Pharmaceutical Technology-I

Colloid-Part II

Lyophobic and Association Colloids

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 <u>hydrophobic</u> 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 colloid

- For preparing lyophobic colloidal sol, the substance in bulk is broken down into particles of colloidal dimensions (Dispersion) or aggregating smaller particles of into particles of colloidal dimensions (condensation).
- To improve the stability of sol creation substances are added to the sol, the substances added are called stabilizers.

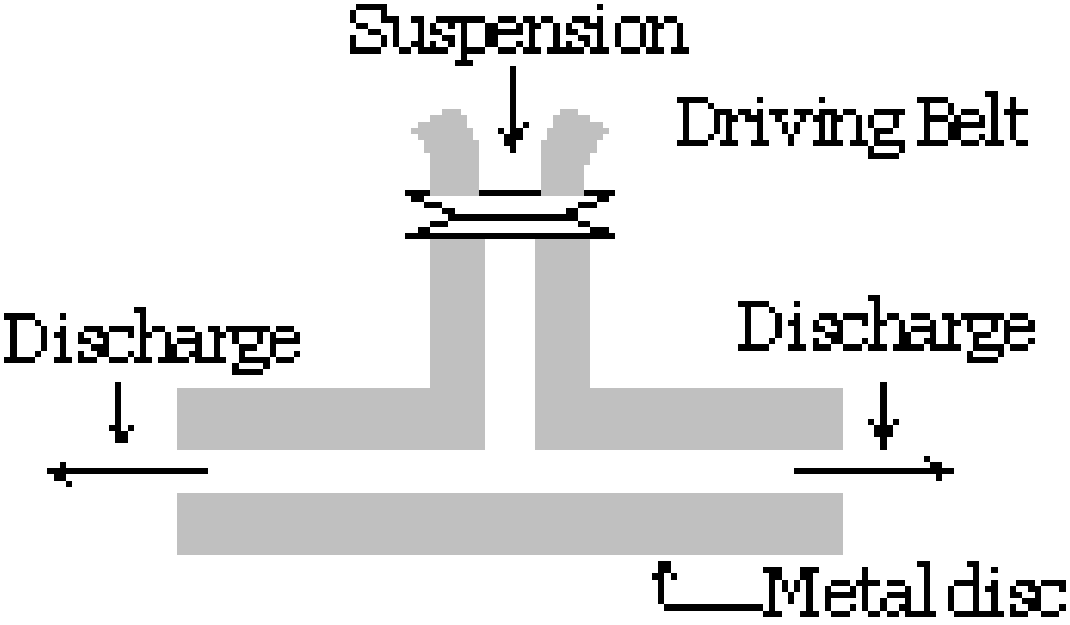
Dispersion methods

- In the dispersion method particle of larger size are broken down to colloidal size in the dispersion medium.
- Starting with the material in massive form, a colloidal dispersion is prepared by using suitable devices to disintegrate it into particles of colloidal size.
- Normally this is carried out by physical methods.
- The dispersion methods used are:

1. Mechanical dispersion
2. Electrical dispersion
3. Ultrasonic dispersion

Mechanical dispersion method

- The substance which is to be dispersed is finely ground. It is then mixed with the dispersion medium, protective materials or stabilizer is also added when a coarse suspension is obtained.
- This suspension is then passed through a colloid mill. A colloid mill consists of two heavy metal discs placed one above the other separated by a very small gap from each other. They are rotated in the opposite directions at a very high speed of about 7000 r.p.m.
- The sol results due to the large shearing effect.
- Protective material used prevents particles from coagulation.



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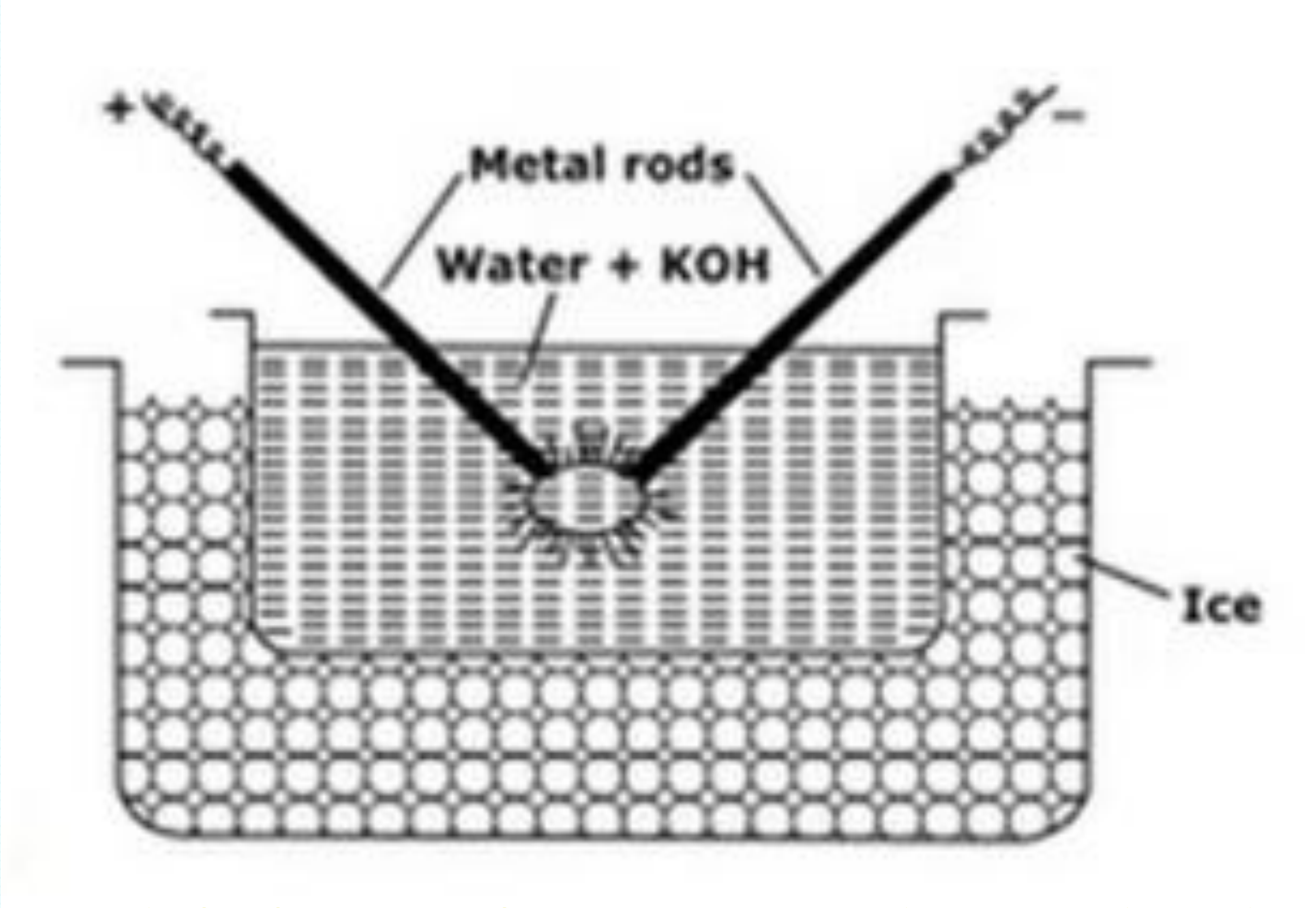
Electrical dispersion or Bredig's Arc method

