

Pharmaceutical Technology

Colloidal Dispersion

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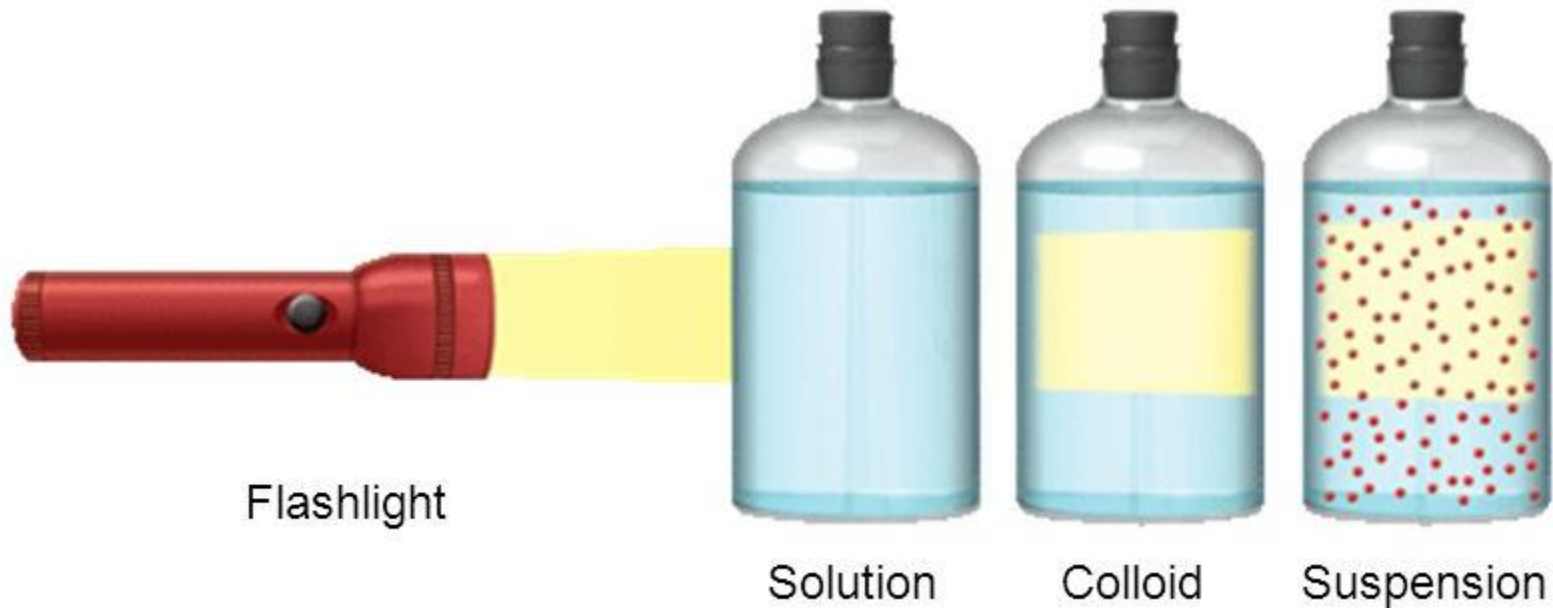
- Although there is no precise point at which the size of a particle in a dispersion can be considered to be “colloidal”, there is a generally accepted size range.
- A substance is said to be colloidal when its particles fall between 1 nm and 1 μ m (or 0.5 μ m).
- Colloidal particles are usually larger than atoms, ions, or molecules and generally consist of aggregates of many molecules, although in certain proteins and organic polymers, single large molecules may be of colloidal dimension and form colloidal dispersions.

Differences between colloidal dispersion and true solution

1. The particle size: the larger particle size of the disperse phase of colloidal type of preparation.
2. The optical properties of the two systems: true solutions do not scatter light and therefore appear clear, but colloidal dispersions contain opaque particles that do scatter light and thus appear turbid. This turbidity is easily seen even with dilute preparations, when the dispersion is observed at right angles to a beam of light passed through the dispersion.

The Tyndall Effect

The scattering of visible light by colloidal particles is called the **Tyndall effect**.



Torch

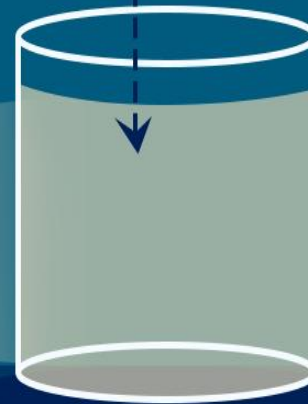
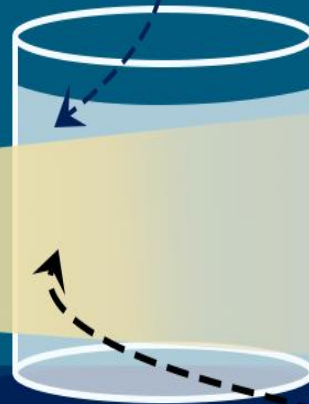


True solution
(No scattering
of light)

Colloidal sol
(Scattering of
light)

Colloidal mixture of
flour and water

Solution of water
and red sugar



Light is scattered through colloid

Properties of colloidal dispersions

- Colloidal dispersions have the following properties:
 1. Visible in electron microscope and often in ultra-microscope, but invisible in ordinary microscope.
 2. Low rate of diffusion.
 3. Undergo Brownian motion.
 4. Pass through filter paper, retained by ultrafilters and dialysis membrane.
 5. Low osmotic pressure.

