UNIT-I

COLLOIDAL DISPERSION

KGRL COLLEGE OF PHARMACY

jahnavi thota
[COMPANY NAME]

COLLOIDAL DISPERSION

Dispersed systems consist of particulate matter (known as the dispersed phase), distributed throughout a continuous phase (known as dispersion medium).

CLASSIFICATION OF DISPERSED SYSTEMS

Based on the mean particle diameter of the dispersed material, three types of dispersed systems aregenerally considered:

a) Molecular dispersions
b) Colloidal dispersions, and
c) Coarse dispersions

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

Example: aqueous solution of salts, glucose

Colloidal dispersions are micro-heterogeneous dispersed systems. The dispersed phases cannot beseparated under gravity centrifugal or other forces. The particles do not mix or settle down. **Example:** aqueous dispersion of natural polymer, colloidal silver sols, jelly

Coarse dispersions are heterogeneous dispersed systems in which the dispersed phase particles arelarger than 0.5µm. The concentration of the dispersed phase may exceed 20%.

Example: pharmaceutical emulsions and suspensions

COMPARISON OF CHARACTERISTICS THREE DISPERSED SYSTEMS

	Moleculardispersions	**Colloidal dispersions**	**Coarse dispersions**
1. Particle size	<1nm	1nm to0.5µm	>0.5µm
2. Appearance	Clear, transparent	Opalescent	Frequentlyopaque
3. Visibility	Invisibleinelectron microscope	Visible in the electron microscope	Visibleunderoptical microscope or **the naked eye**
4. Separation	Pass through a semipermeable membrane,filterpaper	Pas through filter paper but do not pass through semipermeable membrane	Do not pass through normal filter paper and semipermeable membrane
5. Diffusion	Undergorapiddiffusion	Diffuse very slowly	Donotdiffuse
6. Sedimentation	No questionofsetling	Donotsetletdown	Fastsedimentationof dispersed phase gravity or other forces

SHAPE OF COLLOIDAL PARTICLES

The shape adopted by colloidal particles in dispersion is important because the more extended the particle, the greater its specific surface and the greater the opportunity for attractive forces to developbetween the particles of the dispersed phase and the dispersion medium. In a friendly environment,a colloidal particle unrolls and exposes maximum surface area. Under adverse conditions, it rolls upand reduces its exposed area.

The shapes that can be assumed by colloidal particles are: (a) spheres and globules, (b) short rods and prolate ellipsoids (rugby ball-shaped/elongated), (c) oblate ellipsoids (discus-shaped/flattened) and flakes, (d) long rods and threads, (e) loosely coiled threads, and (f) branched threads

The following properties are affected by changes in the shape of **colloidal** particles:

a) Flowability
b) Sedimentation
c) Osmotic pressure
d) Pharmacological action.

TYPES OF COLLOIDAL SYSTEMS

Based on the interaction between the dispersed phase and dispersion medium, colloidal systems areclassified as

(a) **Lyophilic colloids (solvent-loving)** (When the dispersion medium is water, it is called hydrophilic colloids and if the dispersion medium is an organic solvent, it is called hydrophobic colloids)
(b) **Lyophobic colloids (solvent-hating)** (When the dispersion medium is an organic solvent, it is called hydrophilic colloids and if the dispersion medium is a water, it is called hydrophobic colloids)

Difference between Lyophilic colloids and Lyophobic colloids

Lyophilic colloids	**Lyophobic colloids**
Colloidal particles have a greater affinity for the dispersion medium	Colloidal particles have little affinity for the dispersion medium
Owing to their affinity for the dispersion medium, the molecules disperse spontaneously to form a colloidal solution	Material does not disperse spontaneously, and hence lyophobic sols are prepared by dispersion or condensation methods
These colloids form “reversible sols”	These colloids form “irreversible sols”
Viscosity of the dispersion medium is increased greatly by the presence of the lyophobic colloidalparticles	Viscosity of the dispersion medium is not greatly increased by the presence oflyophilic colloidal particles
Dispersions are stable generally in the presence ofelectrolytes; they may be salted out by high concentrations of very soluble electrolytes	Lyophobic dispersions are unstable in thepresence of even small concentrations of electrolytes
Dispersed phase consists generally of large organicmolecules such as gelatin, acacia lying within colloidal size range	Dispersed phase ordinarily consists of inorganic particles, such as gold or silver

Preparation of Lyophilic Colloids:

This simple dispersion of lyophilic material in a solvent leads to the formation of lyophilic colloids.

Preparation of Lyophobic Colloids

The lyophobic colloids may prepared by
(a)Dispersion method
(b) Condensation method

Dispersion methods: This method involves the breakdown of larger particles into

particles of colloidal dimensions. The breakdown of coarse material may be affected by the use of the Colloid mills and ultrasonic treatment in the presence of a stabilizing agent such as a surface active agent.

Condensation method:

In this method, the colloidal particles are formed by the aggregation of smaller particles such as molecules. These involve a high degree of initial supersaturation followed by the formation and growth of nuclei. Supersaturation can be brought about by

(i) **Change in solvent**: For example, if sulfur is dissolved in alcohol and the concentratedsolution is then poured into an excess of water, many small nuclei form in the supersaturated solution. These grow rapidly to form a colloidal sol. If a saturated solution of sulfur in acetone is poured slowly into hot water the acetone vaporizes, leaving a colloidal dispersion of sulfur.

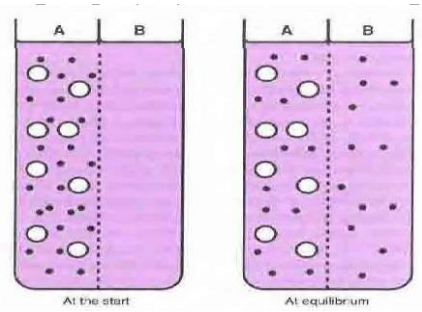
(ii) **Chemical reaction:** For example, colloidal silver iodide may be obtained by reacting together dilute solutions of silver nitrate and potassium iodide. If a solution of ferric chloride is boiled with an excess of water produces a red sol of hydrated ferric oxide byhydrolysis.

Purification of Colloids

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

(a) Dialysis:

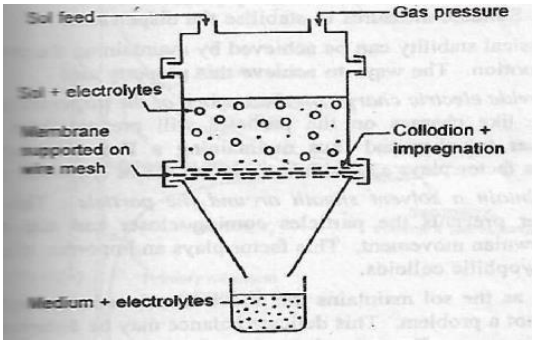
At equilibrium, the colloidal material is retained in compartment A, whereas the sub-colloidal material is distributed equally on both sides of the membrane. By continually removing the liquid in compartment B, it is possible to obtain colloidal material in compartment A which is free from sub-colloidal contaminants. The process of dialysis may be hastened by stirring, to maintain a high concentration gradient of diffusible molecules across the membrane and by renewing the outer liquidfrom time to time.



[**Open circles:** colloidal particles, **solid dots:** electrolyte particles]

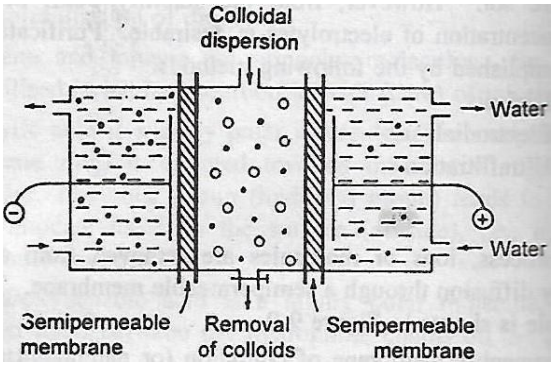
(b) Ultrafiltration

Colloidal dispersion can pass through an ordinary filter because the pore size of the filter is large. If this filter paper is impregnated with collodion (syrupy solution of nitrocellulose), the pore size reduces. Such modified filter papers are called ultrafilters. By applying pressure(or suction). The solvent and small particles may be forced across a membrane but the larger colloidal particles are retained. This process is referred to as ultrafiltration.



(c) Electrodialysis

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



Association/Amphiphilic Colloids

Surface active agents have two distinct regions of opposing solution affinities within the same molecule or ion and are known as *amphiphiles*. When present in a liquid medium at low concentrations, the amphiphiles exist separately and are of sub-colloidal size. As the **concentration** is increased, aggregation occurs over a narrow concentration range. These aggregates, which may contain 50 or more monomers, are called *micelles.* Because the diameter of each micelle is of the order of 50Å, micelles lie within the colloidal **size** range. The concentration of monomer at which micelles are formed is termed *critical micelle concentration (CMC).* The number of monomers that aggregate to form a micelle is known as the *aggregation number* of the micelle.

In water, the hydrocarbon chains of amphiphiles face inward into the micelle to form their hydrocarbon environment. Surrounding this hydrocarbon core are the polar portions of the amphiphiles associated with the water molecules of the continuous phase.

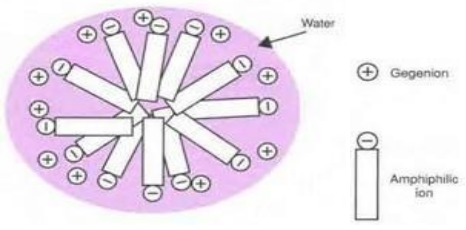


Figure: Spherical micelle of an anionic association colloid in aqueous media

The association colloid can be classified as anionic, cationic, nonionic, or ampholytic (zwitterionic)depending upon the charges on the amphiphiles. The opposite ions bound to the surface of chargedmicelles are termed counter ions or *gegenions,* which reduce the overall charge on the micelles.

The viscosity of the system increases as the concentration of the amphiphile increases because micelles increase in number and become asymmetric. In aqueous solutions, the CMC is reduced by the addition of electrolytes, salting out may occur at higher salt concentrations.

OPTICAL PROPERTIES:

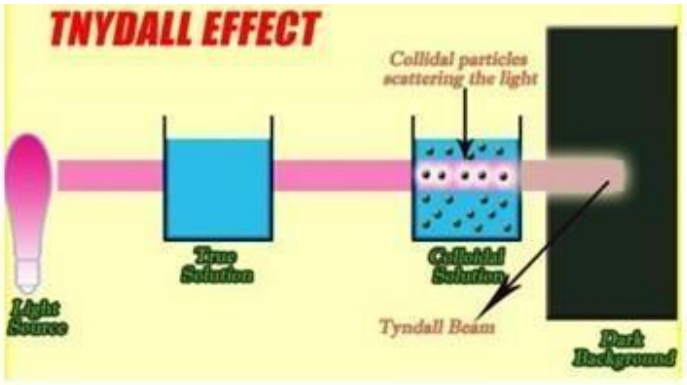
Tyndall effect

When a strong beam of light is passed perpendicularly through two solutions (1) true solution and

(2) colloidal solution placed against a dark background:

1. The path of the light beam is not visible in the case of a true solution.
2. The path of the light beam is visible (scattered) in the case of colloidal solution and further it forms a shadow (beam or cone) on the dark background.

This phenomenon of scattering of light by the colloidal particles is called the **Tyndall effect**. The illuminated beam or cone formed by the sol particles is called the Tyndall beam or Tyndall cone. The Tyndall effect is because colloidal particles scatter light in all directions in space. The scattering of light illuminates the path of the beam in the colloidal dispersion.



KINETIC **PROPERTIES:**

Kinetic properties of colloidal systems relate to the motion of particles concerning the dispersion medium. The kinetic properties are:

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

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

1. Brownian motion

Colloidal particles undergo random collisions with the molecules of the dispersion

medium and follow an irregular and complicated zigzag path. If the particles up to about 0.5 µm diameter are observed under a microscope or the light scattered by colloidal particles is viewed using an ultra-microscope, an erratic motion is seen. This movement is referred to as Brownian motion.

2. Diffusion

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

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

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

The diffusion coefficient of a dispersed material is given by the **Stokes-Einstein equation**

$$D = \frac{RT}{6\pi\eta rN}$$

Where N=Avogadro's number (6.023×10^{23} molecules per mole), R=molar gas constant, and *r* is theradius of the spherical particle.

The analysis of the above equations allows us to formulate three main rules of diffusion:

(i) The velocity of molecules increases with reduction of particle size
(ii) The velocity of molecules increases with increasing temperature
(iii) The velocity of molecules decreases with increasing viscosity of the medium.

3. Osmotic Pressure

Osmosis is the spontaneous net movement of solvent molecules through a semipermeable membrane into a region of higher solute concentration in the direction that tends to equalize the solute concentration on the two sides. The external pressure required to be applied so that there is no net movement of solvent across the membrane is called osmotic pressure.

The osmotic pressure, $\pi$of a dilute colloidal solution is described by the van't Hoff equation:

$$\pi = cRT$$

Where c =molar concentration of solute. This equation can be used to calculate the molecular weightof a colloid in a dilute solution. Replacing c with Cg/M in the above equation, in which cg is the gramsof solute per liter of solution and M is the molecular weight, we obtain

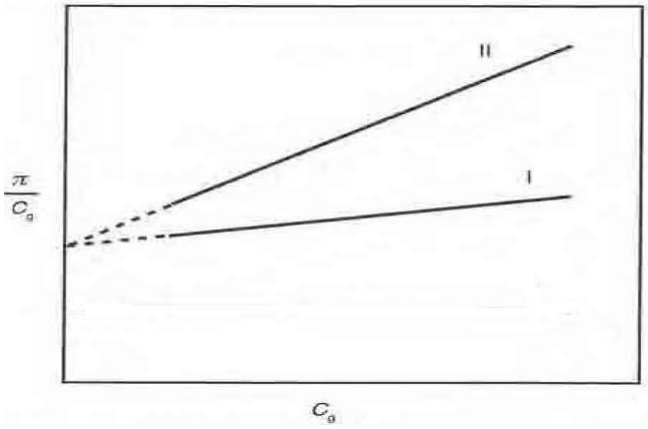
$$\pi = \frac{C_g}{M}RT$$

The above equation is true when the concentration of colloids is low (ideal system).

For linear lyophilic molecules or high molecular weight polymers (real system), the following equation is valid.

$$\frac{\pi}{C} = RI(\frac{1}{M} + BC_g)$$

where *B* is an interaction constant for any particular solvent/solute system. A plot of π/c vs is C_g linear.



The extrapolation of the line to the vertical axis where Cg=0 gives RT/M and if the temperature at whichthe determination was carried out is known, the molecular weight of the solute can be determined. Fromthe slope of the line, the value of interaction constant (B) can be determined.

Line II is typical of a linear colloid in a solvent having a high affinity for the dispersed particles. Type I line is observed for the same collide if it is present in a relatively poor solvent having areduced affinity for the dispersed material.

However, the extrapolated intercept on the y-axis is identical for lines I and II. This indicatesthat the calculated molecular weight is independent of the solvent used.

