fall in temp and a consequent decrease in solubility of solute

e.g.

· Injection of calcium glucconate

· In suspensions crystals settle down and caking occurs and suspension becomes unstable.

Preventive measures: a. A part of calcium gluconate is replaced by calcium saccharate.

b. Selecting suitable storage conditions to reduce fluctuations in ambient temperature.

5. Polymorphic Changes:

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.

Preventive measures: suspending agents such as methyl cellulose are added to prevent the conversion owing to enhanced viscosity and limited diffusion of drug molecules.

6. Colour changes:

Colour changes are of two types.

1. Loss of colour
2. Development of colour

- Loss of colour is due to pH change and presence of reducing agent.
- Development of colour is due to exposure to light

Preventive measures: · 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.

Chemical Degradations:

Decomposition of active ingredient in pharmaceutical dosage forms can occurs through several phathways i.e., hydrolysis, oxidation-reduction, racemization, decarboxylation, ring cleavage and photolysis. Most frequently encountered are hydrolysis and oxidation-reduction.

(A) Hydrolysis : Many pharmaceuticals contain ester or amide functional groups which undergo hydrolysis in solution. Examples of drugs are – Anesthetics, antibiotics, vitamins and barbiturates.

(i) ***Ester hydrolysis :*** Hydrolysis of an ester into a mixture of an acid and alcohol involves rupture of a covalent linkage as given below.

$$R_1 - \underset{\underset{\text{Ester}}{}}{\overset{\overset{O}{\|}}{C}} - OR + H^+ + OH^- \rightarrow R_1 - \underset{\underset{\text{Acid}}{}}{\overset{\overset{O}{\|}}{C}} - OH + HOR \quad \underset{\text{Alcohol}}{}$$

Majority of hydrolysis reactions takes place in presence of a catalyst [catalysts are mineral acids, alkalies or acids etc]. Examples of drugs degrade through ester hydrolysis are procaine, atropine, methyl p–aminobenzoate etc.

Methods to enhance the stability of pharmaceuticals undergoing ester hydrolysis are –

(a) *pH :* If physiologically permissible, the pH of a formulation should be as close as possible to its pH of optimum stability.

(b) *Type of Solvent :* Partial or full replacement of water with a solvent of lower dielectric constant reduces the velocity of hydrolysis. Ex : ethanol, glycols, glucose, mannitol solutions.

(c) *Complexations :* Complex formation, example – caffeine with benzocaine decreases the velocity of reaction. Similarly caffeine complexes with local anesthetics such as procaine, tetracaine, can reduce the velocity of hydrolytic degradation.

(d) *Surfactants :* It has been observed that nonionic, cationic and anionic surfactants stabilize the drug against hydrolysis. A 5 % sodium lauryl sulphate (anionic) causes 18-fold increase in the half life of benzocaine.

(e) *Modifications of chemical structure :* Certain substitutes added to the alkyl or acyl chain of aliphatic or aromatic esters decreases the hydrolytic rate.

(ii) ***Amide Hydrolysis :*** Pharmaceutical compounds containing amide group can undergo hydrolysis. In the amide hydrolysis acid and amine are formed as given below;

Amide Acid Amine

Similar methods are used to protect compound from amide hydrolysis, as given under ester hydrolysis.

(B) ***Oxidation-Reduction :*** A number of pharmaceutical compounds undergo oxidative reaction includes vitamins, steroids, antibiotics, epinephrine etc. These reactions are mediated either by free radicals or by molecular oxygen.

Common form of oxidation is autoxidation; and is defined as the reaction of any material with molecular oxygen. This may be given as follows:

$$A : B \rightarrow A^{\cdot} + B^{\cdot}$$

$$CH_3 : CH_3 \rightarrow 2\,CH_3^{\cdot}$$

These are free radicals and are highly unsaturated and readily takes electrons from other substances causing oxidation. Autoxidation may be described as follows:

Initiation

$$RH \xrightarrow[\text{light heat}]{\text{activation}} R^{\cdot} + (H^{\cdot})$$

Propagation

$$R^{\cdot} + {}^{\cdot}O_2 \rightarrow RO_2$$

$$RO_2^{\cdot} + RH \rightarrow ROOH + R^{\cdot}$$

Hydroperoxide decomposition

$$ROOH \rightarrow RO^{\cdot} + O^{\cdot}H$$

Termination

$$RO_2^{\cdot} + x \rightarrow \text{Inactive products}$$

$$RO_2^{\cdot} + RO_2^{\cdot} \rightarrow \text{Inactive products}$$

The initiation of oxidation reactions can be produced by the thermal decomposition by light. Many oxidations are catalyzed by hydrogen and hydroxyl ions. Oxygen concentration is important in autoxidation process. Examples of drugs undergoing oxidative degradation are prednisolone, morphine, epinephrine, isoamyl nitrite.

Rancidity, which can affect nearly all oils and fats, causes typical off-flavors, due to the autoxidation of unsaturated fatty acids present in fat or oil.

Methods to protect drug from oxidation includes - oxygen content, use of antioxidants (oil soluble and water soluble example Sodium sulphate, sodium meta bisulphate, sodium bisulphate, ascorbic acid, thiourea, thioglycolic acid, propyl gallate, BHT, BHA, Lecithin etc), use of chelating agent (examples – EDTA, citric acid, tartaric acids); adjustment of pH, use of solvent etc.

(C) ***Photolysis :*** Decomposition of drugs due to absorption of radiant energy in the form of light. If the molecules absorbing the radiation take part themselves, in the main reaction, the reaction is said to be a photochemical one. Ex : chlorpromazine hydrochloride, hydrocortisone, prednisolone and methyl prednisolone etc.

(D) Racemization: An optically active substance loses its optical activity without changing its chemical composition. The biological effect of the dextro form can be considerably less than the levo form.

Ex. Levo-adrenaline is 15 to 20 times more active than dextro-adrenaline. Solutions of levo adrenaline form a racemic mixture of equal part of levo, and dextro-adrenaline having pharmacological activity half than pure levo compound.

Influence of Temperature on Drug Decomposition

Arrhenius was the pioneer, who studied the effects of temperature on decomposition of drug. The rate of a reaction doubles with every 10° rise in temperature.

Arrhenius equation illustrates the effect of temperature on reaction rate.

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

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

Taking logarithm on both sides

$$\log K = \log A - \frac{E_a}{2.303\ RT} \qquad \text{.....(8.16)}$$

Frequency factor (A) is the product of the number of collisions and probability of collisions which give a reaction product.

Activation energy (E_a) is the minimum energy that a molecule should possess so as to produce the product.

Estimation of K : The value of K can be found out by conducting the experiment at different temperatures. The concentration values at different time points is calculated and graph is ploted for concentration Vs time. From the slope of line one can calculate the value of K.

Estimation of Activation Energy and Arrhenius Factor : As stated above one can get values of K at different temperatures. Let the value of $K = K_1$ at temperature t_1 and $K = K_2$ at temperature t_2

So Eq. (8.16) can be written as

$$\log K_1 = \log A - \frac{E_a}{2.303\ RT_1} \qquad .....(8.17)$$

$$\log K_2 = \log A - \frac{E_a}{2.303\ RT_2} \qquad .....(8.18)$$

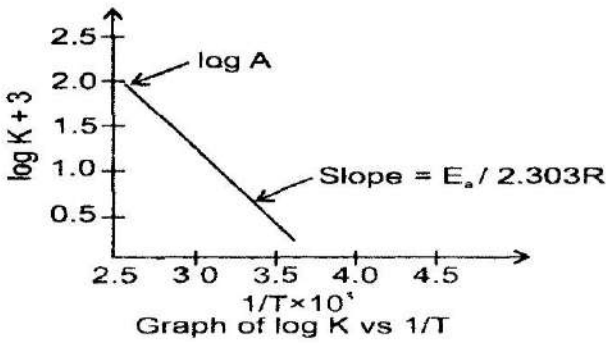
Substracting Eq. (8.17) and Eq. (8.18) yield

$$\log \frac{K_2}{K_1} = \frac{E_a}{2.303\ R}\left(\frac{T_2 - T_1}{T_2\ T_1}\right) \qquad .....(8.19)$$

Now substitute the value of E_a in the equation to obtain value of A.

We can also estimate the value of E_a from the slope of line obtained by drawing the values of log K on y-axis and $\frac{1}{T}$ on x-axis as given in Fig. 8.4.

$$\text{Slope} = \frac{E_a}{2.303\ R}$$



Graph of log K vs 1/T

Fig. 8.4

Factors which govern the rate of chemical reaction

1. Collision theory of reaction rates.
2. Effect of increase temperature on rate of reaction
3. Transition state theory
4. Effect of Solvent – dielectric constant, ionic student strength.
5. Specific and General Acid–Base and pH Effects

Solvent:

The nature of the solvent can also affect the rate of decomposition of drugs. The relation between reaction rate constant and solubility of reactant and products is given by

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

Where

k = observed reaction rate constant

k_o = rate constant in infinitely dilute solution

V = molar volume of solute

$\Delta S_a, \Delta S_b, and\ \Delta S^*$ = difference in solubility parameter of solvent and reactant 'a' reactant 'b'and activated complex respectively.

From this equation it is found that

- 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.

Ionic strength:

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

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

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

ko is rate constant at infinite dilution in which μ = 0

When a plot of log k against $\sqrt{\mu}$ should give a straight line with a slope of 1.02 Z_A Z_B. If one of the reactants is a neutral molecule, Z_A Z_B = 0, and the rate constant, should then be independent of the ionic strength in dilute solutions.

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, extrapolated to infinite dilution where the ionic strength effect is zero is determined by the following equation:

$$In\,k = In\,k_{\varepsilon=\infty} - \frac{Nz_A\,z_B e^2}{RTr^*}\frac{1}{\varepsilon}$$

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

The reaction between ions of opposite sign, an increase in dielectric constant of the solvent results in a decrease in the rate constant. on the other hand, for ions of like charge an increase in dielectric constant results in an increase in the rate of the reaction.

Catalysis:

The rate of a reaction is also influenced by the presence of a catalyst. A catalyst is a substance that either increase or decrease the rate of a reaction but itself remain unchanged chemically. The catalyst only makes the reaction faster, it does not affect the yield of the product. A catalyst that reduces the rate of reaction is called Negative catalyst.

The catalyst with the reactant (substrate) forms an intermediate complex, which then decomposes to regenerate the catalyst and the products. Homogeneous catalysis occurs when the catalyst and the reactants are in the same phase. Acid-base catalysis is the most important type of homogeneous catalysis. Heterogeneous catalysis occurs when the catalyst and the reactants form separate phases in the mixture.

a. Specific Acid Base Catalysis

The number of drugs decomposed on the addition of acids or bases. When the rate law for an accelerated decomposition reaction contains a term involving the concentration of the hydrogen ion or the concentration of the hydroxyl ion, the reaction is called specific acid-base catalysis.

The magnitude of acid base catalyzed reaction varies with pH. For example, hydrogen ion catalysis occurs at lower pH range while hydroxyl ion catalyzes at higher pH range. The general rate law which express the pH dependence of specific acid-base-catalyzed reaction is shown as

$$\mathbf{dP / dt = (k_o + k_1 [H^+] + k_2 [OH^-]) [S]}$$

In this case the observed rate constant is shown as

$$\mathbf{k_{obs} = k_0 + k_1[H^+] + k_2[OH^-]}$$

- At low pH, the term $k_1[H^+]$ is greater than k_o or $k_2[OH^-]$ because of the greater concentration of hydrogen ions, and specific hydrogen ion catalysis is observed.
- Similarly, at high pH, at which the concentration of $[OH^-]$ is greater, the term $k_2[OH^-]$ greater than the k_o and $k_1[H^+]$ terms, and specific hydroxyl ion catalysis is observed.

Sometimes a minimum plateau extends over a limited pH region, it indicates solvent catalysis. Solvent catalysis may occur simultaneously with specific hydrogen ion or specific hydroxide ion catalysis, especially at pH values that are between the pH regions. In this case, the observed reaction rate is shown as

$$k_{obs} = k_o$$

b. General Acid Base Catalysis

Buffers are used to maintain pH of the solution. Buffer salts (i.e acetates, phosphates, borates etc) shows catalytic effects on drug degradation rate in solution. The reaction is said to be general acid catalysis if catalytic component is acidic while reaction is said to be general base catalysis if catalytic component is basic.

In general base catalysis, the proton transfer take place during rate determined step. It generally function with weak base. While the general acid catalysis is operated with weak acid.

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.

Molecular Collison theory:

According to this theory, **a chemical reaction takes place only by collisions between the reacting molecules.** But not all collisions are effective. Only a small fraction of the collisions produces a reaction.

The two main conditions for a collision between the reacting molecules to be productive are:

(1) The colliding molecules must posses sufficient kinetic energy to cause a reaction.

(2) The reacting molecules must collide with proper orientation.

Now let us have a closer look at these two postulates of the collision theory.

Limitations of the Collision Theory

The collision theory of reaction rates is logical and correct. However, it has been oversimplified and suffers from the following weaknesses.

(1) The theory applies to simple gaseous reactions only. It is also valid for solutions in which the reacting species exist as simple molecules.

(2) The values of rate constant calculated from the collision theory expression (Arrhenius equation) agree with the experimental values only for simple bimolecular reactions. For reactions involving complex molecules, the experimental rate constants are quite different from the calculated values.

(3) There is no method for determining the steric effect (*p*) for a reaction whose rate constant has not been determined experimentally.

(4) In the collision theory it is supposed that only the kinetic energy of the colliding molecules contributes to the energy required for surmounting the energy barrier. There is no reason why the rotational and vibrational energies of molecules should be ignored.

(5) The collision theory is silent on the cleavage and formation of bonds involved in the reaction.

TRANSITION STATE THEORY

The **transition state** or **activated complex theory** was developed by Henry Erying (1935). This theory is also called the **absolute rate theory** because with its help it is possible to get the absolute value of the rate constant. The transition state theory assume that simply a collision between the reactant molecules does not really causes a reaction. During the collision, **the reactant molecules form a transition state or activated complex which decomposes to give the products.**
Thus,

Accelerated Stability Studies:

The objective of accelerated stability studies is to predict the shelf life of a product by accelerating the rate of decoposition, preferably by increasing the temperature. Accelerated stability studies are experimental designs.

Objectivies of stability testing:

1. Our concerns for patients welfare.
2. To protect the reputation of the producer.
3. Requirment for regulatory agencies.
4. To provide a database that may be of value in the formulation of other products.
5. Shelf-life & storage condition and labeling specification.
6. Adequate formulation & container closer systems
7. How quality of drug substance or product varies with the time under the influence of various factors.
8. Degradation product & possible degradation pathway
9. Development & validation of stability indicating methodology
10. Prevent great loss by recalling the batch due to stability.
11. To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product
12. Providing evidence on how quality of drug substance or product varies with the time under the influence of various factors like temp, humidity and light.
13. Loss/increase in concentration of API
14. Modification of any attribute of functional relevance, e.g., alteration of dissolution time/profile or bioavailability
15. Loss of pharmaceutical elegance and patient acceptability

Stability method:

Arrhenius equation explains the effect of temperature on rate of a reaction. According to Arrhenius equation, for every 10^o rise in temperature, the speed of reaction increases about 2-3 times.

$$\log k = \log A - Ea/2.303\ RT$$

The preparation is stored at different elevated temperatures (50, 60, 70, 85, 100 and 121^{o}C). Concentration of reactant at each elevated temperature is also determined. In addition, the samples should be studied at 40^{o}C, 75%RH and incubator tempertautre (35-37 ^{o}C). To conform the results obtained from accelerated stability studies, it is necessary to simultaneously conduct experiments at room temperature (i.e.30 ^{o}C, 70%RH) and or refrigerator temperature (4-5 ^{o}C). During different time intervals, samples are withdrawn. The sampling may be done at:

3 months intervals during the first year,

6 months intervals during the second year, and yearly therrafter.

For drug products which may degrade rapidly more frequent sampling is necessary.

Due to diverse climatic conditions prevalent in different countries, mentioning of ambient temperature amy be relevant here. For this purpose, four climatic zones are proposed in ICH guidelines.

The drug content is estimated using a stability indicating assay method.

