SHAMBHUNATH INSTITUTE OF PHARMACY

2nd Year 4th Semester

Pharmaceutics-IV (Physical Pharmacy)

Paper Code: -BOP-242 **Paper I.D.: - -----**

UNIT-1

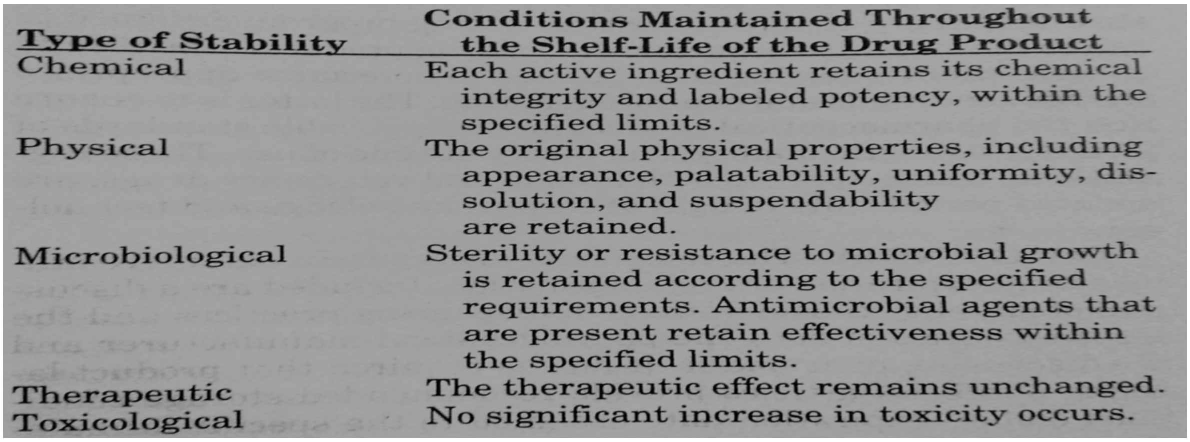
Drug stability

- **Degradative pathways**
- **Influence of……………**
  - ✓ Temperature
  - ✓ Light
  - ✓ Solvent
  - ✓ Catalytic species
  - ✓ Other factor on drug stability
- **Accelerated stability study**
- **Expiration Dating**
- **Buffers……**
  - ✓ Buffered Isotonic Solution
  - ✓ Measurement of tonicity
  - ✓ Calculation and methods of adjusting isotonisity

DRUG STABILITY

- Stability of pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological therapeutic and toxicological specification.
- Assurance that the packed product will be stable for its anticipated self life must come from an accumulation of valid data on the drug in its commercial package.
- These stability data involves selected parameters that taken together from the stability profile. Pharmaceutical products are expected to meet their specification for identifying purity, quality and strength throughout their defined storage period at specific storage condition.
- The stability of pharmaceutical product is investigated throughout the various stages of the development process.
- The stability of the drug substance is first assessed in the preformulation stage.
- At this stage, pharmaceutical scientists determine the drug substance.
- Stability/ compatibility with various solvents, buffered, solutions, and excipents considered for formulation developments
- Optimization of the stable of formulation of a pharmaceutical product is built upon the information obtained from the performulation stage and continues during the formulation development stages.
- Once a pharmaceutical product has gained regulatory approved and is marketed, the pharmacist must understand the proper storage and handling of the drug.
- In some cases a pharmacist may need to prepare stable compounded preparations from this product.
- It is the responsibility of the pharmacist via the information of the manufacture to instruct the patient in the proper storage and handling of the drug product

There are five types of stability that must be consider for each drug



Type of Stability	Conditions Maintained Throughout the Shelf-Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

WHY STABILITY

- Provide a evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as….. temperature, Humidity and light.
- Establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.
- Because physical, chemical or microbiological changes might impact the efficiency and security of the final product.
- **Drug Substances (DS)** ➔ The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.
- **Drug Products (DP)** ➔ The dosage form in the final immediate packaging intended for marketing……. controlled and documented determination of acceptable changes of the drug substance or drug product

What are changes?

- **Physical changes**
  - Appearance
  - Melting point
  - Clarity and color of solution
  - Moisture
  - Crystal modification (Polymorphism)
  - Particle size
- **Chemical changes**
  - Increase in Degradation
  - Decrease of Assay
- **Microbial changes**
- **Forced degradation studies**
  - ✓ Acidic & Basic conditions.
  - ✓ Dry heat exposure
  - ✓ UV radiation exposure
  - ✓ Influence of pH
  - ✓ Influence of temperature
  - ✓ Influence of ionic strength

PHYSICAL CHANGES/INSTABILITY

- Solubility
- pK_a
- Melting point
- Crystal form
- Equilibrium moisture content.
- Example- amorphous materials are less stable than their crystalline counterparts.
- A relatively dense material may better withstand ambient stresses aminobenzylpenicillin trihydrate is more denser and stable than its amorphous form.

DEGRADATION MAY BE OF TWO TYPES

- PHYSICAL DEGRADATION
- CHEMICAL DEGRADATION
  - Oxidation
  - Decarboxylation
  - Photolysis
  - Racemization
  - Hydrolysis

- PHYSICAL DEGRADATION

The physical stability properties includes appearance, palatability ,uniformity ,dissolution and suspend ability are retained . Maintained throughout the shelf life of the drug.

IT INCLUDES FOLLOWING :

- ✓ Loss of water
- ✓ loss of volatile oil
- ✓ Water Absorbance
- ✓ Polymorphism
- ✓ Color change

CHEMICAL DEGRADATION STUDY

- **Hydrolysis-** usually drugs such as esters, amides and lactams undergo hydrolysis.
- **Oxidation Reduction**- loss of electrons, gain of electrons. Auto oxidation also is responsible. Eg -tetracyclines, vit A, vit D, morphine.
- **Photolysis**- Compounds such as ascorbic acid, riboflavin, cyanacobalamine, folic acid undergo degradation on exposure to light. Sometimes coupled with thermal reactions.
- **Isomerisation-**Compounds get converted into a less effective form. Eg-Adrenaline solutions at low pH lose activity since its levo form is more stable than dextro form

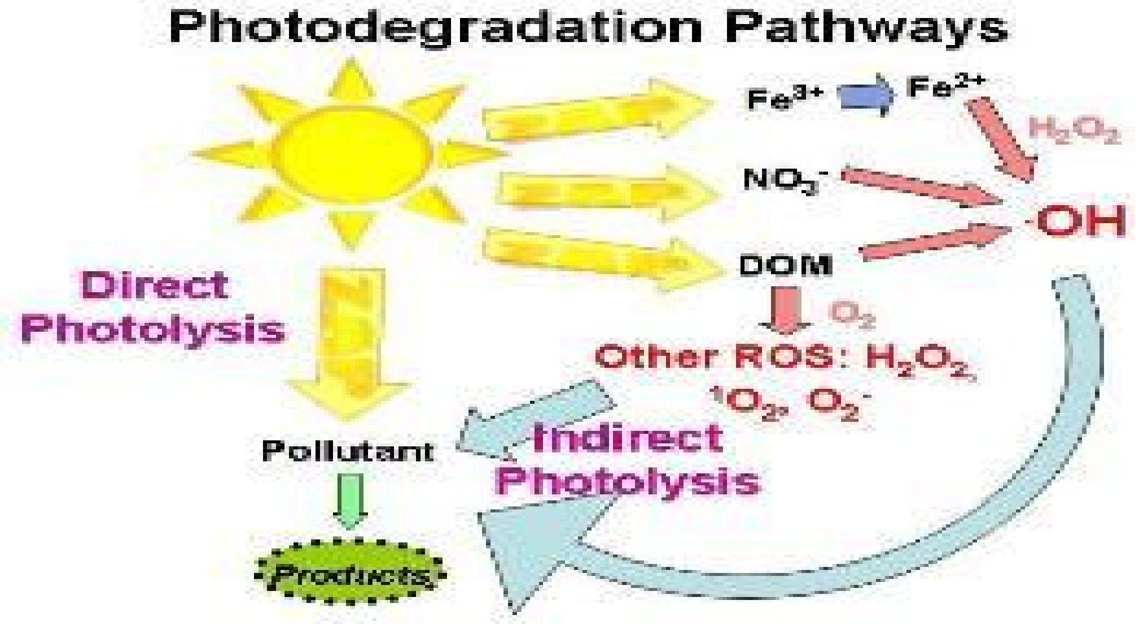
PHOTOLYTIC STABILITY

- Many drugs fade or darken on exposure to light and this leads to an aesthetic problem which can be controlled by using

1 Amber Glass Container

2 Opaque Container

3 Incorporating a Dye



POSSIBLE CHANGES (Visible and invisible)

- Loss of active ingredient
- Alteration in bioavailability
- Loss of content uniformity
- Decline of microbiological status
- Loss of pharmaceutical elegance
- Formation of toxic degradation products
- Loss of package integrity
- Reduction of label quality
- Modification of any factor of functional relevance(dissolution, release, etc)

Stability chamber room

ACCELERATED STABILITY STUDIES

- Storage condition of 40^0C and relative humidity of 75% has been recommended for all the four zones for drug substances and drug products.
- Studies carried out for 6 months.
- Accelerated storage conditions must be at least 15^0C above the expected actual storage temperature and appropriate relative humidity

Climatic Zones / Storage conditions

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	Humidity % RH	Temp °C	Humidity % RH
Climatic Zone I "Temperate" Japan, United Kingdom, Northern Europe, Canada, Russia, United States	20	20	42	21	45
Climatic Zone II "Mediterranean, Subtropical" Japan, United States, Southern Europe	26.4	22	52	25	60

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	Humidity % RH	Temp °C	Humidity % RH
Climatic Zone III "Hot, dry" Iran, Iraq, Sudan	26,4	27,9	35	30	35
Climatic Zone IV "Hot, humid" Brazil, Ghana, Indonesia, Nicaragua, Philippines	26,7	27,4	76	30	70

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	**25°C ± 2°C / 60% ± 5% r.h or** **30°C ± 2°C / 65% ± 5% r.h.**	**12 months**
Intermediate	**30°C ± 2°C / 65% ± 5% r.h.**	**6 months**
Accelerated	**40°C ± 2°C / 75% ± 5% r.h.**	**6 months**

Drug substances - intended for storage in a Refrigerator

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	**5°C ± 3°C**	**12 months**
Accelerated	**25°C ± 2°C / 60% ± 5% r.h.**	**6 months**

Drug products - General case

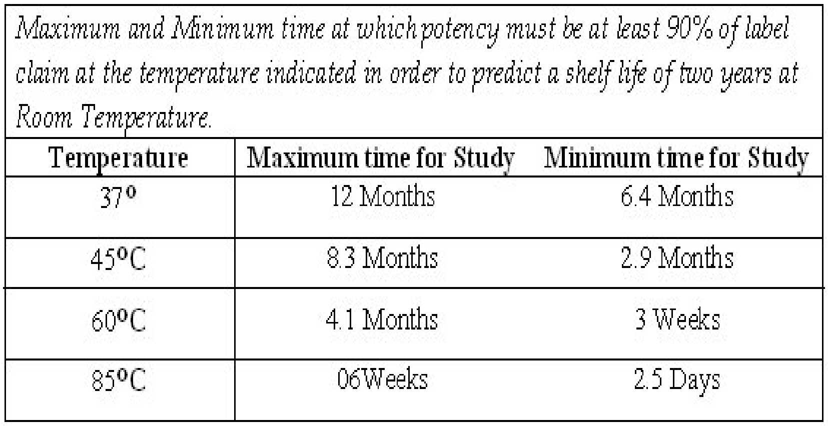
Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term	**25°C ± 2°C / 60% ± 5% r.h. or** **30°C ± 2°C / 65% ± 5% r.h.**	**12 months**
Intermediate	**30°C ± 2°C / 65% ± 5% r.h.**	**6 months**
Accelerated	**40°C ± 2°C / 75% ± 5% r.h.**	**6 months**

Recent development in ICH Guidelines

- For these Climatic Zones, the following standard conditions are recommended:
- **Long-term testing**: 30°C / 65% RH
- **Accelerated conditions**: 40°C / 75% RH
- This means that the "accelerated conditions" remain the same as in the Q1A(R) Guideline and only the "long-term storage conditions" have to be modified.

SHELF LIFE

Self life (referred to as expiration dating period) is the time period during which a drug product is expected to remain within the approved specification for use, provided that it is stored under the conditions defined on the container label



Maximum and Minimum time at which potency must be at least 90% of label claim at the temperature indicated in order to predict a shelf life of two years at Room Temperature.

Temperature	Maximum time for Study	Minimum time for Study
37°	12 Months	6.4 Months
45°C	8.3 Months	2.9 Months
60°C	4.1 Months	3 Weeks
85°C	06Weeks	2.5 Days

Calculation of shelf life

- Example:- self life of Aspirin suspension:
- A prescription for a liquid aspirin is called for, It contains 325mg/5ml or 6.5g/ 100ml.
- Solubility of aspirin at 25^0C is 0.33g/100ml. Therefore the suspension will definitely be a suspension.
- Other ingredients in the prescription cause the product to have a pH of 6.
- The first order rate constant for aspirin degradation in the solution is 4.5×10^{-6} $\sec^{-1}$.
- Calculate the zero order rate constant.
- Determine the self life, t_{90} for the liquid preparation, assuming that the product is satisfactory until at the time at which it has decomposed to 90% of its original concentration (i.e 10% decomposition) at 25^0C.

Ans:- $K_0 = K \times$ [aspirin in solution],

Thus $K_0 = [4.5 \times 10^{-6}\ \sec^{-1}] \times [0.33\text{g}/100\text{ml}]$

$K_0 = 1.5 \times 10^{-6}$ g/100ml $\sec^{-1}$

$$t_{90} = \frac{0.10[A]_0}{K_0}$$

$$= \frac{(0.10)(6.5g/100ml)}{1.5 \times 10^{-6} g/100ml\ sec^{-1}}$$

$$= 4.3\times10^{5}\ sec$$

$$= 5\ days$$

Buffers and Buffer Capacity

Buffers are compounds that resist changes in pH upon the addition of limited amounts of acids or bases. Buffer systems are usually composed of a weak acid or base and its conjugate salt. The components act in such a way that addition of an acid or base results in the formulation of a salt causing only a small change in pH.

The pH of a buffer system is given by the Henderson-Hasselbach equation:

$pH = pKa + \log\frac{[salt]}{[acid]}$ (for a weak acid and its salt)

$pH = pKw - pKb + \log\frac{[base]}{[salt]}$ (for a weak base and its salt)

where [salt], [acid] and [base] are the *molar* concentrations of salt, acid and base.

Buffer capacity is a measure of the efficiency of a buffer in resisting changes in pH. Conventionally, the buffer capacity (β) is expressed as the amount of strong acid or base, in gram-equivalents, that must be added to 1 liter of the solution to change its pH by one unit.

Calculate the buffer capacity as:

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

ΔB = gram equivalent of strong acid/base to change pH of 1 liter of buffer solution

ΔpH = the pH change caused by the addition of strong acid/base

- In general solutions are categorized into:

- **Hypertonic solution**: This is the solution having higher concentration of solute
- **Hypotonic solution**: It's that solution which has lower concentration of solute
- **Isotonic solution**: These are two solutions having similar solute concentration

Isotonic Buffers

The addition of any compound to a solution will affect the isotonicity since isotonicity is a property of the number of particles in solution. So the osmotic pressure of a solution will be affected not only by the drug but also by any buffer compounds that are included in the formulation. But after these compounds have been added, it is still possible that the solution will not be isotonic. It may be necessary to add additional sodium chloride to bring the solution to isotonicity, but that would require doing the calculations as shown above.

