Effect of Surfactant Mixing on Partitioning of Model Hydrophobic Drug, Naproxen, between Aqueous and Micellar Phases

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

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

Received: August 13, 2008; Revised Manuscript Received: October 20, 2008

Mixed surfactants may improve the performance of surfactant-enhanced solubilization of drugs and thus can serve as the tool for increased bioavalaibility, controlled drug release, and targeted delivery. Solubilization of Naproxen by micellar solutions at 25 °C using single and mixed surfactant systems was measured and compared. Solubilization capacity determined with spectrophotometry and tensiometry has been quantified in terms of molar solubilization ratio, micelle−water partition coefficient, and locus of solubilization. Cationic surfactants exhibited higher solubilization capacity than nonionics and anionics, the efficiency increasing with chain length. Mixing effect of surfactants on mixed micelle formation and solubilization efficiency has been discussed in light of regular solution approximation (RSA). Equimolar cationic−nonionic surfactant combinations showed better solubilization capacity than pure cationics or nonionics, which, in general, increased with increase in hydrophobic chain length. Equimolar cationic−nonionic−nonionic ternary surfactant systems exhibited intermediate solubilization efficiency between their single and binary counterparts. Use of RSA has been extended, with fair success, to predict the partition coefficient of ternary surfactant systems using data from binary mixtures. The theoretical micelle−water partition coefficients calculated from the geometric mean equation compared well with experimental values. Locus of solubilization of NAP in different micellar solutions was probed by UV−visible spectroscopy.

Introduction

Poor solubility and hydrophobicity of drugs/bioactives limit their possible applications in drug formulation and delivery development.[1] Up to 40% of new chemical entities (NCEs) discovered by the pharmaceutical industry today are hydrophobic compounds.[2] The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow significantly in the coming years as NCEs are relied upon for a large share of revenue within the pharmaceutical market by innovator companies. Relative to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences including decreased bioavailability, incomplete release from dosage form, and higher interpatient variability.[3] Poorly soluble compounds also present many in vitro formulation obstacles such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the in vivo absorption. These in vivo/in vitro correlations are often sufficiently formidable to halt development of many newly synthesized compounds due to solubility issues.[3] Poorly soluble drugs such as naproxen, nifedipine etc. have motivated the development of drug delivery technologies to overcome the obstacles in their solubilization through either chemical or mechanical modification of the environment surrounding the drug molecule or physically altering the macromolecular characteristics of aggregate drug particles. These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution and spray drying, as well as micellar solubilization, and cyclodextrin-mediated inclusion complexes.[4−6]

Reports on micelle-mediated solubilization of drugs are in abundance.[7−9] The core−corona structure of a micelle is of great importance for solubilizing water-insoluble compounds; the hydrophobic core is able to provide a suitable microenvironment for hydrophobic drugs while the hydrophilic corona acts as a stabilizer for the hydrophillic part in the aqueous environment.[10] Therefore, micellar solubilization serves as an attractive solution for the bioavailability of water-insoluble drug molecules.[11] This constitutes the basis on which surfactants can be exploited in controlled uptake and release of drugs, pollutants, and other compounds in many biological, pharmaceutical, and environmental systems.

Naproxen (NAP), a nonsteroid anti-inflammatory drug,[12] chemically designated as (S)-6-methoxy-α-methyl-2-napthaleneacetic acid,[13] is a well-known anti-inflammatory drug. The main disadvantages of this family of drugs are relatively short plasma half-life and the significant gut- and nephrite toxicities.[16] Moreover, naproxen is a poorly water soluble drug[12] (25 mg/L at 25 °C). Therefore, the development of a drug delivery system allowing the controlled release of naproxen would be useful, especially in high-dose-dependent treatments, including chronic diseases such as rheumatoid arthritis. Studies have been conducted on the solubilization of naproxen in organic solvents,[17,18] supercritical CO_2,[13,19] dyes,[20] oil/water emulsion,[21] polymers,[12,22−26] and polyamidoamine dendrimers.[27] The effect of hydroxylpropylmethylcellulose and hydrogenated castor oil on naproxen release from sustained-release tablets has also been studied.[28] Efforts to study naproxen solubilization in surfactant−polymer mixtures[29] have been made. Enough work, though less detailed, has been done on solubilization of naproxen in single-surfactant systems;[30−37] however, no report of naproxen solubilization in mixed binary and ternary surfactant combinations has been presented. The present work aims at detailed investiga-

* To whom correspondence should be addressed. E-mail: aijaz_n5@yahoo.co.in; Phone: 0194-2424900.

10.1021/jp807229c CCC: $40.75 © 2009 American Chemical Society
Published on Web 01/05/2009

TABLE 1: Critical Micelle Concentration ($cmc_{exp}$and $cmc_{lit.}$) of Single Surfactants, Micellar Composition (X_i^M), Interaction Parameter (β), and Activity Coefficients (f_i) of Equimolar Binary Surfactant Mixtures Using Rubingh's Method and Equimolar Ternary Surfactant Mixtures Using Rubingh−Holland Methods at 25 °C for All Surfactant Mixtures[a]

single surfactant system		mixed surfactant systems system					
system	cmc_{exp} (cmc_{lit})[b] mM	system	cmc_{exp} (cmc_{ideal}) mM	β	$X_1^M/X_2^M/X_3^M$	$f_1/f_2/f_3$	$^{Pred}cmc_{RH}$ (mM)
Brij58	0.006 (0.008)	Brij35−CTAB	0.0771 (0.0830)	−1.03	0.89/0.11	0.99/0.44	
Brij56	0.051 (0.040)	Brij35−TTAB	0.0812 (0.0870)	−2.17	0.93/0.07	0.99/0.15	
Brij35	0.044 (0.050)	Brij35−DTAB	0.0792 (0.0880)	−3.98	0.92/0.08	0.98/0.03	
CTAB	0.764 (0.815)	Brij35−SDS	0.082 (0.0870)	−2.71	0.94/0.06	0.99/0.09	
TTAB	3.800 (3.700)	Brij58−CTAB	0.0109 (0.0121)	−2.99	0.91/0.09	0.98/0.08	
DTAB	14.512 (15.100)	Brij58−TTAB	0.0110 (0.0122)	−4.61	0.930.07	0.97/0.02	
SDBS	2.091 (2.000)	Brij58−DTAB	0.0115 (0.0122)	−5.25	0.95/0.05	0.99/0.01	
SDS	7.593 (8.100)	Brij58−SDS	0.0112 (0.0122)	−5.07	0.94/0.06	0.98/0.01	
		Brij58−Brij35	0.0091 (0.0107)	−1.23	0.78/0.22	0.94/0.47	
		Brij58−Brij35−CTAB	0.0151 (0.0161)		0.77/0.19/0.04	0.92/0.51/0.13	0.0130
		Brij58−Brij35−DTAB	0.0152 (0.0162)		0.78/0.20/0.02	0.93/0.49/0.02	0.0134
		Brij58−Brij35−SDS	0.0152 (0.0162)		0.77/0.16/0.06	0.88/0.58/0.01	0.0126

[a] Error limits of cmc_{exp}, X_i^M, β, and f_i are ±4%. [b] Reference 74 and references therein.