1. Draw a plot by considering some funtion of concentration against time. Examples are c, or log c or x/(a-x) etc. A straght line in a graph permits the etimation of k value at one temperature.
2. Similar experiments should be conducted and grapha are drawn for different elevated temperatures. Linear relationships are obtained and these have different slopes. K value for each temperature are calculated.
3. Log k values are then plotted against reciprocal of absolute temperatures. A linear relations ship is desirable. The energy of activation can be calculated.
4. Extrapolate the straight line to room temperature (25^{o}C or 30^{o}C) or refrigerator temperature (4-8^{o}C) and read the log k value on y axis.

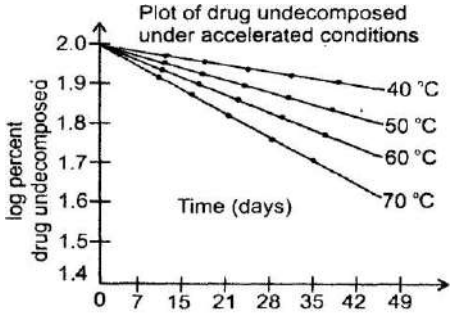


Fig. 8.5

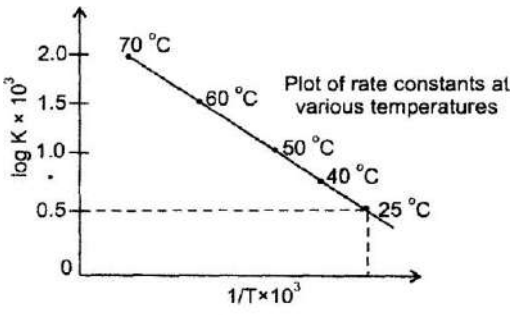


Fig. 8.6

5. Substitute the k_{25} value in the equation of an appropriate order to get shelf life of product under normal shelf life conditions. Assume that 10% deterioration is acceptable. In some cases, the objectionable

decompostion levels such as 30% etc. are defined by manufacctures. The units of shelf life are days, or years.

ICH Guidelines:

ICH stands for"**INTERNATIONAL CONFERENCE ON HARMONISATION**". ICH is a joint initiative involving both regulators and research based industry representative of the European Union, Japan and USA in scientific and technical discussion of the testing procedure required to acess and ensure the quality and efficacy of the medicines.

ICH guidelines are divided in 4 major categories and ICH topic codes are assigned according to this categories:

Q-Quality, S-safety, E-Efficacy and M-Multidisciplinary

ICH Guidelines on stability studies

ICH Guideline	Title
Q1A (R2)	Stability testing of New Drug substances and products
Q1B	Stability Testing: Photo Stability Testing of New Drug substances and Products
Q1C	Stability testing for New Dosage Forms
Q1D	Bracketing and Matrixing Designs
Q1E	Evaluation of Stability Data
Q1F	Stability Data for climatic zone III & IV

Climatic zones with their temperature and Relative humidity values

Zone	Climatic conditions
Zone I	Moderate temperature climate (21^{o}C / 45% RH)
Zone II	Subtropical and Mediterranean Climate (25^{o}C / 60% RH)
Zone III	Hot/Dry Climate (30^{o}C / 35% RH)
Zone IV	Hot/Humid Climate (30^{o}C / 70% RH)

Stability Studies: Storage Condition for product intended to be stored at room temperature

Stability Study Type	Storage condition
Long term stability studies	Duration: 5 Years Temperature: 25 +/- 2^{o}C Relative humidity: 60 +/- 5 %
Intermediate stability studies	Duration: 6 months Temperature: 30 +/- 2^{o}C Relative humidity: 65 +/- 5 %
Accelerated stability studies	Duration: 6 months Temperature: 40 +/- 2^{o}C Relative humidity: 75 +/- 5 %

Limitation of accelerated stability studies:

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 30kcal/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 changges at higher temperautre.

Addition of overages.

- Excess amount of the drug can be added to the preparation to maintain 100% of the labelled amount of during the shelf life of the product.
- Overages are calculated from the accelerated stability studies and added to the preparation at the time of manufacture.
- They should be within the limits compatible with the therapeutics requirment.
- Addition of overages doubles the shelf life of the product.
- Overges are added in multi vitamin preparation.

Applications of Chemical kinetics:

- Study of speed with which a chemical reaction occurs and the factors affecting that speed.
- Provides information about the feasibility of a chemial reaction.
- Provides information about time it takes for a chemical reaction to occur.
- Provides information about the series of elementary steps which lead to the formation of product.

Cold place – it indicates that the product should be stored in a place that maintains any temperature not excedding 8^{o}C. Usually, this temperature is between 2 to 8^{o}C.

Cool place - it indicates that the product should be stored in a place that maintains any temperature between 8^{o}C to 25^{o}C.

Room temperature – The term 'room temperature'indicates the prevailing the temperature in the working area.

Warm – The term 'warm' indicates that the product may be stored in a place that maintains any temperature between 30 to 40^{o}C.

Excessive heat – It indicates that the product may be stored at any temperature above 40^{o}C.

Controlled RT – The working environment of 20 to 25^{o}C, that is being maintained thermostatically is suitable for storage.

Freezer – The product should be stored in a place at which the temperature is maintained thermostatically between -20^{o}C and -10^{o}C

Unit-V Drug Stability

Reaction Kinetics → Rate

* It means Rate of Reaction

↓

It is defined as change in the Concentration of reactant or product at (respective) unit time.

$$\text{Rate of Reaction} = \frac{\text{change in the Conc of Reactant/product}}{\text{Time}}$$

* Rate of Reaction is also defined as the ratio of change in Concentration of Reactant / product per unit time.

$$\text{Rate of Reaction} = \frac{dx}{dt}$$

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Rate Equation

$N_2 + 3H_2 \longrightarrow 2NH_3$

* while writing Rate Equation the Molar Concentration gets Inversed

* The Reactants gets Negative charge because the Concentration of Reactant gradually decreases at the same time the product represent in positive charge as the Concentration gradually increases with time

Rate Equation

$N_2 + 3H_2 \longrightarrow 2NH_3$

$$\frac{dx}{dt} = -\frac{d[N_2]}{dt} = -\frac{1}{3}\frac{d[H_2]}{dt} = \frac{1}{2}\frac{d[NH_3]}{dt}$$

$H_2 + I_2 \longrightarrow 2HI$

$$\frac{dx}{dt} = -\frac{d[H_2]}{dt} = -\frac{d[I_2]}{dt} = \frac{1}{2}\frac{d[HI]}{dt}$$

$\frac{3}{2}A + \frac{2}{5}B + \frac{1}{7}C \longrightarrow 3D + \frac{2}{9}E$

$$\frac{dx}{dt} = -\frac{2}{3}\frac{d[A]}{dt} = -\frac{5}{2}\frac{d[B]}{dt} = -7\frac{d[C]}{dt}$$
$$= \frac{1}{3}\frac{d[D]}{dt} = \frac{9}{2}\frac{d[E]}{dt}$$

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Order of Reaction

↓

It is defined as the Sum of the powers of molar Concentration of Reactants

* For Example to understand the Concept a Casual example

$$A + B + C \longrightarrow \text{Product}$$

A	B	C	Product
↓	↓	↓	↓
Alu	Maida	oil	Samosa
[1Kg]	[500g]	[200ml]	

If Concentration of A Increases & B, C are Constant

$$A + B + C \longrightarrow \text{Product}$$

[Alu] (B, C: Constant) [Samosa]

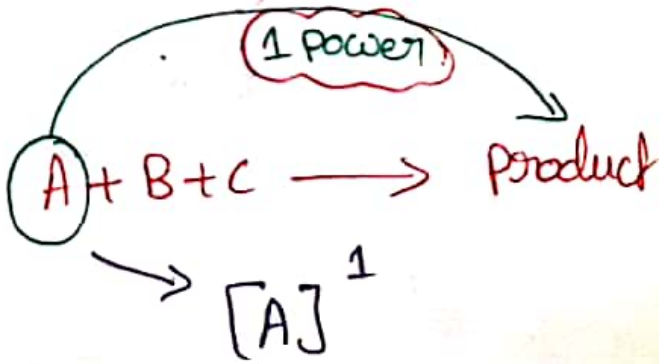
1Kg ⟶ 20

↓

2Kg ⟶ 40

↓

3Kg ⟶ 60



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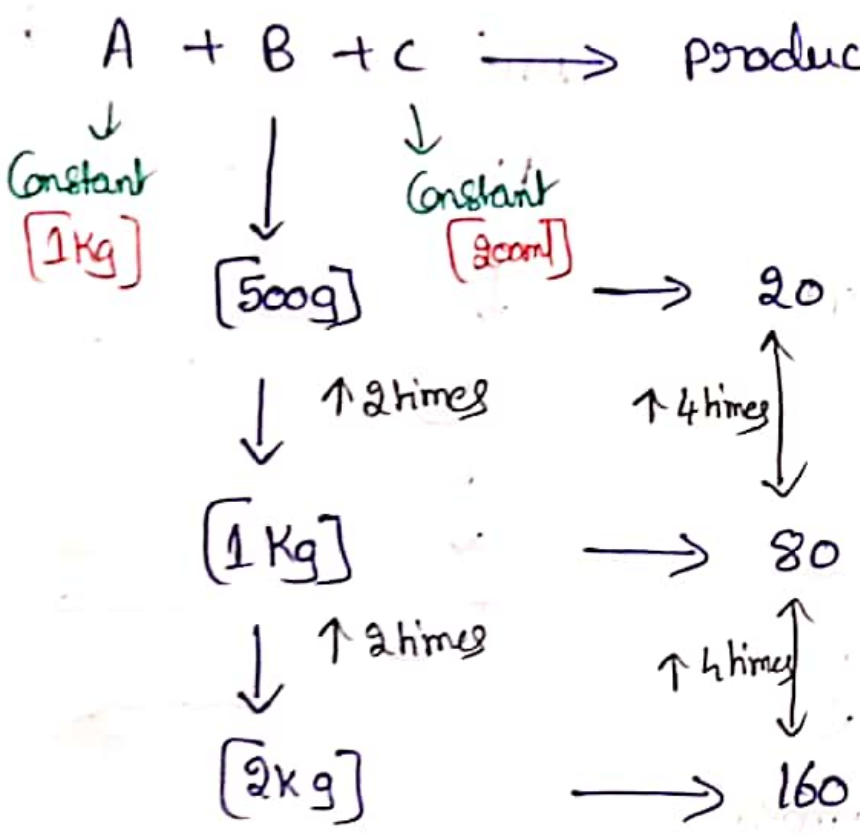
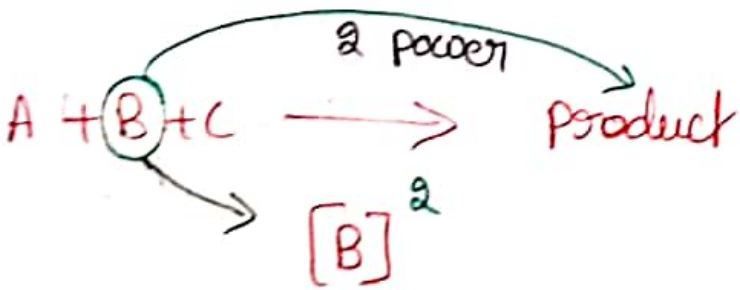
In another Case:

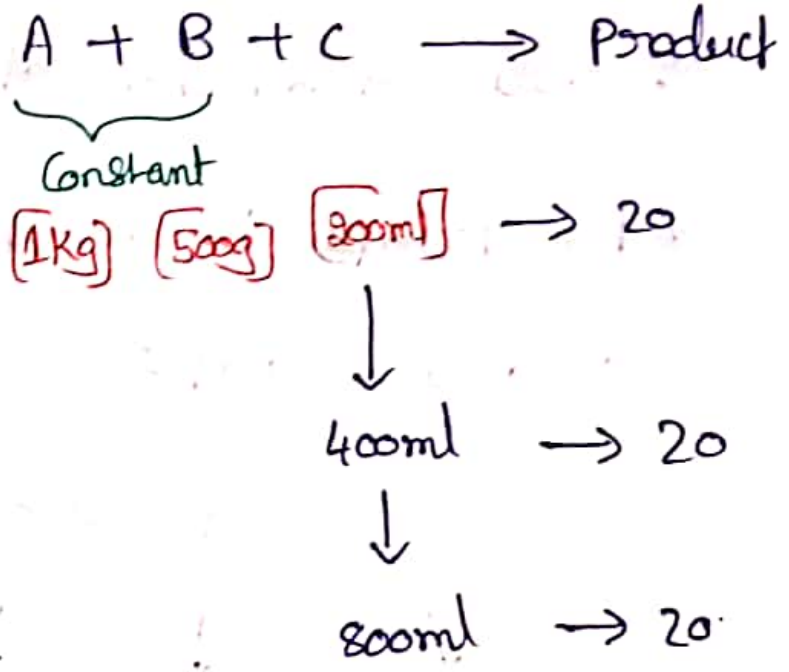
B Concentration Increases, A & C are Constant





In another Case

C Concentration Increases, A & B are Constant.



It shows that the reactant 'C' has no impact on product Concentration.

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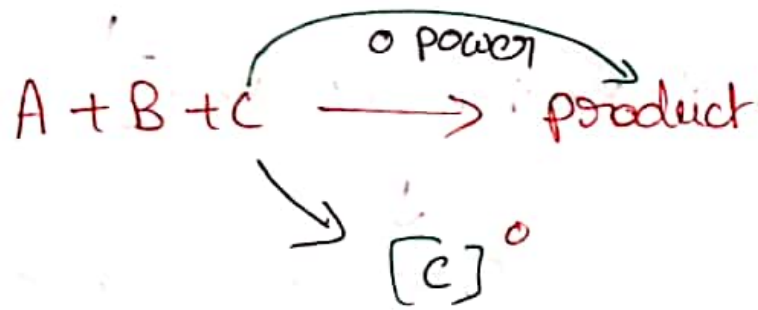
Therefore the the Reactant [C] has zero power on the product Concentration.



Finally the effect of all reactants on product Concentration is

$$[A]^1 + [B]^2 + [C]^0 \propto \text{~~Rate~~ order}$$

$$1 + 2 + 0 = \text{order}$$

$$3 = \text{order of Reaction}$$

Third order of Reaction.

∴ The order of Reaction is Sum of the powers of the Molar Concentration of all the reactants.

$$\text{Rate} \propto [A]^n$$

n = order of Reaction

n = 0 zero order Reaction

n = 1 First order Reaction

n = 2 Second order Reaction

n = 3 Third order Reaction.

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For Example

$A^1 + B^0 + C^0 \longrightarrow$ Product

↓

First order Reaction

$A^1 + B^1 + C^0 \longrightarrow$ product

↓

Second order Reaction

$A^1 + B^1 + C^1 \longrightarrow$ product

↓

Third order Reaction

$A^1 + B^2 + C^0 \longrightarrow$ product

↓

Third order Reaction

First order Reaction

$H_2O_2 \longrightarrow H_2O + \frac{1}{2}O_2$

Rate of Reaction $\propto [H_2O_2]^1$

↓

First order Reaction

$CH_3COOCH_3 + H_2O \rightarrow CH_3COOH + CH_3OH$

Rate of Reaction $\propto [CH_3COOCH_3]^1 [H_2O]^0$

↓

First order Reaction.

In this Case Reactant undergo Hydrolysis in water. The water quantity is not effect the Hydrolys

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of CH_3COOCH_3. Therefore the H_2O has zero power on rate of Reaction.