Terms used for colloidal dispersions

- Sol: is a general term to designate a dispersion of a solid substance in either a liquid, a solid, or a gaseous dispersion medium.
- Hydrosol: a prefix hydro refers to water, means the dispersion medium is water.
- Organosol: dispersion of solid in organic solvent
- Alcosol: a prefix alco refers to alcohol, dispersion medium.
- Aerosol: term for a dispersion of solid or a liquid in a gaseous phase.

Types of colloidal dispersions

- According to the attraction or lack of attraction between the dispersion phase and dispersion medium, colloidal dispersion divided into:
 1. Lyophilic colloid:
 - there is a considerable attraction between dispersed phase and dispersion medium.
 - There is extensive solvation and the system is said to be solvent loving when there is high affinity between the two phases.
 - If the dispersion medium is water then the system is called hydrophilic.
 - For example starch, gelatin, acacia, povidone these swell, disperse, dissolve spontaneously in water.

Official lyophilic dispersion

1. Cellulose and cellulose derivatives
2. Starch
3. Polyelectrolytic polysaccharide
4. Acacia, tragacanth, sodium alginate and agar
5. Synthetic non-ionic water-soluble polymers
6. Polyethylene glycol
7. Povidone (polyvinyl pyrrolidone)
8. Protein and polypeptides
9. gelatin

- If the dispersion medium is of low polarity or low dielectric constant then it is called lipophilic or oleophilic.
- These have good affinity for oils or solvent of low polarity like benzen, CCl_4 .
- Examples of lipophilic dispersion: polymers like polystyrene or gum rubber, they dissolve molecularly in benzene. Magnesium or Aluminum stearate in cotton seed oil.

- Lyophilic colloidal systems are usually:
 1. Easier to prepare, formed spontaneously because of high affinity between dispersed particle and the dispersion medium.
 2. Thermodynamically stable because of high affinity will give small surface area which gives small free energy (ΔF)

$$\Delta F = \gamma \Delta A$$

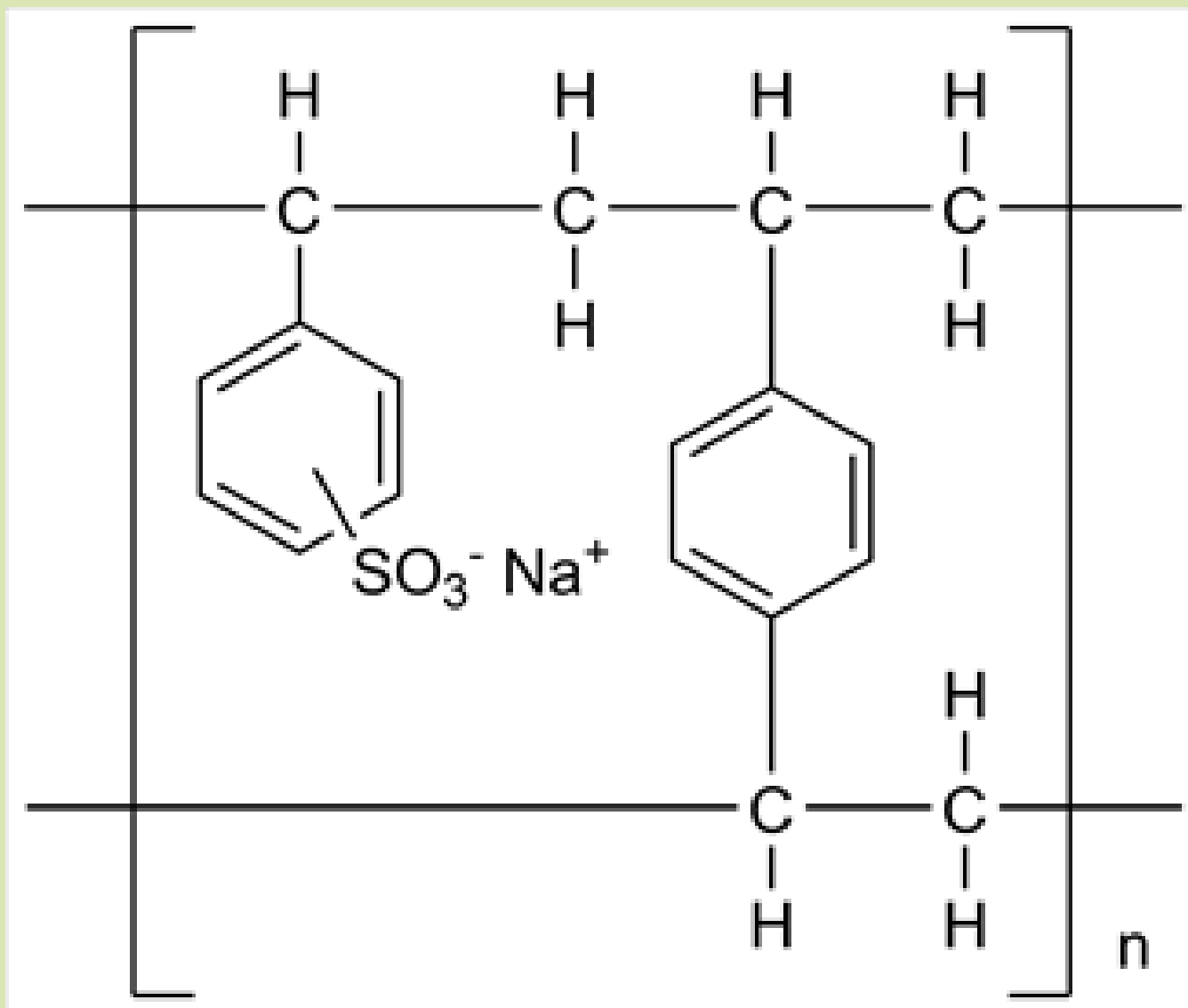
3. Reversible: even if the solvent is removed from the system and then is bring back, the system will formed spontaneously.