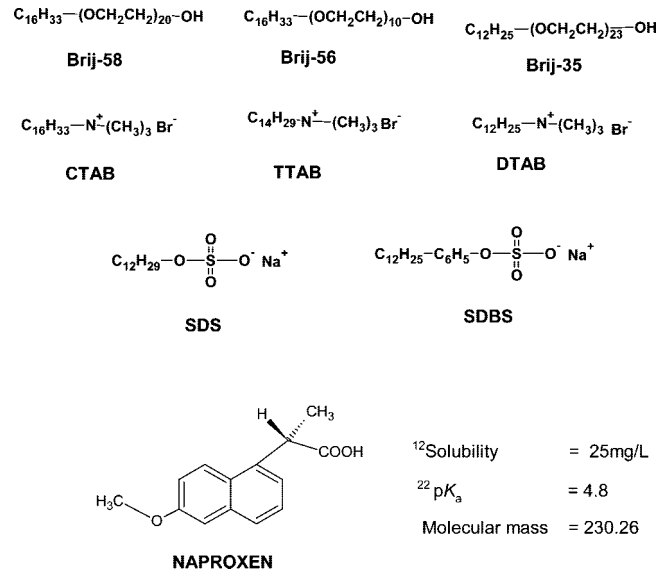
tion of the solubilization of naproxen by single, binary, and ternary surfactant systems. More specifically, the focus of attention has been: (a) effects of difference in hydrophobic chain length and hydrophilic head groups on solubilization; (b) solubilization capabilities of binary and ternary mixtures of various ionic and nonionic surfactants and their intercomparison; (c) correlation of interaction parameter for mixed micelle formation with the solubilization interaction parameter from regular solution approach (RSA); (d) correlation of the experimental micelle−water partition coefficient with the theoretically determined values to test the validity of the geometric mean equation in mixed surfactant systems; and (e) determination of locus of solubilization of solubilized solubilizate molecules in the micelles. The experimental results of this study may be useful in understanding and predicting the solubilization properties of studied binary and ternary surfactant combinations, based on those of single surfactant systems, and provide valuable information for selection of surfactant mixtures for controlled drug release and targeted delivery. Additionally, the study may be helpful in testing the validity of various theoretical models applied to solubilization studies. Although, the ionic surfactants used might be toxic and present restrictions for in vivo use, knowledge of their solubilization characteristics will contribute significantly to the understanding of naproxen solubilization.

Experimental Section

Materials. The nonionic amphiphiles (Brij35, Brij56, and Brij58), cationic amphiphiles (CTAB, TTAB, and DTAB) and anionic amphiphiles (SDS and SDBS), including tetramethylammoniumbromide (TMAB), n-octane, sodium sulfate, diethylether, and methanol, were all Aldrich products and were used as received. Naproxen (NAP) was a Himedia (India, 98%) product. The structures and important properties of the surfactants and naproxen are presented in Scheme 1 and Table 1, respectively.

Methods. The solubility of NAP was measured in different surfactant solutions with concentrations between 0 and 30 mM. Excess amounts of NAP were added to vials containing 1 mL of the surfactant solutions to ensure maximum solubility. The sample vials having 5 mL capacity were sealed with screw caps fitted with Teflon-lined septa to prevent any loss. These samples were then agitated with magnetic pieces for a period of 24 h on a magnetic stirrer at a temperature of 25 ± 0.5 °C. The solutions were subjected to centrifugation at 15 000 rpm to remove the

SCHEME 1: Structure of naproxen and different surfactants used in this study



undisolved drug. The concentration of solubilized drug was determined spectrophotometrically with a Shimadzu spectrophotometer (Model UV-1650) following appropriate dilution of an aliquot of the supernatant with the 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 NAP was determined at its characteristic wavelength of 332 nm using the extinction coefficient 2831.7 M^{-1} cm^{-1}, determined from its calibration curve in methanol. Using this extinction coefficient, solubility of NAP in water was confirmed to be 0.109 mM, which tallied well with the literature value.[12]

The cmc values of all surfactant solutions studied were determined from the surface tension (γ) versus logarithm of surfactant concentration (log C_t) plots in 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}.

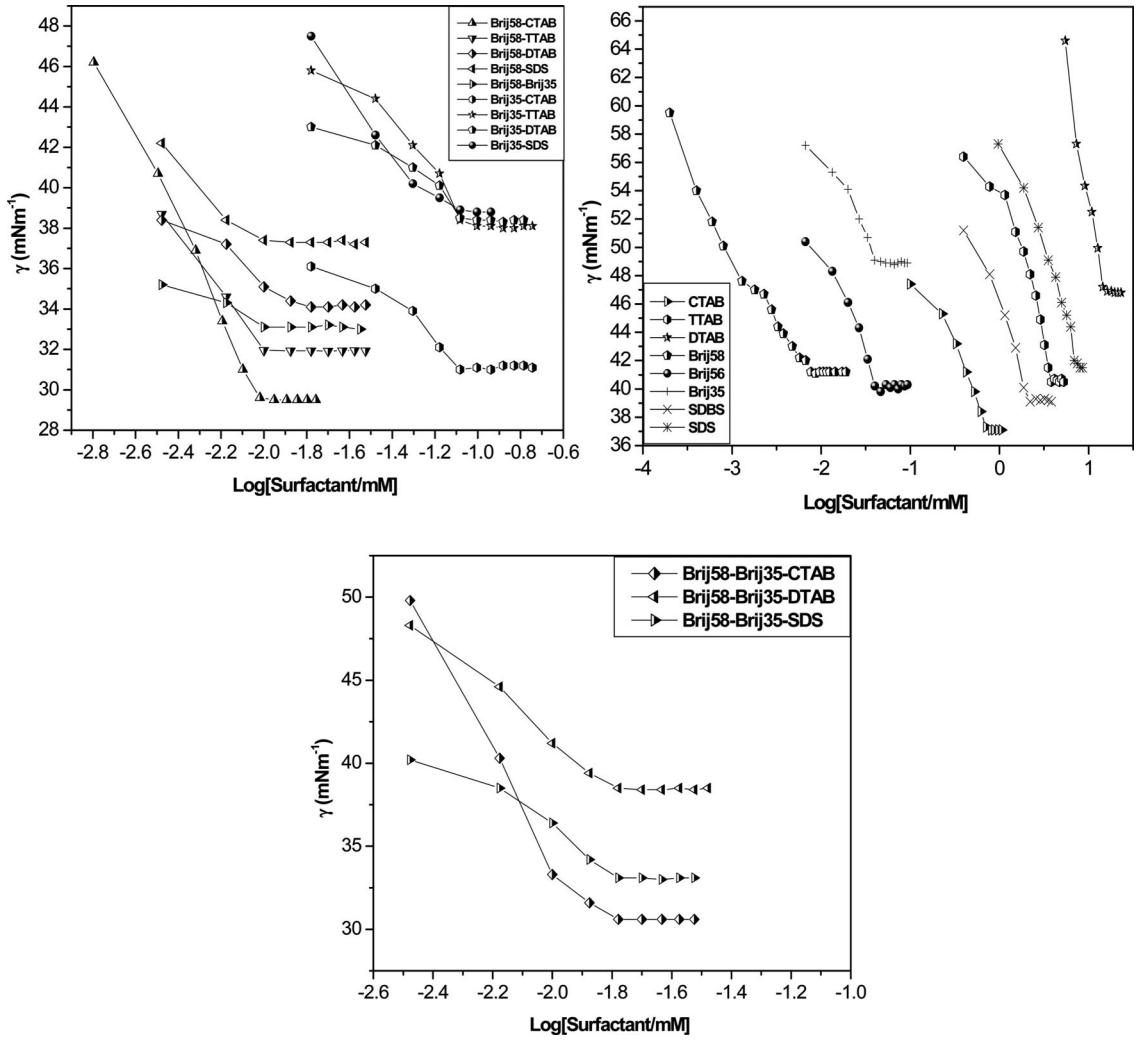


Figure 1. Plots of surface tension vs single and mixed surfactant concentrations.