- This method used to prepared metal sols like platinum, silver, gold, copper in water.
- A dispersion medium (conductivity water) and a trace of sodium hydroxide (the stabilizing agent) is taken in porcelain or glass (non conducting) vessel.
- Metal to be dispersed is dipped in the vessel in the form of electrodes. Electrodes are connected to the high voltage source. The ends of electrodes in the dispersion medium are very near to each other.
- A very high voltage is applied and then an electrical arc is struck between the tips of electrodes. This creates large heat due to which metal rods melt, evaporate and suddenly cooled due to freezing mixture gives rise to the colloidal solution of the metal.
- ➢ Function of the freezing mixtures are

1. Freezing mixture helps in condension of metal vapours forming the colloids
2. It prevents vapourisation of water.
3. It prevents coagulation of colloids, by keeping sol cold.



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Ultrasonic Dispersion

- Ultrasound is a very effective processing method in the generation and application of colloidal size particles.
- High-intensity ultrasonic waves are used for this purpose.
- During sonicating of liquids the ultrasonic waves that propagate through dispersion medium result in alternating high-pressure (compression) and low-pressure (rarefaction) cycles. This mechanical stress causes ultrasonic cavitation in liquids. It creates high-speed liquid jets of up to 100km/h.
- Such jets press liquid at high-pressure between the particles and separate them from each other.
- Smaller particles are accelerated with the liquid jets and collide at high speeds.
- Various substances like oils, mercury, sulphur, sulphides and oxides of metal can be dispersed in a colloidal state by this method.

Condensation methods

- These methods involve chemical reactions.
- In these methods factors like temperature, pressure, concentrations, etc. are properly maintained.
- The unwanted ions present in the sol are removed by dialysis, as these ions may eventually coagulate the sol.
- Condensation methods are:

1. Oxidation method
2. Reduction method
3. Hydrolysis method

Oxidation method

- Preparation of colloidal Sulphur:

  When H_2S in water (aqueous solution) is exposed to air, it slowly gets oxidise to sulphur.
- The sulphur so formed remains in water in the colloidal state and the solution has a slightly milkish appearance.

$$H_2S \quad + \quad O2 \rightarrow H_2O \quad + \quad 2S \text{ (colloidal)}$$

- A sol of sulphur can also be prepared when H_2S gas is bubbled through an aqueous solution of SO_2

$$H_2S \quad + \quad SO_2 \rightarrow 2\,H_2O \quad + \quad 3S \text{ (colloidal)}$$

Reduction Method

- Preparation of Gold Sol:
- A number of metals like silver, gold, platinum, mercury leas can be obtained in the colloidal state by the reduction of their salt solutions (dilute) using suitable reducing agents like hydrogen sulphide, formuldehyde, stannous chloride, tannic acid etc.
- Gold sol can be obtained when $AuCl_3$ (dilute) solution is treated with stannous chloride.

$$2\,AuCl_3 + 3\,SnCl_2 \rightarrow 3\,SnCl_4 + 2\,Au\ \text{(colloidal)}$$

- Similarly, silver, platinum mercury sols are prepared

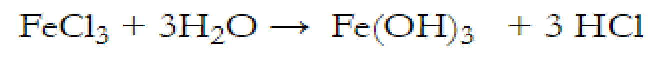
$$AgNO_3 + \text{Tannic acid} \longrightarrow \text{Ag sol}$$

$$AuCl_3 + \text{Tannic acid} \longrightarrow \text{Au sol}$$

Hydrolysis method

1. Preparation of Ferric hydroxide sol:

- A colloidal solution of ferric hydroxide is obtained by boiling a dilute solution of ferric chloride.



$$FeCl_3 + 3H_2O \rightarrow Fe(OH)_3 + 3\,HCl$$

2. Preparation of silicic acid sol:

- By hydrolysis of a dilute solution of sodium silicate with a hydrochloric acid, the colloidal solution of silicic acid H4SiO4 is obtained.

