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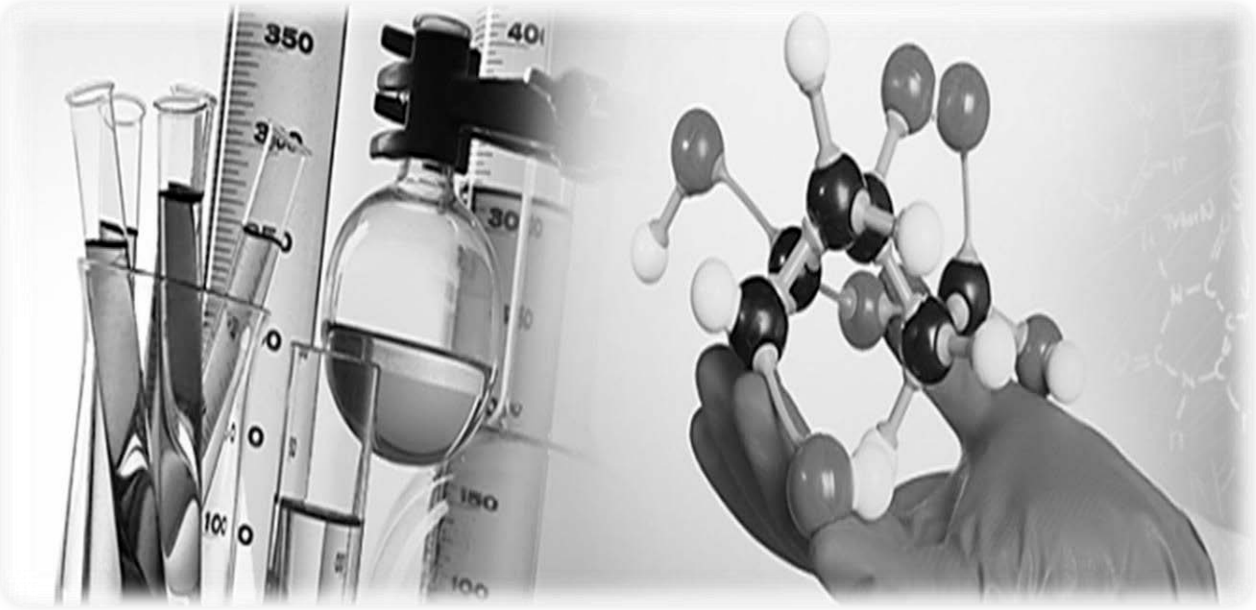
Faculty of Pharmacy
Menoufia University

Physical Pharmacy

For

First Year Pharmacy Students
Second Semester



By Staff Members Of
Pharmaceutical Technology Department

Menoufia University, Faculty of Pharmacy
Course Specifications

Physical Pharmacy
First Year, Second Semester

Professional Information

1. Overall aims of the course

Upon successful completion of this course, the students should be able to:

-Recognize the fundamental aspects of physical pharmacy.

-Elaborate the principles of solubility, surface and interfacial phenomena, rheology, adsorption and complexation.

2. Intended learning outcomes of the course (ILOs)

a- Knowledge and understanding:

Upon successful completion of the course, the graduate should be able to:

- a1- Classify buffers, colloids and complexes.
- a2- Define the solubility and solubilization.
- a3- Describe the interfacial phenomena and surface active agents.
- a4- Describe different types of flow.
- a5- Identify adsorption/desorption phenomena.
- a6- Identify the reaction kinetics and drug degradation pathways.

b- Intellectual skills:

- b1 - Calculate the buffer capacity and isotonicity.
- b2 - Determine the order of reaction.
- b3 - Utilize the fundamental basics of physical pharmacy in dosage form.

c- Professional and practical skills:

- c1 – Detrmine the surface tension and critical micelle concentration.
- c2 – Determine the viscosity, solubility and partition coefficient.
- c3- Recommend the proper storage conditions based on drug degradation pathway.
- c4- Determine the expiration date of drugs.

d- General and transferable skills:

- d1 – Work in groups.

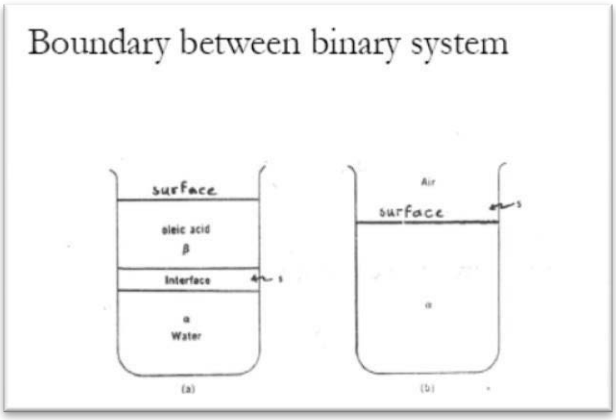
3. Teaching and learning methods

a. Lectures
b. Practical training / laboratory
c. Seminar / Workshop
d. Class Activity

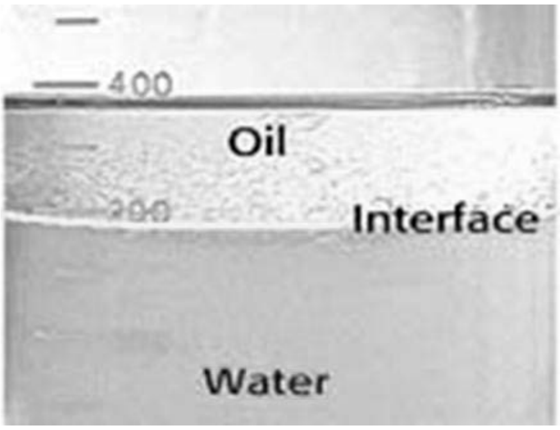
Surface and Interfacial Phenomena

Introduction

- *Interface* is the 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 interfaces can exist depending on whether the two adjacent phases are in solid, liquid or gaseous state.
- Types of boundaries:
- Gas/ Gas (vapour/vapour) v/v
- Liquid/ Liquid (L/L); e.g. oil and water in emulsion
- Liquid/ Vapor (L/V); e.g. water exposed to air
- Solid/ Vapor (S/V); e.g. table top exposed to air
- Solid/ Liquid (S/L); e.g. suspension



Boundary between binary system



Phases	Types and Examples of Interfaces and surfaces
Gas/gas	No interface
Gas/liquid	Liquid surface, water exposed to atmosphere
Gas/solid	Solid surface, table top in contact with atmosphere
Liquid/liquid	Interface, emulsion (oil/water)
Liquid/solid	Interface, suspension (solid suspended in a liquid
Solid/solid	Mixture of powder particles in contact.

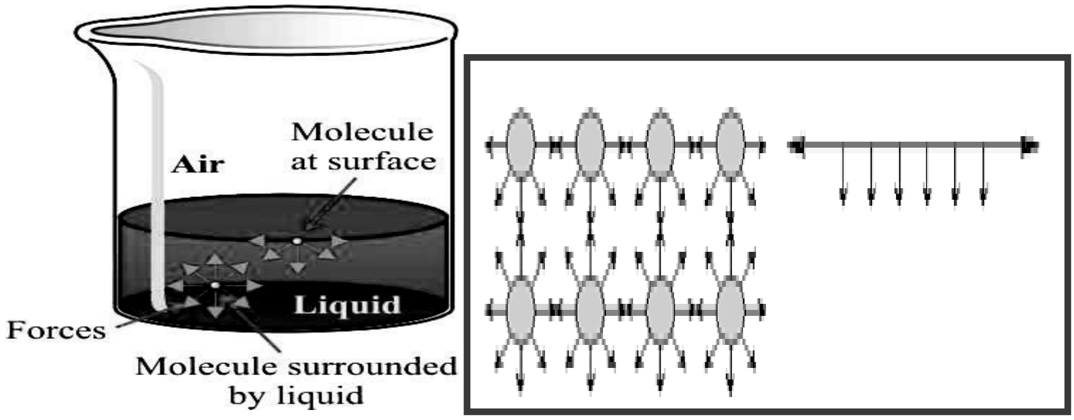
- ☐ Importance of Interfacial phenomena in pharmacy:
- ☐ Adsorption of drugs onto solid adjuncts in dosage forms.
- ☐ Penetration of molecules through biological membranes.
- ☐ Emulsion formation and stability.
- ☐ The dispersion of insoluble particles in liquid media to form suspensions.

Forces of Attractions:

- ☐ Cohesive forces: are the forces that exist between molecules of one phase (i.e. between like molecules).
- ☐ Adhesive forces: are the forces that exist between molecules of two different phases (i.e. between unlike molecules).
- ☐ MISCIBILITY: occurs when cohesive forces are less than adhesive forces, e.g. water and alcohol.
- ☐ IMMISCIBILITY: occurs when cohesive forces are more than adhesive force e.g. water and oil.
- ☐ WETTABILITY: occurs when adhesive forces are more than cohesive force e.g. water and solids

LIQUID INTERFACES

Surface and Interfacial Tensions



- In the liquid state, the cohesive forces between adjacent molecules are well developed.

- For the molecules in the bulk of a liquid

- They are surrounded in all directions by other molecules for which they have an equal attraction.

- For the molecules at the surface (at liquid/air interface)

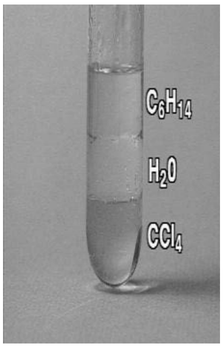
- Only attractive cohesive forces with other liquid molecules which are situated below and adjacent to them.

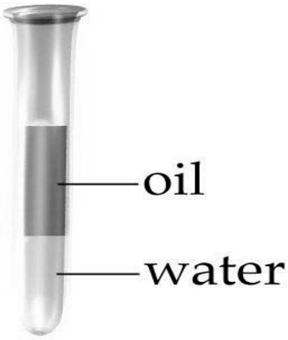
- They can develop adhesive forces of attraction with the molecules of the other phase in the interface

- The net effect is that the molecules at the surface of the liquid experience an inward force towards the bulk of the liquid and pull the molecules and contract the surface with a force F.

- To keep the equilibrium, an equal force must be applied to oppose the inward tension in the surface.

- Thus SURFACE TENSION [γ] is the force per unit length that must be applied parallel to the surface so as to counterbalance the net inward pull and has the units of dyne/cm





- INTERFACIAL TENSION: is the force per unit length existing at the interface between two immiscible liquid phases and has the units of dyne/cm.

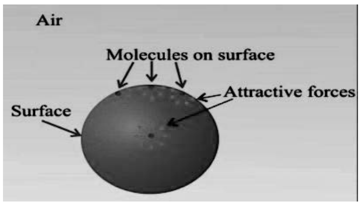
- Interfacial tension is less than surface tension because an adhesive forces, between the two liquid phases forming the interface are greater than when a liquid and a gas phase exist together.

- If two liquids are completely miscible, no interfacial tension exists.

- High surface tension reflects high intermolecular attraction force. So increase in hydrogen bonds or molecular weight causes increase in ST.

$$\mathbf{W = \gamma \, \Delta \, A}$$

- The work W required to create a unit area of surface is known as SURFACE FREE ENERGY/UNIT AREA (ergs/cm2)



- erg = dyne . cm

- It is equivalent to the surface tension γ. Thus the greater the area A of interfacial contacts between the phases, the greater the free energy.

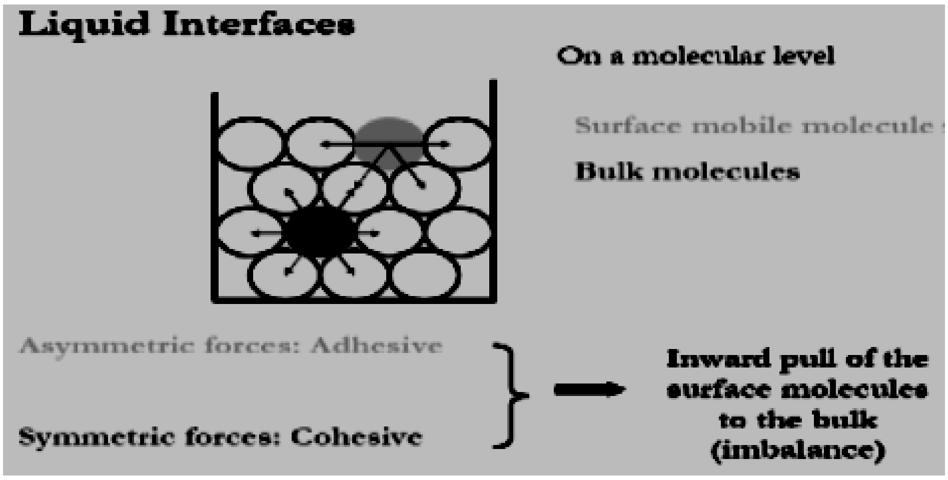
<u>Note : Liquid interfaces</u>

- At the bulk of the liquid;

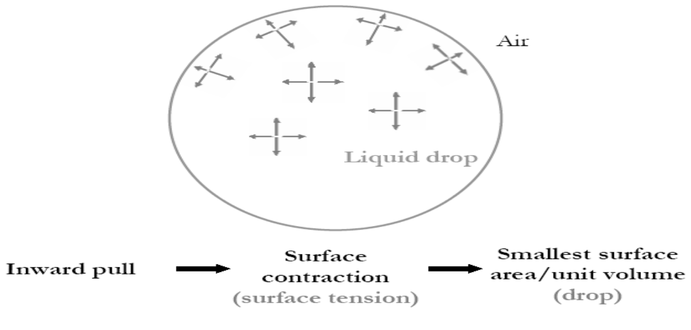
Molecules in the interior experience an attractive force from neighboring molecules which surround on all sides

- At the liquid surface;

Molecules on the surface have neighboring molecules only on one side and thus experience an attractive force which tends to pull them into the interior



- The net effect is that the molecules at the surface of the liquid experience an inward force toward the bulk of the liquid.
- Such force results in what is called Surface Tension.
- Due to this unbalanced forces, the surface of the liquid behaves like a stretched elastic membrane containing the molecules of the liquid inside.
- Since the liquid tends to contract to a minimum area, the surface of the liquid appears to be in a state of tension, so in order to increase the area of the surface it is necessary to do work to bring the molecules from the bulk of the liquid to the surface against the inward attractive force.
- Due to these unbalanced forces the liquid tends to adjust itself to give a minimum surface area, which takes the form of a sphere and for this reason
- Liquid rises in capillary tubes
- Droplets acquire spherical shape



Note: Surface Energy vs. Surface Tension

- For liquids, Surface Tension = Surface Energy
- For solids, the tension depends on the crystal structure of the surface ⇒ surface tension is inhomogeneous.

- Hence, “surface tension” should be used for interfaces involving fluid phases, whereas for interfaces involving solids, “surface energy” should be used.
- The surface free energy and surface tension are numerically equal and dimensionally equivalent.

$$\gamma = \frac{W}{\Delta A} = \frac{erg}{cm^2} = \frac{dyne \times cm}{cm^2} = \frac{dyne}{cm}$$

- Therefore, water has a surface tension of 72.8 dyne/cm and a surface free energy of 72.8 erg/cm^2

Note: Adhesional and cohesional forces

- Adhesional forces: Are forces which act between molecules of different phases.
- Cohesional forces: Are forces which act between molecules of the same phase.
- Cohesional force tend to keep the phases separate while adhesional forces tend to increase the affinity of two phases
  - if Adhesive force > cohesive force
    - Wetting
    - Spreading
    - Rising in the tube

Measurement of surface and interfacial tension

- Methods for measuring surface and interfacial tension
  - 1- Capillary rise method
  - 2- Ring (Du Nouy) tensiometer
  - 3- Drop weight method (Stalagmometer)
- The choice of the method for measuring surface and interfacial tension depend on:
  - Whether surface or interfacial tension is to be determined.
  - The accuracy desired

✓ The size of sample.

Capillary Rise Method

- When a capillary tube is placed in a liquid, it rises up the tube a certain distance. By measuring this rise, it is possible to determine the surface tension of the liquid. It is not possible, to obtain interfacial tensions using the capillary rise method.
- Cohesive force is the force existing between like molecules in the surface of a liquid
- Adhesive force is the force existing between unlike molecules, such as that between a liquid and the wall of a glass capillary tube
- When the force of Adhesion is greater than the cohesion, the liquid is said to wet the capillary wall, spreading over it, and rising in the tube.

$$\gamma = \frac{1}{2} hrdg$$

Where:

γ is the surface tension of the liquid (dyne/cm).

h is the height of liquid in the capillary tube (cm).

r is the radius of the capillary tube (cm).

d is the density of the liquid (g/cm3).

g is the acceleration due to gravity (980 cm/sec2).

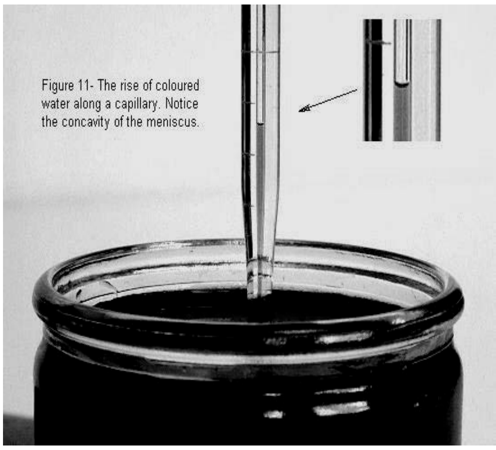
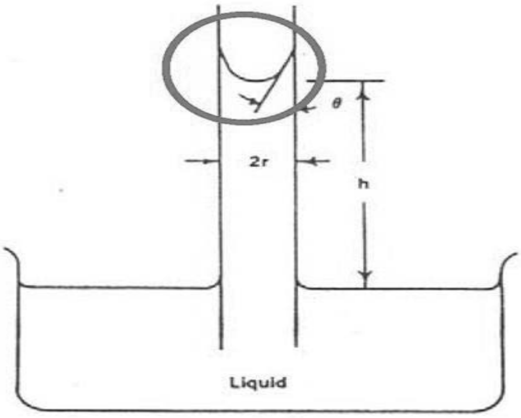
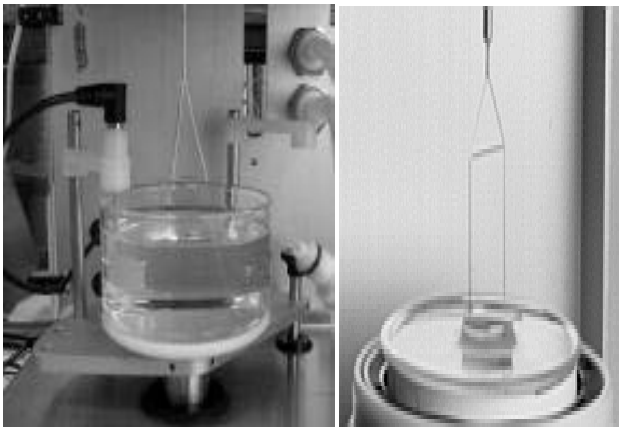


Figure 11- The rise of coloured water along a capillary. Notice the concavity of the meniscus.



Ring method (Du Nouy Tensiometer)

- ❑ Used for measuring the surface and interfacial tension
- ❑ The principle of the instrument depends on the fact that: 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 of detachment is recorded in dynes on a calibrated dial



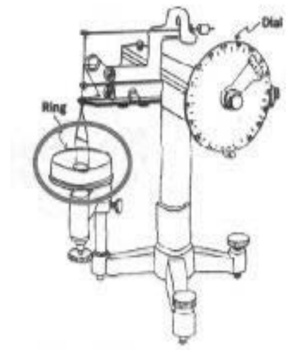
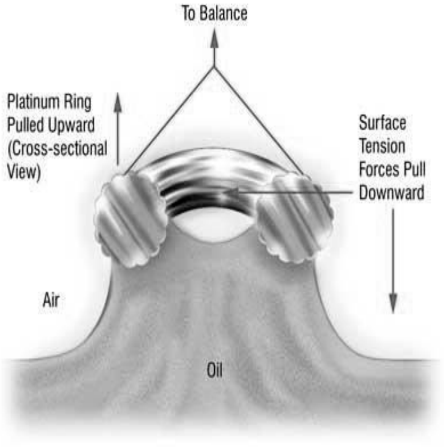
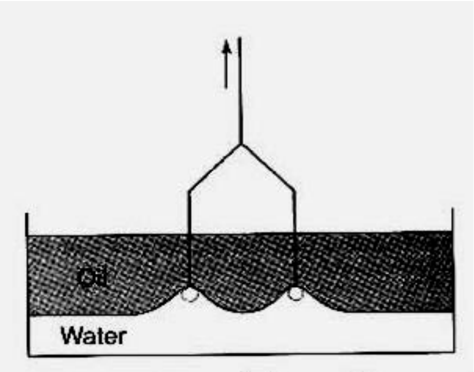


Fig. 16-5. Cenco DuNouy tensiometer





- ❑ The surface tension is given by:

$$\gamma = F / 2\pi (R_1 + R_2)$$

Where: F = the detachment force, R1 and R 2= the inner and outer radii of the ring.

Drop Weight and drop volume method

- ❑ If the volume or weight of a drop as it is detached from a tip of known radius is determined, the surface and interfacial tension can be calculated from

$$\gamma = \frac{\Phi\, mg}{2\pi r} = \frac{\Phi\, V\, pg}{2\pi r}$$

Where

m = the mass of the drop

p = the density of the liquid

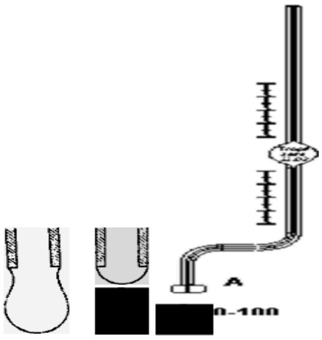
g = the acceleration due to gravity

V = the volume of the drop

r = the radius of the tip

Φ = a correction factor

- ☐ The correction factor is required as not all the drop leaves the tip on detachment
- ☐ The tip must be wetted by the liquid so as the drop doesn't climb the outside of the tube.



Pharmaceutical Application of surface tension

- ☐ The surface tension, and consequently the contact angle, of liquids are very important in:
  - ✓ Preparation of suspension; wetting of insoluble powders so as to prepare suspension.
  - ✓ Preparation of Emulsion, mixing of immiscible liquids.
  - ✓ Granulation, prior to tableting, involve the mixing of powder with a liquid binder.
  - ✓ Film coating of tablets
  - ✓ Successful dissolution of tablet or capsules necessitates penetration of liquid into pores in the dosage form.
  - ✓ Spreading of lotion on the skin surface.
  - ✓ Spreading of ointment in the eye.
  - ✓ Spreading of disinfectant on micro-organism surface.

CONCLUSION

- ☐ The physical and chemical behavior of liquids cannot be understood without taking surface tension into account.

- ☐ It governs the shape that small masses of liquid and the degree of contact a liquid can make with another substance.
- ☐ To perform the previous pharmaceutical process we need to reduce the surface tension, so as to reduce the contact angle and increase the spreading of the material
- ☐ HOW CAN WE REDUCE THE SURFACE TENSION?

Spreading

- ☐ If a small quantity of an immiscible liquid is placed on a the surface of another liquid, it may
  - ✓ spread to cover the surface with a film or
  - ✓ remain as a drop
- ☐ Spreading of a liquid on the surface of another occurs when the work of adhesion between the two liquids exceeds the work of cohesion between the molecules of each liquid.

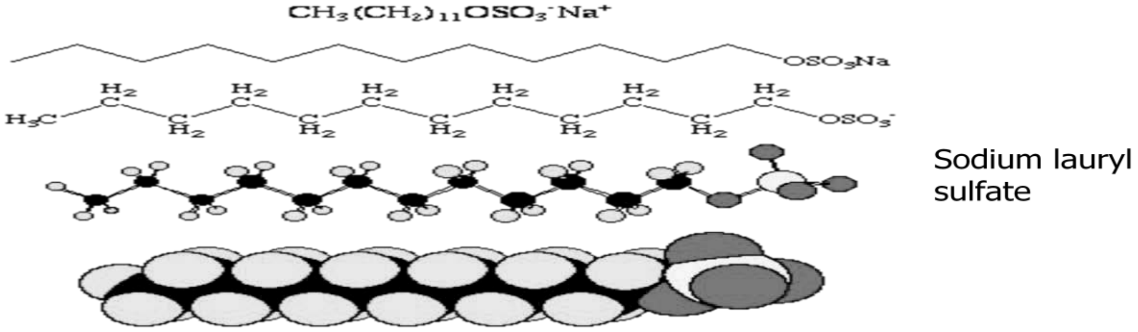
Spreading coefficient

- ☐ The ability of one liquid to spread over another can be assessed in terms of the spreading coefficient (S)
  - ✓ A positive value of spreading coefficient is required for spreading to occur.
  - ✓ If spreading coefficient is negative value, the substance forms globules or a floating drop.
- ☐ Spreading is important for products meant for external application such as lotions, creams,….these should be able to spread freely and evenly on the skin.

Surfactants
(surface active agents SAA)

- ❑ Surfactants are compounds that lower the surface tension of a liquid, the interfacial tension between two liquids, or that between a liquid and a solid.
- ❑ Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants.
- ❑ These agents perform their function by:
  - ✓ Reduction of the surface free energy.
  - ✓ Reduction of surface tension
  - ✓ Reduction of interfacial tension
  - ✓ Increasing the spreading coefficient
- ❑ Surfactants are usually organic compounds that are amphiphilic (contain both hydrophobic and hydrophilic groups). Therefore, a surfactant molecule contains polar part and non-polar part.
- ❑ Surfactant molecules will diffuse in water and adsorb at interfaces between air and water or at the interface between oil and water, in the case where water is mixed with oil
- ❑ Surfactants reduce the surface tension of water by adsorbing at the liquid-gas interface. The decrease in surface tension depends on the number of adsorbed molecules per unit area.

