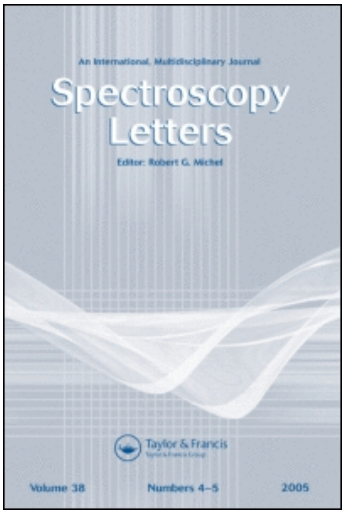

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Solution Behaviour of Rivanol in Micellar Environments

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Abstract: The interaction of the cationic drug rivanol (RIV) with three types of surfactants; [cationic (cetyltrimethylammonium bromide; CTAB), anionic (sodium dodecylsulfate; SDS), and nonionic (*t*-octylphenoxypolyethoxyethanol, TX-100)] has been studied spectrophotometrically as a function of surfactant concentration from the premicellar to the postmicellar region. A comparison of the binding constants calculated from the Benesi–Hildebrand equation indicated that the binding tendency of RIV with TX-100 micelles is higher than that with SDS micelles. The binding constants of RIV to both SDS and TX-100 micelles were found to decrease in the presence of NaCl (0.225% w/v), ethanol (5% v/v), propylene glycol (5% v/v), and glycerin (5% v/v), The addition of the additives to the medium had a pronounced effect on the association of RIV with micelles. They all tended to decrease the binding of RIV to micelles. The inhibitory effect of alcohols followed the order water > glycerin > propylene glycol > ethanol.

Keywords: Binding constant, cosolvent, interaction, micelles, rivanol, surfactants

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INTRODUCTION

Surfactants are known to play a vital role in many processes of interest in both fundamental and applied science.[1–3] An important property of surfactants is the formation of colloidal-sized clusters in solutions, known as micelles, which have particular significance in pharmacy mainly because of their ability to increase the solubility of sparingly soluble substances in water.[4–8] In general, surfactants play an important role in contemporary pharmaceutical biotechnology, because they are largely utilized in various drug dosage forms to control wetting, stability, bioavailability, among other properties.[9] Usually, some surfactants such as sodium dodecylsulfate (SDS), Tweens, and TX-100 used as excipients are added to formulations to facilitate the preparation, patient acceptability, and functioning of the dosage form. They can also be used as disintegrating agents, diluents, suspending agents, and emulsifying agents.[5,10–14]

Micellar media considered as a pseudo model for simple biological mimetic systems have been used to study different aspects of essential bilayer properties and functions.[5,15–17] The physicochemical interactions of drugs with surfactant micelles can be visualized as an approximation for their interaction with biological surfaces. This provides an insight into more complex biological processes such as the passage of drugs through cell membranes. The fundamental event in the interaction of drugs with biological tissues at the molecular level is their binding to membranes.[18,19] This is an important issue because it relates to the mechanism of drug action. Therefore, the study of surfactant micelles and their role in pharmacy is of paramount importance, especially with respect to their ability of solubilizing hydrophobic drugs.[20–26]

Surfactants are used as solubilizers for water-insoluble dyes as well as for water-insoluble drugs. The dye–surfactant interactions have also been the subjects of many studies in view of the fact that they mimic many biological processes taking place between organic molecules and the biomembranes.[27] Knowledge of dye–surfactant interaction has great value in understanding the chemical equilibria, mechanisms, and kinetics of surfactant-sensitized color and/or fluorescence reactions.[28–36] The interaction between ionic dye and charged surface is also of interest in numerous applications ranging from the design of electronic devices to the characterization of drug delivery interest.[37,38] The studies on different type of dyes in aqueous surfactant solutions can give useful information about the mechanism according to which surfactants operate as leveling agents and about the influence of dye-surfactant interactions on thermodynamics and kinetics of dyeing process.[39–41]

Among the various investigation techniques, spectrophotometry has been most widely used to study the complexation equilibria between dyes and surfactants in solution.[21,23,28–30] Extensive research carried out has confirmed that two types of interaction between dye and surfactant may be observed

