Pharmaceutical Technology

Colloidal Dispersion

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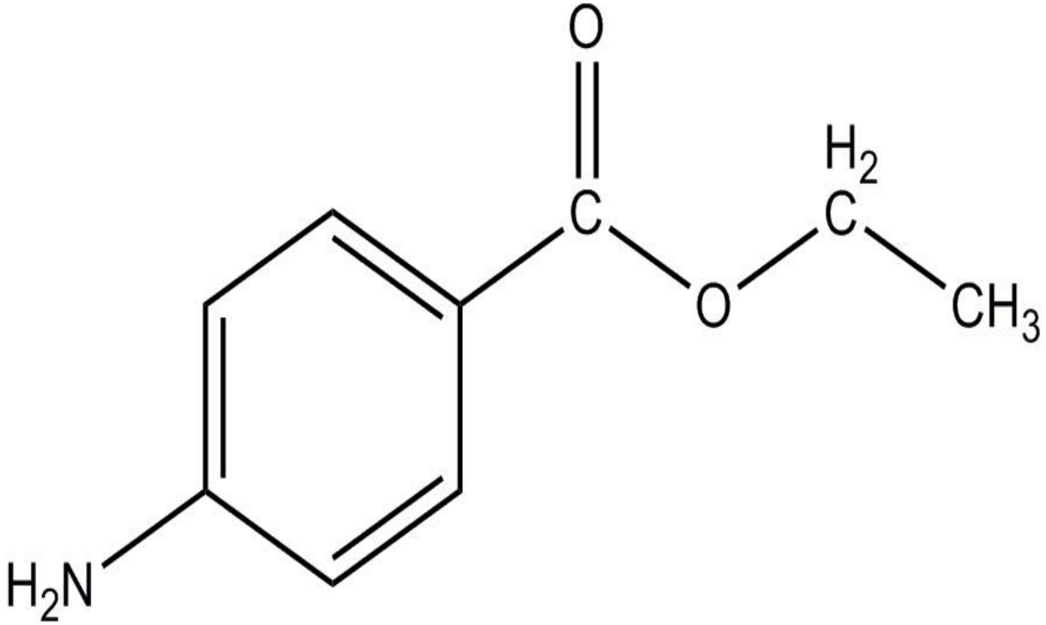
Importance of micelles

- 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.

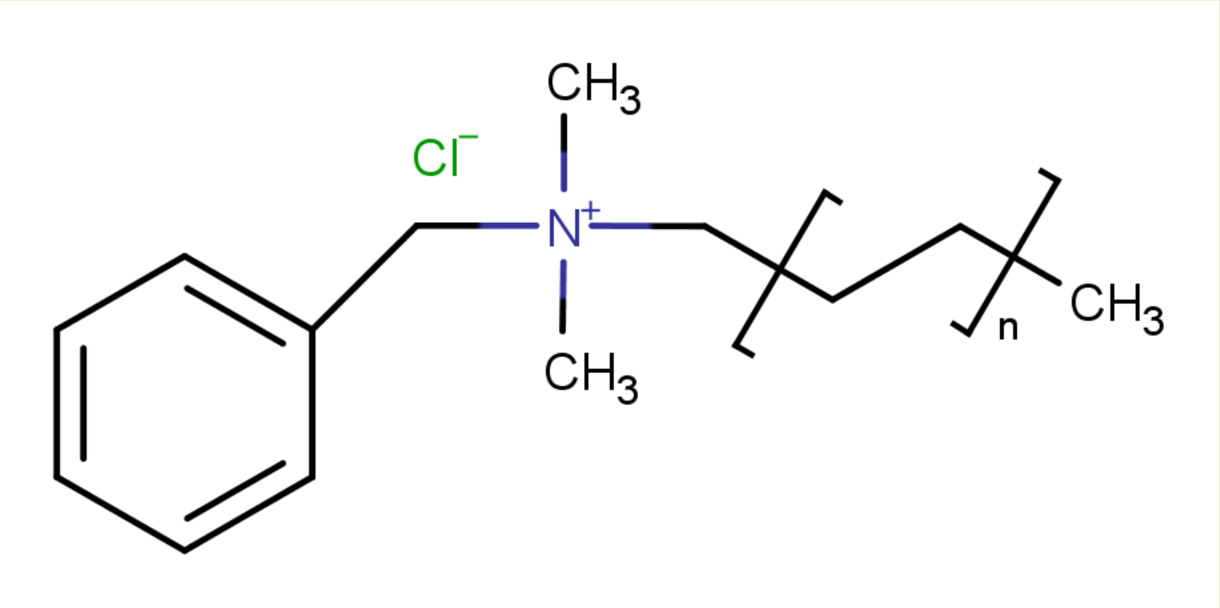
Example of soap is potassium salt of oleic acid or what is called (Green Soap).

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.

