A Cloud Point Study on the Micellar Growth of an Amphiphilic Drug in the Presence of Alcohol and Ionic Surfactant

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Cloud point (CP) measurements have been performed to investigate the influence of alcohols ($C_2–C_{10}OH$) on the micellar growth of amphiphilic drug amitriptyline (AMT) in the presence of salt and surfactant. In the case of shorter-chain alcohols (C_4OH or C_5OH), the CP increased with increasing alcohol concentration in the presence of a small amount of sodium phosphate because they partition very little in AMT micelles. On the other hand, it steeply decreased with increasing alcohol concentration in the case of longer-chain alcohols (C_8OH or $C_{10}OH$) due to their considerable partitioning in AMT micelles. The effect of hindering the micellar aggregation was enhanced as the alcohol chain length increased in the case of shorter-chain alcohols. The CP became less sensitive to addition of C_6OH at higher sodium phosphate concentrations, resulting from incorporation of more C_6OH molecules into the enlarged micelles. Addition of cationic surfactant cetylpyridinium chloride to the AMT micellar solutions increased the CP because cetylpyridinium cations affect electrostatic interactions with the cationic AMT headgroup, while addition of anionic surfactant, sodium dodecyl sulfate, decreased the CP because of penetration of dodecyl chains into the micelles, resulting in a micellar growth.

Introduction

Since many pharmacologically active compounds are amphiphilic, they tend to self-associate as micelles in aqueous solutions and to interact with biological membranes, causing disruption and solubilization in a surfactant-like manner.[1] Drug self-association depends on the molecular structure of the drug, the drug concentration, and physicochemical conditions such as temperature, pH, and electrolyte concentration.[1-4] An understanding of the self-aggregation mechanism of amphiphilic drugs at the molecular level and their solubilization by surfactants is crucial in the rational design of more effective drug delivery systems. Micelles have been widely used as drug delivery vehicles because they have low viscosity, small aggregate size, simple preparation, and long shelf life. Incorporation of an amphiphilic drug into an aggregate, either upon self-association or by intercalation into other micelles, will affect its physicochemical properties such as the degree of ionization and reaction rates.[1]

The cloud point (CP) phenomenon is generally observed in nonionic surfactant micellar solutions when the temperature of the surfactant solution is raised to a certain value.[5-9] The increase in turbidity at the CP is generally considered to be due to formation of large aggregates.[10] There is some debate on the relative importance of micellar interaction and micellar growth to the CP. Corti et al.[11] interpreted the increase in turbidity as being due to critical fluctuations of micellar concentrations and not to a temperature dependence of the micellar size. Glatter et al.[12] showed by SANS measurements

combined with depolarized light scattering and ultralow shear viscosimetry that there are micellar interaction and micellar growth in aqueous solutions of nonionic surfactants of the *n*-alkyl polyglycol ether type near the CP. On the other hand, Laughlin[13] suggested that micellar interaction and micellar growth have no need to relate to the CP because the CP phenomena are also observed in nonsurfactant systems.

Gu and Galera-Gómez[7] investigated the effect of polar organic additives on the CP of Triton X-100 (TX100) in aqueous solutions. They found in their experiments that the addition of the polar organic additives which are infinitely miscible with water increase the CP of TX100, whereas the addition of the polar organic additives which are partially soluble in water decreases the CP of TX100. They thought that the preferential adsorption of the additives at the micelle−water interface is the main factor that determines the changes in the CP and in the micellization of surfactants in the presence of additives. Kumar et al.[14] observed the CP phenomenon in the anionic surfactant SDS solution in combination with symmetrical quaternary bromides. They explained the CP appearance in their system in terms of increased hydrophobic interactions due to the alkyl chains of the quaternary bromides. In their surfactant system, the addition of organic additives such as aliphatic alcohols ($C_6–C_8$), amines ($C_6–C_8$), and hydrocarbons (*n*-hexane and *n*-heptane) decreased the CP. Kabir-ud-Din et al.[15] performed viscosity measurements to study the effect of alcohols and amines on the micellar growth of cetylpyridinium chloride (CPC) in the absence and presence of KCl. They reported that the presence of a salt and an organic additive in their system produces favorable conditions for micellar growth which cannot be obtainable in the presence of either the salt or the additive alone. Kumar et al.[16] made similar viscosity measurements to

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study micellar morphological changes in sodium dodecyl sulfate (SDS) solutions in the presence of salts and additives. They found that palisade solubilization of an organic additive is most important in observing micellar growth in surfactant systems.

