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Effect of Ethanol on Partition and Binding Equilibrium of Phenothiazine in Anionic and Nonionic Micellar Solutions

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ABSTRACT

This work deals with the solution behavior of a poorly soluble model drug, phenothiazine (PHT), under combined use of anionic Sodium Dodecyl Sulfate (SDS) and nonionic surfactants TritonX-100 (TX100) in the presence of various amount of ethanol. The characteristics of interaction and distribution of PHT were studied spectrophotometrically and quantified in terms of binding constants and micelle-water partition coefficients. Surface tension studies have been applied to identify the surface and bulk properties of the drug PHT in water-ethanol medium as a function of surfactant concentration ranging from premicellar to postmicellar region. When various amount of ethanol (v/v) were added to the aqueous surfactant solutions, it has been seen that its effect on the solubility depended on the combination of the surfactant and the ethanol concentration. Both binding and partition of PHT to SDS and TX100 micelles at low concentration diminished and totally inhibited at a certain concentration. Presence of ethanol has more pronounced inhibitory effect on incorporation of PHT to SDS than TX100 micelles. The results obtained from the different approaches and methods are in good agreement for the effect of ethanol on decreasing the interaction of PHT with micelles.

Key words: Phenothiazine, partition coefficient, binding constant, surface tension, solubilization

INTRODUCTION

Surfactants are known to play a vital role in many processes of interest in both fundamental and applied science. One important property of surfactants is the formation of colloidal-sized clusters in solutions, known as micelles which have particular significance in pharmacy because of their ability to increase the solubility of poorly soluble drugs in water (Rangel-Yagui *et al.*, 2005a, b). These aggregates exhibit an interfacial region separating the polar bulk aqueous phase from the hydrocarbon-like interior (Corrigan and Healy, 2002). Hydrophobic groups of surfactants form a micelle core which is liquid hydrocarbon like in character, while their hydrated polar groups constitute a micelle outer shell in contact with water (Florence and Attwood, 2006). While solubilization of very no polar organic substance takes place in the micellar core, relatively high polar molecules tend to be located on outer region that is solubilized in the interfacial region of the micelle. This model implies that an organic substance which is almost completely insoluble in water will be solubilized by micelles while a substance which is more soluble in aqueous media would be

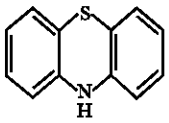

Fig. 1: The molecular structure of PHT

expected to partition between aqueous and micellar phase. As a consequence, micellar solutions consist of a special medium in which hydrophobic, amphiphilic or ionic compounds may be solubilized and reagents may be concentrated or separated in aqueous solution. Therefore, the utilization of aqueous micellar solutions for drug solubilization can be advantageous for drug delivery purposes (Rangel-Yagui *et al.*, 2005a).

The physical chemical interactions of drugs with surfactant micelles can be visualized as an approximation for their interactions with biological surfaces because surfactant micelles and lamellar phases also have been used as mimetics for biomembranes. This provides an insight into more complex biological processes, such as the passage of drugs through cell membranes. An important and fundamental event in the interaction of drugs with biological tissues at the molecular level is their binding to membranes. This is an important issue because it relates to the mechanism of drug action (Fresta *et al.*, 2002; Corrigan and Healy, 2002). An important step to understand such interactions is to characterize in detail the drug interaction sites, as well as the effect of the microenvironment on the drug interaction sites. Physicochemical aspects of the binding of nitrogen-containing heterocyclic drugs to model and natural membranes have been subjects of extensive studies involving a great variety of drugs from different therapeutic categories (Enache and Volanschi, 2010). In recent years some studies have been published on the characterization of phenothiazine derivatives such as thioridazin HCl, promethazine HCl, chlorpromazine HCl in the presence of surfactants (Caetano and Tabak, 1999, 2000; Erdinç *et al.*, 2010; Caetano *et al.*, 2002). There is not much work concern about distribution and binding properties of phenothiazine in the presence of surfactants and effect of cosolvent on these interactions. In this work interaction of sparingly water-soluble drug phenothiazine (PHT) with Sodium Dodecyl Sulfate (SDS) and TritonX-100 (TX100) micelles was studied in the presence of various amount of ethanol (v/v). To the best of our knowledge, the effect of ethanol on the interaction of PHT with various surfactants has not yet been studied. Previously, solubilization of PHT in aqueous surfactant micelles has been studied from a thermodynamic point of view with the theoretical background to a mechanism of solubilization (Moroi *et al.*, 1982). Recently, Liu and Guo reported microenvironment effect on the location distribution of PHT in CTAB/n-pentanol/H_2O and bi-continuous microemulsions using cyclic voltammetry methods (Liu and Guo, 2007).