4. Sedimentation

The velocity, *v*, of sedimentation of spherical particles having a density *ρ,* in a medium of density

P_o and a viscosity η_o is given by *Stoke's law:*

$$\boldsymbol{v = \frac{2r^2(\rho - \rho_o)g}{9\eta_o}}$$

where *g* is the acceleration due to gravity. If the particles are subjected only to the force of gravity,then the lower size limit of particles obeying Stokes's equation is about 0.5 μm. This is because Brownian movement becomes significant and tends to offset sedimentation due to gravity and promotes mixing instead. Consequently, a stronger force must be applied to bring about the **sedimentation** of colloidal particles. A high-speed centrifuge (*ultracentrifuge)*, can produce a forceof about $10^6 g$. In a centrifuge, *g* is replaced by $\omega^2 x$, ω=angular velocity, or angular acceleration=2π

times the speed of the rotor in revolution per second, x= the distance of the particle from the center of rotation.

$$\boldsymbol{v = \frac{dx}{dt} = \frac{2r^2(\rho - \rho_o)\varpi^2 x}{9\eta_o}}$$

5. Viscosity:

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

$$\boldsymbol{\eta = \eta_0(1 + 2.5\phi)}$$

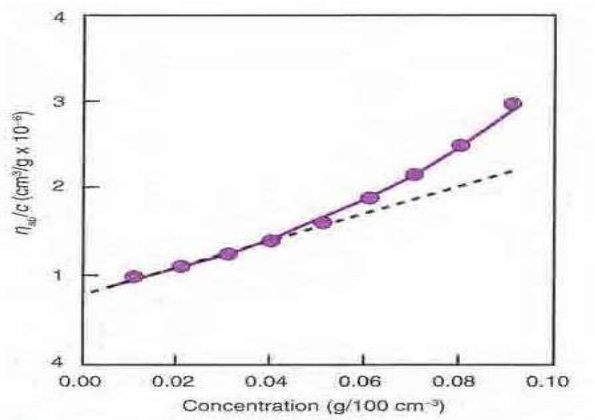
η0 is the viscosity of the dispersion medium, and η is the viscosity of dispersion when the volume fraction ofcolloid particles is ϕ. The volume fraction is defined as the volume

of the panicles divided by the total volume of the dispersion.

Relative viscosity(η_{rel})=η/η_o =1+2.5ϕ
Specific viscosity(η_{sp})=η/η_o-1=2.5ϕ (or) η_{sp}/ϕ=2.5
By determining η at various concentrations and knowing $\eta 0$ the specific viscosity can be calculated.
Because the volume fraction is directly related to concentration, we can write,η_{sp}= K, where *C* = gm of colloid particles per 100ml.
For highly polymeric materials, Huggin's equation is used. Specific viscosity expresses incrementalviscosity due to the presence of polymer in solution. Intrinsic viscosity is a measure of a solute's contribution to the viscosity of a solution or limiting value of a specific viscosity/concentration ratio at zero concentration.

$$\frac{\eta_{SP}}{C} = \eta_i + k\eta_i^2 C$$

If η_{sp}/C is plotted against *C* and the line extrapolated to infinite dilution, the intercept is intrinsicviscosity (ηi).



This constant, commonly known as the intrinsic viscosity η_i and is used to calculate the approximate molecular weights of polymers. According to the so-called **Mark–Houwink equation**

$$\eta_i = kM^a$$

Where *k* and *a* are constants, characteristics of a particular polymer-solvent system and arevirtually independent of molecular weight.

$$\log \eta_i = \log k + a \log M$$

These constants are obtained initially by determining η_i experimentally for polymer fractions whose molecular weights have been determined by other methods such as light scattering, osmotic pressure,or sedimentation.
Then the specific viscosity for each fraction is determined and then intrinsic viscosity can be obtained.

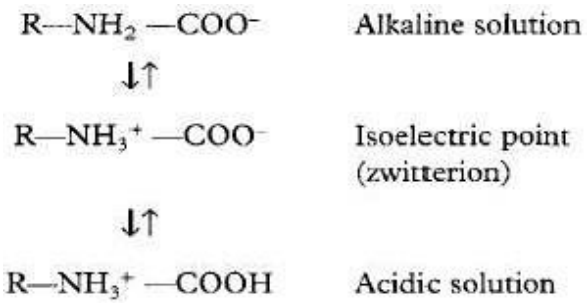
$$\text{If we plot } \log \eta_i \; vs. \log \text{M } then \; the \; slope \; will \; give \; 'a' \; value \; and \; the \; intercept \; will \; give \; 'k' \; value.$$

Then, the molecular weight (M) of unknown fraction of the polymer can be obtained from **Mark– Houwink equation.**

KINETIC PROPERTIES:
The colloidal particles acquire a surface electric charge when brought into contact with an aqueousmedium. The principal charging mechanisms are discussed below.

1. **Surface Ionization**

Here the charge is controlled by the ionization of surface groupings. For example, carboxymethyl cellulose frequently has carboxylic acid groupings at the surface which ionize to give negatively charged particles. Amino acids and proteins acquire their charge mainly through the ionization of carboxyl and amino groups to give $–COO^-$ and NH_3^+ ions. The ionization ofthese groups and hence the net molecular charge depends on the pH of the system. At a pHbelow the pKa of the COO- group the protein will be positively charged because of the protonation of this group, -COO- —> COOH, and the ionization of the amino group $-NH_2 \rightarrow -NH^+$, which has a much higher pKa;whereas at higher pH, where the amino group is no longer ionized, the net charge on the molecule is now negative because of the ionization of the carboxyl group. At a certain definite pH, specific for each individual protein, the total number of positive charges will equal the total number of negative charges and the net charge will be zero. This pHis termed the isoelectric point of the protein and the protein exists as its zwitterion. This may be represented as follows:

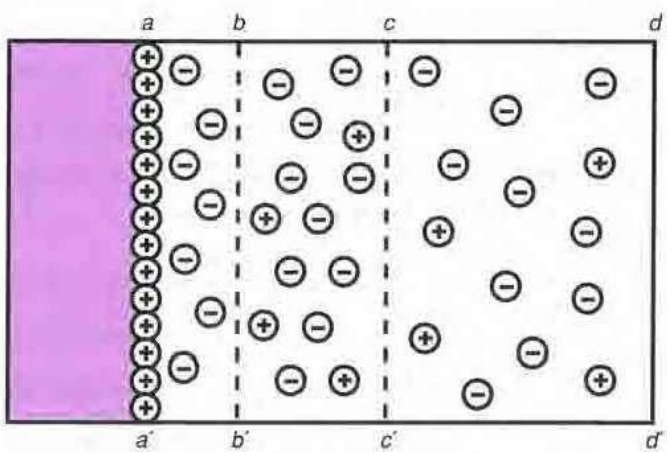


1. Ion Adsorption

Surfaces in water are more often negatively charged than positively charged, because cations are generally more hydrated than anions. Consequently, the former have the greater tendency to reside in the bulk aqueous medium, whereas the smaller, less hydrated and more polarizing anions havea greater tendency to reside at the particle surface; Surface-active agents are strongly adsorbed and have a pronounced influence on the surface charge, imparting either a positive or negative charge depending on their ionic character.

2.Electrical double layer

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



Suppose that some of the cations are adsorbed onto the solid surface (aa') giving it a positive chargeand these are called potential determining ions. Then the counter anions are attracted tothe positively charged surface by electric forces and forms a region called tightly bound layer. In this layer there are fewer anions than cations adsorbed onto the solid surface and hence the potential at bb' is still positive.

In addition to these electrical forces, the thermal motion tends to produce an equal distribution of all the ions in solution. As a result, some of the excess anions approach the surface, whereas the remainders are distributed in decreasing amounts as one proceeds from the charged surface. At a particular distance from the surface, the concentration of anions and cations are equal and form an electrically neutral region. The system as a whole is electrically neutral even though there are regions of unequal distributions of anions and cations.

The region bounded by bb' and cc' is called diffuse second layer where an excess anions are present.Beyond cc', the distribution of ions is uniform and an electrically neutral region exists.

The potential at the solid surface is called Nernst potential and is defined as the difference in potential between actual solid surface and the electrically neutral region of the solution. The potential at plane bb' is called zeta potential and is defined as the difference in potential between surface of tightly bound layer and the electrically neutral region of the solution.

If zeta potential falls below a particular value (+30mV or -30mV), the attractive force exceed the repulsive force and results in aggregation of colloidal particles. The stability of colloidal particles isevaluated based on zeta potential value. Zeta potential decreases more rapidly when the concentration of electrolytes is increased or the valency of counter ions is higher.

The presence and magnitude, or absence, of a charge on a colloidal particle is an important factor in the stability of colloidal systems. Stabilization is accomplished essentially by two means: providingthe dispersed particles with an electric charge, and surrounding each particle with a protective solvent sheath that prevents mutual adherence when the particles collide as a result of Brownian movement. This second effect is significant only in the case of lyophilic sols.

Stability of lyophobic colloids

A lyophobic sol is thermodynamically unstable. The particles in such cols are stabilized only by thepresence of electric charges on their surfaces. The like charges produce a repulsion that prevents coagulation of the particles. Hence, addition of a small amount

of electrolyte to a lyophobic sol tends to stabilize the system by imparting a charge to the particles.

In colloidal dispersions frequent encounters between the particles occur as a result of Brownian movement. Such interactions are mainly responsible for the stability of colloids. There are two types of interactions- van der Waals attraction and electrostatic repulsions. When attractions predominate, the particles adhere after collisions and aggregate is formed. When repulsions predominate, the particles rebound after collisions and remain individually dispersed.

At low electrolyte concentration, repulsive forces predominate so that the particles experience only repulsive forces upon approach. The particles remain independent and the system is considered dispersed or peptized.

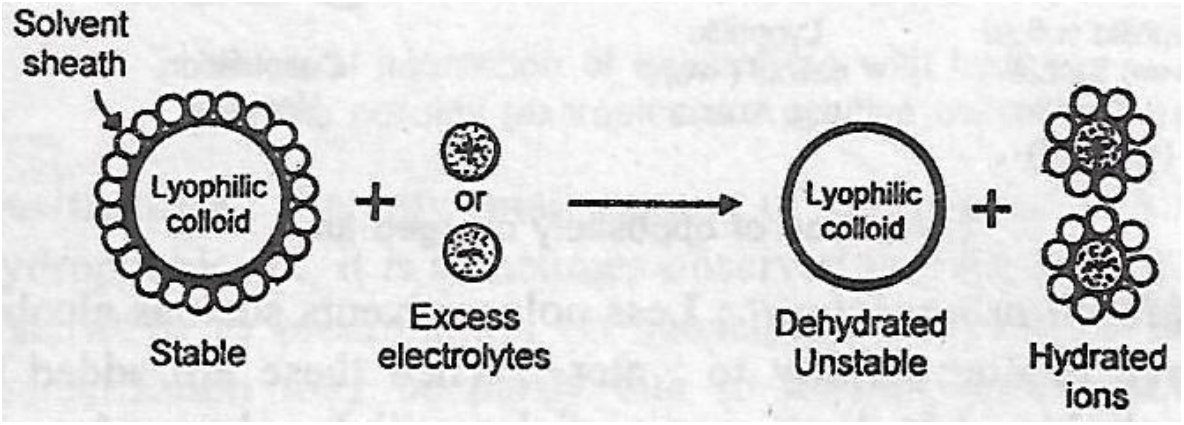
At high electrolyte concentration, the double layer repulsive forces are greatly reduced, so that vande Waals attractive forces predominate. These net attractive forces between particles causethe formation of aggregate of particles, a process known as coagulation.

The concentration of electrolyte necessary, to collapse the repulsive force and permit coagulation depends on the valence of ions of opposite charge. Schulze-hardy rule states that the precipitation power of an ion on dispersed phase of opposite charge increases with increase in valence or chargeof the ion. The higher the valency of ion, the greater is the precipitation power. Cations: Al^{+3}> Ba^{+2}>Na+ Anions: SO^{2-}> Cl^{-}

Stability of lyophilic Colloids

The addition of an electrolyte to a lyophilic colloid in moderate amounts does not result in coagulation, as was evident with lyophobic colloids. . If sufficient salt is added, however, agglomeration and sedimentation of the particles may result. This phenomenon, referred to as "salting out".

In general lyophilic colloids are stable because of the solvent sheath around the particles.



At high electrolyte concentration, ions get hydrated and water is no more available for hydration ofparticles. This results in flocculation or salting out of colloidal particles.

The coagulating power of an ion is directly related to the ability of that ion to separate water molecules from colloidal particles. Hofmeister or lyotropic series ranks cations and anions in orderof coagulation of hydrophilic sols.

Anions: citrate>tartrate>sulfate>acetate>chloride>nitrate> bromine>iodine

Cations: Mg^{+2}>Ca^{+2}>Ba^{+2}>Na^{+}>K^{+}

Less polar solvents such as alcohol, and acetone have greater affinity to water. When these are added to hydrophilic colloids, dehydration of particles occurs. Now the stability

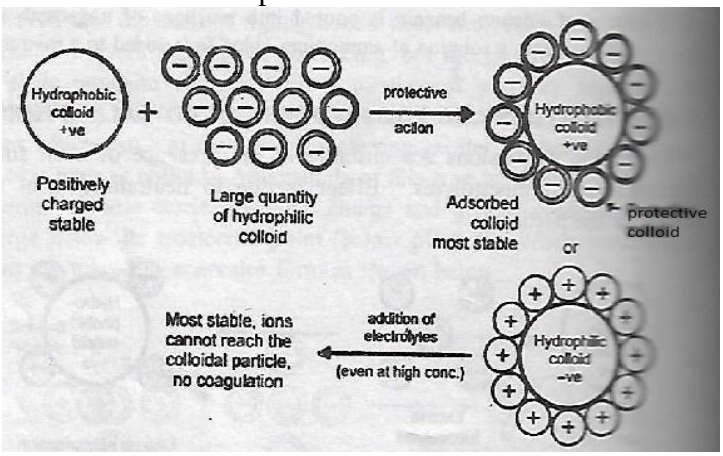
of particles depends on the charge they carry. The addition of even a small amount of electrolytes leads to flocculation or saltingout the colloid easily.

Coacervation

When negatively and positively charged hydrophilic colloids are mixed, the particles may separate from the dispersion to form a layer rich in colloidal aggregates. The colloid-rich layer is knownas a *coacervate* and the phenomenon in which macromolecular solutions separate into two liquid layers is referred to as *coacervation.* As an example, consider the mixing of gelatin and acacia. Gelatin at a pH below 4.7 (its isoelectric point) is positively charged; acacia carries a negative chargethat is relatively unaffected by pH in the acid range, When solutions of these colloids are mixed in acertain proportion, coacervation results. The viscosity of the upper layer, now poor in colloid, is markedly decreased. The lower layer becomes rich in the **coacervate.**

Protective Colloid Action

When a large amount of hydrophilic colloid carrying an opposite charge is added to hydrophobic colloids, these get adsorbed on the hydrophobic particles and form a protective layer around them. Thisadsorbed layer prevents the precipitating ions from reaching the sol particles. Therefore, coagulation is prevented and the system becomes stabilized. The entire colloid behaves like a hydrophilic colloid.The colloid that helps to stabilize the other colloid is known as a protective colloid.



The protective property is expressed most frequently in terms of the *gold number.* The gold numberis the minimum weight in milligrams of the protective colloid (dry weight of dispersed phase) required to prevent a color change from red to violet in 10 mL of a cold sol on the addition of 1 mLof a 10% solution of sodium chloride. The gold numbers for some common protective colloids areGelatin (gold number 0.005-0.01), Albumin (gold number 0.1) Acacia (gold number 0.1-0.2). Gold sol is a hydrophobic colloid and has a red color. When an electrolyte like NaCl is added coagulation of colloid is observed indicating violet color. When protective colloids are added, these stabilize the gold sol and prevent the change to violet color. The lower thegold number, the greater the protective action.

