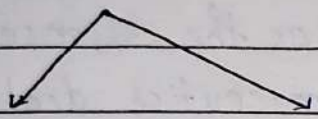
Colloidal Dispersions.

Date: 01/12/21 Page: 05

* Drug
  ↓
  Api (Raw materia)
  ↓
  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.

There 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 heterogenous dispersed systems in which the dispersed phase particles are larger than 0.5 μm. 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	1nm 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, filter paper	Pass through filter paper but do not pass through semipermeable membrane	Do not pass through normal filter paper and semipermeable membrane.
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.

Lyophilic colloids	Lyophobic colloids
• 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 ~~greatly~~ stable generally 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 prepared by.

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

(a) Dispersion methods:

This methods 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 ~~expressed~~ 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 $FeCl_3$ is added to $Fe(OH)_3$, Fe^{3+} ions from $FeCl_3$ are adsorbed by $Fe(OH)_3$

particles. Thus the $Fe(OH)^3$ 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 monomer 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 A° 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 - Sulphanillic acid.

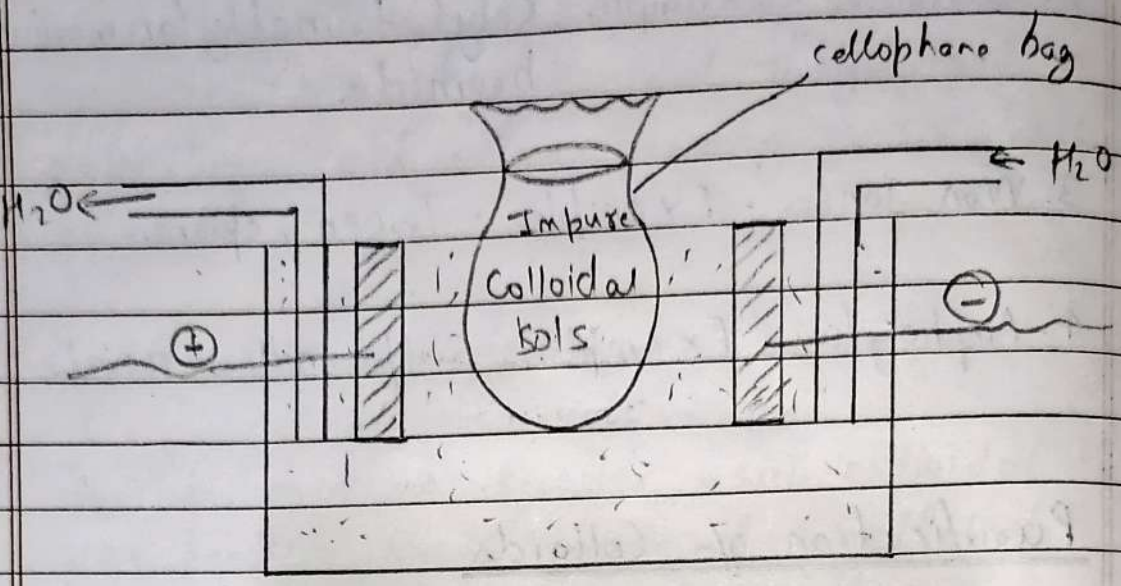
Purification of Colloids

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:**

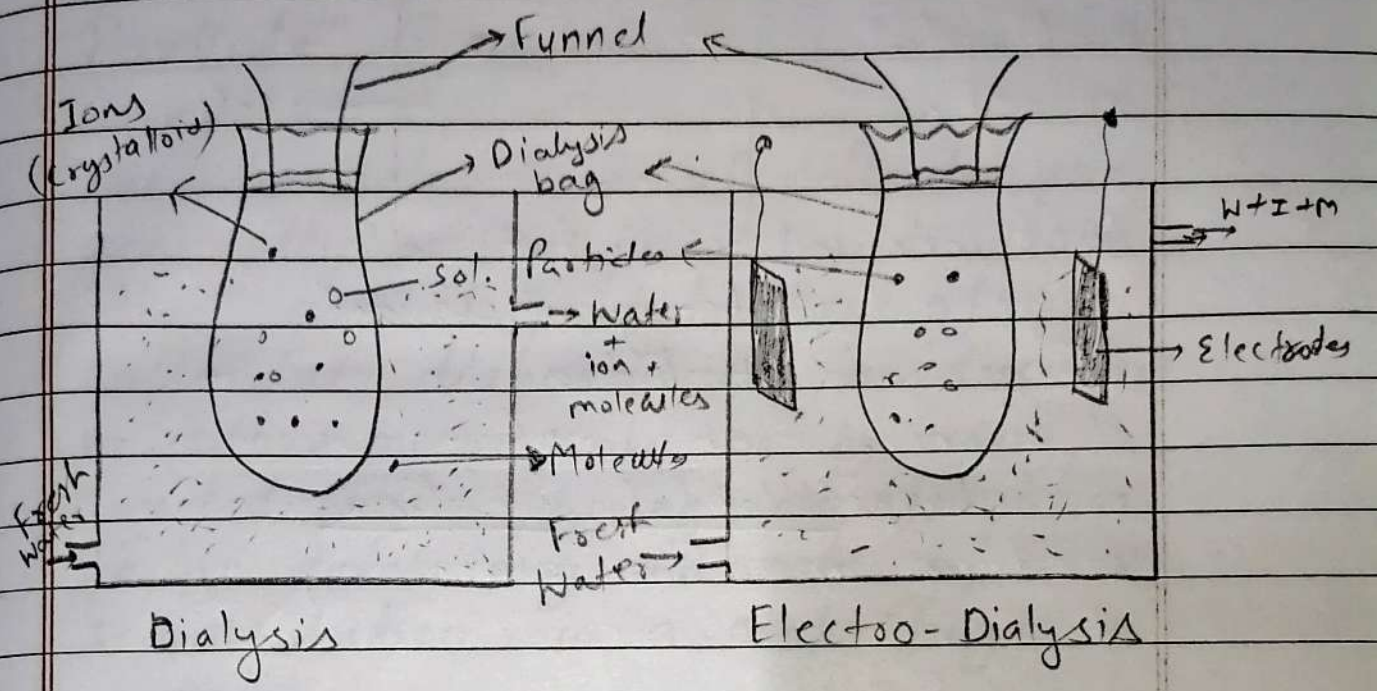
It is a process of removing a dissolved substance from a colloidal solution by diffusion through a suitable membrane in an apparatus called Dialyser.

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.



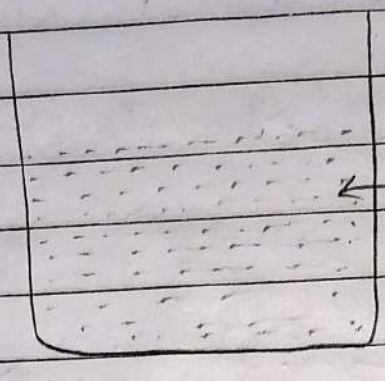
(b) Electrodialysis

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

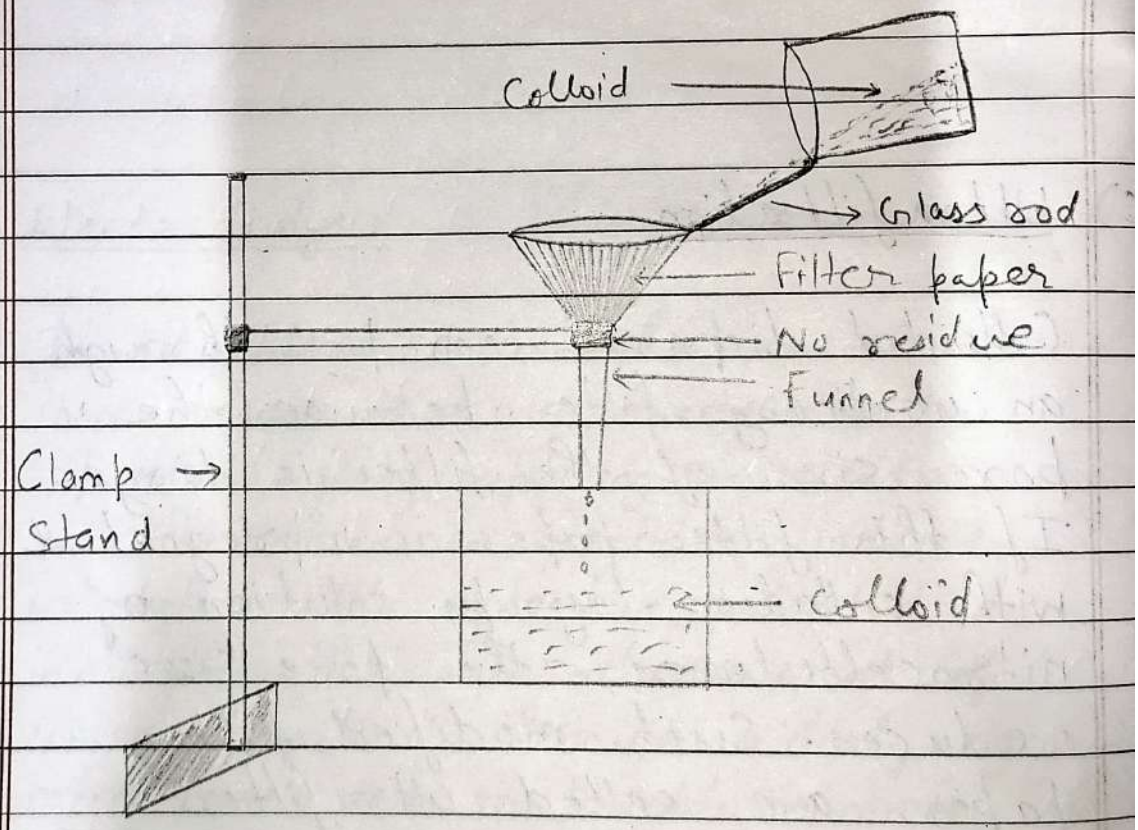


Fig → Filtration of colloidal solution

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 sols 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 ~~se~~ 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. Electromicroscopy:

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 sizie, shape and structure of colloidal particles.

4. Light Scattering:

When beam of light is passed through a colloidal dispersion, some of its 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 ~~refferred~~ 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:

$$D = \frac{RT}{6\pi\eta r N} \cdot \frac{4\pi N}{3MV}$$

Where,
M is the molecular weight
V is the partial specific volume
η 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 determing the molecular weight. The following expression is used for determining molecular weight:

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

Where,
R is the gas constant
T is the absolute temperature
V is the partial specific volume of the polymer.
ρ_o 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:

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

η_0 is the viscosity of dispersion medium, η is the viscosity of dispersion when volume fraction of colloid particles is ϕ. 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, sulpher 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.

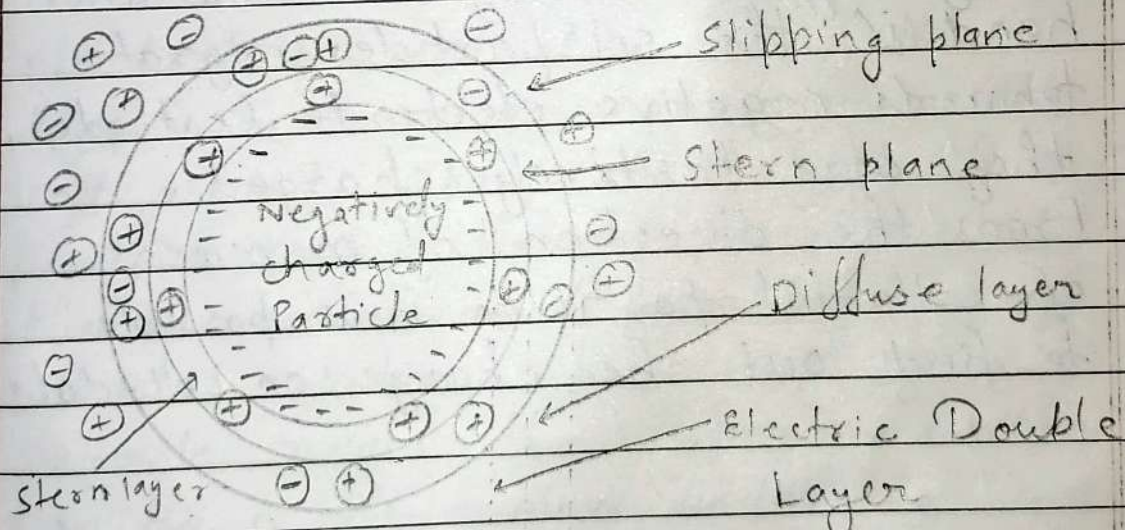
Development of a net charge at the particle surface affects the distribution of ions in the surrounding interfacial region,

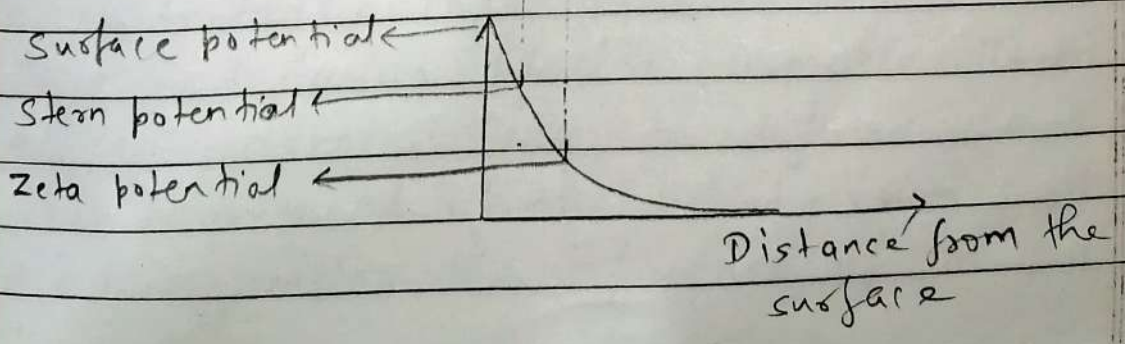
- As a result: concentration of counter ions increase at the surface,
- Thus, an electrical double layer exists around each particle.

Example - $AgNO_3 + NaI \rightarrow AgI + NaNO_3$

Silver iodide sols can be prepared by the reactions, $n\ AgNO_3 + Na\mathbf{1} \rightarrow Ag\mathbf{1} + NaNO_3$. In the bulk of AgI particles 1:1 ratio of Ag^+ and I^-.

If the reaction is carried out with an excess silver nitrate, there will be more Ag^+ than I^- ions in the surface of the particles. The particles will thus be positively charged and the counterions surrounding them will be 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 NaI, there will be more I^- than Ag^+ ions in the surface of the particles. The particles will thus be negatively charged and the counter ions surrounding them will be 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 colloidals.

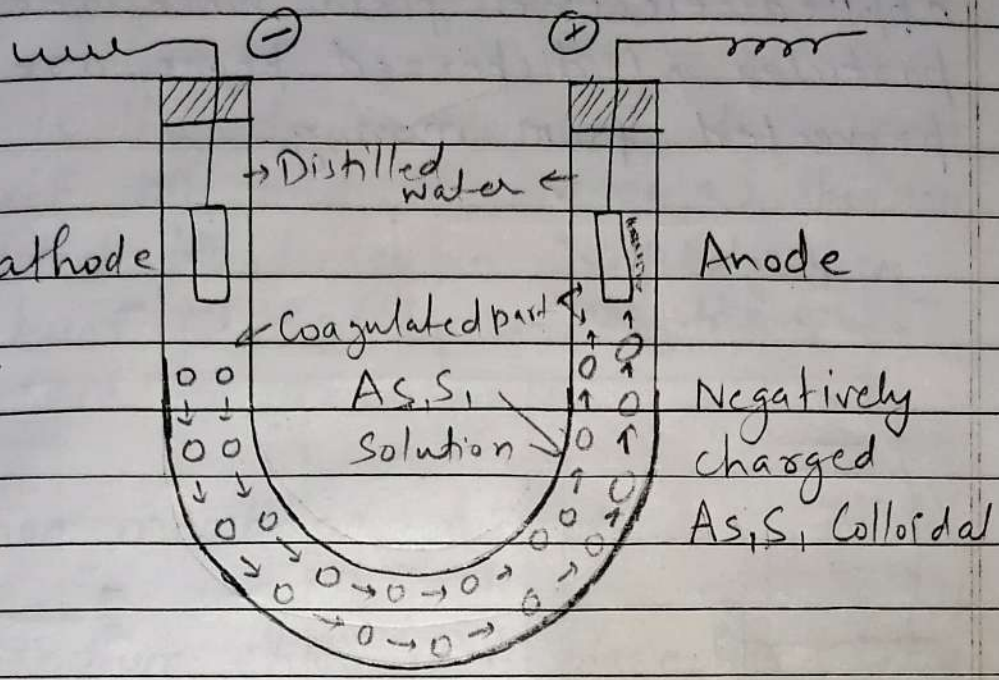


Fig → Electrophoresis

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.

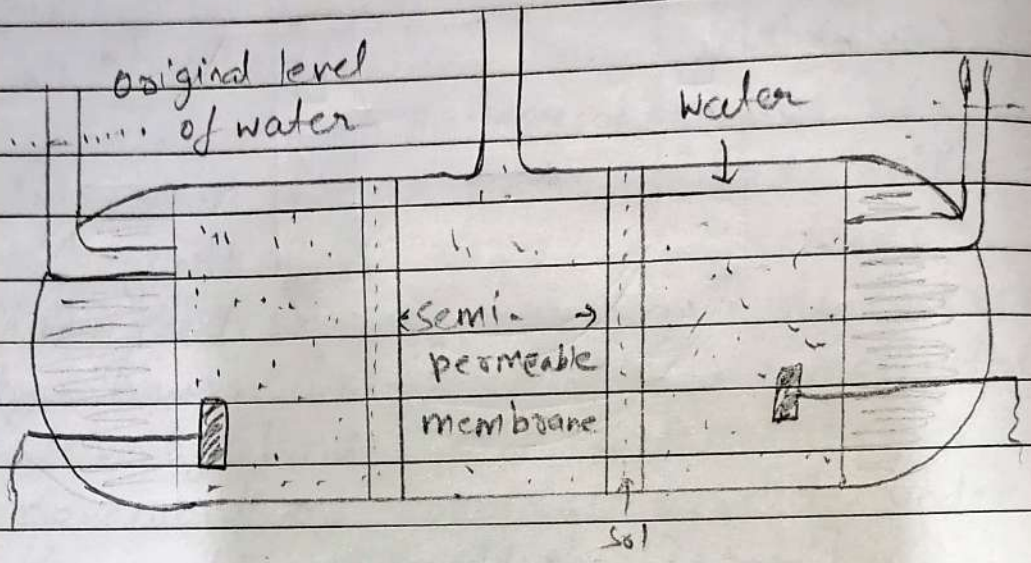


Fig- Electro-osmosis

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 ~~dewasting~~ 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,

Outside (o)	Inside (I)
Na^+	R^-
Cl^-	Na^+
	Cl^-

Na^+, Cl^- are permeable ions
R^- is a non permeable ion

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

i.e., $[Na^+]_o [Cl^-]_o = [Na^+]_i [Cl^-]_i$

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.

i.e. outside : $[Na^+]_o = [Cl^-]_o$
and inside : $[Na^+]_i = [R^-]_i + [Cl^-]_i$

Substituting these in the above first equations, we obtain

$$[Cl^-]_o [Cl^-]_o = ([R^-]_i [Cl^-]_i)[Cl^-]_i.$$

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

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

$$= [Cl^-]_i^2 \, 1 + [R^-]_i / [Cl^-]_i$$

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

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

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 oppositively 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 oppositively 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. Coacervation 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 occur). 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 colloids called protective colloids.

Schulze-Hardy Rule:

Coagulation of colloidal dispersion can be brought about by the addition electrolytes which reduce the zeta-potential. The ~~difference~~ 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.

Al_3^+ is more effective than Mg^{++} and Na^+. Negatively charged arsenious sulfide will be coagulated rapidly with a smaller concentration of $AlCl_3$ than that of $BaCl_2$ or NaCl. Similarly for positively charged sol such as $Fe(OH)_3$, PO_4^{---} is more effective than SO_4^{--} and 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 1ml 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 10ml 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~~ e 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 results 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 tap 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. mdecular 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. eg.
eg. efficiency of kaolin in adsorbing toxins from GIT.
eg. efficiency of aluminium hydroxide as antacid.

7.) Blood plasma substitutes as dextran, PVP 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 anemia.

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.

★ Drug:

It is a bunch of chemicals for the use by patients 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 predication 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 ~~dog~~ drug tend to degrade from the point of manufacture and the expiry date of a product is end point of its self 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 observed 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 pharmaceuticals compounds which undergo photochemical decomposition include riboflavin, phenothiazines, chlordiazepoxide, 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.

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

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_0 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 indude ethanol, Glycerol, propylene glycol, PEN and vegetable oils.

3.) Ionic Strength.

The effect of ionic strength of solution of the rate of degredation 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.

μ 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 charge 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°C in temperature.

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

$$K = A_R^{-E_a/RT}$$

Where,

K is the specific reaction rate constant.

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

Ea is the energy of activation.

R is the gas constant as 1.987 Calories / deg · mole.

T is absolute temp.

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

Expressing the eqn in logarithmic form.

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

Converting to common logarithmic form

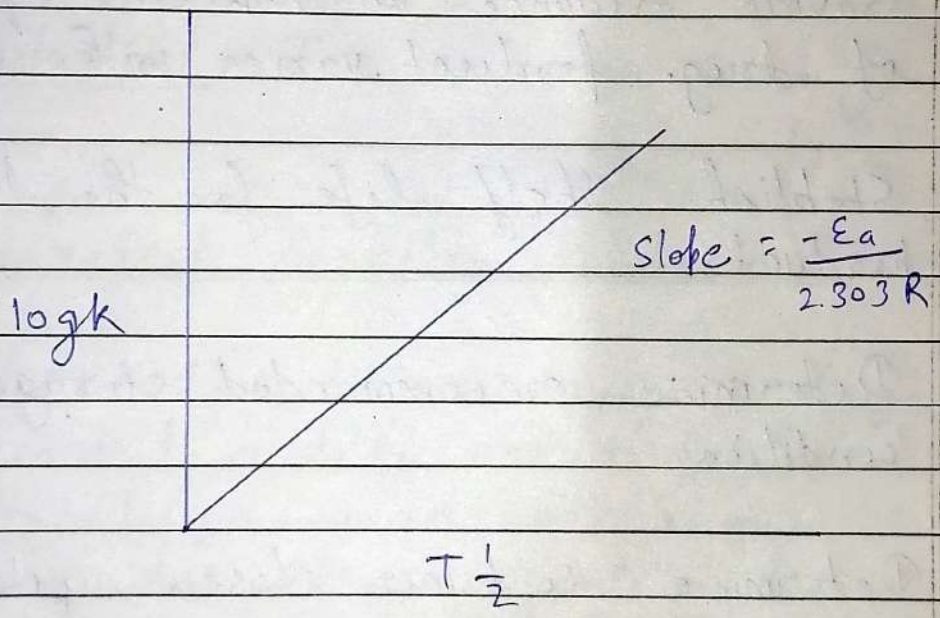
$$\boxed{\log k = \frac{-E_a}{2.303RT} + \log A}$$

Where,

$\log A$ is constant.