Recently, we observed the CP phenomenon in the amphiphilic drug amitriptyline (AMT) solutions.[17] The CP of the AMT solution considerably decreased with increasing pH due to a reduction in electrical repulsion between AMT micelles. Unlike nonionic surfactant systems or anionic surfactant−quaternary bromide systems already reported in the literature, the CP increased on addition of electrolyte due to an increase in electrical repulsion resulting from an increase in the cationic AMT micelle size.

Many studies have been reported on the role of additives in the micellar growth of nonionic surfactants. However, few workers have studied the effect of additives in ionic micellar systems. In the present study, we have investigated the CP behavior of cationic AMT micellar solutions in the presence of alcohol present concurrently with salt and ionic surfactant. The variation in the CP of the AMT micellar solutions relates to the micellar association. We report herein the CP studies performed on aqueous AMT micellar solutions with alcohols (ethanol to decanol) and surfactants (CPC and SDS) in the presence of sodium phosphate. The effect of the additives on the CP of AMT solutions has been discussed in terms of electrostatic and hydrophobic interactions.

Experimental Section

AMT hydrochloride ($\geq 98\%$) supplied by Sigma Chemical Company was used as received. All alcohols (ethanol, C_2OH; 1-butanol, C_4OH; 1-pentanol, $1\text{-}C_5OH$; 2-pentanol, $2\text{-}C_5OH$; 3-pentanol, $3\text{-}C_5OH$; 1-hexanol, C_6OH; 1-octanol, C_8OH; 1-decanol, $C_{10}OH$), and sodium phosphate were of the reagent grade and were obtained from Fisher Scientific. SDS ($\geq 99\%$) and CPC ($\geq 99\%$) were supplied by Sigma Chemical Company. Distilled and deionized water with a resistivity of 18.3 MΩ cm was used to prepare AMT solutions.

The pH of the AMT solutions was measured with an ATI Orion 720A pH meter. The CP measurements were performed in a water bath by immersing the AMT solution in a capped glass tube. The CP was determined visually by noting the temperature at which the continuously heated solution suddenly became cloudy. The temperature was raised at a rate of approximately 0.5 °C/min around the CP. The repeatability of the CP measurements was ±0.2 °C.

Results and Discussion

In the previous study, we explored the effect of addition of electrolyte on the CP of the cationic AMT micellar solution.[17] It was observed that the CP decreased with increasing pH due to a reduction in electrical repulsion between AMT micelles. One of the interesting findings was that addition of electrolyte increased the CP due to an increase in electrical repulsion as a result of the cationic AMT micellar growth. The effect of cations was found to be insignificant compared to anions. The concentrations of AMT considered in this work are above the CMC (36 mM) of AMT[18] where AMT micelles start to form in the aqueous solution. The pH of the AMT solution is fixed at 6.7.

Figure 1 illustrates the effect of alcohol concentration on the CP of 200 mM AMT micellar solutions in the presence of 10 mM sodium phosphate, which has a weak ionic strength. One can see that the variation of CP with alcohol concentration depends strongly on the chain length of the alcohol. The CP is
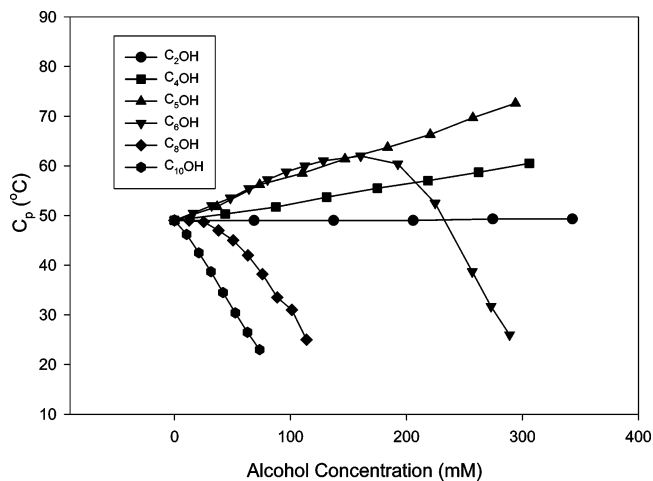