Hydrophilic dispersion classification

1. Soluble material: are soluble in water whether they are linear or branched polymer. Their solution is classified as colloid because the individual molecules are in the colloidal particle size range, they exceed 50-100 Å. For example acacia, povidone.
2. Particulate: represent solids which swell in water, but their primary particles do not dissolve or break down into individual molecules or ions. One subdivision of this class composed of cross-linked polymers, their linear uncross-linked analogues are soluble in water.

Examples

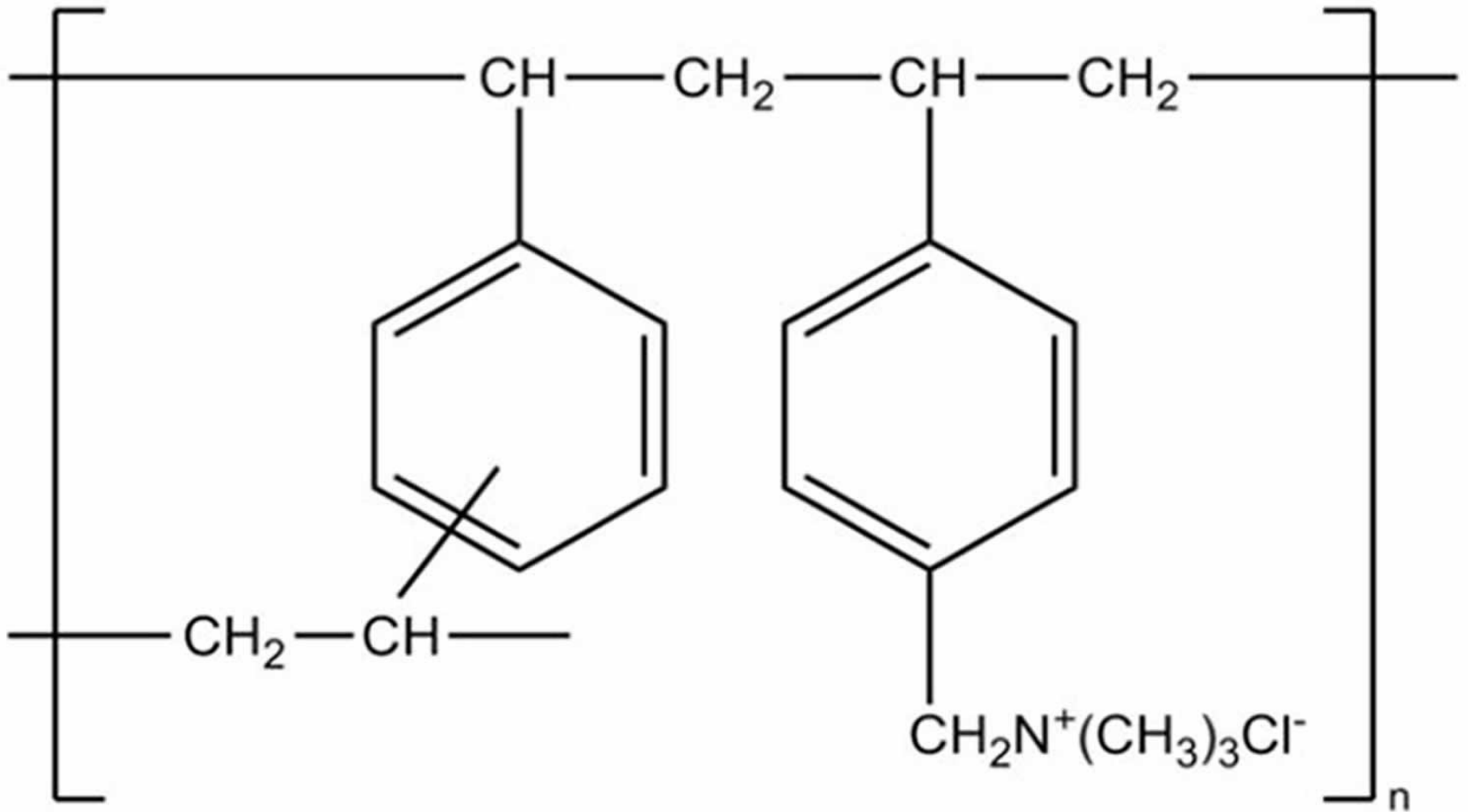
- Sodium polystyrene sulfonate which is used as cation exchange resin and it is water insoluble produced by copolymerization of styrene with few percentage of divinyl benzene and then the product is subjected to sulfonation and neutralization.
- The polymer behaves as single molecule where its atoms are linked together by vinyl bond, they are strong and resist rupture and dissolution.



