A Text Book of

PHYSICAL PHARMACEUTICS - II

⑤

As Per PCI Regulations

SECOND YEAR B. PHARM.

Semester IV

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Contents

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Unit ... 1

COLLOIDAL DISPERSIONS

◆ **LEARNING OBJECTIVES** ◆

After completing this unit, reader should be able to:

- Understand the distinction among colloidal solution, true solution and suspension.
- Identification of colloidal solution phases.
- Classification of colloidal solutions and fabrication techniques of colloids.
- Understand the colloidal solutions properties.

1.1 INTRODUCTION

It is vital that the pharmacist must understand the concept and technology of dispersed systems. Information of interfacial phenomena and understanding with the features of colloids and small particles are important to understand the behaviour of pharmaceutical dispersions. In the pharmaceutical sciences, there are three kinds of dispersed systems come across molecular, colloidal, and coarse dispersions. It is vital to distinguish that the only difference among molecular, colloidal, and coarse dispersions is the size of the dispersed phase and not its composition. Dispersions contain one internal phase that is dispersed in a dispersion medium. A colloid is a mixture in which one substance of microscopically dispersed insoluble particles is suspended through another substance. Occasionally, the discrete substance alone is called the colloid; the term colloidal suspension refers definitely to the overall mixture (although a narrower sense of the word suspension is distinguished from colloids by larger particle size). Disparate a solution, whose solute and solvent found only one phase, a colloid has a dispersed phase (the suspended particles) and a continuous phase (the medium of suspension).

To be suitable as a colloid, the combination essential be one that does not settle or would take a very long time to settle significantly. The dispersed-phase particles have a diameter among nearly 1 and 1000 nanometers. These particles are usually simply visible in an optical microscope, though at the smaller size range ($r < 250$ nm), an ultra-microscope or an electron microscope may be required. Homogeneous mixtures with a dispersed phase in this size range may be called colloidal aerosols, colloidal emulsions, colloidal foams, colloidal dispersions, or hydrosols. The dispersed-phase particles or droplets are affected largely by means of the surface chemistry existing within the colloid. Few colloids are translucent since of the Tyndall effect, which is the scattering of light by particles in the colloid. Other colloids may be opaque or have a slight color. Colloidal suspensions are the subject of interface and colloid science. This arena of study was presented by Scottish scientist Thomas Graham Phases in 1861.

1.2 CLASSIFICATION OF DISPERSED SYSTEMS OF COLLOIDS

Normally, dispersion is composed of two substances, one of which (dispersed phase) is spread in the form of subdivided particles through another substance (continuous phase or dispersion medium). Majorly, dispersed systems are categorized in to three types as follows:

1.2.1 Molecular Dispersions

The molecular dispersion is a true solution of a solute phase present within a solvent. Within molecular dispersion, solutes are in the form of individual molecules equivalently dispersed in the soivent (dispersion medium). The molecule in this phase have size less than 1 nm (4 × 10^{-8} inch). For instance, air is the molecular dispersion (a blend of Oxygen, Nitrogen and some other gases), electrolytes (aqueous solutions of salts). Basically, the particles within molecular dispersion are invisible in electron microscope. They can pass through semipermeable membranes and filter paper. However, particles do not settle down on standing, they undergo rapid diffusion. For example, ordinary ions, glucose.

1.2.2 Colloidal Dispersion

Basically, colloids are the micro-heterogeneous dispersed systems, with the size of the dispersed phase particles within the range of 1-1000 nm (4 × 10^{-8} – 4 × 10^{-5} inch). The gravity, centrifugal or other forces cannot separate the colloids phases. The separation of dispersed phase of colloids from the dispersion medium can be carried out by micro-filtration. The colloidal particles not determined through ordinary microscope, can be identified using electron microscope. These particles can pass through filter paper but not pass through semipermeable membrane. Colloidal particles diffuse very slowly. Some common examples of colloids include fog (aerosol of water micro-droplets in air), milk (emulsion of fat and few other substances in water), opal (colloidal silica), Alumina aerogel monolith, Silica aerogel monolith.

1.2.3 Coarse Dispersions

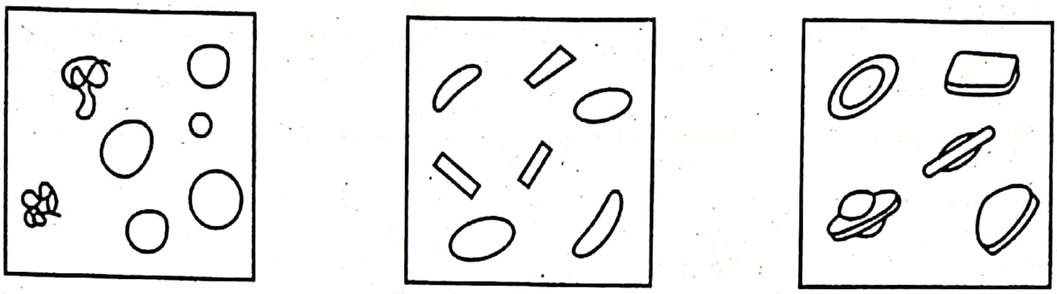
Coarse dispersions (suspensions) are heterogeneous dispersed systems, having dispersed phase particles are larger than 1000 nm (4 × 10^{-5}). These are characterized by comparatively fast sedimentation rate of the dispersed phase produced by means of gravity or other forces. The separation of dispersed phase of coarse dispersions can be simply separated from the constant phase by filtration. The particles within coarse dispersion are visible under ordinary microscope. However, they cannot pass via filter paper or semipermeable membrane.

Particles within the coarse dispersion settle down under gravity. Some common examples of coarse dispersion include suspensions, emulsions and red blood cells.

1.3 GENERAL CHARACTERISTICS OF DISPERSED SYSTEMS

- **Particle shape**

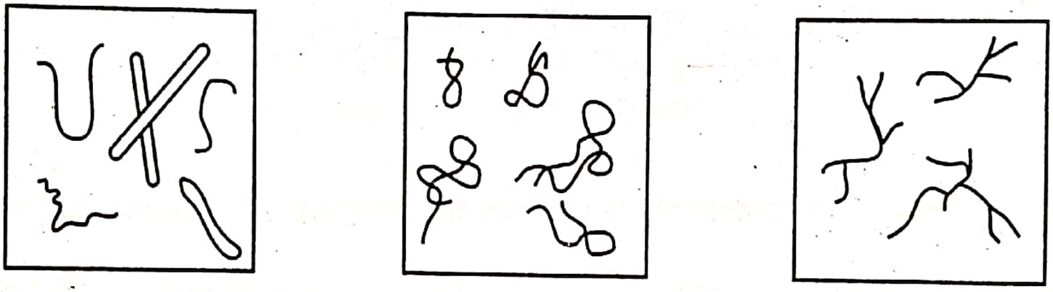
The fabrication technique has significant role in shapes of dispersion particles and affinity of these particles towards dispersion medium. The colour of the dispersion also influenced by the particle shape. It is supposed that spherical gold particles are shown by red colour, while disc like particles of gold shows blue color. Shapes of few colloidal particles are given in Fig. 1.1.



(a) Spheres and globules- surfactants, poliomyelities

(b) Short rods and prolate ellipsoids-serum albumin, microcrystalline cellulose

(c) oblate ellipsoids and flakes-bentonite, kaolin



(d) Long rods and threads- attapulgite, tobacco mosaic virus

(e) Loosely coiled threads

(f) Branched threads celluloses, asbestos

Fig. 1.1: Shapes of Few Colloidal Particles

- **Surface area**

Normally, the colloidal particles have size ranging few micronmeters, thus these particles have huge surface area as compared to coarser particles. Owing to large surface area these particles become effective catalysts. Moreover, increased surface area also improves the solubility of drug particles.

- **Particle size**

The colour of dispersion is influenced by the particle size present within dispersion medium. The wavelength of light absorbed by a particle is roughly associated with its radius. If the particle size is larger, the wavelength of light transmitted is shorter. For instance, colloidal gold (650-750 nm) has a red colour, while intermediate size is in violet colour. The coarse dispersion of gold appears blue (450-490 nm).

- **Surface charge**

Colloidal particles have surface charge on it. The charge on these particles and its environment in a dispersion medium is explained in Fig. 1.2. Few examples of charged particles are Acacia, Tragacanth and Sulphur having negative surface charge and Gelatin, Bismuth and Aluminium having positive charge. The interior of these particles is electronically neutral, however the surface gets charged. Owing to small size, a considerable amount of their atoms, ions and molecules are located on the interface or surface. Generally, the charge on surface of a particle is originated due to,

(i) Surface adsorbs the ions present within the medium. However, in pure water hydronium ions (H_3O^+) or hydroxyl ion (OH^-) may get adsorbed to the surfaces of particles.

(ii) The ionization of functional groups presents on the surface.

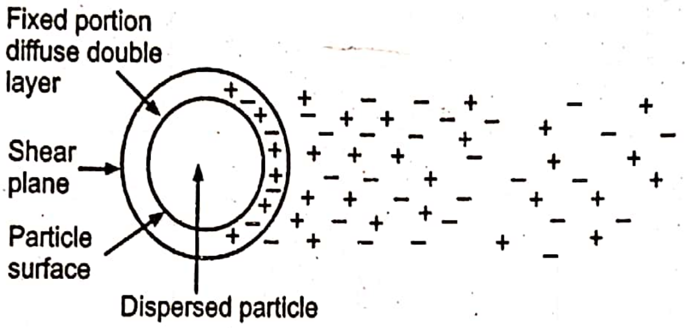


Fig. 1.2: Appearance of Environment and Charge on the Colloidal Surface

1.4 SIZE AND SHAPES OF COLLOIDAL PARTICLES

Particles coming under the colloidal size have comparatively large surface area when linked with the surface area of an equal volume of larger particles. Specific surface is the surface area per unit weight or volume of material. The size and surface area of colloidal particle have significant effect on colloidal properties. The colour of colloidal dispersion can be change with the size of the particles. For instance, on increasing the size of the particles red gold sol changes in to blue colour when the particles increase in size. Platinum is active as catalyst only when occur in colloidal form owing to large surface area which adsorb reactant on their surface. The shape of colloidal particles in dispersion is significant. The more extended the particle the greater its specific surface, the better the attractive force among the particles of the dispersed phase and the dispersion medium. The shape of colloidal particles has direct effect on the flow, sedimentation and osmotic pressure of the colloidal system. Moreover, colloidal particle shape can also effect the pharmacologic action.

1.5 CLASSIFICATION OF COLLOIDS

Colloids are generally classified according to:

1. **The original states of their component parts**

Table 1.1: Types of colloidal dispersions

Dispersion Medium	Dispersion Phase	Common name	Examples
Solid	Solid	Solid Sol	Coloured glasses, Coloured gemstones
Liquid	Solid	Sol	Muddy water, gold sol, starch sol, sulphide sol
Gas	Solid	Aerosol	Dust, Smoke
Solid	Liquid	Gel	Cheese
Liquid	Liquid	Emulsion	Milk
Gas	Liquid	Liquid aerosol	Cloud, Mist
Solid	Gas	Solid foam	Pumice stone, Foam rubber
Liquid	Gas	Foam	Whipped cream

2. **Colloidal solutions can be classified in different ways:**
   (a) Based upon molecular size.
   (b) Based upon interaction among the phases.

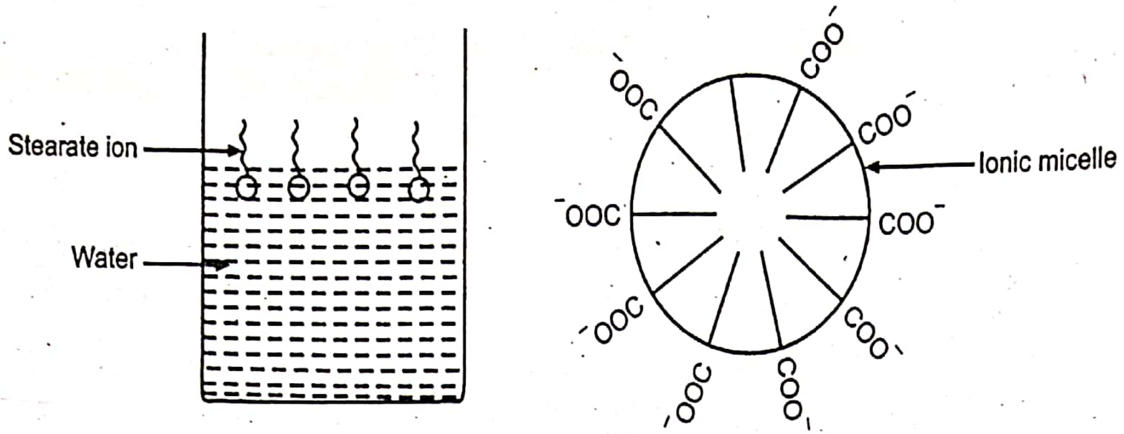
(a) Based upon molecular size

Based upon the molecular size the colloids are further categorized in to:

(i) Macromolecular colloids: In this category of colloids the size of the particles of the dispersed phase are sufficiently large to descent in the colloidal dimension as deliberated earlier (i.e. – 100 nm). Cellulose, starch, proteins etc. are few examples of naturally occurring macromolecular colloids.

(ii) Multi molecular colloids: Here individually the atoms are not of colloidal size but they combined to join together developing colloidal size molecule. For instance, sulphur sol comprises aggregates of S8 molecules which occur in colloidal sizes.

(iii) Associated colloids: Associated colloids are substances which work as usual electrolyte at low concentration but become associated at higher concentration to form micelle and act as colloidal solution. For example, Soap which is sodium salt of long chain fatty acid R COONa. When placed in water, soap forms $RCOO^-$ and Na^+. These $RCOO^-$ ions associate themselves around dirt particles as shown below forming a micelle. Fig. 1.3



Arrangement of stearate ions on the surface of water at low concentrations of soap

(a)

Arrangement of stearate ions inside the bulk of water (ionic micelle) at critical micelle concentrations of soap

(b)

Fig. 1.3: Arrangement of Ions on Inside and on Surface of Soap

(b) Based upon interaction among phases

Based upon the interaction among dispersed phase as well as the dispersion medium colloidal solutions have been categorized into two classes.

(a) **Lyophilic colloids:** (lyo means solvent and philic means loving) these are also called as solvent loving colloids as the dispersed particles interact to an appreciable extent with the dispersion medium. These solutions are those in which the dispersed phases have a great attraction for the dispersion medium. Substances such as gelatin, gum, starch etc. when mixed with appropriate dispersion medium, openly pass into colloidal state and produce colloidal solution. Consequently, this kind of solutions is simply produced by bringing dispersed phase and dispersion medium in direct contact with each other. Though, these colloidal solutions are reversible in nature. The separation of dispersed phase and dispersion medium can be done easily once lyophilic colloidal solution has been formed. Separated phases can be mixed again by remixing the two phases. The viscosity of dispersion medium increases with addition of dispersed phase with solution changing to gel. The stability of these sols is higher and doesn't need addition of stabilizers during the preparation. If water is utilized as a dispersion medium, then it is called as hydrophilic colloid.

(b) **Lyophobic Colloids:** Generally, lyophobic colloids are solvent hating. Lyophobic colloidal solutions are those in which the dispersed phase has no affinity for the dispersion medium. Metals such as gold, silver and their hydroxides or sulphides etc., when basically mixed with dispersion medium do not pass directly into colloidal state. Such sols have to be fabricated through special techniques. Generally, such sols can be freely precipitated and once precipitated they have little affinity to go back into the colloidal state. Therefore, these sols are irreversible in nature. Moreover, they are unstable and need a stabilizing agent to stay in the colloidal form. If water is utilized as a dispersion medium it is named as hydrophobic solutions.

(c) Association Colloids or Amphiphilic Colloids: These are molecules or ions having both polar and non-polar groups. At low concentrations, the amphiphiles exist separately as monomers and having size below colloidal range. As the concentration is increased, the amphiphiles (surfactants) aggregate to form micelles. The minimum concentration at which micelles are formed is termed as Critical Micelle concentration of the surfactant. These are thermodynamically stable colloids and easy to prepare and form spontaneously once the CMC is exceeded. In a polar solvent such as water, polar end of amphiphile in the micelle faces the solvent, whereas in non-polar end faces the solvent. The shape of micelle may be spherical or laminar.

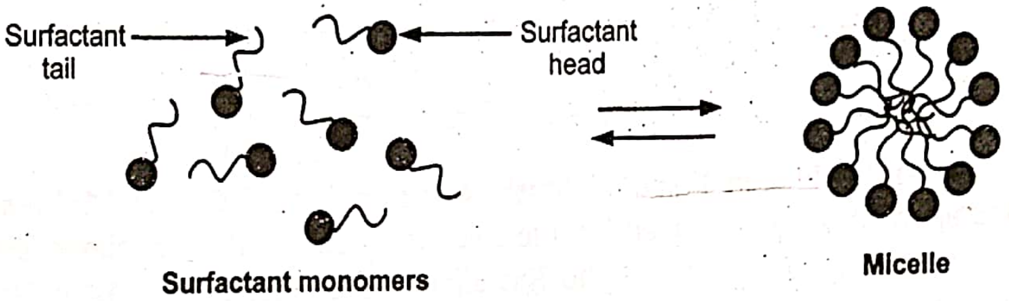
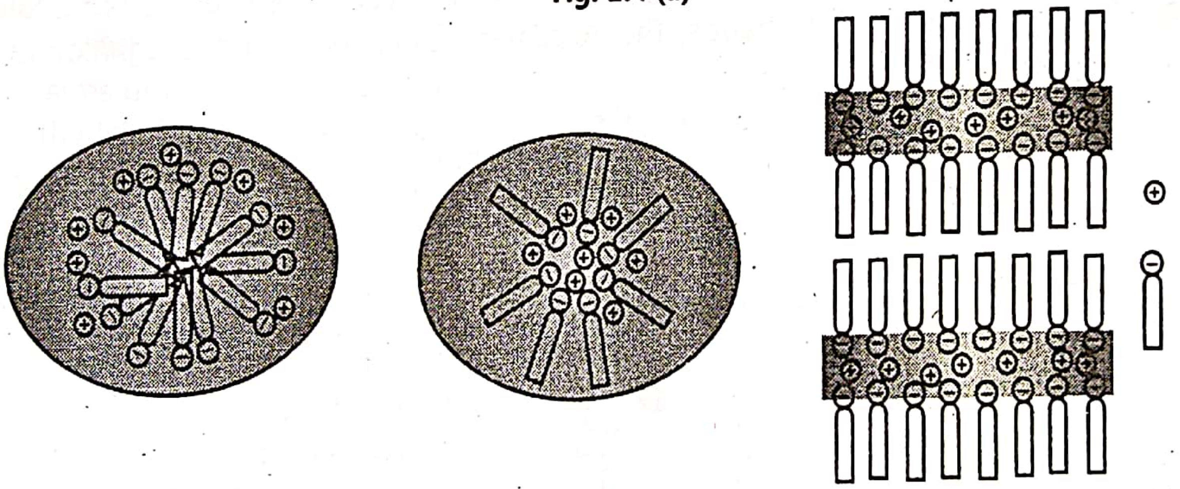


Fig. 1.4 (a)



(a) Spherical micelle in aqueous media

(b) Reversed micelle in non-aqueous media

(c) Laminar micelle, formed at higher amphiphile concentration, in aqueous media

Fig. 1.4 (b)

Micelle form when the polar head and the non-polar tail arrange in a unique way. Micelle form only when the concentration of surfactant is greater than the CMC. The surfactant is any surface active material that can part the surface upon entering. Micelles assume spherical shape near CMC and laminar micelle at higher concentrations.

1.6 COMPARATIVE ACCOUNT OF THEIR GENERAL PROPERTIES OF COLLOIDS

1.6.1 Optical Properties

- **Tyndall effect**

In 1869, scientist Tyndall noticed that if a heavy beam of light is delivered over a colloidal solution then the path of light is illuminated. For instance, when an intense joining beam of light is passed over a colloidal solution kept in dark, the path of the beam gets illuminated with a bluish light. This phenomenon is named as Tyndall Effect and the illuminated path is known as Tyndall cone. Generally, it happens owing to scattering of light through colloidal particles. The similar effect is observed when a light beam come into a dark area through a slit and come to be visible. This occurs owing to the scattering of light through dust particles present in the air.

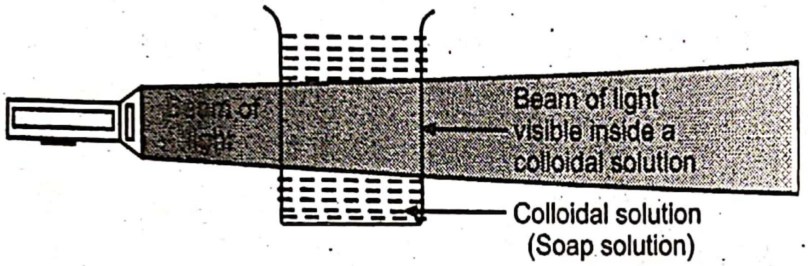


Fig. 1.5: Illumination of Light when Passing through Colloidal Solution

Tyndall effect is not displayed by true solutions. Because the particles existing in a true solution are too minor to scatter light. This effect can be cast-off to differentiate a colloidal solution from a true solution. Moreover, this phenomenon has also been utilized to create an instrument called as ultra-microscope. The instrument is helpful for the recognition of the colloidal particles sizes.

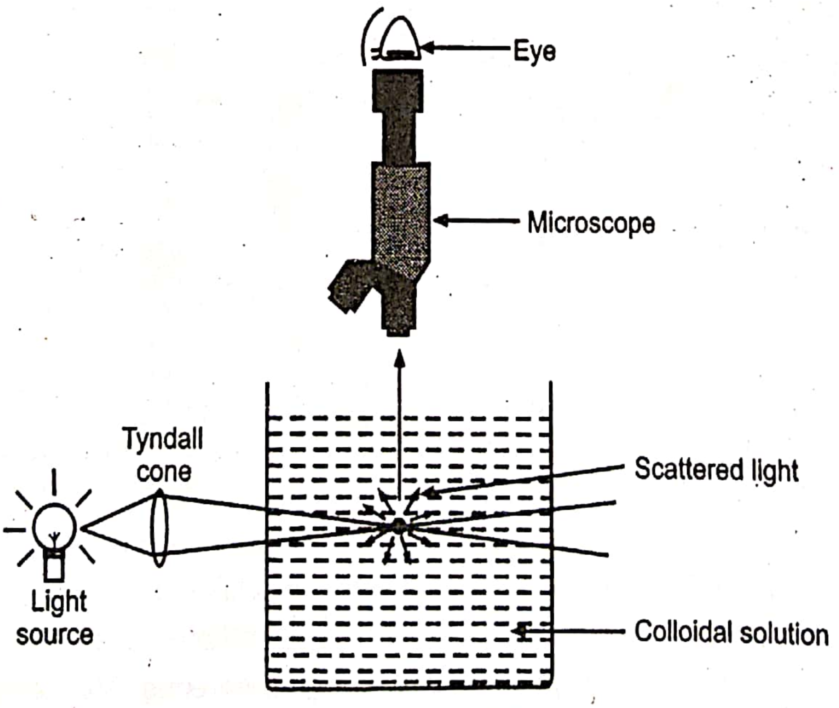


Fig. 1.6: Tyndall Effect

- **Electron microscope**

The usage of ultra-microscope has dropped in yester years as it is unable to determine lyophilic colloids. Thus, electron microscope is proficient of producing images of definite particles shape, size and colloidal particles structure. It has excessive resolving capacity, as its radiation source is a beam of high energy electrons, whereas that of optical microscope is visible light.

Nephelometer: It's used when amount of dispersed particles is low and the intensity of scattered light is measured at right angles to the direction of incident light.

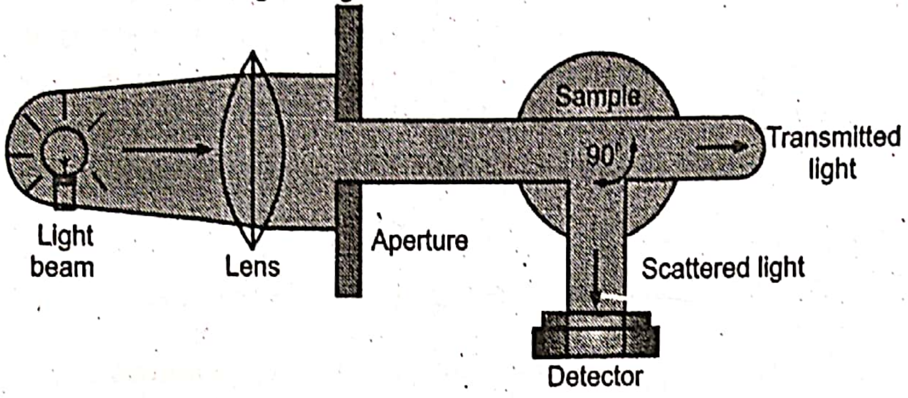


Fig. 1.7

- **Light Scattering**

The light scattering depends on Tyndall effect. Normally, it is utilized to give data regarding particle size and shape and for calculation of molecular weight of colloids. Which are useful to study proteins, association colloids and lyophobic solutions. Scattering termed in terms of turbidity (T). Turbidity is the fractional reduction in intensity owing to scattering as the incident light passes over 1 cm of solution. Turbidity is directly proportional to the molecular weight of lyophilic colloid.

$$\frac{Hc}{T} = \frac{1}{M} + 2Bc$$

Whereas, T: turbidity, C: Conc. of solute in gm/cc of solution,
M: molecular weight,
B: interaction constant,
H: constant for a particular system.

1.6.2 Kinetic Properties

- **Brownian movement**

Brownian movement is also named as Brownian motion and is called after its inventor Robert Brown (a Botanist). Normally, Brownian movement is the zig-zag movement of colloidal particles in continuous random manner (Fig. 1.8). Brownian motion rises since the influence of the molecules present in the dispersion medium on the particles of dispersed phase. The forces are uneven in diverse directions. Therefore, it triggers the particles to travel in a zig-zag manner. The zig-zag motion of colloidal particles is continuous and random. Brownian movement is normally more rapid for smaller particles. It declines with rise in the viscosity of the medium.

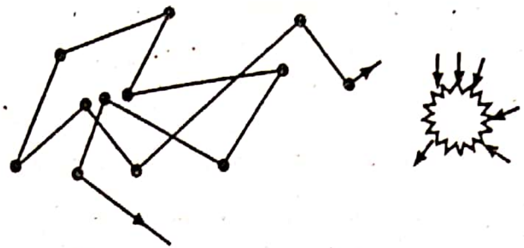


Fig. 1.8: Brownian Movement

- **Diffusion**

Diffusion generally is a movement of particles from an area of higher concentration to the lower concentration. Naturally particles diffuse from a region of higher concentration to one of lower concentration till the concentration of the system becomes uniform completely. Generally, diffusion is an outcome of Brownian motion. Fick's first law utilized to define the diffusion, i.e. The quantity of Dq of substance diffusing in time dt through a plane of area (A) is directly proportional to the change of concentration dc with distance travelled.

$$dq = -DA\left(\frac{dc}{dx}\right)dt$$

Whereas, D-diffusion coefficient, the quantity of the material diffused per unit time through a unit area when $\frac{dc}{dx}$ (conc. gradient) is unity. The measured diffusion coefficient can be employed to govern the molecular weight or radius of particles.

- **Osmotic pressure**

Normally, Van't hoff equation is used to determine the osmotic pressure,

$$\pi = cRT$$

Moreover, it can be used to control the molecular weight of colloid in dilute solution. By replacing c by $\frac{C}{M}$ (where, $C = \frac{\text{The grams of solute}}{\text{Liter of solution}}$, M = molecular weight).

$$\frac{\pi}{C} = \frac{RT}{M}$$

π = Osmotic pressure
R = Molar gas constant

Sedimentation:

Sedimentation is normally settling down of particles below the effect of gravity at a very slow rate. The velocity of sedimentation is set by Stokes 'Law:

$$v = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

Whereas,

V = Rate of sedimentation,
D = Diameter of particles,
ρ = Density of internal phase and external phase,
g = Gravitational constant,
η = Viscosity of medium.

Viscosity: Viscosity of colloids depends upon the shape of colloidal material. Spherical colloidal material yields dispersions of relatively low viscosity. Linear colloids are more viscous. Viscosity increase is due to salvation effect. When degree of salvation is more, the dispersion becomes more viscous. Higher the molecular weight of material, greater will be the viscosity. Therefore, by measuring the viscosity, molecular weight of polymers can be determined.

The Einstein's equation provides a quantitative expression for flow of disperse systems consisting of spherical particles.

Thus, $\eta = \eta_o (1 + 2.5\,\phi)$

Where, η_o = Viscosity of dispersion medium,

η = Intrinsic viscosity of dispersion and

ϕ = Volume fraction of particles.

