

The values of the CMC or CMT collected as a function of temperature or concentration can be used to extract the enthalpic and entropic contributions to the association process. For a closed association mechanism with relatively large aggregation number and a narrow distribution, the standard free energy and standard enthalpy of micelle formation (ΔG° and ΔH° , per mole of the solute in the micelle) are related to the CMC and its temperature dependence in the form (Lindman and Wennerstrom, 1980; Zhou and Chu, 1994).

$$\Delta G^\circ = RT \ln (\text{CMC}) \quad (13.1)$$

$$\Delta H^\circ = R[d \ln (\text{CMC})/d(1/T)] \quad (13.2)$$

where the CMC is in molar concentration, the two standard states are the polymer molecules and micelles in ideally dilute solution at unit molarity. Equation 13.2 can be integrated to yield

$$\ln (\text{CMC}) \approx \Delta H^\circ/RT + \text{constant} \quad (13.3)$$

provided that ΔH° is approximately a constant in the temperature interval involved.

At a given temperature, micellization of copolymers in aqueous solutions depends on their concentration. Therefore, the application of micelles as drug carriers raises the fundamental question about their stability during dissolution by body fluids. The multimolecular micelles are formed at copolymer concentrations equal to or exceeding the CMC, which may serve as a thermodynamic parameter characterizing the micelle stability during dissolution. Temperature can affect the CMC as well as other thermodynamic parameters such as aggregation number and micelle size. Linse and Malmsten (1992) used gel permeation chromatography (GPC) and data obtained from the literature to study the temperature-dependent micellization in aqueous block copolymer solutions. Pluronic 127 was used as the model copolymer in their study. They concluded that temperature has a great effect on micellization of the Pluronic copolymer: with increasing temperature, the CMC decreases, the fraction of polymer molecules in micellar form increases, the average aggregation number increases, and the micelle hydrodynamic radius (size) increases.

Almgren et al. (1992) examined aqueous solutions of Pluronic L-64 with static and dynamic light scattering (DLS), pulsed-gradient spin-echo (PGSE) NMR and fluorescence spectroscopy over a range of concentrations from 0.2% to 25% and temperature from 15°C to 60°C. Relaxation time distributions from DLS show L-64 to be molecularly dissolved at 21°C and to form micelles at higher temperatures. The aggregation numbers at the temperatures 21.0°C, 25.9°C, 40.0°C, and 60.0°C were calculated to be 2, 4, 19, and 85, respectively, indicating a smooth increase with temperature. The data are in agreement with earlier reported results (McDonald and Wang, 1974; Al-Saden et al., 1982). These micelles persist at high concentrations (25%) without the formation of gel or liquid crystalline phases. The temperature where micelle formation starts is strongly concentration dependent, in contrast to the cloud point (CP) that remains fairly constant at 60°C. Similar results were obtained by Pandya using static light scattering (Pandya et al., 1993).

The data from PSGE NMR indicate that the exchange between monomers and micelles is fast and the large aggregates involve only a small fraction of L-64 (Almgren et al., 1992). At low concentrations, the observed diffusion coefficient (D) grows initially with the temperature to a maximum, and decreases steeply thereafter. The decrease in D is due to micelle formation, which starts at a lower temperature when the concentration is high. The steep decrease on approaching the CP is probably due to micelle-micelle interactions.

The pronounced sensitivity of the CMC to temperature, or the CMT to concentration, is commonly found for poloxamers (Zhou and Chu, 1987, 1988), but not for the normal alkyl polyethylene glycol ethers, C_xEO_y (35). The decrease of the hydrophilicity of the PEO blocks with increasing temperature has comparatively little effect on the CMC for C_xEO_y . For $C_{12}EO_8$ the CMC is reported as 9.7×10^{-5} M at 15°C and 5.8×10^{-5} M at 40°C (Megufo et al., 1987). In addition, the number of