Solubilization Capabilities of Some Cationic, Anionic, and Nonionic Surfactants toward the Poorly Water-Soluble Antibiotic Drug Erythromycin

Parvaiz Ahmad Bhat, Aijaz Ahmad Dar, and Ghulam Mohammad Rather*

Department of Chemistry, University of Kashmir, Srinagar-190006, J&K, India

Surfactants can be used to increase the solubility of poorly soluble drugs in water and to increase drug bioavailability. In this article, solubilization of macrolide antibiotic erythromycin is investigated by employing spectrophotometry and tensiometry in micellar solutions of nonionic (Brij56, Brij58, Brij35, Brij30), cationic (cetyltrimethylamonium bromide, CTAB; tetradecyltrimethylammonium bromide, TTAB; dodecyltrimethylammonium bromide, DTAB), and anionic (sodium dodecylbenzenesulfonate, SDBS; sodium dodecylsulfate, SDS) surfactants and then compared. The results showed that irrespective of the surfactant type, the solubility of erythromycin increases linearly with increasing surfactant concentration, as a consequence of association between the drug and micelles. Solubilization capacity has been quantified in terms of molar solubilization ratio ($R_{m,S}$), micelle−water partition coefficient (K_M), binding constant (K_1) between solubilizate monomer and vacant micelle, and the free energy of solubilization (ΔG_s^o) of the drug in the micelles. Cationic surfactants of the same chain length as that of nonionic and anionic surfactants exhibited higher solubilization capacity, probably due to solubilization at the micelle−water interfaces. The order of solubilization powers among nonionic, cationic, and anionic surfactants for erythromycin was found to be Brij56 > Brij58 > Brij35 > Brij30, CTAB > TTAB > DTAB, and SDBS > SDS, respectively. This comparative study can be used to select an appropriate medium for erythromycin solubilization, where nonionic surfactants are advantageous due to their minimal protein binding and retention of their micellar form even after large dilution in blood owing to their very low critical micellar concentration (cmc) values.

Introduction

The solubility of biologically active compounds is often a limiting factor for their applicability. It has been estimated that 40 % or more of newly developed pharmaceutically active substances will be poorly water soluble, often resulting in poor and highly variable bioavailability.[1,2] Therefore, solubility enhancement of drugs is an important task in pharmaceutical technology because it leads to better bioavailability.[3–5] With the recent advent of high-throughput screening of potential therapeutic agents, the number of poorly water-soluble drug candidates has risen sharply, and the formulation of such drugs for either oral or injectable delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industries.[6]

To improve the solubility of drugs in water, technological expedients widely used in pharmaceutics have been proposed,[7,8] for example, micronizing the drug particles, forming water-soluble salts, modifying crystal structure by the formation of various polymorphic forms, adding solubilizing agents, or improving the wettability of the drug powder. However, these methods have not always been sufficient to achieve the goal. The process of solubilization by surfactants, known to form micelles, has been extensively studied. Micelles possess a number of unbeaten advantages as potential drug delivery systems for poorly water-soluble pharmaceuticals.[9] The hydrophobic core of micelles may be used as a cargo space for encapsulation of a variety of sparingly soluble therapeutic and diagnostic agents. Such encapsulation substantially increases their bioavailability, protects them from destructive factors upon parental administration, and beneficially modifies their pharmacokinetics and biodistribution.[9] An additional advantage of micelles as drug carriers from the practical point of view is that they are easy to prepare on a large scale. Though the process of solubilization has been studied in both ionic[10] and nonionic surfactants,[11] the latter have been frequently used in pharmaceutical systems, due to their advantages of compatibility, stability, and minimal binding to proteins.[12,13]

