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Solubility of LIDOCAINE in Ionic, Nonionic and Zwitterionic Surfactants

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Abstract The solubility of an anesthetic drug, LIDOCAINE, in water was investigated in the presence of ionic, nonionic and zwitterionic surfactants at 25 °C, and the solubility was found to increase linearly with the surfactant concentration. The molar solubilization ratio, $R_{m,s}$, and Gibbs free energy, ΔG_s^o values for nonionic surfactants fall in the order DDAO > Brij 35 > Brij 30, whereas for ionic and zwitterionic surfactants the order is DDAPS > DTAB > SDS. The high negative values of the Gibbs energies in the cases of DDAO and DDAPS prove them to be better surfactants for solubilizing this drug as compared to the other surfactants.

Keywords LIDOCAINE · DDAPS · Aqueous solubility · Micelle · Molar solubilization ratio

1 Introduction

Quite a high percentage of pharmaceutically active compounds are nearly insoluble in water thus having low and variable bioavailability [1, 2]. Therefore, several techniques are used to increase the solubility of such drugs, including the use of surfactants/amphiphiles [3–14]. LIDOCAINE is a common local anesthetic and antiarrhythmic drug. Its IUPAC name is 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide. LIDOCAINE is used topically to relieve itching, burning and pain from skin inflammations, is injected as a dental anesthetic and in minor surgery. LIDOCAINE is approximately 90% metabolized (de-ethylated) in the liver by CYP1A2 (and to a minor extent CYP3A4) to form the pharmacologically active metabolites monoethylglycinexylidide and glycinexylidide [15]. The half life of LIDOCAINE is approximately 1.5–2 hours in most patients, but its presence can be prolonged because of hepatic impairment (average 343 minutes) or congestive heart failure (average 136 minutes) [16].

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$C_{12}H_{25}(OCH_2CH_2)_{23}OH$ Brij-35

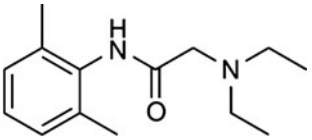
$C_{12}H_{25}(OCH_2CH_2)_4OH$ Brij-30

$C_{12}H_{31}NO$ DDAO

$C_{12}H_{25}SO_4Na$ SDS

$C_{12}H_{25}N^+(CH_3)_3Br^-$ DTAB

$C_{12}H_{25}N^+(CH_3)_2(CH_2)_3SO_3^-$ DDAPS



Lidocaine

Scheme 1 Structure of LIDOCAINE and formulae of the investigated surfactants

However, LIDOCAINE is practically insoluble in water [17, 18] and a number of attempts have been made to solubilize it in various media [19–21]. Although the controlled release of LIDOCAINE from polymeric micelles and its solubility in liquid supercritical carbon dioxide have been reported, its solubility in surfactants micelles, the most important materials in this respect, has not yet been investigated [22, 23]. This fact has, therefore, prompted us to investigate the solubility of LIDOCAINE in various ionic, nonionic and zwitterionic surfactant solutions in order to identify appropriate surfactants for its delivery and solubility enhancement.

2 Experimental

2.1 Materials

N-Dodecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate (DDAPS) (97%) was purchased from Fluka Biokemika, Dorset, UK. Dimethyldodecylamine-*N*-oxide (DDAO) (99%), dodecyltrimethylammonium bromide (DTAB) (98%), and LIDOCAINE (Product No. L-7757-25G) were obtained from Sigma, Dorset, UK. LIDOCAINE has the polarizability, molar volume and density values 28.71×10^{-24} cm^3 [24], 228.3 cm^3·mol^{-1} [25] and 1.026 g·cm^{-3} [25], respectively. Sodium dodecylsulfate (SDS), specifically purified for biochemical purpose, was purchased from BDH, UK, while Brij 30 and Brij 35 (98%) were obtained from Merck, Germany. The chemical formulae are provided in Scheme 1. All of the chemicals were used as obtained from the suppliers.