Phenothiazines are a group of basic drugs including a phenothiazine ring with different substituents attached at the 2-and 10-position, which are used as antipsychotics, neuroleptics and antihistamines. The parent of the phenothiazines, PHT is a typical and useful organic compound with an N atom that easily looses one electron to form cationic radical (Kamat and Seetharamappa, 2004). The molecular structure of PHT is illustrated in Fig. 1.

MATERIALS AND METHODS

The research was carried out between 2007/2008 and 2009/2010 academic sessions in Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Marmara University, Istanbul. All the chemicals were of analytical reagent grade. SDS, TritonX-100 and PHT were obtained from

Sigma. As solvent, doubly distilled water, water-ethanol mixtures containing 5, 10, 20, 30, 40, 50% (v/v) of ethanol (absolute ethanol Ridel de Haen) were used. Spectroscopic measurements were carried out using a UV-Visible Spectrophotometer (Shimadzu 2100S) with a matched pair of cuvettes of 1 cm path length in a thermostated cell holder. The reproducibility for λ_{max} of spectra was ±0.1 nm. All measurements were done at least in triplicate at 298 K during the study. A PHT solution with a given concentration was prepared in ethanol-water mixture. Absorption spectra of PHT in aqueous solution with a varying wide concentration range of SDS and TX100 in the presence of various concentrations of ethanol (v/v) have been recorded at 298 K (±0.1), keeping the concentration of PHT (1.0×10^{-5} mol dm^{-3}) fixed in each one. Drug/micelle binding constant, K_b, was determined from the absorbances at 250 nm of a series of solutions containing a fixed concentration of PHT in the presence of various amount of ethanol and increasing concentrations of SDS and TX100. Micelle/water partition coefficients, K_x, were determined from the absorbances at the same wavelength (λ = 250 nm) of a series of solutions containing a fixed concentration of PHT in the presence of various amount of ethanol and increasing concentrations of SDS and TX100. In this study the CMC determination is based on the surface tension measurements. The surface tension of surfactant solutions was determined using an automatic tensiometer, KSV Instruments, model Sigma 701 (Helsinki, Finland) employing the Wilhelmy plate method to determine the CMC and observe the variation surface tension of surfactants in the presence of 1.0×10^{-5} mol dm^{-3} PHT at various ethanol-water mixtures.

RESULTS AND DISCUSSION

The hydrophobic cationic drug PHT exhibit two maximum absorption bands at 250 and 315 (±0.1) nm in the presence of 5, 10, 20, 30, 40 and 50% (v/v) ethanol concentrations. The change in absorbance value at 250 nm has been used to study the interaction between PHT and surfactants. The molar absorption coefficients (ε_0) of PHT at 250 nm in the concentration range of 1.0×10^{-5} to 8.0×10^{-5} mol dm^{-3} were calculated as 35607, 35656, 35669, 35834 and 35909 mol^{-1} dm^3 cm^{-1} at 298 K (±0.1), respectively. The linear relation between absorbance and PHT concentration (r: 0.9999) indicates that the validity of Lambert-Beer Law. The absorption spectra of 1.0×10^{-5} mol dm^{-3} PHT at various selected concentrations of SDS and TX-100 in the presence of 5% (v/v) ethanol concentrations are shown in Fig. 2a and b, respectively, as an example.

A similar behavior i.e., progressive enhancement in absorbance at the surfactant concentration above the CMC was observed for SDS and TX100 in the presence of 5, 10, 20 and 30% concentrations of ethanol. Addition of surfactants did not influence the spectral characteristics of PHT in the presence of various ethanol concentrations. The value of λ_{max} was constant regardless of the surfactant concentration. In the case of SDS a decrease in the absorbance was observed at the concentration below the CMC which indicates the molecular complex formation between cationic PHT and anionic surfactant molecules due to the electrostatic interaction. At the concentrations below the CMC the absorbance of PHT remained almost constant for nonionic surfactant TX100. As seen in Fig. 2a and b, the increase in surfactant concentration above CMC is regarded to be caused by the incorporation of PHT molecules to micelles. PHT may be adsorbed on the surface or may be trapped in the hydrocarbon core of the type of the surfactant. As more drug molecules are incorporated to micelles the absorbance values of λ_{max} reaches a limiting value and becomes almost constant. The increase in ethanol concentration the micelle formation of both surfactants diminished and micellization totally inhibited when ethanol concentration reached a certain value.

