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Original Article

Solubilization of Insoluble and Poorly-Water Soluble Drugs in Micellar Systems

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Abstract

Introduction: This study investigates the micellar solubilization of several insoluble and poorly soluble drugs—clopidogrel bisulfate, ganciclovir sodium, miconazole nitrate, brinzolamide, brimonidine tartarate, and dexamethasone—using sodium dodecyl sulfate (SDS), aerosol-OT (AOT), dodecyl trimethylammonium bromide (DTAB), and cetyltrimethylammonium bromide (CTAB) as surfactants.

Methods: The micellar solubilization experiments were conducted by preparing solutions of the drugs in the presence of SDS, AOT, DTAB, and CTAB micelles. Spectrophotometric measurements were performed at a constant temperature of 298 K to analyze the solubilization efficiency of each surfactant. Phase-solubilization graphs were plotted to visualize the relationship between drug solubility and surfactant concentration.

Results: The results indicated that hydrophobic interactions play a critical role in surfactant solubilization power. AOT was identified as the most effective surfactant among those tested. The solubility tendencies of the drugs in the presence of micelles were discussed based on the calculated K_M values and the spectral behavior of drug molecules.

Conclusion: Micellar solubilization offers a promising approach to characterize drugs with varying solubility profiles—ranging from slightly soluble to insoluble in water. Additionally, surfactant micelles serve as effective biomimetic models for membrane systems in pharmaceutical research. the findings from this study hold implications for drug formulation and design, particularly in addressing solubilization challenges and optimizing pharmaceutical dosage forms.

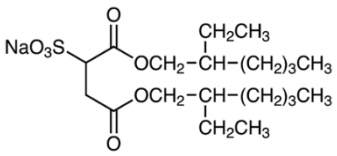
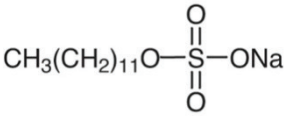
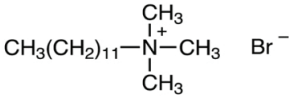
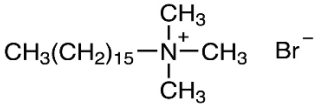
Keywords: Surfactant, poorly soluble drugs, critical micelle concentration, micelle, solubilization

1. Introduction

Solubility is of great importance in developing drug formulations and regulatory standards. Especially insoluble or poorly water-soluble drugs bring about problems in drug formulations at appropriate doses. The many pharmaceutical substances that have limited solubility in water present formidable problems to the acceptable dosage forms e.g. incomplete dissolution in body fluids. Therefore, solubility problems that make transport of drugs difficult are also present in many existing drugs. Solubility is a crucial chemical parameter in developing a drug, since of the current drugs in the industry are either insoluble or sparingly soluble in water. For this purpose, the dissolution method is usually performed to formulate. Among the most preferred methods are pH adjustment, cosolvents, solubilization with micelles (micellar solubilization), and complexation. One of the common methods in pharmaceutical applications practice to improve hydrophobic drugs' solubility is to use micelles since surfactants have many different structures and properties (1-7).

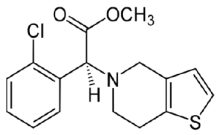
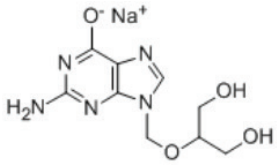
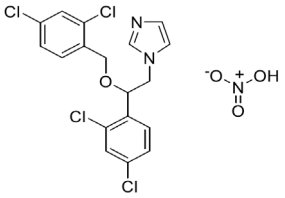
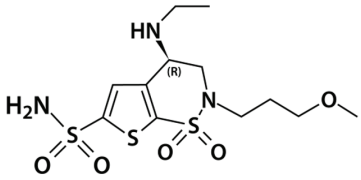
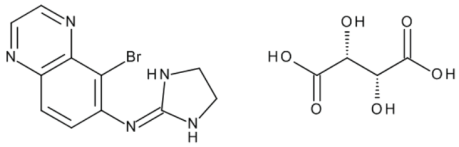
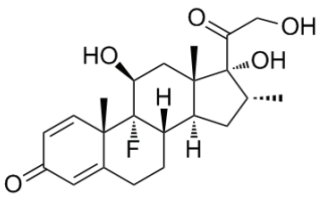
Molecules of surfactant composed of hydrophobic and hydrophilic parts associate in water to form colloidal aggregates called micelle if the concentration exceeds the critical micelle concentration (CMC). Owing to their unique structure and properties, surfactant micelles create a different microenvironment by binding organic ions and molecules in the solution with hydrophobic and/or electrostatic interaction and enhancing the solubility behaviour of molecules. From this point of view, surfactants and their role in pharmaceutical applications are paramount, especially concerning their ability to solubilize hydrophobic drugs. In recent years, there have been numerous studies on micellar solubilization of drugs to improve their

Table 1. CMC and molecular structures of surfactants

Surfactant	Molecular structure	CMC (mmol/L)
AOT $C_{20}H_{37}NaO_7S$		3.30
SDS $C_{12}H_{25}SO_4Na$		8.00
DTAB $C_{15}H_{34}BrN$		10.0
CTAB $C_{19}H_{42}BrN$		0.92

CMC: Critical micelle concentration.