Reference:

Martin's Physical Pharmacy and Pharmaceutical Sciences: physical, chemical, and biopharmaceutical principles in the pharmaceutical sciences. 6th edition. Editors: Patrick J Sinko, Yashveer Singh. Wolters Kluwer Health, Lippincott Williams & Wilkins, Philadelphia, 2006.

UNIT-II

RHEOLOGY

KGRL COLLEGE OF PHARMACY

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RHEOLOGY

The term ‘rheology' was derived from the Greek words *rheo* (flow) and *logos* (science) and is used to describe the flow of liquids and the deformation of solids. Viscosity is an expression of the resistance of a fluid to flow: the higher the viscosity, the greater the resistance.

Importance of Rheology in Pharmacy

Manufacturers of medicinal and cosmetic creams, pastes, and lotions must be capable of producing products with acceptable consistency and smoothness and reproducing these qualities each time a new batch is prepared.

Rheology is involved in

- the mixing and flow of materials,
- their packaging into containers, and
- their removal before use, whether this is achieved by pouring from a bottle, extrusion from a tube, or passage through a syringe needle.

The medicinal and cosmetic creams, pastes, and lotions must have an acceptable consistency and smoothness. These qualities must be reproducible each time a new batch is prepared. The rheology of a particular product, which can range in consistency from fluid to semisolid to solid, can affect patient acceptability, physical stability, and biological availability (for example, viscosity has been shown to affect absorption rates of drugs from the gastrointestinal tract).

Rheologic properties of a pharmaceutical system can influence the selection of processing equipment used in its manufacture. Inappropriate equipment from this perspective may result in an undesirable product, at least in terms of its flow characteristics.

Newton’s Law of Flow

Newton was the first to study now properties of liquids in a quantitative way. **Newton’s Law of Flow** states that the shear stress between adjacent fluid layers is proportional to the velocity gradient between two layers or shear rate.

Two-plate model

The two-plate model provides a mathematical description of viscosity. There are two plates with fluid placed in between. The lower plate does not move. The upper plate drifts aside very slowly and subjects the fluid to stress, which is parallel to its surface: the shear stress. The force applied to the upper plate divided by this plate’s area defines the shear stress (F’/A). Force/area results in the unit N/m^2, which is named Pascal [Pa]

The two-plate model allows for calculating another parameter: the shear rate (*dv/dr*). The shear rate is the velocity of the upper plate divided by the distance between the two plates. Its unit is [1/s] or reciprocal second [s^{-1}].

Dynamic viscosity is shear stress divided by shear rate.

$$\frac{F}{A} = \eta^1 \frac{dv}{dr}$$

where η is the coefficient of viscosity or simply viscosity or absolute viscosity or dynamic viscosity.

where η is the coefficient of viscosity or simply viscosity or absolute viscosity or dynamic viscosity.

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

For a Newtonian system, a representative flow curve or rheogram, by plotting *F* versus *G* is shown below where a straight line passing through the origin is obtained.
The cgs unit of viscosity is the *poise* (dyne sec/cm^2 or g cm^{-1} sec^{-1}), defined as the shearing force required to produce a velocity of 1cm/sec between two parallel planes of liquid each 1 cm^2 in area

and separated by a distance of 1 cm. A more convenient unit for most work is the *centipoise* (cp), 1P
= 100cP. The SI unit is Pascal.sec (Pa.s or N.s/m^2 or kg/m.s). 1P=0.1Pa.s

Fluidity, ϕ is defined as the reciprocal of viscosity: □=1/η

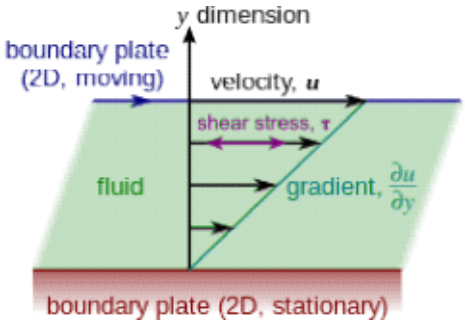
Kinematic viscosity is the absolute viscosity divided by the density of the liquid, ρ at a specific temperature:

□□□□□□□□□□ □□□□□□□□□□ = □/□

The cgs unit of kinematic viscosity is *stoke* (s) or cm^2/sec and *centistoke (cs)* and SI unit of kinematic viscosity is m^2/sec.

Two-plate model to calculate the shear stress. Shear stress is the force moving the upper plate divided by the plate's area.

Two-plate model to calculate the shear rate. The shear rate is the velocity of the moving plate divided by the distance between the plates.



Influence of Temperature and Pressure on Viscosity

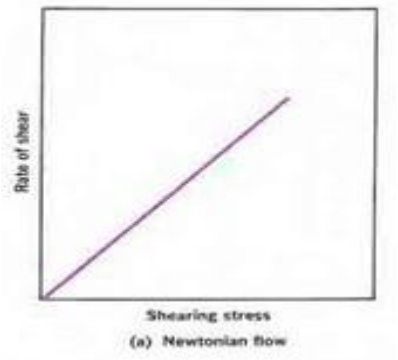
Apart from the shear rate, temperature strongly influences a fluid's viscosity. A substance's viscosity decreases with increasing temperature. As temperature is raised, the fluidity of a liquid (the reciprocal of viscosity) increases with temperature. This inversely proportional relation applies to all substances. Any temperature change always influences viscosity, but for different fluids, the extent of this influence varies. Even a 1 K (1 °C) temperature increase can raise the viscosity by 10%.

Normally, an increase in pressure causes a fluid's viscosity to increase however, fluids are not dramatically affected if the applied pressure is low or medium: liquids are almost non-
compressible in this pressure range. Most liquids react to a significantly altered pressure (from 0.1 MPa to 30 MPa) with a viscosity change of about 10%.

In case the pressure goes up from 0.1 MPa to 200 MPa, the viscosity can rise to 3 to 7 times the original value. This applies to most low-molecular liquids. Highly viscous mineral oils react with a viscosity increase of times 20000 under identical circumstances.

[**Conversion of pressure units:** 1 bar = 0.1 MPa = 105 Pa = 105 N/m^2]

In most liquids, pressure reduces the free volume in the internal structure, and thus limits the movability of molecules. Consequently, internal friction and viscosity increase



This is the simplest form of a rheograrn is produced by Newtonian systems. A *rheogram* is a plot of shear rate, *G*, as a function of shear stress, *F*. Rheograms are also known as consistency curves or flow curves. For this system, the greater the slope of the line, the greater is the fluidity or, conversely, the lower the viscosity.

Fluids that obey Newton's law of viscosity are called **Newtonian fluids** or a fluid whose viscosity does not change with the shear rate or a **Newtonian fluid** is one where there is a linear relationship between shear stress and shear rate

Non-Newtonian Systems

The majority of fluid pharmaceutical products do not follow Newton's law of flow. These systems are referred to as *non-Newtonian.* Non-Newtonian behavior is generally exhibited by liquid and solid heterogeneous dispersions such as colloidal solutions, emulsions, liquid suspensions, and ointments.

Non-Newtonian Flow

(a) Plastic
(b) Pseudoplastic
(c) Dilatant

(a) Plastic Flow

The materials that exhibit plastic flow, such materials are known as *Bingham bodies.* Plastic flow curves do not pass through the origin but rather intersect the shearing stress axis (or will if the straight part of the curve is extrapolated to the axis) at a particular point referred to as *the yield value.* A Bingham body does not begin to flow until a shearing stress corresponding to the yield value is exceeded. At stresses below the yield value, the substance acts as an elastic material. The **slope** of the rheogram is termed the *mobility*, analogous to fluidity in Newtonian systems, and its reciprocal is known as the *plastic viscosity, U.* The equation describing plastic flow is

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

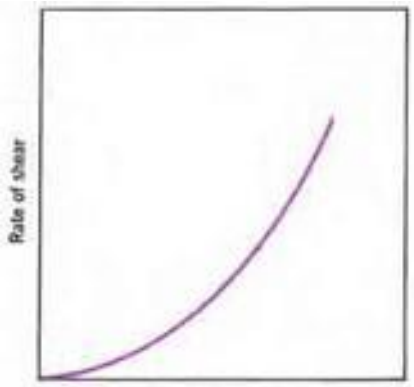
where *f* is the yield value, or intercept on the shear stress axis in dynes/cm^2

(b) Simple plastic flow

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions. As a result, a continuous structure is set up throughout the system. A yield value exists because of the contacts between adjacent particles (brought about by van der Waals forces), which must be broken down before flow can occur. Consequently, the yield value is an indication of force of flocculation: The more flocculated the suspension, the higher will be the yield value. Frictional forces between moving particles can also contribute to yield value. Once the yield value has been exceeded, any further increase in shearing stress (*F - f*) brings about a directly proportional increase in *G*, rate of shear. In effect, a plastic system resembles a Newtonian system at shear stresses above the yield value.

Pseudoplastic Flow

Many pharmaceutical products, including liquid dispersions of natural and synthetic gums (tragacanth, sodium alginate, methylcellulose. and sodium carboxymethyl cellulose) exhibit pseudoplastic flow. Pseudoplastic flow is typically exhibited by polymers in solution in contrast to plastic systems, which are composed of flocculated particles in suspension. The consistency curve for a pseudoplastic material begins at the origin (or at least approaches it at low rates of shear). Therefore, there is no yield value.



(c) Simple pseudoplastic flow

Furthermore, because no part of the curve is linear, the viscosity of a pseudoplastic material cannot be expressed by any single value. The viscosity of a pseudoplastic substance decreases with an increasing rate of shear and this system is known as a shear thinning system.

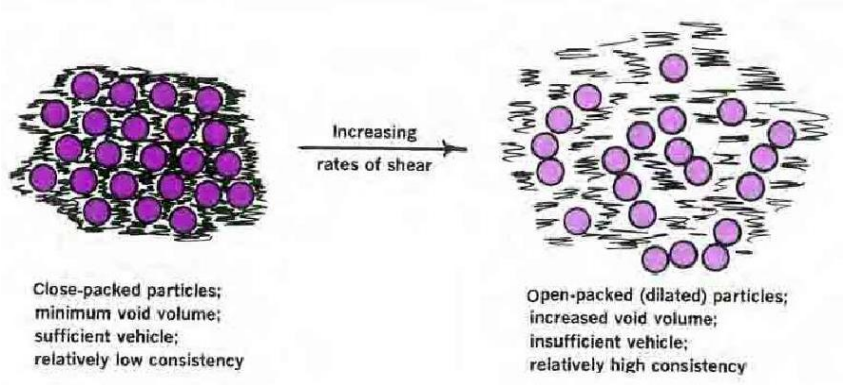
As shearing stress is increased, normally disarranged molecules begin to align their long axes in the direction of flow. This orientation reduces the internal resistance of the material and allows a greater rate of shear at each successive shearing stress. In addition, some of the solvent associated with the molecules may be released, resulting in an effective lowering of both the concentration and the site of the dispersed molecules. This, too, will decrease apparent viscosity.

Dilatant Flow

Certain suspensions with a high percentage of dispersed solids exhibit an increase in resistance to flow with increasing rates of shear. Such systems increase in volume when sheared and are hence termed *dilatants.* This type of flow is the inverse of that possessed by pseudoplastic systems. Whereas pseudoplastic materials are frequently referred to as "shear-thinning systems," dilatant materials are often termed "shear-thickening systems." When stress is removed, a dilatant system returns to its original state of fluidity.

Substances possessing dilatant flow properties are invariably suspensions containing a high concentration (about 50% or greater) of small, deflocculated particles.

Dilatant behavior can be explained as follows. At rest, the particles are closely packed with minimal inter-particle volume (voids). The amount of vehicle in the suspension is sufficient, however, to fill voids and permit particles to move relative to one another at low rates of shear. Thus, a dilatant suspension can be poured from a bottle because under these conditions it is reasonably fluid.



As shear stress is increased, the bulk of the system expands or dilates; hence the term *dilatant.* The particles, in an attempt to move quickly past each other, take on an open form of packing, as depicted in the above figure**.** Such an arrangement leads to a significant increase in inter-particle void volume. The amount of vehicle remains constant and, at some point, becomes insufficient to fill the increased voids between particles. Because the particles are no longer completely wetted or lubricated by the vehicle, the resistance to flow increases. Eventually, the suspension will set up as a firm paste.

Thixotropy

Thixotropy is defined as the progressive decrease in viscosity with time for a constant applied shear stress followed by a gradual recovery when the stress is removed.

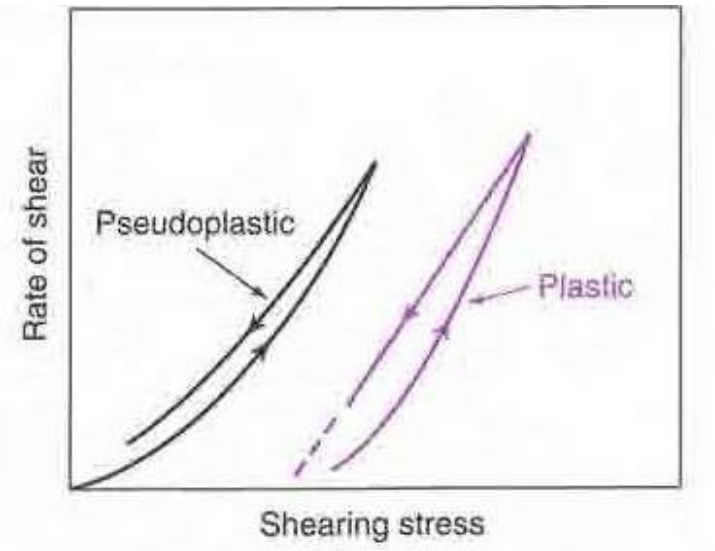
Thixotropy is a time-dependent shear thinning property.

Thixotropy can be defined as an isothermal and slow recovery of material consistency, lost

through shearing.

If the rate of shear is reduced once the desired maximum is reached, the down-curve would be superimposable on the up-curve. This is true for Newtonian systems.

In case of non-Newtonian systems, the down-curve can be displaced relative to the up-curve. With shear-thinning systems (i.e., pseudoplastic), the down-curve is frequently displaced to the left of the up-curve, showing that the material has a lower consistency at any one rate of shear on the down-curve than it had on the up-curve. This indicates a breakdown of structure (and hence shear thinning) that does not reform immediately when stress is removed or reduced. This phenomenon is known as *thixotropy*. Typical rheograms for plastic and pseudoplastic systems exhibiting this behavior are shown below.



Thixotropic systems usually contain asymmetric particles. These particles set up a loose three-dimensional network in the sample through numerous points of contact. At rest, this structure confers some degree of rigidity on the system, and it resembles a *gel*. As shear is applied and flow starts, this structure begins to break down as points of contact are disrupted and particles become aligned. The material undergoes a gel-to-sol transformation and exhibits shear thinning. On removal of stress, the structure starts to reform. This process is not instantaneous. Rather, it is a progressive restoration of consistency as asymmetric particles come into contact with one another by undergoing random Brownian movement.

The most apparent characteristic of a thixotropic system is the hysteresis loop formed by the up-curves and down-curves of the rheogram. The **area enclosed** between the "up" and "down" **curves** (the **hysteresis loop**) is an indication of the extent of **thixotropy** of the **material**. This relates to the energy needed to break down the reversible microstructure of tested material. Thus, a highly thixotropic material is characterized by having a large area within the loop. If up and down- curves coincide perfectly, the material is non-thixotropic. In a thixotropic system, the nature of the rheogram largely depends on the rate at which shear is increased or decreased. Typically, the period over which the shear rate is increased (up-curve) is equal to the period over which it is decreased (down curve). The response in terms of material shear stress is recorded and plotted against

time.