1.6.3 Electrical Properties

The colloidal solutions exhibit electrical properties. The particles within colloidal solution are electrically charged and transmit the charge similar charge, either positive or negative. The dispersion medium has an equal and opposite charge. The colloidal particles so resist each other and do not gathered together to settle down. For instance, gold sol, arsenious sulphide sol, silver sol, etc. comprise negatively charged colloidal particles while ferric hydroxide, aluminium hydroxide etc. contain positively charged colloidal particles. Source of charge on colloidal particles is owing to:

(a) Carrying a charge by micelles on them.

(b) Better adsorption of cations or anions by colloidal particles.

(c) Through the formation of colloids particularly by Bredig arc technique, colloidal particles capture electrons and get charged. The presence of charge on a colloidal particle is revealed by a method called electrophoresis.

Electric Double Layer:

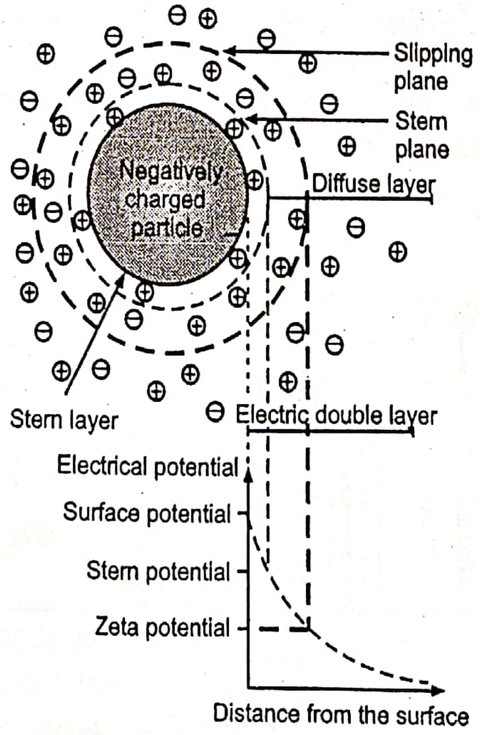


Fig. 1.9

Particles dispersed in liquid may become charged as a result, dispersed solid particles usually are surrounded by a double layer of electric charge made of ions.The electric double layer consists of layer of ions bonded firmly to the surface is called stern layer, surrounded by oppositely charged ions that form a loose diffuse layer in the adjacent liquid phase. The surface separating the two layers is called shear plane. The region outside the double layer with equal anions and cations is called electro-neutral region.

Nernst and Zeta Potential:

The electro-thermodynamic (Nernst) potential (E) is the difference in potential between the actual surface and the electro-neutral region of the solution.

The electro-kinetic potential (Zeta) is the difference between the surface of the stern layer and the electro-neutral region of the solution. The zeta potential is measured to monitor and predict the stability of dispersion systems.

- **Electrophoresis**

It is a method which comprises the movement of colloidal particles either to cathode or anode under the impact of electrical field. The device utilized is as revealed in Fig. 1.10.

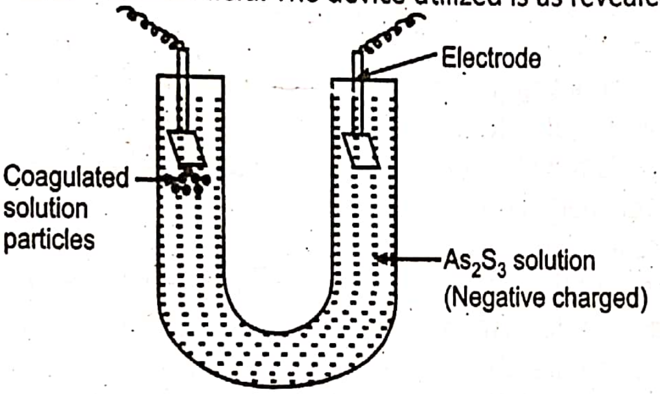


Fig. 1.10: A Typical Electrophoresis Set

- **Electrosmosis**

Electrosmosis is the movement of dispersion medium below the impact of an electric field in the condition when the movement of colloidal particles is prohibited with the assistance of an appropriate membrane. Throughout electrosmosis, colloidal particles are checked and it is the dispersion medium that transfers to the oppositely charged electrode. (Fig. 1.11).

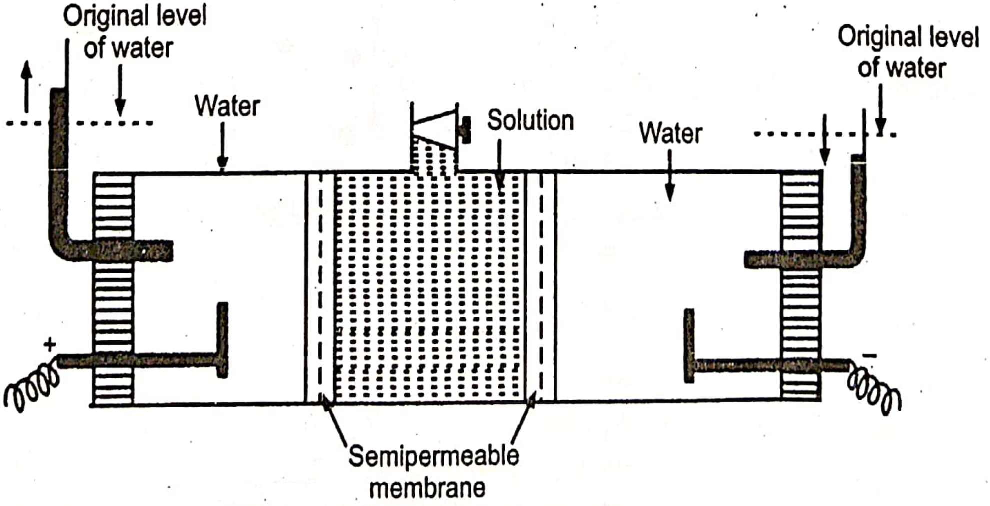


Fig. 1.11: Electrosmosis

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

Streaming Potential is the technique is used to measure the zeta potential of relatively coarse solids which would sediment rapidly in an electrophoresis cell. The liquid is forced through a plug of the powdered solid at a constant rate and the potential difference across this plug is measured.

Donnan Membrane Effect: The presence of charged molecules on one side of a semi-permeable membrane affects the diffusion of small ions such as drug ions through the membrane. This effect is due to the electrical gradient across the membrane and as a consequence, the charged drug ions of same charge as the macromolecules are driven to the opposite side of the membrane altering the concentration of the drug ions. This is termed as Donnan membrane equilibrium. It is used to enhance the absorption of drugs and retard drug absorption.

1.7 EFFECT OF ELECTROLYTES

Precipitation or coagulation is the condition in which settling of dispersed phase and flocculation (aggregation) is noticed. The electrolytes have significant effect on this instability of the colloidal dispersion.

(i) **Addition of excess electrolytes:** On addition of excess of electrolytes, particles precipitate after a specific concentration. Generally, it takes places owing to accumulation of oppositely charged particles.

Hofmeister or Lyotropic series: It states that the precipitating power of an ion is directly related to the ability of that ion to separate water molecule from the colloidal particles.

Coagulating power of anions or cations on hydrophilic colloids arranged by hofmeister series.

E.g., cations : $Mg^{2+} > Ca^{2+} > Ba^{2+} > Na^{+} > K^{+}$

E.g., Anions: citrates > tartarates > sulfates >acetates > chlorides > nitrates > bromides.

(ii) **Removal of electrolytes:** If the electrolytes are present in the minimum quantity, the repulsion among the particle declines and the potential of electrical double layer drops below critical value. The repulsions among the approaching particles are declined to such extent that those colliding with certain viscosity. Therefore, coagulation occurs.

(iii) **Electrolytes of opposite charge:** For maintaining the electrostatic repulsions, particle needs charge. The mixing of opposite charge substance prompts the coagulation of particles. Schulze-Hardy rule is applied within this phenomenon, which states that the precipitating power of an ion on a dispersed phase of opposite charge surges with increase in the valence or charge of the ion.

The precipitation power of an electrolyte is expressed as flocculation value. Higher the flocculation value, higher the precipitation power. Hydrophobic colloids require less amount of electrolyte for precipitation, whereas the hydrophilic colloids need a large amount of electrolytes as the hydration layer around the particles is removed.

Cations: $Al^{3+} > Ba^{2+} > Na^{+}$

Anions: $[Fe(CN)_6]^{3-} > SO_4^{2-} > Cl^{-}$

(iv) Addition of colloids having opposite charge: On addition of a hydrophilic or a hydrophobic colloid, with an opposite charge with a hydrophobic colloid, coagulation of colloidal particles is detected.

1.8 COACERVATION

Coacervation is the method of combining negatively and positively charged hydrophilic colloids, and therefore the particles discrete from the dispersion to form a layer abundant in the colloidal aggregates i.e. coacervate. The phenomenon which involves separation of macromolecular solutions into two liquid layers is called as coacervation. To cite an example, take the mixing of acacia and gelatin. Gelatin at a pH below 4.7 is positively charged; acacia have a negative charge which is comparatively unaffected through pH in the acid range. Once solutions of these colloids are mixed in a definite amount, coacervation occurs. The upper layer viscosity, normally poor in colloid, is distinctly declined under that of coacervate, and normally it is considered as a physical incompatibility. Coacervation not required the contact of charged particles; the coacervation of gelatin may also be brought about by adding of sodium sulphate, a macromolecular substance like starch, alcohol.

1.9 PEPTIZATION

It is the method accountable for the development of stable dispersion of colloidal particles in dispersion medium. Generally, it is the method of changing a precipitate in to colloidal sol via shaking with dispersion medium in the existence of slight quantity of electrolyte. The electrolytes utilized in this method are known as peptizing agents. Some freshly precipitated ionic solids are dispersed into colloidal solution in water by the addition of small amounts of electrolytes, principally those comprising a common ion. The precipitate adsorbs the common ions and electrically charged particles then split from the precipitate as colloidal particles. Normally, Peptization is the reverse of coagulation of a sol. Preparation of sols through peptization is described by following examples, Ferric hydroxide, Fe(OH), produces a sol through adding ferric chloride (Fe' existence as a common ion), Silver Chloride, Ag-Cl, can be changed into a sol by addition of hydrochloric acid (Cl remains common ion).

1.10 PROTECTIVE ACTION

The addition of some quantity of the hydrophilic or hydrophobic colloid of opposite charge tends to sensitize or even coagulate particles. On addition of large amount of hydrophilic colloid (hydrophile) which carries opposite to hydrophobic colloids, these get adsorbed on hydrophobic particles and form protective layer around it. This adsorption layer inhibits the precipitating reaching the sol particle. Thus, coagulation is prohibited now the complete colloid may act like a hydrophilic colloid, which is thermodynamically stable. The colloid which supports to stabilize other colloid is called protective colloid.

The concept of protection is defined as a method through which the solution particles are prevented from coagulation prompted by an electrolyte owing to prior mixing of some lyophilic sol. For instance, hydrophobic sol for injection, like colloidal gold (198 Au) injection must be sterically stabilized, in this case by gelatin the defensive action of it is expressed in terms of gold number.

The gold number is the minimum weight in mg of protective colloid (dry weight of dispersed phase) essential to stop a colour modification from red to violet in 10 ml of gold sol on addition of 1 ml of 10 % Nacl solution. Higher the gold number, lower the protective action and vice-versa. Gold numbers of some protective colloids are given below,

Table 1.2: Protective colloids with their gold numbers

Protective colloid	Gold number
Gelatin	0.0005-0.01
Albumin	0.1
Acacia	0.1-0.2
Sodium oleate	1-5
Tragacanth	2

Coacervation is the method of combining negatively and positively charged hydrophilic colloids.

DLVO Theory: (Derjaguin, Landau,Verway and Overbeek Theory)

According to this theory, the distance between two dispersed particle influences particle-particle interactions. In a colloidal dispersion, the Brownian motion results in frequent collisions between particles. Interactions like attractions and repulsions are responsible for stability of colloids. When attractive forces are dominant, particles adhere after collision and aggregate. When repulsive forces are dominant, particles rebound and remain dispersed. It is used to determine the amount of electrolyte required to precipitate or stabilize a colloid.

The interactions between particles are described as follows:

(a) Van Der Waals attraction forces: Depend on chemical nature and size of the particle. These are London type forces and potential energy of attraction is represented by VA.

(b) Electrostatic repulsive forces: Depend on density, surface charge and thickness of double layer. Indicates magnitude of zeta potential, represented by V_R.

(c) Net energy of interaction (V_T).

Conclusions drawn from energy curves:

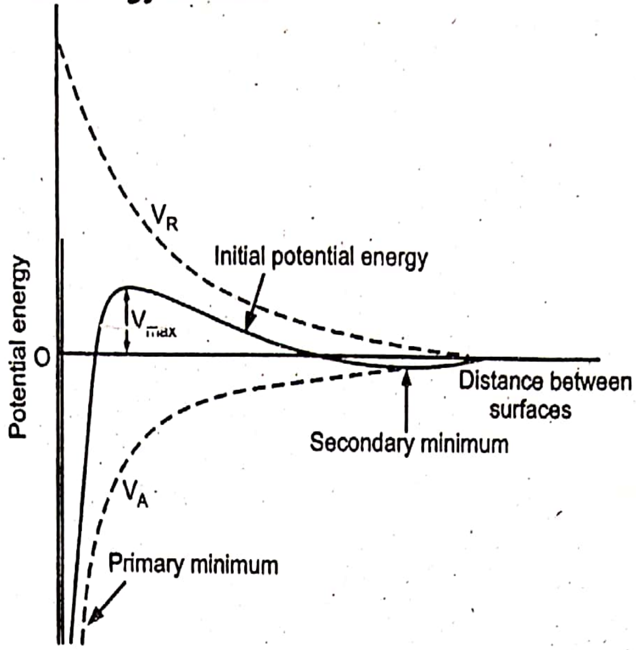


Fig. 1.12

(i) Primary minimum (precipitation) when particles are in close proximity, atomic orbital overlap and penetrate each other. Indicated by a rise in potential energy and net result is stronger attraction leading to precipitation.

(ii) Net energy peak (stability): At intermediate distance appreciable repulsive forces operate. At this peak, minimum potential is designated by V_m. The potential barrier makes particles to move in Brownian motion, which imparts stability to the colloidal dispersion.

(iii) Secondary minimum (aggregation): This is observed when the particles are separated by long distances and have attraction forces and form aggregates. The presence of secondary minimum is taken advantageously in controlled flocculation of a coarse dispersion.

The coagulation of colloidal particles may be accelerated by two ways i.e., by reducing the height of potential barrier and by increasing the kinetic energy of particles.

Applications of Colloids:

- **Stability:** Coating of colloidal dispersion of gelatin on solid dosage and granules protects the medicaments from adverse condition of the atmosphere. Dispersion of surfactants improves stability of liquid dosage forms.
- **Diagnostic Agents:** Gold solution is used to detect syphilis in patients.
- **Toxicity:** Colloidal iodine less toxic than their ionic salts. Colloidal dispersion Amphotericin B in children reduces renal toxicity and colloidal iron is less astringent.
- **Absorption:** Due to larger surface area colloidal dispersions shows better absorption. Colloidal sulfur shows faster absorption than coarse dispersion. Colloidal aluminium hydroxide better neutralization of stomach acid.
- **Targeted drug delivery:** Liposomes are of colloidal range are preferentially taken-up by liver and spleen. Micro-emulsions are used for targeting and controlled release of different pharmaceutical agents.

- **Therapeutic Effect:** Colloidal dispersions show better therapeutic effect. Colloidal silver used germicidal, colloidal copper as anticancer agent and colloidal mercury as anti-syphilis agent.
- **Parenteral:** Dextran injection a colloidal dispersion is used as plasma substitute. Intramuscular injection of Colloidal gold, calcium, and manganese used in treatment of tuberculosis and rickets.

EXERCISE

Multiple Choice Questions:

1. A ...... is a mixture in which one substance of microscopically dispersed insoluble particles is suspended through another substance.
   (a) Suspension (b) Colloid
   (c) Emulsion (d) None of the above
2. Few colloids are translucent because of the ......
   (a) Tyndall effect (b) Splitting effect
   (c) Scattering (d) None of the above
3. The comparatively fast sedimentation rate of the dispersed phase produced by means of gravity or other forces this is characteristic of ......
   (a) Colloidal dispersion (b) Coarse dispersion
   (c) Both of the above (d) None of the above
4. The molecule in the molecular dispersion phase have size ......
   (a) Less than 10 nm (b) More than 1 nm
   (c) Less than 1 nm (d) More than 10 nm
5. The ...... colloids have strong attraction towards solvents.
   (a) Lyophilic (b) Lyophobic
   (c) Associated (d) None of the above
6. ...... is the method accountable for the development of stable dispersion of colloidal particles in dispersion medium.
   (a) Coacervation (b) Peptization
   (c) Flocculation (d) Coagulation
7. The phenomenon which involves separation of macromolecular solutions into two liquid layers is called as ......
   (a) Liquid separation (b) Coagulation
   (c) Flocculation (d) Coacervation
8. ...... is directly proportional to the molecular weight of lyophilic colloid.
   (a) Solubility (b) Turbidity
   (c) Density (d) None of the above
9. ...... is the movement of dispersion medium below the impact of an electric field in the condition when the movement of colloidal particles is prohibited with the help of an appropriate membrane.
   (a) Electrosmosis (b) Osmosis
   (c) Photosmosis (d) None of the above
10. ...... is the method of combining negatively and positively charged hydrophilic colloids.
    (a) Coacervation (b) Peptization
    (c) Flocculation (d) Coagulation

Keys

1. (b)	2. (a)	3. (b)	4. (c)	5. (a)
6. (b)	7. (d)	8. (b)	9. (a)	10. (a)

Short Questions Answer:

1. **Enlist names of colloids based upon molecular size.**

Ans. (i) Macromolecular colloids, (ii) Multimolecular colloids, (iii) Associated colloids.

2. **What Lyophilic colloids?**

Ans. The lyophilic colloids have strong attraction towards solvents. These solutions are those in which the dispersed phase have a great attraction for the dispersion medium. Substances such as gelatin, gum, starch etc. when mixed with appropriate dispersion medium, openly pass into colloidal state and procedure colloidal solution. Consequently, this kind of solutions are simply produce by bringing dispersed phase and dispersion medium in direct contact with each other.

3. **What is Coacervation?**

Ans. Coacervation is the method of combining negatively and positively charged hydrophilic colloids, and therefore the particles discrete from the dispersion to form a layer abundant in the colloidal aggregates i.e. coacervate. The phenomenon which involves separation of macromolecular solutions into two liquid layers is called as coacervation.

4. **What do you mean by Peptization?**

Ans. It is the method accountable for the development of stable dispersion of colloidal particles in dispersion medium. Generally, it is the method of changing a precipitate in to colloidal sol via shaking with dispersion medium in the existence of slight quantity of electrolyte. The electrolytes utilized in this method are known as peptizing agents. Some freshly precipitated ionic solids are dispersed into colloidal solution in water by the addition of small amounts of electrolytes, principally those comprising a common ion.

5. **Explain in short about colloidal dispersion.**

Ans. Colloids are the micro-heterogeneous dispersed systems, with the size of the dispersed phase particles within the range of 1-1000 nm ($4 \times 10^{-8} - 4 \times 10^{-5}$ inch). The gravity, centrifugal or other forces cannot separate the colloids phases. The separation of dispersed phase of colloids from the dispersion medium can be carried out by micro-filtration.

Long Question Answer:

1. **Discuss in detail classification of dispersed systems?**

Ans. Refer Point No. 1.2.

2. **Enlist and explain general characteristics of dispersed systems.**

Ans. Refer Point No. 1.3.

3. **Enlist and explain classification of colloids.**

Ans. Refer Point No. 1.6.

4. **Explain optical properties of colloids.**

Ans. Refer Point No. 1.6.1.

5. **Explain in detail protective action of colloids.**

Ans. Refer Point No. 1.10.

***

Unit ... 2

RHEOLOGY

◆ LEARNING OBJECTIVES ◆

After completing this unit, reader should be able to:

- To understand the conceptions of viscosity, kinematic viscosity, thixotropy. Shear rate, fluidity, Yield point, dilatancy, plasticity.
- To provides the property of Newtonian and Non-Newtonian fluids.
- To understand the deformation of solids.
- It also helps to understand the various apparatus used for determination of viscosity.

2.1 INTRODUCTION

Rheology term is originated from the Greek words rheo, means "to flow," and logos, means "science." Rheology comprises the scientific study of the flow properties and deformation of matter which is normally measured by a rheometer. The rheological properties measurement is valid from fluids like dilute solutions of polymers and surfactants to rigorous protein formulations, to semi-solids like creams and pastes, to solid polymers and asphalt. The measurement of rheological properties can be done from bulk sample deformation by a mechanical rheometer or on a micro-scale through a microcapillary viscometer or an optical method like microrheology.

Several normally utilized materials and formulations display complex rheological properties, whose viscosity and viscoelasticity able to change reliant on the exterior environment applied, like a strain, stress, timescale as well as temperature.

Rheology involved in mixing and flow of materials, their packing into containers, and their removal prior to use achieved by pouring form bottle, extrusion from tube or passage through a syringe needle.

The deformation that results from the stress applied can be divided into two types:

- Elastic deformation: (spontaneous and reversible deformation).
- Plastic deformation: (permanent or irreversible deformation).

Rheological properties have significant effect at all stages of material used in numerous industries from formulation development and stability to processing as well as product performance. The type of remoter essential for determining these properties is often reliant on the relevant shear rates and timescales as well as sample size and viscosity. Below there are some examples of rheological measurements:

- Improving and measuring stability of dispersion.
- Thixotropy determination of paints and coatings for product application and final finish quality.
- To study effect of polymer molecular structure on viscoelasticity for processing and end-use performance.
- Pre-formulation screening for therapeutics, mainly bio-pharmaceuticals.

2.2 NEWTONIAN SYSTEMS

2.2.1 Law of Flow

Newtonian law states that the shear stress in the plane of contact of layers of fluid is directly proportional to the derivative of the rate of flow in the direction of normal to these planes. Liquids that obey the law are called Newtonian fluids.

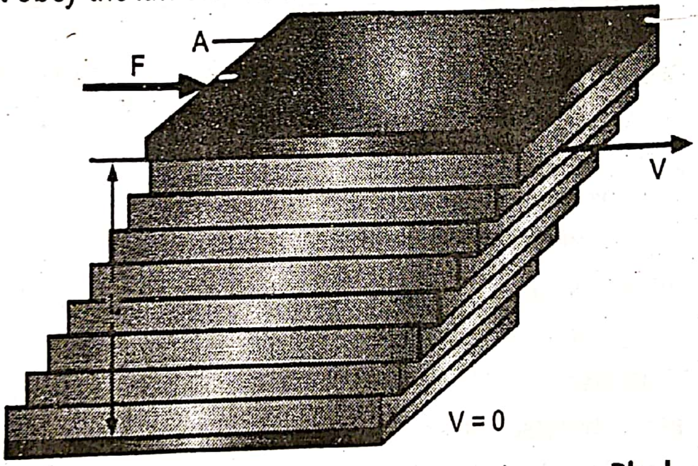


Fig. 2.1 (a) : Representation of Shearing Force Acting on a Block of Material

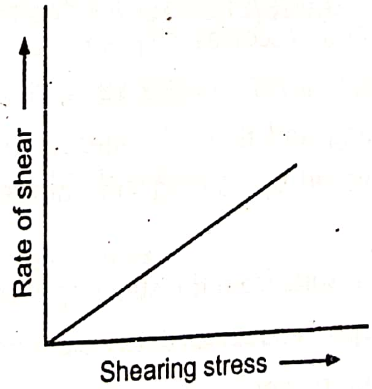


Fig. 2.1 (b) : Relationship between Shear Stress-Shear Rate (Rheogram)

Shear stress-shear rate relationship is generally explained in the form of curve i.e. rheogram or consistency curve. When figures are schemed through taking F on x axis and G on y axis a flow curve is achieved. The rheogram passes over the origin and the slope offers the coefficient of viscosity. Systems that obey this linear relationship are called as Newtonian fluids. The viscosity of these fluid is constant at a given temperature and pressure. This category comprises liquids such as chloroform, water solution of syrup, glycerine very dilute colloidal solution.

Consider a block of liquid consisting parallel plates of molecules as shown in the figure. The bottom layer is fixed and the top plane of liquid is moved at a constant velocity, each layer will move with a velocity directly proportional to its distance from the stationary bottom layer. During moving ahead the first layer induces flow in the second layer. The velocity of second layer is less than that of first layer. In the same way velocity of third layer will be less than that of second layer. This phenomenon continues and the bottom layer remains stationary. Hence liquid resists flow when force is applied.

Shear stress is defined as the force per unit area $\frac{F'}{A}$, which is applied to bring flow.

Shear stress, $F = \frac{F'}{A}$

Velocity gradient or rate of shear, $\frac{dv}{dr}$ is defined as the change in velocity, dv with an infinitesimal change in distance, dr.

Rate of shear, $G = \frac{dv}{dr}$

Greater the viscosity of liquid, greater is the force per unit area required to produce certain rate of shear.

Therefore, shear stress α Rate of shear

$$\frac{F'}{A} \propto \frac{dv}{dr}$$

or $$\frac{F'}{A} = \eta \times \frac{dv}{dr}$$

or $$F = \eta G$$

Where, η is the coefficient of viscosity

Viscosity is calculated by:

$$\eta = \frac{F}{G}$$

Coefficient of viscosity is defined as the force per unit area required to maintain unit difference between two parallel layers in the liquid, 1 cm apart. The unit of viscosity is poise or centipoises (cp). The C.G.S. unit for poise is dyne sec cm^{-2} or g cm^{-1} sec^{-1}.

2.2.2 Kinematic Viscosity

In several conditions, the ratio of the inertial force to the viscous force is the main concern, earlier, this ratio is characterized by the fluid density ρ. This ratio is considered via the kinematic viscosity, stated as follows:

$$\nu = \frac{\mu}{\rho}$$

The SI unit of ν is m^2/s. The SI unit of ρ is kg/m^3.

The cgs physical unit for kinematic viscosity is the stokes (St), which termed after George Gabriel Stokes. Occasionally, it is expressed in terms of centistokes (cSt).

2.2.3 Effect of Temperature

As the temperature increases, the viscosity of liquid decreases. However, viscosity of gas increases with increase in a temperature and the liquid fluidity surges with temperature. The dependency of the viscosity of a liquid on temperature is stated nearly for several elements through an equation similar to the Arrhenius equation of chemical kinetics,

$$\eta = Ae^{EvRT}$$

Where, A is constant dependent on the molecular weight and molar volume of the liquid and Ev is an activation energy essential to initiate flow among molecules.

Other Terms for Viscosity:

Different terminology is used to express the resistance to flow of liquids, when different substances are added to a solvent or a vehicle.

- **Relative viscosity (η_r):** It is defined as the ratio of the viscosity of a solution (η) to the viscosity of the solvent used (η_s).

$$\eta_r = \frac{\eta}{\eta_s}$$

- **Specific Viscosity (η_{sp}):** It is defined as the relative increase in the viscosity of the dispersion over that of the solvent alone.

$$\eta_{sp} = \frac{\eta - \eta_s}{\eta_s}$$

- **Intrinsic viscosity:** It is defined as the limiting value of the reduced viscosity at infinite dilution of polymer. It is determined at various concentrations of a substance and the results are potted. Extrapolating the resulting linear relationship to obtain the intercept.
- **Reduced viscosity:** It is defined as the ratio of the specific viscosity to the mass concentration of the polymer.

$$\text{Reduced viscosity} = \frac{\eta_{sp}}{c}$$

2.3 NON-NEWTONIAN SYSTEMS

The substances which are unable to obey Newton's law are deliberated as Non-Newtonian bodies. These are solid, liquid, heterogeneous dispersions like colloidal solutions, emulsions, liquid suspensions as well as ointments. Normally, they are divided into 3 kinds of flow, Pseudo plastic, Plastic, Dilatant.

2.3.1 Pseudo Plastic Flow

The curve for a pseudo plastic material starts at the origin (or at least lines it at small shear rate). The curved rheogram for pseudo plastic materials is owing to shearing action on the long chain molecules of materials like linear polymers. In which curve is passing from origin (Zero shear stress), so no yield value is Obtained. So, in psedoplastic flow as shear stress increases, shear rate increases but not linear.

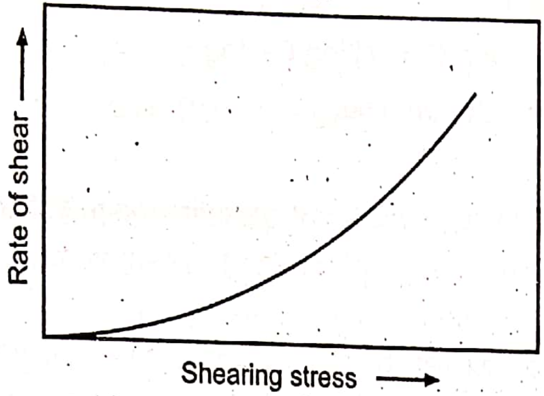


Fig. 2.2: A Rheogram for Pseudo Plastic Flow

By increasing the shearing stress, the disordered molecules turn themselves in the specific flow direction, hence reducing friction and allow an improved shear rate at every shearing stress. Some of the solvent linked will be unrestricted triggering reduced viscosity. Such kind of flow behaviour is also termed as shear thinning system. Long chain molecules of polymer, are useful to explain the pseudo plastic flow.