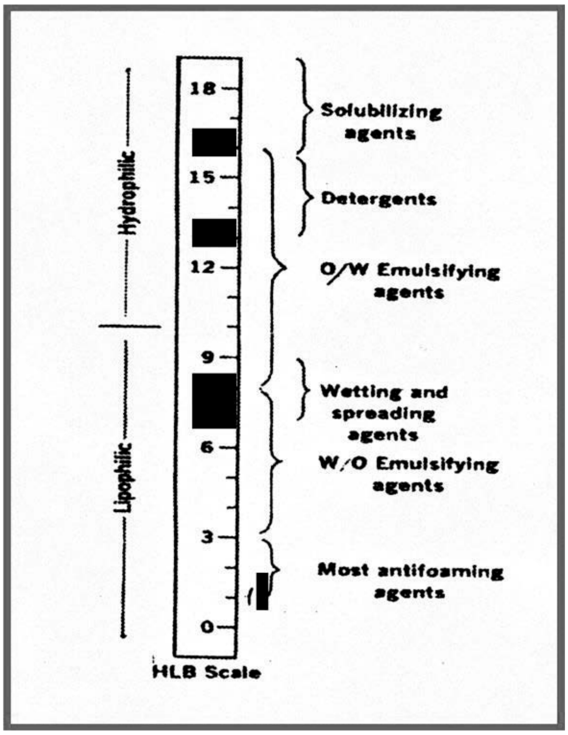
A surfactant molecule



- It is the amphiphilic nature of surface active agents which causes them to be adsorbed at interfaces, whether these are liquid/gas or liquid/liquid.
- Depending on the number and nature of the polar and nonpolar groups present, the amphiphile may be hydrophilic, lipophilic or be reasonably well-balanced between these two extremes. This is expressed as Hydrophilic Lipophilic Balance (HLB).

Hydrophilic-Lipophilic Balance (HLB)

- It is an arbitrary scale from 0 to 18 introduced by Griffin (Griffin's scale) to measure the Hydrophilic/Lipophilic properties of surfactants.
- The higher the number the greater the hydrophilicity and vice versa.
- Low HLB surfactants are more oil soluble.
- High HLB represents good water solubility.
- A scale showing classification of surfactant function on the basis of HLB values of surfactants.
- The higher the HLB of a surfactant the more hydrophilic it is.
- Example: Spans with low HLB are lipophilic. Tweens with high HLB are hydrophilic.



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

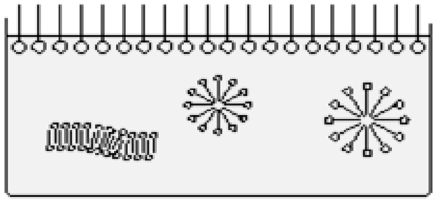
$$HLB = E / 5$$

- By splitting the various surfactants molecules into their component group (Davis Method):

$$HLB = \sum (\text{hydrophilic group No.}) - \sum (\text{lipophilic group No.}) + 7$$

Oriented adsorption of surfactant at interfaces

- As a Surface active substance contains a hydrophilic and a hydrophobic portions, it is adsorbed as a monolayer at the interfaces.
- At water-air interface surfactant molecules will be adsorbed at water-air interfaces and oriented so that the hydrocarbon chains are pushed out of the water while the polar groups are inside the water. Perhaps the polar groups pull the hydrocarbon chains partly into the water.



- **At low surfactant concentrations:**

The hydrocarbon chains of surfactant molecules adsorbed in the interface lie nearly flat on the water surface.

- **At higher concentrations:**

They stand upright because this permits more surfactant molecules to pack into the interfacial monolayer.

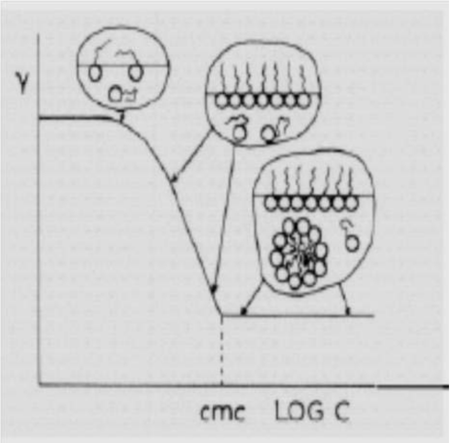
As the number of surfactant molecules adsorbed at the water-air interface increased, they tend to cover the water with a layer of hydrocarbon chains. Thus, the water-air interface is gradually transformed into an non polar-air interface. This results in a decrease in the surface tension of water.

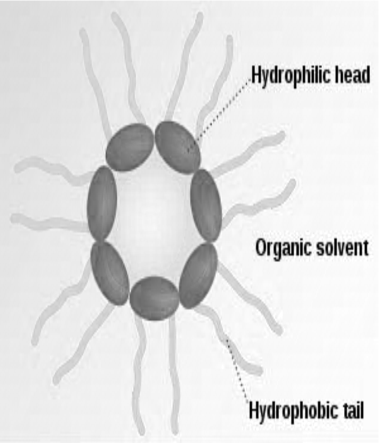
Micelle formation

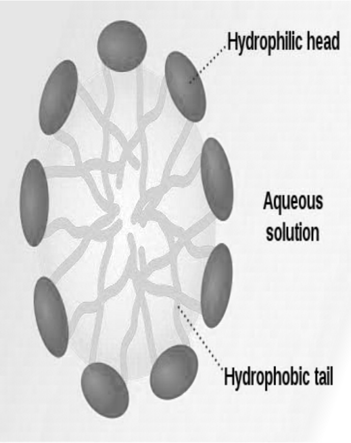
- When the surfactant molecules adsorbed as a monolayer in the water-air interface have become so closely packed that additional molecules cannot be accommodated, the polar groups pull the hydrocarbon chains partly into the water.
- At certain concentration the interface and the bulk phase become saturated with monomers. Excess surfactants added will begin to agglomerate in the bulk of the solution forming aggregates called micelles and the free energy of the system is reduced
- The lowest concentration at which micelles first appear is called the critical micelle concentration [CMC]

Critical micelle concentration can (CMC) be defined as:

- The concentration of surfactant at which the micelles are formed.
- The concentration of surfactant after which the surfactant added has no effect on surface tension.
- The concentration at which the surface of solution becomes completely saturated with SAA
- The concentration of surfactant at which a dramatic change in physicochemical properties of solution occur.







Micelle formation

- At a given concentration, temperature, and salt content, all micelles of a given surfactant usually contain the same number of molecules, i.e. they are usually monodisperse.

- For different surfactants in dilute aqueous solutions, this number ranges approximately from 25 to 100 molecules.

- The diameters of micelles are approximately between 30 and 80 Ao. Because of their ability to form aggregates of colloidal size, surfactants are also called association colloids.

- Micelles are not permanent aggregates. They form and disperse continually.

- Normal spherical micelles :

In dilute aqueous solutions micelles are approximately spherical. The polar groups of the surfactants are in the periphery and the hydrocarbon chains are oriented toward the center, forming the core of the micelles

- Inverted spherical micelles:

In solvents of low polarity or oils micelles are inverted. The polar groups face inward to form the core of the micelle while the hydrocarbon chains are oriented outward

Shape of micelles

- Inverted micelles

- Cylindrical and lamellar micelles

In more concentrated solutions of surfactants, micelles change from spherical either to cylindrical or lamellar phase.

Factors affecting CMC

- **For ionic surfactants:**

The CMC are higher for ionic than nonionic surfactants. The charges in the micelle of ionic surfactant are in close contact. To overcome the resulting repulsion an electric work is required. In contrast, nonionic surfactants have no electric repulsion to overcome in order to aggregate.

- **Effect of electrolytes on the CMC of ionic surfactants**

The addition of salts to ionic surfactant solutions reduces the electric repulsion between the charged groups and lower CMC values.

Effect of Surfactant's structure on CMC

- **Branched chain systems and double bonds raise CMC**
  - Since the chains must come together inside the micelles.
- **Length of hydrocarbon chain and polarity of Surfactants**
  - Increase in chain length of hydrocarbon facilitate the transfer from aqueous phase to micellar form cause decrease in CMC
  - Greater interaction with water will retard micelle formation thus ionized surfactants have higher CMC in polar solvents than nonionic surfactants.

In polar solvent	
↑ Polarity of Surfactant molecules	↑ CMC
↑ Length of hydrocarbon chain	↓ CMC
In non-polar solvents	
↑ **Polarity of Surfactant molecules**	↓ **CMC**
↑ **Length of hydrocarbon chain**	↑ **CMC**

Application of Solubilization by Micellization in Pharmacy

- **1. vitamin preparations**
  - Administration of oil soluble vitamins which otherwise be unpleasant for infants or children.
  - In addition, vitamin preparations are liable to oxidation and solubilized vitamin is more stable than oily solution.
  - Examples; vitamin D and E are solubilized by nonionic surfactants
- **2. Solubilization of oil soluble drugs as progesterone.**
- **3. Hormones and anti-inflammatory agents taken by injections.**
- **4. Oily solutions may be used but modern dermatological practice is to use water washable solution**

Classification of surfactants:

a- Functional classification

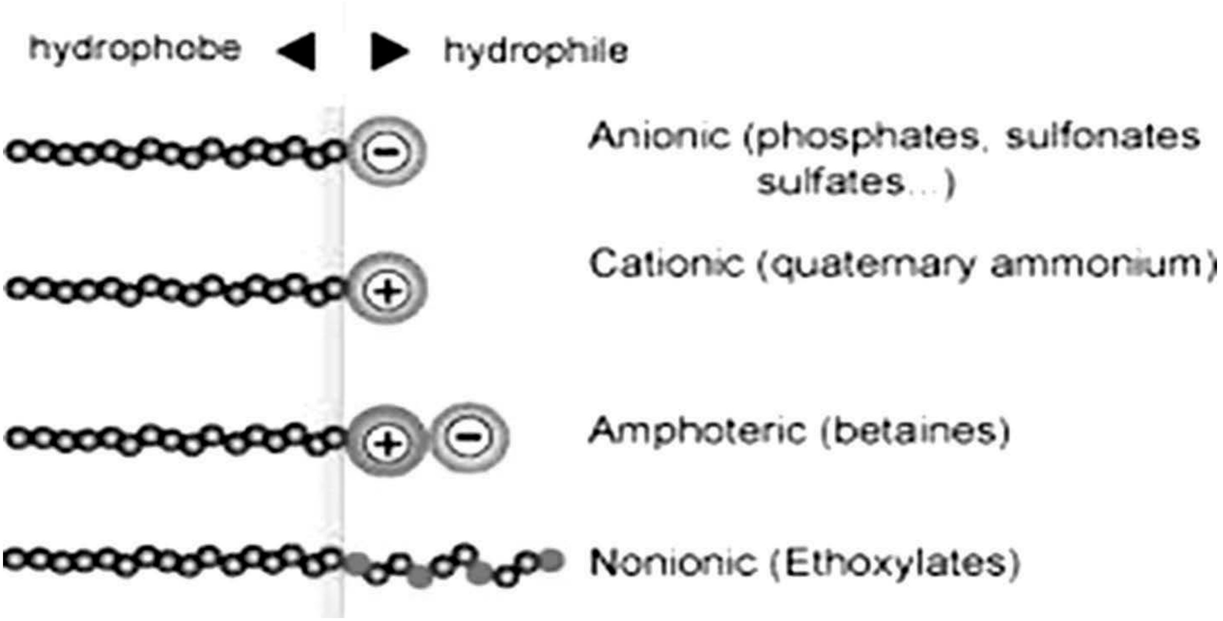
- If you know HLB value, you can determine surfactant suitability as:

- ✓ Anti-foam agent (HLB=1-3)
- ✓ Emulsifying agent w/o (HLB=3-8)
- ✓ Wetting/spreading agent (HLB=7-9)
- ✓ Emulsifying agent o/w (HLB=8-16)
- ✓ Solubilising agent (HLB>16)
- ✓ Detergent (HLB=13-16)

b- Structural classification

❑ **According to polarity:**

- A. Ionic
    - Anionic
        - Soaps (alkali soaps, metallic soaps and amine soaps).
        - Sulfuric acid esters (sulfated compounds)
    - Cationic
        - Simple amine salts
        - Quaternary ammonium salts
- B. Nonionic (ester linkage, ether linkage or ester-ether linkage)
- C. Ampholytic (zwitterionic).



Anionic surfactants

- Ionize in water and possess anion as the active part of the molecule.

A- Soaps

  - These are salts of long chain fatty acids

- **1. Alkali soaps**
  - Prepared from fatty acids having 12-18 carbon atoms with monovalent bases of sod, pot or ammonium.

(e.g. sodium stearate) $C_{17}H_{35}COONa \longrightarrow C_{17}H_{35}COO^- + Na^+$

- Disadvantages
  - Sensitive to hard water (no calcium tolerance).
  - Incompatible with acidic drugs.
  - Temperature sensitive:
    - ❖ Soap micelles break at high temperature and the system converts to true solution.
- **2. Metallic soaps**
  - These are soaps of polyvalent cations with fatty acids $[(RCOO)_2M^{++}]$
  - They are hydrophobic due to the presence of two or more lipophilic groups.
- **3. Amine soaps**
  - Formed from organic amines with fatty acids (e.g. triethanolamine oleate)

B- Sulfuric acid esters

  - They are sulfated compounds and have general formula of RSO_4M such as sodium lauryl sulfate

C- Sulfonic acid derivatives

  - They are sulfonated compounds such as dioctyl sodium sulfosuccinate.

Cationic surfactants

  - Dissociated in water into an amphiphilic cation and an anion, most often of the halogen type.

- A very large proportion of this class corresponds to nitrogen compounds such as fatty amine salts and quaternary ammoniums, with one or several long chain of the alkyl type, often coming from natural fatty acids.

Cetylpyridinium chloride:

- Used in some types of mouthwashes, toothpastes, lozenges, throat sprays, breath sprays, and nasal sprays.
- It is an antiseptic that kills bacteria and other microorganisms.
- It has been shown to be effective in preventing dental plaque and reducing gingivitis.

Benzalkonium chloride:

- Used as preservative in eye drops.
- Used in skin care products and in aftershave, deodorants, hair products and cosmetics.
- Skin antiseptics, such as Bactine and Dettol

Cetrimide (Cetrimonium bromide) (cetyl trimethyl ammonium bromide):

- Used as topical antiseptics, and may be found in selected cosmetic products due to its high cost.

Nonionic surfactants

- Do not dissociate in water. They are the most widely used in pharmaceutical formulations.
- Classified according to the linkage the polar and non-polar groups into:

1- Ether linkage

- **Brijs**

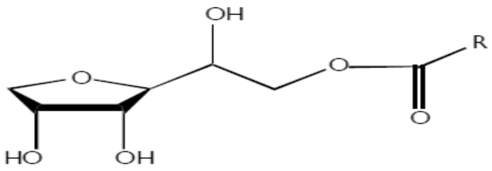
These are ethoxylated fatty alcohols R - $(OCH_2\ CH_2)n$ - OH

- ✓ Being ether they can resist hydrolysis.
- ✓ Can thus be formulated in a variety of pH values.
- ✓ Their HLB values increase by increasing the degree of ethoxylation.
- ✓ They work better when used in combination.
- ✓ Used as detergent and as emulsifiers

2- Ester linkage (Spans and Tweens)

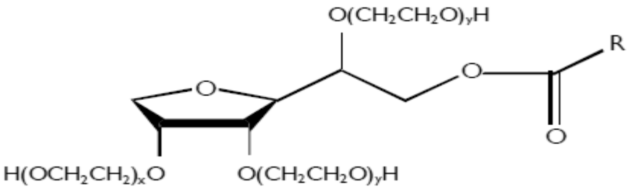
- ✓ They are stable in mild acids, alkalis and electrolytes and do not react with ionic ingredients.
- ✓ They can be combined at different ratios to produce mixtures of the required HLB.
- ✓ They are effective as emulsifiers, solubilizers, dispersing and wetting agents

- ■ **Spans (sorbitan fatty acid esters)**

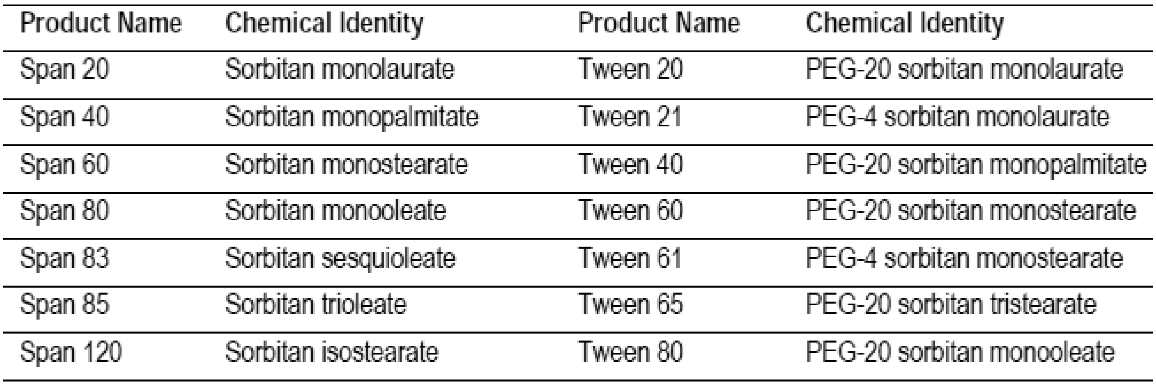


- ✓ Produced by dehydration of sorbitol followed by esterification. Further esterification produces polyesters.
- ✓ Spans are immiscible with water. They have low HLB.
- ✓ HLB decreases by increasing the degree of esterification.
- ✓ They form water in oil (W/O) emulsion.

- ■ **Tweens (polyoxyethylene sorbitan esters) (polysorbates)**



- ✓ They are hydrophilic. With higher HLB.
- ✓ The hydrophilicity increases by increasing the degree of ethoxylation.
- ✓ For fixed degree ethoxylation the water solubility decreases by increasing the number of ester groups.
- ✓ For fixed degree ethoxylation and estrification, the water solubility decreases by increasing the molecular weight of fatty acid.
- ✓ Produce oil in water (O/W) emulsion



Product Name	Chemical Identity	Product Name	Chemical Identity
Span 20	Sorbitan monolaurate	Tween 20	PEG-20 sorbitan monolaurate
Span 40	Sorbitan monopalmitate	Tween 21	PEG-4 sorbitan monolaurate
Span 60	Sorbitan monostearate	Tween 40	PEG-20 sorbitan monopalmitate
Span 80	Sorbitan monooleate	Tween 60	PEG-20 sorbitan monostearate
Span 83	Sorbitan sesquioleate	Tween 61	PEG-4 sorbitan monostearate
Span 85	Sorbitan trioleate	Tween 65	PEG-20 sorbitan tristearate
Span 120	Sorbitan isostearate	Tween 80	PEG-20 sorbitan monooleate

Incompatibilities of surfactants

Nonionic surfactants

- Nonionic surfactants have few incompatibilities with drugs and are preferred over ionic surfactants. even in formulations for external use, except when the germicidal properties of cationic and anionic surfactants are important.
- Nonionic surfactants form weak complexes with some preservatives as phenols, including esters of phydroxybenzoic acid (Parabenzes) and with acids like benzoic and salicylic via hydrogen bonds. This reduces the antibacterial activity of these compounds.

Ionic surfactants

- Ionic surfactants capable of reacting with compounds possessing ions of the opposite charge. These reactions may bind the surface active ions, sometimes with precipitation.
- Incompatibility of surface active quaternary ammonium compounds with bentonite, kaolin, talc, and other solids having cation exchange capacity.

Anionic surfactants

- React with Cationic drugs (alkaloidal salts, local anesthetics, most sympathomimetic, cholinomimetic, adrenergic blocking, skeletal muscle relaxants, antihistamines, many tranquilizing and antidepressant agents) cause precipitation or the drugs lose potency or availability

Cationic surfactants

- Form complex with water soluble polymers containing negatively charged groups, as natural gums (acacia, tragacanth, agar, carrageenin), alginate, sodium carboxy methylcellulose, and Carbopol.

Rheology

Introduction

- ☐ Rheology is the science of the flow and deformation of matter (liquid or "soft" solid) under the effect of an applied force.
- ☐ Deformation → change of the shape and the size of a body due to applied forces (external forces and internal forces).
    - ✓ Flow → irreversible deformation (matter is not reverted to the original state when the force is removed).
    - ✓ Elasticity → reversible deformation (matter is reverted to the original form after stress is removed).
- ☐ Viscosity is an expression of the resistance of a fluid to flow.
- ☐ The higher the viscosity the greater the resistance to flow.
- ☐ Dynamic (absolute) viscosity:
    - ✓ The resistance to flow encountered when one layer or plane of fluid attempts to move over another identical layer or plane of fluid at a given speed. Dynamic viscosity is also called absolute viscosity.

Application of rheology:

- ☐ Formulation of medicinal and cosmetic creams, pastes and lotion.
- ☐ Formulation of emulsion, suspension, suppositories and tablet coatings.
- ☐ Fluidity of solutions for injection.
- ☐ In mixing and flow of materials, packaging into containers, their removal prior to use, whether by pouring from a bottle, extrusion from a tube, or passage through a syringe needle.
- ☐ Can affect patient acceptability, physical stability, and even biological availability.

Types of flow

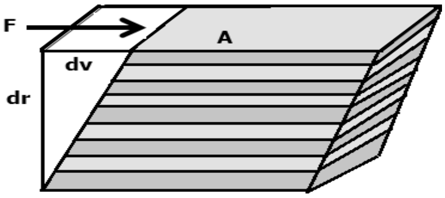
Newtonian System

- ✓ These are systems the flow of which follows Newton`s law

Non-Newtonian System

- These are systems in which the flow pattern does not follow Newton`s law

Newtonian systems



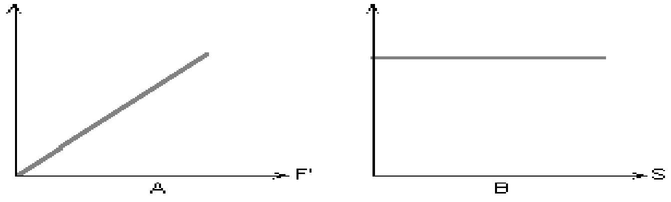
Newton`s law of flow

- Consider a block of liquid consisting of parallel plates of molecules as in the above figure.
- If the bottom layer is fixed and the top plane of liquid is moved at constant velocity, each lower layer will move with velocity directly proportional to its distance from the stationary bottom layer.

Definitions

- **Shear:** is the movement of material relative to parallel layer.
- **Shear stress (F’):** is the force per unite area required to bring about flow (F/A). dynes /cm^2
- **Shear rate (S)** difference in velocity dv, between two planes of liquids separated by distance dr (i.e. dv/dr) sec^{-1}

- According to this law F’ α S thus F’= h S
  - Where h is the viscosity.
  - According to this law the viscosity is constant and is independent on the shear rate



Simple Newtonian rheogram

- **slope = 1/η**

Absolute (dynamic) viscosity

- $$\text{Viscosity} = h = \frac{F'}{S} = \frac{\text{shear stress}}{\text{shear rate}} = \frac{\text{dyne x cm}}{\text{cm2x cm/sec}} = \text{dyne cm-2 sec}$$
- The fundamental unit of viscosity measurement is the poise (dyne cm^{-2} sec). 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 centipoise.

To summarize:

- Viscosity is the resistance of a fluid to flow. The higher the viscosity, the greater the resistance.
- Poise: shearing force required to produce a velocity of 1cm/sec between two parallel planes of liquid each having area of 1 cm^2 and separated by a distance of 1cm

Fluidity; it is the reciprocal of viscosity

$$\mathbf{Ø = 1/\eta}$$

Kinematic Viscosity:

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

$$\textbf{Kinematic viscosity} = \eta / p$$

- Where ***p*** is the density of the liquid
- The unite is Stock (s) or centistock (cs)

Relative viscosity:

- Is the relation of the solution viscosity η to the viscosity of the solvent “standard” η_o
- $$\eta_{rel} = \eta / \eta_o$$

Specific Viscosity (reciprocal of relative viscosity)

- $$\eta_{sp} = \eta_{rel}^{-1}$$

Example

A) The viscosity of acetone at 25°C is 0.313 cp, its density at 25°C is 0.788 g/cm^3. What is its kinematic viscosity at 25°C?

B) Water is usually used as a standard of liquids. Its viscosity at 25°C is 0.89 cp. What is the viscosity of acetone relative to that of water (relative viscosity, η_{rel}) at 25°C?

Solutions:

a) Kinematic viscosity = 0.313 cp ÷ 0.788 g/cm^3= 0.397 cs

b) Relative viscosity h_{rel} = 0.313 cp ÷ 0.8904 cp = 0.352 (dimensionless)

Absolute Viscosity of Some of the Commonly Used Liquids

Liquid	***Viscosity (cp)***
Castor oil	1000
Chloroform	0.563
Ethyl alcohol	1.19
Glycerol	400
Olive oil	100
Water	1.0019

Non-Newtonian systems

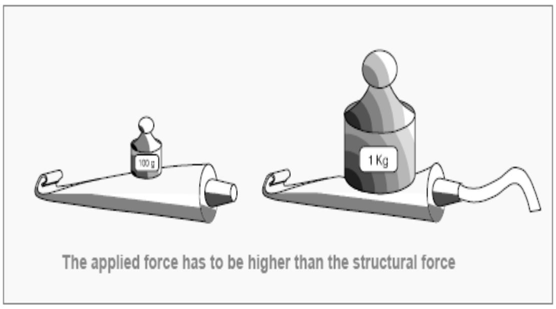
- A non-Newtonian fluid is defined as one for which the relationship between F' and S is not linear.
- In other words, when the shear rate is varied, the shear stress doesn't vary in the same proportion. The viscosity of such fluids will therefore change as the shear rate is varied.
- It can be seen in liquid and solid heterogeneous dispersions such as colloids, emulsions, liquid suspensions and ointments.
- Three classes of flow are recognized:

✓ 1. Plastic 2. Pseudoplastic 3. dilatant

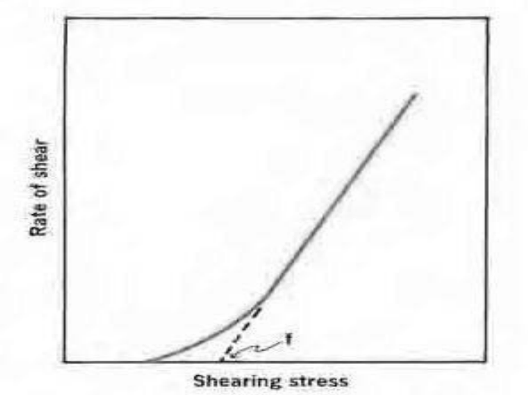
1. Plastic Flow

- 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, tooth past.