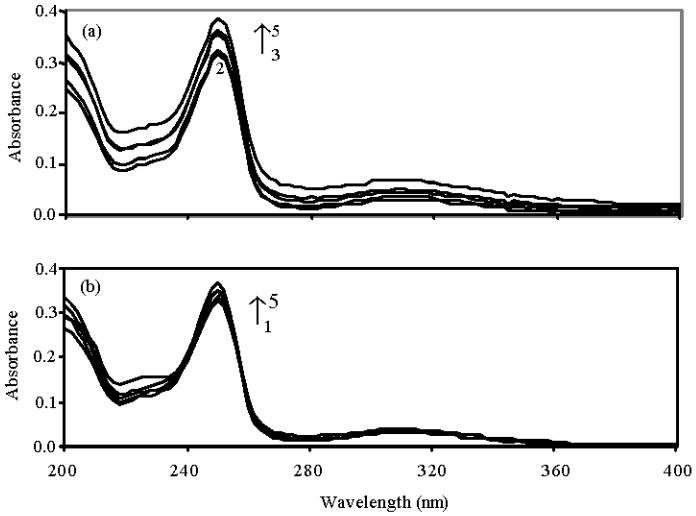

Fig. 2: (a) The absorption spectra of 1.0×10^{-5} mol dm^{-3} PHT at various concentrations of SDS in the presence of 5% (v/v) ethanol at 298 K. Concentrations of SDS; 1: no SDS, 2: 5.10^{-5}, 3: 3.10^{-4}, 4: 8.10^{-4}, 5: 1.10^{-3} mol dm^{-3} (b). The absorption spectra of 1.0×10^{-5} mol dm^{-3} PHT at various concentrations of TX100 in the presence of 5% (v/v) ethanol at 298 K. Concentrations of TX100; 1: no TX100, (2): 1.10^{-5}, (3): 8.10^{-5}, (4) 1.10^{-4} (5) 5.10^{-4} mol dm^{-3}

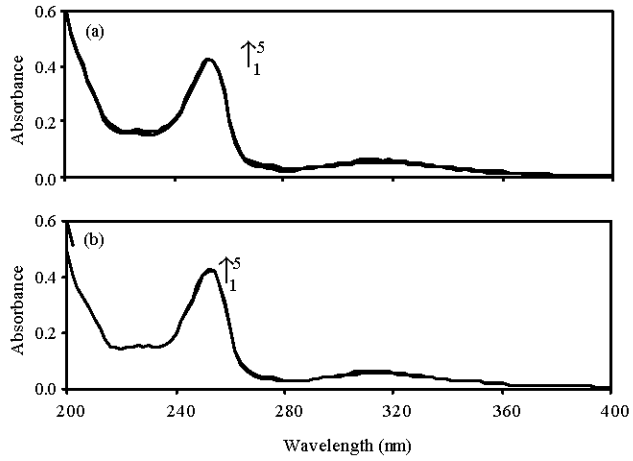

Fig. 3: (a) The absorption spectra of 1.0×10^{-5} mol dm^{-3}PHT at various concentrations of SDS in the presence of 40% (v/v) ethanol at 298 K. Concentrations of SDS; 1: no SDS, 2: 1.10^{-4}, 3: 5.10^{-3}, 4: 8.10^{-3}, 5: 1.10^{-2} mol dm^{-3} (b). The absorption spectra of 1.0×10^{-5} mol dm^{-3} PHT at various concentrations of TX100 in the presence of 40% (v/v) ethanol at 298 K. Concentrations of TX100; 1: no TX100, (2): 8.10^{-5}, (3): 1.10^{-4}, (4) 4.10^{-4} (5) 1.10^{-3} mol dm^{-3}

The absorption spectra of PHT at various concentrations of SDS and TX100 in the presence of 40% (v/v) ethanol were shown in Fig. 3a and b, respectively. As seen in these figures even at high surfactant concentrations there was no interactions observed.

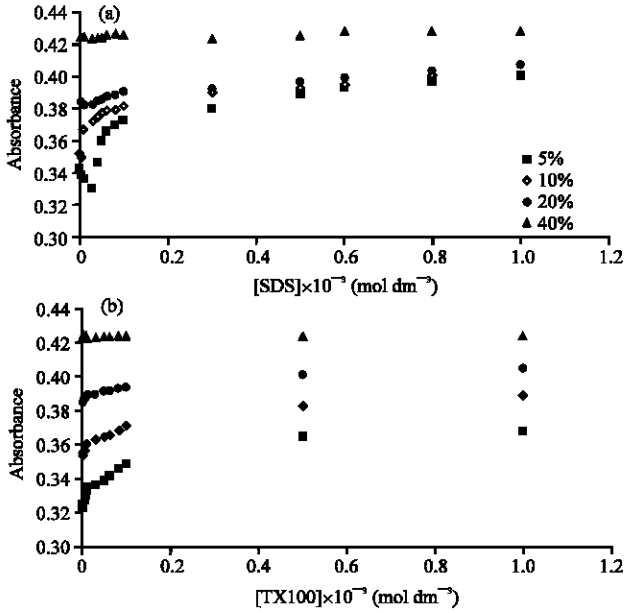

Fig. 4: (a) The absorbance change of 1.0×10^{-5} mol dm^{-3} PHT with concentration of SDS in the presence of 5, 10, 20 and 40% (v/v) ethanol. (b) The absorbance change of 1.0×10^{-5} mol dm^{-3} PHT with concentration of TX100 in the presence of 5, 10, 20 and 40% (v/v) ethanol

The absorbance change of 1.0×10^{-5} mol dm^{-3} PHT with concentration of SDS and TX100 in the presence of 5, 10, 20 and 40% concentrations of Ethanol was shown in Fig. 4a and b, respectively.