Physical methods
By exchange solvent method

- There are a number of substances whose colloidal solution can be prepared by taking a solution of the substance in one solvent and pouring it into another solvent in which is relatively less soluble.
- Preparation of sulphur or phosphorous sol: If a solution of sulphur or phosphorous prepared in alcohol is poured into water, a colloidal solution of sulphur or phosphorus is obtained due to the low solubility of sulphur or phosphours in water

By change of physical state

- A colloidal solution of certain elements such as mercury and sulphur are obtained by passing their vapours through cold water containing a stabilizer (an ammonium salt or a citrate).

Excessive cooling method

- A colloidal solution of ice in an organic solvent like ether or chloroform can be prepared by freezing a solution of water in the solvent. The molecules of water which can no longer be held in solution, separately combine to form particles of colloidal size.

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.

- The effect of micellization on some of the physical properties of solutions containing surface-active agents as shown in the Figure 16-3. Note particularly that surface tension decreases up to the CMC. From the Gibbs' adsorption equation, this means increasing interfacial adsorption.
- Above the CMC, the surface tension remains essentially constant, showing that the interface is saturated and micelle formation has taken place in the bulk phase.

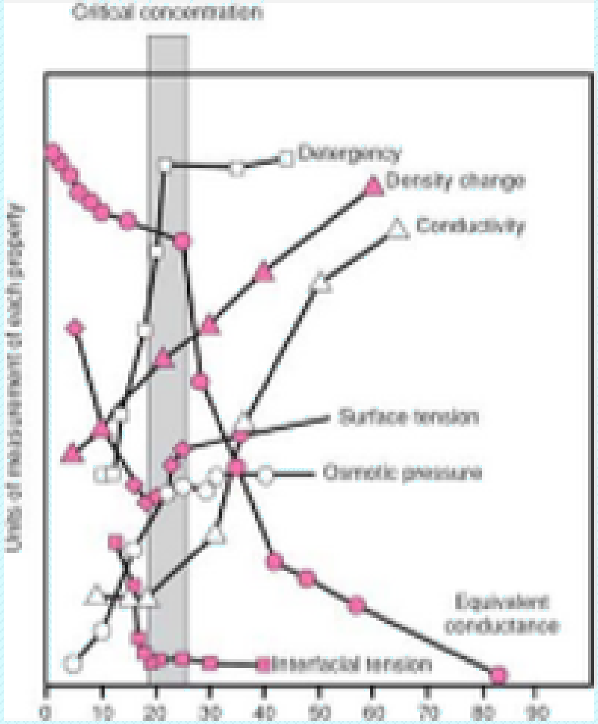


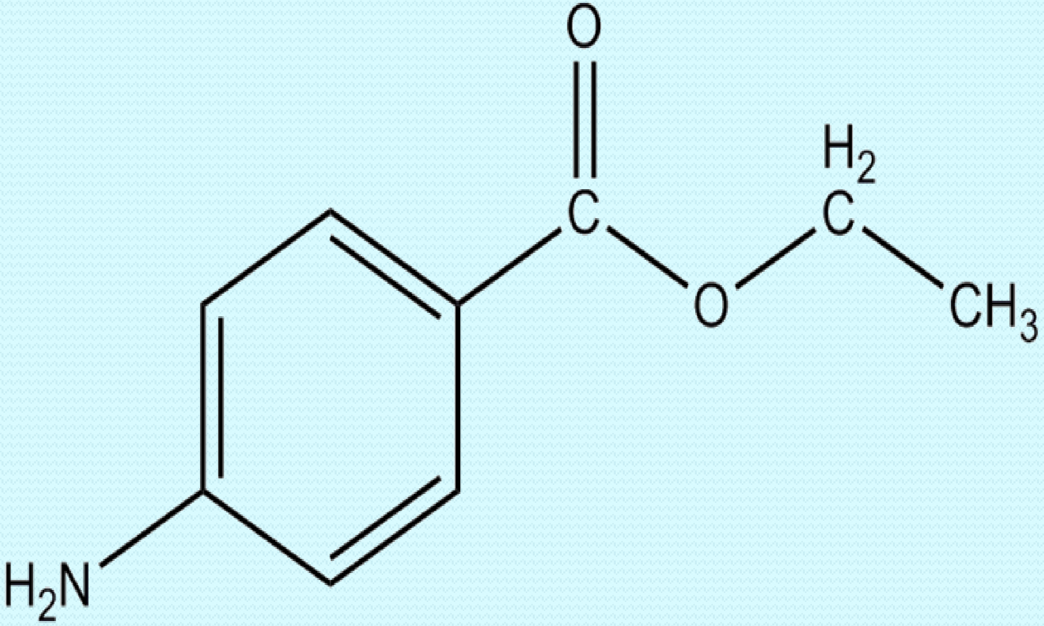
Fig. 16-3. Properties of surface-active agents showing changes that occur sharply at the critical micelle concentration. (Modified from W. J. Preston, Phys. Coll. Chem. **52,** 85, 1948.)

Importance of micelles

- Micelles practically are important for two purposes:

1. To solubilize 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.

Example: 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. $C_{12}H_{25}O.SO_2O^- Na^+$

- It is used in toothpaste and ointments.

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

$CH_3(CH_2)_nCOO^- M^+$

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.