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

Plot a graph of $\log k$ versus $T\frac{1}{2}$ gives a straight line with slope equal to $-E_a/2.303R$ 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 closer system to remain its physical, chemical, microbiological, therapeutic, toxicological specification.

Need for Stability Testing :-

i) Provide evidence as how the equality of drug product varies with time.

ii) Stablish shelf life for the drug product.

iii) Determine recommended storage condition.

iv) Determine container closer system suitability.

v) Safety point of view of Patients.

vi) Prevention of economical refresion.

vii) Essential quality attributes.

According to USP 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 ~~withd~~ 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 emit similar radiation as the sunlight.

* Limitation of Accelerated stability Analysis.

1) Stability Predication 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 degredation in hydrogels of various natural and semi-synthetic polymer.

Stability of solid Dosage forms:-

The effect 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 ~~desired~~ described by ~~vast~~ 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 quiet high, the decomposition of drug in solid dosage form becomes similar to that in a saturated solution i.e. 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 dry 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). stated 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 ~~in~~ 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 37th 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_2) 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_2)	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 estrems tested. The ~~uses~~ uses of this design is in appropriate if the selected sample are not the estrems.

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 ratest period or shelf life proposed for labeling.

This study is generally performed at 25°C/60% or 30°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 ± 3°C and for freezer stored carried out at -20 ± 5°C.

Climatic zones	Recommended Conditions for long term stability studies in general case	
	Temperature (°C)	Humidity (%)
I and II	25 ± 2°C	60 ± 5%
III and IV	30 ± 2°C	65 ± 5%

Table : Recommended Conditions for long term stability studies.

(2) Accelerated Stability Studies :-

For accelerated stability studies; A storage condition of 40°C ± 2°C and RH of 75 ± 5% has been recommended for all the four zones for drug substances and drug products at 25°-30°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 30°C ± 2°C and 65% ± 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 ± 2°C and 60 ± 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 eg. (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 reciere 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 degredation 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 not acceptence 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 patients is entitled to reciene 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 ~~sod~~ 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 lactems.

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

eg. 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 manufactures, 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 anasthesia) 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 pharmacentical preparation are due to ~~oxidation~~ oxidative ~~degregat~~ degredation of the active ingredient of this preparation when exposed to atmospheric oxygen.

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

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

Protection against oxidation.

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

eg. vit-E, C or Hydrogen peroxide, Halogen etc.

ii) The effectiveness of antioxidant can be increase through the use of ~~synergists~~ 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.

iv) 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.

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

Ascorbic acid is also an antioxidant agent.

3) Photolysis.

Many pharmacentical compounds including ascorbic acid, ~~Nitrogen~~ riboflenin, ~~hydrocardisat~~ Hydrocortisone, Prednisolone Nifedipine etc undergo degradation when it posses to light. Its posses 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 degration. 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 therapeutidy 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 parcentage 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 Order

Plasma conc.: 100

1 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% → Rate of elimination.

i) Rate of elimination

ii) Clearance .: = Rate of elimination / plasma concentration

iii) Half life ($t_{\frac{1}{2}}$) :- It is the time ~~at~~ 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. $CL \propto \frac{1}{PC}$
iii) Half life is constant	iii) Half life is directly proportional to plasma conc. $(T\frac{1}{2})$ 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

$$aA + bB \rightarrow \text{Products}$$

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.

'-' signs 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 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 :

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

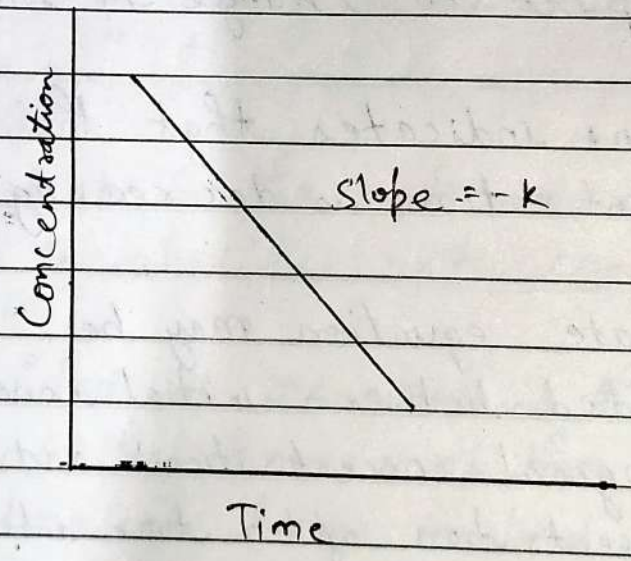


Fig:→ 6.1: Plot of concentration versus time for a zero order reaction.

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

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,

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

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

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

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

Shelf 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,

$$A_t = 0.9A.$$

Substituting this in the above equation we get,

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

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

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 of a first order reaction is given by.

$$-dc/dt = kC$$

$$dc/c = -k\,dt$$

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

$$\int_{C_0}^{C} dc/c = -k \int_{0}^{t} dt$$

$$\ln c - \ln C_0 = -k(t-0)$$

$$-\ln c = \ln C_0 - kt.$$

Converting to common logarithmic form, we get,

$$\log c = \log C_0 - kt/2.303.$$

$$\boxed{k = \frac{2.303}{t} \log \frac{C_0}{C}}$$

In exponential form, the equation becomes:

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

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

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

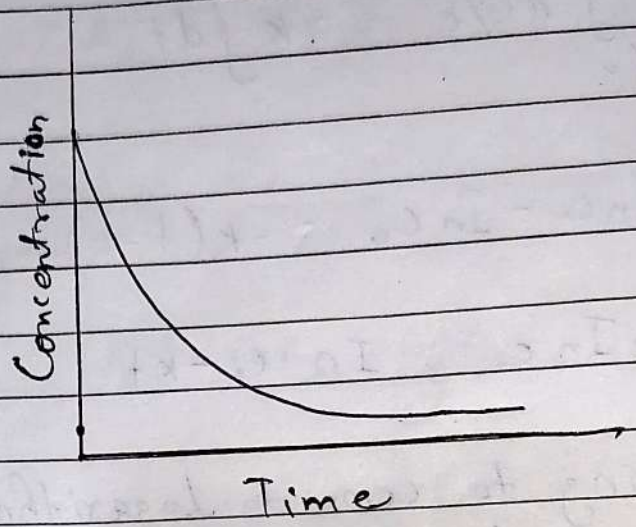


Fig :-6.2 : Plot of concentration versus time for a first order equation.

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)

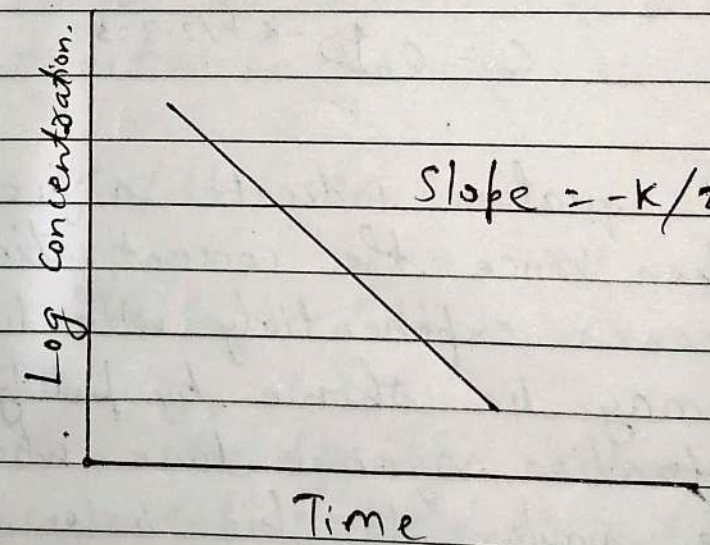


Fig 6.3 : Plot of log concentration versus time for a first order reaction.

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 sec^{-1} (or $time^{-1}$).

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.

Shelf life of a first order reaction

$$t_{0.9} = \frac{2.303}{K} \log \frac{C_0}{0.9C_0}$$

$$= 2.303/K \times 0.0457$$

$$= 0.1052/K$$

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.

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

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 in 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:

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

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

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

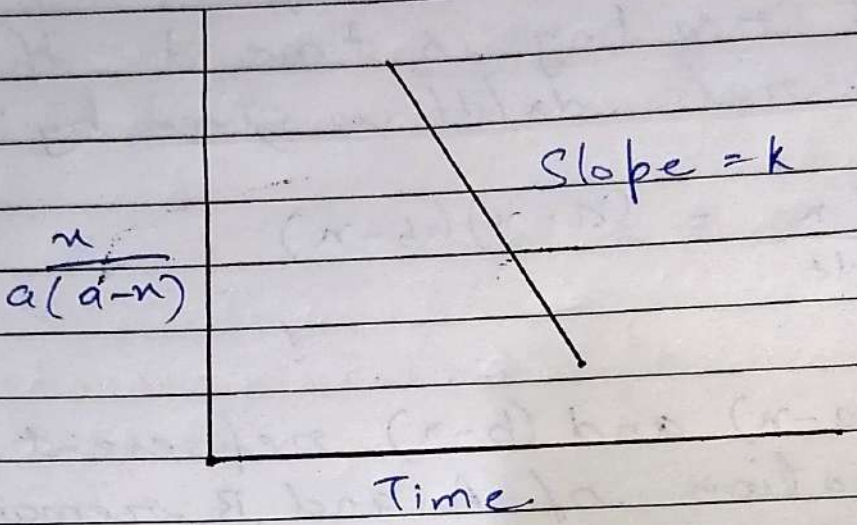


Fig: 6.4. Plot of $x/a(a-x)$ versus time for a second order reaction.

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

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:

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

In such a case, plot of $\log b(a-x)/a(b-x)$ 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, $litre \cdot mole^{-1} sec^{-1}$.

Half life of a Second order Rxn

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

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

PSUEDO 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

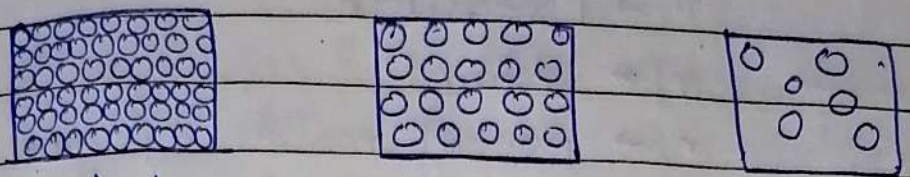
Date: _____ Page: 9
PDF-Start

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 i- solid, liquid and gase. 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 vapours.



Solid Liquid Gas.

✱ The Gaseous State

The physical behaviours of gases is independed of chemical nature of the molecules. the molecule in a gas are always in a state of vigorous and rapid motion, these travel are 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 → Pressure
V → volume
n → no. of moles of gas
R → Gas constant (0.821)
T → Absolute temp.

The ideal law desived 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 are 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~~ 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 results 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.
eg. at 0°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.
eg:- at 100°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.

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

The amount of water vapour in 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. Mixture of such substances are k/a Eutectic mixture.

The mixture of substance that melts 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, the point A and B represent the melting point of two components. As increasing quantities of B are added to A, and ~~rice~~ vice-versa. The freezing point A fall as curve ~~A C B~~ AC and B fall as curve BC at the particular composition C, known as Eutectic point.

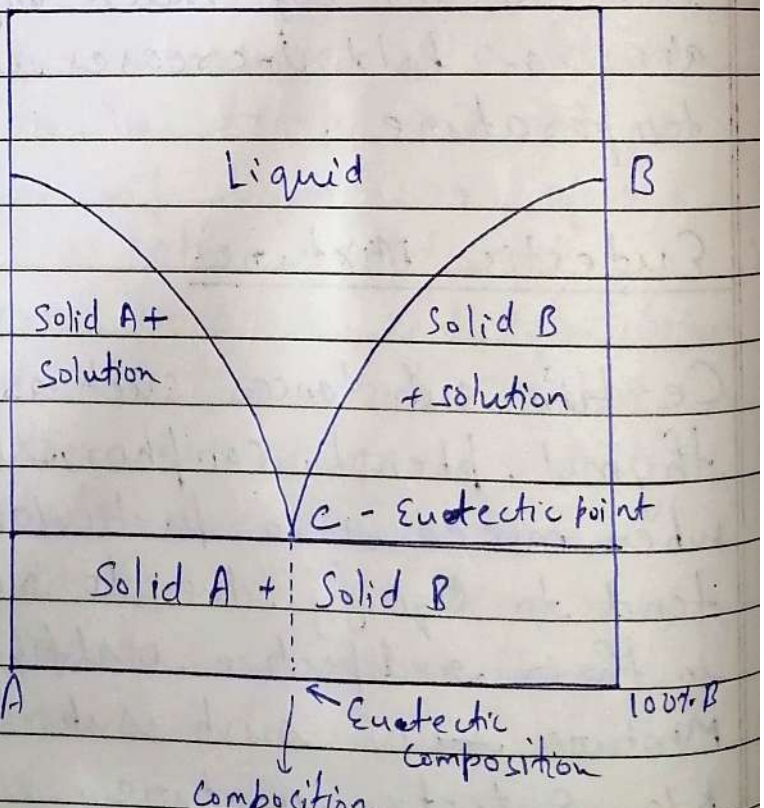


Fig:- Phase diagram of Eutectic system.

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.

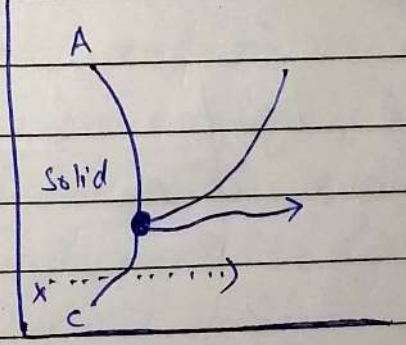
eg:- Aspirin - acetaminiphen (37% and 63%)
Urea - acetaminophen (46% and 54%) and
griseofulvin - succine (55% and 45%)

✱ 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, napthalene, ice is also.

Principle:-



The curve AD represents the melting point of the solid phase of the substance at different pressure. Along ~~long~~ 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 equillibrium with each other and this is k/a Triple point.

The point x below the table 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 ~~glass~~ 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 propellent, 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-propallent mixture is expelled out due to the excess pressure inside the container. The propallent used ~~on~~ 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 quality of propellant is forced into the container under pressure.

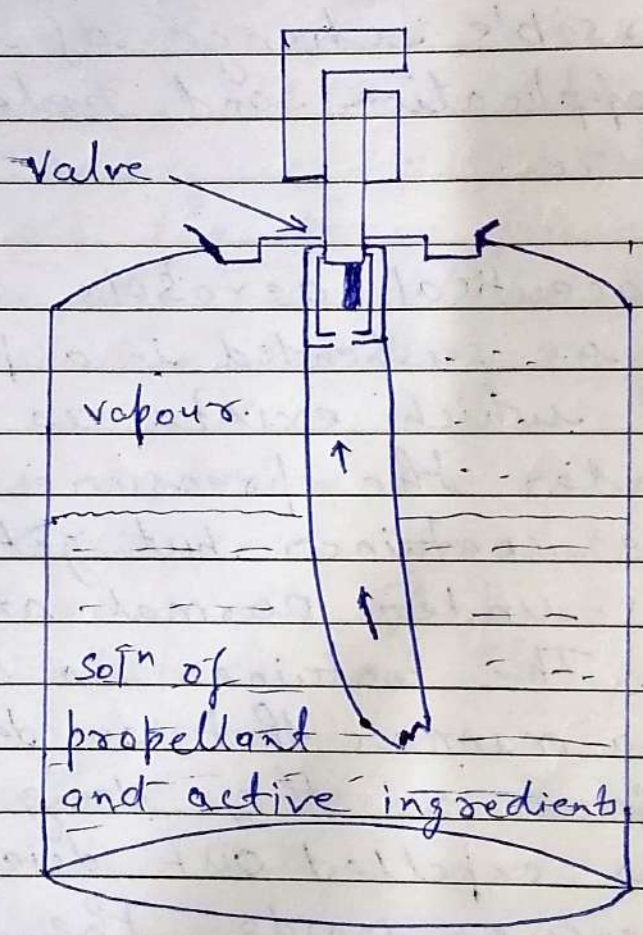


Fig :- An Aerosol System

The Solid State

Solid have the stoongest intermolecular forces. Their ~~stuu~~ 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 stoong 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).

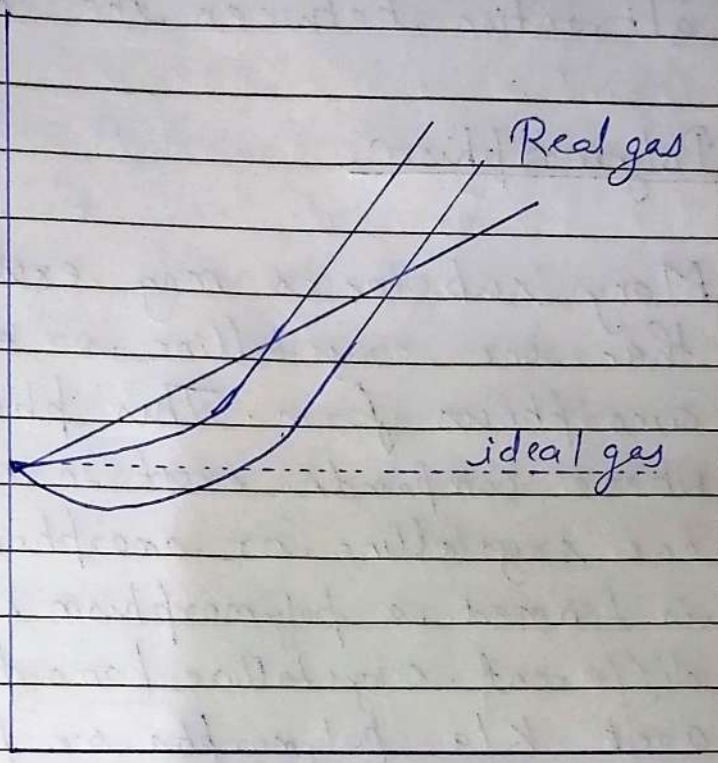
☆ The Liquid State.

The liquid state may be intermodiate state as matter. Liquid can be considered as highly compressed gases or slightly released solids. The molecules of 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 reduced 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. Liquefication 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°C or 647°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 vander 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 intermolecule force of attraction between the molecules.

☆ Polymorphism.

Many substances may exist in more than one crystalline or ~~amorph~~ amorphous form. This phenomenon where compounds exist in more than one crystalline or amorphous forms is termed a 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 show 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.

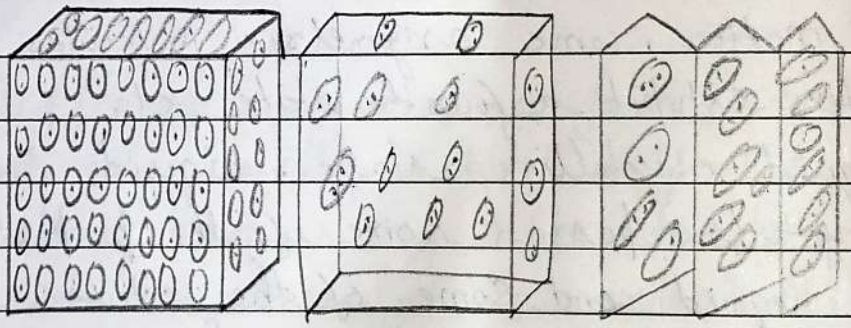
For example: Different polymorphic forms of drug like paracetamol, carbamazepine, phenylbutazone etc. have exhibited different mechanical properties such as compressibility, flowability, hardness, bonding strength etc.

★ Liquid Crystal

In addition to the three states of matter, some assymetric molecules often exhibit a fourth state kla liquid crystalline state. Liquid crystals posses some of the properties of liquid and some of the solids. eg - liquid crystals posses the property of mobility and rotation and can be considered to have the flow properties of liquids. On the other hand, These also posses 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 kla the cholestric crystals exist but may be considered as a special case of the nanematic type.



Smectic Nematic Cholestric

Fig: Liquid crystalline phase

The liquid crystalline state is found widespread in nature in nerve, brain tissue and blood vessels. Atherosclerosis is throughout 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 ~~three~~ these may be involved in the formation of gall stones.

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

⇒ When a liquid is heated in a open atmosphere the vapour pressure is increased. On further heating its vapour pressure ~~becomes~~ 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.

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Buffer

PHYSICAL PHARMACEUTICS

UNIT-5

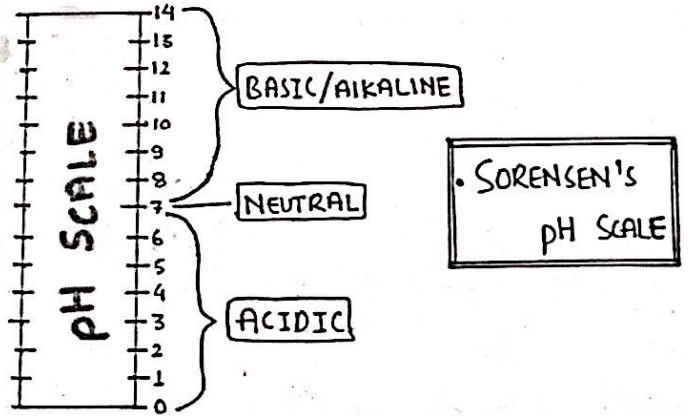
pH, BUFFERS AND ISOTONIC SOLUTIONS

- Sorensen's pH scale, pH determination (electrometric and colorimetric)

- pH → potential/power of Hydrogen
- It is given by Sorensen, so it is also called as Sorensen's pH scale.
- p → (potenz means power) and H → (Hydrogen).
- pH defined as negative logarithm of the hydrogen ion concentration.

$$pH = -\log[H^+]$$

- The concentration of the hydrogen ion is a measure of its acidity or basicity of a aqueous soln at a specific solution.
- Acidic solution have a higher relative number of H^+ ion.
- Basic/Alkaline solution have a higher relative number of OH^- ion.
- pH scale help to measure the acidity and basicity of any solution.