Table 2. Solubility, IUPAC name and molecular structures of the drugs.

Drug	Solubility in water	IUPAC Name
Clopidogrel bisulfate (CBS)	practically insoluble	methyl (2S)-2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c] pyridin-5-yl)acetate;sulfuric acid 
Ganciclovir sodium (GS)	soluble	sodium;2-amino-9-(1,3-dihydroxypropan-2-yloxymethyl)purin-6-olate 
Miconazole nitrate (MN)	limited soluble	1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl] imidazole;nitric acid 
Brinzolamide (BRZ)	limited soluble	(4R)-4-(ethylamino)-2-(3-methoxypropyl)-1,1-dioxo-3,4-dihydrothieno[3,2-e]thiazine-6-sulfonamide 
Brimonidine tartarate (BRT)	practically insoluble	5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)quinoxalin-6-amine;(2R,3R)-2,3-dihydroxybutanedioic acid 
Dexamethasone (DEX)	practically insoluble	(8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one 

efficiency in solutions (8-12). Among the various experimental methods, spectrophotometry is the most preferred technique for the interaction of drugs with surfactants as well as micellar solubilization of hydrophobic drugs (8, 9-14). By considering all above points, the present study examines the solubilization of slightly soluble drugs using sodium dodecyl sulfate (SDS), aerosol-OT (AOT), dodecyltrimethylammonium bromide (DTAB) and cetyltrimethylammonium bromide (CTAB) micelles (Table 1). The properties and molecular structures of pharmaceutical compounds were given in Table 2. The obtained experimental data have been used to plot phase-solubility graphs of all drugs in aqueous solutions of surfactants according to the Higuchi-Connors method (15). Using the phase solubility graphs of drugs in different micellar media, the solubilizing capacity of micelles (K_M) was determined and the drug solubilization capacities of the studied surfactant micelles were compared.

2. Methods

2.1. Materials

CBS, GS, MN, BRZ, BRT, and DEX were supplied from World Medicine Pharmaceutical Company. SDS, AOT, DTAB and CTAB purchased from Sigma Co. All solutions were prepared using doubly distilled conductivity water. DMSO, methanol, and ethanol were of analytical grade. UV-visible spectrophotometer computer connected (Shimadzu 1700) was used to record the UV spectra of drugs in the absence and presence of surfactants.

2.2. Method

Phase-solubility experiments of CBS, GS, MN, BRZ, BRT, and DEX in aqueous solutions of AOT, SDS, DTAB and CTAB were conducted to the shake-flask method of Higuchi and Connors (1965) (15). Surfactant solutions in various quantities in water were prepared depending on their CMC i.e. at below the CMC (premicellar region) and well above the CMC (post micellar region) of surfactants. The concentrations of surfactants varied from 0.1 mM to 50 mM (from premicellar to micellar region). Then an excess of the drug was added in glass flasks and shaken up with surfactant at 298 K for 24 h to reach the equilibrium. After filtration, the total solubilized concentration of the drugs was analysed by UV absorbance spectroscopy. The calibration curve of drugs was constructed using UV-visible spectrophotometer absorption data. The drug concentrations dissolved in the presence of surfactants were determined using the calibration curves of the drugs constructed in appropriate solvents such as methanol, ethanol or DMSO. The detailed micellar solubilization experimental procedure has been previously reported. (8,9,15).

2.2.1. Determining the solubilizing capacity of micelles (K_M)

The solubility of a substance in the presence of a surface active agent can be explained by the two-phase model which assumes that micellization only occurs above the CMC and that the monomer concentration remains constant, independent of the total surfactant concentration, as described by the following equation (8,10,11,16,17).

$$S_m = K_M (C_S - C_{CMC}) + S_0$$

Here, CS is the surfactant concentration and CCMC is the critical micelle concentration of each surfactant. Sm and S0 are solubility of the drug in the presence and absence of surfactants, respectively. Determining the slope of the solubilization curve the solubilizing capacity of micelles (K_M) can be calculated and given in mmol/L (mM).