Binding constant of PHT in the presence of micelles: The binding constant is quantitatively determined in terms of the pseudo-phase model (phase separation approximation) in which micelles and water are considered as separate pseudo-phases. Equilibrium scheme of PHT and micelle can be assumed as:

$$PHT + M \underset{}{\overset{K_b}{\rightleftharpoons}} (PHT)M$$

Benesi-Hildebrand (B-H) method was initially put forward by Benesi and Hildebrand (1949) and has become popular method for determining the binding constant using various spectroscopic techniques (UV-vis, fluorescence, infrared, etc.). The extended B-H equation (Gokturk and Tunçay, 2003; Benesi and Hildebrand, 1949; Erdinç *et al.*, 2004) is shown below using UV-vis data:

$$\frac{l[PHT]}{A - A_0} = \frac{1}{\varepsilon_m - \varepsilon_o} + \frac{1}{K_B[S_m](\varepsilon_m - \varepsilon_o)} \quad (1)$$

where, [PHT] and $[S_m]$ (S_m = total surfactant concentration-CMC) are the initial molar concentrations of PHT and the micellized surfactant concentration, respectively, *l* is the optical path length of the solution. A and A_0 are the absorbances of PHT in the presence and absence of

Table 1: The physical parameters for the interaction of 1.0×10^{-5} mol dm^{-3} PHT with SDS and TX100 micelles at various ethanol concentrations % (v/v)

	SDS				TX100			
Ethanol % (v/v)	K_b	K_s	K_x	f*	K_b	K_s	K_x	f*
5	6900	6200	344000	0.7963	10250	10100	560000	0.8651
10	3350	3050	170000	0.6258	10133	9876	548000	0.8451
20	2683	2514	140000	0.5796	8700	8251	460000	0.7569
30	297	221	120000	0.1242	7783	7254	400000	0.7412

*Limit values of f at the 5.0×10^{-4} mol dm^{-3} surfactant concentration. Error limit in K (dm^3 mol^{-1}) values is ±5%. The correlation coefficients are higher than 0.9980

surfactant, respectively. ε_m, is the molar absorption coefficient of the drug fully bound to micelles determined in large excess of the micelles. The plot of l [PHT]/($A-A_0$) against 1/[S_m] were used to calculate K_b values at different ethanol concentrations (v/v) from the slope and intercept and were given in Table 1. From Table 1, it can be seen that the binding constant of PHT with micelles decreases with the increase in ethanol concentration. The results mean that the rise of ethanol concentration is unfavorable to the interaction between PHT and micelles. A more precise comparison can be provided from amount of solubilized PHT by micelles. The concentration of the solubilized PHT was also calculated from the relationship (Bielska *et al.*, 2009).

$$[D_m] = \frac{A_0 - A}{\varepsilon_0 - \varepsilon_m} \quad (2)$$

where, D_m is the concentration of PHT solubilized in the micelle.

Figure 5a and b represent the variation of amount of solubilized PHT with SDS and TX100 micelles in the presence of various ethanol concentrations, respectively. As seen in Fig. 5a and b the amount of solubilzed PHT decreased with increase in ethanol concentration.

Partition coefficient of PHT between micelles and aqueous phase: Absorbance values obtained at λ_{max}, can be also used for the calculation of partition coefficient, K_x, defined according to the pseudo-phase model as (Sepulveda *et al.*, 1986; Kawamura *et al.*, 1989; Sepulveda, 1974):

$$K_x = \frac{X^m_{PHT}}{X^w_{PHT}} \quad (3)$$

where, X^m_{PHT} and X^w_{PHT} are the mole fractions of cationic dye PHT in micellar and aqueous phase, respectively. They are related with concentrations of species in the solubilization system:

$$X^m_{PHT} = \frac{C^m_{PHT}}{C^M_{PHT} + C^m_{surfactant}} \quad (4)$$

$$X^w_{PHT} = \frac{C^w_{PHT}}{C^w_{PHT} + C_{surfactant} + n_W} \quad (5)$$

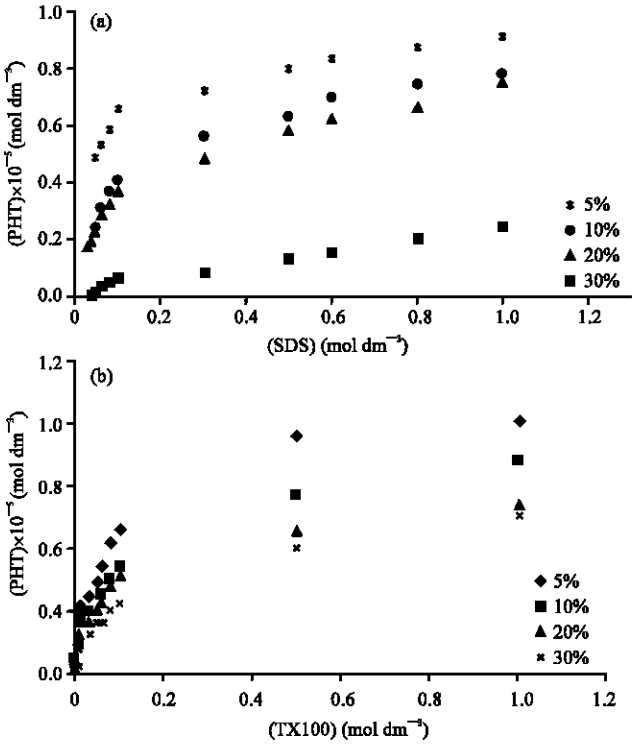

Fig. 5: (a) Solubility curve of 1.0×10^{-5} mol dm^{-3} PHT as a function of SDS concentration in the presence of various amount of ethanol (v/v), (b) Solubility curve of 1.0×10^{-5} mol dm^{-3} PHT as a function of TX100 concentration in the presence of various amount of ethanol (v/v)

where $C^{m}_{surfactant}$ and $C^{w}_{surfactant}$ represent concentrations of surfactant in micellar and monomeric states and $n_w = 55.5$ mol dm^{-3} is the molarity of water. Under the present experimental conditions $C^{m}_{PUT}+C^{w}_{surfactant} << n_w$, if we express $K_s = K_x/n_w$, we get the equation:

$$K_S = \frac{C^{m}_{PHT} / (C^{m}_{PHT} + C^{m}_{surfactant})}{C^{w}_{PHT}} \quad (6)$$

the fraction of the associated PHT (f) may be defined as:

$$f = \frac{C^{m}_{PHT}}{C_{PHT}} \quad (7)$$

At a certain C_{PHT}, f is equal to zero in the non-micellar region up to CMC and increases with increasing the concentration of surfactant above CMC. As $C_{surfactant}$ increases up to infinity, f approaches unity since all added drug should be solubilized in micelles. f can be directly calculated from the experimental data:

$$f = \frac{\Delta A}{\Delta A^{\infty}} \quad (8)$$

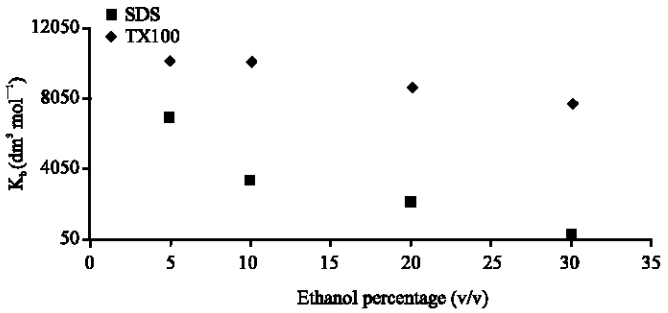

Fig. 6: Variation of binding constants value of PHT to SDS and TX100 micelles in the presence of ethanol concentrations (v/v)

where, $\Delta A = A\text{-}A_{water\text{-}ethanol}$ and $\Delta A^{\infty} = A^{\infty}\text{-}A_{water\text{-}ethanol}$, A^{∞}being the absorbance of PHT completely bound micelles. The change in f with ethanol percentages (v/v), at the concentrations of 5.0×10^{-4} mol dm^{-3} for TX100 and SDS micelles were given in Table 1. It can be seen in Table 1, the increase in ethanol concentration caused to decrease the fraction of PHT with two types of micelles. By using Eq. 5-8 can be written in linear form:

$$\frac{1}{\Delta A} = \frac{1}{\Delta A^{\infty}} + \frac{1}{K_S \Delta A^{\infty}(C_{PHT} + C_{surfactant} - CMC)} \tag{9}$$