A certain shear stress has to be applied in order to let the sample flow



Examples:
Pastes (tomato paste, chilli paste, tooth pastes)



- The flow curve does not pass through the origin. Extrapolation of the linear portion intersects with the shear stress at a value equal to the yield value.
- The slope of the rheogram is termed Mobility, analogous to fluidity in Newtonian system, and its reciprocal is known as Plastic viscosity, U

U =(F’ – f) / S (Where f is the yield value)

- **Plastic systems are shear-thinning systems**

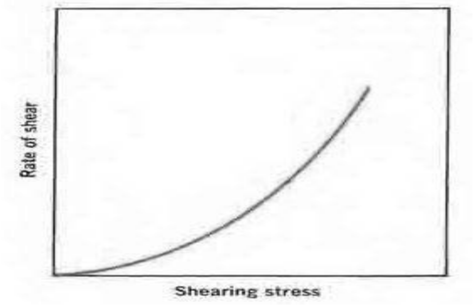
Problem

- A plastic material was found to have a yield value of 5200 dyne.cm-2. At a shearing stress above yield value, F was found to increase linearly with S. If the rate of shear was 150 sec-1 when F was 8000 dyne.cm-2. Calculate the plastic viscosity of the sample.

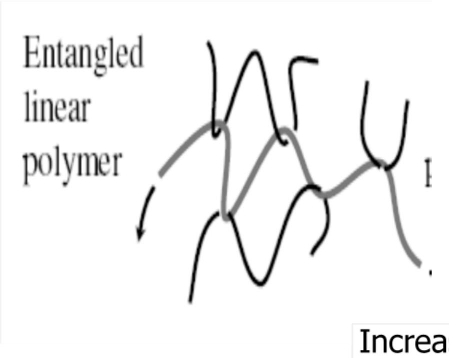
Solution:

U = (F – f)/ S = (8000 – 5200) / 150 = 18.67 poise

2. Pseudoplastic Flow (shear-thinning)



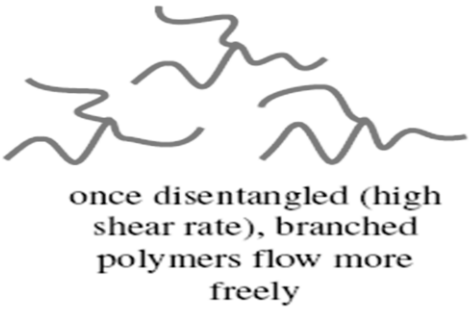
- The curve begins at the origin (or approaches it), there is no yield value.
- Occurs in dispersion of polymers (e.g. syenthetic or natural gum, cellulose derivatives)
- As the shearing stress is increased, disarranged molecules orient themselves to the direction of flow. This orientation reduces internal friction and resistance of the molecules.
- The viscosity decreases by increasing shear rate
- 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



-Chains line up in the direction of the Applied stress
-Layers move over each other more easily
-More vehicle available

Increased stress

-Random arrangement polymer chains
-Solvent interact with polymer
- Chain entanglement



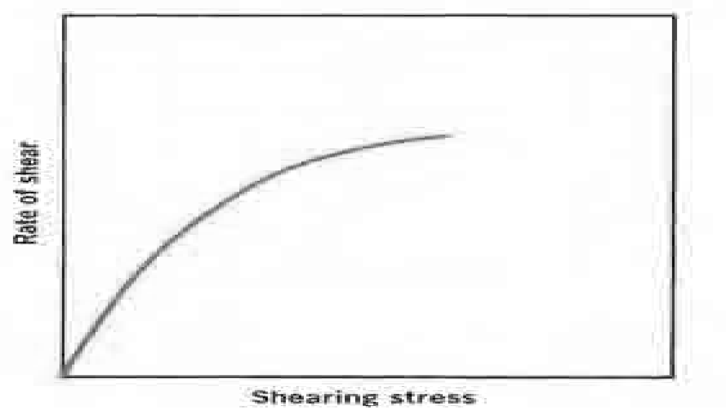
- The curve begins at (or near) the origin, there is no yield value
- Apparent viscosity at any shear rate is determined from the slop of a tangent to the curve at that point.

Examples; creams, some gels, paints, nail polish

- For comparison between two pseudoplastic systems the viscosity value at fixed shear rate can be used. Another approach is to apply the following exponential formula:
- $F^N = \eta S$
- Where N is the exponent value. N increases as the flow becomes increasingly non-Newtonian. If N = 1, the system will be Newtonian.
- $\text{Log } S = N \text{ Log } F - \text{Log } \eta$
- A straight line is obtained when log S is plotted against log F

3. Dilatant Flow (shear-thickening)

- 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.



Reasons for Dilatancy

1. At rest particles are closely packed with minimal inter-particle volume (void), so the amount of vehicle is enough to fill in voids and permits particles to move at low rate of shear.
2. Increase shear stress, the bulk of the system expands (dilates), and the particles take an open form of packing.

3. The vehicle becomes insufficient to fill the voids between particles. Accordingly, particles are no longer completely wetted (lubricated) by the vehicle.

4. Finally, the suspension will set up as a firm paste.

5. This process is reversible.

Characters of dilatant system

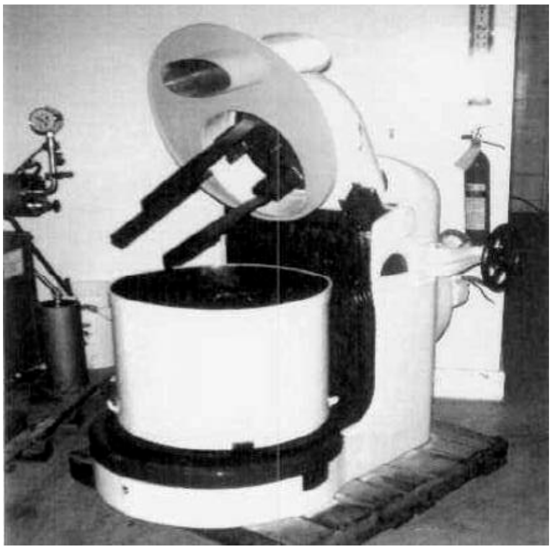
Resting	**Sheared**
- Closed packed particles	Open packed particles
- Minimum void volume	Increased void volume
- Sufficient vehicle	Insufficient vehicle
- Relatively low consistency	Relatively high consistency

Significance of Dilatancy:

❑ Such behaviour suggests that appropriate precautions should be used during processing of dilatant materials.

❑ Mixing (powder + granulating liquid) is usually conducted in high speed mixers, dilatant materials may solidify under these conditions thereby damage the equipment.

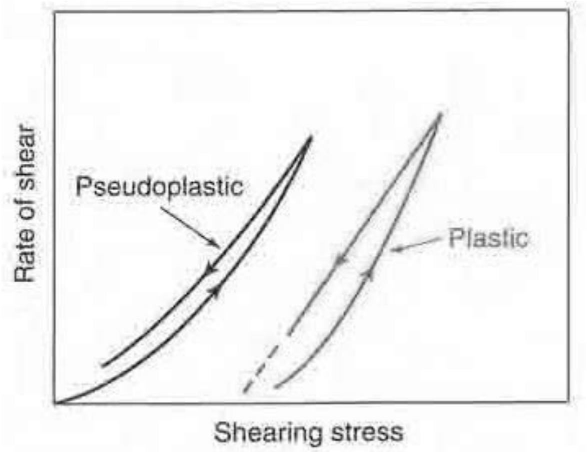
❑



Thixotropy

- It is a Non-Newtonian, Time Dependent behaviour.
- Thixotropy is the reversible, isothermal, time-dependent decrease in viscosity when a fluid is subjected to increased shear stress or shear rate. The system will slowly recover its viscosity after removal of shear.
- **Gel** $\rightleftarrows$ **Sol**
- 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 contains asymmetric particles forming a loose network through sample. At rest, this structure impart rigidity to system resembling gel. As shear applied, the structure begin to break and the material undergo Gel-to-Sol transformation. Finally, at rest the structure is restored again (Sol-to Gel).
- It happens with pseudoplastic materials (shear-thinner)
- It is reversible process

Rheogram of thixotropic system



- **Thixotropy**: characterized by hysteresis loop in which the downward curve does not superimpose over the upward curve.
- The down curve is displaced to the left of the upward curve.
- E.g., for plastic systems showing thixotropy; bentonite and petrolatum
- E.g., for pseudplastic systems showing thixotropy; dispersion of synthetic suspending agents

Thixotropy in Formulation

- In suspension, particles will not settle down in the container (gel form), will become fluid (sol) on shaking for a dose to dispense. At rest, it will retain its consistency to maintain the particles suspended. This is also applied to emulsions, lotions and creams.
- Parenteral suspensions used for intramuscular depot therapy, e.g. procaine penicilline G (40-70% w/v in water)

Rheopexy

- An increase 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. Also called Anti-thixotropy or negative thixotropy.

Factors affecting viscosity

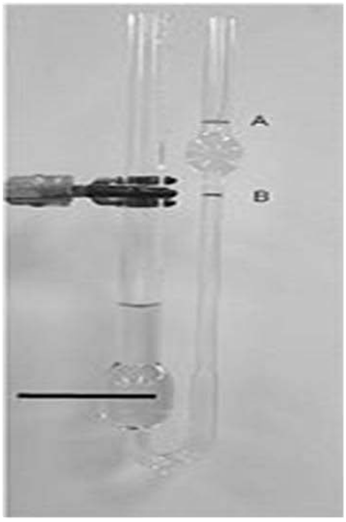
- Temperature; inverse relationship
- Shape of particles;
  - e.g. spheroid colloids is less viscous than linear colloids, as the latter tend to form a network within the dispersion medium.
- Concentration; direct relationship

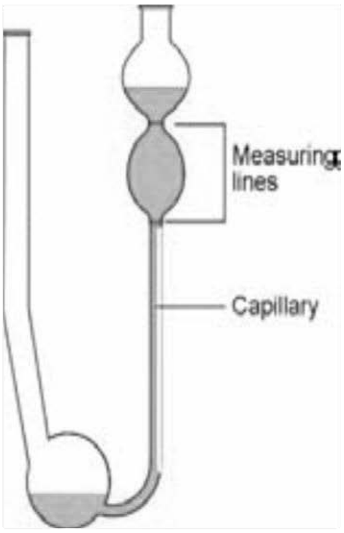
Determination of Viscosity

- U-tube viscometers
- Falling sphere viscometers
- Rotation viscometers

1. Cappilary viscometers

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





2. 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

- The principle of this instrument is based on Stoke's law which states that when a body falls through a viscous medium, it experiences a resistance which opposes the motion of the body.

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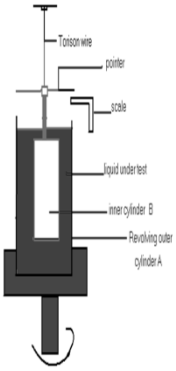
2. Rotational Rheometers

1. Concentric cylinder rheometer

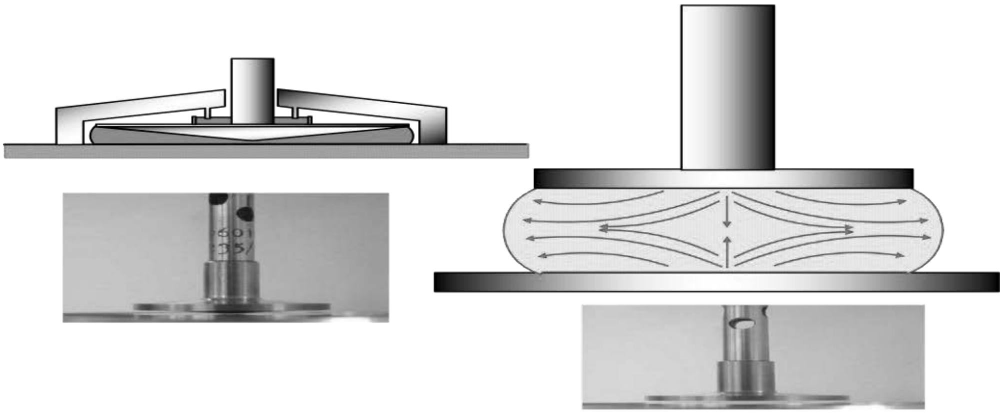


Cup and Bob Viscometer

- ❑ It consists of two coaxial cylinders of different diameters. The outer cylinder forms the cup into which the inner cylinder or the bob is fixed centrally.
- ❑ The sample to be analyzed is sheared in the space between the outer wall of the bob and the inner wall of the cup.
- ❑ There are two classical geometries in "cup and bob" viscometers, known as ;
  - ✓ the cup is rotated
  - ✓ the bob is rotated
    - E.g., Brookfield viscometer

3. <u>Rotational Rheometers</u>

2. Cone and plate type



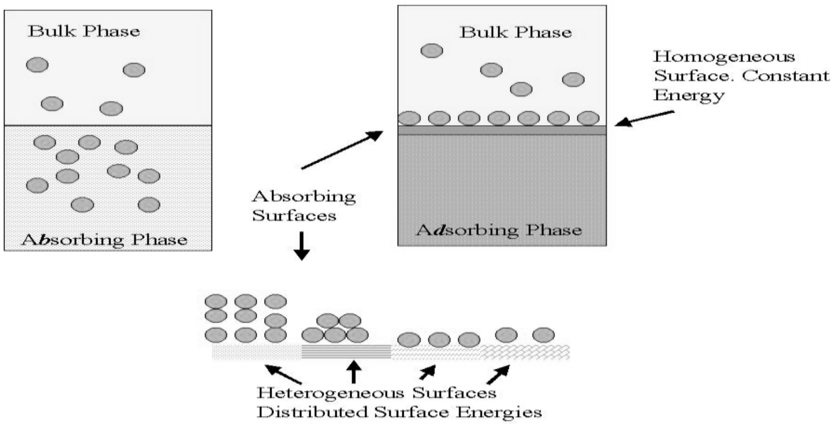
- ❑ The cone is driven by a speed motor and the sample is sheared in the narrow gap between the stationary plate and the rotating cone.

- ❑ Advantages over cup and bob viscometer
  - ✓ Time saved in cleaning
  - ✓ The small sample size
  - ✓ More suitable for semisolid preparations
  - ✓ Rate of shear is constant throughout the sample

ADSORPTION AT SOLID INTERFACE

Adsorption

- Adsorption is the process in which matter is extracted from one phase and concentrated at the surface of a second phase. (Interface accumulation). This is a surface phenomenon as opposed to
- Absorption where matter changes solution phase,(penetration of absorbing material by molecules of the absorbed substance) e.g. gas transfer.



- A gas or liq. is adsorbed on solid surface (having high surface free energy so as to reduce this free energy).
- The material used to adsorb gas or liq (solid) is known as adsorbent (material doing the adsorbing).
- The substance that is attached to the surface of the solid is called adsorbate (material being adsorbed).
- The degree of adsorption of gas by a solid depends on
    - ✓ Nature of adsorbent and its surface area.
    - ✓ Nature of adsorbate and the partial pressure of gas.
    - ✓ Temp.

Thermodynamics of surface adsorption

- ☐ In solutions certain particles tend to concentrate at the surface. These particles are those that have low affinity for the water (solvent).
- ☐ These are hydrophobic molecules (they have low affinity for the solvent) they can get to the surface easily since they have low bond energy in the bulk phase.
- ☐ The water system prefers to have these molecules at the surface because the placement at the surface requires less energy than a water molecule -- hydrophobic molecules decrease surface energy (surface tension) relative to a pure water system.
- ☐ On the other hand if a particle has a high affinity for the solvent phase (hydrophilic) it will tend to remain in the bulk solution because of its strong bond with water. In fact, this bonding makes the water bonding stronger and, therefore, there is a larger energy required to get water molecules to the surface-- therefore, hydrophilic molecules increase surface tension, e.g. salts such as NaCl.
- ☐ As particles concentrate at surface there becomes a "surface excess".

Types of adsorption.

Physical adsorption	*Chemical adsorption*
Reversible	**Irreversible**
Weak van der Waals forces	**Strong chemical bond**
Common at low temp	**Occurs at high temp**
Non-specific	**More specific**
Heat of adsorption is low (20 to 40 kj/mole)	**Heat of adsorption is high (40 to 400 kj/mole)**
Adsorbed as mono- or multi-layers	**Adsorbed as mono layer**
Fast adsorption rate, since it is a non-activated process	**Slow adsorption rate**
e.g. adsorption of gases on charcoal	**e.g. adsorption of oxygen on silver or gold**

- Combination of both type of adsorption is known as sorption.
- Desorption: adsorbed molecules or ions are removed from the solid surface.
- Generally some combination of physical and chemical adsorption is responsible for activated carbon adsorption in water and waste water.

Adsorption at solid/gas interface

Adsorption of gas is important in following area

- Removal of objectionable odors from the room.
- Prevention of obnoxious gases entering in to the body (gas masks)
- Estimation of surface area and particle size of powders.
- Decolorizing solution
- Adsorption chromatography
- Detergency
- Wetting

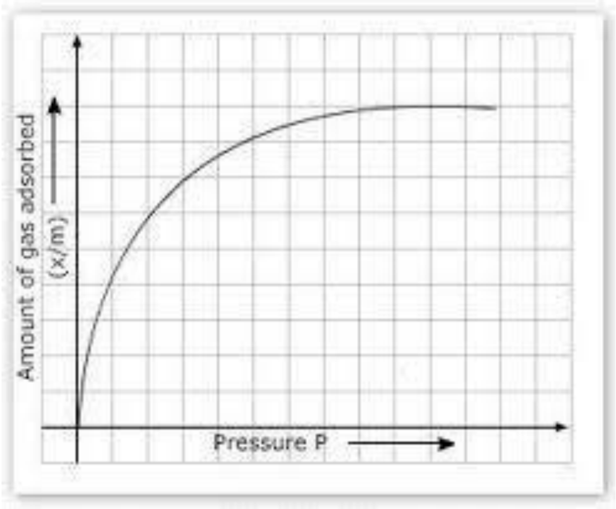
Adsorption equilibria

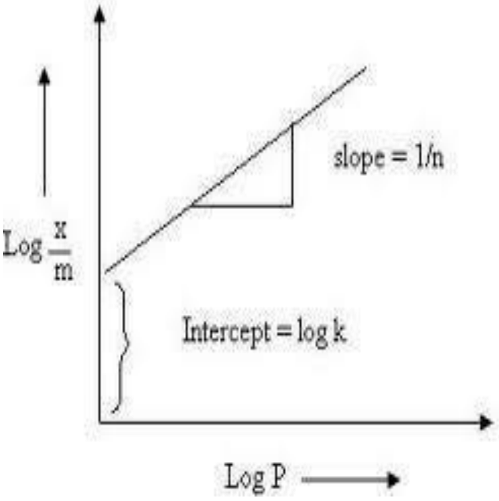
- If the adsorbent and adsorbate are contacted long enough an equilibrium will be established between the amount of adsorbate adsorbed and the amount of adsorbate in solution. The equilibrium relationship is described by isotherms (The graph of amt of gas ad./unit A or m of solid Vs pressure)
- The process of adsorption is usually studied through graphs know as adsorption isotherm. It is the graph between the amounts of adsorbate (x) adsorbed on the surface of adsorbent (m) and pressure at constant temperature.
- Different adsorption isotherms have been Freundlich, Langmuir and BET theory.

Freundlich isotherm

- The relationship between pressure of the gas and amt adsorbed at constant temp has been expressed by freundlich isotherm eqn: $y = x/m = kP^{1/n}$
- Where y = wt of gas adsorbed (x) per unit wt of adsorbent, (m) P= equilibrium pressure, k and n = constant
- This eqn gives curvilinear graph when (x/m) is plotted against pressure p.

- The constant k and n are evaluated from the exp and they depends on temp and nature of the adsorbent and adsorbate.





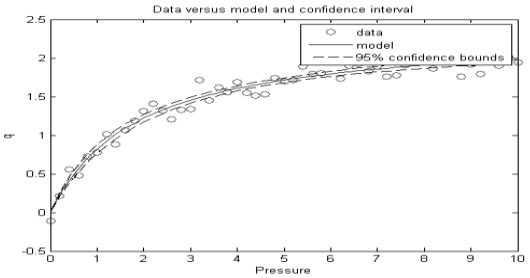
- Convert the eqn. into logarithmic form Log x/m = log k + 1/n log P
- Thus, plotting log (x/m) versus log p gives a straight line with the slope (1/n) and the intercept on the y axis is log k.
- Liquefiable gases such as CO2, NH3, SO2, HCl get more readily adsorbed than other gases such as O2, H2 and N2.
- Higher the critical temp of the gas, more is the adsorption of gases

■ Langmuir Adsorption

- The following assumptions are made for this:

1. The surface of solid has fixed number of active sites for the adsorption of gases.
2. Adsorbed molecules do not interact
3. At max adsorption, the gas layer that is found around the solid is of only one molecule thick.
4. The rate of adsorption (condensation) is proportional to number of unoccupied sites.
5. The rate of evaporation (desorption) is proportional to the number of occupied sites.

- The adsorption of gas on the solid surface depends on the pressure of the gas in the experimental conditions.
- $\Theta = \alpha.P/(1+ \alpha.P)$ At a particular gas pressure (p)



❑ Fraction of site occupied : Θ

❑ Fraction of sites unoccupied: (1-Θ)

❑ Rate of adsorption: $v_{ad} = k_1 p(1-\theta)N$

❑ Rate of desorption: $v_{de} = k_{-1}\theta N$

❑ Where k_1 and k_{-1} are proportionality constants for the process of adsorption and desorption

❑ **<u>Langmuir's model of the structure of the adsorbed layer</u>**

❑ The black dots represent possible adsorption sites, while the white and mauve ovals represent adsorbed molecules.

■ Multimolecular adsorption (*BET isotherm)*

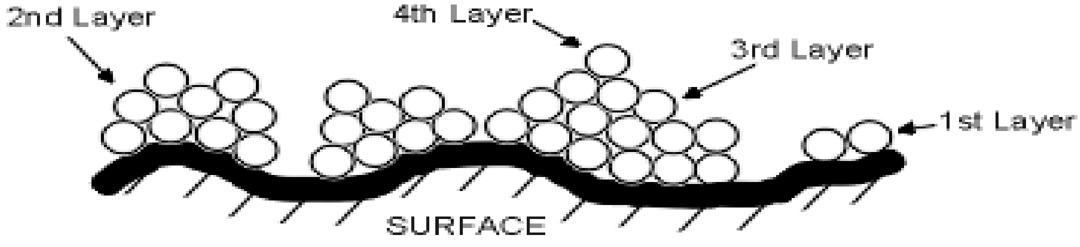
❑ Sometimes, gases adsorb as multi-molecular layers on solids.

❑ Braunauer, Emmette and Teller (BET) have extended equation as:

- ✓ $P/y(Po – P)=1/(y_m b) + (b-1)/y_m b * P/ Po$

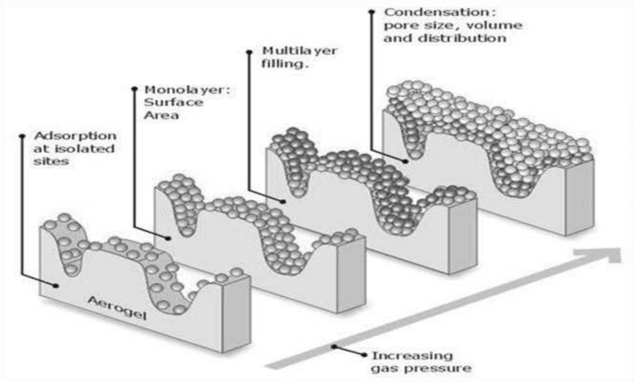
Where P = pressure of adsorbate, mmHg

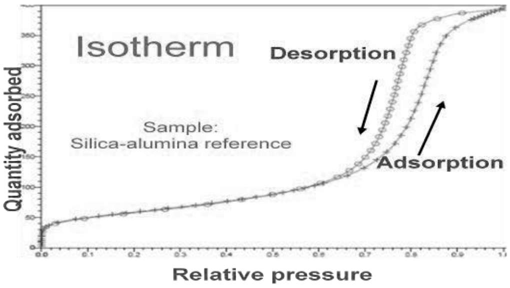
- ✓ y = mass of vapor adsorbed per gram of adsorbent
- ✓ P_o = vapor pressure at saturation (monolayer)
- ✓ Y_m = is the mass of vapor adsorbed per gram of adsorbent, when the surface is covered with monomolecular layer.
- ✓ b = constant, proportional to the difference between the heat of adsorption of vapor and the latent heat of condensation of subsequent layers.



❑ The assumptions underlying the simplest BET isotherm are:

- ✓ (1) Gas adsorbs on a flat, uniform surface of the solid
- ✓ (2) There is no lateral interaction between the adsorbed molecules and the heat of formation of monolayer is equal to heat of condensation
- ✓ (3) Adsorption is multilayer.





■ <u>Adsorption Isotherms</u>

❑ Adsorption isotherms are defined as the plots drawn between the amount of gas adsorbed on a solid against the equilibrium pressure or conc at constant temp.

$$P/y(P_o - P) = 1/(y_m b) + (b-1)/y_m b * P/P_o$$

■ ***Types:***

Type I Type II Type III Type IV Type V

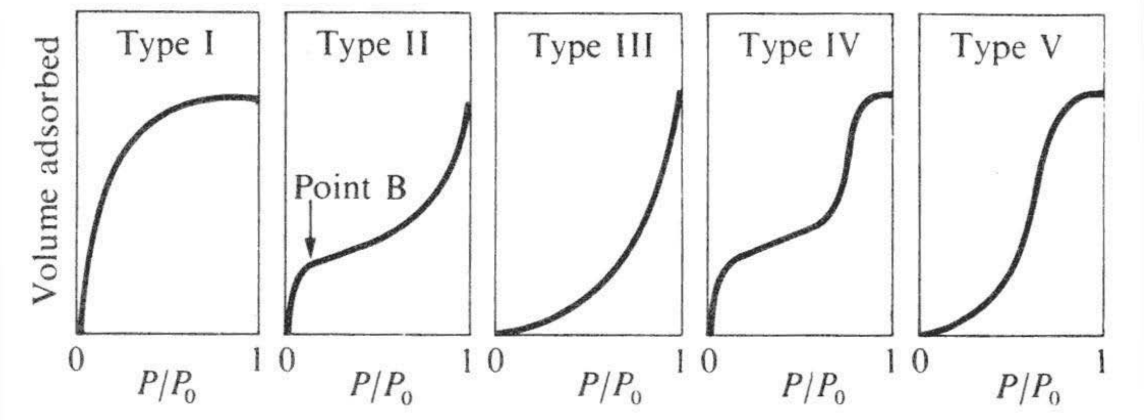


FIG. 2.5 Classification of isotherms according to the BET theory.