2.2 Methods

2.2.1 Critical Micelle Concentration Determinations

The critical micelle concentration, CMC, of the surfactants was determined from surface tension measurement. The surface tension measurements were made using a Lauda (TE III) tensiometer made in Germany. The tensiometer was first calibrated with a known weight provided by the supplier, and further tested for the surface tension of pure deionized water. During the measurements, the temperature was kept constant at 25.00 ± 0.01 °C by a Lauda (E200) water, bath made in Germany.

Table 1 Surface tension of aqueous solutions of different surfactants as a function of concentration at 25 °C

Concentration of DDAO ($mmol \cdot L^{-1}$)	Surface tension of DDAO ($mN \cdot m^{-1}$)	Concentration of SDS ($mmol \cdot L^{-1}$)	Surface tension of SDS ($mN \cdot m^{-1}$)	Concentration of DTAB ($mmol \cdot L^{-1}$)	Surface tension of DTAB ($mN \cdot m^{-1}$)
1.0	51.60	7.0	43.25	7	42.51
1.2	49.60	7.2	41.95	9	40.82
1.4	47.65	7.4	40.61	11	39.15
1.6	45.54	7.6	39.02	13	37.52
1.8	43.58	7.8	37.65	15	35.71
2.0	43.50	8.0	36.23	16	34.81
2.2	43.50	8.2	36.21	17	34.82
2.4	43.50	8.4	36.21	18	34.80
2.6	43.50	8.6	36.22	19	34.81
2.8	43.50	8.8	36.22	20	34.82

2.2.2 Solubility Estimation

The solubility of LIDOCAINE in different surfactants solutions was determined spectroscopically using an Irmeco UV/Vis spectrophotometer (model U2020), USA. For this purpose, 1 mL of surfactant solution was saturated with LIDOCAINE in order to ensure maximum solubility of this drug. Vials containing an excess amount of the drug and surfactants solution were sealed with screw caps having Teflon lined septa to prevent solvent losses from the samples through evaporation. These samples were then agitated using a magnetic stirrer for 24 hrs at 25 ± 0.5 °C. These solutions were then subjected to centrifugation at 15,000 rpm by using an ultracentrifuge machine supplied by Sigma, UK. Aliquots were diluted to the required concentration using surfactant solutions of the same concentration. The UV measurements were made at the wavelength 263 nm (λ_{max}) for LIDOCAINE. The blanks used were the respective surfactant solutions having the same surfactant concentration. The concentration of the drug was obtained using the Beer–Lambert equation. The calculated extinction coefficient in ethanol at this wavelength is 382 $L \cdot mol^{-1} \cdot cm^{-1}$ [19].

3 Results and Discussion

The surface tension of the surfactant solutions was measured as a function of concentration and depicted in Table 1. The results were plotted as a function of concentration which gave the expected curves (Fig. 1). The CMC obtained from these curves are listed in Table 2 and agree well with their corresponding literature values [26–29].

The solubility of LIDOCAINE measured in the surfactant solutions showed very small increase with increasing surfactant concentration, up to their CMC. However, by further increasing the surfactant concentration beyond the CMC, an abrupt increase in solubility was observed. Normally, the solubilization of any substance in surfactants is expressed as the molar solubilization ratio, $R_{m,s}$ and the micellar–water partitioning coefficient, K_M. The molar solubilization ratio, $R_{m,s}$ is defined as the amount of drug that can be solubilized by one mole of micellar surfactant. It is given as [26, 30, 31]:

$$R_{m,s} = (S_{tot} - S_{CMC})/(C_{surf} - CMC) \quad (1)$$

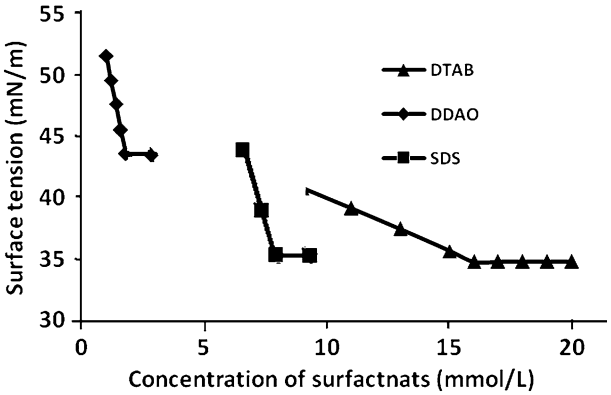


Fig. 1 Surface tension of aqueous solutions of DDAO, SDS and DTAB as a function of their concentration (mmol·L^{-1}) at 25 °C

