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Research article

Self-assembling of surface active drug amitriptyline hydrochloride in association with additives: Role of surface activity in the pharmaceutical applications

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Abstract

The self-assembling of surface active antidepressant drug amitriptyline hydrochloride (AMT) has been studied to determine the micellar solution behavior in the presence of polar (methanol and ethanol), dipolar aprotic solvents (acetone and 1,4 dioxane), salt (NaCl) and water structure-breakers (urea) at 298 K using surface tension and electrical conductivity measurements. The counterion binding parameter and the ionization degree of AMT micelles have been determined by electrical conductivity measurements. To better analyze the influences of additives on micellar behavior of AMT, surface features of AMT were defined using Gibbs Adsorption Isotherm in water and in association with various amounts of additives conducted by surface tension measurements. Both conductometric and surface tension experiments were also used to detect the critical micelle concentration (CMC) of AMT. The experimental results indicated that CMCs of AMT were influenced in the presence of additives. Self-aggregation of AMT was totally inhibited when methanol, ethanol, acetone, 1,4 dioxane, and urea concentration is attained to a certain value while the CMC of AMT reduced with the increase in concentration of NaCl.

Keywords: *Amitriptyline hydrochloride; amphiphilic drugs; conductivity; critical micelle concentration; surface active drugs; surface tension*

1. Introduction

Most of drug molecules are surface active and tend to aggregate in aqueous solution due to their surface activities and these features of them relate well with their pharmacological action (Attwood and Florence, 1983; Attwood et al., 1989; Attwood, 1995; Schreier et al., 2000; Taboada et al., 2000; Junquera et al., 2001; Srivastava and Nagappa, 2005; Alam et al., 2008). Amitriptyline hydrochloride (AMT), one of the surface active drugs, is a member of tricyclic antidepressant drugs (TCA). There is an alkyl amine side chain in its molecular structure conferring on “surfactant-like” behavior with its planar tricyclic ring system (Fig. 1). Among the numerous studies of amphiphilic drugs, the study of their aggregation properties represent an area of continued research interest (Din et al., 2010; Ali et al., 2013; Rub et al., 2013, 2014; Sharma et al., 2014). Within this scope, excellent studies on micellization behavior of AMT are already available, thus this study aims to make an effort to indicate effects of additives which are contributing to the mechanism of surface activity on micelle formation of AMT

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in detail. Surface activity of AMT also relates with its pharmacological action because of exerting its activity by interacting with biological membranes. Furthermore, the mechanism of the self-assembling of amphiphilic drugs plays a crucial role in the pharmaceutically important process such as drug delivery systems. However, it is essential to have extent practice of the process about the associations of drugs since drugs are always used in combination with different additives (Erdinc et al., 2010; Alam et al., 2011; Gokturk and Var, 2012; Ozcam, 2015; Ozan and Gokturk, 2021). This study deals with describing the association of AMT with the additives in order to express the effects of additives on micellization behavior and interfacial properties of AMT using surface tension and conductivity measurements. Both of these methods were performed to observe the micelle formation of AMT alone and in the presence of various amounts of methanol (MeOH), ethanol (EtOH), acetone (Ace), dioxane (Diox), urea, and NaCl in aqueous media at 298 K. MeOH and EtOH which form H bonds with water were used to examine the effect on micelle formations of AMT. To see the influence of dipolar aprotic solvents on micelle formation of AMT Ace and Diox which form strong H bonds with water were used. Urea, known as a water structure breaker, were also used to see its effect on the micelle formation mechanism of AMT. In order to find out the effect of physiologic additives such as salt utilized in drug administration, similar experiments were employed in the presence of 0.45% (w/v), 0.9% NaCl (w/v).

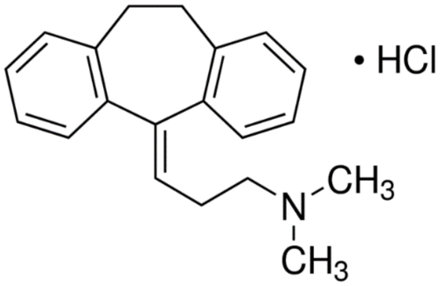

Fig. 1. Chemical structure of AMT.

2. Materials and methods

AMT was provided from Sigma (Germany) using without purification (>98.0%purity). Methanol (MeOH), ethanol (EtOH), acetone (Ace), dioxane (Diox), and urea were purchased from E. Merck. NaCl was supplied from Merck. The chemicals are spectroscopic grade products. All experiments were performed with doubly distilled conductivity water.