■ Adsorption Isotherm Type I

- ☐ It represents increase in adsorption with increase in pressure followed by a leveling off.
- ☐ Shown by adsorbents with microporous structure
- ☐ This leveling off is due to the saturation of available specific chemical groups or entire surface is covered by a monomolecular layer.
- ☐ Same as Freundlich and Langmuir adsorption isotherm.
- ☐ E.g. adsorption of N_2 gas on carbon and ammonia on charcoal

■ Adsorption Isotherm Type II

- ☐ Sigmoidal in shape (S shaped) and occurs when gases undergo physical adsorption onto nonporous solid.
- ☐ shows large deviation from Langmuir model of adsorption
- ☐ 1st inflection point represents formation of monolayer.
- ☐ As pressure increases multilayer formation occurs.
- ☐ Represented by a BET eqn.
- ☐ E.g. adsorption of N2 gas on iron or platinum catalyst at 78 ^{o}C.

■ Adsorption Isotherm Type III

- ☐ Shows a curve that is convex to the pressure axis
- ☐ It is seen rarely and shows large deviation from Langmuir model and represented by BET equation
- ☐ This isotherm explains the formation of multilayer
- ☐ The heat of adsorption of gas in the first layer is less than the latent heat of condensation of subsequent layers (weak interaction lead to low adsorption at low pressure till formation of first layer then strong interaction resulting in accelerated adsorption at higher pressure).
- ☐ E.g. adsorption of bromine on silica or alumina

■ Adsorption Isotherm Type IV

- ☐ Represents the adsorption of gases on porous solids.
- ☐ First point of inflection when extrapolated to zero pressure represents the amount of gas required to form a monomolecular layer on the solid surface.

- ❑ Condensation within the pores of the solid are responsible for the multimolecular layer before reaching saturation pressure.
- ❑ E.g. adsorption of benzene on silica gel

■ Adsorption Isotherm Type v

- ❑ Like type III show convex curve to the pressure axis indicating weak adsorbate – adsorbent interaction.
- ❑ Like type IV capillary condensation is responsible for further adsorption that reaches a limiting value before Po (saturation pressure) is attained.
- ❑ E.g. adsorption of water vapor on charcoal at 100 °C.

■ Applications

1. Q.A.C **2. Adsorption chromatography**

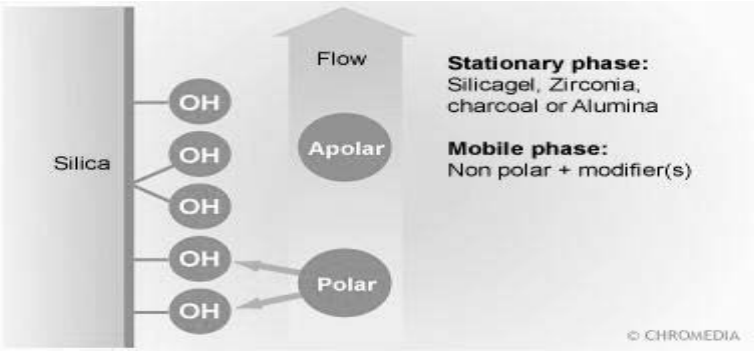
2. Detergents **3. Wetting agents**

■ 1. Quaternary ammonium compounds

- ❑ E.g. cetrimide and benzalkonium chloride
- ❑ Effective antimicrobial agents for application to skin and mucous membrane
- ❑ These compounds may be inactivated by certain ingredients in the formulation (kaolin and talc that are lubricant) through adsorption process

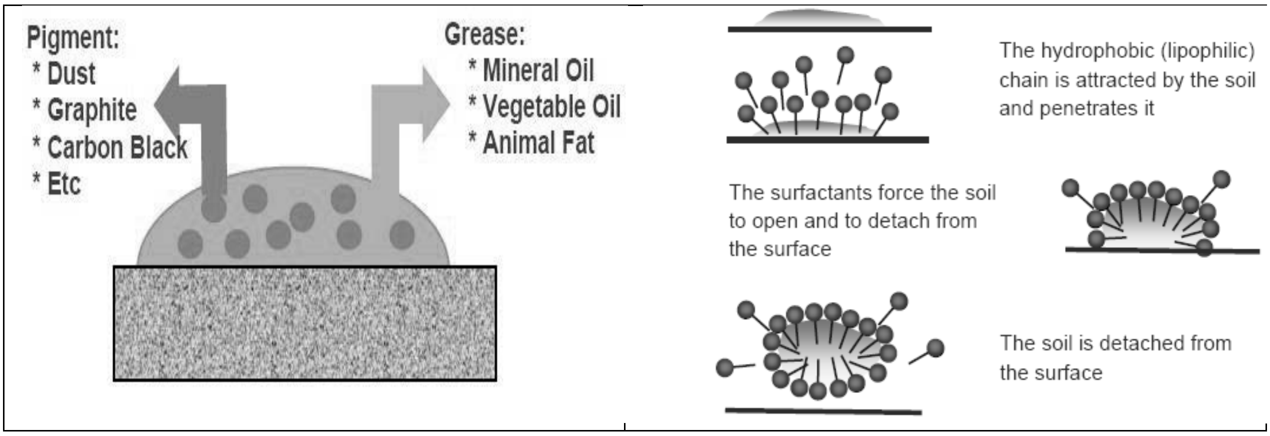
■ 2. Adsorption chromatography

- ❑ Solutes present in the solution will come off at the bottom of the column in the reverse order of their
- ❑ adsorptive affinity for the particular adsorbent used
- ❑ Thus solutes with little or no affinity for the solid phase will pass through the column and present in the initial effluent while strongly adsorbed solutes will pass out in the final effluent



3. Detergents

- Detergents are surfactants or a mixture of surfactants with cleaning properties in dilute solutions used for removal of dirt.
- They are amphiphilic - partly hydrophilic (polar) and partly hydrophobic (non-polar). Their dual nature facilitates the mixture of hydrophobic compounds (like oil and grease) with water.
- Because air is not hydrophilic, detergents are also foaming agents to varying degrees
- Detergency involves:
  - ✓ Initial wetting of the dirt and the surface to be cleaned
  - ✓ Deflocculation and suspension, emulsification or solubilization of the dirt particles
  - ✓ Finally washing away the dirt

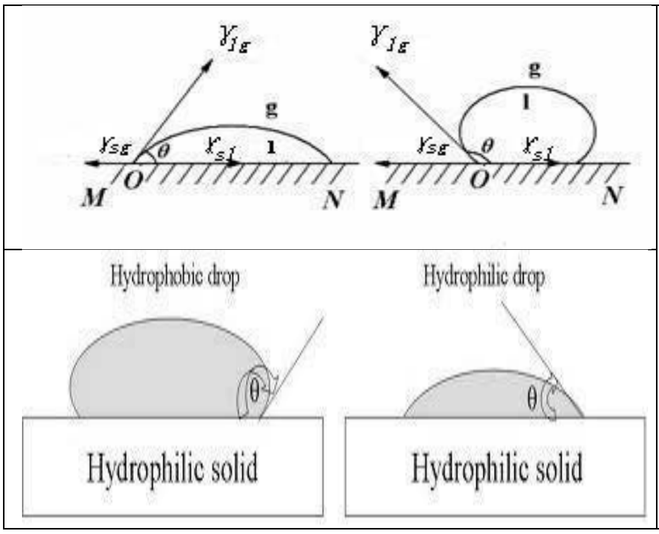


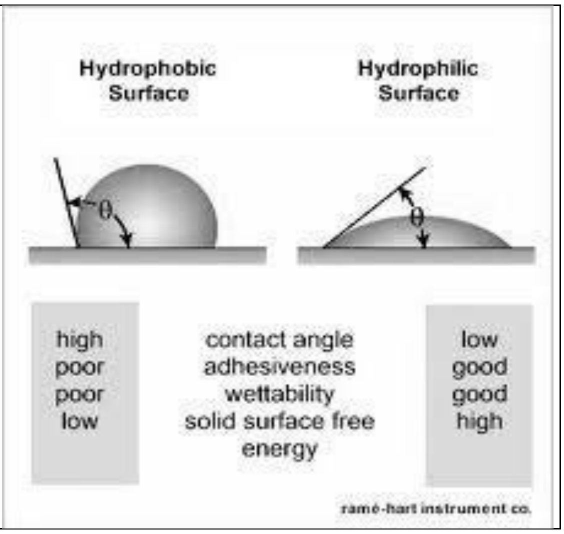
4.Wetting agents

- Wetting agent is a surfactant that when dissolved in water, lower the contact angle and aids in displacing the air phase at the surface and replacing it with a liquid phase. (contact angle: is the angle which a small droplet of liquid makes when placed on a solid surface)
- Based on this concept: a good wetting agent to be one which reduces the surface tension of a liquid to a value below the solid critical surface tension.
- According to the nature of the liquid and the solid, a drop of liquid placed on a solid surface will adhere to it or no. which is the wettability between liquids and solids.
- When the forces of adhesion are greater than the forces of cohesion, the liquid tends to wet the surface and vice versa. Place a drop of a liquid on a

smooth surface of a solid. According to the wettability, the drop will make a certain angle of contact with the solid.

- A contact angle is lower than 90°, the solid is called wettable
- A contact angle is wider than 90°, the solid is named non-wettable (Teflon is an example of lipophilic solid 180 angle).
- A contact angle equal to zero indicates complete wettability



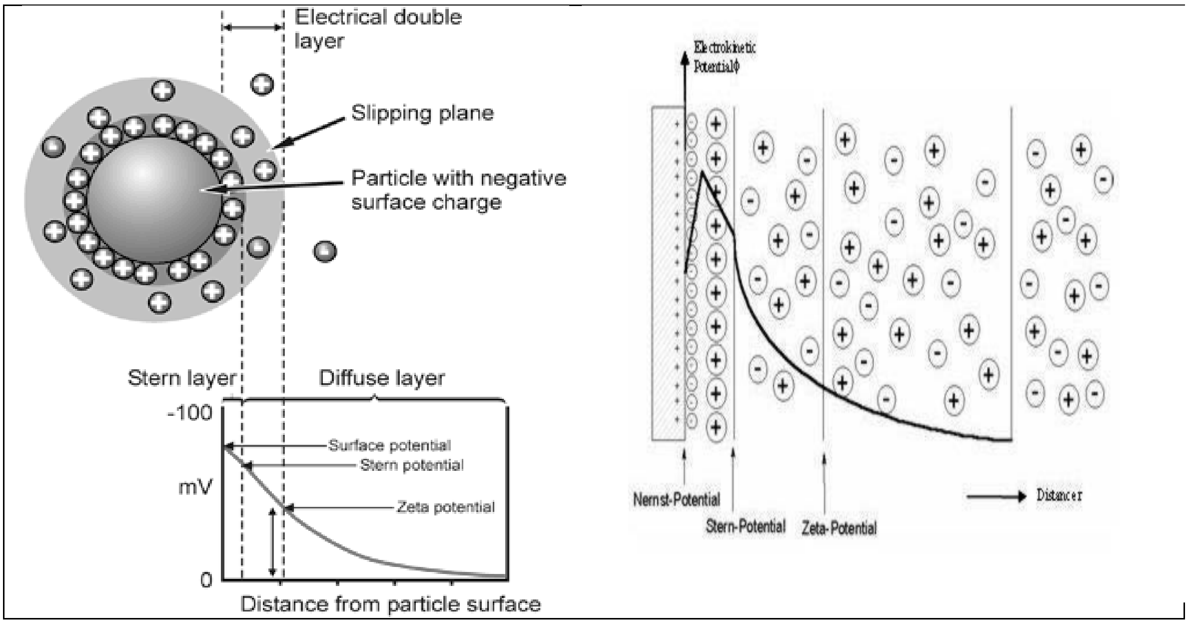


■ Electrical Properties of Interfaces

Particles dispersed in liquid media become charged as a result of

- Adsorption of ionic species present in the solution (added ions), hydronium ion or hydroxyl ion (more common) of pure water
- Ionization of particle groups :
  1. Polystyrene latex has carboxylic group so ionize giving negatively charged particles
  2. Acidic drugs as nalidixic acid and ibuprofen acquire negative charge
  3. Amino acids and proteins their charge depend on the pH of the medium (ionization may give +ve amino group or –ve carboxylic group).
- Zeta potential is the electrical potential that exists at the shear plane of a particle, which is some small distance from the surface.
- Colloidal particles dispersed in a solution are electrically charged due to their ionic characteristics and dipolar attributes.

- The development of a net charge at the particle surface affects the distribution of ions in the neighboring interfacial region, resulting in an increased concentration of counter ions (ion of charge opposite to that of the particles) close to the surface
- Each particle dispersed in a solution is surrounded by oppositely charged ions called fixed layer.
- Outside the fixed layer, there are varying compositions of ions of opposite polarities, forming a cloud-like area.
- Thus an electrical double layer is formed in the region of the particle-liquid interface
- This double layer may be considered to consist of two parts: a inner region which includes ions bound relatively strongly to the surface and an outer, or diffuse region in which the ion distribution is determined by a balance of electrostatic forces and random thermal motion.
- The potential in this region, therefore, decays with the distance from the surface, until at a certain distance it becomes zero.
- When a voltage is applied to the solution in which particles are dispersed, particles are attracted to the electrode of the opposite polarity, accompanied by the fixed layer and part of the diffuse double layer.
- The potential at the boundary between this unit, that is to say at the above-mentioned shear plane between the particle with its ion atmosphere and the surrounding medium, is known as the Zeta Potential.
- Zeta potential is a function of the surface charge of a particle, any adsorbed layer at the interface and the nature and composition of the surrounding medium in which the particle is suspended.
- The principle of determining zeta potential is very simple. A controlled electric field is applied via electrodes immersed in a sample suspension and this causes the charged particles to move towards the electrode of opposite polarity.
- Viscous forces acting upon the moving particle tend to oppose this motion and an equilibrium is rapidly established between the effects of the electrostatic attraction and the viscosity drag.
- The particle therefore reach a constant terminal velocity



■ Electrical Double Layer

<u>The electric double layer is electrically neutral.</u>

❑ It consists of three parts:

1. Surface charge - charged ions (commonly negative) adsorbed on the particle surface
2. Stern layer – counter-ions (charged opposite to the surface charge) attracted to the particle surface and closely attached to it by the electrostatic force.
3. Diffuse layer (a film of the dispersion medium (solvent) adjacent to the particle) that contains free ions with a higher concentration of the counter-ions. The ions of the diffuse layer are affected by the electrostatic force of the charged particle.

❑ It is sensitive to electrolytes and temperature.

❑ The electrical potential has the maximum value on the particle surface (Stern layer).

❑ The potential drops with the increase of distance from the surface and reaches 0 at the boundary of the Electric Double Layer.

❑ When a colloidal particle moves in the dispersion medium, a layer of the surrounding liquid remains attached to the particle.

❑ The boundary of this layer is called slipping plane (shear plane).

- ☐ The value of the electric potential at the slipping plane is called Zeta potential, which is very important parameter in the theory of interaction of colloidal particles.

- ☐ A phenomenon, which plays a fundamental role in the mechanism of the electrostatic stabilization of colloids.

- ☐ It has a combination of charged surface.

- ☐ Unequal distribution of co-ions and counter-ions near the surface.

- ☐ Colloidal particles gain negative electric charge when negatively charged ions of the dispersion medium are adsorbed on the particles surface.

- ☐ A negatively charged particle attracts the positive counter-ions surrounding the particle.

- ☐ Electric Double Layer is the layer surrounding a particle of the dispersed phase and including the ions adsorbed on the particle surface and a film of the counter-charged dispersion medium.

■ Significance Of Zeta Potential

- ☐ It plays an important role in theory of aggregative stability. Electrostatic repulsion between particles depends on the value of zeta potential.

- ☐ The higher the zeta potential, the stronger the repulsion, the more stable the system becomes. For instance, high zeta potential of the fat droplets in milk prevents them against coalescence. Reduction of it due to addition of acid would lead to cheese formation from coalescence droplets

- ☐ # slipping plane associated with tangential motion of the liquid relative to the surface. Liquid underneath of the slipping plane remains attached to the surface. Electric potential corresponding to the slipping plane is " Zeta potential "

■ Applications of adsorption

- ☐ **Production of high vacuum**

- ☐ **In gas masks*:*** this apparatus is used to adsorb poisonous gases (e.g. Cl2 ,CO oxide of sulphur etc.) and thus purify the air for breathing

- ☐ **For desiccation or dehumidification*:*** These substances can be used to reduce/remove water vapors or moisture present in the air (Silica gel and alumina are used for dehumidification in electronic equipment).

- ☐ **Removal of coloring matter from solution:**

- ✓ Animal charcoal removes colors of solutions by adsorbing colored impurities.
- ✓ Animal charcoal is used as decolorize in the manufacture of cane sugar (remove brown color)

- ☐ **Softening of hard water**
  - ✓ i) The hard water is made to pass through a column packed with zeolite (sodium aluminium silicate)
  - ✓ ii) Ca^{++} & Mg^{++} ions which are responsible for hardness, get adsorbed on zeolite, exchanging sodium ions
  - ✓ iii) The exhausted zeolite is regenerated with 10% of sodium chloride solution .

- ☐ **De-ionization of water**
  - ✓ Water can be de-ionized by removing all dissolved salts with the help of cation and anion-exchanger resin .

- ☐ **Medical use:**
  - ✓ kaolin: formed of aluminum hydroxide residue adsorb both basic and acidic intestinal toxins by ion exchange (less value will occur in the lower part of the GIT)

Solubilization

- Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at certain temperature, and in qualitative way it can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.
- Solubility is defined as the molecular dispersion of solute in the solvent.
- Solubilization can be defined as the preparation of a thermodynamically stable solution of a substance normally insoluble or very slightly soluble in a given solvent by the introduction of an additional component or components
- The process of solubilization involves the breaking of inter-ionic or inter-molecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

1: Holes opens in the solvent

2: Molecules of the solid breaks away from the bulk

3: The freed solid molecule is integrated into the hole in the solvent

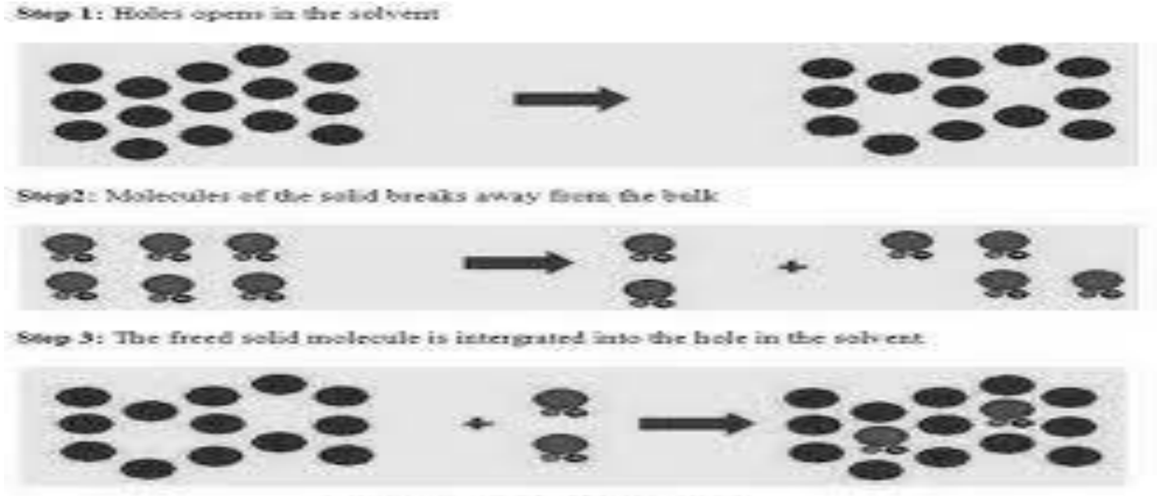


Fig. 1 Process of solubilisation

Importance of solubilization:

- The solubility behavior of a drug candidate can be regarded as one of the most important aspects of preformulation testing for poorly soluble compound.
- For parenteral formulations, the drug must be soluble in a pharmaceutically acceptable vehicle.

- ❑ For oral formulations, the drug must have an adequate solubility and dissolution rate to achieve suitable bioavailability.
- ❑ Solubility is an important physico-chemical property of a drug.
- ❑ In order for a drug to enter systemic circulation and to exert a therapeutic effect it must first be in solution form.

■ Terms of approximate solubility

Term	**Parts of solvent required for one part of solute**
Very soluble	**Less than 1 part**
Freely soluble	**1 to 10 parts**
Soluble	**10 to 30 parts**
Sparingly soluble	**30 to 100 parts**
Slightly soluble	**100 to 1000 parts**
Very slightly soluble	**1000 to 10000 parts**
Practically insoluble	**More than 10000 parts**

■ Types of Solubilization

1. **Co-solvency**
2. **Hydrotropy**
3. **Complex formation**
4. **Micelle solubilization**
5. **Solid state manipulation**
6. **Drug derivatisation**

■ Solubilization By Cosolvents

- ❑ During chemical processing, a second solvent is added to the original solvent, generally in small concentrations, to form a mixture that has greatly enhanced solvent powers due to synergism
- ❑ Weak electrolytes and non polar molecules frequently have poor aqueous solubility.
- ❑ Their solubility in water is increased by addition of water miscible solvents in which drug has good solubility.
- ❑ This process is called cosolvency and the added solvents are called cosolvents.
- ❑ The cosolvents such as propylene glycol, polyethylene glycol, ethanol, glycerin aids to solubilize drug in aqueous vehicle.
- ❑ The solubilizing effect by cosolvency is primarily dependent upon the polarity of drug with respect to solvent and cosolvent
- ❑ Mechanism responsible for solubility enhancement through cosolvency is by reducing the interfacial tension (reduce the polarity differences) between the predominantly aqueous solution and hydrophobic solutes and reduces the contact angle between solid and liquid.
- ❑ Cosolvents can increase the solubility of a nonpolar drug up to several orders of magnitude compared to its aqueous solubility.
- ❑ When delivered parenterally or orally, a drug in solution has more bioavailability compared to a solid dosage form.
- ❑ It must meet certain requirements, such as non toxicity, compatibility with blood, non sensitizing, non irritating, and above all physically and chemically stable and inert.
- ❑ Ex. For Co-solvency :

1. The solubility of diazepam can be increased by using mixture of 10% ethanol and 40% propylene glycol.
2. Phenobarbitone is relatively insoluble in water but its solubility can be increased by using mixture of water, alcohol and glycerin
3. Nitrocellulose is greatly dissolved by a mixture of ether and alcohol
4. Cellulose acetate is readily dissolved by a mixture of alcohol and tetrachloroethane
5.

■ Hydrotropic Solubilization

- ☐ Addition of large amount of a second solute results in an increase in the aqueous solubility of another solute.
- ☐ Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs
- ☐ Hydrotropic agents exhibit many solubilizing mechanisms e.g. solubilization by sodium benzoate derivatives is due to: complex formation or salting in
- ☐ Potassium iodide is a hydrotropic agent for iodine by the formation of complex ion
- ☐ Advantages:

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification

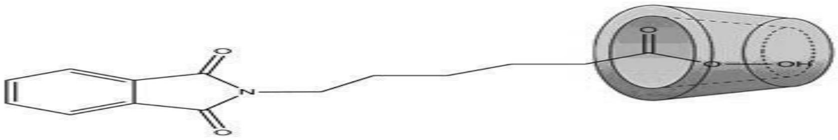
2. It only requires mixing the drug with the hydrotrope in water.

3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system

Drug	***Hydrotropic agent***
Riboflavin	***Procaine HCl , PABA HCl , Cinchocaine HCl , Resorcinol, Pyrogallol***
Chartreusin	***Sodium benzoate, Sodium p- hydroxybenzoate ,*** ***Sodium m- hydroxybenzoate ,*** ***Sodium o- hydroxybenzoate***
Diazepam, Medazepam , Oxazepam , Nitrazepam , Clonazepam	***Sodium salicylate***

Solubilization by Complexation

- It is defined as the reversible association of a substrate and ligand to form a new species with a well defined stoichiometry.
- Complexation relies on relatively weak forces such as hydrogen bonding and hydrophobic interactions
- Example: solubilization of tetracycline and oxytetracycline by complexation with no. of compound such as sodium salicylate, sodium saccharin, caffeine, sodium hydroxybenzoate and methyl pyrrolidone
- The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide
- Insertion of the nonpolar region of one molecule into the cavity of another molecule e.g.: cyclodextrins
- Cyclodextrins are unique since they increase the water solubility of poorly soluble drugs by fitting them into the hydrophobic cavity of the cyclodextrin molecule.
- These cyclodextrins have the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility.



- Surfactant molecules accumulate in the interfaces between water and water insoluble compound.
- Their hydrocarbon chains penetrate the outermost layer of insoluble compound which combine with the water insoluble molecules.
- Micelles form around the molecules of the water insoluble compound (inside the micelles' cores) and bring them into solution in an aqueous medium. This phenomenon is called micellar solubilization.
- The inverted micelles formed by oil soluble surfactant which dissolves in a hydrocarbon solvent can solubilize water-soluble compound which is located in the center of the micelle, out of contact with the solvent
- Micelles of nonionic surfactants consist of an outer shell containing their polyethylene glycol moieties mixed with water and an inner core formed by their hydrocarbon moieties.

- Some compounds like phenols and benzoic acid form complexes with polyethylene glycols by hydrogen bonding and/or are more soluble in liquids of intermediate polarity like ethanol or ethyl ether than in liquids of low polarity like aliphatic hydrocarbons.

- These compounds locate in the aqueous polyethylene glycol outer shell of nonionic micelles on solubilization.

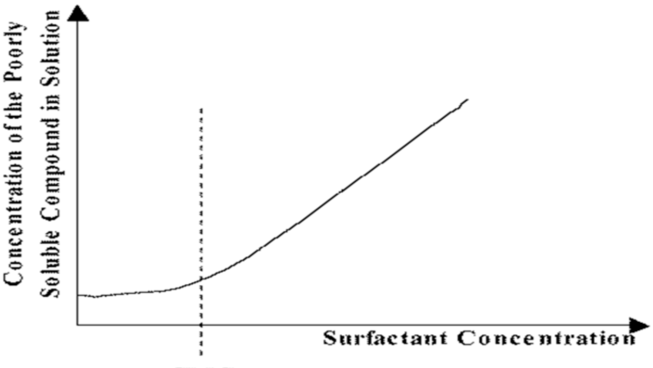
- Drugs which are soluble in oils and lipids can be solubilized by micellar solubilization

- As Micellar solubilization depends on the existence of micelles; it does not take place below the CMC. So dissolution begins at the CMC.