Thixotropy can be measured by two methods:

(a) At constant shear rate

(b) At variable shear rate

Determination of viscosity

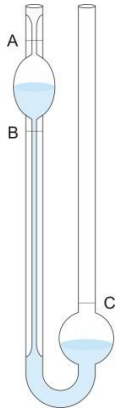
(a) For Newtonian systems, single-point instruments that operate at a single shear rate are used. Example: **Ostwald viscometer** and **falling sphere viscometer**.

(b) For non-Newtonian systems, multi-point instruments operate at a variety of shear rates are used. For example: a single-point determination is virtually useless in characterizing its flow properties. Example: **Brookfield viscometer**

Therefore, although all viscometers can be used to determine the viscosity of Newtonian systems, only those with variable-shear-rate controls can be used for non-Newtonian materials.

Capillary Viscometer

The viscosity of a Newtonian liquid can be determined by measuring the time required for the liquid to pass between two marks as it flows by gravity through a vertical capillary tube known as an *Ostwald viscometer.*



The time of flow of the liquid under test is compared with the time required for a liquid of known viscosity (usually water) to pass between the two marks. If η_1 and η_2 are the viscosities of the unknown and the standard liquids, respectively, ρ_1 and ρ_2 are the respective densities of the liquids, and t_1 and t_2 are the respective flow times in seconds, the absolute viscosity of the unknown liquid, η_1 is determined by substituting the experimental values in the equation

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1 \square 1}{\rho_2 \square 2}$$

The ratio η_1/η_2 is known as the relative viscosity of the liquid under test.

The above equation is obtained from Poiseuille's law for a liquid flowing through a capillary tube as follows.

$$5 = \frac{\square\square^4\square\Delta\square}{8\square\square}$$

where *r* is the radius of the inside of the capillary, *t* is the time of flow, *ΔP* is the pressure head (dynes/cm^2) under which the liquid flows, *l* is the length of capillary and V is the volume of liquid flowing. The radius, length, and volume of a given capillary viscometer are constants and can be combined into a constant, K. Then the equation can be written as:

$$5 = \square\square\Delta\square$$

The pressure head ΔP depends on density, ρ of the liquid being measured, the acceleration of gravity, and the difference in heights of liquid levels in the two arms of the viscometer (hydrostatic pressure = *hρg*). Acceleration of gravity is a constant, however, and if the levels in the capillary are kept constant for all liquids, these terms can be incorporated in the constant and the viscosities of the unknown and the standard liquids can be written as

$$5_1 = \square'\square_1\square_1$$

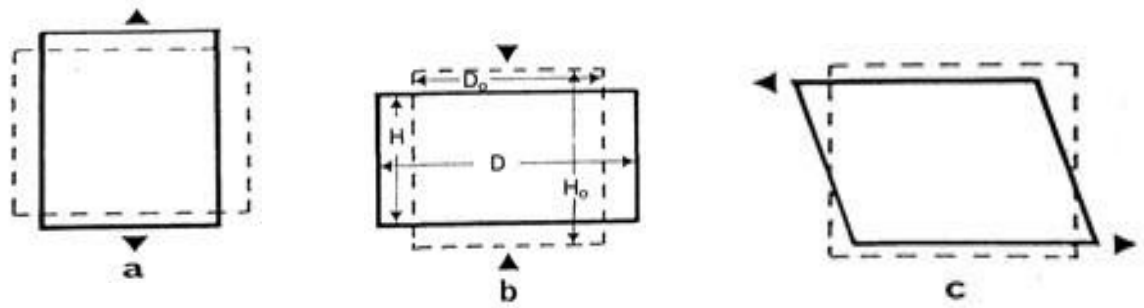
$$5_2 = \square'\square_2\square_2$$

Therefore, when flow periods for two liquids are compared in the same capillary viscometer, the two equations give the following relationship:

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1\square_1}{\rho_2\square_2}$$

Deformation of Solids

Deformation means change in the form of materials upon application of force. When any solid body is subjected to opposing forces, there is a finite change in its geometry, depending upon the nature of the applied load. The relative amount of deformation produced by such forces is a dimensionless quantity called strain. The deformation of a solid due to stress is strain. Three of the most common types of strain are illustrated below:



The diagram shows the change in geometry (strain) of a solid body resulting from various types of applied force: tensile strain (a), compressive strain (b), and shear strain (c)

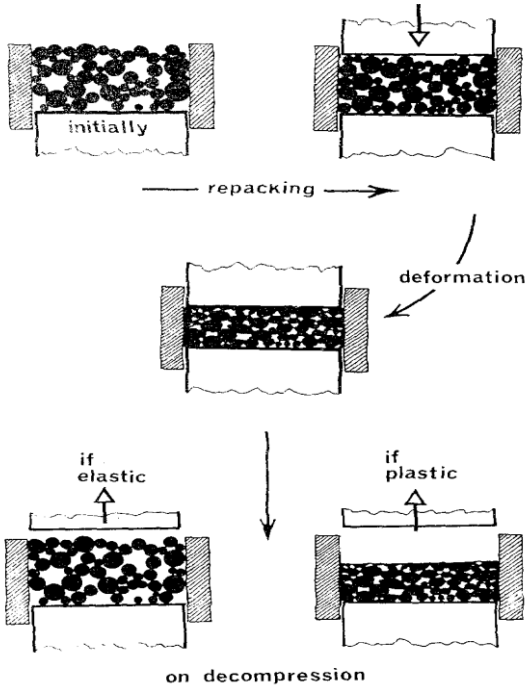
For example, if a solid rod is compressed by forces acting at each end to cause a reduction in length of ΔH from an unloaded length of H_0 (Diagram *b*), then the compressive strain *Z* is given by the equation:

$$Z = \frac{\Delta H}{H_O}$$

The ratio of force, *F* necessary to produce this strain to the area *A* over which it acts is called the stress σ, which is

$$\sigma = \frac{F}{A}$$

The deformation may be **plastic** or **elastic**. A deformation that does not recover completely after the release of stress is known as plastic deformation. A deformation that returns to its original shape upon release of stress is known as elastic deformation. The force required to initiate a plastic deformation is known as yield stress.



The particle size distribution and shape of the granules determine initial packing or bulk density as the granulation is delivered into the die cavity. At low pressure, the granules flow concerning each other, with the finer particles entering the void between the larger particles, and the bulk density of the granulation is increased. Spherical particles undergo less particle rearrangement than irregular particles as spherical particles assume a close packing arrangement initially. When the particles of granulation are so closely packed that no further filling of the void occurs, a further increase in compression force causes deformation at the points of contact. Deformation increases the area of true contact, thereby increasing potential

bonding areas.

HECKEL EQUATION (1961):

The Heckel analysis is the most useful method for estimating volume reduction under compression pressure (in compression of tablets).

Heckel plots can be affected by

- Time of compression
- Degree of lubrication
- Size of die

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

The Heckel equation is expressed as:

$$\int [\frac{1}{1-D}] = KP + A$$

Whereas, D= relative density of the tablet

(ratio of tablet density and true density of powder)

P = pressure

K = slope of straight line

A = constant represents the rearrangement of particles.

APPLICATIONS:

1. The crushing strength of tablets can be correlated with values of K of Heckel plots.
2. Larger K values usually indicate harder tablets
3. It information helps in binder selection when designing tablet formulation.

ELASTIC MODULES:

The constant of proportionality depends on the material being deformed and the nature of the deformation. This constant is called Elastic modules.

It determines the amount of force required per unit of deformation.

A material with a large elastic modulus is difficult to deform, while one with a small elastic modulus is easier to deform.

UNIT-III

COARSE DISPERSION

KGRL COLLEGE OF PHARMACY

jahnavi thota
[COMPANY NAME]

COARSE DISPERSION

A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium (usually water or water-based vehicle). Generally, the particleshave diameters greater than 0.5µm. The concentration of the dispersed phase may exceed 20%.

SUSPENSIONS:

Some desirable qualities of suspension include the following:

1. The suspended material should not settle rapidly. If the particles settle to the bottom of the container, they must not form a hard cake but should be readily redispersed into a uniform mixture when the container is shaken.
2. The suspension must not be too viscous to pour freely from the orifice of the bottle in case of oral suspension or to flow through a syringe needle in case of parenteral suspension. In the case of lotion, the product must be fluid enough to spread easily over the affected area and yet must not be so mobile that it runs off the surface to which it is applied.
3. The suspension should have optimum physical, chemical, and pharmacologic properties.

Interfacial properties of suspended particles

The work must be done to reduce a solid to small particles and disperse them in a continuous medium. The large surface area of the particles that results from the size reduction is associated with surface-free energy that makes the system ***thermodynamically unstable***. It means that the particles arehighly energetic and tend to regroup in such a way as to decrease the total area and reduce the surface-free energy. The particles in a liquid suspension therefore tend to *flocculate*, that is, to form light, fluffyconglomerates that are held together by weak van der Waals forces. Under certain conditions, the particles may adhere to stronger forces to form *aggregates*. Caking often occurs through the growth andfusing of crystals in the precipitates to produce a solid aggregate.

The formation of any type of agglomerates either floccules or aggregates are taken as a measure of thesystem's tendency to reach a more thermodynamically stable state. An increase in the work, W, or surface free energy, ΔG, brought about by dividing the solid into smaller particles and consequentlyincreasing the total surface area, ΔA, is given by

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

where γ_{SL} is the interfacial tension between the liquid medium and the solid particles.

Therefore, the system tends to reduce the surface free energy to reach a stable state, and equilibrium is

reached when ΔG=0. This condition can be accomplished by

(i) a reduction of interfacial tension

(ii) a decrease in interfacial area

The decrease of interfacial area leads to flocculation or aggregation which can be desirable or undesirable in pharmaceutical suspension.

The interfacial tension can be reduced by the addition of a surfactant but cannot ordinarily bemade equal to zero. A suspension of insoluble particles, then, usually possesses a finite positive interfacial tension, and the particles tend to flocculate.

The forces at the surface of a particle affect the degree of flocculation and agglomeration in a suspension. Forces of attraction are of the van der Waals type; the repulsive forces arise from the interaction of the electric double layers surrounding each particle.

When the particles approach each other, they experience repulsive forces because the

particles carry a finite charge on their surface. When repulsion energy is high, the potential barrier is also high, and collision of the particles is opposed and aggregation of particles is prevented. So the solids are present as individual particles and the sedimentation of particles is very slow. This system is called a deflocculated system.

When the particles are separated by a longer distance (10-20 nm), a weak attractive force existsjust beyond the range of double-layer repulsive forces. This region is called secondary minimum and is responsible for flocculation of particles i.e. the formation of loose fluffy aggregates or open network of aggregated particles (flocs or floccules). This system is called flocculated suspension.

Deflocculated suspension	Flocculated suspension
Pleasant appearance due to uniform dispersion of particles	Unsightly sediment and clear supernatant layer
Supernatant remains cloudy	Supernatant is clear
Particles experience repulsive force	Particles experience weak attractive force
Particles exist as separate entities	Particles form loose aggregates
Rate of sedimentation is slow	Rate of sedimentation is higher as flocs are the collection of smaller particles
Particles settle independently and separately	Particle settle as flocs
The sediment is closely packed and form hard Cake	The sediment is loosely packed open network and does not form hard cake
Hard cake cannot be re-dispersed	Sediment is easy to re-disperse

Settling in suspension

The physical stability in pharmaceutical suspensions is concerned with keeping the particles uniformly distributed throughout the dispersion. The velocity of sedimentation is expressed by Stoke's law:

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

where v is the sedimentation velocity in cm/sec. d is the diameter of the particle in cm, ρ_s and ρ_0, are the densities of the dispersed phase and dispersion medium, respectively, g is the acceleration due to gravity, and η_0 is the viscosity of the dispersion medium inpoise. Stokes law is useful in fixing factors that can be utilized in the formulation of suspension.

1. *Particle size:* if particle size is reduced to half of its original size, the rate of sedimentation decreases by a factor of 4.
2. *Viscosity of medium:* The higher the viscosity, the lower the rate of sedimentation. High viscosity enhances physical stability by preventing sedimentation, inhibits crystal growth, and prevents the transformation of metastable crystals to stable crystals. However, high viscosity hinders drug absorption from suspension and creates problems in handling.
3. *Density of the medium:* The density of solids used in suspension is generally from 1.5 to 2.0 gm/cc.

If the density of the medium is equal to the density of solids, the rate of settling becomes zero. In general, the medium density is about 1gm/cc due to the aqueous phase. Therefore, there is a need to increase the viscosity of the medium, so that the differences in densities will be minimal. The density of the medium can be increased by using PVP, glycerin, and sorbitol.

A combination of these yields improved suspension but they should be used inhigh concentration, though the improvement in density is less. Hence, this is not a viable factor to decrease the rate of settling.

Sedimentation of Flocculated Particles

The extent of sedimentation is quantitatively expressed by two parameters:

1. **Sedimentation volume or sedimentation height**
2. **Degree of flocculation**

These are normally used for the comparison of different suspensions and apply to flocculated suspensions only. The term *subsidence* is sometimes used to describe settling in flocculated systems and refers to the descending of the boundary between the sediment and clear supernatant above it. When sedimentation is studied in flocculated systems, it is observed that the flocs tend to falltogether, producing a distinct boundary between the sediment and the supernatant liquid. Theliquid above the sediment is clear because even the small particles present in the system areassociated with the flocs. Such is not the case in deflocculated suspensions having a range ofparticle sizes, in which, by Stokes's law, the larger particles settle more rapidlythan the smaller particles. No clear boundary is formed and the supernatant remains turbid for aconsiderably longer period. Whether the supernatant liquid is clear or turbid during theinitial stages of settling is a good indication of whether the system is flocculated or deflocculated,respectively.

Sedimentation volume:

The sedimentation volume, *F,* is defined as the ratio of the final or ultimate volume of the sediment, V_u, to the original volume of the suspension, V_0, before settling. H_u represents the height of the sediment. Thus,

$$F = \frac{V_u}{V_o} = \frac{H_u}{H_o}$$

For ideal suspension, $V_u = V_0$, because there is no sedimentation and hence F=1. Normally, the F value liesbetween 0 and 1. In general, the higher the sedimentation volume, the better the physical stability.

Degree of flocculation

The sedimentation volume gives only a qualitative account of flocculation because it lacks a meaningful reference point. A more useful parameter for flocculation is β, the degree of flocculation.

If we consider a suspension that is completely deflocculated, the ultimate volume of the sediment willbe relatively small. Writing this volume as V_∞, we can write

$$F_\infty = \frac{V_\infty}{V_O}$$

Where, F_∞ =sedimentation volume of deflocculated or peptised suspension

$$\text{Degree of flocculation } \beta = \frac{F}{F_\infty}$$

$$\beta = \frac{v_u/v_o}{v_\infty/v_o} = \frac{v_u}{v_o}$$

We can therefore say that,

$$\text{Degree of flocculation } (\beta) = \frac{\textbf{ultimate sediment volume of flocculated suspension}}{\textbf{ultimate sediment volume of deflocculated suspension}}$$

Formulation of Suspensions

The formulation of a suspension depends upon whether the desired suspension is flocculated or deflocculated. Two approaches are commonly used. One approach involves the use of structured vehicles to keep particles in a deflocculated state. The second approach keeps particles in a flocculatedstate to prevent cake formation. The third method uses a combination of earlier approaches toprevent settling.

Suspensions are prepared by levigating or grinding the insoluble materials in the mortarto a smooth paste with a vehicle containing the wetting agent such as hydrophilic polymers- sodium CMC, water-miscible solvents like glycerin, propylene glycol, alcohol and water-insoluble but hydrophilic materials such as bentonite, aluminum-magnesium silicates, colloidal silica, surfactants (HLB 7-9) either alone or in combination.