Results and Discussions

Surfactant−Surfactant Interactions. The cmc values of the studied single as well as mixed surfactant systems are presented in Table 1. The values for pure surfactants are in good agreement with the literature values. The ideal cmc values, cmc_{ideal}, for mixed surfactant systems calculated using the Clint equation[14] are also included in Table 1. All of the observed cmc values were found to be lower than ideal cmc values, indicating negative deviation from ideal behavior for mixed micelle formation. The estimate of negative deviation of experimental cmc values from cmc_{ideal} and, hence, nonideality of mixed binary surfactant systems can be made in light of Rubingh's equation[15] based on regular solution theory. The interaction parameter, β, accounts for deviation from ideality and is an indicator of the degree of interaction between two surfactants in mixed micelles. The values of β along with the micellar mole fraction, X_i^M and activity coefficient, f_i, of the ith surfactant within mixed micelles calculated using Rubingh treatment are presented in Table 1 for the selected equimolar binary surfactant systems. The negative values of β indicate synergistic interactions. It is well-known[38,39] that, for ionic-nonionic mixed surfactant systems, significant electrostatic self-repulsion of ionics and weak steric self-repulsion (depending on the headgroup size) of nonionics before mixing are weakened by dilution effects after mixing and that the electrostatic self-repulsion of the ionic surfactant is replaced by the ion−dipole interactions between the hydrophilic head groups of ionic and nonionic surfactants. For the same nonionic surfactant in different cationic−nonionic mixtures, the magnitude of β increases with decrease in chain length of cationic surfactant, a fact attributed to the more favorable self-interaction in longer CTAB chains compared to that in DTAB and TTAB and reflected in its lower cmc and hence higher propensity to form micelles. As a result, its intermixing with nonionic surfactants may become less favorably reflected by its lower β values in the cationic−nonionic mixtures. The less negative value of β in Brij35−ionic surfactant system than their Brij58−ionic counterparts may be attributed to the larger headgroup size of Brij35 (OE = 23) than Brij58 (OE = 20), thereby making a larger steric self-repulsion contribution toward interhead group interaction. The repulsion will be more effective in small-sized micelles of Brij35 compared to that in Brij58. Moreover, these mixed micelles are dominated by nonionic surfactants as indicated by X_i^M values in Table 1, in conformity with the results of other studies on different ionic−nonionic mixed systems.[40,41]

Holland and Rubingh[42] have proposed a generalized muticomponent nonideal mixed micelle model based on a pseudophase separation approach. It has been successfully applied in the case of many ternary surfactant systems[43,44] for evaluation of micellar composition, activity coefficients, and cmc values. It makes an effective use of net interaction parameters determined experimentally from cmc measurements on binary systems. In the

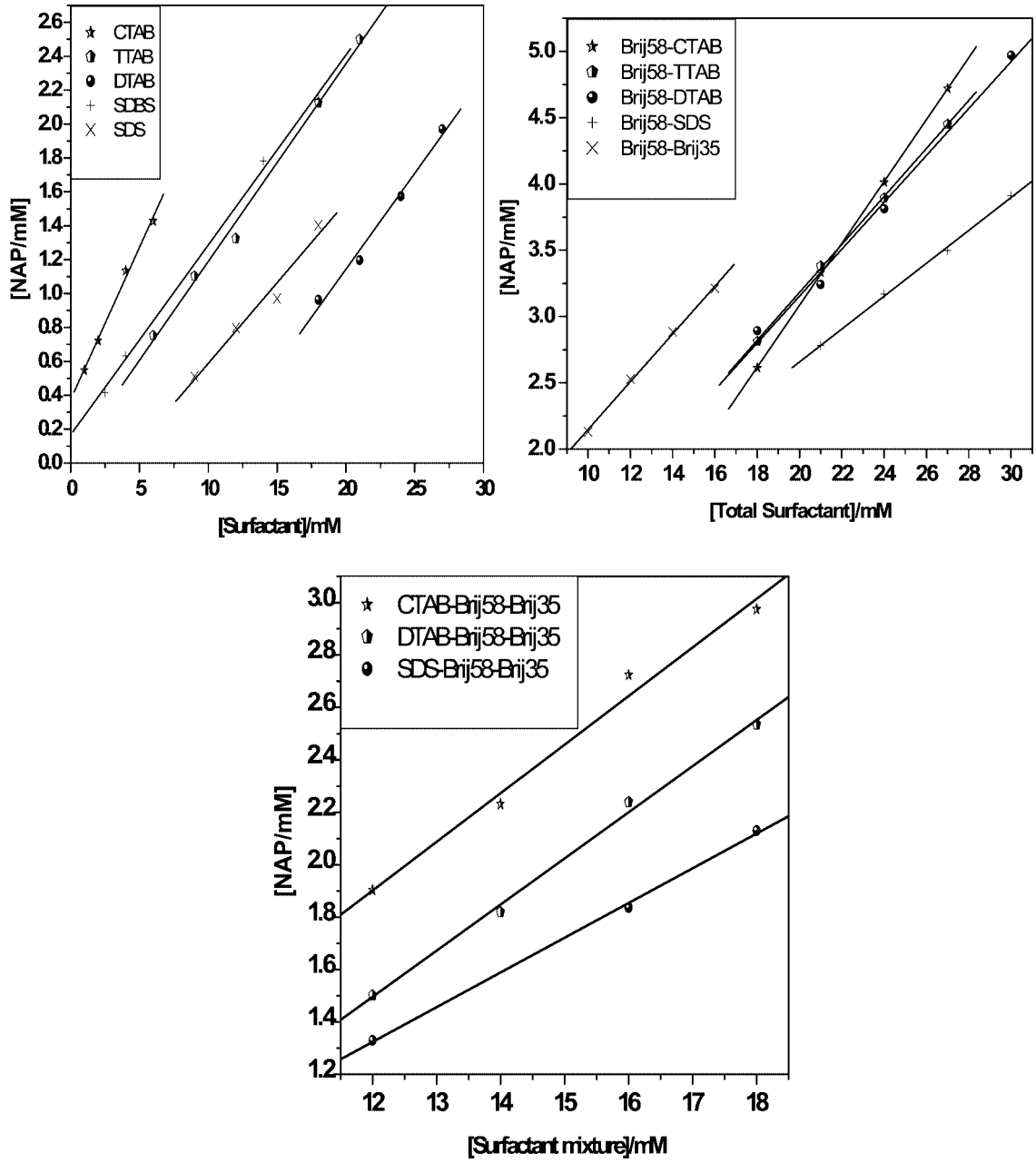


Figure 2. Plots of Naproxen concentration vs surfactant concentration.

present study, values of binary interaction parameters—β_{12}, β_{13}, and β_{23}—following Rubingh's method and cmc values of pure surfactants (Table 1) were used in the equations of Rubing—Holland (RH) formulation[42] to evaluate activity coefficients—f_1, f_2, and f_3—and the micellar mole fractions—X_1^M, X_2^M, and X_3^M. These values were then used to predict the cmc of ternary system, cmc_{RH}, according to Rubing—Holland (RH) formulation. The results are presented in Table 1.

The composition of mixed micelles (X) differs from the bulk composition (α): $X_{cationic}$ values are much lower than $\alpha_{cationic}$. The activity coefficients of cationics are very low but are close to unity for nonionics. The cmc_{RH} values are found to differ significantly from experimental cmc values, probably due to the calculation of β values of binary surfactant mixtures at a single mole fraction. However, when the β value is calculated over the whole mole fraction range, the agreement between the two is found to be good.[44] Moreover, other factors such as changes in ionic strength, etc. might also have their influence. It has been reported[45] that for nonionic—ionic surfactant mixtures, a single β value is sufficient to represent mixed micellization when the number of oxyethylene (OE) groups in nonionic surfactant varies between 10 and 20. However, for the extreme cases of OE = 20 and OE = 23, as in our systems, the values show variation.