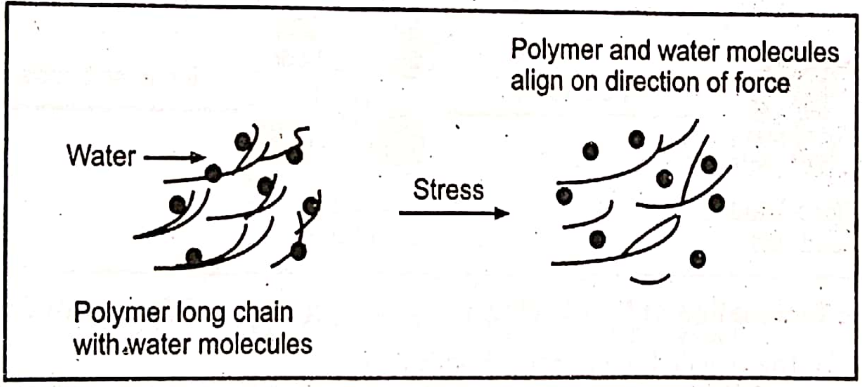


Fig. 2.3: Explanation of Psedoplastic Flow by Taking Example of Long Chain Polymer Molecules

On putting F/A, shearing stress molecules (water and polymer) organize long axis in the route of force applied. Such stress decreases internal resistance and solvent molecules released form polymer molecules. Then reduce the concentration and size of molecules with decrease in viscosity.

The Following equation displays this flow

$$FN = \eta G$$

N = Number of specified exponent,

η = Viscosity coefficient

- In case of pseudo plastic flow, where N > 1.

  i.e. More N >1, the greater pseudo plastic flow of material.
- If N = 1, the flow is considered as Newtonian.

  By taking Log on both sides,

  i.e. $N \log F = \log \eta + \log G$

  On reordering, we attain

$$\log G = N \log F - \log \eta$$

This equation provides a straight line.

2.3.3 Plastic

In plastic flow, rheogram curve does not pass via origin, at first the substance acts as an elastic body and it fails to flow, on application of minimum stress. On increasing the stress, the rate of shear increase non-linearly but after that curve is linear. The linear portion extrapolated intersects the x axis at the point termed as yield value thus, plastic flow displays newtonian flow beyond the yield point. The curve signifies plastic flow; these kinds of materials are termed as Bingham bodies. These bodies do not flow till the shearing stress is analogous to yield value surpassed. Consequently, yield value is significant property of definite dispersions. The reciprocal of mobility is Plastic viscosity. For instance, paints and ointments, ZnO in mineral oil, definite pastes and Plastic flow described through flocculated particles in concentrated ointments, suspensions, pastes as well as gels.

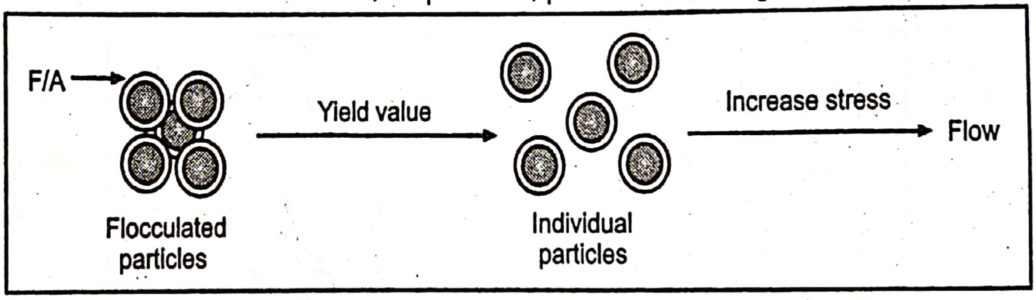


Fig. 2.4: Explanation of Plastic Flow by Taking Example of Flocculated Particles

The curve for the plastic flow is described below.

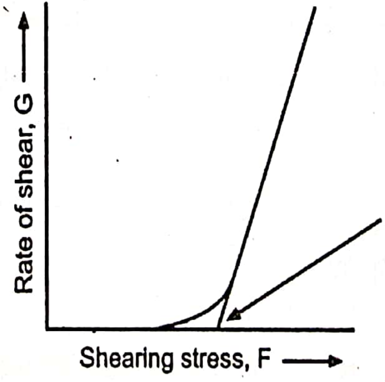


Fig. 2.5: A Rheogram for Plastic Flow

The equation describing plastic flow is,

$$U = \frac{F - f}{G}$$

Where,

f = Yield value,
F = Shearing stress,
G = Rate of shear

2.3.2 Dilatant

Some suspensions with an increased percentage of dispersed solids shows a surge in resistance to flow with increasing shearing rates. These systems essentially increase in volume when sheared and are therefore called as a dilatant.

Such flow is the inverse of that controlled by pseudoplastic systems. While pseudoplastic materials are regularly stated to as "shear-thinning methods," dilatant materials are frequently called as "shear-thickening systems." On removing stress, a dilatant system come backs to its original state of fluidity.

Graph for dilatant flow is like this,

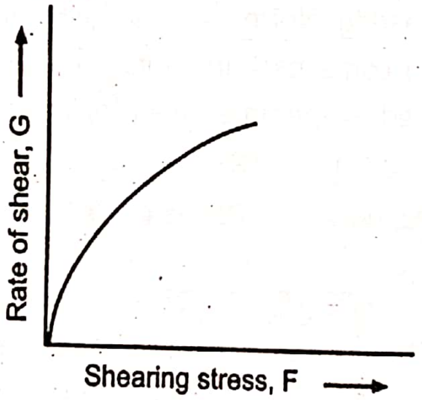


Fig. 2.6: A Rheogram for Dilatant Flow

In this rheogram, curve is passing through origin (Zero shear stress), so no yield value is attained. Non-linear surge in shear rate. Shearing rate increases on increasing resistance to flow on.

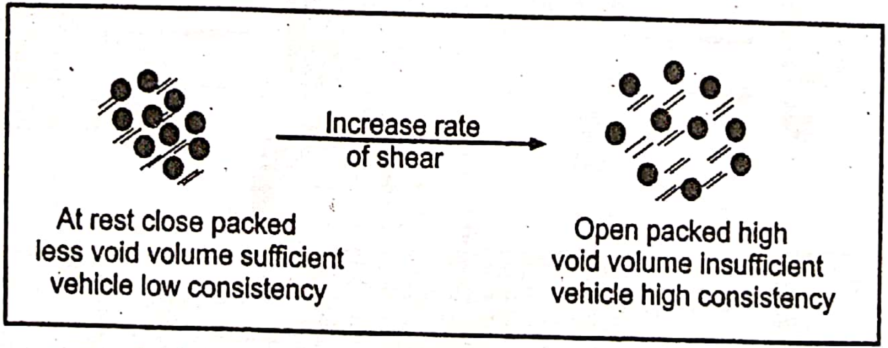


Fig. 2.7: Effect of Increased Rate of Shear on Particle Flow

In dilatant, particles are thoroughly packed with less voids spaces, also some quantity of vehicle is enough to fill the void volume. Owing to this, particle move relative to one another at low shear rate. Thus, dilatant suspension can be transferred from bottle as in these condition it is fluid. After increasing stress, the particles show the open packing and bulk of system (void volume is increase) is increased. However, the quantity of vehicle is deficient to plug this void space. Therefore, particles are not wetted or lubricated and improve resistance to flow. Lastly, system display consistency such as the paste. Due to this behaviour, the dilatant suspension can be process through high speed mixers, blenders or mills.

This flow is shown by the exponential equation,

$$FN = \eta G$$

where, N = Number of given exponent.

η = Viscosity coefficient.

In which $N < 1$, and decrease as the dilatancy increase. If $N = 1$, the system is Newtonian flow.

2.4 THIXOTROPY

Thixotropy is the isothermal and moderately slow recovery on standing of material of which stability lost owing to shearing. Normally, it is shear thinning system, on agitating and keeping apart it is estimated to come back in to its original fluidity state, but takes longer duration to improve as compared to the time taken for agitation. Thixotropic behaviour can be exposed by plastic and pseudo plastic system.

- **Thixotropy Concept (Particle – Particle Interactions) (Gel – Sol – Gel Transformation)**

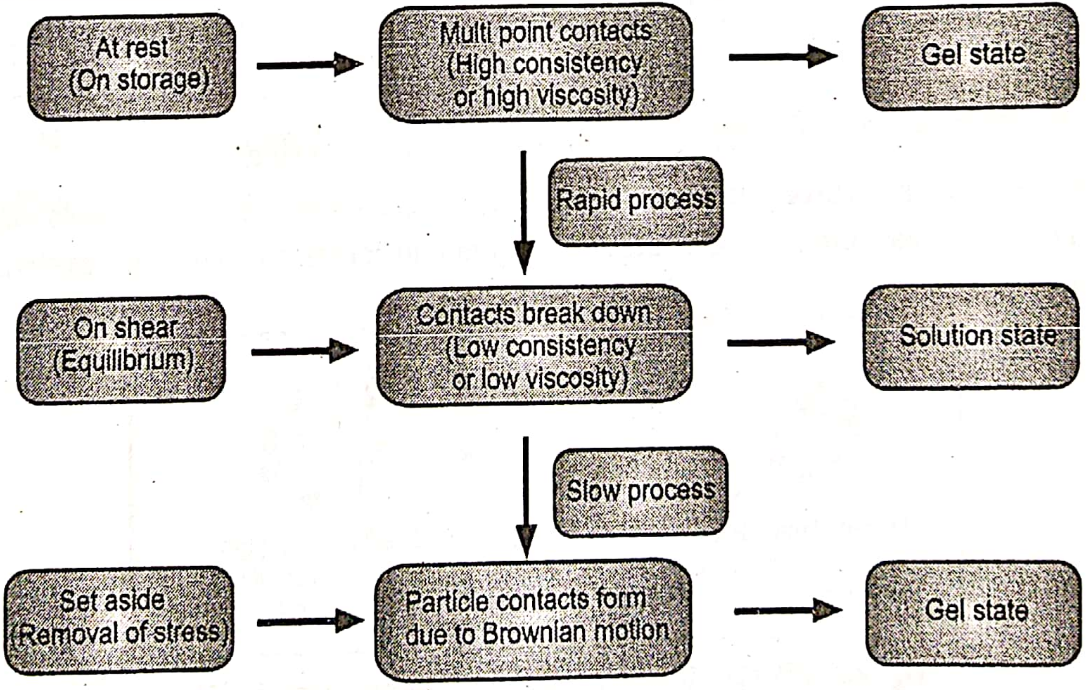


Fig. 2.8: Schematic Explanation of Thixotropy Concept

The Rheogram of thixotropic material determined by:

(i) Rate at which shear increased or decreased.

(ii) Duration through which sample is exposed to any one shear rate.

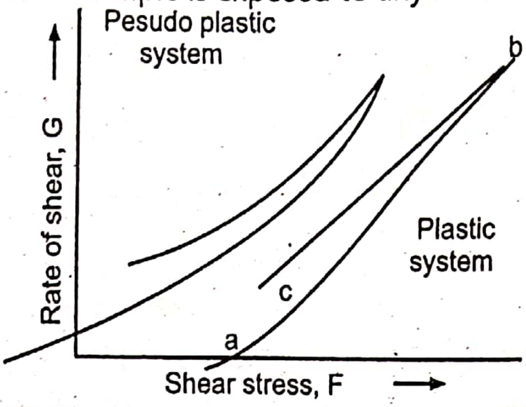


Fig. 2.9: The Rheogram of Thixotropic Material

The Thixotropy phenomena can be observed by constructing consistency curves. From the graph up curve ab is attained, up to maximum point b. If the rate of shear is condensed, then down curve bc is obtained. Moreover, in non-newtonian system, the down curve is moved to left of the up curve. Within this graph, the material has low consistency at any shear rate on down curve likened to that exposed on up curve. The thixotropic curves raised for pseudo plastic system. However, within newtonian system, the superimposition of down curve take place on up curve.

- **Anti-thixotropy (-Ve Thixotropy)**

Anti-thixotropy signifies a rise in uniformity (high viscosity) rather reduction in uniformity in the down curve. The surge in thickness or flow resistance with increase shear time detected for (magnesia magma). Anti-thixotropy is flocculated system comprising low solid content (1 – 10%). Dilatancy system is deflocculated system comprising solid content (> 50%).

- **Anti-thixotropy concept**

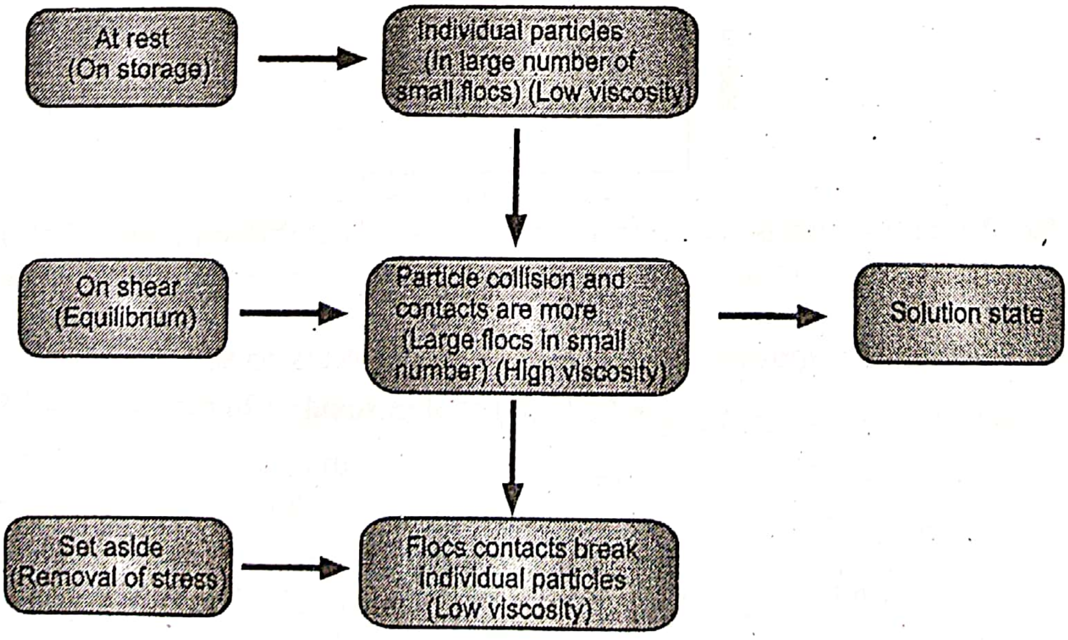


Fig. 2.10: Schematic Explanation of Anti-thixotropy Concept

The anti-thixotropy phenomena can be exposed through Magnesia Magma,

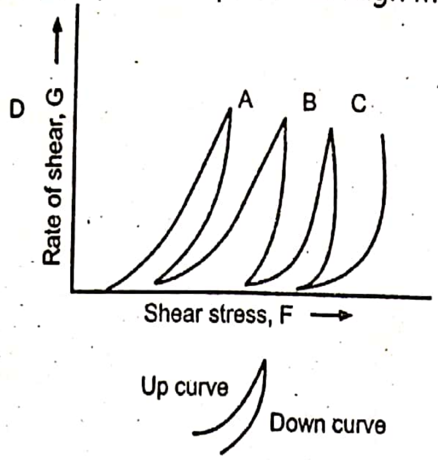


Fig. 2.11: The Rheogram of Anti-thixotropic Material

As soon as magnesia gel is sheared alternatively with increasing and decreasing shear rates, the gel thickens. As the cycle proceeds, the extent of increase in the thickening reduces slowly and reaches equilibrium finally. There will be no change in the consistency curves on further cycles of shear rate. The anti-thixotropic character is magnesia gel is shown in Fig. 2.12. The equilibrium system was gel like, with great suspendability and was readily pourable. When allowed to stand, the substance was sol-like.

Rheopexy: It is rare property of some Non-Newtonian fluids to show a time-dependent increase in viscosity; the longer the fluid undergoes shearing force, higher its viscosity. "It is phenomenon in which a solution transforms to a gel state more readily rather than keeping a solution at rest".

Measurement of Thixotropy:

1. **Measurement of structural break-down due to increasing rate of shear:**

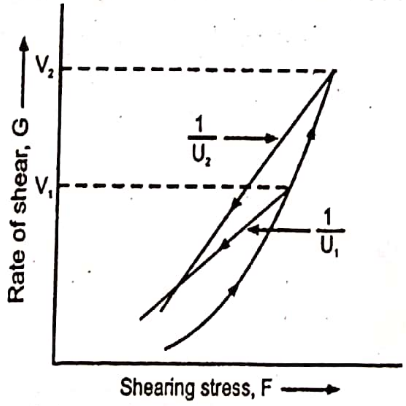


Fig. 2.12: Structural Breakdown in Plastic Materials at Different Shear Rates

The coefficient of thixotropic breakdown of plastic materials 'M', the loss in shear stress per unit increase in shear rate.

The co-efficient of thixotropic breakdown 'M' is than calculated as:

$$M = \frac{2\,(U_1 - U_2)}{ln\left(\frac{V_2}{V_1}\right)^2} \qquad \dots (10)$$

'M' is in dynes sec cm^{-2},

Where, U_1 and U_2 are plastic viscosity of the down-curves having shearing rates of V_1 and V_2 respectively.

2. Measurement of structural break-down with time at constant rate of shear:

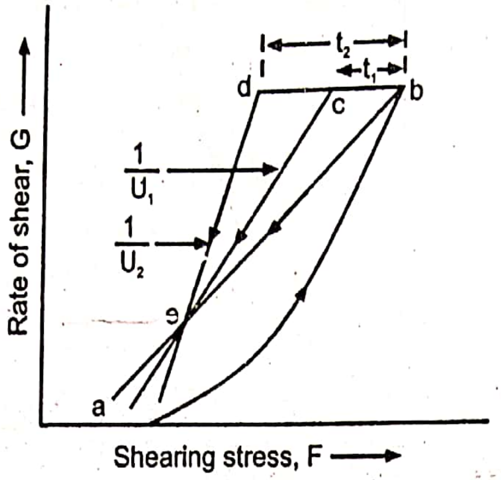


Fig. 2.13: Structural Breakdown with Time in Plastic Materials Possessing Thixotropy

Thixotropic co-efficient 'B' is calculated as:

$$B = \frac{(U_1 - U_2)}{ln\left(\frac{t_2}{t_1}\right)} \quad \text{... (11)}$$

Where, U_1 and U_2 are plastic viscosity of the two down-curves calculated after shearing at a constant rate for t_1 and t_2 secs, respectively.

Shear rate held constant for a certain period of time t_1 (abce) and if held constant for t_2 (abcde).

Bulges and Spur:

Bulge is a hysteresis loop with a characteristic bulge in the up-curve. A concentrated aqueous bentonite gel, 10% to 15% by weight, produces a hysteresis loop with a characteristic bulge in the up-curve. It is presumed that the crystalline plates of bentonite form a "house of cards structure" that causes the swelling of bentonite magmas.

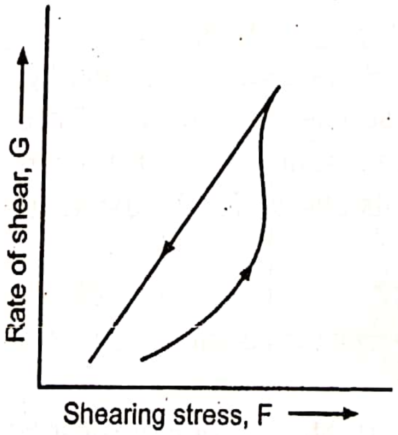


Fig. 2.14: Rheogram of a Thixotropic Material Showing Bulge in the Hysteresis Loop

Spur is a sharp point of structural breakdown at lower shear rate in up-curve. It is a rheogram wherein the bulged cure may develop into a spur like protrusion. Penicillin gels have definite spur values, forming intra-muscular depots upon injection that afforded prolonged blood levels of the drug.

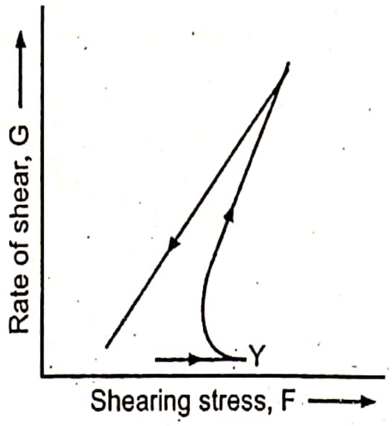


Fig. 2.15: Rheogram of a Thixotropic Material Showing A Spur in the Hysteresis Loop

2.5 THIXOTROPY IN FORMULATION

Thixotropy is a beneficial property in liquid pharmaceutical systems that preferably should have an increased consistency in the container, which can be pour as well as spread simply. For instance, a good-prepared thixotropic suspension will not settle out freely within the container, will convert fluid after shaking, and will persist long adequate for a dose to be distributed. At last, it will recover consistency quickly sufficient so as to sustain the particles in a suspended state. An analogous behaviour is necessary with lotions, emulsions, ointments, creams, and parenteral suspensions to be used for intramuscular depot therapy.

If we take a look towards suspension stability, there is a connection among degree of thixotropy as well as sedimentation rate; If the rate of thixotropy is greater then, rate of settling is lower. Degree of thixotropy may alter over time and end with a poor formulation. Thixotropic systems are compound, and it is impractical to imagine that rheological alterations can be expressively trailed through the use of single factor. Therefore, in a study related with the aging effects of thixotropic clay, Levy13 found it essential to follow variations in viscosity of plastic, hysteresis area, yield value, and spur value.

2.6 DETERMINATION OF VISCOSITY

Effective determination and assessment of rheological properties of one specific scheme rest on choosing the precise instrumental technique. Since, the shear rate in a newtonian system is directly proportional to shearing stress, instruments that operate at a single shear rate can be used. The instruments utilized for the determination of viscosity classified in to two types

[A] Single point viscometer

(i) Capillary viscometer [Ostwald viscometer]

(ii) Falling sphere viscometer

Within this type of viscometers, Stress α rate of shear Equipment works at Single rate of shear.

[B] Multi point viscometer

(i) Cup and bob viscometer

(ii) Cone and plate viscometer

Within this type of viscometers, viscosity det. at several rates of shear to get consistency curves

2.6.1 Capillary Viscometer [Ostwald Viscometer]

The capillary viscometer is utilized to calculate the viscosity of Newtonian fluid. The viscosity of Newtonian fluid is calculated by measuring time necessary for the fluid to pass amongst two marks.

Principle: The principle behind capillary viscometer includes, when a liquid flows by gravity, the time needed for the liquid to pass among two marks (A and B) over the vertical capillary tube. The flow time of the liquid in test is likened with time necessary for a liquid of known viscosity (Water). Thus, the viscosity of unknown liquid (η_1) can be determined by using following equation:

$$\eta_1 = \frac{\rho_1 t_1}{\rho_2 t_2} \eta_2 \qquad \text{... (2.1)}$$

Where,

ρ_1 = Unknown liquid density
ρ_2 = Known liquid density
t_1 = Flow time for unknown liquid
t_2 = Flow time for known liquid
η_2 = Known liquid viscosity

Equation (2.1) is established on the basis of Poiseuille's law, shows the resulting connection for the liquid flow over the capillary viscometer.

$$\eta = \frac{\pi r_2 \Delta P}{8lV} \qquad \text{... (2.2)}$$

Where,

r = Radius of capillary,
t = Flow time,
ΔP = Pressure head dyne/cm^2,
l = Length of capillary cm,
V = Volume of liquid flowing, cm^3

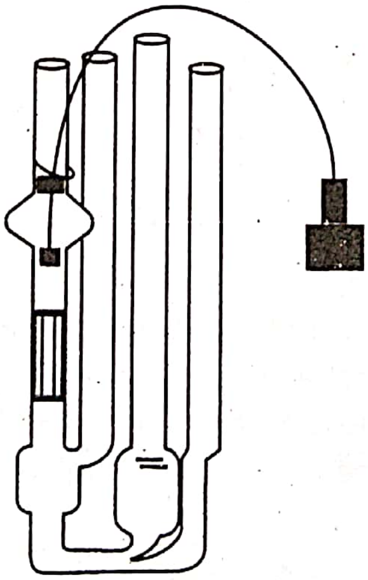


Fig. 2.16: Capillary Viscometer

For a specified capillary viscometer, the r, V and l are combine into constant (K), then equation (2.2) can change in to equation where the pressure head ΔP (shear stress) rest on the density of liquid being measured, acceleration owing to gravity (g) and change in heights of liquid in viscometers. Acceleration of gravity is constant and if the levels in capillary are retained constant for all liquids, if these constants are including into the equation (2.3) then, viscosity of liquids may be stated as:

$$\eta_1 = K' t_1 \rho_1 \quad \text{... (2.4)}$$

$$\eta_2 = K' t_2 \rho_2 \quad \text{... (2.5)}$$

By dividing of equations (2.4) and (2.5) provides the equation (2.1), which is specified in the principle,

$$\eta_1 = \frac{\rho_1 t_1}{\rho_2 t_2} \eta_2 \quad \text{... (2.6)}$$

Equation (2.6), may be utilized to control the relative and absolute viscosity of liquid. This viscometer, gives only mean value of viscosity since one value of pressure head is possible. Capillary viscometer is utilized for highly viscous fluid i.e. Methyl cellulose Dispersions.

2.6.2 Falling Sphere Viscometer

Falling sphere viscometer is also called as Hoeppler falling sphere viscometer. Falling sphere viscometer is worked on the principle, a glass or ball moves down in vertical glass tube comprising the test liquid at a known constant temperature. The rate at which the ball of specific density and diameter falls is an inverse function of viscosity of sample.

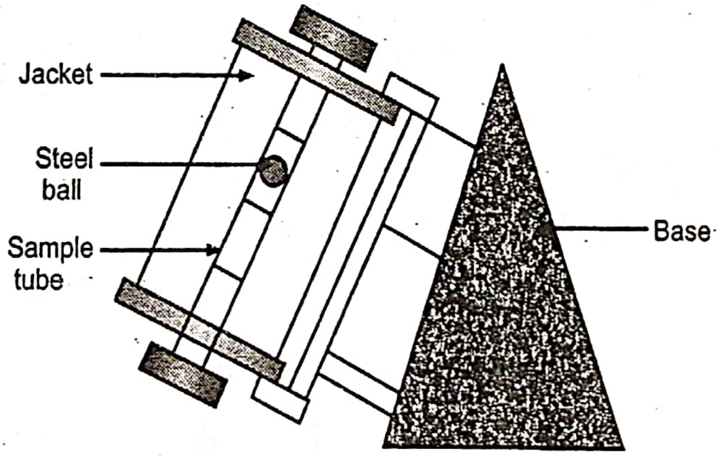


Fig. 2.17: Falling Sphere Viscometer

The working of falling sphere viscometer involves a glass or steel ball is plunged into the liquid and permitted to reach equilibrium with temperature of outer jacket. The tube with jacket is then upturned so that, ball at top of the inner glass tube. The time taken by the ball to fall between two marks is calculated, frequent method for a number of times to acquire contemporary outcomes. For superior results select ball which proceeds not less than 30 sec. to fall among two marks.

$$\eta = t (S_b - S_f) B$$

Where,

t = Time in sec. for ball to fall between two marks,
S_b and S_f = Specific ball gravities and fluid under examination,
B = Constant for particular ball.

2.6.3 Rotational Viscometers

2.6.3.1 Cup and Bob Viscometer

It involves shearing of the sample among the outer wall of a bob and inner wall of a cup in to which the bob fits. The Fig. 2.14 shows its principle. Depending on the torque obtaining from the cup and bob rotation several instruments are available now-a-days.

- The *Couette* type viscometer involves the rotation of cup. Owing to the sample, the viscous drag on bob to cause its turning. The obtainable torque is directly related with the sample viscosity.
- The *Searle* type of viscometer utilizes a stationary cup and a rotating bob. The torque resulting from the various drag of the system under examination is normally calculated by a spring or sensor in the drive to the bob.