- The pH scale ranges from 0 to 14.
- The scale start with a zero pH indicates that the solution is strongly acidic, and end with 14 (fourteen) indicates that

the solution is strongly alkaline(basic).

- The central point pH in the scale is 7 indicates that the solution is neutral (neither acidic nor basic).

⇒ Three Region

(0 - below 7) → Acidic

(7) → Neutral

(Above 7 - 14) → Basic/Alkaline

- Determination of pH

- The pH value is determine by following methods :-

i) pH paper

ii) Electrometric method

iii) Calorimetric method

i) **pH paper** ⇒

- for routine work pH of a solution is determined by pH paper.

- Take a one pH paper and dip into sample solution (which we have to determine the pH).

- Then compare the pH paper color (which change in soln) with standard color of pH paper in which pH number is written with color.

- Acc. to pH value we determined, that the solution is acidic or basic or neutral.

ii) **Electrometric Method** ⇒

- Apparatus is know as pH meter

- It consist a voltmeter which connected with two electrodes :-

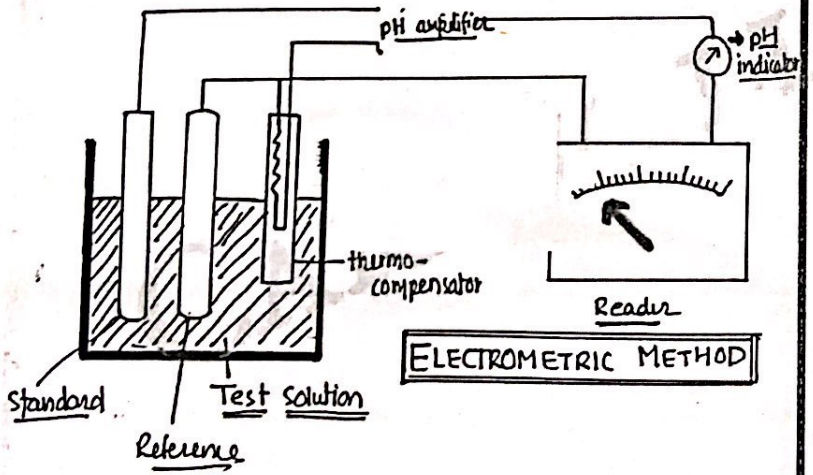
i) Standard Electrode → known as potential

ii) Special(probe) Electrode → which enclosed in a glass membrane that allow migration of H^+ ions, and it contain reference solution of dilute HCl.

→ Working →

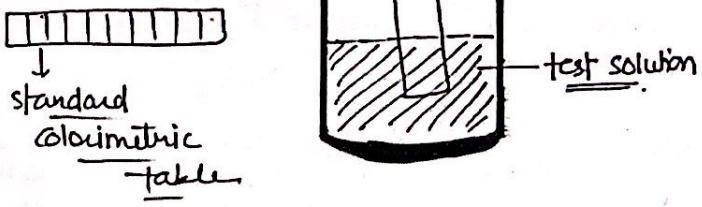
- The Electrodes (both) are dipped in the solution to be tested.

- If the solution's pH differ from probe solution's pH, then probe passes electric signals to a meter that display the reading in pH units.
- A change in temp can cause an error in the pH reading. To prevent this, a temp. compensation resistance (thermocompensator) include in a circuit and immersed in the solution.



ii) **Colorimetric method** ⇒

- Take a colorimetric paper and dip into sample solution (which we have to determine the pH).
- Then obtained color is computed with the standard table of colorimetric.
- Then pH value is obtained acc. to their color.
- Acc. to pH value we determined, that the solution is acidic or basic or neutral.



• Buffer Solution

- The solution that are able to resist the change in pH value termed as buffer solution.

Types:—

i) Acidic ⇒ Acidic buffers are those buffer solution which is used in acidic solution.

→ Composition → weak acid and its salts [weak acid + strong base]

eg. [$CH_3COOH + CH_3COONa$]

— Acetic acid and Sodium acetate

ii) Basic ⇒ Basic or Alkaline buffers are those which used in basic solution.

• Composition → weak base and its salts [weak base + strong acid]

eg. [$NH_4OH + NH_4Cl$]

Ammonium hydroxide — Ammonium chloride

⇒ If Buffer solution is added in any solution, then it resist the change in pH of that solution, whether we add small amount of acid or alkali/base to it in that solution.

• Applications of Buffers

i) Biochemical assay → Enzyme activity depends on pH, so the pH during enzyme assay must stay constant (Buffer helps).

ii) Maintenance of life → Most of the biochemical processes work within a relatively small pH range

The body have its own buffer solution which maintain a constant pH.

eg. Blood contain a bicarbonate buffers that keep the pH close to 7.4.

iii) Callibrate pH meters → Buffer solutions is used to callibrate pH meter.

iv) Textile Industry → Buffer solution also used in textile industry.

eg. Many dyeing processes use buffer to maintain the correct pH for various dyes.

v) Food Industry → Buffers are used in food industry to maintain the acidity of food, and also for microbiological stability of food.

- **Buffer Equation**

It is used to calculate the pH of a buffer solution and the change in pH with the addition of an acid/base

- Acidic Buffer (weak acid & its salts)

The pH of acidic buffer can be calculated from the dissociation constant (K_a) of the weak acid and the concentration of the acid and salt used.

- Dissociation of weak acid & salt expressed as →

$HA \rightleftharpoons H^+ + A^-$ (weak acid)

$BA \longrightarrow B^+ + A^-$ (its salts)

↳ Common ion effect.

- By applying law of mass action,

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

On Rearrange,

$$[H^+] = K_A \frac{[HA]}{[A^-]}$$

$HA \rightarrow$ Acid and $[A^-] \rightarrow$ Salt

$$[H^+] = K_a \frac{[Acid]}{[Salt]}$$

→ Taking $-\log$ on both sides,

$$-\log [H^+] = -\log \left[K_a \frac{[Acid]}{[Salt]}\right]$$

$$-\log [H^+] = -\log K_a - \log \frac{[Acid]}{[Salt]}$$

$-\log (H^+) = pH$ and $-\log K_a = pK_a$

$$pH \Rightarrow pK_a - \log \frac{[Acid]}{[Salt]}$$

On Rearrange,

$$pH = pK_a + \log \frac{[Salt]}{[Acid]}$$

This relationship is also called as **Handerson-Hasselbatch Equation.**

- Basic Buffer (weak base and its salts)

In similar way Buffer equation for a basic buffer can be written as

$$pOH = pk_b + \log \frac{[Salt]}{[Base]}$$

- **Buffer Capicity**

The amount of acid or base that must be added to the buffer to produce a unit change of pH.

- It helps to know the effectiveness of a buffer on a quantitative basic

$$\beta = \frac{\Delta B}{\Delta pH}$$

where, β = Buffer Capicity, ΔB = Amount of Acid/Base

ΔpH = Change in pH.

- **Buffer in pharmaceutical and biological system**

- Pharmaceutical system

The buffer play an important role in pharmaceutical preparation to ensure pH condition for the medicinally active compound :-

- **Solubility** of compounds can be frequently controlled by providing a medium of suitable pH, and required pH is adjusted by buffers.
- **Patient comfort** Injectable and preparations for internal or external use become irritating if their pH is different greatly from that normal. So, it is maintained by buffers.

eg.

- Sorensen proposed mixture of salt of Sodium phosphate for pH 6 to 8.
- Mixture of [boric acid and monohydrate ~~solution~~ Sodium carbonate] buffers with pH 5 to 9.

- Biological System

• Body fluids in biological system (body) are having balance quantity of acid or base (pH).

• The biochemical reaction that takes place in living system are very sensitive to even small change in pH (acidity or basicity).

• So, the maintenance of the normal pH range within the body fluids become essential.

- The pH value of some body fluids with the buffer system to maintain pH in body

Body fluids	pH value	Buffer system
• Blood	7.4 - 7.5	Bicarbonate
• Urine	4.5 - 8.0	Phosphate
• Interstitial fluids	7.2 - 7.4	Bicarbonate
• Intracellular fluids	6.5 - 6.9	Protein and Phosphate

• **Buffered Isotonic Solution**

• Pharmaceutical buffer solution that are meant for applications of body should be adjusted to same osmotic pressure as that of the body fluids

eg. Blood = 0.9% w/v Nacl solution.

• there are three types of solutions :—

i) Isotonic → A buffer solution have same osmotic pressure as body fluid (0.9% Nacl)

ii) Hypotonic → A buffer solution have less concentration of solute (osmotic pressure) than 0.9% Nacl.

iii) Hypertonic → A buffer solution have high concentration of solute (osmotic pressure) than 0.9% Nacl.

• We have to make **buffer isotonic solution**, which have same osmotic pressure as body fluids or same conc of solute as 0.9% w/v Nacl.

• Method to determine Isotonicity

i) Cryoscopic method. (Colligative method).

ii) Hemolytic method.

i) Cryoscopic method → This method is depends upon colligative properties of solution such as their freezing point, boiling point, vapour pressure and temp. difference

- Take two solution. one standard isotonic sol (0.9% NaCl) and other is test solution (which we have to determine the isotonicity).
- Now compare their colligative properties with standard solution and determine the tonicity or solution

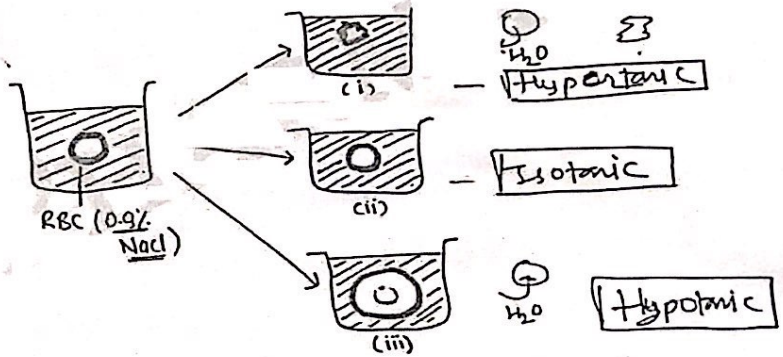
eg.
f.p. of std. 0.9% NaCl → -0.52°C

Compare
- freezing point
- Boiling point
- Vapour pressure

Same → Isotonic
>0.9% → Hypertonic
<0.9% → Hypotonic

ii) Hemolytic method →

The effect of various solution of the drug was observed on the appearance of red blood cells suspended in solution.



(Acc. to Osmosis, solvent particle move from low concentration to high concentration.

i) → conc of solution > conc of RBC (0.9%)

So, solvent (H_2O) move from low to high or RBC to solution, this cause cell shrinkage → Hypertonic solution

ii) → Conc. of solution = conc of RBC (0.9%)

So, cell (RBC) remain same or constant.

→ Isotonic solution

iii) → conc of solution < conc. of RBC cell (0.9%)

So, solvent(H_2O) move/diffuse from solution to RBC cells, this cause cell swelling.

↓

Hypotonic solution

- Method of adjusting tonicity

i) Class Ist and ii) Class IInd

i) Class I →

a) Cryoscopic method (freezing point depression method).

b) Sodium chloride Equivalent. (E).

a) Cryoscopic method :— This method is used for hypotonic solution.

Conc of solution is less than 0.9% w/v NaCl.

- Sodium chloride is added to solution to make it isotonic.

$$W\% = \frac{0.52 - a}{b}$$

where,

W = amount of adjusting substance

a = freezing point of 1% solution of unadjusted sol^n.

b = freezing point of 1% solution of adjusting sol^n.

b) Sodium Chloride Equivalent (E). :—

Used for hypotonic solution and add sodium chloride in solution to make it isotonic

$$f = \frac{17 \times Liso}{M}$$

where,

f = Sodium chloride equivalent or amount of NaCl required.

Liso → Liso value

M = Molecular weight of drug solution.

ii) **Class - II**

This method is used for hypertonic solution. Add water in solution to make it isotonic

a) White - vincent method :—

$$V = W.E.111.1$$

where,

V = volume of water added in solution to make it isotonic

W = weight of drug in gram.

E = Equivalent weight of drug (Sodium chloride Equivalent).

b) Sprowls method :—

Simplification of white and vincent method. Here weight of drug(w) is set to constant value of 0.3.

$$V = 0.3.E.111.1 \longrightarrow V = 33.33E$$

— x — x — x —

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Complexation

INTRODUCTION

Complexes are compounds that result from donor–acceptor mechanisms between two or more chemical species.

Complexes can be divided broadly into three classes depending the type of the acceptor substance:

1. Metal ion complexes
2. Organic molecular complexes
3. Inclusion complexes

Intermolecular forces involved in the formation of complexes:

1. Van der Waals forces.
2. Hydrogen bonds (important in molecular complexes).
3. Coordinate covalence (important in metal complexes).
4. Charge transfer.
5. Hydrophobic interaction.

Introduction

Types of Complexes

Metal Ion Complexes

A. Inorganic type
B. Chelates
C. Olefin type
D. Aromatic type

II. Organic Molecular Complexes

A. Quinhydrone type
B. Picric acid type
C. Caffeine and other drug complexes
D. Polymer type

III. Inclusion Compounds

A. Channel lattice type
B. Layer type
C. Clathrates
D. Monomolecular type
E. Macromolecular type

Metal ion complex (coordination complex) consists of a transition-metal ion (e.g. cobalt, iron, copper, nickel and zinc) linked or coordinated with one or more counter ions or molecules to form a complex.

The ions or molecules (e.g. Cl^-, NH_3, H_2O, Br^-, I^-, CN^-, etc.) directly bound with the metal are called ligands.

The interaction between the metal and the ligand represents a Lewis acid-base reaction in which the metal ion (Lewis acid) combines with a ligand (Lewis base) by accepting a pair of electrons from the ligand to form the coordinate covalent or electrostatic forces:

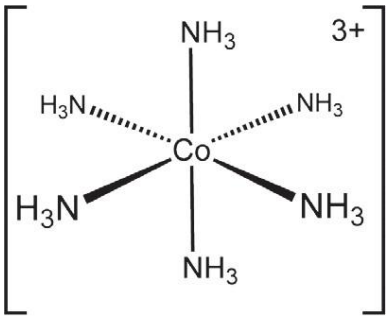
$$Co^{3+} + 6\ (:NH_3) \rightarrow [Co(NH_3)_6]^{3+}$$

Metal ion Complexes

Inorganic Complexes

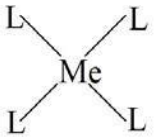
The number of ligands bound to the metal ion is defined as coordination number.

The coordination number of cobalt is six, since it complexed with six NH_3 groups.

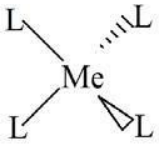


Coordination number usually determine the geometry of the complex.

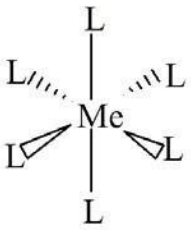
CN = 2 (linear)



CN = 4 (square planar)



CN = 4 (tetrahedral)

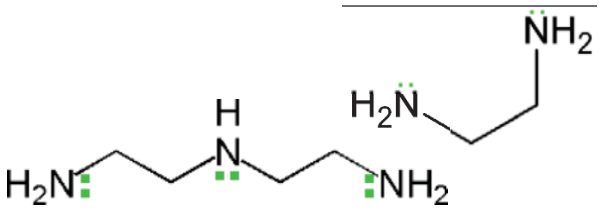


CN = 6 (octahedral)

Compound (e.g. NH_3) which has a single pair of electrons for bonding with the metal ion, is called unidentate ligand.

Ligands with two or three groups are known as bidentate or tridentate respectively.

Ethylenediaminetetraacetic acid (EDTA) has six points for attachment (two nitrogen and four oxygen donor groups) and is called hexadentate.

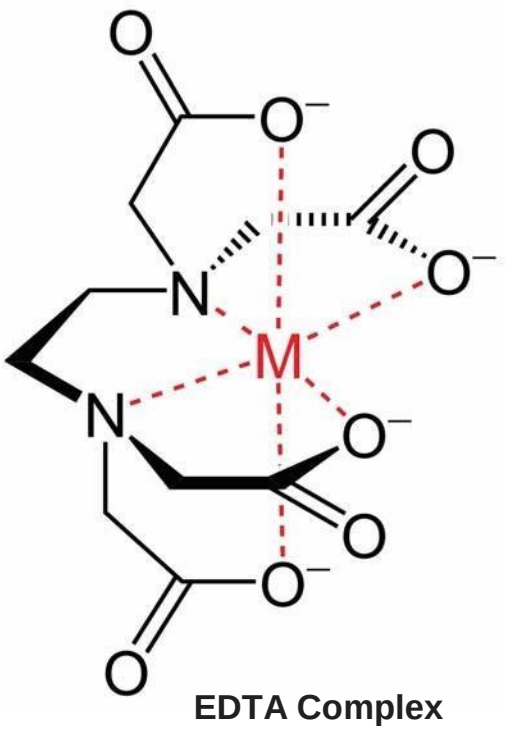


Metal ion Complexes

Chelates

Chelation is the formation of two or more coordinate bonds between a multidentate ligand (organic compound called chelating agent) and a single central atom.

The bonds in the chelate may be ionic, primary covalent, or coordinate type.



EDTA Complex

Organic Molecular Complexes

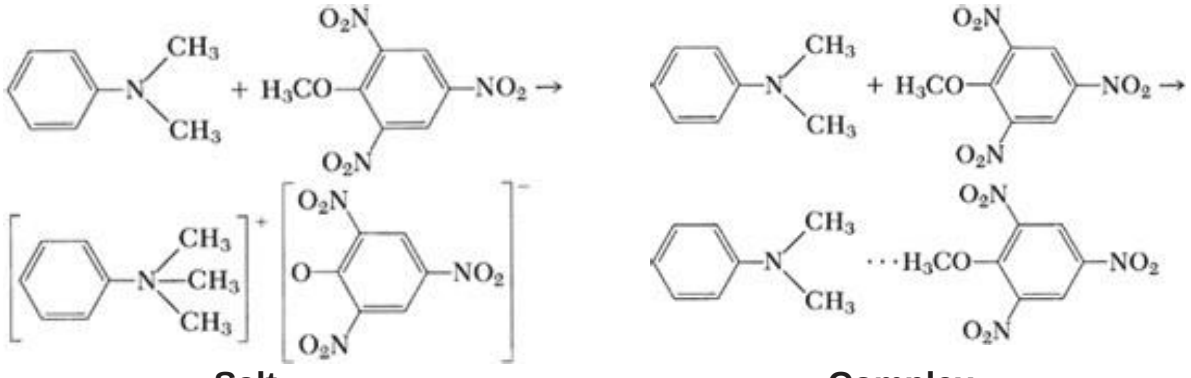
Organic molecular complexes are formed as a result of non-covalent interactions between a ligand and a substrate.

The interactions can occur through van der waals forces, charge transfer, hydrogen bonding or hydrophobic effects.

Many organic complexes are so weak that they cannot be separated from their solutions as definite compounds, and they are often difficult to detect by chemical and physical means.

Complexation differs from the formation of organic compounds in the forces between the constituents:

E.g. Dimethylaniline and 2,4,6-trinitroanisole react in the cold to give a molecular complex. However at elevated temperature, they react to yield a salt, in which the molecules are held together by primary valence bonds.



Salt **Complex**

Organic Molecular Complexes

Charge transfer complex is an association of two or more molecules in which a fraction of electronic charge is transferred between the molecular entities.

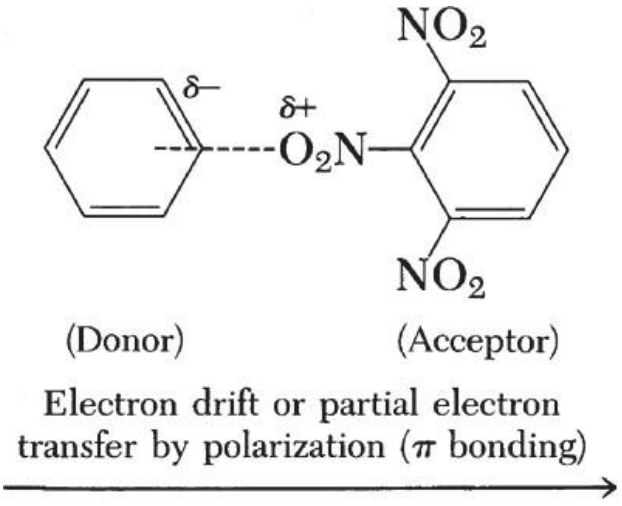
The molecules from which the charge is transferred is called the electron donor and the receiving species is called the electron acceptor

Attraction in charge-transfer complexes is weaker than in covalent forces.

Usually these complexes is formed by sharing of w-electrons

E.g. Complex between benzene and trinitro benzene (1:1 type). (polar nitro group of trinitro benzene induce a dipole in the readily polarizable benzene molecules, resulting in electrostatic attraction).

The difference between a *donor–acceptor* and a *charge transfer* complex is that in the latter type, resonance makes the main contribution to complexation, whereas in the former, London dispersion forces contribute more to the stability of the complex.

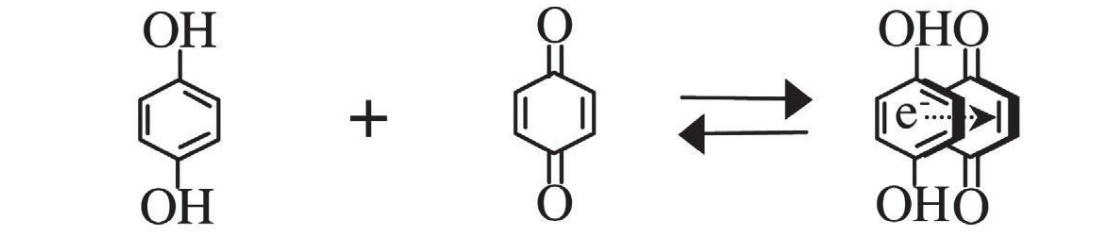


Organic Molecular Complexes

Quinhydrone Complex

This molecular complex is formed by mixing equimolar quantities of benzoquinone with hydroquinone.

Complex formation is due to overlapping of the w-framework of the electron-defficient benzoquinone with the w-framework of the electron-rich hydroquinone (charge transfer).