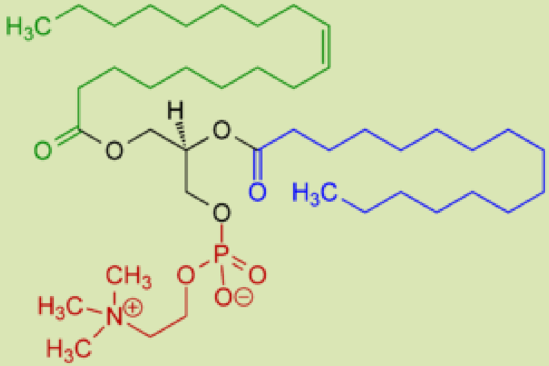
Ampholytic surfactants

- 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.

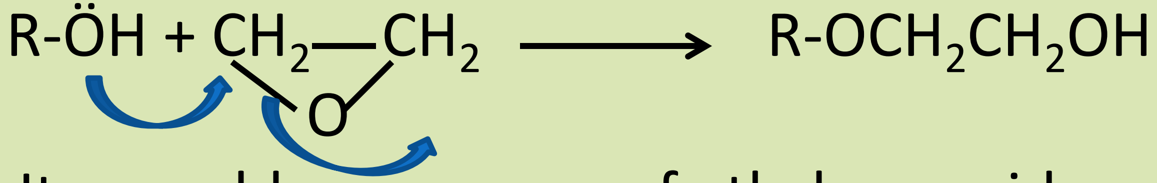
   $CH_3(CH_2)_{11}\text{-}NH_2^+\text{-}CH_2CH_2COO^-$

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.



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

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

- 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.

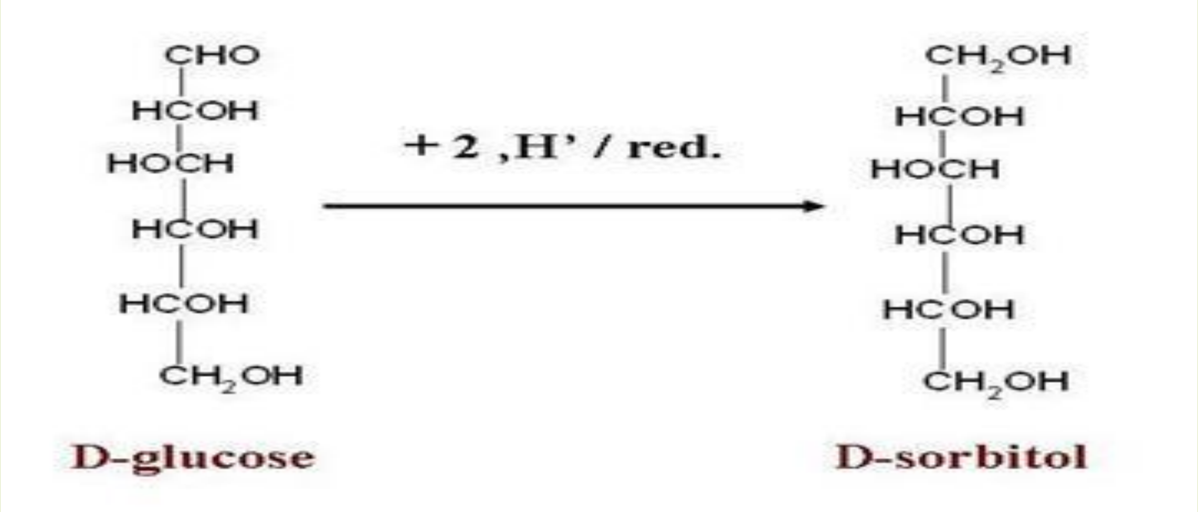
- The dispersion of emulsion containing this type of surfactant is destroyed if heated above the cloud point, can not be back or re-used.
- This type of surfactant is called “polyoxyethylated non-ionic surfactant.
- An important examples on nonionic SAA are: Span 20, 40, 60, 80, ---- + 20 molecules of 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:

1. Spans are less water-soluble while tweens are highly water-soluble.
2. Although, they differ in viscosity, e.g., span 20 for example is less viscous than span 80.