3. Results

3.1. Clopidogrel bisulfate (CBS)

CBS was practically insoluble in water. The maximum absorbance of CBS was recorded at 203 nm in methanol, based on the valid concentration range of Lambert-Beer Law. To compare the influence of micelles, the corresponding absorption spectra of CBS in the absence and the presence of DTAB, CTAB, SDS and AOT micelles are shown in Fig 1.

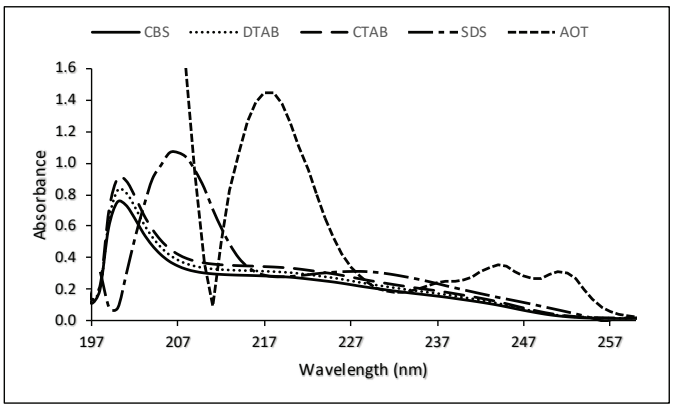


Figure 1. Absorption spectra of CBS in micellar solutions of DTAB, CTAB, SDS, AOT and in methanol.

As seen in Fig 1 the λmax of CBS shifted from 203 nm to 207 nm in the presence of SDS micelles while a significant red shift was observed from 203 nm to 219 nm in the presence of AOT micelles. In addition, as the surfactant concentration increased, an increase in the absorbance of CBS was observed. However, no significant shift was observed for CBS in the presence of DTAB and CTAB micelles. The solubility of CBS increased with the increase in AOT and SDS micelle concentration. The solubilization capacities (K_M) of AOT and SDS micelles were determined and are presented in Table 3. The variation in the solubility of CBS as a function of the micelle concentration of DTAB, CTAB, AOT, and SDS is shown in Fig. 2.

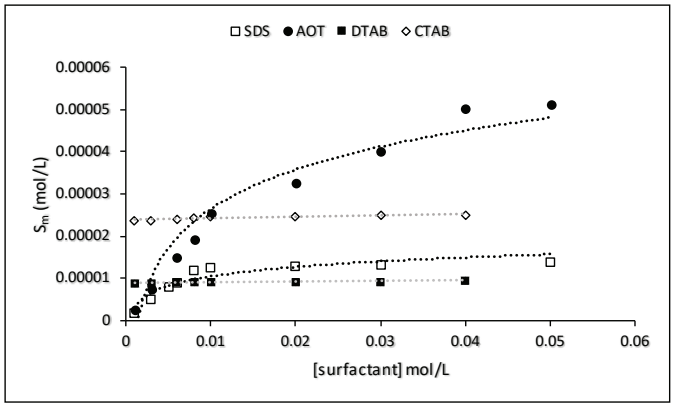


Figure 2. Phase–solubility plot of CBS in DTAB, CTAB, SDS and AOT micelles (298 K)

3.2. Brimonidine tartrate (BRT)

Brimonidine tartrate (BRT) was practically insoluble in water. The maximum absorbance of BRT was recorded at 247 nm in DMSO, based on the valid concentration range of Lambert-Beer Law. In order to compare the influence of micelles, the corresponding absorption spectra of BRT in the absence and the presence of DTAB, CTAB, SDS and AOT micelles are shown in Fig 3.

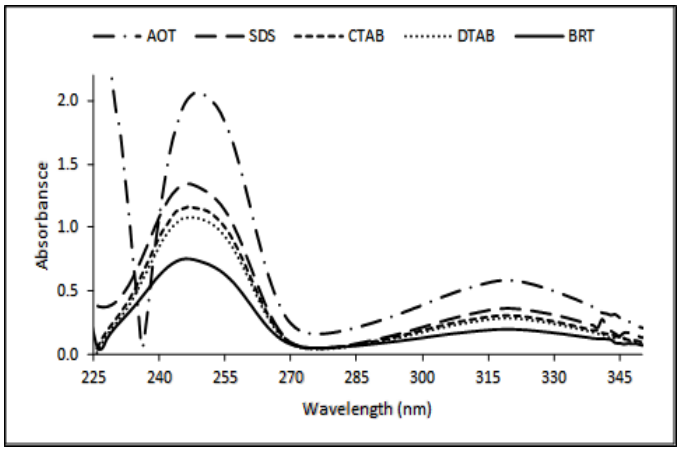


Figure 3. Absorption spectra of BRT in micellar solutions of DTAB, CTAB, SDS, AOT and in DMSO.