Examples

- Cholestramin resin USP, which has the same backbone of the cross-linked polystyrene chain but they contain quaternary ammonium chloride group instead of sodium sulfonate group, so it acts as anion exchange resin.

Cholestyramine



3. Gels (sometimes called jellies) are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jelly like by the addition of a gelling agent.
- Among the gelling agents used are synthetic macromolecules, such as carbomer 934; cellulose derivatives, such as carboxymethylcellulose or hydroxypropyl methylcellulose; and natural gums, such as tragacanth.
 - Carbomers are high molecular weight water-soluble polymers of acrylic acid cross-linked with allyl ethers of sucrose and/ or pentaerythritol.

- There are two properties for substances to form gel:
 1. The particle must be extensively solvated
 2. They must be able to adhere to each other at the point of contact.
- A gel consists of two continuous phases mixed together and interpenetrating, the solid matrix and the immobilized liquid.
- A gel is formed when the polymer substances are present at high concentration and/ or at a temperature where their solubility is low.
- Examples of such hydrogel are gelatin and starch, which will form gel on cooling. While methylcellulose will form gel on heating.

- Gel is considered as a semisolid or solid dispersion.
- Gels owe their rigidity to an intertwining network of the disperse phase which entraps and holds the dispersion medium.
- A change in the temperature can cause certain gels to resume the sol or liquid state. Also, some gels may become fluid after agitation and resume their solid or semisolid state after remaining undisturbed for a period of time, a phenomenon known as thixotropy.
- Gels may thicken on standing, forming a thixotrope, and must be shaken before use to liquefy the gel and enable pouring.

Lyophobic Dispersion (Colloid)

1. A system in which there is little attraction between dispersed phase and dispersion medium. It is called solvent-hating.
2. Unlike lyophilic colloids, lyophobic materials do not spontaneously disperse, but must be encouraged to do so by special individualized procedures.
3. Their addition to the dispersion medium does not greatly affect the viscosity of the vehicle.

- When the dispersion medium is water then the system called hydrophobic and this system consists of a particle which is not hydrated by water, so water molecules attract to each other to solvate particle.
- This system includes aqueous dispersion of
 1. Oleophilic materials such as polystyrene, gum rubber, steroids, paraffin wax and
 2. Some other organic lipophilic materials like Magnesium stearate
 3. There is an exception for materials that are not lipophilic and form hydrophobic dispersion, these are AgCl and gold.

- Lyophobic dispersions are intrinsically unstable because of the lack of attraction between the dispersed phase and continuous phase, and they are irreversible.
- The instability is also due to the large surface area, which gives large surface free energy, which is not lowered by solvation.
- The dispersion process does not take place spontaneously and once the dispersed phase is separated from the dispersion medium the dispersion is not easily reconstituted.

Preparation of lyophobic dispersion

- It involves the use of many instruments, like colloid mills, ultrasonic vibrators and electric arcs inside the liquid.
- These electric arcs cause evaporation of materials, then followed by condensation process, which is either physical or chemical.
- Example on physical condensation is the precipitation of sulfur from its solution in alcohol by the addition of water.
- Example of chemical condensation is the reaction between strong acid and sodium thiosulfate or reaction between hydrogen sulfide and sulfur dioxide, reaction between strong acid and Ca-polysulphite, all these reactions produce elemental colloidal sulfur.
- A reduction may also takes place like the reduction of salts of gold, silver and copper producing sols of these elements.

- Precipitation may occur between BaCl_2 and sodium sulfate which results in precipitation of Ba sulfate sol.
- Precipitation whether physical or chemical occurs in two stage:
 1. Nucleation: is the formation of sub-microscopic nuclei or seeds.
 2. Particle growth: results from deposition of precipitated materials onto these nuclei.

- There are three conditions that produce colloidal precipitate:
 1. Dilute system with low supersaturation: there are few nuclei but the total precipitating material is low, so no nucleus can grow very large.
 2. Concentrated system with high supersaturation. In this system, many nuclei are formed so quickly, so that the precipitating material per nucleus is still low.
 3. Intermediate concentrated system with moderate supersaturation. The number of nuclei is small compared with the total material precipitated, so the nucleus can grow into large particles.