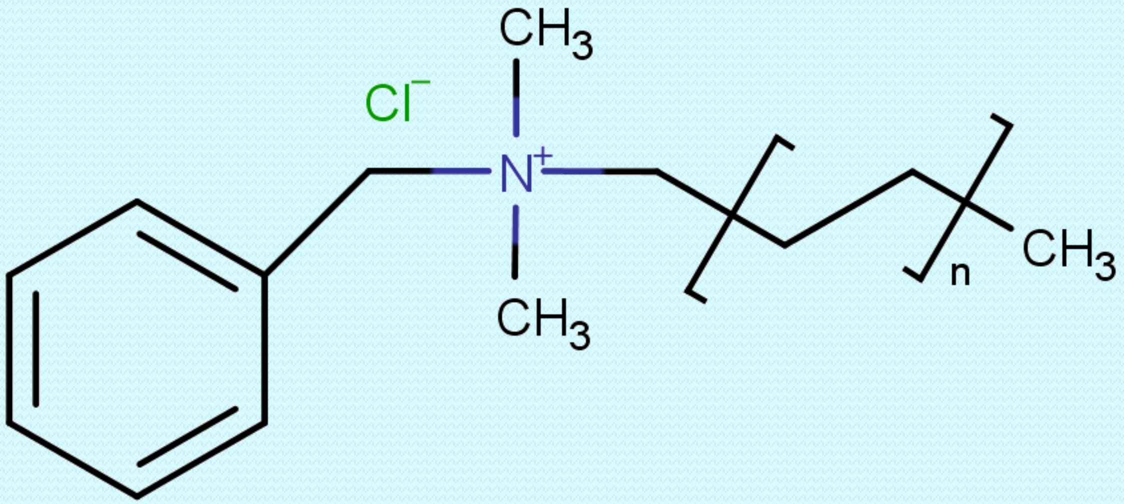
Example of soap is potassium salt of oleic acid or what is called (Green Soap).

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 laysis of the cell.
- So used as antiseptic and as preservative.

Benzalkonium chloride



What is benzalkonium chloride and why is it used as an excipient?

- Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of other cationic surfactants.
- It is also used as an antimicrobial preservative for pharmaceutical products. For most multidose aqueous nasal, ophthalmic and otic products, benzalkonium chloride is the preservative of choice.
- It has been used in eye drops as a preservative since the 1950's and it is still the most common preservative used in ophthalmic solutions at a concentration of 0.01–0.02%.
- It is an effective bactericidal and fungicidal agent that helps to minimise the growth of organisms in multidose containers.

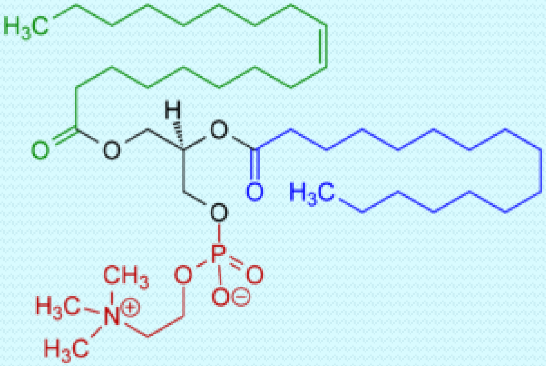
Ampholytic surfactants

- Ampholytic surfactant are molecules as a whole containing both negative and positive charged groups and they exist a zwitter ion.
- Examples:

1. Dodecyl β-alanine.

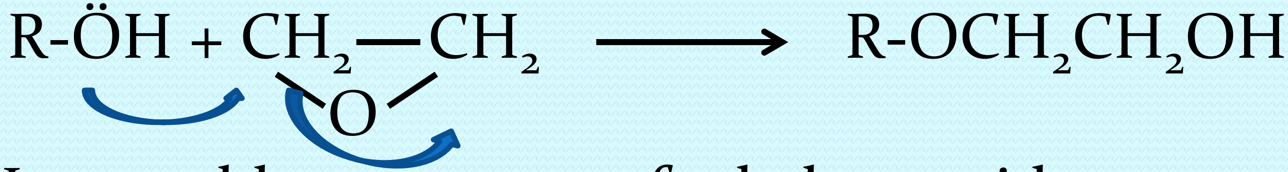
$CH_3(CH_2)_{11}-NH_2^+-CH_2CH_2COO^-$

2. 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 NH_2 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.



$$R\text{-}\ddot{O}H + \underset{O}{CH_2\text{—}CH_2} \longrightarrow R\text{-}OCH_2CH_2OH$$

- It can add many more of ethylene oxide
- An example of nonionic compound is

$$CH_3(CH_2)_{11}\text{-}O\text{-}(\text{-}CH_2CH_2O)_8H$$

- 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 with ionic surfactant (i.e., ionic SAA are more soluble than non-ionic one).