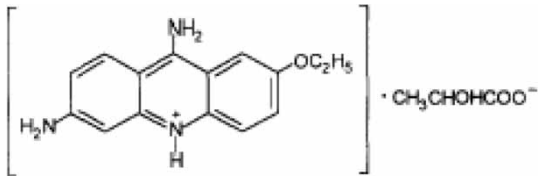
depending on the chemical structure of both dye and surfactant. At concentrations below the critical micelle concentration (CMC), decrease in the absorbance with appearance of a new band indicates formation of a complex between dye and surfactant molecules, whereas increase in absorption coefficient at high micelle concentrations indicates incorporation of dye to micelle.[42–48]

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.[49–51] Various studies indicated that presence of neutral salts lead to decrease in the CMC of ionic surfactants while the salt effects on nonionic surfactants are specific and depend on the nature of the ion. Organic additives are known to affect the micellization characteristics of both ionic and nonionic surfactants.[52–54] Mixed alcohol–water systems have particularly been investigated because of their importance in the preparation of microemulsions.[55,56] The studies have shown that the incorporation of alcohols into the micelles produces noticeable changes in the micellar shape and in their transport properties.[57] In general, 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 and dye molecules.[58] Several authors have shown that the presence of cosolvents may diminish the micelle formation and totally inhibit micellization when cosolvent concentration reaches a certain value.[59,60]

Although there are a number of studies about the effect of medium on micellization process, there is very little attention directed toward the effect of added organic and inorganic solutes on the interaction between dyes or drugs and micelles.[58,61–64] Bracko et al.[58] studied the interactions between an anionic dye and two cationic surfactants by conductumetry at different temperatures in water–ethanol mixed solvent. We have recently reported the interaction of Safranin-O, a cationic dye, with various surfactants both at premicellar and postmicellar region in the presence of various cosolvents such as dimethylformamide (DMFA), dioxan (DX), and methanol[65,66] and also studied the effect of NaCl and glucose on binding of epirubicin HCl, cationic drug, to various micelles.[67]

In the current paper, we report on the interaction of rivanol (RIV) with various surfactants as anionic (SDS), cationic (CTAB), and nonionic TX-100. RIV (6,9-diamino-2-ethoxyacridine lactate), usually known as ethacridine, is a cationic dye as well as a cationic drug and a potent antimicrobial agent that has been employed as an amebicide in the treatment of human dysentery and as a bactericide in the treatment of bovine streptomastitis.[68] Its solution prepared in glycerin is used in ear-drop formulation.[69] RIV is also potentially interesting as an absorbing and fluorescing probe of nucleic acid structure and of the interaction of aromatic cations with nucleic acids.[70]

The structure of RIV is given in Scheme 1.



Scheme 1. Structure of RIV.

In view of this interest, we have undertaken this study to understand the interaction of RIV with various micelles and the role of the additives that are used in pharmaceutical applications of RIV solution such as NaCl (0.225% w/v) ethanol (5% v/v), propylene glycol (5% v/v), and glycerin (5% v/v).

In this work, considering the effect of cosolvents on micellar systems and their practical application in drug formulation, special attention has been given to the interaction between RIV and various micelles in the presence of these additives.

MATERIALS AND METHODS

All the chemicals were of analytical reagent grade. SDS, Triton X-100, and CTAB were from Sigma (Germany) products. RIV was obtained from Fluka (Switzerland). The solvents ethanol, propylene glycol, and glycerin used were spectroscopic-grade products from E. Merck (Germany). NaCl was also obtained from Merck. Doubly distilled conductivity water was used. Visible absorption spectra were recorded with UV-Visible Spectrophotometer (UV-1601, Shimadzu, Japan) with a matched pair of cuvets of 1 cm optical length placed in a thermostated cell holder at 298 K (± 0.1). The absorption spectra of 5.0×10^{-5} M RIV solution containing surfactants in the concentration range from 1.0×10^{-5} to 2.0×10^{-2} M were recorded, and the reproducibility for λ_{max} of the spectra was ± 0.1 nm. All measurements were done at least in triplicate during the study.