Several methods are used to adjust isotonicity of pharmaceutical solutions.

- One of the most widely used methods is the **sodium chloride equivalent method**. The NaCl equivalent (E) is the amount of NaCl which has the same osmotic effect (based on number of particles) as 1 gm of the drug.
- In the Second approach, the drug is dissolved in an appropriate volume of water (V-value) to make the solution isotonic. Then the remaining volume needed in the formulation is supplied by an isotonic buffer

UNIT-II

Micromeritics and powder Rheology

- Particle size and distribution
- Average particle size
- Number and weight distribution
- Method for determining particle volume
- Optical microscopy
- Sieving
- Sedimentation
- Measurement………..Particle shape, specific surface
- Method for determining surface area……….
    - ✓ Air permeability method
    - ✓ Adsorption method
- Derived properties of powders……………….
    - ✓ Porosity
    - ✓ Packing arrangement
    - ✓ Densities
    - ✓ Bulkiness
    - ✓ Flow properties

Micromeritics

Definition: It is the science and technology of small particles.

*The unit of particle size used is the micrometer, µm,micron, µ, and equal to 10-6 m.

The knowledge and control of the size of particles is of importance in pharmacy and materials science. The size & hence the surface area of a particle can be related to the physical, chemical & pharmacologic properties of drugs.

Release & dissolution:

Particle size & 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 & increases the drug solubility & dissolution.

2- Absorption & drug action:

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

3- Physical stability:

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

4- Dose uniformity:

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

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.

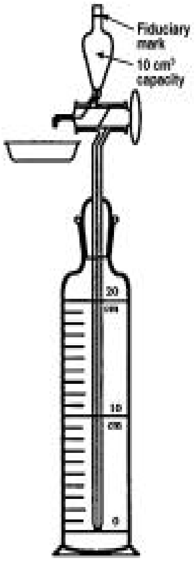
2- Sieving (range: 40 – 9500µm):

-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 which is too fine for it to pass through. 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.

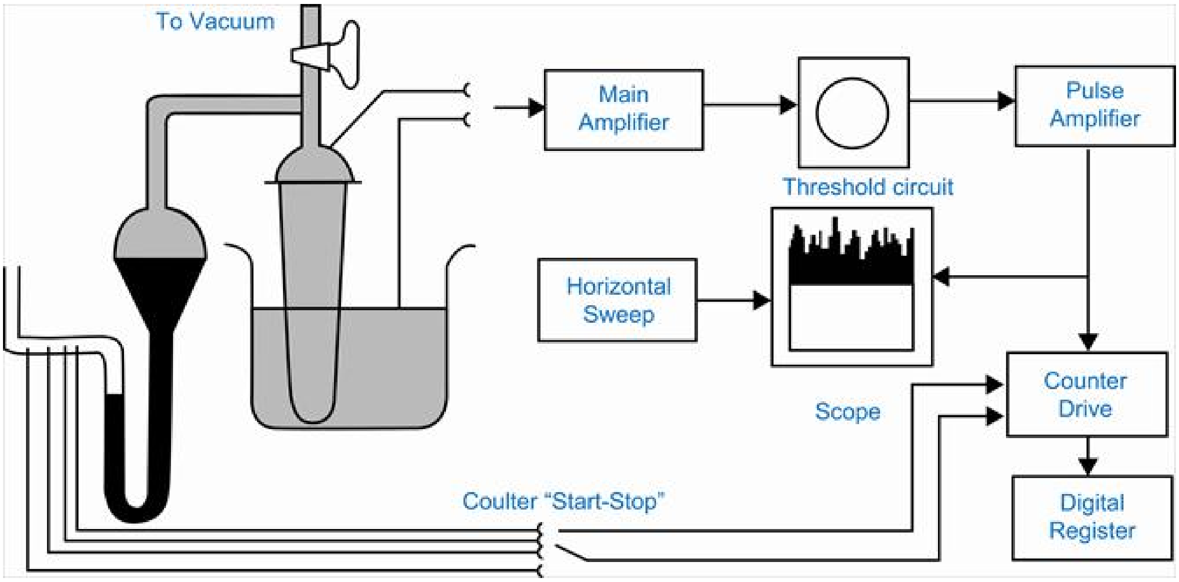
3- Sedimentation (range: .08 –300µm):

by measuring the terminal settling velocity of particles through a liquid mediumin a gravitational centrifugal environment using Andreasen apparatus.



Particle volume measurement (range: .5 - 300 um):

Principle- 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.



coulter counter apparatus

A Coulter counter is an apparatus for counting and sizing particles suspended in electrolytes. It is used for cells, bacteria,prokaryotic cells and virus particles.[3]

A typical Coulter counter has one or more microchannels that separate two chambers containing electrolyte solutions. As fluid containing particles or cells is drawn through each microchannel, each particle causes a brief change to the electrical resistance of the liquid. The counter detects these changes in electrical resistance.

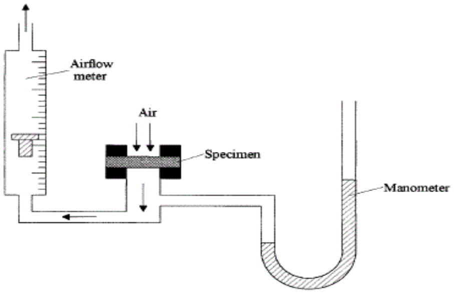
Particle specific surface area measurement

1- By Air permeability Method 2- By adsorption method

Air permeability Method

The air permeability specific surface of a powder material is a single-parameter measurement of the fineness of the powder. The specific surface is derived from the resistance to flow of air (or some other gas) through a porous bed of the powder. The SI units are $m^2 \cdot kg^{-1}$ ("mass specific surface") or $m^2 \cdot m^{-3}$ ("volume specific surface").

Measurement consists of packing the powder into a cylindrical "bed" having a known porosity (i.e. volume of air-space between particles divided by total bed volume). A pressure drop is set up along the length of the bed cylinder. The resulting flow-rate of air through the bed yields the specific surface by the Kozeny–Carman equation:[



$$S = \frac{7d}{\rho(1-\epsilon)}\sqrt{\frac{\epsilon^3 \pi \, \delta P}{l \eta Q}}$$

where: S is specific surface, $m^2 \cdot kg^{-1}$

d is the cylinder diameter, m

ρ is the sample particle density, $kg \cdot m^{-3}$

ε is the volume porosity of the bed (dimensionless)

δP is the pressure drop across the bed, Pa

l is the cylinder length, m

η is the air dynamic viscosity, Pa·s

Q is the flowrate, $m^3 \cdot s^{-1}$

It can be seen that the specific surface is proportional to the square root of the ratio of pressure to flow. Various standard methods have been proposed:

- ✓ Maintain a constant flowrate, and measure the pressure drop
- ✓ Maintain a constant pressure drop, and measure the flowrate
- ✓ Allow both to vary, deriving the ratio from the characteristics of the apparatus.

Derived properties of powders:

1 - Porosity:

Suppose a nonporous powder, is placed in a graduated cylinder:

the total volume occupied is known as the bulk volume Vb .

bulk volume = true volume + volume of spaces between particles.

The volume of the spaces, the **void volume, V = Vb - Vp**

Vp is the **true volume** of particles.

The porosity or voids ε of powder is determined as the ratio of void volume to bulk volume.

$$\textbf{Porosity} = \varepsilon = \frac{\textbf{Vb} - \textbf{Vp}}{\textbf{Vb}} = \frac{1 - \textbf{Vp}}{\textbf{Vb}}$$

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.

3- Bulkiness = Specific bulk volume = reciprocal of bulk density:

- It is an important consideration in the packaging of powders.
- The bulk density of calcium carbonate vary from 0.1 to 1 .3, and the lightest (bulkiest) type require a container about 13 times larger than that needed for the heaviest variety. (Bulkiness increases with a decrease in particle size).
- In mixture of materials of different sizes, the smaller particles sift between the larger ones and tend to reduce bulkiness.

4- 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 hopper.

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

3- Uneven powder flow → increase particle's friction with die wall causing lubrication problems, and increase dust contamination risks during powder transfer.

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 (%) =

$$\frac{\text{Tapped density} - \text{Poured or bulk density x 100}}{\text{Tapped density}}$$

Bulk density = weight / bulk volume

Tapped density = weight / true volume

Relationship between powder flowability and % compressibility

Flow description	**% compressibility**
Excellent flow	5 – 15
Good	16 – 18
Fair	19 – 21
Poor	22 – 35
Very poor	36 – 40
Extremely poor	> 40

2- Hausner ratio:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured or bulk density}}$$

Hausner ratio was related to interparticle friction:

Value less than 1 .25 indicates good flow (= 20% Carr).

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

Value greater than 1 .5 indicates poor flow (= 33% Carr).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.

3- The angle of repose φ:

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

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

$\tan \varphi = \mu$ $\quad \tan \varphi = h / r$ $\quad r = d / 2$

The sample is poured onto a 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.

- Angle of repose less than 20 (excellent flow)
- Angle of repose between 20-30 (good flow)
- Angle of repose between 30-34 (Pass flow)
- Angle of repose greater than 40 (poor flow)

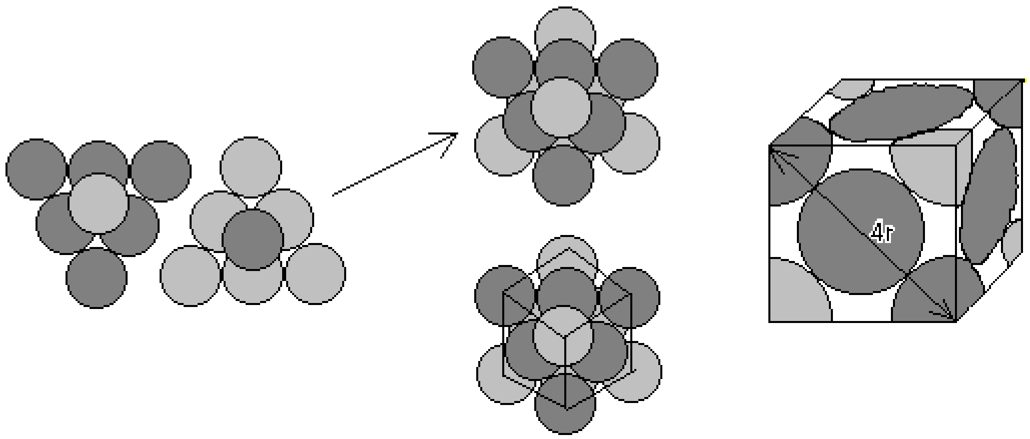
*****The rougher and more irregular the surface of the particles, the higher will be the angle of repose.**

PACKING ARRANGMENT

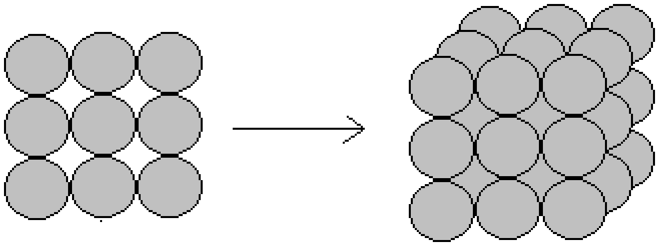
In geometry, close-packing of equal spheres is a dense arrangement of congruent spheres in an infinite, regular arrangement (or lattice). Carl Friedrich Gauss proved that the highest average density – that is, the greatest fraction of space occupied by spheres – that can be achieved by a lattice packing is

$$\frac{\pi}{3\sqrt{2}} \simeq 0.74048.$$

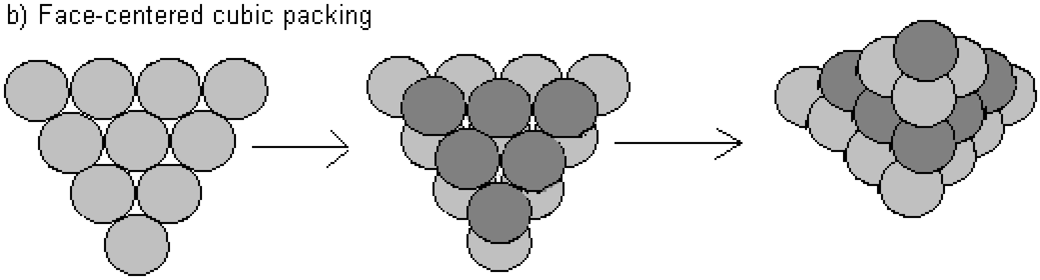
The same packing density can also be achieved by alternate stackings of the same close-packed planes of spheres, including structures that are aperiodic in the stacking direction. The Kepler conjecture states that this is the highest density that can be achieved by any arrangement of spheres, either regular or irregular. Many crystal structures are based on a close-packing of a single kind of atom, or a close-packing of large ions with smaller ions filling the spaces between them



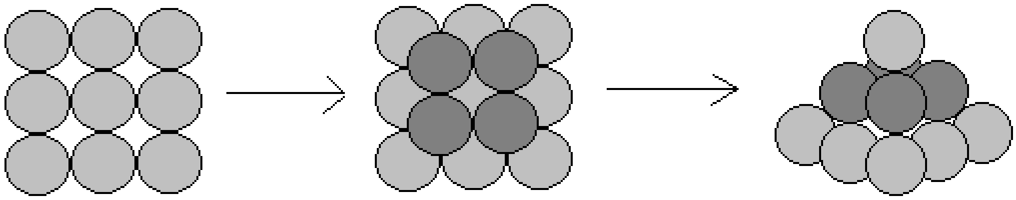
a) Simple cubic packing



b) Face-centered cubic packing



c) Hexagonal packing



UNIT-III

Surface and Interfacial Phenomenon

- Liquid interface
- Surface and interfacial tension
- Surface free energy
- Measurement of surface and interfacial tension
- Spreading coefficient
- Adsorption at liquid interface
- Surface active agent
- HLB Classification
- Solubilization
- Detergency
- Adsorption at solid-liquid interface
- Complex film
- Electrical properties of interface and application

Surface and Interfacial Phenomenon

- Surface is a boundary between solid or liquid phase and a vacuum.
- Interface is a boundary between two phases.
- Surface free energy is the work required to increase the area of the surface by 1cm2.