Amphiphilic or association colloids

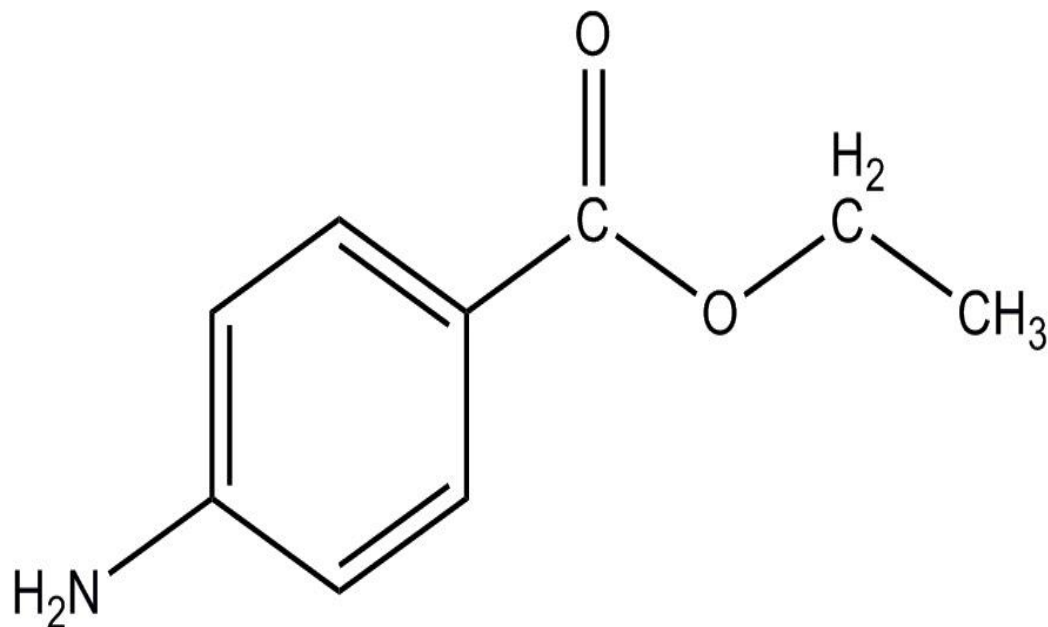
- Association colloid is formed by the grouping or association of molecules that exhibit both lyophilic and lyophobic properties.
- Amphiphilic colloids form dispersions in both aqueous and non aqueous media.
- Depending upon their individual character and the nature of the dispersion medium.
- However, they generally cause an increase in the viscosity of the dispersion medium with an increase in concentration.
- Example of association colloids are surfactant micelles (aggregation of surfactant molecules).

- These aggregates, which may contain 50 or more monomers, are called micelles. Because the diameter of each micelle is of the order of 50 Å, micelles lie within the size range we have designated as colloidal.
- The concentration of monomer at which micelles form is termed the critical micelle concentration(CMC). The number of monomers that aggregate to form a micelle is known as the aggregation number of the micelle. The phenomenon of micelle formation can be explained as follows.
- Below the CMC, the concentration of amphiphile undergoing adsorption at the air–water interface increases as the total concentration of amphiphile is raised.

- Eventually, a point is reached at which both the interface and the bulk phase become saturated with monomers. This is the CMC.
- Any further amphiphile added in excess of this concentration aggregates to form micelles in the bulk phase, and, in this manner, the free energy of the system is reduced.

Importance of micelles

- Micelles practically are important for two purposes:
 1. To solubilize their insoluble compounds or slightly soluble compounds, e.g., vit. A, D, steroids, and volatile oils, these compounds are incorporated in the non polar region of the surfactant.
 2. To protect compounds from acid and base hydrolysis by the incorporation in the non-polar region of the surfactant. An ester is hydrolyzed in acidic or basic media.
 3. Benzocaine (lipophilic compound) have been solubilized in micelle and its solubility was increased



Benzocaine

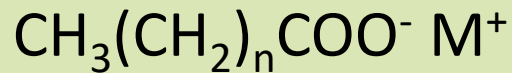
[Benzoic acid, 4-amino-, ethyl ester]

- Surfactant or surface active agents can be classified in two different ways:
 1. Functional classification: they are classified according to uses into wetting agents, detergents, emulsifying agent, solubilizing agents, suspending agents, foaming agents and anti foaming agents.
 2. Structural classification: the most important surfactants are those which are water-soluble, they are classified according to chemical structure into three groups: ionic surfactant, non ionic surfactants and ampholytic surfactants.

Anionic surfactants

- Anionic surfactants which contain (+) charged counter ion.
- Counter ion: an ion having a charge opposite to that of the substance with which it is associated.
- it is the ion that accompanies an ionic species in order to maintain electric neutrality.
- Examples:
 1. Sodium lauryl sulfate, sodium ion is the counter ion. $\text{C}_{12}\text{H}_{25}\text{O}.\text{SO}_2\text{O}^- \text{Na}^+$
- It is used in toothpaste and ointments.

2. Soaps: are salts of long chain fatty acid, they have general formula



Where: M = Na^+ or K^+ or triethanolamine

Fatty acid:

Lauric acid, n= 10

Myristic acid, n =12

Palmitic acid, n = 14

Stearic acid, n = 16

Oleic acid, n = 16 + monounsaturated

Ricinoleic acid, n = 16 + monounsaturated + one OH^- group.

Example of soap is potassium salt of oleic acid or what is called (Green Soap).

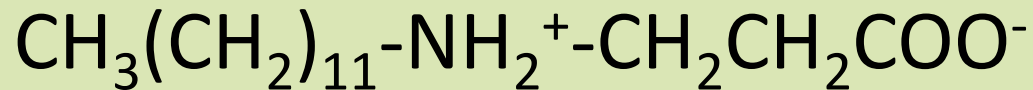
3. Bile salt: sodium glycocholate, which is used to solubilize monoglycerides, which is essential step in fat metabolism.