Surfactants aid in dispersion by reducing the interfacial tension between solid particles and the vehicle. As a result, the contact angle is lowered and air is displaced from the surface of solids.

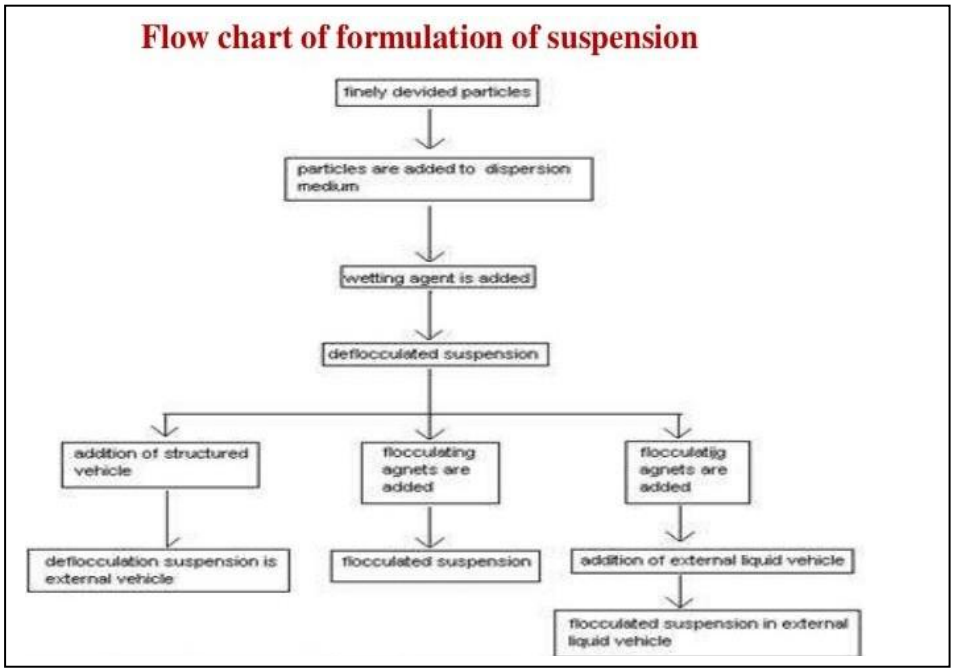
All soluble ingredients are dissolved in some portions of the vehicle and added to the smoothpaste to get a slurry. The slurry is transferred to a graduated cylinder; the mortar is rinsed with successive portions of the vehicle.

Then decide whether the solids are suspended in a structured vehicle or flocculated or flocculated and then suspended. Add the vehicle containing the suspending agent or flocculating agent in the order mentioned in the diagram. Then make the dispersion to the final volume.

It is frequently difficult to disperse the powder owing to an adsorbed layer of air. The powder is not readily wetted, and although it may have a high density, it floats on the surface of the liquid. Finely powdered substances are particularly susceptible to this effect because of entrained air,and they fail to become wetted even when forced below the surface of the suspending medium. The wettability of a powder can be ascertained easily by observing the contact angle that the powder makes with the surface of the liquid. The angle is approximately 90º when the particles are floating well out of the liquid. A powder that floats low in the liquid has a lesser angle, and one that sinks shows no contact angle. Powders that are not easily wetted by water and accordingly, show a large contact angle such as sulfur, charcoal, and magnesium stearate are saidto be *hydrophobic*. Powders that are readily wetted by water when free of adsorbed contaminants arecalled *hydrophilic*. Zinc oxide, talc, and magnesium carbonate belong to the latter class.

The degree of flocculation is a more fundamental parameter than F because it relates the volumeof flocculated sediment to that in a deflocculated system. We can therefore say that

$$\beta = \frac{\text{ultimate sediment volume of flocculated suspension}}{\text{ultimate sediment volume of deflocculated suspension}}$$



Structured vehicle-deflocculated suspension

Many pharmaceutical products, including liquid dispersions of natural and synthetic gums (e.g., tragacanth, sodium alginate, methylcellulose. and sodium carboxymethyl cellulose) exhibit pseudoplastic flow. Pseudoplastic flow is typically exhibited by polymers in solution in contrast to plastic systems which are composed of flocculated particles in suspension. The viscosity of a pseudoplastic substance decreases with increasing rate of shear.

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions. As a result, a continuous structure is set up throughout the system. A yield value exists because of the contacts between adjacent particles (brought about by van der Waals forces), which must be broken down before flow can occur. Consequently, the yield value is an indication of the force of flocculation: The more flocculated the suspension, the higher will be the yield value.

Structured vehicles are vehicles that exhibit pseudoplastic or plastic behavior. Moreover, they should possess some degree of thixotropic behavior i.e. gel-sol-gel transformation. Such a behavior improves the physical stability of suspensions. During storage, a shear thinning system acquires a gel-like structure so that particles do not settle. On shaking, viscosity decreases andthe suspension becomes a sol so that uniform dispersion of solid can be achieved. If left aside,the suspension regains its gel-like structures. Structured vehicles are extremely used for the preparation of deflocculated suspensions. Structured vehicles are generally prepared using hydrocolloids like carbopol, sodium CMC, bentonite, MC, and HPMC.

Controlled flocculation-flocculated suspension

Once the powders are properly wetted and dispersed in a medium, flocculation can be produced by the gradual addition of flocculating agents such as electrolytes, polymers, and surfactants.

Most dispersed particles have a surface charge. The intensity of this charge can be reduced by the addition of agents with oppositely charged electrolytes. As a result, the zeta potential decreasesand particles establish attractive forces between adjacent particles.
Surfactants and polymers are long-chain compounds. These substances act by adsorbing a part of their chains on the particle surface and projecting out the remaining part into the medium, this type of bridging promotes the formation of flocs. The hydrophilic polymers form a mechanical barrier or sheath around the particles and induce flocculation. This mechanism is more useful to improve the appearance of flocculated suspension.

Flocculation in structured vehicle:

In a flocculated suspension, the supernatant becomes clear rapidly. This is an undesirable property. Hence the principles of flocculation and structured vehicles are combined to get an improved suspension. The flocculating agents facilitate the formation of aggregates of uniform size, while the structured vehicles prevent the aggregates or flocs from settling. Consequently, in practice, a suspending agent is frequently added to retard the sedimentation of flocs. Such agents are CMC, Carbopol 934, tragacanth, and bentonite have been employed, either alone or in combination.

EMULSIONS:

An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules (the dispersed phase) in the other liquid phase (the continuous phase), stabilized by the presence of an emulsifying agent.

Either the dispersed phase or the continuous phase may range in consistency from that ofa mobile liquid to a semisolid. Thus, emulsified systems range from lotions of relatively low viscosity to ointments and creams, which are semisolid. The particle diameter of the dispersed phase may extend from about 0.01 to 10 μm.

When the oil phase is dispersed as globules throughout an aqueous continuous phase, the system is referred to as an oil-in-water (o/w) emulsion. When the oil phase serves as the continuous phase, the emulsion is referred to as water-in-oil (w/o) emulsion. Medicinal emulsions for oral administration are usually of the o/w type and require the use of water-soluble emulsifying agents such as nonionic surfactants, acacia, tragacanth, sodium lauryl sulfate, tri-ethanolamine stearate, monovalent soaps such as sodium oleate.

Pharmaceutical w/o emulsion is used almost exclusively for external application and may contain one or several of the following emulsifiers: polyvalent soaps such as calcium palmitate, sorbitan esters (Spans), cholesterol, and wool fat.

Two additional types of emulsions are oil-in-water-in-oil emulsion (o/w/o) and water-in-oil-in-water (w/o/w) type emulsion. Such emulsions are known as multiple emulsions.

Theories of emulsification

When two immiscible liquids are agitated together so that one of the liquids is dispersed as small droplets in the other, the liquids separate rapidly into two clearly defined layers. The failure of two immiscible liquids to remain mixed is explained by the fact that the cohesive force between the molecules of each separate liquid is greater than the adhesive force between the two liquids. When one liquid is broken into small particles, the interfacial area of the globules constitutes a surface that is enormous compared with the surface area of the original liquid. The surface free energy increase (W) is given by the equation: $W = \gamma_{ow}$

$\times \Delta A$ and $\gamma_{o/w}$ is the interfacial tension between oil and water.
The increase in energy, associated with this enormous surface is sufficient to make the system thermodynamically unstable hence the droplets tend to coalesce. To prevent coalescence or at least to reduce its rate to negligible proportions, it is necessary to introduce an emulsifying agent that will form a film around the dispersed globules.
Emulsifying agents can be divided into three groups, as follows:

1. **Surface-active agents** (Spans, Tweens), which are adsorbed at oil-water interfaces toform monomolecular films and reduce interfacial tension.
2. **Hydrophilic colloids** (acacia, gelatin), form a multi-molecular film around the dispersed droplets of oil in an o/w emulsion.

Finely divided solid particles (bentonite-hydrated aluminum silicate, Veegum-magnesium aluminum silicate), which are adsorbed at the interface between two immiscible liquid phases form a film of particles around the dispersed globule.

Monomolecular Adsorption

Surface-active agents reduce interfacial tension because of their adsorption at the oil-water interface to form monomolecular films. Because the surface free energy increase, W, equals $\gamma o/w \times \Delta A$ and we must retain a high surface area for the dispersed phase, any reduction in $\gamma o/w$, the interfacial tension, will reduce the surface free energy and hence the tendency for coalescence.

Further, the dispersed droplets are surrounded by a coherent monolayer that helps prevent coalescence between two droplets as they approach one another. Ideally, such a film should be flexible so that it is capable of reforming rapidly if broken or disturbed. An additional effect promoting stability is the presence of a surface charge, which will cause repulsion between adjacent particles.
The type of emulsion is a function of the relative solubility of the surfactant, the phase in which it is more soluble being the continuous phase. This is sometimes referred to as the rule of Bancroft. Thus, an emulsifying agent with a high HLB is preferentially soluble in water and results in the formation of an o/w emulsion. The reverse situation is true with surfactants of low HLB which tend to form w/o emulsions. In general, o/w emulsions are formed when the HLB of the emulsifier is within the range of about 8 to 16, and w/o emulsions are formed when the rangeis about 3 to 6.

Multi-molecular Adsorption and Film Formation

Hydrophilic colloids differ from the synthetic surface-active agents in that (a) they do not cause anappreciable lowering of interfacial tension and (b) they form a multi- rather than a monomolecular film at the interface. Their action as emulsifying agents is due mainly to the formation of multi-molecular layer film which is strong enough to resist coalescence. An auxiliary effect promoting stability is the significant increase in the viscosity of the dispersion medium. Because the emulsifying agents that form multilayer films around the droplets are invariably hydrophilic, they tend to 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 can act as emulsifying agents. The solid particles concentrate at the interface, where they produce a particulate film around the dispersed droplets to prevent coalescence. Powders that are wetted preferentially by water form *o/w* emulsions, whereas those more easily wetted by oil form *w/o* emulsions.

Physical stability of an emulsion

A pharmaceutical emulsion becomes unstable due to the following reasons:

1. **Creaming**
2. **Flocculation**
3. **Coalescence**
4. **Phase inversion**

1. Creaming

Under the influence of gravity, the emulsion droplets tend to rise or sediment depending on the difference in densities between the phases and this phenomenon is known as creaming.

According to Stoke's law, if the dispersed phase is less dense than the continuous phase as in the case of *o/w* emulsions, an upward *creaming* results. If the internal phase is heavier than the external phase as in the case of *w/o* emulsions, the globules settle and result in *downward creaming.*

In the case of pharmaceutical emulsions, creaming results in a lack of uniformity of drug dose unless the preparation is thoroughly shaken before administration. The visual appeal of an emulsion is also affected by creaming.

Creaming is a reversible process. The cream floccules can be re-dispersed easily, and a uniform mixture is reconstituted from a creamed emulsion by agitation because the oil globules are still surrounded by a protective sheath of emulsifying agent. Creaming can be prevented or reduced in the following ways:

The rate of creaming is a function of the square of the radius of the globules. Thus, larger particles creammore rapidly than smaller particles.

Reduction of particle size to a diameter below 5 µm, Brownian motion helps the particles to settle or cream more slowly.

The viscosity of the external phase can be increased without exceeding the limits of acceptable consistency by adding a ***viscosity improver or thickening agent*** such as methylcellulose, tragacanth, or sodium alginate.

2. Flocculation

Flocculation is defined as a reversible aggregation of droplets of internal phases in the form of three-dimensional clusters. Flocculation may take place before, during, or after creaming.

Flocculation can be prevented or reduced in the following ways:

An emulsion can be stabilized with the use of ionic surfactants at a particular concentration. The droplets remain deaggregated in the form of single droplets as a result of repulsion between charged droplets.

Uniform-size globules also prevent flocculation.

If the viscosity of the external medium is increased, the globules become relatively immobile and flocculation can be prevented.

The following factors promote flocculation. An increase in ionic strength with electrolytes or an increase in emulsifier concentration tends to promote flocculation. A high internal phase volume and tight packing of the dispersed phase tend to promote flocculation.

1. Coalescence

Coalescence is a growth process during which the emulsified droplets fuse to form larger particles. In this process, the emulsifier film around the globules is destroyed to a certain extent. This step is recognized by increased globule size and reduced number of globules. The coalescence can be prevented by the formation of thick interfacial film from macromolecules or from particulate solids. This is the reason a variety of natural gums and proteins are as useful as auxiliary emulsifiers when used in low concentrations but can be used as primary emulsifiers at higher concentrations.

If the globule sizes are not uniform, globules of smaller size occupy the spaces between largerglobules. This type of close packing induces greater cohesion of globules which leads to coalescence. Any evidence for the formation of larger droplets suggests that the emulsion will separate into oiland aqueous phase; this is called ***breaking of emulsion***. It is an irreversible process; simplemixing failed to re-suspend the globules into a uniform emulsion.

2. Phase inversion

Phase inversion means a change of emulsion type from *o/w* to *w/o* or vice versa. For instance, an *o/w* emulsion is prepared using sodium stearate. Then, calcium chloride is added to form calcium stearate, which is oil-soluble. Therefore, the oil phase becomes the continuous phase, and *w/o* emulsion is produced. Inversion can also be produced by alterations in the phase-volume ratio. The temperature at which phase inversion occurs depends on emulsifier concentration and is called phase inversion temperature (PIT).

PRESERVATION OF EMULSIONS

Certain undesirable changes in the properties of the emulsion can be brought about by the growth of microorganisms. These include physical separation of the phases, discoloration, gas, and odor formation, and changes in rheologic properties. Emulsions for parenteral use obviously must be sterile.

The propagation of microorganisms in emulsified products is supported by one or more of the components present in the formulation. Thus, bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and vegetable gums present as thickeners, with a consequent deterioration of the emulsion. As a result, emulsions must be formulated to resist microbial attack by including an adequate concentration of preservatives in the formulation. However, the main problem is obtaining an adequate concentration of preservatives in the product. Some of the factors that must be considered to achieve this end are presented here.

Emulsions are heterogeneous systems in which partitioning of the preservative will occur between the oil and water phases. Mainly the bacteria grow in the aqueous phase of emulsified systems, with the result that a preservative that is partitioned strongly in favor of the oil phase may be virtually useless at normal concentration levels because of the low concentration remaining in the aqueous phase. The phase-volume ratio of the emulsion is significant in this regard. In addition, the preservative must he in an un-ionized state to penetrate the bacterial membrane. Therefore, the activity of weak acid preservatives decreases as the pH of the aqueous phase rises.

