

# Syllabus

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## PHARMACEUTICS - I

### (Physical Pharmacy)

#### 1. Matter, Properties of Matter :

State of matter, change in the state of matter, latent heats and vapour pressure, sublimation - critical point, Eutectic mixtures, gases, aerosols - inhalers, relative humidity, liquid, complexes, liquid crystals, glassy state, solids - crystalline, amorphous and polymorphism.

#### 2. Micrometric and Powder Rheology:

Particle size and distribution, average particle size, number and weight distribution, particle number, methods for determining particle volume, optical microscopy, Asieving, sedimentation, measurement, particle shape, specific surface, methods for determining surface area, permeability, adsorption, derived properties of powders, porosity, packing arrangement, densities, bulkiness, and flow properties.

### 3. Surface and Interfacial Phenomenon

Liquid interface, surface and interfacial tensions, surface free energy, measurement of surface and interfacial tensions, Spreading coefficient, adsorption at liquid interfaces, surface active agents, HLB classification, solubilization, defoaming, adsorption at solid interfaces, solid-gas and solid-liquid interfaces, complex films and electrical properties of interface.

### 4. Viscosity and Rheology:

Newtonian systems, Law of flow, kinematic viscosity, effect of temperature, non-Newtonian systems, pseudoplastic, dilatant, plastic, thixotropy in formulation, determination of viscosity, capillary, falling ball, rotational viscometers, thixotropy,

### 5. Dispersion Systems:

Colloidal Dispersions:-

Definition, types, properties of colloids, protective colloids, applications of colloids in pharmacy.

## Suspensions and Emulsions:

Interfacial properties of suspended particles, settling in suspensions, theory of sedimentation, effect of Brownian movement, sedimentation of flocculated particles, sedimentation parameters, wetting of particles, controlled flocculation, flocculation in structured vehicles, rheological considerations.

Emulsions - types, theories, physical stability.

## 6. Complexation:

Classification of complexes, methods of preparation and analysis, applications.

## 7. Kinetics and Drug Stability:

General considerations and concepts, half-life determination, Influence of temperature, light, solvent, catalytic species and other factors, Accelerated stability study, expiration dating.

## 8. Buffers:

Buffer equations and buffer capacity in general, buffers in pharmaceutical systems, preparation, stability, buffered isotonic solutions, measurements of tonicity, calculations and methods of adjusting isotonicity.

# Colloidal Dispersions.

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\* Drug

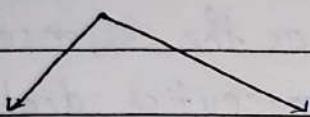


Api (Raw material)



Active Pharmaceutical Ingredient

\* Medicine



Api + Additives / Excipients



Flavouring agent,

Colouring agent,

Sweetening agent,

Lubricating agent,

Bulking agent

Diluent,

Binding agent.

\* Lab Requirement :- Practical file,

Observation copy,

Synopsis copy,

Scissor,

Sachet,

Transparent tape.

\* Theory → Theory copy.

Q. What is pharmaceutics?

⇒ Pharmaceutics is the science of pharmacy which deals with the process of turning a new chemical entity or old drug into medication to be used safely and effectively by patient.

Pharmaceutics are also known as the science of doses form design. Pharmaceutics deals with formulation of pure drug substance into dosage form.

These are different branches of pharmaceutics:

- ① Pharmaceutical formulation
- ② Pharmaceutical manufacturing
- ③ Pharmaceutical technology.
- ④ Dispensing pharmacy.
- ⑤ Physical pharmacy.
- ⑥ Pharmaceutical jurisprudence.

### \* Physical Pharmacy

Physical pharmacy is the branch of pharmacy that concentrate on the application of physics and chemistry to the study of pharmacy.

In other words, it is the study of the effect dosage form have on their environment by addressing issue at their molecular level. It forms the basis for design, manufacture and distribution of drug product and serve as the foundation for the stable and proper use of medical drugs.

## Colloidal Dispersion

A Dispersed systems is defined as a system in which one phase (known as the dispersed phase) is distributed throughout a continuous phase (known as dispersion medium).

### Classification of Dispersed Systems:

On the basis of mean particle diameter of the dispersed material, three types of dispersed systems are generally considered:

- (a) Molecular dispersions
- (b) Colloidal dispersions, and
- (c) Coarse dispersions.

#### (a) Molecular dispersions.

Molecular dispersions are the true solutions of a solute phase in a solvent. The solute is in the form of separate molecules homogeneously distributed throughout the solvent.

Example:- aqueous solution of salts, glucose.

## (b) Colloidal dispersions:

Colloidal dispersions are micro-heterogeneous dispersed systems. The dispersed phases cannot be separated under gravity or centrifugal or other forces. The particles do not mix or settle down.

Example: aqueous dispersion of natural polymer, colloidal silver sols, jelly.

## (c) Coarse dispersions

Coarse dispersions are heterogeneous dispersed systems in which the dispersed phase particles are larger than  $0.5\text{ }\mu\text{m}$ .

The concentration of dispersed phase may exceed 20%.

Example:- Pharmaceutical emulsions and suspensions.

## Comparison of Characteristics Three Dispersed Systems.

	Molecular dispersion	Colloidal dispersion	Coarse dispersion
1. Particle size	< 1 nm	1 nm to 0.5 μm	> 0.5 μm
2. Appearance	Clear, transparent	Opalescent	Frequently opaque
3. Visibility	Invisible in electron microscope	Visible in electron microscope	Visible under optical microscope or naked eye.
4. Separation	Pass through semipermeable membrane, but do not pass filter paper	Pass through paper and semipermeable membrane	Do not pass normal filter paper
5. Diffusion	Undergo rapid diffusion	Diffuse very slowly	Do not diffuse.
6. Sedimentation	No question of settling	Do not settle down	Fast sedimentation of dispersed phase by gravity or other.

## Types of Colloidal Systems.

Based on the interaction between dispersed phase and dispersion medium, colloidal systems are classified as.

(a) Lyophilic colloids (solvent-loving).

(When the dispersion medium is water, it is called hydrophilic colloids and if the dispersion medium is an organic solvent, it is called hydrophobic colloids).

(b) Lyophobic colloids (solvent-hating).

Difference between Lyophilic colloids and Lyophobic colloids.

<u>Lyophilic colloids</u>	<u>Lyophobic colloids</u>
• Colloidal particles have greater affinity for the dispersion medium.	• Colloidal particles have little affinity for the dispersion medium.
• Owing to their affinity for the dispersion medium, the molecules disperse spontaneously to form colloidal solution.	Material does not disperse spontaneously, and hence lyophobic sols are prepared by dispersion or condensation methods.

- |                                                                                                                                                 |                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| • These colloids form "reversible sols".                                                                                                        | • These colloids form "irreversible sols".                                                                      |
| • Viscosity of the dispersion medium is increased greatly by the presence of the lyophobic colloidal particles.                                 | • Viscosity of the dispersion medium is not greatly increased by the presence of lyophilic colloidal particles. |
| • Dispersions are generally stable in the presence of electrolytes; they may be salted out by high concentrations of very soluble electrolytes. | • Lyophobic dispersions are unstable in the presence of even small concentrations of electrolytes.              |
| • Dispersed phase consists generally of large organic molecules such as gelatin, acacia lying within colloidal size range.                      | • Dispersed phase ordinarily consists of inorganic particles, such as gold or silver.                           |

## Preparation of Lyophilic Colloids.

This simple dispersion of lyophilic material in a solvent leads to the formation of lyophilic colloids. Preparation of Lyophobic colloids. The lyophobic colloids may be prepared by .

- (a) Dispersion method.
- (b) Condensation method.

### (a) Dispersion methods :

This method involves the breakdown of larger particles into particles of colloidal dimensions. The breakdown of coarse material may be effected by the use of the colloid mills, Ultrasonic treatment in presence of stabilizing agent such as a surface active agent.

These methods may involve the use of such mechanical methods as :

- (i) Mechanical dispersion
- (ii) Electro-dispersion
- (iii) Ultrasonic dispersion
- (iv) Peptization.

### (i) Mechanical dispersion:

The substance to be dispersed is ground as finely as possible by the usual methods. It is shaken with the dispersion medium and thus obtained in the form of a coarse suspension.

This suspension is now passed through a colloid mill. The simplest type of colloid mill called disc mill, consists of two metal discs nearly touching each other and rotating in opposite directions at a very high speed.

The suspension passing through these rotating discs is exposed to a powerful shearing force and the suspended particles are apart to yield particles of colloidal size. Colloid mill are widely used in the industrial preparation of paints, cement, food products, pharmaceutical products etc.

### (ii) Electro-dispersion:

These methods are employed for obtaining colloidal solutions of metals like gold, silver, platinum etc. An electric arc is struck between the two metallic electrodes placed in a container of water. The intense heat of the arc converts the metal into vapours, which

are condensed immediately in the cold water bath. This results in the formation of particles of colloidal size. We call it as gold sol.

(iii) Ultrasonic dispersion:

Ultrasonic vibrations (having frequency more than the frequency of audible sound) could bring about the transformation of coarse suspension to colloidal dimensions. Claus obtained mercury sol by subjecting mercury to sufficiently high frequency ultrasonic vibration.

(iv) Peptization:

Peptisation is the process of converting a freshly prepared precipitate into colloidal form by the addition of a suitable electrolyte. The electrolyte is called peptising agent. For example when Ferric chloride is added to a precipitate of ferric hydroxide, ferric hydroxide gets converted into reddish brown coloured colloidal solution. This is due to preferential adsorption of cations of the electrolyte by the precipitate. When  $\text{FeCl}_3$  is added to  $\text{Fe(OH)}_3$ ,  $\text{Fe}^{3+}$  ions from  $\text{FeCl}_3$  are adsorbed by  $\text{Fe(OH)}_3$ .

particles. Thus the  $\text{Fe(OH)}_3$  particles acquire +ve charge and they start repelling each other forming a colloidal solution.

(B) Condensation method :

In this method, smaller or sub colloidal size particle are condensed together to form a colloidal size range that is achieved through chemical reaction.

(C) Association colloids

Amphiphiles are molecules or ions showing affinity towards both polar and non polar solvent. In water, they exhibit action of surface active agent in form of monomers or colloidal size. As their concentration increases these monomers come together and get aggregated in form of micelles. Each micelles contain approx. 50 monomer of  $50 \text{ A}^\circ$  -size and make colloidal system.

Association colloids are also further classified as :

1. Anionic - Example - sodium lauryl sulphate

2. Cationic - Example - Cetyl trimethylammonium bromide.

3. Non ionic - Example - Tween, span.

4. Ampholytic - Example - Sulphanilic acid.

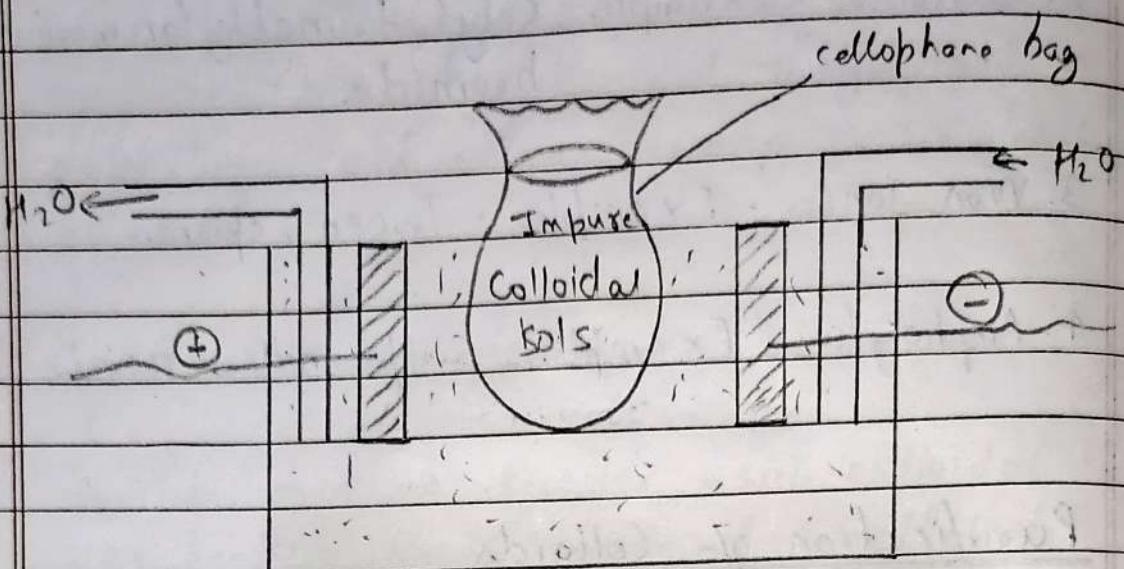
### Purification of Colloids

When a colloidal solution is prepared, it often contains certain electrolytes which tend to destabilize it. The following methods are used for purification of colloids:

#### (a) Dialysis:

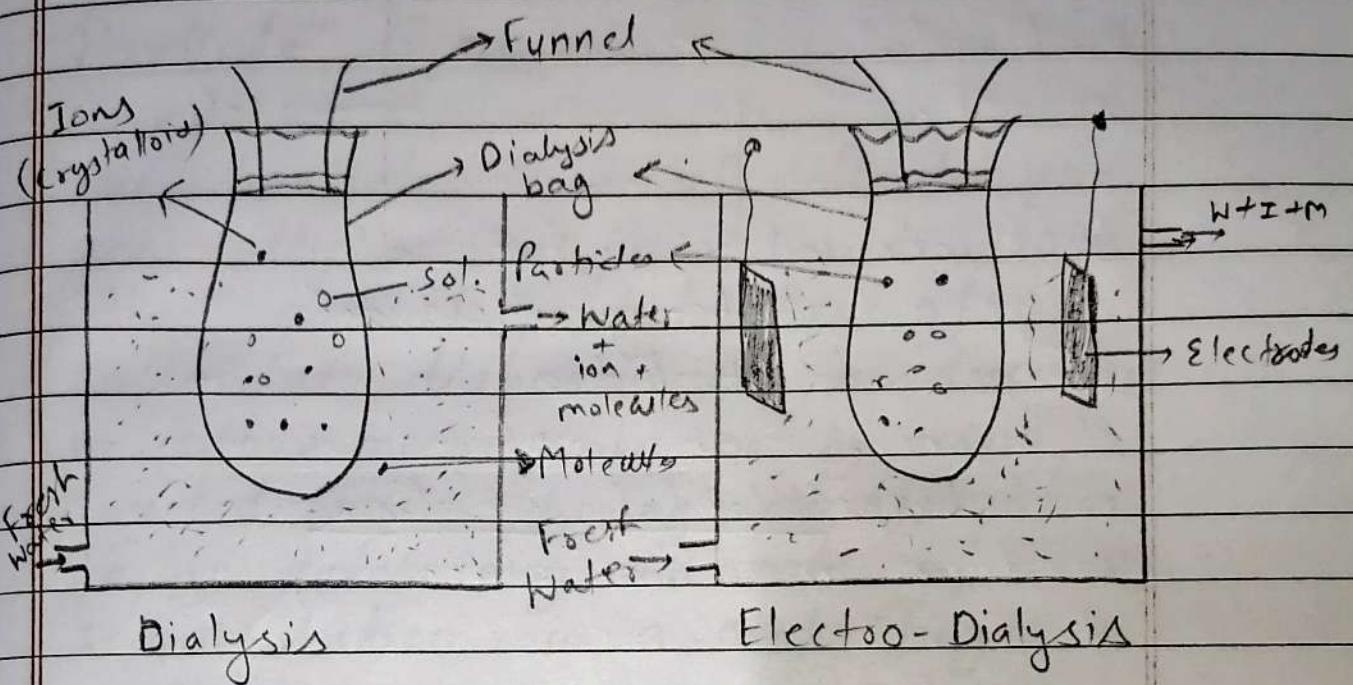
It is a process of removing a dissolved substance from a colloidal solution by diffusion through a suitable membrane in a ~~an~~ apparatus called Dialyser.

A bag of suitable membrane like animal bladder or cellophane sheet containing the colloidal solution is suspended in vessels in which fresh water is flowing continuously. The molecule and ions diffuse through membrane into the outer water and pure colloidal solution is left behind.



### (b) Electrodialysis

In the dialysis unit, the movement of ions across the membrane can be speeded up by applying an electric current through electrodes induced in solution. The electric potential increases the rate of movement of ionic impurities through a dialysing membrane and so provide a more rapid means of purification. The dialysis membrane allows small particles (ions) to pass through but the colloidal size particles (haemoglobin) do not pass through the membrane.

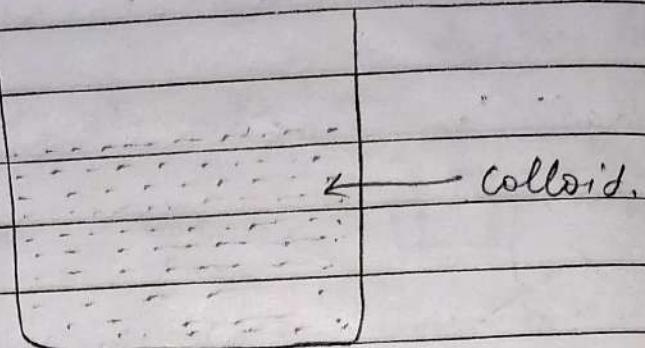


### (c) Ultrafiltration

Colloidal dispersion can pass through an ordinary filter, because the pore size of the filter is large.

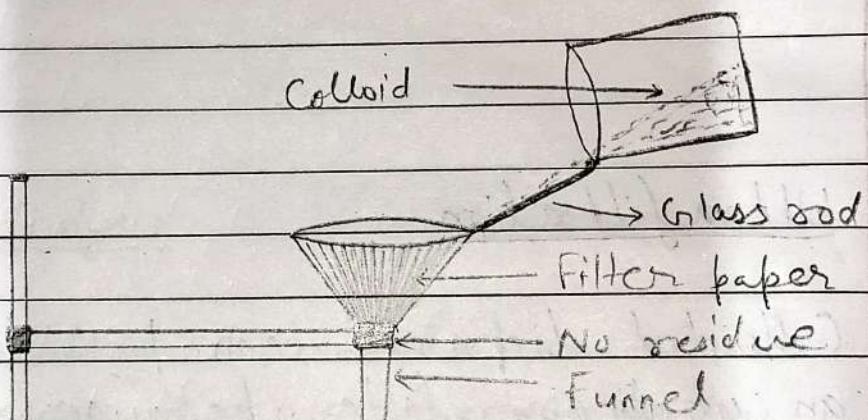
If this filter paper is impregnated with collodion (syrupy solution of nitrocellulose), the pore size reduces. Such modified filter papers are called ultrafilters.

By applying pressure (or suction) the solvent and small particles may be forced across a membrane but the larger colloidal particles are retained. This process is referred to as ultrafiltration.



Heterogenous and turbid.

Fig. Colloidal Solution



Clamp →  
Stand

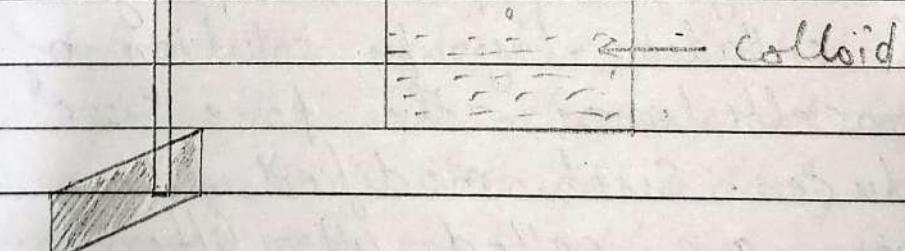


Fig. Filtration of colloidal solution

## OPTICAL PROPERTIES OF COLLOIDS

### A. Particle Size:

The particle sizes of colloids are generally varies from 1nm to 100nm.

The actual particle size of colloidal dispersion can be determined by ultra-microscope or by using graded filters during ultrafiltration or by determining the rate of sedimentation in a centrifuge.

### B. OPTICAL PROPERTIES

#### 1. Tyndall effect:

When a strong beam of light is passed perpendicularly through two solutions

(1) True solution

(2) Colloidal solution place against a dark background.

1) The path of light beam is not visible in case of true solution.

2. The path of light beam is visible (scattered) in case of colloidal solution and further it is forming a shadow (beam or cone) at the

dark background. This phenomenon of scattering of light by the colloidal particles is called Tyndall effect.

Difference in refractive indices of dispersed phase and dispersed dispersion medium, larger the difference in the refractive indices of dispersed phase and dispersion medium, more is scattering of light. Therefore, lyophobic sols exhibit more scattering as compare to lyophilic sols.

The illuminated beam or cone formed by the sol~~s~~ particles is called Tyndall beam or Tyndall cone.

The Tyndall effect is due to the fact that colloidal particles scatter light in all directions in space. The ~~so~~ scattering of light illuminates the path of beam in the colloidal dispersion.

## 2. Ultramicroscopy.

The colloidal particles are too small to be seen with an optical microscope. However, when a cell containing a colloidal dispersion is

Viewed through an ultramicroscope against a dark background at right angle to an intense beam of incident light, the particles appear as bright spots against the dark background. The ultramicroscope is used in the technique of microelectrophoresis for measuring the particle size.

### 3. Electron microscopy:

Ultramicroscope are sometimes not able to resolve some lyophilic colloids and hence electron microscope are employed for studying the colloidal dispersions.

The electron microscope is useful in getting picture of actual particles and help in the study of the size, shape and structure of colloidal particles.

### 4. Light scattering:

When beam of light is passed through a colloidal dispersion, some of it is absorbed, some is scattered and the remainder is transmitted undisturbed through the sample. The absorbed light is responsible for the highly coloured nature of certain colloids.

## C. KINETIC PROPERTIES

Kinetic properties of colloidal systems relate to the motion of particles with respect to the dispersion medium.

The kinetics properties are:

1. Brownian motion
2. Diffusion
3. Osmotic pressure
4. Sedimentation
5. Viscosity.

The motion may be thermally induced (Brownian movement, diffusion, osmosis). Gravitational force induced (sedimentation), or applied externally (viscosity).

### 1. Brownian motion:

Colloidal particles undergo random collisions with the molecules of the dispersion medium and follow an irregular and complicated zigzag path. If the particles up to about 0.5 μm diameter are observed under a microscope or the light scattered by colloidal particles is viewed using an ultramicroscope, an erratic motion

is seen. This movement is referred to as Brownian motion.

## 2 Diffusion:

As a result of Brownian motion colloidal particles spontaneously diffuse from a region of higher concentration to one of lower concentration. The rate of diffusion is expressed by Fick's first law:

$$\frac{dq}{dt} = -DS \frac{dc}{dx}$$

According to the law, the amount,  $dq$  of substance diffusing in time,  $dt$  across a plane of area ( $S$ ) is directly proportional to the change of concentration,  $dc$ , with distance travelled,  $dx$ .  $D$  is diffusion coefficient and has dimension of area per unit time,  $dc/dx$  is concentration gradient. The minus sign denotes that the diffusion takes place in the direction of decreasing concentration.

It is possible to determine the molecular weight of approximately spherical particles from the diffusion

by substituting the data obtained from diffusion experiments in the following expression:

$$D = \frac{RT}{6\pi\eta rN} \cdot \frac{4\pi N}{3Mv}$$

Where,

$M$  is the molecular weight

$v$  is the partial specific volume

$\eta$  is the viscosity of the solvent

$R$  is the molar gas constant

$T$  is the absolute temperature

$r$  is the radius of spherical particle  
and

$N$  is the Avagadro's number.

### 3. Osmotic Pressure:

Osmosis is the spontaneous net movement of solvent molecules through semipermeable into a region of higher solute concentration in the direction that tends to equalize the solute concentration on the two

sides. The external pressure required to be applied so that there is no net movement of solvent across the membrane is called osmotic pressure.

The osmotic pressure can be used to calculate the molecular weight of colloidal material.

$$P = \frac{C}{M}$$

P is the osmotic pressure

C is the concentration in gram solute per liter solvent

M is the molecular weight

R is the gas constant

T is the temperature in kelvin.

#### 4. Sedimentation

In normal dispersion, the dispersed particle tend to settle under the influence of gravity but in case of colloidal dispersion, the Brownian movement tends to offset this sedimentation but promotes mixing instead. Therefore, stronger force must be applied to bring about sedimentation of colloidal particles.

Ultracentrifuge is generally used for bringing about and studying sedimentation in colloidal dispersions.

In an ultracentrifuge, the particles settle according to their movement molecular weight and hence this is also helpful in determining the molecular weight. The following expression is used for determining molecular weight:

$$M = \frac{RTS}{D(1 - VP_0)}$$

Where,

R is the gas constant

T is the absolute temperature

V is the partial specific volume of the polymer.

$P_0$  is the density of the solvent.

S is the Svedberg sedimentation coefficient determined at 20°

D is the diffusion coefficient obtained by calculation from diffusion data at 20°.

## 5. Viscosity:

The viscosity of colloids depends upon the shape of colloidal material. Spherical colloidal material yields dispersions of relatively low viscosity. Linear colloids are comparatively more viscous. Viscosity increase due to solvation effect. When the degree of solvation is more,

the dispersion becomes more viscous. Viscosity studies provide a mean of detecting changes in the shape of flexible colloidal particles and macromolecules. Viscosity studies also provide a mean of determining the molecular weight of colloidal particles.

Einstein equation of flow for the colloidal dispersions of spherical particles is given by :

$$\eta = \eta_0 (1 + 2.5 \phi)$$

$\eta_0$  is the viscosity of dispersion medium,  
 $\eta$  is the viscosity of dispersion when volume fraction of colloid particles is  $\phi$ . The volume fraction is defined as the volume of the particles divided by the total volume of the dispersion.