Preparation of Spans and Tweens

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

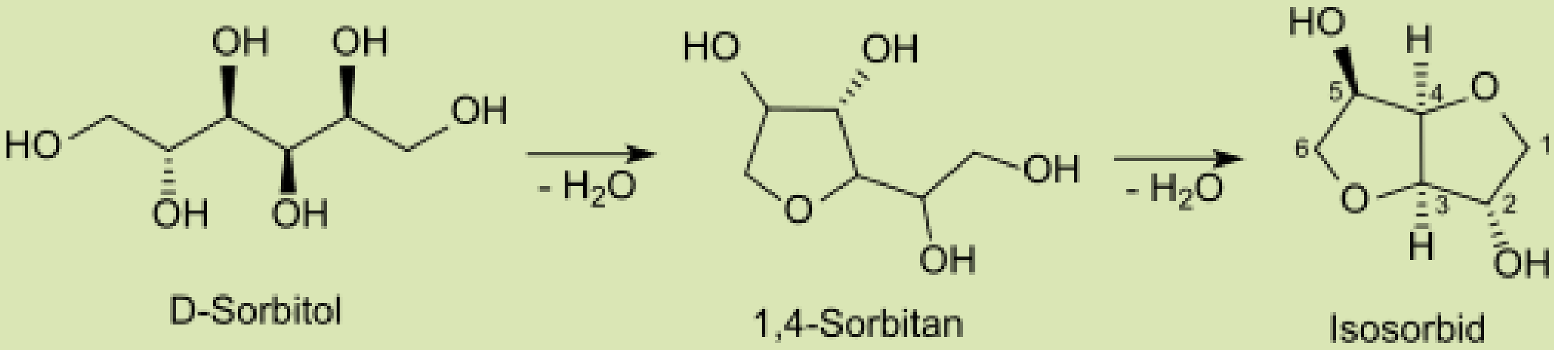


D-glucose D-sorbitol

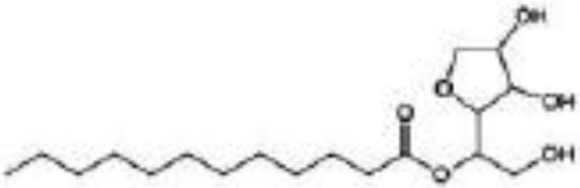
- Then by dehydration it gives mixture of 5- and 6- member ring compounds called sorbitan which has the following structure: they have the same chemical formula.

Sorbitan

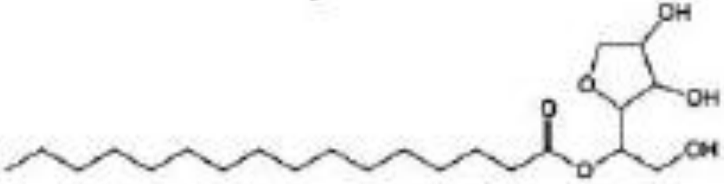
- Sorbitan is produced by the dehydration of sorbitol and is an intermediate in the conversion of sorbitol to isosorbide. The rate of formation of sorbitan is typically greater than that of isosorbide, which allows it to be produced selectively, providing the reaction conditions are carefully controlled.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


HO
OH
OH
OH
OH
OH
D-Sorbitol
- H_2O
HO
OH
O
OH
OH
1,4-Sorbitan
- H_2O
HO
H
5
4
O
6
1
O
3
2
H
OH
Isosorbid

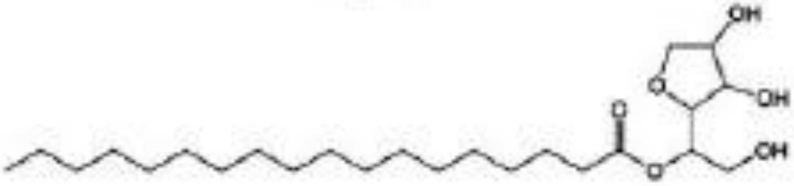
- Esterification of primary alcohol of sorbitan with lauric acid (10C) gives sorbitan mono laurate (Span 20).
- Esterification of primary alcohol of sorbitan with palmitic acid (14 C) gives sorbitan mono palmitate (Span 40).
- Esterification of primary alcohol of sorbitan with stearic acid (16C) gives 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



