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As the concentration is increased above the level required to completely occupy the surface (known as the critical micelle concentration or the critical micellization concentration and abbreviated as CMC), reversible self-association structures form in solution. These soluble aggregates, which may contain up to 50 or more monomers, are called micelles. Therefore, micelles are small, generally spherical structures composed of both hydrophilic and hydrophobic regions of surfactant molecules. In an aqueous bulk solution environment, the hydrophobic region is embedded on the inside (Figure 10.3). Conversely, in a hydrophobic, lipid, or lipophilic bulk solution, the hydrophilic region is embedded on the inside. The surfactant monomers in micelles are in dynamic equilibrium with free molecules (monomers) in solution, resulting in a continuous flux of monomers between the solution and the micellar phase. Figure 10.3 Types of micelles. Spherical micelles are formed when the concentration of monomers in the aqueous solution reaches the critical micelle concentration (CMC). Elongation of spherical micelles at high concentration leads to the formation of a cylindrical micelle. Reverse micelles are formed in a nonpolar solvent. Types of micelles The shape of micelles formed by a particular surfactant is greatly influenced by the geometry of the surfactant molecules. At high concentrations, some micellar structures can also form. A bilayer structure forms if the surfactant has two hydrophilic groups. This occurs because one end of the molecule is attracted toward water away from the solvent and toward the center, which may also enclose some water (Figure 10.3). Micelles versus liposomes Micelles are unilayer structures of surfactants, whereas liposomes have a lipid bilayer structure that encloses the solvent medium (water) (Figure 10.3). Although both micelles and liposomes are formed from amphiphilic monomers, the structure and properties of the monomers play a role in determining which of these structures forms. In addition, liposomes are not formed spontaneously—they require an input of energy and are typically formed by the application of one or more of agitation, ultrasonication, heating, and extrusion. Colloidal properties of micellar solutions Micellar solutions are different from other types of colloidal solutions (such as colloidal suspensions of particles), since micelles are association colloids; that is, the associated surfactant molecules are colloidal in size in solution. The micelles are formed by reversible self-association of monomers. The minimum concentration of a monomer at which micelles are formed is called the critical micelle concentration or the critical micellization concentration (CMC). The number of monomers that aggregate to form a micelle is known as the aggregation number of the micelle. The size of micelles depends on the number of monomers per micelle and the size and molecular shape of the individual monomers. Factors affecting the formation of micelles include temperature, pH, electrolyte concentration, and nature of the surfactant. Some factors affect the CMC, while others do not. Surface tension of a solution progressively increases, the properties of the solution change gradually. Not all surfactants form micelles. In the case of surfactants that form micelles, a sharp inflection point in the physical properties of the solution is observed at the CMC. The properties that are affected include the following: Surface tension: As illustrated in Figure 10.4, surface tension of a surfactant solution decreases steadily up to the CMC but remains constant above the CMC. Table 10.4 Critical micellization concentration and number of surfactant molecules per micelle Figure 10.4 Micellization of an ionic surfactant (a) and its effect on conductivity and surface tension (b). This is attributed to the saturation of surface occupation of a surfactant above the CMC. Below the CMC, as the surfactant concentration in the solution is increased, more and more surfactant molecules partition into the surface or interface, leading to a steady reduction in surface tension. Above the CMC, the surface or interface is already completely full or saturated with the surfactant. Thus, further addition of the surfactant leads to minimal changes in surface tension. The excess surfactant added to the solution forms micelles in the bulk of the liquid. Conductivity: The conductivity of a solution due to the presence of non-valent inorganic ions is affected by the surfactant's concentration, since the polar head group of the surfactant can bind the ions, leading to reduced number of free ions available for conduction. As a surfactant is added to the solution, some of the surfactant occupies surface and some is available in the bulk of the solution, binding the counterions. Thus, solution conductivity reduces steadily as the surfactant concentration increases until it reaches the CMC. Above the CMC, the big part of the surfactant is in the form of micelles, so there is no significant change in conductivity. Surface area: The surface area occupied by the surfactant in the solution increases slightly with the surfactant concentration below the CMC but shows significant and sharp increase above the CMC. Below the CMC, an increase in the solubility of a hydrophobic drug results from changes in the characteristics of the solvent medium (such as dielectric constant) and drug-surfactant interaction. Above the CMC, additional drug solubilization results from the hydrophobic drug getting incorporated into the micelles. Osmotic pressure: Micelles, formed above the CMC, act as association colloids, leading to an increase in the osmotic pressure of the colloidal solution. Light-scattering intensity: Light scattering shows a sharp increase above the CMC due to the formation of colloidal micelles that scatter light. Factors affecting critical micelle concentration and micellar size Size and structure of hydrophobic group: An increase in the hydro-carbon chain length causes a logarithmic decrease in the CMC. This is because an increase in hydrophobicity reduces aqueous solubility of the surfactant and

there was an increase in the solubilizing capacity of a series of polysorbates for selected barbiturates as the alkyl chain length was increased from C12 (polysorbate 20) to C18 (polysorbate 80). An increase in the alkyl chain length increases the hydrophobicity of the core and micellar radius, reduces pressure inside the micelle, and increases the diffusive entry of the hydrophobic drug into the micelle. In addition, the solubilization of the poorly soluble drug tropicamide increased with increase in the oxyethylene content of poloxamer. On the other hand, an increase in the ethylene oxide chain length of a polyoxyethylated nonionic surfactant led to an increase in the total amount solubilized per mole of surfactant because of the increasing number of micelles. Thus, the effect of increase in the number of micelles of the same (smaller) size can be very different than increase in the size of micelles.