where, K_S and K_x ($K_s = K_x/n_w$) is obtained from the slope of the plot of $1/\Delta A$ versus $1/(C_{PHT}+C_{surfactant}\text{-}CMC)$. The results at the different ethanol concentrations are summarized in Table 1. In the presence of 1.0×10^{-5} mol dm^{-3} PHT, as seen in Table 1 CMC values are always significantly lower than the corresponding CMC values of SDS at all the studied ethanol concentrations. This confirms that PHT is capable of interacting with SDS, inducing the formation SDS aggregates. As seen in Table 1 PHT interacts with SDS more hardly and weakly with increasing in ethanol concentrations. It is also clearly seen in Fig. 6, as the ethanol concentration increases the tendency of drug-micelle association decreases. More pronounced inhibitory effect of ethanol on binding of PHT to SDS micelles than TX100 micelles can be roughly explained by decreasing electrostatic interaction as well as decreasing hydrophobic attraction as a result of incorporation of ethanol molecules in the palisade layer of micelles.

It is well known that the properties of surfactant solutions such as micellization, micellar size and properties are affected markedly by the presence of organic or inorganic additives (Florence and Atwood, 2006). Organic additives are known to affect the micellization characteristics of both ionic and nonionic surfactants (Zana, 1995). Mixed alcohol-water systems have particularly been investigated because of their importance in the preparation of microemulsions (Liu and Guo, 2007). The studies have shown that the incorporation of alcohols into the micelles produces noticeable changes in the micellar shape and their transport properties.

The inhibitory effect of cosolvent on binding can be explained in a very qualitative manner in terms of decreasing hydrophobic attraction if the effect of the cosolvent on the micelles is considered. It is well known the presence of cosolvents has a negative influence on hydrophobic interaction due to its destructive action on structured water molecules around the hydrophobic parts of the surfactant (Zana, 1995). In our system there are many factors responsible for the influence of ethanol on interaction such as changing water structure, preferential solvation of PHT, changing

dielectric constant of the media, changing cohesive energy, changing micellar size and properties due to the incorporation of ethanol molecules to micelles and etc. The distribution (or interaction) of PHT between aqueous ethanol mixture and micellar phase is a complex phenomenon since the quaternary systems (e.g., water-surfactant-cosolvent-substrate) are too complicated to study quantitatively. The quaternary system contains water, ethanol, SDS (or TX100) and PHT in this study. The latter may interact with surfactant monomers, micelles and ethanol and also ethanol may interact with micelles. All of these shift the CMC and influence the size and shape of the micelles and of course changes the physicochemical properties of the bulk. Very low CMC values obtained in case of SDS supports this explanation.

The higher K_b and K_x in the case of TX100 than in the case of SDS can be attributed to higher hydrophobicity of TX100 than that of SDS. The dependence of K values with amount of ethanol can be related to partition of the alcohol between micellar pseudophase and bulk aqueous phase. The decrease in binding and partition coefficients with increase in ethanol concentrations can be explained by incorporation of the alcohol to the micellar surface. Lastly, the partition of alcohol between the micellar pseudophase and the intermicellar solution, which decreases with increase in ethanol concentration, may affect K values.

In order to interpret the inhibiting efficiency of ethanol the interactions between surfactants and ethanol have been taken into consideration separately. Surface tension measurements of SDS and TX100 were performed in the presence of varying concentrations of ethanol in the absence and presence of 1.0×10^{-5} mol dm^{-3} PHT. The surface tension (γ) versus logarithm of concentrations curves of SDS and TX100 in ethanol-water mixtures are shown in Fig. 7. The CMC values of SDS and TX100 were obtained from the intersection point between the straight lines in water and ethanol-water mixtures. The results are summarized in Table 2. The CMC values obtained in water for both surfactants are in agreement with previous values reported in literature i.e., $CMC_{SDS} = 8.2\times10^{-3}$ mol dm^{-3} and $CMC_{TX100} = 0.3\times10^{-3}$ mol dm^{-3} (Florence and Atwood, 2006).

As seen in Fig. 7 and Table 2, CMC values of SDS and TX100 obtained from the surface tension results clearly indicate that the effect of ethanol on micelle formation. The difference in ethanol effects on CMC can be ascribed to the difference of surfactant types. The CMC of SDS was depressed in ethanol-water mixtures. The depression of CMC of SDS is due manly to the decrease in the thickness of the electric double layer surrounding the ionic head-groups and consequent