Micellization of AMT in the presence of various amount of MeOH, EtOH, Ace, Diox, urea, and NaCl have been studied and the experiments were conducted by surface tension and electrical conductivity measurement analyses at 298 K.

2.1. Surface tension measurements

Sigma 701 KSV Instruments computer-controlled tensiometer (Helsinki, Finland) was used to study surface tension measurements. The Wilhelmy-plate method was employed. The presented surface tension values in this study are mean quantities and all surface tension reading were taken in triplicate. The standard deviation of the mean did not deviate ±1.1%. The accuracy of measurements within was 0.01 mN/m. The data of surface tension of AMT in water and the presence of various amounts of additives were used to specify the minimum area per molecule (A_{min}) and maximum surface excess concentration (Γ_{max}) of surface active drug AMT based on a plot of the surface tension (γ) against AMT concentrations in water and in the presence of additives. Gibbs Adsorption Isotherm was applied to analyze the changes of surface properties i.e.Γ_{max} and A_{min}. Here, C is the concentration of AMT, T is the temperature in Kelvin and R is the gas constant.

$$\Gamma_{\max} = -\frac{1}{RT}\left(\frac{d\gamma}{d\ln C}\right) \tag{1}$$

A_{min} (Å^2 molecule^{-1}) is determined from the value of Γ_{max} by the Eq.2. (N_A is the Avogadro constant);

$$A = \frac{1}{N_A \Gamma_{\max}} \tag{2}$$

(Florence and Atwood 1998; Gokturk and Tamer, 2018).

2.2. Electrical conductivity measurements

WTW Inolab (pH/Cond 740) (automatic temperature compensated) conductivity meter were used for electrical conductivity measurements. The cell constant is 1.0 cm^{-1} with ± 1% uncertainty in measurement. Standard KCl solutions was used to calibrate the constant of the conductivity cell and checked at least three times during the study. The specific conductivity (κ) measurements provided useful knowledge on the electrical conductivity of the AMT solutions in water and in the presence of additives. The conductometric method describes the concentration dependence of conductivity on the basis of attaining of a breaking point on the curves. The breaking point seen in the plot corresponds to micelle formation. There are two straight lines having different slopes in the concentration dependence of specific conductivity (κ) plots. From these plots, the counterion binding parameter (β) can be determined from the ratio of the slopes of the two intersecting lines. The values of the ionization degree of the micelles (α) can also be calculated by;

$\beta = 1 - \alpha$ (Hiemenz and Rajogopalan, 1986; Gokturk and Aslan, 2014).

3. Results and discussion

The CMC of amphiphilic drug AMT was determined by measuring a change in the surface tension and electrical conductivity with various concentrations of AMT in water and in the presence of additives as described in detail previously (Florence and Atwood 1998; Gokturk and Aslan, 2014; Gokturk and Tamer, 2018). The CMC of AMT obtained through different measurements are consistent with the values in literature (3.48x10^{-2} mol/L) (Schreier et al., 2000). The CMC values of AMT determined by conductometry and tensiometry techniques in water and the presence of additives were presented in Table 1. The micellization characteristics of AMT in the absence and presence of additives in aqueous solutions have been conducted by (i) surface tension, and (ii) electrical conductivity measurements, and the effects of various concentrations of additives (MeOH, EtOH, Diox, Ace, urea and NaCl) on micellar and interfacial properties of AMT were discussed.

3.1. Determination of surface properties of AMT (Γ_{max} and A_{min})

The influence of additives on the interfaces of AMT has been detected by using surface tension measurements. The surface excess amount of AMT was found by applying the Gibbs adsorption isotherm (Eq. 1 and Eq. 2). The effects of additives on surface properties of amphiphilic drug AMT were plotted by the surface tension (γ) against AMT concentration (Fig. 2, 3, 4, 5, 6 and 7). The values of AMT obtained from tensiometry in the presence of additives were observed to be lower than those in the absence of all amount of studied additives except for urea.

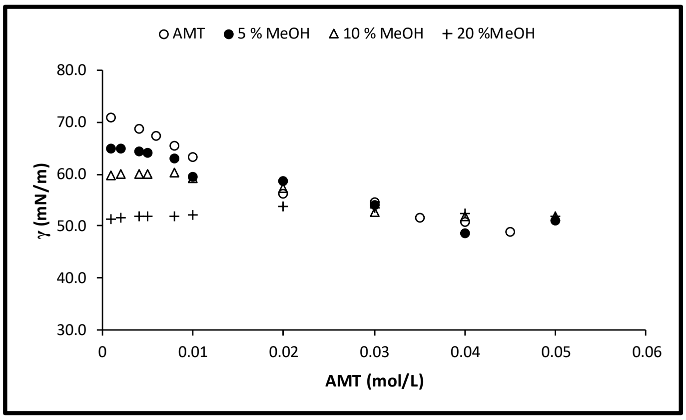

Fig. 2. Surface tension measurements vs. molar concentration of AMT in water and the presence of 5, 10 and 20 % (v/v) MeOH at 298 K.