In this paper, CMC determination is based on the change in absorption spectrum of RIV, which indicates the onset of micelle formation as described previously.[65,67]

RESULTS AND DISCUSSION

The cationic drug RIV, having the structure shown in Scheme 1, exhibits two maximum absorption bands at 363 and 411 nm. The change in absorbance value at 363 nm has been used to study the interaction between RIV and CTAB, SDS, and TX-100. The molar absorption coefficient of RIV at

363 nm, ε_o, was calculated as 1.40 ($\pm$0.01) $\times$ 10^4 M^{-1} cm^{-1} at 298 K ($\pm$0.1) in the concentration range of 1.0 $\times$ 10^{-5} to 8.0 $\times$ 10^{-5} M. The linear relation between absorbance and RIV concentration (r: 0.9990) indicates the validity of Beer's law.

The absorption spectra of RIV in the presence of various selected concentrations of SDS and TX-100 are shown in Figs. 1a and 1b, respectively. As seen in Fig. 1a, for SDS concentrations up to 3.0 $\times$ 10^{-3} M, absorbance of RIV sharply decreased with a slight red shift. This initial decrease in absorbance with a slight red shift indicates complex formation between RIV and SDS molecules. When SDS concentration reached 8.0 $\times$ 10^{-3} M, the shape of spectrum changed. With further increase of SDS concentration from 8.0 $\times$ 10^{-3} M to 2.0 $\times$ 10^{-2} M, the λ_{max} at 363 nm shifted to 371 nm and the λ_{max} at 411 nm shifted to 414 nm, and a shoulder appeared at 432 nm. At the concentrations of TX-100 below the CMC, no spectral changes were observed, and the absorbance of RIV remained almost constant. As seen in Fig. 1b, the λ_{max} values of RIV at 363 and 411 nm shifted to 374 and 434 nm, respectively, and a shoulder appeared at 433 nm in the presence of TX-100 above the CMC. A similar behavior, that is, a progressive enhancement in absorbance with a red shift at the surfactant concentrations above the CMC, was observed for both surfactants. The shifted λ_{max} values of RIV in the presence of TX-100 and SDS micelles are listed in Table 1. There was no interaction between RIV and CTAB micelles due to electrostatic repulsion.

The absorbance change of 5.0 $\times$ 10^{-5} M RIV at 363 nm with the varying concentration of SDS and TX-100 (below and above CMC) is shown in Fig. 2. As seen in Fig. 2, with initial increase in SDS concentrations well below the CMC, a decrease in absorbance was observed, and with further addition of SDS, onset of enhanced absorbance considered as CMC, whereas the lack of change in absorbance of RIV at the concentrations of TX-100 below the CMC indicates absence of interaction between RIV and TX-100 molecules until the concentration of TX-100 reached 0.4 mM, which corresponds with the CMC of TX-100. The absorbance increase with a red shift above the CMC indicates incorporation of RIV into both SDS and TX-100 micelles.

Determination of Binding Constant

The binding constant is quantitatively determined in terms of the pseudophase model in which micelles and water are considered as separate pseudophases.[71,72] The equilibrium scheme of RIV and micelle can be assumed to follow

$$\mathrm{RIV} + \mathrm{M} \overset{K_B}{\rightleftharpoons} (\mathrm{RIV})\mathrm{M}$$

where (RIV)M and K_B represent RIV–micelle associate and binding constant, respectively. K_B and molar absorption coefficient ε_m can be determined using