Antibiotics are useful not only as therapeutic agents but also as important tools for blocking and analyzing functional steps of protein synthesis.[14] Among antibiotics, macrolides have played a key role in the treatment of bactericidal infections. Erythromycin, a macrolide antibiotic, has gained importance for its potential use in the treatment of gastrointestinal disorders and inflammatory diseases as well as for the synthesis of ketolides used in the treatment of emerging drug-resistant bacterial strains.[14] Erythromycin easily degrades in acidic conditions giving inactive compounds 8,9-anhydro-6,9-hemiketal and erythromycin-6,9,12-spiroketal.[15] However, the water solubility of erythromycin, $1.96 \cdot 10^{-6}$ mol·dm^{-3}, is very low (Drug Bank) thereby making it less bioavailable. To increase its acid stability and bioavailability, erythromycin is needed to convert into several forms including estolate, ethylsuccinate, and stearate.[15] To our conception, micellar solubilization of erythromycin may increase its bioavailability and stability, since surfactants are largely utilized in various drug dosage forms to control wetting, and offer stability and bioavailability.[16] Therefore, the design of a formulation for erythromycin is a challenging task, and it requires preliminary investigations on its solubility behavior in surfactant systems to select an appropriate medium

* Corresponding author. E-mail: gmrather2002@yahoo.com. Tel.: 0194-2424900.

10.1021/je700659g CCC: $40.75
Published on Web 04/26/2008

to enhance its solubility. The investigation of solubility of erythromycin has not received much attention so far, although efforts to study its solubilization in pure solvents, actone + water binary mixtures,[17] and supercritical CO_2[18] have been made. Moreover, the reports show that erythromycin−acetone solvates are metastable and get converted into its dihydrate.[19] Efforts have also been made to separate erythromycin from its closely related substances[20] and for its extraction from aqueous solutions using micelles.[21] But to our knowledge, no study for solubilization of erythromycin using micelles has been reported. Keeping the above points in consideration, this paper focuses on a preliminary solubilization study of erythromycin using different surfactants with the aim to choose an appropriate medium for its solubility enhancement. The solubility of erythromycin in aqueous medium as investigated using spectrophotometry is presented at 298.15 K in different nonionic, cationic, and anionic surfactants and then compared. Important solubilization characteristics, viz., molar solubilization ratio ($R_{m,S}$), micelle−water partition coefficient (K_M), free energy of solubilization (ΔG_s^o), interaction parameter between surfactant and solubilizate (K_1), and number of solubilizate molecules per micelle (S^M), have been evaluated and analyzed.

The determination of the solubility of erythromycin (EM) in different surfactant solutions holds particular interest because the solubility determines its fate in the body and may help us in understanding the mechanism involved in its delivery and controlled release. This article may also help with regard to pharmacokinetics of EM, involving its release, transport, extent of absorption in the body, and other pharmacodynamic properties. Further, in pharmaceutical industries, knowledge of the partitioning of drugs in different media of the human body (log K_M) is important at the early stages of the drug design process. Hence, proper information of K_M would be valuable for predicting partitioning of EM in solutions that contain different surfactants.

Experimental Section

Materials. The nonionic (Brij30, Brij35, Brij56, Brij58), cationic (CTAB, DTAB, and TTAB), and anionic (SDS and SDBS) amphiphiles were all Aldrich products and used as received. The antibiotic drug erythromycin was a Himedia (India, 98 %) product. The structures and important properties of the surfactants and erythromycin ($V_{m,EM}$ molar volume, solubility, M_{EM} molecular weight of erythromycin) are presented in Scheme 1 and Table 1, respectively.

Methods. Solubility Experiments. The solubility of erythromycin was measured in different surfactant solutions between (0 and 30) mmol·dm^{-3}. Excess amounts of erythromycin were added to vials containing 1 mL of the surfactant solutions to ensure maximum solubility. The 5 mL sample vials were sealed with screw caps fitted with Teflon lined septa to prevent any loss. These samples were then agitated for a period of 24 h on a magnetic stirrer at a temperature of (25 ± 0.5) °C, using magnetic Teflon pieces previously placed in the vials. The solutions were subjected to centrifugation at 15 000 rpm to remove the undissolved drug. The concentration of solubilized drug was determined spectrophotometrically with a Schimazdu spectrophotometer (model UV-1650) following appropriate dilution of an aliquot of the supernatant with corresponding surfactant concentration. The surfactant concentration was kept the same in both the reference and the measurement cells to eliminate the effect of surfactant on UV absorbance. The solubility of erythromycin was determined at its characteristic wavelength, 286 nm, at which its calculated extinction coefficient was 142.53 M^{-1}·cm^{-1}, from the slope of the absorbance vs the concentration curve of the drug in methanol. Using this extinction coefficient, the solubility of erythromycin in water was confirmed to be 2·10^{-6} mol·dm^{-3} which tallied well with the literature value.