2. Nature of solubilizate (drug being solubilized): The location of solubilizates in the micelles is closely related to the chemical nature of the solubilizate. In general, nonpolar, hydrophobic solubilizates are localized in the micellar core. Compounds that have both hydrophobic and hydrophilic regions are oriented with the hydrophobic group facing out in the core and the hydrophilic or polar groups facing toward the surface. For a hydrophobic drug solubilized in a micelle core, an increase in the lipophilicity or the lipophilic region or surface area of the drug leads to solubilization near the core of the micelle and enhances drug solubility. Unsaturated compounds are generally more soluble than their saturated counterparts. Solubilizates that are located within micellar core tend to increase the size of the micelles. Micelles become larger not only because their core is enlarged by the solubilizate but also because the number of surfactant molecules per micelle increases in an attempt to cover the swollen core.

3. Effect of temperature: In general, the amount of the drug solubilized increases with an increase in temperature (Figure 10.5). The effect is particularly pronounced with some nonionic surfactants, where it is a consequence of an increase in the micellar size with increasing temperature.

4. Effect of pH: The main effect of pH on solubilizing ability of non-ionic surfactants is to alter the equilibrium between ionized and unionized drugs. The overall effect of pH on drug solubilization is a function of proportion of ionized and unionized forms of the drug in solution and in micelles, which is determined by (1) the pKa value of the ionizable functional group(s), (2) the solubility of the ionized and unionized forms in the solution, and (3) the solubilization capacity of the micelles for the ionized and unionized forms. Generally, the unionized form is the more hydrophobic form and is solubilized to a greater extent in the micelles than the ionized form.

Figure 10.5 Effect of temperature and surfactant type on the micellar solubilization of griseofulvin and hexocresol. (Modified from Bates, T.R, Gilbaldi, M. and Kanig, J.I. J. Pharm. Sci., 55, 191, 1966. With Permission.)

2. Pharmaceutical applications Several insoluble drugs have been formulated by using micellar solubilization. For example:

- Phenolic compounds, such as cresol, chlorocresol, and chloroxylenol, are solubilized with soap to form clear solutions for use as disinfectants.
- Polysorbates have been used to solubilize steroids in ophthalmic formulations.
- Polysorbate are used to prepare aqueous injections of the water-insoluble vitamins A, D, E, and K.
- Nonionic surfactants are efficient solubilizers of iodine.

3. Thermodynamics/spontaneity Micellar solubilization involves partitioning of the drug between the micellar phase and the aqueous solvent. Thus, the standard free energy of solubilization, ΔG_s , can be computed from the partition coefficient, K , of the drug between the micelle and the aqueous medium: $\Delta G_s = -RT \ln K$ (10.1) where: R is the gas constant T is the absolute temperature Change in free energy with micellization can be expressed in terms of the change in enthalpy (ΔH_s) and entropy (ΔS_s) as: $\Delta G_s = \Delta H_s - T \Delta S_s$ (10.2) Thus, $\Delta H_s - T \Delta S_s = -RT \ln K$ Or, $\ln K = -\Delta H_s/R \cdot 1/T + \text{constant}$ where the constant is $\Delta S_s/R$, assuming that the change in entropy from micellization is constant. Thus, experimental determination of enthalpy of micellization can be a useful tool to predict ΔG_s , which, in turn, indicates whether micellar incorporation of a drug would be spontaneous. When ΔG_s is negative, solubilization process is spontaneous. When ΔG_s is positive, solubilization does not occur.

Example 1: Given $\Delta H_s = 2830 \text{ cal/mol}$ and $\Delta S_s = -26.3 \text{ cal/K mol}$, does ammonium chloride spontaneously transfer from water to micelles? $\Delta G_s = \Delta H_s - T \Delta S_s = 2830 \text{ cal/mol} - (298K)(-26.3 \text{ cal/kmol})$ which is positive, indicating that micellar solubilization (transfer) would not occur.

Example 2: Given $\Delta H_s = -1700 \text{ cal/mol}$ and $\Delta S_s = 2.1 \text{ cal/K mol}$, does amobarbital spontaneously transfer from water to a micellar solution (sodium lauryl sulfate, 0.06 mol/L)? $\Delta G_s = \Delta H_s - T \Delta S_s = 1700 \text{ cal/mol} - (298K)(2.1 \text{ cal/kmol}) = -2326 \text{ cal/mol}$ which is negative, indicating that micellar solubilization (transfer) would indeed spontaneously occur.