Finally

$A \longrightarrow$ product

Rate of Reaction $\propto [A]^1$

$$\frac{-d[A]}{dt} \propto [A]$$

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

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

$$\frac{d[A]}{[A]} = -K\,dt$$

Integrate on both sides

$$\int_{A=0}^{A} \frac{d[A]}{dt} = -K \int_{0}^{t} dt$$

$$\ln[A] - \ln[A_0] = -K[t-0]$$

$$\ln[A] - \ln[A_0] = -K \cdot t$$

Apply logarithm

$$\log[A] - \log[A_0] = \frac{-K\,t}{2.303}$$

$$\ln[A] = \ln[A_0] - K \cdot t$$

Apply logarithm

$$\log[A] = \log[A_0] - \frac{K \cdot t}{2.303}$$

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$$\log [A] = \log [A_0] - \frac{K \cdot t}{2.303}$$

$$\frac{K \cdot t}{2.303} = \log [A_0] - \log [A]$$

$$\frac{K \cdot t}{2.303} = \log \frac{[A_0]}{[A]}$$

$$\log \frac{[A_0]}{[A]} = \frac{Kt}{2.303}$$

$$K = \frac{2.303}{t} \cdot \log \frac{[A_0]}{[A]}$$

Half Life

It is defined as the time at which the concentration of reactant reduced to half of its Initial Concentration.

$$\log \frac{[A_0]}{[A]} = \frac{Kt}{2.303}$$

$A = A_0/2 \quad t = t_{1/2}$

$$\log \frac{[A_0]}{\left[\frac{A_0}{2}\right]} = \frac{K t_{1/2}}{2.303}$$

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$$\log \frac{[A_0] \times 2}{[A_0]} = \frac{k\, t_{Y_2}}{2.303}$$

$$\log [2] = \frac{k\, t_{Y_2}}{2.303}$$

$$0.3010 = \frac{k \cdot t_{Y_2}}{2.303}$$

$$t_{Y_2} = \frac{0.3010 \times 2.303}{k}$$

$$t_{Y_2} = \frac{0.693}{k}$$

Zero order

Zero order reaction is defined as a reaction in which the rate does not depend on the Concentration of reactant i.e the rate of reaction Cannot be increased by increase in the Concentration of reactant.

$$A \longrightarrow \text{Product}$$

$$\text{Rate of Reaction} \propto [A]^0$$

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$$-\frac{d[A]}{dt} = K \cdot [A]^0$$

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

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

$$d[A] = -K \cdot dt$$

Integrating on both sides

$$\int_0^A d[A] = -K \cdot \int_0^t dt$$

$$A - A_0 = -Kt$$

Half Life

$$[A] - [A_0] = -K \cdot t$$

$$A = [A_0/2] \quad t = t_{1/2}$$

$$[A] - [A_0] = -K \cdot t$$

$$\frac{[A_0]}{2} - [A_0] = -K \cdot t_{1/2}$$

$$\frac{A_0 - 2[A_0]}{2} = -K \cdot t_{1/2}$$

$$\frac{-[A_0]}{2} = -K \cdot t_{1/2}$$

$$\frac{[A_0]}{2} = K \cdot t_{1/2}$$

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$$\frac{[A_0]}{2} = K \cdot t_{1/2}$$

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

Second order

* It is defined as the reaction in which the rate depends on the Concentration of two reactants each raised to be power one.

$$A + B \longrightarrow \text{Product}$$

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} \propto [A]^1 [B]^1$$

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = K [A]^1 [B]^1$$

let a and b are initial Concentration of A & B and x be the Concentration of each species reaching in time t

$$\frac{dx}{dt} = K [a-x] [b-x]$$

If $a = b$

$$\frac{dx}{dt} = K [a-x] [a-x]$$

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$$\frac{dx}{dt} = K[a-x]^2$$

$$\frac{dx}{(a-x)^2} = K \cdot dt$$

Integrate of above equation

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

$$\frac{1}{(a-x)} - \frac{1}{(a-0)} = K \cdot (t-0)$$

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

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

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

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

If $a \neq b$

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

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Half Life

put $(a-x) = a/2$

$$t = t_{y_2}$$

$$x = a/2$$

$$K = \frac{1}{a \cdot t_{y_2}} \cdot \frac{a/2}{a/2}$$

$$K = \frac{1}{a \cdot t_{y_2}}$$

$$t_{y_2} = \frac{1}{a \cdot K}$$

Units of order of Reaction

Here iam giving a Trick to find the unit of different order of Reaction

$$\text{Mol}^{1-n} \quad \text{litre}^{n-1} \quad \text{sec}^{-1}$$

Here n = order of Reaction

If $n = 0 \Rightarrow$ zero order Reaction

$n = 1 \Rightarrow$ First order Reaction

$n = 2 \Rightarrow$ Second order Reaction.

$n = 3 \Rightarrow$ Third order Reaction

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For zero order Reaction

$Mol^{1-n}\ litre^{n-1}\ sec^{-1}$

Here $n = 0$

$Mol^{1-0}\ litre^{0-1}\ sec^{-1}$

$Mol\ litre^{-1}\ sec^{-1}$

$\Downarrow$

$Mol / litre \cdot sec$

For First order Reaction

$n = 1$

$Mol^{1-1}\ litre^{1-1}\ sec^{-1}$

$Mol^{0}\ litre^{0}\ sec^{-1}$

$\Downarrow$

sec^{-1}

For Second order Reaction

$n = 2$

$Mol^{1-n}\ litre^{n-1}\ sec^{-1}$

$Mol^{1-2}\ litre^{2-1}\ sec^{-1}$

$Mol^{-1}\ liter^{1}\ sec^{-1}$

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For Third order Reaction:

$$Mol^{1-n}\ litre^{n-1}\ Sec^{-1}$$

$n=3$

$$Mol^{1-3}\ litre^{3-1}\ Sec^{-1}$$

$$Mol^{-2}\ litre^{2}\ Sec^{-1}$$

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Physical & Chemical Factors Influencing the chemical degradation of pharmaceutical products

1) Temperature

* Generally → The speed of many reactions can be increased by 2 to 3 times with each increase of 10°C in temperature.

* The effect of temperature on reaction rate is given by Arrhenius Equation.

Arrhenius Equation

$$K = A\, e^{-Ea/RT}$$

K = Specific reaction rate Constant

A = Frequency Factor also known as Arrhenius Factor

Ea = Activation Energy

R = Gas Constant [1.987 Cal/deg mol]

T = Absolute Temperature.

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* The Frequency Factor [A]

is a measure of Frequency of Collisions b/n reacting molecules.

* The Activation Energy [Ea]

is Energy required for effective Collision to cause reaction

* Expressing the Arrhenius Equation in logarithmic form

on Integration of Equation.

$$K = A \cdot e^{-Ea/RT}$$

$$\ln K = -\frac{Ea}{RT} + \ln A$$

Converting to Common log

$$\log K = -\frac{Ea}{2.303\,RT} + \log A$$

* The value of Constants A & Ea can be determined by determining K at various Temperatures.

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* E_a Can be attained by determining K_1 at T_1 and K_2 at T_2.

$$\log \frac{K_2}{K_1} = \frac{E_a}{2.303\,R} \frac{(T_2 - T_1)}{T_2 \cdot T_1}$$

2) Effect of Solvent

The effect of Solvents on rate of decomposition of drugs is generally related to relative Solubility of reactants and the products in the given Solvents

For a Reaction

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

The quantitative relationship b/n Reaction Rate Constant & Solubility of reactants & products given by

$$\log K = \log K_0 + \frac{V}{2.303\,R} \frac{1}{T} [\Delta S_A + \Delta S_B - \Delta S$$

K = observed Reaction Rate Constant

K_0 = Reaction rate Constant in an infinity dilute solution

↓ Ideal Behaviour

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V = Approximation for molar volume of reactant A & B and the activated Complex Formed during reaction.

S_A, S_B & S^* = Solubility parameters of Reactant A, B and Activated Complex respectively.

* If polarity of product > polarity of Solvent

↓

Reaction Rate increases if the Solvent is more polar.

* If the polarity of Product < Polarity of Reactant

↓

Reaction rate increases if the Solvent is less polar.

* If the polarity of Product & polarity of Solvent is Completely different then the Reaction rate decreases.

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3) Effect of Ionic Strength.

* The effect of ionic strength on rate of decomposition of drug is expressed as

$$\log K = \log K_0 + 1.02\, Z_A Z_B \sqrt{\mu}$$

where

K = Degradation rate Constant

K_0 = Reaction rate Constant at infinite dilution.

$Z_A + Z_B$ = charges carried by reactant A & B

μ = Ionic Strength of Solution

* According to Equation

An increase in ionic strength of a solution

↓

Decrease the rate of reaction b/n oppositely charged ions

Increase the rate of reaction b/n similar charged ions.

* If one of the Reactant is neutral molecule $Z_A \cdot Z_B = 0$

↓

Then rate Constant is independent of Ionic Strength.

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4) Effect of Dielectric Constant of Solvent

* Dielectric Constant of Solvent has a Significant effect on rate of reaction.

* For a reaction involving

A charged reactant and

Another ionic species $[H^+ \& OH^-]$

↓

The effect of dielectric Constant on reaction rate is given by

$$\ln K = \ln K_{E=\infty} - \frac{N Z_A Z_B e^2}{RT r^*} \cdot \frac{1}{\varepsilon}$$

where

K = observed reaction rate in a Solvent of dielectric Constant ε

$K_{\varepsilon=\infty}$ = Reaction rate Constant in a Solvent of Infinite dielectric Constant

N = Avagadro's Number

$Z_A \& Z_B$ = Charge on two ionic species

e = unit of electric charge

r^* = distance b/n ionic Species in Activated Complex.

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ε = Dielectric Constant of the Solution

* So reactions involving ions of opposite charge.

↓

Results in accelerated rate of reaction by Solvents of low Dielectric Constant

[Vice-versa]

* If reactions involving ions of Similar charge

↓

Results in accelerated rate of reaction by Solvents of High Dielectric Constant

5) Effect of Catalysis

A Catalyst is defined as

↓

The Substance which increases or decreases the rate of reaction without itself being altered chemically.

(a) Specific Acid-Base Catalysis

A number of drugs in Solution Form

↓

undergo Hydrolytic degration

[Upon Addition of Acid / Base]

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So the reaction may be Considered to be Catalysed by Hydrogen / Hydroxyl ions.

↓

i.e these are Called Specific Acid-Base Catalysis Reaction.

* The effect of H^+ or OH^- Concencentration on specific acid or Base Catalysed reactions Can be expressed as

$$dP/dt = K_0 + K_1[H^+] + K_2[OH^-][B]$$

↙

Conc of Substrate

For which observed rate Constant

$$K_{obs} = K_0 + K_1[H^+] + K_2[OH^-]$$

At low pH

$[H^+]$ is very High, so $K_1[H^+]$ is greater than $K_0 + K_2[OH^-]$

↓

So observed reaction rate Constan becomes

$$K_{obs} = K_1[H^+]$$

[Reaction is specific Hydrogen ion Catalysed / Acid Catalysed]

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At higher pH

$[OH^-]$ is high, So $K_2[OH^-]$ is greater than

$$K_0 + K_1[H^+]$$

So observed Reaction rate Constant become

$$K_{obs} = K_2[OH^-]$$ [Reaction is specific Hydroxyl ion or Base Catalysed]

At Intermediate pH

$[H^+]$ and $[OH^-]$ are low or product of

$K_1[H^+]$ and $K_2[OH^-]$ are Small.

In this Condition observed reaction rate is

$$K_{obs} = K_0$$ [reaction is Solvent Catalyst]

* The effect of pH on degradation may be determined by ↓

Obtaining the pH rate profile for specific acid-base Catalysed reaction.

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b) General Acid-Base Catalysis

* The Acid-Base Catalysis in Solution

↓

IS not restricted to H^+ and OH^- but often undissociated acids or Base also produce a Catalytic effect on reaction

* Such reactions are said general acid-Base Catalysed reaction.

For Example → Most of the pharmaceutical formulations have Buffers to maintain pH of the Solution often one of the Component of buffer Catalyse the rate of reaction

* If Catalytic Compound is Acidic, the reaction is said to be

↓

General Acid Catalysed

* If the Component is Basic the reaction is said to be

↓

General Base Catalysed

* Common buffer Salts have a Catalytic effect include.

Acetate, phosphate & Borate Buffers

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Accelerated Stability Testing

* This method is designed to predict Stability and Shelf life of formulations under normal or recomended storage Conditions by Carrying out the Study under accelerated Conditions of

- Temperature
- Moisture
- light

* The Stability testing is done to predict the time period upon which the quality of product remain Satisfactory under prescribed Storage Condition.

Shelf life

It is defined as the time required for the Concentration of reactant to reduce to 90% of its Initial Concentration.

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Objectives of Accelerated Stability Testing

1) To Serve a rapid means for Selection of best Formulation from a Series of Similar Formulations.

2) To predict the Shelf life [expiry] of the product.

3) To Serve as a rapid means of quality Control.

Common High Stress during Stability Testing.

- Temperature
  - ↑ Temp Increases Degradation
- Light
  - effect of Sun light.
- Humidity
  - Decomposition from Hydrolysis

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Steps Involved in Accelerated Stability Testing

1) The preparation is stored at different elevated temperatures such as [40°C, 50°C, 60°C & 70°]

2) The Concentration of reactant at each elevated Temperature is also Determined.

3) Samples are withdrawn at different time intervals.

4) The rate of reaction is determined by plotting the Concentration against time and linear relationship is determined.

5) The 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 of ~~each~~ at

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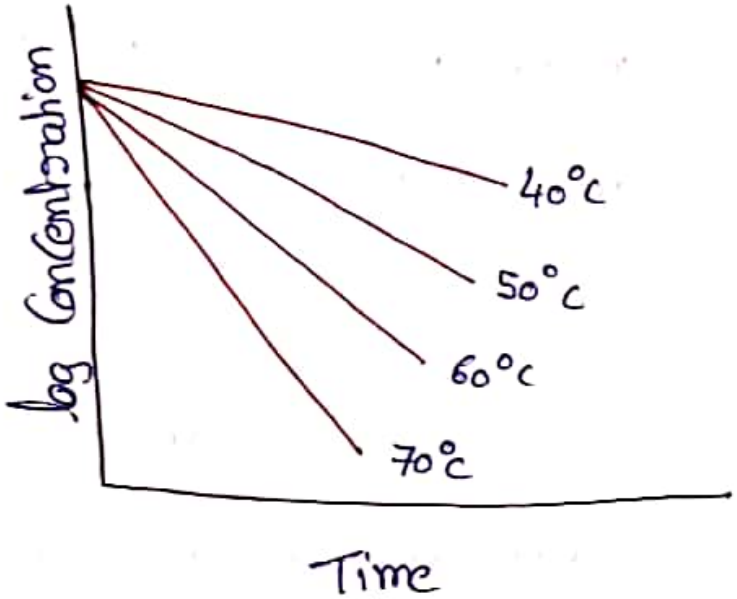
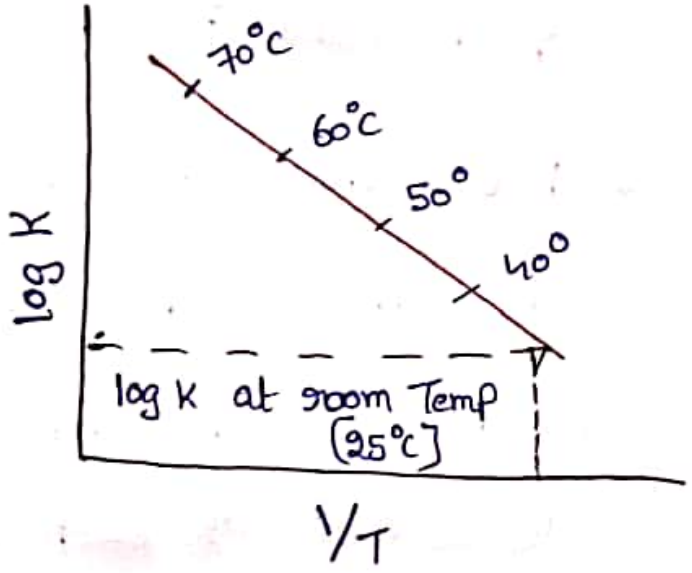
each elevated temperature is calculated.





Limitations of Accelerated Stability Testing

1) Stability predictions based on Arrhenius Equation.

↓

Valid only when energy of activation for thermal decomposition lies b/n 10 - 30 K Cal/mole.

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

↓

For simple reactions only

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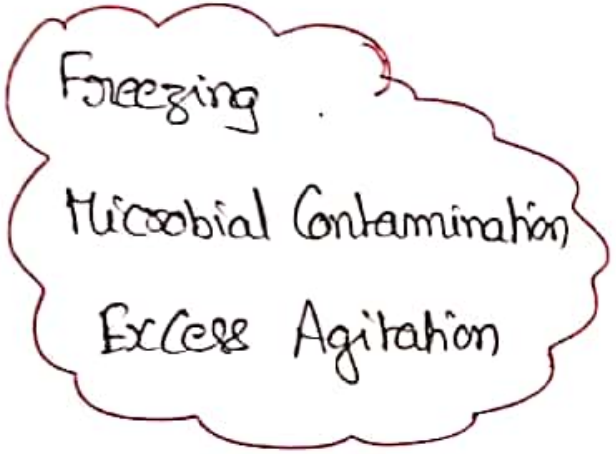
3) This method is not applicable if degradation is due to



4) The product which loose their physical Integrity at elevated Temperatures is not Suitable for this method Such as Converting from Solid to liquid (or) liquid to Gas at elevated Temperature

5) This method is not valid when order of reaction changes at higher temperature.