Scheme 1. Structure of Erythromycin (EM) and Different Surfactant Molecules Used in this Study

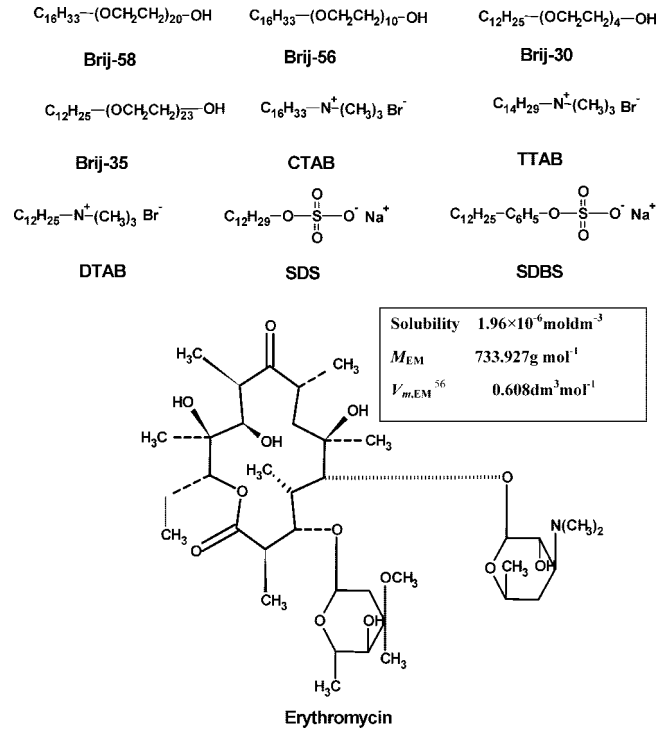

Table 1. Critical Micellar Concentration (cmc), Hydrophilic−Lipophilic Balance (HLB) Number, and Aggregation Number (N) of Various Surfactants Used in this Study

surfactant	cmc^{exptl}/mmol·dm^{-3}	cmc^{lit}/mmol·dm^{-3}	HLB	N
Brij58	0.0061	0.0081[a]	15.7[j,k]	65[a]
Brij56	0.051	0.04[m]	12.9[j,k]	141[b]
Brij30	0.0382	0.0351[a]	9.7[k]	101[a]
Brij35	0.044	0.05[d]	16.9[j,k]	40[b]
CTAB	0.764	0.815[a]	10[h]	90[q]
TTAB	3.80	3.7[g]	40[i]	80[l]
DTAB	14.5	15.1[c]	27[p]	74[o]
SDBS	2.09	2[f]	30[n]	51[e]
SDS	7.59	8.1[d]	40[i,l]	62[l]

[a] Ref 24. [b] Ref 42. [c] Ref 24. [d] Ref 44. [e] Ref 43. [f] Ref 45. [g] Ref 46. [h] Ref 47. [i] Ref 48. [j] Ref 49. [k] Sigma Aldrich, India. [l] Ref 50. [m] Ref 51. [n] Ref 52. [o] Ref 53. [p] Ref 54. [q] Ref 55. Error limits of cmc^{exptl} are ± 4 %.

Critical Micelle Concentration Determination. The cmc (c_M) values of all surfactants studied were determined from the surface tension (γ) vs logarithm of surfactant concentration (c_t) plots (Figure 1). Surface tension measurements were made with a Krüss 9 tensiometer by the platinum ring detachment method. Surfactant concentration was varied by adding concentrated surfactant solution in small installments using a Hamilton microsyringe, and readings were taken after thorough mixing and temperature equilibration. Temperature was maintained at the desired value (within ± 0.1 °C) by circulating water from a HAAKE GH thermostat. The accuracy of measurements was within ± 0.1 dyn·cm^{-1}.