Table 2 CMCs and aggregation numbers of different surfactants used in this study

Surfactants	CMC$_{exptt}$ [a] (mmol·L^{-1})	CMC^{lit} [b] (mmol·L^{-1})	Aggregation number
Brij 35	0.051	0.050 [24]	40
Brij 30	0.034	0.035 [23]	101
DDAO	1.820	1.800 [25]	76
SDS	8.200	8.050 [24]	62
DTAB	14.700	14.650 [23]	74
DDAPS	2.500	2.500 [27]	67

[a]Experimental CMC value from this research

[b]Literature CMC value

Here S_{CMC} and S_{tot} are the solubility of drug at the CMC and total solubility of the drug, respectively. C_{surf} and CMC denote the molar concentration in solution and critical micelle concentration of surfactant, respectively. Beyond the CMC, the surfactants monomer concentration is equal to the CMC, hence the term (C_{surf} − CMC) is equal to the surfactant concentration occurring in micellar form. Therefore, $R_{m,s}$ is equal to the ratio of the drug concentration in micelles to the surfactant concentration in the micellar form.

The micelle–water partition coefficient is defined as the ratio of drug concentration in the micelle to the drug concentration in water, for a particular surfactant concentration, and is given by [32]:

$$K_M = x_M/x_a \tag{2}$$

Here x_M and x_a are the mole fractions of the drug in the micellar and aqueous phases, respectively. These quantities are further given by:

$$x_M = R_{m,s}/(1 + R_{m,s}) \tag{3}$$

$$x_a = S_{CMC}V_m \tag{4}$$

where V_m (= 0.01805 L·mol^{-1}) is molar volume of water. By substituting these relations for x_M and x_a in Eq. 2 we get another expression for K_M:

$$K_M = R_{m,s}/S_{CMC}V_m(1 + R_{m,s}) \tag{5}$$

Table 3 Molar solubilization ratio ($R_{m,s}$), partition coefficient (K_M), and equilibrium Gibbs energy change (ΔG_s^o) of LIDOCAINE in various aqueous surfactant solutions at 25 °C

Surfactants	$R_{m,s}$	$S_{cmc} \times 10^3$ (mol·L^{-1})	$K_M \times 10^{-3}$	ΔG_s^o (kJ·mol^{-1})
Brij 30	0.026	0.41	3.53	−20.0
Brij 35	0.301	3.05	3.62	−20.6
DDAO	0.460	3.12	3.75	−21.3
SDS	0.211	3.92	3.39	−19.3
DTAB	0.220	3.08	3.51	−20.0
DDAPS	0.350	2.97	3.68	−21.0

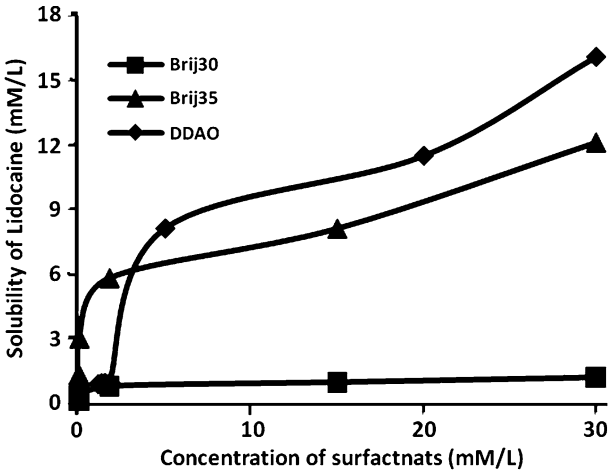


Fig. 2 Solubility of LIDOCAINE (mmol·L^{-1}) in aqueous nonionic surfactant solutions at 25 °C