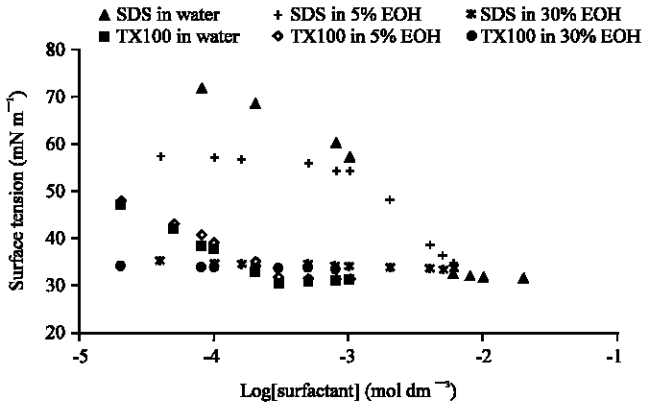

Fig. 7: Variation of surface tension of SDS and TX100 in the absence and presence of 5 and 30 % (v/v) ethanol concentrations

Table 2: Effect of ethanol concentrations (v/v) on the CMC values of SDS and TX100 determined from surface tension measurements in the absence and presence of 1.0×10^{-5} mol dm^{-3} PHT

	SDS		TX100	
Ethanol % (v/v)	CMC[a] (mol dm^{-3})	CMC[b] (mol dm^{-3})	CMC[a] (mol dm^{-3})	CMC[b] (moldm^{-3})
0	8.0×10^{-3}	-	3.0×10^{-4}	-
5	8.0×10^{-4}	2.0×10^{-4}	3.0×10^{-4}	5.0×10^{-4}
10	1.0×10^{-3}	5.0×10^{-4}	3.0×10^{-4}	5.0×10^{-4}
20	2.0×10^{-3}	1.0×10^{-3}	3.0×10^{-4}	5.0×10^{-4}

[a]The CMC values in the absence of PHT. [b]The CMC values in the presence of 1.0×10^{-5} mol dm^{-3}PHT

decreased electrical repulsion between them in the micelle. On the other hand the CMC of TX100 did not show significant change in ethanol-water mixtures. This nonionic surfactant has a polyoxyethylene hydrophilic head group that interacts with water through hydrogen bonds. Therefore, the CMC does not change in the presence of ethanol. The effect of alcohols on critical micelle concentration is well documented in the literature (Zana *et al.*, 1981; Ionescu *et al.*, 1984). Ethanol is a border case between short-chain and long-chain alcohols (with more than four carbons in the alcohol molecule), showing an increase of the CMC with ethanol concentration or presenting a minimum, depending on the surfactant (Zana,1995). The common effect of ethanol on these systems is totally inhibiting micellization of both surfactants at a certain concentration of ethanol 30%(v/v). Several authors have shown that the presence of cosolvents may diminish the micelle formation and totally inhibit micellization when cosolvent concentration reaches at a certain value (Ionescu *et al.*, 1984; Zana, 1995; Gokturk and Tunçay, 2003; Gokturk *et al.*, 2006). This can be explained by the greater the similarity between surfactant and solvent the harder the micelle formation. In the presence of 1.0×10^{-5} mol dm^{-3} PHT the CMC of SDS were lowered, whereas no significant change but slightly increased was observed for the CMC of TX100. In this respect it has been described that molecules solubilized in the outer portion of the micelle core are most effective in reducing the CMC than ones solubilized in the inner core. It can be said that PHT should be located near the inner core of TX100 micelles, as a result of hydrophobic interactions with the surfactant tail while in the presence of SDS PHT should be located outer portion of micelle. The surface tension (γ) versus logarithm of concentrations curves of SDS and TX100 containing 1.0×10^{-5} mol dm^{-3} PHT in ethanol-water mixtures are shown in Fig. 8a and b, respectively. As seen in Fig. 8a and b the increase in ethanol concentration diminished the micelle formation of both surfactants and inhibited at the ethanol concentration of 30% (v/v). As a conclusion there is a reasonable agreement with the value obtained by spectrophotometric measurements in terms of inhibitory effect of ethanol on interaction between PHT and both surfactants studied (Table 1).

In order to gain further insight about the solubilization of 1.0×10^{-5} mol dm^{-3} PHT it has been monitored the dependence of surface tension of PHT in the presence of different ethanol-water mixtures. The variation of surface tension of 1.0×10^{-5} mol dm^{-3} PHT as a function of ethanol concentration has been shown in Fig. 9. It was observed that with the increase in ethanol concentration the surface tension of PHT significantly decreased. This is also supported that there is an interaction between PHT and ethanol apart from surfactant-ethanol interaction. In other words there is preferentially solvation of PHT by ethanol i.e., co-solubilization effect of ethanol. The parallelism between molar extinction coefficients and surface tension values of PHT in the presence of various amount of ethanol demonstrate that significant influence of polarity change on micellar binding and partition.