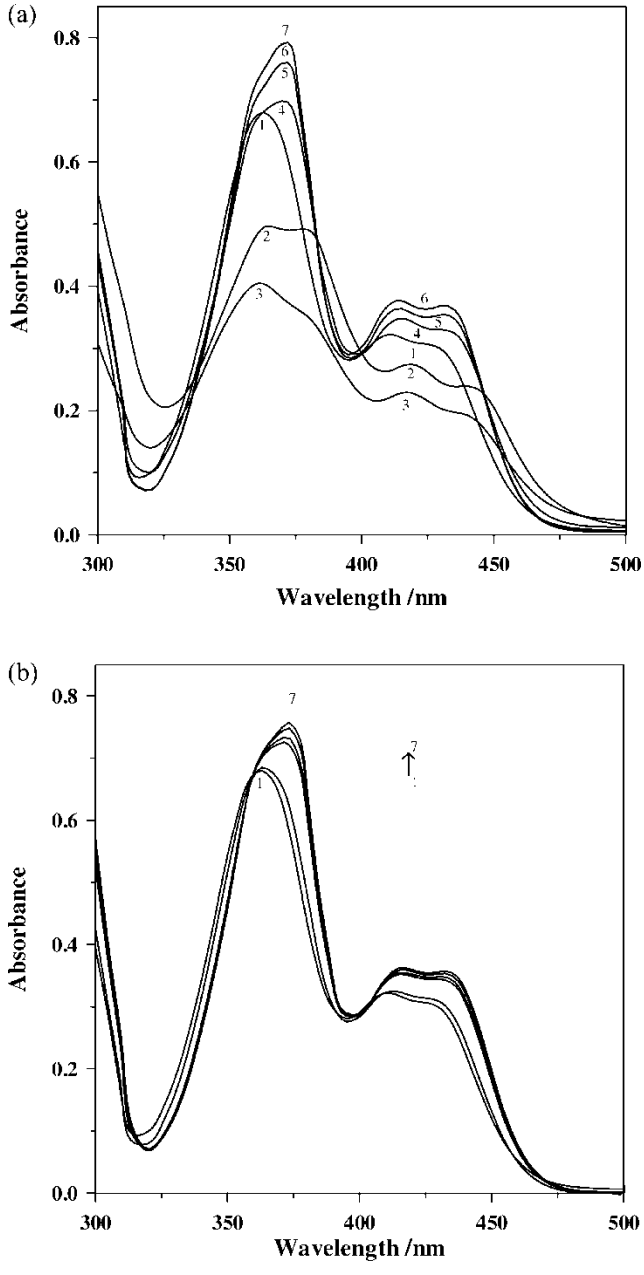


Figure 1. (a) Visible absorption spectra of RIV (5.0×10^{-5} M) at various concentrations of SDS at 298 K: (1) 0.0; (2) in 1.0; (3) in 3.0; (4) in 8.0; (5) in 10.0; (6) in 15; (7) in 20 mM SDS. (b) Visible absorption spectra of RIV (5.0×10^{-5} M) at various concentrations of TX-100 at 298 K: (1) 0.0; (2) in 1.0; (3) in 3.0; (4) in 6.0; (5) in 8.0; (6) in 1.0; (7) in 2.0 mM TX-100.

Table 1. Physical parameters of 5.0×10^{-5} M RIV in SDS and TX-100 at 298 K

Surfactant	CMC_0[a] (mM)	CMC[b] (mM)	λ_{max}[c] (ε_m)	K_B (M^{-1})
SDS	8.00	3.0	371 (17,350)	854
TX-100	0.33	0.4	374 (17,200)	1381

[a]The CMCs were taken from literature.[49,51]

[b]The CMCs were obtained from spectrophotometric determination in the presence of 5.0×10^{-5} M RIV.

[c]λ_{max} is in nm and ε_m is in M^{-1} cm^{-1}; error limit in ε_m is $\pm 1\%$.

the Benesi–Hildebrand equation, which is valid for high surfactant concentrations [65,73] in the following modified form

$$\frac{[RIV]\,l}{\Delta A} = \frac{1}{\varepsilon_m - \varepsilon_o} + \frac{1}{K_B[S_m](\varepsilon_m - \varepsilon_o)} \tag{1}$$

where $[RIV]$ and $[S_m]$ (S_m = total surfactant concentration – CMC) are the initial molar concentrations of RIV and the micellized surfactant concentration, respectively, l is the optical path length of the solution, ΔA is the