Molar Solubilization Ratio (MSR) and Micelle-phase/Aqueous-phase Partitioning of NAP. Water solubility of NAP by both single- and mixed-surfactant solutions were evaluated and compared. The variation of solubilities of NAP versus total surfactant concentrations is plotted in Figure 2. The solubilities increase linearly over the range of single- or mixed-surfactant concentrations above cmc, indicating solubilization of the drug within single/mixed-surfactant micelles. Solubilization capacity of different surfactant systems for NAP above cmc was quantified by the molar solubilization ratio (MSR)[46] defined as the amount (moles) of solute dissolved per mole of surfactant. The micelle—water partition coefficient, K_m,[46] a thermodynamic parameter that represents the affinity of a given solubilizate with the micellar phase

TABLE 2: Molar Solubilization Ratio (MSR), log K_m, Deviation Ratio (R), Experimental Interaction Parameter (B) for Single- and Mixed-surfactant Systems at 25 °C[a]

system	MSR (MSR_{ideal})	log K_m	B	R
Brij58	0.173	4.23		
Brij56	0.122	4.09		
Brij35	0.112	4.07		
CTAB	0.180	4.23		
TTAB	0.117	4.09		
DTAB	0.113	4.06		
SDBS	0.112	4.14		
SDS	0.095	4.08		
Brij58−CTAB	0.234 (0.176)	4.98	21.99	1.33
Brij58−TTAB	0.181 (0.145)	4.89	22.37	1.25
Brij58−DTAB	0.177 (0.143)	4.88	34.29	1.24
Brij58−SDS	0.124 (0.134)	4.75	20.57	0.93
Brij35−CTAB	0.193 (0.146)	4.92	18.87	1.32
Brij35−TTAB	0.141 (0.114)	4.80	25.60	1.23
Brij35−DTAB	0.126 (0.113)	4.75	21.41	1.12
Brij35−SDS	0.109 (0.104)	4.70	25.75	1.05
Brij58−Brij35	0.180 (0.143)	4.89	9.39	1.26
Brij58−Brij35−CTAB	0.186 (0.153)	4.90 (5.19)		1.21
Brij58−Brij35−DTAB	0.176 (0.131)	4.88 (5.08)		1.34
Brij58−Brij35−SDS	0.133 (0.125)	4.77 (5.25)		1.06

[a] Error limits in the measurement of MSR and log K_m are ±7% and ±4%, respectively.

relative to the aqueous phase, is used to determine the amount of drug molecules solubilized by the micelles and to define the stability of the drug−micelle complex against dilution in drug delivery applications. The values of K_m were calculated using eq 1,[46]

$$K_m = \mathrm{MSR}/\{[S_{cmc}]V_m(1 + \mathrm{MSR})\} \quad (1)$$

where V_m is the molar volume of water (0.01805 L/mol at 25 °C) and S_{cmc} is the apparent solubility of NAP at cmc. MSR values are calculated from slopes of the curves in Figure 2, and K_m values thus obtained are presented in Table 2.

Treiner et al.[47] have suggested that the partition coefficient of a neutral organic solute between the micelle and aqeous phase in a mixed surfactant system may be presented by the relationship shown in eq 2

$$\ln K_{m12} = X_1^M \ln K_{m1} + (1 - X_1^M) \ln K_{m2} + BX_1^M(1 - X_1^M) \quad (2)$$

where K_{m12}, K_{m1}, and K_{m2} are the micelle−water partition coefficients of the solute in mixed and single surfactants systems and X_1^M (X_2^M) represents the micelle mole fraction of surfactant 1 (2). B has the same origin as β in the Rubingh model.[15] B, as per Zhu et al.,[39] is an empirical parameter incorporating both surfactant−surfactant and surfactant−solute interactions. For $B = 0$, there would be no mixing effect of surfactants on partitioning of a solute between aqueous and micellar phases. As per the RSA of Treiner,[48] for solute containing polar moiety, attractive interactions between the surfactants (β = −ive) in mixed micelle must lead to less solubilization efficiency ($B < 0$) of mixed micelle. According to Nishikido,[49] there are at least three solubilization sites in mixed ionic−nonionic surfactant systems: the hydrophobic core, the region of interaction between the ionic headgroup and the polar moieties, and finally the fraction of the polar chain with no interaction with ionic head groups. For the correlation suggested by Treiner[48] between B and β to exist, the solubilization site of the solute must be closer to the micellar surface, since only this region is associated with the β value. Therefore, for polar solubilizates where micellar surface solubilization is expected, the relationship between B and β should follow RSA. In the present study, for all ionic−nonionic surfactant mixtures showing β = −ive, B has been found to be positive for NAP solubilization, which is in contrast to the expectation using the above approach. However, this observation is in tune with the reports in literature[50,51] for ionic−nonionic mixtures, where B has been found to be positive for polar solubilizates inspite of β = −ive for surfactant mixtures.

The partition coefficient of a solubilizate in a ternary surfactant system, K_{m123}, can be represented by eq 3.[46]

$$\ln K_{m123} = X_1^M \ln K_{m1} + X_2^M \ln K_{m2} + X_3^M \ln K_{m3} + B_{12}X_1^MX_2^M + B_{13}X_1^MX_3^M + B_{23}X_2^MX_3^M \quad (3)$$

The values of X_i^M (Table 1) from the Rubing−Holland formulation of ternary systems and B_{12}, B_{13}, and B_{23} values (Table 2) as described above for binary surfactant mixtures can be used in eq 3 to give predicted log K_{m123} values given in parenthesis for cationic−nonionic−nonionic and anionic−nonionic−nonionic ternary systems in Table 2 along with the experimentally observed values. The remarkable results indicate that the experimental interaction parameters of binary surfactant systems may be used along with the micellar mole fraction values from RH treatment to predict the K_m values of ternary surfactant systems. Further validation from the literature could not be made since no data presenting solubilization of NAP or any other polar hydrophobic molecule in mixed ternary surfactant systems are available.

Figure 2 and Table 2 show that among single-surfactant systems, cationic surfactants of a given chain length exhibit higher solubilizing power for NAP, followed by nonionic and anionic surfactants. NAP, being an acidic drug ($pK_a = 4.8$),[22] is repelled by the headgroup of anionic micelles, thereby limiting its solubilization. Similar results have been observed for ibuprofen[52] and sulfanilamide[53] in anionic surfactants. One way of lowering the repulsion between SDS micelles and NAP may be to lower the pH value, in order to favor the molecular form of the drug. The extent of its solubilization increases at higher SDS concentrations, which may be due to the increase in the concentration of micelles. The higher values of MSR and K_m of NAP in SDBS micelles may be due to the presence of benzene ring in SDBS. Electrostatic attraction between the cationic surfactant head groups and negatively charged drug would lead to larger values of K_m and MSR, a phenomenon supported by the solubilization of the cationic drug trifluoperazine in SDS micelles.[54] Nonionic surfactants, however, have intermediate MSR and K_m values for NAP between those of same chain length cationic and anionic surfactant micelles due to their very low cmc values. Similar results have been reported for ibuprofen[52] (cationc > nonionic > anionic). However, the MSR and K_m values for NAP in various single-surfactant systems decrease in general with the decrease in hydrocarbon chain length. The higher solubilization power of Brij58 compared to Brij56 may be related to the greater number of oxyethylene (OE) units in it, which may facilitate solubilization of semipolar compounds due to hydrogen bonding between NAP and OE head groups at the interfacial region. Moreover, the large micellar concentration of Brij58, owing to its lower cmc, may also be the reason.

NAP solubilization has been found to increase with increased single-surfactant concentration as per the literature available,[30−37] in agreement with the results of our system. For example, Hearan Suh et al.[32] found that at a particular pH, NAP release across the membrane was inversely proportional to the surfactant (PF-127) concentration. Yiyun et al.[37] observed that 82 mM Tween 20 (C_{12}) enhances NAP solubility to 3160 mg/L, and 20 mM Brij35 (C_{12}) in our system increases it to 642 mg/L.