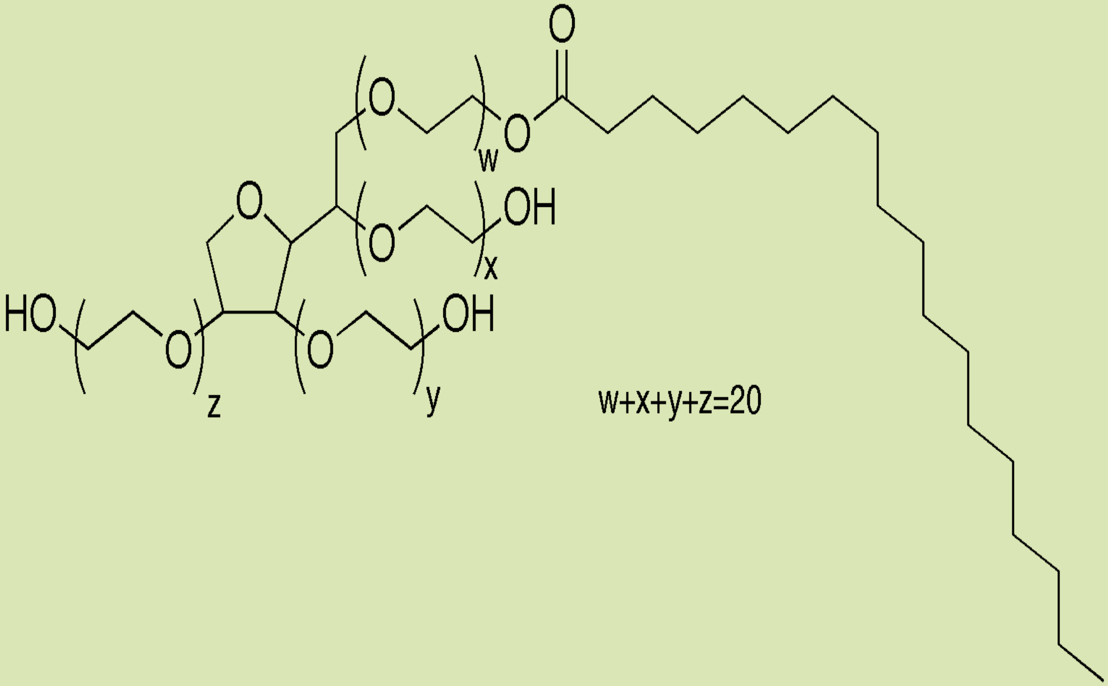
Span 40

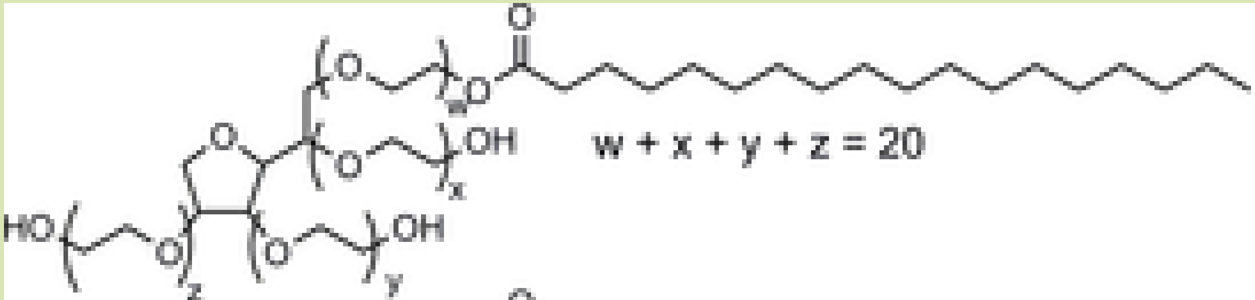


Span 60

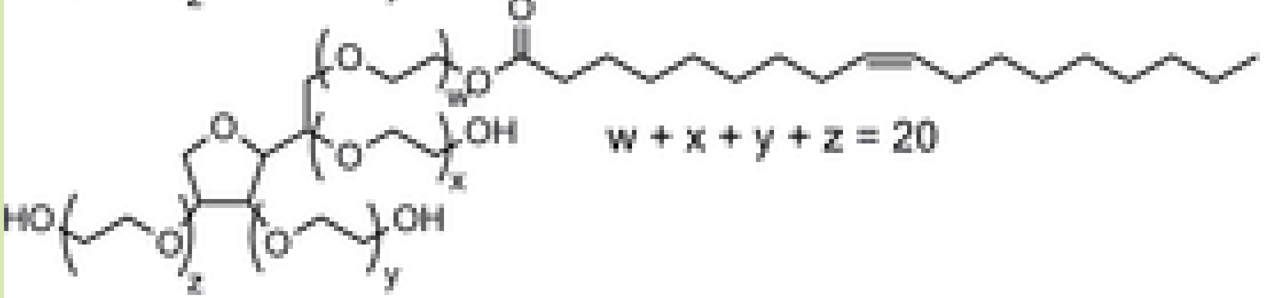
Span 80

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





Tween 60



Tween 80

Span 60

Span 80

- 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:

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

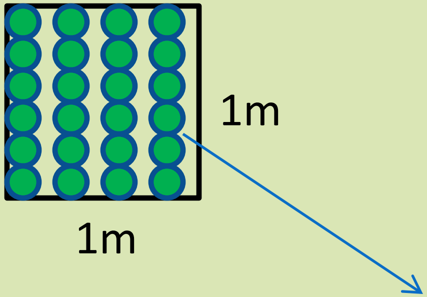
- Γ: surface concentration of surfactant/ unit area, mole/cm^2, found in the surface in excess of that in the bulk.
- C: concentration of surfactant in the bulk.
- R: gas constant,
- T: absolute temperature,
- dϒ/dc: the change in surface tension by change in concentration.

- Surface Tension: is the work in erg that needs to generate one cm^2 of the surface.
- $\Delta F = ϒ . \Delta A$
- $Erg/cm^2 = dyne.cm/cm^2 = dyne/cm$
- 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.