Results and Discussion

The solubility of erythromycin (EM) was found to increase with an increase in surfactant concentration, with a slow increase

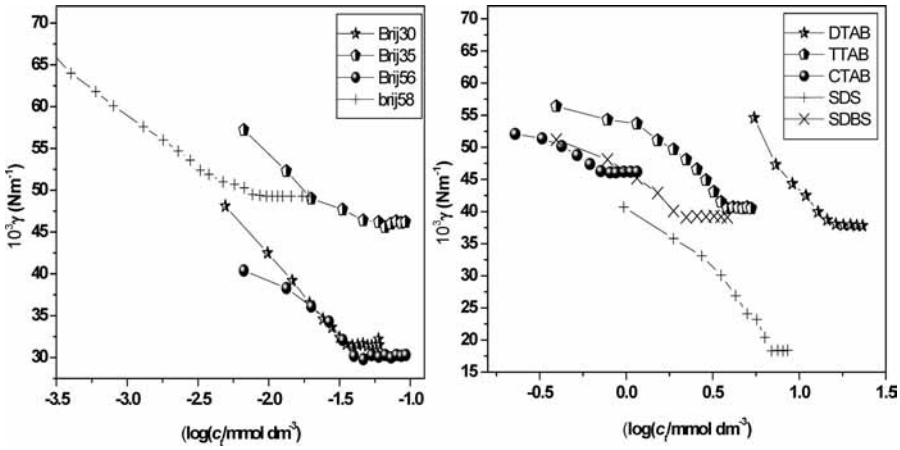

Figure 1. Plots of surface tension (γ) vs the total surfactant concentration (c_t) of various surfactants.

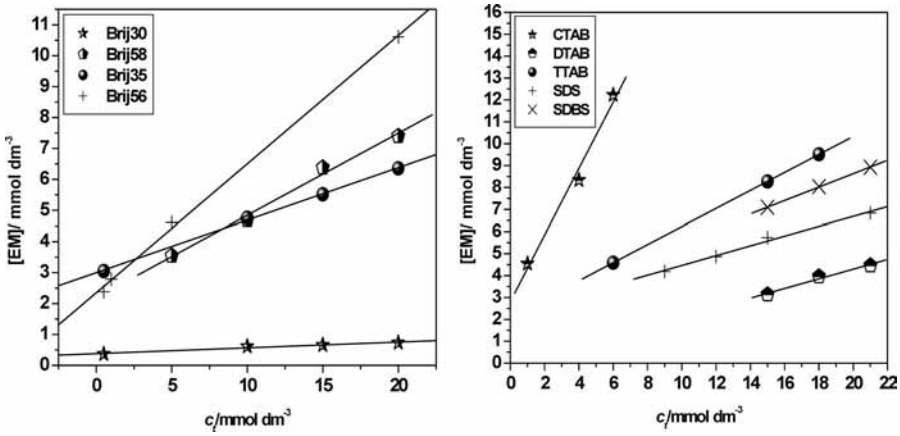

Figure 2. Variation of solubility of erythromycin (EM) vs surfactant concentration for various surfactants at 25 °C.

up to cmc followed by an abrupt increase in the postmicellar region. The cmc values of different surfactants, determined by tensiometry, are presented in Table 1 along with the reported values in the literature, revealing fair agreement. Table 1 also includes the literature values of their aggregation numbers.

Solubilization of a substance by a surfactant can be evaluated using two descriptors, the molar solubilization ratio $R_{m,S}$ and the micelle−water partition coefficient K_M. The $R_{m,S}$ value is defined as the amount of solute (drug) that can be solubilized by one mole of micellar surfactant and characterizes the ability of the surfactant to solubilize the drug. It is given by[22–24]

$$R_{m,S} = \frac{s_t - s_{cmc}}{c_t - c_M} \quad (1)$$

where s_{cmc} and s_t are solubility at cmc and total solubility of the drug, respectively, and c_t is the total surfactant concentration. Since ($c_t - c_M$) indicates the concentration of surfactant in micellar form, $R_{m,S}$ is equal to the ratio of drug concentration solubilized in micelles to the surfactant concentration in the micellar form and is obtained from the slopes of the curves that result when solubilizate concentration is plotted against surfactant concentration. The variation of solubility of EM in nonionic, cationic, and anionic surfactant series is plotted in Figure 2. The intercept of such plots is not expected to give the aqueous solubility of EM ($2 \cdot 10^{-6}$ mol·dm^{-3}) because we observed a linear, although very slow, increase in solubility of EM with surfactant concentration below cmc. This premicellar solubility may owe its existence to the interaction between surfactant and polar EM. For example, in aqueous CTAB, the solubility of EM showed a 2-fold increase in the premicellar