Figure 1. Cloud point of 200 mM AMT micellar solutions as a function of *n*-alcohol concentration. The concentration of sodium phosphate is 10 mM.

found to remain nearly constant on addition of C_2OH. It increases linearly with increasing shorter-chain alcohol (e.g., C_4OH or C_5OH) concentration. In addition, the CP increases with increasing chain length from C_2 to C_5 at a given alcohol concentration. These shorter-chain alcohols are hydrophilic molecules and decrease the polar character of the solution medium. They partition very little in AMT micelles. These alcohol molecules may be adsorbed preferentially at the micelle−water interface.[7] Since most of them are placed outside of the micelles, addition of these alcohols would hinder the micellar aggregation leading to an increase in CP with alcohol concentration. For C_6OH, the CP increases at first with alcohol concentration and then decreases at higher alcohol concentrations above 150 mM, showing a peaked behavior. It is worth noting that there is no actual difference in CP between C_5OH and C_6OH up to 150 mM, indicating that some of C_6OH molecules partition in the micelles. Large-chain alcohols usually partition in the headgroup region, with the alkyl chain penetrating into the micellar core.[14] The partitioning of alcohol would replace the amount of water near the headgroup region with a lower temperature required to obtain the CP phenomenon. This partitioning is not significant at low alcohol concentrations, thus the CP increases with C_6OH concentration. At higher C_6OH concentrations, the partitioning becomes significant, resulting in a decrease in CP with alcohol concentration. In the case of larger-chain alcohols (C_8OH or $C_{10}OH$), the CP monotonically decreases with increasing alcohol concentration. The CP decreases more steeply for a larger-chain alcohol ($C_{10}OH$). Increasing the alkyl chain length of alcohol has a distinct effect on the CP, which is due to the replacement of more water from the micellar surface. Gu and Galera-Gómez[7] observed a similar trend in CP behavior with alcohol in the TX100 nonionic surfactant system. However, the CP of the TX100 aqueous solution decreased with alcohol concentration when the alcohol chain length was larger than C_3. In addition, they did not observe a maximum CP behavior in their system.

There are two competing factors affecting the AMT micellar growth in the presence of alcohols. One is the electrical repulsion originating from intermicellar and intramicellar Coulombic interactions which favors AMT micelles with a high surface area per headgroup. The other is due to the hydrophobic interactions between the hydrocarbon parts of the AMT monomers which try to achieve aggregates with tightly packed chains.[19] The larger-chain alcohols (e.g., C_8OH or $C_{10}OH$) would get easily embedded between AMT monomers comprising a

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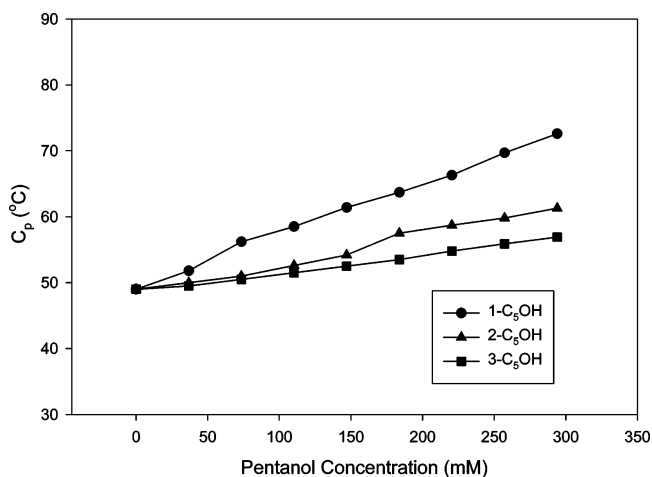

Figure 2. Cloud point of 200 mM AMT micellar solutions as a function of pentanol isomer concentration. The concentration of sodium phosphate is 10 mM.