The λmax of BRT shifted slightly from 247 nm to 250 nm in the presence of all micelles. However, with AOT and SDS concentration increased and also an increase in the absorbance of BRT was observed. Since no significant change was observed in the absorbance of BRT in the presence of DTAB and CTAB micelles, K_M values could not be calculated. Solubility of BRT increased with the increase in AOT and SDS micelle concentration. The solubilization capacity (K_M) of SDS and AOT micelles were calculated and are given in Table 3. The variation of solubility of CBS as a function of micelles concentration of DTAB, CTAB AOT and SDS are shown in Fig 4.

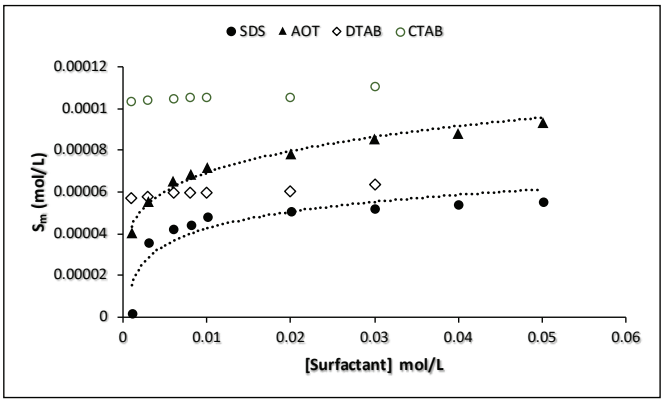


Figure 4. Phase–solubility plot of BRT in DTAB, CTAB, SDS and AOT micelles (298 K)

3.3. Dexamethasone (DEX)

Dexamethasone (DEX) was practically insoluble in water. The maximum absorbance of DEX was recorded at 242 nm in ethanol, based on the valid concentration range of Lambert-Beer Law. In

order to compare the influence of micelles, the corresponding absorption spectra of DEX in the absence and the presence of DTAB, CTAB, SDS and AOT micelles are shown in Fig 5.

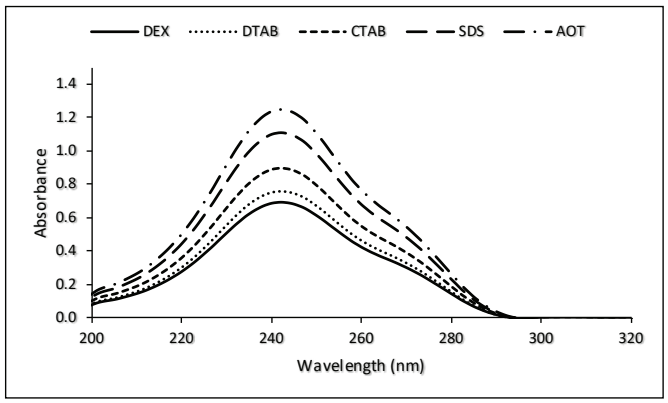


Figure 5. Absorption spectra of DEX in micellar solutions of DTAB, CTAB, SDS, AOT and in ethanol.

As seen in Fig 5 the λmax of DEX did not change in the presence of micelles but with the surfactant concentration increased and also an increase in the absorbance of DEX was observed. However, the solubility of DEX enhanced with the increase in DTAB, CTAB, SDS, and AOT micelle concentration. The solubilization capacity (K_M) of micelles were calculated and given in Table 3. The variation of solubility of DEX as a function of micelles concentration of DTAB, CTAB, AOT and SDS are shown in Fig 6.

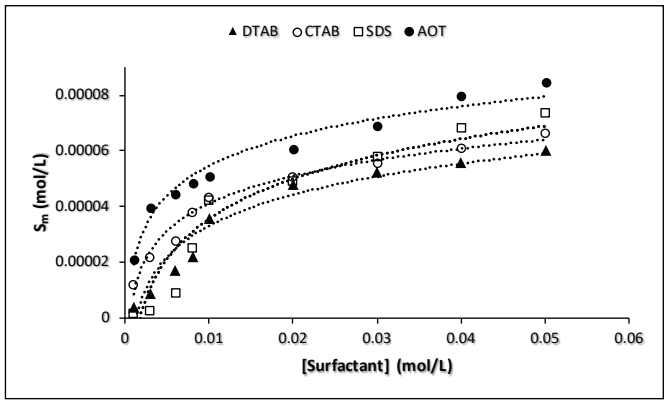


Figure 6. Phase–solubility plot of DEX in DTAB, CTAB, SDS and AOT micelles (298 K)