All the equimolar nonionic−cationic binary surfactant mixtures show greater MSR and K_m values than those of single surfactant systems indicating synergism in NAP solubility enhancement. This may be due to the larger effective solubilization area in mixed micelles as reported by Tokuota et al.[55] In the mixed cationic−nonionic systems, the solubilization power for NAP increases with the increase in chain length of either of the surfactants. The results are well in conformity with early findings,[46] with PAHs as solubilizates. The higher solubilization capacity of equimolar nonionic−nonionic, Brij58−Brij35 (C_{16}−C_{12}), system compared to the ionic−nonionic (C_{16}−C_{12}) systems may be due to a large micelle concentration owing to the low mixed cmc value. Similar observation is evident in the case of equimolar cationic−nonionic−nonionic ternary surfactant mixtures. However, their MSR and K_m values are lower than their equimolar cationic−nonionic binary counterparts. On the contrary, anionic−nonionic−nonionic ternary systems show greater MSR and K_m values than their equimolar anionic−nonionic binary counterparts. However, these binaries showed intermediate MSR and K_m values between those of their single surfactant systems. In cationic−nonionic mixed micelles, as only a small fraction of cationic (Table 1) is present, and also the degree of counterion binding is negligible;[40] a slight positive charge on mixed micelles facilitates micelle−water interface adsorption in addition to solubilization in the palisade layer by nonionics. Consequently, we expect larger MSR and K_m values than individual surfactants. However, addition of one more nonionic surfactant may decrease the micelle−water interfacial adsorption due to charge dispersal, thus decreasing the MSR and K_m values. On the other hand, in case of anionic−nonionic surfactant mixtures, a slight negative charge on mixed micelles would exclude the possibility of palisade layer solubilization as well as micelle−water interface adsorption of the negatively charged drug. Because enhancement of solubility of NAP by these systems compared to water solubility is observed, as depicted by MSR values, the locus of solubilization may therefore be the mixed micelle core. This inference is corroborated by the results discussed in a later section. An increase in micellar aggregation number upon surfactant mixing has also been reported in such systems.[56] The effect of large solubilization area,[55] greater aggregation number,[56] and enhanced micellar mole fractions of nonionics in such mixtures may oppose the effect of the slight negative charge on mixed micelles. The two compensating effects may, therefore, be the reason for the observed MSR values. However, addition of one more nonionic surfactant to the binary mixture may increase the micelle−water adsorption due to dispersal of negative charge, thus increasing the MSR and K_m values for such ternary systems.

The discussion presented above shows a significant and different mixing effect in cationic−nonionic and anionic−nonionic mixtures, which can be quantified in terms of the deviation ratio (R), defined as the ratio of experimental MSR, MSR_{exp}, to the ideal value, MSR_{ideal}, where $MSR_{ideal} = \Sigma_i\ MSR_i\alpha_i$. MSR_i is the experimental MSR value of solubilizate in pure ith surfactant solution whose bulk mole fraction in the mixture is α_i. Values of R, which characterize the mixture nonideality with respect to solubilization, are also presented in Table 2. $R > 1$ implies positive mixing effect of surfactants on solubilization. R values for NAP are significantly greater than unity in all binary and ternary surfactant mixtures, except in systems containing anionic surfactant, where R is close to unity. The micelle concentration in mixed ionic−nonionic surfactant systems increases considerably over that of pure ionic systems. Meanwhile, MSR values in mixed ionic−nonionic surfactant systems may also increase over the ideal MSRs (R > 1). For our cationic-nonionic systems, an increase in K_m/MSR is coupled with a decrease in cmc, the conjunct effect of which results in greater positive deviation of MSR values from ideal behavior, leading to R values greater than unity. However, in case of the anionic−nonionic surfactant systems, only a decrease in cmc is noted, whose conjunct effect with K_m (MSR) results in R values close to unity. It is observed that in the case of cationic−nonionic systems, the B value is consistently large and positive, in tune with the values of $R > 1$. However, in case of anionic−nonionic systems, the value of B is also largely positive in spite of the fact that R is close to unity. As per Zhu et al.,[39] the parameter B could not be utilized as the sole factor to account for the mixing effect of surfactants on solubilization, as they observed negative B values with R values significantly greater than unity for solubilization of pyrene in various anionic−nonionic systems. It may, therefore, be concluded that R is the more relevant factor to discuss the mixing effect of surfactants on solubilization than B.

Theoretical Estimation of Partition Coefficient, K_M by Geometric Mean Equation. Researchers have developed many methods to evaluate and/or predict surfactant-enhanced solubilization of hydrophobic organic compounds (HOCs). Recently, a simple method to estimate K_M of hydrocarbons in micellar solutions was developed by Liu et al.[57] The authors assume that the two liquid phases, arenes with water and arenes with micelles, are in a typical quasi-crystalline state (lattice array) and that the intermolecular force effectively acts on the surface area of nearest neighbor molecules. Their equation to predict the surfactant enhanced solubilization of HOCs is

$$\log K_M = \left(\frac{N}{2.3RT}\right)(\pi_{20}\pi_{cmc})^{1/2}(\mathrm{TSA}) \qquad (4)$$

In this equation, K_M values of HOCs in the dilute solution range are estimated from the product of the geometric mean, $(\pi_{20}\pi_{cmc})^{1/2}$, of the two surface tension reductions (π_{cmc} is surface pressure at cmc and π_{20} is the surface tension reduction equal to 20 dyn/cm) by the surfactant solution and the total molecular surface area (TSA) of the arenes. The rationality is that the interfacial tension reduction, a macroproperty of the solution, is a reflection of a microproperty of the surfactant solution and that the total molecular surface area of the arene is a measure of the hydrophobicity of the arenes. The authors tested the validity of the equation in various single surfactant systems and found good agreement between the $^{pred}\log K_M$ values (from geometric mean equation) and $\log K_m$ values for nonpolar hydrocarbons. However, a significant difference was obtained when the compounds were polar. No report is available regarding the validity of the equation in mixed surfactant systems. The endeavor of the present work is to test the validity of the geometric mean equation for both nonpolar (pyrene, anthracene, and naphthalene) using the earlier published data[46] and polar (NAP) solubilizates in mixed surfactant systems.

K_M of Nonpolar Solubilizates. The previously published[46] $\log K_m$ values of arenes, which include naphthalene, anthracene

TABLE 3: Comparison of $^{pred}\log K_M$ and $^{exp}\log K_m$ Values of Anthracene, Pyrene, Napthalene and Naproxen

		napthalene		anthracene		pyrene	
surfactant system	π_{cmc}(exp)/dyncm$^-$	$^{pred}\log K_M$	$\log K_m$	$^{pred}\log K_M$	$\log K_m$	$^{pred}\log K_M$	$\log K_m$
$C_{12}Br$	34.1	4.30	4.46	5.57	5.95	5.88	6.40
$C_{12}EBr$	36.5	4.44	4.49	5.77	6.02	6.09	6.48
Brij30	40.6	4.69	4.54	6.08	6.23	6.42	6.52
$C_{12}EBr-C12Br$	35.5	4.38	4.48	5.69	5.96	6.01	6.42
$C_{12}Br-Brij30$	42.2	4.78	4.59	6.20	6.31	6.55	6.62
$C_{12}EBr-Brij30$	44.9	4.93	4.62	6.40	6.4	6.75	6.66
$C_{12}EBr-C12Br-B30$	43.4	4.84	4.56	6.29	6.26	6.64	6.56

		naproxen	
surfactant system	π_{cmc}(exp)/dyncm$^-$	$^{pred}\log K_M$	$\log K_m$
Brij58	30.0	6.69	4.23
Brij56	33.0	7.01	4.09
Brij35	23.0	5.86	4.07
CTAB	34.9	7.22	4.23
TTAB	31.0	6.80	4.09
DTAB	25.0	6.10	4.06
SDBS	31.5	6.85	4.14
SDS	30.5	6.74	4.08
Brij58−CTAB	42.7	7.97	4.98
Brij58−TTAB	40.2	7.74	4.89
Brij58−DTAB	37.4	7.47	4.88
Brij58−SDS	34.5	7.17	4.83
Brij35−CTAB	41.0	7.82	4.92
Brij35−TTAB	33.9	7.11	4.80
Brij35−DTAB	33.5	7.07	4.75
Brij35−SDS	33.3	7.05	4.73
Brij58−Brij35	38.9	7.61	4.89
Brij58−Brij35−CTAB	41.0	7.82	4.90
Brij58−Brij35−DTAB	39.1	7.63	4.88
Brij58−Brij35−SDS	33.7	7.08	4.77