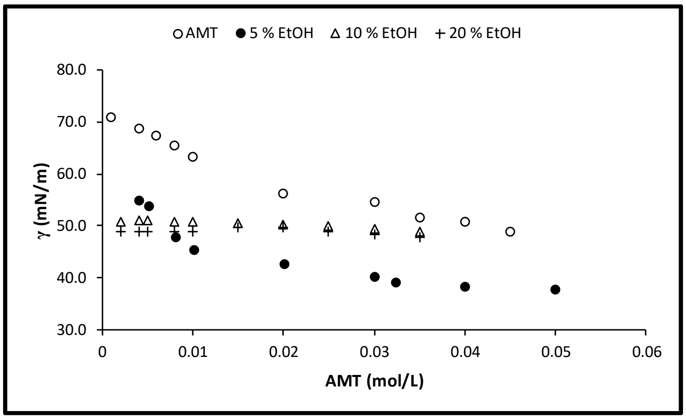

Fig. 3. Surface tension measurements vs. molar concentration of AMT in water and the presence of 5, 10 and 20 % (v/v) EtOH at 298 K.

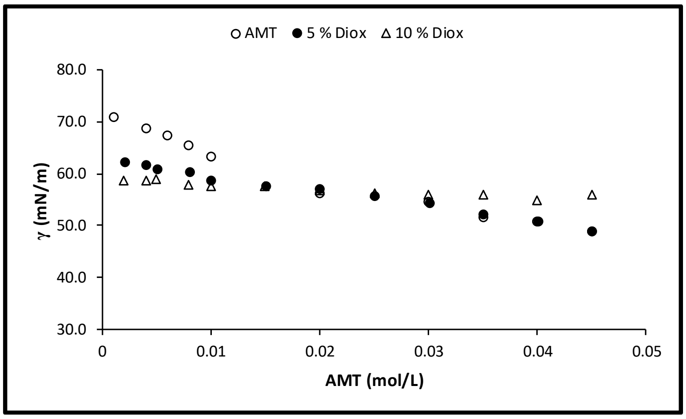

Fig. 4. Surface tension measurements vs. molar concentration of AMT in water and the presence of 5 and 10 % (v/v) Diox at 298 K.

As seen in Fig. 2, 3, 4 and 5, with the increase in MeOH, EtOH, Diox and Ace concentrations, micellization of AMT diminished, and inhibited at the additive concentration of 10 % (v/v). As presented in Table 1, the presence of NaCl decreased the CMC of AMT. On the other hand, the CMC of AMT increased in the presence of MeOH, EtOH, Diox and Ace. In the case of urea there was seen no significant decrease in surface tension values of AMT. However, the CMC of AMT increased depending on the urea concentration due to its modifying influence on the aqueous solution properties.

The adsorbed amount and the adsorbed area of AMT were specified based on Eq. 1. Applying Gibbs Equation to determine

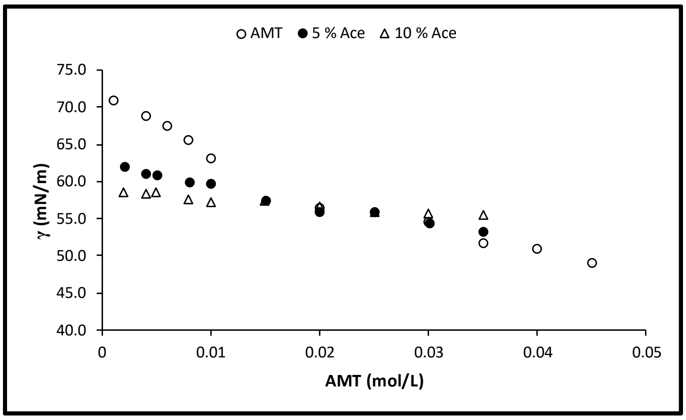

Fig. 5. Surface tension measurements vs. molar concentration of AMT in water and the presence of 5 and 10 % (v/v) Ace at 298 K.