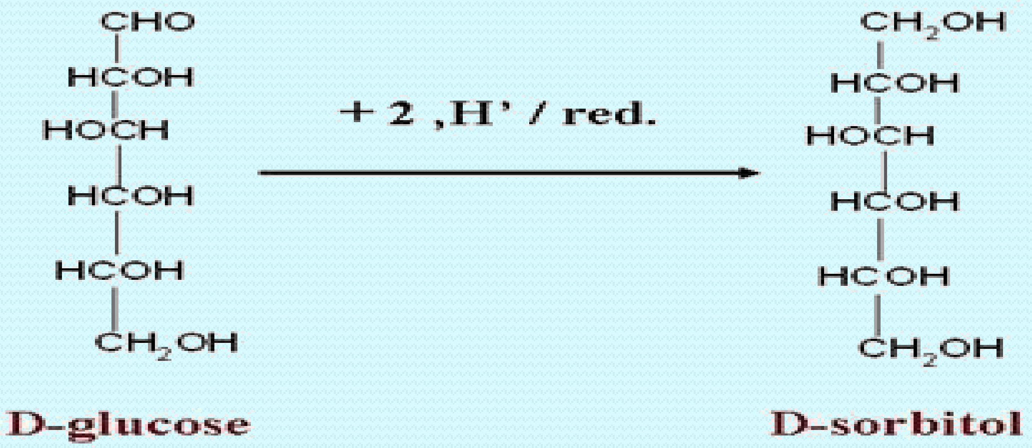
- Hydration process is an exothermic process, when the temperature increases, hydration decreases and the SAA becomes less soluble, its solution becomes turbid, this characteristic temperature is called cloud point.
- This solution becomes clear again if cooled down below the cloud point because it becomes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

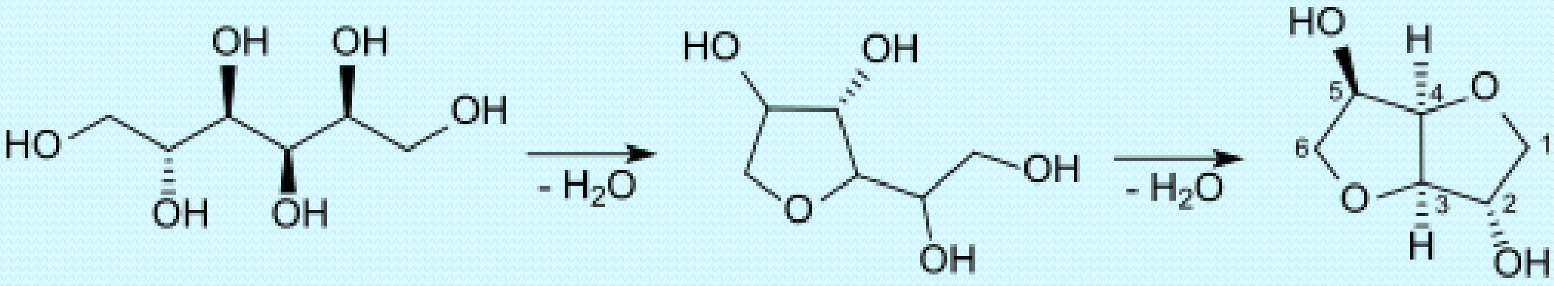
Spans are less water-soluble while tweens are highly water-soluble

Preparation of Spans and Tweens

- The electrolytic reduction (H^+) of glucose yields the hexa hydroalcohol (sorbitol)



- Then by dehydration it gives mixture of 5- and 6- member ring compounds called sorbitan which has the following structure: they have the same chemical formula.



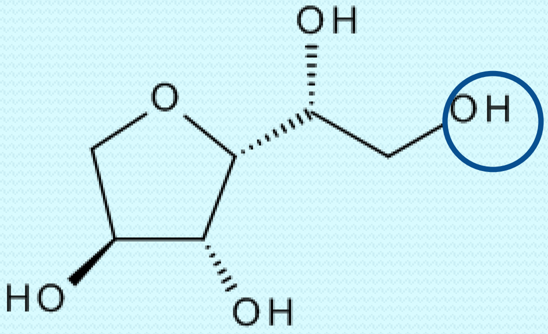
D-Sorbitol

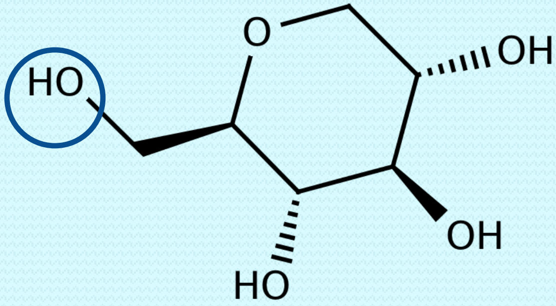
1,4-Sorbitan

Isosorbid

Sorbitan

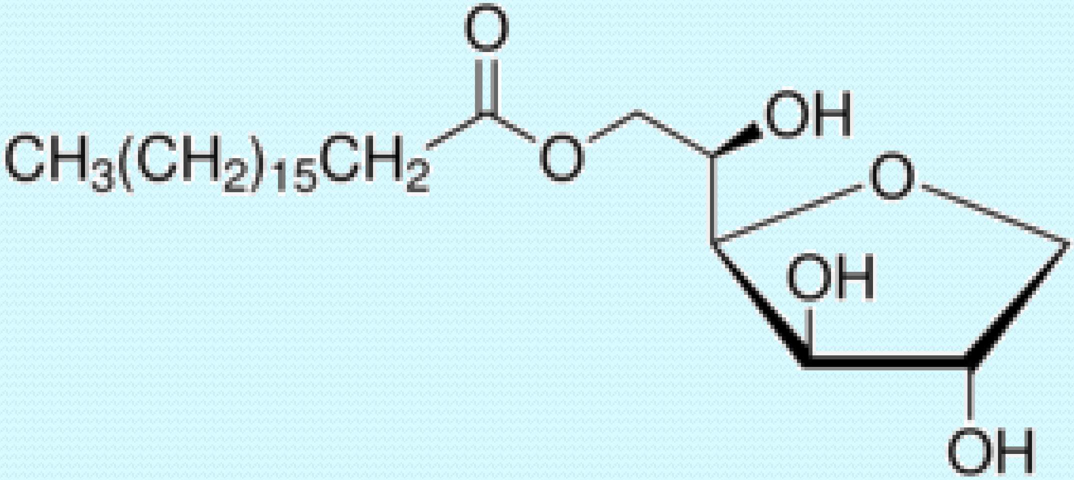
- Sorbitan is produced by the dehydration of sorbitol and is an intermediate in the conversion of sorbitol to isosorbide. The rate of formation of sorbitan is typically greater than that of isosorbide, which allows it to be produced selectively, providing the reaction conditions are carefully controlled. The dehydration reaction has been shown to work even in the presence of excess water.