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Photolytic Degradation

* When molecules or drugs are exposed to electromagnetic radiation they absorb light [Photons] at characteristic wavelength which causes increase in energy which can cause degradation/ decomposition.
* Exposure to light cause substantial degradation of drug molecule
* Natural Sun light lies in wavelength range [290 - 780nm] of which only higher energy UV range [210 - 320nm] cause photodegradation of drugs.

Example of photoxic Drugs

Furosemide, Acetozolamide, Cyanocobalamine.

Photolysis Example

* Sodium Nitroprusside in aqueous solution
* If protected from light it is stable to atleast 1 year.
* If exposed to normal Room light has a shelf life for 4 hours.

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Prevention

* use of amber Colored bottles
* Store the product in dark, packaging in Cartons also act as physical barrier of light
* Coating of Tablets with polymer

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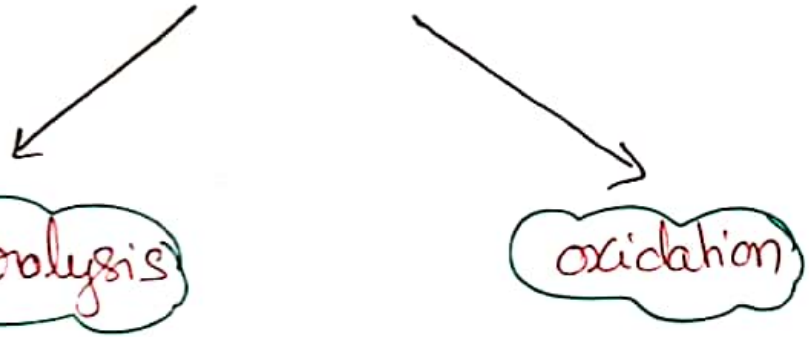
Causes of Instability in Pharmaceutical Products + their Prevention

* The two main Common Causes of Instability or Degradation or Decomposition of pharmaceutical products / Drugs are



Hydrolysis

* The problem is more important in System Containing water.

Such as Syrups, Emulsions, Suspensions etc.

* Also for drugs which are affected by traces of moisture
* The main (~~Cau~~s) classes of drugs that undergo Hydrolysis are

Esters
Amides
lactams

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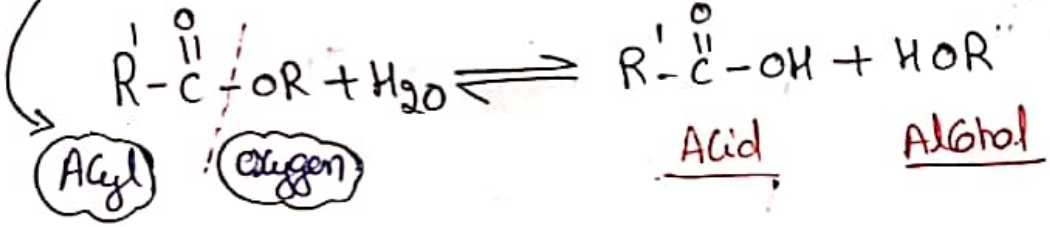
A) Ester Hydrolysis

The most Common type is

↓

acyl - oxygen Cleavage

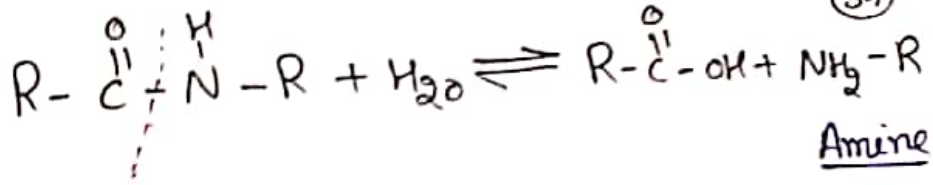


Examples of Drugs

Procaine, Tetracaine, Atropine & Aspirin

B) Amide Hydrolysis

Usually involves Cleavage of amide linkage to give amine



Examples

Dibucaine, Ergometrine, Chloramphenicol, Niaciramide & Barbiturates

C) Ring Hydrolysis

Proceed by ring cleavage with subsequent attack by Hydrogen or Hydroxyl ions

Examples

Benzodiazipenes, Nitrazepam, Chlordiazepoxide, penicillins and Cephalosporin

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Protection against Hydrolysis

(i) Hydrolytic reactions in Solid drug products.

↓

Prevented by avoiding their Contact with moisture at the time of manufacturing, packaging in Suitable (Container) moisture resistant packs Such as Strip packs and Stored in Controlled Humidity & Temperature Conditions

↓

By incorporating Suitable dessicant

Silica Gel Bags

(ii) In Case of liquid dosage form

↓

The main emphasis is on reducing rate of Hydrolysis

↓

Since Hydrolysis is Acid or Base Catalysed an optimum pH for maximum stability should be selected & maintained with buffering agents.

(iii) General Acid-Base Catalysed Hydrolysis is due to Components of buffer Can be minimized by Keeping buffer Concentration

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minimum required for maintaining the pH (Caffeine) to drug solution.

(iv) Hydrolytic reactions can be minised by

↓

Altering the dielectric constant of system by partial or complete replacement of water with non-aqueous solvents such as (Alcohol, Glycerine & propylene Glycol)

(v) Hydrolysis of certain drugs such as Benzocaine and procaine can be decreased by the

↓

Addition of specific complexing Agents like

(vi) Since only that portion of a drug which is in solution form undergoes Hydrolysis it is possible to supress degradation of drug by making them less ~~Hydrolysis~~ soluble.

(vii) Micellar concentration of certain drugs such as (Benzocaine)

↓

By use of surfactants protects ~~from~~ them from Hydrolysis.

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(viii) Hydrolysis of Susceptible drugs

Such as (Penicillin & its derivatives)

Can be prevented by formulating them in the form of ~~dry constituents~~ drug powder for reconstitution.

↓

It means that it should mix with water for Injection at the time of administration.

(xi) Refrigeration of drugs & drug solutions also retard Hydrolytic reactions.

Oxidation

* Instability of number of pharmaceutical preparations are due to oxidative degradation of Active pharmaceutical Ingredients [API] when exposed to atmospheric oxygen.

↓

Involves either addition of oxygen or Removal of Hydrogen

* oxidation & Reduction reactions generally occur simultaneously

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oxidation is the loss of electrons

Reduction is the Gain of electrons

* Autooxidation (require a small amount of oxygen) is most common Form of oxidative degradation.

↓

which Involves a Free radical chain process

* Heavy metals Such as Copper, Iron, Cobalt and Nickel

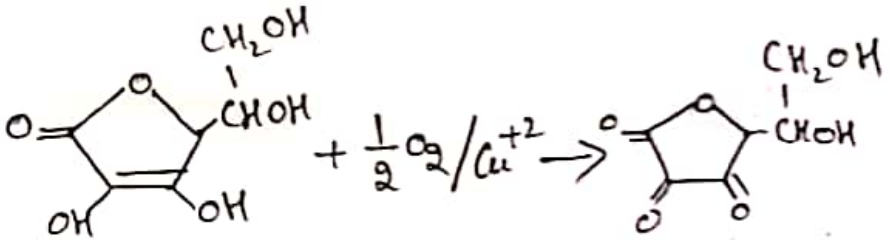
↓

Catalyse the oxidative degradation

* Examples of drugs which undergo oxidative deComposion are

↓

ASCorbic Acid, Morphine, Epirephrine, Heparin paraldehyde, Tetracycline, Vitamin A, D and K



ASCorbic Acid

Dehydro ASCorbic Acid.

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Protection Against oxidation

(i) The most Common approach

↓

To include Suitable antioxidants

(ii) The oxygen in pharmaceutical Containers Should be Replaced with Nitrogen (or) Carbondioxide

(iii) The Contact of drug with Heavy metals ions Such as [Iron, Cobalt (or) Nickel which Catalyse oxidation]

Should be avoided and Stored at reduced temperatures.

(iv) Reducing agents Such as Sodium metabisulfite are used to prevent oxidation.

(v) The ~~pH of optimum~~ Stability must

(v) oxidation of Fats and oils may be retarded by Hydrogenation

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* Methods generally used to determine → particle Size and particle Size Distribution. are

- Microscopic Method
  - Optical Microscopy
  - Electron Microscopy
- Sieving Method
- Sedimentation method (Andreason pipette)
- Coulter-Counter Method. (Particle volume Determination)

(1) Microscopic Technique :- (Range 0.2 to 100 μm)

* Optical microscopy → generally used for particle Size Measurment
  ↓
  in the range of 0.2 μm to 100 μm.

* At least 300 to 500 particles must be counted
  ↓
  for good size distribution analysis.

Method :- A dilute suspension of powder is prepared in a liquid vehicle in which it is insoluble.
↓
a drop of suspension is mounted on slide
↓
observed under the microscope
(eyepiece is fitted with micrometer)
↓

↓

estimate the particle size and counted through eye piece.

↓

Data scientifically represented as Size - frequency distribution curve.

from the data → average particle size. and
↘ Size distribution is determined.

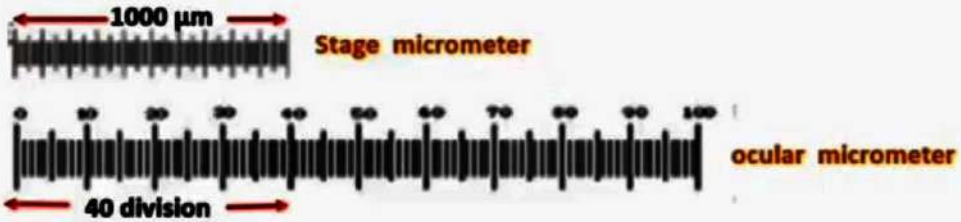
* for ease in counting → field viewed is projected on screen.
or
↘ photographed for latter measurment.

* for very small particles → Electron microscope or
↘ Scanning electron microscope may be used.

Advantage:- Agglomerates or contamination can be detected.

Disadvantage:- * Slow and boring method.
* The measured diameter is two dimensions only
↓
length and breadth
(depth is not obtained)

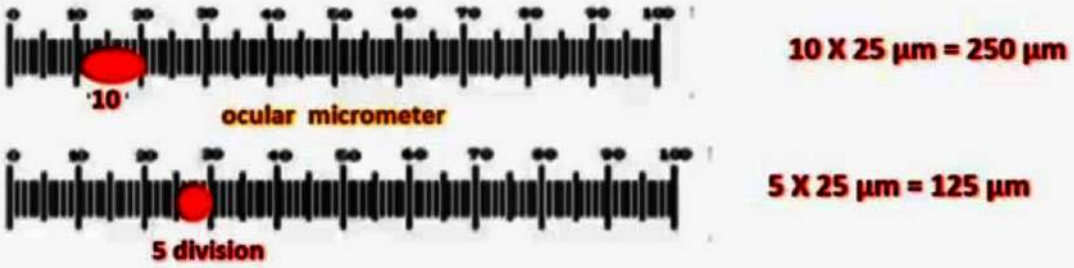
At 40 X magnification



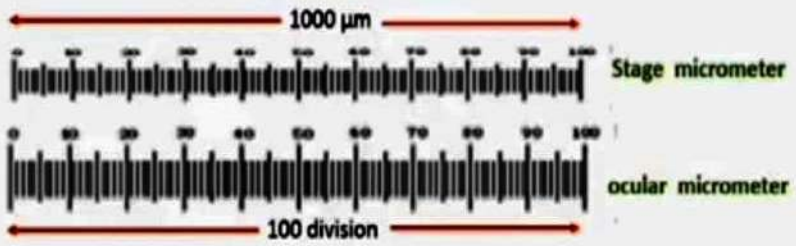
40 division of ocular micrometer = 1000 µm of stage micrometre

Then 1 divisions of ocular micrometre = $\frac{1000\ \mu m}{40}$ = 25 µm

Size of particle = number of divisions covered X value of one division at any specific magnificatio



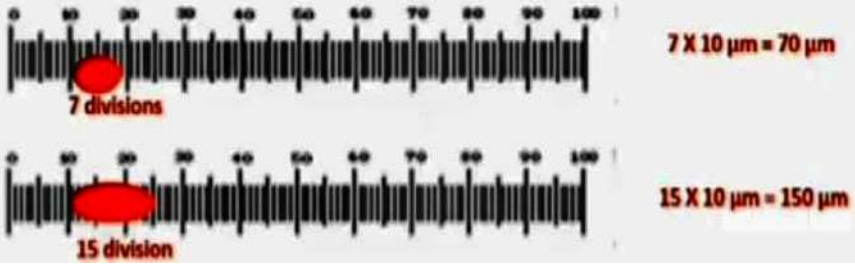
At 100 X magnification



100 division of ocular micrometer = 1000 µm of stage micrometre

Then 1 divisions of ocular micrometre = $\frac{1000\ \mu m}{100}$ = 10 µm

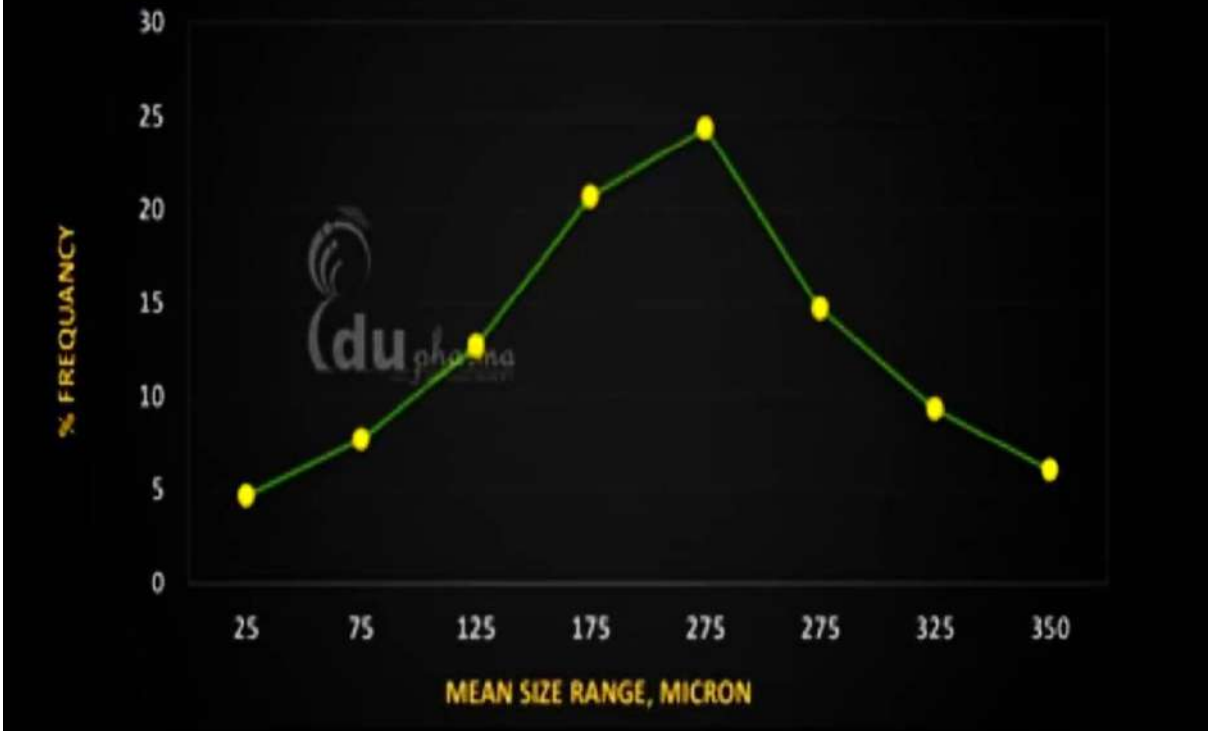
Size of particle = number of divisions covered X value of one division at any specific magnification



Observation

Size range (µm)	Mean of size range µm (d)	Number of Particles (n)	% Particles	Cumulative % frequency	nd	nd^2
00 - 50	25	14	4.67	4.67	350	8750
50 - 100	75	23	7.67	12.33	1725	129375
100 - 150	125	38	12.67	25.00	4750	593750
150 - 200	175	62	20.67	45.67	10850	1898750
200- 250	275	73	24.33	70.00	20075	5520625
250 - 300	275	44	14.67	84.67	12100	3327500
300 - 350	325	28	9.33	94.00	9100	2957500
350 - 400	350	18	6.00	100.00	6300	2205000
		Σn= 300			Σnd= 65250	Σnd^2= 16641250

Frequency distribution curve



(2) Sieving Technique :- (50 μm to 1500 μm)

* Sieving method is an ordinary and simple method
* In this method a series of standard sieves are used
  ↓
  placed on a mechanical shaker
  (Sieve of largest aperture on the top followed by sieves of gradually decreasing pore size)

Method :- The powder whose particle size is to be determined is placed on the nest of sieves
↓
The powder is shaken for a definite time
↓
powder retained on sieves is collected and weighed
↓
The data obtained is analysed and particle size and Size distribution is calculated.