#### D. ELECTRICAL PROPERTIES

The colloidal particles carry a electrical charge of either positive or negative type. Negatively charged colloidal particles include that of kaolin, sulphur and arsenious sulphide while positively charged ones include ferric oxide and other metal hydroxide colloidal dispersion. In certain colloidal

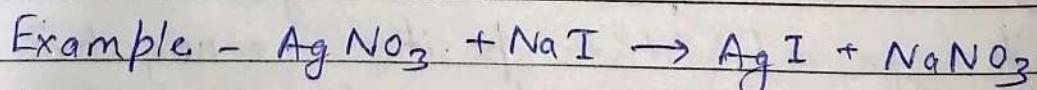
dispersion such as that of protein, the charge on the particles may be positive, negative or neutral depending upon the pH of the medium.

### 1. Electrical double layer:

The theory of the electrical double layer deals with this distribution of ions and hence with the magnitude of the electric potentials that occur in the locality of the charged surface. Consider a solid charged surface in contact with an aqueous solution of electrolyte.

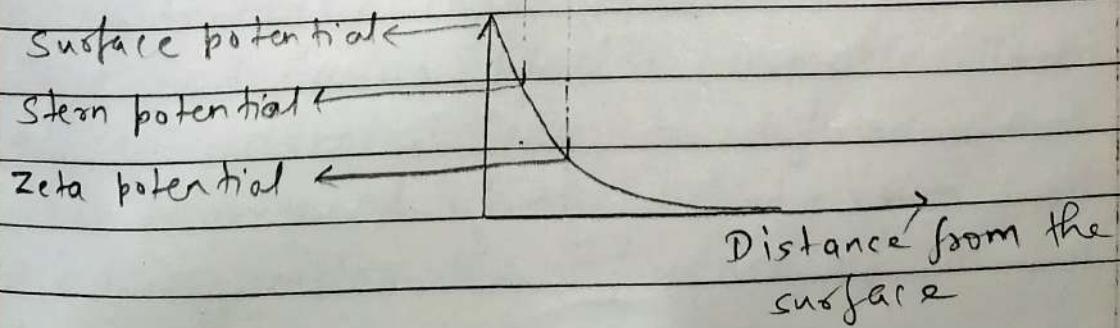
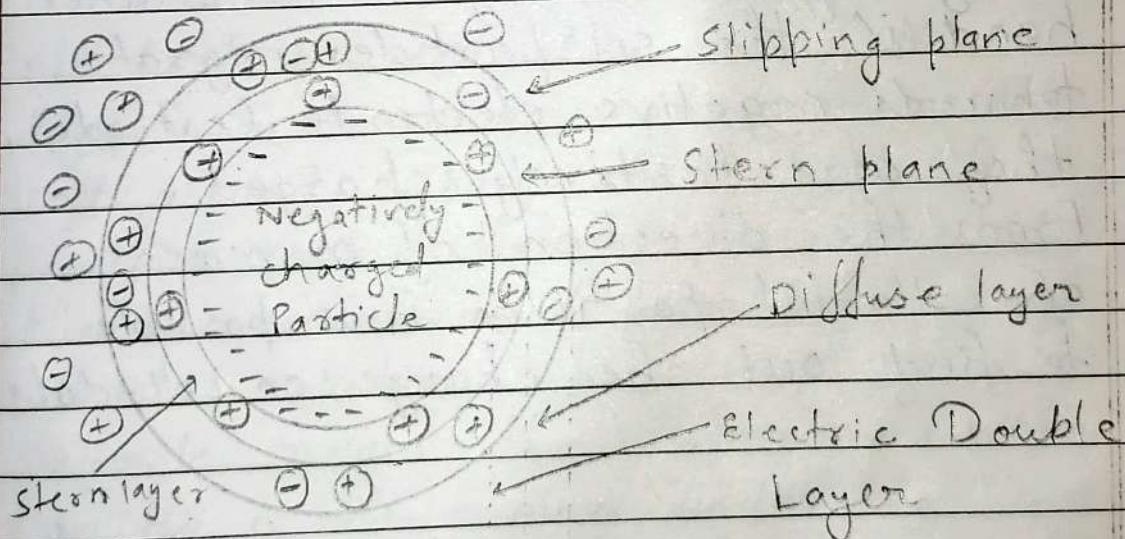
Development of a net charge at the particle surface affects the distribution of ions in the surrounding interfacial region,

- As a result: concentration of counter ions increase at the surface,
- Thus, an electrical double layer exists around each particle.



Silver iodide sols can be prepared by the reaction,  $n \text{AgNO}_3 + \text{NaI} \rightarrow \text{AgI} + \text{NaNO}_3$ . In the bulk of AgI particles 1:1 ratio of  $\text{Ag}^+$  and  $\text{I}^-$ .

If the reaction is carried out with an excess silver nitrate, there will be more  $\text{Ag}^+$  than  $\text{I}^-$  ions in the surface of the particles. The particles will thus be positively charged and the counterions surrounding them will be  $\text{NO}_3^-$ . The combination of the positively charged surface and the atmosphere of counter ions surrounding it is called the electric double layer. If the reaction is carried out with an excess  $\text{NaI}$ , there will be more  $\text{I}^-$  than  $\text{Ag}^+$  ions in the surface of the particles. The particles will thus be negatively charged and the counter ions surrounding them will be  $\text{Na}^+$ .



## 2. Electrophoresis :

When a potential difference (electric field) is applied across two platinum electrodes immersed in a colloidal solution, the particles of dispersed phase move towards either the positive or negative electrode.

This observation was first discovered by Rauss in 1807 and was investigated later by Linder and Picton. The movement of colloidal particles under the action of electric field is known as Electrophoresis. If the colloidal particles move towards the positive electrode (Anode) they carry negative charge. On the other hand if the sol particles migrate towards negative electrode (cathode), they are positively charged.

From the direction of movement of colloidal particles it is possible to find out the charge on colloids.

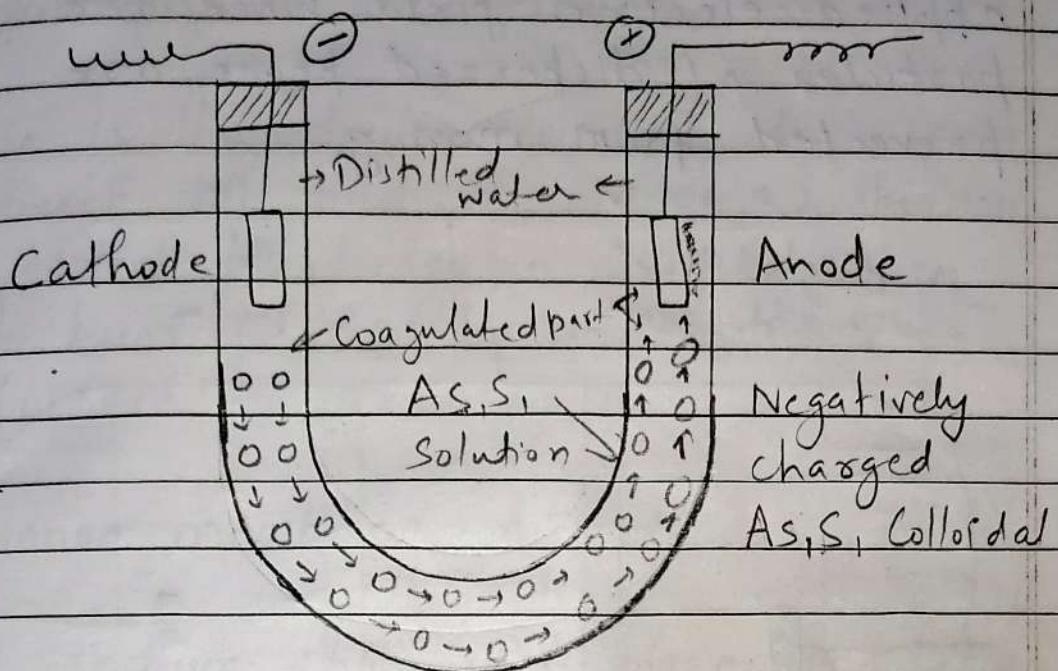


Fig → Electrophoresis.

### 3. Electro-Osmosis :

A colloidal solution as a whole is electrically neutral in nature i.e., dispersion medium carries an equal and opposite charge to that of the particles of dispersed phase. When the movement of dispersed phase of colloidal solution is prevented by suitable means, the dispersion medium can be made to move under the influence of an applied electric field or potential. This phenomenon is referred to as Electro-Osmosis. Thus electro-osmosis may be defined as the movement of the dispersion medium under the influence of an

applied electric field when the particles of dispersed phase are prevented from moving.

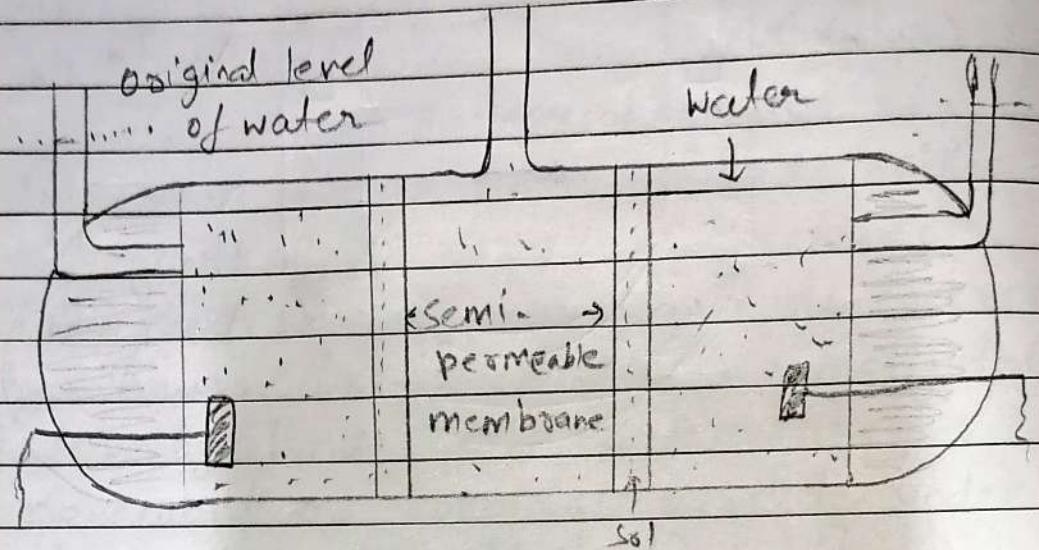


Fig- Electro-osmosis

If the particles carry positive charge, the dispersion medium would start moving towards the anode and the level of water in the side tube T would be seen to rise, indicating the presence of negative charge on the dispersion medium. If the particles carry negative charge, the dispersion medium would be seen to move towards cathode and water in the side tube T would start rising.

Electro osmosis is utilizing for dewatering dewatering moist clay and drying of dye pastes.

#### 4. Sedimentation potential :

This is the difference set up between top and bottom of a suspension of solid particles in a liquid when the particles settle under the influence of gravity.

#### 5. Donnan membrane effect:

If sodium chloride is placed in solution on one side of a semipermeable membrane and a negatively charged colloid together with its counter ions  $R^- Na^+$  is placed on the other side, the sodium and chloride ions can pass freely across the barrier but not the colloidal anionic particles. The system at equilibrium is represented in the following diagram, in which R is the non-diffusible colloidal anion and the vertical line separating the various species represents the semipermeable membrane. The volumes of solution on the two sides of the membrane are considered to be equal. After equilibrium has been established, the concentration in dilute solutions (more correctly the activity) of sodium chloride must be the same on both sides of the

membrane, according to the principle of escaping tendencies. Therefore,

<u>Outside (o)</u>	<u>Inside (I)</u>
$\text{Na}^+$	$\text{R}^-$
$\text{Cl}^-$	$\text{Na}^+$ $\text{Cl}^-$

$\text{Na}^+$ ,  $\text{Cl}^-$  are permeable ions

$\text{R}^-$  is a non permeable ion

In accordance with the principle of escaping tendencies, the concentration of the drug ( $\text{Na}^+$ ,  $\text{Cl}^-$ ) must balance on both sides of the membrane.

$$\text{i.e., } [\text{Na}^+]_o [\text{Cl}^-]_o = [\text{Na}^+]_i [\text{Cl}^-]_i$$

Where o and i indicate outside and inside respectively.