3.4. Miconazole nitrate (MN)

The solubility of miconazole nitrate (MN) in water was limited. MN exhibited two maximum absorbance at 231 and 238 nm in DMSO. Based on the valid concentration range of Lambert-Beer Law, the absorbance variation of MN was observed at 231 nm. To compare the influence of micelles, the corresponding absorption spectra of MN in the absence and the presence of DTAB, CTAB, SDS and AOT micelles were shown in Fig 7. As seen in Figure 7, no shift was observed in the presence of cationic DTAB and CTAB micelles while the presence of SDS and AOT affected the absorbance spectrum of MN with a significant red shift. Besides the λmax of MN at 238 nm disappeared.

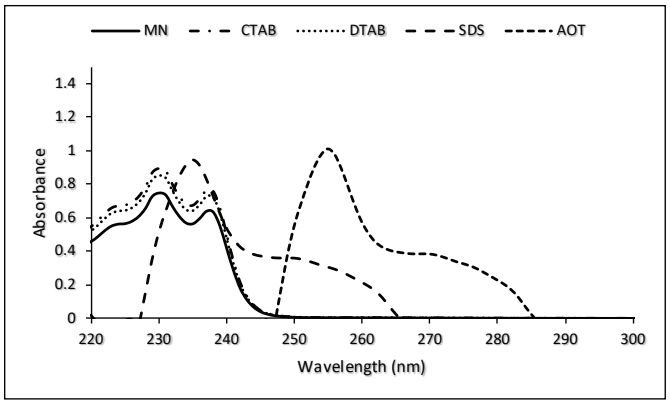


Figure 7. Absorption spectra of MN in micellar solutions of DTAB, CTAB, SDS, AOT and in DMSO.

The solubility of MN enhanced with the increase in DTAB, CTAB, SDS, and AOT micelle concentration. The solubilization capacity (K_M) of micelles were calculated and given in Table 3. The variation of solubility of MN as a function of micelles concentration of DTAB, CTAB AOT and SDS are shown in Fig 8.

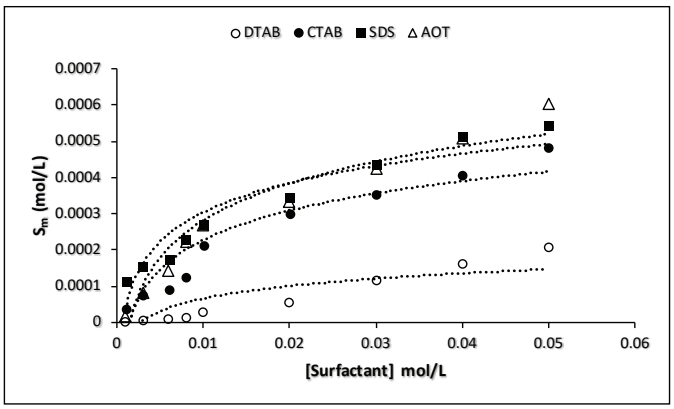


Figure 8. Phase–solubility plot of MN in DTAB, CTAB, SDS and AOT micelles (298 K)

3.5. Brinzolamide (BRZ)

The solubility of Brinzolamide (BRZ) in water was limited. The maximum absorbance of BRZ was recorded at 255 nm in ethanol, based on the valid concentration range of Lambert-Beer Law. In order to compare the influence of micelles, the corresponding absorption spectra of BRZ in the absence and the presence of DTAB, CTAB, SDS and AOT micelles are shown in Fig 9.

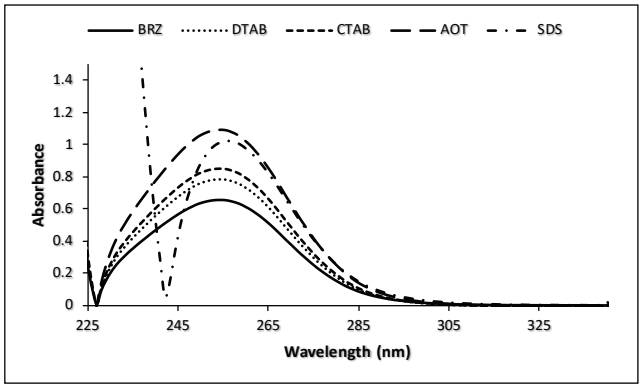


Figure 9. Absorption spectra of BRZ in micellar solutions of DTAB, CTAB, SDS, AOT and in ethanol.