Figure 3. Cloud point of 200 mM AMT micellar solutions as a function of n-hexanol concentration at various fixed sodium phosphate concentrations.

Figure 4. Cloud point of AMT micellar solutions as a function of n-hexanol in the presence of 500 mM sodium phosphate. The AMT concentration varies from 50 mM to 200 mM.

micelle. The penetration of these alcohols into the palisade layer reduces headgroup repulsion by holding these alcohol molecules between headgroups of similar charge. This leads to the decrease in surface area occupied per surfactant headgroup (A_o). As a result, the Mitchell-Ninham parameter[20] $R_p = V_c/l_c A_o$ (V_c being the volume of hydrophobic portion of the AMT monomer, and l_c its length) increases. The penetration of alkyl chain of alcohol will increase the volume of the micelle, which corresponds to increasing the V_c.[21] This may result in an increase in R_p.[22] Accordingly, AMT/larger-chain alcohol would form enlarged micelles, as being reflected by the decrease in the CP on addition of larger-chain alcohols (C_8OH or $C_{10}OH$) to 200 mM AMT micellar solutions. Furthermore, an increase in R_p is greater with $C_{10}OH$ than with C_8OH due to the larger hydrophobic volume of $C_{10}OH$, resulting in the formation of larger micelles and the greater decrease of the CP.

Figure 2 depicts the effect of pentanol isomer on the CP of 200 mM AMT micellar solutions in the presence of 10 mM sodium phosphate. One can see that the CP monotonically increases with increasing C_5OH concentration for all C_5OH isomers. At a given alcohol concentration, 1-C_5OH yields the highest CP while 3-C_5OH provides the lowest CP. The chain length of the C_5OH isomers is in the order: 1-C_5OH > 2-C_5-OH > 3-C_5OH. As discussed previously, most of C_5OH molecules remain outside of the micelles, thus addition of C_5-OH may hinder micellar aggregation, resulting in an increase in CP. This hindering effect is enhanced as the chain length of the alcohol increases. The effect of C_5OH isomers on the CP is also correlated to the solubility of C_5OH isomers. Comparison of Figures 1 and 2 tells us that the CP with C_4OH is actually equal to that with 2-C_5OH at a given alcohol concentration because C_4OH and 2-C_5OH have the same chain length. Note that C_4OH gives higher CP than 3-C_5OH. The results of Figure 2 are consistent with those of Figure 1.