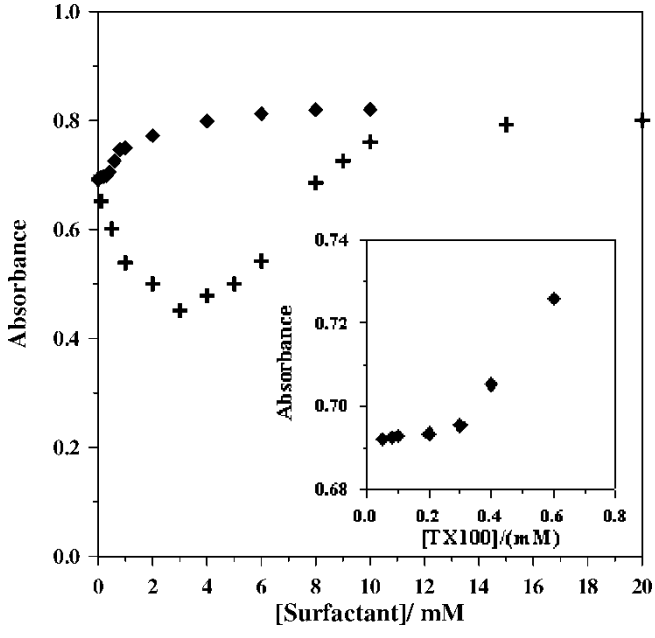


Figure 2. The absorbance change of 5.0×10^{-5} M RIV at 363 nm with concentration of surfactants: (◆) TX-100; (+): SDS. Inset: The absorbance change of 5.0×10^{-5} M RIV at 363 nm below the CMC of TX-100.

difference between A and A_0, which is the absorbance of RIV in the presence and absence of surfactants, respectively. ε_m is the molar absorption coefficient of the dye fully bound to micelles determined in large excess of the micelles. The plot of $[RIV]l/(\Delta A)$ against $1/[S_m]$ was found to be linear in all cases. The K_B values related to the extent of RIV–surfactant interaction, calculated from the slope and intercept, are shown in Table 1. Computations of binding constants reveal that binding in the case of nonionic is stronger than that of anionic. Combined electrostatic and hydrophobic forces take place in binding onto anionic micelles, whereas hydrophobic interaction plays the main role in binding onto nonionic. Therefore, it has been expected that the interaction between RIV and anionic SDS micelles would be strongest because of the opposite charge of the components. The lack of interaction between RIV and CTAB supports this expectation. However, TX-100 formed complexes with RIV more strongly than SDS. It is considered that compared with anionic site on SDS micelles, the aqueous mantle of the TX-100 micelles (composed of polyoxyethylene oxide residues, 9.5 EO units) is more favorable for location of RIV.

In this work, the effect of NaCl (0.225% w/v) on the interaction between RIV and both SDS and TX-100 micelles were studied. The nature of the spectrum of RIV in the presence of NaCl (0.225% w/v) with varying surfactant concentrations remained the same as in the absence of NaCl. This shows that same type of interaction between RIV and SDS and TX-100 took place both in the absence and presence of NaCl.

Micelles are sensitive to any changes in the properties of the aqueous solution. It is well-known that presence of neutral salts may lead to decrease in the CMC of ionic surfactants. The effects of salts on nonionics are specific depending on the nature of the ion, some capable of "salting out" reduce the CMC, whereas others capable of "salting in" increase the CMC.[50,51] In this work, it has been found that presence of 5.0×10^{-5} M RIV decreased the CMC of SDS. Presence of RIV has a neutral salt effect on SDS micelle solutions reducing the mutual electrostatic repulsion of charged head-groups. The increasing in CMC of TX-100 in the presence of 5.0×10^{-5} M RIV can be explained in terms of salting in effect. Presence of NaCl (0.225% w/v) caused further decrease in the CMC of SDS while the CMC of TX-100 slightly increased. In the presence of 5.0×10^{-5} M RIV, the apparent CMC of SDS varied from 3 mM in water to 1 mM in NaCl solution (0.225 % w/v). The CMC of TX-100 in the presence of 5.0×10^{-5} M RIV, changed from 0.4 mM in water to 0.5 mM in NaCl solution (0.225% w/v).

The presence of NaCl has an inhibitory effect on binding of RIV to both SDS and TX-100 micelles. K_B values diminished from 854 M^{-1} to 687 M^{-1} for SDS micelles and from 1381 M^{-1} to 1048 M^{-1} for TX-100 micelles. The decrease in binding constant in the case of TX-100 can be explained by decreasing hydrophobic interaction parallel to decreasing micellar size (i.e., salting in effect), whereas in the case of SDS it can be related to the electrostatic screening effect rendered by Na^+ ions.[52,74]

Effect of Alcohols

In this work, effect of glycerin, propylene glycol, and ethanol at 5% (v/v) on binding of RIV to both SDS and TX-100 micelles was studied. It was found that the presence of these alcohols increased the CMC and decreased the binding of RIV to micelles. The results in Table 2 show that K_B values vary indirectly with CMC. The increase in CMC of both SDS and TX-100 in the presence of alcohols followed the order ethanol > propylene glycol > glycerin > water.