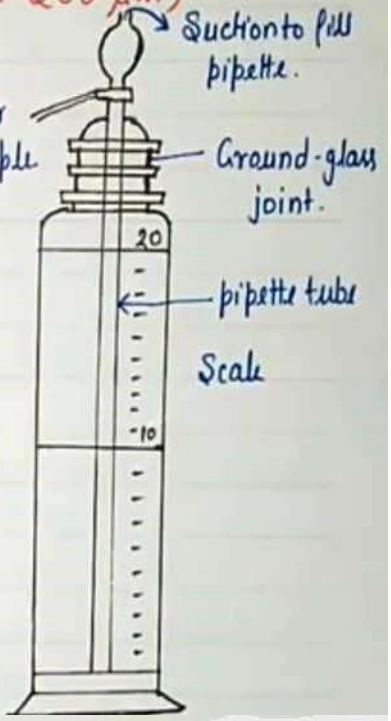
* This technique generally used for coarse particles
  ↓
  more than 50 μm in size.

Advantage :- Simple and inexpensive method.

Disadvantage :-
* Particles below 50 μm difficult to measure.
* Chances of clogging of sieve.
* Chances of attrition during sieving.
* Need large amount of powder.

Weight of sample taken		2000		Specification
S. no.	Sieve Designation	Weight Retained (g)	Cummulative Wt retained (g)	Cumm. Wt retained (%)
1	10.00 mm	0	0	0
2	4.75mm	1	1	0.05
3	2.36mm	637	638	31.9
4	1.18mm	448	1086	54.3
5	600 microns	125	1211	60.55
6	300 microns	389	1600	80
7	150 microns	91	1691	84.55

(3) Sedimentation Method :- (1 μm to 200 μm)
(Andreason pipette)



* The apparatus consists of a 550 ml cylindrical vessel about 5.5 cm internal diameter. (with scale graduated from 0-20 cm).

* Stopper has 10 ml bulb pipette fitted with two way stopcock.
  ↓
  Side tube for draining sample.

Method:- 1 or 2 % suspension of the powder is prepared
↓
The suspension is introduced into vessel upto 550 ml mark.
↓
vessel is stoppered and shaken
↓
pipette is then placed and vessel is kept undisturbed at a constant temp.
↓
at various intervals, 10 ml samples of suspension are withdrown through two way stopcock
↓

samples are evaporated and weighed

* The particle diameter at various time periods is calculated by using Stoke's equation

$$V = \frac{h}{t} = \frac{d_{st}^2 (\rho_s - \rho_0) g}{18 \eta_0}$$

$$d_{st}^2 = \frac{18 \eta_0 h}{(\rho_s - \rho_0) g t}$$

or $$d_{st} = \sqrt{\frac{18 \eta_0 h}{(\rho_s - \rho_0) g t}}$$

where V = is rate of settling
h = distance of fall in time t.
d_{st} = mean diameter of particle.
ρ_s and ρ_0 = density of particle and medium respectively.
η_0 = viscosity of medium
g = acceleration due to gravity.

Advantage:- * Simple and inexpensive.
* The result obtained are precise.

Disadvantage:- * Method is laborious → separate analysis for each sample.
* Very small particles cannot be determined.

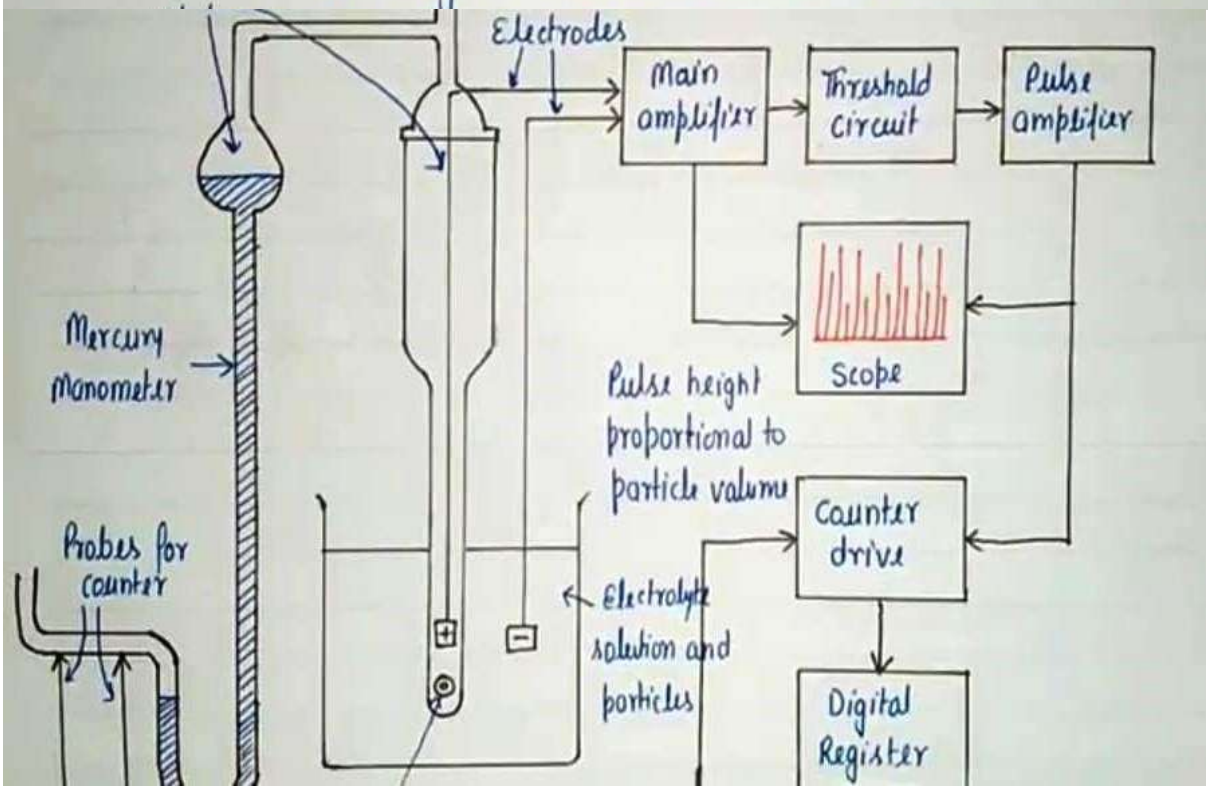
(4) Coulter Counter Method :-

* Used for measuring particle volume.

Principle :- When a particle suspended in a conducting liquid passed through a small orifice. (on either side of which are electrodes)

↓

a change in electric resistance occures.



* A known volume of a dilute suspension is pumped through the orifice
(electrodes located on either side of the apparatus)

↓

a constant voltage is applied through electrodes to produce a current

↓

The change in the electrical signal that occurs when particle occupies the orifice and displaces its own volume of electrolyte.

↓

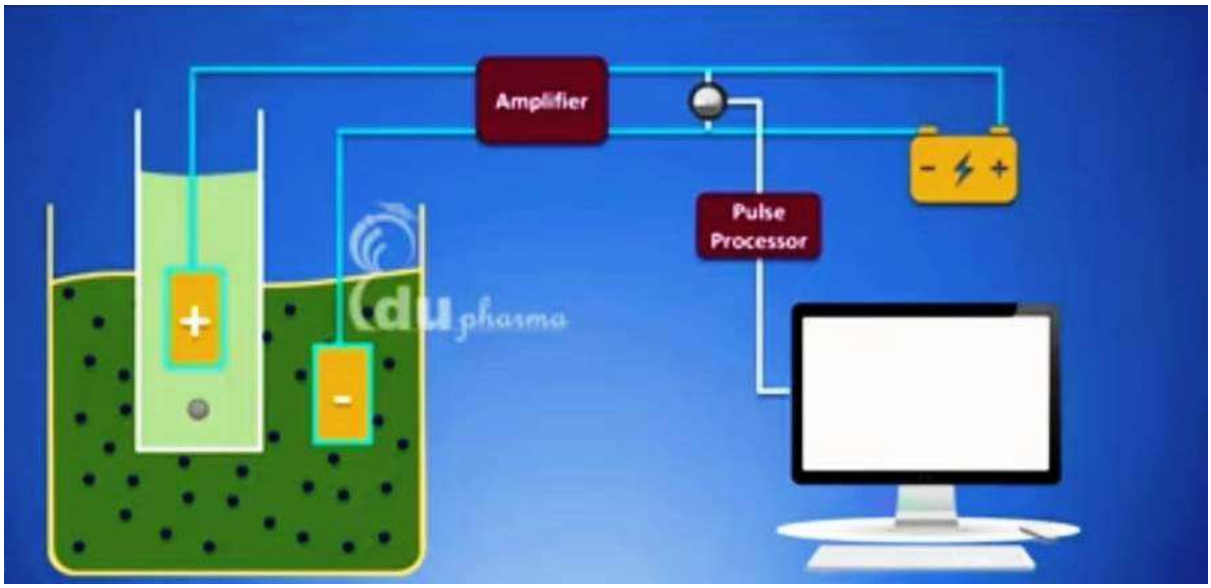
change in resistance b/w electrodes cause voltage pulse

change in resistance b/w electrodes cause voltage pulse
which is amplified and processed electronically.

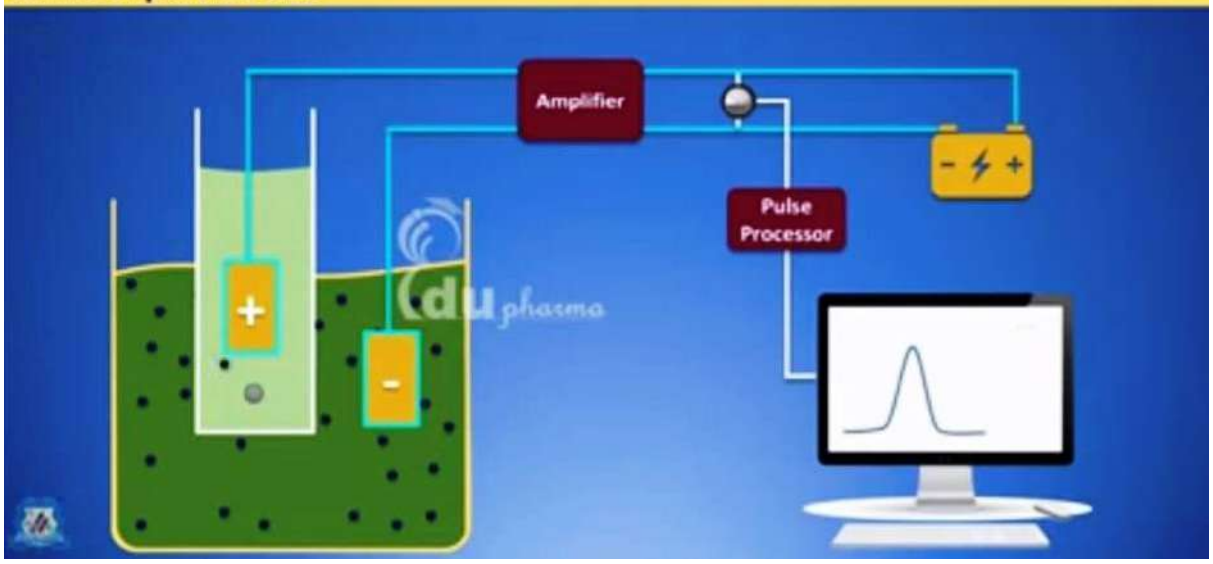
* The magnitude of pulse is generated which is proportional to the volume of particles.

Advantages:- * It is one of the precise and accurate method.
* Analysis range is wide.

Disadvantages:- * Aggregation of particle produce wrong result.
* Coarse particles blocking orifice.



The change in resistance, which is related to the particle volume, causes a voltage pulse that is amplified and fed to a pulse-height analyzer calibrated in terms of particle size



Methods for Determining Surface area

* The surface area of a powder can be determined indirectly from knowledge of → particle size Distribution
  ↘ volume determined by coulter counter.

* The surface area can directly determined by two methods
  (1) The adsorption method and
  (2) The air permeability method

(1) Adsorption Method :-

* Particles with a large specific surface (small particle size) are
  ↓
  good adsorbents of gases and solute from solution.

* The amount of gas or solute adsorbed on powder sample to form a monolayer
  ↓
  is found out and from this data surface area of the powder is determined.

(a) By using a solute which forms a monolayer :-

In this method, a solution of solute is prepared in a medium in which adsorbent powder is insoluble.
↓
a known amount of powder is then added and content was stirred for a sufficient time. (till equilibrium)
↓
the powder is filtered and amount of solute remaining in solution is determined. (by suitable method)

(b) By Using adsorption of gas on powder :-

Instrument is used is called Quantasorb

* The powder whose surface area to be determined is introduced into a cell in the instrument and

↓

nitrogen which is the adsorbate gas and helium which is an inert gas (not absorbed) passed through the powder in the cell.

↓

A thermal conductivity detector measure the amount of nitrogen adsorbed at every equilibrium pressure

↓

a bell shaped curve is obtained

→ Signal height gives rate of adsorption of nitrogen

→ area under curve provides ampunt of gas adsorbed

The volume of nitrogen gas Vm in cm^3 absorbed by 1 gram of powder (when monolayer formed)

↓

given by Brunauer, Emmett, and Teller (BET) equation.

$$\frac{P}{V(P_o - P)} = \frac{1}{V_m\, b} + \frac{(b+1)\,P}{V_m\, b\, P_o}$$

where

V = volume of gas in cm^3 adsorbed per gram of powder at pressure P

* The specific surface of the powder is obtained by -

$$S_w = \frac{A_m N}{m/\rho} \times V_m$$

where

m/ρ = molar volume of gas = 22,414 cm^3/ mole

N = Avogadro's number 6.02×10^{23}

A_m = area of single close packed gas molecule adsorbed as a monolayer on surface of powder particles

for nitrogen the value is 16.2×10^{-16} cm^2

(2) Air Permeability Method :-

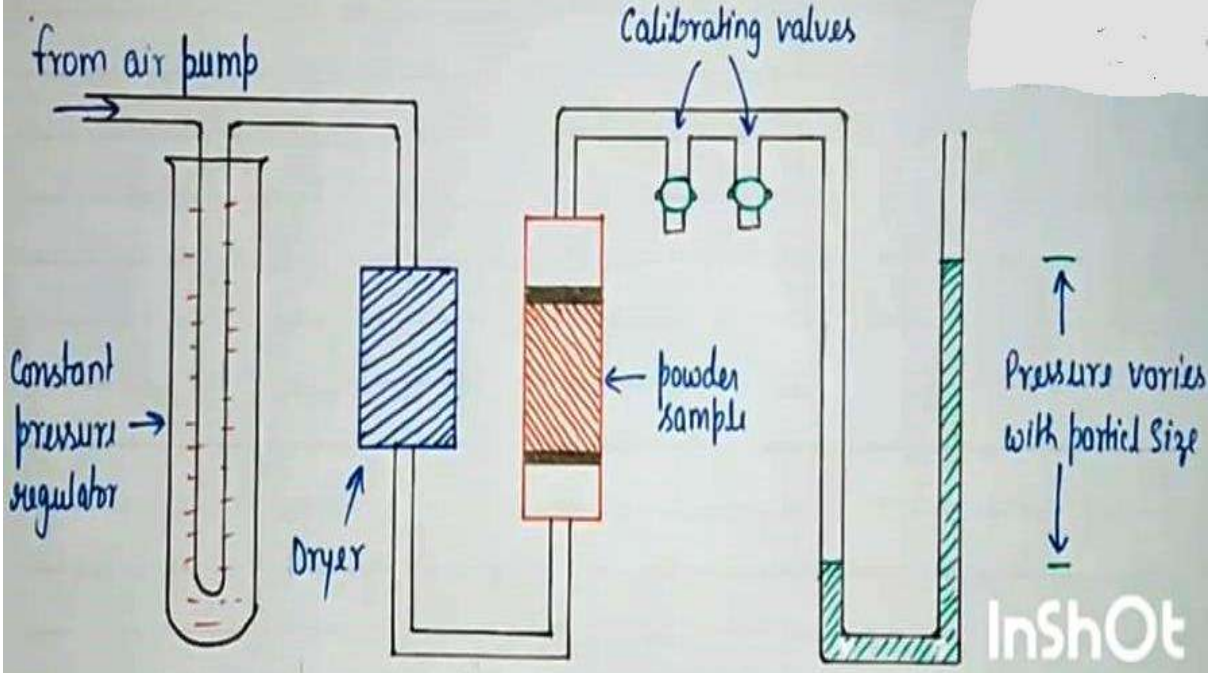
* This method is based on the principle that

↓

The resistance offered to the flow of fluid (air) through a plug of compacted powder is proportional to the surface area of the powder.