Figure 3 shows the variation of the CP of 200 mM AMT micellar solutions as a function of C_6OH concentration at various fixed sodium phosphate concentrations. The CP monotonically increases with C_6OH concentration in the absence of sodium phosphate while it reaches a maximum value and then decreases on further addition of C_6OH in the presence of sodium phosphate. It is important to note that the CP becomes less sensitive to addition of C_6OH at higher sodium phosphate concentrations above 250 mM. The presence of a phosphate counterion (PO_4^{3-}) is responsible for the decrease in surface
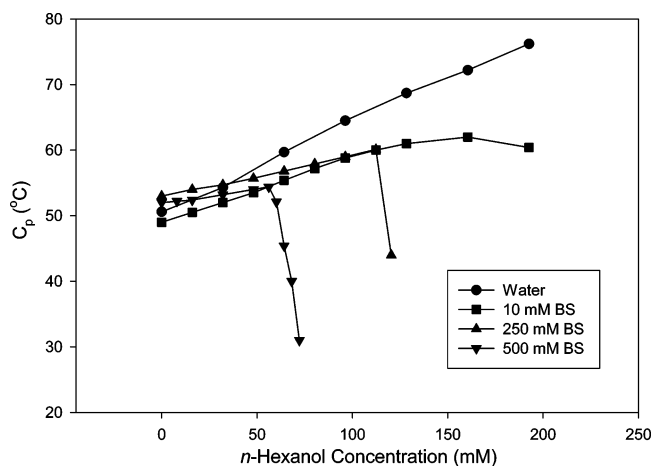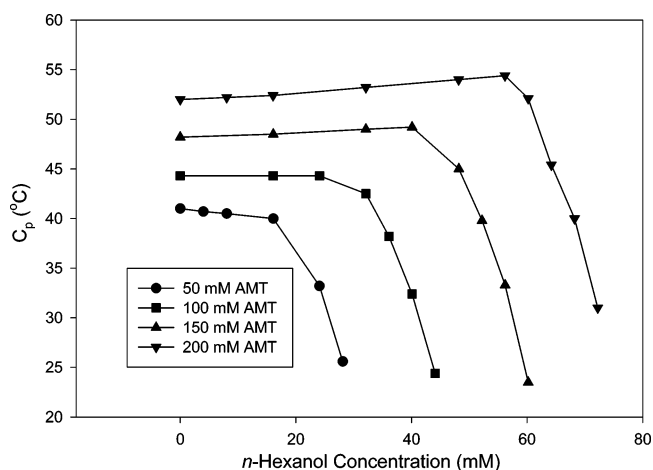
area occupied per AMT monomer headgroup (A_o), with a simultaneous increase in the Mitchell-Ninham parameter R_p of the AMT monomer. A decrease in A_o seems to result in an increase in R_p and micellar growth. More C_6OH molecules are able to get embedded in larger micelles. In general, the aggregation number (N) of ionic micelles increases with increasing electrolyte concentration.[1,23] The degree of counterion binding has an effect on the size and shape of micelles.[18,24] Furthermore, the salting-out nature of sodium phosphate will cause C_6OH molecules to move from the outside of the micelle to the headgroup region of the micelle. Accordingly, more C_6-OH molecules partition in the micelles at higher sodium phosphate concentrations. As mentioned above, C_6OH remaining in the bulk phase prevents micelles from aggregating, resulting in an increase in CP while the partitioning of C_6OH in the micelles causes a decrease in CP. At higher sodium phosphate concentrations above 250 mM, these two effects are almost balanced, resulting in a slight increase in CP with C_6OH concentration until the CP reaches a maximum above which the CP sharply decreases on further addition of C_6OH. The maximum CP shift toward lower C_6OH concentration with increasing sodium phosphate concentration implies that micellar growth is accelerated at higher sodium phosphate concentrations resulting from the combined effect of a decrease in A_o and incorporation of more C_6OH molecules into the micelles. This
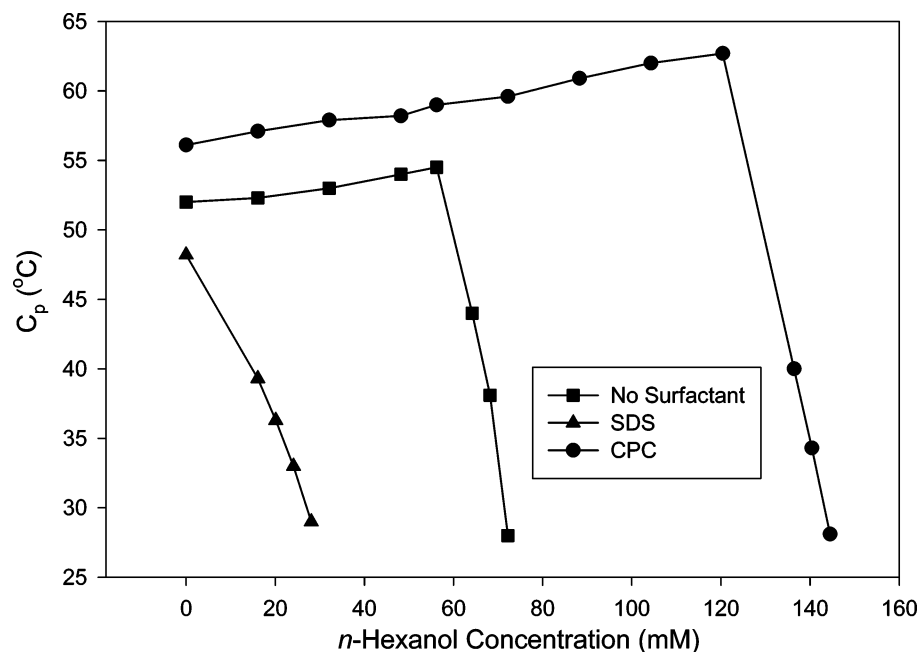
Figure 5. Cloud point of 200 mM AMT micellar solutions as a function of *n*-hexanol concentration in the presence of 500 mM sodium phosphate and surfactants.