Effectiveness of alcohols as inhibitors on binding RIV to both SDS and TX-100 micelles followed the order $K_{B(water)} > K_{B(glycerin)} > K_{B(propylene\ glycol)} > K_{B(ethanol)}$.

The inhibitory effect of alcohols on binding can be explained in a very qualitative manner in terms of decreasing hydrophobic attraction related to increasing number of OH groups which can be clearly seen in the increase in CMC order. Comparison of the dielectric constant of alcohols indicates the order of the polarity of the media follow the trend water > glycerin–water > propylene glycol–water > ethanol–water. This follows the same decreasing order of binding constant. A decreased in the dielectric constant of the aqueous phase would result in a decreased hydrophobic effect leading to smaller micelles and resulting in smaller binding constants. Although the parallelism between polarity of the medium and micellar binding demonstrates significantly the influence of polarity change on micellar binding, the behavior of dye–surfactant system in different cosolvents may not be influenced only by the dielectric constant of the alcohols but also by its other characteristics such as changing water structure, preferential solvation of RIV, changing micellar size and properties due to the incorporation of alcohol molecules to micelles, and so forth. The most inhibitory effect was seen in the presence of ethanol. Literature survey indicates that the presence of ethanol has a negative influence on hydrophobic interactions due to its destructive action on structured water molecules around the hydrophobic

Table 2. Experimental data of CMCs and values of K_B in the presence of cosolvents for interaction of RIV and surfactants

	SDS		TX-100	
	K_B (M^{-1})	CMC (mM)	K_B (M^{-1})	CMC (mM)
Water	854	3.0	1381	0.4
Glycerin	730	4.0	1200	0.5
Propylene glycol	540	5.0	830	0.6
Ethanol	420	6.0	574	0.8

parts of the surfactant and dye molecules.[52,58] Moreover, a number of studies were reported that the increase in ethanol concentration totally inhibits micellization.[59,60,65]

Polarity of the Micellar Microenvironment and Probable Location of RIV

Micelles are characterized by three distinct regions: a nonpolar core formed by the hydrocarbon tails of the surfactant, a compact Stern layer having the head groups, and a relatively wider and diffuse Gouy–Chapman layer that encompasses a majority of the counterions. Depending on the nature of the dye and the micelle, a dye molecule may bind either to the nonpolar core of micelles or to the micelle–water interface.[5,21,52]

Our data showed that upon going from the aqueous solution to the more hydrophobic micellar environment, RIV underwent a red shift in the absorption maximum. The red shift is a clear indication of the transfer of RIV to less polar site of micelles.[75,76]

In order to gain further insight about the localization of RIV in SDS and TX-100 micelles, we have studied the spectrophotometric behavior of RIV in water–dioxane (DX) mixture of varying composition, because the water–DX mixture resembles the micellar environment. Especially these mixtures resemble nonionic micelles as nonionic surfactants contain polyethylene oxide groups, which are involved in hydrogen bonding with water molecules.[77]

The spectrum of 5.0×10^{-5} M RIV in DX–water solutions as a function of various selected percentages of DX (v/v) is shown in Fig. 3. Similar changes in absorption properties were observed in the presence of DX–water solutions as in the presence of SDS and TX-100 micelles. As the DX portion in DX–water mixture increased (i.e., as the polarity of the medium decreased), the absorption band intensity increased with a progressive red shift (Fig. 4). Both the red shift and increase in molar absorption coefficient indicates a decrease in the polarity or dielectric constant of the medium surrounding the RIV molecule.

Comparison of the red-shifted values obtained in the presence of SDS and TX-100 micelles (8 and 11 nm, respectively) with the red shift values obtained in DX–water mixtures indicates that RIV transferred to less polar (i.e., more hydrophobic) site of the TX-100 micelles.