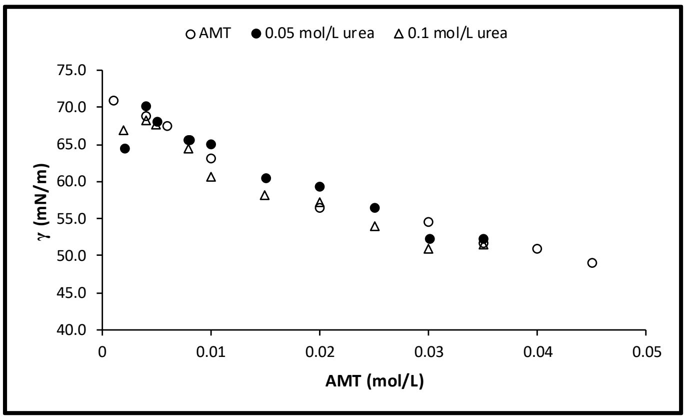

Fig. 6. Surface tension measurements vs. molar concentration of AMT in water and the presence of 0.05 M and 0.1 mol/L urea at 298 K.

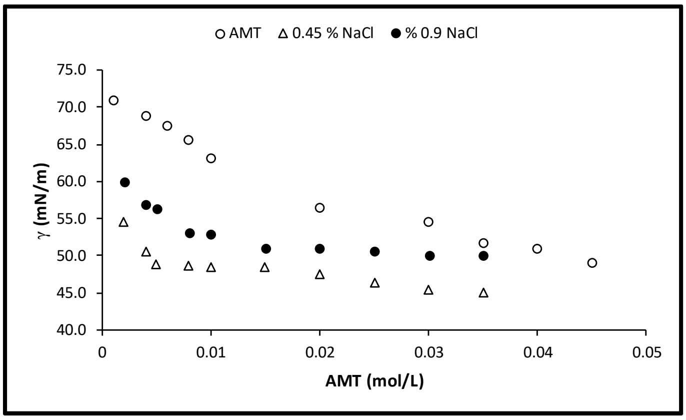

Fig. 7. Surface tension measurements vs. molar concentration of AMT in water and the presence of 0.45 and 0.9 (w /v) NaCl at 298 K.

quantitative surface properties was depicted in Fig. 8 and 9 for EtOH and NaCl, respectively, as representative plots. Table 1 indicates the calculated Γ_{max} and A_{min} values. As seen in the data given in Table 1 Γ_{max} value of AMT was reduced and A_{min} increased in the presence of various amounts of additives. The change in tensiometry values and estimated surface parameters showed the incorporation tendency of AMT increased in the presence of additives. This can be explained by the addition of additives decreasing the electrostatic repulsion between the head groups of AMT, and thereby incorporating much more AMT molecules at the interface. This is correlated with the fact that greater value of A_{min} i.e. additives increased the penetration of AMT at the interface. No marked shift on surface parameters of AMT observed in the presence of urea which can also be explained by its superior water structure breaker properties for the interaction of AMT compared to that of MeOH, EtOH, Ace, Diox and NaCl.

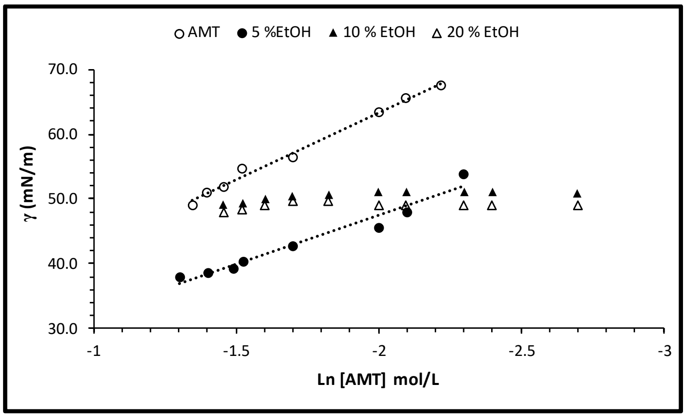

Fig. 8. Gibbs Adsorption Isotherm plots of AMT in water and the presence of 5, 10 and 20 % EtOH at 298 K.