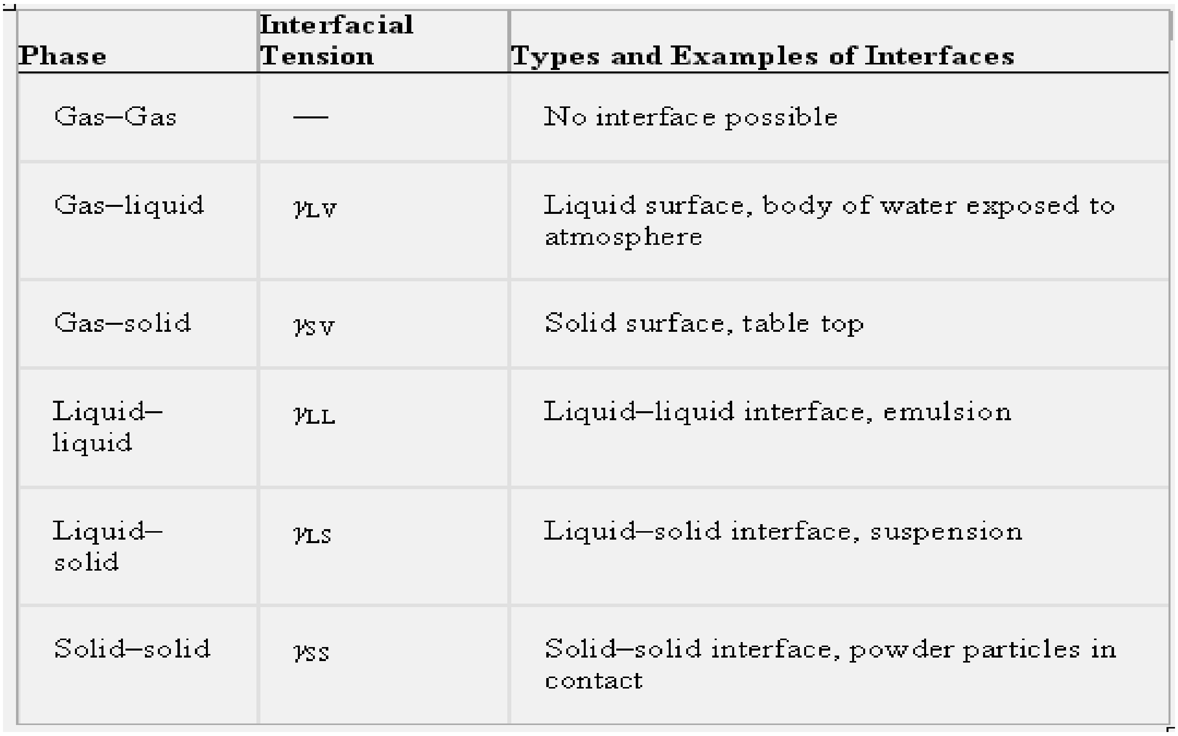
Interface

- Interfaceisthe boundary between two or more phases exist together
- The properties of the molecules forming the interface are different from those in the bulk that these molecules are forming an interfacial phase.
- Several types of interface can exist depending on whether the two adjacent phases are in solid, liquid or gaseous state.

Important of Interfacial phenomena in pharmacy:

- Adsorption of drugs onto solid adjuncts in dosage forms
- Penetration of molecules through biological membranes
- Emulsion formation and stability
- The dispersion of insoluble particles in liquid media to formulation.
- **The term *surface* is used when referring to either a gas–solid or a gas–liquid interface.**

Types of interface

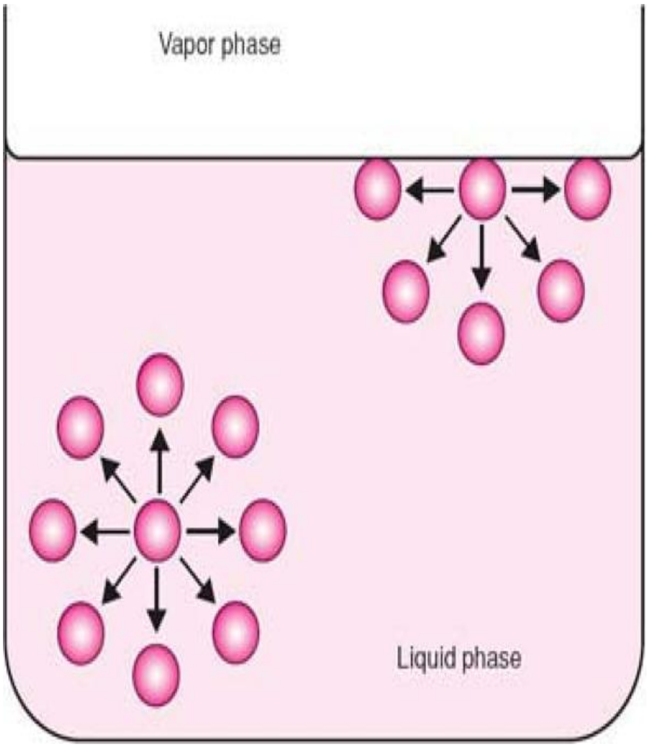


Phase	Interfacial Tension	Types and Examples of Interfaces
Gas–Gas	—	No interface possible
Gas–liquid	γ_{LV}	Liquid surface, body of water exposed to atmosphere
Gas–solid	γ_{SV}	Solid surface, table top
Liquid–liquid	γ_{LL}	Liquid–liquid interface, emulsion
Liquid–solid	γ_{LS}	Liquid–solid interface, suspension
Solid–solid	γ_{SS}	Solid–solid interface, powder particles in contact

Liquid Interfaces

Surface and Interfacial Tensions

- Molecules in the bulk liquid are surrounded in all directions by other molecules for which they have an equal attraction.
- Molecules at the surface (i.e., at the liquid–air interface) can only develop attractive cohesive forces with other liquid molecules that are situated below and adjacent to them. They can develop adhesive forces of attraction with the molecules constituting the other phase involved in the interface, although, in the case of the liquid–gas interface, this adhesive force of attraction is small.
- The net effect is that the molecules at the surface of the liquid experience an inward force toward the bulk.
- Such a force pulls the molecules of the interface together and, as a result, contracts the surface, resulting in a surface tension.



- Interfacial tension is the force per unit length existing at the interface between two immiscible liquid phases.

The surface and interfacial tensions, have the units of dynes/cm or N/m

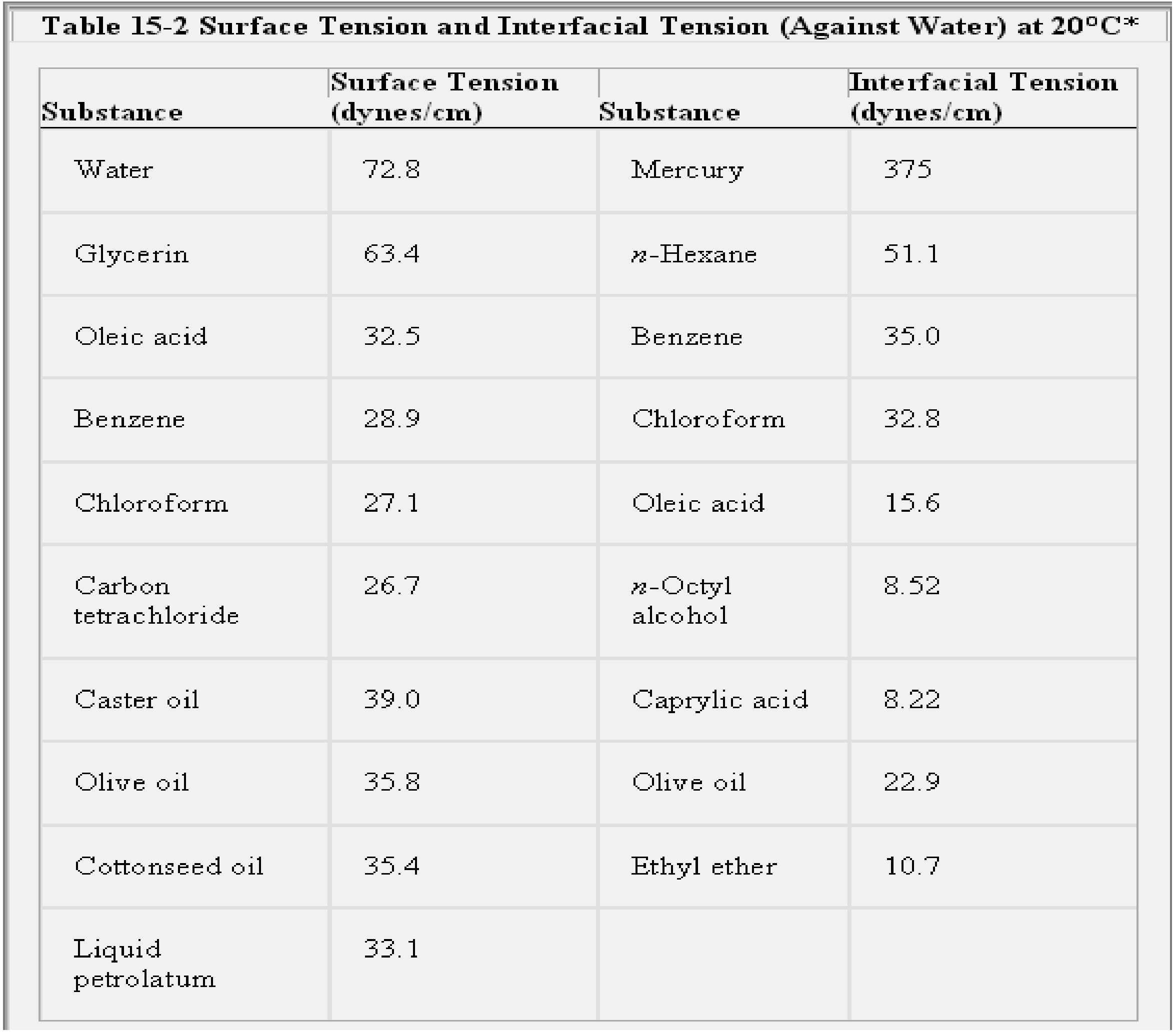


Table 15-2 Surface Tension and Interfacial Tension (Against Water) at 20°C*

Substance	Surface Tension (dynes/cm)	Substance	Interfacial Tension (dynes/cm)
Water	72.8	Mercury	375
Glycerin	63.4	*n*-Hexane	51.1
Oleic acid	32.5	Benzene	35.0
Benzene	28.9	Chloroform	32.8
Chloroform	27.1	Oleic acid	15.6
Carbon tetrachloride	26.7	*n*-Octyl alcohol	8.52
Caster oil	39.0	Caprylic acid	8.22
Olive oil	35.8	Olive oil	22.9
Cottonseed oil	35.4	Ethyl ether	10.7
Liquid petrolatum	33.1		

- The surface tensions of most liquids decrease almost linearly with an increase in temperature, that is, with an increase in the kinetic energy of the molecules.
- In the region of its critical temperature, the surface tension of a liquid becomes zero.
- The surface tension of water at 0°C is 75.6, at 20°C it is 72.8, and at 75°C it is 63.5 dynes/cm.

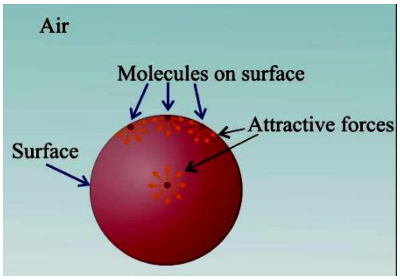
Surface Free Energy and Surface Tension

- The surface layer of a liquid possesses additional energy as compared to the bulk liquid.
- Surface free energy is the work required to increase the area of the surface by 1cm2.
- This energy increases when the surface of the same mass of liquid increases and is therefore called surface free energy
- The work W required to create a unit area of surface is known as SURFACE FREE ENERGY/UNIT AREA (ergs/cm^2)

erg = dyne . cm

$$\boxed{W = \gamma \Delta A}$$

- Its equivalent to the surface tension γ
- Thus the greater the area A of interfacial contact between the phases, the greater the free energy.
- For equilibrium, the surface free energy of a system must be at a minimum.
- Thus Liquid droplets tend to assume a spherical shape since a sphere has the smallest surface area per unit volume



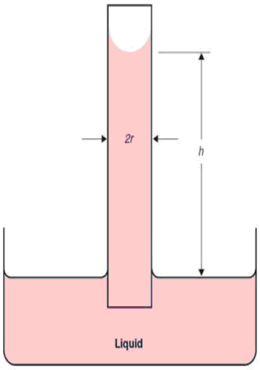
Measurement of Surface and Interfacial Tensions

1. Capillary Rise Method.
2. The DuNoüy Ring Method
3. Drop weight method (Stalagmometer)

Capillary Rise Method

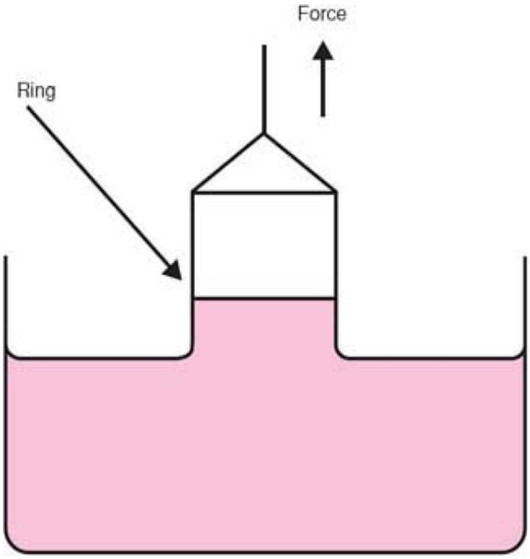
- When a capillary tube is placed in a liquid contained in a beaker, the liquid generally rises up the tube a certain distance.
- By measuring this rise in a capillary, it is possible to determine the surface tension of the liquid. It is not possible, however, to obtain interfacial tensions using the capillary rise method.
- Because of the surface tension, the liquid continues to rise in the tube, but because of the weight of the liquid, the upward movement is just balanced by the downward force of gravity

$$\gamma = \frac{1}{2} r h \rho g \qquad (15\text{–}12)$$



The DuNoüy Ring Method

- The DuNoüy tensiometer is widely used for measuring surface and interfacial tensions.
- The force necessary to detach a platinum–iridium ring immersed at the surface or interface is proportional to the surface or interfacial tension.
- The force required to detach the ring in this manner is provided by a torsion wire and is recorded in dynes on a calibrated dial.



$$\gamma = \frac{\text{Dial reading in dynes}}{2 \times \text{Ring circumference}} \times \text{Correction factor, } \beta \qquad (15\text{–}14)$$

- A correction factor is necessary because the simple theory does not take into account certain variables such as the radius of the ring, the radius of the wire used to form the ring, and the volume of liquid raised out of the surface.