* The greater the surface area per gram of powder,
  ↳ the greater is the resistance to flow.

* Instrument is called - fisher subsieve sizer.



* According to Poiseuille's equation

$$V = \frac{\pi d^4 \Delta P t}{128 l \eta}$$

Where V = volume of air flow
l = length
d = internal diameter
t = time
ΔP = Pressure difference
η = viscosity of fluid (air)

* When air flow through plug of compacted powder
↓
resistance to flow of air occurs.

* This resistance is related to surface area of the powder

* So as per Kozeny-Carman equation.- derived from Poiseuille's equation

$$V = \frac{A}{\eta S_w^2} \times \frac{\Delta P t}{K l} \times \frac{\varepsilon^3}{(1-\varepsilon)^2}$$

Where A = Cross sectional area of plug.
K = constant (usually 5.0 ± 0.5)
ε = porosity

from this equation specific surface (S_w) can be calculated.

Particle Shape:- A sphere has a minimum surface area per unit volume.

↓

more asymmetric the particle → the greater is the surface area per unit volume.

* A sphere is characterised by its diameter.

* An asymmetric particle is more difficult to characterise in terms of surface diameter

↓

so asymmetric particle's surface diameter is measured in terms of some equivalent spherical diameter.

Surface area of sphere $S = \pi d^2$

Volume of sphere $V = \pi d^3/6$

{ where d = diameter of particle }

* So to estimate surface area or volume of an asymmetric particle → it is necessary to choose a diameter that relates this to surface area or volume of a sphere through a correction factor.

* Suppose → the particle size is determined microscopically

↓

the projected diameter is d_p

So, Surface area $= \alpha_s d_p^2 = \pi d_s^2$

Where α_s = surface area factor

d_s = equivalent surface diameter.

Volume $= \alpha_v d_p^3 = \pi d_v^3/6$

Where α_v = volume factor
d_v = equivalent volume diameter.

* for a sphere

$$\alpha_s = \pi d_s^2 / d_p^2 = 3.142$$

$$\alpha_v = \pi d_v^3 / 6 d_p^3 = 0.524$$

* The ratio α_s / α_v is used to characterise particle shape

When particle is spherical $\alpha_s / \alpha_v = 6$

$$\frac{\alpha_s}{\alpha_v} = \frac{3.142}{0.524} = 6$$

* The ratio α_s / α_v is used to characterise particle shape.

When particle is spherical $\alpha_s / \alpha_v = 6$

$$\frac{\alpha_s}{\alpha_v} = \frac{3.142}{0.524} = 6$$

* If this ratio exceeds the minimum value of 6

↓

particles deviate from being spherical.

* More this ratio exceeds from 6 → more asymmetric

Specific Surface :-

* The specific surface of a powder is defined as
↓
the surface area per unit volume (S_v) or per unit weight (S_w)

* The specific surface area per unit volume is given by

$$S_v = \frac{\text{Surface area of particles}}{\text{Volume of particles}}$$

$$S_v = \frac{n \alpha_s d^2}{n \alpha_v d^3} = \frac{\alpha_s}{\alpha_v d} \quad \text{——— (1)}$$

where

N = number of particles
d = volume-surface mean diameter

* The surface area per unit weight is

$$S_w = S_v / \rho$$

where ρ = true density of particles

* Putting the value of S_v from equation (1)

$$S_w = \frac{\alpha_s}{\rho d_v \alpha_v}$$

$$S_w = S_v / \rho$$

where ρ = true density of particles

* Putting the value of S_v from equation ①

$$S_w = \frac{\alpha_s}{\rho \, d_{vs} \varepsilon_v}$$

for spherical or nearly spherical particles -

$$S_w = \frac{6}{\rho \, d_{vs}}$$

(as $\alpha_s / \varepsilon_v = 6$ for a sphere)

Particle Number

* Particle number N is defined as

↓

the number of particles per unit weight of a powder.

* Assuming that

→ particles of the powder are spherical
→ Volume of a single particle is → $\pi d_{vn}^3 / 6$
→ mass of a single particle is → volume x density

↓

$\pi d_{vn}^3 \rho / 6$

Where d_{vn} is mean diameter
ρ is density of particle.

* So number of particles per gram can be obtained by -

$$N = \frac{1 \text{ gm of the powder}}{\text{Mass of one particle.}}$$

$$N = \frac{1}{\pi d_{vn}^3 \rho / 6}$$

$$N = \frac{6}{\pi d_{vn}^3 \rho}$$

Q.1 The mean volume number diameter of a sample of powder is 3.62 mm, If density of the powder is 3.0 g/cm³, what is number of particles per gm?

Solution:- Volume number mean diameter (d_{vn}) = 3.62 mm = 3.62×10^{-4} cm

Density of the powder (ρ) = 3.0 g/cm³

$$N = \frac{6}{\pi d_{vn}^3 \rho} = \frac{6}{3.14 \times (3.62 \times 10^{-4})^3 \times 3.0} = \frac{6}{3.14 \times 47.44 \times 3.0 \times 10^{-12}} = 1.34 \times 10^{10}$$

RHEOLOGY

Rheology is a branch of science which deals with the deformation of materials or matter under the influenced of stress. The term rheology has its origin from the Greek "rheo" means flow and "logos" means science. So, the definition can further be simplified as "The science which deals with the flow of fluid type preparations. Flow property of a simple liquid is expressed in terms of viscosity. Quantitively, viscosity is an index of resistance of a liquid to flow. The higher the viscosity of a liquid, the greater is the resistance to flow.

Applications:

- **Standards of liquids:** The viscosity of common liquids of pharmaceutical importance are standardized and reported. For example, liquid paraffin has the viscosity of less than 64 centistokes at 37.8 ^{0}C.
- **Manufacture of dosage form:** Materials undergo process such as mixing, flowing through pipes, filling into the containers etc. Flow related changes influence the selection of mixing equipment. The manufacture of simple liquids, gels, ointments, creams and pastes are influenced. If the material is highly viscous, large amount of energy is required for mixing. Sometimes, heat is applied to convert gel – like consistency to liquid – like consistency, so that mixing can be effective under low viscosity conditions.
- **Handling of drugs for administration:** The syringibility of the medicines, pouring of liquid from containers, extrusion of ointment from tubes, all depend on the changes in flow behavior of dosage forms. This also ensures compliance of the patient. The words on the label such as 'shake well before use' also indicate that flow behavior changes. After shaking, the liquid flows out well through the neck of the container. These helps in achieving patient compliance.
- **Quality control tools for product evaluation:** The performance of the product is evaluated routinely for maintaining the behavior and to reduce batch to batch variability. For example, dextran 40 and dextran 110 injections are analysed by determining the viscosity ratios at 37 ^{0}C. most of the cases, compendial testing is limited to fluids following Newtonian type.
- **Determination of molecular mass (molecular weight):** Molecular weight of polymers such as albumin, insulin and dextran can be determined from the viscosity measurements.
- **Viscosity improving substances:** Hydrocolloids and polymers are added to vehicle for maintaining the product consistency, in preparing suspensions and emulsions. The influence of these additives and their concentrations are selected, to maintain the desired flow behavior. These influence the physical stability and bioavailability of the drug.
- **Identification of diseases:** A change in consistency of the body fluids, mucus, blood, saliva etc. is used as an indicator of the severeness of the diseases.
- **Model for treatment of diseases:** The effectiveness of drugs against diseases such as mucoviscidosis can be tested by studying the consistency changes.

Newton's law of flow:

Deformation is a result of force applied on the body. In addition, gravity or inertia also produces deformation. The stress and its influences on the flow can be expressed as mathematical expression namely newton's law of flow.

Shear stress is defined as the force per unit area, which is applied to bring about the flow.

$$\text{Shear stress, } F = \frac{F'}{A}$$

Where F = force, N/m^2 (Pa)

F' = Shear stress, N

A = area, m^2

When stress is applied, the body changes its shape, strain. It may be regarded as rate of shear. Velocity gradients or rate of shear is defined as the change in velocity between the top and bottom places of liquid separated by a distance, dr.

$$\text{Rate of shear, } G = \frac{dv}{dr}$$

Where v = velocity, m/s

r = distance, m

G = rate of shear, S^{-1}

The velocity gradient occurs in the sample during flow. The higher the shear, the greater is the rate of shear. Hence, the relationship between shear stress and rate of shear is given as:

Shear stress α Rate of shear (strain)

$$\frac{F'}{A} \alpha \frac{dv}{dr}$$

The viscosity is a constant and does not depend on the shear rate or on time. In several cases, the stress – strain relationship is not equal, but the flow line pattern is curved. Therefore, proportionality constant is included.

$$\frac{F'}{A} = \eta \frac{dv}{dr}$$

$$F = \eta G$$

Where $\eta = N.s.m^{-2}$ (Pa.S)

The η is the coefficient of viscosity, and usually referred to as viscosity. Viscosity is calculated by

$$\eta = \frac{F}{G}$$

Coefficient of viscosity is defined as the force per unit area required to maintain unit area required to maintain unit difference in velocity between two parallel layers in the liquid, one meter apart.

In CGS units, viscosity is expressed as poise, named after poiseulle for his valuable contribution to the study of rheology. It is also expressed as dy/cm^2. In SI system, the units are pascal second (Pa.S).

Fluidity: It is denoted by phi (ϕ). It is the reciprocal of viscosity.

$$\Phi = \frac{1}{\eta}$$

So the bodies with less viscosity have high values of fluidity and vice-versa.

The other types of viscosities include:

(a) Kinematic Viscosity: it is defined as viscosity (η) divided by the density (ρ)of the liquid.

Viscosity is expressed in terms of kinematic viscosity in the official pharmacopoeias, IP, BP, USP and National Formulary. It is expressed mathematically as:

$$\text{Kinematic viscosity} = \frac{\eta}{\rho}$$

The unit of kinematic viscosity is stokes (s) and centistokes (cs). In SI system, kinematic viscosity is expressed as m^2/s.

Dynamic viscosity (η): it is defined as resistance provided to a layer of liquid when it moves over another layer of liquid.

$$\eta = \frac{c}{dv/dr}$$

(b) Relative Viscosity: The coefficient, abbreviated, η_r is defined as the ratio of viscosity of the dispersion (η) to that of the solvent, η_0 (vehicle). It is mathematically expressed as:

$$\text{Relative viscosity, } \eta_r = \frac{\eta}{\eta 0}$$

(c) Specific viscosity: This term is defined as the relative increase in the viscosity of the dispersion over that of the solvent (vehicle) alone. It is mathematically expressed as:

$$\text{Specific viscosity, } \eta_{sp} = \frac{\eta - \eta 0}{\eta 0}$$

(d) Reduced viscosity: This term is defined as the ratio of specific viscosity to the concentration (c). It is mathematically expressed as:

$$\text{Reduced viscosity, } \eta_{red} = \frac{\eta sp}{c}$$

Factors influencing the viscosity:

Intrinsic factors:

- Chemical nature, i.e., molecular size, shape and intermolecular forces, influences the viscosity. The heavier the molecule of the given liquid, the greater will be the viscosity.
- Liquids with large and irregularly shaped molecules are generally known to be viscous compared to small and symmetric molecules.
- Molecular collisions between larger molecules are not elastic, i.e. involve loss of kinetic energy.
- Thus, intermolecular interactions are stronger and the molecules tend to stick to each other thereby increasing the viscosity of the liquid.
- The higher the intermolecular forces, the higher is the viscosity. Molecules with spherical shape are expected to slide past one another, and thus have low viscosity.

Extrinsic factors:

- Pressure, temperature and added substances also influences the viscosity.
- An increase in pressure enhances the cohesive forces of interactions, leading to an increase in the viscosity.
- In general, small quantities of nonelectrolytes like sucrose, glycerin and alcohol when added to the water, the solution exhibits increased viscosity.
- Similarly, polymers and other macromolecules enhance the viscosity of solvents such as water.
- On the other hand, small amounts of strong electrolytes decrease the viscosity. As the temperature increases, the system acquires thermal energy which facilitates the breaking of the cohesive forces.
- The viscosity of liquid decreases. In case of gases, an increase in temperature increases the viscosity owing to the increased molecular collisions and interactions.

Newtonian flow:

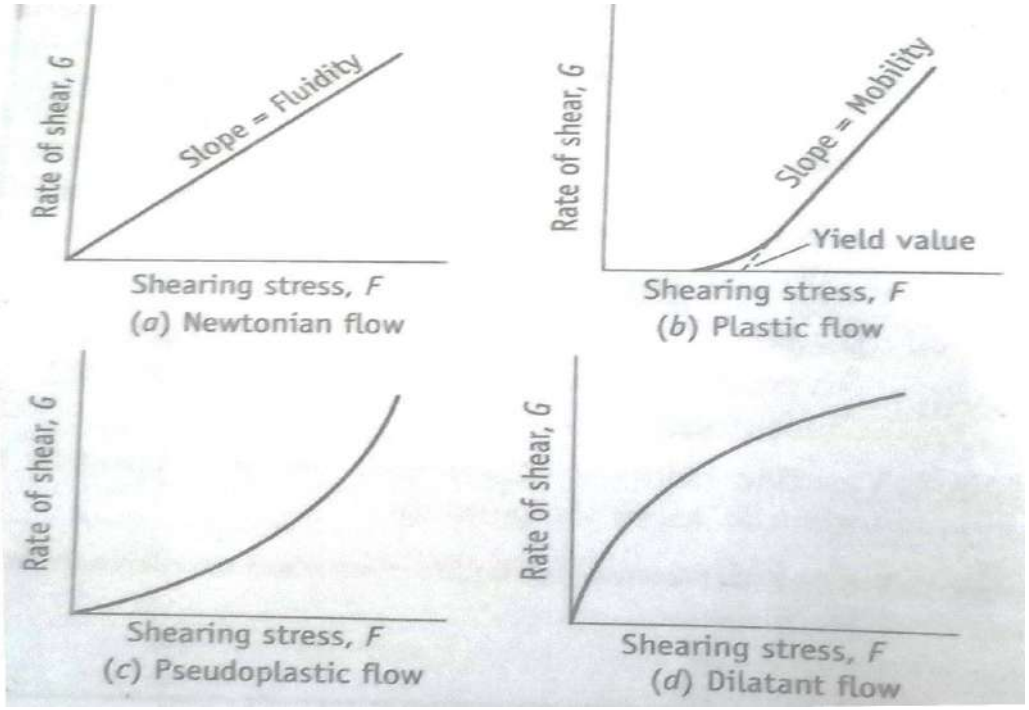
Newton was the first to study the flow properties of liquid in quantitative terms. Liquids that obey newton's law of flow are called as Newtonian fluids. Newtonian equation for the flow of a liquid is.

$$F = \eta G$$

Shear stress – shear rate relationship is normally represented in the form of a curve namely rheogram or consistency curve. When data are plotted by taking F on x axis and G on y axis, a flow curve is obtained. The rheogram passes through the origin and the slope gives the coefficient of viscosity. Systems that follow this linear relationship are called as Newtonian fluids. The viscosity of such a fluid is constant at a given temperature and pressure.