Cationic surfactant

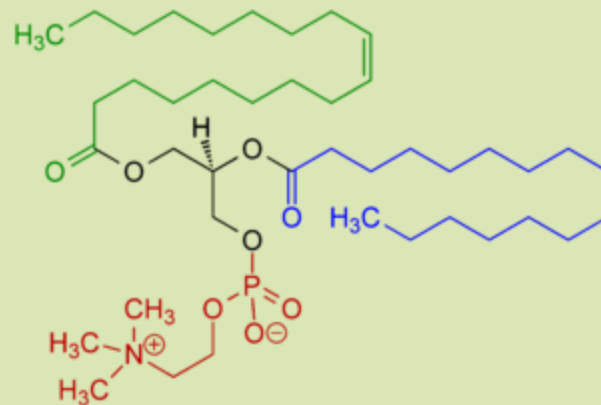
- Cationic surfactant contain (-) charged counter ion.
- Example: Benzalkonium chloride which is a quaternary ammonium compound used as bacteriostatic agent because it combines with carboxyl group of the cell wall of micro organism causes lysis of the cell. So used as antiseptic and as preservative.

Ampholytic surfactants

- Ampholytic surfactants are molecules as a whole containing both negative and positive charged groups and they exist as a zwitterion.
- Examples: Dodecyl β -alanine.

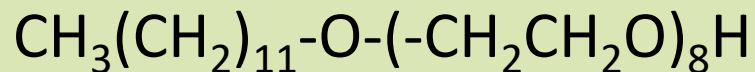


- Lecithin



II-Nonionic S.A.A

- Non ionic S.A.A are mostly additional products of ethylene oxide, the addition process is initiated by active hydrogen which is present in aliphatic or phenolic OH, COOH, SH, and NH₂ group.
- All these compounds contain active hydrogen that can produce ring-opening reaction for ethylene oxide and the reaction is produced by alkaline catalyst, example on the formation of nonionic S.A.A. is R-OH compounds containing active hydrogen added to ethylene oxide.
- $R-OH + CH_2-OCH_2 \rightarrow R-OCH_2CH_2OH$
- It can add many more of ethylene oxide
- An example of nonionic compound is



- The reaction is like many polymerizations, some molecules may grow faster than another, the polyethylene glycol portion is the hydrophilic moiety, each ether oxygen can add two water molecules by hydrogen bonding and these water molecules in turn can add many more water molecules.
- As a result, hydration and solubilization of surfactant takes place, but this hydration is not as efficient as introduction of cationic group into ionic surfactant (i.e., ionic SAA are more soluble than non-ionic one).

- Hydration process is an exothermic process, when the temperature increases, hydration decreases and the SAA becomes less soluble, its solution becomes turbid, this characteristic temperature is called cloud point.
- This solution becomes clear again if cooled down below the cloud point because it becomes hydrated and soluble.

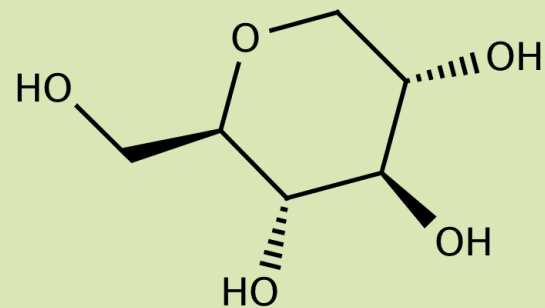
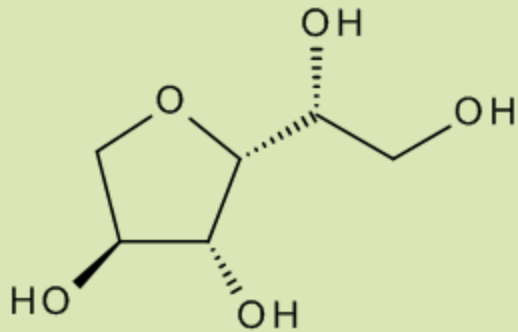
- Cloud point is independent on concentration of the solution but depends on its composition e.g., cloud point increases as the no. of ethylene oxide units/ molecule increase at constant hydrocarbon portion, while the cloud point decreases as the hydrocarbon chain length increases at constant ethylene oxide unit no.

- The dispersion of emulsion containing this type of surfactant is destroyed if heated above the cloud point, can not be back orre-used.
- This type of surfactant is called “polyoxyethylated non-ionic surfactant.
- An important examples on nonionic SAA are:
Span 20, 40, 60, 80, ---- + 20 molecules of ethylene oxide \longrightarrow Tween 20, 40, 60, 80, ---
- Each span is converted to tween by the addition of 20 molecules of ethylene oxide.

- Properties of spans are different from tweens:
- Spans are water-insoluble while tweens are water-soluble.
- The number besides spans and tweens doesnot indicate anything but the companies give them numbers to differentiate one span from another and one tween from another.
- Although, they differ in viscosity, e.g., span 20 is less viscous than span 80.

Preparation of Spans and Tweens

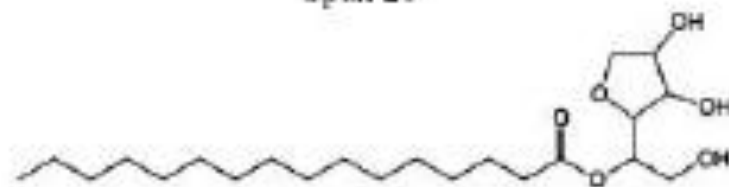
- The electrolytic reduction (H^+) of glucose yields the hexahydroalcohol (sorbitol) then by dehydration it gives mixture of 5- and 6-member ring compounds called sorbitan which has the following structure: It has the same chemical formula.