Gibbs adsorption equation

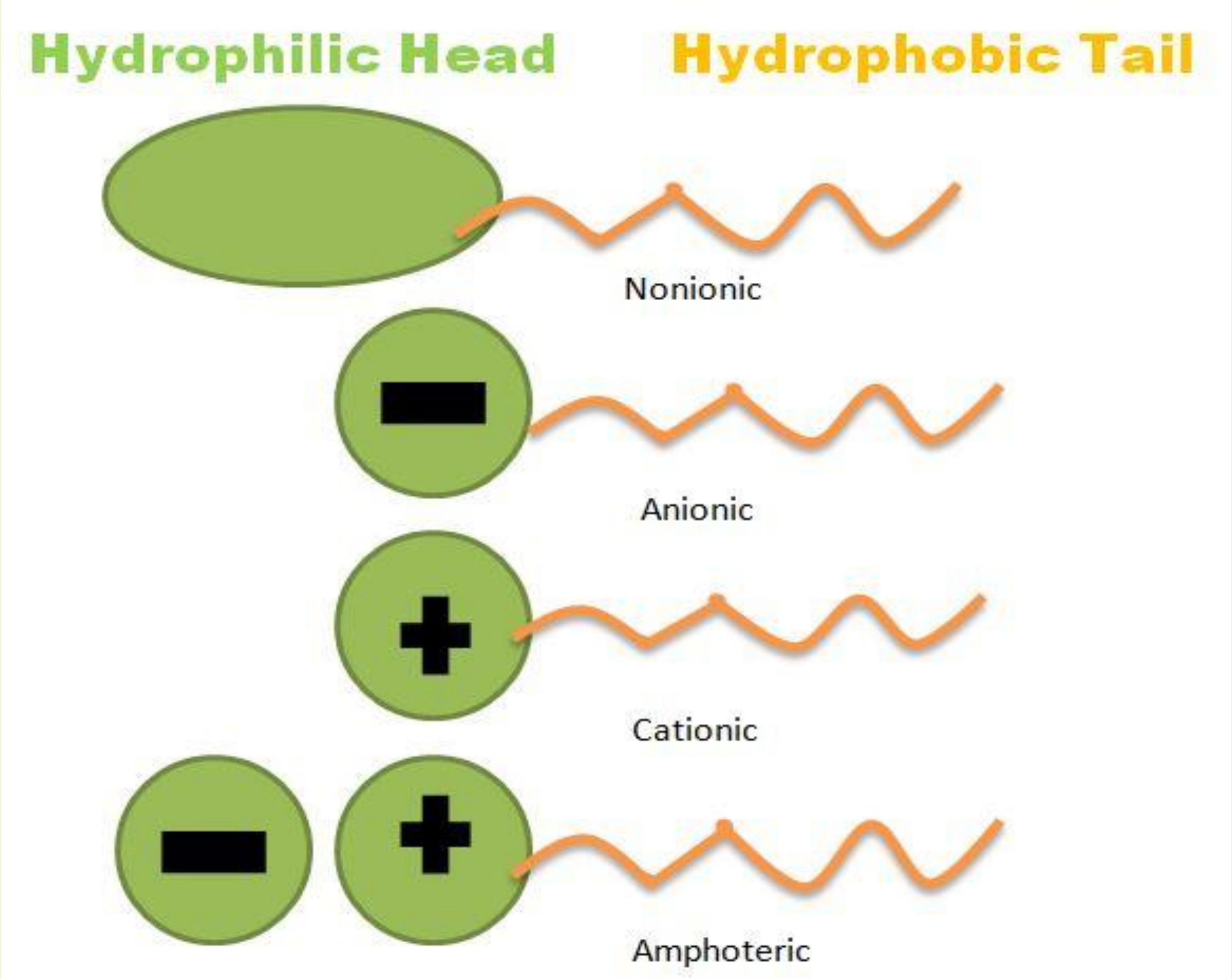
- Application of the Gibbs equation
- Just below the cmc, surfactant molecules are closely packed in the surface.
- The area A that each molecule occupies at the surface

$$A = \frac{1}{N_A \Gamma}$$



- Γ : The amount of component on the surface (of moles / m^2)
- N_A : The Avogadro constant

* Physiochemical Principles of Pharmacy 4th edition
Alexander T Florence and David Attwood