Applying electroneutrality on both sides, the concentration of positively charged ions must balance the concentration of negatively charged ions.

$$\text{i.e. outside : } [\text{Na}^+]_o = [\text{Cl}^-]_o$$

$$\text{and inside : } [\text{Na}^+]_i = [\text{R}^-]_i + [\text{Cl}^-]_i$$

Substituting these in the above first equations, we obtain

$$[C_1^-]_o [C_1^-]_o = ([R^-]_i [C_1^-]_i) [C_1^-]_i$$

$$[C_1^-]^2_o = [R^-]_i [C_1^-]_i + [C_1^-]_i [C_1^-]_i$$

$$[C_1^-]^2_o = [C_1^-]^2_i + [R^-]_i [C_1^-]_i$$

$$= [C_1^-]^2_i 1 + [R^-]_i / [C_1^-]_i$$

$$\frac{[C_1^-]^2_o}{[C_1^-]^2_i} = 1 + \frac{[R^-]_i}{[C_1^-]_i}$$

$$\text{or, } \frac{[C_1^-]_o}{[C_1^-]_i} = 1 + \frac{[R^-]_i}{[C_1^-]_i}$$

From the above equation which represents the ratio of concentrations of diffusible drug anion outside and inside the membrane at equilibrium, it may be understood that a charged polyelectrolyte (i.e., macromolecules of colloidal dimensions) inside a semi-permeable membrane sac would affect the equilibrium concentration ratio of a diffusible anion. That is, it tends to drive the ion (drug ion) of like

charge on its side to the opposite side through the semipermeable membrane.

### Interaction of colloids :

#### 1. Mutual Precipitation :

When two oppositely charged hydrophilic colloid are mixed, precipitation takes place. Charges necessary for stability get neutralized by each other and attractive forces between particles dominate.

#### 2. Coacervate formation :

When oppositely charged hydrophilic colloids are mixed, a colloid rich layer separates which is called as coacervate. This phenomenon in which macro-molecular dispersion, on mixing, separate into two liquid layers is called coacervation.

Gelatin at pH below 4.7 (iso-electric point) is positively charged while acacia is negatively charged. When the two are mixed together, two layer are formed, the upper layer

of low viscosity having a poor concentration of colloidal material and lower layer of higher viscosity containing high concentration of colloidal material. Coagulation can also be brought about by the addition of alcohol, sodium sulphate or a macromolecular substance such as starch and the mechanism may not involve interaction of charged particles but mechanism such as dehydration of the solvated layer in the case of alcohol.

### 3. Sensitisation :

In the presence of very small amount of hydrophilic colloid, the hydrophobic colloids may become even more susceptible to precipitation from electrolytes. Sensitization is attributed to a reduction in zeta below the critical value (the value at which coagulation occurs). It is also reasoned that it is due to reduction in the thickness of the ionic layer surrounding the colloidal particles.

#### 4. Protection :

Larger concentration of hydrophilic colloids increases the stability of hydrophobic colloid towards precipitation by electrolytes. The hydrophilic colloids on the surface of hydrophobic colloids particles and form a protective layer thus preventing them from precipitation on addition of an electrolyte.

This phenomenon is called protection. The hydrophilic sol used for the purpose of protecting hydrophobic colloid is known as protective colloid.

#### Stability of Colloids

Colloidal particles, though larger than ions and molecules, yet are stable, and do not settle under gravity. There are at least three good reasons for the stability of colloidal sols.

##### i) Brownian motion :

Like the molecules or ions in a solution, the colloidal particles of a sol are in a state of continuous rapid motion.

The intensity of Brownian motion falls rapidly with increase in the particle

size, yet it is high enough to offset  
of gravity in case of colloidal particles.

### ii) Electric Charge:

As we know that the colloidal particles  
in a sol are all either positively  
charged or negatively charged.

Therefore, the force of repulsion  
keeps the particles scattered and even  
upon close approach they will not  
collide and coalesce. Hence similar  
charge on all the particles of a  
colloid accounts for the stability  
due to mutual repulsion in the solution.

### iii) Solvation:

The colloidal particles of a sol are  
often highly hydrated in solution.

The resulting hydrated "shell" prevents  
close contact and cohesion of colloidal  
particles. Comparatively the addition  
of small amounts of a lyophilic colloid  
called protective colloids.

## Schulze - Hardy Rule:

Coagulation of colloidal dispersion can be brought about by the addition electrolytes which reduce the zeta-potential. The effectiveness of an electrolyte to cause precipitation depend not only on the concentration but also on the valence of the active ion (ion causing coagulation). The higher the valency of the ion, the greater is the precipitating power. This is known as Schulze - Hardy Rule.

$\text{Al}_3^+$  is more effective than  $\text{Mg}^{++}$  and  $\text{Na}^+$ . Negatively charged arsenious sulfide will be coagulated rapidly with a smaller concentration of  $\text{AlCl}_3$  than that of  $\text{BaCl}_2$  or  $\text{NaCl}$ . Similarly for positively charged sol such as  $\text{Fe(OH)}_3$ ,  $\text{PO}_4^{3-}$  is more effective than  $\text{SO}_4^{2-}$  and  $\text{Cl}^-$ .

Generally hydrophobic colloids need very small amount of electrolyte for coagulation whereas hydrophilic colloids need a larger amount because the hydration layer surrounding the dispersed particles has to be removed.

## Gold Number:

Gold Number is a measure of the protective ability of hydrophilic colloid. It is defined as the number of milligram of hydrophilic colloid which when added to 10 ml of red gold sol prevents the change in colour from red to violet on the addition of 1 ml of 10% solution of sodium chloride.

The change in the colour is due to the change in particle size.

The lower the gold number, higher is the protective ability of the colloid. The gold number of protective colloid, gelatin, albumin, acacia and tragacanth are 0.01, 0.1, 0.2 and 2.0 respectively. Thus, gelatin is the most effective protective colloid of the above four.

## Determination of Gold number:

For the determination of gold number, a series of test tube containing 10 ml of gold sol are taken. To each of the test tube is added a protective colloid in increasing concentration.

To each of the test tubes is then added 1 ml of 10% sodium chloride

solution. The test tubes are left undisturbed. At higher concentration of the protective colloid, the gold sol does not change its color while at lower concentration, the gold sol changes color from red to violet. The test tube containing the minimum quantity of colloid which prevents the change in color of the gold sol is the gold number of the protective colloid.

### DLVO Theory:

DLVO theory is a theory of colloidal dispersion stability in which zeta potential is used to explain that as two particles approach one another their ionic atmospheres begin to overlap and a repulsion force is developed. In this theory, two forces are considered to impact on colloidal stability: van der Waals forces and electrical double layer forces.

The total potential energy is described as the sum of the attraction potential and the repulsion potential. When two particles approach each other, electrostatic repulsion increases and the interference between their

electrical double layers increases.

However, the van der Waals attraction also increases as they ~~get~~ get closer.

At each distance, the net potential energy of the smaller value is subtracted from the larger value.

At very close distances, the combination of these ~~factors~~ forces result in a deep attractive well, which is referred to as the primary minimum. At larger distances, the energy profile goes through a maximum, or energy barrier, and subsequently passes through a shallow minimum, which is referred to as the secondary minimum.

At the maximum of the energy barrier, repulsion is greater than attraction. Particles rebound after interparticle contact, and remain dispersed throughout the medium.

The maximum energy needs to be greater than the thermal energy.

Otherwise, particles will aggregate due to the attraction potential. The height of the barrier indicates how stable the system is. Since particles have to overcome this barrier in order to aggregate, two particles on a

collision course must have sufficient kinetic energy due to their velocity and mass. If the barrier is cleared, then the net interaction is all attractive, and as a result the particles aggregate. This inner region is often referred to as an energy trap since the colloids can be considered to be trapped together by van der waals forces.

For a colloidal system, the thermodynamic equilibrium state may be reached when the particles are in deep primary minimum. At primary minimum, attractive forces overpower the repulsive forces at low molecular distances. Particles coagulate and this process is not reversible. However, when the maximum energy barrier is too high to overcome, the colloid particles may stay in the secondary minimum. Particles where particles are held together but more weakly than in the primary minimum. Particles form weak attractions but easily redispersed. Thus, the adhesion at secondary minimum can be reversible.

## Pharmaceutical applications of colloids:

- 1.) Colloidal silver iodide, silver chloride and silver protein are effective germicides and not cause irritation as ionic silver salts.
- 2.) Colloidal copper used in cancer.
- 3.) Colloidal gold used as diagnostic agent.
- 4.) Colloidal mercury used in syphilis.
- 5.) Association colloids (SAA) are used to increase solubility and stability of certain compounds in aqueous and oily pharmaceutical preparations.
- 6.) Efficiency of certain substances is increased when used in colloidal form due to large surface area. e.g.  
eg. efficiency of kaolin in adsorbing toxins from C.I.T.  
eg. efficiency of aluminium hydroxide as antacid.
- 7.) Blood plasma substitutes as dextran, PRP and gelatin are hydrophilic colloids used to restore or maintain blood volume.
- 8.) Iron-dextran complex form non-ionic hydrophilic sols used for treatment of anaemia.

# Kinetics and Drug Stability

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## \* Kinetics

The means of kinetics is study the rate of chemical or biochemicals reaction. It is a branch of chemistry or biochemistry deals with measuring and study the rate of chemical reaction.

## \* Doug:

It is a bunch of chemicals for the use by patient in people for the prevent or care or treatment of disease. and also both physical and chemical ability.

## \* Stability:

It is a condition or stage that preserve or store capacity of dry substance or drug moiety.

- Chemical Kinetics is the study of the rate of chemical change takes place during chemical reaction, As applied to pharmaceutical formulation, this includes a study of physical and chemical reaction in drugs and dosage forms. Factor influencing the rate of these

chemical reaction, accelerated, stability testing and prediction of shelf life of formulation.

### \* Shelf life:

The time period from the product was manufactured to its expiry date:

The time period of the product is expected to be safe, effective and fit for purpose to provided. It has been packaged and stored in recommended condition throughout this period.

All ~~drugs~~<sup>drugs</sup> tend to degrade from the point of manufacture and the expiry date of a product is end point of its shelf life taking into account a tolerance of degradation (normally less than 10%).

### \* Half life

This is usually a reference to the time taken for the body to eliminate 50% of the dosage of drug after the time of administration.

It varies with varies with different drugs and between individual patients but average half life of drugs may

be found in the literature most penicillins -  $\frac{1}{2}$  life around 20min.

\* Factors affecting rate of reaction of kinetic and drug stability.

i). Light

Light energy may be absorbed by certain molecules which becomes sufficiently activated ~~for~~ to undergo reaction. Mostly visible and U.V. light cause photochemical reaction.

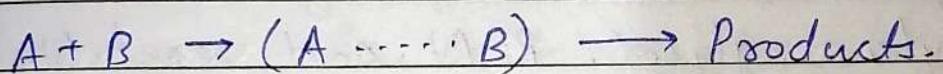
Photochemical reaction don't depend on temperature for activation of the molecules. While, once a molecule has absorbed a quantum of radiant energy, it may collide with other molecules raising their kinetic energy which results in the increase in temperature of the system.

Hence, Photochemical reaction are often followed by Thermal reaction, photochemical reaction are, in general, complex reaction and proceed by a series of steps:-

Example of pharmaceutical compounds which undergo photochemical decomposition include riboflavin, phenothiazines, chlorodiazepoxide, nifedipine etc.

## 2) Solvent :-

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



The quantitative relationship between the reaction rate constant and stability of reactants and products is given by the equation.

$$\log k = \log k_0 + \frac{v}{2.303} \cdot \frac{1}{T} (\Delta S_A + \Delta S_B - \Delta S^*)$$

where,

k is the observed reaction rate constant.

k<sub>0</sub> is the reaction rate constant in infinity dilute solution

$V$  is a molar volumes of the reactants.

A and B is activated complex form during reaction.

$S_A$ ,  $S_B$  and  $S^*$  is the solubility parameters of the reactants if the products formed are less polar than the reactants then the reaction proceeds better in solvent.

Commonly used non-aqueous solvents for drugs include ethanol, Glycerol, propylene glycol, PEG and vegetable oils.

### 3.) Ionic Strength.

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

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

Where,

$k$  is the degradation rate constant for the reaction.

$K_0$  is the reaction rate constant of infinite dilution.

$Z_A$  and  $Z_B$  are the charge carried by the real A and B in solution respectively.

$\mu$  is the ionic strength of the solution.

According to the above equation, An increase in the ionic strength of the solution would tend to decrease the rate of reaction involving interaction b/w oppositely charged ions and increase the rate of reaction b/w similarly ions.

#### 4) Temperature

Generally the speed of many reaction can be increased two or three times with increase in  $10^{\circ}\text{C}$  in temperature.

The effect of temp. on reaction rate is given by Arrhenius equation in (as exponential form).

$$K = A e^{-E_a/RT}$$

Where,

$k$  is the specific reaction rate constant.

$A$  is the frequency factor also  $K/a$  Arrhenius factor.

$E_a$  is the energy of activation

$R$  is the gas constant as 1.987 calories/deg.mole

$T$  is absolute temp.

The frequency factor  $A$  referred to above is a measure of frequency of collisions.