Emulsion Formulation by HLB Method

HLB measures the polar and non-polar nature of the surfactant. Each emulsifying agent is given a number on the HLB scale. The *o/w* emulsifying agent has an HLB value of 8-16 and the *w/o* emulsifyingagent has an HLB of 3-6. High numbers indicate hydrophilic

properties while low numbers represent hydrophobic properties. Emulsifying agents with high numbers give *w/o* emulsion and those with low numbers give *w/o* emulsion.
The HLB required for emulsifying oil in water can be determined by trial and error. Prepare emulsion with emulsifiers having a range of HLB values and then determine the HLB value that yields the best emulsion. However, a list of required HLB values is given that are of interest in pharmaceutical preparations. The knowledge of required HLB (RHLB) permits the selection of an emulsifier or a combination of emulsifiers.
To ensure satisfactory emulsion, oils, fats, and waxes require emulsifying agents of suitable HLB value. Therefore, required HLB values are calculated for oily materials, depending on whether*o/w* or *w/o* emulsions are required.

Table: Required HLB values of oils and waxes

	w/o	**o/w**
Beeswax	4	12
Cetyl alcohol	-	15
Liquid paraffin	5	12
Soft paraffin	5	12
Wool fat	8	10

When several oils and fats are included in a formula the total required HLB may be calculatedand an emulgent or blend of emulgents is selected accordingly. The formulation of an *o/w*emulsified lotion illustrates the procedure.

Formula:

Liquid paraffin..... 35
Wool fat 1
Cetyl alcohol..... 1
Emulgent.....7
Water to..... 100

Required HLB values of the first three ingredients are respectively 12, 10, and 15 for an *o/w* emulsion. The total percentage of the oil phase is 35+1+1=37 %, and the proportions of the oil phase ingredients are-
Liquid paraffin: 35/37*100=
94.6%Wool fat: 1/37*100=
2.7%
Cetyl alcohol: 1/37*100=2.7%
The total required HLB value is obtained as follows:
Liquid paraffin: 94.6/100*12=11.4
Wool fat: 2.7/100*10= 0.3
Cetyl alcohol: 2.7/100*15=0.4
Total RHLB= 12.1
Say, a mixture of Span 80 (HLB=4.3) and Tween 80 (HLB=15) is to be used as an emulgent blend. The proportions of these two substances that will provide the RHLB value of 12.1 are calculatedas follows:
Let x = % of Span 80 in the
mixture. Then 100-x = % of Tween

80 Contribution from span 80=
4.3*x/100
Contribution from span 80= 15*(100-x)/100
Since total contribution must be 12.1, the expression for calculating x is:
4.3*x/100 + 15*(100-x)/100=12.1
4.3x+1500-15x=1210
290=10.7x or x=27%
Hence, the percentages of emulsifying agents in the mixture are: Span 80: 27; Tween 80: 73 Since the total percentage of the mixed emulgents is the formula is 7, the percentages of individual substances are Span 80= 7*27/100=1.89; Tween 80= 7-1.89=5.11

Microemulsion

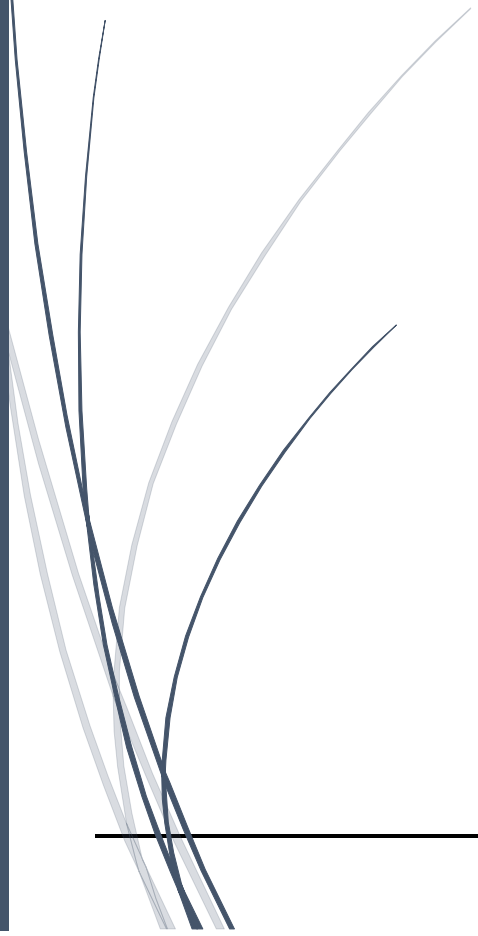
Microemulsion is an isotropic, clear, and transparent liquid, representing a state intermediate between solution and ordinary emulsion. Microemulsion contain droplets with diameters of about 10 to 200 nm, and the volume fraction of the dispersed phase varies from 0.2 to 0.8. In addition to an emulsifying agent, a co-surfactant is used in the preparation of microemulsion. The addition of co-surfactant (pentanol) temporarily reduces the surface tension to approximately zero, allowing spontaneous emulsification. Both surfactant and co-surfactant molecules form an adsorbed film on the microemulsion particles to prevent coalescence.

Microemulsion can be used to increase the bioavailability of poorly soluble drugs. Microemulsions have also been considered as topical drug delivery systems. For example, *water-in-oil* microemulsion can be used to incorporate polar drugs in the aqueous internal phase. The microemulsion helps in deeper penetration of these compounds into the skin.

UNIT-IV

MICROMERITICS

KGRL COLLEGE OF PHARMACY



jahnavi thota
[COMPANY NAME]

MICROMERITICS

Micromeritics study in different formulations • Colloidal dispersion is characterized by particles that are too small to be seen in the ordinary microscope. • The particles of pharmaceutical emulsion and suspension and the "fines" of powder fall in the range of the optical microscope. • Particles having the size of coarser powder, tablet granulation, and granular salts fall within the sieve range. Control of particle size and the size range of a drug can be significantly related to its physical, chemical, and pharmacological properties. Bioavailability and physical stability in some dosage forms can also be affected by particle size. Micromeritics is the science and technology of small particles. The unit of particle size most frequently used in micromeritics is a micrometer, also called a micron.

Applications

1**) Release & Dissolution Particle size** & surface area influence the release of a drug from a dosage form that is administered orally, rectally parenterally & topically. The higher surface area brings about intimate contact of the drug with the dissolution fluids in vivo & increases the drug's solubility & dissolution.
2)Absorption & Drug Action Particle size & surface area influence the drug absorption & subsequently the therapeutic action. The higher the dissolution, the faster the absorption & hence quicker & greater the drug action.

3)Physical Stability Micromeritc properties of a particle i.e. the particle size in a formulation influence the physical stability of the suspensions & emulsions. The smaller the size of the particle, the better the physical stability of the dosage form owing to the Brownian movement of the particles in the dispersion

Factors influenced by particle size

Surface area: increased S.A. affects the therapeutic efficiency of medicinal compounds that possess a low solubility in body fluids by increasing the area of contact between the solid and the dissolving fluid. This compound dissolves in a shorter time.
Extraction: the time required for extraction is shortened by the increased area of contact between the solvent and solid and the reduced distance the solvent has to penetrate the material.
Dissolution: the time required for dissolution of solid chemicals is shortened by the use of smaller particles
Drying: the drying of wet mass may be facilitated by milling, which increases the S.A. and reduces the distance the moisture must travel within the particle to reach the outer surface.
Mixing: the mixing of several solid ingredients of a pharmaceutical is easier and more uniform if the ingredients are approximately the same and small in size.
Lubrication: lubricants used in compressed tablets and capsules function by their ability to coat the surface of granulation or powder.

Properties of powder based on particle size and shape

Porosity: the porosity or voids of powder is defined as the ratio of the void volume to the bulk volume of packing. (v)
Є= Vb-Vp particle Vb
Here; Vb – Vp = void volume
Vb = bulk volume

Vp = true volume

Packing arrangements; powder beds of uniform-sized spheres can assume two ideal packing arrangements. closest or rhombohedral most open, loosest, or cubic packing the theoretical porosity of powder of uniform spheres in closest packing is 26% and for loosest packing is 48%.

Density (ρ): density is universally defined as weight per unit volume.

Three types of densities can be defined True density, Granule density, Bulk density

Bulkiness: Specific bulk volume, the reciprocal of bulk density, is often called bulkiness or bulk. Bulkiness increases with a decrease in particle size.

Flow properties: powder may be free-flowing or cohesive. Factors that affect the Flow properties are particle size, shape, surface texture, porosity, and density. The angle of repose (φ) has been used as an indirect method for quantifying powder flowability. $\varphi = \tan^{-1}(h/r)$ Here: h = height of pile r = radius of pile.

Compression: The strength of a compressed tablet depends on several factors, the most important are which are particle size and compression. As the compression increases the tablet hardness and fracture resistance also increase.

Particle size and the lifetime of a drug • In production: particle size influences the production of formulated medicines as solid dosage forms both tablets and capsules are produced.

Powders with different particle sizes have different flow and packing properties which alter the volume of powder during each encapsulation or table compression event.

In Body: after administration of the medicine, the dosage should release the drug into to solution at an optimum rate.

This depends on several factors, one of which will be the particle size of the drug.

Particles having small dimensions will tend to increase the rate of solution

Conclusion Particle size is an important parameter for producing medicines containing particulate solids and in the efficacy of the medicine administration.

Methods for determining particle size:

1. Optical microscopy (range: 0.2 –100 um): • The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated.

2. Sieving (range: 40 – 9500μm): -Standard-sized sieves are available to cover a wide range of sizes. These sieves are designed to sit in a stack so that material falls through smaller and smaller meshes until it reaches a mesh that is too fine for it to pass through.

The result achieved will depend on the agitation's duration and the agitation's manner.

The fraction of the material between pairs of sieve sizes is determined by weighing the residue on each sieve.

The stack of sieves is mechanically shaken to promote the passage of the solids.

3. Sedimentation (range: .08 –300μm): by measuring the terminal settling velocity of particles through a liquid medium in a gravitational centrifugal environment using

• Andreasen apparatus.

4. **Particle volume measurement** (range: .5 - 300 um): - In this type of machine the powder is suspended in an electrolyte solution. This suspension is then made to flow through a short insulated capillary section between two electrodes and the resistance of the system is measured. When a particle passes through the capillary there is a momentary peak in the resistance, the amplitude of the peak is proportional to the particle size. Counting is done by a computer.

Derived properties of powders:

The porosity or voids ε of powder is determined as the ratio is the true volume of particles.
bulk volume = true volume + volume of spaces between particles.
The volume of the spaces, the void volume, $V = V_b - V_p$
the total volume occupied is known as the bulk volume V_b.
Suppose a nonporous powder, is placed in a graduated cylinder:

Derived properties of powders:
1.Porosity: AContinue of void volume to bulk volume.
Porosity = ε = Vb – Vp/Vp = 1 – Vp/Vb
Porosity is frequently expressed in percent, ε x 100.
2- Densities of particles: Density is defined as weight per unit volume (W/V).
Types of densities:
A- true density: The true density, or absolute density, of a sample, excludes the volume of the pores and voids within the sample.
B- bulk density (w/v) the bulk density: value includes the volume of all of the pores within the sample
Densities of particles • During tapping, particles gradually pack more efficiently, the powder volume decreases, and the tapped density increases.
(Bulkiness increases with a decrease in particle size). In a mixture of materials of different sizes, the smaller particles sift between the larger ones and tend to reduce bulkiness.The bulk density of calcium carbonate varies from 0.1 to 1.3, and the lightest (bulkiest) type requires a container about 13 times larger than that needed for the heaviest variety. It is an important consideration in the packaging of powders. volume = reciprocal of bulk density.

Flow properties: Powders may be free-flowing or cohesive ("sticky"). Many common manufacturing problems are attributed to powder flow: •
1. Powder transfer through large equipment such as a hopper.

2. Uneven powder flow → excess entrapped air within powders →capping or lamination.

3. Uneven powder flow → increases particle friction with the die wall causing lubrication problems, and increasing dust contamination risks during powder transfer.

Derived properties of powders:
non-uniformity (segregation) in blending
powder flow problems
Tests to evaluate the flowability of a powder:

1. **Carr's compressibility index** • A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measured.
   • Carr's index (%) =Tapped density – Poured or bulk density x 100/Tapped density
   • Bulk density = weight/bulk volume
   • Tapped density = weight / true volume
2. **Tests to evaluate the flowability of a powde**r: Flow description % compressibility Excellent flow 5-15
   Good- 16-18
   Fair -19-21

Poor- 22-35
Very poor- 36-40
Extremely poor >40.

Between 1.25 and 1.5, added glidant normally improves flow.

A value greater than 1.5 indicates poor flow (= 33% Carr). More cohesive, less free-flowing powders such as flakes.

The powder with low interparticle friction, such as coarse spheres.

A value less than 1.25 indicates good flow (= 20% Carr).

Hausner ratio=Tapped density /Poured or bulk density

The hausner ratio was related to interparticle friction:

Tests to evaluate the flowability of a powder:

2- Hausner ratio: > 1.5 added glidant doesn't improve flow.

r = d / 2 tan φ = h / r tan φ = μ □ϕ

ϕ= the maximum angle possible between the surface of a pile of powder and horizontal plane = coefficient of friction μ between the particles:

The frictional forces in a loose powder can be measured by the angle of repose φ.

The angle of repose φ

Tests to evaluate the flowability of a powder:

The user normally selects the funnel orifice. The sample is poured onto a horizontal surface and the angle of the resulting pyramid is measured.

3- The angle of repose φ: The rougher and more irregular the surface of the particles, the higher will be the angle of repose.

The angle of repose greater than 40 (poor flow)

Angle of repose between 30-34 (Pass flow)

Angle of repose between 20-30 (good flow)

The angle of repose is less than 20 (excellent flow) fice through which the powder flows slowly and reasonably constantly.

Alteration of Particle size & size distribution can also be altered to improve flowability by removing a proportion of the fine particle fraction or by increasing the proportion of coarser particles, such as occurs in granulation. Coarse particles are more preferred than fine ones as they are less cohesive. Distribution There is a certain particle size at which the powder's flow ability is optimum.

Alteration of Particle Shape & texture Particle's Shape:

Generally, more spherical particles have better flow properties than more irregular particles.

- Spherical particles are obtained by spray drying, or by temperature cycling crystallization.

- Particle texture: particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth-surfaced particles.

Hygroscopic powders are stored and processed under low humidity conditions.
Drying the particles will reduce the cohesiveness and improve the flow.
Adsorbed surface moisture films tend to increase bulk density and reduce porosityMoisture content of particles greatly affects powder's flowability.

Reduction of electrostatic charges can improve powder flowability

Electrostatic charges can be reduced by altering process conditions to reduce frictional contacts. Alteration of Surface Forces

Formulation additives (Flow activators):

• Flow activators are commonly referred to as glidants.

• Flow activators improve the flowability of powders by reducing adhesion and cohesion.

• e.g. talc, maize starch, and magnesium stearate
Factors affecting the flow properties of powder

1. Alteration of Particle's size & Distribution

2. Alteration of Particle shape & texture

3. Alteration of Surface Forces

4. Formulation additives (Flow activators)

Factors affecting the flow properties of powder Alteration of Particle's Size & Distribution

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Importance of Study of Micromeritics

Knowledge and control of the size and the size range of particles is of profound importance in pharmacy. Size and surface area can be related to the physical, chemical, and pharmacological properties of a drug.