Value of K_M of LIDOCAINE in different surfactants systems are given in Table 3. The trend is the same for all of the investigated systems. The solubility of LIDOCAINE in different surfactants has been plotted in Figs. 2 and 3. The results show that among the investigated nonionic surfactants, the order of solubilization of drug is dimethyldodecylamine-*N*-oxide > Brij 35 > Brij 30. Although the aggregation numbers of pure Brij 30 surfactants are higher than for Brij 35, but the solubility is higher in Brij 35 solution. This trend can be attributed to differences in the number of OE units [33]. However, the solubility of the drug in DDAO solutions is high due to the possible interactions of the amino oxide group of DDAO with LIDOCAINE. It is further noted that the $R_{m,s}$ and K_M values for Brij 30, Brij 35, and DDAO indicate that the solubilization of this drug with intermediate polarity occurs in the polyoxyethylene head groups (POE) micelles [34, 35], and in the palisade layer between the hydrophilic groups and the first few carbon atoms of hydrophobic groups (that is, in the outer core [35]). Apart from this, the LIDOCAINE molecule is also solubilized at the micelle–water interface due to hydrogen bonding between the NH group and the C=O group of LIDOCAINE and the OE group of surfactants [33].

The solubilization order among ionic and zwitterionic surfactants is DDAPS > DTAB > SDS. As all these surfactants have the same hydrophobic chain length but different head groups, the differences in solubility of LIDOCAINE is considered to be mainly due to the difference in interactions with the head groups of the surfactants. DDAPS has the ability to solubilize more drug than DTAB due to its longer chain.

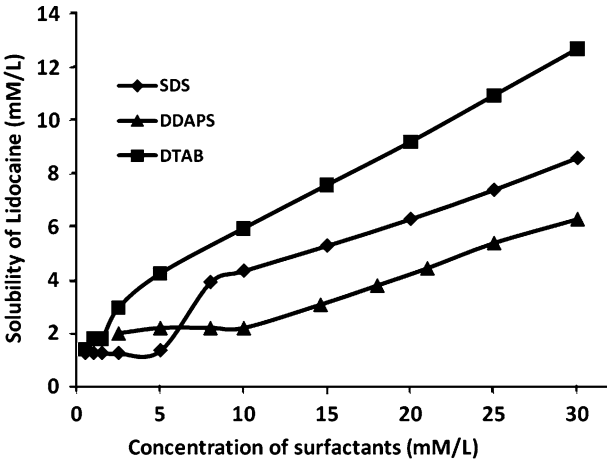


Fig. 3 Solubility of LIDOCAINE (mmol·L^{-1}) in ionic and zwitterionic surfactant solutions at 25 °C

Knowledge of the thermodynamic properties that control the solubilization process is quite helpful in understating the process of solubilization. For example, the solubilzation of drugs occurs by partitioning of drug molecules among the micelle and aqueous phases, and the standard Gibbs free energy of solubilization, ΔG_s^o, can be calculated by using the expression [36]:

$$\Delta G_s^o = -RT \ln K_M \tag{6}$$

where R is the gas constant, T is the absolute temperature and K_M is the mole-fraction-based partition coefficient between the micelle and aqueous phases. The calculated values of ΔG_s^o are reported in Table 2. All of the systems investigated displayed negative values of ΔG_s^o, indicating spontaneous solubilization, and the solubility is directly related to the Gibbs energy.