As seen in Fig 9 the λmax of BRZ did not change in the presence of DTAB and CTAB micelles but with the surfactant concentration increased and also an increase in the absorbance of BRZ was observed. However, λmax of BRZ shifted from 255 to 257 nm in the presence of SDS and AOT micelles. The solubility of BRZ enhanced with the increase in DTAB, CTAB, SDS, and AOT micelle concentration. The solubilization capacity (K_M) of micelles were calculated and are given in Table 3. The variation of solubility of BRZ as a function of micelles concentration of DTAB, CTAB AOT and SDS are shown in Fig 10.

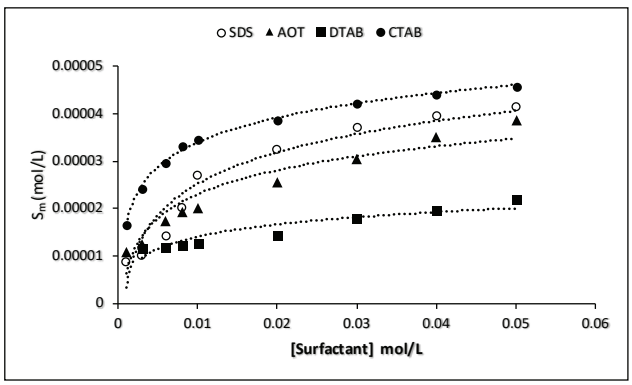


Figure 10. Phase–solubility plot of BRZ in DTAB, CTAB, SDS and AOT micelles (298 K)

3.6. Ganciclovir sodium (GS)

Ganciclovir sodium (GS) was freely soluble drug in water. The maximum absorbance of GS was recorded at 255 nm in water based on the valid concentration range of Lambert-Beer Law. In order to compare the influence of micelles, the corresponding absorption spectra of GS in the absence and the presence of DTAB, CTAB, SDS and AOT micelles were shown in Fig 11.

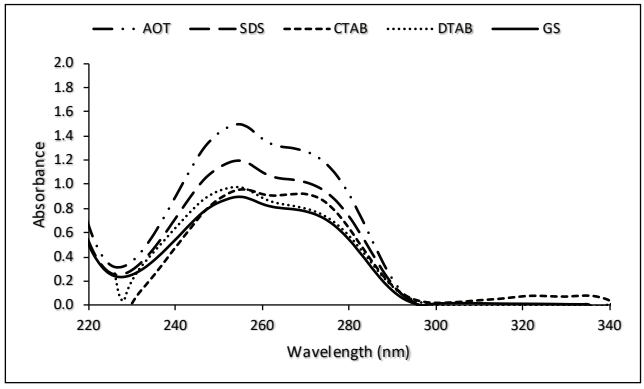


Figure 11. Absorption spectra of GS in micellar solutions of DTAB, CTAB, SDS, AOT and in water.

The λmax of GS did not change in the presence of DTAB, CTAB, SDS and AOT micelles but with the surfactant concentration increased an increase in the absorbance of GS was observed. The solubility of GS enhanced with the increase in DTAB, CTAB, SDS, and AOT micelle concentration. The solubilization capacity (K_M) of micelles were calculated and given in Table 3. The variation of solubility of GS as a function of micelles concentration of DTAB, CTAB AOT and SDS are shown in Fig 12.

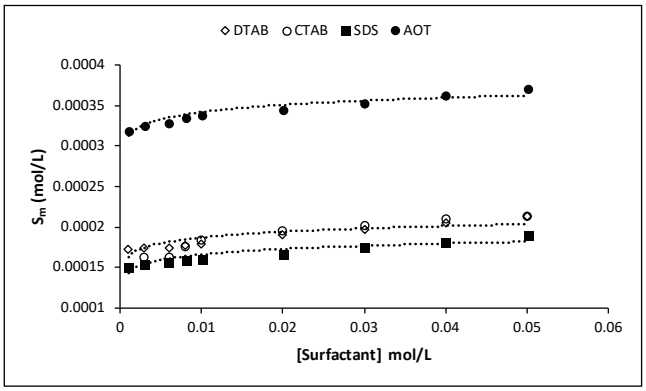


Figure 12. Phase–solubility plot of GS in DTAB, CTAB, SDS and AOT micelles (298 K)

4. Discussion

Each of the drugs used in this study had different chemical structures and properties. CBS, BRT and DEX were practically insoluble in water whereas MN and BRZ were sparingly soluble in water. Only GS was freely soluble in water among the drugs studied. It was observed that the solubility of drugs, in general, was almost constant until CMC. Then the significant increase observed after CMC indicated the solubilization of each drug molecule by the micelles. The solubilization capacities (K_M) of the selected micelles as models were calculated from the linear relationship between C_M and Sm which was valid for the postmicellar region and are given in Table 3. Fig 13 has illustrated C_M versus Sm as an example of determining the solubilization capacity of micelles.