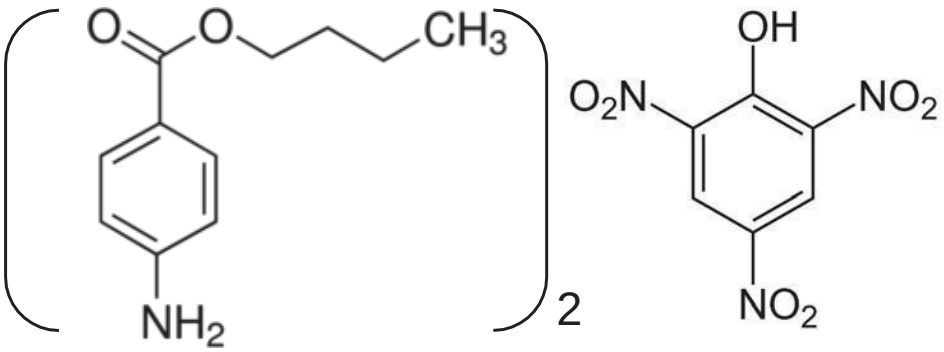
Hydroquinone (colorless) Benzoquinone (yellow) Quinhydrone (purple)

Organic Molecular Complexes

Picric Acid Complexes

Picric acid (2,4,6-trinitrophenol), is a strong acid that forms complexes with many weak bases such as poly-nuclear aromatic compounds.

An example is Butesin picrate (local anaesthetic) which is a complex formed between two molecules of butyl p-aminobenzoate with one molecule of picric acid.



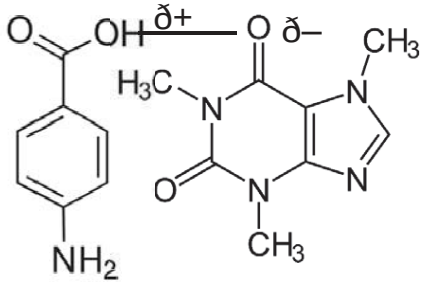
Organic Molecular Complexes

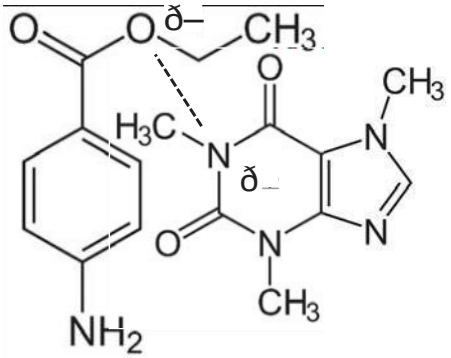
Caffeine Complexes

Caffeine forms complexes with a number of drugs owing to the following factors:

Hydrogen bonding between the polarizable carbonyl group of caffeine and the hydrogen atom of the acidic drugs such as p-amino benzoic acid and gentisic acid.

Dipole-dipole interaction between the electrophilic nitrogen of caffeine and the carboxy oxygen of esters such as benzocaine or procaine





Organic Molecular Complexes

Caffeine Complexes

Caffeine forms water soluble complexes (more soluble than caffeine itself) with organic acid *anions*, but the complexes formed with organic acids, such as gentisic acid, are less soluble than caffeine alone.

Such insoluble complexes provide caffeine in a form that masks its normally bitter taste in chewable tablets.

Organic Molecular Complexes

Polymer Complexes

Polymeric materials such as eudragit, chitosan, polyethylene glycols (PEG), polyvinylpyrrolidone (PVP) and sodium carboxymethyl cellulose (CMC), which are usually present in liquid, semisolid and solid dosage forms, can form complexes with a large number of drugs.

Such interactions can result in precipitation, flocculation, solubilization, alteration in bioavailability or other unwanted physical, chemical, and pharmacological effects.

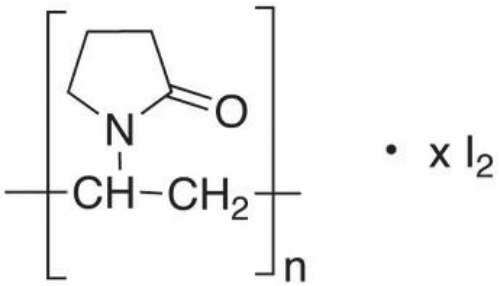
Organic Molecular Complexes

Polymer Complexes

Polymer–drug complexes however can also be used to modify biopharmaceutical parameters of drugs.

Polymeric complex between naltrexone and eudragit improves the dissolution rate of naltrexone.

Povidine-iodine is a stable complex of PVP and iodine, which possess superior antibacterial activity.



Inclusion Complexes

An inclusion compound is a complex in which one chemical compound (the ‘host’) forms a cavity in which molecules of a second compound (‘guest’) are entrapped.

These complexes generally do not have any adhesive forces working between their molecules and are therefore also known as no-bond complexes.

Inclusion Complexes

Channel Lattice Type

In this complex, the host component crystallizes to form channel-like structure into which the guest molecule can fit.

The guest molecule must possess a geometry that can be easily fit into the channel-like structure

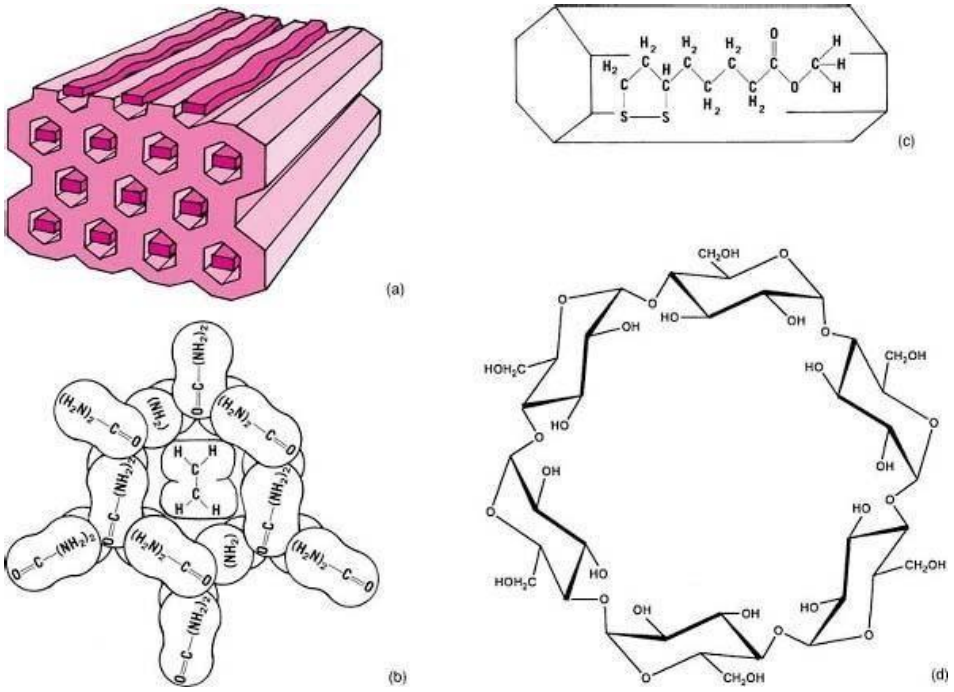
Channel lattice complexes provides a mean of separation of optical isomers.

The cholic acids (bile salt) is an example of this complex type. The crystals of deoxycholic acid are arranged to form a channel into which the complexing molecule can fit.

The well-known starch–iodine complex is a channel-type complex consisting of iodine molecules entrapped within spirals of the glucose residues

Inclusion Complexes

Channel Lattice Type



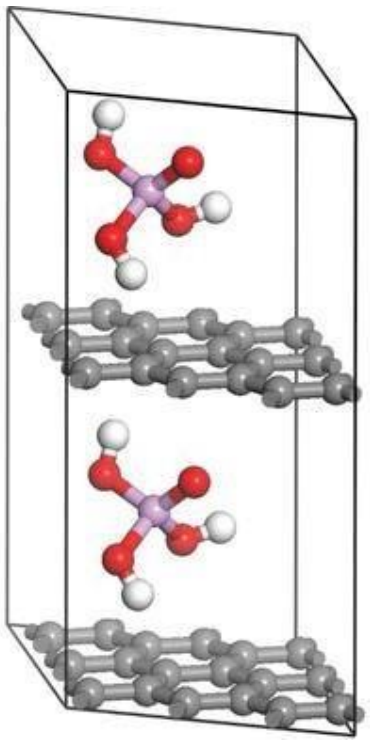
Inclusion Complexes

Layer Type

Layer type complex (or intercalation compound) is a type of inclusion compound in which the guest molecule is diffused between the layers of carbon atom, to form alternate layers of guest and host molecules.

Montmorillonite, the principal constituent of bentonite, can trap hydrocarbons, alcohols, and glycols between the layers of their lattices.

Graphite can also intercalate compounds between its layers.



Inclusion Complexes

Clathrates

The clathrates are compounds that crystallize in the form of a cage-like lattice in which the coordinating compound is entrapped.

One official drug, warfarin sodium, is in the form of crystalline clathrate containing water and isopropyl alcohol.

Clathrates can be used to separate optical isomers.

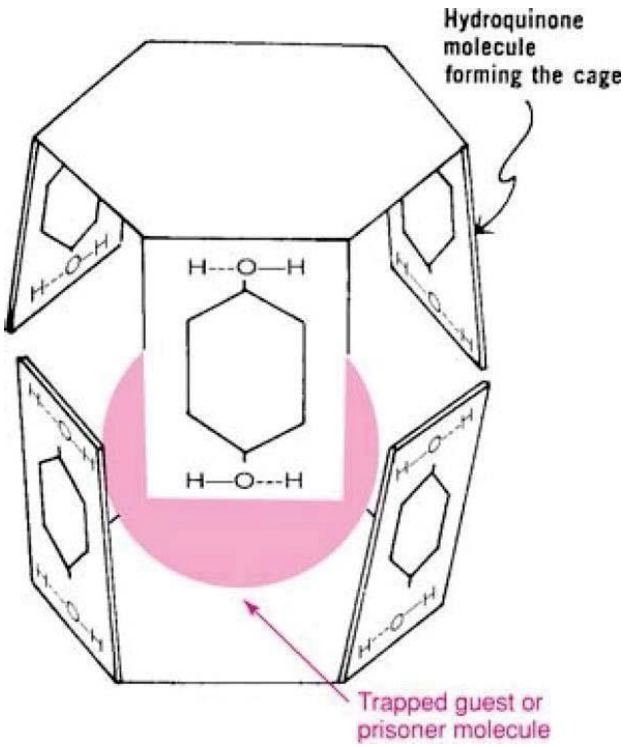
Inclusion Complexes

Clathrates

Hydroquinone crystallizes in a cage-like hydrogen-bonded structure, in which small molecules such as methyl alcohol, CO_2, and HCl may be trapped in these cages.

Size of the guest molecule is important for complex formation.

If the size is too small, the guest molecule will escape from the cage of the host and if the size is too big, it will not be fit inside the cage.



Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

Monomolecular inclusion complex involves the entrapment of guest molecules into the cage-like structure formed from a single host molecule.

Cyclodextrins are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides)

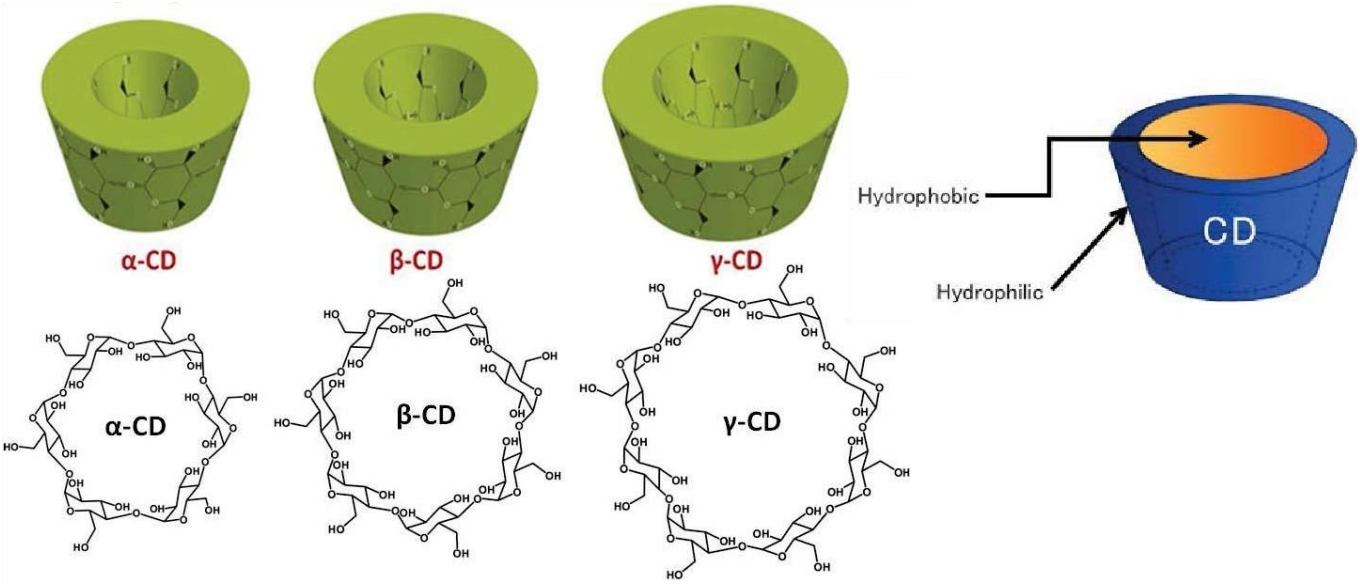
They consist of 6, 7, and 8 units of glucose referred to as a, þ, and ç cyclodextrins, respectively.

Cyclodextrin type	Glucose units	Internal diameter	Aqueous solubility	USP name
a-cyclodextrins	6	4.7-5.3 Å	14.5 g/100 mL	Alfadex
þ-cyclodextrins	7	6.0-6.5 Å	1.85 g/100 mL	Betadex
ç-cyclodextrins	8	7.5-8.3 Å	23.2 g/100 mL	Gammadex

Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

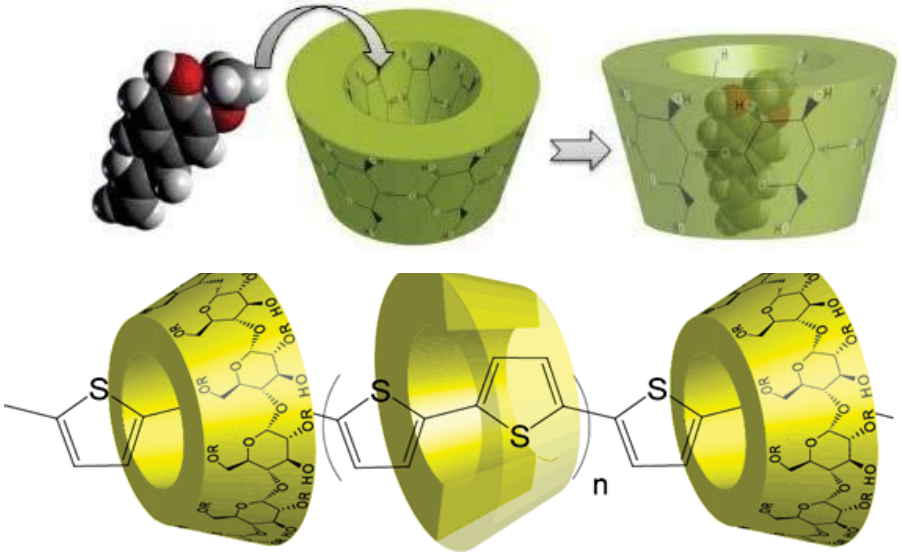
Cyclodextrons have truncated cone structure with a hydrophobic interior cavity because of the CH_2 groups, and a hydrophilic exterior due to the presence of hydroxyl group.



Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

Molecules of appropriate size and stereochemistry get entrapped in the cyclodextrin cavity by hydrophobic interaction by squeezing out water from the cavity.



Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

Cyclodextrins can enhance the solubility and bioavailability of hydrophobic compounds due to the large number of hydroxyl groups on the CDs.

Cavity size is the major determinant as to which cyclodextrin is used in complexation.

yclodextrins have small cavities that are not capable of accepting many molecules. ç-Cyclodextrins have much larger cavities than many molecules to be incorporated.

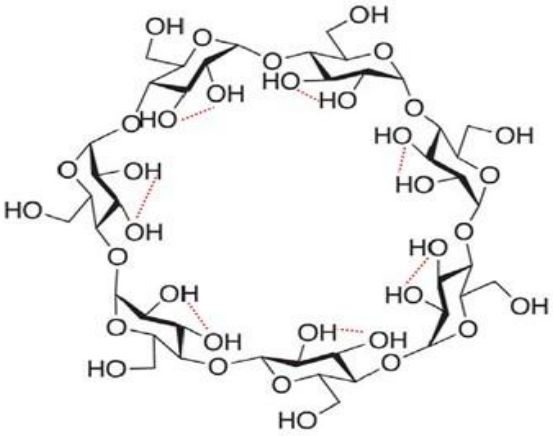
The cavity diameter of þ-cyclodextrins has been found to be the most appropriate size for most drugs. For this reason, þ-cyclodextrin is most commonly used as a complexing agent

Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

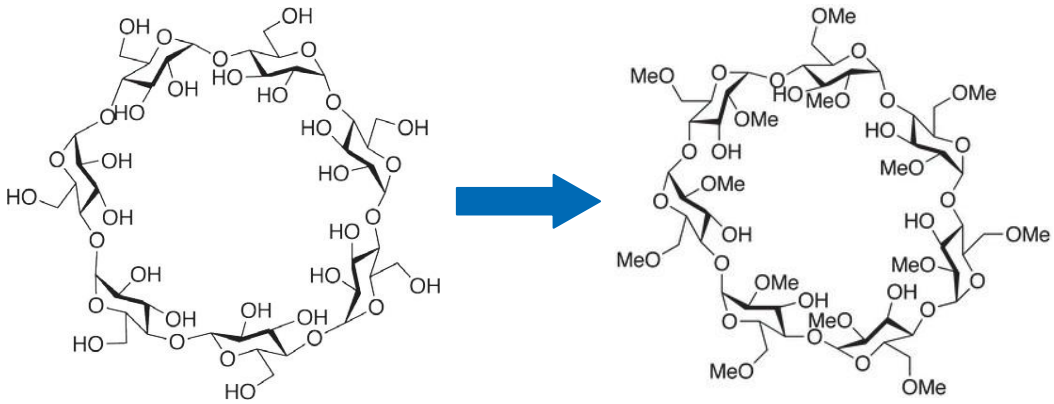
Although þ-CD contains a high number of hydroxyl groups, þ-CD solubility is the lowest compared to the a-CD or ç-CD.

This is due to the formation of an internal hydrogen bond network between the secondary hydroxyl groups.



Monomolecular Inclusion Compounds: Cyclodextrins

Partial alkylation of some of the OH groups in CD reduces the intermolecular hydrogen bonding, leaving some OH groups free to interact with water, thus increasing the aqueous solubility of CD.



Inclusion Complexes

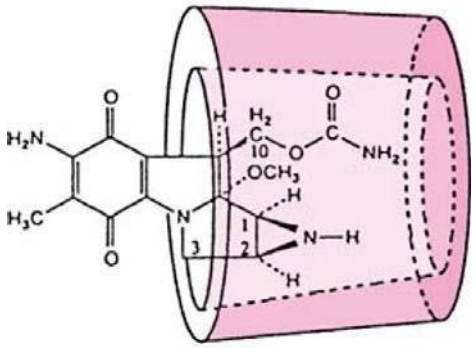
Monomolecular Inclusion Compounds: Cyclodextrins

In addition to hydrophilic derivatives, hydrophobic forms of þ-CD have been used as sustained release drug carriers.

Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

In addition to improving the solubility of compounds, complexation with cyclodextrin has been used to improve the stability of many drugs by inclusion of the compound and protecting certain functional groups from degradation.



Complexation with cyclodextrins has also been used to mask the bitter taste of certain drugs such as femoxetine.

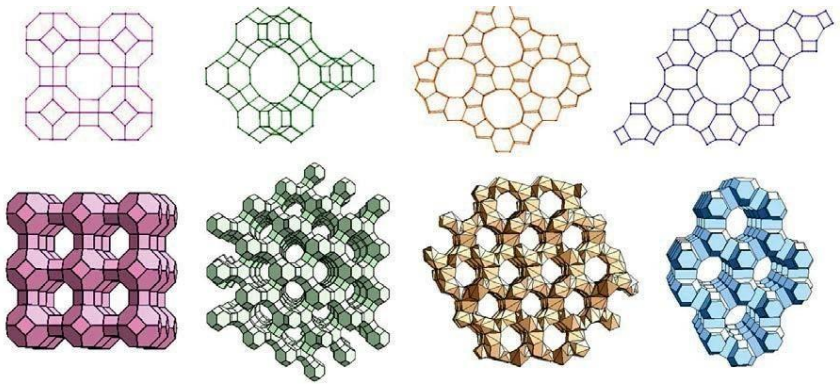
Inclusion Complexes

Macromolecular Inclusion Compounds

Macromolecular inclusion compounds, (*molecular sieves*) include substances such as zeolites, dextrins, and silica gel.

The atoms are arranged in three dimensions to produce cages and channels in which the guest molecules are entrapped.

Synthetic zeolites can be made to a definite pore size to separate molecules of different dimensions.



Methods of Analysis

Method of Continuous Variation PH
Titration
Distribution Method Solubility
Method Spectroscopy

Methods of Analysis

A determination of the **(1) *stoichiometric ratio*** of ligand to metal (or donor to acceptor) and the **(2) *stability constant*** for complex formation are important in the study and application of complexes.

Several methods for estimation of these parameters have been developed:

1. **Method of continuous variation**
2. **pH Titration method**
3. **Distribution Method**
4. **Solubility Method**
5. **Spectroscopy**

The stoichiometry of a metal–ligand complexation reaction can be determined by three methods:

(A) Job's method (B) Mole ratio method (C) Slope ratio method

Job's Method

In **Job's method**, a series of solution are prepared with variable ratios of metal and ligand but with fixed total concentrations (the total ligand + metal concentration are the same for all solutions).