would result in a rapid decrease in CP. Kabir-ud-Din et al.[15] reported that the magnitude of the viscosity increase with organic additive becomes substantial in the presence of electrolyte.

Figure 4 illustrates the effect of C_6OH addition on the CP of AMT micellar solutions in the presence of 500 mM sodium phosphate, which has a strong ionic strength. Here the AMT concentration varies from 50 mM to 200 mM. It is seen that the CP increases with increasing AMT concentration, which is opposite to the trend obtained in nonionic surfactants. The micellar size increases with increasing AMT concentration. Since the ionization constant, pK_a, of AMT is 9.4,[25] ionized AMT molecules prevail at pH of 6.7. Electrical repulsion between cationic AMT micelles would become greater for larger micelles, resulting in an increase in CP. The CP behavior is found to be similar at all AMT concentrations. The CP at first remains almost constant with C_6OH concentration and then it steeply decreases. It is interesting to note in Figure 4 that the CP remains almost constant until the C_6OH concentration reaches about 30% of the AMT concentration.

Figure 5 shows the effect of C_6OH addition on the CP behavior of 200 mM AMT micellar solutions in the presence of surfactant and 500 mM sodium phosphate. The concentration of the surfactant added is 20 mM. One can see that addition of cationic surfactant CPC to the AMT micellar solution increases the CP, while addition of anionic surfactant SDS decreases the CP. In the case of CPC, cetylpyridinium cations may affect electrostatic interactions with the cationic AMT headgroup, which will hinder the micellar aggregation as reflected by the increase in CP. On the other hand, in the case of SDS, alkyl (dodecyl) chains could penetrate into the micelle, with polar groups (sulfate anions) remaining in the headgroup region, resulting in a micellar growth leading to a reduction in CP. Moreover, addition of CPC to the AMT solution does not change the trend in CP behavior except that the C_6OH concentration where the CP becomes a maximum increases from 60 mM to 120 mM. Kumar et al.[19] investigated the effect of benzene addition on the viscosity behavior of cetylpyridinium bromide (CPB) micellar solutions containing quaternary ammonium salts. Their results showed that the salting-in nature of these salts progressively removes the effective benzene content from the

headgroup region of the CPB micelles. The maximum CP shift toward higher C_6OH concentration seems to relate to the salting-in nature of CPC. In the presence of SDS in the AMT solution, the CP monotonically decreases on addition of C_6OH.

Mechanisms for micellar interactions and micellar growth discussed above are a qualitative explanation. Further studies employing light scattering and fluorescence measurements are needed to make a thorough interpretation of the data.

Conclusions

We have performed CP measurements to study the effect of alcohols on the micellar growth of amphiphilic drug AMT in the presence of salt (sodium phosphate) and surfactants (sodium dodecyl sulfate, cetylpyridinium chloride). The CP behavior in the presence of a small amount of sodium sulfate depended strongly on the chain length of alcohol. The CP monotonically increased with increasing shorter-chain alcohol (C_4OH or C_5-OH) concentration because of the negligible partitioning of alcohol in AMT micelles. C_6OH showed a maximum behavior. In the case of larger-chain alcohols (C_8OH or $C_{10}OH$), the CP steeply decreased with increasing alcohol concentration due to the considerable partitioning of alcohol in AMT micelles, resulting in a micellar growth. The effect of C_5OH isomer concentration on the CP of AMT micellar solutions is in the order: $1-C_5OH > 2-C_5OH > 3-C_5OH$. The CP became less sensitive to addition of C_6OH at higher sodium phosphate concentrations above 250 mM. The micellar growth is accelerated at higher sodium phosphate concentrations resulting from a decrease in A_o and incorporation of more C_6OH molecules into the micelles. The CP increased with increasing the AMT concentration due to greater electrical repulsion between larger cationic AMT micelles. Addition of cationic surfactant CPC to the AMT micellar solution increases the CP because cetylpyridinium cations affect electrostatic interactions with the cationic AMT headgroup. On the other hand, addition of anionic surfactant SDS decreased the CP because dodecyl chains penetrate into the micelle, with polar groups (sulfate anions) remaining in the headgroup region resulting in a micellar growth.