Table 3. K_M (mmol/L) values of DTAB, CTAB, SDS and AOT for CBS, GS, MN, BRZ, BRT and DEX at 298 K. (Error limit in K_M ± 3%. The correlation coefficients are good in all cases (R^2 >0.9987).

CBS			
DTAB (mmol/L)	CTAB (mmol/L)	SDS (mmol/L)	AOT (mmol/L)
-	-	0.03	0.9
BRZ			
DTAB (mmol/L)	CTAB (mmol/L)	SDS (mmol/L)	AOT (mmol/L)
0.2	0.3	0.4	0.5
DEX			
DTAB (mmol/L)	CTAB (mmol/L)	SDS (mmol/L)	AOT (mmol/L)
0.4	0.6	0.8	0.9
MN			
DTAB (mmol/L)	CTAB (mmol/L)	SDS (mmol/L)	AOT (mmol/L)
5.1	6.4	7.2	8.5
BRT			
DTAB (mmol/L)	CTAB (mmol/L)	SDS (mmol/L)	AOT (mmol/L)
-	-	0.2	0.6
GS			
DTAB (mmol/L)	CTAB (mmol/L)	SDS (mmol/L)	AOT (mmol/L)
0.7	0.7	0.8	0.9

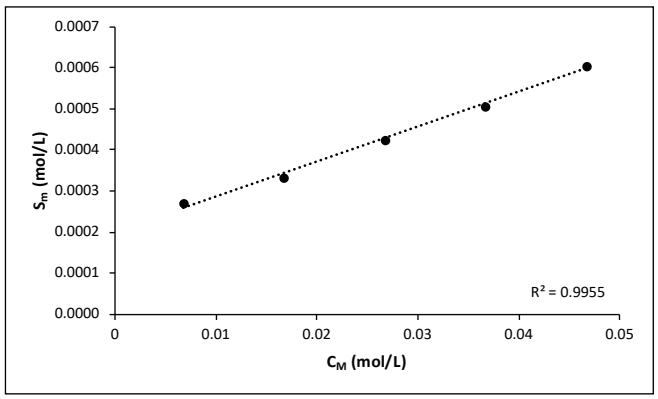


Figure 13. A representative plot determining the solubilization capacity of AOT micelles for MN.

As seen in Table 3, the solubilization capacities of the micelles contributed to the solubilization of drugs. On the other hand, the solubilization capacities of water-insoluble drugs CBS and BRT could not be calculated because no significant change was observed in their absorbance in the presence of cationic DTAB and CTAB. However, DEX, which is also insoluble in water, showed a tendency to dissolve in the presence of both types of surfactant micelles. This can be explained by hydrophobic and/or electrostatic interactions which constitute the basis of the interactions between drugs and surfactants. Surfactant micelles create a different microenvironment for substances by binding ions and molecules of drug to themselves through hydrophobic and/or electrostatic interaction. Therefore, the interaction of the drug with the micelle, their orientation varied in this microenvironment. While electrostatic attraction played a major role in the incorporation of drug ions into oppositely charged micelles, there was also a hydrophobic interaction depending on the structure of the drug. Mostly, the hydrophobic interaction assumes the role of driving force in solubilization, and in many cases, especially in environments where electrostatic repulsion was present, the hydrophobic interaction often predominated. All drugs used in the study were cationic (basic) except DEX which was strongly acidic). Accordingly, the low solubility tendency or no solubility tendency observed in the presence of DTAB and CTAB could be explained by the dominance of the hydrophobic interaction by the electrostatic repulsion forces between drug and micelles. For instance; since CBS and BRT had cationic character, the lack of solubilization tendency with DTAB and CTAB cationic micelles could be explained by the dominance of electrostatic repulsion over hydrophobic interaction. The solubilization tendency of DEX in the presence of DTAB and CTAB micelles might be expressed by the fact that DEX had an anionic character and therefore electrostatic attraction forces with DTAB and CTAB micelles played a role together with the hydrophobic interaction. However, the solubilization efficiency with anionic SDS and AOT micelles was a result of the dominant character of both electrostatic attraction and hydrophobic interaction. The strongest solubilization capacity observed in the presence of AOT could be explained by the fact that CMC of AOT (3.3 mmol/L) had more hydrophobic character than SDS (CMC: 8.0mM mol/L) (3).