- Particle size affects its release from dosage forms that are administered orally, parenterally, rectally, and topically
- Physical stability and pharmacologic response of suspensions, emulsions, and tablets depends on particle size.
- It is also important in flow properties and proper mixing of granules and. powders in tableting.
- Both Tablets and capsules are produced using equipment that controls the mass of the drug and other particles by volumetric filling. Therefore any interference with the uniformity of fill volumes may alter the mass of the drug incorporated into the tablet or capsules. Thus reducing the uniformity of the medicine.
- Powders with different particle sizes have different flow and packing properties which alter the volumes of powder during each encapsulation or tablet compression.
- The rate of solution depends on several factors. One factor is the particle size. Thus particles having small dimensions will tend to increase the rate of solution. For example:
    - Griseofulvin has a low solubility by oral administration but is rapidly distributed following absorption. The solubility of Griseofulvin can be greatly increased by particle size reduction.
    - Reduction of particle size also increases the rate of absorption of tetracycline, Aspirin, and Sulphonamides.
    - Reduction of particle size of nitrofurantoin increased the rate of absorption. Therefore the toxic effect is due to rapid absorption.

Different means of expressing particle size.

There are different means of expressing particle size:

Millimeter (mm)……. 10^{-3} meter
Micrometer (µ m) ……. 10^{-6} meter
nanometer (nm)…….. 10^{-9} meter
pico meter .....10^{-12} meter
fanto meter .....10^{-15} meter

Particle Dimension in Pharmaceutical Disperse System

Particle size Micrometer (µ m)	Millimeter (mm)	Disperse systems
0.5-10	0.0005 - 0.010	Suspension, fine emulsion
10-50	0.010- 0.050	Coarse emulsion, flocculated suspension
50- 100	0.50- 0.100	Lower range of sieve range, fine powder range
150-1000	0.150-1.000	Coarse powder range
1000- 3360	1.000- 3.360	Average granule size

Methods of determining particle size

- Optical microscopy
- Seiving methods
- Sedimentation methods.

Particle volume measurement

- Coulter Counter Method (Electrical stream sensing method)
- Laser light scattering methods.

Methods of determining surface area:

- Adsorption method
- Air permeability method

Sieving Method

The sieving method is ordinary and simple. It is widely used as a method for the particle size analysis.

Range of analysis:

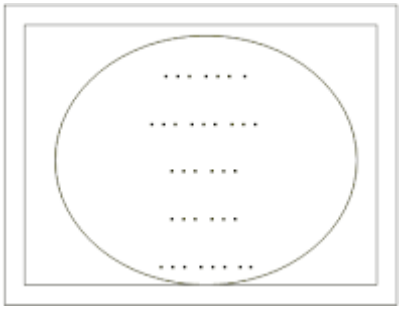
The International Standards Organization (ISO) sets the lowest sieve diameter of 45 µm and since powder is usually defined as having a maximum diameter of 1000 µm, this could be considered to be the upper limit.

In practice, sieves can be obtained for size analysis over a range from 5 to 125 000 µm.

Sample preparation and analysis condition

1. Sieve analysis is usually carried out using dry powders.

2. Although, for powders in liquid suspension or which agglomerate during dry sieving, a process of wet sieving can be used.



Principle of Measurement:

Sieve analysis utilizes a woven, punched, or electroformed mesh often in brass, bronze, or stainless steel with known aperture (hole) diameters which form a physical barrier to particles. Most sieve analyses utilize a series, stack (Load /Mountain or nest (layer) of sieves which have the smallest mesh above a collector tray followed by meshes that get progressively coarser towards the top of the series.

A sieve stack usually comprises 6-8 sieves with a progression based on a $\sqrt{2}$ or $2\sqrt{2}$ change in diameter between adjacent apertures.

The powder is loaded onto the coarsest sieve of the assembled stack and the nest is subjected to mechanical vibration for, say 20 minutes

After this time, the particles are considered to be retained

on the sieve mesh with an aperture corresponding to the minimum or sieve diameter

A sieving time of 20 minutes is arbitrary and BS 1796 recommends sieving to be continued until less than 0.2% of material passes a given sieve aperture in any 5-minute interval.

Advantages:

- This is a very simple method.
- Not expensive
- Easy to repair

Disadvantages:

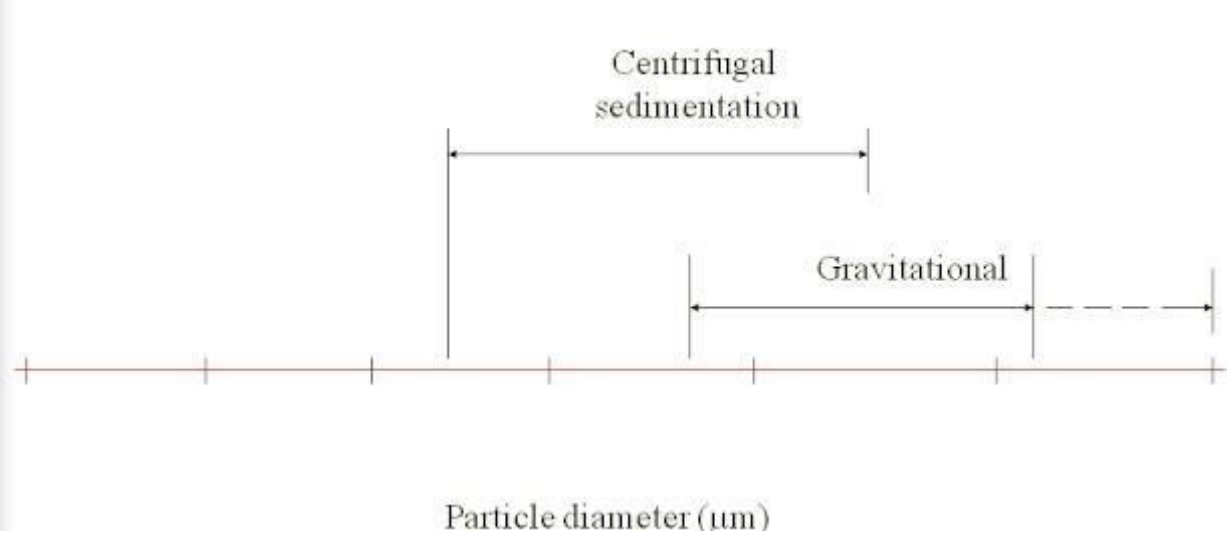
- Not too much precise value
- Not applicable for all dispersed systems.

Sedimentation Methods

The Sedimentation Method is also ordinary and simple.

It is widely used as a method for the particle size analysis.

Range of analysis:



Sample preparation and analysis conditions

In this method, particle size can be determined by examining the powder as it sediments out.

(a). In cases where the powder is not uniformly dispersed in a fluid it can be introduced as a thin layer on the surface of the liquid.

(b). If the powder is lyophobic, e.g. hydrophobic in water, it may be necessary to add a dispersing agent to aid wetting of the powder.

(c). In case where the powder is soluble in water it will be necessary to use non-aqueous liquids or carry out the analysis in a gas.

Principle of Measurement

Particle size analysis by sedimentation method can be divided into two main categories according to the method of measurement used.

1. One of the types is based on the measurement of particles in a retention zone.
2. Another type uses a non-retention measurement zone.

An example of a non-retention zone measurement is known as the pipette method.

In this method, known volumes of suspension are drawn off and the concentration differences are measured for time.

One of the most popular pipette methods was developed by *Andreasen and Lundberg and is commonly called the Andreasen pipette.*

The Andreasen fixed-position pipette consists of a 200 mm graduate cylinder that can hold about 500 ml of suspension fluid.

A pipette is located centrally in the cylinder and is held in position by a ground glass stopper so that its tip coincides with the zero level.

A three-way tap allows fluid to be drawn into a 10 ml reservoir which can then be emptied into a beaker or centrifuge tube.

The amount of powder can be determined by weight following drying or centrifuging.

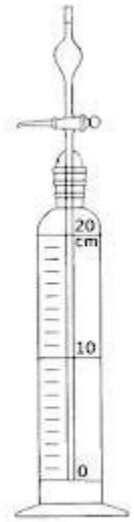


Fig. 16–8. Andreasen apparatus for determining particle size by the gravity sedimentation method.

The weight of each sample residue is therefore called the weight of undersize and the sum of the successive weight is known as the cumulative weight of undersize. It can be expressed directly in weight units or percent of the total weight of the final sediment.

The data of cumulative weight of undersize is used for the determination of particle weight distribution, number distribution,

The largest particle diameter in each sample is then calculated from *Strokes' Law.*

The particle size may be obtained by gravity sedimentation as expressed in *Strokes'law.*

$$V=h/t$$

$$\frac{h}{t} \quad \frac{d_{st}^2(\rho_s-\rho_o)g}{18\eta_o}$$

$$\frac{18\eta_o h}{(\rho_s-\rho_o)gt}$$

Where,

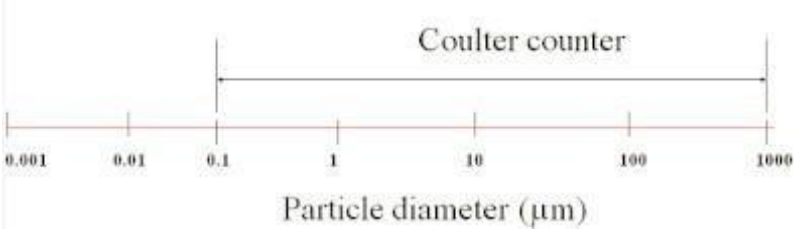
v = rate of settling
h = Distance of the fall in time, t
d_{st} = the mean diameter of the particles based on the velocity of sedimentation ρ_s= density of the particles
ρ_o = density of the dispersion medium g = Acceleration due to gravity
ηo = Viscosity of the medium

Note: The question holds spheres falling freely without hindrance and at a constant rate

Coulter Counter Method (Electrical stream sensing zone method)

The Coulter Counter Method (Electrical stream sensing zone method) is sophisticated. It is a precise and accurate method.

Range of analysis:



Sample preparation and analysis conditions

1. Powder samples are dispersed in an electrolyte to form a very dilute suspension

2. The suspension is usually subjected to ultrasonic agitation for a period to break up any particle agglomerates.
3. A dispersant may also be added to aid particle deagglomeration.

Principle of Measurement

1. The particle suspension is drawn through an aperture accurately drilled through a sapphire crystal set into the wall of a hollow glass tube.

2. Electrodes, situated on either side of the aperture and surrounded by an electrolyte solution.

3. Monitor the change in the electrical signal that occurs when a particle momentarily occupies the orifice and displaces its volume of electrolyte.

4. The volume of suspension drawn through the orifice is determined by the suction potential created by a mercury thread rebalancing in a convoluted U tube.

5. The volume of electrolyte fluid that is displaced in the orifice by the presence of a particle causes a change in electrical resistance between the electrodes which is proportional to the volume of the particle.
6. The change in resistance is converted into a voltage pulse which is amplified and processed electronically.
7. Pulses falling within pre-calibrated limits or thresholds are used to split the particle size distribution into many different size ranges.

- To carry out size analysis over a wide diameter range it will be necessary to change the orifice diameter used, to prevent
- Coarse particles block a small diameter orifice. Conversely, finer particles in a large diameter orifice will cause too small a relative in volume to be accurately quantified.

Advantages:

1. It is one of the most precise and accurate methods.
2. The analysis range is wide.

Disadvantages:

1. It is a sophisticated method.
2. It is an expensive method.

Micromeritics Applications

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

. **Release and dissolution**

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

Absorption and drug action

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

Physical stability

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

Dose uniformity

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

Methods for determining particle size

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

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

Range of particle sizes A guide to the range of particle sizes applicable to each method
Particle size Method 1 µm Electron microscope, ultracentrifuge, adsorption 1 – 100 µm Optical microscope, sedimentation, coulter counter, air permeability >50 µm Sieving
Optical microscopy (range: 0.2-100 µm) The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated
• According to the optical microscopic method, an emulsion or suspension is mounted on a ruled slide on a mechanical stage.
• The microscope eyepiece is fitted with a micrometer by which the size of the particles can be estimated.
• The ordinary microscope is used for measurement of the particle size in the range of 0.2 to about 100 µm.

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Disadvantage of the microscopic method

1. The diameter is obtained from only two dimensions of the particle.

2. The number of particles that must be counted (300- 500) to obtain a good estimation of the distribution makes the method somewhat slow and tedious wide range of sizes.
. • These sieves are designed to sit in a stack so that material falls through smaller and smaller meshes until it reaches a mesh that is too fine for it to pass through Sieving (range: 40-9500 µm)
• The stack of sieves is mechanically shaken to promote the passage of the solids.
• The fraction of the material between pairs of sieve sizes is determined by weighing the residue on each sieve.
• The result achieved will depend on the duration of the agitation and the manner of the agitation.
Sedimentation (range: 0.08-300 µm)
• By measuring the terminal settling velocity of particles through a liquid medium in a gravitational centrifugal environment using the Andreasen apparatus.
Particle volume measurement (range: 0.5-300 µm)
• In this type of machine the powder is suspended in an electrolyte solution.
• This suspension is then made to flow through a short insulated capillary section between two electrodes and the resistance of the system is measured.
When a particle passes through the capillary there is a momentary peak in the resistance, the amplitude of the peak is proportional to the particle size.
• Counting is done by a computer.

Particle volume measurement (range: 0.5-300 µm)

Density of powders
• Density is defined as weight per unit volume (W/V).
• During tapping, particles gradually pack more efficiently, the powder volume decreases, and the tapped density increases.
Types of Density
1. True density: The true density or absolute density of a sample excludes the volume of the pores and voids within the powder sample.
2. Bulk density: The bulk density value includes the volume of all of the pores within the powder sample.
Flow properties of powders
• Powders may be free-flowing or cohesive (Sticky).
• Many common manufacturing problems are attributed to powder flow.
Powder transfer through large equipment such as a hopper.
Uneven powder flow → excess entrapped air within powders → capping or lamination.
Uneven powder flow → increases particle friction with the die wall causing lubrication problems and increasing dust contamination risks during powder transfer.
5. Powder storage, which for example results in caking tendencies within a vial or bag after shipping or storage time.
6. Separation of a small quantity of the powder from the specifically just before the creation of individual doses such as during tableting, encapsulation, and vial filling which affects the weight uniformity of the dose (under or over dosage Powder flow problems

Flow properties of powders
• Tests to evaluate the flowability of a powder.
- Carr's compressibility index.
- Hausner ratio.
- The angle of repose (θ).

Carr's compressibility index • A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measured.
Tapped density- Poured or bulk density
Carr's index (%)= X 100 Tapped density Bulkdensity=weight/bulk volume
Carr's compressibility index Flow description % Compressibility
Excellent flow 5 – 15
Good 16 – 18
Fair 19 – 21
Poor 22 – 35
Very Poor 36 -40
Extremely poor > 40
Relationship between powder flowability and % Hausner ratio and Tapped density
Hausner ratio = Poured or bulk density
Hausner ratio was related to interparticle friction:
• A value less than 1.25 indicates good flow

Hausner ratio
• The powder with low interparticle friction, such as coarse spheres.
• A value greater than 1.5 indicates poor flow (= 33% Carr's Compressibility Index)).
• More cohesive, less free-flowing powders such as flakes.
• Between 1.25 and 1.5 added glidant normally improves flow.
• > 1.5 added glidant doesn't improve flow.
The angle of repose (θ)
• The sample is poured onto the horizontal surface and the angle of the resulting pyramid is measured.
• The user normally selects the funnel orifice through which the powder flows slowly and reasonably constantly.