- Above the CMC, the amount solubilized is directly proportional to the surfactant concentration because all surfactant added to the solution in excess of the CMC exists in micellar form, and as the number of micelles increases the extent of solubilization increases .

- Compounds that are extensively solubilized increase the size of micelles in two ways:
    - ✓ The micelles swell because their core volume is augmented by the volume of the solubilization.
    - ✓ The number of surfactant molecules per micelle increases.

- ***Insoluble drugs incorporation into micelles by: O/W Emulsion Method :***

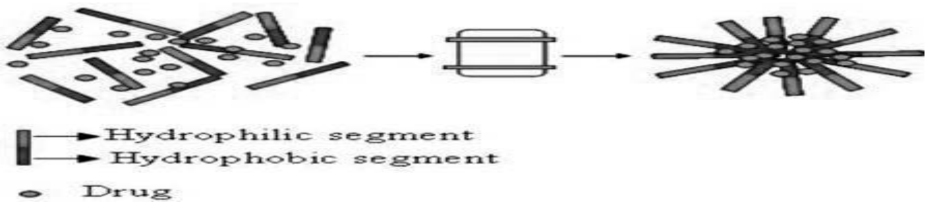


- ***This method consists first of preparing an aqueous solution of the polymer.***
- ***To this add a solution of the drug in a water-insoluble volatile solvent (e.g., chloroform).***
- ***The micelle-drug complex forms as the solvent evaporates***

- Hydrophilic drugs can be adsorbed on the surface of the micelle

- Drugs with intermediate solubility should be located in intermediate positions within the micelle such as between the hydrophilic head groups and in the palisade layer between the hydrophilic groups and the first few carbon atoms of the hydrophobic group, that is the outer core

- Completely insoluble hydrophobic drugs may be located in the inner core of the micelle.



■ 5. Solid State Manipulation

- Many organic molecules will naturally occur (or are compounds, especially capable of being manipulated to exist) in more than one form as solid.

Homogenous solid phases	*Heterogeneous solid phases*
❑ *Crystalline forms (polymorphism)* ❑ *Non crystalline forms (amorphous)*	❑ *Solvates* ❑ *Retardation of phase transformation* ❑ *Drug dispersed in matrix (solid dispersions, eutectic mixtures)*

■ 5.1. Polymorphic modifications

- Solubility of each form depends on the ability of the molecules to escape from the crystal to solvent.

- The stable form posses the lower free energy at a particular temperature and therefore has the lower solubility or escaping tendency whereas the meta stable forms posses higher free energy hence has higher solubility.

- About fifty to hundred percent increase in the dissolution rate can be achieved through polymorphic modifications.

Meta-stable form: exhibit poorly organized and weakly bounded crystal forms (low melting point, higher solubility and high dissolution rate)

- ☐ Examples: Chloramphenicol palmitate (form B) Methyl prednisolone (form 2) Chlortetracycline (form B)
- ☐ Chloramphenicol palmitate: when the metastable form of the drug is formulated as a suspension was found to have higher solubility, dissolution rate and absorption compared to the stable form.

■ 5.2. Non Crystalline Solutes (Amorphous)

- ☐ They will not contain internal crystal lattice structure.
- ☐ These are thermodynamically unstable.
- ☐ Amorphous solid forms give faster dissolution rates and higher solubility than polymorphic modifications. E.g.: Novobiocin (amorphous form possess high absorption (10 time in 0.1 N HCl) while crystalline form of the same drug was found to be poorly absorbed).
- ☐ Thus, the order for dissolution of different solid forms of drug is Amorphous >Metastable >Stable

■ 5.3. Solvates (Pseudo Polymorphism)

- ☐ The recrystallization of many drug substances from solution will results in the formation of solids containing solvent molecules as an integral part of their crystal structure.
- ☐ Majority of these crystalline materials referred as pseudo polymorphs, contain stoichiometric amount of solvent.

Anhydrates > hydrates

Organic solvates > organic non-solvates

- ☐ Enhances the solubility of drug markedly.
- ☐ Examples: pentanol solvates of fludrocortisone, chloroform solvates of griseofulvin, cephalexin hydrate (better absorption than the same drug asolvate)
- ☐ The anhydrous form of ampicillin, when taken orally in a hard gelatin capsule formulation was found to possess higher dissolution rates and higher absorption rates than ampicillin trihydrate
- ☐ Hydration is used if the solvent was water while solvation if it was any other solvates (organic solvent)
- ☐ Asolvate : drug molecule crystals containing no solvent molecules trapped between them

- ☐ Anhydrates > hydrates this is bcz the anhydrous forms of the drug reacts more extensively with water compared to the already hydrated form which is considered to have a level of water saturation already

■ 5.4. Retardation of Phase Transformation

- ☐ PVP, pectin, acacia, gelatin, methylcellulose, carboxymethyl cellulose, surfactants retard phase transformation.
- ☐ These materials retard phase transformation by inhibiting crystal growth by adsorbing on to the surface of nucleated crystals or by increasing viscosity which in turn retards the diffusion that control the process of crystallization.
- ☐ This retardation has improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility

■ 5.5. Solid Dispersions

- ☐ The term solid dispersion is applied to those systems in which the dispersion of one or more active ingredients in an inert excipient or matrix (hydrophilic), prepared by fusion or melting-solvent method. where the active ingredients could exist in finely crystalline or amorphous states.
- ☐ Solid dispersions may also be called “solid state dispersions”.
- ☐ Solid dispersion provides particle size reduction and increased rates of dissolution
- ☐ Examples:
    - ✓ polyethylene glycols -Oxazepam, Nefidipine, Ketoprofen
    - ✓ Maltodextrins-Piroxicam solid dispersions

Hot Melt method

- ☐ Drug and carrier were melted together then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved, another important requisite is the thermo stability of the drug and carrier.

Solvent Evaporation Method

- ☐ Drug and carrier are dissolved in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion.

Eutectic Mixtures:

When two materials are completely miscible in there molten state they will solidify to form a eutectic mixture.

- At the eutectic composition, both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug.
- The process of eutectic formation may cause the drug to crystallize in a metastable state.
- Urea and succinic acid have been found to form simple eutectics with a wide variety of drugs

■ 6. Drug Derivatisation

- To increase the solubility of poorly soluble drugs

6.1. Prodrug approach:

- Prodrug is a compound that must undergo bioconversion before exerting its pharmacological effect.
- The functional groups-esters, thioesters, amides, acetals, and ketals are used.

6.2. Salt Formation:

- In general, aqueous solubility is a function of chemical structure, and salts represent the class of drugs that are most likely to attain the desired extent of solubility in water.
- Salts have improved solubility and dissolution characteristics in comparison to the original drug.
- An alkaloidal base is slightly soluble in water, but if the pH of medium is reduced by addition of acid, the solubility of the base is increased as the pH continues to be reduced.
- The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water.
- Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are water-soluble than the parent drug.
- The solubility of slightly soluble acid is increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates).

compound	***Solubility (mg/ml)***
Naproxin	***0.07***
Naproxin sodium	***266***
Tolmetin	***0.10***
Tolmetin sodium	***163***

■ Other Methods Include

Micronization:

- The solubility of drug is often intrinsically related to drug particle size.
- By reducing the particle size, the increased surface area improve the dissolution properties of the drug.

Solubilizing agents:

- The solubility of poorly soluble drugs can also be improved by various solubilizing materials.
- PEG 400 improves the solubility of hydrochlorthiazide.
- Solubility enhancement of poorly soluble drug, nimodipine by modified karaya gum.
- The aqueous solubility of halofantrine is increased by the addition of caffeine and nicotinamide.

COLLOIDS

Dispersed systems consist of :

a) Particulate matter (dispersed phase).

b) Dispersion medium (continuous medium).

- **Classification of dispersed systems (according to particle**

COARSE DISPERSION	**COLLOIDAL DISPERSION**	**MOLECULAR DISPERSION**
- Greater than 500 um	- 1 um to 500 um	- Less than 1 um
- Don't diffuse e.g. suspension & emulsion	- Very slow diffusion e.g. colloidal silver sol.	- Particles undergo rapid diffusion e.g. O2 & glucose
- Particles are visible under ordinary microscope.	- Particles resolved by electron microscope.	- Particles invisible in electron microscope.
- Do not pass through filter paper or semipermeable membrane.	- Pass through filter paper but not pass through semipermeable membrane.	- Pass through semipermeable membranes and filter paper.

Type of colloids depends on the medium and the dispersed phase

Dispersing medium	***Dispersed matter***	***Type of colloid***	***examples***
Gas	***Liquid***	***Aerosols***	***Fog, aerosol spray***
	solid	***Aerosols***	***smoke***
liquid	***Gas***	***Foam***	***Whipped cream***
	Solid	***Suspension***	***Mayonnaise***
	liquid	***Sol/Emulsion***	***paint***
solid	***Gas***	***Solid foam***	***Marshmallow***
	Solid	***Solid foam***	***Butter***
	liquid	***Solid sol***	***Ruby glass***

Types of colloidal systems

- According to the interaction between particles of dispersed phase & those of dispersion medium:
    - Lyophilic (solvent loving): the dispersed phase has high affinity for the dispersion medium
    - Lyophobic (solvent hating): the dispersed phase has low affinity for the dispersion medium
    - Association (amphiphilic).

hydrophilic and hydrophobic is used when the dispersion medium is aqueous.

1) Lyophilic colloids

- Colloidal particles interact to an appreciable extent with the molecules of the dispersion medium (solvent loving).
- Obtained simply by dissolving the material in the solvent (due to the high affinity)

Types of lyophilic colloids;

(According to type of solvent)

Hydrophilic colloids	Lipophilic colloids
Solvent: water.	Solvent*: non- aqueous, organic.*
Example: acacia, insulin. in water.	Example*: **rubber & polystyrene.***

- So: material that form lyophilic colloid in a certain solvent may not do so in another solvent, e.g.;
    - acacia + water ---------- lyophilic colloid (hydrophilic type).
    - acacia + benzene ------------ No lyophilic colloid formed.
- The dispersed phase does not precipitate easily (need neutralization of charge and removal of water layer)
- Addition of liquid less polar than water (acetone or alcohol) with small amount of electrolytes facilitate coagulation due to dehydration of the particles
- The sols are quite stable as the solute particle surrounded by two stability factors:

    - ✓ a- Negative or positive charge
    - ✓ b- Layer of solvent

- ☐ If the dispersion medium is separated from the dispersed phase, the sol can be reconstituted by simply remixing with the dispersion medium. Hence, these sols are called reversible sols
- ☐ Ammonium sulphate the most widely used electrolyte suitable for fractional precipitation of serum protein (at low conc. precipitate globulins while at high conc. precipitate albumin)
- ☐ Heat, acids, alkalies and some salts cause denaturation of lyophilic colloidal materials (not reversible)
- ☐ Similarly charged hydrophilic colloid easily mixed with no precipitation while that of different charge interact together with precipitation (e.g antigen antibody reaction)
- ☐ More viscous than the dispersion medium due to swelling of the particles by the solvent (concentrated sols form gels)
- ☐ Gels: e.g. lyophilic sol of gelatin or agar in water which is elastic in behavior and the sol-gel transformation is reversible (depend on temp.).
- ☐ Gel structure is broken on shaking but gel reform on stand (thixotropy)
    - ✓ 50 % suspension of zinc oxide in paraffin
    - ✓ Oily injection of procaine penicillin
    - ✓ Ferric hydroxide gelled by addition of Sod. Chloride, bentonite,
- ☐ Dried gelatin or agar swell with water (the volume of swollen gel is less than that of water and dried gel) by a process called imbibition while liberation of water on storage called synersis
- ☐ Ca++ and Zn ++ ions increase gel strength of bentonite which is negatively charged while peptizing agents will liquefy gels

However rigid gel contains chemical bonds between molecules of the dispersed phase which give irreversible gelling process e.g. silica gel (drying of the gel has great affinity to water so silica gel is a drying agent)

<u>2) Lyophobic colloids</u>

- ☐ Colloidal particles have very little or no attraction for the dispersion medium (solvent hating).

- Colloidal particles: inorganic particles (e.g. gold, silver, sulfur….) Dispersion medium: water.
    - These colloids are easily precipitated on the addition of small amounts of electrolytes, by heating or by shaking
    - Less stable as the particles surrounded only with a layer of positive or negative charge which lead to repulsion between particles
    - Once precipitated, it is not easy to reconstitute the sol by simple mixing with the dispersion medium. Hence, these sols are called irreversible sols.
- Not obtained simply i.e need special method for preparation
- Addition of small amount of lyophilic or lyophobic colloid to a lyophobic colloid of opposite charge make the latter more sensitive to coagulation by electrolytes
- Addition of excess lyophilic sol to a lyophobic sol (less precipitation of lyophobic by electrolyte)
    - e.g. tincture of benzoin + ammonium chloride soln lead to coagulation while in the presence of water mucilage of tragacanth no coagulation occur (mucilage of tragacanth is a lyophilic sol that protect the lyophobic resin sol).
- lyophilic sol with weak opposite charge than lyophobic one give better protection where neutralization of the charge occur and the residual charge of the lyophobic particles enable them to retain colloidal condition and behave like lyophilic sol.

3. Association colloids:

- Certain molecules or ions termed amphiphile (surface active agent SAA) are characterized by two distinct regions of opposing solution affinities within the same molecules or ions.
- At low concentration: amphiphiles exist separately (subcolloidal size)
- At high concentration: form aggregates or micelles (50 or more monomers) (colloidal size)
- As with lyophilic sols, formation of association colloids is spontaneous, provided that the concentration of the amphiphile in solution exceeds the CMC.
- Amphiphiles may be

- ✓ 1. Anionic (e.g., Na. lauryl sulfate)
- ✓ 2. Cationic (e.g., cetyl triethylammonium bromide)
- ✓ 3. Nonionic (e.g., polyoxyethylene lauryl ether)
- ✓ 4. Ampholytic (zwitterionic) e.g., dimethyl dodecyl ammoniom propane sulfonate.

Comparison of properties of colloidal sol

	Lyophilic (solvent-loving).	**Lyophobic (solvent-hating).**	**Association (amphophilic).**
Dispersed phase	Large organic molecules lying within colloidal size	Inorganic particles such as gold or silver	Aggregates (micelles) of small organic molecules or ions whose size is below the colloidal size
Solvation	Solvated	little	Hydrophilic or lipophilic portion of the molecules is solvated depending on the medium
Preparation	Spontaneous by dissolving in solvent	Needs special procedure	Spontaneous when conc. of amphiphiles exceeds CMC
Viscosity	Viscosity increased as the conc. increase. At certain conc. Gel sol gel formation	Not greatly increased due to un solvation	Increased as conc. of amphiphile increase as micelles no. increase & become asymmetric.
Effect of electrolytes	Stable in presence of electrolytes Desolvation and salting out in high conc.	Unstable due to neutralization of charges on particles	Cmc is reduced and salting out occur at high salt conc

Preparation of colloids

- ❑ Lyophilic sols and association colloidal sols are usually prepared by dissolving the dispersed phase in water

❑ While lyophobic colloids were prepared by :

- ✓ Condensation process:
  - ❖ 1) Change of solvent   2) Double decomposition
  - ❖ 3) Reduction   4) Oxidation
- ✓ Dispersion methods: coarse particles are reduced in size by:
  - ❖ 1) Ultrasonic generator   2) Electric arc.
  - ❖ 3) Colloid mill.   4) peptization

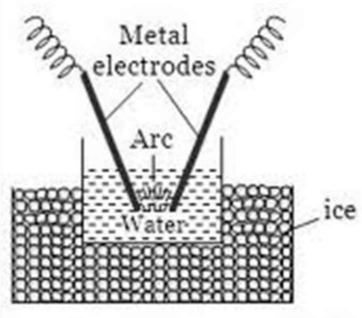
2) Lyophobic colloids (Dispersion methods)

1)Ultrasonic generator:

❑ • Dispersion achieved by high intensity UG at frequency more than 20,000 cycles/second e.g. colloidal dispersions containing graphite, mercury, metal oxides and sulphur

2) Electric arc:

• Involves production of an electric arc within the liquid and dispersion achieved by intense heat generated by the arc so some metal of the electrodes dispersed as vapor then condense to colloidal particles e.g. colloidal solutions of metals as copper, gold, mercury, silver.



Bredig's arc method

3) Colloidal mill:

❑ • Material sheared between 2 rapidly rotating close plates (in opposite directions).

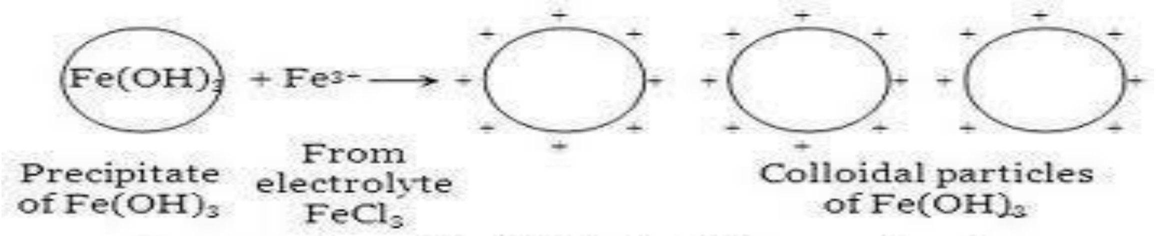
❑ • Low efficiency & reduce the size of small proportion of particles only and mix with a dispersing agent as protective colloids, peptizing agent, soap (act as a colloidal stabilizer)

4) peptization:

❑ Achieved by addition of electrolytes to precipitates that carry a small net charge.

e.g. negatively charged precipitates may be dispersed by the addition of alkali

Precipitate that contain large quantity of electrolyte may be peptized by washing with water (dialysis) to remove some electrolyte



Preparation of colloidal sol by peptization

2) Lyophobic colloids (Condensation methods)

- Materials of sub colloidal dimensions are caused to aggregate into particles with colloidal size range by:

1) Change in solvent:

- • Change in solvent leading to super saturation that will result in formation & growth of nuclei. (colloidal system formation) e.g. sulfur and alcohol in excess of water, simple tincture of benzoin is poured in water.

2) Oxidation:

- Hydrogen sulfide by oxidation result in sulfur atoms that give sulfur sol,
- Colloidal iodine prepared by oxidizing sod. iodide with sodium nitrate in acid solution containing glucose.

3) Double decomposition:

- Hydrogen sulfide + arsenous acid Double decomp. Arsenous sulfide sol (yellow sol transparent to transmitted light and turbid to reflected light).

4) Reduction:

- Colloidal silver is prepared by reduction of silver oxide with tannic acid
- Ammonia was added drop wise to silver nitrate solution (until 1st precipitate just redissolves) then dilute water and 2% tannic solution
- Colloidal silver is brown solution that is greenish by reflected light, can be stabilized with albumin

Purification of colloids

- Many lyophobic sols contain more or less material in true solution. which may be undesirable for number of reasons; e.g., electrolyte impurities : cause the flocculation of the sol.
- a) Dialysis. b) Electro dialysis. c) Ultra filtration

a)- Dialysis

- Depend on difference in size between colloidal particles & molecular particles (impurities).

- **Technique*;***

1) use semi-permeable membrane

e.g. collodion (nitrocellulose), cellophane.

2) pore size of used semi-permeable membrane prevent passage of colloidal particles & permit passage of small molecules & ions (impurities) such as urea, glucose, and sodium chloride.

- A type of dialysis equipment; “Neidle dialyzer”

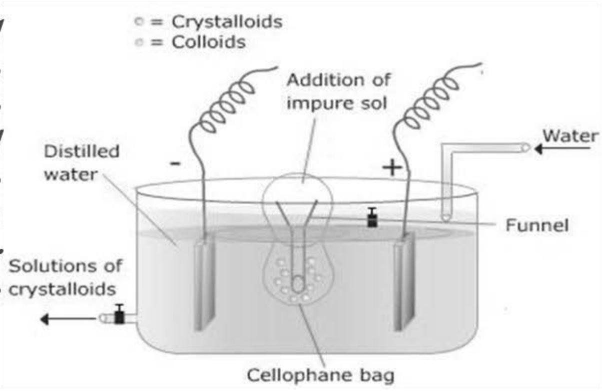
At equilibrium, the colloidal material is retained in one compartment, while the sub-colloidal material is distributed equally on both sides of the membrane.

By continually removing the liquid in other compartment, it is possible to obtain colloidal material in 1st compartment that is free from sub-colloidal contaminants.

B) Electro dialysis

- An electric potential may be used to increase the rate of movement of ionic impurities through a dialyzing membrane and so provide rapid purification.
- Electrodialysis is carried out in a three compartment vessel with electrodes in the outer compartments containing water and the sol in the center compartment

- *Application of electrical potential causes cations to migrate to the negative electrode compartment and anions to move to the positive electrode compartment, in both of which running water ultimately removes the electrolyte.*

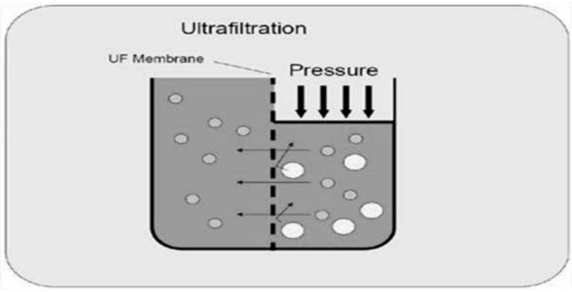


c) Ultra filtration

- Apply pressure (or suction) result in ------- Solvent & small particles forced across a membrane while colloidal particles are retained.
- The membrane must be supported on a sintered glass plate to prevent rupture due to high pressure.

- Pore size of the membrane can be increased by soaking in a solvent that cause swelling

e.g. Cellophane swell in zinc chloride solution.
e.g. Collodion (nitrocellulose) swell in alcohol.



- Purification of pepsin enzyme is an example of using dialysis in pharmacy. Where pepsin is prepared by scraping off the lining mucosa of the pig stomach then put in HCl acid and precipitated by sat. soln. of sodium chloride, filtrate, redissolve in water and dialysis to separate acid and salt leaving pepsin in colloidal soln. that then precipitated by the addition of alcohol

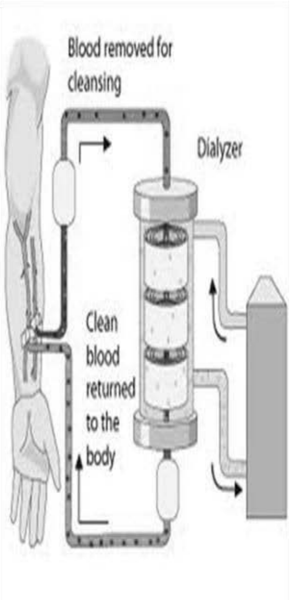
Artificial kidney machine

patient's blood (arterial) pass through cellophane coils (ideal semi permeable membrane for haemodialysis).

- ***cellophane pass urea, glucose, electrolytes but don't pass plasma proteins & blood cells***
- ***pure dialyzed blood enter the body again through a vein.***

N.B.

- ***success of the artificial kidney machine depends on its ability to reduce blood urea.***
- ***Cellophane coils are supported on a drum rotating in electrolyte solution (rinsing fluid).***



Importance of the rinsing solution:

- Substances present in excess in blood (e.g. urea) diffuse from blood to the rinsing solution.
- Substances which are deficient in blood (e.g. bicarbonate) diffuse from the rinsing solution to blood.
- Substances which are present in normal amounts in blood are kept unaltered have the same conc. in both blood and rinsing solution.

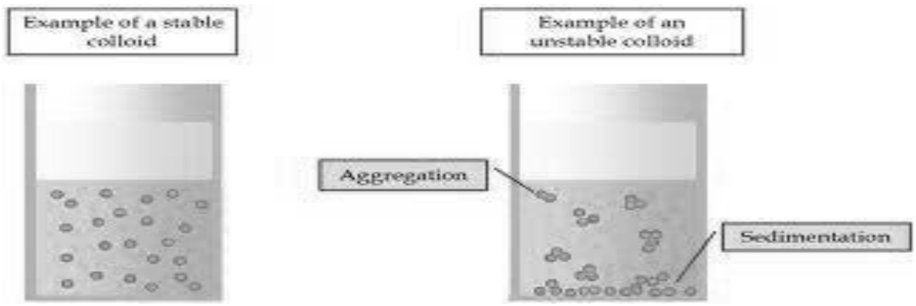
Stabilization of colloid

Electrostatic repulsion

- A colloid is neutral
- BUT, when a colloid is placed in an electric field, the particles all migrate to the same electrode.
- The colloid attracts ions of the same charge which surround the colloid particle.
- Ions of the opposite charge surround the first layer of ions.
- Being surrounded by ion, the colloid particles repel other colloid particles, and so are unable to aggregate to precipitate out

To destroy a colloid (coagulation)

- Heat the colloid
    - Heating increases velocities of particles
    - Particles can collide with enough energy to knock off the ion barriers, thus allowing the colloid particles to aggregate and precipitate out.
- Add an electrolyte
    - the electrolyte will neutralize the ion layers
    - Ex: deposition of clay where a river reaches the ocean. The high salt content of the seawater causes the suspension of clay particles to coagulate.



Shape of colloidal particles

- Particles are present in different shapes as spherocolloids (may not be perfectly spherical) or linear colloids (in the form of rods, coils or branched threads)
- E.g albumin present as a fiber coiled up into globule however after denaturation it becomes extended into a fiber.

- ☐ The more extended the particle, the greater its specific surface & the greater the opportunity for attraction.
- ☐ Properties of colloids as flow, sedimentation rate & O.P. are all affected by the shape of the particles.
- ☐ The viscosity of linear colloid is high because of forming a network with the dispersion medium while spherocolloids have lower viscosity.
- ☐ Particles in the colloidal state are of a size range that they possess a surface area which is enormous compared with the surface area of an equal volume of larger particles (6 m2 become up to 60 m2 total surface area)
- ☐ The color of certain substance depend on particle size e.g. antimony and arsenic trisulpides are red in color in coarse powder form, as the particles are reduced in size the color change to yellow.
- ☐ With regard to the size of the material in the colloidal state colloidal particles may be separated from subcolloidal material such as small molecules or ions by dialysis

Properties of colloids

1. **Optical properties.**
2. **Kinetic properties.**
3. **Electrical properties**

- ☐ **Optical properties:**

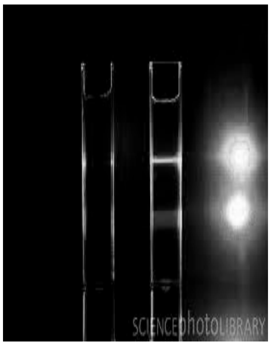
    - ✓ 1) Light scattering (Tyndall effect).
    - ✓ 2) Ultra microscope.
    - ✓ 3) Electron microscope.