Expressing the eqn in logarithmic form.

$$\ln k = -\frac{E_a}{RT} + \ln A$$

Converting to common logarithmic form

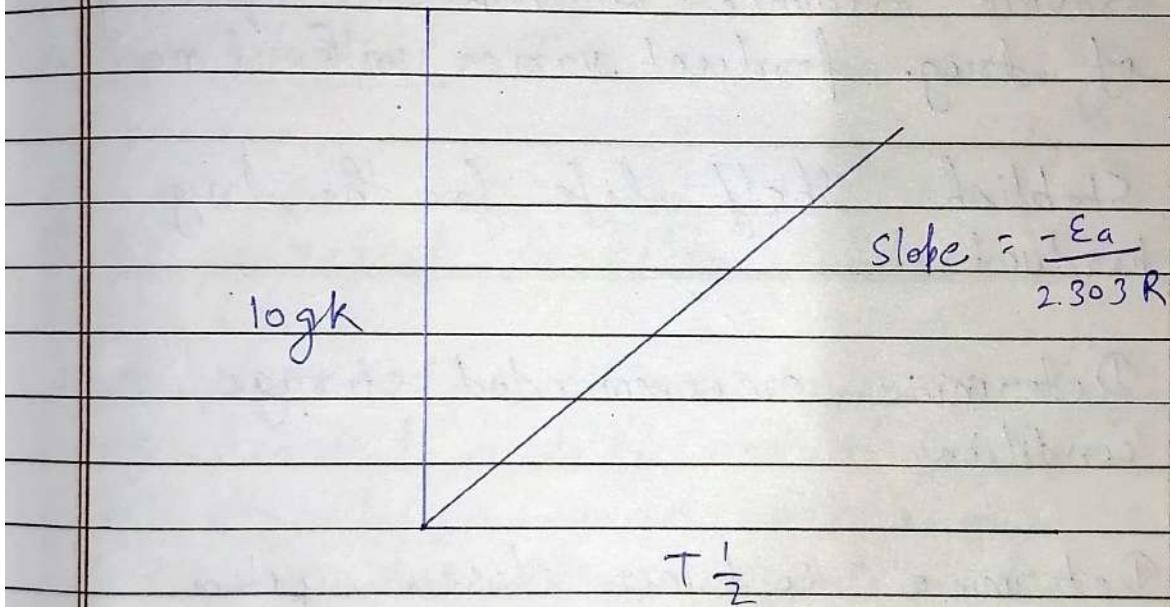
$$\log k = \frac{-E_a}{2.303RT} + \log A$$

Where,

$\log A$  is constant.

The value of constant  $A$  and  $E_a$  can be determined by determining at various temp.

Plot a graph of  $\log K$  versus  $T^{\frac{1}{2}}$  gives a straight line with slope equal to  $-E_a / 2.303 R$  and y-axis intercept is equal to  $\log A$ .



Arrhenius plot.

## ★ Stability

Stability of pharmaceutical product may be defined as the capability of particular formulation in a specific container or closure system to remain its physical, chemical, microbiological, therapeutic, toxicological specification.

### Need for Stability Testing:-

- i) Provide evidence as how the quality of drug product varies with time.
- ii) Establish shelf life for the drug product.
- iii) Determine recommended storage condition.
- iv) Determine container closure system suitability.
- v) Safety point of view of Patients.
- vi) Prevention of economical regression.
- vii) Essential quality attributes.

According to use types of stability.

### Types:

1. Chemical :- Chemical integrity and labelled potency.
2. Physical - Appearance, uniformity.
3. Microbiological - Sterility
4. Therapeutic - Drug action remains unchanged.
5. Toxicological - Increase in toxicity

### \* Accelerated Stability Analysis.

Accelerated stability analysis is designed to predict stability and shelf life of formulation under normal or recommended storage condition by carrying out the study under accelerated condition of temp., moisture and light.

### Objective of accelerated Stability Analysis

- Acc. stability testing is generally undertaken with the following objectives.

- i) To serve as a rapid means of selecting the best ~~formulations~~ formulations from amongst a series of similar formulation of product.
- ii) To predict the shelf life of the product.
- iii) To serve as a rapid means of quality control.
- (iv) Determine recommended storage condition.

★ Common High Stresses during stability Testing :-

⇒ Preparation are generally subjected to the following high stresses during stability testing.

1. Temperature:

Increase in the temp., increase degradation. Hence, preparation are subjected to different elevated temp. At various time ~~to~~ intervals, samples are withdrawn, extent and nature of degradation is determined.

## 2. Humidity:

High humidity condition accelerates decomposition that results from Hydrolysis. Product without container are exposed to high humidity condition usually in humidity chambers and analysed at regular intervals.

## 3. Light:

Artificial light of varying intensity can be used to accelerate the effect of sunlight. The light source should be however limit <sup>similar</sup> radiation as the sunlight.

## \* Limitation of Accelerated stability analysis.

1) Stability Prediction based on Arrhenius equation are valid only when energy of activation for the thermal decomposition lies within the range of 10 - 30 kcal/mole.

2) Certain reactions which usually don't take place under normal conditions of storage may take place under accelerated or high stress conditions and hence actual information may

not be obtained.

- 3) The order of reaction may be different in real and acc. conditions
- 4) Accelerated testing can't be used if the decomposition is due to freezing, contamination by micro-organisms, excessive agitation during transport.
- 5) Products such as emulsions may appear to be more stable at elevated temperature which may not be the case at normal storage conditions.

#### \* Stability of semi-solid Dosage forms:-

- Stability of active ingredients incorporated into ointments or creams often depends upon the nature of ointments and creams base used in formation. Cream bases containing water are more active to decomposition of drugs which proceeds via hydrolysis [The chemical breakdown of a compound due to reaction with water].

Dilution of ointment and creams by the user with untested diluents can further lead to instability problems.

Diluents containing oxidizing agents could cause chemical degradation.

Incorporation of drugs into gel structure lead to change in their stability. Penicillin G sodium has been shown to undergo increased degradation in hydrogels of various natural and semi-synthetic polymer.

### Stability of solid Dosage forms:-

The effect of ~~of~~ various factors on the stability in solid dosage forms are following.

#### 1) Temperature :

The kinetic of decomposition in the solid state is different from that in solution. The temperature dependence of the rate constant usually follows the Arrhenius equation.

Exception to this rules are those solids in which decomposition exhibits an approach to equilibrium as in case of vitamin A in gelatin beadlets and vitamin E in lactose base tablets.

In this case, the effect of temperature is derived described by ~~vant~~ Vant Hoff equation:-

$$\ln K = -\frac{\Delta H}{RT} + \text{constant}$$

## 2. Moisture.

Moisture has a significant effect on the kinetics of decomposition of solid dosage forms. When the moisture content is quite high, the decomposition of drug in solid dosage form becomes similar to that in a saturated solution i.e.  $\rightarrow$  zero under kinetic.

## 3. Chemical interaction :-

Chemical interaction between components in solid dosage form may often lead to increased decomposition. In APC tablets [Aspirin, Phenacetin, and caffeine], Phenacetin was replaced by paracetamol but this led to an unexpected decrease in stability. A number of tablet excipient have also found to decrease the stability of the active ingredient.

## International Regulatory Guideline for Stability studies.

Stability testing of drug substance and day products has long been a concern area for both the pharmaceutical industry as well as the regulatory agencies world wide.

The first effort of technical requirements for pharmaceutical stability, ICH (International council Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) (ICH). Started in 1990 at brussels. The ICH steering committee has since been meeting regularly and atleast twice a year. Harmonization of stability requirement guideline in stability testing of new drug substance and products in 1993. This guideline describe the stability testing requirements for registration of pharmaceutical products in Europe, Japan and USA.

The World Health Organization (WHO) being the observer of the ICH process felt that the ICH parent guideline Q1A was not to address the requirements in

my country having extreme climatic condition to existing drug product.

- ◎ Q1A → guideline is a stability testing of new drug substance and products.

It published a separate guideline on stability testing of pharmaceutical product containing well established drug substances in conventional dosage forms; updated in the report of 32<sup>th</sup> meeting of WHO in October 2001.

#### (4) ICH and WHO guideline for stability studies

The ICH released six guideline for stability studies. The parent guideline Q1A has been raised twice and the current version Q1A (R<sub>2</sub>) lays down the requirements pertaining to registration application within the three regions of the Europe, Japan and USA.

The Q1B guideline gives the recommendation for photostability testing of new drug substance and drug products.

The Q1C guideline for stability testing of New dosage forms.

The Q1D guidelines explain the bracketing and matrixing designs for stability testing of drug substances and products.

The Q1E guideline explain the principle of the parent guideline and gives specific stability requirement for other regions of the world.

### ICH guideline

### Title

1. Q1A (R<sub>2</sub>)      Stability testing of new drug substance and products.

2. Q1B      Stability testing - photostability of new drug substances and products.

3. Q1C      Stability testing for new dosage forms.

4. Q1D      Bracketing and matrixing design for stability testing of drug substances and products.

5. Q1E Evaluation of stability data.

6. Q1F Stability data package for registration application in climatic zone.

### Bracketing:

It assumes that the stability of the intermediate is represented by the stability of the extremes tested. The ~~was~~ uses of this design is appropriate if the selected sample are not the extremes.

### Matrixing:

It is use to confirm a prediction of the stability information.

### ICH guideline on stability studies

### Climatic zones:-

As per the ICH and WHO guideline on stability studies. The world has been divided into four zones as per annual climatic condition of temp. and humidity.

Zone I - temperature:

Zone II - Subtropical with possible high humidity

Zone III - hot, dry

Zone IV - hot, humid.

### Types of stability studies.

#### 1) Long term stability studies

ICH guideline Q1A (R2) defines long term studies as stability studies under recommended storage condition for the greatest period or shelf life proposed for labeling.

This study is generally performed at  $25^{\circ}\text{C}/60\%$  or  $30^{\circ}\text{C}/65\%$ . RH.

Ideally 12 months data is to be generated. 5x month data is also acceptable.

For drug substances recommended to be stored in a refrigerator, the long term stability study is carried out  $5 \pm 3^{\circ}\text{C}$  and for freezer stored carried out at  $-20 \pm 5^{\circ}\text{C}$ .

Climatic zones	Recommended Conditions for long term stability studies in general case	
	Temperature (°C)	Humidity (%)
I and II	$25 \pm 2^{\circ}\text{C}$	$60 \pm 5\%$
III and IV	$30 \pm 2^{\circ}\text{C}$	$65 \pm 5\%$

Table : Recommended Conditions for long term stability studies.

## (2) Accelerated Stability Studies :-

For accelerated stability studies, A storage condition of  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and RH of  $75 \pm 5\%$  has been recommended for all the four zones for drug substances and drug products at  $25 - 30^{\circ}\text{C}$ . The studies carried out for 6 month storage. At intermediate storage conditions additional testing where significant change occurs at any time during 6 month storage at  $230^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and  $65\% \pm 5\%$ .

RH (Relative humidity) should be conducted.

For drug substances and drug products intended to be stored in a refrigerator, studies carried out at  $25 \pm 2^{\circ}\text{C}$  and  $60 \pm 5\%$  RH.

### 3) Testing Frequency

The frequency of testing at the long term storage condition should normally be every 3 month over the first year, every 6 month over the 2nd year and annually through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time point e.g. (0, 3 and 6 months) from a 6-months study is recommended.

### 4) Packaging container

Stability studies should be carried out in the final packaging proposed for marketing. Additional testing of unprotected finished product can form a useful part of the stress testing and pack evaluation.

### 5. Stability Testing

A study of drug stability and of stability testing technique is essential for the following main reasons.

### i) Patient Safety:

Pharmaceutical Industry produces highly specific, chemically complex, Potent drugs. The patient should receive a uniform dosage of the drug throughout the shelf life of the product. The drug may have shown to be safe but the decomposition product may not be safe.

### ii) Drug activity:-

In addition to the formation of toxic products, determination deterioration will also lead to reduce activity of the compound or preparation. And hence the therapeutic benefits of the preparation will be reduced. Microbial contamination may be also cause degradation and be otherwise harmful.

### iii) Legal requirement.

Preparation formulated according to official compendia must comply with requirement for identify, strength, purity and quality of the drug. This is true of the product not only when it is manufactured but throughout

its shelf life..

iv) Bad image for the manufacturers:-

A poorly formulated or unstable product may show problems like fading or darkening of colour, caking of suspension or breaking of emulsions. This will result in non-acceptance by the user community that is doctor, pharmacists etc. And it will be a poor advertisement for the manufacturers. From economic point of view it will result in financial loss resulting from non-sale, withdrawal, reformulation etc.

v) Patients Economy .

A patient is entitled to receive what he is paying for. Stability testing is generally done to ensure that the determination deterioration does not exceed and acceptable level and the activity of the drug and safety of the patients is ensured.

### \* 3). Cause of instability and prevention

The most common cause of instability and decomposition of drug are :-  
Hydrolysis and oxidation.

Photochemical decomposition and isomerization lead to instability of some drug.

#### 1) Hydrolysis :

This problem is most important in system containing water such as emulsion, suspension, solution etc. Also for drug which are affected by traces of moisture in the form of water vapour from the atmosphere.

The main class of drugs that undergo hydrolysis are the esters, amides and lactams.

\* Any insoluble substance present in liquid form ~~is~~ is called suspension.

e.g. Antacids (oral).