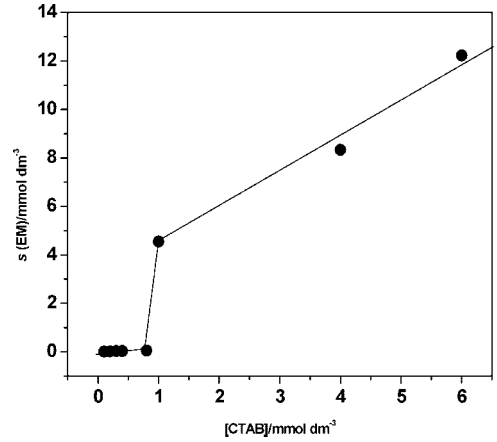

Figure 3. Variation of solubility of erythromycin (EM) vs concentration of CTAB in its pre- and postmicellar concentration regions at 25 °C.

surfactant range of (0.1 to 0.3) mmol·dm^{-3}, but it exhibited a 95-fold increase in the postmicellar concentration range from (0.8 to 1) mmol·dm^{-3} due to micellar solubilization (Figure 3).

Thus, the aqueous solubility of erythromycin increases quite fast and linearly over the range of surfactant concentrations above cmc (premicellar region not shown), indicating a very significant solubility enhancement over that in water. This phenomenon is presumably due to the micellar solubilization,[25] although the cosolvent effect of surfactant[26] may not be ruled out. The $R_{m,S}$ values from the above plots are presented in Table 2 for all the surfactants used in the study. The solubilizing power

Table 2. Molar Solubilization Ratio ($R_{m,S}$), Partition Coefficient (K_M), Equilibrium Free Energy Change (ΔG_s^o), Binding Constant (K_1), and Number of Solubilizate Molecules Per Micelle (S^M) of Erythromycin in Various Surfactant Systems at 25 °C[a]

surfactant	$R_{m,S}$	$10^3 s_{cmc}$ / mol·dm^{-3}	log K_M	ΔG_s^o / kJ·mol^{-1}	$10^{-2} K_1 N^{-1}$ / mol^{-1}·dm^3	$10^{-4} K_1$ / mol^{-1}·dm^3	S^M
Brij56	0.42	2.32	3.85	−22.0	1.79	2.52	58.6
Brij35	0.17	2.91	3.44	−19.7	0.61	0.24	7.0
Brij58	0.26	2.15	3.73	−21.3	1.23	0.80	17.2
Brij30	0.02	0.36	3.43	−19.6	0.55	0.56	2.02
CTAB	1.51	3.96	3.93	−22.4	3.83	3.44	136.3
TTAB	0.41	3.36	3.68	−21.0	1.22	0.98	32.8
DTAB	0.23	2.95	3.53	−20.1	0.75	0.55	16.4
SDBS	0.31	3.02	3.63	−20.7	1.01	0.52	15.6
SDS	0.22	3.92	3.41	−19.5	0.57	0.35	13.8

[a] Error limits in the measurement of $R_{m,S}$, s_{cmc}, K_1, log K_M, S^M, and ΔG_s^o are ± 7 %, ± 4 %, ± 4 %, ± 4 %, ± 7 %, and ± 5 %, respectively.

of nonionic surfactants follows the order Brij56 > Brij58 > Brij35 > Brij30, while in cationic and anionic surfactants the order is CTAB > TTAB > DTAB and SDBS > SDS, respectively.