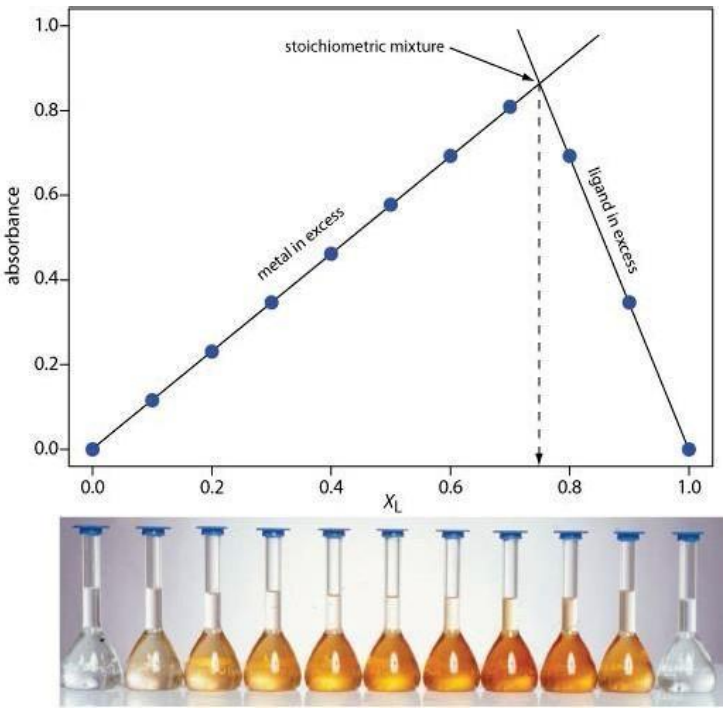
An additive property that is proportional to the concentration of the formed complex (e.g. absorbance) is measured and plotted against the mole fraction from 0 to 1 for one of the components of a mixture (e.g. Ligand).

Method of Continuous Variation

Job's Method

For a constant total concentration of *A* and *B*, the complex is at its greatest concentration at a point where the species *A* and *B* are combined in the ratio in which they occur in the complex.

The line therefore shows a break or a change in slope at the mole fraction corresponding to the complex.



Job's Method

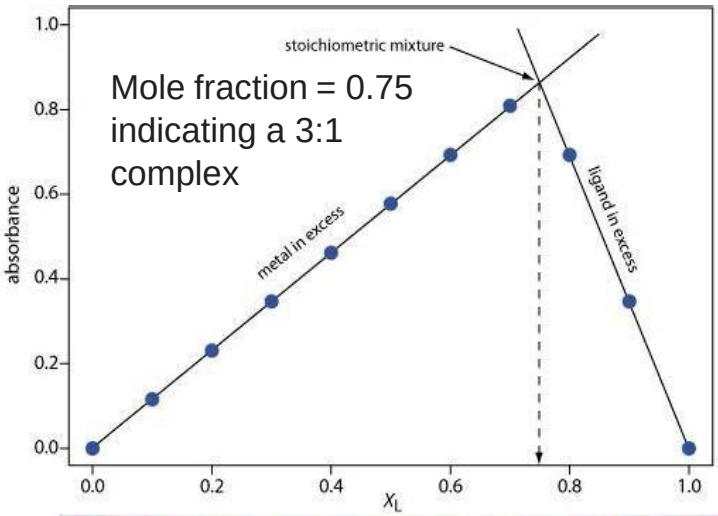
E.g. the change in slope occurs at a mole fraction of 0.75:

$$\frac{X_L}{X_M} = \frac{0.75}{1 - 0.75} = 3$$

This indicate a complex formation of the 3:1 type (ligand : metal).

The calibration curve flattens out when there is no longer enough ligand to react with all of the metal ions.

Job's method is restricted to the formation of a single complex



Method of Continuous Variation

Mole Ratio Method

In the **mole ratio method**, a series of solutions are prepared with a fixed amount of the metal and a variable amount of the ligand (or vice versa).

An additive property that is proportional to the concentration of the formed complex (e.g. absorbance) is measured and plotted against the mole ratio of the component with the variable amounts (e.g. Ligand).

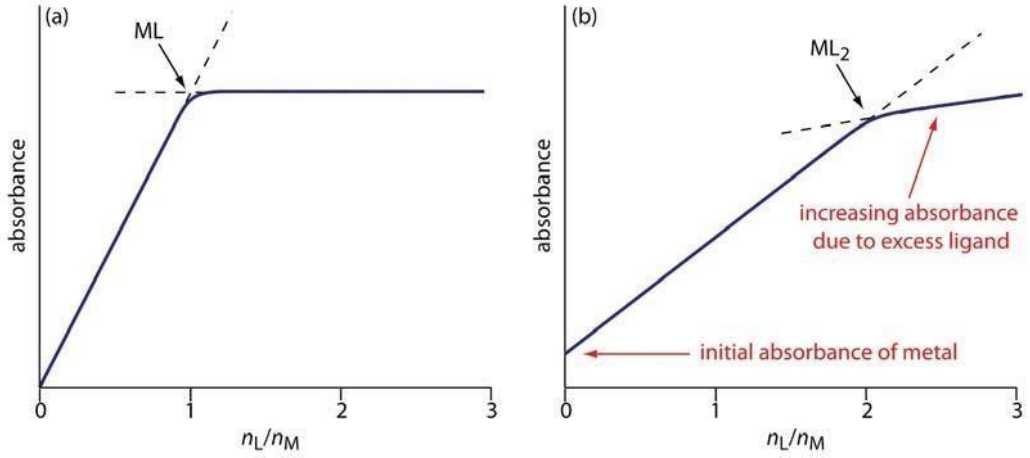
The formed complex is at its greatest concentration at a point where the species *A* and *M* are combined in the ratio in which they occur in the complex (indicated by a change in the slope at the mole ratio that forms the complex).

Method of Continuous Variation

Mole Ratio Method

The change in slope (a) occurs at a mole ratio of 1 indicating a complex of the 1:1 type, while the change in slope (b) occurs at a ratio of 2 indicating a complex of the 2:1 type.

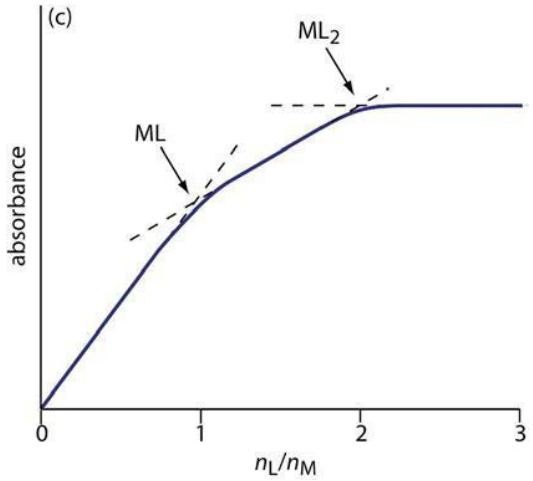
The calibration curve flattens out when there is no longer enough ligand to react with all of the metal ions.



Method of Continuous Variation

Mole Ratio Method

Unlike Job's method, the mole-ratio method can be used to investigate the formation of higher complexes in solution.



Slope Ratio Method

In the **slope-ratio method** two sets of solutions are prepared:

The first set of solutions contains a large excess of metal and a variable concentrations of ligand (all the ligand reacts in forming the metal–ligand complex).

The absorbance of the formed complex is plotted against the ligand concentration and the slope of the line is determined.

A second set of solutions is prepared with a large excess of ligand and a variable concentration of metal (all the metal reacts in forming the metal–ligand complex). .

The absorbance of the formed complex is plotted against the metal concentration and the slope of the line is determined.

Method of Continuous Variation

Slope Ratio Method

The stoichiometric ratio of metal to ligand is inversely proportional to the ratio of the slopes:

$$\textit{Stoichiometric ratio}\,\textbf{(L:M)} = \frac{\text{Slope}_M}{\text{Slope}_L}$$

E.g. The slope of the first line (variable metal) is 1.56×10^{-3} and the slope of the other line (variable ligand) is 5.3×10^{-4}. What is the stoichiometric ratio of this complex?

$$\textit{Stoichiometric ratio}\,\textbf{(L:M)} = \frac{\text{Slope}_M}{\text{Slope}_L} = \frac{1.56 \times 10^{-3}}{5.3\times 10^{-4}} = 3$$

$$\textit{Stoichiometric ratio}\,\textbf{(L:M)} = 3{:}1\ (\text{L:M})$$

The slope-ratio method also is limited to systems in which only a single complex is formed.

pH Titration Method

pH titration method can be used whenever the complexation is accompanied by a change in pH.

E.g. The chelation of the cupric ion by glycine:

$$Cu^{2+} + 2NH^{+}_{3}CH_2COO^{-} = Cu(NH_2CH_2COO)_2 + 2H^{+}$$

Because 2 protons are formed in the reaction, the addition of glycine to Cu^{2+} solution should result in a decrease in pH.

Titration curves can be obtained by adding a strong base to a solution of glycine alone and to another solution containing (glycine + copper salt) and plotting the pH against the volume of base added.

pH Titration Method

The curve for the metal-glycine mixture is well below that for the glycine alone.

The difference in pH for a given quantity of base added indicates the occurrence of a complex.

Distribution Method

The method of distributing a solute between two immiscible solvents can be used to determine the stability constant for certain complexes.

The complexation of by potassium iodide is an example to illustrate this Method.

$$I_2 + I^- \prec I^-_3$$

The distribution method iodine has been used to study caffeine and polymer complexes with a number of acidic drugs such as benzoic acid, salicylic acid, and acetylsalicylic acid.

Note: This method is described in details in "lab. 2 Complexation".

Solubility Method

Solubility method is the most widely used method is the study the inclusion complexation.

According to the solubility method, excess quantities of the drug are placed in well-stoppered containers, with a solution of the complexing agent in various concentrations.

The bottles are agitated in a constant temp. bath until equilibrium is reached. Then, the supernatant liquid are removed and analyzed to obtain the total drug concentration.

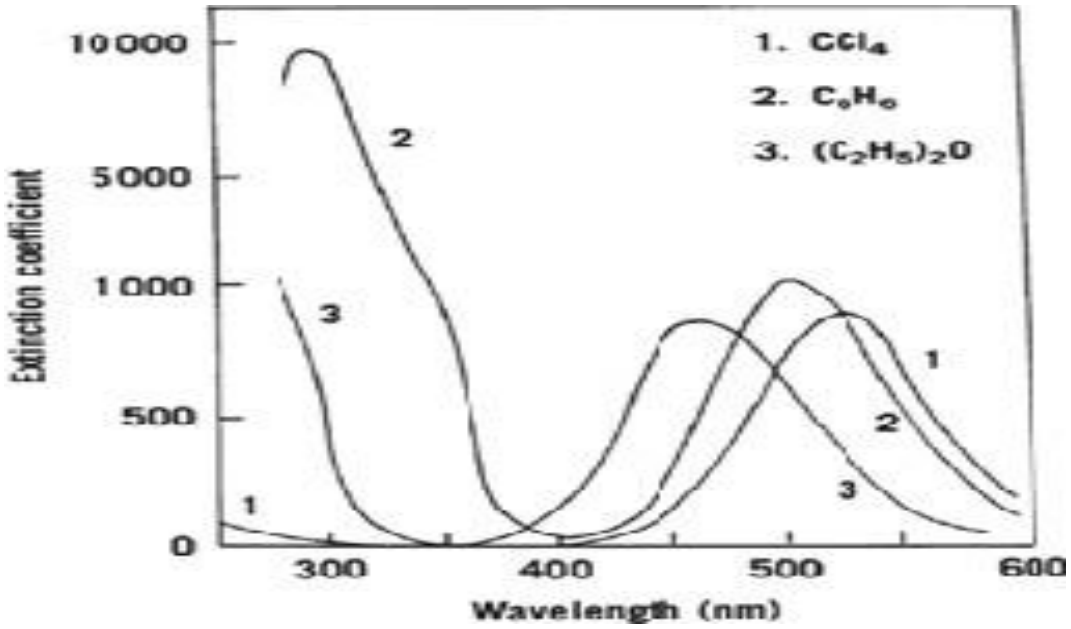
The concentration of the drug is plotted against the concentration of caffeine to obtain a curve that can be used to calculate the stability constant.

This method is used for charge transfer complexes.

When Iodine is analyzed with non-complexing solvent (e.g. CCl_4) a curve is obtain with a single peak at about 520 nm.

A solution of iodine in benzene exhibits a maximum shift to 475 nm, and a new peak with higher intensity at 300 nm.

A solution of iodine in diethyl ether shows a still greater shift to lower wavelength and the appearance of a new maximum.



SPECTROSCOPY

In benzene and ether, iodine is electron acceptor and the organic solvent is donor, while in CCl_4, no complex is formed.

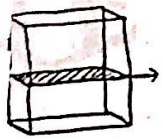
The shift towards the UV region becomes greater as the electron donor solvent becomes a stronger electron-releasing agent.

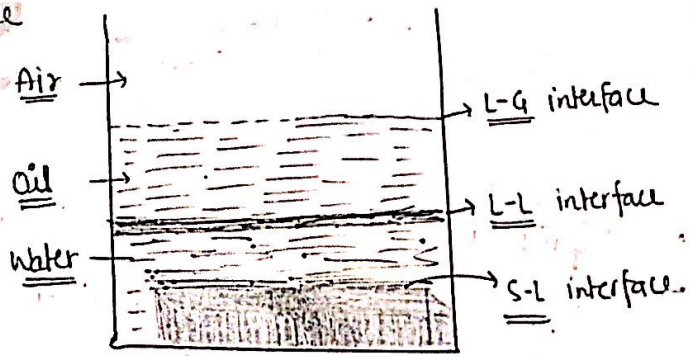
PHYSICAL PHARMACEUTICS || UNIT - 3rd

SURFACE & INTERFACIAL PHENOMENA

- **Interface :-** It forms when two or more immiscible substance contact with each other.

eg:-





- **Surface :-** The outside part of something, but here, surface is the liquid-gas interface or any interface in which Gas is on opposite site.

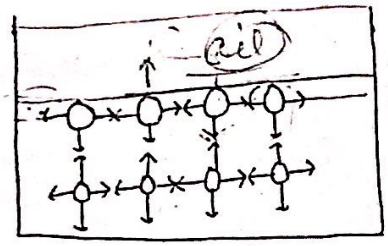
- **Interfaces :-**
  - Solid-liquid interface :- It forms b/w solid and Liquid.
  - Liquid-liquid interface :- It forms b/w liquid and liquid, but liquids does not miscible with each other.
  - Liquid-Gas interface (surface) :- It form b/w liquid and gas (air) and it is called as surface
  - Solid-Gas interface (surface) :- It form b/w solid and gas and it is also called surface

- **Liquid interface :-** It form when liquid is contact or mix with other states of matter (solid and gas) or itself (liquid).

  eg :- Oil in water (liquid-liquid interface) etc.

- **Importance :-**
  - Emulsion formation and stability
  - Adsorptions of drugs onto solid adjuncts in dosage forms. etc.

Surface and Interfacial tensions :-



In Liquid, state, liquid molecules are attached or attracted with each other through cohesive force. (vaudarwall forces)

It is a intermolecular force which attract each other from every side. & make them stable at equilibrium

- **Surface tension** → It is the force per unit length that must be applied parallel to the surface.

$$\gamma = \frac{\text{force}}{\text{length}}$$

Gamma

γ (Gama) = surface tension , Unit = N/m

- **Interfacial tension** → Same as surface tension, but it is happened between two immiscible liquid.

- SURFACE & INTERFACIAL PHENOMENON

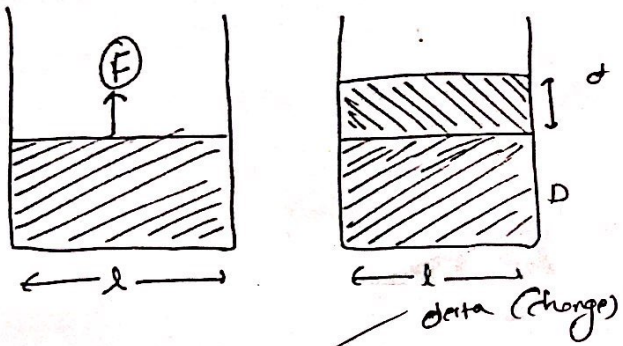
- SURFACE FREE ENERGY
- Measurement of surface and Interfacial tensions
  - i) Capillary Rise method
  - ii) Drop count method
  - iii) Drop weight method
  - iv) Wilhelmy plate method
  - v) Ring detachment method

① Surface free energy ⇒

Those energy which want to ⊗ increase our surface.

The molecules near the surface of liquid have more potential energy as compared to the molecules in the bulk of the liquid, this means that as surface area of liquid increase, the more molecules have this excessive potential energy. This energy is proportional to the

size of the free surface, it is called a surface free energy.



$W = f \times \Delta d$

$W = S \times l \times \Delta d \quad [f = S \times l]$

$W = S \times \Delta A$

S → Surface tension.

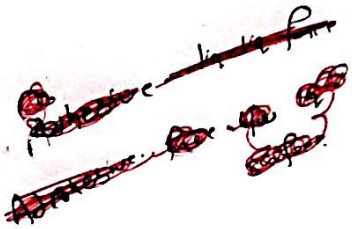
$\boxed{W = \gamma \times \Delta A}$ $\left[\Delta A = \frac{\text{change of}}{\text{surface}} \text{ area}\right]$

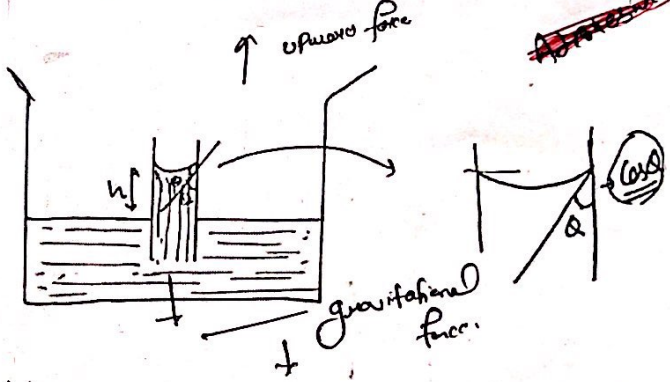
where, W = Surface free energy (work done)
γ = Surface tension, ΔA = Increase in area

- Measurement of Surface and Interfacial tension.

1) **Capillary rise method** :-

It is used to measure surface tension.





Principle :- When a thin glass tube (capillary) is placed in b/w liquid, liquid rises up in the capillary tube upto certain height.

- It is because adhesive force between capillary and liquid is more than

the cohesive force b/w intermolecular molecules of liquid.

- Due to surface tension liquid rises but some gravitational force is also apply on liquid which pull downward liquid.
- When both forces are equal liquid is an equilibrium and stable in that situtation.

- **Derivation :-**

— Upward force →

$f = 2\pi r \cdot \gamma \cos\theta$ —— (i)

(Capillary is circular that's why $2\pi r$ Gamma)

$\boxed{f = 2\pi r \cdot \gamma}$

where,

$2\pi r$ = Circumference of that capillary.

$\gamma\cos\theta$ = Surface tension & angle of contact

— Downward force →

$f = mgh + w$ —— (ii)

where,

mgh = potential energy with respect to gravitational force

w = weight of liquid.

we know that,

density = mass / volume (easy)

$\rho = \frac{m}{v} \Rightarrow \frac{m}{\pi r^2}$ $[v = \pi r^2]$ (new)

where,

ρ = density of liquid

m = mass

v = volume (new)

$\boxed{m = \rho \cdot \pi r^2}$ —— (iii)

Put eqn (iii) value in eqn (ii)

$f = \rho \pi r^2 gh + w$

Now,

Liquid is in equilibrium. means both forces are equal.

So,

Upward force = Downward force

$$2\pi r\gamma\cos\theta = \rho\pi r^2 gh + \omega$$

$$2\pi r\gamma\cos\theta = \rho\pi r^2 gh + \omega$$

for water,

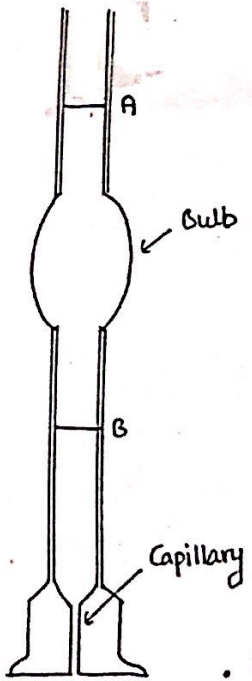
$$\gamma = \frac{1}{2}(\rho ghr + \omega)$$

where,

γ = surface tension
ρ = density
g = gravitation
h = height of rising liquid
r = radius of that liquid
ω = weight of

ii) **Drop count method** :-

It is used to measure the surface tension of liquid.



• Stalagmometer

In this method, we find out surface tension through comparing.

i) firstly take known liquid, which we know the surface tension.

ii) then fill stalagmometer with that liquid at point A. then stalagmometer closed from buttom from or with the help of finger.

iii) Now, Release liquid slowly-slowly dropwise from capillary untill liquid reached at point B. and continously count no. of drop, then note it.

iv) Now, Do same with other liquid, which we have to find surface tension.

v) So, on comparing both, by using formula we find out surface tension (r).

Let's see how??

-Derivation of formula ⇒

we know that

$W = 2\pi r\gamma$ ---Gamma

where, $2\pi r$ = circumference of capillary

1st case → when we take water [known surface tension]

$W_1 = 2\pi r \gamma_1$

$\gamma_1 = \frac{W_1}{2\pi r \cdot n_1}$ [∵ r = radius is same for both liquid]

2nd case → when we take unknown S.T. liquid.

$W_2 = 2\pi r \gamma_2$

$\gamma_2 = \frac{W_2}{2\pi r \cdot n_2}$ [where n = no. of drop]

Now,
we know that

$w = m.g$ & $\rho = \frac{m}{v} \Rightarrow m = \rho.v$

(mass, gravitational force, density)

$\boxed{w = \rho.v.g}$

where, ρ = density of liquid
v = volume of liquid
g = gravitational force

- Put these value in main eqn

$$r_1 = \frac{\rho_1 v g}{2\pi r n_1}$$

$$r_2 = \frac{\rho_2 v g}{2\pi r n_2}$$

On Comparing both,

$$\frac{r_1}{r_2} = \frac{\frac{\rho_1 v g}{2\pi r n_1}}{\frac{\rho_2 v g}{2\pi r n_2}}$$

So,

$$\boxed{\frac{r_1}{r_2} = \frac{\rho_1}{\rho_2} \times \frac{n_2}{n_1}}$$

where, r = surface tension
ρ = density of liquid
n = no. of drop count

→ So, in this we know ρ_1, ρ_2, n_1, n_2 and r_1, so we can easily find out the surface tension, by putting these value

iii) **Drop weight method** :-

It is same as drop count method, in which we use same capillary or stalagmometer.

Difference is that,

In which we weight the drop (one drop), firstly those liquid

D

which we know surface tension, then weight the other liquid's drop which we have to find out the surface tension.