## Protection against hydrolysis.

Hydrolysis or solvolytic reactions may be retarded by the following approaches.

- i) Hydrolytic reaction in solid drug products such as tablets, capsules, powders and granules may be prevented by avoiding their contact with moisture at the time of manufacture, packaging in suitable moisture resistant packs such as strip packs and storage in controlled humidity and temp. cond. Extra protection can be achieved by incorporating a suitable desiccant in the pack such as silica gel bags.
- ii) Hydrolysis of certain drugs such as benzocaine and procaine (local anaesthesia) can be decreased by addition of specific complexing agent like caffeine to the drug solution.
- iii) In case of liquid dosage form such as solution, suspension and emulsion, The main emphasis is on reducing the rate of hydrolysis.

iv) Refrigeration of drug solution and drugs also retards hydrolytic reaction.

## 2) Oxidation

Instabilities in a number of pharmaceutical preparation are due to oxidation oxidative degradation degradation of the active ingredient of this preparation when exposed to atmospheric oxygen.

Oxidation involves either the addition of oxygen or removal of hydrogen. ~~Oxy~~ oxidation and reduction reaction generally occurs simultaneously. Oxidation is the loss of electrons while reduction is the gain of electron.

Auto-oxidation is a most common form of oxidative degradation that occurs in many pharmaceutical preparation and involves a free radical chain process. In an auto-oxidative degradation, only a small quantity or amount of oxygen is required for initiating the reaction and thereafter oxygen concentration is relatively important.

## Protection against oxidation.

i) The most common approach to prevent oxidation in pharmaceutical preparation is to include antioxidants in the preparation. An antioxidant is an agent that has lower oxidation potential than the drug.

e.g. vit-E, C or Hydrogen peroxide, Halogens etc.

ii) The effectiveness of antioxidant can be increase through the use of synergists such as chelating agent like EDTA, citric acid and tartaric acid which react with impurities such as those of heavy metals which may catalyst the oxidation reaction.

EDTA = Ethylene diamine tetraacetic acid;

[Examples of drug which undergo oxidation decomposition are - Ascorbic acid, Morphine, Heparin, Paraldehyde, Tetracycline, Vitamin - A, D and K.]

iii) When oxidation is catalysed by hydrogen and hydroxyl ion the pH of optimum stability must be ensure.

- ii) Replacement of air from the container of the drug preparation by an inert gas such as - Nitrogen can also prevent oxidation.
- v) Oxidation of fat and oils may be retarded by hydrogenation.
- vi) Protection from light.

e.g.: - Packaging in amber coloured bottle or container and storage at low temp. can also minimize oxidation-reduction in certain preparation.

Ascorbic acid is also <sup>an</sup> antioxidant agent.

### \* 3) Photolysis.

Many pharmaceutical compounds including ascorbic acid, nitrogen nifoflenin, hydrocortisate, Hydrocortisone, Prednisolone, Nifedipine etc undergo degradation when it passes to light. Its波es of light may produce oxidation-reduction, ring arrangement or modification and polymerisation. The shorter the wavelength of light the greater is the effect of light in initiating the chemical reaction because of higher energy.

#### 4) Isomerisation

Isomerisation is the process of conversion of a drug into optical or geometric isomer. Since different isomers of a drug have different activities, such a conversion from one form to another may be regarded as a form of degradation. Resulting in serious loss of therapeutic activity.

"For example, there is an appreciable loss of activity of adrenaline solution at low pH due to the conversion of its therapeutically active laevo-rotatory form to the less active dextro-rotatory form, the process often known as racemisation".

#### \* PH :-

Acidic and alkaline pH influence the rate of decomposition of most drugs. Many drugs are stable between pH 4 and 8. Weakly acidic and basic drugs show good solubility when they are ionized and they also decompose faster when they are ionised.

## \* Drug Kinetics

\* Drug follows two kind of kinetics:

- i) First order
- ii) Zero order.

### i) First order:

→ In first order, fraction is constant.  
It means in same time, some fraction will be eliminated. That is in same time, some percentage of drug will be eliminated. Suppose initial plasma concentration of drug is 100.

### ii) Zero order

→ Amount ~~of~~ is constant. It means in same time, same amount will be remove not percentage.

First order:Zero OrderPlasma conc.: 1001 hr | 20

80

1 hr | 20

60

1 hr | 20

40

1 hr | 20

20

1 hr | 20

0

First order.

100

1 hr | 50/100

50      50%

1 hr | 25/100

25      50%

1 hr | 12.5/100

12.5      50%

1 hr | 6.25/100

6.25      50%

It means 50% per hr.

50%  $\rightarrow$  Rate of elimination.

i) Rate of elimination

ii) Clearance = Rate of elimination  
plasma concentrationiii) Half life ( $t_{1/2}$ ) :- It is the time at which plasma concentration become half.

First order	Zero Order
i) Rate of elimination is directly proportional to plasma conc.	i) Constant
ii) Clearance is constant.	ii) Clearance is inversely proportional to plasma conc.
iii) Half life is constant	iii) Half life is directly proportional to plasma conc. $\boxed{CL \propto \frac{1}{PC}}$ $\boxed{(T^{\frac{1}{2}}) \text{ Half life} \propto PC}$

Zero order eg

W - Warfarin

A - Alcohol, Aspirin

T - Theophylline

T - Tolbutamide

Power - Zero Phenytoin.

\* If enzymes is the limiting factor then it follow zero order kinetics.

## Rates and order of Reactions

### Rate of Reaction

⇒ The rate of a chemical reaction is defined as the velocity with which a reactant or reactants undergo chemical change. The rate of a reaction can therefore be measured by measuring the change in the concentration of a reactant or product in a particular period of time.

The rate of a reaction is given by.

$$\boxed{\pm \frac{dc}{dt}}$$

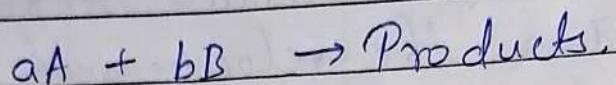
The + or - sign indicates an increase or decrease respectively in concentration  $dc$  within a time interval  $dt$ .

### ④ Rate constant and order of Reaction.

⇒ According to the law of mass action, the rate of a chemical reaction is proportional to the product of the molar concentration of the reactants each raised to a power usually equal to the number of molecules,  $a$  and  $b$ .

of the substance A and B undergoing reaction.

Thus, in the reaction



the rate of the reaction is given by:

$$\text{Rate} = \frac{-1}{a} \frac{d[A]}{dt}$$

OR

$$\boxed{\text{Rate} = \frac{-1}{b} \frac{d[B]}{dt} = k[A]^a [B]^b}$$

in which  $k$  is the rate constant also known as specific rate constant.

The order of reaction is the ~~term~~  
sum of the powers of the concentration terms involved in the eq.

Thus the order of the above reaction is  $(a+b)$ . The order of a reaction determines the way in which the conc. of a reactant or reactants influences the rate of a chemical reaction.

## Zero Order Reaction

If the rate of a reaction is independent of the concentration of the reacting species, the reaction is said to be a zero-order reaction.

The rate of a zero-order reaction is given by:

$$-\frac{dA}{dt} = k.$$

Where,

$dA$  is the change in concentration with respect to change in time  $t$ .

'-' sign indicates that the concentration is decreasing.

This rate equation may be integrated between initial concentration  $A_0$  (original concentration) and  $A_t$ , the concentration after time interval  $t$ .

$$\int_{A_0}^{A_t} dA = -k \int_0^t dt$$

$$A_t - A_0 = -kt.$$

$$A_t = A_0 - kt$$

This being the equation of a straight line, the plot between  $A_t$  on y-axis against  $t$  on x-axis gives a straight line with slope equal to  $-k$ .

Unit of  $k$  for a zero order reaction is moles/litre/second.

The above equation can also be written as :

$$k = \frac{A_0 - A_t}{t}$$

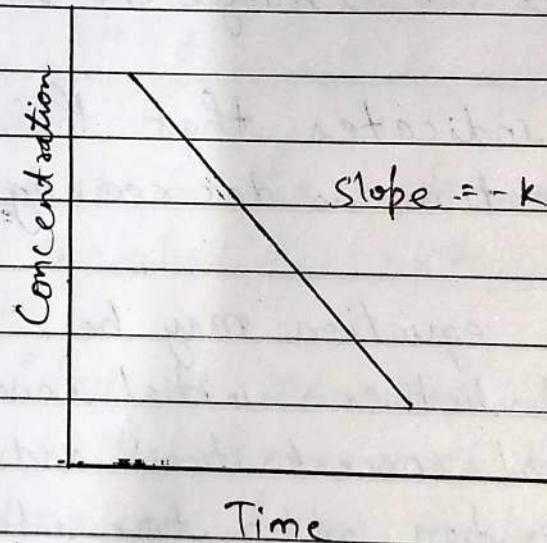


Fig: 6.1: Plot of concentration versus time for a zero order reaction.

or  $t = \frac{A_0 - A_t}{k}$

## 5 Half Life of a zero-order Reaction.

Half life ( $t_{\frac{1}{2}}$ ) of a chemical reaction is the time required for the initial concentration of a reactant to get reduced to half, i.e.,

$$A_t = \frac{1}{2} A_0$$

Substituting this in the above equation, we get,

$$\frac{A_0}{2} = A_0 - k t_{\frac{1}{2}}$$

$$\frac{A_0}{2} - A_0 = -k t_{\frac{1}{2}}$$

$$-\frac{A_0}{2} = -k t_{\frac{1}{2}}$$

$$t_{\frac{1}{2}} = \frac{\frac{1}{2} A_0}{k}$$

## Half life of a zero-order Reaction

An expression of importance in the pharmaceutical field is  $t_{0.9}$ , i.e., the time required for the drug to decompose by 10% (i.e. to 90% of its original conc.)

Thus,

$$A_t = 0.9 A_0$$

Substituting this in the above equation, we get.

$$t_{0.9} = \frac{A_0 - 0.9 A_0}{K}$$

$$t_{0.9} = \frac{0.1 A_0}{K}$$

### First Order Reaction

When the rate of a reaction is directly proportional to the first power of the concentration of a single reactant, the reaction is said to be of first order with respect to the single reactant.

In this type of reaction if a first order reaction is given by.

$$-\frac{dc}{dt} = k c$$

$$\frac{dc}{c} = -k dt$$

Integrating the equation between the limits of concentration  $c_0$  at time  $t = 0$  and conc.  $c$  at time  $t = t$ , we, get,

$$\int_{C_0}^C \frac{dc}{c} = -k \int_0^t dt$$

$$\ln C - \ln C_0 = -kt$$

$$-\ln C = \ln C_0 - kt$$

Converting to common logarithmic form, we get,

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

$$K = \frac{2.303}{t} \log \frac{C_0}{C}$$

In exponential form, the equation becomes:

$$C = C_0 e^{-kt}$$

$$C = C_0 10^{-kt/2.303}$$

These equations indicate a first order reaction since the concentration decreases exponentially with time and this may be shown by plotting concentration against time when a curve similar to fig. below.

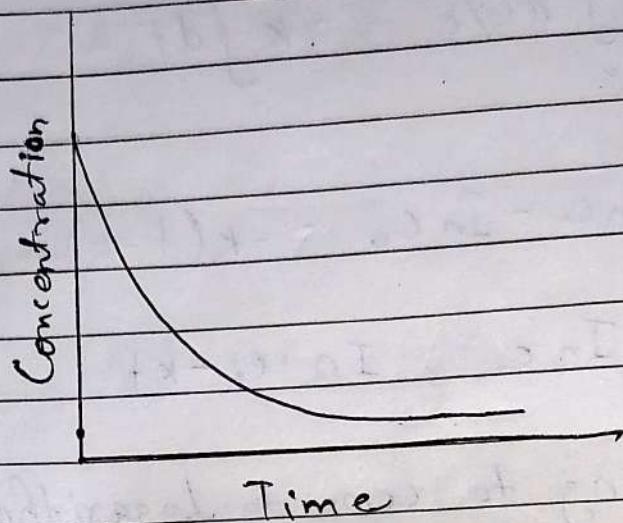


Fig :- 6.2 : Plot of concentration versus time for a first order equation.

If  $\log c$  is plotted against  $t$ , a straight line is obtained with slope equal to  $-k/2.303$ . The rate constant  $k$  can then be obtained from the slope of the line (fig. 6.3)

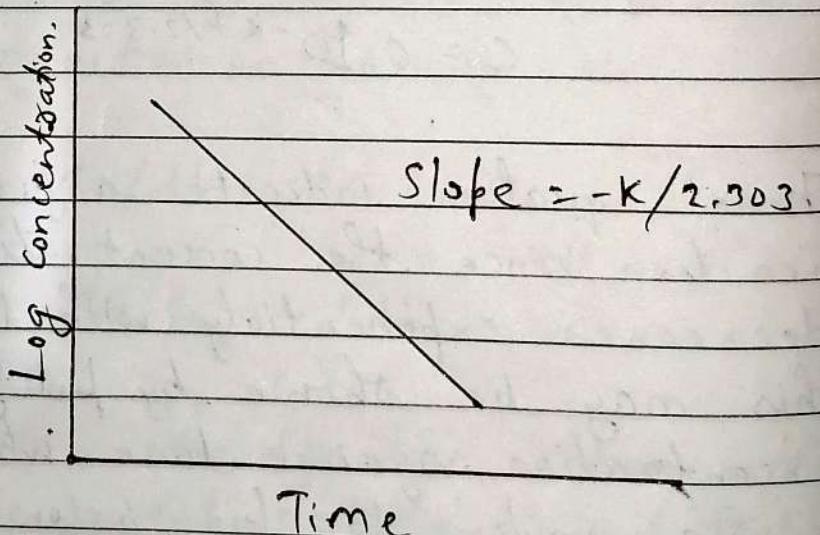


Fig 6.3 : Plot of log concentration versus time for a first order reaction.