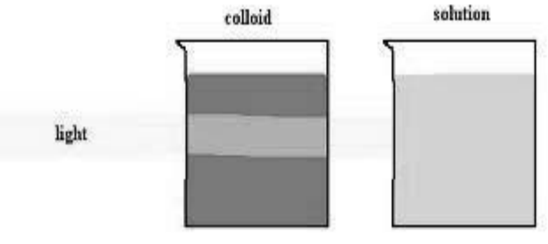
1) Light scattering (Tyndall effect)

- ☐ True solutions do not scatter light and appear clear but colloidal dispersions contain opaque particles that scatter light and thus appear turbid.
- ☐ Tyndall effect: when a beam of light pass through a colloidal sol, scattered light cause the sol to appear turbid.
- ☐ Importance of light scattering measurements:
    - ✓ 1) Estimate particle size.

✓ 2) Estimate particle shape.

✓ 3) Estimate particles interactions.





A beam of light shining toward the solution and the colloid. The light particles are suspended when passing through the colloid's large particles, but not when passing through the solution's smaller particles.

2) Ultra microscope:

☐ Particles appear as bright spots of light against the dark background of the microscope.

☐ Used in the technique of micro electrophoresis for measuring particle charge.

3) Electron microscope:

☐ Give actual picture of the particles (up to 5A).

☐ Used to observe the size, shape and structure of sols.

☐ High energy electron beams are used. (have greater resolving power)

☐ One disadvantage is; only dried samples can be examined. not give information on solvation.

☐ **B) Kinetic properties**

Which relate to the motion of the particles within the dispersion medium as following:

✓ Brownian motion.

✓ Diffusion.

✓ Osmotic pressure.

✓ Light scattering

✓ Sedimentation.

✓ The Donnan membrane effect.

✓ Viscosity.

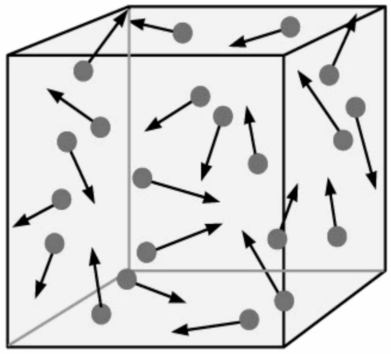
1) Brownian motion

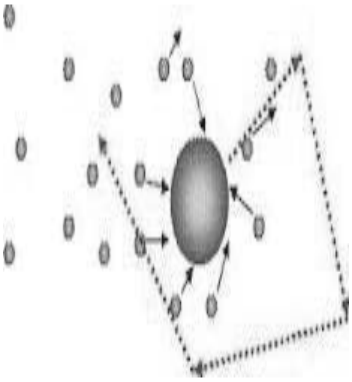
☐ Definition: colloidal particles are subjected to random collision with molecules of the dispersion medium (solvent) so each particle move in irregular and complicated zigzag pathways.

☐ First observed by Robert Brown (1827) with pollen grains suspended in water.

☐ The velocity of particles increases with decreasing particle size and viscosity.

☐ Increasing the viscosity of dispersion medium (by glycerin) decrease then stop Brownian motion.





2) Diffusion:

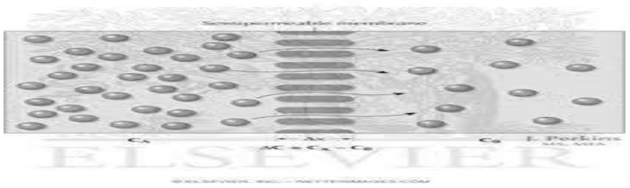
☐ Definition: As a result of Brownian motion particles pass (diffuse) from a region of higher concentration to one with lower conc. until equilibrium is attained.

☐ Rate of diffusion is expressed by; Fick’s first law: $dm/dt = -DA\ dc/dx$

Where dm is the mass of substance diffusing in time dt across an area A under the influence of a concentration gradient dC/dx. D is the diffusion coefficient.

☐ The minus sign denotes that diffusion takes place in the direction of decreasing concentration.

☐ The rate of diffusion decrease as medium viscosity increase.

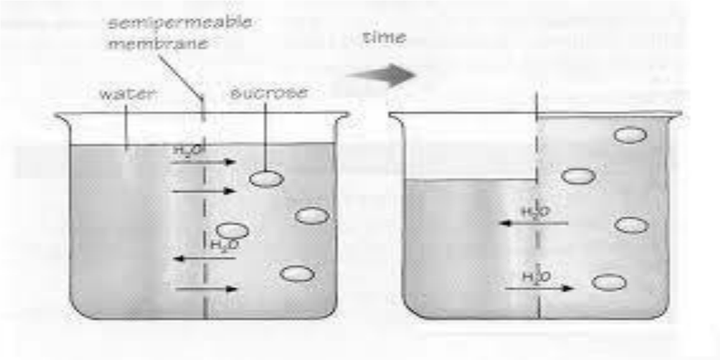


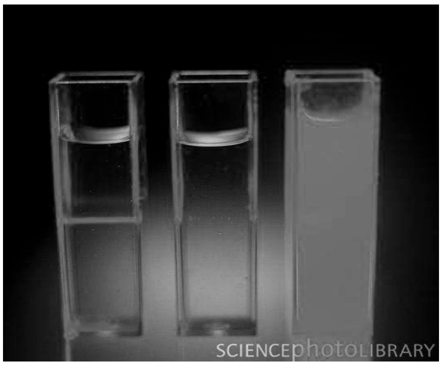
3) Osmotic pressure

- The method is based on Van's Hoff's law; $P = RTC / M$

From the equation; a) The osmotic pressure (P) depends on molar conc. of the solute (C) & on absolute temp. (T). b) The osmotic pressure is inversely proportional to molecular weight (M). R= molar gas constant

- The equation is valid for true solution and very dilute solutions in which the molecules do not interact mutually (e.g. egg albumin and glycogen).
- For linear colloid use $P = RTC / M + Bc$ where b is the interaction factor (this interaction between solvent and solute lead to increase in the solute concentrations)





4) Light scattering

- Optical technique used for determination of particle size or molecular weight of spherocolloidal material
- Using electron microscope attached to a photometer where the decrease in the intensity of the transmitted light is proportional to colloidal particle size
- Laser light passing first through tap water is revealed as a single beam. On passing through distilled water (middle), so little dispersion of light occurs that the beam can hardly be seen at all. At right the colloidal suspension of gelatin has caused total dispersion of the light,

5) Sedimentation

- Stoke's law: $V = 2r^2(p-p_o) g / 9 \eta$
  - ✓ v: velocity of sedimentation of spherical particles.
  - ✓ p: density of the spherical particles.
  - ✓ p_o: density of the medium.
  - ✓ η: viscosity of the medium.
  - ✓ g: acceleration due to gravity.

- ☐ At small particle size (less than 0.5 um) Brownian motion is significant & tend to prevent sedimentation due to gravity & promote mixing instead. So, we use an ultracentrifuge which provides stronger force so promote sedimentation in a measurable manner.

6) viscosity

- ☐ Definition: The resistance of a system to flow under an applied pressure
- ☐ Viscosity of colloid allows
  - ✓ 1- Calculation of the molecular weight.
  - ✓ 2- Provide useful information about the shape of the colloidal particles.

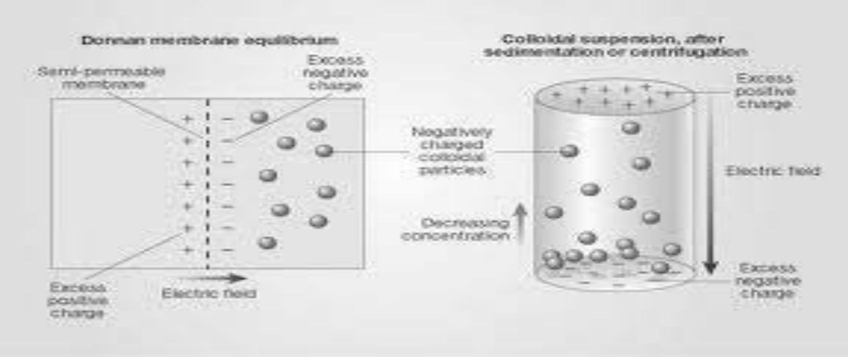
Spherocolloidal dispersions are of relatively low viscosity.

On the other hand linear colloidal dispersions are of high viscosity.

If linear colloidal particles coil up into spheres the viscosity of the system falls due to changing the shape (resemble spherocolloidal).

7) The Donnan membrane effect.

- ☐ Definition: Diffusion of small ions through a membrane will be affected by the presence of a charged macromolecule that can't penetrate the membrane due to its size.
- ☐ Application: Facilitating the absorption of ionizable drugs from GIT by co-administration of macromolecules of same charge so mutual ionic repulsion occurs.e.g co-administration of anionic macromolecule e.g. sodium carboxy methyl cellulose, with a diffusible anion e.g. potassium benzyl penicillin to enhance diffusion of the later across body membranes.



- ☐ **C) Electrical properties**
  - ✓ Electrical properties of interfaces.
  - ✓ The electrical double layer

1) Electrical properties of interfaces

- Most surfaces acquire a surface electric charge when brought into contact with an aqueous medium, the principal charging mechanisms being as follows:
  - 1) Ion dissolution.
  - 2) Ionization.
  - 3) Ion adsorption.
- Ion dissolution
- Surface charge of colloidal particle is controlled by the charge of ion present in excess in the medium.
- Example; 1) AgNo3 + NaI -------- AgI +NaNo3
  - Silver iodide in a solution with excess iodide Particles acquire – ve charge & vice versa. if excess Ag the charge will be +ve since the conc of Ag and I determine the electric potential
  - Aluminum hydroxide in a solution with excess hydroxide ------------ particles acquire – ve charge & vice versa
  - Potential determining ions: ions whose conc. determine the electric potential at the particle surface (e.g. Ag+ , I -, H+, OH-)
- 2) Ionization
- Surface charge of colloidal particle is controlled by the ionization of surface groupings examples:
  - a) polystyrene latex has carboxylic acid group at the surface, ionize to give negatively charged particles.
  - b) acidic drugs as ibuprofen & nalidixic acid acquire surface negative charge.
  - c) Amino acids & proteins have carboxyl & amino groups whose ionization depend on the pH as follow;
- NH2-R-COO -------- NH3-R-COO --------- NH3-R-COOH

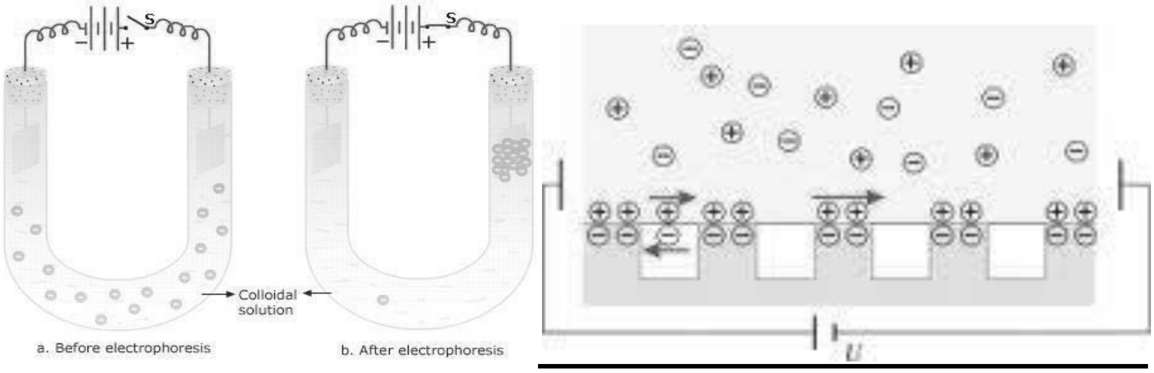
at high pH	zwitter ion	at low pH
alkaline medium	iso-electric point	acidic medium
Negatively charged	zero charge	positively charged

- ☐ A protein is least soluble at its iso-electric point and is readily precipitated e.g. insulin is precipitated from aqueous alcohol by adjusting the solution to the iso-electric point (pH 5-6)
- ☐ Iso electric point:
  - ✓ pH at which +ve charges = -ve charges,
  - ✓ i.e. net charge of the amino acid = zero.
  - ✓ It is a definite pH specific for each protein.
  - ✓ At this pH protein is least soluble& precipitated.
- ☐ Q; How can you precipitate insulin???
- ☐ BY ADJUSTING THE pH OF THE SOLUTION TO THE ISO ELECTRIC POINT OF INSULIN (PH 5.2).
- ☐ 3) Ion adsorption
- ☐ Surface charge of colloidal particle is controlled by the unequal adsorption of oppositely charged ions
- ☐ Examples;
  - ✓ Surfaces of sol in water are more often –ve charged than +ve charged?!!!
  - ✓ Because cations are more hydrated than anions so cations reside in the bulk while less hydrated anions adsorbed on the surface.

2) The electrical double layer

- ☐ 1) Electrophoresis: The movement of colloidal particles under the influence of electric field.
- ☐ When an electric field is applied across the colloidal solution, the colloidal particles migrate to oppositely charged electrode where they get neutralized
- ☐ The colloidal particles move with respect to the liquid upon maintaining a potential difference across the sol. Used generally for separation of protein using paper electrophoresis
- ☐ The movement rate of protein is dependant on zeta potential, molecular size and potential gradient where a mixture of proteins can be resolved into separate zones if the mobilities of the individual proteins are different
- ☐ # The electrophoretic mobility of a protein at the iso-electric point is zero

- 2) Electro-osmosis: Is the movement of the liquid with respect to the particles under the influence of potential gradient. The dispersion medium itself begins to move in an electric field.



Pharmaceutical applications of colloids

- 1) Colloidal silver iodide, silver chloride & silver protein are effective germicides & not cause irritation as ionic silver salts.
- 2) Colloidal copper used in cancer.
- 3) Colloidal gold used as diagnostic agent.
- 4) Colloidal mercury used in syphilis.
- 5) Association colloids (SAA) are used to increase solubility & stability of certain compounds in aqueous & oily pharmaceutical preparations e.g. oil soluble vitamins A, D and K also essential oils and phenols of low water solubility.
- 6) Efficiency of certain substances is increased when used in colloidal form due to large surface area.
    - ✓ e.g. efficiency of kaolin in adsorbing toxins from GIT.
    - ✓ e.g. efficiency of aluminum hydroxide as antacid.
- 7) Blood plasma substitutes as dextran, PVP & gelatin are hydrophilic colloids used to restore or maintain blood volume.
- 8) Iron - dextran complex form non-ionic hydrophilic sols used for treatment of anemia.
- 9) Artificial rain: Cloud consists of charged particles of water dispersed in air. These particles are neutralized by spraying oppositely charged particles over a cloud. These neutralized particles of water combine to form large water drops. Thus, artificial rain is caused by the aggregation of minute particles of water to form large particles .

- 10) Food items: Large numbers of food articles which we use in our daily life are colloidal in nature. For example, milk, butter and ice creams are colloidal in nature

- 11)The product is made of nano material and high-performance resin by nano technology, it can naturally decompose the organism and be anti-dust in air and on the surface of glass and other basic material, so the building and glass surface can be water-proof, hydrophilic, anti-dust, anti-fog and air purifying effects. and they realize self cleaning

SOLUBILITY and DISSOLUTION

Solutions

- ***Solutions*** are homogeneous mixtures of two or more pure substances.
- In a solution, the solute is dispersed uniformly throughout the solvent.

State of Solution	State of Solvent	State of Solute	Example
Gas	Gas	Gas	Air
Liquid	Liquid	Gas	Oxygen in water
Liquid	Liquid	Liquid	Alcohol in water
Liquid	Liquid	Solid	Salt in water
Solid	Solid	Gas	Hydrogen in palladium
Solid	Solid	Liquid	Mercury in silver
Solid	Solid	Solid	Silver in gold

Definitions

- ***Dissolution:*** The transfer of molecules or ions from a solid state into solution.

- ***Solubility*** **-** how much of a particular solute can dissolve in a certain solvent at a specified temperature

- The solubility of NaCl at 25 ° C is 36.2 g per 100 ml of water

---

Ways of Expressing Solubility & Concentrations of Solutions

Percentage

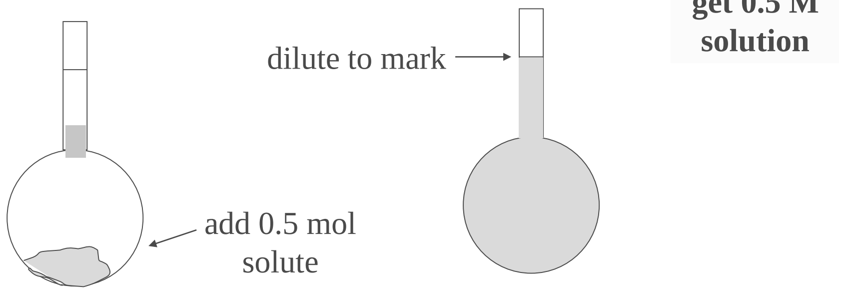
$$\underset{(\%\ \text{w/v})}{\text{Concentration}} = \frac{\text{Weight of solute}}{\text{Volume of solution}} \times 100$$

Molarity (M): the number of moles of solute contained in 1 Litre of solution

$$\text{Molarity}\ (\text{mol}/L) = \frac{\text{moles of solute}}{\text{liters of solution}}$$

Convenient way to prepare solution in lab,

1Litre flask (1000.0 mL)



Molarity

- ***Examples:***

1. What is the molarity (M) of a solution containing 1.5 mols of sugar in 200 mL of solution?

n = 1.5 mol   V = 200 ml = 0.2L

$$M = n / V$$

= 1.5 mol / 0.2 L   =**7.5 mol/L**

2. How many moles of sugar are needed to prepare 620 ml of 2.0 M sugar solution? (**1.24 mol)**

***Molality* (*m*)**: the number of moles of solute divided by the mass of solvent

$$m\ (mol/Kg) = \frac{\text{mol of solute}}{\text{Kg of solvent}}$$

- More <u>**precise**</u> description of concentration because it is not affected by temperature.

Parts: the number of parts of solute dissolved in a stated number of parts of solution.

e.g. 5ppm *means:*

5 gm of solute dissolved in 10^6 ml of solution.

Mole Fraction (X)

The number of moles of solute divided by the total number of moles of solute and solvent.

$$X_A = \frac{moles\ of\ solute}{moles\ of\ solute+moles\ of\ solvent}$$

THE PROCESS OF DISSOLUTION

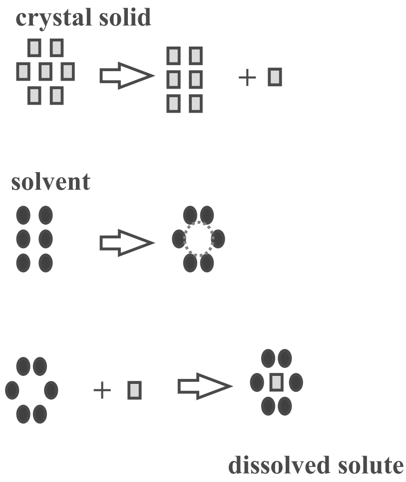
1- interfacial reaction:

A-Removal of drug molecules from a solid, so, the solvent/solute forces of attraction overcome the cohesive forces between solid molecules

B- drug molecules incorporated within the solvent

2- Diffusion through the boundary layer:

Transport of drug molecules away from solid/liquid interface into bulk of liquid



The process of solubilization involves the breaking of inter-ionic or inter-molecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

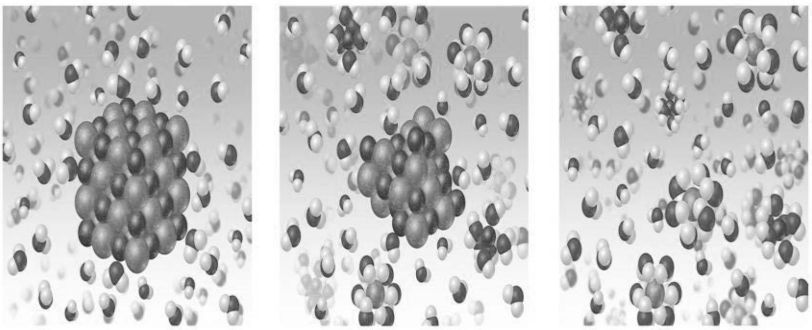
1: Holes opens in the solvent

2: Molecules of the solid breaks away from the bulk

3: The freed solid molecule is integrated into the hole of the solvent

How Does a Solution Form?

1. Solvent molecules attracted to surface ions.
2. Each ion is surrounded by solvent molecules.
3. Energy change



Ionic solid dissolving in water

Energy Changes in Solution

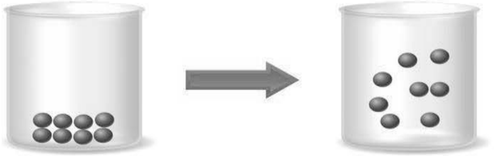
To determine the enthalpy change, we divide the process into 3 steps.

1. Separation of solute particles ($\Delta H1$).
2. Separation of solvent particles to make ‘holes’ ($\Delta H2$).
3. Formation of new interactions between solute and solvent ($\Delta H3$).

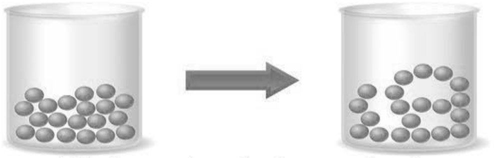
- We define the enthalpy change in the solution process as

  $\Delta H_{soln} = \Delta H1 + \Delta H2 + \Delta H3$

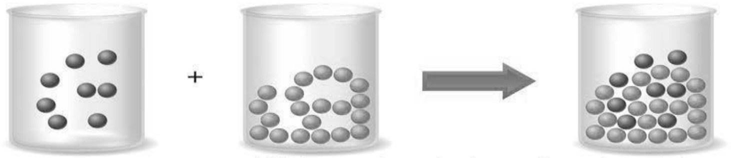
- ΔH_{soln} can either be positive or negative depending on the intermolecular forces



ΔH_1: Separation of solute molecules



ΔH_2: Separation of solvent molecules



ΔH_3: Formation of solute-solvent interactions

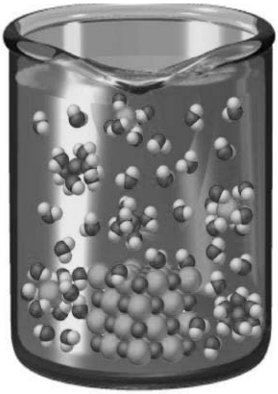
Energy Changes in Solution (cont.)

- The reaction may be ***exothermic*** when heat is released as a result of solubility process, and the flask gets warm (less common). *negative* ΔH_{soln}

- The reaction may be ***endothermic*** when the system consumed heat to do the solubility process, and the flask gets cold . *positive* ΔH_{soln}

- Dissolution process is ***spontaneous.*** $\Delta H_{soln} = 0$

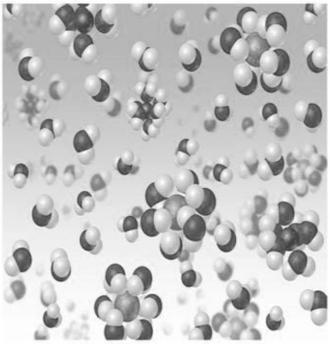
Degree of saturation



- ***Saturated solution***
  - ➢ Solvent holds as much solute as is possible at that temperature.
  - ➢ Undissolved solid remains in flask.
  - ➢ Dissolved solute is in dynamic equilibrium with solid solute particles.

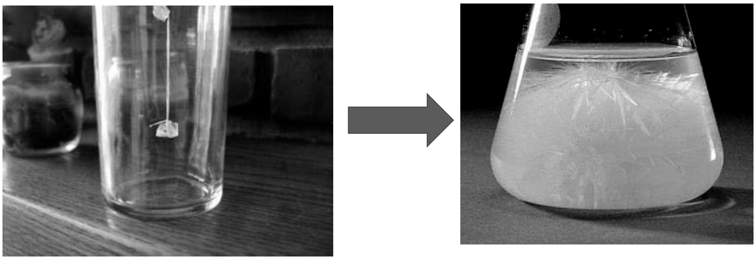
Degree of saturation

- ***Unsaturated Solution***
  - ➢Less than the maximum amount of solute for that temperature is dissolved in the solvent.
  - ➢No solid remains in flask.



Degree of saturation

- ***Supersaturated***
  - Solvent holds *more* solute than is normally possible at that temperature.
  - These solutions are unstable; **crystallization can often be stimulated by *adding a "seed crystal" or scratching the side of the flask.***

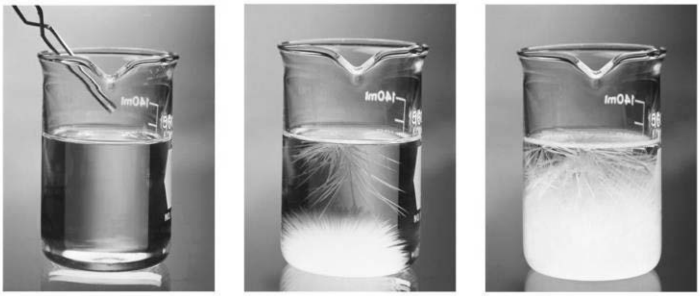


Crystallization: **opposite of the solution process (solute becomes reattached to surface of crystal)**

$$\textbf{Solute} + \textbf{Solvent} \underset{\text{crystallize}}{\overset{\text{dissolve}}{\rightleftharpoons}} \textbf{Solution}$$

Saturated solution: no more solid will dissolve and a dynamic equilibrium exists between the solution and the undissolved solid

Degree of saturation



Unsaturated, Saturated or Supersaturated?

⇒ Depends on How much solute can be dissolved in a solution

Unsaturated Solution:

A solution that contains less solute than a saturated solution

Example: you dissolved some salt into a cup of water. If you try to add more, it will still dissolve.

Saturated Solution:

A solution that contains the maximum amount of dissolved solute

Example: you dissolved all of the salt that you can into a cup of water. If more is added, it falls to the bottom and won't dissolve.