References and Notes

(1) Schreier, S.; Malheiros, S. V. P.; de Paula, E. *Biochim. Biophys. Acta* **2000**, *1508*, 210.

(2) Attwood, D.; Natarajan, R. *J. Pharm. Pharmacol.* **1981**, *33*, 136.

(3) Atherton, A. D.; Barry, B. W. *J. Colloid Interface Sci.* **1985**, *106*, 479.

(4) Attwood, D. *Adv. Colloid Interface Sci.* **1995**, *55*, 271.

(5) Gu, T.; Galera-Gómez, P. A. *Colloids Surf. A* **1995**, *104*, 307.

(6) Al-Ghamdi, A. M.; Nasr-El-Din, H. A. *Colloids Surf. A* **1997**, *125*, 5.

(7) Gu, T.; Galera-Gómez, P. A. *Colloids Surf. A* **1999**, *147*, 365.

(8) Schott, H. *Colloids Surf. A* **2001**, *186*, 129.

(9) Shigeta, K.; Olsson, U.; Kunieda, H. *Langmuir* **2001**, *17*, 4717.

(10) Paradies, H. H. *J. Phys. Chem.* **1980**, *84*, 599.

(11) Corti, M.; Degiorgio, V.; Hayter, J. B.; Zulauf, M. *Chem. Phys. Lett.* **1984**, *109*, 579.

(12) Glatter, O.; Fritz, G.; Lindner, H.; Brunner-Popela, J.; Mittelbach, R.; Strey, R.; Egelhaaf, S. U. *Langmuir* **2000**, *16*, 8692.

(13) Laughlin, R. G. *The aqueous phase behavior of surfactants*; Academic Press: London, 1994.

(14) Kumar, S.; Sharma, D.; Kabir-ud-Din. *Langmuir* **2000**, *16*, 6821.

(15) Kabir-ud-Din; Kumar, S.; Kirti; Goyal, P. S. *Langmuir* **1996**, *12*, 1490.

(16) Kumar, S.; Naqvi, A. Z.; Kabir-ud-Din. *Langmuir* **2000**, *16*, 5252.

(17) Kim, E. J.; Shah, D. O. *Langmuir* **2002**, *18*, 10105.

(18) Attwood, D.; Florence, A. T. *Surfactant systems: Their chemistry, pharmacy and biology*; Chapman and Hall: New York, 1983.

(19) Kumar, S.; Bansal, D.; Kabir-ud-Din. *Langmuir* **1999**, *15*, 4960.

(20) Mitchell, D. J.; Ninham, B. W. *J. Chem. Soc., Faraday Trans. 2* **1981**, *77*, 601.

(21) Lin, Z.; Cai, J. J.; Scriven, L. D.; Davis, H. T. *J. Phys. Chem.* **1994**, *98*, 5984.

(22) Israelachvili, J. N.; Mitchell, D. J.; Ninham, B. W. *J. Chem. Soc., Faraday Trans. 2* **1976**, *72*, 1525.

(23) Evans, D. F.; Wennerstörm, H. *The Colloidal Domain: Where Physics, Chemistry, and Biology Meet*, 2nd ed.; Wiley-VCH: New York, 1999.

(24) Rosen, M. J. *Surfactants and Interfacial Phenomena*, 2nd ed.; Wiley: New York, 1989.

(25) Hansch, C. *Comprehensive medicinal chemistry: The rational design, mechanistic study & therapeutic application of chemical compounds*; Pergamon Press: New York, 1990.