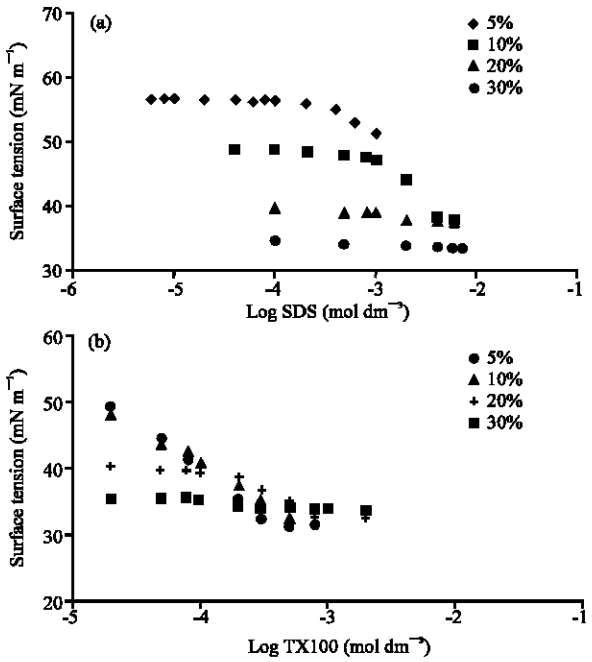

Fig. 8: (a) Surface tension of SDS in the presence of 1.0×10^{-5} mol dm^{-3} PHT at various ethanol concentrations % (v/v). (b) Surface tension of TX100 in the presence of 1.0×10^{-5} mol dm^{-3}PHT at various ethanol concentrations % (v/v)

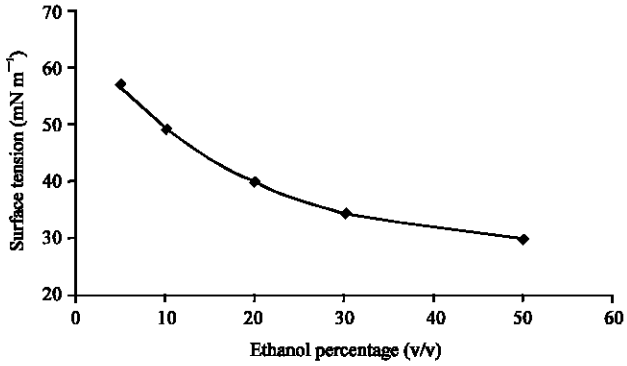

Fig. 9: Surface tension of $1.0x10^{-5}$ mol dm^{-3} PHT in the presence of various concentrations of ethanol % (v/v)

It might be said that the solubility of PHT increased as a function of EOH concentration. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, cosolvents reduce waters ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility (Millard *et al.*, 2002).

The importing finding here is that the addition of ethanol generally did not contribute much to improving solubilization in the presence of two types of micelles SDS and TX100. Moreover the

addition of ethanol decreased the solubility or drug-micelle incorporation as observed our system. When ethanol concentration increased the dramatic decrease was observed for SDS-PHT system. On the other hand, it might be said that the addition of ethanol to TX100-PHT solutions had only minor effect on the solubilization of PHT. However addition of ethanol with the drug to the surfactant solutions generally offered an advantage due to decreasing CMC and caused to low toxicity of surfactants to formulation. In conclusion much attention is required when surfactant and cosolvents are formulated together because the cosolvents affect the micelle characteristics significantly.

CONCLUSIONS

This study reports the results obtained from a series measurements of the binding and partition coefficient of PHT between two types of micelles i.e., anionic (SDS) and nonionic (TX100) and aqueous phase in the presence of various amount of ethanol (v/v). The addition of ethanol reduces drug-surfactant association. Its influence can be interpreted in two ways: firstly, the increase of the ethanol content in the water-ethanol mixed solvent causes a decrease of the dielectric constant of the aqueous phase and thereby causes an increase of attractive electrical interactions; secondly ethanol is known for its negative influence on hydrophobic interactions because of its ability to break down the structured water molecules around the hydrophobic parts of solute. According to the results the first influence might be dominated by the second one as the equilibrium constants of the PHT-surfactant systems examined decrease with increasing amount of ethanol. Irrespective of surfactant type micellization decreased with the increase in ethanol concentration and totally inhibited at 30% (v/v) ethanol concentration. The results show that the binding constants and partition coefficients decreased with the increase of ethanol percentages. Thus, the rise of ethanol concentration is unfavorable to the PHT distribution in the micelles phase. Apart from decrease in hydrophobic interaction decrease in electrostatic attraction occurs in binding of PHT to SDS micelles, more pronounced effect of ethanol on the binding constants obtained for SDS supports this explanation. The greater binding constants of PHT for neutral TX100 than for ionic SDS indicate that the former micelle provides a more hydrophobic environment to PHT. Inhibitory effect of ethanol on binding to micelles can be explained by decreasing hydrophobic attraction as a result of incorporation of alcohol molecules to micelles.

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