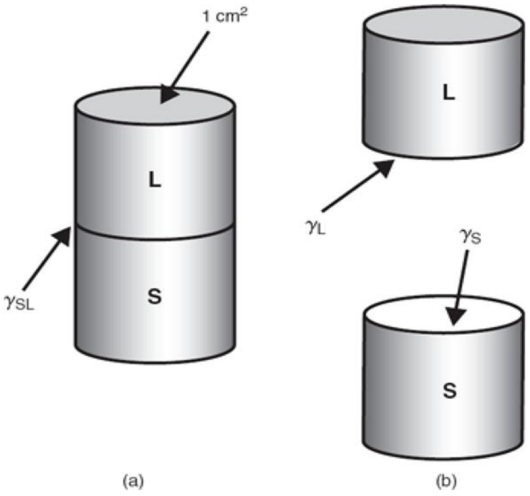
Errors as large as 25% may occur if the correction factor is not calculated and applied

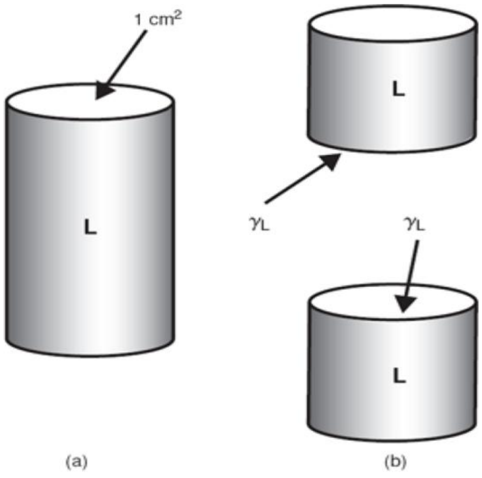
Spreading coefficient

Adhesion and cohesion

The work of adhesion between two immiscible liquids is equal to the work required to separate unit area of the liquid-liquid interface and form two separate liquid-air interfaces (Figure: Work of adhesion (a) and of cohesion (b), and is given by the Dupre equation

$$W_a = \gamma_A + \gamma_B - \gamma_{AB}$$





When a drop of an insoluble oil is placed on a clean water surface, it may behave in one of three ways:

1. Remain as a lens, as in Figure (non-spreading).

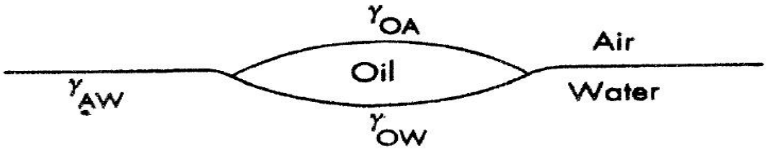


Figure 4.16 A drop of non-spreading oil on a water surface

2. Spread as a thin film, which may show interference colours, until it is uniformly distributed over the surface as a 'duplex' film. (A duplex film is a film which is thick enough for the two interfaces - i.e. liquid-film and film-air - to be independent and possess characteristic surface tensions.)

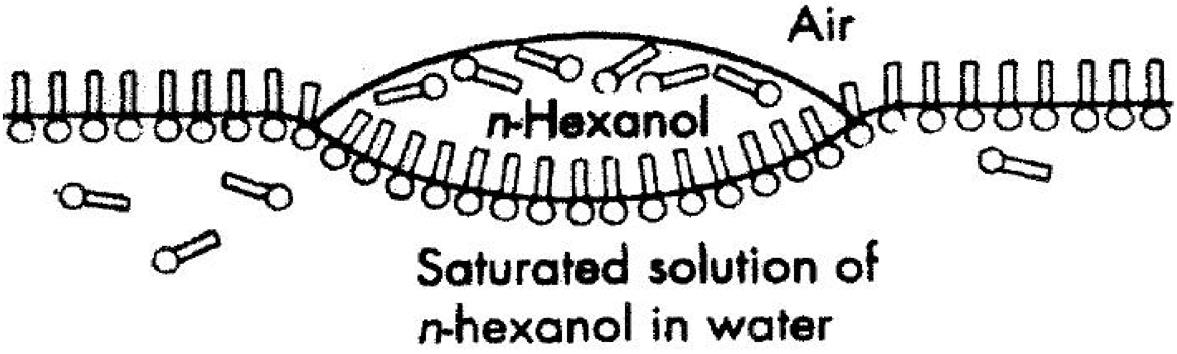


Figure 4.17 Spreading of *n*-hexanol on a water surface

- ✓ The term (Wa - Wc) is known as the spreading coefficient, S;
- ✓ if it is positive, the oil will spread over a water surface.

$$S = (Wa - Wc)$$

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

- ✓ γ_S is the surface tension of the sublayer liquid,
- ✓ γ_L is the surface tension of the spreading liquid,

γ_{LS} is the interfacial tension between the two liquids

- ✓ spreading occurs (S is positive) when the surface tension of the sublayer liquid is greater than the sum of the surface tension of the spreading liquid and the interfacial tension between the sublayer and the spreading liquid.

If $(\gamma_L + \gamma_{LS})$ is larger than γ_S, the substance forms globules or a floating lens and fails to spread over the surface. An example of such a case is mineral oil on water

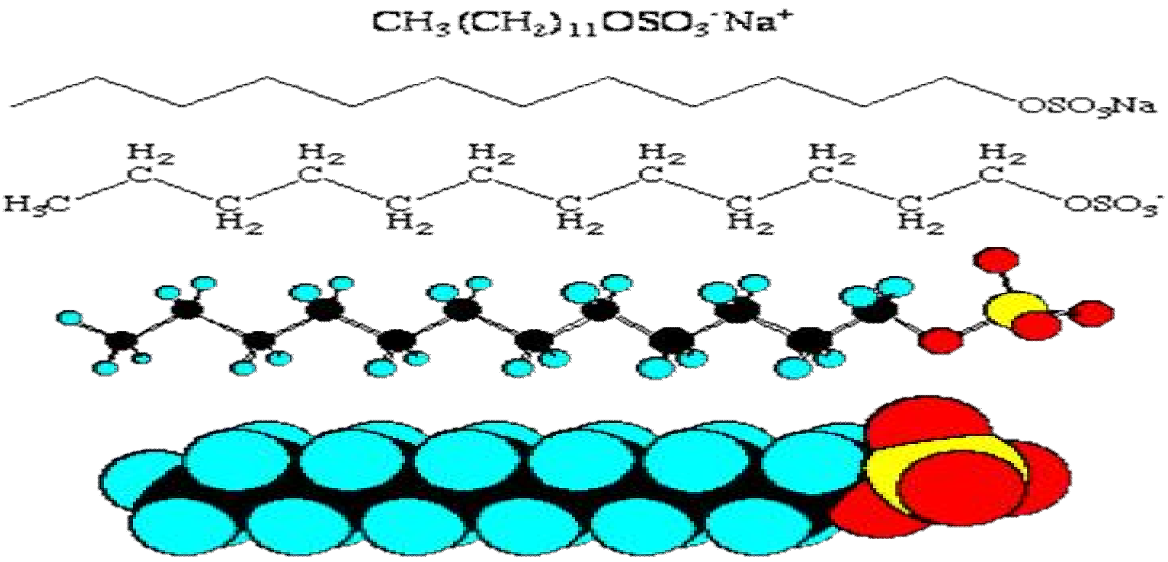
Adsorption at Liquid Interfaces

- Certain molecules and ions, when dispersed in the liquid, move of their own accord to the interface.
- the surface free energy and the surface tension of the system are automatically reduced.
- Molecules and ions that are adsorbed at interfaces are termed surface-active agents or surfactants. An alternative term is amphiphile,

Surface Active Agents (Surfactant)

A surfactant molecule is depicted schematically as a cylinder representing the hydrocarbon (hydrophobic) portion with a sphere representing the polar (hydrophilic) group attached at one end.

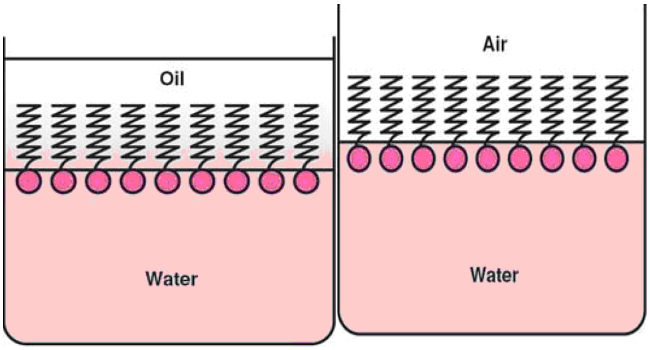
The hydrocarbon chains are straight because rotation around carbon-carbon bonds bends, coils and twists them.



- ✓ It is the amphiphilic nature of surface-active agents that causes them to be absorbed at interfaces.
- ✓ Thus, in an aqueous dispersion of amphiphile, the polar group is able to associate with the water molecules. The nonpolar portion is rejected, As a result, the amphiphile is adsorbed at the interface.
- ✓ The situation for a fatty acid at the air–water and oil–water interface:
- ✓ At the oil–water interface, the lipophilic chains are directed upward into the air;

at the air–oil interface, they are associated with the oil phase.

- ✓ For the amphiphile to be concentrated at the interface, it must be balanced with the proper amount of water- and oil-soluble groups.
- ✓ If the molecule is too hydrophilic, it remains within the body of the aqueous phase and exerts no effect at the interface.
- ✓ if it is too lipophilic, it dissolves completely in the oil phase and little appears at the interface



Systems of Hydrophile–Lipophile Balance (HLB Classification)

- ✓ The higher the HLB of an agent, the more hydrophilic it is.
- ✓ The Spans, sorbitan esters , are lipophilic and have low HLB values (1.8–8.6);
- ✓ The Tweens, polyoxyethylene derivatives of the Spans, are hydrophilic and have high HLBvalues (9.6–16.7

Hydrophilic Lipophilic Balance

Determination of HLB

- Polyhydric Alcohol Fatty Acid Esters (Ex. Glyceryl monostearate)

HLB = 20 (1 – S / A)

S = Saponification number of the ester

A = Acid number of the fatty acid

- Surfactants with no Saponification no(Ex. Bees wax and lanolin)

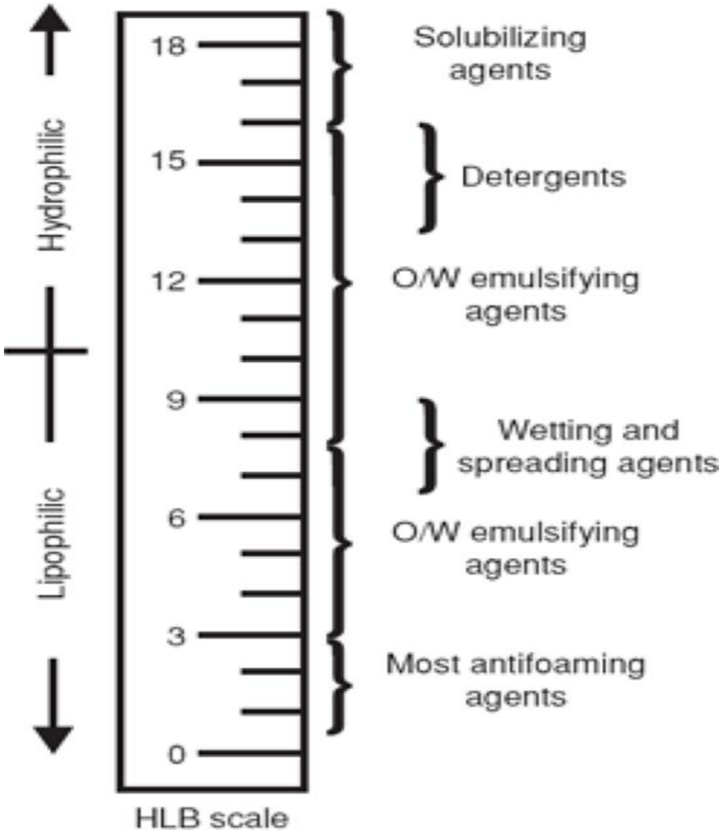
HLB =E + P / 5

E = The percent by weight of ethylene oxide

P=The percent by weight of polyhydric alcohol group in the molecules

- Surfactants with hydrophilic portion have only oxyethylene groups

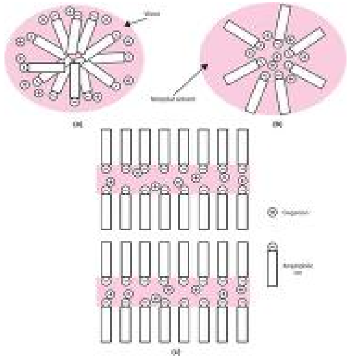
HLB =E / 5



Micelles and the Critical Micelle Concentration

- When present in a liquid medium at low concentrations, the amphiphiles exist separately.
- As the concentration is increased, aggregation occurs. These aggregates, which may contain 50 or more monomers, are called micelles

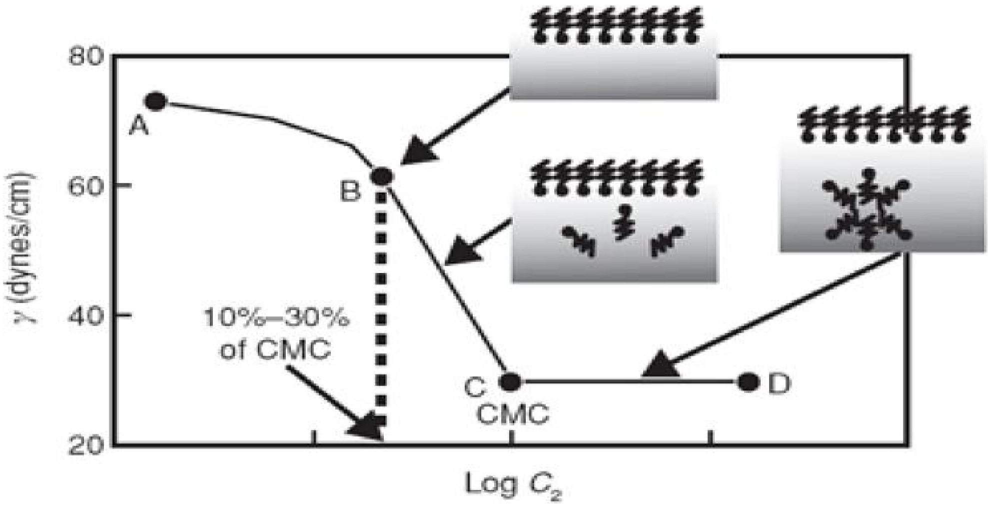
The concentration of monomer at which micelles form is termed the critical micelle concentration(CMC).



a) spherical micelle in aqueous media,

(b) reversed micelle in nonaqueous media,

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



- ✓ The surface tension decreases up to the CMC .
- ✓ When the surface tension, γ, of a surfactant is plotted against the logarithm of the surfactant activity or concentration, log c_2, the plot takes on the shape shown in Figure.
- ✓ The point C corresponds to the critical micelle concentration (CMC), the concentration at which micelles form in the solution.
- ✓ Beyond the CMC, the line becomes horizontal because further additions of surfactant are no longer being accompanied by a decrease in surface tension.

Adsorption at Solid Interfaces

- ✓ Solid–gas adsorption:
- ✓ The removal of objectionable odors from rooms and food,
- ✓ The operation of gas masks,
- ✓ The measurement of the dimensions of particles in a powder.
- ✓ Solid–liquid adsorption:
- ✓ Decolorizing solutions,
- ✓ Adsorption chromatography,
- ✓ Detergency, wetting

The adsorbent :→ the material used to adsorb the gas)

The adsorbate:→ the substance being adsorbed

Types of adsorption:

1. **physical adsorption:**

- ✓ Associated with van der Waals forces,
- ✓ Reversible,
- ✓ The removal of the adsorbate from the adsorbent being known as desorption. A physically adsorbed gas can be desorbed from a solid by increasing the temperature and reducing the pressure.