- Esterification of primary alcohol of sorbitan with lauric acid (10C) gives sorbitan mono laurate (Span 20).
- Esterification of primary alcohol of sorbitan with palmitic acid (14 C) gives sorbitan mono palmitate (Span 40).
- Esterification of primary alcohol of sorbitan with stearic acid (16C) gives sorbitan mono stearate (Span 60).
- Esterification of primary alcohol of sorbitan with oleic acid (16 C and unsaturated) gives sorbitan mono oleate (Span 80)



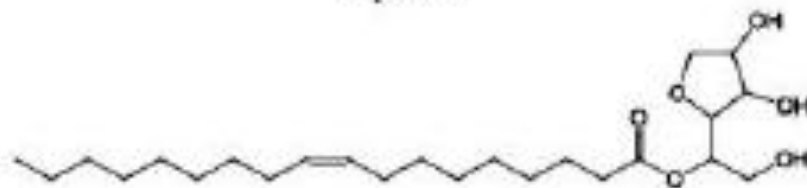
Span 20



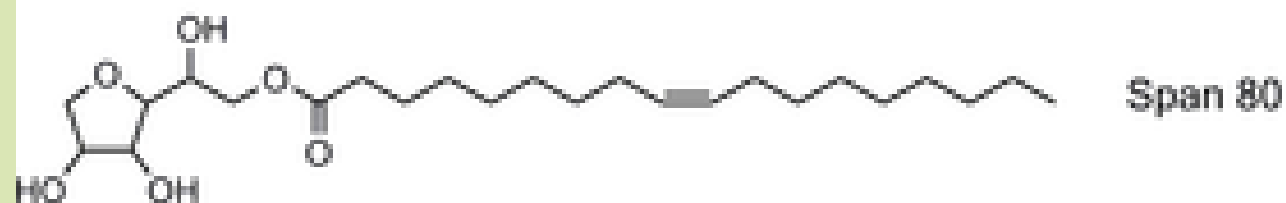
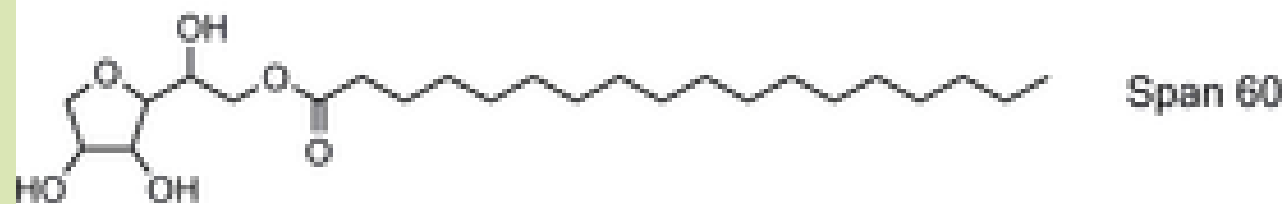
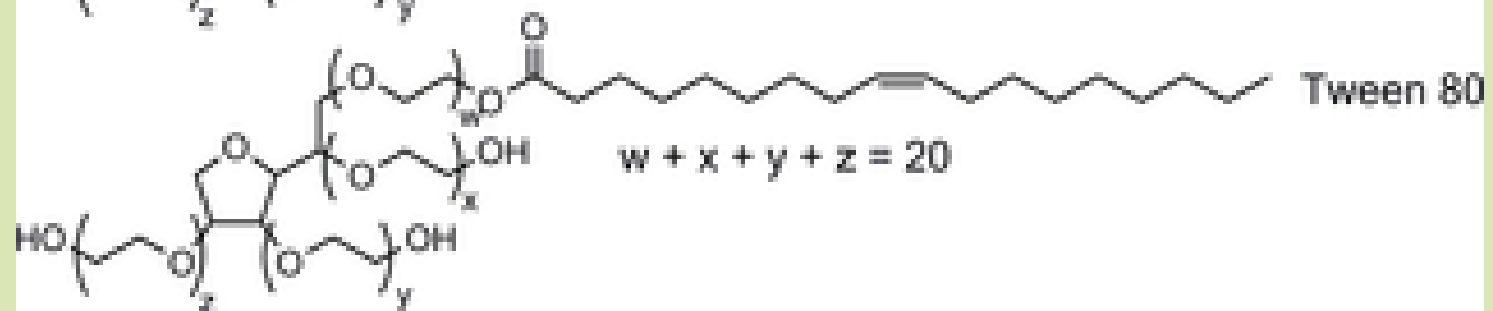
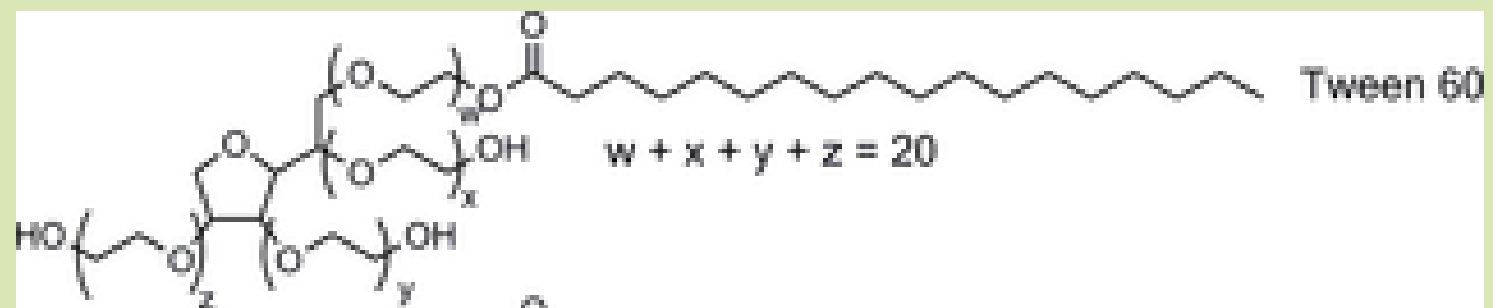
Span 40