The above equation is also written as:

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

Where,

$a$  is the initial conc. equal to  $c_0$ .  
 $x$  is the decrease in conc. in time  $t$ .  
 $(a-x)$  is the concentration remaining at time  $t$  and is equal to  $c$  in the above reaction.

Unit of  $K$  for a first order reaction is  $\text{sec}^{-1}$  (or  $\text{time}^{-1}$ ).

Half life of a first order reaction

$$t_{\frac{1}{2}} = \frac{2.303}{K} \log \frac{c_0}{c}$$

$$= \frac{2.303}{K} \log \frac{c_0}{\frac{1}{2} c_0}$$

$$= 2.303 / K \log 2$$

$$= 0.693 / K$$

Thus, half life of a first order reaction is a constant independent of the concentration.

## Half life of a first order reaction

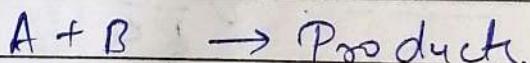
$$t_{0.5} = \frac{2.303}{k} \log \frac{C_0}{0.5 C_0}$$

$$= 2.303/k \times 0.0952$$

$$= 0.1052/k$$

## Second Order Reaction

A reaction is said to be of second order if the experimentally determined rate of reaction is proportional either to the second power of the concentration of a single reactant or to the first power of the concentration of the two reactants.



If the reaction is one mole per basis of A and B rate of decomposition of A = rate of decomposition of B.

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

If  $a$  and  $b$  represents the initial concentrations of A and B respectively and  $x$  is the amount of each of A and B reacting in time  $t$ , the reaction rate  $dx/dt$  is given by:

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

where  $(a-x)$  and  $(b-x)$  represent the concentration of A and B remaining unreacted at time  $t$ .

1. If the initial concentration of A and B are equal, i.e.,  $a=b$ , the above equation can be written as :

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

On integrating between the limits  $x=0$  at  $t=0$  and  $x=dx$  at  $t=t$ , we get:

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

$$\frac{1}{(a-x)} - \frac{1}{(a-0)} = kt.$$

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

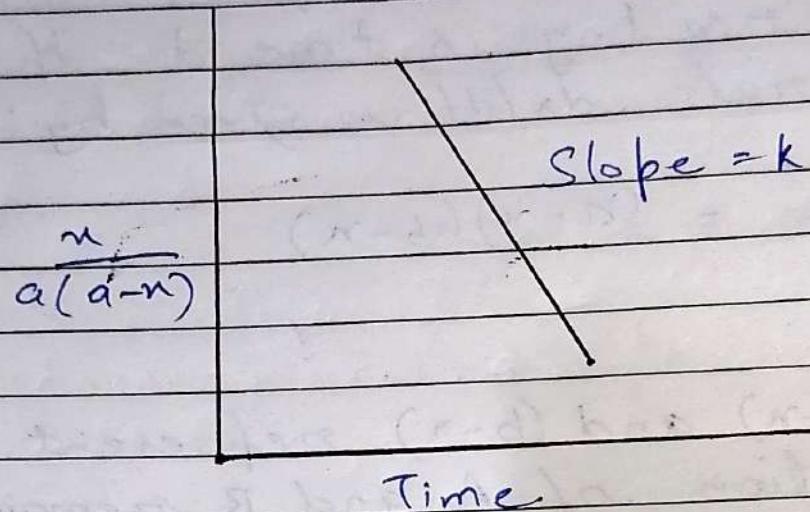


Fig: 6.4. Plot of  $n/a(a-n)$  versus time for a second order reaction.

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

Plot of  $x/a(a-x)$  against  $t$  gives a straight line with slope equal to  $K$  (fig. 6.4.).

2. If the concentration of A and B are not equal, i.e.  $a \neq b$ , integration of equation (i) gives:

$$Kt = \frac{2.303}{(a-b)} \log \frac{b(a-n)}{a(b-n)}$$

In such a case, plot of  $\log b(a-n)/a(b-n)$  against  $t$  yields a straight line with slope equal to  $(a/b)k/2.303$ .

The rate of constant  $k$  for a second order reaction has the units,  
 $\text{litre} \cdot \text{mole}^{-1} \text{sec}^{-1}$

### Half life of a Second order Rxn.

The half-life for a second order reaction (only when  $a=b$ ) is given

by:

$$\boxed{t_{\frac{1}{2}} = 1/ak}$$

### PSEUDO FIRST ORDER REACTION

In a second order rxn if the conc. of one reactant is in such large excess that is virtually remain constant, when the rate of change of concentration follows first order. Hydrolysis reaction are common example of pseudo first order reaction. Also if a buffer is use to maintain the pH, the reaction proceeding of an addition of an acid or a base is pseudo first order.

# States of Matter

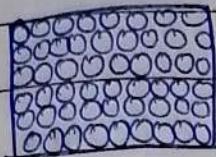
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Pharmaceutics is a branch of pharmacy in which we study with the formulation, manufacture, stability and effectiveness of pharmaceutical dosage forms. It is systematic approach to get an effective and stable formulation without disturbing its quality. It deals with technology involve in large scale manufacturing.

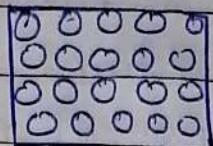
## Introduction :

Matter are normally exists in the three states :- liquid solid, liquid and gas. However, there is no sharp borderline between the various states and in most cases a substance may be made to exists in any of three states. The factor effecting in which matter exist are the intermolecular forces, the temperature and pressure. Solid have strong intermolecular forces and gases have the weakest. When temp. increases solid matter converted to liquid and liquid to gases.

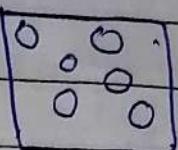
eg. Solid ice liquid water and water vapors.



Solid



Liquid



Gas.

### \* The Gaseous State

The physical behaviour of gases is independent of chemical nature of the molecules. The molecule in a gas are always in a state of vigorous and rapid motion, these travel over random paths, collide with one another with the wall of the container. They occupy completely all the space available in the containers.

### Ideal and Non-ideal gases:-

The general behaviour of an ideal gas with variations of pressure, volume and temperature can be given by the ideal gas equation.

$$PV = nRT$$

Where,

$P \rightarrow$  Pressure

$V \rightarrow$  volume

$n \rightarrow$  no. of moles of gas

$R \rightarrow$  gas constant (0.0821)

$T \rightarrow$  Absolute temp.

The ideal law derived by combining the gas law formulated by Gay Lussac, Boyle's, Charles and Avogadro's -

The ideal gas law is clear that the volumes of a gas is directly proportional to the number of moles of the gas, and absolute temp. is inversely proportional to the pressure.

Non-ideal gas is called Real and actual gases which do not obey the ideal gas law.

### Change in the State of Matter.

The molecules, atoms or ions in a solid are strongly held by intermolecular, interatomic or ionic forces respectively. As the temperature of solid substance is raised, the particle acquire

sufficient energy to disrupt the ordered arrangement and pass into the liquid state. On further increasing the temperature, the molecules pass into the gaseous state. Sometimes, the solid directly converted to the gaseous state. This term is called sublimation.

### Latent Heat.

When a change in the state of materials occurs, the temp. usually remains constant but heat is absorbed. This heat will result in the change of matter without increasing the temperature is called latent heat.

When this heat result in the change of state from a solid to a liquid, it is known as the latent heat of fusion.

e.g. at  $0^{\circ}\text{C}$  the heat required to change ice to water.

When a liquid change into a vapour form, that latent heat is known as latent heat of vapourisation.

e.g.: - at  $100^{\circ}\text{C}$  the heat required to change water into vapour.

## Vapour Pressure

When temp. applied to a liquid is kept in a closed evacuated container, molecules from its surface continuously leave and keep walking into the free space, this is called vapourisation. Some molecules returns to the surface depending on their conc. in the vapour (condensation). At last a condition of equilibrium gets established when the rate of escape of molecule become equal to the rate of return. The vapour is then said to be saturated and the pressure exerted by the vapour at equilibrium is called the vapour pressure.

The vapour pressure of a liquid depends on the temp. and not on the amount of liquid or vapour as long as both liquid and vapour are present and equilibrium maintained. At the temp. raised, more of the liquid goes into the vapour state and the vapour pressure increase. The density of vapour increase and then liquid density decrease.

The temp. at which this happens is called critical temp. and above this temp. there is no liquid phase.

## Relative Humidity.

Relative humidity may be defined as the ratio of amount of water vapour in air at a specific temp. to the maximum amount that the air could hold at that temp. expressed as a percentage.

$$\text{Relative humidity} = \frac{\text{actual water vapour pressure}}{\text{saturated water vapour pressure}} \times 100\%$$

The amount of water vapour the air can hold increases with temperature.

## \* Eutectic Mixture.

Certain substances such as menthol, thymol, phenol, camphor, sol etc. when mixed in a particular proportion tend to liquify due to reaction in their respective melting points. Mixtures of such substances are known as eutectic mixture.

The mixture of substance that melt or solidifies at a single temperature that is lower than the melting point of either of the constituents.

### Principle

We considered two substances A and B, where point A and B represent the melting point of two components. As increasing quantities of B are added to A, and vice versa.

The freezing point A fall as curve ~~AC~~ and B fall as curve BC at the particular composition C, known as Eutectic point.

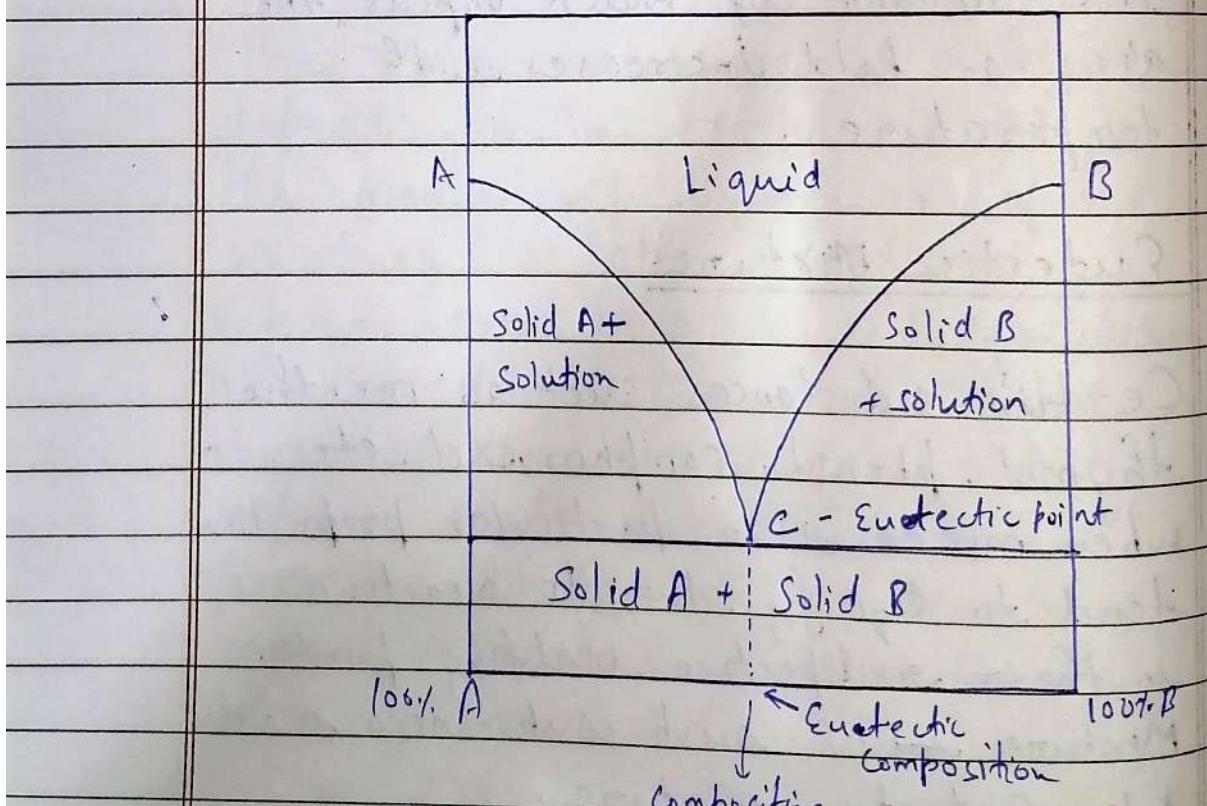


Fig:- Phase diagram of Eutectic system.