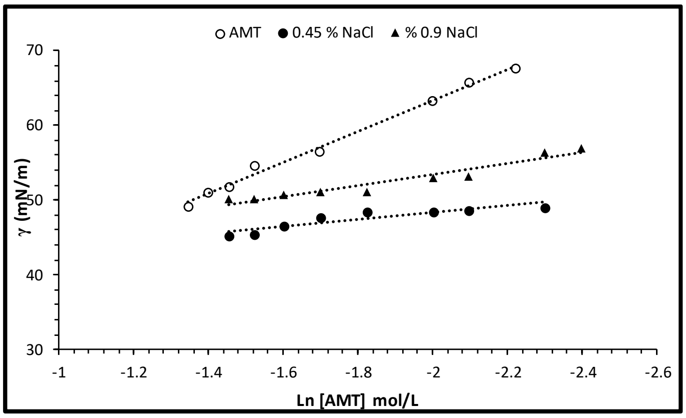

Fig. 9. Gibbs Adsorption Isotherm plots of AMT in water and the presence of 0.45 and 0.9 % (w/v) NaCl at 298 K.

3.2. Determination of degrees of ionization and counterion binding parameter (α and β)

In order to see the influence of electrostatic interactions on solution behavior of AMT molecules conductivity measurements were performed. For this purpose, variation of conductivity of AMT was monitored in the absence and presence of various concentrations of additives in aqueous solutions. The measured specific conductivities were plotted versus the AMT concentration. Since the same behavior was observed, only the influence of various concentrations of EtOH, Diox and NaCl on the electrochemical properties of AMT are shown in Figs. 10, 11 12 and 13 respectively, as representative plots. As seen in these figs. there is a significant loss of ionic charges since a fraction of the counterions is limited to the micellar surface.

β values estimated from the ratio of the slopes gives the average number of counterions per AMT ion in the micelle (Evans, 1956; Rosen, 1978; Gokturk and Aslan, 2014). Calculated α and β values of AMT were listed in Table 1. In the presence of additives, the same behavior has been observed. β values increased and α values decreased in comparison with the absence of additives in solutions.

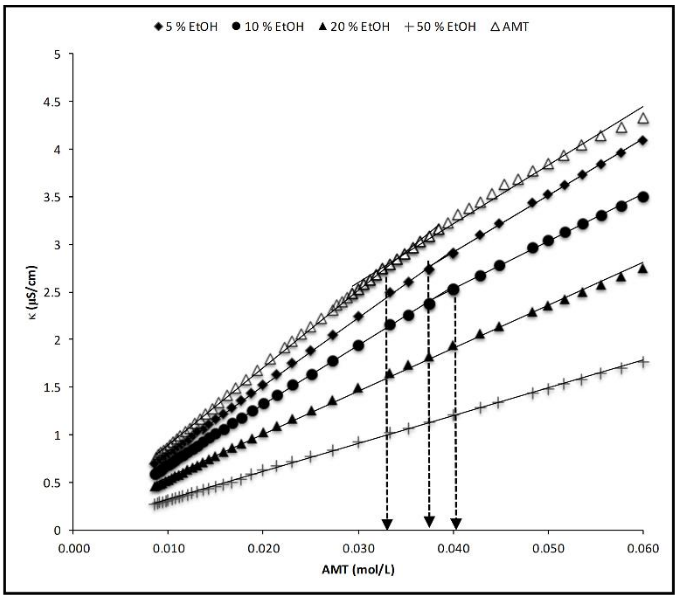

Fig. 10. Specific conductivity vs. molar concentration of AMT in water and the presence of 5, 10, 20 and 50 % (v/v) EtOH and CMC at 298 K (arrows show the CMC).

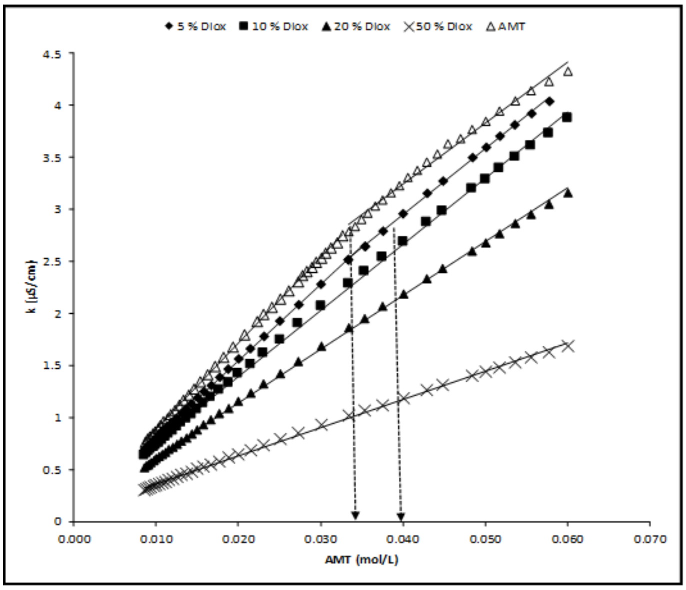

Fig. 11. Specific conductivity vs. molar concentration of AMT in water and the presence of 5, 10, 20 and 50 % (v/v) Diox and CMC at 298 K (arrows show the CMC).