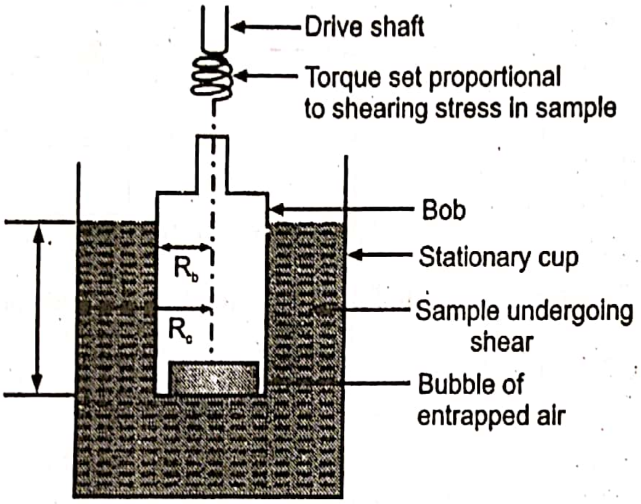


Fig. 2.18: Principle of Cup and Bob Viscometer

Plug Flow:

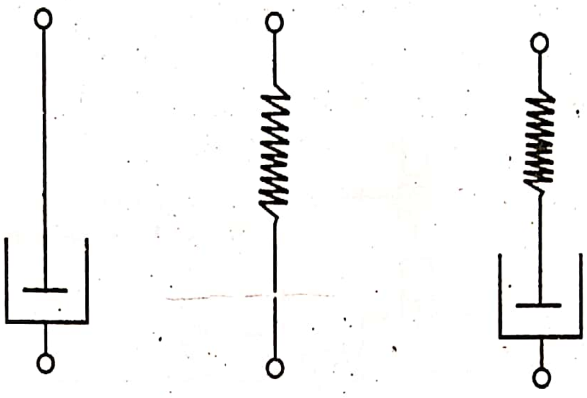
Plug flow is developed during analysis of plastic material which requires a definite yield value to be exceeded before flow can begin. One potential disadvantage of cup and bob viscometers is variable shear stress across the sample between bob and cup. In Searle type instruments, where bob rotates the shear stress exerted near the wall of the bob is high when compared to the stress exerted at the inner wall of the cup. The shear stress lies below the yield value, so the material in this region remains as solid plug and there will be error in measuring viscosity. Plug flow is minimized by using the largest bob possible with a cup of definite diameter and reducing the gap between cup and bob.

Visco-elasticity:

The materials which exhibit both viscous property of liquid and elastic property of solid are known as viscoelastic. Examples of viscoelastic materials are lotions, creams, blood, sputum etc. When stress is applied for short time, they undergo slight deformation and once the stress is removed they show elastic property by returning to original shape. If stress is applied for long time, the deformation increases and becomes more permanent. As the steady shear in rotational viscometers yield large deformations and produce false results, oscillatory and creep methods used for evaluating the viscoelastic property of pharmaceutical preparations.

Maxwell Element:

The behaviour of a semi-solid body can be described by combination of dashpot and spring. The combination of spring and shock absorber in "a car" provides a smooth ride over rough roads. When dashpot and spring are combined in series, it is called Maxwell element. As a constant stress is applied to the Maxwell unit, there is stress on the material that can be thought of as a displacement of the spring. The applied stress can be thought of as also producing a movement of the piston in the dashpot due to viscous flow. Removal of stress leads to complete recovery of spring, but the viscous flow shows no recovery i.e. no tendency to return to its original state.



(a) Dashpot (b) Spring (c) Dashpot and spring in series (Maxwell unit)

Fig. 2.19: Mechanical Models to Represent Viscoelasticity

Voigt Element:

It consists of a dashpot combined in parallel with a Hooke spring. It is useful in modeling viscoelastic property termed as creep, which is change in strain under a constant stress as a function of time. Once constant stress is applied, the drag of the viscous fluid in a dashpot influences the extension and compression of the spring which characterizes nature of solid material.

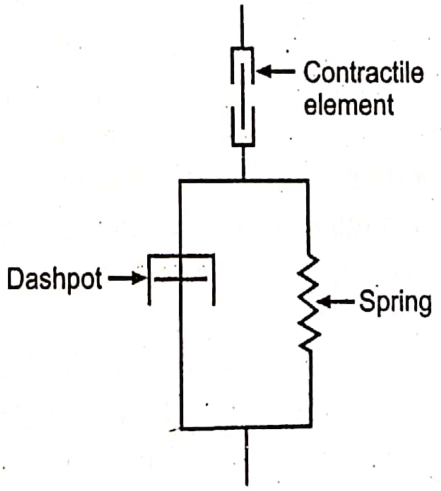


Fig. 2.20: Voigt Element

Creep Testing:

Creep the viscoelastic property is measured by the Creep viscometer. In this, sudden stress is applied on the material and is maintained constant for a prolonged time. The resultant deformation produced in material is measured and plotted to obtain a characteristic curve called as creep curve.

2.7 DEFORMATION OF SOLIDS

Deformation is the alteration in the shape and the size of a body owing to applied (external forces and internal forces). Flow is the irreversible deformation (matter is not returned to the original state when the force is removed). Elasticity is the reversible deformation (herein, matter is returned to the original state after removing the stress). Solids as well as liquids in rest retain their shape unchanged. On application of forces on these bodies, deformation can arise if the force used is larger than the internal forces keeping the body in its original form.

Deformation Forces:

The deformation forces (also referred as loading) which act on a solid or a liquid body can be

- **Static:** It is the force acting continually and its direction and magnitude are constant (constant loading).
- **Dynamic:** It is within this force, direction of the force(s) are variable as a function of time (variable loading).
- **Strain:** It is the deformation in terms of relative displacement of the particles comprising the body.
- **Stress:** It measures the internal forces acting within a (deformable) body.
- **Shear:** It is the deformation of a body in only single direction (subsequent from the action of a force per unit area τ =shear stress) and devising a specified perpendicular gradient (γ = Shear strain).

2.7.1 Plastic and Elastic Deformation

- **Plastic deformation**

Plastic deformation is a method in which permanent deformation is produced through an adequate load. It yields a permanent modification in the shape or size of a solid body deprived of any fracture to the body, causing from the use of continued stress outside the elastic limit. Plastic deformation can be employed in the manufacturing of numerous metal, plastic, concrete items. Generally, plastic deformation is also called as plasticity. The mechanisms that cause plastic deformation can change extensively. At the crystal level, plasticity in metals is normally a result of disruptions. In brittle materials such as rock, concrete and bone, plasticity is produced mainly through slippage at micro cracks. Plastic materials with hardening demand progressively advanced pressures to effect in extra plastic deformation.

Pressures as well as heat are normally utilized to shape objects into the preferred form. So, plastic deformation employed in the fabrication of goods includes carefully monitoring heat and pressure, permitting the material structure to adjust to the different conditions and incrementally winding till the favoured shape is attained. Initially, elastic deformation is occurring when an object goes in plastic deformation, which is reversible, Hence the object may recover its original shape. Soft thermoplastics have a large plastic deformation range, as do ductile metals such as copper, silver and gold. Steel does, too, but not cast iron. Hard thermosetting plastics such as rubber, crystals and ceramics have negligible plastic deformation series. Below tensile stress, plastic deformation is categorized through a strain-hardening area and a necking region and lastly, fracture, which is also named as rupture.

- **Elastic Deformation**

It is a short-term material shape deformation which is self-reversing subsequently eliminating the load or force. Elastic deformation changes the shape of a material with the application of a force in its elastic limit. This physical property confirms that elastic materials will recover their original dimensions succeeding the release of the practical load. At this point deformation *is* reversible and non-permanent. Generally, elastic deformation of metals and ceramics is observing at low strains; their elastic behaviour is normally linear. Elastic deformation can be formed by applying shear forces or tension or compression stress. However, in plastic deformation when these stresses are adequate to lastingly deform the metal. In plastic deformation, breaking of bonds is produced due to the dislocation of atoms. The elastic deformation of material permits them to recover from stress and restore their normal functionality. But these properties damage over time and in some conditions the material can become brittle and lose their ductility. Materials become less pliable when cold or exposed to hardening chemicals that inhibit with their elasticity.

2.8 HECKEL EQUATION

The variations in the volume with the applied pressure are defined by way of numerous equations among them the "The Heckel Theory" is the most vital. Heckel measured that the decline in the voids follows the first order kinetics connection with the applied pressure. For the compressional method Heckel has suggested the following equation known as the "Heckel Equation".

$$ln\frac{V}{V - V_\alpha} = KP + \frac{V_o}{V_o - V_\alpha} \qquad \ldots (2.1)$$

Where,

V = Volume at the applied pressure "P",

V_o = Original volume of the powder including the voids,

V_α = Volume of the Solid Powder excluding the voids,

K = A constant related to the "yield pressure" of the powder,

P = Applied pressure

As we know, porosity "E" is the ratio of the total volume of the void space to the bulk volume of the powdered material.

i.e.
$$E = \frac{V - V_\alpha}{V}$$

From the equations (2.1) and (2.2) we get,

$$ln\frac{1}{E} = KP + \frac{V_0}{V_o - V_\alpha} \quad \text{... (2.3)}$$

This is the reorganized or moderate form of Heckel Equation.

2.9 STRESS

Stress is a physical pressure or strain applied to a material, which can frequently leads to corrosion damage. Stress can be produced through crevice loads, passed on through stress concentration or other things such as the materials' structure type or remaining stresses from cold working as well as different kinds of manufacturing. Stress can trigger cracks in materials, which can spread dependent on the harsh ions' diffusion rate. Cracks that proliferate along structures fluctuate reliant on the smeared stress levels. When stress is combined with a harsh surroundings, corrosion can take place, arising slowly initially, and then rising more quickly. As the crack spreads, breaks occur, subsequent in total constituent failure. In order to stop this from happening, selection of materials that can limit the level of stress should be implemented as early as the design phase. When a constituent is impaired and is displaying signs of corrosion owing to stress, treatments comprise: Removal of rivets, removal of visible damage, applying doublers, applying coatings. The improvement of different alloys could also benefit to diminish stress levels by making materials more resistant to the damaging effects of corrosion.

2.10 STRAIN

Normally, it is the deformation rate triggered through strain in a material in an equivalent time. This measures the rate where expanses of materials alter within a distinct time period. It includes both the rate where a definite material increases and shears, constructing it a normal measurement in the examination of the corrosion method. Strain rate contains the rate wherein a material shrinks or enlarges and the rate of deformation obtained by progressive shearing without a change in volume. In metallurgy precise measurement of strain rate is very helpful. As materials may experience deformation in numerous rates and directions, learning how to gauge strain rate with respect to certain elements such as time, velocity and others is important in the determination of the material strength and the point at which corrosion, exactly stress corrosion cracking, could take place. The usage of lower strain rate is nowadays an extensively utilized technique in assessing the reaction of material in contradiction of stress. This must be sensibly deliberated and executed in the field in order to produce precise results. Using following formula, the strain rate can be calculated:

$$\text{Strain Rate} = \frac{\text{Change in Strain}}{\text{Change in Time}}$$

2.11 ELASTIC MODULUS

It is the ratio of stress, less than the proportional limit, to the resultant strain. It is the amount of rigidity or stiffness of a material. In relations with the stress-strain curve, the modulus of elasticity is the slope of the stress-strain curve in the range of linear proportionality of stress to strain. The larger the modulus, the stiffer the material, or the lesser the elastic strain that results from the use of a given stress. The modulus is a vital design factor utilized for calculating elastic deflections. Sometimes it is also stated to as Young's modulus. Elastic modulus is a material property that designates its stiffness and is then most vital property of solid materials. It is the ratio of stress to strain when deformation is totally elastic. Elastic modulus may be thought of as a material's resistance to elastic deformation. A stiffer material has a greater elastic modulus. For most typical metals the magnitude of this modulus ranges among,, 45 gigapascals, for magnesium, and 407 gigapascals, for tungsten.

Generally, there are three types of moduli available:

(i) Elastic Modulus (Young's Modulus): The longitudinal ratio of stress to strain.

(ii) Shear Modulus: It is the ratio of tangential force per unit area to the angular deformation of the body.

(iii) Bulk modulus: It is the ratio of stress to the fractional decrease in the volume of the body.

The stress-strain curve is utilized to measure elastic modulus and shear modulus. The parameters utilized to define the stress-strain curve of a material are tensile strength (ultimate strength), yield strength (or yield point), percent elongation and reduction of area. A material having higher elastic modulus is supposed to be stiffer than one with a lesser elastic modulus. Elasticity modulus has the similar dimension as stress since it results from separating the stress by strain. Values of the elastic modulus for ceramic materials are about the same as for metals, However, they are minimum for polymers. These variances are a direct result of the diverse kinds of atomic bonding in the three material types. Moreover, with increasing in temperature, the modulus of elasticity reduces.

EXERCISE

Multiple Choice Questions:

1. A shear stress-shear rate relationship is generally explained in the form of curve i.e. or ......

(a) Rheogram	(b) Consistency curve
(c) Both of the above	(d) None of the above

2. The cgs physical unit for kinematic viscosity is the stokes (St) ......

(a) Stokes (St)	(b) Pascale (PS)
(c) Newton	(d) None of the above

3. As the temperature increases, the viscosity of liquid ......

(a) Decreases	(b) Increases
(c) Sustainly increases	(d) Remains constant

4. The curve for a pseudo plastic material rheogram ......
   (a) starts at the origin (b) starts at the top
   (c) both of the above (d) none of the above
5. In psedoplastic flow as shear stress increases, shear rate ......
   (a) Increases (b) Increases but linear
   (c) Increases but not linear (d) Decreases
6. Dilatant materials are frequently called as ......
   (a) strain-thinning systems (b) shear-thickening systems
   (c) shear-thinning systems (d) strain-thinning systems
7. The Rheogram of thixotropic material determined by ......
   (a) Duration through which sample is exposed to any one shear rate.
   (b) Rate at which shear increased or decreased.
   (c) Both of the above
   (d) None of the above
8. ...... is the isothermal and moderately slow recovery on standing of material of which stability lost owing to shearing.
   (a) Thermochemistry (b) Viscosity
   (c) Entiotropy (d) Thixotropy
9. ...... is the alteration in the shape and the size of a body owing to applied external forces and internal forces.
   (a) Deformation (b) Formation
   (c) Conjugation (d) None of the above
10. ...... is the deformation in term of relative displacement of the particles comprising the body.
   (a) Strain (b) Stress
   (c) Shear (d) State

Keys

1. (c)	2. (a)	3. (a)	4. (a)	5. (c)
6. (b)	7. (c)	8. (d)	9. (a)	10. (a)

Short Questions Answer:

1. Enlist names of colloids based upon molecular size.

Ans. Rheology term is originated from the Greek words rheo, means "to flow," and logos, means "science." Rheology comprises the scientific study of the flow properties and deformation of matter which is normally measured by a rheometer.

2. What is pseudo plastic flow?

Ans. The curve for a pseudo plastic material starts at the origin (or at least lines it at small shear rates). The curved rheogram for pseudo plastic materials is owing to shearing action on the long chain molecules of materials like linear polymers. In which curve is passing from origin (Zero shear stress), so no yield value is Obtained. So, in psedoplastic flow as shear stress increases, shear rate increases but not linear.

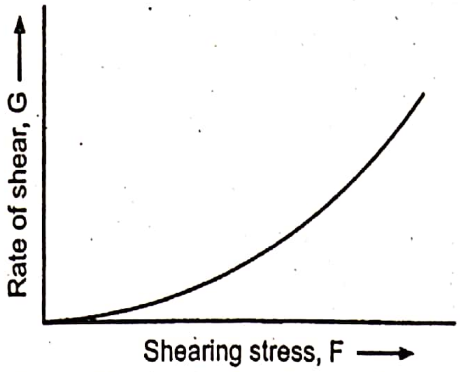


Fig. 2.21: A Rheogram for Pseudo Plastic Flow

3. What is Thixotropy?

Ans. Thixotropy is the isothermal and moderately slow recovery on standing of material of which stability lost owing to shearing. Normally, it is shear thinning system, on agitating and keeping apart it is estimated to come back in to its original fluidity state, but takes longer duration to improve as compared to the time taken for agitation. Thixotropic behaviour can be exposed by plastic and pseudo plastic system.

4. Enlist various instruments used for viscosity determination?

Ans. [A] Single point viscometer

(i) Capillary viscometer [Ostwald viscometer]
(ii) Falling sphere viscometer

[B] Multi point viscometer

(i) Cup and bob viscometer
(ii) Cone and plate viscometer

5. Explain in short about Plastic deformation.

Ans. Plastic deformation is a method in which permanent deformation is produced through an adequate load. It yields a permanent modification in the shape or size of a solid body deprived of any fracture to the body, causing from the use of continued stress outside the elastic limit. Plastic deformation can be employed in the manufacturing of numerous metal, plastic, concrete items. Generally, plastic deformation is also called as plasticity.

Long Question Answer:

1. Discuss in detail Non-Newtonian systems?

Ans. Refer Point No. 2.3.

2. Explain in detail about Thixotropy.

Ans. Refer Point No. 2.4.

3. Enlist various instruments used for determination of viscosity and explain capillary viscometer.

Ans. Refer Point No. 2.6.

4. Explain plastic and elastic deformation.

Ans. Refer Point No. 2.7.1.

5. Explain in detail about Newtonian systems.

Ans. Refer Point No. 2.2.

⁂

Unit ... 3

COARSE DISPERSION

◆ **LEARNING OBJECTIVES** ◆

After completing this unit, reader should be able to:

- Learn the potentials of pharmaceutical suspensions and emulsions.
- Understand the factors that affect the stability of suspensions and emulsions.
- Describe settling and sedimentation theory and calculate sedimentation rates.
- Learn pharmaceutical emulsion instability.

3.1 INTRODUCTION

In pharmaceutical dispersions, one substance is dispersed in a different substance. In pharmaceutical sector, dispersions are establishing in an extensive range of dosage forms as well as in nearly all routes of drug administration. The examples of such dispersions ranges from solutions of very big molecules (macromolecules) like albumin and polysaccharides, to liquid suspensions of "nano"-sized crystals (nanocrystals) and of "micro"-sized droplets (microemulsions), to coarse (bigger particle) emulsions and suspensions.

3.2 SUSPENSION

Suspensions are a type of dispersed system in which a magnificently divided solid is uniformly dispersed within a liquid dispersion medium. Depending on the particles size, suspensions are categorized as coarse or colloidal dispersion, Normally, the suspensions having particle size greater than ~1 mm are categorized as coarse suspension, though those under 1 mm are stated as colloidal suspension. When the particles comprising the internal phase of the suspension are therapeutically active, the suspension is called as pharmaceutical suspension. There are several advantages behind formulating pharmaceutical suspension. The drug remains insoluble in the delivery vehicle; it masks the bitter drug taste, increases stability of drug and attain controlled/sustained drug release. A suitable suspension has few desirable qualities, comprising prolonged settling time less viscous to pour freely from the orifice of the bottle or to flow through a syringe needle. For pharmaceutical intentions, physical stability of suspensions may well-defined as the conditions which do not involve aggregation of particles in which they remain uniformly dispersed through the dispersion.

3.2.1 Interfacial Properties of Suspended Particles

3.2.1.1 Surface Potential

The existence of surface potential has significant impact on stability of lyophobic colloidal systems. Surface potential exists when dispersed solid particles in a suspension retain charge in relation to their adjoining liquid medium. Solid particles may become charged by diverse methods. If the suspension comprises electrolytes, selective adsorption of a specific ionic species through the solid particles is a possibility. This will lead to produce charged particles.

Moreover, the charging of solid particles can also have done by ionizing of functional group of the particles. In this circumstance, the total charge is a function of the pH of the adjacent vehicle. Dispersed particles of peptide and protein molecules ionize due to presence of ionizable groups like $-COOH$ and $-NH_2$. Dispersed particles of these types of molecules will ionize. The sign and magnitude of the ionization generally rest on the pH of the vehicle.

3.2.1.2 Surface Free Energy

Magnificently divided solid materials give larger surface area which is characteristically related with large amount of free energy on the surface. The relation among the surface free energy and the surface area can be stated through

$$\Delta G = \gamma \Delta A$$

where, ΔG is the increase in surface free energy, ΔA is the increase in surface area and γ is the interfacial tension among the dispersion medium and particles. The ΔG of the suspension is lesser, then suspension is more thermodynamically stable. So, a system with very fine particles is thermodynamically unstable as of high total surface area. Therefore, the system tends to agglomerate in order to decrease the surface area and thus the excess free energy. Surface free energy may also be reduced to evade the agglomeration of particles, which can be proficient through decreasing interfacial energy. When a wetting agent is mixed to the suspension preparation, it is adsorbed at the interface. This will decrease interfacial tension, and produces more stable system.

3.2.1.3 Electric Double Layer

Degree of flocculation in suspension is affected by the forces acting on the suspended particles. Forces of attraction are of the London, Van der Waals type and the repulsive forces arise from the interaction of the electric double layers surrounding each particle. The potential energy of two particles is plotted in Figure as a function of the distance of separation. The curves are depicting the energy of attraction, the energy of repulsion, and the net energy which has a peak and two minima. Collision of the particles is opposed due to high repulsion energy and high the potential barrier energy. The system remains deflocculated and the particles form a close-packed arrangement with the smaller particles filling the voids between the larger ones and enter into primary minimum. The particles at the bottom get compressed by the weight of the particles in the upper layer and also by dispersion medium. Thus the energy barrier is overcome, allowing the particles to come in close contact with each other. In order to re-suspend and re-disperse these particles, it is again necessary to overcome the high energy barrier. This is not achieved by agitation, the particles tend to remain strongly attracted and form a hard cake.

When the particles are flocculated, the energy barrier is still too large to be overcome and the particles remain separated by a distance ranging between 1000 to 2000 A° in secondary minimum. This distance is adequate to form the loosely structural flocs. Therefore, flocculated particles are weakly bonded settle rapidly, do not form a cake, and are re-suspended. The deflocculated particles settle slowly and eventually form sediment in which aggregation occurs to form a hard cake which is difficult to re-suspend.

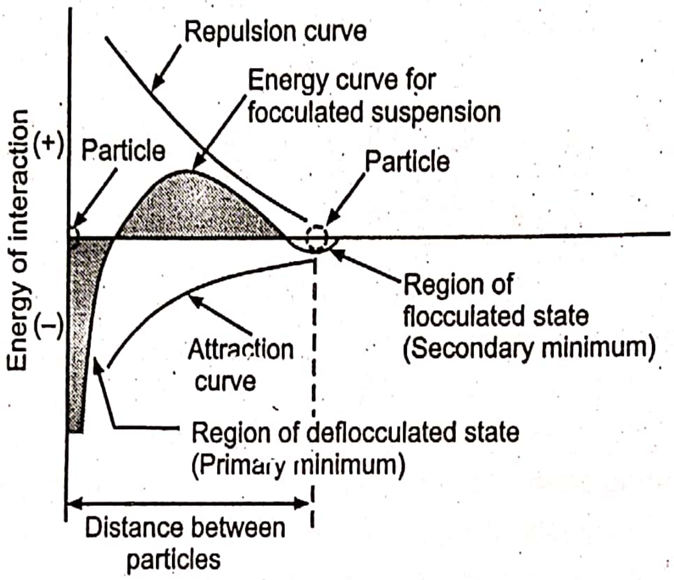


Fig. 3.1: Potential Energy Curve for Particle Interactions in Suspensions

3.2.1.4 Zeta Potential

Normally, it is the difference in potential among the tightly bound layer surface (shear plane) and electro-neutral solution region.

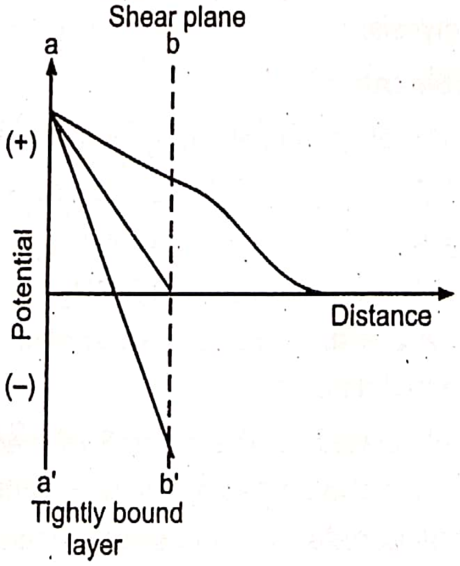


Fig. 3.2: Zeta Potential

As the potential drops-off rapidly at first, followed more gradual decrease as the distance from the surface increases. This is because of the counter ions close to the surface acts as a screen that decrease the electrostatic attraction among the charged surface and those counter ions further away from the surface. Zeta potential has useful application in stability of systems containing dispersed particles. Since this potential, rather than the Nernst potential, directs the degree of repulsion among the equally charged, adjacent, dispersed particles. The value of the zeta potential if declined below a definite level, the attractive forces go beyond the repulsive forces, and the particles gather together. This phenomenon is called as flocculation. The flocculated suspension is one in which zeta potential of particle is -20 to +20 mV. Therefore, the phenomenon of flocculation and de flocculation depends on zeta potential carried by particles.

3.2.1.5 Wetting

Wetting of solids can be governed by means of Young's equation.

$$\cos\theta = \frac{\gamma_{S/N} - \gamma_{S/L}}{\gamma_{L/N}}$$

where, θ is the contact angle, γ is the interfacial tension among the different phases, vapour (V), solid (S), and liquid (L). Wetting agents can reduce $\gamma_{S/L}$ and $\gamma_{L/V}$ and therefore decrease the contact angle. Surfactants having HLB value in the range of 7 and 9 can function as wetting agents. Several surfactants are used at concentrations up to 0.1% as wetting agents. Normally utilized wetting agents for oral application are polysorbates and sorbitan esters. For external application SDS is an example of a surfactant that is used. Parenteral preparation may comprise polysorbates, some of the poloxamers, and lecithin, among others. High concentration of the surfactant may yield foam or deflocculated systems, both of which may be unwanted. Hydrophilic polymers can also be utilized to rise the wetting of solid materials. For instances, acacia, tragacanth, xanthan gum, bentonite, aluminium–magnesium silicates. Wetting can also be improved by using hygroscopic solvents, like alcohol, glycerol, and glycols, specially, propylene glycols.

3.2.1.6 Electro kinetic Phenomena

The occurrence of interfacial potentials may arise presence of four electrokinetic phenomena, which are electrophoresis, electrosmosis, sedimentation potential, and streaming potential. All of these properties are basically the direct results of the movement of a charged surface with respect to an adjacent liquid phase.

- Electrophoresis determines the movement of charged particles via a liquid under the impact of an applied potential difference.
- Electrosmosis perhaps deliberated as the reverse to electrophoresis. Further, charged solid particles move relative to the dispersion medium with an applied potential, whereas in electrosmosis, the solid is reduced immobile but the liquid moves relative to the charged surface when a potential is concerned.

- Sedimentation potential is produced when particles experience sedimentation. So, mainly it is the reverse method of electrophoresis.
- The streaming potential is basically the reverse method of electrosmosis, is produced by forcing a liquid to course through a stationary solid phase (for example, plug or bed of particles).

3.2.2 Settling in Suspensions

- **Theory of Sedimentation**

The velocity of sedimentation is stated through Stoke's law:

$$v = \frac{d^2 (\rho_s - \rho_o) g}{18 \eta_o}$$

Where, v is the terminal velocity in cm/sec, d is the particle diameter in cm, ρ_s and ρ_o are the densities of the dispersed phase and dispersion medium, correspondingly, g is the acceleration due to gravity, and η_o is the dispersion medium viscosity in poise.

Within dilute suspensions, the particles do not interfere with one another throughout sedimentation, and free settling occurs. Several pharmaceutical suspensions that contain dispersed particles in concentrations of 5%, 10% or higher percentages, the particles display hindered settling. The particles interfere with one another as they fall, and Stoke's law no longer applies. Under these conditions, some estimation of physical stability can be attained through diluting the suspension so that it comprises about 0.5% to 2.0% w/v of dispersed phase. This is not always suggested, though, since the stability picture attained is not essentially that of the original suspension. The addition of a diluent may disturb the degree of flocculation (or deflocculation) of the system, thus efficiently changing the particle-size distribution.

- **Brownian Movement Effect**

The particles having a diameter of about 2 to 5 μm (dependent on the particle density and the density and viscosity of the suspending medium), Brownian movement counters sedimentation to an assessable extent at room temperature through maintaining the dispersed material in random motion. The critical radius, r, under which particles will be retained in suspension through kinetic bombardment of the particles by the molecules of the suspending medium (Brownian movement) was worked out by Burton. It can be seen in the microscope that Brownian movement of the smallest particles in a field of particles of a pharmaceutical suspension is usually eliminated when the sample is dispersed in a 50% glycerine solution, having a viscosity of about 5 centipoises. Therefore, it is doubtful that the particles in a normal pharmaceutical suspension comprising suspending agents are in a state of vigorous Brownian motion.