1st case → know liquid.

$$w_1 = 2\pi r T_1$$

$$T_2 = \frac{w_1}{2\pi r}$$

2nd case → Unknow

$$w_2 = 2\pi r T_2$$

$$T_2 = \frac{w_2}{2\pi r}$$

[r = radius is same due to same capillary]

On comparing both,

$$\frac{T_1}{T_2} = \frac{\cancel{w_1}/\cancel{2\pi r}}{\cancel{w_2}/\cancel{2\pi r}}$$

$$\boxed{\frac{T_1}{T_2} = \frac{w_1}{w_2}}$$

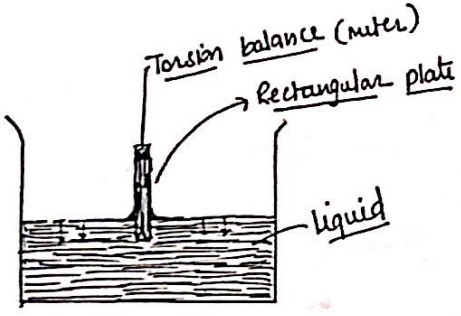
where,

T = surface tension

w = weight of the drop.

iv) **Wilhemy plate method** :-

It is used to used to measure surface tension.



- firstly we put the rectangular plate in that liquid, which we have to find out the surface tension.
- Now, Surface tension is applied on plate which pulled plate downward in the liquid.
- And we pulled rectangular plate upward with some force and surface tension is also oppose this.
- Now, that condition, when we pulled (detached) out plate from liquid, that time the force we applied is same as the surface tension of liquid.

$$\gamma = \frac{f}{L\cos\theta}$$

where,

γ = surface tension of liquid

f = force applied

L = length of plate (perimeter)

θ = angle of contact,

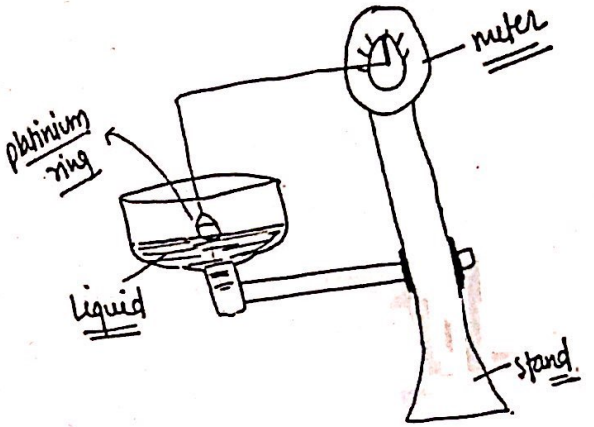
[$\cos\theta = 1$ for water]

v) **Ring detachement method :-**

It is used for measure both surface and interfacial tension.

→ It is also known as du nuoy method.

- In this method, a slowly lifting ring, often made up of platinium it attached from the surface of liquid
- The force f, required to raise the ring from the liquid's surface is measured and related to the liquid's surface tension.



$$\gamma = \frac{f}{2\pi(r_1 + r_2)}$$

where,

γ = surface tension

f = force applied

r_1 = radius of outer surface

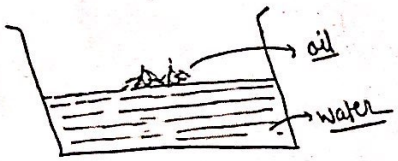
r_2 = radius of inner surface

- Spreading Coefficient
- Adsorption of liquid interface.

1) Spreading Coefficient :-

In two immiscible liquid, when we placed first's liquid drop on the surface of other it will spread as a film. And the ability of one liquid to spread over another liquid is calculated as spreading coefficient.

Eg:- Emulsion, oil in water, etc.



And it occurs, when adhesive force is more than cohesive force

i.e. $\boxed{S = W_A - W_C}$ ——— (1)

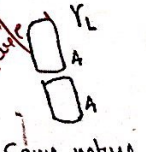
where, S = spreading coefficient
W_A = Work done of adhesive force
W_C = Work done of cohesive force

- Adhesive force :- It applied on the different nature's liquid.
- Cohesive force :- It applied on the same nature's liquid.

Derivation,

1st case → for Cohesive force

Two drop of liquid with same nature



Same nature liquid

$W_C = \gamma_L \Delta A + \gamma_L \Delta A$ [∵ γ_L = Surface tension of water, ΔA = Area of drop]

$W_C = 2\gamma_L \Delta A$

If $\Delta A = 1 cm^2$, then

$\boxed{W_C = 2\gamma_L}$ ——— (11)

Adsorption - Surface ↑.

Absorption - absorb.

2nd Case :- for different nature's liquid. (Adhesive force).

$$W_A = \gamma_L \cdot \Delta A + \gamma_S \cdot \Delta A - \gamma_{LS} \cdot \Delta A$$

If $\Delta A = 1 cm^2$

$$\boxed{W_A = \gamma_L + \gamma_S - \gamma_{LS}} \quad \text{— (iii)}$$

Now, put value of eqn (ii) & (iii) into (i)

$$S = W_A - W_C$$

$$S = \gamma_L + \gamma_S - \gamma_{LS} - 2\gamma_L$$

$$\boxed{S = \gamma_S - (\gamma_L + \gamma_{LS})}$$

If, $\gamma_S > (\gamma_L + \gamma_{LS})$, then spreading occurs,

$\gamma_S < (\gamma_L + \gamma_{LS})$, the spreading does not occurs,

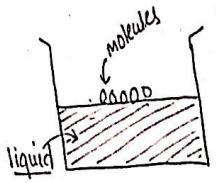
Adsorption of Liquid surfaces :-

Adsorption is defined as the deposition of some molecules or ions [molecular species] onto the surface of liquid.

Positive Adsorption

→ molecules deposite on the surface of liquid.

→ surface free energy & surface tension decreased. ↓

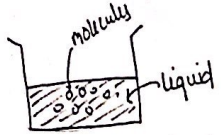


→ molecules settle down on surface.

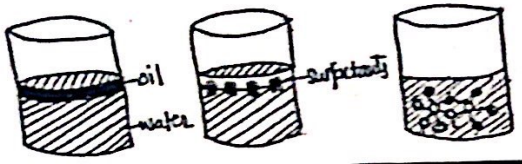
Negative Adsorption (Absorption)

→ Molecules does not deposite on surface it mix with the liquid.

→ surface free energy & surface tension increase. ↑



→ molecules mixed with liquid.

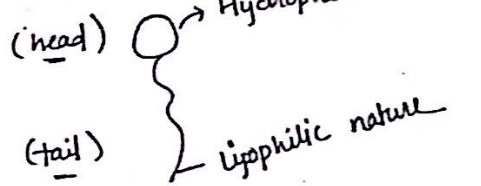


Surface Active agents (Surfactants)

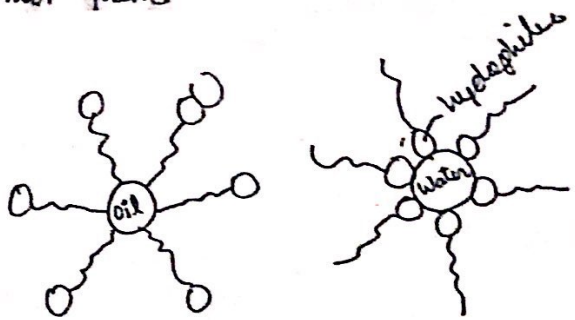
These are those agents (substances) which reduced the surface tension and interfacial tension b/w two liquids.

Detergents, soaps, emulsifier etc

eg:- It helps in mixing of oil into water..



If we add oil & water in any container, then it is immiscible, so we used surfactants to reduced interfacial tension and helps to mix them



(micelle)

→ oil (lipophilic), so attached with lyophilic part of surfactants.

→ Water (hydrophilic), so attached with hydrophilic part of surfactants.

→ And on which temperature micelle formed is called craft temperature

Types of Surfactants :-

I) Anionic
II) Cationic
III) Ampholytic
IV) Non-ionic

I) Anionic surfactants :- It contain organic tail with negative charge head and small positive molecules like ammonia.
- these are unpleasant taste. so not suitable for internal use
eg:- Alkali metals and ammonium soaps (sodium stearate) (O/W)

II) Cationic surfactants :-
It contain organic tail with positive charge head and small negative molecules like chloride
- these are sometimes used on the skin for cleansing of wounds.
eg:- Benzalkonium chloride ~~Acid~~ etc

III) Amphoteric surfactants :- (Ampholytic)
Ampholytic and Amphoteric surfactants sometimes reffered to as zwitter ionic molecules surfactants that possess both cationic and anionic group in the same molecules.
- they depends on the pH of the systems
- they mostly used as co-surfactants that boosts the detergency and the foaming power of anionic surfactants
eg:- Lecithin, Amino acetic acid etc

iv) Non-ionic surfactants :-

They are non-ionic, so they does not ionize in water, because their hydrophilic part consist of non-dissociable molecules.

→ These are mostly used in pharmaceutical industry.

→ They are resistant to pH change.

eg :- Glycerol

• **HLB System** :- [Hydrophilic - Lipophilic Balance System]

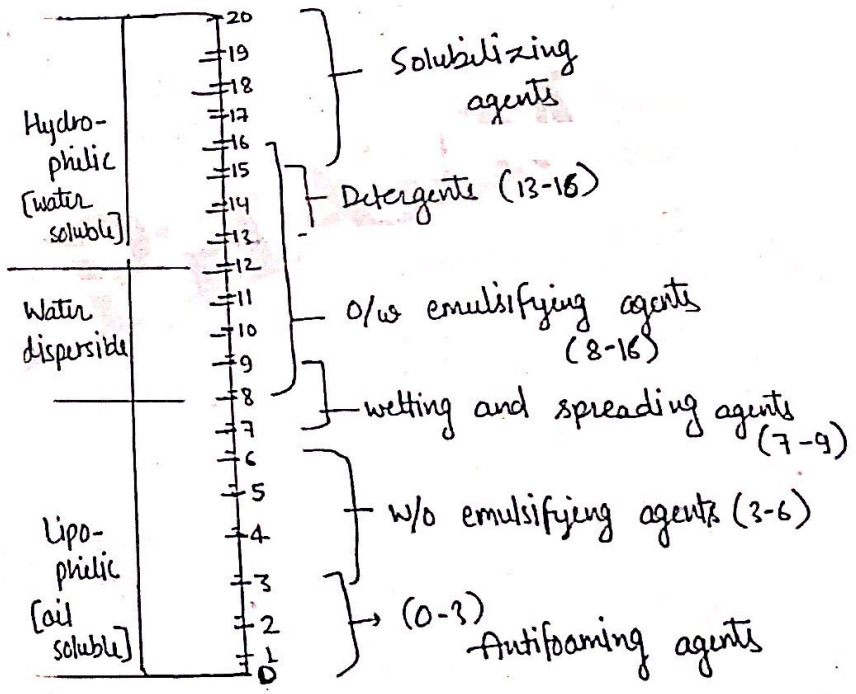
Thise system consist of arbitatory scale in which values are assigned to different surfactants according to their nature

→ HLB value of 1 indicates → Surfactants is lipophilic & soluble in oil.

→ HLB value of 20 indicates → Surfactants is hydrophilic & soluble in water.

$$HLB = \frac{\text{Hydrophilic}}{\text{Lipophilic}}$$

• HLB SCALE •



- **Solubilization :-**

It is the process in which, Solubility of organic compound is increased in aqueous medium with the help of surface active agents (surfactants), this phenomena is known as solubilization.

- It is used in many industries for the mixing of two immiscible liquid & help in making of drugs

- **Detergency :-**

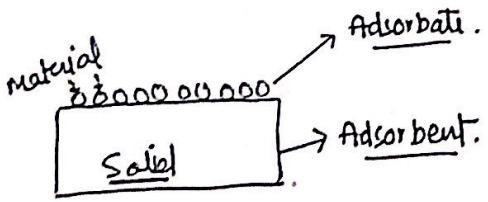
It is the process or phenomenon in which dirt (oil and solid objects) remove from the surface with the help of ~~surface~~ detergent.
And these detergent are basically made up with Surfactants or itself surfactants.

- It work that, it reduce the adhesive force, so dirt particles easily remove from the surface

Adsorption at Solid interface :-

- When substance (material) deposite on the surface of solid is called the adsorption at solid interfaces.

- The material (substance) which deposit on the surface of solid is called adsorbate.
- The material (substance) on whose surface the process takes place is called adsorbent.



Now, adsorbent and adsorbate are attached with each other with some attraction forces

- On the basis of attraction forces adsorption divided into two.
  - i) Physisorption (Physical adsorption)
  - ii) Chemisorption (chemical adsorption)

i) Physisorption :- When adsorbent and adsorbate is attached with each other with some weak bonds as like as, Vandarwall forces, and
- these are reversible
- And these have weak force of attraction as compared to chemisorption
- It is less energy consuming

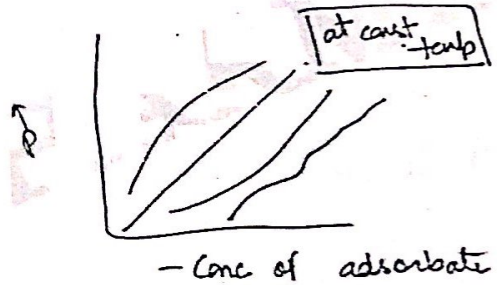
II) Chemisorption :-

When adsorbati and adsorbent are attached with each other with some strong chemical bond, as like as, covalent bond, Ionic bond.

- they are irreversible
- they have strong force of attraction b/w adsorbent and ~~ab~~ adsorbati.
- It is more energy consuming as compared to physisorption.

Adsorption Isotherm

→ At constant temperature, graph b/w pressure & conc of adsorbate.



Freundlich theorem

Langmuir theorem

i) Freundlich theorem →

Let, When adsorbate is attached on the adsorbent

that time, (let)

x = mass of adsorbate

M = mass of adsorbent

and their

fraction of adsorption = $\frac{x}{m}$

and an increasing amount of adsorbate, fraction of adsorption increase and an increasing pressure, fraction of adsorption increased.

So, acc. to Freudlich

$$\frac{x}{m} \propto p^{1/n}$$

$$\boxed{\frac{x}{m} = Kp^{1/n}}$$

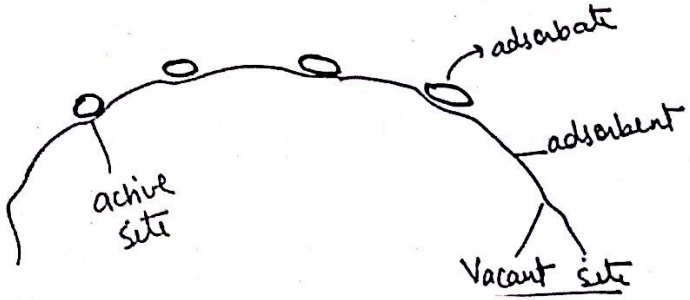
→ It is based on Chemisorption.

ii) Langmuir theorem :-

→ It is based on physisorption.

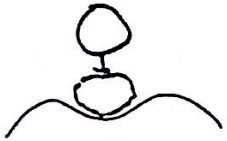
In this case,

we let their are some vacant site on which particles attached,



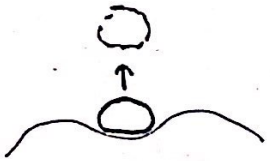
Active site, on which particles attached

Vacant site, when particles detached from active site after adsorption



adsorption

[attachment of particles on surfa]



desorption

[detachment of particles from surface]

let,

r_1 = rate of adsorption

r_2 = rate of desorption

let,

θ = filled site

$(1-\theta)$ = Vacant site

→ Rate of adsorption is dipend on vacant site, because the more vacant site, the more particles attached.

So, $r_1 \propto (1-\theta) \times P$

$r_1 = k_1(1-\theta) \times P$

[where, r_1 = rate of adsorption
k_1 = constant
P = pressure which help in adsorption]

→ Rate of disorption is dipend on active site. because the more particle attached get more detached.

So, $r_2 \propto \theta$ [pressure is not required for detachment]

$r_2 = k_2\theta$

At equilibrium, $r_1 = r_2$

$\therefore k_1(1-\theta) \times P = k_2\theta$

$k_1P - k_1\theta P = k_2\theta$

$k_1P = k_2\theta + k_1\theta P$

$\boxed{k_1P = \theta[k_2 + k_1P]}$ — this is Langmuir equation.

MICROMERITICS

Definition:

- Micromeritics is the science and technology of small particles. Knowledge and control of the size and the size range of particles are of significant importance in pharmacy because the size and surface area of a particle related to the physical, chemical and pharmacologic properties of a drug.
- The particle size of a drug can affect its release from dosage forms that are administered orally, parenterally, rectally and topically.
- In the area of tablet and capsule manufacture, control of the particle size is essential in achieving the necessary flow properties and proper mixing of granules and powders.

Applications:

1. Release and dissolution.
2. Absorption and drug action.
3. Physical stability.
4. Dose uniformity.

1. Release and dissolution.

Particle size and surface area influence the release of a drug from a dosage form. Higher surface area allows intimate contact of the drug with the dissolution fluids in vivo and increases the drug solubility and dissolution.

2. Absorption and drug action.

Particle size and surface area influence the drug absorption and subsequently the therapeutic action. Higher the dissolution, faster the absorption and hence quicker and greater the drug action.

3. Physical stability

The particle size in a formulation influences the physical stability of the suspensions and emulsions. Smaller the size of the particle, better the physical stability of the dosage form.

4. Dose uniformity.

Good flow properties of granules and powders are important in the manufacturing of tablets and capsules.

Particle size and size Distribution: When a powder sample contains of uniform size, it is said to be monodisperse. In collection of particles of more than one size, it is said to be polydisperse. The pharmaceutical powders are almost always be polydisperse and hence it is necessary to charcterise particle size and their distribution. For characterisation two properties are important i.e., (a) the shape and surface area of the individual particles, and (b) the size range and number or weight of particles present and hence, the total surface area. The size of a sphere can completely be expressed in terms of its diameter. When particle is asymmetrical the diameter which is related to an equivalent spherical diameter, which relates the size of the particles to the diameter of a sphere having the same surface area, volume or diameter

The size of particles may be expressed as:

(i) Surface diameter, ds : Is the diameter of a sphere having the same surface area as that of the asymmetric particle.

(ii) Volume diameter, dv : Is the diameter of of a sphere having same volume as that of the asymmetric particle.

(iii) Projected diameter, dp : Is the diameter of sphere having the same observed area as the particle when viewed normal to its most stable plane.

(iv) Stokes'diameter, dst : Is the diameter of an equivalent sphere undergoing sedimentation at the same rate as the asymmetric particle.

(v) Sieve diameter, d sieve: Is the diameter of a sphere that will just pass through the same square or sieve aperture as the particle.

(vi) Volume-surface diameter; dvs : Is the diameter of a sphere that has the same volume to surface area ratio as the asymmetric particle.

Frequency distribution curve:

In this type, number or weight of particles lying within particular size range is plotted against the mean particle size. In general the normal distribution curve is expected to be symmetrical (bell shaped) around the mean, which is also the mode. In this type of distribution, the positive and negative deviations from the mean are uniform and it is represented by standard deviation. Larger particles obtained by granulation can be described by normal distribution. In this case, arithmetic mean and standard deviation are considered.

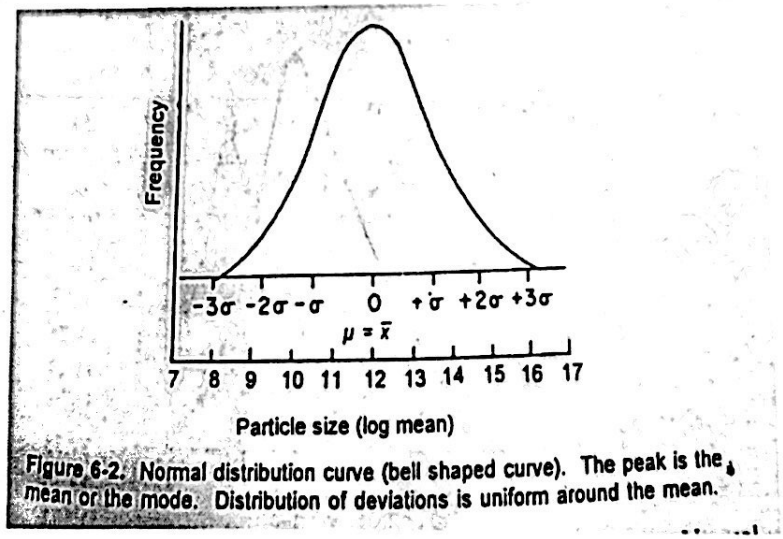


Figure 6-2. Normal distribution curve (bell shaped curve). The peak is the mean or the mode. Distribution of deviations is uniform around the mean.

Normal distribution is usually not found in pharmaceutical powders because of uneven size reduction process. The distribution of particles in a powder is termed as unsymmetric or skewed, i.e. uneven around the mean. If frequency curve is elongated towards higher size range, the pattern is known as positive skewness. If frequency curve is elongated towards lower size, the pattern is known as negative skewness. It is normally shows a long tail of larger particle size.

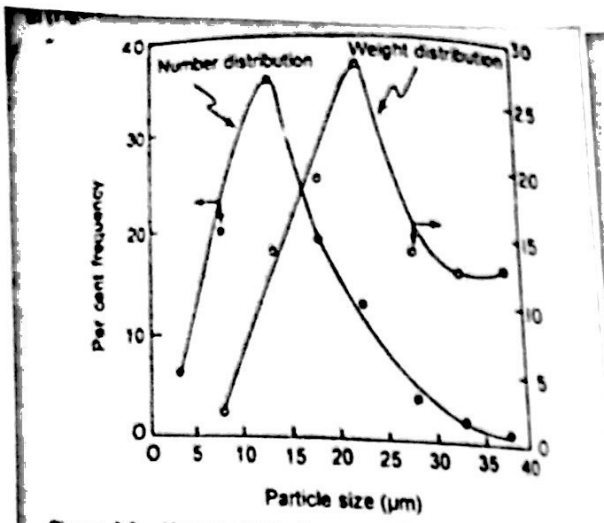
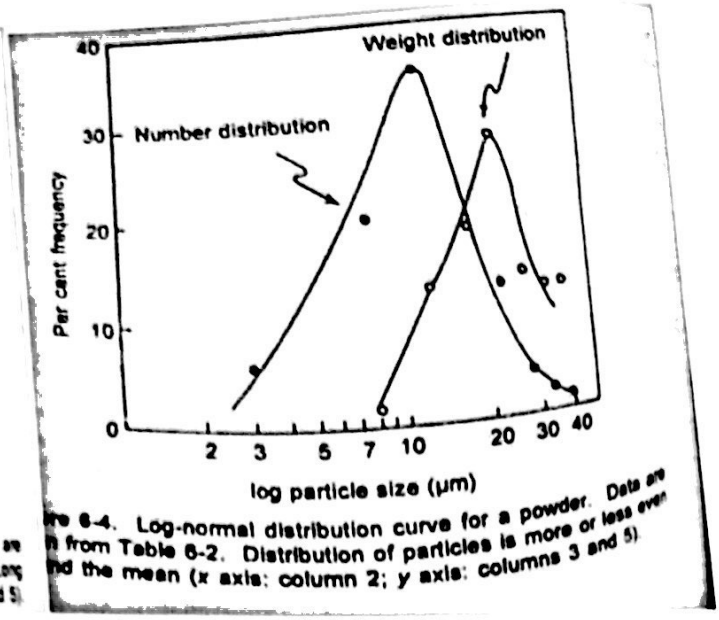


Figure 6-3. Normal distribution curve for a powder. Data are taken from Table 6-1. Uneven distribution around the mean. Long tail of larger particles (x axis column 2, y axis: columns 4 and 5)



...re 6-4. Log-normal distribution curve for a powder. Data are ...n from Table 6-2. Distribution of particles is more or less even ...nd the mean (x axis: column 2; y axis: columns 3 and 5)

Log-normal distribution curve:

In this type, frequency on y axis is plotted against log mean particle size on x axis. Advantage of this curve is that the distribution pattern is made symmetrical. When compared to normal distribution curve. Powders obtained by crystallization and milling methods exhibit log-normal distribution. Powder blend obtained from granulation may have different type of distribution.