The rate of neutralized charges in a micelle to the total number of surfactant molecules in the micellar phase is defined as the incorporation degree of counterion to the micelle (Stellner and Scamehorn, 1989). The surfactant molecules show different behavior in aqueous solutions depending on their concentration. The low concentration of surfactant solutions behaves as simple electrolyte that involve free monomers in the aqueous solutions. Besides, solution behavior changes with the increase in surfactant concentration. At the concentrations above the CMC, most of the surfactant molecules aggregate to form micelles and the total monomer concentration remains almost constant. Accordingly, after the CMC the gradient of conductivity decreases which means that a larger area of micelle surface, for a certain amount of counterions and the incorporation of additives to AMT micelles occurs more remarkably.

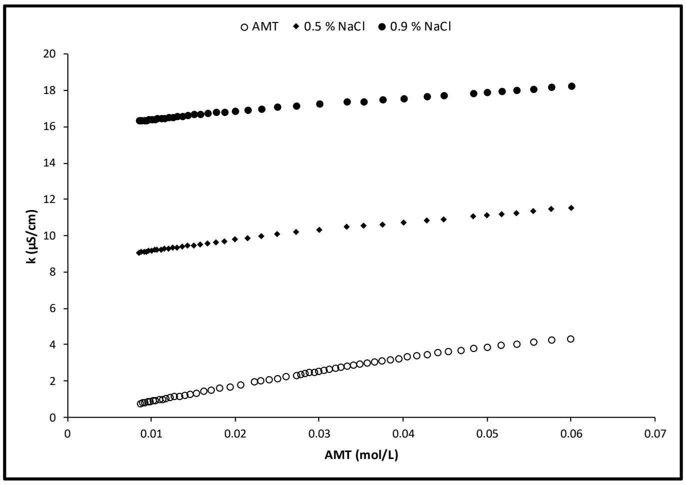

Fig. 12. Specific conductivity vs. molar concentration of AMT in water and the presence of 0.45 and 0.9 % (w/v) NaCl at 298 K.

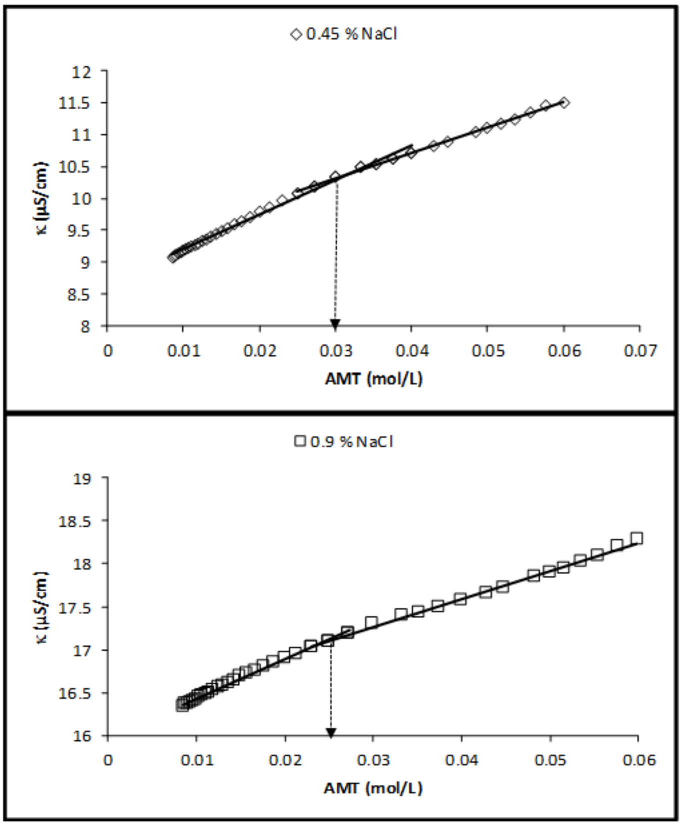

Fig. 13. Specific conductivity vs. molar concentration of AMT in water and the presence of 0.45 and 0.9 % (w/v) NaCl and CMC at 298 K (arrows show the CMC).