2. Chemical adsorption or chemisorptions

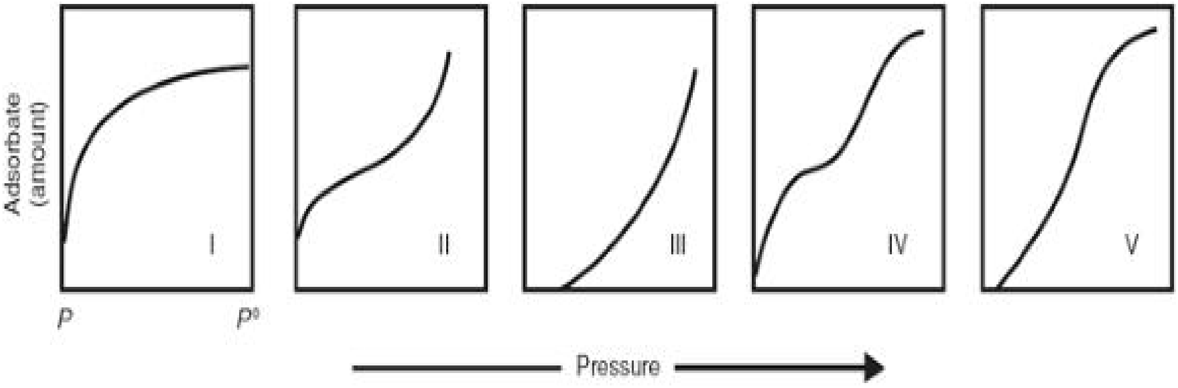
- ✓ The adsorbate is attached to the adsorbent by primary chemical bonds,
- ✓ Irreversible unless the bonds are broken.

The degree of adsorption of a gas by a solid depends on:

1. The chemical nature of the adsorbent and the adsorbate
2. The surface area of the adsorbent,
3. The temperature,
4. The partial pressure of the adsorbed gas

The relationship between the amount of gas physically adsorbed on a solid and the equilibrium pressure or concentration at constant temperature yields an adsorption isotherm when plotted

The number of moles, grams, or milliliters, x, of gas adsorbed on, m, grams of adsorbent at standard temperature and pressure is plotted on the vertical axis against the equilibrium pressure of the gas in mm Hg on the horizontal axis,



The Freundlich isotherm

$$y = \frac{x}{m} = kp^{1/n} \tag{15–49}$$

- x is the mass of gas adsorbed
- m is the mass of adsorbent,
- y is x/m
- k and n are constants that can be evaluated from the results of the experiment.

The logarithmic form,

$$\log \frac{x}{m} = \log k + \frac{1}{n} \log p \tag{15–50}$$

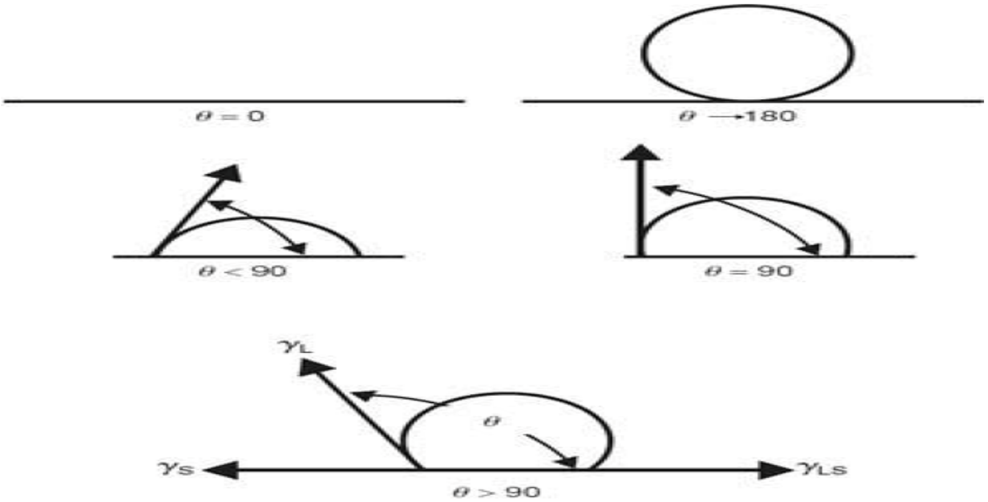
- which yields a straight line when plotted.
- The constant, log k, is the intercept on the ordinate,
- 1/n is the slope of the line.

Wetting Phenomena

- Adsorption at solid surfaces is involved in the phenomena of wetting and detergency.
- When a liquid comes into contact with the solid, the forces of attraction between the liquid and the solid phases begin to play a significant role.
- In this case, the behavior of the liquid will depend on the balance between the forces of attraction of molecules in the liquid and the forces of attraction between the liquid and the solid phases.
- In the case of mercury and glass, attractive forces between molecules of mercury and glass are much smaller than the forces of attraction between molecules of mercury themselves.
- As a result, mercury will come together as a single spherical drop.
- In contrast, for water and glass (or mercury and zinc), attractive forces between the solid and liquid molecules are greater than the forces between molecules of liquid themselves, and so the liquid is able to wet the surface of the glass.
- The contact angle is the angle between a liquid droplet and the surface over which it spreads.
- The contact angle between a liquid and a solid may be 0° signifying complete wetting, or may approach 180°, at which wetting is insignificant.

$$S = \gamma_L(\cos\theta - 1) \tag{15–60}$$

- The most important action of a wetting agent is to lower the contact angle between the surface and the wetting liquid.
- A wetting agent is a surfactant that, when dissolved in water, lowers the advancing contact angle, aids in displacing an air phase at the surface, and replaces it with a liquid phase



The application of wetting Phenomena

- The displacement of air from the surface of sulfur, charcoal, and other powders for the purpose of dispersing these drugs in liquid vehicles;
- The displacement of air from the matrix of cotton pads and bandages so that medicinal solutions can be absorbed for application to various body areas;
- The displacement of dirt and debris by the use of detergents in the washing of wounds;
- The application of medicinal lotions and sprays to the surface of the skin and mucous membranes
- Wettability of tablet surfaces influences disintegration and dissolution and the subsequent release of the active ingredient(s) from the tablet.
- The influence of tablet binders on wettability of acetaminophen tablets

Electric Properties of Interfaces

- Particles dispersed in liquid media may become charged mainly in one of two ways:
    1. The selective adsorption of a particular ionic species present in solution.

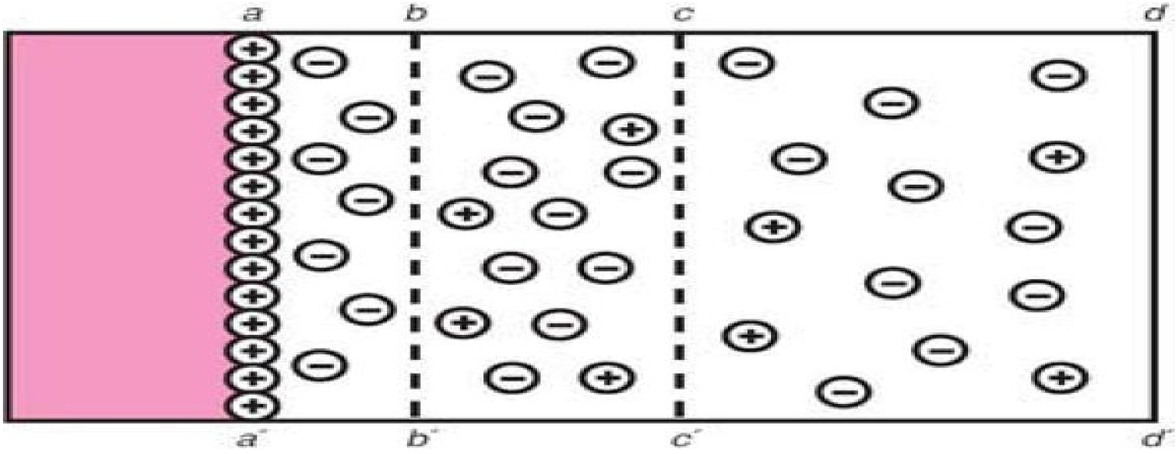
- This may be an ion added to the solution or, in the case of pure water, it may be the hydronium or hydroxyl ion.
- The majority of particles dispersed in water acquire a negative charge due to preferential adsorption of the hydroxyl ion

2. Charges on particles arise from ionization of groups (such as COOH) that may be situated at the surface of the particle. In these cases, the charge is a function of pK and pH.

- A third, less common origin for the charge on a particle surface is thought to arise when there is a difference in dielectric constant between the particle and its dispersion medium.

The Electric Double Layer

- Consider a solid surface in contact with a polar solution containing ions, for example, an aqueous solution of an electrolyte.
- suppose that some of the cations are adsorbed onto the surface, giving it a positive charge.
- Remaining in solution are the rest of the cations plus the total number of anions added
- As a result, an equilibrium situation is set up in which some of the excess anions approach the surface, whereas the remainders are distributed in decreasing amounts as one proceeds away from the charged surface.
- At a particular distance from the surface, the concentrations of anions and cations are equal, that is, conditions of electric neutrality prevail
- The system as a whole is electrically neutral, even though there are regions of unequal distribution of anions and cations



- ✓ aa′ is the surface of the solid.
- ✓ The adsorbed ions that give the surface its positive charge are referred to as the potential-determining ions.

- ✓ Immediately adjacent to this surface layer is a region of tightly bound solvent molecules, together with some negative ions, also tightly bound to the surface.
- ✓ The limit of this region is given by the line bb′ .
- ✓ These ions, having a charge opposite to that of the potential-determining ions, are known as counterions or gegenions.
- ✓ In the region bounded by the lines bb′ and cc′, there is an excess of negative ions.
- ✓ The potential at bb′ is still positive because, as previously mentioned, there are fewer anions in the tightly bound layer than cations adsorbed onto the surface of the solid.
- ✓ Beyond cc′, the distribution of ions is uniform and electric neutrality is obtained.
- ➢ Thus, the electric distribution at the interface is equivalent to a double layer of charge:

1. The first layer (extending from aa′ to bb′) tightly bound
2. A second layer (from bb′ to cc′) that is more diffuse.

- ✓ The so-called diffuse double layer therefore extends from aa′ to cc′.

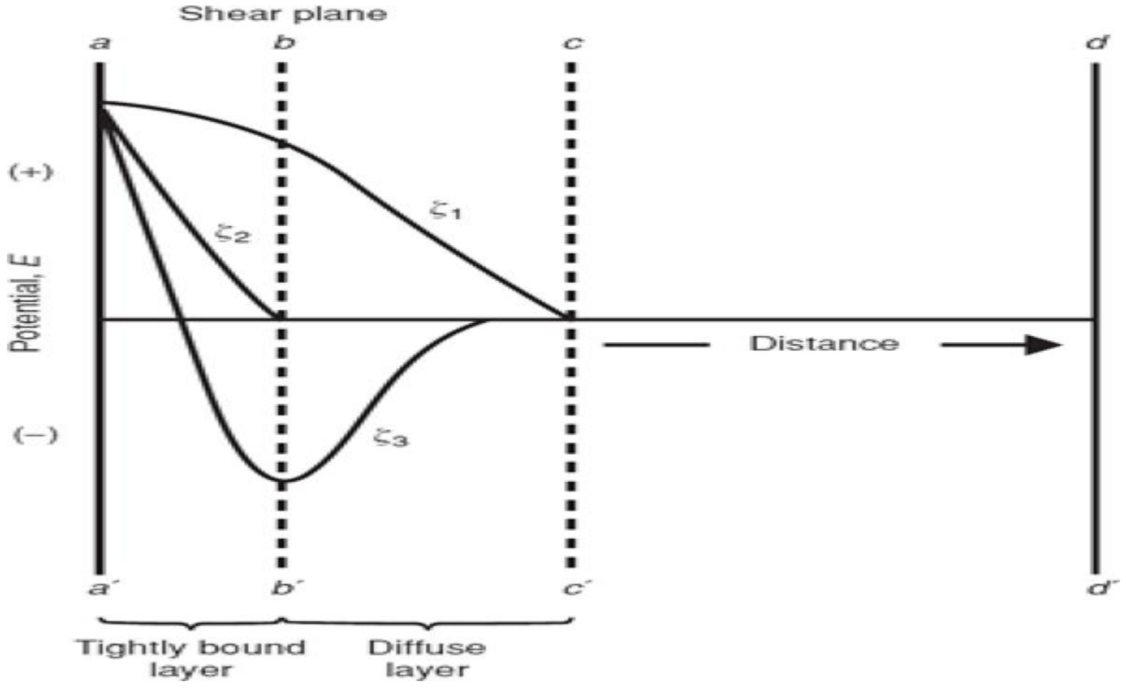
Nernst and Zeta Potentials

- ✓ The changes in potential with distance from the surface for the various situations:
- ✓ The potential at the solid surface aa′ due to the potential-determining ion is the electrothermodynamic (Nernst) potential, E,
- ✓ Defined as the difference in potential between the actual surface and the electroneutral region of the solution.
- ✓ The potential located at the shear plane bb′ is known as the electrokinetic, or zeta, potential, ζ.

The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electroneutral region of the solution

- ✓ the potential initially drops off rapidly, followed by a more gradual decrease as the distance from the surface increases.

- ➢ This is because the counterions close to the surface act as a screen that reduces the electrostatic attraction between the charged surface and those counterions further away from the surface



- The zeta potential has practical application in the stability of systems containing dispersed particles because this potential governs the degree of repulsion between adjacent, similarly charged, dispersed particles.
- If the zeta potential is reduced below a certain value (which depends on the particular system being used), the attractive forces exceed the repulsive forces, and the particles come together. This phenomenon is known as flocculation

UNIT-IV

Viscosity and Rheology

- Newtonian systems
- Law of flow
- Kinematic viscosity
- Factors affecting viscosity of formulation
- Non-Newtonian systems
  - ✓ Pseudoplastic
  - ✓ Dilatants
  - ✓ Plastic
  - ✓ Thixotrophy
- Determination of viscosity by-
  - ✓ Falling sphere viscometer
  - ✓ Rotational viscometer

Rheology

- ✓ Rheo – to flow
- ✓ logos – science
- ✓ ology – the study of.
- ➢ Study of deformation and flow of matter

- ➢ “Rheology is the study of the flow of materials that behave in an interesting or unusual manner. Oil and water flow in familiar, normal ways, whereas mayonnaise, peanut butter, chocolate, bread dough, and silly putty flow in complex and unusual ways. In rheology, we study the flows of unusual materials.”

- ➢ All normal or Newtonian fluids (air, water, oil, honey) follow the same scientific laws. On the other hand, there are also fluids that do not follow the Newtonian flow laws. These non-Newtonian fluids, for example mayo, paint, molten plastics, foams, clays, and many other fluids, behave in a wide variety of ways. The science of studying these types of unusual materials is called rheology”

Objective of Rheology

- ➢ Establishing the relationship between applied forces and geometrical effects induced by these forces at a point (in a fluid).

- ➢ The mathematical form of this relationship is called the rheological equation of state, or the constitutive equation.

- ➢ The constitutive equations are used to solve macroscopic problems related to continuum mechanics of these materials.

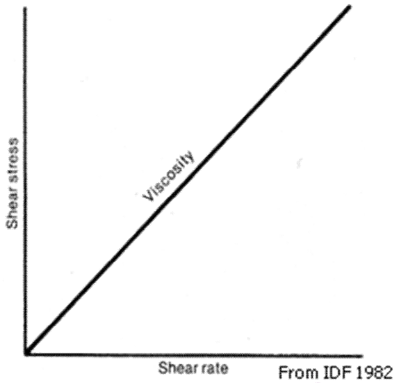
- ➢ Any equation is just a model of physical reality

- ➢ Establishing the relationship between rheological properties of material and its molecular structure (composition). Related to:

- ✓ Estimating quality of materials
- ✓ Understanding laws of molecular movements
- ✓ Intermolecular interactions
- ✓ Interested in what happens inside a point during deformation of the medium

Newton and Simple Fluids

- Newtonian behaviour: Viscosity remains constant no matter what the shear rate.