Hydrophilic Head
Hydrophobic Tail
Nonionic
Anionic
Cationic
Amphoteric

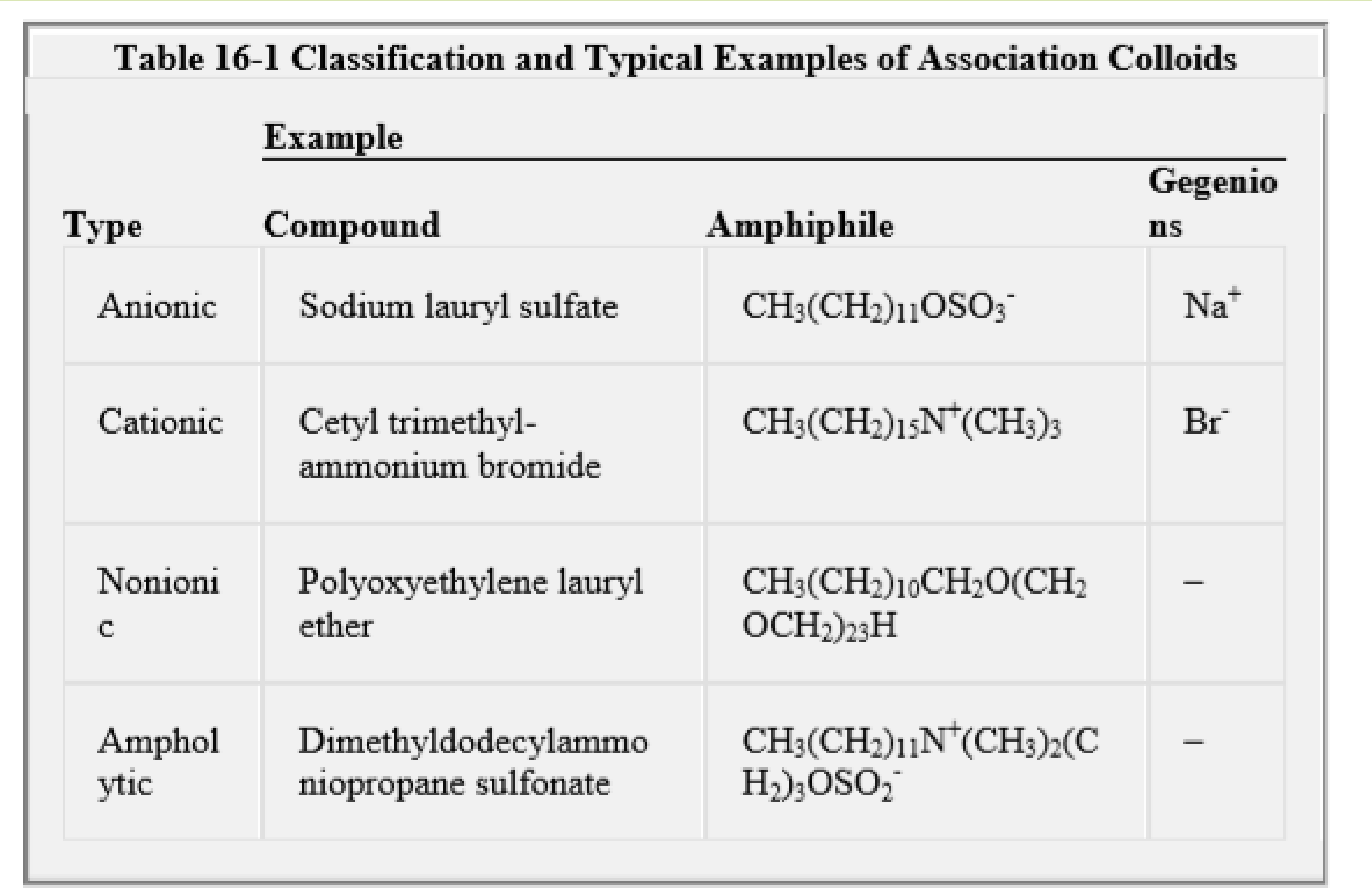


Table 16-1 Classification and Typical Examples of Association Colloids

Type	Example		
	Compound	Amphiphile	Gegenions
Anionic	Sodium lauryl sulfate	$CH_3(CH_2)_{11}OSO_3^-$	Na^+
Cationic	Cetyl trimethylammonium bromide	$CH_3(CH_2)_{15}N^+(CH_3)_3$	Br^-
Nonionic	Polyoxyethylene lauryl ether	$CH_3(CH_2)_{10}CH_2O(CH_2OCH_2)_{23}H$	–
Ampholytic	Dimethyldodecylammoniopropane sulfonate	$CH_3(CH_2)_{11}N^+(CH_3)_2(CH_2)_3OSO_2^-$	–