Cumulative frequency distribution curve:

In this plot, cumulative percentage over size (or under size) is drawn against particle size. If summation of frequencies is carried out from the bottom upward, the result expressed as the percentage particle over size. Summation downwards gives percentage undersize. Data yield a sigmoid curve with the mode, i.e. particle size at the greatest slope. The advantage of this plot is that one can directly read the percentage within any given size range without any difficulty. The disadvantage is that scattering of points cannot be identified.

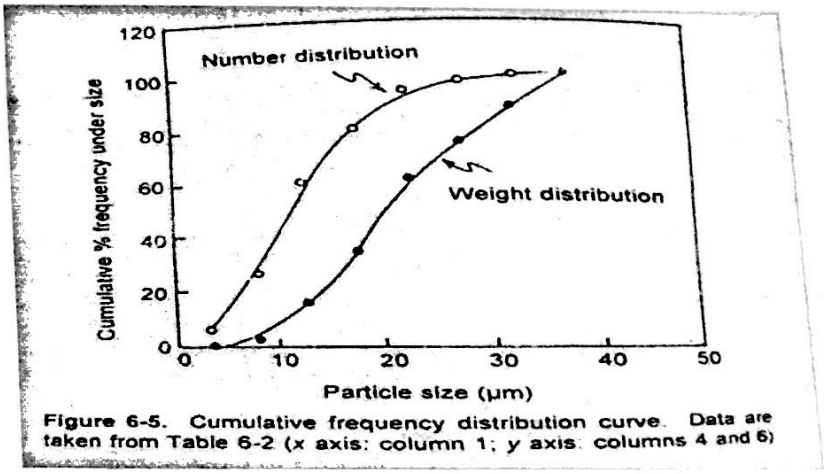


Figure 6-5. Cumulative frequency distribution curve. Data are taken from Table 6-2 (x axis: column 1; y axis: columns 4 and 6)

Log –Probability plot:

A plot is drawn by taking log particle size on x axis and cumulative percent frequency of the probability scale on y axis. In this plot, the cumulative curve is converted into a straight line. A straight line is completely defined by one point and the slope. For the number distribution, slope gives geometric standard deviation σg. The reference point gives geometric mean diameter, dg, which is equal to the median or the diameter at 50% on probability scale.

Probability plot is necessary when certain data points are not well defined. For example, in the sieve analysis, how much material has passed through the top sieve is known. For this data point, we have to identify the midpoint interval of the top, which is not known.

The advantages of probability graph are:

1. Error of data points are averages by taking a best fit line.
2. Linearity or lack of linearity can be identified.

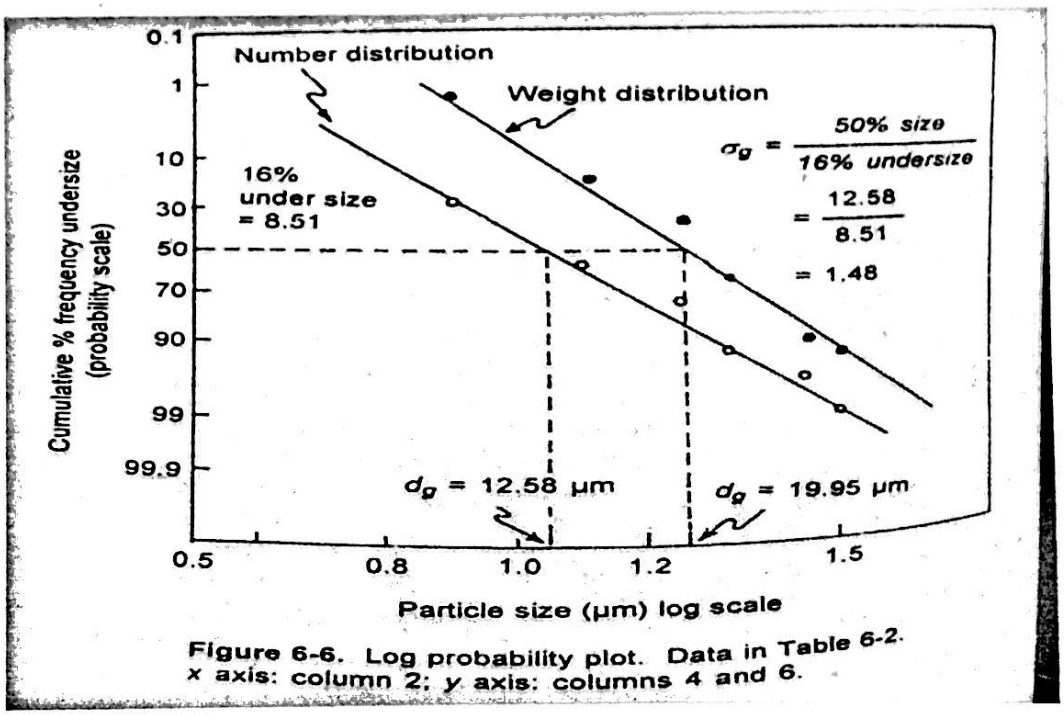


Figure 6-6. Log probability plot. Data in Table 6-2. x axis: column 2; y axis: columns 4 and 6.

Particle size determination-Methods:

Many methods available for determining particle size such as optical microscopy, sieving, sedimentation and particle volume measurement.

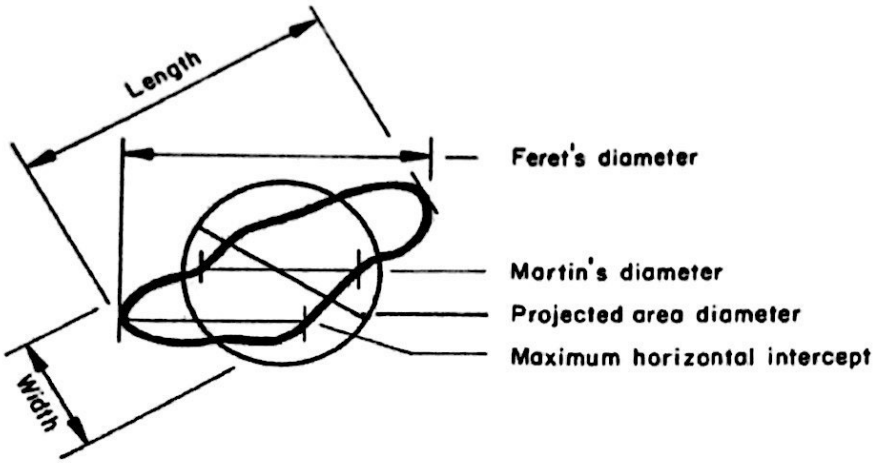
1. Optical microscopy (range: 0.2-100 μm).
2. Sieving (range: 40-9500 μm).
3. Sedimentation (range: 0.08-300 μm).
4. Particle volume measurement or conductivity method (range: 0.5-300 μm).

1. Optical microscopy:

The optical microscopy can be used to measure the particles size in the range of 0.2 μm to about 100 μm. In this method the size is expressed as d_p projected diameter. By this method the number distribution data can be obtained and it can be converted to weight distribution. The

resolving power of optical microscope is less as compared to ultramicroscope or electron microscope. In this method, an emulsion or suspension, diluted or undiluted, is mounted on a slide or ruled cell. Eye-piece of the microscope is fitted with a micrometer, called ocular micrometer. The eyepiece or ocular micrometer is calibrated using a stage micrometer. The slide or ruled cell is placed on a mechanical stage. The size of particle is determined with the help of ocular micrometer. The field can be projected onto a screen where particles are measured more accuratly and photograph can be taken. The optical microscopy method can be used to determine the particle size analysis in suspensions, in aerosols or in emulsion (droplet size). In order to get statistically valid results the counting of particles should be in the range of 500 to 1000 particles for every sample.

From the obtained data the size frequency distribution curves, cumulative frequency curves are plotted. Other popular measurements includes - Feret diameter, the Marti diameter and projected area diameter.



Popular measurements:

Feret's Diameter— The distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale.

Martin's Diameter— The diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas.

Projected Area Diameter— The diameter of a circle that has the same projected area as the particle.

Length— The longest dimension from edge to edge of a particle oriented parallel to the ocular scale.

Width— The longest dimension of the particle measured at right angles to the length

Advantages

1. Microscopy method allows the direct observation (shape and size) of particles
2. The field can be projected and a photograph can be taken.
3. Aggregation of particles can be easily detected.
4. Provides accurate results and reproduciability.

5. Simple and economic.
6. Easy to handle.

Disadvantages

1. Diameter is obtained from only two dimensions of the particle i.e., length and breadth. No estimation of depth (thickness) of particle.
2. The method is slow and tedious, because the number of particles that must be counted (300-500) to obtain a good estimation of the distribution.
3. Time consuming method.
4. Large sample is required.

2. Sieving method:

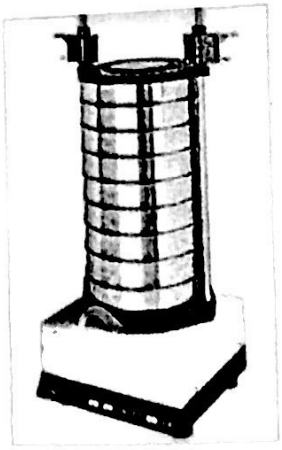
Particles having size range between 40 to 9500μm are estimated by sieving method. In this method, the size is expressed as d_{sieve}, which describes the diameter of a sphere that passes through the sieve aperture as the asymmetric particle. This method directly gives **weight distribution**. This method is also known as **analytical sieving**.

The sieving method finds application in dosage form development of tablet and capsules. Normally 15% of fine powder should be present in granulated mass to get as proper flow and achieve good compaction in tabletting. Therefore, percent of coarse or fine powder can be quickly estimated. In addition, sieving also separated the powder can be quickly estimated. In addition, sieving also separates the powder into fractions of desired size.

Sieves for pharmaceutical testing are considered from wire cloth with square meshes, woven from wire of brass, bronze, stainless steel or any other suitable material. Sieves should not be coated or plated. There must be no reaction between the material of construction of the sieve and the substance to be sieved.

Method:

Standard sieves of different mesh numbers are available commercially as per the specification of IP and USP. Sieves are arranges in a nest with the coarsest at the top. A sample of the powder is places on the top sieve. This sieves set is placed in the mechanical shaker apparatus and shaken for a certain period of time. The powder retained on each sieve is weighed. Frequently, the powder is assigned the mesh number of the screen through which it is passed or on which it is retained. It is expressed in terms of **arithmetic or geometric mean** of the two sieves. Data are analyzed for normal, log-normal, cumulative percent frequency distribution and probability curves. The relevant diameter such as geometric mean weight diameter and standard deviation can be obtained.



Advantages

1. It is simple for handling.
2. It is inexpensive and rapid.
3. Provides reproducible results.
4. Specially useful for weight distribution.
5. It can be used for very small particles having particle diameter upto 5J.lm.

Disadvantages

1. It cannot used for very small particles is below 5J/m.
2. The powder sample should be dried every time, otherwise it may clog with particles, resulting improper sieving.
3. During shaking, attrition of particles may cause reduction of particle size. This may leads to errors in estimation.
4. Time consuming method.
5. Approximate results can be obtained.

3. Sedimentation method:

The sedimentation method can be used for formulation and evaluation of suspensions. emulsions and determination of molecular weight of polymers. The particle size in the subsieve range may be obtained by gravity sedimentation and is expressed as stokes' diameter, dst' in Stokes' law.

$$d_{st} = \sqrt{\frac{18\mu h}{(\rho_s - \rho_l)gt}}$$

Where,

d_{st} = Stokes diameter of the particle

μ= viscosity of the medium

h = height of fall in time

Ps = density of the particles

Pl= density of the medium

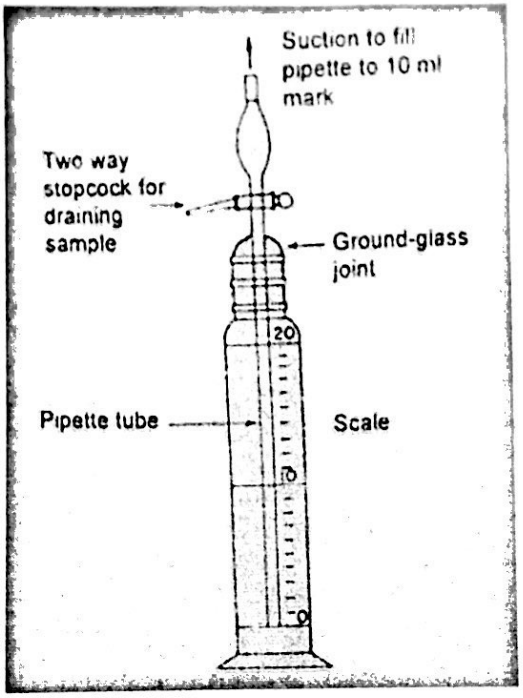
g = acceleration due to gravity

t = time interval

The apparatus usually consists of 550ml vessel containing a 10ml pipette sealed into a ground glass stopper. When the pipette is in place in the cylinder, its lower tip is 20cm below the surface of the suspension.

The procedure is as follows:

1 or 2% suspension of powder in a suitable medium firstly prepared and to that add suitable deflocculating agent. Transfer this mixture (suspension) into the Andreasen vessel. Place the stopper and shake the vessel to distribute the particles uniformly throughout the suspension and the apparatus is place in a constant temperature bath. Remove the stopper and attach two-way stopcock. At various time intervals, 10ml samples are withdrawn and discharged by means of the two way stopcock. The samples are evaporated and weighed or analyzed by any method, correcting for the deflocculating agent that has been added. The weight or the amount of particles obtained in each time interval is referred to as weight undersize. The weights are converted into cumulative weight undersize.



4. Particle volume measurement or conductivity method:

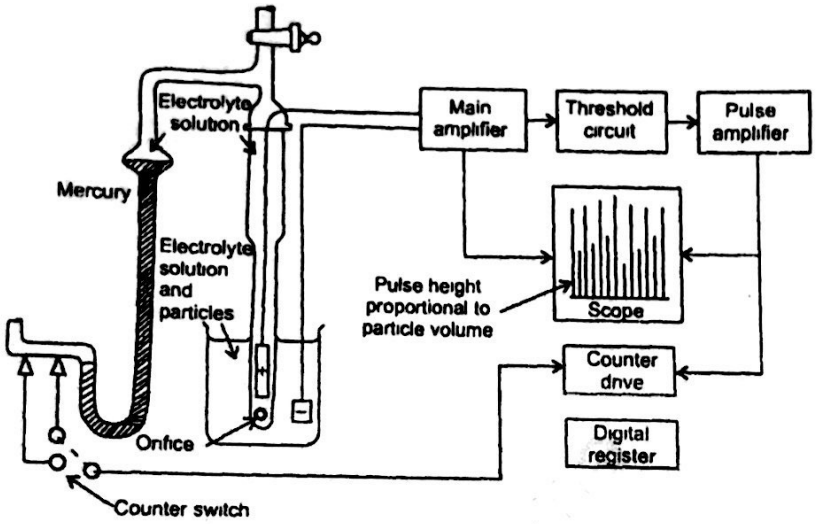
The popular instrument to measure the volume of particles is the coulter counter. This method gives number distribution. Here the particle volume is measured and is converted into particle diameter, and size is expressed as volume diameter d_v. The method is useful in the study of particle growth in suspension and solutions, useful in dissolution studies and to study the effect of antibacterial agents on the growth of microorganisms. This method gives quick and accurate results.

The working principle of coulter counter is that when a particle suspended in a liquid containing electrolyte (sodium chloride) passed through a small orifice, and maintains contact

with the external medium. Generally, a known volume of a dilute suspension is pumped through the orifice. The suspension is sufficiently diluted so that only one particle can pass at a time through an orifice. A constant voltage is applied across the two electrodes. Here the current produces. When a suspended particle travels through the orifice, it displaces its own volume of electrolyte. The resistance, between two electrodes increases. The net result is a change in the electrical resistance, which is related to the particle volume, causes a voltage pulse. The voltage pulse are amplified and fed to a pulse height analyzer calibrated in terms of particle size.

The pulses are electronically counted for a given threshold value. By adjusting the threshold setting the number of particles of each size range is obtained. Thus the particle size distribution can be obtained.

The instrument is capable of counting particles at the rate of approximately 4000 per second. The data may be converted from a volume distribution to a weight distribution.



Coulter counter apparatus

Advantages

1. It gives very fast results [approximately 4000 particles per second].
2. Short period of time is required for size distribution analysis.
3. It provides accurate results.
4. It can be used to measure particulate contamination in parenteral solutions.
5. Submicron particle sizing instrument, the coulter Model N4 has been developed for analyzing particles in the range of 0.003 to 0.3 μm.
6. It is used in the study of the clustering process and the packing of the mineral components of renal stones.
7. It is also useful in quality control of large volume parenteral [LVP] solutions.

Disadvantages

1. It is not suitable for polar and highly water soluble materials due to solvation.
2. It is expensive method.

Specific surface:

Specific surface is defined as the surface are per unit weight (Sw) or unit volume (Sv) of the material.

Determination of surface area:

The commonly used methods are:

1. Adsorption method
2. Air permeability method

Specific Surface

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

$$= \frac{\text{number of particles} \times \text{Surface area of each particle}}{\text{number of particles} \times \text{Volume of each particle}}$$

$$= \frac{\eta \alpha_s d^2}{\eta \alpha_v d^3} = \frac{\alpha_3}{\alpha_v d}$$

$$S_w = \frac{\text{Surface area}}{\text{Weight}} = \frac{\text{Surface area}}{\text{Density} \times \text{Volume}}$$

$$S_w = \frac{S_v}{\rho} = \frac{\eta \alpha_s d_{vs}^2}{\eta \alpha_v d_{vs}^3 \times \rho}$$

$$= \frac{\alpha_s}{\alpha_v \, d_{vs} \, \rho}$$

When the particles are spherical, above equation simplifies to

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

Since $\frac{\alpha_S}{\alpha_v} = 6.0$ for a sphere.

Adsorption method:

Principle: A large specific surface allows good adsorption of gas and/or solutes from a solution. The volume of gas (in m^3) adsorbed per gram of adsorbent (solid) can be plotted against the pressure of gas introduced at constant temperature. At low pressure, the gas adsorbs on the surface of adsorbent and form a monolayer. At saturation, the amount of adsorbed is a function of surface area of powder. At high pressure, the adsorbed layer becomes multi-molecular. The completion of mono-molecular film can be identified using BET equation. At that stage, the volume (y_m) adsorbed per one gram can be obtained.

$$\frac{p}{v(p_0 - p)} = \frac{1}{v_m b} + \frac{(b - p)}{v_m b} \frac{p}{p_0} \quad (12)$$

where p = pressure of the adsorbate, mmHg
v = volume of vapor (gas) per gram, g
p_0 = vapor pressure at saturation (monolayer), mmHg
v_m = amount of vapor adsorbed per unit mass of adsorbent when the surface is covered with monomolecular layer, g
b = constant, proportional to heat of adsorption and latent heat of condensation of subsequent layers

When, $p/p_0 = 1$, the vapor pressure p is equal to saturation vapor pressure. Quinsorb QS-16 is used for obtaining the data needed to calculate the surface area.

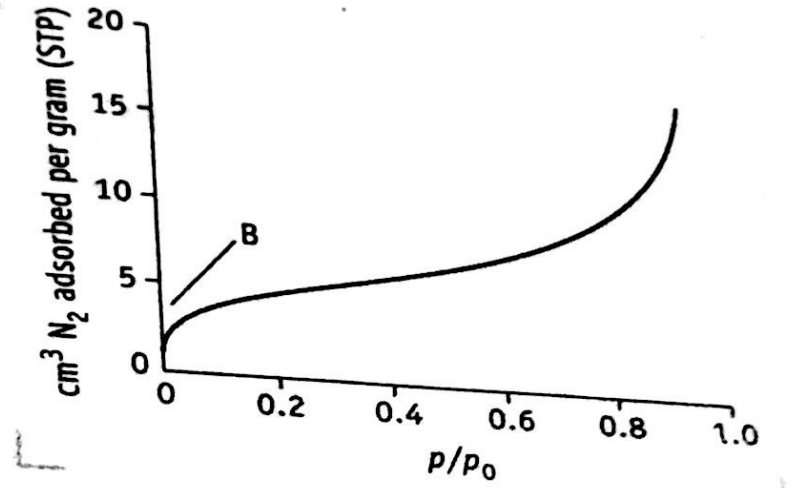


Fig. 6-12 Adsorption isotherm showing the volume of nitrogen gas absorbed on the powder. The first inflection point, B, represents the completion of monomolecular layer (v_m).

Procedure : A known weight of powder is introduced into the sample tube. The sample is mounted to the out-gassing station to remove gas. Then the sample tube is mounted to the analysis station. A mixture of helium and nitrogen are used as adsorbate gas. Nitrogen gas adsorbs on the powder and helium does not adsorb (inert). Vapour dosing options are available with the instrument. A mixture of gases is passed through sample tube (containing powder) at a specific pressure and temperature (thermostat facility). The amount of nitrogen gas adsorbed and desorbed is measured using a thermal conductivity detector. The signal height is proportional to the rate of adsorption or desorption of nitrogen gas. The area under the curve is proportional to the gas adsorbed on the particles. The adsorption is measured, at several

pressures, so that BET equation plot can be obtained. Gaussian or bell shaped curve is plotted on a strip chart recorder.