4 Conclusion

The solubility of LIDOCAINE was investigated in ionic, nonionic and zwitterionic surfactant solutions at 25 °C. The results show that the solubility is considerably increased if the concentration of surfactant is higher than the CMC of the surfactant, and the order for the molar solubilization ratio, $R_{m,s}$, and Gibbs energy, ΔG_s^o, values for nonionic surfactants is DDAO > Brij 35 > Brij 30 while for ionic and zwitterionic surfactants it is DDAPS > DTAB > SDS. The high negative values of the Gibbs energy in the cases of DDAO and DDAPS proved them to be better surfactants for solubilizing the drug as compared to the other surfactants. It was therefore concluded that LIDOCAINE can be solubilized in surfactants and the extent of the solubility increase depends upon both the hydrophilic and hydrophobic groups.

References

1. Lipinski, C.A.: Avoiding investment in doomed drugs. Curr. Drug Discov. **14**, 17–19 (2001)
2. Lipinski, C.A.: Poor aqueous solubility—An industry wide problem in drug delivery. Am. Pharm. Res. **19**, 1894–1900 (2002)

3. Yalkwosky, S.H., Valvani, S.C.: Solubility and partitioning: Solubility of nanoelectrolytes in water. J. Pharm. Sci. **69**, 912–922 (1980)
4. Hoerter, D., Dressman, J.B.: Influence of physiochemical properties on dissolution of drugs in the gastrointestinal tract (review). Adv. Drug Deliv. Rev. **25**, 3–14 (1997)
5. Leuner, C., Dressman, J.: Improving drug solubility for oral delivery using solid dispersions. J. Pharm. Biopharm. **50**, 47–60 (2000)
6. Desai, K.G.H., Kulkarni, A.R., Aminabhavi, T.M.: Solubility of Rofecoxib in the presence of methanol, ethanol, and sodium laurylsulfate at (298.15, 303.15, and 308.15) K. J. Chem. Eng. Data **48**, 942–945 (2003)
7. Yumiko, N., Kozo, T., Kimio, H.: Promoting effect of O-ethylmenthol on the percutaneous absorption of Ketoprofen. Int. J. Pharm. **145**, 29–36 (1996)
8. Vergote, G.J., Vervaet, C., Driessche, I.V.: An oral controlled release matrix pellet formulation containing nano crystalline Ketoprofen. Int. J. Pharm. **219**, 81–87 (2001)
9. Zhonggao, G., Anatoly, N., Lukyanov, S., Anurag, P., Torchilin, V.: Diacyllipid–polymer micelles as nanocarriers for poorly soluble anticancer drugs. Nano Lett. **2**, 979–982 (2002)
10. Lui, C., Groud, K., Desai, H.: Solubility of Valdecoxib in the presence of ethanol & sodium laurylsulfate at (298.15, 303.15, 308.15) K. J. Chem. Eng. Data **49**, 1847–1850 (2004)
11. Cheng, Y., Yang, J.: Solubilization of non-steroidal anti-inflammatory drugs in the presence of tween series surfactants. Phys. Chem. Liq. **44**(3), 249–256 (2006)
12. Florence, A.T., Attwood, D.: Le Basi Chemico-Fisiche Della Technologia Farmaceuit. EdiSES, Napoli (2002)
13. Iked, K., Tomida, H., Yotsuyanagi, T.I.: Micellar interaction of tetracycline antibiotics. Chem. Pharm. Bull. **25**, 1067–1072 (1977)
14. Ullah, I., Baloch, M.K., Durrani, G.F.: Solubility of nonsteroidal anti-inflammatory drugs (NSAIDs) in aqueous solution of non-ionic surfactants. J. Solution Chem. **40**, 1341–1348 (2011)
15. Murphy, J.E.: Clinical Pharmacokinetics, 4th edn. Am. Soc. Health System Pharmacists, Tucson (2008)
16. Thomson, P.D., Melmon, K.L., Richardson, J.A., Cohn, K., Steinbrunn, W., Cudihee, R., Rowland, M.: LIDOCAINE pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. Ann. Intern. Med. **78**(4), 499–508 (1973)