The angle of repose (θ)
1. Angle of repose less than 20 (Excellent flow).
2. Angle of repose between 20-30 (Good flow).
3. Angle of repose between 30-40 (Pass flow).
4. The angle of repose is greater than 40 (Poor flow).
• The rougher and more irregular the surface of the particles, the higher will be the angle of repose.

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1. Textbook of Physical Pharmaceutics by CVS Subramanyam.
2. Textbook of Physical Pharmacy By Albert Martin.

UNIT-V

DRUG STABILITY

KGRL COLLEGE OF PHARMACY

KGRL COLLEGE OF PHARMACY
DEPARTMENT OF PHARMACEUTICS

KINETICS

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

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

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

Drug A $\longrightarrow$ drug B

The rate of forward reaction is expressed as;

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

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

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

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

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

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

where, k = Rate constant

n = order of reaction

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

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

Unimolecular Reaction: This reaction involves only one molecule.

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

Bimolecular Reaction: This involves reaction between two molecules

Eg : $H_2 + I_2 \longrightarrow 2HI$

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

Zero Order Reaction:

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

Examples:

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

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

$$dc/dt = - K_0C^0 = -K_0$$

Rearranging the above equation

$$dc = - K_0 dt$$

Integrating on both sides

$$C - C_0 = - K_0t$$

Or

$$C = C_0 - K_0 t$$

C_0 = Concentration of drug at t = 0,

C = Concentration of drug to undergo reaction at time t

Half life:

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

The half-life equation can be derived as follows.

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

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

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

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

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

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

Shelf life:

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

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

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

Substitute the above values in

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

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

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

First order kinetics:

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

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

By rearranging the above equation

$$dc/c = - K_1dt$$

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

$$\int_{C_0}^{C_t} dc/c = - K_0 \int_0^t dt$$

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

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

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

Converting eq 2 into logarithm to the base 10

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

By rearranging eq 3

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

Half life:

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

The half life equation can be derived as follows.

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

Substituting $C = C_0/2$, $t = t_{½}$

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

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

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

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

Shelf life:

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

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

$$C_t = \left(\frac{90}{100}\right) C_0$$

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

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

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

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

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

Second order:

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

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

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

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

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

If a = b then

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

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

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

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

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

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

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

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

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

If $a \neq b$

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

Half life:

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

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

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

$$K_2 = \frac{1}{a.t1/2}$$ ……..3

$t1/2 = 1/ak$

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

Apparent or Pseudo zero order reaction:

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

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

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

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

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

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

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

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

Pseudo first order reaction:

Pseudo first order reaction is defined as a reaction which is originally a second order, but is made to behave like a first order reaction.

In second order reaction, the rate depends on the concentration terms of two reactants. Therefore the rate equation would be

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

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

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

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

Examples:

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

Differences between order and molecularity

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

Determination of Order:

1. **Substitution Method**: In this method, different initial concentrations of the reactant (a) are taken. The values of concentration (a - x) at regular intervals of time (t) were noted. These values a, (a - x), and t thus obtained from the experiment are substituted into the integrated rate equations for the first, second, and third order. The equation that yields a constant value of K corresponds to the order of the reaction.

2. Half-life Method: In this method, half-life is determined as a function of concentration. The order is considered unity if the half-life is independent of concentration. The half-life of a reaction is inversely proportional to the concentration term raised to the power (n - 1) where n = order of a reaction.

So, half life $\propto = 1/\{A\}$ (for 2nd order reaction)

Half life $\propto = 1/\{A\}^2$ (for 3rd order reaction)

For n^{th} order reaction; $1/\{A\}^{n-1}$

If two different reactions are run at different concentrations, a_1 and a_2, the half lifes $t_{1/2}$ (1) and $t_{1/2}(2)$ are as follows:

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

Or in logarithmic form finally, we get,

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

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

$$\text{In } C_O/C_1 = K_1 t$$

(or)

$$\text{In } (C_t) = \text{In}(C_o) - kt$$

$$Y = C - mx$$

So for the values of two variables In C_{0}/C_{1} (vs) t if we obtain a straight line then the corresponding reaction is said to be first order. If a curve is obtained then the reaction is not a first-order reaction.

For the second order similarly, we plot for values of 1/(a - x) versus t.

The line obtained has an equation

$$1/(a - x) - kt + 1/a$$

$$y = mx + c$$

In case we get a curve for values of 1/(a - x) versus t then it is not a second order reaction.

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

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

Let's consider the reaction

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

The order of reaction concerning three reactants is given by

$$n = n_A + n_B + n_C$$

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

DRUG STABILITY:

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

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

Physical Degradation:

Definition:

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

Types:

Types of physical degradation are as under

➤ Loss of volatile components

➤ Loss of H_2O

➤ Absorption of H_2O

➤ Crystal growth

➤ Polymorphic changes

➤ Colour changes

1. Loss of volatile components:

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

E.g.: Nitroglycerine from drugs evaporates.

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

2. Loss of water:

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

• Water evaporates causing crystalline growth.

• This will result in an increase in potency & decrease in weight.

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

e.g. water evaporates from efflorescent salts such as Na2SO4, borax

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

3. Absorption of H_2O :

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

Depends on temp and humidity of the surrounding material

e.g.

• Glycerin suppositories may become opaque

• Gelatin capsule may soften

Some deliquescent salts are calcium chloride and potassium citrate.

Preventive measures: products stored in air-tight containers and kept in a cool place.

4. Crystal growth:

In solutions after supersaturation crystal growth occurs. The reason may be the fall in temp and a consequent decrease in solubility of solute

e.g.

• Injection of calcium gluconate

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

Preventive measures:

a. A part of calcium gluconate is replaced by calcium saccharate.

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

5. Polymorphic Changes:

In polymorphic changes, crystal forms are changed. A stable crystal form loosens. This may cause alteration in solubility and possibly crystalline growth in aqueous suspensions.

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

6. Colour changes:

Colour changes are of two types.

1. Loss of colour

2. Development of colour

Loss of colour is due to pH change and the presence of a reducing agent.

Development of colour is due to exposure to light

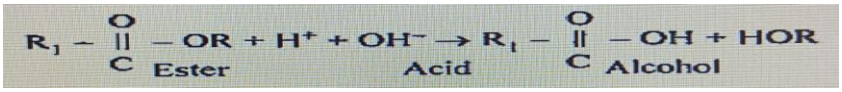
Preventive measures: pH should not be changed, and Exposure to light should be avoided an attempt has been made to prevent the fading by incorporating UV light-absorbing material.

Chemical Degradations:

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

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

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



The majority of hydrolysis reactions take place in the presence of a catalyst [catalysts are mineral acids, alkalies or acids etc]. Examples of drugs that degrade through ester hydrolysis are procaine, atropine, methyl p-aminobenzoate etc.

Methods to enhance the stability of pharmaceuticals undergoing ester hydrolysis are

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

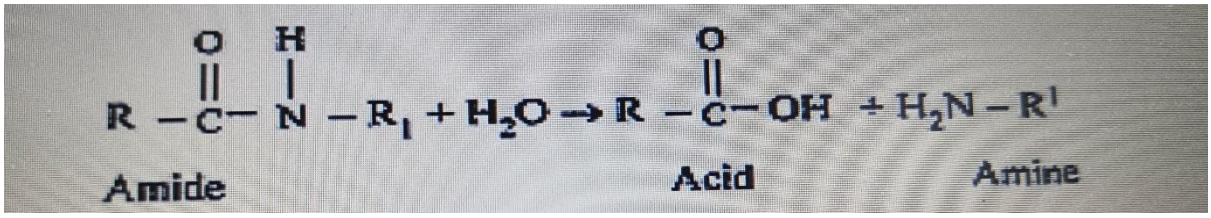
b) Type of Solvent: Partial or full replacement of water with a solvent of lower dielectric constant reduces the velocity of hydrolysis. Ex ethanol, glycols, glucose, mannitol solutions.

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

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

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

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



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

(B) Oxidation-Reduction:

Several pharmaceutical compounds undergo oxidative reactions including vitamins, steroids, antibiotics, epinephrine etc. These reactions are mediated either by free radicals or by molecular oxygen.

A common form of oxidation is autoxidation which is defined as the reaction of any material with molecular oxygen. This may be given as follows:

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

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

These are free radicals and are highly unsaturated and readily take electrons from the other substances causing oxidation.

Autoxidation may be described as follows:

Initiation: $RH \xrightarrow[\text{Light bond}]{\text{addition}} R^- + (H^-)$

Propagation: $R^- + O_2 \rightarrow RO_2$

$$RO_2 + RH \rightarrow ROOH + R$$

Hydroperoxide decomposition: $ROOH \rightarrow RO + OH$

Termination: $RO_2 + x \rightarrow$ inactive products

$RO_2 + RO_2 \rightarrow$ inactive products

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

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

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

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

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

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

Influence of Temperature on Drug Decomposition

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

Arrhenius's equation illustrates the effect of temperature on reaction rate.

Where $K = Ae^{-E_a/RT}$

K = Specific rate constant

A = Frequency factor or Arrhenius factor.

E = Activation energy

R = Ideal gas constant (1.987cal / mol.deg)

T = Absolute temperature

Taking logarithms on both sides

$$logK = logA - \frac{E_a}{2.303RT}$$

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

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

Estimation of K: The value of K can be found by experimenting with different temperatures. The concentration values at different time points are calculated and the graph is plotted for concentration Vs time. From the slope of a line, one can calculate the value of K.

Estimation of Activation Energy and Arrhenius Factor:

As stated above one can get values of K at different temperatures. Let the value of $K=K_1$

So the above equation can be written as

$$logk_1 = logA - \frac{E_a}{2.303RT_1}$$

$$logk_2 = logA - \frac{E_a}{2.303RT_2}$$

Subtracting the above two equations to yield

$$log\frac{k_2}{k_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2T_1}\right)$$

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

We can also estimate the value of E_a from the slope of the line obtained by drawing the values of log K on the y-axis and 1/T on the x-axis as given in the below figure.

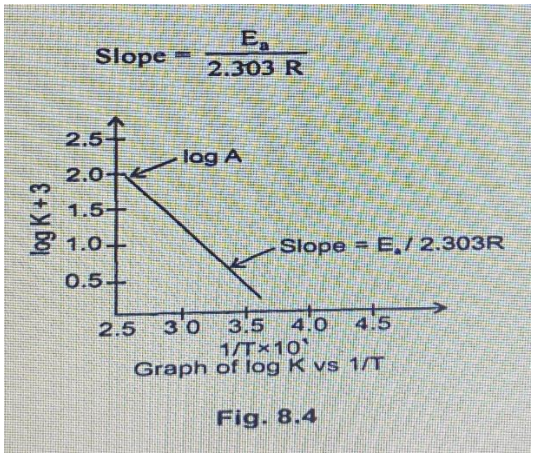


Fig. 8.4

Factors which govern the rate of chemical reaction

1. Collision theory of reaction rates.

2. Effect of increased temperature on the rate of reaction

3. Transition state theory

4. Effect of Solvent - dielectric constant, ionic student strength.

5. Specific and General Acid-Base and pH Effects

Solvent:

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

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

Where

k = observed reaction rate constant

k_o = rate constant in infinitely dilute solution

V = molar volume of solute

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

From this equation it is found that

- If polarity of product > polarity of reactant then reaction rate increases if the solvent is more polar.
- If polarity of product < polarity of reactant then reaction rate increases if the solvent is less polar.

Ionic strength:

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

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

Where

Z_A and Z_B are the charges on reactant A and B respectively.

μ is the ionic strength

k is rate constant of degradation

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

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

Dielectric constant:

The dielectric constant is used to measure polarity of the solvent. Dielectric constant shows significant effect on the rate of reaction. The effect of the dielectric constant on the rate constant of an ionic reaction, extrapolated to infinite dilution where the ionic strength effect is zero is determined by the following equation:

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

Where

$k\varepsilon = \infty$ is the rate constant in a medium of infinite dielectric constant

k is observed rate constant in medium of dielectric constant ε

N is Avogadro's number,

Z_A and Z_B are the charges on the two ions, e is the unit of electric charge,

r* is the distance between ions in the activated complex

ε is dielectric constant of the solution

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

Catalysis:

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

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

a. Specific Acid Base Catalysis

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

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

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

In this case the observed rate constant is shown as

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

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

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

$$k_{obs} = k_o$$

b. General Acid Base Catalysis

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

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

The evaluation of a general acid or general base catalysis can be done by determining the degradation rates of a drug in a series of buffers having the same pH but they should be prepared with increasing concentration of buffer species.

Molecular Collison theory:

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

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

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

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

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

Limitations of the Collision Theory

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

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

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

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

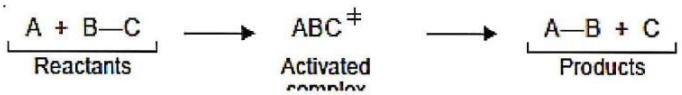
(4) In the collision theory it is supposed that only the kinetic energy of the colliding molecules contributes to the energy required for surmounting the energy barrier. There is no reason why the rotational and vibrational energies of molecules should be ignored.

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

TRANSITION STATE THEORY

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

Thus,



Accelerated Stability Studies:

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

Objectivies of stability testing:

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

Stability method:

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

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

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

3 months intervals during the first year,

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

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

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

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

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

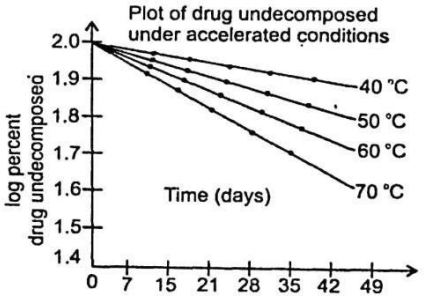


Fig. 8.5

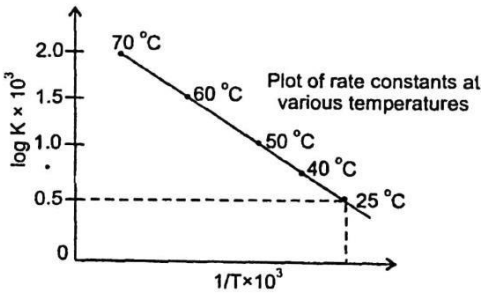


Fig. 8.6

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

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

ICH Guidelines:

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

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

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

ICH Guidelines on stability studies

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

Climatic zones with their temperature and Relative humidity values

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

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

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

Limitation of accelerated stability studies:

1. This method is not used in case of complex reactions because arrhenius equation consist of only one rate constant therefore it is applicable to simple decomposition mechanism.
2. This method is not applicable if degradation is due to freezing, microbial contamination, excess agitation etc.
3. This method is valid only if energy of activation lies between 10 to 30kcal/mole.
4. The products which loose their physical integrity at elevated temperature is not suitable for accelerated testing.
5. This method is not valid when order changges at higher temperautre.

Addition of overages.

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

Applications of Chemical kinetics:

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

Cold place – it indicates that the product should be stored in a place that maintains any temperature not excedding 8ºC. Usually, this temperature is between 2 to 8ºC.
Cool place - it indicates that the product should be stored in a place that maintains any temperature between 8ºC to 25ºC.
Room temperature – The term 'room temperature'indicates the prevailing the temperature in the working area.
Warm – The term 'warm' indicates that the product may be stored in a place that maintains any temperature between 30 to 40ºC.
Excessive heat – It indicates that the product may be stored at any temperature above 40ºC.
Controlled RT – The working environment of 20 to 25ºC, that is being maintained thermostatically is suitable for storage.
Freezer – The product should be stored in a place at which the temperature is maintained thermostatically between -20ºC and -10ºC