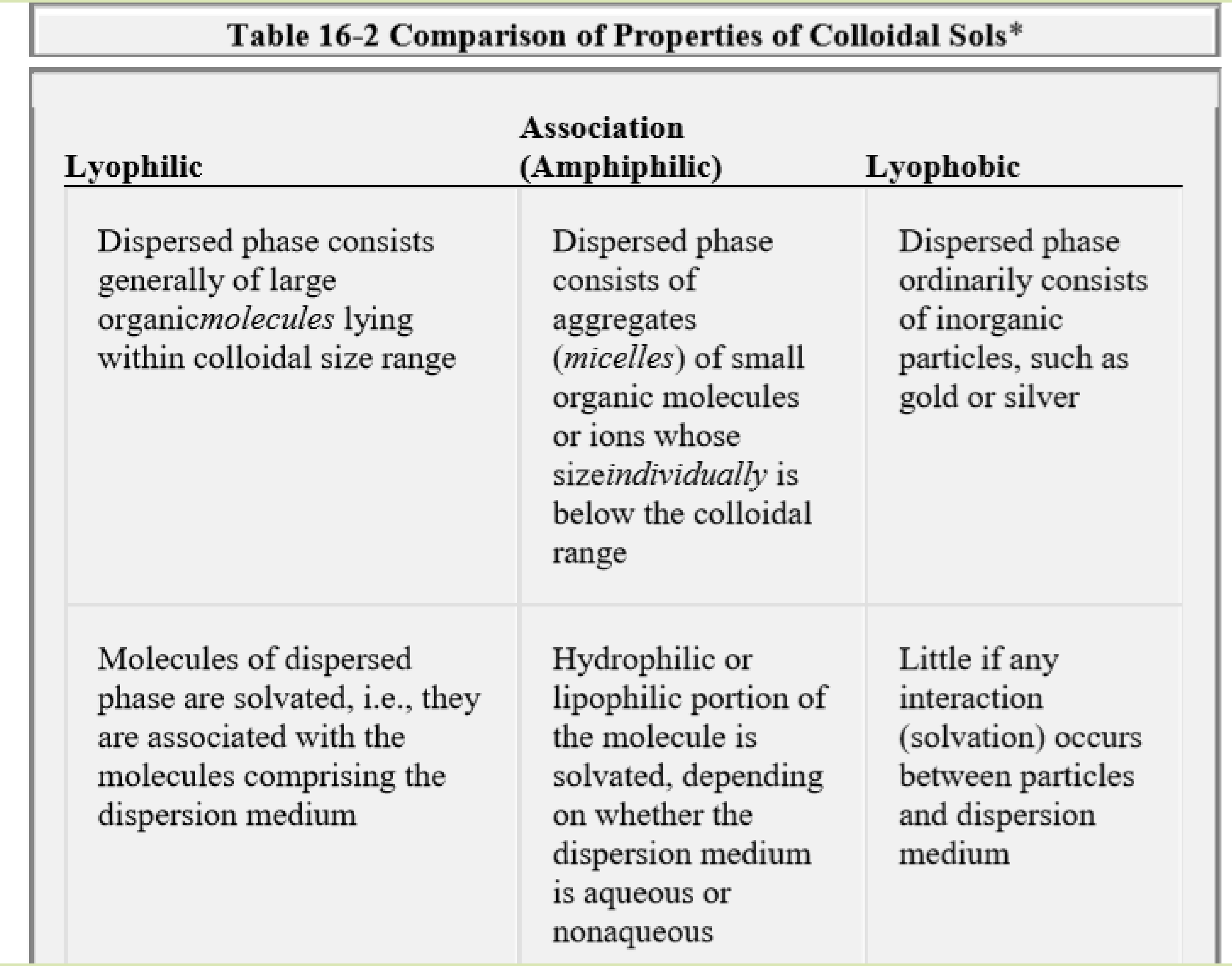
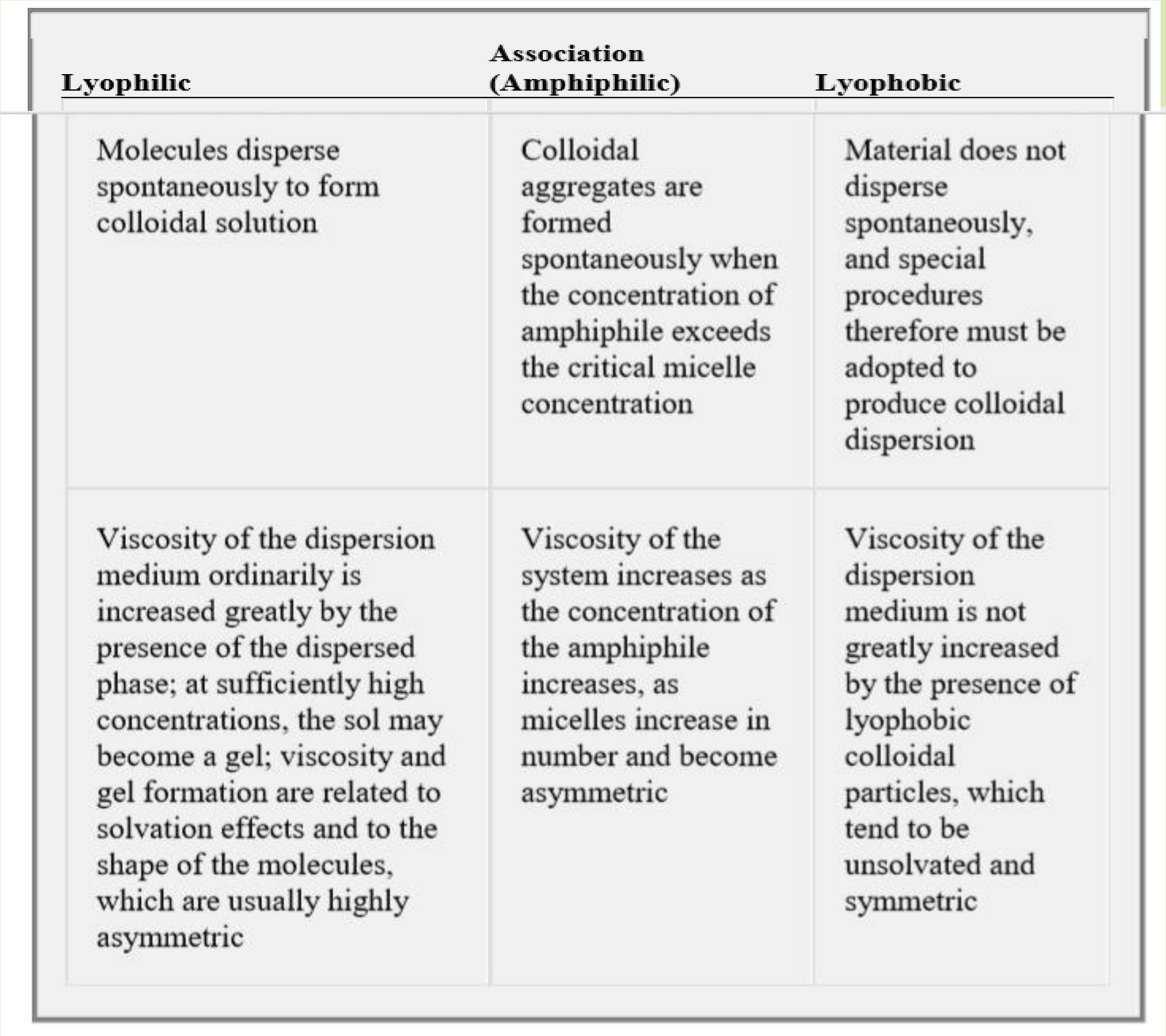
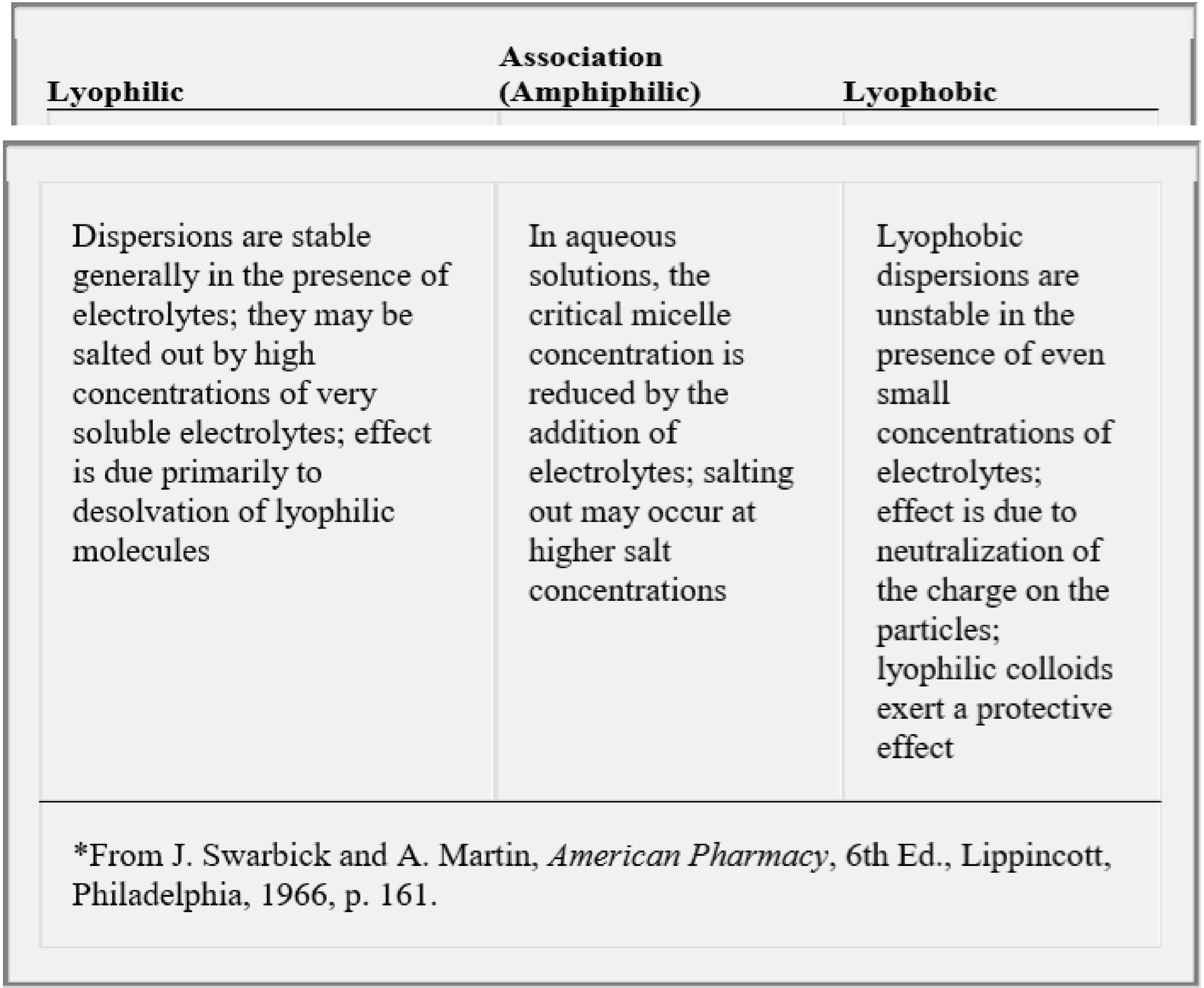


Table 16-2 Comparison of Properties of Colloidal Sols*

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.