In addition to monitoring variation of the absorbance change in spectrophotometric measurements used in solubilization and interaction studies, changes in the observed wavelength provided information about the degree of interaction. The shift of the wavelength at which a molecule exhibits maximum absorbance towards red (bathochromic effect) and shorter wavelengths in the presence of surfactant micelles was called blue shift (hypsochromic effect). There were changes in the absorption spectrum of the substance depending on the degree of interaction of the substance with the surfactant micelles, that was, where the substance is located in the micelle. A schematic representation of the micellar solubilization of a pharmaceutical compound was illustrated in Fig 14.

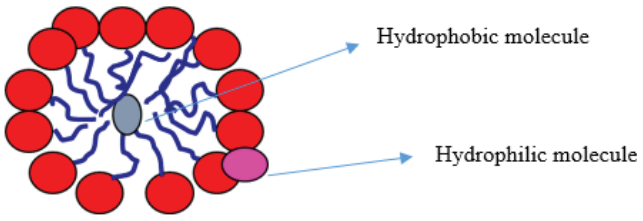


Figure 14. Possible location of a drug molecule in micelles

The further the wavelength of the substance shifts toward the red side in the presence of micelles, indicating that it moves toward the micelle core, i.e. the more hydrophobic region (8-10,18) This can be clearly seen when the absorption spectrum graphs of drugs in the presence of micelles are examined.

GS was the only water-soluble drug used in the study and has hydrophilic character. No significant shift in the wavelength of GS was observed in the presence of micelles. While the wavelength at which GS showed maximum absorbance did not change in the presence of DTAB and CTAB, it shifted from 255 to 256 and 257 nm in the presence of SDS and AOT, respectively. Whereas, MN, which had limited solubility in water, exhibits maximum absorbance at 231 and 238 nm. While no significant change was observed in the presence of CTAB and DTAB, it was observed that the wavelength shifted to 235 and 255 nm in the presence of SDS and AOT, respectively. This showed that the solubilization mechanism of MN was towards the micelle core in the presence of anionic micelles. The same situation applied to BRT, which had limited solubility in water. While no significant change was observed in the presence of DTAB and CTAB, the wavelength at 247 nm shifted to 249 nm in the presence of anionic micelles. The small shift in the wavelength of BRT observed in the presence of micelles indicates that the solubilization mechanism occurs at the micelle surface. When the solubilization results of water-insoluble CBS were examined, an increase in absorbance was observed in the presence of anionic and cationic micelles, while no significant shift was observed at the maximum absorbance wavelength of 201 nm. The solubilization results of water-insoluble CBS also showed, an increase in absorbance in the presence of anionic and cationic micelles, but no significant shift was observed at the maximum absorbance wavelength of 201 nm. This behaviour indicated that the solubilization mechanism of CBS into micelles occurs on the micelle surface. The same situation was applied to the solubilization mechanism of water-insoluble BRZ. While no change was observed in the presence of DTAB and CTAB, it was observed that the wavelength of BRZ at 255 nm, shifted to 257 nm in the presence of SDS and AOT micelles i.e. solubilization mechanism occurs on the micelle surface. Among the water-insoluble drugs, the most significant wavelength shift was observed in the case of DEX. The wavelength of DEX at 247 nm shifted to 253 nm in the presence of SDS and AOT micelles. This shift in the observed wavelength indicated that the solubilization mechanism occured from the micelle interface toward the micelle core.

Experimental data obtained from the presented study showed that as the hydrophobicity of surfactants increases the micellar solubilization of drugs is enhanced, especially for insoluble or poorly soluble drugs in water. The lower the CMC value of a surfactant, the more hydrophobic the micelles. The micellar solubilization efficiency followed the order for cationic micelles DTAB < CTAB and for anionic micelles SDS < AOT micelles. The most effective surfactant was also found to be AOT which has a two-branched hydrophobic tail that contributes to the highest micellar solubilization capacity. From this perspective, AOT had a low CMC value and the highest hydrophobic character to solubilize drug molecules with micelles. Therefore, it could be concluded that AOT played a very important role in increasing the solubility of drugs from a pharmacological point of view.

5. Conclusion

Micellar solubilization provided the potential to characterize slightly, sparingly, poorly, and insoluble drugs in water. Furthermore, surfactant micelles have been widely used as a biomimetic model for membrane systems in pharmaceutical research. The main purpose of this paper was to deal with the solubilization of different kinds of drugs by the various types of micelles. In our point of view, the results of this study can be used in drug formulation and design related to solubilization problems as well as assessing the pharmaceutical dosage forms.

Conflicts of interest: The authors have no conflicts of interest to declare.

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