From IDF 1982

Consistency curve for a Newtonian fluid.

- Newtonian fluids are the simplest type of fluid and contain no particles larger than a molecule. In an Newtonian fluid, such as water or oil, the shear stress is directly proportional to the shear rate, while the fluid is in laminar flow

Newtonian (Newtonian Law of Flow)

- ✓ "The higher the viscosity of a liquid, the greater is the force per unit area (shearing stress) required to produce a certain rate of shear"
- ✓ Shear – as a stress which is applied parallel or tangential to a face of a material, as opposed to a normal stress which is applied perpendicularly.
- ✓ *Shear stress* -Measured in (SI unit): pascal
- ✓ Commonly used symbols: τ
- ✓ Expressed in other quantities: **τ = F / A**
- ✓ A simple equation to describe Newtonian fluid behavior is where

$$\tau = \mu(\Delta v/\Delta y) \qquad (2\text{–}1)$$

τ is the shear stress exerted by the fluid ("drag") [Pa]
μ is the fluid viscosity - a constant of proportionality [Pa·s]
du is the velocity gradient perpendicular to the direction *dy* of shear [s−1]

- For a Newtonian fluid, the viscosity, by definition, depends only on temperature and pressure (and also the chemical composition of the fluid if the fluid is not a pure substance), not on the forces acting upon it.

Viscosity (η)

- Viscosity (η) is the resistance of a fluid material to flow under stress. The higher the viscosity, the greater the resistance.

Absolute (dynemic) viscosity

Viscosity= η = F'/s = shear stress/ shear rate = dyn m-2/ sec-1 = dyn m-2 s

- The fundamental unit of viscosity measurement is the *poise*. A material requiring a shear stress of one dyne per square centimeter to produce a shear rate of one reciprocal second has a viscosity of one poise, or 100 centipoi

Fluidity; it is the reciprocal of viscosity

$$Ø = 1 / \eta$$

Kinematic Viscosity:

It is the absolute viscosity divided by the density of liquid at a specified temperature

Kinematic viscosity = η / ρ

Where ρ is the density of the liquid

The unite is Stock (s) or centistock (cs)

- **Relative viscosity:**

  Is the relation of the solution viscosity h to the viscosity of the solvent "standard" h o

  $$\eta_{rel} = \eta / \eta_o$$

  _ Specific Viscosity $\eta_{sp} = \eta_{rel} - 1$

FACTORS AFFECTING VISCOSITY

1-Temperature; --------(inverse relationship) The former effect causes a decrease in the shear stress while the latter causes it to increase. The result is that liquids show a reduction in **viscosity** with increasing **temperature**. With high temperatures, viscosity increases in gases and decreases in liquids, the drag force will do the same.

2-Shape of particles; e.g. spheroid colloids is less viscous than linear colloids, as the latter tend to form a network within the dispersion medium.

3-Concentration; direct relationship

Non-Newtonian -

- A **non-Newtonian fluid** is a fluid whose flow properties are not described by a single constant value of viscosity.

- ✓ If the relation between shear stress and shear rate is not linear: non-newtonian viscosity

- ✓ Viscosity varies with the shear: $\eta = f(\tau)$ or $\eta = f(D)$

- ✓ Most viscous materials are non-newtonian

- ✓ Non-newtonian behavior depends on the micro- or nanostructure of the material (breakdown, arrangement, or entanglement)

- Many polymer solutions and molten polymers are non-Newtonian fluids, as are many commonly found substances such as ketchup, starch suspensions, paint, blood and shampoo.

- In a Newtonian fluid, the relation between the shear stress and the strain rate is linear (and if one were to plot this relationship, it would pass through the origin), the constant of proportionality being the coefficient of viscosity.

- A In a non-Newtonian fluid, the relation between the shear stress and the strain rate is nonlinear, and can even be time-dependent. Therefore a constant coefficient of viscosity cannot be defined.

- **Strain:** deformation in term of relative displacement of the particles composing the body
  - **Stress**: measure of internal forces acting within a (deformable) body
  - **Shear:** deformation of a body in one direction only (resulting from the action of a force per unit area
  τ=shear stress) and having a given perpendicular gradient (γ=shear strain)

- A ratio between shear stress and rate of strain (or shear-dependent viscosity) can be defined, this concept being more useful for fluids without time-dependent behavior

- An inexpensive, non-toxic example of a non-Newtonian fluid is a suspension of starch (e.g. cornflour) in water

Type of non- Newtonian flow:

- ✓ Plastic flow
- ✓ Pseudoplastic flow
- ✓ Dilatant flow

- **Plastic Flow**

- Plastic flow is associated with the preparation of flocculation or aggregations of particles in concentrated suspension, also known as ***Bingham bodies.***

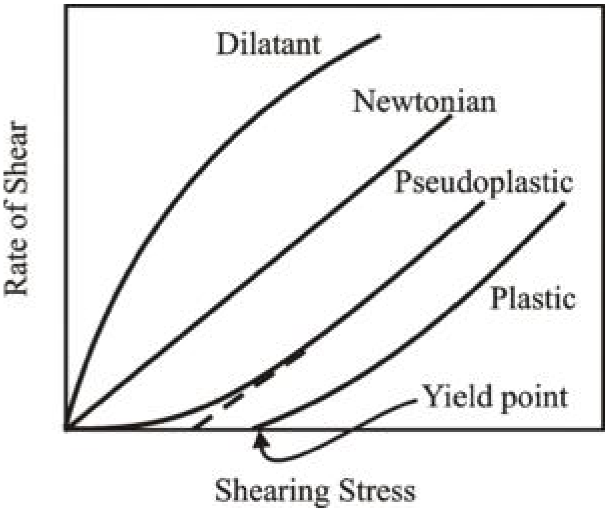
- A *Bingham body* does not begin to flow until a shearing stress corresponding to the yield value is exceeded.

- *Yield value (f);* is an indication of the force that must be applied to a system to convert it to a Newtonian System.

- Examples; suspension of Zno in mineral oil, certain paints, ointments. clay suspensions, drilling mud, toothpaste, mayonnaise, chocolate, and mustard. The classic case is ketchup which will not come out of the bottle until you stress it by shaking.

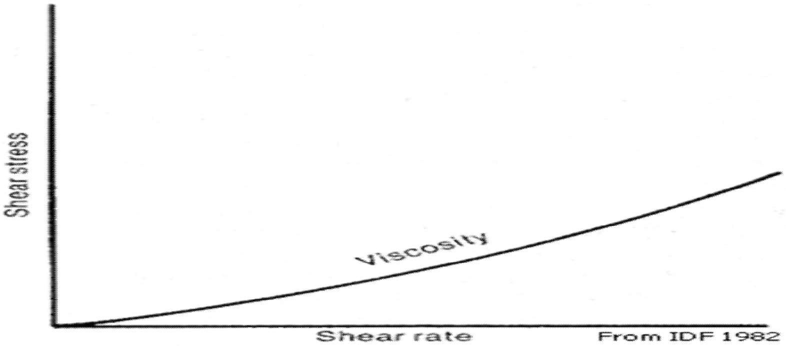
- he slope of the rheogram is termed *Mobility*, analogous to fluidity in Newtonian system, and its reciprocal is known as *Plastic viscosity, U*

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



Pseudoplastic Flow

- ✓ pseudoplastic fluids **Shear thinning** is an effect where viscosity decreases with increasing rate of shear stress. Materials that exhibit shear thinning are called pseudoplastic.



The consistency curve for a Pseudoplastic fluid.

- ✓ The curve begins at the origin (or approach it), there is no yield value.
  Occurs in dispersion of polymers (e.g. syenthetic or natural gum, cellulose derivatives)

- ✓ As the shearing stress is increased, disarranged molecules orient themselves to the direction of flow. This orientation reduces internal friction and resistance of the molecules and allows a greater rate of shear at each shear stress.

- ✓ Some of the solvent associated with molecules will be released resulting in decreasing the viscosity.

- ✓ This type of flow behavior is sometimes called shear-thinning.

- ✓ Pseudoplasticity can be demonstrated by the manner in which shaking a bottle of ketchup causes the contents to undergo an unpredictable change in viscosity. The force causes it to go from being thick like honey to flowing like water.

- ✓ Viscosity decreases with an increase in shear thinning

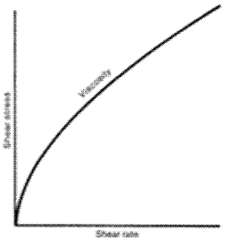
- ➢ Eg. Blood plasma, latex, inks Polymers in solutions such as tragacant, sodium alginate, methylcellulose

Dilatant Flow

- ✓ Certain suspensions with a high percentage (up to 50%)%) of deflocculated solids exhibit an increase in resistance to flow with increasing rate of shear.
- ✓ Such systems actually increase in volume when sheared and hence termed *dilatant.*
- ✓ This type of flow behavior is sometimes called *shear-thickening*.
- ✓ When stress is removed, a dilatent system returns to its original state of fluidity. E.g. corn starch in water
- ✓ The plot of shear stress versus velocity gradient lies below the straight line for Newtonian fluids. The curve begins with a low slope, indicating a low apparent viscosity. Then, the slope increases with increasing velocity gradient.

  Eg. Starch in water, TiO_2

Equation for dilatants flow is $F^N = \eta G$



From IDF 1982

Consistency curve for a typical non-Newtonian fluid.

THIXOTROPY

- ➢ Thixotropiy is the property of some non-Newtonian pseudoplastic fluids to show a time-dependent change in viscosity; the longer the fluid undergoes shear stress, the lower its viscosity.
- ➢ A thixotropic fluid is a fluid which takes a finite time to attain equilibrium viscosity when introduced to a step change in shear rate.
- ➢ A decrease in apparent viscosity with time under constant shear rate or shear stress, followed by a gradual recovery, when the stress or shear rate is removed. – Such system contain asymmetric particles forming a loose network through sample. At rest, this structure impart rigidity to system resembling gel.

- As shear applied, the structure begins to break and the material undergoes Gel-to-Sol transformation. Finally, at rest the structure is restored again (Sol-to Gel).
- The term is sometimes applied to pseudoplastic fluids without a viscosity/time component. Many gels and colloids are thixotropic materials, exhibiting a stable form at rest but becoming fluid when agitated.
- A thixotropic fluid displays a decrease in viscosity over time at a constant shear rate.
- A shear thinning fluid displays decreasing viscosity with increasing shear rate.
- Some fluids are anti-thixotropic: constant shear stress for a time causes an increase in viscosity or even solidification. Constant shear stress can be applied by shaking or mixing. Fluids which exhibit this property are usually called rheopectic. They are much less common.

Determination of Viscosity

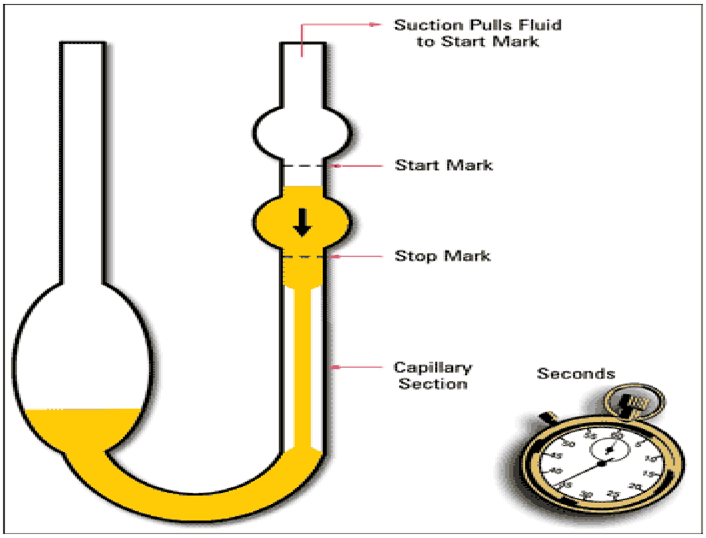
- ✓ **U-tube viscometers**
- ✓ **Falling sphere viscometers**
- ✓ **Rotation viscometers**

A **viscometer** (also called **viscosimeter**) is an instrument used to measure the viscosity of a fluid. For liquids with viscosities which vary with flow conditions, an instrument called a rheometer is used. Viscometers only measure under one flow condition.

U-tube viscometers

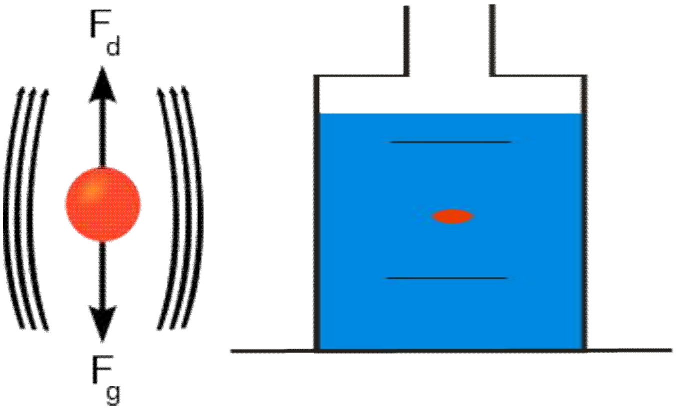
These devices are also known as glass capillary viscometers or **Ostwald viscometers**, named after Wilhelm Ostwald. Another version is the Ubbelohde viscometer, which consists of a U-shaped glass tube held vertically in a controlled temperature bath. In one arm of the U is a vertical section of precise narrow bore (the capillary). Above there is a bulb, with it is another bulb lower down on the other arm. In use, liquid is drawn into the upper bulb by suction, then allowed to flow down through the capillary into the lower bulb. Two marks (one above and one below the upper bulb) indicate a known volume. The time taken for the level of the liquid to pass between these marks is proportional to the kinematic viscosity. Most commercial units are provided with a conversion factor, or can be calibrated by a fluid of known properties. The time required for the test liquid to flow through a capillary of a known diameter of a certain factor between two marked points is measured. By multiplying the time taken by the factor of the viscometer, the kinematic viscosity is obtained.

- Rotation viscometer Also known as Ostwald (U-tube(viscometer of glass capillary viscometer.
- Used for Newtenian flow
- Classified as direct flow and reverse flow viscomenters



Falling sphere viscometers

A glass or steel ball of known size and density is allowed to descend through the liquid hold stationary in a vertical glass tube.The rate at which the ball falls inversely proportion to the viscosity. - Electrical sensor is used for opaque liquids



Falling sphere viscometers

Principle-Stokes' law is the basis of the falling sphere viscometer, in which the fluid is stationary in a vertical glass tube. A sphere of known size and density is allowed to descend through the liquid. If correctly selected, it reaches terminal velocity, which can be measured by the time it takes to pass two marks on the tube. Electronic sensing can be used for opaque fluids. Knowing the terminal velocity, the size and density of the sphere, and the density of the liquid, Stokes' law can be used to calculate the viscosity of the fluid. A series of steel ball bearings of different diameter are normally used in the classic experiment to improve the accuracy of the calculation. The school experiment uses glycerine as the fluid, and the technique is used industrially to check the viscosity of fluids used in processes. It includes many different oils, and polymer liquids such as solutions.