It is well known that organic and inorganic additives significantly influence the properties of surfactant solutions, especially CMC and micellization (Atwood and Florence, 1998). Studies on mixed alcohol-water systems have gained more attention due to their interest for designing of micro-emulsions (Liu and Guo, 2007). These studies reported that the association of alcohols with the micelles produces significant alteration in the micellar shape and their transport properties. The blocking effect of cosolvent and diminishing micellization at a certain concentration can be accounted for by reducing hydrophobic forces due to its destructive action on structured water molecules around the hydrophobic parts of the surfactant (Zana, 1995).

The decrease in both conductivity and surface tension values of AMT in the presence of various concentrations of MeOH, EtOH, Ace and Diox supports this assessment. Apart from preferential solvation of AMT in these cosolvents, changing water structure, alteration the polarity of the media (dielectric constant), cohesive energy changing are such responsible factors on diminishing micellization of AMT and inhibiting it at a certain concentration.

On the contrary, presence of NaCl decreased the CMC value of AMT, while the presence of urea increased the CMC of AMT (Table 1). The CMC of ionic surfactants reduces in the presence of inorganic salts. The addition of inorganic salt causes to break the hydration film and so the diffuse double is packed in the region of the ionic head groups. Monomers in the micellar surface layer can aggregate more closely, accordingly micelle formation can be formed easily at lower concentrations because of the decreasing the electrostatic repulsion with the addition of salt (Rosen, 1978).

However, as seen in Table 1, an increment in the CMC of AMT in the presence of urea can be expressed by the disruptive power of the iceberg structure, except for any big alteration in the micellar state by reducing the standard chemical potential. The increase in CMC suggests a decrease in hydrophobic attraction, followed by a great increase in the solubility of the hydrocarbon tails in the participation of urea. Based on the direct mechanism, urea increases the solubility of hydrophobic solutes which is attributed to an enhanced solvation as a result of the dislocation of the water molecules by a large number of urea molecules in the solvation layer (Kuharski and Rossky, 1984; Mizutani et al., 1989).

4. Conclusions

In this study, using surface tension and conductivity measurements provided useful and important information on the effect of additives for micellization process of AMT in aqueous media. The experimental results obtained from surface tensiometry studies are compatible with electrical conductivity measurements. The CMC of AMT increased with the addition of MeOH, EtOH, Ace and Diox in different concentrations, and micellization of AMT were totally inhibited at an exact concentration of cosolvents (~10% in volume). Obtained from conductivity measurements, it was determined that the value of counterion binding parameter (β) increased and α values decreased. This can be supported by the data obtained from surface tension measurements. Γ_{max} of AMT decreased and A_{min} increased with the addition of MeOH, EtOH, Ace and Diox (v/v).

The self-aggregation of surface active molecules is expla-

Table 1
CMC values and estimated parameters for AMT by conductometry and surface tension measurements in water and the presence of additives at 298 K.

MeOH % (v/v)	**Conductivity**			**Surface tension**		
	α	β	CMC (mol/L)	Γ_{max} (mmol/m^2)	A_{min} x10^{-2} (Å)^2	CMC (mol/L)
0	0.2776	0.7224	3.48x10^{-2}	8.380	1.982	3.50x10^{-2}
5	0.2133	0.7867	3.55x10^{-2}	6.196	2.680	3.55x10^{-2}
10	0.1788	0.8211	3.75x10^{-2}	4.026	4.120	4.00x10^{-2}
20	-	-	-	-	-	-
50	-	-	-	-	-	-
EtOH % (v/v)	α	β	CMC (mol/L)	Γ_{max} (mmol/m^2)	A_{min} x10^{-2} (Å)^2	CMC (mol/L)
0	0.2776	0.7224	3.48x10^{-2}	8.380	1.982	3.50x10^{-2}
5	0.1807	0.8193	3.75x10^{-2}	6.029	2.750	3.70x10^{-2}
10	0.1754	0.8246	4.00x10^{-2}	-	-	-
20	-	-	-	-	-	-
50	-	-	-	-	-	-
Acetone % (v/v)	α	β	CMC (mol/L)	Γ_{max} (mmol/m^2)	A_{min} x10^{-2} (Å)^2	CMC (mol/L)
0	0.2776	0.7224	3.48x10^{-2}	8.380	1.982	3.50x10^{-2}
5	0.1619	0.8381	4.20x10^{-2}	3.680	4.510	4.0x10^{-2}
10	-	-	-	-	-	-
20	-	-	-	-	-	-
50	-	-	-	-	-	-
Diox % (v/v)	α	β	CMC (mol/L)	Γ_{max} (mmol/m^2)	A_{min} x10^{-2} (Å)^2	CMC (mol/L)
0	0.2776	0.7224	3.48x10^{-2}	8.380	1.982	3.50x10^{-2}
5	0.1585	0.8415	4.00x10^{-2}	3.807	4.360	4.50x10^{-2}
10	-	-	-	-	-	-
20	-	-	-	-	-	-
50	-	-	-	-	-	-
Urea (mol/L)	α	β	CMC (mol/L)	Γ_{max} (mmol/m^2)	A_{min} x10^{-2} (Å)^2	CMC (mol/L)
0	0.2776	0.7224	3.48x10^{-2}	8.380	1.982	3.50x10^{-2}
0.05	0.2869	0.7137	4.00x10^{-2}	7.412	2.240	4.00x10^{-2}
0.1	0.3025	0.6975	4.50x10^{-2}	7.142	2.320	4.50x10^{-2}
1.0	0.2281	0.7719	5.00x10^{-2}	7.210	2.450	5.0x10^{-2}
NaCl % (w/v)	α	β	CMC (mol/L)	Γ_{max} (mmol/m^2)	A_{min} x10^{-2} (Å)^2	CMC (mol/L)
0	0.2776	0.7224	3.48x10^{-2}	8.380	1.982	3.48x10^{-2}
0.45	0.3399	0.6601	3.00x10^{-2}	1.868	8.890	3.00x10^{-2}
0.9	0.3000	0.6999	2.50x10^{-2}	2.976	5.580	2.00x10^{-2}