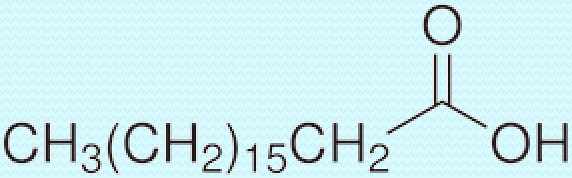




- Esterification of primary alcohol of sorbitan with lauric acid gives sorbitan mono laurate (Span 20).
- Esterification of primary alcohol of sorbitan with palmitic acid gives sorbitan mono palmitate (Span 40).
- Esterification of primary alcohol of sorbitan with stearic acid gives sorbitan mono stearate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

Span 60

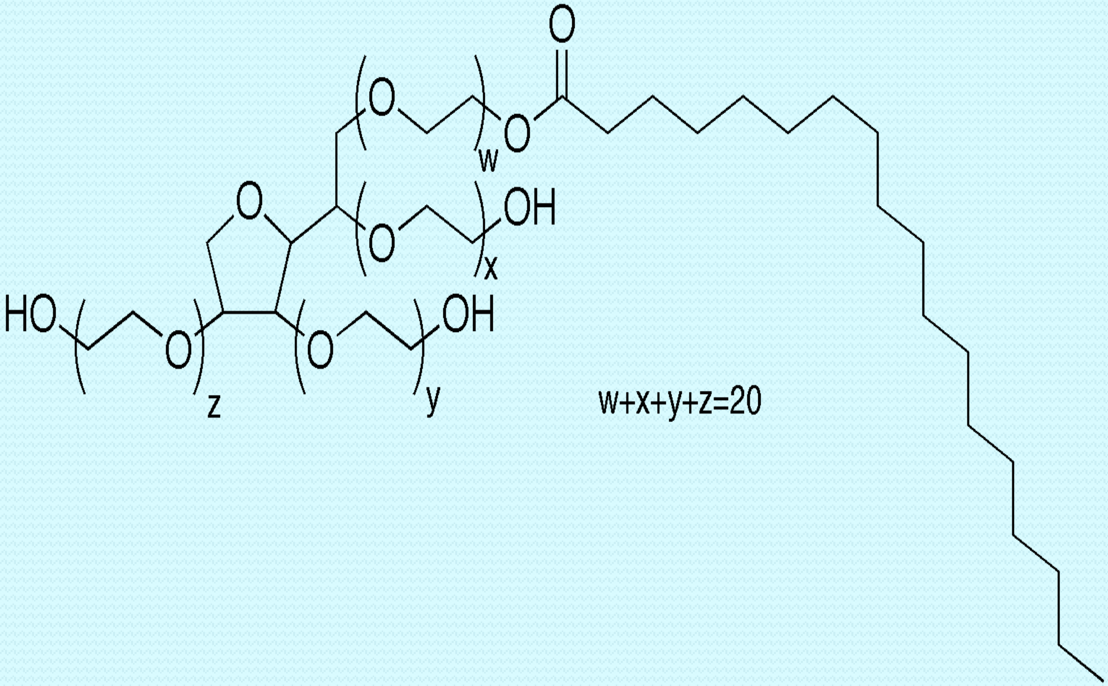




$CH_3(CH_2)_{15}CH_2C(=O)OH$

Stearic acid

- Then by addition of 20 molecules of ethylene oxide, it gives the corresponding Tween:
- For example Tween 60 (polysorbate 60)



$w+x+y+z=20$

- Addition of ethylene oxide increases the water solubility so tween is more soluble in water than span.
- 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:

$$\Gamma = -\frac{c}{RT} \times \frac{dY}{dc}$$

- Γ: surface concentration of surfactant/ unit area, mole/cm^2, found in the surface in excess of that in the bulk.
- C: concentration of surfactant in the bulk.
- R: gas constant,
- T: absolute temperature,
- $d\Upsilon/dc$: 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.
- $\Delta F = \Upsilon . \Delta A$
- $Erg/cm^2 = dyne.cm/cm^2 = dyne/cm$
- Tension between two immiscible liquids is called interfecial 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.