Examples: Water, glycerin, chloroform, solutions of syrups & very dilute colloidal solution.

Molten Vaseline behaves Newtonian, whereas Vaseline is classified as non-Newtonian at room temperature.



Non – Newtonian flow:

Simple liquids exhibit Newtonian flow. Rheologic properties of heterogenous dispersions such as emulsions, suspensions and semisolids are more complex and do not obey newton's equation of flow.

Non-Newtonian phenomena may be time independent or time dependent. These are:

Time independent:

- Plastic flow
- Pseudoplastic flow
- Dilatant flow

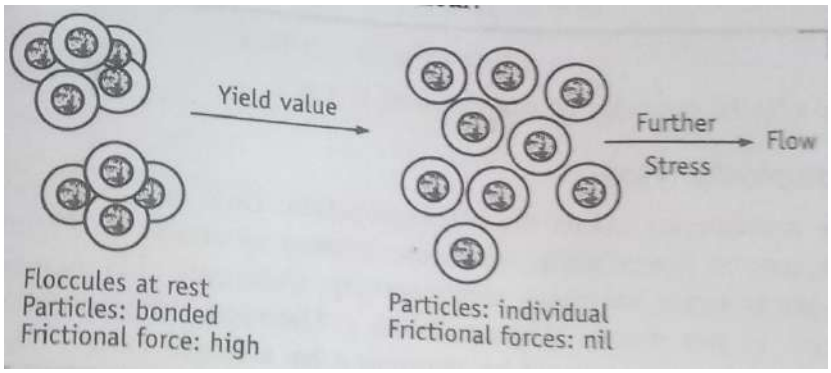
Time dependent:

- Thixotropy
- Rheopexy

Plastic flow: The curve does not pass through the origin. The substances initially behaves like an elastic body and fails to flow when less amount of stress is applied. Further increase in shear stress leads to a nonlinear increase in the shear rate which progressively gets linearized. The linear portion when extrapolated intersects the x axis at a point called yield value. Plastic flow can be adequately expressed in terms of yield value and plastic viscosity.

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions, butter, certain ointments, pastes and gels.

Floccules are the aggregation of particles with inter-particle contacts. This structure is maintained when the system is at rest. Yield value represents the stress required to break the inter-particles contacts so that particles behave individually. Therefore, yield value is indicative of the forces of flocculation. Frictional forces between moving particles also contribute to the yield value. Once the yield value exceeds, further increase in shearing stress (F-f) will bring about a proportional increase in the rate of shear.



Materials that exhibit plastic flow are often called as Bingham bodies, in honour of Bingham, who carried out many of the early studies on these materials. The quantitative behavior is expressed in terms of Bingham equation. The slope of the rheogram is termed as mobility and its reciprocal is known as plastic viscosity, U and expressed as

$$U = \frac{F-f}{G}$$

Where F = shear stress, N/m^2

f = yield value, N/m^2

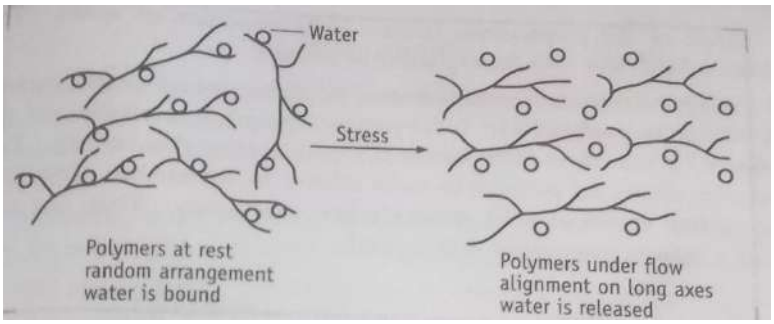
G = rate of shear, S^{-1}

Yield value, f, is the intercept on the shear stress axis and has the units dy/cm^2.

Pseudoplastic flow:

The consistency curve for a pseudoplastic flow begins at the origin. As the shear stress increases progressively, shear rate also increases, but the trend is not linear. Therefore, the viscosity of a pseudoplastic system cannot be expressed by a single value. The entire curve is the most satisfactory representation of the pseudoplastic material. Pseudoplastic flow can be found in emulsions, suspensions etc. in general, pseudoplastic flow is exhibited by polymer dispersions such as tragacanth in water, sodium alginate in water, methylcellulose in water, sodium carboxy methylcellulose in water.

The materials are known as shear thinning materials. Mechanistic explanation for the observed behavior is as follows. Under normal storage conditions, the long chain molecules of the polymers are randomly arranged in the dispersion. On applying a shear stress, these molecules begin to arrange their long axes in the direction of force applied. This stress molecules begin to arrange their long axis in the direction of force applied. This stress induced orientation reduces the internal resistance of the material. In addition, the solvent molecules which were earlier associated with the polymer molecules will also be released. Thus, the effective concentration and size of the molecules are lowered. Now, the material allows greater shear rate on progressive increase in the shearing stress.



Pseudo plastic flow rheogram can be described by the following exponential formula.

$$F^N = \eta' G$$

Where N is a number given to the exponent and η' is the viscosity coefficient, In case of pseudoplastic fluids, N is higher than 1 and rises as the flow becomes increasingly non-Newtonian. The greater the value of N above unity, the greater the pseudoplastic behavior of the material. Taking logarithms of both sides the above equation can be written as:

$$N \log F = \log \eta' + \log G$$

On rearrangement of equation

$$\log G = N \log F - \log \eta'$$

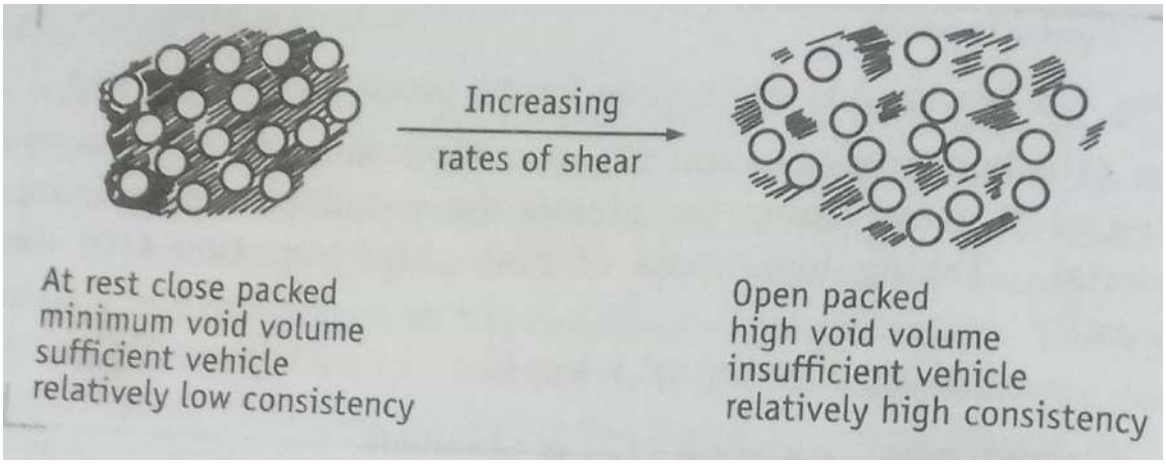
The above equation represents a straight line. This is a simplified approach because some fluids do not obey above equation, though they exhibit pseudoplastic flow.

Dilatant flow:

The system exhibits enhanced resistance to flow with increasing rate of shear. When sheared, these systems increase their volume and hence are called as dilatant. Dilatant materials are also often termed as shear thickening system because of increased apparent viscosity at higher rates of shear. When the stress is removed, the system returns to its initial state of fluidity. Dilatant flow is exhibited by:

- Suspension containing high concentration of solids (>50%) of small, deflocculated particles.
- Suspension of starch in water.
- Inorganic pigments in water eg. Kaolin 12% in water, zinc oxide 30% in water.

Most of the preparation contain high proportion of solids. The dilatant behavior may be explained as follows.



When the dilatant system is at rest, the molecules are closely packed. A minimum void volume is available and the amount of vehicle is sufficient to fill the void volume. This situation allows the particles to move relative to one another. Therefore, the system at rest exhibits relatively low consistency. Thus, one may pour a dilatant suspension from a bottle.

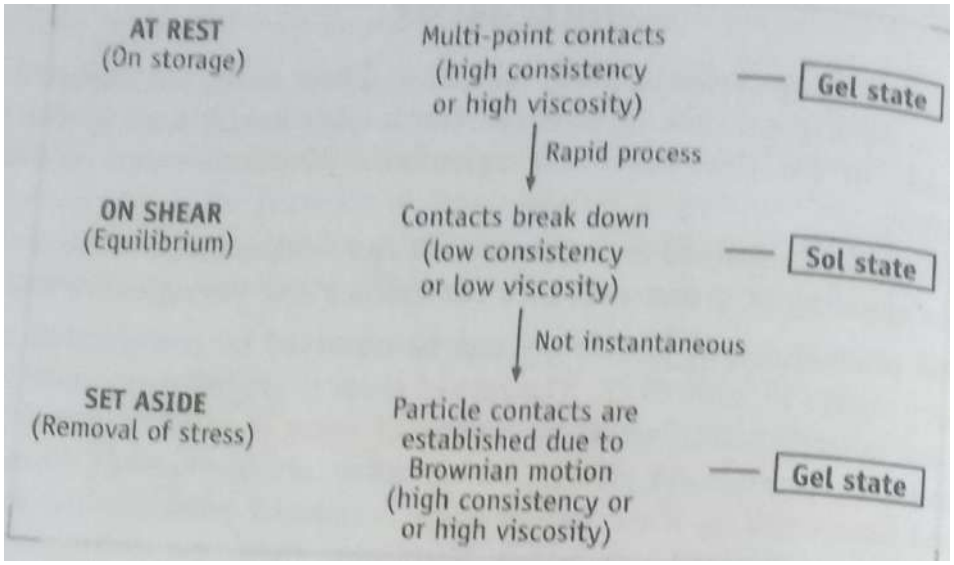
When shear stress is applied, the particles assume open form of packing and the bulk of the system expands or dilates, i.e. the void volume significantly increases. But the amount of vehicle is insufficient to fill this expanded void space. Thus, the particles are not wetted or lubricated and develop resistance to flow. Finally, the system will show a paste like consistency. For this reason one has to be cautions in selecting equipment in the manufacture of dispersion system of a dilatant type.

The sediment in the deflocculated suspension is dilatant and resists any attempt of stirring or shaking. This effect is known as caking or claying of suspension. This behavior should be avoided. In this case, N is less than 1 and decreases as the degree of dilatancy increases.

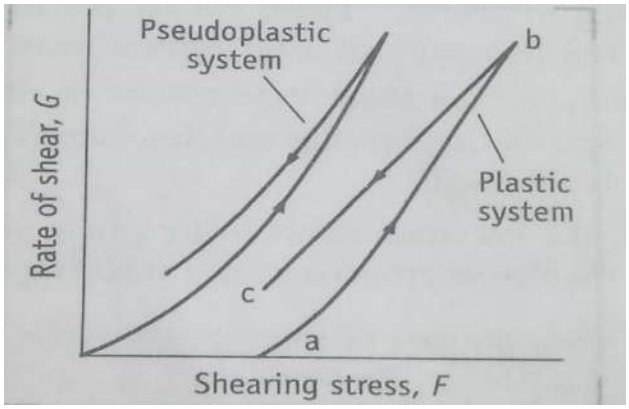
Thixotropy:

Thixotropy is defined as an isothermal and comparatively slow recovery of a system whose consistency is lost through shearing.

Example of pseudoplastic system showing thixotropy include HPMC (Hydroxy propyl methyl cellulose) in water. Initially, HPMC form random network of hydrated elongated particle i.e. Gel and viscosity get increased. On application of shearing stress these particles align themselves parallel to the direction of flow and interparticle attractions are broken. Then gel get converted into solution and viscosity get decreases. On removal of shearing forces, again gel network is reformed and viscosity also increases, not immediately but after some time lag.



The rheogram shows that a hysteresis loop is obtained. On applying shearing stress an upcurve is obtained while on removal of shear stress a down-curve is obtained. But these curves are not super-imposable. The viscosities of down curve are lower than the upcurve.



Bulges:

In case of concentrated aqueous magma (gel) of bentonite (10-15% w/w) produces a hysteresis loop with a characteristic bulge in the up-curve. This may be due to the arrangement of crystalline plates of bentonite in the form of "house-of-cards structure" that causes the swelling of bentonite magmas. This three-dimensional structure result in a bulged hysteresis loop as observed.

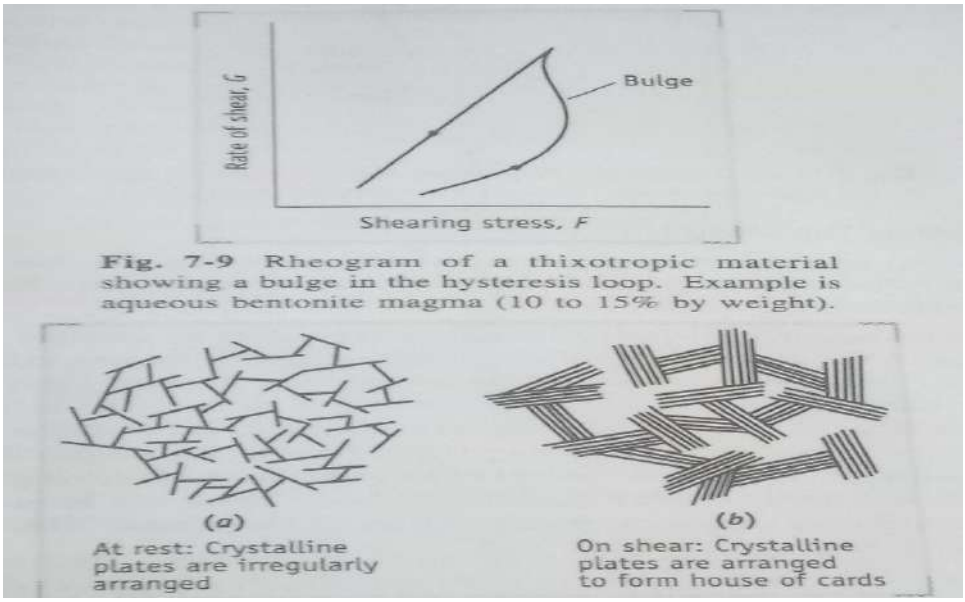
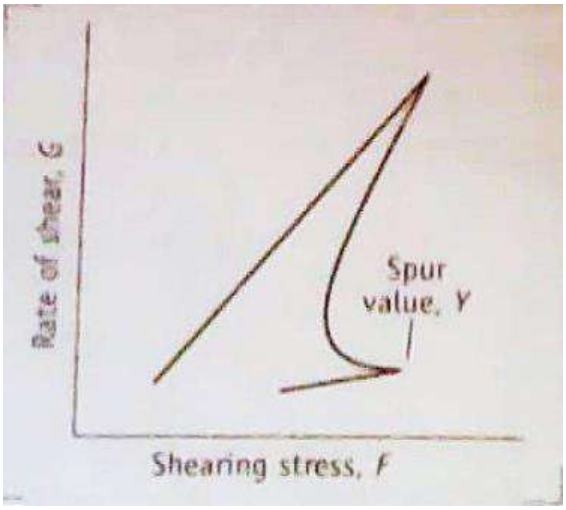


Fig. 7-9 Rheogram of a thixotropic material showing a bulge in the hysteresis loop. Example is aqueous bentonite magma (10 to 15% by weight).