CONCLUSIONS

The current study clearly demonstrated that the spectral properties of RIV are affected in the presence of anionic SDS and nonionic TX-100 surfactants. The change of spectra at the concentrations above the CMC indicated incorporation of RIV to SDS and TX-100 micelles, while owing to electrostatic

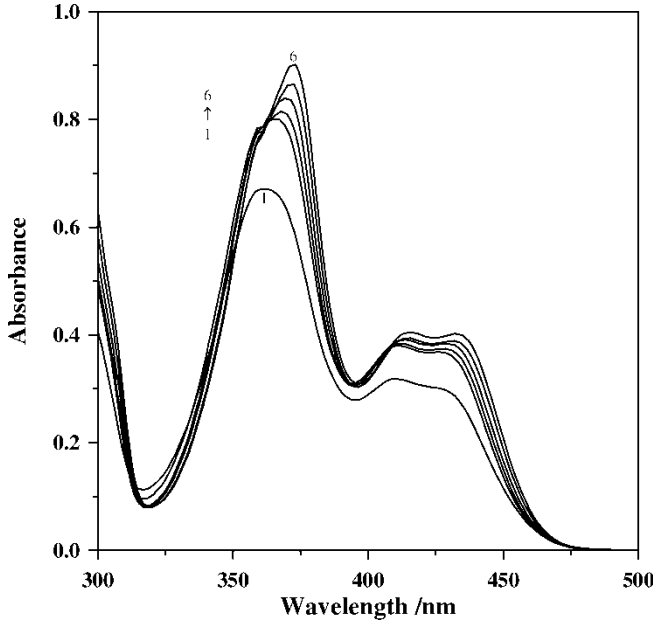


Figure 3. Visible absorption spectra of RIV (5.0×10^{-5} M) in various water–DX mixtures (v/v) at 298 K: (1) 0.0; (2) in 10% (3) in 20% (4) in 30% (5) in 50% (6) in 70% (v/v).

repulsion and insufficient hydrophobic attraction, no binding between cationic RIV and cationic surfactant CTAB were observed. The binding of RIV to SDS and TX-100 micelles was calculated by means of Benesi–Hildebrand equation. It has been found that the binding tendency of RIV to TX-100 micelles is higher than that of SDS micelles.

Comparison of the red shift in SDS and TX-100 micelles with that in DX–water mixtures indicated that RIV transferred from aqueous solution to the more hydrophobic micellar environment of TX-100 and SDS micelles. Electrostatic attraction between the cationic RIV and anionic micelles would favor location of RIV closer to the head group of the respective micelles.

The presence of NaCl has an inhibitory effect on binding of RIV to both SDS and TX-100 micelles (i.e., K_B values decreased in both cases).

Presence of alcohols as glycerin, propylene glycol, and ethanol did not affect the characterizations of absorption spectra of RIV in SDS and TX-100 micelles, indicating the same type of interaction between RIV and micelles as compared with that of pure water. Results show that the addition of alcohols leads to higher CMC values. The binding constant of RIV to both SDS and TX-100 micelles decreased with the presence of these alcohols. Both change in CMC and binding constant depends on the incorporation of alcohols with micelles, and the degree of incorporation depends on the

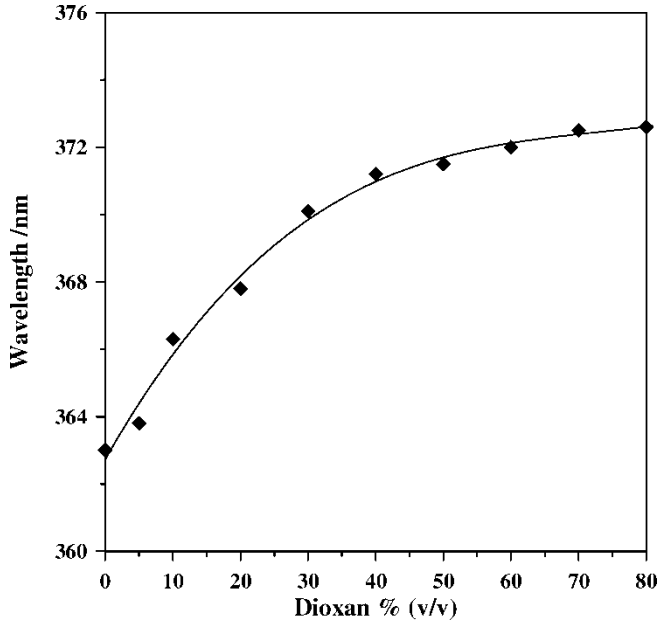


Figure 4. Variation of λ_{max} values of RIV (5.0×10^{-5} M) as a function of DX concentrations (v/v).

number of OH groups in alcohols. The changes in binding constants follow the trend water > glycerin–water > propylene glycol–water > ethanol–water.

Inhibitory effect of alcohols 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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