ined by hydrophobic association within the nonpolar hydrocarbon part, and the electrostatic attraction of the ionic polar head groups thereby forming aggregates. The tendency of micelle formation in the presence of polar solvents, instead of water, is called solvophobic interaction. The Gibbs free energy of the system decreases due to micelle formation in the aqueous media, associating the hydrophobic parts of the surfactant molecules and repelling the water molecules around them. The main factor directing micelle formation in aqueous solution is entropy. The water structure, which is organized around the surface active molecules, returns to its former disorder with the formation of micelles. Based on these statements reduction in conductivity values of AMT in the presence of MeOH, EtOH, Ace and Diox can be explained by solvophobic interaction. As a matter of fact, the same solvents rise the CMC of AMT up to a certain concentration and then diminished micelle formation which can be explained by decreasing the intermolecular attraction density of water or the solubility parameter. The presence of MeOH, EtOH, Ace, and Diox lower the dielectric constant of the medium, increasing the repulsion between the ionic head groups in the ionic AMT micelles, thus increasing CMC and making micelle formation difficult. It is also well known that entropy change is an important factor in micelle formation in aqueous media. Therefore, urea was used as a water structure breaker in order to see its influence on the structure of water. The presence of urea also increased the CMC of AMT due to increased hydration of the hydrophilic group with the breaking down of the water structure and making micellization difficult. The presence of electrolytes in aqueous media caused a reduction in the CMC of AMT, since especially ionic surface active agents are very sensitive to small changes in the ionic strength of aqueous solutions as in the case of cationic amphiphilic drug AMT. The presence of NaCl in the environment decreases the CMC by decreasing the electrostatic repulsion between the head groups of AMT due to the screening effect. Thereby, adding different concentrations of NaCl to ionic AMT solutions reduced the CMC since less electricity is required for micelle formation. In case of NaCl, the rise in conductivity values of AMT can be explained by an increase the salt concentration decreasing the electrical repulsions and affecting the balance of the forces on which the micelle size is dependent and causing the micelle size to grow.

Surface tension measurements provided very useful information on the surface activity of amphiphilic drug molecule AMT at surfaces and interfaces that elucidate the penetration behavior of AMT molecules at air-liquid interface in the absence and presence of additives. Decreasing Γ_{max} values and increasing A_{min} values can be attributed to the presence of additives increasing the incorporation of AMT at the interface. The higher A_{min} and the lower Γ_{max} values are consistent with β and α parameters obtained from conductivity measurements. All parameters obtained from both experimental techniques supported that amphiphilic AMT molecules can be incorporated at the interface.

The results presented in this study can provide important knowledge in elucidating the role of additives that contribute to their practice in the relevant pharmaceutical processes as active pharmaceutical additives. The determination of interfacial properties of amphiphilic drugs and their associations with pharmaceutically important additives are considered significant to enhance their utilization in pharmaceutical processes. Taking into consideration the micellar systems especially used in the drug delivery systems, the presented data here also provide important knowledge for the development of new dissolution process concerning suitable pharmaceutical additives.

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Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The authors declare that this manuscript did not involve human or animal participants and informed consent was not collected.

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