and pyrene in cationic−cationic, cationic−nonionic, and cationic−cationic−nonionic micellar solutions, are listed in Table 3, along with the $^{pred}\log K_M$ values using eq 4. Table 3 also lists the surface tension reduction, π_{cmc} values of different surfactant solutions used. It is clear from Table 3 that the predicted log K_M values of arenes are almost the same as the published values. The average absolute difference between the predicted log K_M values and the published values of these arenes is less than 0.3 log units, indicating that the developed equation is genuinely valid in mixed micellar solutions for nonpolar solubilizates. It seems that the geometric mean equation can be generalized for its application to predict log K_M values of the arenes in both single as well as mixed surfactant systems.

K_M of Naproxen. The log K_m and $^{pred}\log K_m$ values of NAP in various surfactant systems of the present study are also listed in Table 3. A significant difference exists between these values, although the trend in solubilization is not changed. The possible reason is that the carboxylic group of NAP straddling between the polar and nonpolar positions may contribute to the interfacial tension between water and the outer layer of micelles and produce different values of $(\pi_{20}\pi_{cmc})^{1/2}$. Also, because the behavior of polar solubilizates like NAP in two pseudophases is complex,[6,58] the validity of eq 4 to predict the log K_m values of NAP and other polar solubilizates is questionable. Liu et al.[57] also observed a significant difference between the log K_m and those predicted by eq 4 for polyhalogenated compounds. The amphiphilic nature of NAP makes the micellar solutions and the interactions involved more complex, limiting the applicability of eq 4 for polar solubilizates. Further, the TSA of solubilizates required to be put into eq 4 represents only the hydrophobic surface area. The hydrophobic surface area of NAP may be supposed to be the TSA of napthalene (155.8),[57] and if this value is substituted in eq 4 in place of total surface area of NAP, fair agreement between the experimental and predicted log K_M values is observed with the maximum absolute difference of 0.5 log units. This further indicates that the developed equation, although more applicable for nonpolar solubilizates, may be used for polar solubilizates as well, if TSA is taken to be only the hydrophobic surface area. Considering that the measurement of π_{cmc} is much easier than the analysis of solubility of solubilizates in surfactant solutions, the developed equation may in practice have better applicability. Because this is the first time that eq 4 has been used to predict the micelle−water partition coefficient of solubilizate in mixed surfactant systems, more research is needed to validate its use, especially for predicting the K_M of polar solubilizates.

Locus of Solubilization. The sites of solubilization of aromatic molecules such as benzene and its alkyl derivatives in micelles have been a matter of some controversy.[59,60] NMR[60] studies have indicated that benzene, when present in polar environment at low concentration, is localized at the micellar surface only, and at the saturated concentration solubilization in the interior core has been suggested. The location of incorporated molecules within a micelle determines the extent of solubilization, the chemical reactivity of solubilizates,[60] as well as the rate of their release from the micelles.[61] It is also a measure of the strength of specific interactions between the solubilizate and the micelle. Several experimental methods,[60−63] such as NMR, UV−visible spectroscopy, fluorescence measurements, and solubility in model solvents, have been used to determine the locus of solubilization of various solubilizates. A micelle can at least provide three thermodynamically distinguishable microenvironments for solubilization: the micelle core, the corona, and the core−corona interface. The highly nonpolar core is considered as the locus of solubilization for nonpolar molecules such as alkanes.[64,65] For more polar solubilizates such

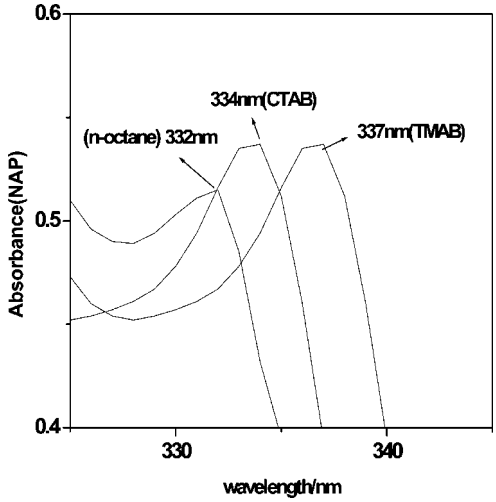


Figure 3. Plot showing wavelength of maximum absorption of NAP in different solvents.

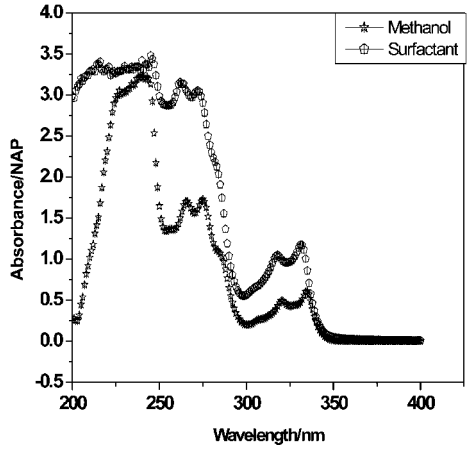


Figure 4. Plot showing unchanged behavior of NAP in methanol and surfactants.

as ketones[66] or substituted phenols,[67,68] the interfacial region is generally the solubilization site. The corona, on the other hand, is rarely involved in the solubilization of hydrophobic molecules. The information about the locus of solubilization can be obtained by comparing λ_{max} of the drug in micellar solutions to that in model solvents that mimic the polarity of different regions of the micelle. In the present study, because of similarity in structure and polarity, tetramethylammonium bromide (TMAB) was chosen to mimic the polar headgroup of cationics (CTAB, TTAB, and DTAB), sodium sulfate (Na_2SO_4) for SDS and SDBS, ether for OE nonionics, and n-octane to resemble the nonpolar micellar core. The UV-spectra of NAP in CTAB, TMAB, and n-octane are shown in Figure 3. When solubilized in aqeous cationic surfactants, NAP absorbs at $\lambda_{max} = 334$ nm, which is intermediate of that in TMAB ($\lambda_{max} = 337$ nm) and in n-octane ($\lambda_{max} = 332$ nm). Such a shift in the λ_{max} indicates that solubilized NAP molecules are residing in the microenvironment of intermediate polarity as compared to n-octane and TMAB. However, it is also conceivable that the absorption band in the micellar solution is a superposition of two unresolved peaks, one representing the absorption in the micelle core (n-octane-like environment), and the second representing the absorption in aqueous TMAB-like environment, the micelle−corona. This possibility is eliminated because the absorption peak in the micellar solutions is not sufficiently broad to be considered as a superposition of the peak in n-octane and that in aqueous TMAB solution. This suggests that micellar interface in cationics is the most reasonable site for the solubilizate molecules like NAP having ampiphilic character. Solubilization at the interface would allow the polar groups of drug molecules to interact with the exterior aqueous solution, while at the same time maintaining the possibility of hydrophobic interactions between nonpolar parts of the drug molecules and the micelle core.