Advantages : Quintasorb is versatile in the sense that it permits the use of a number of gases (or gas mixtures) over a range of temperatures. It allows the evaluation of characteristics of porous material. In addition, it can be used to measure true density of the powder, pore size and pre volume distribution. These can be used for studying physisorption and chemisorption. It is applicable to a wide range of surface areas.

Air Permeability Method – Fisher-Subsieve Sizer

Air permeability method is offical in IP. This method also used to estimate surface diameter, d_s.

Principle : Powder is packed in the sample holder as a compact plug. In this packing, surface-surface contacts between particles appear as a series of capillaries. The surface of these capillaries is a function of the surface area of the powder. When air is allowed to pass, air travel through these capillaries and thus this method is related to surface area of powder. When air is allowed to pass at a constant pressure, the bed resists the flow of air. This results in a pressure drop. The greater the surface area per gram of the powder, S_w, the greater the resistance to flow. The permeability of air for a given pressure drop is inversely proportional to specific surface.

The *Kozeny-Carman* equation is used to estimate the surface area by this method. This is based on the principle of Poiseulle's equation.

$$V = \frac{A}{\eta S_w^2} \cdot \frac{\Delta P t}{K l} \cdot \frac{\varepsilon}{(I - \varepsilon)^2} \qquad ...(19)$$

where A = cross sectional area of the bed (pack), m^2

ΔP = pressure difference of the plug, Pa (or mmHg)

t = time of flow, s

l = length of the sample holder, m

ε = porosity of the powder

S_w = surface area per gram of the powder, m^2/g

h = viscosity of the air Pa.s

K = a constant (5.0±0.5) that accounts the irregular capillaries

V = volume of air flowing through the bed, m^3

Poiseulle's equation is same as that used in Ostwald's viscometer, the principle of flow of liquids through the capillary tube. Fisher subsieve sizer instrument is commercially available.

Method : Assembling of the apparatus is shown in Figure 6-13. It consists of a sample tube containing the packed powder sample with one end connected to an air pump through a constant pressure regulator. The other end is attached to a calibrated manometer containing a suitable liquid of low viscosity and negligible vapor pressure.

The air pump builds up air pressure and is connected to a constant pressure regulator. Air is passed through the dryer to remove any moisture. Air is then allowed to flow through the packed powder in the sample tube. The flow of air is measured by the manometer. The level of the fluid in the manometer is related to the average diameter of the particles. The higher the surface area, the greater is the resistance, the pressure drop is higher and manometer level decreases. Commercial equipment is standardized to eliminate the mathematical computation. Average particle diameter can be read from the calculator charts supplied with the equipment.

The porosity of the powder (ε) and viscosity of air (η) are estimated separately. A and l are constants represent sample holder. ΔP and V can be obtained from the experiment and substituted in equation (19) in order to estimate the surface area.

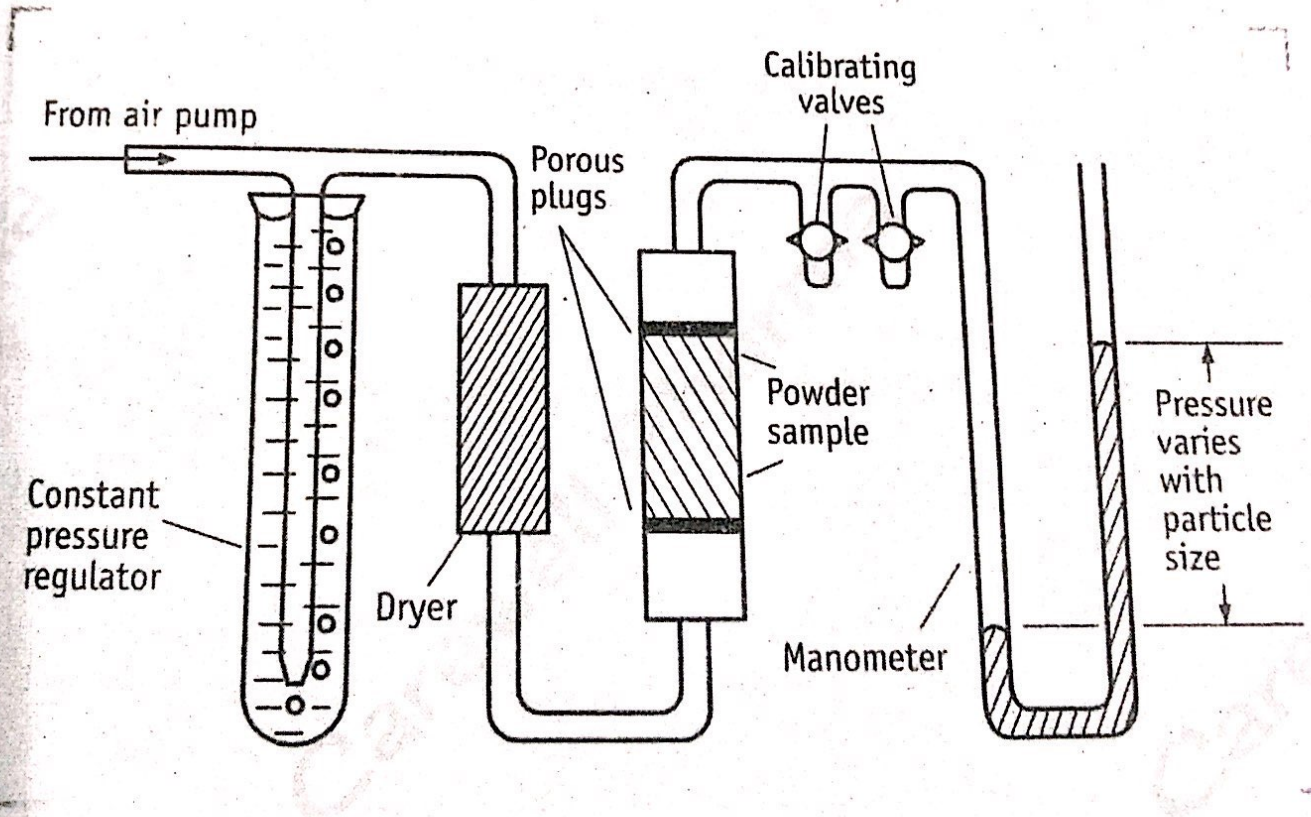


Fig. 6-13 The Fisher subsieve sizer.

If the powder has decreased porosity, the d_{vs} also decreases. Therefore, over a range of porosities, the minimum value of diameter is achieved.

Advantages

1. Simple instrumentation and high speed, it is widely used pharmaceutically for specific surface determinations.
2. Bephenium hydroxynaphthoate, official in the B.P.C., 1973 is standardized by air permeability method.
3. Activity of some drugs is related to the specific surface. Ex: Anthelmintic drugs in suspension dosage form must possess a surface area of not less than 7000 cm^2/g. As the specific surface of the material is reduced, the activity of the drug also falls.
4. Air permeability method, officially in U.S. pharmacopoeia used for determining the specific surface area of griseofulvin.
5. This method is also used for measuring the fineness of Portland cement.

Derived properties of powders:

True density: it is the density of the material itself. It is defined as:

True density, $\rho p = \frac{weight\ of\ powder}{true\ volume\ of\ powder}$

The density is dependent on the type of atoms in a molecule, arrangement of the atoms in a molecule and the arrangement of molecules in the sample. Apart from true density, powder is also characterized by granule density and bulk density.

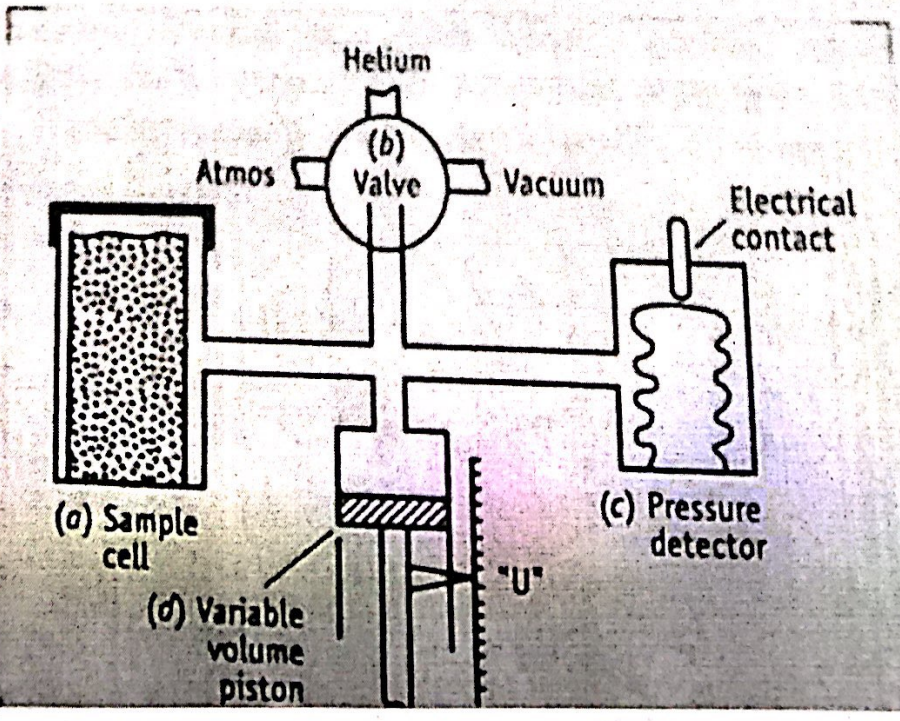
Volume occupied by voids and intraparticle pores are not included in true density. The most common methods used in the determination of the true density are gas (helium or nitrogen) displacement, liquid displacement and flotation in a liquid. Helium and nitrogen gases obey the ideal gas law at ambient temperatures and pressures. However, helium is preferred because of its smaller size. Both gases do not adsorb on the material.

Volume occupied by voids (inter-particle spaces) and intraparticle pores are not included in true density (Figure 6-15). The true densities of some pharmaceutically important powders are listed in Table 6-7.

The most common methods used in the determination of the true density are gas (helium or nitrogen) displacement, liquid displacement and flotation in a liquid. Helium and nitrogen gases obey the ideal gas law at ambient temperatures and pressures. However, helium is preferred because of its smaller size. Both gases do not adsorb on the material.

Porous solids—Helium displacement method : Helium penetrates the smallest pores and crevices. Therefore, this method gives a value closer to its true density. This is a valuable tool to estimate the true density, particularly for porous solids.

Method : The schematic representation of helium pycnometer is shown in Figure 6-16. It consists of a sample holder (A), which can be sealed after placing the sample. The valve (B) is connected to the sample holder. It has provisions for removing the air from the sample holder and introducing the helium gas. Helium gas is selected as it does not adsorb on the solid sample. A pressure detector (C) is included in order to maintain preset constant pressure. It has sealed bellows which maintains the electric contact at a particular pressure. A piston (D) is attached in order to read the corresponding pressure, which is also related to the volume of the powder.



Initially, the volume of empty pycnometer is determined. The air present in the sample holder is removed by applying vacuum. Then, helium gas is passed into the apparatus through the valve (B). The pressure is adjusted and set a particular value with the help of a movable piston (D). At this position, the reading on the scale denotes U_1. This represents the volume of empty cell.

In the next step, pycnometer is calibrated by placing a standard sample of known true volume (V_s) (stainless steel spheres) in the sample holder. The sample holder is sealed and air is removed. The same amount (as used in the first step) of the helium gas is introduced. Pressure is adjusted to preset value by moving the piston suitably. At this stage, the scale reading is denoted by U_2. The difference between U_1 and U_2 gives the volume occupied by the sphere.

The last step involves the determination of volume of the sample. The stainless steel sphere is replaced by the test sample powder. The air in the pycnometer is replaced by helium gas (same quantity as used in earlier steps). The pressure is adjusted with the help of piston. At this state, the piston reading is denoted by U_s. The difference between U_1 and U_s gives the volume occupied by the sample.

The operating equation for the instrument is:

$$V_t = \frac{V_s}{U_1 - U_2}[U_1 - U_s] \qquad ...(21)$$

where V_t = true volume of the sample, cm^3.

True volume and weight of the sample are substituted in equation (20) gives the true density.

Liquid displacement method : Liquids such as water and ethyl alcohol cannot occupy the pores and crevices. If the powder is nonporous, this method is used. Select a solvent in which the powder is insoluble and heavy. Normally, the values obtained are somewhat lower than the helium displacement method.

Method : Pycnometer or specific gravity bottle may be used.

Weight of pycnometer = w_1

Weight of pycnometer + sample (or glass beads) = w_2

Weight of sample = $w_3 = w_2 - w_1$

Weight of pycnometer with powder and filled with solvent = w_4

Weight of the liquid displaced by solids (related to volume of liquid displaced) = $w_4 - w_2$

$$\text{True density} = \frac{w2-w1}{w4-w2}$$

Compressed powders: The powder sample is compressed into a tablet using a punching machine with 1,00,000 lb/sqin. Now estimate the true density.

Weight of the tablet = w_1

Volume of the tablet = V

$$\text{True density} = \frac{w1}{V}$$

Granule density: Granule density is determined for the granules that are employed in the manufacture of tablet.

Granule density is defined as:

$$\text{Granule density, } \rho g \frac{Granule\ density}{Granule\ volume}$$

The volume of granules can be measured by mercury displacement method. Mercury is suitable because it fills the voids, but fails to penetrate the internal pores of the particles. The use of mercury is also based on its high contact angle of about 140^0 and its nonwetting characteristics.

Bulk density: It is defined as:

$$\text{Bulk density } (\rho_b) = \frac{mass\ of\ a\ powder\ (w)}{bulk\ volume\ (Vb)}$$

When particles are packed loosely, lots of gaps between particles are observed. Hence bulk volume increases making the powder light. Based on bulk volume, powders are classified as "light" and "heavy". Light powders have high volume.

Tapped volume: The powder is passed through a standard sieve no. 20. The weighed powder (100gm) is transferred into a 250ml measuring cylinder. The level of powder is made without compacting. The unsettled apparent volume is measured (V_0) to the nearest graduated unit. The cylinder is fixed on the bulk density apparatus and the timer knob is set for 100 tapping. The cylinder is tapped and volume readings are taken until little further volume change is observed.

$$\text{Tapped density } = \frac{mass\ of\ a\ powder\ (m)}{volume\ of\ the\ powder\ bed\ at\ zero\ tapping\ (V0)}$$

Applications:

1. Bulk density is used to check the uniformity of bulk chemicals.
2. The size of the capsule is mainly determined by bulk volume for a given dose of material. The higher the bulk volume, lower will be bulk density and bigger the size of the capsule.

$$\text{Capsule volume} = \frac{capsule\ fill\ weight\ of\ formulation}{tapped\ bulk\ density}$$

3. It helps in selecting the proper size of a container, packing material, mixing apparatus in the production of tablets and capsules. The capacity of a mixing bowl is usually expressed in cubic feet or liter. Normally, the volume of formulation and an excess of 10% of the volume is considered for the selection of container for the mixing process.

$$\text{Capacity of mixing bowl} = \frac{weight\ of\ batch}{bulk\ volume}$$

Porosity:

True volume = Volume of the powder itself.

Granule volume = Volume of the powder itself + volume of interparticle spaces.

Bulk volume = Volume of the powder itself + volume of interparticle spaces + volume of inter-particles spaces (voids)

if the powder is nonporous i.e. no internal pores or capillary spaces, the bulk volume consists of true volume plus the volume of spaces between the particles, i.e. void volume,

Void volume = V= bulk volume - true volume or Vb – Vp

The porosity or solids, ε, of the powder is defined as:

Porosity or voids $\varepsilon = \frac{void\ volume}{bulk\ volume}$

$$\varepsilon = \frac{bulk\ volume - true\ volume}{bulk\ volume} = \frac{Vb - Vp}{Vb}$$

Porosity is frequently expressed in per cent.

Percent, $\varepsilon = 1 - \frac{Vp}{Vb}$ X 100

The above equation can also be expressed in terms of density values.

Percent, $\varepsilon = \frac{\rho p - \rho b}{\rho b}$ X 100

Applications:

Certain powders contribute immensely to the porosity of the tablet. Porosity influences the rate of disintegration and dissolution. The higher the porosity, the faster the rate of dissolution. Based on porosity values, solids can be classified as porous and nonporous. Porosity is applied in the studies on adsorption and diffusion of drug materials.

FLOW PROPERTIES:

Flowability is the ability of a powder to flow through reliably. Flow properties influence mixing and de-mixing of powders. These also influence the design of formulation and selection of process equipment.

Angle of repose:

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

By definition

$$\tan\theta = \frac{h}{r}$$

$$\theta = tan - 1\ \frac{h}{r}$$

Where h = height of pile, cm

r = radius of the base of the pile, cm

θ = angle of repose.

The lower the angle of repose, the better the flow property. Rough and irregular surface of particles gives higher angle of repose.

Procedure: A glass funnel is held in place with a clamp on a ring support over a glass plate. The glass plate is placed on a micro-lab jack. Approximately 100 gm of powder is transferred into the funnel keeping the orifice of the funnel blocked by the thumb. As the thumb is removed, the lab-jack is adjusted to lower the plate and maintain about 6.4 mm gap between the bottom of the funnel stem and the top of the powder pile. When the powder is emptied from the funnel, the angle of the heap to the horizontal plane is measured with a protractor.

The height of the pile (h) and the radius of the base (r) is measured with the ruler. The angle of repose is this estimated. Cohesive powders yield better results if measurements are carried out using a funnel with a 30 mm stem opening.

Scale of flowability

Angle of repose	Flow property
25-30	Excellent
31-35	Good
36-40	Fair, aid is not needed
41-45	Passable, may hang up
46-55	Poor, must agitate or vibrate
56-65	Very poor
> 66	Very very poor

ANGULAR TESTS: Angular tests are applicable to relatively free flowing powders containing particles larger than 100 µm. such powders cannot be investigated satisfactory using shear cells and tensile strength apparatus.

- If granulation is tested for flow, then flow meter is the method of choice.
- If known forces are utilized during the flow, shear cell is a method of choice.

These are strictly empirical between the degree of compaction and powder flow. Based on experimental variables, one of the following can be used.

- Height of funnel is fixed, but the height of powder varies, as the pile is formed.
- Base diameter is fixed or diameter is fixed or diameter of powder cone may be allowed to change, as the pile is formed.

Angular properties of powders also depend on the details of the measurement. Angle of repose is not an intrinsic property of a powder and is primarily a function of surface roughness. Angle of repose provides qualitative information.

- Rough and irregular surface of particles give higher angle of repose.
- Cohesive particles tend to form higher heaps, which cannot spread out. Angle of repose of such powders will be higher or poor flow.

Drained angle: It is the angle observed, when powder flows from a conical surface onto a flat bottomed container, if the powder is discharged through the orifice in the base. The drained angle is affected by the degree of consolidation of the material in the hopper. Method – wise it is like angle of repose.

Poured angle: The poured angle of repose can be measured, when the powder is allowed to pour onto the flat surface. The angle is measured from the height of the heap. A protector is commonly used for measurement. In this case, the word conical surface was not mentioned. For the some powder, drained angle is larger than the poured angle. In case of poured angle, the particles slide and roll down from the powder surface. In case of drained angle, convergence occurs, i.e. particles get mixed up with the remaining pile and nesting in the container.

Dispersibility: Dispersibility of a powder is the ability of a material to flow or pour easily over a plane. Dispersibility, dustiness and flow ability are inter-related terms.

Method: Weigh approximately 10 gm of the sample. The material is dropped enmasse from a total weight on to a tarred watch glass through a hollow cylinder placed vertically 102 mm above the watch glass. The cylinder is secured to a support stand by 102 mm diameter support rings placed above and below the cylinder. The drop point is approximately 178 mm vertically above the top of the cylinder. The material landing within the watch glass is weighed. Any loss of powder during the fall is the result of dispersion. The percent Dispersibility is calculated using the relationship.

$$\text{Dispersibility (\%)} = \frac{weight\ of\ powder\ in\ watch\ glass}{initial\ weight\ of\ the\ sample}\ X\ 100$$

Carr's index: It is defined as:

$$\text{Consolidated index} = \frac{tapped\ density - fluff\ density}{tapped\ density}\ X\ 100$$

This property is known as compressibility. It is indirectly related to the relative flow rate, cohesiveness, particle size, shape and moisture content. It is simple, fast and popular method of predicting powder flow characteristics.

Fluff density is the ratio of mass of powder to the fluff volume. Fluff volume is the volume occupied by a certain mass, when gently poured into a measuring cylinder. This is known as aerated density.

Tapped density is the ratio of mass of powder to the tapped volume. Tapped volume is the volume occupied by the same mass of powder after a standard tapping of a measure.

Compressibility index can be a measure of the potential strength that a powder could build up in its arch in a hopper and the ease with which such an arch could be broken. It is a simple and fast method.

Method: using a suitable adhesive, the base of a 10 ml. tarred measuring cylinder is fixed to the standard rubber bung at the top of the 250 ml cylinder. A powder sample is transferred into the tarred 10 ml cylinder with the help of a funnel. The 250 ml measuring cylinder is placed on the tapping apparatus. The initial volume occupied by the powder is denoted as V_0.

The contents are tapped in the following order., 2,4,6,8,10,20,30 and 50 taps. After completing the tapping, the volume is denoted as V_2, V_4 …..V_{50}.

The powder is carefully collected from the cylinder and weighed (W).

$$\text{Fluff density } (\rho b, minimum) = \frac{W}{V0} g/cm3$$

$$\text{Tapped density } (\rho b, maximum) = \frac{W}{V50} g/cm3$$

Hausner ratio: It is defined as:

$$\text{Hausner ratio} = \frac{V_0}{V_f}$$

Where V_0 = volume of the powder bed at initial stage, ml

V_f = volume of the powder bed after tapping, ml

Hausner ratio is related to the morphological behavior. For example, flow properties increasing sphericity. The V_f means repeated taps or as needed, until the difference between the successive measurements is less than 2%.

Particle Number: The particle number is important in dose of drugs specially for potent drugs or drugs having low dose. Knowledge of particle number is important in preparation of tablets and capsules. The number of particles per unit weight, N, is expressed in terms of volume-number mean diameter, dvn. Assuming that the particles are spheres, the volume of a single particle is $\frac{\pi dvn^3}{6}$ and the mass (volume x density) is $\frac{\pi d^3 vn\rho}{6}$ gram per particle. The number of particles per gram may be obtained from following relationship.

$$\frac{(\pi d_{vn}{}^3)/6g}{\text{Particle}} = \frac{1g}{N}$$

So,

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