Sedimentation of Flocculated Particles:

For investigating sedimentation in flocculated systems, it is detected that the flocs incline to fall collectively, creating a distinct boundary among the sediment and the supernatant liquid. Normally, the liquid above the sediment is clear since even the small particles present in the system are related with the flocs. This is not the case in deflocculated suspensions devising a range of particle sizes, in which, in harmony with Stoke's law, the larger particles settle more quickly as compared to the smaller particles. No clear boundary is made (if only one size of particle is present), and the supernatant rests turbid for a substantially longer time duration. If the supernatant liquid is clear or turbid through the initial stages of settling is a good indication of whether the system is flocculated or deflocculated, separately. According to Hiestand, the initial settling rate of flocculated particles is determined by the floc size and the porosity of the aggregated mass. Then, the rate depends on compaction and rearrangement courses within the sediment. The term subsidence is occasionally used to define settling in flocculated systems.

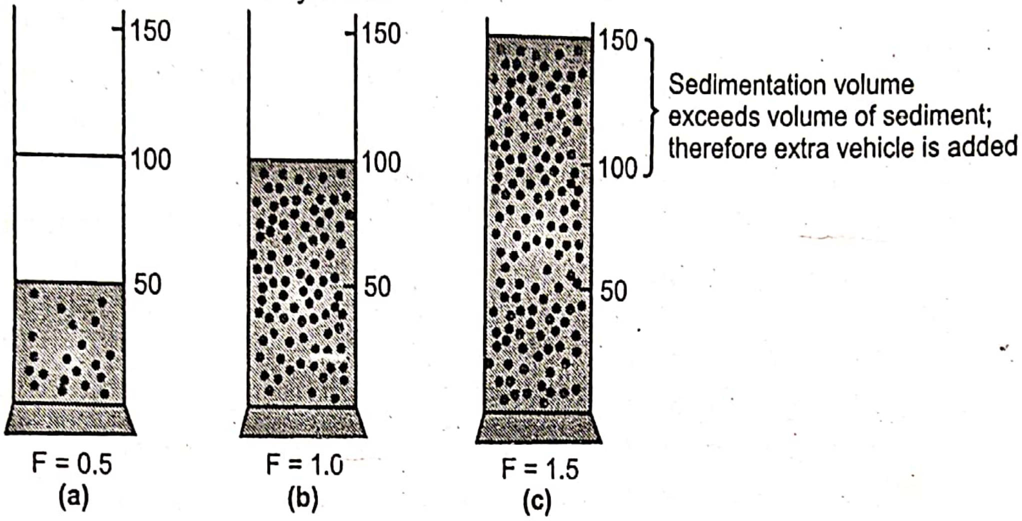


Fig. 3.3: Sedimentation Volumes Produced by Adding Varying Amounts of Flocculating Agent. Examples (b) and (c) are Pharmaceutically Acceptable

3.2.3 Formulation of Flocculated and Deflocculated Suspensions

Flocculated Suspensions:

Within flocculated suspension, formed flocs (loose aggregates) will arise surge in sedimentation rate owing to increase in size of sedimenting particles. Therefore, flocculated suspensions sediment more quickly. At this point, the sedimentation rest on size of the flocs and the porosity of flocs.

Deflocculated suspensions:

Deflocculated suspension involves individual particle settling. Owing to this the rate of sedimentation is slow, which inhibits entrapping of liquid medium which creates it difficult to re-disperse through agitation. This phenomenon is termed as 'caking' or 'claying'. In deflocculated suspension larger particles settle fast and smaller stay in supernatant liquid so supernatant looks cloudy.

- **Formulation of Suspensions:**

The formulation of a suspension rest on the flocculated or deflocculated nature of suspension.

Three approaches are normally including, use of structured vehicle, use of controlled flocculation, and combination of both of the methods. Structured vehicles are also termed as thickening or suspending agents. They are aqueous solutions of natural and synthetic gums. Generally, they surge the suspension viscosity. It is valid only to deflocculated suspensions. For instance, methyl cellulose, sodium carboxy methyl cellulose, acacia, gelatin and tragacanth. These structured vehicles act by entrapping the particle and decreases. Therefore, the usage of deflocculated particles in a structure vehicle may produce solid hard cake upon long storage. Too high viscosity is not necessary as, it sources exertion in pouring and administration. It may affect drug absorption since they adsorb on the surface of particle and suppress the dissolution rate. Occasionally suspending agents can be mixed to flocculated suspension to impede sedimentation. For example, Carboxymethylcellulose (CMC), Carbopol 934, Veegum, and bentonite. Controlled flocculation of particles is obtained by adding flocculating agents, such as electrolytes, surfactants and polymers.

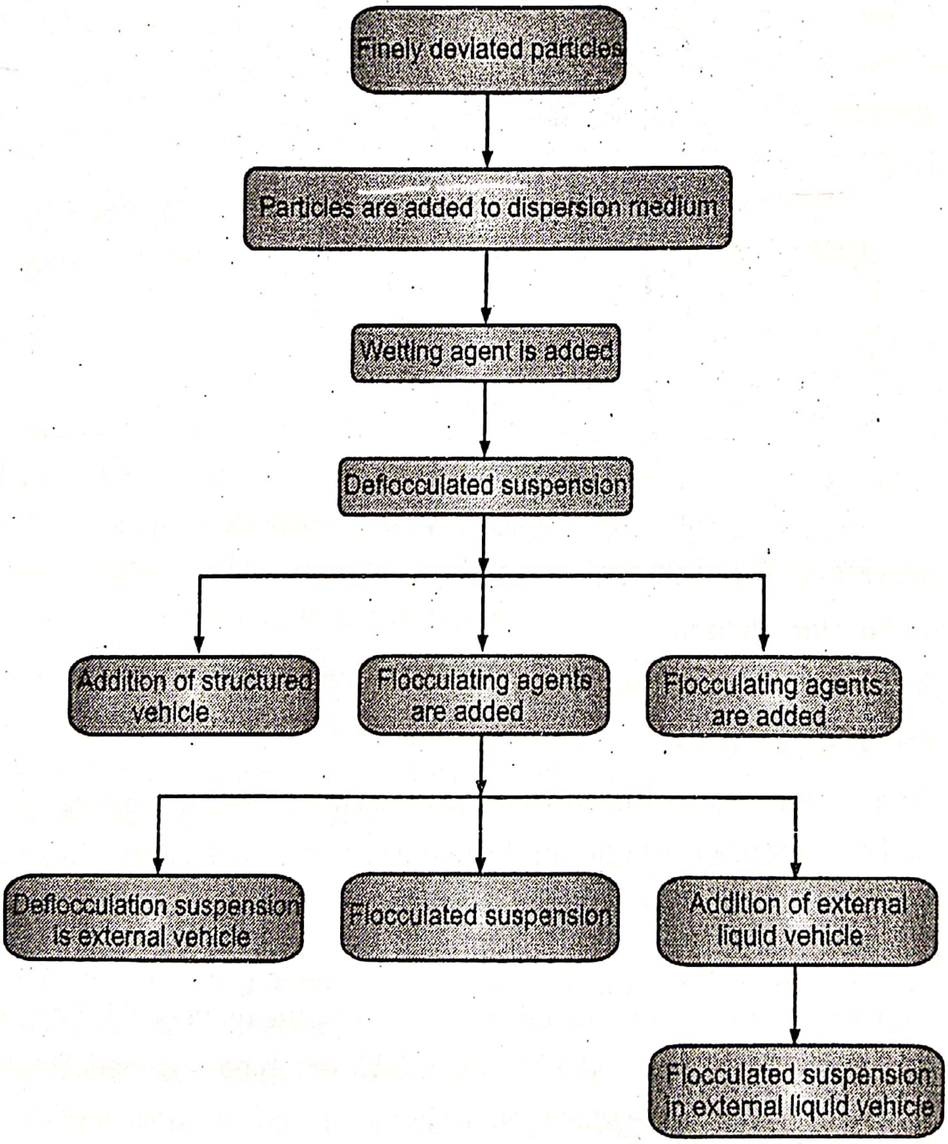


Fig. 3.4: Flow Chart of Formulation of Suspension

3.3 EMULSIONS

An emulsion is a thermodynamically unstable system comprising of at least two immiscible liquid phases, one is dispersed as globules (the dispersed phase) in the other liquid phase (the continuous phase), stabilized by the existence of an emulsifying agent. Either the dispersed phase or the continuous phase may vary in uniformity from that of a mobile liquid to a semisolid. Therefore, emulsified systems available from lotions of moderately low viscosity to ointments and creams, which are semisolid in nature. The particle diameter of the dispersed phase normally ranges from about 0.1 to 10 μm, however particle diameters as small as 0.01 μm and as large as 100 μm are not rare in some preparations.

An emulsion is a dispersion of at least two immiscible liquids, one of which is dispersed as droplets in the other liquid, and stabilized by an emulsifying agent. Two basic types of emulsions are the oil-in-water (O/W) and water-in-oil (W/O) emulsion. Though, differing upon the need, more complex systems described to as "double emulsions" or "multiple emulsions" can be prepared. These emulsions have an emulsion as the dispersed phase in a continuous phase and they can be either water-in-oil-in-water ($W_1/O/W_2$) or oil-in-water-in-oil ($O_1/W/O_2$).

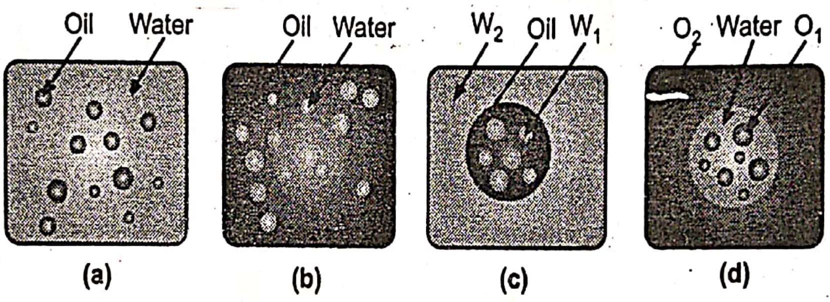


Fig. 3.5: Types of Emulsions

3.3.1 Theories of Emulsification

(A) Surface Tension Theory:

Emulsification can be achieved by lowering the surface tension.

(B) Oriented-Wedge Theory:

According to this theory, monovalent soap such as sodium stearate give o/w type emulsion and divalent soap like calcium stearate give w/o type emulsion. This was described through successful modification of the soap molecules to yield the type of emulsion.

(C) Interfacial Film Theory:

According to this theory the added emulsifying agent reduces the interfacial tension among the oil and water phases and therefore a stable emulsion is formed. This theory could not explain the formation of type of emulsion.

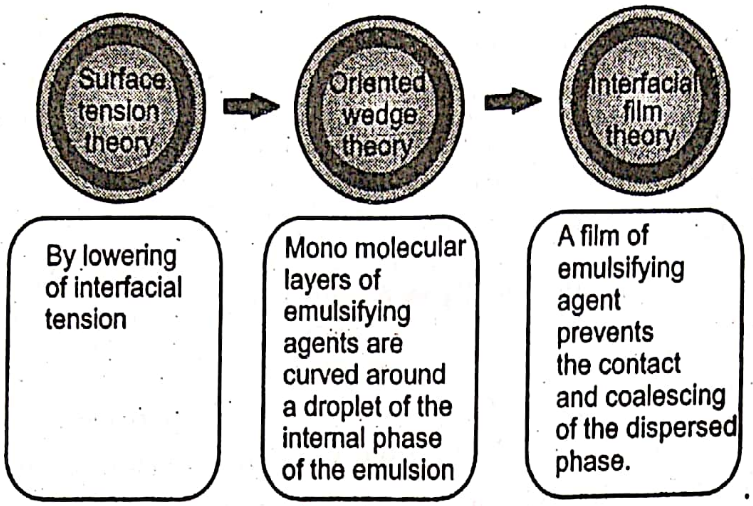


Fig. 3.6: Theories of Emulsification

Monomolecular Adsorption:

Surface-active agents, or amphiphiles, reduce interfacial tension because of their adsorption at the oil-water interface to form monomolecular films. The emulsifying agents which reduce both the surface free energy and interfacial tension will reduce the tendency for coalescence. Also the dispersed droplets which are surrounded by a coherent monolayer that helps to prevent coalescence between the droplets. This film should be flexible and should be capable of reforming rapidly if busted. The stability of emulsion is further promoted due to presence of a surface charge which will cause repulsion between neighboring particles. The combinations of emulsifiers rather than single agents are used most frequently today in the preparations, which will form closely packed and complex film at the interface to produce an excellent emulsion. In general, o/w emulsions are formed when the HLB value of the emulsifier is in the range of 9 to 12, and w/o emulsions are formed when the range is about 3 to 6. Therefore, an emulsifying agent with a high HLB value is preferentially soluble in water and forms o/w emulsion and vice-versa with surfactants of low HLB value to form w/o emulsion.

Multimolecular Adsorption and Film Formation:

Hydrophilic lyophilic colloids have been used for years as emulsifying agents; their use is limited due to availability of the large number of synthetic surfactants. They differ from the synthetic surface-active agents in two ways:

(1) They do not cause an appreciable lowering of interfacial tension, and

(2) They form a multi-rather than a monomolecular film at the interface.

Their action as emulsifying agents is due mainly to the latter effect, for the films thus formed are strong and prevent coalescence. An auxiliary effect promoting stability is due to significant increase in the viscosity of the dispersion medium. Since the emulsifying agents that form multilayer films around the droplets are invariably hydrophilic and promote the formation of o/w emulsions.

Solid Particle Adsorption:

Finely divided solid particles that are wetted to some degree by both oil and water act as emulsifying agents. This results from their being concentrated at the interface, where they produce a particulate film around the dispersed droplets so as to prevent coalescence. Powders that are wetted preferentially by water form o/w emulsions and those wetted by oil form w/o emulsions.

3.3.2 Microemulsions and Multiple Emulsions

Micro Emulsions:

"A micro-emulsion is a system, of water, oil and an amphiphilic which is a single optically isotropic and thermodynamically stable liquid solution." In some parts, micro emulsions can be considered as small scale versions of emulsions. i.e. droplet type dispersions either of oil-in-water (o/w) or of water in oil (w/o) with a size range in the order of 5-50 nm in drop radius.

Depending on the composition, three types of micro emulsions can be prepared:

(i) Oil in water micro emulsions in which oil droplets are dispersed in the continuous aqueous phase.

(ii) Water in oil micro emulsions where water droplets are dispersed in the continuous oil phase.

(iii) Bi-continuous micro emulsions where in micro domains of oil and water are inter dispersed within the system.

In all three types of microemulsions, the interface is stabilized through an appropriate grouping of surfactants and/or co-surfactants.

Multiple Emulsions:

Within this type of emulsion system, the dispersed phase comprises smaller droplets that have the same composition as the external phase. It is occur owing to double emulsification hence the systems are also termed as "double emulsion". Like simple emulsions, the multiple emulsions are also considered to be of two types:

- Oil-in-Water-in-Oil (O/W/O) emulsion system.
- Water-in-Oil-in-Water (W/O/W) emulsion system.

O/W/O Emulsion:

In O/W/O systems an aqueous phase (hydrophilic) separates internal and external oil phase. In different words, O/W/O is a system in which water droplets may be surrounded in oil phase, which in true encloses one or more oil droplets.

W/O/W Emulsion:

In W/O/W systems, an organic phase (hydrophobic) separates internal and external aqueous phases. In different words, W/O/W is a system in which oil droplets may be enclosed by an aqueous phase, which in turn encloses one or several water droplets.

3.3.3 Stability of Emulsions

The supreme vital consideration in relation to pharmaceutical and cosmetic emulsions is the finished product stability. Generally, the stability of emulsion is characterized by the absence of coalescence of the internal phase, absence of creaming, and maintenance of elegance with respect to appearance, odour, colour, and other physical properties. Many researchers define instability of an emulsion only in terms of agglomeration of the internal phase and its separation from the product. Creaming, causing from flocculation and concentration of the globules of the internal phase, sometimes is not measured as a sign of instability. An emulsion is a dynamic system, though, and flocculation and resultant creaming denote potential steps to complete coalescence of the internal phase. Moreover, in relation to pharmaceutical emulsions, creaming outcomes in a lack of uniformity of drug distribution and, if the preparation is thoroughly shaken before administration, leads to variable dosage.

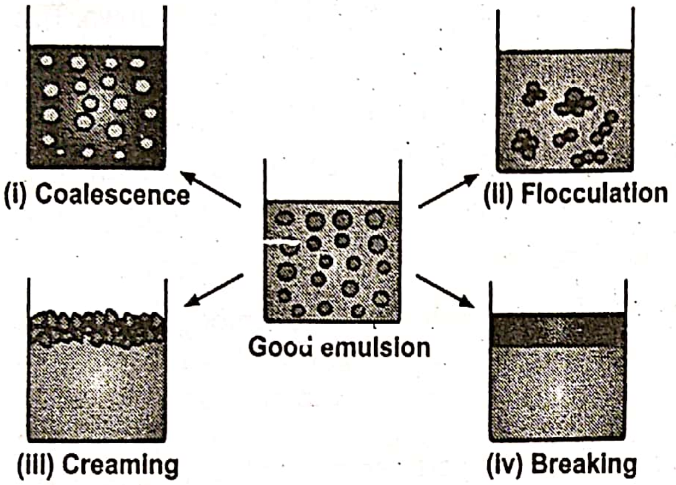


Fig. 3.7: Instabilities of Emulsion

Types of Physical Instability:

(i) Flocculation:

Flocculation involves the gathering of neighbouring globules to each other and form groups in the continuous phase. This combination of globules is not clearly visible. This is the primary phase that leads to instability. Flocculation of the dispersed phase may take place formerly, through or after creaming. The reversibility of flocculation depends upon strength of interaction among particles as determined by the chemical nature of emulsifier, the phase volume ratio, the concentration of dissolved substances, particularly electrolytes and ionic emulsifiers. The size of flocculation of globules rest on the globule size distribution, charge on the globule surface, viscosity of the external medium.

(ii) Creaming or sedimentation:

Creaming is the upward movement of dispersed droplets of emulsion relative to the continuous phase (owing to the density difference among two phases). Creaming is the concentration of globules at the top or bottom of the emulsion. Droplets larger than 1 mm may settle favourably to the top or the bottom under gravitational forces. Creaming can also be detected on reason of the change of individual globules. Creaming can be observed by a difference in color shade of the layers. Actually, it is a reversible procedure, i.e., cream can be re-dispersed easily through agitation, this is probable because the oil globules are still enclosed by the protective sheath of the emulsifier. Creaming triggers lack of uniformity of drug distribution. This causes variable dosage. Therefore, the emulsion should be shaken thoroughly before use.

Generally, there are two types of creaming,

- **Upward creaming:** Within this type of creaming the dispersed phase is less dense than the continuous phase. This is usually observed in o/w emulsions. The velocity of sedimentation becomes negative.
- **Downward creaming:** It arises if the dispersed phase is heavier than the continuous phase. Owing to gravitational pull, the globules settle down. This is generally observed in w/o emulsions.

There are several strategies, which can reduce the creaming,

1. Reducing the particle size by means of homogenization.
2. Increasing the viscosity of the external phase through adding the thickening agents like methyl cellulose, tragacanth or sodium alginate.
3. Decreasing the difference in the densities among the dispersed phase and dispersion medium.

(iii) Aggregation or Coalescence:

Within aggregation dispersed particles gather together but do not fuse. Coalescence is the technique by which emulsified particles combine with each to form large particles. This type of closed packing prompts greater cohesion which leads to coalescence. In this procedure, the emulsifier film nearby the globules is damaged to a definite amount. This step can be identified through increased globule size and reduced globules number. Coalescence is observed owing to inadequate quantity of the emulsifying agent. Altered separating of the emulsifying agent and incompatibilities among emulsifying agents.

(iv) Phase inversion:

Phase inversion includes the change of emulsion type from o/w to w/o or vice versa. When we expected to prepare one type of emulsion say o/w, and if the final emulsion turns out to be w/o, it can be designated as a sign of instability. Normally, it occurs due to change in temperature as well as composition.

The phase inversion can be prevented by selecting right emulsifying agents in appropriate concentrations. Wherever possible, ensure that the volume of internal phase does not exceed 74% of the total volume of the emulsion. However, a phase-volume ratio of 50 : 50 (which approximates loose packing) results in about the most stable emulsion.

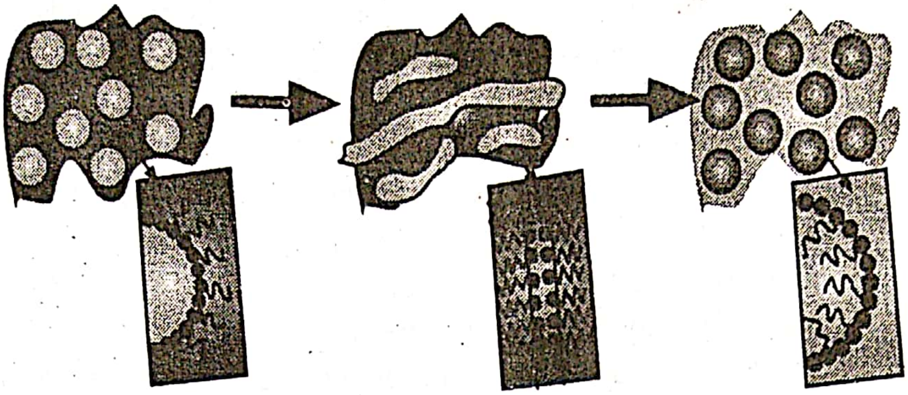


Fig. 3.8: Phase Inversion

3.3.4 Preservation of Emulsions

Owing to the growth of micro-organisms few undesirable variations in the properties of the emulsion arises. These comprise physical separation of the phases, discoloration, gas and odour formation, and alterations in rheologic properties. The proliferation of micro-organisms in emulsified products is maintained by one or more of the constituents present in the formulation. Therefore, bacteria have been shown to destroy non-ionic and anionic emulsifying agents, glycerine, and vegetable gums present as thickeners, with a resultant deterioration of the emulsion. As an outcome, it is vital that emulsions be framed to resist microbial attack by comprising a sufficient amount of preservative in the formulation.

The preservative has integral action contrary to the contamination come across, the main problem is gaining an adequate concentration of preservative in the product. Emulsions are heterogeneous systems in which partitioning of the preservative will occur between the oil and water phases. In the main, bacteria grow in the aqueous phase of emulsified systems, with the result that a preservative that is partitioned strongly in favour of the oil phase may be nearly useless at normal concentration levels since of the low concentration lasting in the aqueous phase. The phase volume ratio of the emulsion is important in this respect. Moreover, the preservative must be in an un-ionized state to enter the bacterial membrane. Therefore, the activity of weak acid preservatives declines as the pH of the aqueous phase increases. Lastly, the preservative molecules must not be bound to other constituents of the emulsion, since the complexes are ineffective as preservatives. Only the concentration of free, or unbound, preservative is active. Normally, Microbial contamination may arise owing to contamination through development or production of emulsion or through its use. usage of impure raw materials, poor sanitation conditions, Invasion by an opportunistic microorganism. The antimicrobial agents the preservative must be, less toxic, stable to heat and storage, chemically compatible with reasonable cost and should be effective against fungus, yeast and bacteria. Examples of antimicrobial preservatives utilized to preserve emulsified systems comprise Parahydroxybenzoate esters like methyl, propyl and butyl parabens, organic acids like ascorbic acid and benzoic acid, organic mercurials such as phenyl mercuric acetate and phenyl mercuric nitrate, quaternary ammonium compounds such as cetrimide. Antioxidants also used as preservative agents for emulsions. The anti-oxidants used must be nontoxic, non-irritant, effective at low concentration under the expected conditions of storage and use, soluble in the medium and stable. Antioxidants for use in oral preparation should also be odourless and tasteless. Some of the commonly used antioxidants are gallic acid, propyl gallate, butylated hydroxyl toluene and butylated hydroxyl anisole.

3.3.5 Rheological Properties of Emulsions

Some flow associated characteristics are needed for the overall performance of an emulsion. Removal of an emulsion from a bottle or tube, Flow of an emulsion in a hypodermic needle, Spreadability of an emulsion on the skin, Stress prompted flow changes during manufacture. The rheology of emulsions has numerous same features to that of suspensions. Though, they vary in three key aspects,

(i) The liquid/liquid interface that comprises surfactant or polymer layers' presents are response to deformation and one has to consider the interfacial rheology.

(ii) The dispersed phase viscosity relation to that of the medium has an influence on the rheology of the emulsion.

(iii) The deformable nature of the dispersed phase droplets, principally for large droplets, has an effect on the emulsion rheology.

Generally, dilute emulsions show "Newtonian flow". As the viscosity of the emulsion rises, flocculation of globules will be reduced since the mobility of globules is restricted, leads to creaming. Owing to this antagonistic effect, an optimum viscosity is necessary for good stability. Concentrated emulsions display "non-Newtonian flow". Multipoint viscometers are utilized for viscosity analysis.

3.3.6 Emulsion Formulation by HLB Method

Hydrophilic lipophilic balance (HLB) is the ratio among the hydrophilic portion of the molecule to the lipophilic portion of the molecule. The higher the HLB of an agent the more hydrophilic it is. Spans are lipophilic and have low HLB. Tweens are hydrophilic and have high HLB. An HLB number (1-20) represents the relative proportions of the lipophilic and hydrophilic parts of the molecule. High numbers (8-18) specify a hydrophilic molecule, and produce an o/w emulsion. Low numbers (3-6) indicate a lipophilic molecule and produce a w/o emulsion. Oils and waxy materials have a 'required HLB number' which helps in the selection of appropriate emulsifying agents when formulating emulsions. Liquid paraffin, for example, has a required HLB value of 4 to obtain a w/o emulsion and 10.5 for an o/w emulsion.

EXERCISE

Multiple Choice Questions:

1. The suspensions having particle size ...... are categorized as coarse suspension.

   (a) Greater than ~1 mm (b) Greater than ~10 mm

   (c) Both of the above (d) None of the above

2. ...... exists when dispersed solid particles in a suspension retain charge in relation to their adjoining liquid medium.

   (a) Surface area (b) Surface potential

   (c) Surface volume (d) None of the above

3. The equal distribution of all the ions in solution retain by ......
   (a) Electric forces (b) Thermal motion
   (c) Both of the above (d) None of the above
4. The flocculated suspension is one in which zeta potential of particle is ......
   (a) −05 to +05 mV (b) −10 to +10 mV
   (c) −20 to +20 mV (d) −30 to +30 mV
5. ...... determines the movement of charged particles via a liquid under the impact of an applied potential difference.
   (a) Electrophoresis (b) Electrosmosis
   (c) Surface charge (d) Static movement
6. ...... is produced by forcing a liquid to course through a stationary solid phase.
   (a) Electrosmosis (b) Electrophoresis
   (c) The sediment potential (d) The streaming potential
7. The flocculated suspensions sediment ......
   (a) Slowly (b) Quickly
   (c) More quickly (d) None of the above
8. ...... suspension involves individual particle settling.
   (a) Flocculated (b) Deflocculated
   (c) Both of the above (d) None of the above
9. Structured vehicles are also termed as or ......
   (a) Thickening (b) Suspending agents
   (c) Both of the above (d) None of the above
10. ...... is the concentration of globules at the top or bottom of the emulsion.
   (a) Creaming (b) Cracking
   (c) Phase inversion (d) State

Keys

1. (a)	2. (b)	3. (c)	4. (c)	5. (a)
6. (d)	7. (c)	8. (b)	9. (c)	10. (a)

Short Questions Answer:

1. **What do you mean by flocculated and deflocculated suspensions?**

Ans. Flocculated Suspensions: Within flocculated suspension, formed flocs (loose aggregates) will arise surge in sedimentation rate owing to increase in size of sedimenting particles. Therefore, flocculated suspensions sediment more quickly. At this point, the sedimentation rest on size of the flocs and the porosity of flocs.

Deflocculated suspensions: Deflocculated suspension involves individual particle settling. Owing to this the rate of sedimentation is slow, which inhibits entrapping of liquid medium which creates it difficult to re-disperse through agitation. This phenomenon is termed as 'caking' or 'claying'. In deflocculated suspension larger particles settle fast and smaller stay in supernatant liquid so supernatant looks cloudy.

2. What is Micro Emulsions?

Ans. "A micro emulsion is a system, of water, oil and an amphiphilic which is a single optically isotropic and thermodynamically stable liquid solution." In some parts, micro emulsions can be considered as small scale versions of emulsions. i.e. Droplet type dispersions either of oil-in-water (o/w) or of water in oil (w/o) with a size range in the order of 5-50 nm in drop radius.

3. Enlist types of Physical instability?

Ans. (i) Flocculation
(ii) Creaming or sedimentation
(iii) Aggregation or coalescence
(iv) Phase Inversion

4. What is the difference between upward creaming and downward creaming?

Ans.
- **Upward creaming:** Within this type of creaming the dispersed phase is less dense than the continuous phase. This is usually observed in o/w emulsions. The velocity of sedimentation becomes negative.
- **Downward creaming:** It arises if the dispersed phase is heavier than the continuous phase. Owing to gravitational pull, the globules settle down. This is generally observed in w/o emulsions.

5. Enlist Interfaciai properties of suspended particles.

Ans.