The effectiveness of solubilization can also be expressed in terms of the micelle−water partition coefficient, K_M, of the solubilizate between the micelle and aqueous phases and defined as $K_M = x_M/x_a$, the ratio of mole faction of solubilizate in the micellar phase, x_M, to that in aqueous phase, x_a. The value of x_M in terms of $R_{m,S}$ can be written as $x_M = R_{m,S}/(1 + R_{m,S})$, where $x_a = s_{cmc}V_m$, V_m being the molar volume of water equal to 0.01805 dm^3·mol^{-1} at 298 K. With these expressions, K_M becomes[24]

$$K_M = R_{m,S}/\{s_{cmc}V_m(1 + R_{m,S})\} \quad (2)$$

The obtained values of log K_M of erythromycin in different micellar systems are presented in Table 2. The trend in log K_M values is similar to that observed for $R_{m,S}$ in the selected surfactant systems.

Among nonionic surfactant series, the higher solubilization power of Brij56 may be due to its higher aggregation number (Table 2), a potential consequence of its larger hydrophobic content.[11] Brij58, although containing the same hydrophobic chain length as that of Brij56, has a comparatively lower $R_{m,S}$ value which may be attributed to its lower aggregation number. Both Brij56 and Brij58 have higher $R_{m,S}$ and K_M values than Brij35 and Brij30, due to greater hydrophobic chain lengths (C_{16} in Brij56 and Brij58, C_{12} in the case of Brij35 and Brij30). The higher solubilization power of Brij35 than Brij30 (with the same hydrophobic tail) may be a result of greater oxyethylene (OE) content in Brij35 (23) than in Brij30 (4), although the aggregation number of Brij30 (101) is greater than that of Brij35 (40). This indicates that in nonionic surfactants with the same hydrophobic tail solubilization of erythromycin increases with the increase of OE content as reported for other polar solubilizates.[27] The inference seems to contradict the higher solubilization power of Brij56 than Brij58 where the number of OE units is more in the latter surfactant. The contradiction may be explained on the basis of the relative values of aggregation number and number of OE units after proper understanding of the mechanism of EM solubilization. The solubilization site of drugs with intermediate polar character is found to be between the hydrophilic head groups of polyoxyethylene (POE) micelles[28] and in the palisade layer between the hydrophilic groups and the first few carbon atoms of the hydrophobic groups, that is, in the outer core.[29] Apart from this, EM molecules may also get solubilized on the micelle−water interface due to hydrogen bonding between −OH and $-NH_2$ groups of EM and OEs of surfactants. In this context, solubilization of EM should increase with an increase in number of OE units in POE surfactants as well as with an increase in micellar volume/aggregation number of surfactants, a fact well-known for polar solubilizates.[27] Therefore, it may be argued that between two POE surfactants involving an increase in the number of OE units and a decrease in aggregation number the balance between these two opposing factors should explain the observed trend of solubilization. In case the percentage change in opposing factors is similar, then we may argue that the effect of aggregation number would predominate as it affects both micellar volume and number of OE head groups on micelle surfaces. Also, micellar sizes are known to increase with a decrease in OE content.[30] Hence, experimental observation in our study can be easily explained. The percentage increase in aggregation number (117 %) and percentage decrease in OE content (100 %) between Brij58 and Brij56 have almost similar magnitude, and the effect of aggregation number would be dominant resulting in more solubilization power for Brij56. On the contrary, the percentage increase in aggregation number (152 %) of Brij35 to Brij30 is very low compared to the percentage decrease in the number of OE units (475 %), and dominance of the latter results in more solubilization power of Brij35. Thus, although the increased OE content of Brij35 decreases the micellar size and hence solubilization of EM molecules into the micelle core, the surface solubilization due to enhanced OE content more than compensates this decrease, leading to an overall enhanced solubilizing efficiency. Moreover, there would be a larger number of smaller sized micelles when molar concentrations are considered.[30] The compensation between effects of increased OE content and decreased aggregation number to explain solubilization of polar solubilizates is well supported in the literature.[30–36] For the similar number of OE units in Brij35 and Brij58, the greater $R_{m,S}$ and K_M values of the latter can be traced to its greater hydrophobic content and lower cmc.