When solubilized in nonionics, NAP absorbs at $\lambda_{max} = 330$ nm, which is the same as its $\lambda_{max} = 330$ nm observed in diethylether, indicating that the solubilization site of NAP in nonionics is not the micellar core ($\lambda_{max} = 332$ nm) but somewhere near or between the OE head groups.The interaction of the carboxylic group of NAP with the OE headgroup of nonionic surfactant may drag the NAP molecules to the interfacial region. In cationics and nonionics, considering that the micellar core has certain affinity for the drug molecules, one might expect the incorporation of the drug molecules to occur inside the micellar core, in addition to the interface. One can speculate that with increasing drug concentration, as the micellar interface saturates, the micelle core would participate in the solubilization of the drug molecules, as also reported for other polar solubilizates.[57,68,69] This would be reflected by a shift in λ_{max} of the drug in micellar solutions with the extent of solubilization. In the present system, however, no such shift was observed, and the wavelength of maximum absorption of the drug in micellar solution was independent of the drug concentration, indicating that solubilization occurs at the same site for all levels of solublizate concentrations. A similar behavior has been observed for solubilization of anilinium cations in sodium dodecylsulfate micelles,[61] 2-nitrodiphenylamine in block copolymer micelles,[70] and short chain phenols in POE nonionics.[71]

The λ_{max} of NAP in anionics was found to be 332 nm, the same value as in n-octane, and differs from that in Na_2SO_4 (329.5 nm), indicating that NAP is localized inside the core of anionic micelles. This may be due to the reluctance of NAP molecules to adsorb at the negatively charged micellar surface. Any solubilized species is likely to be exposed to water at the interface to some extent, on a statistical basis, unless it is actually repelled from the surface.[70]

Total Interfacial Area of the Micelles. In this section we determine if sufficient micellar surface area is available for the interfacial solubilization of the drug molecules in cationics and nonionics. To do so, we determined the area of one drug molecule using a molecular model (ChemSW) and compared the area required to accommodate all of the drug molecules incorporated at saturation to the total surface area of the micelles. The radius of CTAB and C_{16} nonionics, using the Tanford equation,[73] was calculated to be approximately 20.48 Å, hence the micellar surface area is 5.3×10^3 Å^2. At saturation, the number of drug molecules solubilized per CTAB micelle, using the appropriate equation,[46] comes out to be 16.4. Because the estimated area of one drug molecule is 259 Å^2, the incorporation of all the drug molecules would require an area of $16.4 \times 259 = 4.3 \times 10^3$ Å^2 per micelle, which corresponds to 81% of the total micellar interfacial area. Considering that the drug molecules are not expected to pack on the surface with a crystal like precision and that the emanating hydrophilic head groups represent a significant perturbation to the packing efficiency, 81% coverage at saturation does not seem unreasonable. For Brij56, the total covered interfacial surface at saturation is 83%. For all other cationics and nonionics, the interfacial area coverage was even lower. As already explained that in the case

of anionic surfactants, the reasonable solubilization site is the micellar core. Interfacial solubilization in such micelles may be hindered by the repulsion between negatively charged head groups of surfactants and NAP molecules. To determine whether sufficient micellar core volume is available to accommodate all the solubilized NAP molecules, the volume of one NAP molecule (354.5 Å^3) was determined using the molecular model and their total volume was compared with the volume of the micellar core. For SDS micelles, the volume of the micellar core according to the Tanford equation[73] is 15.35×10^3 Å^3, which is sufficient to accommodate, on average, 5.6 NAP molecules per SDS micelle calculated using the appropriate equation.[46] The volume thus occupied would be equal to $5.6 \times 354.5 = 1.99 \times 10^3$ Å^3, which is just 13% of the micellar core volume. Thus, the micellar core can act as solubilization site for NAP molecules. The percentage values indicate that anionic surfactants are less effective in solubilizing NAP compared to cationics and anionics.

Further, it is expected from the unchanged behavior of UV-spectra of surfactant-solubilized NAP compared to that in methanol and other solvents including water that the interaction of NAP with surfactants does not damage its structure as indicated by the UV-spectrum of NAP in methanol and surfactant shown in Figure 4.

Conclusions

This study investigates the solubilization of NAP in single- and mixed-surfactant systems varying in hydrophobic chain length and hydrophilic heads. The solubilization capacity has been quantified in terms of MSR and log K_m values. The thermodynamic K_m values, when compared with the $^{pred}K_M$ values from geometric mean equation, reveal significant differences indicating that the geometric mean equation can not be generalized for polar solubilizates, although it may give fair results after assuming TSA to be the hydrophibic surface area of solubilizates. In general, cationics exhibited higher solubilization capacity for NAP due to electrostatic attraction. Increase in the hydrophobic chain length of the surfactant enhances the solubilization capacity. All mixed surfactant systems exhibited better solubilization capacity than those of single-surfactant systems, indicating their mixing effect on solubilization of NAP. Equimolar cationic−nonionic mixtures are better solubilizers than equimolar cationic−nonionic−nonionic mixtures. However, anionic−nonionic mixtures indicate lower solubilization capacity than their ternary counterpart.

This study also gives insight into the applicability of RSA as applied to the solubilization by binary surfactant systems to be extended to multicomponent system in analogy with its more frequent use to mixed micelle formation. This treatment has led to the prediction of log K_m values of ternary surfactant systems using the experimental interaction parameter B of binary surfactant systems. The analysis has yielded fair results and can, therefore, provide valuable information for the selection of mixed surfactants for increased bioavailability, controlled drug release, and targeted delivery. Spectroscopic data evidenced the locus of solubilization as the interfacial site in cationic and nonionic surfactant solution and micellar core in anionic micelles for hydrophobic but polar solubilizates like NAP.

Acknowledgment. Constant encouragement and inspiration by Professor M. A Qurishi, Head, Department of Chemistry, University of Kashmir, Srinagar, is gratefully acknowledged.