Supersaturated Solution:

A solution that contains more dissolved solute than a saturated solution.

Example: you dissolved all of the salt that you can into a cup of water. You heat it up and dissolve more. When it cools down, it is supersaturated.

Solubility

Rule to determine solubility

LIKE DISSOLVES LIKE

Compounds of similar polarity dissolve in one another

i.e. **Water** can dissolve **polar substances**, such as alcohol and ionic compounds. However, it is **not** a good solvent for **nonpolar** materials.

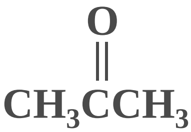
Prediction of solubility

Solubility definitions[3,4, 5]:

Definition	**Parts of solvent required for one part of solute**
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

SOLUBILITY OF LIQUID IN LIQUID

Polar liquids tend to dissolve in polar solvents due to dipole-dipole and H-bonding interactions



$$CH_3\overset{\overset{O}{\|}}{C}CH_3$$

acetone

CH_3CH_2OH

ethanol

Miscible: soluble in all proportions (liquids)

Immiscible: do not dissolve in one another

Nonpolar liquids tend to be insoluble in polar liquids; e.g. hexane (C_6H_{14}) does not dissolve in water.

Increasing the nonpolar character of a substance will decrease its solubility in water.

Solubility and Polarity	Solubility in	Solubility in
Alcohol	**H_2O**	**C_6H_{14}**
CH_3CH_2OH	∞	0.12
$CH_3CH_2CH_2OH$	∞	∞
$CH_3CH_2CH_2CH_2OH$	0.11	∞
$CH_3CH_2CH_2CH_2CH_2OH$	0.030	∞
$CH_3CH_2CH_2CH_2CH_2CH_2OH$	0.0058	∞
mol alcohol/100 g solvent		

SOLUBILITY OF GASES IN LIQUID

SOLUBILITY OF GASES IN LIQUID

- In general, the solubility of gases in water increases **with increasing mass.**

Why?

- Larger molecules have stronger dispersion forces.

- Usually, **increase pressure** will increase gas solubility

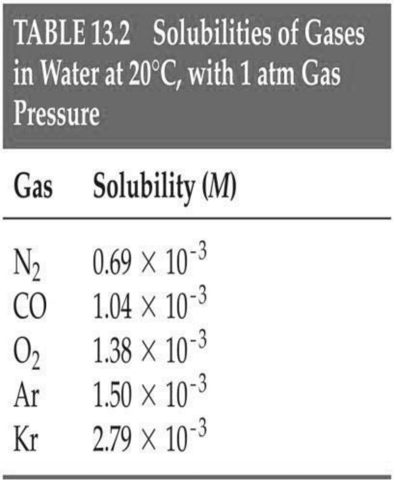


TABLE 13.2 Solubilities of Gases in Water at 20°C, with 1 atm Gas Pressure

Gas	Solubility (*M*)
N_2	0.69×10^{-3}
CO	1.04×10^{-3}
O_2	1.38×10^{-3}
Ar	1.50×10^{-3}
Kr	2.79×10^{-3}

FACTORS AFFECTING SOLUBILITY

- **Molecular structure of solute**
- **Temperature**
- **Pressure (gas solute only)**
- **Molecular size of solute**
- **Polarity**
- **Polymorphs**

1.**Effect of Structure**

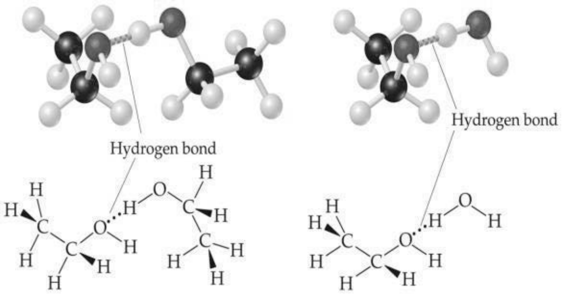
- Introduction of hydrophilic hydroxyl group…….large improvement in water solubility

(phenol vs. benzene)

- Conversion of weak acid into its salt…..increase ionic dissociation and hence increase water solubility

(salicylic vs. its sodium salt)

1. Effect of Structure (cont.)



The stronger the intermolecular attractions between solute and solvent, the more likely the solute will dissolve.

Example: ethanol in water

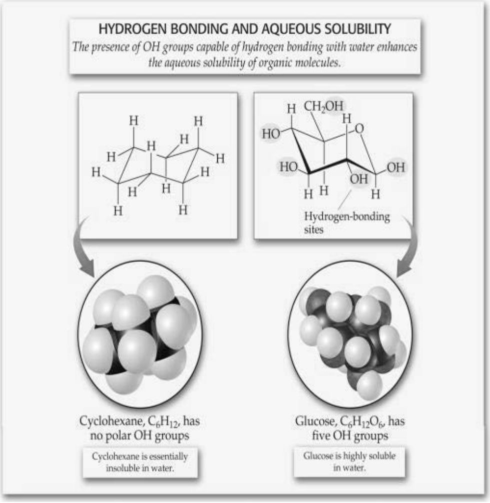
Ethanol = CH_3CH_2OH

Intermolecular forces = H-bonds; dipole-dipole; dispersion (Van der Waal bond)
Ions in water also have ion-dipole forces.

1. Effect of Structure (cont.)

Glucose (which has hydrogen bonding) is very soluble in water.

Cyclohexane (which only has dispersion forces) is not water-soluble.



HYDROGEN BONDING AND AQUEOUS SOLUBILITY

The presence of OH groups capable of hydrogen bonding with water enhances the aqueous solubility of organic molecules.

Cyclohexane, C_6H_{12}, has no polar OH groups

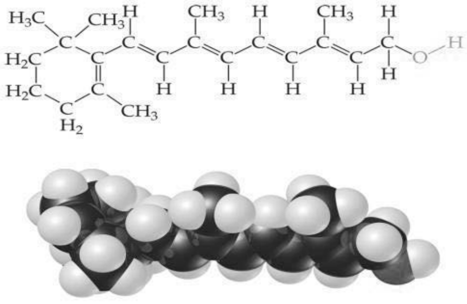
Cyclohexane is essentially insoluble in water.

Glucose, $C_6H_{12}O_6$, has five OH groups

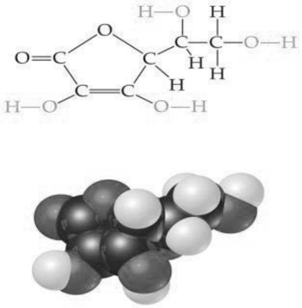
Glucose is highly soluble in water.

1. Effect of structure (cont.)

- Vitamins A, D, K and E is soluble in nonpolar compounds (like fats).
- Vitamins B and C is soluble in water.

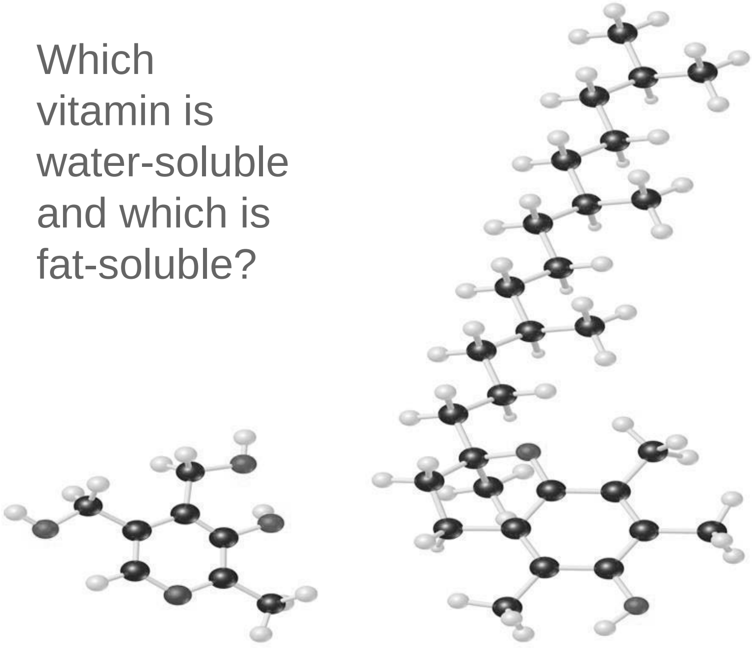


Vitamin A



Vitamin C

Which vitamin is water-soluble and which is fat-soluble?



Vitamin B_6 Vitamin E

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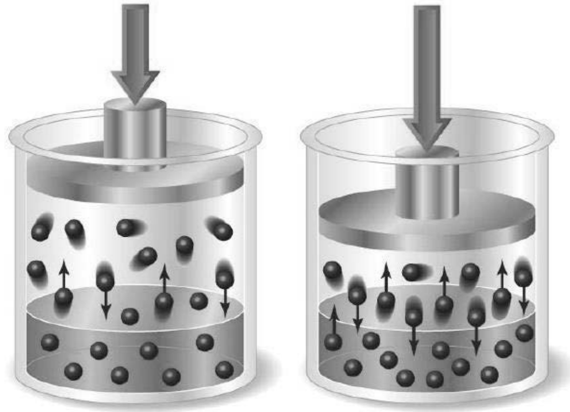
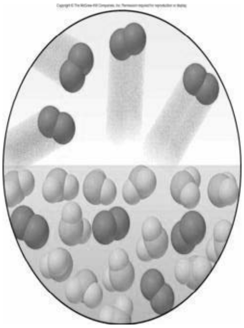
2. Effect of Pressure on solubility

Increasing pressure above solution forces more gas to dissolve.





2. Effect of Pressure (cont.)

- **The solubility of liquids and solids does not change appreciably with partial pressure.**

- **But, the solubility of a gas in a liquid is directly proportional to the partial pressure above that gas.**
- **Effect of pressure is significant.**

2. Effect of Pressure (cont.)

- Solubility of a gas in a liquid is a function of the pressure of the gas.
- The higher the pressure, the more molecules of gas are **close** to the solvent and the greater the chance of a gas molecule **striking** the surface and entering the solution.
  - Therefore, the higher the pressure, the greater the solubility.
  - The lower the pressure, the fewer molecules of gas are close to the solvent and the lower the solubility

2. Effect of Pressure (cont.)

Henry's Law:

at constant temperature, the amount of a gas dissolved in a solution is directly proportional to the pressure of the gas above the solution

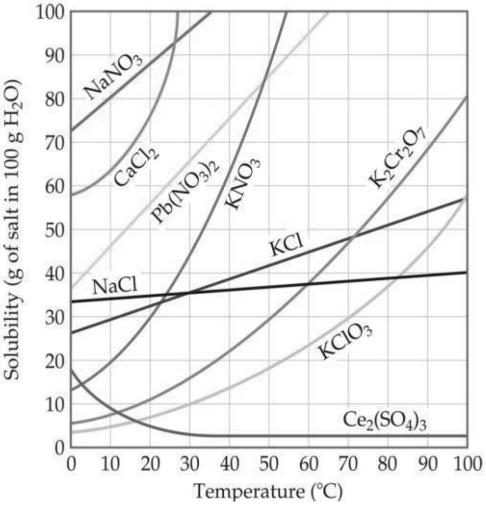
$$\mathbf{W} = \boldsymbol{kP}$$

where

- W is the mass of gas dissolved in the solvent (Mol fraction);
- *k* is the Henry's law constant for that gas in that solvent;
- *P* is the partial pressure of the gas above the liquid.

When pressure is released when the cap is opened, what happens to the solubility of CO_2?

3. Effect of Temperature on Solubility

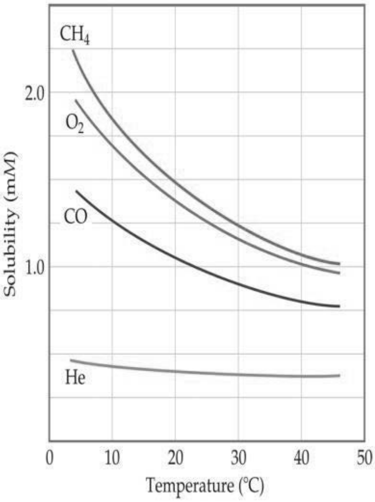


Generally, the solubility of **solid** solutes in liquid solvents **increases** with increasing temperature.

i.e. endothermic

Temperature

- The opposite is true of gases.
- Higher temperature drives gases out of solution.
  - Carbonated soft drinks are more "bubbly" if stored in the refrigerator.
  - Warm lakes have less CO2 & O_2 dissolved in them……. not available for plants or animals (thermal pollution)
  - Water for injection free from carbon dioxide prepared by boiling water



Effect of molecular size

- **Molecular size will affect the solubility.**

The larger the molecule or the higher its molecular weight……. the less soluble the substance.

- Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

- In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Effect of polarity

- ***The polar solute*** molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules.

This is a type of intermolecular force known as *dipole-dipole interaction.*

- All molecules also have a type of intermolecular force much weaker than the other forces called *London Dispersion forces* where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules

Effect of polymorphs

- ***Polymorphism*** is the ability of an element or compound to crystallize in more than one crystalline form.
- Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc.
- *Examples:* steroids, sulphonamides

IMPROVEMENT OF AQUEOUS SOLUBILITY

IMPROVEMENT OF AQUEOUS SOLUBILITY

(1) COSOLVENCY

- The solubility of poorly soluble drugs can be improved by the addition of water miscible solvent in which the compound is soluble.

- Vehicles used in combination to increase the solubility of a drug are called ***COSOLVENTS***.

- The choice of suitable cosolvents is **limited** for pharmaceutical use because of toxicity and irritancy.

IMPROVEMENT OF AQUEOUS SOLUBILITY

- Most commonly used blends is water/ethanol blend, other suitable solvents are *glycerol, propylene glycol, sorbitol and syrup.*
- ***Examples;***
  - a blend of PG/water is used to improve the solubility of co-trimoxazole.
  - elixir of paracetamol use ethanol/water blend

IMPROVEMENT OF AQUEOUS SOLUBILITY

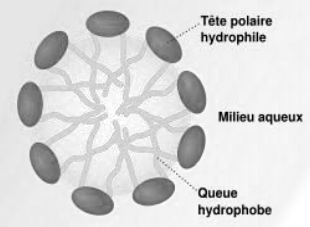
(2) pH Control:

- If the drug is a weak acid or weak base, its solubility in water can be controlled by the pH of the system.
- The solubility of weak acid can be increased by increasing the pH, and that of weak based is increased by lowering the pH.
- The pH of maximum solubility does not usually coincide with pH for optimum stability.
- Avoid pH extremes in solutions for parenterals (SC and IM), ophthalmic use, mucus membrane and abraded skin due to irritation and pain.

IMPROVEMENT OF AQUEOUS SOLUBILITY

(3) Solubilization:

- The solubility of poorly soluble drug is increased by the use of surface active agent (SAA). this phenomenon is known as *Micellar solubilization*.
- The concentration of SAA must be above the Critical Micelle Concentration (CMC).
- The increased solubility is due to drug partitioning between the aqueous phase and the micelle.



IMPROVEMENT OF AQUEOUS SOLUBILITY

(4) complexation:

- It is the interaction between the poorly soluble drug and a soluble material to form a soluble complex.
- Being a macromolecules, the formed complex should be reversible so that the free drug is released during or before contact with biological membrane.

Solubilization by Complexation

- *It is defined as the reversible association of a substrate and ligand to form a new species with a well defined stoichiometry.*
- ***Complexation relies on relatively weak forces such as hydrogen bonding and hydrophobic interactions***
- ***Example: solubilization of** tetracycline and oxytetracycline **by complexation with no. of compound such as sodium salicylate, sodium saccharin, caffeine, sodium hydroxybenzoate and methyl pyrrolidone***
- ***The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide***

Solubilization by Complexation

- ***Insertion of the nonpolar region of one molecule into the cavity of another molecule e.g.: <u>cyclodextrins</u>***
- ***Cyclodextrins are unique since they increase the water solubility of poorly soluble drugs by <u>fitting them into the hydrophobic cavity of the cyclodextrin molecule.</u>***
- ***These cyclodextrins have the ability to form <u>molecular inclusion complexes</u> with hydrophobic drugs having poor aqueous solubility.***

IMPROVEMENT OF AQUEOUS SOLUBILITY

<u>(5) Chemical modification:</u>

- The drug may be chemically modified to produce a water soluble derivative (usually salt form).
- *Examples;*

  - sodium phosphate salt of hydrocortisone

  - chloramphenicol sodium succinate as parenteral solution. This solution has no antibacterial but produce high blood level after which it is converted to the active base

IMPROVEMENT OF AQUEOUS SOLUBILITY

(6) Particle size control:

- As particle size decrease the drug solubility increased.

DISSOLUTION RATES OF SOLIDS IN LIQUID

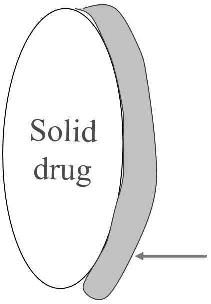
DISSOLUTION MECHANISM

- ***1. Interfacial reaction*** that results in liberation of solute molecule from the solid phase, The solution in contact with solid will become saturated ***(Cs).***

- ***2. The solute molecules migrate*** through the boundary layers surrounding the crystal to the bulk of solution, at which concentration is ***(C)***.

- **Boundary layer** is nearly static and surround all wetted surface of the solid.
- Mass transfer is slowly through the boundary layer to the bulk of solution.

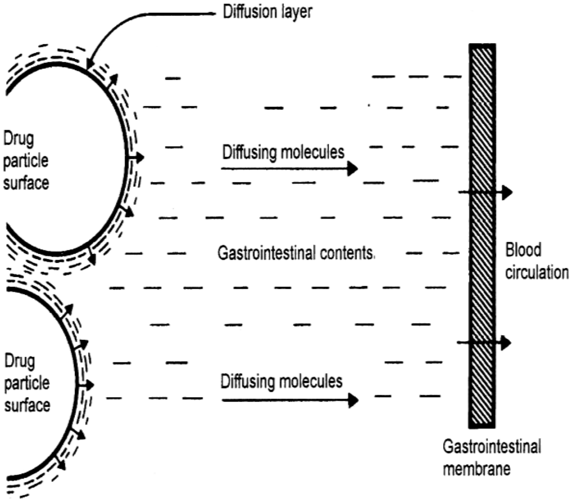
DISSOLUTION MECHANISM



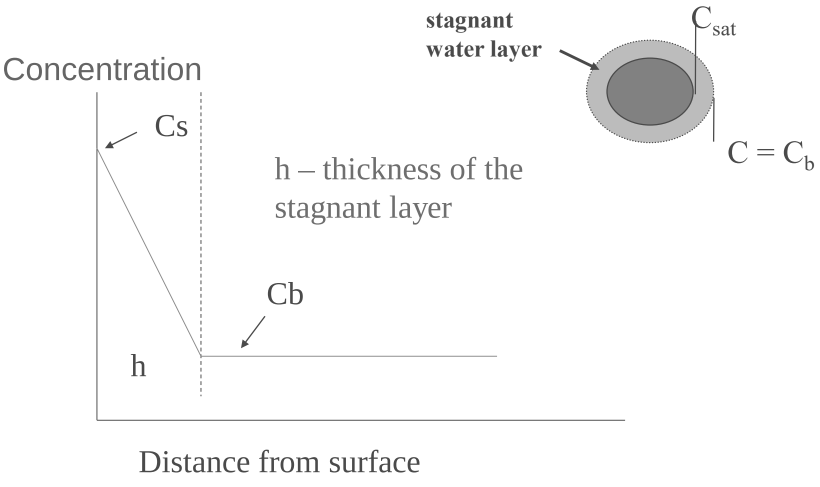
Bulk solution

Boundary layer: Small film of liquid surrounding drug particle

DISSOLUTION MECHANISM



Plot of concentration gradient



DISSOLUTION MECHANISM

- The rate of dissolution will depend on the slowest step, migration through boundary layer, and obeys ***Fick's law:***

$$dC/dt = K\,\Delta C$$

Where K: the dissolution rate constant

ΔC: the difference in concentration of solution at the solid surface (Cs) and the bulk solution (Cb).

DISSOLUTION RATE

- NOYES-WHITNEY EQUATION

$$dm/dt = DAC_s/\,h$$

- ◌́where **dm/dt** is the rate of mass transfer of solute molecule through the diffusion layer
- **Cs** is the concentration of the solute at surface available for migration
- **D** is the diffusion coefficient (m^2/s)
- **A** is the area available for molecular migration
- **h** is the thickness of the boundary layer

Factors affecting dissolution rate :

Surface area of solid (A):

1-Size of solid particles

- When the total **surface area** of the solute particles is **increased,** the solute dissolves more rapidly because the action takes place only at the surface of each particle. Breaking a solute into smaller pieces **(milling) increases its surface area and hence its rate of solution.**

2- Porosity

- Pores must be large enough to allow access of dissolution medium and outward diffusion of dissolved solute molecules

Factors affecting dissolution rate :

Solubility of solid in dissolution medium (C_s):

1- Temperature

- Higher temperature makes the solvent molecules move faster and contact the solute harder.
- Higher temperature increases the amount of solute that will dissolve

2- Nature of dissolution medium

- Presence of cosolvents, pH ……affect the dissolution rate

3- Molecular structure of solute

E.g. salts of weakly acidic or basic drugs increase the dissolution rate

Factors affecting dissolution rate :

4- Crystalline form

E.g. polymorphs, hydrates, solvates, amorphous

5- Presence of other compounds

E.g. complexing agents, solubilizing agents

Concentration of solute in solution at time t (C) :

1- Volume of dissolution medium

- Large dissolution medium…….C negligible (sink condition)

2- Any process that removes dissolved solute from the dissolution medium:

Factors affecting dissolution rate :

Diffusion coeffecient of solute in the dissolution medium:

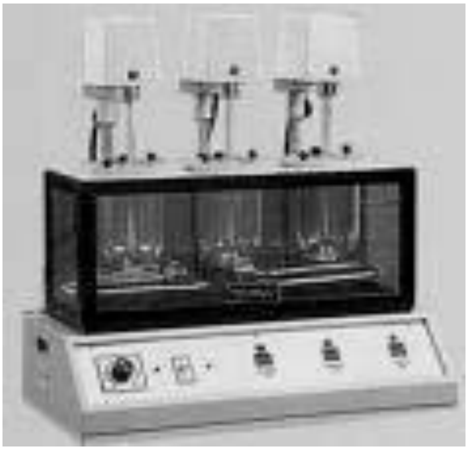
1- Thickness of boundary layer

- Decreased by increasing the rate of Stirring

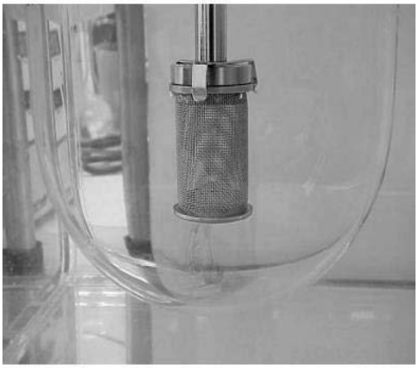
2- viscosity of dissolution medium

Measurement of dissolution rates

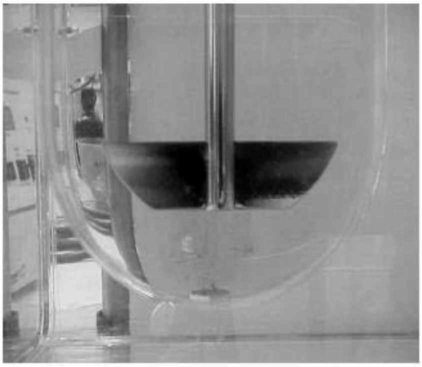
- Beaker method
- Flask-stirrer method
- Rotating basket method (pharmacopeal)
- Paddle method (pharmacopeal)



Measurement of dissolution rate

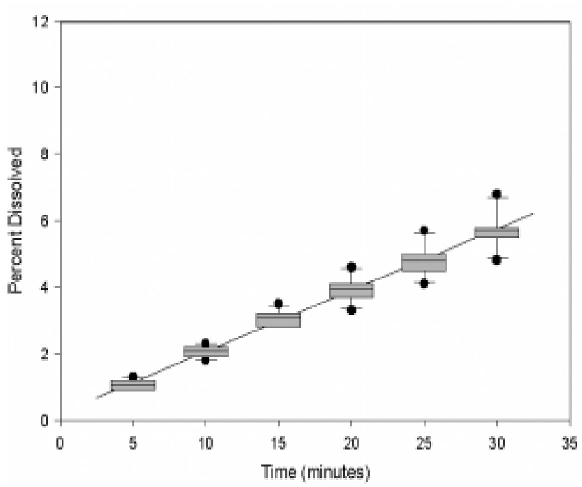


Rotating basket



Paddle method

Measurement of dissolution rate



Buffers

Buffers

Definition:

- ***A buffered solution is one that <u>resists changing pH</u> when acid or bases is added.***
- ***A buffer solution is an aqueous solution consisting of a mixture of a <u>weak acid and its conjugate base</u> or <u>a weak base and its conjugate acid</u>.***
- ***The resistance to a change in pH is known as <u>buffer action</u>.***

Criteria of a good buffer

- *The buffering capacity in the desired pH range with the ability to maintain constant pH during fixation.*
- ***Suitable ionic concentration so that materials are neither extracted nor precipitated during fixation.***
- ***Maximum solubility in water and minimum solubility in all other solvents.***
- ***Reduced ion effects.***
- ***Dissociation of buffer least influenced by buffer concentration, temperature and ionic composition.***
- ***Suitable osmolarity so that cells neither swell nor shrink during fixation.***

Criteria of a good buffer

- ***Resistance to oxidation (stable).***
- ***Inexpensive and easy to prepare.***

Type of buffer solutions

- ***Acidic buffer solutions***
- ***Alkaline buffer solutions***

Acidic buffer solutions:-

- *An acidic buffer solution is simply one which has a pH less than 7.*
- ***Acidic buffer solutions are commonly made from a weak acid and one of its (conjugate base) salt.***
- ***A common example would be a mixture of acetic acid and sodium acetate in solution***

Type of buffer solutions

Alkaline buffer solution

- *An alkaline buffer solution has a pH greater than 7*
- *Alkaline buffer solutions are commonly made from a weak base and one of its salts.*
- *A frequently used example is a mixture of ammonia solution and ammonium chloride solution.*
- *If these were mixed in equal molar proportions, the solution would have a pH of 9.25.*

Common Buffers

Phosphate Buffer (Sorenson's buffer) pH 5.8-8.