In 1851, George Gabriel Stokes derived an expression for the frictional force (also called drag force) exerted on spherical objects with very smallReynolds numbers (e.g., very small particles) in a continuous viscous fluid by changing the small fluid-mass limit of the generally unsolvableNavier-Stokes equations:

$$F = 6\pi r \eta v$$

where:

- ✓ F is the frictional force,
- ✓ r is the radius of the spherical object,
- ✓ η is the fluid viscosity, and
- ✓ v is the particle's velocity.

If the particles are falling in the viscous fluid by their own weight, then a terminal velocity, also known as the settling velocity, is reached when this frictional force combined with the buoyant force exactly balance the gravitational force. The resulting settling velocity (or terminal velocity) is given by:

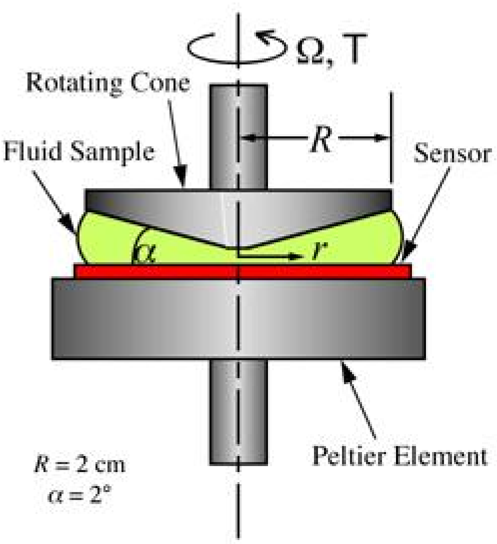
$$V_s = \frac{2}{9}\frac{r^2 g(\rho_p - \rho_f)}{\mu}$$

where:
V_s is the particles' settling velocity (m/s) (vertically downwards if $\rho_p > \rho_f$, upwards if $\rho_p < \rho_f$),
r is the Stokes radius of the particle (m),
g is the gravitational acceleration (m/s^2),
ρ_p is the density of the particles (kg/m^3),
ρ_f is the density of the fluid (kg/m^3), and
μ is the (dynamic) fluid viscosity (Pa s).

Rotational viscometers

Rotational viscometers use the idea that the torque required to turn an object in a fluid is a function of the viscosity of that fluid. They measure the torque required to rotate a disk or bob in a fluid at a known speed.

'Cup and bob' viscometers work by defining the exact volume of a sample which is to be sheared within a test cell; the torque required to achieve a certain rotational speed is measured and plotted. There are two classical geometries in "cup and bob" viscometers, known as either the "Couette" or "Searle" systems - distinguished by whether the cup or bob rotates. The rotating cup is preferred in some cases because it reduces the onset of Taylor vortices, but is more difficult to measure accurately in instrument 'Cone and Plate' viscometers use a cone of very shallow angle in bare contact with a flat plate. With this system the shear rate beneath the plate is constant to a modest degree of precision and deconvolution of a flow curve; a graph of shear stress (torque) against shear rate (angular velocity) yields the viscosity in a straightforward manner.



Cone and plate Viscometer

UNIT-V

Dispersion system

- **Colloidal dispersion**
  - Brief introduction to colloids
  - Type and application in pharmacy
- **Suspension**
  - Settling in suspension
  - Theory of sedimentation
  - Effect of Brownian movement
  - Sedimentation of flocculated particles
  - Sedimentation parameters
  - Wetting of particles
  - Controlled flocculation
  - Flocculation in controlled vehicles
  - Rheological considerations
- **Emulsions**
  - Theories
  - Physical stability

DISPERSE SYSTEMS

- The term "Disperse System" refers to a system in which one substance (The Dispersed Phase) is distributed, in discrete units, throughout a second substance (the continuous Phase or vehicle).
- Each phase can exist in solid, liquid, or gaseous state

Classification of Dispersed Systems

Class	Range of particle size	Characteristics of the system	Examples
Molecular Dispersion	Less than 1.0nm (mμ)	Invisible in SEM, pass through ultra filters	Oxygen molecules, ordinary ions, Glucose
Colloidal Dispersion	1.0nm to 0.5μm	Could be detected under SEM	Colloidal silver solution
Coarse Dispersion	Greater than 0.5μm (μ)	Visible under microscope, not pass through normal filter	

Colloidal dispersion

- Colloidal systems are a kind of dispersed system in which the size of dispersed phase particles is less than 1 micron.
- A colloid is a solution that has particles ranging between 1 and 1000 nanometers in diameter, yet is still able to remain evenly distributed throughout the solution.
- These are also known as colloidal dispersions because the substances remain dispersed and do not settle to the bottom of the container.
- Colloidal system or colloidal dispersion is a heterogeneous system which is made up of Dispersed phase and Dispersion medium.
- In colloidal dispersion one substance is dispersed as very fine particles in another substance called dispersion medium. In case of dust, solid particles are dispersed in air as dispersion medium.

Types of Colloidal Dispersions

- ✓ Homogenous colloidal system - lyophilic dispersion.
- ✓ Heterogenic colloidal system – lyophobic dispersion
- ✓ Amphiphilic (this colloidal dispersion is formed by association of molecules that exhibit both lyophilic and lyophobic properties.)

- Dispersed phase and dispersion medium can be solid, liquid or gas. Depending upon the state of dispersed phase and dispersion medium, eight different types of colloidal dispersions can exist.

Eight Different **Types of Colloidal Dispersions** are:

1. Foam
2. Solid foam
3. Liquid Aerosol
4. Emulsions
5. Gels
6. Solid Aerosol
7. Sol (Colloidal suspension)
8. Solid sol (Solid suspension)

Properties of colloid dispersion

Optical Properties

- ✓ Particles are visible only by ultramicroskop or electron microskop – Brown motion.
- ✓ Dispersion of passing light (Tyndall efect).

Kinetic Properties

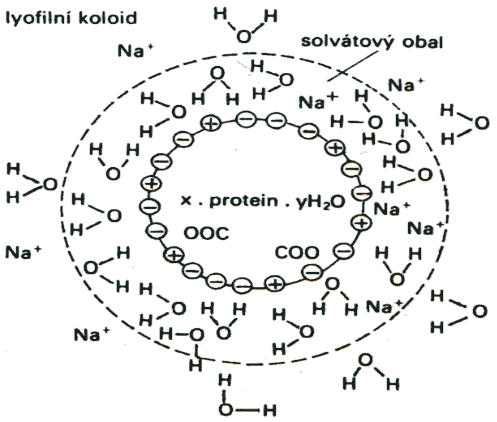
- ✓ They do not sedimentate, pass through common filters (but not through semipermeable membrane).
- ✓ Brownian motion
- ✓ Viscosity
- ✓ Diffusion
- ✓ Produce osmotic pressure

Electrical Properties

- ✓ Electrokinetics Phenomena

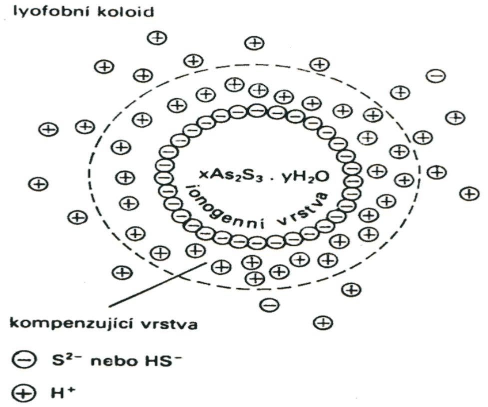
Lyophilic colloids

- Lyophilic particles are mixed with the suitable solvent. Particles have high affinity to the solvent.
  - High force of attraction exists between colloidal particles and liquid.
  - This result in formation of very stable solution called lyophilic sol.
  - Attraction forces (solvate cover) stabilize lyophilic colloid, defense their clustering to the larger complexes



Lyophobic colloid

- ✓ Colloid particles do not have affinity to the molecules of solvent
- ✓ Mostly complexes of inorganic particles which do not have affinity to the solvent
- ✓ They are prepared by artificial dispersion - $Fe(OH)_3$, As_2S_3



Method of preparation of colloidal dispersion

1-Condensation Method: by-

- ✓ Solven removal
- ✓ Electrochemical method

2-Dispersion method:by

- ✓ Ball mill
- ✓ Micronizer
- ✓ Homogenizer

Pharmaceutical Applications

1) In Therapy— Colloidal system are used as therapeutic agents in different areas.

- ✓ Example- Silver colloid-germicidal
- ✓ Copper colloid-anticancer
- ✓ Mercury colloid-Antisyphilis

2) Stability—

- ✓As already stated, charges play an important role in determining the stability of a colloidal system.
- ✓Colloids, especially lyophobic colloids having like charges on particle surface repel each other and prevent flocculation in suspensions.
- ✓e.g- Colloidal dispersion of gelatin is used in coating over tablets and granules which upon drying leaves a uniform dry film over them and protect them from adverse conditions of the atmosphere.

3) Absorption—

- ✓As colloidal dimensions are small enough, they have a huge surface area. Hence, the drug constituted colloidal form is released into the vicinity in large amount.
- ✓e.g- sulphur colloid gives a large quantity of sulphur and this often leads to sulphur toxicity.

4) Dissolution —

- ✓ Due to huge surface area, the dissolution rate is very large as stated by Noyes-Whitney equation.

$$dC/dT=DA(Cs-Cb)/Ln$$

5) Targeted Drug Delivery—

- ✓Liposomes are of colloidal dimensions and are preferentially taken up by the liver and spleen. Hence, principle of colloids is also used in targeted drug delivery system.

SUSPENSION

- ➢ A suspension: is a disperse system in which one substance (the disperse phase) is distributed in particulate form throughout another (the continuous phase) .
- ➢ Mixture of two substances, one of which is finely divided and dispersed in the other.

Suspensions: may be

- ✓ S-S,
- ✓ L-S (OR S-L),
- ✓ G-S

Colloidal suspension > 1 nm to 0.5 µm

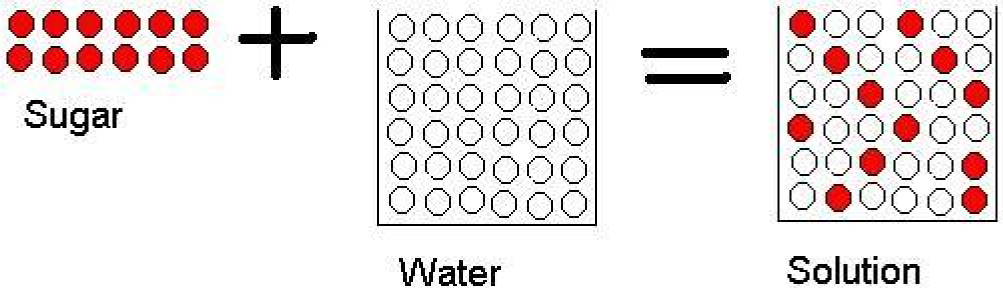
Coarse suspension > 1 to 100 µm

- ➢ A suspension of liquid droplets or fine solid particles in a gas is called an aerosol.
- ➢ Blood is an example of suspensions

- ➢ Suspensions are useful for administering insoluble or poorly soluble drugs or in situations when the presence of a finely divided form of the material in the GI tract is required.

The Difference Between Solution & Suspensions

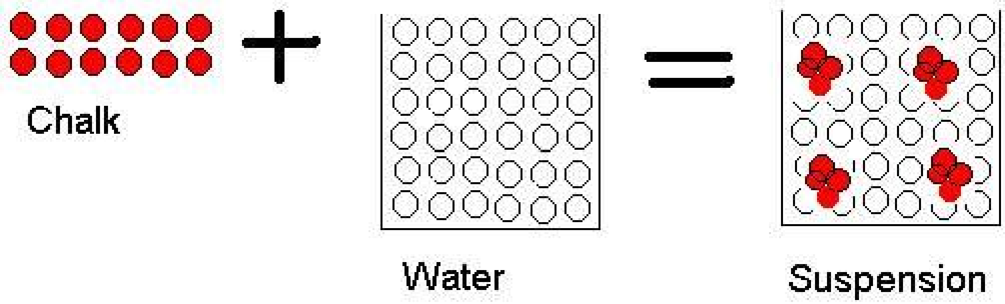
- ✓ When the 2 substances totally mix it is called a solution.
- ✓ E.g. Solute + Solvent = Solution
- ✓ (sugar) + (water) = Solution



We then say sugar is soluble in water, it has dissolved

Suspensions

- ✓ Sometimes when we mix substances they stay in clusters. We therefore say it is insoluble in water.
- ✓ E.g. Chalk + Water = Suspension



- ✓ Eventually the particles sink to the bottom to form sediment

Uses of Suspensions

- ✓ To administer an insoluble compound as a liquid.
- ✓ To lessen the unpleasant taste of an insoluble compound by:
  - formulating a vehicle in which the drug is not soluble
  - using an insoluble form of the drug (ie. salt form or prodrug)
  - adsorbing the drug onto an insoluble carrier
- ✓ To modify the release rate of the drug.
- ✓ To improve the stability by reducing the fraction of drug in solution

Properties of an Ideal Suspension are:

- Uniform dispersion
- Palatable
- Pleasing odor and color
- No grittiness
- Easy to pour yet not watery
- No cap-lock
- Temperature insensitive
- Particles should settle slowly
- Formulation should allow the easy redispersion of sedimented particles
- A flocculated suspension is desirable than a deflloculated suspension
- A suspension should not be too viscous to reduce the sedimentation rate

Routes of Administration

- ✓ Oral
- ✓ Ocular
- ✓ Rectal
- ✓ Parenteral
- ✓ Topical

Examples of Pharmaceutical Suspensions

1. Antacid oral suspensions
2. Antibacterial oral suspension
3. Dry powders for oral suspension (antibiotic)
4. Analgesic oral suspension
5. Anthelmentic oral suspension
6. Anticonvulsant oral suspension
7. Antifungal oral suspension

Preparation of suspension

- ✓ Large scale: colloid mill
- ✓ Small scale by mortar and pestle
- ✓ Witting agents: alcohol, glyrecin (hygroscopic liquids

METHODS OF PREPARATION

(1) use of controlled flocculation .

(2) use of structured vehicle.

Packaging and Storage of Suspensions

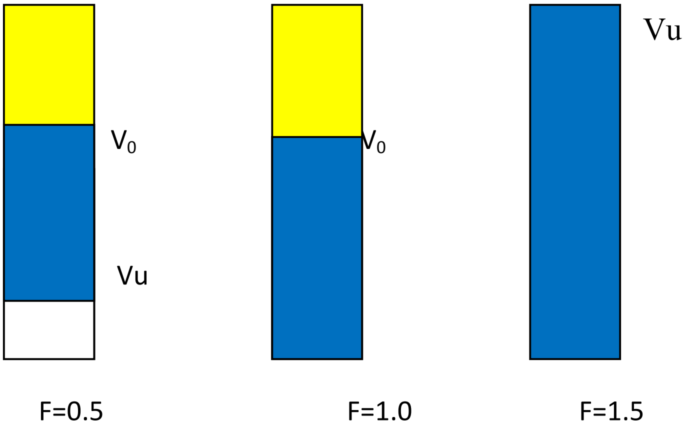
1. Should be packaged in wide mouth containers having adequate air space above the liquid.
2. Should be stored in tight containers protected from:
   - ✓ freezing.
   - ✓ excessive heat & light.
3. Label: "**Shake Before Use**" to ensure uniform distribution of solid particles and thereby uniform and proper dosage.