The mixture of the two substances has the lowest melting point. This composition of the two substance is k/a Eutectic mixture.

The phenomenon of eutectic formation has been used in pharmaceutical practice to improve the dissolution behaviour of certain drugs.

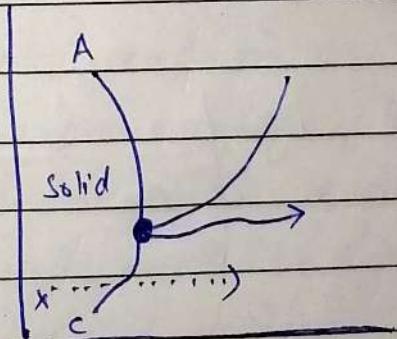
eg:- Aspirin - acetaminophen (37% and 63%)  
Urea - acetaminophen (46% and 54%) and  
griseofulvin - succin (55% and 45%)

### \* Sublimation

It is defined as the process of transformation of solid directly into the vapour phase without passing the intermediate liquid phase.

eg. Camphor, menthol, naphthalene, ice is also.

### Principle :-



The curve AD represents the melting point of the solid phase of the substance at different pressure. Along the curve AO, the solid exists in equilibrium with its liquid phase. The BO represents the liquid exist form and liquid exists in equilibrium with its vapour.

The curve CO represents the vapour pressure of the solid at various temp. and k/a sublimation curve. There is exist one point (O) where all the three phases of the materials are in equilibrium with each other and this is k/a triple point.

The point X below the stable point where substance is present in the form of a solid, if heat is applied to the substance at the point it will pass directly in the vapour phase without passing through the liquid state. This process is called sublimation.

## \* Aerosols :-

Liquification of gas can be achieved by applying pressure on it and keeping the temperature below the critical temperature. When the pressure is reduced, the molecule expand and the liquid reverts back to the gaseous state.

Aerosols are based on this principle of reversible change of state on the application and release of pressure.

In pharmaceutical aerosols, drug is classified or suspended in a propellant, a material which exists as a solid liquid under the pressure conditions inside the container but gets converted to a gas under normal atmospheric conditions. The container is designed in such a manner that on depressing a valve, some of the drug-propellant mixture is expelled out due to the excess pressure inside the container.

The propellant used on such products are generally fluorinated hydrocarbons. Although gases such as Nitrogen and carbon dioxide also used.

The Aerosol containers are filled either by cooling the propellant and dry to a low temp. within the container which is then sealed with the valve. The drug is sealed in the container at Room. temp. and the required quantity of propellant is forced into the container under pressure.

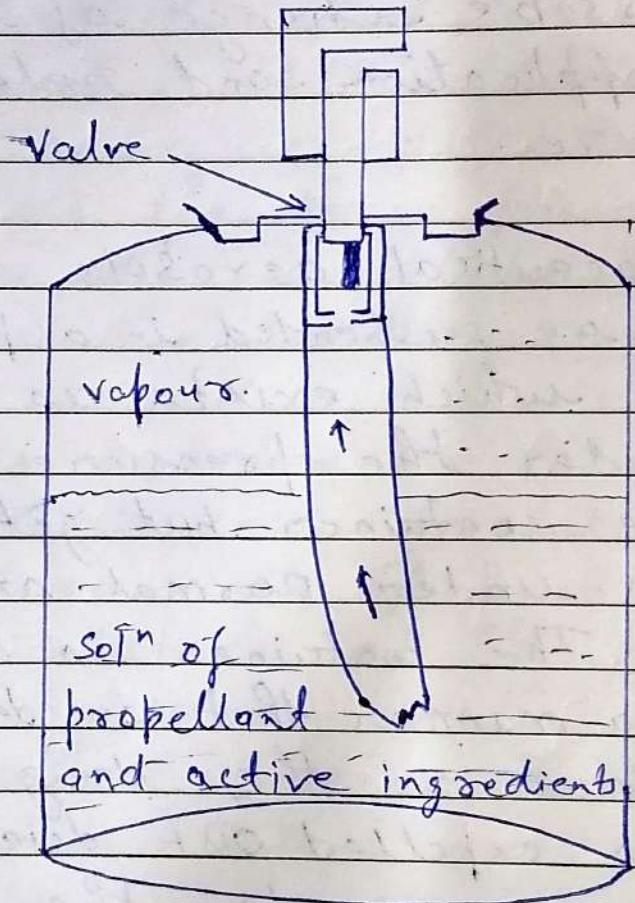


Fig :- An Aerosol System

## The Solid State

Solids have the strongest intermolecular forces. Their structure may be crystalline and lattice-like or non-crystalline such as glass which are not lattice-like structure.

The molecules of a solid are held together by strong bonds which impart a high melting point to these substances.

### Crystalline Solids:-

Crystalline solids generally exhibit a definite shape and an orderly arrangement of units, it arranged in fixed geometric patterns or lattice. The crystalline solids have been divided into seven distinct forms including cubic form (eg - NaCl), tetragonal form (eg - Urea), hexagonal form (eg - iodoform), orthorhombic form (eg - iodine), monoclinic form (eg - sucrose), Trigonal form (eg - calamine) and triclinic form (eg - boric acid).

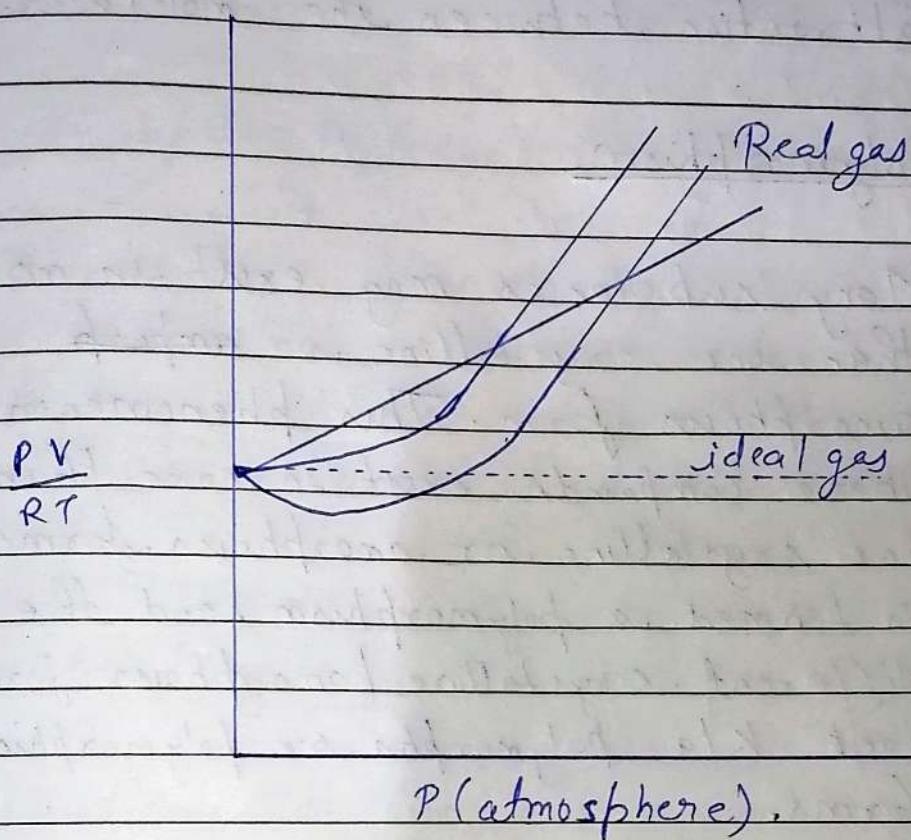
## \* The Liquid State.

The liquid state may be intermediate state as matter. Liquid can be considered as highly compressed gases or slightly released solids. The molecules of a gas are in a state of rotation owing to their kinetic energy which is proportional to the absolute temp. of the gas.

When gas is cooled, its reduced their kinetic energy gradually. As the temp. reduced, a stage is reached where the molecules almost loose their kinetic energy. As a result, the gas molecules come closer and ultimately the gas gets converted into the liquid state. Liquefaction of gas can also by increasing the pressure on the gas, but pressure is effective only below a certain temp.

Those certain temp. which are gas converted to the liquid states is called critical temp. The critical pressure is the pressure required to liquify a gas at its critical temp. The critical temp. of water is  $374^{\circ}\text{C}$  or  $692^{\circ}\text{K}$  and its critical pressure is 218 atmosphere.

Departure of real gases from ideality can be demonstrated by means of plots such as that shown in figure.



- $PV/RT$  is a function of pressure for 1 mole of each gas.

A better approximation to the real behaviour may be obtained by the using of van der waals equation.

$$\left( P + \frac{an^2}{v^2} \right) (v-nb) = nRT$$

Where,

$a$  and  $b$  are constants for a particular gas.  $\frac{a}{v^2}$  accounts for the internal pressure per mole resulting from the intermolecular force of attraction between the molecules.

### ★ Polymorphism.

Many substances may exist in more than one crystalline or amorphous form. This phenomenon where compounds exist in more than one crystalline or amorphous forms is termed as polymorphism and the different crystalline / amorphous forms are K/a polymorphs or polymorphic forms.

Different polymorphic forms of substance usually exhibit different melting points, x-ray diffraction pattern, solubilities, dissolution behaviour, stability and biological activity. A number of pharmacologically active substances such as chloramphenicol, furosemide, sulphonamide, barbiturates, testosterone, Prednisolone, (steroids) etc. have been shown to exhibit a number of polymorphic forms differing their solubility, stability and pharmacological

activity. The most stable polymorph. Polymorphism can affect the mechanical properties of drug particles and can therefore affect the manufacturing manufacturability and physical attributes of dosage forms like, tablet.

For example : Different polymorphic forms of drug like paracetamol, carbamazepine, phenylbutazone etc. have exhibited different mechanical properties such as compressibility, flowability, hardness, bonding strength etc.

### \* Liquid Crystal

In addition to the three states of matter, some asymmetric molecules often exhibit a fourth state i.e liquid crystalline state. Liquid crystals possess some of the properties of liquid and some of the solids.

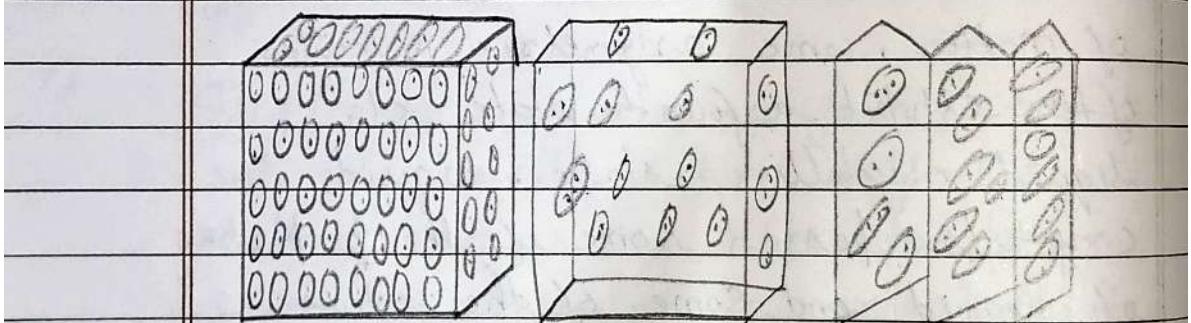
e.g - liquid crystals possess the property of mobility and rotation and can be considered to have the flow properties of liquids. On the other hand, These also possess the property of birefringence, A property associated with solid crystals. In birefringence,

the light passing through a material is divided into two components. Components with different velocities and different refractive index.

The two main types of structure of liquid crystals are smectic (soap or grease like) and Nematic (thread like). In Smectic state, the molecules are mobile in two directions and show rotation about one axis.

In the nematic state, the molecules are mobile in three dimensions.

A third type are ~~ka~~ the cholesteric crystals exist but may be considered as a special case of the nematic type.



Smectic      Nematic      Cholesteric

Fig: Liquid crystalline phase

The liquid crystalline state is found widespread in nature in nerve, brain tissue and blood vessels. Atherosclerosis is thought to result from the deposition of lipid in the liquid crystalline state on the walls of blood vessels. The three components of bile, the cholesterol, the bile salts and water, when present in a definite proportion can result in formation of smectic crystals and these may be involved in the formation of gallstones.

Q. Define boiling point, melting point and freezing point.

When a liquid is heated in an open atmosphere the vapour pressure is increased. On further heating its vapour pressure becomes equal to the atmospheric, the temperature at which the vapour pressure of a liquid equal to the atmospheric is known as boiling point.

Melting point:

The temperature at which a solid passes into a liquid state under atmospheric pressure is known

as its melting point.

### Freezing Point:-

The melting point is referred to as freezing point if the liquid passes into the solid state.