Spurs:

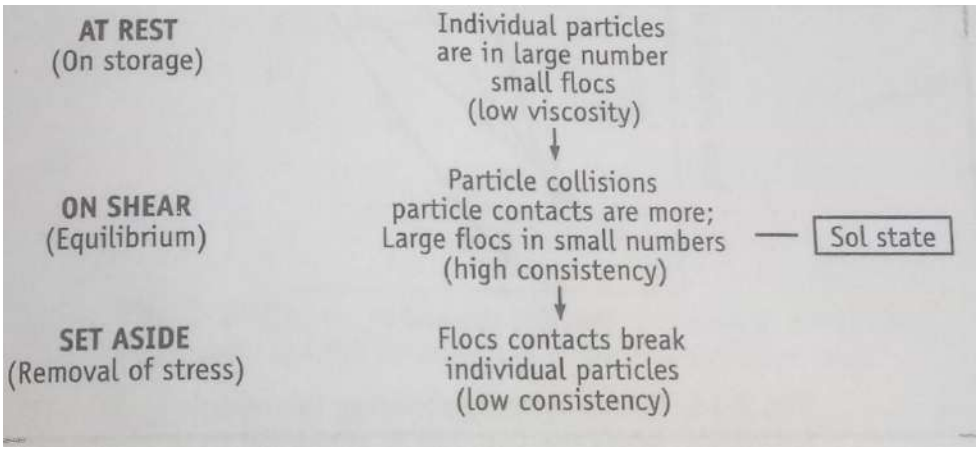
The gel formulations containing procaine pencillin gel shows a typical rheogram with a characteristic spur-like protrusion. The spur represents a sharp point of structural breakdown at low shear rate. The structure demonstrates a high yield or spur value, y, that traces out a bowed up-curve when the three-dimensional structure breaks in the viscometer.



Negative thixotropy and Antithixotropy:

Negative thixotropy is a phenomenon in which there is increase in viscosity on down curve. Example of negative thixotropy include suspension containing less number of floccules while more number of deflocculated particles. On application of shear stress number of flocculated particles increase and as a result viscosity also increases. The viscosity obtained on down curve is greater than that of up-curve.

The rheogram of negative thixotropy shows that the down-curve appears above the up-curve. The graph also shifts toward right indicating that system is gaining viscosity. But it is up to a limit. Beyond the limit, if the shear stress increases, there will be no increase in viscosity.



Rheopexy:

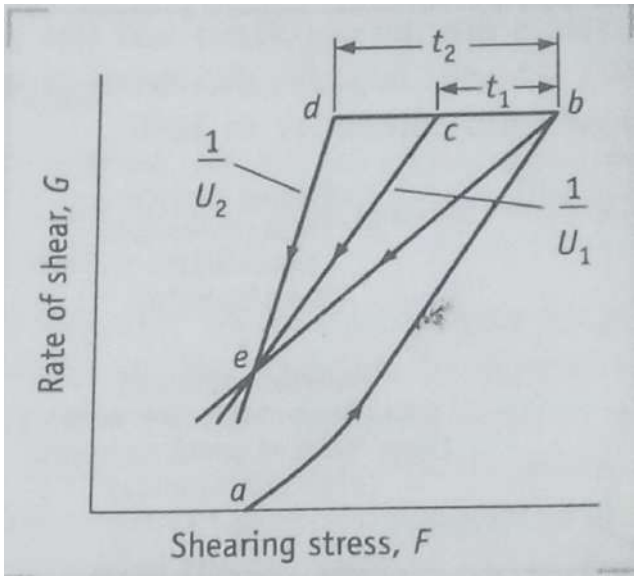
Rheopexy is a phenomenon in which solid substance forms a gel more readily when shaken gently or sheared. The system exists in gel state at equilibrium unlike antithixotropic substances which exists in sol form.

Magnesia magma and clay suspensions may show a negative rheopexy, analogous to negative thixotropy.

Measurement of thixotropy:

a. The measure of area of hysteresis loop formed by the up and down curves in a thixotropic material gives the value of thixotropic break down. This value can be obtained by using a planimeter.

b. In a thixotropy system, the nature of rheogram largely depends on the rate at which shear is increased or decreased. Consider a material that follows plastic flow. Suppose shear rate is increased at a constant rate on the system upto a point 'b' and then decreased. When the results are plotted, ábc' rheogram is obtained. If the shear rate is maintained at b for time t_1 seconds and then decreased, ábce' rheogram is obtained. Similarly at point 'b' if the shear rate is maintained for time t_2 seconds and then decreased, a'bde' curve is obtained. The structural breakdown with respect to time at constant rate of shear gives the rheogram. Based on such rheogram, the thixotropic coefficient, B, is calculated using following equation.



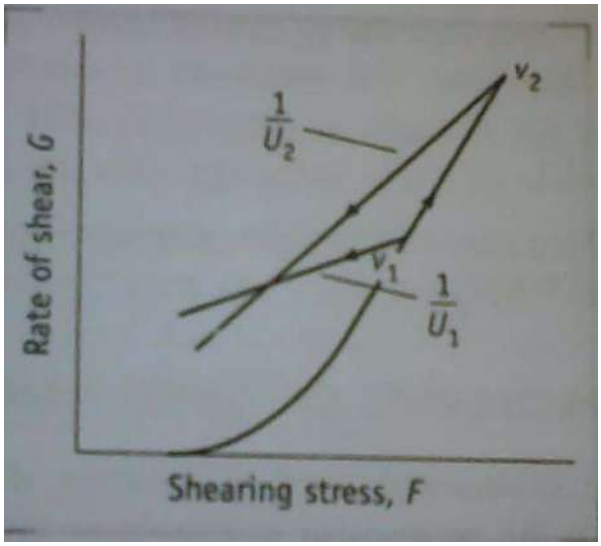
$$B = \frac{(U1-U2)}{\ln(\frac{t2}{t1})}$$

Where U_1 and U_2 are the plastic viscosities of the two down curves. Thixotropic coefficient, B, represents the rate of breakdown with time at constant shear rate.

c. In this method, the system is subjected to different rates of shear (say, v_1 and v_2) and the rheogram is obtained, which shows two hysteresis loops. The thixotropic coefficient, M, is calculated using the following equation.

$$M = \frac{2(U1-U2)}{\ln(\frac{v2}{v1})2}$$

Where M is in dy.s/cm^2. U_1 and U_2 are the plastic viscosities of the down-curves having shearing rates of v_1 and v_2 respectively. Thixotropic coefficient, M, represents the loss in shearing stress per unit increase in shear rate.



The limitations of this approach are that the value of M shows considerable variation and it depends on the proper selection of the rates of shear.

(Thixotropic coefficient is a simple test for analyzing the time -dependent behavior of samples.)

Thixotropy in formulations:

1. The greater the thixotropy, the higher is the physical stability of the suspension. During storage, a suspension should have high consistency in the container, so that the suspended particles do not settle rapidly.

   On moderate shaking the suspension should become fluid (sol), so that the contents can be poured easily from the container. Thus, the principles of thixotropy are useful in dispensing and administration of a dose. At rest, the suspension regains its original consistency. This gel-sol-gel transformations improve the physical stability of dosage form.

2. The degree of thixotropy is related to the specific surface of penicillin used. Parenteral suspension containing 40 to 70% of procaine penicillin G in water has higher inherent thixotropy. While injecting the preparation, the structure of the suspended particles breaks down so that the product can pass through the hypodermic needle. After the injection, the original structure of gel will be rebuilt. This leads to depot of the procaine penicillin G at the site of injection in the muscle, from which it is slowly released so as to provide sustained levels of drug in the body.

DETERMINATION OF VISCOSITY:

Viscometers are used to determine viscosity. Viscometers are classified as

1. Capillary viscometer
2. Falling sphere viscometer
3. Rotational viscometers-cup-bob, cone-plate viscometers

Capillary viscometer:

Ostwald viscometer is used to determine the viscosity of a Newtonian liquid. Both dynamic and kinematic viscosities can be obtained.

Principle: When a liquid flow by gravity, the time required for the liquid to pass between two marks through a vertical capillary tube is determined. The time of flow of the liquid under test is compared with the time required for a liquid of known viscosity. The viscosity of the unknown liquid (η_1) is determined using following equation.

$$\eta_1 = \frac{\rho 1\, t1}{\rho 2\, t2}\, \eta_2$$

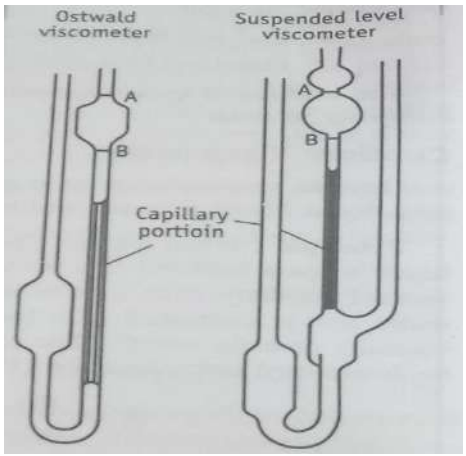
Where ρ_1 = density of the unknown liquid, kg/m^3

t_1 = time of flow of unknown liquid, s

ρ_2 = Density of the known liquid, kg/m^3

t_2 = time of flow of unknown liquid, s

η_2 = viscosity of the known liquid, Pa.s



Procedure:

1. A clean and dry Ostwald viscometer should be selected and fixed firmly to a stand in vertical position.
2. With the help of a pipette, a fixed amount of water is transferred through a wide limb. Through the rubber tube, water is sucked to the level above the upper mark A.
3. Then water is allowed to flow down. When water meniscus reaches mark A, the stop clock is started. When the meniscus reaches the mark B, the stop clock is stopped.

4. The difference in time represents the flow of time for a given liquid, water. An average of three determinations may give true value, t_2 sec.
5. Similarly, the above procedure is repeated with the liquid under test. The time of flow for the liquid represents t_1 sec.
6. The densities of water and liquid are estimated by a suitable method. Substituting this data in above formula gives the viscosity of the unknown liquid.

Applications:

a. Ostwald viscometer method is used for quality control purposes in the formulation and evaluation of pharmaceutical dispersion systems such as colloids, dilute suspensions, emulsions etc.
b. The study of flow of liquids through a capillary tube throw light upon the circulation of the blood.

Falling sphere viscometer:

The principle involved in falling sphere viscometer is based on the Hoeppler viscometer. The apparatus consists of glass tube positioned vertically. A constant temperature jacket with provision for water circulation is arranged around the glass tube. The test liquid is placed in the glass chamber. A glass or steel ball is dropped into the liquid and allowed to reach equilibrium with the temperature of the outer jacket. The tube with the jacket is then inverted, which places the ball at the top of the inner glass tube. The time taken for the ball to fall between two marks is accurately measured. This process is repeated several times to obtain concurrent results. The viscosity of a Newtonian liquid is calculated from the following equation.

$$\eta_1 = t\,(S_b - S_f)\,B$$

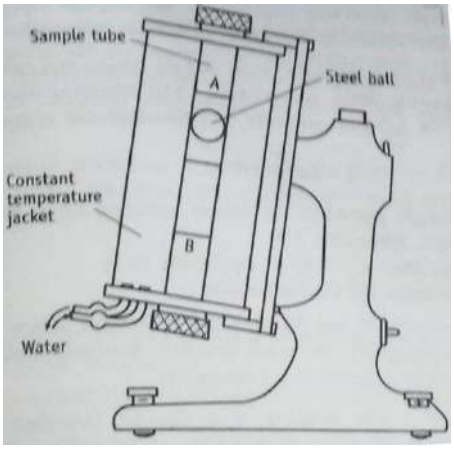
where t = time taken for the ball to fall between the two points, s

S_b = specific gravity of the ball

S_f = Specific gravity of the test fluid

B = constant for a particular ball, N/m^2 (Pa)

Depending on the diameter and material of construction of ball, this instrument can be used over a range of 0.5 to 20,000 Pa.s. For better results, select a ball which takes not less than 30 seconds to fall between the two marks. The largest possible diameter ball should be employed.



Cup and Bob viscometer:

This is multipoint viscometer and belongs to the category of rotational viscometers.

Principle:

The sample is placed in the cup and the bob is placed in the cup upto an appropriate height. The sample is accommodated between the gap of cup and bob. Now, either the cup or bob is made to rotate and the torque resulting from the viscous drag is measured by a spring or sensor in the drive of the bob.

Couette type: revolving cup type – Mac Michael viscometer

Searle type: revolving Bob type – Stomer viscometer

The number of revolutions (rpm) and the torque represent the rate of shear and shearing stress, respectively. The following equation is used to calculate the apparent viscosity of a pseudoplastic system.

$$\eta = k_v \frac{w}{v}$$

where w = weight placed on the hanger, shearing stress, N/m^2 (Pa)

v = rpm, shear rate, s^{-1}

η = apparent viscosity of the liquid, Pa.s

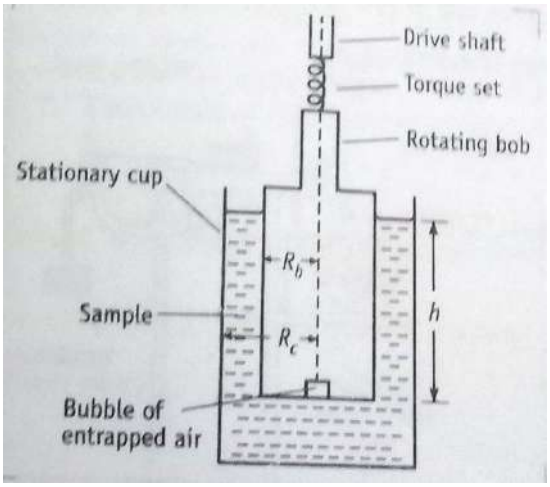
k_v = constant for the instrument

Apparent viscosities can be obtained at several points of shearing stress. Then a rheogram can be constructed. Similarly, a plastic system can be evaluated by constructing a rheogram.

Method:

The standard liquid for calibration or sample under study is placed in the space between the cup and bob and is allowed to reach temperature equilibrium. The temperature is to be maintained constant as it influences the viscosity. A weight is placed on the hanger, and the time taken for the bob to rotate 100 times is recorded by the operator. The data are then converted to rpm. This value represents the shear rate at one point of shearing stress.

The same procedure is repeated by increasing the weights. In this way, a rheogram cane be constructed by plotting rpm versus weights added. The rpm values can be converted to actual rates of shear and weights can be converted into the units of shear stress, by using appropriate constants.



Plug Flow: Cup and Bob viscometer suffers from disadvantage of plug flow, which is due to variable shear stress across the sample i.e., the values of shear stress of the sample close to bob may be sufficiently higher than the yield value but the shear stress of the sample close to the inner wall of cup may be below the yield value. This results in formation of solid plug and hence erratic values of viscosity. To avoid this largest bob that fits in to cup should be chosen. The plug flow is important in the flow of pastes and concentrated suspension through an orifice e.g., the extrusion of toothpaste from a tube.

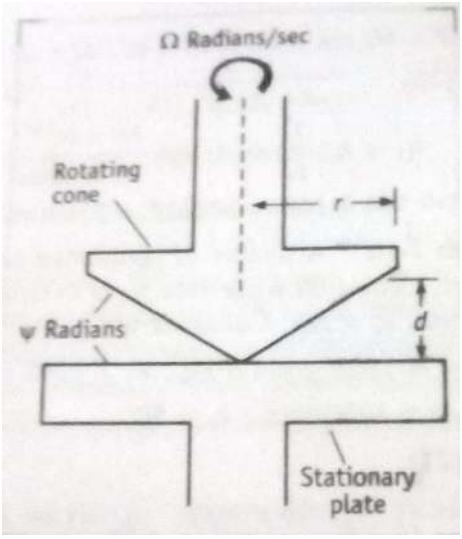
Cone and plate viscometer:

Cone and plate viscometer possesses several advantages.

1. The rate of shear is constant throughout the entire sample being sheared. Plug flow is not observed.
2. The sample required is small, 0.1 to 0.2 ml
3. Cleaning and filling easy.
4. Less time is required for temperature equilibration.

Principle:

The sample is placed at the center of the plate, which is then raised into a positon under the cone. The cone is driven by a variable-speed motor and the sample is sheared in the narrow gap between the stationary plate and the rotating cone. The rate of shear in rpm is increased and decreased by a selector dial and the viscous traction or torque produced on the cone is read in the indicator scale. A plot of rpm versus scale reading may thus be constructed in the usual manner.



Newtonian systems:

The viscosity is estimated by following equation.

$$\eta = C\frac{T}{V}$$

where C is the instrument constant, T is the torque reading and v is the speed of the cone (rpm).

Plastic viscosity: The viscosity (U) is estimated using following equation

$$U = Cf.\frac{T - Tf}{v}$$

And yield value (f) = C_f X T_f

In which T_f is the torque at the shearing stress axis and C_f is an instrumental constant.

Brookfield viscometer:

Brookfield viscometer is also a rotational viscometer. The construction of the instrument is similar to cup and bob viscometer. This viscometer is used to evaluate the rheological properties of suspensions with some modifications such as helipath arrangements (T spindle).