FACTORS TO BE CONSIDERED

- ✓ Sedimentation.
- ✓ Particle size.
- ✓ Nernst and zeta potential.
- ✓ Deflocculation and flocculation.
- ✓ Electrokinetic Properties.
- ✓ Density of the vehicle.
- ✓ Viscosity of the vehicle

Sediment Volume

$F=\{\text{volume of sediment } V_u\}/\{\text{original volume } V_o\}$



- ✓ Sedimentation volume-

  F = Vsed/Vtot

- ✓ The value of F normally lies between 0 to 1 for any pharmaceutical suspension.
- ✓ The value of F provides a qualitive knowledge about the physical stability of the suspension.
- ✓ Sedimentation equilibrium: Gravity is neutralized by Brownian movement

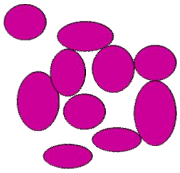
- The rate of sedimentation of a suspended phase depends on several factors which may be controlled by pharmaceutical manipulation. Assuming that all dispersed particles are of uniform shape and size and that the particles are sufficiently far apart so that the movement of one does not affect the neighboring particles, the rate of sedimentation can be estimated by Stoke's equation:

$$V = \frac{d^2(\rho_1 - \rho_2)g}{18\,\eta_o}$$

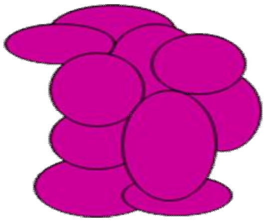
- where **V** is the sedimentation rate (cm/sec), d the diameter of the suspended particles (cm), r_1 its density and r_2 is the density of the medium (g/cm^3), g is the acceleration of gravity (980.7 cm/sec^2) and h_o is the viscosity of the external phase in poises (g/cm sec).

Settling & Aggregation

- The suspension shall form loose networks of **flocks** that settle rapidly, do not form cakes and are easy to resuspend.
- Settling and aggregation may result in formation of **cakes** (suspension) that is difficult to resuspend or phase separation (emulsion).



flocks



cake

Nernst potential

The difference in electric potential between the actual surface of the particle and the electroneutral region is referred to as Nernst potential

Deflocculation

- Deflocculation of particles is obtained when the zeta potential is higher than the critical value and the repulsive forces supersede the attractive forces.
- These deflocculated particles when sediment form a close packed arrangement with the smaller particles filling the voids between the larger ones. -SOLID HARD CAKE

Flocculation

- ✓ When this zeta potential goes below the critical value, the attractive forces supersede the repulsive forces and flocculation occurs.
- ✓ These loosely packed particles or floccs settle faster than the defflocculated particles because of their larger sizes.
- ✓ But unlike deffloculated particles this sediment of floccs does not form solid cake.
- ✓ This sediment of floccs is easy to redisperse by minute agitation.
- ✓ Degree of flocculation-

$$\text{ß} = F_{floc}/F_{defloc} = \frac{(V_{sed}/V_{tot})_{floc}}{(V_{sed}/V_{tot})_{defloc}}$$

- When the total volume of both the flocculated and the deflocculated suspensions are same, the degree of flocculation,

$$\text{ß} = (V_{sed})_{floc}/(V_{sed})_{defloc}$$

Difference between flocculated and deflocculated suspension

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

Controlled flocculation

Assuming that the powder is properly wetted and dispersed attention may now be given to the various means by which controlled flocculation may be produced so as to prevent compact sediment which is difficult to redisperse. Controlled flocculation can be described in terms of the materials used to produce flocculation I suspensions, namely, (i) electrolytes, (ii) surfactants, and (iii) polymers.

- Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta-potential and formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

- Example: When bismuth subnitrate is suspended in water it has been found (by electrophoretic studies) that they possess a large positive charge, or zeta potential. Because of the strong forces of repulsion between adjacent particles, the system remains in deflocculated (peptized) state. The addition of monobasic potassium phosphate (KH_2PO_4) to the suspension causes the positive zeta-potential to decrease owing to the adsorption of the negatively charged phosphate anion. The particles then can come closer to form aggregates.

- Surfactants both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical since these compounds may also act as wetting agents to achieve dispersion.
- Polymers are long chain, high molecular weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.

- hydrophilic polymers also acts as protective colloids and particles coated in this manner are less prone to cake than are uncoated particles.

Flocculation in structured vehicle

Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close to or equal to 1. So a suspending agent is added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth or bentonite have been employed, either alone or in combination.

These may lead to incompatibilities, depending on

(i) The initial particle charge
(ii) The charge carried by flocculating agent and
(iii) The charge carried by suspending agent.

Wetting of particles

The insoluble medicament may be :

- Diffusible solids (dispersible solids): These are insoluble solids that are light and easily wetted by water. They mix readily with water, and stay dispersed long enough for an adequate dose to be measured. After settling they redisperse easily. Examples include magnesium trisilicate, light magnesium carbonate, bismuth carbonate and light kaolin.
- Indiffusible solids: Most insoluble solids are not easily wetted, and some particles may form large porous clumps in the liquid, whereas others may remain on the surface. These solids will not remain evenly distributed in the vehicle long enough for an adequate dose to be measured. They may not redisperse easily. Examples for internal use includes aspirin, phenobarbital, sulfadirnidine and chalk, and for external use calamine, hydrocortisone, su1phur and zinc oxide.
- Because of the high interfacial tension between indiffusible solids and water; air may be trapped in these poorly wetted particles which causes them to float to the surface of the preparation and prevents them from being readily dispersed throughout the vehicle.
- Wetting of the particles can be encouraged by reducing the interfacial tension between the solid and the vehicle, so that adsorbed air is displaced from solid surfaces by liquid.
- Suitable wetting agents have this effect, but decrease inter-particular forces thereby affecting flocculation
- **Wetting agents:**
- Hydrophilic colloids such as acacia and tragacanth can act as wetting agents. However, care should be taken when using these agents as they can promote deflocculation.
- Intermediate HLB (hydrophilic-lipophilic balance) surfactants such as polysorbates (tweens) and sorbitan esters (spans) are used for internal preparations. Sodium lauryl sulphate and quillaia tincture are used in external preparations.
- Solvents such as ethanol, glycerol and the glycols also facilitate wetting.

Rheological Properties of Suspension)

Rheological consideration are important in

(i) The viscosity of a suspension as it affects the settling of particles. As viscosity increases rate of sedimentation of the particles reduces.

(ii) The change in flow properties of the suspension when the container is shaken and when the product is poured out off the bottle.

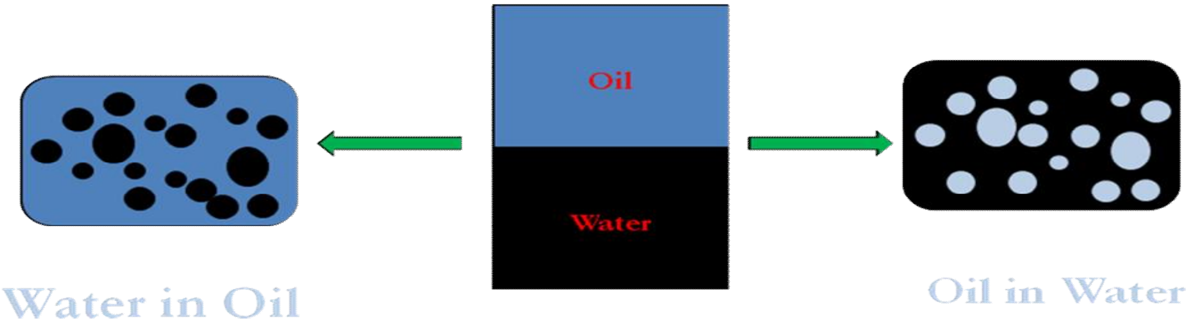
(iii) The spreading quality of the lotion when applied to the affected area.

(iv) During the manufacture of the suspensions.

- A thixotropic suspension is the one which is viscous during storage but loses consistency and become fluid upon shaking.
- A well-formulated thixotropic suspension would remain fluid long enough for the easy dispense of a dose but would slowly regain its original viscosity within a short time.

Emulsion

- Emulsion consists of two immiscible liquids one of which is uniformly dispersed throughout the other as droplets of diameter greater than 0.1μm.
- To prepare a stable emulsion a third phase, an emulsifying agent, is required.
- Emulsions is a useful way to present oils and fats in a palatable form.
- Emulsions for external use are known as a lotion



Emulsion Types

- Oil in Water, (O/W) the oil phase distributed as globules in the aqueous phase (continuous phase).
- Water in oil, (W/O) the water is distributed through out the oil phase (continuous phase).
- Pharmaceutical emulsion usually O/W emulsion.

Determining the type of emulsion

1. Water soluble dye to be dusted on the surface of the emulsion:
    - ■O/W the dye will be dissolve the color & diffuse through the system.
    - ■W/O, the dye will stay on as clumps on the tope of the emulsion.
    - ■Dilution of the emulsion with water, if the emulsion mixed freely with water, thus it is O/W

Pharmaceutical Applications of emulsion

1. Convenient of orally water insoluble liquids, when the dispersed phase has unpleasant taste.
2. Increase the absorption (some ingredients such as vitamins are absorbed completely when emulsified with emulsifying agent).
3. For patients how can’t getting medicine and nutrition's orally. (I.V Emulsion)
4. In many cosmetics preparations (dermatological products, lotions and creams) because the ability for spreading is high over the skin.
5. In diagnostic agents in x-ray examination.
6. In aerosols preparation for producing foams.
7. To prepare stable and homogeneous mixtures of two immiscible liquids.
8. It permits the administration of a liquid drug in a form of globules.
9. Reduce the droplet size of the oil, make it more readily absorbed.
10. If the active ingredients irritating the skin, are less irritant when used as internal phase

Ideal Emulsion

1. Colorless
2. Odorless.
3. Tasteless.
4. Non-toxic.
5. Non irritant.
6. Able to produce stable emulsions at low concentration.

Theories of Emulsification

- **Surface-tension theory**
- **Oriented-wedge theory**
- **Plastic or interfacial film theory**

Surface-tension theory

- All liquids have a tendency to assume a shape having the least amount of surface area exposed.
- For a drop of a liquid, it is a spherical shape.
- In the spherical drop of liquid there are internal forces which promote the association of the molecules to resist the distortion of the drop into a less spherical form
- If two or more drops of the same liquid come into contact with one another, the tendency is for them to join or to coalesce, making one large drop having less surface area.
- This tendency of liquids may be measured quantitatively, and when the surrounding of the liquid is air, it is referred to as **Liquid's surface tension.**

Oriented-wedge theory

- Assume monomolecular layers of emulsifying agent curved around a droplet of the internal phase of the emulsion.
- Certain emulsifying agents orient themselves about and within a liquid in a manner reflective of their solubility in the particular liquid.
- In a system containing two immiscible liquids, presumably the emulsifying agent would be preferentially soluble in one of the phases and would be embedded more deeply and strongly in that phase then the other
- This theory based on:
- emulsifying agent have a hydrophilic or water loving portion and a hydrophobic or oil loving portion.
- The molecules will position themselves into each phase.
- Depending on the shape and size of the molecules, their solubility characteristics and their orientation,
- the wedge-shape arrangement envisioned for the molecules will cause the surrounding of either oil globules or water globules

- No universal theory of emulsification.
- Because emulsion can be prepared using several different types of emulsifying agent, each of which depends for its action on a different principles to achieve a stable products.
- Any theory to be acceptable should explain the followings:
  1. The stability of the product.
  2. The type of emulsion formed.

What happened when two immiscible liquids are agitated together?

- ✓ Failure the two liquids to remain mixed, because :
- ✓ The cohesive force between the molecules of each separate liquid is greater than the adhesive force between the two liquids.
- ✓ The increase in the surface energy makes the system thermodynamically unstable,

Hence the droplets have a tendency to coalesce.

Emulsion stability – Stability to resist changes in its physicochemical properties with time.

Mechanisms of emulsion breakdown:

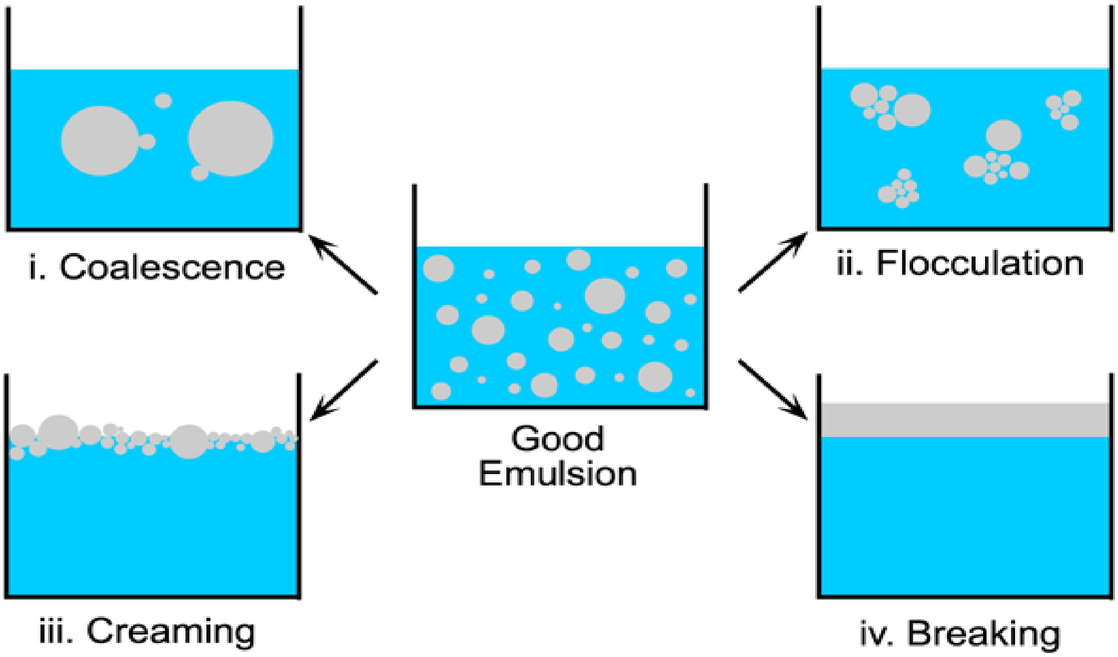
Creaming – the process in which droplets move upwards (droplets density < density of continuous phase)

Sedimentation - the process in which droplets move downwards (droplets density > density of continuous phase)

Flocculation– the process in which two or more droplets “stick” together to form an aggregate (but the droplets still retain their individual integrity)

Coalescence - the process in which two or more droplets merge together to form a single larger droplet.

Phase inversion – the process in which o/w emulsion changes to w/o emulsion, or vice versa.



- **Emulsion stability can be achieved by using**

  1-emulsifiers (surfactants) 2- stabilizers:

Emulsifiers –

- Compounds that facilitate the formation of emulsion by lowering the oil/ water interfacial tension & imparting shortterm stability by forming a protective film around the droplets.
- Emulsifiers, because of their amphiphilic nature, adsorb at the interface between oil & water & form an interfacial film reduction of interfacial tension

Stabilizers –

1--Compounds that are not (or only slightly) surface active but impart long-term stability to emulsions by restricting interfacial interactions.

2--The reduction of interfacial tension through addition of emulsifiers allows emulsion formation with considerably less energy input.