1. Surface Potential	2. Surface Free Energy
3. Electric Double Layer	4. Zeta Potential
5. Wetting	6. Electro kinetic Phenomena

Long Question Answer:

1. Discuss in detail interfacial properties of suspended particles?

Ans. Refer Point No. 3.2.1.

2. Explain in detail Microemulsions and multiple emulsions.

Ans. Refer Point No. 3.3.2.

3. Enlist various instabilities of emulsions.

Ans. Refer Point No. 3.3.3.

4. Explain Preservation of emulsions.

Ans. Refer Point No. 3.3.4.

5. Explain in detail about settling in suspensions.

Ans. Refer Point No. 3.2.2.

***

Unit ... 4

MICROMERETICS

♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- Understanding the impact of particle sizes on pharmaceutical processing/preparation.
- Learning of different methods used for characterization of particles, particle size.
- Discussion of the characteristics and significance of surface area and particle shape.
- Techniques utilized for determining the particle surface area.
- Derived properties of a powder.

4.1 INTRODUCTION

Information and mechanism of the size as well as the size range of particles have vital significance in pharmacy. Therefore, size as well as surface area of a particle directly affects the physical, chemical, and pharmacologic properties of a drug. Moreover, particle size can alter the drug release patterns that are administered parenterally, rectally, topically and orally. The effective formulation of suspensions, emulsions, and tablets, from the perspectives of mutually physical stability and pharmacologic response, also determined by the particle size attained in the product. In the tablet and capsule production sector, control of the particle size is important in attaining the essential flow properties and accurate mixing of granules and powders. Micromeritics is the science and technology of small particles. The unit of particle size used in then micrometer (µm), micron (µ) and equal to 10^{-6} m.

4.2 PARTICLE SIZE AND DISTRIBUTION

There is a lot of difference in actions and evaluation parameters of particles of different sizes. The below mentioned table 4.1 depicts the relationship among particle size as well as instances of which products might comprise that size particle. Normally, colloids contain the smallest particles while the largest particles of interest to the pharmaceutical industry are utilized in the production of tablets and capsules.

Table 4.1 (a): Dimensions of Particles in Pharmaceutical Dispersed System

Particle size, Diameter		Approximate sieve size	Examples
Micrometers (μm)	Millimeters		
0.5-1.0	0.0005-0.010	-	Emulsions, Suspensions.
10-50	0.010-0.050	-	Upper limit of sub sieve range, coarse emulsion particles, flocculated suspension particles.
50-100	0.050-0.100	325-140	Lower limit of sieve range, fine powder range.
150-1000	0.150-1.000	100-18	Coarse powder range.
1000-3360	1.000-3.360	18-6	Average granule size.

In a collection of particles of more than one size in other words, in a polydispersed sample, two properties are vital, specifically,

(a) The shape and surface area of the individual particles.

(b) The size range and number or weight of particles present.

The size of a sphere is freely stated in terms of its diameter. However, there is no one distinctive diameter for a particle. Alternative must be made to the use of an equivalent spherical diameter, which transmits the size of the particle to the diameter of a sphere having the same surface area, volume, or diameter. Normally, there are four types of diameter.

- **The surface diameter (ds):** It is the diameter of a sphere having the same surface area as the particle in question.
- **The volume diameter (dv):** It is the diameter of a sphere having the same volume as the particle.
- **The projected diameter (dp):** It is the diameter of a sphere having the same observed area as the particle when viewed normal to its most stable plane.
- **The Stokes diameter (dst):** The size can often have expressed as the stokes diameter, which defines an equivalent sphere suffering sedimentation at the same rate as the asymmetric particle.

4.3 MEAN PARTICLE SIZE NUMBER AND WEIGHT DISTRIBUTION, PARTICLE NUMBER

Any gathering of particles is commonly polydispersed. Hence, it is essential to have information regarding the size of a particle and the number of particles of the same size present in the sample. Therefore, it is necessary to evaluate the size range existing and the amount or weight fraction of each particle size. Generally, this is the particle-size distribution;

owing to this we can calculate mean particle size for the sample. If a researcher wishes to work with nearly uniform size particles (mainly monodisperse rather than polydispersed), researcher may get bunches of latex particles as small as 0.060 μm (60 nm) in diameter with a standard deviation (SD), σ, of ±0.012 μm and particles as large as 920 μm (0.920 nm) with σ = ±32.50. This kind of uniform size particle are utilized in medical field for numerous diagnostic examinations; as particle-size standards for particle analyzers; for the accurate identification of pore sizes in filters; and such as uniformly sized surfaces upon which antigens can be coated for effective immunization. Nano sphere are existing in 22 sizes, from 21 nm (0.021 μm) to 900 nm (0.9 μm or 0.0009 mm) in diameter for instrument calibration and quality control in the manufacture of submicron-sized products like liposomes, nanoparticles, and microemulsions.

- **Particle number**

Particle number is an important expression in particle technology. Generally, it is the number of particles per unit weight, N, which is stated in terms of (dvn). Normally, we can obtain the number of particles per unit weight by following expressions. For instance, assume that the particles are spheres, the volume of a single particle is π d3vn/6, and the mass (volume × density) is (π dvn3ρ)/6 g per particle. Thus, the number of particles per gram is then achieved from the proportion,

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

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

Average Particle Size:

After microscopic examination of a powder sample, record the data for number of particles lying in each size range. Such data for a sample is given the table 4.1 (b).

Table 4.1 (b): Particle Size Distribution Data obtained by Microscopic Method

Size Range (μm)	Mean Size Range (μm) (d)	Number of particles in each size range (n)	nd	nd^2
0.5-1.0	0.75	3	2.25	1.68
1.0-1.5	1.25	15	18.75	23.44
1.5-2.0	1.75	31	54.25	94.94
2.0-2.5	2.25	58	130.5	293.63
2.5-3.0	2.75	18	49.5	136.13
3.0-3.5	3.25	5	16.25	52.81
3.5-4.0	3.75	2	7.5	28.13
		$\sum n = 132$	$\sum nd = 279$	$\sum nd^2 = 630.76$

Edmundson derived a general equation for average particle size, whether it is arithmetic, a geometric, or a harmonic mean diameter:

$$d_{mean} = \left(\frac{\sum nd^{p+f}}{\sum nd^{f}}\right)^{1/p}$$

where, n = number of particles in a size whose mid-point, d, is one of the equivalent diameters, p = index related to the size of an individual particle. When p = 1, p = 2 or p = 3 is an expression of the particle length, surface or volume respectively. The p value decides whether the mean is arithmetic (p is positive), geometric (p is zero) or harmonic (p is negative).

Arithmetic mean: Arithmetic mean of a powder is defined as the sum of the particle sizes divided by the number of particles. Types of arithmetic mean sizes are as follows:

Table 4.1 (c): Important Arithmetic diameters

Mean diameter	Equation	Comments
Length-number mean	$d_{ln} = \frac{\sum nd}{\sum n}$	Satisfactory if size range is narrow and distribution is normal. Rarely seen in pharmaceutical powders.
Volume surface mean diameter	$d_{vs} = \frac{\sum nd^3}{\sum nd^2}$	Inversely related to specific surface area.
Volume weighted mean diameter	$d_{wm} = \frac{\sum nd^4}{\sum nd^3}$	Limited Pharmaceutical significance.
Mean weight diameter (volume-number mean)	$d_{vn} = \sqrt[3]{\frac{\sum nd^3}{\sum n}}$	The number of particles per gram of material.
Surface-number mean diameter	$d_{sn} = \sqrt{\frac{\sum nd^2}{\sum n}}$	Refers to particle having average surface area.

Particle Size Distribution:

When the number or weight of particles lying within a certain range is plotted against the size range or mean particle size, a so-called frequency distribution curve is obtained.

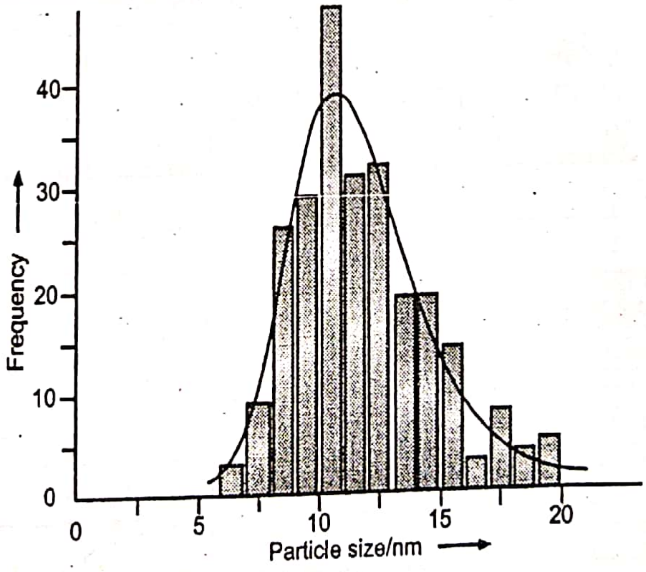


Fig. 4.1

When the number (or weight) of particles lying within certain range is plotted against the mean particle size, a frequency distribution curve is obtained. Histogram plotted gives visual representation of the distribution, which an average diameter cannot achieve. The particle size distribution in two powder samples have same average diameter, but differ in the distribution of sizes above and below the mean. From frequency distribution curve gives the number of particles within particular size range is referred as mode.

When number of particles lying in particular size range is plotted against mean particle size, a symmetrical (bell shaped) curve is obtained and is called as normal distribution curve. Normal distribution is usually not found in pharmaceutical powders due to uneven size reduction.

When the number of particles is plotted against the mean particle size, the curve is called as number frequency distribution curve. When the weight of particles is plotted versus the mean particle size, the curve is called as the weight distribution frequency curve. When size distributions are not symmetrical, the frequency distribution of such powder sample exhibit skewness as in figure 4.2 (a). If distribution is skewed, it can be frequently made symmetric if the sizes are replaced by the logarithms of particle sizes as in figure 4.2 (b).

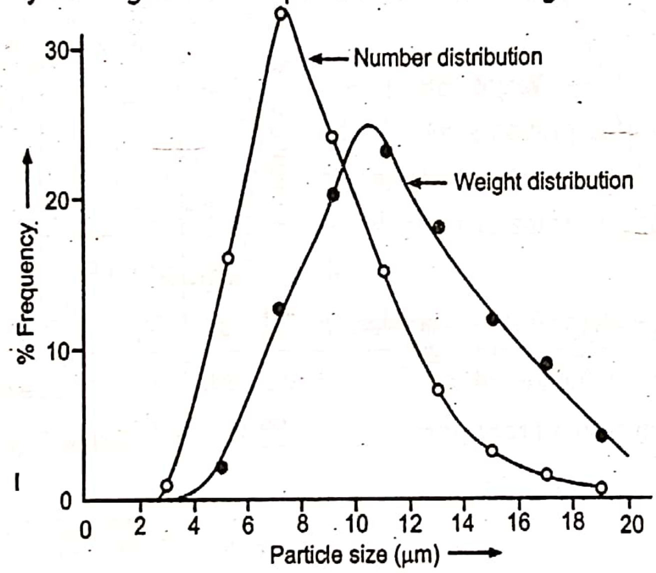


Fig. 4.2 (a): Normal Distribution Curve

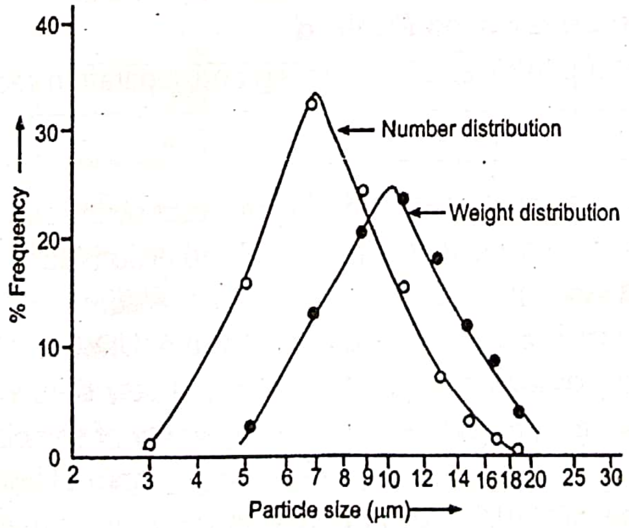


Fig. 4.2 (b): Log-normal Distribution Curve

When cumulative percentage under (or over) a particular size plotted against the particle size, this gives a sigmoidal curve as in figure 4.2 (c) with the mode being the particle size of the greatest slope.

When the logarithm of the particle size is plotted against the cumulative frequency on a probability scale, a linear relationship is observed as in figure 4.2 (d). A straight line is completely by one point and the slope. The reference point used is the logarithm of the particle size equivalent to 50% on the probability scale i.e., the 50% size, this is known as geometric mean diameter (d_g). The slope is given by the geometric standard deviation (σ_g) which is a quotient of the ratio of undersize or oversize / 50% size or 50% size / undersize or oversize.

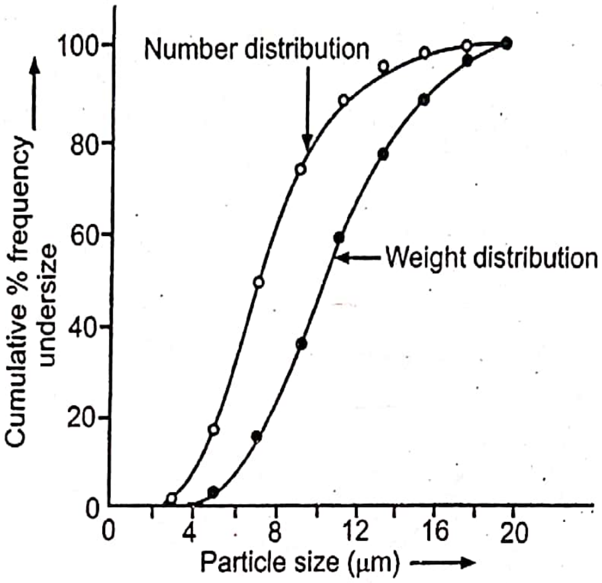


Fig. 4.2 (c): Cummulative Frequency Distribution Curve

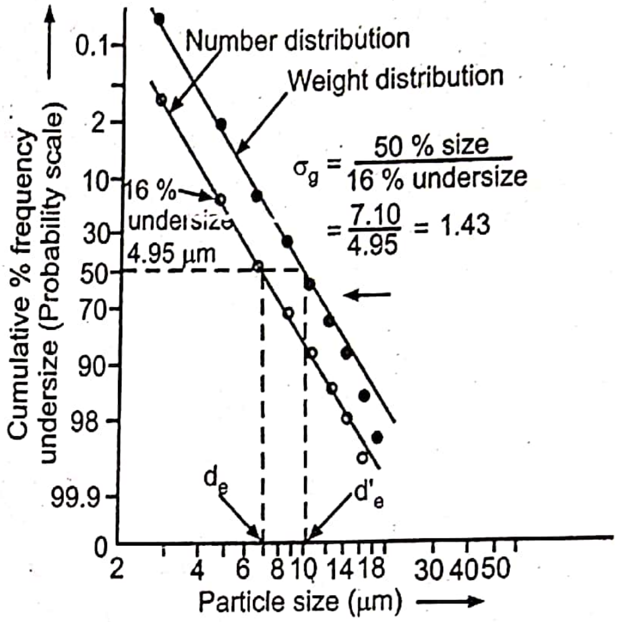


Fig. 4.2 (d): Log Probability Plot

4.4 METHODS FOR DETERMINING PARTICLE SIZE BY DIFFERENT METHODS

4.4.1 Counting and Separation Method

The determination of particle size by counting and separation technique involves several methods in it,

- **Microscopy**

The determination of particle size by utilizing microscopy based on the principle of Optic or electronic measures. It involves two dimensional projections such as projection screen or circles and image analysing programs. Generally, it measures feret diameters and equal circles. It can measure particle size range 0.001-1000 µm. Using microscopy, we can obtain particle number average, or area average. Microscopy is very simple and natural method. It also facillates shape information within reasonable quantity of sample. The microscopes like Light microscope (1-1000 µm), Fluorescence microscope, Confocal laser scanning microscopy and Electron microscope (SEM (0.05-500 µm), TEM (Å-0.1 µm)) are used in this technique.

- **Sieving**

Sieving method is normally a separation technique. Sieving method can measure projected perimeter-square and circle and particle size ranging 5-125000 µm. Air-jet sieving involves individual sieves with an under pressure and air stream under the sieve which blows away oversize particles. This technique gives weight average.

Table 4.2: Separation methods Powder Grades According to BP

Description	Sieve diameter µm	Sieve that do not allow more than 40% to pass µm
Coarse	1700	355
Moderate coarse	710	250
Moderate fine	355	180
Fine	180	
Very fine	125	

The particle size ranging between 50-1500 µm are estimated by this method and expressed as d_{sieve}. The sieves are constructed with wire having square meshes, woven from wire of brass, bronze or stainless steel. The sieves should not be coated or plated and there should be no interaction between sieve material and the sample. Standard sieves and their dimensions as per IP are given below the table.

Table 4.3: Designation and Dimensions of I.P Specification Sieves

Sieve Number	Aperture size Micrometer	Sieve Number	Aperture size Micrometer
10	1700	44	325
12	1400	60	250
16	1000	85	35
22	710	100	36
25	600	120	34
30	500	150	36
36	425	170	35

Method: The powder sample is placed on the nest of standard sieves stacked over one another. The coarsest sieve is placed on the top followed by sieves of decreasing pore size. The nest of sieves with the sample is placed on the mechanical shaker and shaken for a fixed period of time. Powder passes through a particular sieve and is retained on the next sieve is collected and weighed. The weight of the powder that passes through a given sieve and retained on the next sieve is determined. For example, a powder passing through sieve number 80 and retained on 100 is assigned an arithmetic mean diameter. This is reported as undersize.

Advantages:

- Easy to perform and inexpensive.
- Wide size range.

Disadvantages:

- Abrasion between particles leads to size reduction during shaking.
- Aggregation of particles due to generation of electrostatic charge.
- Presence of moisture leads to improper sieving and particles clogged.

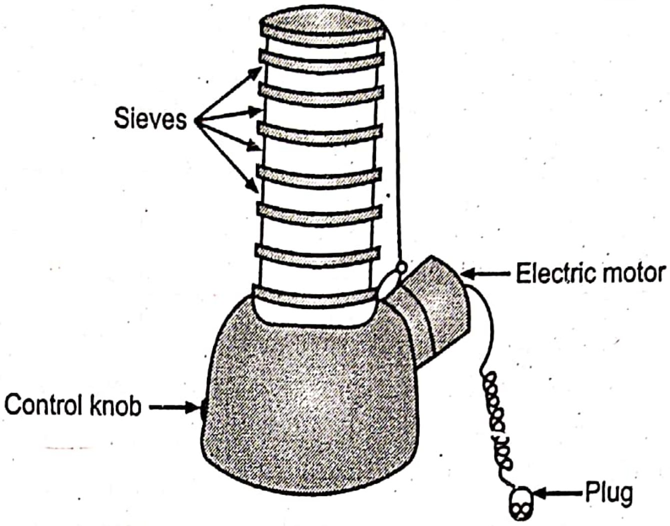


Fig. 4.3

Sedimentation Method:

This method is used over a size range of 1-200µm, size expressed as Stoke's diameter (d_{st}). This Method finds application in formulation, evaluation of suspensions, emulsions, and determination of molecular weight of polymers.

Rate of settling of particles in a suspension or emulsion may be obtained by Stoke's law:

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

where, h = distance of fall in time, t,

η_0 = viscosity of the medium,

ρ_s = density of particles,

ρ_0 = density of dispersion medium and

g = acceleration due to gravity.

Method: The apparatus used for this method is called Anderason pipette. It consists of 550 ml cylindrical vessel containing vertical scale graduated from 0-20 cm. The cylindrical vessel has stoppered 10 m bulb pipette fitted with two-way stopcock and a side tube for removing the sample. When pipette is placed in the cylinder its lower tip is 20 cm below the surface of the suspension. Prepare1 or 2% suspension of a powder sample in a suitable medium. A deflocculating agent is added to help uniform dispersion. The cylindrical vessel is stoppered and the vessel is shaken for uniform distribution of the suspension. Remove the stopper and place the two-way pipette and place the whole apparatus undisturbed in a constant temperature bath. At different time intervals, 10ml samples are withdrawn using two-way pipette and collect in a watch glass. The samples collected in a watch glass are evaporated and weighed.

The residue of dried sample is the weight fraction having particles of size less than the size obtained by the Stoke's law and weight of each sample residue is called as the weight undersize.

Advantages:

- Equipment required can be relatively simple and inexpensive.
- Can measure a wide range of sizes with accuracy and reproducibility.

Dis-advantages:

- Sedimentation analysis must be carried out at concentrations which are sufficiently low for interactive effects between particles to be negligible.
- Large particles create turbulence, are slowed and are recorded undersize.
- Careful temperature control is necessary to suppress convection currents.
- Particle re-aggregation during extended measurements.
- Particles have to be completely insoluble in the suspending liquid.
- The long settling time required for very fine particles and separate tests should be performed for each sample.

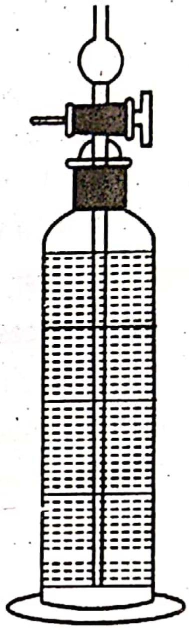


Fig. 4.4

Conductivity Method or Coulter Counter Method:

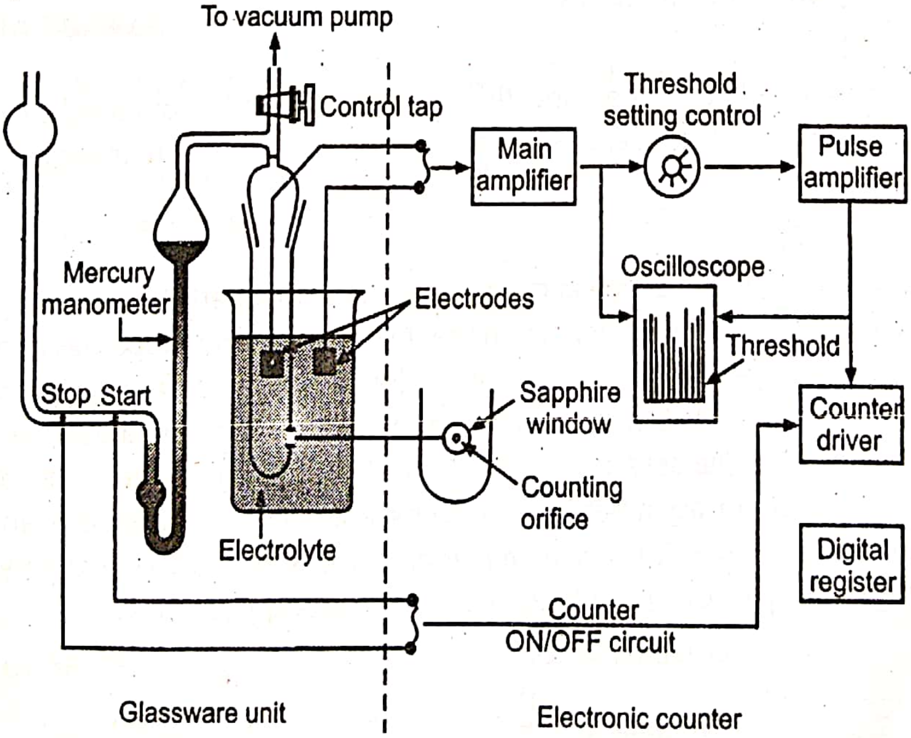


Fig. 4.5

It is used for measuring particle volume which is converted into diameter. The particles ranging from 0.5-500 μm can be measured by this method and gives number distribution. The size expressed as volume diameter (d_v).

Method: It consists of two electrodes one of which is immersed into a beaker containing the particle suspension in an electrolyte (NaCl). The other electrode is immersed into the electrolyte contained in a glass tube and this tube is immersed into the beaker containing the particle suspension in the electrolyte. This dispersion is filled in the sample cell which has as an orifice and maintains contact with the external medium. A known volume of suspension is passed through the orifice so that only one passes at a time. A constant voltage is applied across the electrodes so as to produce current. When a suspended particle travels through orifice, it displaces its own volume of electrolyte into the beaker. The change in electrical resistance is proportional to the volume of the particle is converted into a voltage pulse that is amplified and processed electronically.

Advantages:

- The process is rapid and completed in a short time.
- True volume distribution and high resolution
- Wide range of measurement: particle diameter from approx. 0.5-400 μm

Dis-advantages:

- Expensive and needs calibration
- Medium must be an electrolyte and Low particle concentration
- Errors with porous particles and orifice blocking troublesome.
- Particles below minimum detectable size go unnoticed.
- Difficult with high density materials.

Chromatography:

Chromatography technique measures the hydrodynamic radius of particle. Normally, it is based on the principle of Size exclusion and porous gel beads. It measures size range 0.001-0.5 μm.

4.4.2 Particle Shape

The information regarding shape and the surface area of a particle is very important. The shape of the compound has direct impact on the flow and packing properties of a powder as well as having some impact on the surface area. Normally, sphere has smallest surface area per unit volume. If the particle is more asymmetric, then the surface area per unit volume will be greater. Normally, the characterization of spherical particle is carry out by its diameter. As the particle converts more asymmetric, it converts gradually tough to allot an expressive diameter to the particle. Thus, it is a simple matter to attain the surface area or volume of a sphere since for such a particle. It can be find out by following equations

$$\text{Surface area} = \pi d^2$$

and

$$\text{Volume} = \frac{\pi d^3}{6}$$

Where, d is the diameter of the particle. Thus, the surface area of a spherical particle is proportional to the square cube of the diameter and the volume of spherical particle is proportional to cube of the diameter.

To get information of the surface or volume of a non-spherical particle, the diameter is taken in to consideration as a characteristic of the particle and relates this to the surface area or volume by a correction factor. If we view the particles microscopically, if we wanted to calculate the surface area and volume from the expected diameter, dp, of the particles. The square and cube of the selected dimension are directly proportional to the surface area and volume, correspondingly. Using proportionality constants, we can write as

$$\text{Surface area} = \alpha_s d_p^2 = \pi d_s^2$$

Where, d_s are the equivalent surface diameter, α_s is the surface area factor. For calculating volume we can write down,

$$\text{Volume} = \alpha_v d_p^3 = \frac{\pi d_v^2}{6}$$

Where, α_v is the volume factor and d_v is the equivalent volume diameter.

Generally, the shape factors (surface area and volume) are the ratio of one diameter to another. Thus, for a sphere, $\alpha_s = \pi\, ds^2/dp^2 = 3.142$ and $\alpha_v = \pi\, dv^3/6\, dp^3 = 0.524$. There are as several of these volume and shape factors as there are pairs of equivalent diameters. The ratio $\frac{\alpha_s}{\alpha_v}$ is also utilized to characterize particle shape. When the particle is spherical, $\frac{\alpha_s}{\alpha_v} = 6.0$. The more asymmetric the particle, the more this ratio exceeds the minimum value of 6.

4.4.3 Specific Surface

The volume or surface area per unit weight is a vital characteristic of a powder while performing surface adsorption and dissolution rate studies. The specific surface is the surface area per unit volume, S_v, or per unit weight, S_w, and can be obtained from above described equations. Generally, for asymmetric particles where the characteristic dimension is not clear.

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

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

Where, n is the number of particles. Therefore, the surface area per unit weight is

$$S_w = \frac{S_v}{\rho}$$

Where, ρ is the true density of the particles. The general equation can be obtained by substituting equation of S_v in S_w:

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

Where, the dimension is stated as dv_s, the volume surface diameter characteristic of particular surface.

When the particles have spherical or (somehow spherical), above equation converts in to

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

As, for a sphere $\frac{\alpha_s}{\alpha_v}$ is 6.0.

4.5 METHODS FOR DETERMINING SURFACE AREA

The calculation of surface area of a powder sample can be done from the information obtained from particle-size distribution. Generally, two techniques are normally used for the calculation of surface area. In one technique, the quantity of a gas or liquid solute that is adsorbed on the sample of powder to form a monolayer is a direct function of the surface area of the sample. The second technique is subjected to on the fact that the rate at which a gas or liquid permeates a bed of powder is linked, amongst other issues, to the surface area exposed to the permeant.

4.5.1 Permeability

Air permeability technique is utilized for estimation of surface diameter d_s. This technique is vital in regulating batch to batch variations in production of powders. The instrument engaged in this technique is simple and carry out quick determination. In this technique, within the sample holder, powder is packed as a compact plug. In this packing, surface-surface contacts between particles appear as a series of capillaries. The surface of these capillaries and therefore this technique is associated with the surface area of powder. After permitting the air through powder bed at constant pressure, the bed resists the flow of air and owing to this pressure drop arises. As the surface area per gram of the powder is maximum S_w, the resistance to flow is greater. Generally, the permeability of air for a given pressure drop is inversely proportional to specific surface.