Among the cationic surfactants, the solubilizing order is CTAB > TTAB > DTAB. This is obviously a manifestation of their hydrophobic content, all having the same hydrophilic head. Among anionic surfactants, $R_{m,S}$ and K_M values of SDBS appear to be higher than those of SDS, which may be attributed to the presence of a benzene ring in SDBS. For the same hydrophobic chain length, both cationic and anionic surfactants have higher $R_{m,S}$ and K_M values than nonionic surfactants. This might be related to the presence of electrostatic interaction between the charged ionic surfactants and polar erythromycin, the magnitude of which is low in the case of nonionic surfactants.[37] It has been reported that solubilized drug molecules decrease the repulsive forces between the head groups of surfactant molecules, thereby decreasing the cmc value.[27] The polar character of the EM becomes obvious by comparing the limiting solubilities of anthracene ($2.53 \cdot 10^{-7}$ mol·dm^{-3})[24] and pyrene ($6.57 \cdot 10^{-7}$ mol·dm^{-3})[24] with that of EM ($2 \cdot 10^{-6}$

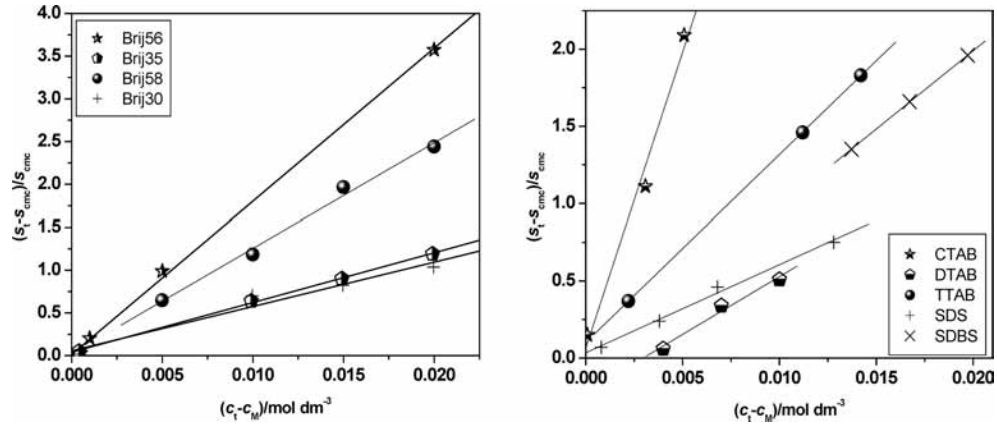

Figure 4. Variation of $(s_t - s_{cmc})/s_{cmc}$ of EM vs surfactant concentration in micellar form $(c_t - c_M)$ in different surfactant systems.

mol·dm^{-3}) in water, indicating EM is less hydrophobic than anthracene and pyrene. Thus, erythromycin solubilization can be a manifestation of its polar character as well as its nonpolar content. Large hydrophobic content and significant polar character of surfactant would lead to a high value of $R_{m,S}$ for erythromycin due to its solubilization both into micellar interior and adsorption at the micelle−water interface,[38,39] evidenced by the high $R_{m,S}$ value in CTAB compared to both TTAB and Brij56. The higher $R_{m,S}$ value in SDBS (C_{12}) than in DTAB (C_{12}) as well as in SDS (C_{12}) may be attributed to the benzene ring of SDBS and to the large micellar concentration owing to its lower cmc.

Knowledge of the thermodynamic parameters controlling solubilization is helpful for a better understanding of the mechanisms involved in this process. From the thermodynamic point of view, solubulization can be considered as a normal partitioning of the drug between the two phases, micelle and aqueous, and the standard free energy of solubilization, ΔG_s^o can be represented by the following expression[27,37]

$$\Delta G_s^o = -RT \ln K_M \quad (3)$$

where R is the gas constant; T is the absolute temperature; and K_M is the molar partition coefficient between the micelle and aqueous phase. The ΔG_s^o values thus calculated are presented in Table 2. For all the systems, ΔG_s^o is negative, indicating spontaneous solubilization. The largest negative value was observed for the CTAB micellar system, showing that the solubilization of EM is energetically more favorable in cationic micellar systems, due to electrostatic interaction. On the contrary, the lowest negative value was obtained for the Brij30 micellar system.