17. Martindale Extra Pharmacopoeia, 27th edn. Pharmaceutical Press, London (1978)
18. Remington's Pharmaceutical Sciences, 15th edn. Mack, Easton (1975)
19. Cereda, C.M., Brunetto, G.B., de Araújo, D.R., de Paula, E.: Liposomal formulations of prilocaine, LIDOCAINE and mepivacaine prolong analgesic duration. Can. J. Anaesth. **53**, 1092–1097 (2006)
20. Carlfors, J., Blute, I., Schmidt, V.: LIDOCAINE in microemulsion—A dermal delivery system. J. Dispersion Sci. Technol. **12**, 467–482 (1991)
21. Scherlund, M., Brodinand, A., Malmsten, M.: Micellization and gelation in block copolymer systems containing local anesthetics. Int. J. Pharm. **211**, 37–49 (2000)
22. Liu, H., Farrell, S., Uhrich, K.: Drug release characteristics of unimolecular polymeric micelles. J. Control. Release **68**, 167–174 (2000)
23. Weinstein, R.D., Muske, K.R., Moriarty, J., Schmidt, E.K.: The solubility of benzocaine, lidocaine, and procaine in liquid and supercritical carbon dioxide. J. Chem. Eng. Data **49**, 547–552 (2004)
24. Drug Bank: http://www.drugbank.ca/drugs/DB00281
25. Hare, G.M., Nqan, J.C.: Density determination of local anaesthetic opioid mixture for spinal anaesthesia. Can. J. Anaesth. **45**, 341–346 (1998)
26. Dar, A.A., Rather, G.M., Das, A.R.: Mixed micelle formation and solubilization behaviour towards polycyclic aromatic hydrocarbons of binary and ternary cationic-nonionic surfactant mixtures. J. Phys. Chem. B **111**, 3122–3132 (2007)
27. Akbas, H., Taliha, M.: Effect of polyoxyethylene chain length and electrolyte on the viscosity of mixed micelles. Turk. J. Chem. **27**, 357–364 (2003)
28. Rathman, J.F., Christian, D.S.: Determination of surfactant activities in micellar solutions of dimethyldodecylamine oxide. Langmuir **6**, 391–395 (1990)
29. Cholewa, E., Burgess, I., Kunze, J., Lipkowsk, J.: Adsorption of N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate (DDAPS), a model zwitterionic surfactant, on the Au(111) electrode surface. J. Solid State Electrochem. **8**, 693–705 (2004)
30. Attwood, D., Florence, A.T.: Surfactant Systems: Their Chemistry, Pharmacy and Biology, pp. 794–795. Chapman and Hall, New York (1983)
31. Stephenson, B.C., Rangel-Yagui, C.O., Adalberto, P., Leoberto, C., Beers, T., Blankschtein, K.: Experimental and theoretical investigation of the micellar-assisted solubilization of Ibuprofen in aqueous media. Langmuir **22**, 1514–1525 (2006)
32. Edwards, D.A., Luthy, R.G., Liu, Z.: Solubilization of polycyclic aromatic hydrocarbons in micellar nonionic surfactant solutions. Environ. Sci. Technol. **25**, 127–133 (1991)

33. Parvaiz, A.B., Aijaz, A.D., Ghulam, M.R.: Solubilization capabilities of some cationic, anionic, and nonionic surfactants toward the poorly water-soluble antibiotic drug Erythromycin. J. Chem. Eng. Data **53**, 1271–1277 (2008)
34. Rangel-Yagui, C.O., Adalberto, P., Leoberto, C.T.: Micellar solubilization of drugs. J. Pharm. Pharmaceut. Sci. **8**, 147–163 (2005)
35. Allen, T.M., Hansen, C.B., Menenez, D.E.: Pharmacokinetics of long-circulating liposomes. Adv. Drug Deliv. Rev. **16**, 267–274 (1995)
36. Canto, G.S., Dalmora, S.L., Oliveira, A.G.: Piroxicam encapsulated in liposomes: characterization and in vivo evaluation of topical anti-inflammatory effect. Drug Dev. Ind. Pharm. **25**, 1235–1239 (1999)