References and Notes

(1) Hoerter, D.; Dressman, J. B. *Adv. Drug. Delivery Rev.* **1997**, *25*, 3.
(2) Lipinski, C. A. *Am. Pharm. Rev.* **2005**, *5*, 82.
(3) Gupta, U.; Agashe, H. B.; Asthama, A.; Jain, N. K. *Biomacromolecules* **2006**, *7* (3), 649.
(4) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug. Delivery Rev.* **2001**, *46*, 3.
(5) Kubinyi, H. *Pharmazie* **1995**, *50*, 647.
(6) Rangel-Yagui, C. O.; Pessoa, A., Jr.; Tavares, L. C. *J. Pharm. Pharmaceut. Sci.* **2005**, *8* (2), 147.
(7) Samaha, M. W.; Gadalla, M. A. F. *Drug Dev. Ind. Pharm.* **1987**, *13*, 93.
(8) Whitworth, C. W.; Carter, E. R. *J. Pharm. Sci.* **1969**, *58*, 1285.
(9) La, S. B.; Okano, T.; Kataoka, K. *J. Pharm. Sci.* **1996**, *85*, 85.
(10) Tang, Y.; Lui, S. Y.; Armes, S. P.; Billingham, N. C. *Biomacromolecules* **2003**, *4*, 1636.
(11) Lui, C.; Desai, K. G. H.; Lui, C. *J. Chem. Eng. Data* **2004**, *49*, 1847.
(12) Cirri, M.; Maestrelli, F.; Corti, G.; Furlanetto, S.; Mura, P. *J.Pharm. Biomed. Anal.* **2006**, *42*, 126.
(13) Simon, S. T. T.; Staurt, J. M.; David, L. T.; Neil, R. F. *Ind. Eng. Chem. Res.* **1993**, *32*, 1471.
(14) Clint, J. H. *J. Chem Soc., Faraday Trans* **1 1975**, *71*, 1327.
(15) Rubingh, D. N. In *Solution Chemistry of Surfactants*; Mittal, K. L. Ed.; Plenum Press: New York, 1979; Vol 1, p 337.
(16) Simo, C.; Gallard, A.; Sanroman, J.; Barbas, C.; Cifuentes, A. *J. Chromatog. B.* **2002**, *767*, 35.
(17) Mora, C. P.; Martinez, F. *Fluid Phase Equilib.* **2007**, *255*, 70.
(18) Maheshwari, R. K.; Chaturvedi, S. C.; Jain, N. K. *Indian. J. Pharm. Sci.* **2007**, *69*, 101.
(19) Garmoodi, A.; Hassan, J.; Yamini, Y. *J. Chem. Eng. Data* **2004**, *49*, 709.
(20) Fini; Fazio, G.; Feroci, G. *Int. J. Pharm.* **1995**, *126*, 95.
(21) Correa, M. A.; Scarpa, M. V.; Franzini, M. C.; Oliveira, A. G. *Colloids Surf. B* **2005**, *43*, 108.
(22) Mura, P.; Furlanetta, S.; Curri, M.; Maestrelli, F.; Corti, G.; Pizauti, S. *J. Pharm. Biomed. Anal.* **2005**, *37*, 987.
(23) Kumar, R.; Chen, M. H.; Parmar, V. S.; Samuelson, L. A.; Kumar, J.; Nicolsi, R.; Yoganathan, S.; watterson, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 10640.
(24) Paola, M.; Francesca, M.; Marzia, C. *Int. J. Pharm.* **2003**, *260*, 293.
(25) Bhise, K. S.; Dhumal, R. S.; Chauhan, B.; Paradkar, A.; Kadam, S. S. *AAPS PharmSci Tech.* **2007**, *8* (2), 3.
(26) Bettinettig, G.; Mura, P. *Drug Dev. Ind. Pharm.* **1994**, *20*, 1353.
(27) Yiyun, C.; Tongwen, X. *Eur. J. Med. Chem.* **2005**, *40*, 1188.
(28) Amaral, M. H.; Sousa Loba, J. M.; Ferreira, D. C. *AAPS PharmSci Tech.* **2001**, *2*, 1. article 6.
(29) Mura, P.; Faucci, M. T.; Manderioli, A.; Bramanti, G.; Parrini, P. *Drug Dev. Ind. Pharm.* **1999**, *25*, 257.
(30) Rao, V. M.; Nerurkar, M.; Pinnamaneni, S.; Rinaldi, F. *Int. J. Pharm.* **2006**, *319*, 98.
(31) Zgoda, M. M.; Lukosek, M.; Nachajski, M. *J. Polim. Med.* **2006**, *36*, 13.
(32) Hearan, S.; Jun, H. W. *Int. J. Pharm.* **1996**, *129*, 13.
(33) He, Y.; Yalkowsky, S. H. *Int. J. Pharm.* **2006**, *314*, 15.
(34) Gerakis, A. M.; Koupparis, M. A.; Efstathiou, C. E. *J. Pharm. Biomed. Anal.* **1993**, *11*, 33.
(35) Cheng, X.; Zhao, L.; Lui, M.; Lin, J. M. *Anal. Chem. Acta* **2006**, *558*, 296.
(36) Sharma, P. K.; Bhartia, S. R. *Int. J. Pharm.* **2004**, *278*, 361.
(37) Yiyun, C.; Jiepin, Y. *Phys. Chem. Liq.* **2005**, *44*, 249.
(38) Zhou, Q.; Rosen, M. J. *Langmuir* **2003**, *19*, 4555.
(39) Zhou, W.; Zhu, L. *J. Hazard. Mater. B* **2004**, *109*, 213.
(40) Dar, A. A.; Chatterjee, B.; Das, A. R.; Rather, G. M. *J. Colloid Interface Sci.* **2006**, *298*, 395.
(41) Errico, G.; Ortona, O.; Paduano, L.; Tedeschi, A.; Vitagliano, V. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5317.
(42) Holland, P. M.; Rubingh, D. N. *J. Phys. Chem.* **1983**, *87*, 1984.
(43) Ghosh, S. *J. Colloid Interface Sci.* **2001**, *244*, 128.
(44) Dar, A. A.; Rather, G. M.; Ghosh, S.; Das, A. R. *J. Colloid Interface Sci.* **2008**, doi: 10.1016/j.jcis.2008.03.022.
(45) Carrion Fite, F. *Comun. Jorn. Com. Esp. Deterg.* **1994**, *15*, 379.
(46) Dar, A. A.; Rather, G. M.; Das, A. R. *J. Phys. Chem. B* **2007**, *111*, 3122.
(47) Treiner, C.; Nortz, M.; Vaution, C. *Langmuir* **1990**, *6*, 1211.
(48) Treiner, C. *Chem. Soc. Rev.* **1994**, *23*, 349.
(49) Nishikido, N.; Moroi, Y.; Matuura, R. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1387.
(50) Carlfors, J.; Stilbs, P. *J. Colloid Interface Sci.* **1985**, *103*, 332.
(51) Abe, M.; Mizogushi, K.; Kondo, Y.; Ogino, Y.; Uchiyama, H.; Scamehorn, J. F.; Tucker, E. E.; Christian, S. D. *J. Colloid Interface Sci.* **1993**, *160*, 16.
(52) Rangel-Yagui, C. O.; Ling Hsu, H. W., Jr.; Tavares, L. C. *Braz. J. Pharm. Sci.* **2005**, *41*, 237.
(53) Mall, S.; Buckton, G.; Rawlins, D. A. *J. Pharm. Sci.* **1996**, *85*, 75.

(54) Cacteno, W.; Gelamo, E. L.; Tabak, M.; Itri, R. *J. Colloid Interface Sci.* **2002**, *248*, 149.

(55) Tokuota, Y.; Uchiyama, H.; Abe, M.; Christian, S. D. *J. Phys. Chem.* **1994**, *98*, 6167.

(56) Tokiwa, F.; Aigami, K. *Kolloid-z. z. Polym.* **1970**, *239*, 687.

(57) Liu, G. G.; Roy, D. *Langmuir.* **2000**, *16*, 3595.

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

(59) Mukerjee, P. *J. Pharm. Sci.* **1971**, *60*, 1528.

(60) Mukerjee, P. *Adv. Colloid Interface Sci.* **1967**, *1*, 241.

(61) Kim, B. J.; Im, S. S.; Oh, S. G. *Langmuir* **2001**, *17*, 565.

(62) Teng, Y.; Morrison, M. E.; Munk, P.; Webber, S. E.; Prochazka, *Macromolecules* **1998**, *31*, 3578.

(63) Goldenberg, M. S.; Bruno, L. A.; Rennwantz, E. L. *J. Colloid Interface Sci.* **1993**, *158*, 351.

(64) Cang, H.; Brace, D. D.; Fayer, M. D. *J. Phys. Chem. B* **2001**, *105*, 10007.

(65) Tian, M.; Arca, E.; Tuzar, Z.; Webber, S. E.; Munk, P. *J. Polym. Sci.,Part B: Polym. Phys.* **1995**, *33*, 1713.

(66) Chaiko, M. A.; Nagarajan, R.; Ruckenstein, E. *J. Colloid Interface Sci.* **1984**, *99*, 168.

(67) Hruska, Z.; Piton, M.; Yekta, A.; Duhamel, J.; Winnik, M. A.; Riess. ; Croucher, M. D. *Macromolecules* **1993**, *26*, 1825.

(68) Bunton, C. A.; Sepulveda, L. *J. Phys. Chem.* **1979**, *83*, 680.

(69) Heindl, A.; Strnad, J.; Kohler, H.−H. *J. Phys. Chem.* **1993**, *97*, 742.

(70) Won, Y.-Y.; Davis, H. T.; Bates, F. S. *Science* **1999**, *283*, 960.

(71) Choucair, A.; Eisenderg, A. *J. Am. Chem. Soc.* **2003**, *125*, 11993.

(72) Nakagawa, T. *Nonionic Surfactants*; Schick, M. J. Ed.; Dekker: New York, 1967; Ch. 17.

(73) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; Wiley and Sons: New York, 1980.

(74) Bhat, P. A.; Dar, A, A.; Rather, G, M. *J. Chem. Eng. Data* **2008**, *53*, 1271.

JP807229C