Span 60



Span 80



- Addition of ethylene oxide increases the water solubility so tween is more soluble than span in water.
- In any practice, the best surfactant is obtained by mixing certain quantity of span with certain quantity of tween according to HLB system (hydrophilic-lipophilic balance system).
- HLB system is scale contain values for span and tween and other surfactants.

Adsorption of surfactant

- Surfactant are adsorbed at the interface between two immiscible liquids with the polar portion toward the aqueous phase and non-polar portion oriented toward the non-polar phase.
- Surfactant can form spherical micelles at concentration called critical micelle concentration (CMC) and if the concentration of surfactant is increased above CMC, then the shape of aggregate is changed from spherical to lamellar.
- The adsorption of surfactant is governed by Gibbs adsorption equation, which state that:

$$\Gamma = - \frac{c}{RT} \frac{d\gamma}{dc}$$

- Γ : surface concentration of surfactant/ unit area, mole/cm², found in the surface in excess of that in the bulk.
- C : concentration of surfactant in the bulk.
- R : gas constant,
- T : absolute temperature,
- $d\gamma/dc$: the change in surface tension by change in concentration.

- Surface Tension: is the work in erg that needs to generate one cm^2 of the surface.
- $\Delta F = \gamma \cdot \Delta A$
- $\text{Erg}/\text{cm}^2 = \text{dyne}\cdot\text{cm}/\text{cm}^2 = \text{dyne}/\text{cm}$
- Tension between two immiscible liquids is called interfacial tension.
- For example, normal-octyl alcohol with water, have more interaction than n-octane with water.
- Interfacial tension in first one = 8 dyne/cm, while in second = 50 dyne/ cm.

Table 16-1 Classification and Typical Examples of Association Colloids

Type	Example		
	Compound	Amphiphile	Counterions
Anionic	Sodium lauryl sulfate	$\text{CH}_3(\text{CH}_2)_{11}\text{OSO}_3^-$	Na^+
Cationic	Cetyl trimethyl-ammonium bromide	$\text{CH}_3(\text{CH}_2)_{15}\text{N}^+(\text{CH}_3)_3$	Br^-
Nonionic	Polyoxyethylene lauryl ether	$\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{O}(\text{CH}_2\text{OCH}_2)_{23}\text{H}$	—
Amphotytic	Dimethyldodecylammonio propane sulfonate	$\text{CH}_3(\text{CH}_2)_{11}\text{N}^+(\text{CH}_3)_2(\text{CH}_2)_3\text{OSO}_2^-$	—

Table 16-2 Comparison of Properties of Colloidal Sols*

Lyophilic	Association (Amphiphilic)	Lyophobic
Dispersed phase consists generally of large organic <i>molecules</i> lying within colloidal size range	Dispersed phase consists of aggregates (<i>micelles</i>) of small organic molecules or ions whose size <i>individually</i> is below the colloidal range	Dispersed phase ordinarily consists of inorganic particles, such as gold or silver
Molecules of dispersed phase are solvated, i.e., they are associated with the molecules comprising the dispersion medium	Hydrophilic or lipophilic portion of the molecule is solvated, depending on whether the dispersion medium is aqueous or nonaqueous	Little if any interaction (solvation) occurs between particles and dispersion medium

Lyophilic	Association (Amphiphilic)	Lyophobic
Molecules disperse spontaneously to form colloidal solution	Colloidal aggregates are formed spontaneously when the concentration of amphiphile exceeds the critical micelle concentration	Material does not disperse spontaneously, and special procedures therefore must be adopted to produce colloidal dispersion
Viscosity of the dispersion medium ordinarily is increased greatly by the presence of the dispersed phase; at sufficiently high concentrations, the sol may become a gel; viscosity and gel formation are related to solvation effects and to the shape of the molecules, which are usually highly asymmetric	Viscosity of the system increases as the concentration of the amphiphile increases, as micelles increase in number and become asymmetric	Viscosity of the dispersion medium is not greatly increased by the presence of lyophobic colloidal particles, which tend to be unsolvated and symmetric

Lyophilic**Association
(Amphiphilic)****Lyophobic**

Dispersions are stable generally in the presence of electrolytes; they may be salted out by high concentrations of very soluble electrolytes; effect is due primarily to desolvation of lyophilic molecules

In aqueous solutions, the critical micelle concentration is reduced by the addition of electrolytes; salting out may occur at higher salt concentrations

Lyophobic dispersions are unstable in the presence of even small concentrations of electrolytes; effect is due to neutralization of the charge on the particles; lyophilic colloids exert a protective effect

*From J. Swarbrick and A. Martin, *American Pharmacy*, 6th Ed., Lippincott, Philadelphia, 1966, p. 161.