In this technique, normally the flow rate through the plug or bed is affected by:

1. **Capillary irregularity:** If the capillaries are not circular and longer than the length of bed then it normally affects the flow rate.
2. **Degree of compression:** If the plug is more compact, porosity will be low and increased air flow resistance.

The surface area is calculated by this technique using the Kozeny-Carman equation

$$V = \frac{A}{\eta S_w^2} \cdot \frac{\Delta Pt}{Kl} \cdot \frac{\varepsilon^2}{(1-\varepsilon)^2}$$

Where, A = Cross sectional area of bed (cm^2)

Σ = Porosity of the cake (bed).

S_w = Specific surface of the particles comprising the cake.

K = Kozeny constant (usually taken as 5).

T = Time of flow, in seconds.

P = Pressure difference of the plug.

V = Volume of air flowing via bed, cm^3.

Generally, Fisher subsieve sizer apparatus is employed in the course of air permeability technique.

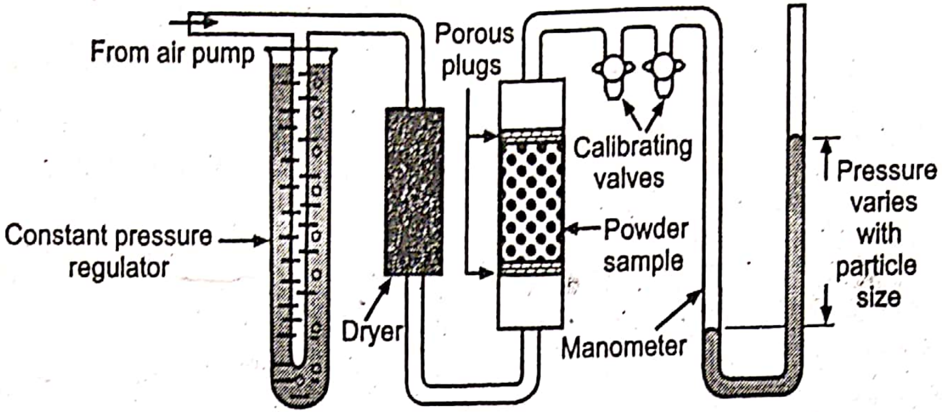


Fig. 4.6: Fisher Subsieve Sizer Apparatus

4.5.2 Adsorption

Particles with enormous specific surfaces are good adsorbents of gases and solution. Quantity of gas that is adsorbed to from a monomolecular layer on the adsorbent is a function of surface area of the powder. The calculation of the specific surface is done by this principle. Adsorption technique also utilized to assess surface diameter, ds. In governing the surface of the adsorbent, the volume in cubic centimeters of gas adsorbed per gram of adsorbent can be plotted in contradiction of the pressure of the gas at constant temperature to give a type II isotherm shown in Figure 4.7.

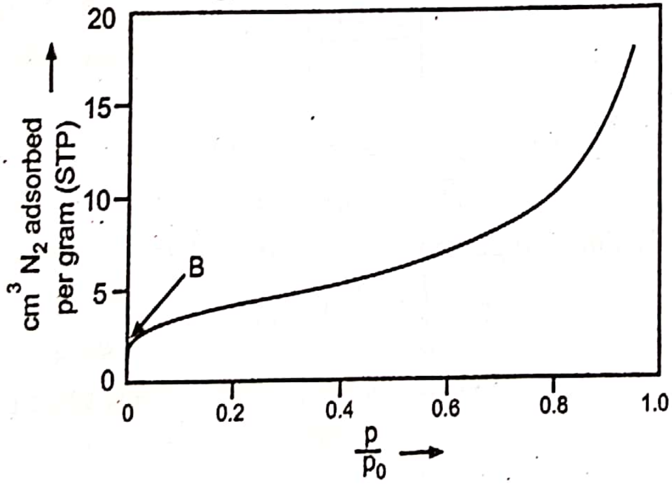


Fig. 4.7: Isotherm showing the Volume of Nitrogen Adsorbed on a Powder at Increasing Pressure Ratio. Point *B* represents the Volume of Adsorbed Gas Corresponding to the Completion of a Monomolecular Film. Key: STP = Standard Temperature and Pressure

Normally, the adsorbed layer is monomolecular at low pressures and converts multimolecular at higher pressures. The completion of the monolayer of nitrogen on a powder is shown as point B in Figure 4.2. The volume of nitrogen gas, V_m, in cm^3 that 1 g of the powder can adsorb when the monolayer is complete is more accurately given by using the Brunaver, Emmett, and Teller (BET) equation, which can be described as:

$$\frac{p}{V\,(p_0 - p)} = \frac{1}{V_m b} + \frac{(b - 1)\,p}{V_m b p_0}$$

Where, V is the volume of gas in cm^3 adsorbed per gram of powder at pressure p, p_0 is the saturation vapor pressure of liquefied nitrogen at the temperature of the experiment, and b is a constant that expresses the difference between the heat of adsorption and heat of liquefaction of the adsorbate (nitrogen). Note that at $\frac{p}{p_0} = 1$, the vapour pressure, p, is equal to the saturation vapor pressure.

4.6 DERIVED PROPERTIES OF POWDERS

Few derived properties of powder which help in quantification of vital variables are

4.6.1 Porosity

Voids are the gaps among the particles in a powder. The volume used by means of such voids is called as void volume.

$$\text{Void volume } (V_v) = \text{Bulk volume} - \text{True volume}$$

The ratio of the void volume to the bulk volume of the packing is called as the porosity of the powders. Or, the ratios of the total volume of void spaces (V_v) to the bulk volume of the material.

$$\text{Porosity (E)} = \frac{\text{Void volume}}{\text{Bulk volume}}$$

$$= \frac{V_v}{V_b}$$

$$= \left[\frac{V_b - V_t}{V_b}\right]$$

(As, $V_v = V_b - V_t$)

$$= 1 - \left(\frac{V_t}{bt}\right)$$

Porosity is normally stated in percent

$$E = \left[\frac{1 - V_t}{V_b}\right] \times 100$$

The relation among porosity and compression is significant since porosity regulates the rate of disintegration, dissolution and drug absorption.

4.6.2 Packing Arrangement Densities

Density is the ratio of mass to volume (ρ) of the material through considering the three sorts of volume of powders. Further, densities are divided as:

- **Bulk density (ρ_b):** Bulk density is the ratio of total mass of the powder to the bulk volume of the powder. It is measured via driving the weighed powder into a measuring cylinder and the volume is noted.

It is stated in gm/ml and is shown by: $\rho b = \frac{M}{V_b}$

Whereas, V_b is the Bulk Volume of the powder, M is the total mass of the powder.

- **Granular density (ρ_g):** Granular density is the ratio of mass of the powder to the granule volume of the powder.

$$\text{Granular density, } \rho_g = \frac{M}{V_g}$$

- **True density (ρ_t):** True density is the ratio of mass of the powder to the true volume of the powder.

$$\text{True density, } \rho_t = \frac{M}{V_t}$$

4.6.3 Bulkiness and Flow Properties

Bulkiness or bulk is the reciprocal of bulk density, which is an important consideration in the packaging of powder. The bulk density of calcium carbonate can differ from 0.1 to 1.3 and the lightest or bulkiest type would need. A container nearly 13 times greater than that required for the heaviest range. As the particle size decreases the bulkiness increases within a mixture of material of diverse size. Though, the minor particle shifts among the lager one and incline to relief the bulkiness.

To acquire weight consistency of the tablet, the powder must possess a better flow property. Flow properties of the powders rest on the:

1. Shape.
2. Particle size.
3. Porosity and density.
4. Moisture of the powder.

1. Shape:

The flow properties are enhanced by spherical, smooth particles. Owing to cohesiveness as well as friction, surface roughness leads to poor flow. As a result, flat and elongated particles tend to pack loosely, hindering the flow.

2. Particle size

The rate of flow of powder is directly proportional to the diameter to the particles. Beyond specific point the increase in particle size declines the flow properties. Since in small particle (10 µ) the Van der Waal's, electrostatic and surface tension forces lead to cohesion of the particles causing poor flow. Increase in particle size, influences the gravitational force on the diameter which increases the flow property. But suitable mixtures of fines and coarse increases flow characteristic, as the fines get absorbed and coarse particle decrease friction.

3. Porosity and density

Particles with low internal porosity and high density incline to have better flow properties.

4. Moisture

Moisture has significant effect on the flow property. Since, moisture leads to poor flow property due to cohesion and adhesion.

- **Angle of repose**

Angle of repose measures the flow characteristic. Angle of repose is the maximum angle probable among the horizontal plane and the surface of a pile of powder.

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

$$\phi = \tan^{-1}\left(\frac{h}{r}\right)$$

Wherever, ϕ = Angle of repose, h = Height of pile, r = Radius of the base of pile

The calculation of angle of repose is done by calculating the height and radius of heap of powder formed. The frictional forces in a loose powder can be measured by Angle of repose. The lower the angle of repose, improved will be flow property.

The values of angle of repose are given below

Table 4.3: The values of angle of repose

Angle of repose (in °)	Type of flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

- **Carr's Consolidation (Compressibility) Index (CI)**

Carr's consolidation index specifies powder flow properties. It is stated in percentage. It is defined as:

$$\text{Consolidation Index} = (\text{CI}) = \text{Tapped density} - \frac{\text{Poured density}}{\text{Tapped density}}$$

$$\text{Therefore} = \left(D_t - \frac{D_b}{D_t}\right) \times 100$$

Wherever, D_t = Tapped density of the powder

D_b = Poured density of the powder

Determination of Tapped density and Poured density:

Normally, it is determined through passing a fixed amount of powder into a measuring cylinder and the volume is noted. CI can be calculated by finding out by tapped density and Poured density of powder.

Table 4.4: Powder grading for their flow properties according to their Carr's index

Percent (%) Carr's index	Type of flow
5-15	Excellent
12-18	Good
18-21	Fair to passable
23-25	Poor
33-38	Very Poor
> 40	Very Very Poor

EXERCISE

Multiple Choice Questions:

1. The physical, chemical, and pharmacologic properties of a drug are directly affected by ……
   (a) Size (b) Surface area
   (c) Both of the above (d) None of the above
2. …… is the science and technology of small particles.
   (a) Micromeritics (b) Microscopy
   (c) Rheology (d) None of the above
3. The unit of particle size used is in ……
   (a) Kilometer (km) (b) Centimeter (Cm)
   (c) Millimeter (mm) (d) Micrometer (µm)
4. 1 micrometer (µm) is equal to ……
   (a) 10^{-5} m (b) 10^{-6} m
   (c) 10^{-7} m (d) 10^{-8} m
5. Particle size with diameter of 0.5-1.0 Micrometers (µm) is useful for ……
   (a) Emulsions (b) Suspensions
   (c) Both of the above (d) None of the above
6. The size of a sphere is freely stated in terms of its ……
   (a) Area (b) Diameter
   (c) Radius (d) Volume
7. …… is the diameter of a sphere having the same observed area as the particle when viewed normal to its most stable plane.
   (a) The surface diameter (d_s) (b) The projected diameter (d_p)
   (c) The volume diameter (d_v) (d) The Stokes diameter (d_{st})
8. …… is the number of particles per unit weight.
   (a) Particle volume (b) Particle number
   (c) Particle mean (d) Particle weight
9. …… technique is utilized for estimation of surface diameter d_s.
   (a) Air permeability (b) Vacuum
   (c) Filtration (d) Weighing
10. The ratio of the void volume to the bulk volume of the packing is called as the ……
    (a) Tap density (b) Bulk density
    (c) Followability (d) Porosity

Keys

1. (c)	2. (a)	3. (d)	4. (b)	5. (c)
6. (b)	7. (b)	8. (b)	9. (a)	10. (d)

Short Questions Answer:

1. Enlist four types of diameter.

Ans. (a) The surface diameter (ds).

(b) The projected diameter (dp).

(c) The volume diameter (dv).

(d) The Stokes diameter (dst).

2. What do you mean by stockes diameter (dst)?

Ans. The size can often have expressed as the stokes diameter, which defines an equivalent sphere suffering sedimentation at the same rate as the asymmetric particle.

3. What is Particle number?

Ans. Particle number is an important expression in particle technology. Generally, it is the number of particles per unit weight, N, which is stated in terms of (d_{vn}). Normally, we can obtain the number of particles per unit weight by following expressions.

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

4. What do you mean by porosity?

Ans. The ratio of the void volume to the bulk volume of the packing is called as the porosity of the powders. Or, the ratios of the total volume of void spaces (Vv) to the bulk volume of the material.

$$\text{Porosity (E)} = \frac{\text{Void volume}}{\text{Bulk volume}}$$

5. What do you mean by angle of repose?

Ans. Angle of repose measures the flow characteristic. Angle of repose is the maximum angle probable among the horizontal plane and the surface of a pile of powder.

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

$$\phi = \tan^{-1}\left(\frac{h}{r}\right)$$

Wherever, ϕ = Angle of repose, h = Height of pile, r = Radius of the base of pile

Long Question Answer:

1. Discuss in detail methods for determining particle size?

Ans. Refer Point No. 4.4.

2. Explain methods for determining surface area.

Ans. Refer Point No. 4.5.

3. Enlist and explain derived properties of powders.

Ans. Refer Point No. 4.6.

****

Unit ... 5

DRUG STABILITY

♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- Define the average and instantaneous rate of a reaction.
- Distinguish molecularity and order of a reaction as well as simple and complex reactions.
- Define the reaction rate in terms of change in concentration of either of the reactants or products with time.
- Discuss the dependence of rate of reactions on concentration, temperature and catalyst.
- Derive integrated rate equations for the zero and first order reactions.

5.1 INTRODUCTION

Formally, stability is stated as the time period through which a bioactive (API) or drug product (FPP) maintains its same properties and characteristics (i.e. Physical, Chemical, Microbiological, Therapeutic and Toxicological orders to retain its character, power, quality, and purity) that it obsessed during manufacturing period. According to the USP, pharmaceutical product stability is defined as, "amount to which a product preserves with in specified limits and through its period of storage and use (i.e. shelf life).

Shelf life is the time necessary for the concentration of the reactant to decrease to 90% of its original concentration. Shelf life is represented as t_{90} and the units of time /conc.

$$t_{90} = \frac{(a - 0.9\,a)}{k_o} = \frac{0.1\,a}{k_o}$$

Where, a = Initial concentration,

k_o = Specific rate constant for zero order reaction.

Generally, Stability testing is employed for,

(i) Delivering evidences of the change in quality of the drug product with time.

(ii) Governing endorsed storage conditions.

(iii) Confirming shelf life for the drug product.

(iv) Determining container closure system suitability.

5.2 REACTION KINETICS

In chemical kinetics, reaction order with in relation with specific reactant is stated as the index, or exponent, to which its concentration term in the rate equation is raised.

For instance, given a chemical reaction with a rate equation,

$$2A + B \rightarrow C$$

$$r = k[A]^2[B]^1$$

The reaction order with respect to A in this case is 2 and in relation to B in this case is 1; the general order of reaction is 2 + 1 = 3. It is not essential that the reaction order must be a whole number, zero and fractional order values are apparent. However, these orders tend to be integers.

Molecularity of Reaction:

Molecularity: It refers to the number of molecules, atoms or ions reacting or colliding in process to form products.

Unimolecular reaction: in such reactions, molecularity is one as single molecules participate in the reaction.

Example: Conversion of trans-Vitamin A to Cis-Vitamin A.

Bimolecular Reaction: In such rections, Molecularity is two as two molecules participate in the reaction.

$$H_2 + I_2 \rightarrow 2HI$$

Order of Reaction: This is the number of concentration terms that determine the rate. Consider the reaction:

$$A + B \rightarrow C + D$$

The rate of the reaction is proportional to the concentration of A to the power of x, $[A]^x$ and also the rate may be proportional to the concentration of B to the power of y, $[B]^y$.

The overall equation is; Rate = k $[A]^x$ $[B]^y$

The overall order of reaction is x + y.

5.2.1 Zero Order Reaction

A zero-order reaction is a reaction having rate independent of concentration of reactant. In different terms, increasing or decreasing the reactants concentration will not have direct effect on reaction. i.e. concentration of reactant will not speed-up or slow down the reaction. This means that the reaction rate is equal to the rate constant, k, of that reaction.

$$\text{Rate} = -\frac{d[A]}{dt} = k\,[A]^0 = k = \text{Constant}$$

If we plot rate as a time function, we can attain the graph given below. This only defines a narrow time region. The slope of the graph is equivalent to k, the rate constant. Thus, k is constant with time. Moreover, we can notice that rate of the reaction is totally independent of how much quantity of reactant you added. Rate vs. time of a zero-order reaction. The rate constant, k, has units of mole L^{-1} sec^{-1}.

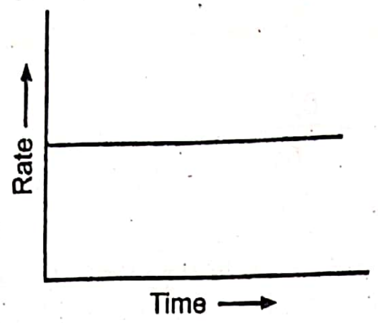


Fig. 5.1: A graph for zero-order reaction

Derivation of Zero Order Reaction:

$$K_0 = \frac{-dA}{dt} \qquad \text{... (5.1)}$$

Integrating equation 1 between initial concentration A_0 at t = 0 and concentration A_t at t = t.

$$\int_{A_0}^{A_t} dA = -K_1 \int_0^t dt$$

$$A_t - A_0 = -K_t$$

$$K_0 = A_0 - \frac{A_t}{t} \qquad \text{... (5.2)}$$

Initial concentration is expressed as 'a' and the concentration at any time t, is 'c'. Thus equation (5.2) changes to

$$K_0 = \frac{(a - c)}{t} \qquad \text{... (5.3)}$$

Half Life of Zero Order Reaction: It is the time required for the concentration of reactant to reduce to half of its initial concentration.

Where , $c = \frac{a}{2}$ and $t = t_{1/2}$

Substituting above values in equation (5.3)

$$t_{1/2} = \frac{a - c}{K_0}$$

$$t_{1/2} = \frac{(a - a/2)}{K_0} = \frac{\left(\frac{1}{2}a\right)}{K_0}$$

$$t_{1/2} = \frac{a}{2K_0} \qquad \text{... (5.4)}$$

Shelf-life of zero order reaction: It is the time required for the concentration of the reactant to reduce to 90% of its reactant.

Where, $c = \frac{90\ a}{100}$ and $t = \frac{t}{90}$

Substituting these values in equation (5.3) gives:

$$t_{90} = \frac{(a - 0.9\ a)}{K_0}$$

$$t_{90} = \frac{0.1\ a}{K_0} \qquad \text{... (5.5)}$$

5.2.2 Pseudo-zero Order Reaction

Several drugs in the solid state, decompose permitting to pseudo-zero order rates as reactions occur among the drug and moisture in the solid dosage form. The system performs as a suspension, and because of the occurrence of excess solid drug, the first-order reaction rate converts in to a pseudo-zero-order rate, and loss rate is linear with time.

$$r = \frac{dCa}{dt} k_1 Ca$$

In suspension formulations the concentration of the drug. The aqueous phase remains constant (i.e. saturated) until the suspended drug particles are completely exhausted.

5.2.3 First Order Reaction

A first-order reaction is a reaction that continues at a rate that depends linearly only on one reactant concentration. Rate is the reaction rate and k is the reaction rate coefficient. In first order reactions, the units of k are 1/s. Though, the units can change with other order reactions.

$$\text{Rate} = -\frac{d[A]}{A} = k[A]^1 = k[A]$$

The succeeding graph symbolizes concentration of reactants vs. time for a first-order reaction.

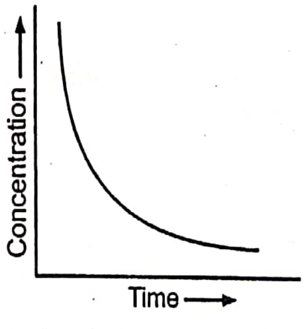


Fig. 5.2: A Graph for First-Order Reaction

Derivation of First Order Reaction Equation:

Consider the reaction.

$$A \rightarrow \text{Products} \qquad \text{... (5.6)}$$

Rate of expression for first order is:

$$\frac{-dc}{dt} = K_1 C$$

Or

$$\frac{-dc}{C} = K_1\, dt \qquad \text{... (5.7)}$$

Integrating equation (5.7) between concentration C_o at time t = 0 and concentration C_t at time t = t gives equation:

$$\int_{C_0}^{C_t} \frac{dc}{C} = -K_1 \int_{0}^{t} dt$$

$$\ln C_1 - \ln C_0 = -K_1 (t - 0)$$

$$\ln C_1 = \ln C_0 - K_1 t \qquad \text{... (5.8)}$$

Changing equation (5.3) to logarithm to the base 10 gives

$$\text{Log } C_t = \text{Log } C_0 - K_1 t / 2.303 \qquad \text{... (5.9)}$$

Rearranging equation (5.9):

$$K_1 = \frac{2.303}{t}\left(\frac{\text{Log } C_0}{C_t}\right) \qquad \text{... (5.10)}$$

(Using log rule $\ln\left(\frac{x}{y}\right) = \ln x - \ln y$)

Equation (5.10) used for calculation of rate constant. Rate constant can be obtained from a graph of log concentration Vs time. Slope of the line is equal to K_1 / 2.303, from which K_1 can be calculated.

Equation (5.10) is written also as:

$$K_1 = \frac{2.303}{t}\left(\log \frac{a}{a - x}\right) \qquad \text{... (5.11)}$$

Where 'a' is as C_0 and 'x' is the concentration of the reactant consumed in time t. Now, (a − x) is C_t.

Unit of K_1 for first order is time^{-1} i.e. SI unit is $(\text{sec})^{-1}$ because K is inversely proportional to t.

Half-Life for First Order Reaction: The half-life, $t_{1/2}$, of a drug is the time required for 50% of drug to degrade and can be calculated as follows:

$$t_{1/2} = \frac{2.303}{K_1} \bullet \log \frac{C_0}{C_t} = \frac{2.303}{K_1} \bullet \log \frac{100}{50}$$

$$t_{1/2} = \frac{2.303}{K_1} \bullet \log 2 = \frac{2.303}{K_1} \bullet 0.3010$$

Therefore,

$$t_{1/2} = \frac{0.693}{K_1} \qquad \text{... (5.12)}$$

Shelf Life for First Order Reaction: The time required for 90% of the drug to degrade is an important value to know, since it represents a reasonable limit of degradation of active ingredients. The $t_{90\%}$ value can be calculated as:

Where $t = t_{90}$ and $C_t = C_0 \left(\frac{90}{100}\right)$

Substituting these in equation (5.10), gives:

$$K_1 = \frac{2.303}{t_{90}}\left(\frac{\text{Log } C_0}{0.9\ C_0}\right)$$

$$t_{90} = \frac{2.303}{K_1}\left(\frac{\text{Log } 10}{9}\right)$$

$$t_{90} = \frac{0.105}{K_1} \quad \text{... (5.13)}$$

5.2.4 Second Order Reaction

In a second-order reaction, the sum of the exponents in the rate law is equal to two. The two most common forms of second-order reactions are following:

Case 1: Two of the same reactant (A) combine in a single elementary step.

$$A + A \rightarrow P$$

$$2\,A \rightarrow P$$

The reaction rate for this step can be written as

$$\text{Rate} = -\frac{d[A]}{A} = k[A]\,[A] = k[A]^2$$

Where, k is a second order rate constant with units of $M^{-1}min^{-1}$ or $M^{-1}s^{-1}$.

Case 2: Two different reactants (A and B) combine in a single elementary step.

$$A + B \rightarrow P$$

The rate of reaction for this stage can be written as

$$\text{Rate} = -\frac{d[A]}{A} = k[A]\,[B]$$

Where, the reaction order with respect to each reactant is 1.

For a second-order reaction, the rate of reaction increases with the square of the concentration, generating an upward curving line in the rate concentration plot.

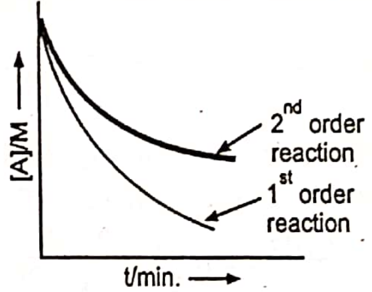


Fig. 5.3: A Graph for Second-Order Reaction

Derivation of Second Order Reaction Equation:

The rate equation for second order is

$$-\frac{dA}{dt} = -\frac{dB}{dt} = K_2\,(A)\,(B) \quad \text{... (5.14)}$$

If concentration of A and B at time t = 0 are 'a' and 'b' respectively and concentration of each substance that has reacted after time t is equal to 'x'. Then concentration of A and B remaining will be (a – x) and (b – x) respectively. Then

$$\frac{dx}{dt} = K_2\,(a - x)\,(b - x) \quad \text{... (5.15)}$$

Case where a = b, equation (5.15) changes to

$$\frac{dx}{dt} = K_2 (a - x)^2 \qquad \text{... (5.16)}$$

Integrating equation (5.16) employing the conditions x = 0 at t = 0 and x = x at t = t

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

$$\left[\frac{1}{(a-x)}\right] - \left[\frac{1}{(a-0)}\right] = K_2 (t - 0)$$

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

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

OR

$$K_2 = \left(\frac{1}{at}\right)\left(\frac{x}{a-x}\right) \qquad \text{... (5.17)}$$

Equation (5.17) used for calculation of rate constant. Rate constant can be obtained from a graph of $\frac{x}{a\,(a-x)}$ Vs time gives a straight line with slope equal to K_2.

If the initial concentrations of A and B are not equal, a ≠ b, integration of equation (5.17) gives

$$K_2 = \frac{2.303}{t\,(a-b)} \cdot \frac{\log b(a-x)}{a\,(b-x)} \qquad \text{... (5.18)}$$

When log $\frac{b\,(a-x)}{a\,(b-x)}$ against yields a straight line with slope equal to $\frac{(a-b)\,K_2}{2.303}$, thus K_2 can be calculated.

Unit of second order reaction is $\text{conc.}^{-1}\ \text{time}^{-1}$ and SI unit is $\text{mol}^{-1}\ \text{sec}^{-1}$.

Half Life of a Second Order Reaction:

Where $(a - x) = \frac{a}{2}$, $t = t_{1/2}$ and $x = \frac{a}{2}$

$$K_2 = \left(\frac{1}{at}\right)\left(\frac{x}{a-x}\right) \text{ changes to}$$

$$K_2 = \left(\frac{1}{at_{1/2}}\right)\left(\frac{a/2}{a/2}\right)$$

$$K_2 = \left(\frac{1}{at_{1/2}}\right)$$

OR

$$t_{1/2} = \frac{1}{aK_2} \qquad \text{... (5.19)}$$

The units for half life for second order are time/conc.

5.3 UNITS OF BASIC RATE CONSTANTS

For a general reaction

$$aA + bB \rightarrow cC + dD$$

$$\text{Rate} = k\,[A]^x\,[B]^y$$

Where x + y = n = order of the reaction

$$k = \frac{\text{Rate}}{[A]^x[B]^y}$$

$$= \frac{\text{Concentration}}{\text{Time}} \times \frac{1}{\text{Concentration}^n}$$

where, [A] [B]

Taking SI units of concentration, mol L^{-1} and time, s, the units of k for different reaction order are listed in Table 5.1.

Table 5.1: Different Orders of Reaction with their Units

Reaction	Order	Units of rate constants
Zero order reaction	0	$\frac{\text{mol } L^1}{s}\frac{1}{\text{mol } L^0}\text{ml } L^1 s^1$
First order reaction	1	$\frac{\text{mol } L^1}{s}\frac{1}{\text{mol } L^1}s^1$
Second order reaction	2	$\frac{\text{mol } L^1}{s}\frac{1}{\text{mol } L^2}\text{mol}^1\ Ls^1$

5.4 DETERMINATION OF REACTION ORDER

Normally, order of reaction can be determined by following methods,

(i) Half Life Method
(ii) Graphical Method
(iii) Initial Rate Method
(iv) Van't Hoff Differential Method

(i) Half Life Method

This technique is utilized only when the rate law involved by only single concentration term.