The higher solubilization power of Brij56 and Brij58 among nonionic surfactants is very important from the pharmacological point of view, due to their lower cmc values and minimal protein binding since, upon dilution with a large volume of blood, considering intravenous administration, only micelles of surfactants with low cmc value still exist. The micelles from surfactants with high cmc values may dissociate into monomers, and their content may precipitate in the blood.[40]

The binding constant K_1 of EM with surfactant systems is related to the total surfactant concentration, c_t, micelle concentration [M_t], cmc, and aggregation number, N, of micelles through the equation[37,41]

$$(s_t - s_{cmc})/s_{cmc} = K_1/N(c_t - c_M) \quad (4)$$

K_1 serves as the interaction parameter between the solubilizate and surfactant. The value of K_1/N is obtained from the slope of $(s_t - s_{cmc})/s_{cmc}$ vs $(c_t - c_M)$ plots as shown in Figure 4. Knowing the aggregation number of a surfactant, K_1 can be evaluated and further used to calculate the average number of solubilizate molecules per micelle, S^M, according to the equation[24,41]

$$S^M = (s_t - s_{cmc})/[M_t] = K_1 s_{cmc} \quad (5)$$

The values of K_1/N, K_1, and S^M are presented in Table 2. The K_1/N values can also serve as the parameter to determine solubilization powers of different surfactants, and the values are well in conformity with the values of $R_{m,S}$ and K_M. The volume of the micellar core of CTAB according to the Tanford equation[24] comes out to be 42117.6 Å^3. Incorporation of 136 EM molecules in such a micelle would lead to a volume increase of 1009·136 = 137224 Å^3 which is comparatively too large a value indicating impossibility of such incorporation into the micelle core (volume of one EM molecule $V_{m,EM}/N_A$ = 1009 Å^3). However, in addition to the solubilization in the core of the micelle, EM may be solubilized on the surface of micelles due to hydrogen bonding. Further, as the number of surfactant molecules goes on increasing in a micelle, a larger number of EM molecules may get solubilized on its surface.

Solubilization capabilities of surfactant solutions toward nonpolar hydrocarbons (HOCs) differ significantly from that for polar EM. While the former is solubilized deep into the micellar core only, the latter is solubilized both in the core as well as on the micellar surface. For example, the polar compound, yellow OB (1-*o*-tolyl-azo-2-napthylamine)[31] and other polar dyes[30–36] are solubilized into the core as well as on the micelle−water interface, while the nonpolar HOCs (pyrene, anthracene, naphthalene)[23] are solubilized into the core only. In the present study, the results show that the volume of solubilized EM molecules is greater than the volume of the micelle core indicating that the solubilization assisted by surface adsorption would be more predominant than the micellar core solubilization. Such solubilization at the interface would allow the polar groups of EM to interact with exterior aqueous solution, possibly with OE groups, while at the same time maintaining the possibility of hydrophobic interactions between nonpolar parts of EM and the micellar core. Thus, while the extent of solubilization of EM is dependent on both total interfacial area of aggregates and weight of surfactants constituting the micelle core, it depends only on the weight of the surfactant in the case of nonpolar HOCs.

Conclusion

The present work investigates the solubilization of EM in different surfactants. The cationic surfactant CTAB showed the highest molar solubilization capacity for EM due to electrostatic attractions. The enhanced solubility of EM in nonionic micellar solution is a consequence of its interaction with POE surfactant head groups and also the molar fraction of surfactants in micellar form. Keeping in view the toxic effects of cationic surfactants, the nonionic surfactants could be considered as the best alternative for solubilization of EM as well as of other drugs. This class of surfactants provides a reasonable molar solubilization capacity combined with low cmc values. Moreover, the low toxicity of nonionic surfactants makes them particularly interesting for solubilization and drug delivery purposes.

Acknowledgment

We are thankful to Dr. Rayees, Lecturer Dept. of Biotechnology, Kashmir University, for providing facilities in his department for carrying out part of this work. In addition, constant encouragement and inspiration by Prof. M. A Qurishi, Head, Department of Chemistry, University of Kashmir, Srinagar, are gratefully acknowledged.

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Received for review November 13, 2007. Accepted March 23, 2008.

JE700659G