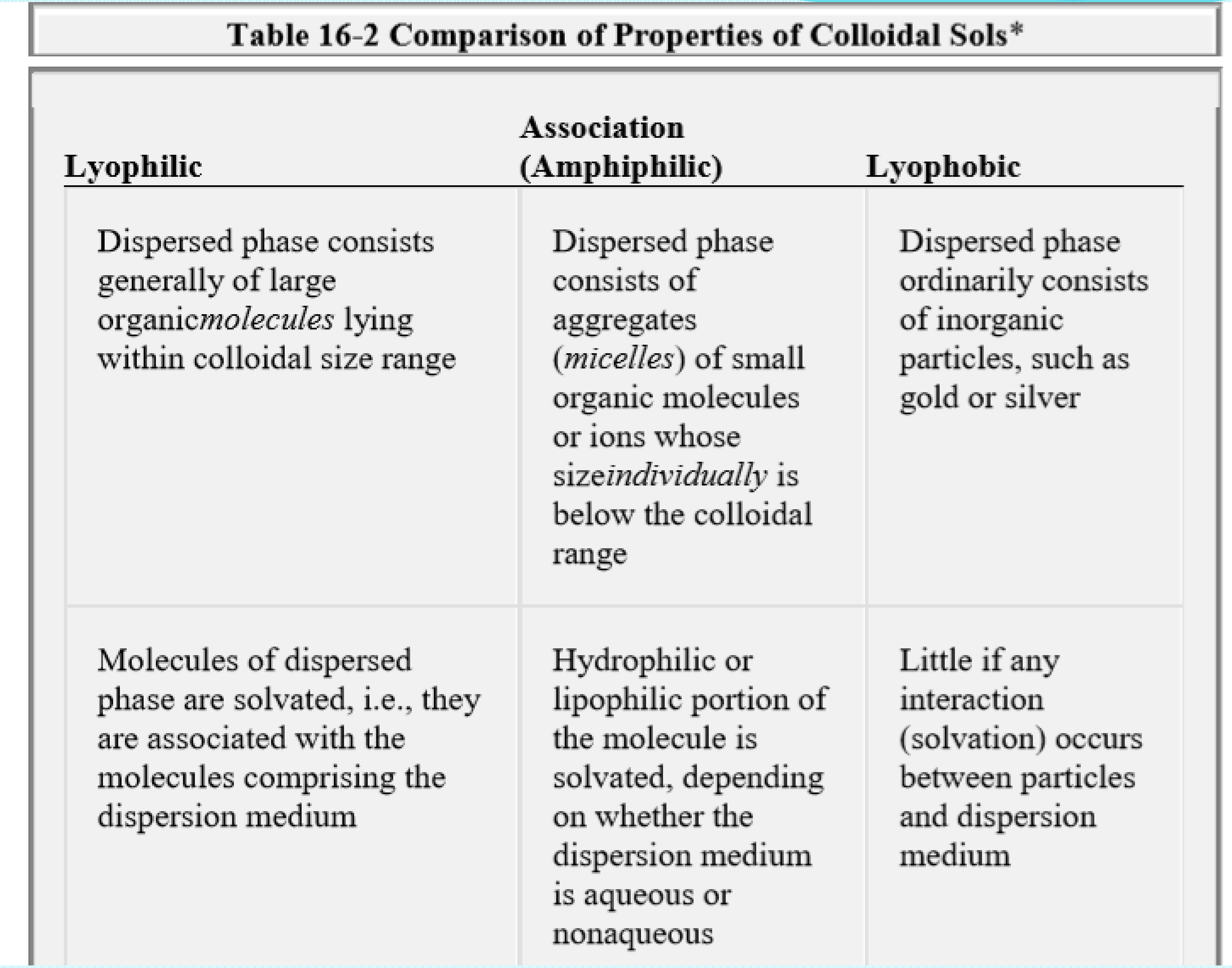
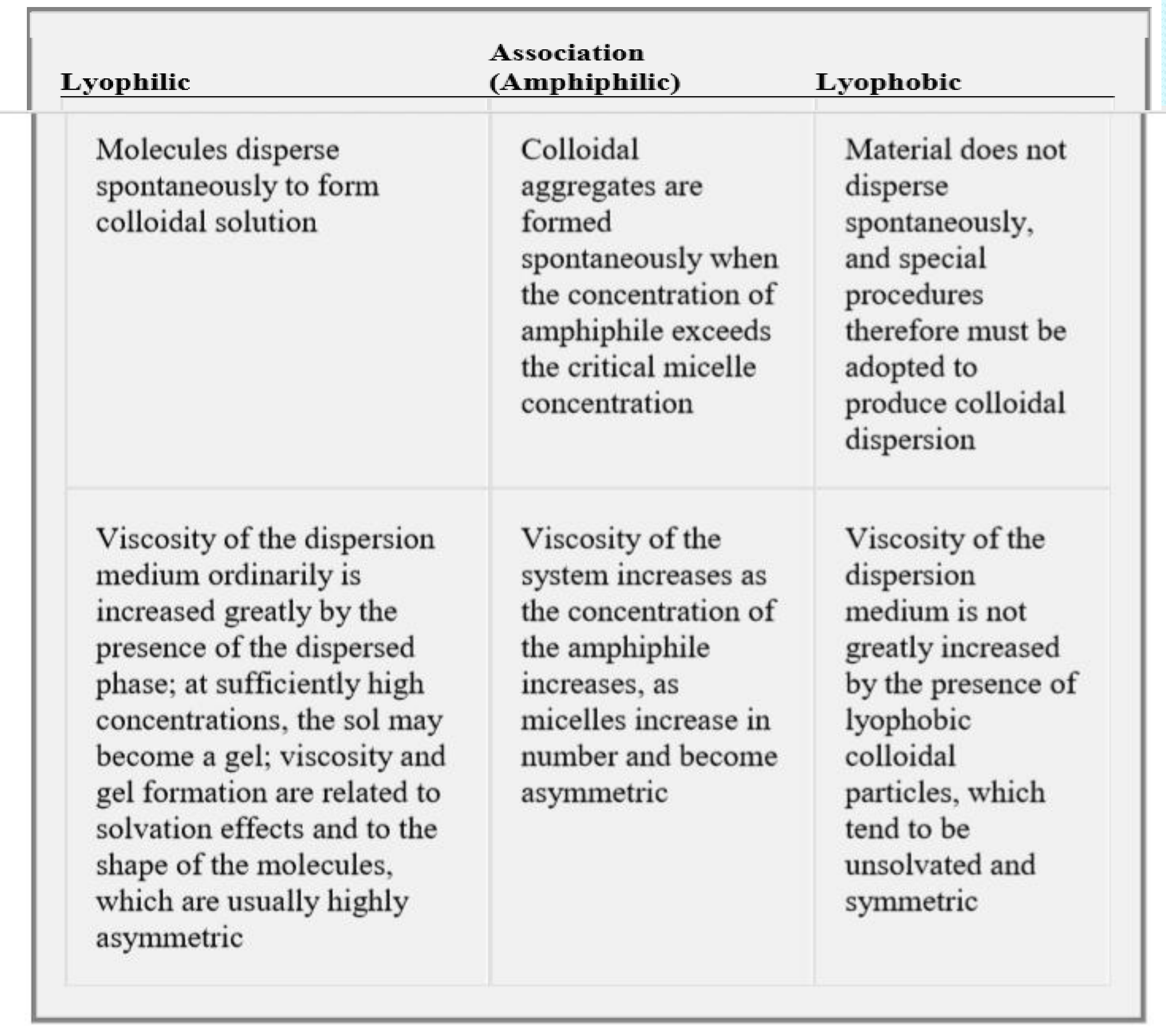
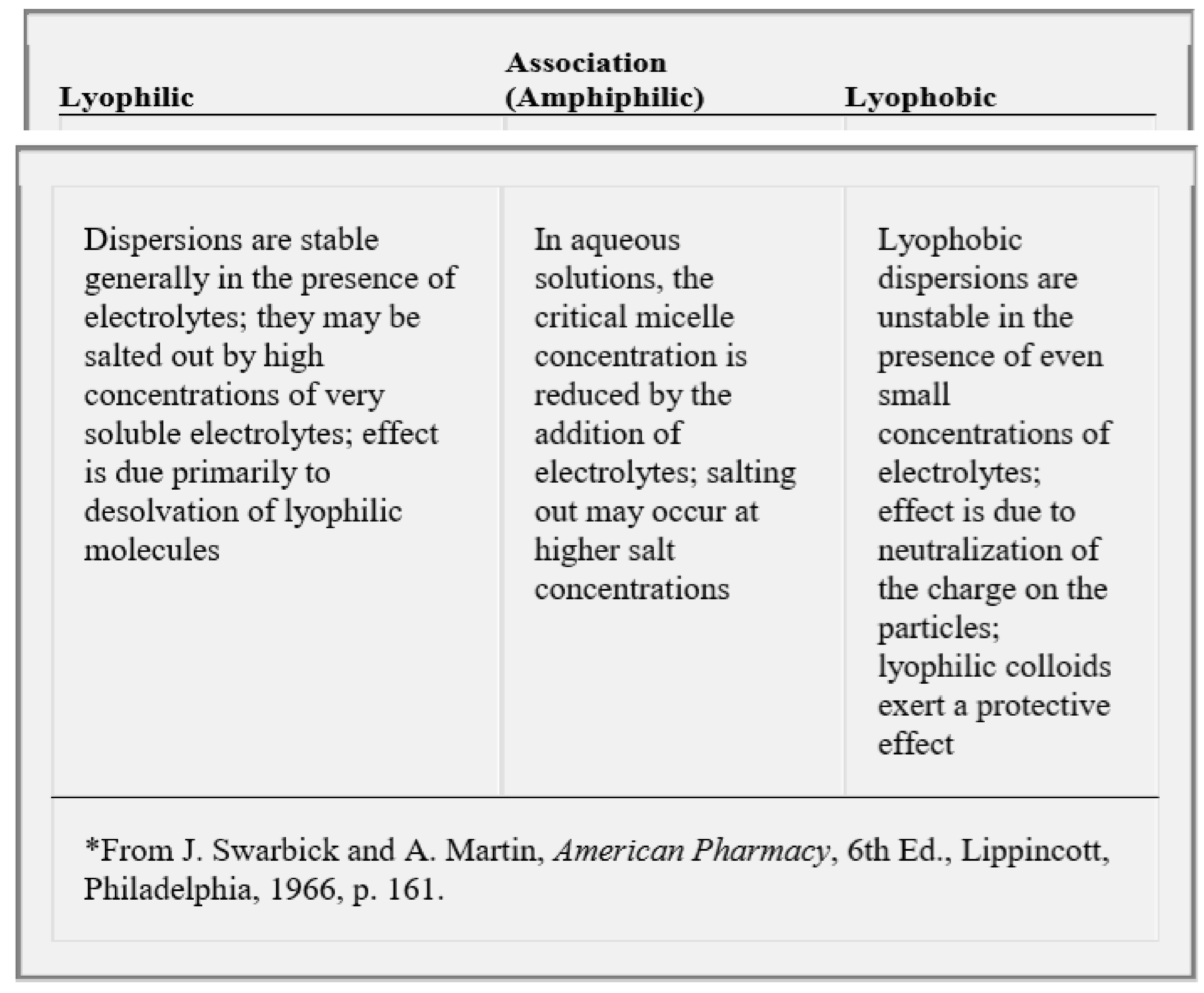


Table 16-2 Comparison of Properties of Colloidal Sols*

Lyophilic	Association (Amphiphilic)	Lyophobic
Dispersed phase consists generally of large organic*molecules* lying within colloidal size range	Dispersed phase consists of aggregates (*micelles*) of small organic molecules or ions whose size*individually* 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. Swarbick and A. Martin, *American Pharmacy*, 6th Ed., Lippincott, Philadelphia, 1966, p. 161.