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

$$t_{(1/2)} = k'\frac{1}{a^{n-1}}$$

$$\log t_{(1/2)} = \log k' + (1 - n)\,a$$

Graph of log $t_{1/2}$ vs log a, displays a straight line with slope (1 − n), where 'n' is the order of the reaction. Defining the slope we can find the order (n). If half-life at different concentrations is given, then

$$(t_{1/2})\ \alpha\ \frac{1}{a_1^{n-1}}$$

and

$$(t_{1/2})\ \alpha\ \frac{1}{a_2^{n-1}}$$

∴

$$\frac{(t_{1/2})_1}{(t_{1/2})_2} = \left(\frac{a_2}{a_1}\right)^{n-1}$$

Taking logarithm and rearranging

$$n = 1 + \frac{\log (t_{1/2}) - \log (t_{1/2})_2}{\log a_2 - \log a_1}$$

Plots of half-lives concentration ($t_{1/2}\ \alpha\ a^{1-a}$):

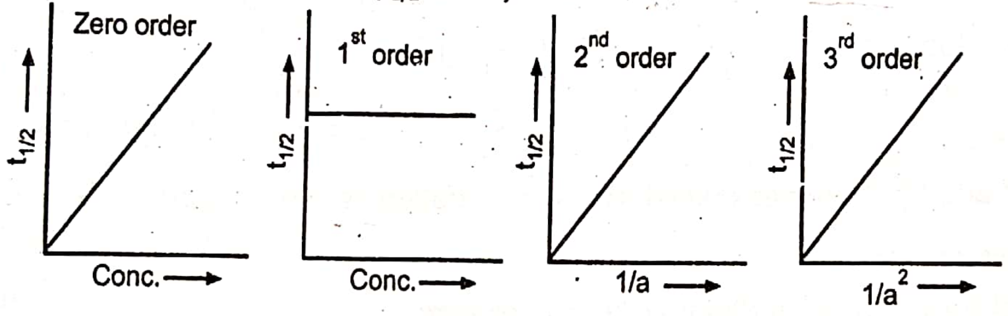


Fig. 5.4

This reaction can be used to determine order of reaction 'n'.

(i) Graphical Method:

This technique is utilized in presence single reactant. If the plot of log [A] vs t is a straight line, the reaction follows first-order. If the plot of $\frac{1}{[A]}$ vs t is a straight line, the reaction follows second order. If the plot of $\frac{1}{[A]^2}$ is a straight line, the reaction follows third order. Normally, for a reaction of nth order, a graph of $\frac{1}{[A]}$ (n − 1) vs t must be a straight line. Here [A] is the concentration of reactant at any given time of the reaction (other t = 0). [A] = (a − x) where a is the initial concentration and x is the extent of reaction at time t.

(ii) Initial Rate Method:

In this technique, initial reaction rate is governed through changing the concentrations of one reactant though keeping others are constant.

$$R = k[A]^x[B]^y[C]^z$$

if [B] and [C] = Constant then for two different initial concentrations of A we have,

$$R_{0_1} = k[A_0]_1^a$$

and $$R_{0_2} = k[A_0]_2^a$$

$$\Rightarrow \quad \frac{R_{0_1}}{R_{0_2}} = \left(\frac{[A_0]_1}{[A_0]_2}\right)_n$$

(iii) Van't Hoff Differential Method:

Generally, the reaction rate changes as the nth power of the concentration of the reactant where, 'n' is the order of the reaction. Thus, for two different initial concentrations C_1 and C_2, equations can be written in the form

$$\log\left(\frac{dC_1}{dt}\right) = \log k + n \log C_1 \quad \ldots \text{(i)}$$

and $$\log\left(\frac{dC_2}{dt}\right) = \log k + n \log C_2 \quad \ldots \text{(ii)}$$

Taking logarithms, substracting equation (ii) from equation (i),

$$\log\left(\frac{dC_1}{dt}\right) - \log\left(\frac{dC_2}{dt}\right) = n(\log C_1 - \log C_2)$$

or $$n = [\log(-(dC_1/dt) - \log((dC_2)/dt)] \div [\log C_1 - \log C_2] \ldots \text{(iii)}$$

$\frac{-dC_1}{dt}$ and $\frac{-dC_2}{dt}$ are determined from concentration vs. time graphs and the value of 'n' can be determined.

Chemical Degradation of Pharmaceutical Product:

Substitution Method:

Data obtained from kinetic experiment is substituted in respective integrated equations.

Zero order: $K_0 = \frac{A_0 - A_t}{t}$

First order: $K_1 = \frac{2.303}{t}\left(\log \frac{C_0}{C_t}\right)$

Second order: $K_2 = \left(\frac{1}{at}\right)\left(\frac{x}{a - x}\right)$

5.5 PHYSICAL AND CHEMICAL FACTORS INFLUENCING THE CHEMICAL DEGRADATION OF PHARMACEUTICAL PRODUCT

5.5.1 Temperature

Endothermic Reaction: If we increase the temperature in the endothermic reaction the rate of reaction will increase and vice versa.

Exothermic Reaction: If we increase the temperature in the exothermic reaction the rate of reaction will decrease and vice versa.

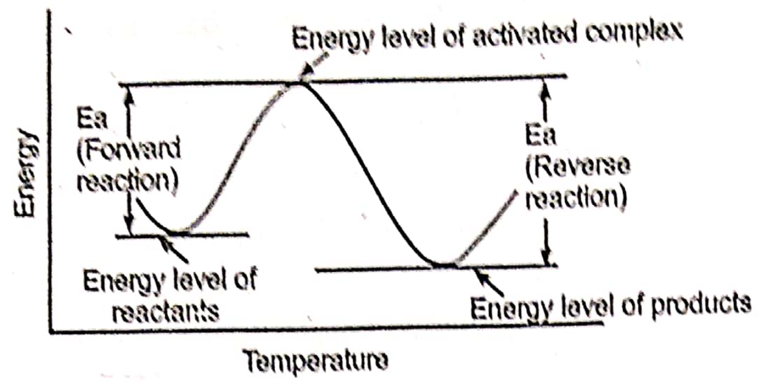


Fig. 5.5: Reaction Between Activation and Energy Levels of Reactants, Products and Activated Complex

5.5.2 Solvent

The quantitative relationship among the reaction rate and the solubility of reactants and products is given by equation.

$$\log k = \log K_0 + \frac{V}{2.303} R \cdot \frac{1}{T} (\Delta S_A + \Delta S_B - \Delta S^*)$$

In different words, a polar solvent inclines to increase the rate of those reactions in which product formed is more polar than reactants. If the products are less polar then it tends to decrease the rate of such reactions. Normally used non-aqueous solvents for drugs comprise ethanol, glycerol and vegetable oil etc.

5.5.3 Ionic Strength

The De-bye Huckel equation may be used to demonstrate that increased ionic strength would be expected to decrease the rate of reaction between oppositely charged ions and increase the rate of reaction between similarly charged ions. Thus, the hydrogen ions catalyzed hydrolysis of sulphate esters is inhibited by increasing electrolyte concentration.

$$ROSO_3 + H_2O \rightarrow ROH + HSO_4^-$$

5.5.4 Dielectric Constant

The dielectric constant (or relative permittivity) of solvent has an important effect on the rate of reaction. Dielectric constant of an ionic reaction is given by

$$\log K = \log K_{\varepsilon=\infty} - K Z_A Z_B/\varepsilon$$

If the reacting ions are of opposite charges, then it will result in increased rate of reaction. If ions of similar charges involve in reaction it will decrease rate of reaction.

5.5.5 Specific and General Acid Base Catalysis

- **Acid-Base Catalysis:**

In acid catalysis and base catalysis a chemical reaction is catalyzed by an acid or a base. The acid is often the proton and the base is often a hydroxyl ion. Typical reactions catalyzed by proton transfer are esterification and aldol reactions. In these reactions the conjugate acid of the carbonyl group is a better electrophile than the neutral carbonyl group itself. Catalysis by either acid or base can occur in two different ways: specific catalysis and general catalysis.

- **Specific catalysis:**

In specific acid catalysis taking place in solvent S, the reaction rate is proportional to the concentration of the protonated solvent molecules SH^+. The acid catalyst itself (AH) only contributes to the rate acceleration by shifting the chemical equilibrium between solvent S and AH in favour of the SH+ species.

$$S + AH \rightarrow SH+ + A^-$$

- For example, in an aqueous buffer solution the reaction rate for reactants R depends on the pH of the system but not on the concentrations of different acids.

$$\text{Rate} = -\frac{d[R_1]}{dt} - k[SH^+][R_1][R_2]$$

This type of chemical kinetics is observed when reactant R_1 is in a fast equilibrium with its conjugate acid R_1H^+ which proceeds to react slowly with R_2 to the reaction product; for example, in the acid catalysed aldol reaction.

- **General Catalysis:**

In general acid catalysis all species capable of donating protons contribute to reaction rate acceleration. The strongest acids are most effective. Reactions in which proton transfer is rate determining exhibit general acid catalysis, for example, diazonium coupling reactions.

$$\text{Rate} = -\frac{d[R_1]}{t} - k_1[SH^+][R_1][R_2] + k_2[AH^1][R_1][R_2] + k_3[AH^2][R_1][R_2] + \ldots\ldots$$

When keeping the pH at a constant level but changing the buffer concentration a change in rate signals a general acid catalysis. A constant rate is evidence for a specific acid catalyst.

5.6 SIMPLE NUMERICAL PROBLEMS

1. Calculate the overall order of a reaction which has the rate expression

   (a) Rate = $k[A]^{1/2}[B]^{3/2}$

   (b) Rate = $k[A]^{3/2}[B]^{-1}$

   (a) Rate = $k[A]^x[B]^y$

   Order = $x + y$

   So order $= \frac{1}{2} + \frac{3}{2} = 2$ i.e. second order

   (b) Order $= \frac{3}{2} + (-1) = \frac{1}{2}$ i.e. half order.

2. The initial concentration of N_2O_5 in the following first order reaction $N_2O_5(g) \rightarrow 2NO_2(g) + \frac{1}{2}O_2\ (g)$ was 1.24×10^{-2} mol L^{-1} at 318 K. The concentration of N_2O_5 after 60 minutes was 0.20×10^{-2} mol L^{-1}. Calculate the rate constant of the reaction at 318 K.

   For a first order reaction

$$\log \frac{[R]_1}{[R]_2} = \frac{k\,(t_2 - t_1)}{2.303}$$

$$k = \frac{2.303}{(t_2 - t_1)} \log \frac{[R]_1}{[R]_2}$$

$$= \frac{2.303}{(60\ \text{min} - 0\ \text{min})} \log \frac{1.24 \times 10^{-2}\ \text{mol L}^{-1}}{0.20 \times 10^{-2}\ \text{mol L}^{-2}}$$

$$= \frac{2.303}{60} \log 6.2\ \text{min}^{-1}$$

$$k = 0.0304\ \text{min}^{-1}$$

3. Identify the reaction order from each of the following rate constants.
   (i) $k = 2.3 \times 10^{-5}$ L mol^{-1} s^{-1}
   (ii) $k = 3 \times 10^{-4}$ s^{-1}
   (i) The unit of second order rate constant is L mol^{-1} s^{-1}, therefore $k = 2.3 \times 10^{-5}$ L mol^{-1} s^{-1} represents a second order reaction.
   (ii) The unit of a first order rate constant is s^{-1} therefore, $k = 3 \times 10^{-4}$ s^{-1} represents a first order reaction.

4. A first order reaction is found to have a rate constant, $k = 5.5 \times 10^{-14}$ s^{-1}. Find the half-life of the reaction.

   Half-life for a first order reaction is

$$t_{1/2} = \frac{0.693}{k}$$

$$t_{1/2} = \frac{0.693}{5.5 \times 10^{-14}\ s^{-1}} = 1.26 \times 10^{13}\ s$$

5.7 STABILIZATION OF MEDICINAL AGENTS AGAINST COMMON REACTIONS LIKE HYDROLYSIS AND OXIDATION.

5.7.1 Hydrolysis

Hydrolysis is most significant in systems comprising water like suspension, emulsion, solutions etc. Also for drugs which are affected via. moisture (water vapour) from atmosphere. It is generally catalysed through hydrogen ion (acid) or hydroxyl ion (base). In this active drug is decomposed with solvent. Commonly solvent is water, few time reactions may include pharmaceutical cosolvents like ethyl alcohol or poly ethylene glycol. Main categories of drugs that experience hydrolysis are the esters, amide, alkali, acid.

(i) Ester Hydrolysis

It involves acyl–acid cleavage. Example of drugs: aspirin, atropine, procaine.

$$R.COOR\ (ester) + H_2O \rightarrow RCOOH\ (acid) + ROH\ (alcohol)$$

(ii) Amide Hydrolysis

Amide hydrolysis is more stable than ester, liable to particular and common acid base hydrolysis. It includes cleavage of amide linkage to give an amine instead of alcohol as in case of esters. For instance, drug like chloramphenicol, barbiturates.

$$R.CONHR\ (amide) + H_2O \rightarrow RCOOH + NH_2R(amine)$$

- **Protection against Hydrolysis**
  - (i) Drug should be packed in appropriate moisture resistant packs like strip packs and storage in meticulous humidity as well as temperature. In liquid dosage form since, hydrolysis is acid or base catalyzed, an optimal pH for better stability should be selected and the formulation should be stabilized at this pH by inclusion of appropriate buffering agents.
  - (ii) By preventing contact with moisture at time of production.
  - (iii) Hydrolysis of definite drugs like procaine and benzocaine can be reduced by the addition of particular complexing agent such as caffeine to the drug solutions.
  - (iv) Hydrolysis susceptible drugs like penicillin and derivatives can be prohibited through formulating them in the dry powder form for reconstruction or dispersible tablets as a substitute of a liquid dosage form like solutions or suspensions.

5.7.2 Oxidation

Oxidation is measured by environment i.e., light, trace elements, oxygen and oxidizing agent. Oxidation arises when exposed to atmospheric oxygen. Moreover, the addition of oxygen or exclusion of hydrogen. Oxidation is the loss of electrons while reduction is the gain of electrons.

- **Autoxidation**

The reaction among the compounds and molecular oxygen is essential for starting the chain reaction is called autoxidation. Free radicals formed through initial reaction are extremely reactive and further catalyze the reaction produce additional free radicals and triggering a chain reaction. Heavy metals like copper, iron, cobalt and nickel have been known to catalyze the oxidative degradation. Heat and light further effect the kinetics of oxidative degradation procedures.

- **Steps involved oxidation reaction**

(i) Initiation

In first step, formation of free radicals is taken place.

$$R - H \rightarrow R' + [H']$$

(ii) Propagation

In propagation the free radical is restored and react with more oxygen.

$$R' + O_2 \rightarrow R'—O^+$$

$$R'O_2 + RH \rightarrow ROOH + R'$$

(iii) Hydro peroxide Decomposition

$$ROOH \rightarrow RO' + OH'$$

(iv) Termination

In last step, free radicals react with each other resulting in inactive products.

$$R'–O_2 + X \rightarrow \text{Inactive product}$$

$$RO_2 + RO_2 \rightarrow \text{Inactive product}$$

There is some example of components decomposed by oxidation pathways like Archis oil, clove oil, Ascorbic acid, ethyl oleate, Morphine, Heparin, Vitamin A, Vitamin B12 etc.

- **Protection against oxidation**

It involves use of antioxidants mainly of three types,

1. The first class perhaps prevents the oxidation by responding with free radicals. For instance, tocopherol, butylated hydroxyl anisole (BHA), butylated hydroxyl toluene's (BHT) with concentration 0.001 – 0.1%.
2. The second class containing the reducing agents, which have a lower redox potential than the drug or other substance that they should preserve and are therefore more readily oxidized. For instance, ascorbic acid and iso-ascorbic acid, potassium or sodium salts of metabisulfite.
3. The third class has less antioxidant effect themselves but improve the action of true antioxidant. Example -- Citric acid, tartaric acid.

Moreover, chelating agent like heavy metals also catalyze oxidation. Chelating agents like EDTA, citric acid, tartaric acid form complexes.

5.7.3 Photo-degradation or Photolysis

The pharmaceutical compounds undergo degradation when exposed to light. Thus the degradation of pharmaceutical compounds from light can be prevented by storing them in amber colored bottle or storing the product in dark. Some examples of drugs which degrade on exposure to light are riboflavin, ascorbic acid, morphine sulfate injection etc.

5.7.4 Isomerization

The Inter-conversion of one stereochemical form into another form produces inactive compound. The optically active D-isomer gets converted to L-isomer or Cis form may get converted into trans form. This type of degradation can prevented by storing them in containers protected from light, heat and optimum pH should be maintained.

For example, (–) Adrenaline (active) → (+) Adrenaline (inactive or less active).

5.8 ACCELERATED STABILITY TESTING IN EXPIRATION DATING OF PHARMACEUTICAL DOSAGE FORMS

Stability study is performed to detect the product shelf life, via accelerating the rate of decomposition, rather by increasing the temperature of reaction conditions. With the progress in branch of kinetics, shelf life of a dosage form can be projected within months based on accelerated stability reports. Preparations are exposed to high stresses through stability testing. Common high stresses comprise temperature, humidity and light.

- **Arrhenius equation**

It describes the effect of temperature on rate of a reaction. According to Arrhenius, for every 10° increase in temperature, the speed of reaction surges about 2-3 times.

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

A - Arrhenius factor, -Ea - Energy of activation, RT - Ideal gas constant

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

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

- **Estimation of k value**

The reaction is carryout at numerous temperatures. Firstly, Concentration of reactants is determined and suitable graphs are drawn for the kinetic data. Then, data is managed for all the orders. The order of the reaction is identified. At last from the slopes of the lines, k values are calculated for all temperatures.

- **Estimation of energy of activation**

Activation energy is the minimum energy that a molecule should possess so that the molecular collisions yield the product. A graph can be drawn by taking log k on y-axis and reciprocal temperature $\left(\frac{1}{T}\right)$ on x-axis. A straight line is acquired, the slope of the line is negative and the magnitude is $\frac{E_a}{2.303\ R}$. The intercept corresponds to log A. All the constants in the Arrhenius equation can be obtained from the graph.

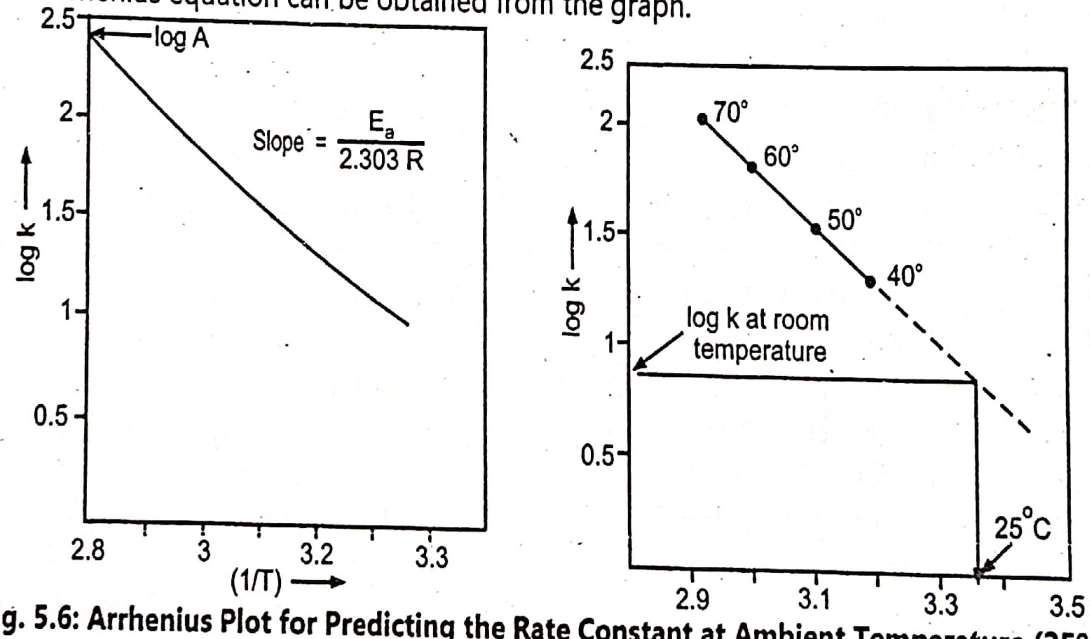


Fig. 5.6: Arrhenius Plot for Predicting the Rate Constant at Ambient Temperature (25°C)

- **Steps involved in Accelerated Stability Testing**
  (i) The preparation is kept at different elevated temperatures, to accelerate the degradation.
  (ii) Samples are taken at different time intervals.
  (iii) The Order of the reaction is calculated by plotting the suitable concentration function against time and linear relationship is determined.

(iv) Straight line in a graph allows the estimation of k value from the slope.

(v) Similarly graphs are drawn for different elevated temperatures and calculations of K value for each temperature are calculated.

(vi) By using Arrhenius relationship, Log k values are plotted against reciprocal of absolute temperature, energy of activation can be calculated.

(vii) Extrapolate the straight line to room temperature (k_{25}) or refrigerated temperature and read the log k value on y-axis.

(viii) Substitute the k value in the appropriate equation to get the shelf life of the product.

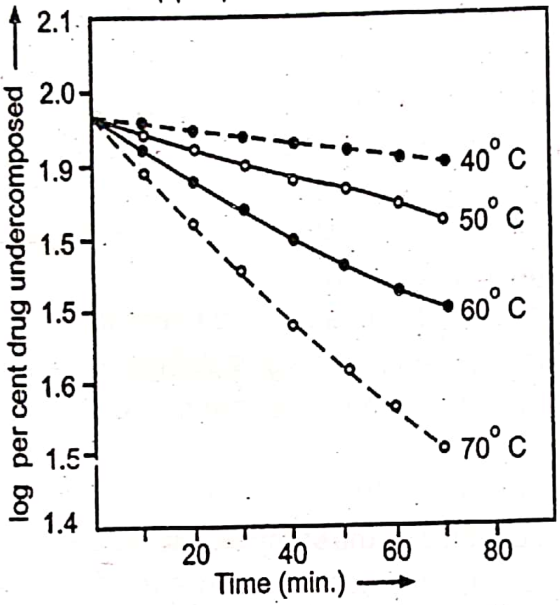


Fig. 5.7: Graph of Log % Drug Undecomposed at Different Time Intervals

Table 5.2: Overview of Storage Conditions and Storage Period for Solid, Semisolid and Liquid Dosage Forms

Stability investigation	Dosage form	Storage condition	Storage period
Organoleptic and physiochemical stability	Solid	Storage in open container until equilibrium is reached at 25°C/60%, 30°C/70%, 40°C.75%	1-2 weeks
	Semisolid	5°C ≥ −10°C 5°C-40°C temperature cycle within 24 hours	4 weeks 4 weeks 2 weeks 3 months
	Liquid	40°C (content uniformity)	
		5°C ≥ −10°C	4 weeks 4 weeks
Photostability	All	Xenon lamp	48 hours
Chemical stability	Solid Semisolid Liquid	40°C, 50°C, 60°C, 70°C 30°C, 40°C, 50°C 40°C, 50°C, 60°C, 70°C	3 months 3 months 3 months

- **Accelerated tests for Suspensions**

  In suspensions, Cake formation is enhanced by centrifugation. Thus, high speed centrifugation is not favoured; low speed centrifugation is utilized to study the physical stability. A Freeze-Thaw cycling technique is one of the stress testing. This cycling treatment endorses particle growth and has primary importance for changes in absolute particle size, particle size distribution and crystal habit.

- **Accelerated stability testing in emulsions**

  An emulsion is kept at elevated temperature. This drops viscosity of the continuous phase. If the emulsion withstands this stress it is expected to be stable at normal conditions of storage. Centrifugation technique is utilized for this concern. Creaming and flocculation are slow methods. Centrifugation accelerates rate of creaming and flocculation in emulsions. The emulsion is subjected to different centrifugal speeds and separation of phases is observed at different time phases. Bad emulsion separates oil instantly. Good emulsion does not show noticeable separation of oil phase till definite time period.

- **Accelerated Tests for moisture absorption**

  In this technique, products are located in an environment of high relative humidity and controlled temperature. Their physical and chemical stabilities are assessed. The results will specify whether the product is susceptible to moisture and also whether the container needs to offer a high degree of protection.

- **Limitations**

  (i) The energy of activation attained in the study should be between 10 to 30 kcal/mole.

  (ii) Stability estimates based on Arrhenius equation are effective only when the break down depends on temperature.

  (iii) In case of disperse systems, when temperature is elevated viscosity is decreased and this may lead errors in the prediction of stability.

  (iv) When the product loses its physical integrity at higher temperatures.

  (v) When degradation arises owing to microbial contamination photochemical reactions.

5.9 PHOTOLYTIC DEGRADATION AND ITS PREVENTION

The drug molecule is degradate by exposure of light it affects substantial degradation of drug molecule. When molecules are exposed to electromagnetic radiation they absorb light (photons) at characteristic wavelength which cause increase in energy which triggers decomposition, retained or transferred and result in light emission at a new wavelength (fluorescence, phosphorescence). Natural sun light lies in wavelength range (290-780 nm) of which only higher energy (UV) range (290-320) cause photo degradation of drugs. Examples of phototoxic drugs include furosemide, acetazolamide and cyanocobalamin.

- **Example**

  Sodium nitroprusside in aqueous solution (which is administered by IV infusion for management of acute hypertension). If protected from light it is stable to at least 1 year. If exposed to normal room light it has a shelf life of 4 hrs.

- **Protection**

  (i) Use of amber coloured bottles.

  (ii) Storing the product in dark, packaging in cartons also act as physical barrier to light.

  (iii) Coating of tablets with polymer films.

EXERCISE

Multiple Choice Questions:

1. ...... is the time necessary for the concentration of the reactant to decrease to 90% of its original concentration.
   (a) Product life (b) Shelf life
   (c) Half life (d) None of the above
2. Generally, Stability testing is employed for ......
   (a) Delivering evidences of the change in quality of the drug product with time.
   (b) Confirming shelf life for the drug product.
   (c) Determining container closure system suitability.
   (d) All of the above
3. A zero-order reaction is a reaction having rate of concentration of reactant.
   (a) Dependent (b) Partially dependent
   (c) Independent (d) None of the above
4. In a second-order reaction, the sum of the exponents in the rate law is equal to ......
   (a) Zero (b) One
   (c) Two (d) Three
5. ...... technique is utilized only during determination of order of reaction, when the rate law involved by only single concentration term.
   (a) The concentration (b) The half of the concentration
   (c) The square of the concentration (d) None of the above
6. ...... technique is utilized only when the rate law involved by only single concentration term for determination of order of reaction.
   (a) Half Life Method (b) Graphical Method
   (c) Initial Rate Method (d) Van't Hoff Differential Method
7. ...... technique is utilized in presence single reactant for determination of order of reaction.
   (a) Half Life Method (b) Graphical Method
   (c) Initial Rate Method (d) Van't Hoff Differential Method
8. In exothermic Reaction, if we increase the temperature in the exothermic reaction the rate of reaction will ......
   (a) Increases (b) Decrease
   (c) Remains constant (d) None of the above
9. If ions of similar charges involve in reaction it will ...... rate of reaction.
   (a) Increases (b) Decreases
   (c) Remains constant (d) None of the above
10. The drug molecule is degradate by exposure of light it affects substantial degradation of drug molecule this phenomenon is known as ......
    (a) Photolytic degradation (b) Chemical degradation
    (c) Physical degradation (d) None of the above

Keys

1. (b)	2. (d)	3. (c)	4. (c)	5. (c)
6. (a)	7. (b)	8. (b)	9. (b)	10. (a)

Short Questions Answer:

1. **What is shelf life of a drug?**

Ans. Shelf life is the time necessary for the concentration of the reactant to decrease to 90% of its original concentration. Shelf life is represented as t_{90} and the units of time/conc.

$$t_{90} = \frac{(a - 0.9\,a)}{k_o} = \frac{0.1\,a}{k_o}$$

Where,

a = Initial concentration,

k_o = Specific rate constant for zero order reaction

2. **What are different orders of reaction with their units?**

Ans. Refer Table No. 5.1.

3. **What is Coacervation?**

Ans. Coacervation is the method of combining negatively and positively charged hydrophilic colloids, and therefore the particles discrete from the dispersion to form a layer abundant in the colloidal aggregates i.e. coacervate. The phenomenon which involves separation of macromolecular solutions into two liquid layers is called as coacervation.

4. **Enlist the methods for determination of order of reaction?**

Ans. (i) Half Life Method

(ii) Graphical Method

(iii) Initial Rate Method

(iv) Van't Hoff Differential Method

5. **Explain in short about effect of dielectric constant on reaction rate.**

Ans. The dielectric constant (or relative permittivity) of solvent has an important effect on the rate of reaction. Dielectric constant of an ionic reaction is given by;

$$\log K = \log K_{\varepsilon=\infty} - K\,Z_A Z_B/\varepsilon$$

If the reacting ions are of opposite charges, then it will result in increased rate of reaction. If ions of similar charges involve in reaction it will decrease rate of reaction.

Long Question Answer:

1. **Discuss in detail about reaction kinetics?**

Ans. Refer Point No. 5.2.

2. **Enlist and explain methods used for determination of reaction order.**

Ans. Refer Point No. 5.4.

3. **Enlist and explain physical and chemical factors influencing the chemical degradation of pharmaceutical product.**

Ans. Refer Point No. 5.5.

4. **Explain effect of hydrolysis and oxidation stability.**

Ans. Refer Point No. 5.7.

5. **Explain in detail accelerated stability testing in expiration dating of pharmaceutical dosage forms.**

Ans. Refer Point No. 5.8.

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