Advantages:

1. *Most physiological of common buffers.*
2. *Non-toxic to cells.*
3. *pH changes little with temperature.*
4. *Stable for several weeks at 4 °C*

Disadvantages:

1. *Precipitates more likely to occur during fixation.*
2. *Tends to form precipitates in presence of calcium ions*
3. *Becomes slowly contaminated with microorganisms.*

Common Buffers

Acetate buffer	pH 4- 5.6
Citrate buffer	pH 3- 6.2
Borate Buffer	pH 7.4-9.2
Dimethylglutarate Buffer	pH 3.2-7.6
Succinate Buffer	pH 3.8-6
Maleate Buffer	pH 5.2-6.8
Imidazole Buffer	pH 6.2-7.8
Veronal-acetate Buffer (Michaelis buffer)	
Cacodylate Buffer (arsenate buffer)	pH 5-7.4

Buffers

- *The common ion effect and buffer equation for a weak acid and its salt :*
- *Let's consider a solution containing a week acid, HAc, and its salt, NaAc.*
- ***Salts are strong electrolytes, so NaAc will completely dissociate in solution:***
- $NaAc\ (aq) \Longrightarrow Na^+(aq) + Ac^-(aq)$
- ***The weak acid exists in equilibrium with its ions:*** $HAc(aq) + H_2O\ (l) \Longleftrightarrow H_3O^+(aq) + Ac^-(aq)$

The ionization constant for the acid

- *Ka = $[H_3O^+][Ac^-]$ / [HAc] =1.75* 10^{-5}*
- *Since we are dealing with weak acids, very little conjugate base (Ac^-) in solution comes from the acid.*
- *The acetate ion supplied by the salt increases the [Ac-].*
- ***To reestablish the constant Ka the hydrogen ion term $[H_3O^+]$ decrease with formation of HAc.***
- ***Further, the presence of the salt in solution reduces the ability of the acid to ionize (common ion effect).***
- *The major source of Ac- is from the salt.*

The ionization constant for the acid

- *Ka = $[H_3O^+]$ [salt] / [acid]*
- *log Ka = log $[H_3O^+]$ + log [salt] – log [acid]*
- ***-pKa= -pH + log [salt] – log [acid]***
- ***# The Henderson-Hasselbalch equation may be derived from this expression:***

  pH = pKa + log([salt] / [acid])
- *Ka is dissociation exponent.*

Buffer equation for a Weak bases and its Salt

- *Buffer solution are not ordinarily prepared from weak base and their salt because of volatility and instability of the base and because of the dependence of their pH on pKw.*
- *pKw is affected by change in temp.*
- ***$[OH^-] = Kb [Base] / [Salt]$***
- ***$pOH = pKb + \log ([Salt]/[Base])$***
- ***And using the relationship $[OH^-] = Kw / [H_3O^+]$***
- ***$pH = pkw - pKb + \log[Base]/[Salt]$***

Factors influencing pH of buffer

- *Addition of small amount of water:*
  - *Cause small +ve or –ve deviation because it alters activity coefficient and water itself behave as a weak acid or weak base.*
  - ***Dilution value** is the change in pH on diluting the buffer solution to one half of its original strength.*
  - *+ve dilution value: pH rises with dilution*
  - *-ve dilution value :pH falls with dilution.*
- *Temp. : pH of acetate buffer increase with rise in temp, pH of boric acid- sodium borate buffer decrease with temp.*
- *The pH of basic buffer more markedly changed with temp due to the Kw that appears in the equation of the basic buffers change with T.*

Factors influencing pH of buffer

<u>SALT EFFECT:</u>

- ***Addition of neutral salt to dilute buffer solution lower the pH by lowering the activity coefficient and pH of basic increases. changes the pH of the solution by altering the ionic strength***

Buffer capacity

- ***The magnitude of the resistance of a buffer to changes is referred to <u>as a buffer capacity β.</u>***
- ***Known as a <u>buffer efficiency, buffer index, buffer value.</u>***
- ***<u>It is the ratio of the increment of strong acid or base to the small changes in pH brought about by this addition (Van Slyke).</u>***
- $\beta = \Delta B / \Delta pH$
- ***where ΔB is small increment in gram equivalent / liter of strong base or acid added to the buffer solution to produce a pH change.***

Calculation of Buffer Capacity

- Consider acetate buffer containing 0.1 M HAc and 0.1 M NaAc in 1 liter of solution. To this 0.01 M NaOH is added.
- $HAc_{(0.1-0.01)} + NaOH_{(0.01)} \longleftrightarrow NaAc_{(0.1+0.01)} + H_2O$
- pH = pKa + log([salt]+[Base]/ [acid]-[Base])
- Before addition pH= 4.76 + log (0.1/ 0.1)=4.76
- After addition pH= 4.76 + log (0.1+0.01/ 0.1-0.01) =4.85
- pH increased from 4.76 to 4.85 or Δ pH of 0.09

Moles of NaOH Added	pH of Solution	Buffer Capacity, β
0	4.76	
0.01	4.85	0.11
0.02	4.94	0.11
0.03	5.03	0.11
0.04	5.13	0.10
0.05	5.24	0.09
0.06	5.36	0.08

Influence of concentration on buffer capacity

- Buffer capacity is not a fixed value for a given buffer system.
- Addition of more NaOH the buffer capacity decrease rapidly till all the acid was converted to acetate ions, [Base] / [Salt]=1 so pH = pKa
- Buffer capacity depend on:

1. Ratio of conc of [salt]/[acid]: depend on the amount of base added, it changes as log [salt] / [acid] increase with the added base.
2. Magnitude of the individual concentration of buffer components (buffer become more efficient as the acid and salt concentrations are increased)

Calculation of Buffer Capacity

- *The buffer capacity is also influenced by an increase in total concentration of buffer constituents.*
- ***More exact equation to calculate the buffer capacity (Van Slyke)***
- $\beta = 2.3\ C^* Ka^* [H_3O^+]/(Ka + [H_3O^+])^2$
- *Where C = total buffer concentration i.e. the sum of the molar concentration of the acid and salt.*
- *This equation permit one to compute the buffer capacity at any hydrogen ion concentration.*

Max Buffer Capacity

- $\beta = 2.3\ C^* Ka^* [H_3O^+]/(Ka + [H_3O^+])^2$
- *The max buffer capacity occurs when pH=pKa or when* $[H_3O^+] = Ka$.
- *Substituting* $[H_3O^+]$ *for Ka in both the numerator and denominator of equation*
- $\beta\ max = 2.3\ C^* [H_3O^+]^2/(2[H_3O^+])^2$
- $\beta\ max = 2.3\ C/4$
- $\beta\ max = 0.576\ {}^*C$
- *where C is total buffer concentration (the sum of the molar concentration of the acid and salt).*

Buffers In Pharmaceutical And Biological Systems

In Vivo Biological Buffer System

- *Blood is maintained at a pH of about 7.4 by primary buffers in plasma and secondary buffers in the erythrocyte.*
- ***The plasma contains carbonic acid/ bicarbonate and acid / alkali sodium salts of phosphoric acid as buffers.***
- ***Plasma proteins, which behave as acids in blood, can combine with base and so act as buffer.***
- ***In erythrocyte, the two buffer system consist of hemoglobin/oxyhemoglobin & acid/alkali potassium salts of phosphoric acid.***

In Vivo Biological Buffer System

- *The dissociation exponent pK1 for the first ionization stage of carbonic acid in the plasma at body temp. and ionic strength of 0.16 is about 6.1. the buffer eqn. for the carbonic acid and bicarbonate buffer of the blood is* $pH= 6.1 + \log ([HCO_3^-]/[H_2CO_3])$
- ***Where*** $[H_2CO_3]$ ***represents the conc. of*** CO_2 ***present as*** H_2CO_3 ***dissolved in blood.***
- *The ratio of bicarbonate to carbonic acid in normal blood plasma is* $\log ([HCO_3^-]/[H_2CO_3]) = 7.4-6.1= 1.3$
- *When pH of the blood goes below 7.0 or above 7.8 life is in danger (in diabetic coma it is below 6.8)*

In Vivo Biologic Buffer System

- *The lacrimal fluid or tears have a good buffer capacity.*
- ***The pH of tear is 7.4 with range of 7 to 8.(It is generally thought that eye drops within a pH range of 4 to 10 will not harm the cornea. However, discomfort and a flow of tears will occur below pH 6.6 and above pH 9.0***
- *Pure conjunctival fluid is more acidic than that of tear fluid (due to loss of* CO_2 *from tear fluid during analysis)*
- *Urine: The urine of a normal adult has a pH of about 6.0 with the range of 4.5 to 7.8*
- *When the pH of the urine is below normal values, hydrogen ions are excreted by the kidneys*

Pharmaceutical Buffers

- *Buffer solutions are used in formulations of ophthalmic solutions.*
- *__Per Gifford:__ mixing various proportions of boric acid and monohydrated sodium carbonate they yield buffer solutions with pH range 5 to 9.*
- ***Sorenson** proposed mixture of salt of sodium phosphate for buffer of pH 6 to 8.*
- *Sodium chloride is added to each buffer to maintain isotonicity.*
- *A buffer system suggested by Palitzsch consist of boric acid, sodium borate and NaCl was used for ophthalmic solution with pH range 7 to 9.*

Pharmaceutical Buffers

- *The buffers of clark and Lubs were determined at 20 °C and re-determined at 25 °C.*
- *The mix and their pH ranges are:*

1. *HCl and KCl, 1.2 to 2.2.*
2. *HCl and KHP, 2.2. to 4.0*
3. *NaOH and KHP, 4.2 to 5.8*
4. *NaOH and KH_2PO_4, 5.8 to 8*
5. *H_3BO_3, NaOH, and KCl, 8 to 10.*

- *Below pH 2 HCl alone has considerable buffer efficiency and KCl is neutral salt and is added to adjust the ionic strength*

Preparations

- *Steps to develop a new buffer solution.*
- *Select a weak acid having a pKa near to a pH at which the buffer is to be used to ensure a max buffer capacity.*
- *Calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer eqn is satisfactory for approximate calculation within the pH range of 4 to 10.*
- *Consider the individual concentration of the buffer salt and acid needed to obtain a suitable buffer capacity.*
- *A conc of 0.05 to 0.5 M is usually sufficient and buffer capacity of 0.01 to 0.1 is generally adequate.*
- *Availability of chemicals, sterility of the final solution, stability of the drug and buffer on aging, cost of materials, and freedom from toxicity should be considered.*
-

Preparations

- *E.g. a borate buffer, bcz of its toxic effects, certainly can not be used to stabilize a solution to be administered orally or parenterally.*
- *Determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter*
- *When the electrolyte conc is high, the pH calculated by use of the buffer eqn is somewhat different from the experimental value.*
- *It is to be expected when activity coefficient are not taken in to account.*

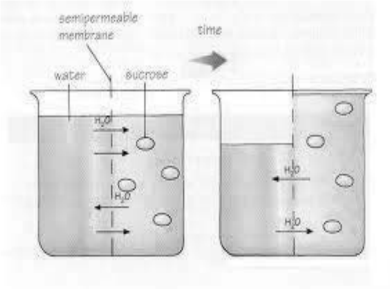
pH and Solubility

- At low pH the base is in the ionic form, which is usually very soluble in aqueous media.
- As the pH is raised more undissociated base is formed.
- When the amount of base exceeds the limited water solubility of this form, free base precipitates from the solution.
- So the solution should be buffered at sufficiently low pH to maintain the stabilization against precipitation.

Isotonicity

Osmosis

- Osmosis is the diffusion of solvent through a semi-permeable membrane.
  - Water always flows from lower solute concentration [dilute solution] to higher solute concentration until a balance is produced
- Osmotic pressure is the force that cause this diffusion
- Tonicity is a measure of the osmotic pressure of two solutions separated by a semi-permeable membrane



Isotonicity

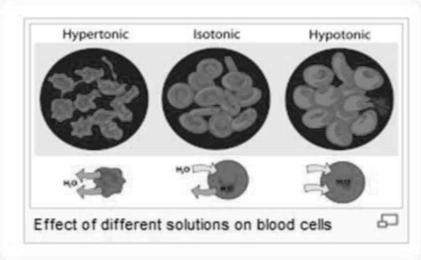
- If a living cell is placed in a surrounding of a distilled water, then significant osmotic pressure appears due the difference in the concentration of a solute in the cell and surrounding.
- As a result the cells swell and can be lysed.
- To avoid the effects of osmotic pressures the "isotonic solutions" are used in biology and pharmaceutics.
- Isotonic - having the same osmotic pressure as body fluids
- Hypotonic - osmotic pressure is lower than in the body fluids
- Hypertonic - osmotic pressure is higher than in the body fluids

Isotonic solution

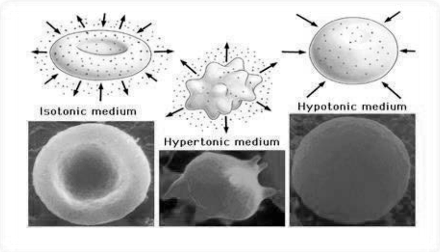
- *A solution which has the same tonicity as the other solution with which it is compared.*
- ***Like osmotic pressure, tonicity is influenced only by solutes that cannot cross the membrane, as only these exert an osmotic pressure.***
- *Solutes able to freely cross the membrane do not affect tonicity because they will always be in equal concentrations on both sides of the membrane.*
- ***Osmotic pressure is the pressure that must be applied to a solution to prevent the inward flow of water across a semipermeable membrane.***

Types Of Tonicity

Hypotonic	isotonic	Hypertonic
NaCl 0.2%	NaCl 0.9%	NaCl 2%
solute Inside ❯ solute outside	solute Inside = solute outside	solute Inside ❮ solute outside
swelling	equilibrium	shrinkage



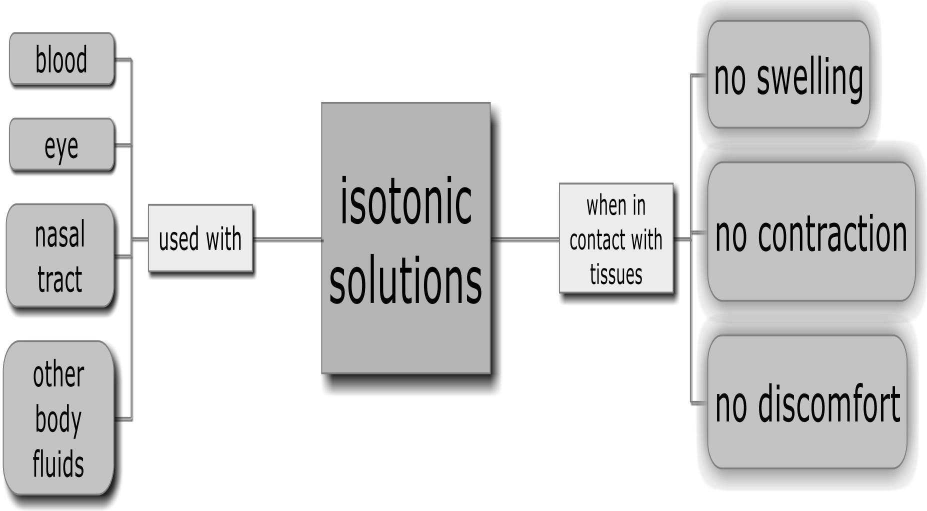
Effect of different solutions on blood cells



Buffered isotonic solutions

- *The RBC membrane permit the passage of water molecules, urea, ammonium chloride, alcohol, boric acid.*
- *A 2.0 % boric acid solution is isosmotic to blood cell.*
- *The molecules of boric acid pass freely through the erythrocyte membrane regardless of conc. (as a result boric acid solution is hypotonic and cause hemolysis).*
- ***So the solution containing quantity of drug calculated to be isosmotic with blood is isotonic only when blood cells are impermeable to solute molecules and permeable to solvent molecules.***
- ***Mucous lining of the eye is true semi permeable to boric acid solutions and hence 2 % boric acid solution is isotonic ophthalmic preparation.***

Why We Use Isotonic Solutions



Calculations for solutions isotonic with blood

1. based on freezing point data:

- ***Depend on two colligative properties which are <u>osmotic pressure and depression of freezing point</u> (determination of the depression of the freezing point is simpler and more accurate than direct measurement of osmotic pressure)***
- ***<u>The same freezing point the same concentration and hence the same tonicity</u>***

Freezing point depression (FPD) "cryoscopic method".

- *F.P. of blood & tears = - 0.52ºC*
- *Any solution have F.P. = - 0.52ºC is isotonic.*
- ***Any solution have F.P. › - 0.52ºC is hypotonic (- 0.4ºC) and -0.6ºC is hypertonic).***
- ***Add solute to hypotonic solution to reach f.p.d of blood (- 0.52ºC)***
- ***The percentage w/v of adjusting substance needed***
- ***a : f.p.d of unadjusted substance at X percentage strength***
- ***b: f.p.d of 1% of adjusting substance (table)***

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

Freezing point depression (FPD) "cryoscopic method".

- *# find the proportion of NaCl required to render 1% solution of cocaine HCl isotonic with blood plasma*

- *From the table the freezing point of 1% cocaine HCl is 0.099 °C and that of 1% NaCl is 0.576 °C.*

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

- *% w/v = 0.52- 0.099/0.576= 0.746 %w/v*

- *# 200 ml of eye wash containing 1% boric acid are to be dispensed (F.P. of 1% boric acid was 0.29 °C and that of 1 % sodium chloride solution was 0.58 °C)*
- *Solution: %w=0.52-0.29/0.58= 0.39 %*
- *W= the weight in gram of the added substance in 100 ml of the final solution.*
- *The working formula for 200 ml of the eye wash will be:*

1. *boric acid (1% for 200 ml)= 1g*2= 2g*
2. *NaCl (0.39% for 200 ml) = 0.39 *2= 0.78g*
3. *Purified water q.s. 200 ml*

Calculations For Solutions Isotonic With Blood

- *2. Based on molecular concentration:*
- ***Refers to the no. of units i.e. molecules or ions or both present in solution (osmotic pressure is proportional to this units which is molecular concentration)***
- ***Aqueous solution has molecular concentration of 1% depress the freezing point to -18.6 ºC, blood plasma freeze at -0.52 ºC***
- ***Therefore a depression of -0.52 ºC is given by a molecular concentration = 1*0.52/18.6= 0.03%***
- ***A solution has a molecular concentration of 0.03% is isotonic with blood plasma***

2. Based on molecular concentration

- ***To convert gram-molecules to grams it is necessary to multiply by the molecular weight. e.g. molecular weight of dextrose is 180, so isotonic solution contains 0.03%*180= 5.4%***
- ***For non ionizing substances use:***

%w = 0.03%* gram molecular weight

- *For ionizing substances use:*

%w = 0.03%* gram molecular weight/no. of dissociated ions

- ***Find the proportion of NaCl required to form an isotonic solution***

0.03*58.5/2 = 0.88% (0.9 % official)

Calculations for solutions isotonic with blood

- ***3. Based on comparison with isotonic sol. of NaCl :***

*% of substance required = (0.9*2/58.5)*(mol. Wt of substance/ no. of ions yielded)*

- *Example: find the weight of sodium sulphate required for 4 ounces of solution isotonic with the blood plasma.*
- *% sod sulphate required = (0.9*2/58.5)*(322/3)= 3.3%*

Then the quantity required for 4 ounces 58 g.

Neutralization curves and buffer capacity

- *Consider a titration curves of strong acid and weak acids when they are mixed with increasing quantity of alkali.*
- *The reaction of an equivalent of acid with an equivalent of base is called neutralization.*
- *The neutralization reactions are written as*
- *H3O+ (Cl-) + (Na+)OH- =2H20 + Na+ + Cl-*
- *HAc + (Na+)OH- =H20 + Na+ Ac-*
- *Where H3O+ (Cl-) is hydrated form of HCl in water*
- *Neutralization curves and buffer capacity The neutralization of strong acid by a strong base simply involves a reaction between hydronium and hydroxyl ions*

Neutralization curves and buffer capacity

- *$H_3O^+ + OH^- = 2\ H_2O$*
- *The reaction between strong acid and strong base proceeds to completion.*
- *The reaction between weak acid and strong base is incomplete bcz Ac- reacts in part with water to regenerate free acid.*
- *The neutralization of 10 ml of 0.1 N HCl and 10 ml of 0.1 N HAc by 0.1 N NaOH can be shown by plotting pH versus ml of NaOH added.*

Neutralization curves and buffer capacity

- *The buffer capacity of a solution of strong acid is shown by Van Slyke to be directly proportional to the hydrogen ion conc.*
- $\beta = 2.303\ [H_3O^+]$
- *The buffer capacity of a solution of strong base is similarly proportional to the hydroxyl ion conc.*
- $\beta = 2.303\ [OH^-]$
- *The total buffer capacity of water solution of a strong acid or base at any pH is sum of the separate capacities.*
- $\beta = 2.303\ ([H_3O^+] + [OH^-])$

- *If the pharmacist has been asked to supply 200 ml of eye wash of boric acid ?*
- *1g of boric acid lower F.P. by 0.29 °C*
- *Then lowering of 0.52 in F.P. will be caused by 1.8 g of boric acid to prepare 100 ml of eye wash*
- *The working formula will be:*
- *Boric acid (1.8% for 200 ml) = 1.8*2= 3.6 g and purified water q.s. 200 ml.*

Based on colligative properties

- *This method is based on the measurement of slight temp differences in the vapor pressure of thermally insulated samples contained in constant humidity chambers.*
- *The freezing point of blood and lacrimal fluid is -0.56 °C .*
- *This temp corresponds to the freezing point of 0.9% Nacl solutions, which is therefore considered as a isotonic with both blood and lacrimal fluids*
- *Freezing point depressions for solutions of electrolytes of both the weak and strong type are greater than those calculated from eqn.* $\Delta T_f = K_f c$,

Calculating Tonicity using Liso values

- ***New factor L=iKf is introduced to overcome difficulty.***
- ***$\Delta Tf = Lc$***
- ***The L value can be obtained from the freezing point lowering of solutions of representative compounds of a given ionic type at conc c that is isotonic with body fluids.***
- ***The sp value of L is written as Liso***
- ***The Liso value for a 0.90 % (0.154 M) solutions of NaCl, which has freezing point depression of 0.52 °C is Liso = $\Delta Tf/c = 0.52/0.154 = 3.4$***
- ***For dilute solutions of non electrolytes, Liso is nearly equal to Kf value.***

Methods for adjusting Tonicity & pH

1. Class I methods :

- ***NaCl or another substance is added to the solution of the drug to lower the freezing point of solution to -0.52 °C and thus make isotonic with body fluid. E.g. Cryoscopic method NaCl equivalent method***

2. Class II methods:

- ***Water is added to the drug in sufficient amount to form isotonic solution.***
- ***The preparation is then brought to its final volum with isotonic or buffered isotonic dilution solution. E.g. White Vincet method and Sprows***

Cryoscopic Method

- *The freezing point depression of number of drugs is determined theoretically and experimentally.*
- ***How much NaCl is required to render 100 ml of 1% solutions of apomorphine HCl isotonic with blood serum.***
- ***Solutions having freezing point lowering value 0.52 °C is isotonic solutions***
- ***Knowing the molecular weight of the drug and the L(iso) value of the ionic class***
- ***Sodium chloride equivalent method***
- ***$E \equiv 17\, L_{iso} / M$***
- ***Where M is the molecular weight***

Cryoscopic Method

- ***1 % solutions of apomorphine HCl have freezing point lowering value 0.08 °C (std)***
- ***Additional Nacl is added to reduce freezing point lowering value by an additional 0.44 (0.52-0.08)***
- ***For 0.58 freezing point lowering 1 % Nacl required (std)***
- ***So 0.44 freezing point lowering x % Nacl required $0.44 * 1\% = 0.58 * X \quad X = 0.76\ \%$***
- ***The solution is prepared by dissolving 1.0 g of drug and 0.76 g of NaCl in sufficient amt of water to make 100 ml of***

NaCl / Tonicic equivalent method

- *The NaCl equivalent (E) is amount of NaCl that is equivalent to 1 g of drug.*
- *E value can be calculated from Liso value or freezing point depression of the drug.*
- *For solutions containing 1g of drug in 1000 ml of solution, the conc c= 1g / M.W*
- *And $\Delta Tf = Liso * c = Liso\ 1\,g / M.W$*
- *Now E is the wt For NaCl with same freezing point depression as 1 g of the drug.*
- $\Delta Tf = 3.4 * E/58.45$
- $Liso / M.W = 3.4 * E/58.45$
- *Multiply the quantity of each drug with its NaCl equivalent and subtract the value from the conc of NaCl that is isotonic with body fluids , 0.9 %*

White –Vincet Method

- ***water is added to the drug in sufficient amount to form isotonic solution.***
- ***The preparation is then brought to its final vol with isotonic or buffered isotonic dilution solution.***
- ***How to make 30 ml of 1% solution of procaine HCl isotonic with body fluid.***
- ***The wt of the drug w, is multiplied by the NaCl equivalent, E : 0.3g*0.21(W*E) = 0.063g***
- ***This is the quantity of NaCl osmotically equivalent to 0.3 g of drug.***

White –Vincet Method

- For 0.9 g NaCl 100 ml water required
- For 0.063 g NaCl X ml water required
- $X = 0.063 * 100/ 9 = 7.0$ ml
- The value of the ratio $100/0.9 = 111.1$
- So the eqn $X = W * E * 111.1$
- Where X is vol in ml of isotonic solution that may be prepared by mixing the drug with water.
- For the problem $X = 0.3 * 0.21 * 111.1 = 7.0$
- To complete the isotonic solution, enough isotonic NaCl solution or an isotonic buffered diluting solution is added to make 30 ml of finished pdt.

The Sprowls Method

- The eqn $X = 0.3 * 0.21 * 111.1$ could be used to construct a table of values of X when the wt of the drug w is fixed.
- Sprowls chose the wt of drug 0.3 g, the quantity for 1 fluid ounce of 1% solution.
- Compute the vol X of isotonic solutions of 0.3 g drug with sufficient water for drugs commonly used in ophthalmic and parental preparations.

- $[H+] = Ka\ [Acid]/[Base] = K\ [Acid]/[Base]$.
- Taking negative logarithms of both sides of the above equation gives:
- $-\log([H+]) = -\log(Ka) - \log([Acid]/[Salt])$
- or $pH = pKa - \log([Acid]/[Salt])$.
- Upon inversion of the argument the last log term becomes positive, as:
- $pH = pKa + \log([Salt]/[Acid])$.