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Influence of molecular structure on the micellar and interfacial behavior of binary mixtures of amphiphilic drugs and polyoxyethylene ethers

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ABSTRACT

The interactions of cationic amphiphilic drugs (CADs) imipramine hydrochloride (IMP) and promethazine hydrochloride (PMT) with nonionic polyoxyethylenes (Brij 35, 56, 58) have been investigated using tensiometry at four different temperatures ranging from 288.15 to 303.15 K. Despite the attractive interactions (of ion–dipole type) between cationic amphiphilic drugs and nonionic surfactants there occurs an increase in values of A_{min} in the mixed monolayer. Steric factor appears to play an important role during interaction when surfactant molecular structure varies in size of the headgroup. The temperature has been observed to be vital in controlling the dehydration and thermal agitation which, in turn, makes an environment conducive for aggregational behavior of the drug–surfactant mixtures in aqueous solution.

1. Introduction

Not only pharmaceutical excipients such as emulsifiers, solubilizing agents and wetting agents, but also a great number of drugs possess an amphiphilic molecular structure. The drugs are surface active and are also able to form micelles in aqueous solutions at concentrations higher than the critical micelle concentration (cmc). The self-association of amphiphilic drugs is governed by hydrophobic interactions of the apolar and ionic/polar headgroups with themselves.

Due to the widespread applications of surfactants in the pharmaceutical field, especially with respect to surfactant micelle stability, to solubilize hydrophobic drugs, their interactions with drugs have received increased attention [1–4]. Interactions between these components can influence the physico-chemical properties of the dosage form and may alter the stability of formulations and the liberation of active components. The interactions of drugs with surfactant micelles can be visualized as an approximation for their interactions with biological membranes.

The study of the properties of mixtures of surface active drugs in solution provides an opportunity to investigate the influence of the molecular structure of the hydrophobe on the nonideality of mixing because of wide variation in the structure of this moiety. A major influence on the nonideality of mixing in amphiphile mixtures is the nature of the charges of the two amphiphiles. Structural differences between the amphiphiles, e.g., difference in alkyl chain length or length of the oxyethylene chain of nonionic surfactant may also influence the nonideality of mixing. Imipramine hydrochloride (IMP) and promethazine hydrochloride (PMT) are cationic amphiphilic drugs (CADs, Scheme 1) belonging to the first generation of antidepressant drugs [5] which suffer from several drawbacks such as being anticholinegic, and having cardiovascular, and antiarrhythmic side effects [5]. These undesirable side effects of CADs may be reduced if the drugs are properly vectored to the organism. Several vehicles such as cyclodextrins, mixed micelles and vesicles/liposomes are known to overcome these problems; serving as suitable drug vectors in aqueous media. Among all additives, surfactants are widely used in drug delivery to enhance drug aqueous solubility by micelle binding, reduce drug toxicity, facilitate control of drug uptake and improve bioavailability of drugs [6]. The detailed physicochemical understanding of the drug–surfactant mixtures helps in rationalizing materials for pharmaceutical development and formulations. In the present study, we have focused on the micellar (cmc, interaction parameters, micellar composition, activity coefficients, free energy of micellization, etc.) and interfacial properties (surface excess, minimum area per molecule and free energy of adsorption) besides other parameters of binary amphiphilic mixtures of polyoxyethylene ethers (Brij 58, 56, 35) with PMT and IMP at four different temperatures viz. 288.15, 293.15, 298.15, and 303.15 K. The selected amphiphilic systems have dissimilar hydrophobic chain lengths and hydrophilic groups. From a toxicological point of view, nonionic surfactants are generally regarded as most suitable for pharmaceutical formulation. Presently, most of the nonionic surfactants from the Brij series have been explored in vesicle drug delivery concepts [7]. Among them, Brij-58 has obtained special importance due to its stability to form inverted vesicles, which are useful for studying ion-pump activity at the plasma membrane. A recent study [8] showed that Brij-35 forms stable niosomes, having high drug entrapment efficiency. In the

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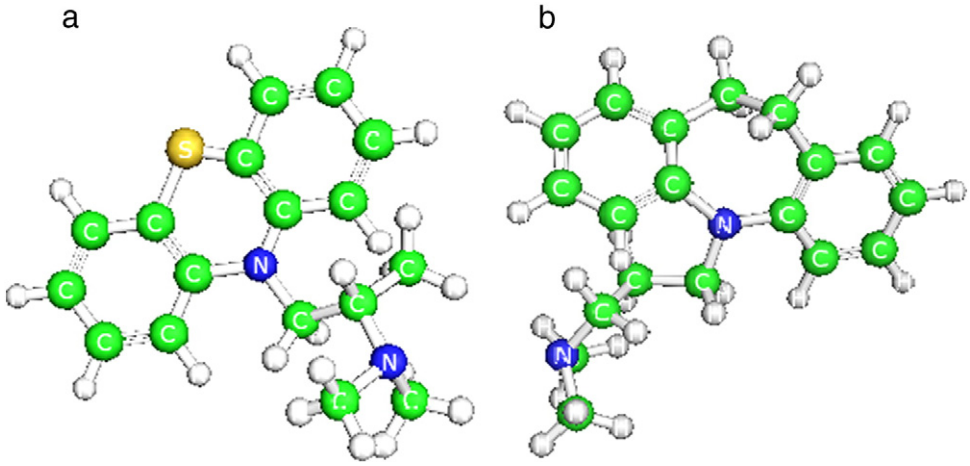

Scheme 1. Structures of PMT (a) and IMP (b).

present study, we have analyzed the amphiphile–amphiphile interactions within the mixed micelles and at interface using the theories of Clint [9], Rubingh [10], Motomura [11], Maeda [12] and Rosen [13,14]. The Clint model is based on the phase separation model and assumes ideal mixing of the amphiphiles in the micellar phase whereas Rubingh's treatment is based on regular solution theory (RST) for nonideal solutions. Maeda introduced the term ΔG_{Maeda} which is a measure of stability for mixed ionic–nonionic systems. Apart from this, Rosen has extended the treatment of Rubingh to estimate (from the surface tension data) the surfactant molecular interaction and also the composition in the mixed adsorbed monolayer at the air/water interface.

2. Experimental

2.1. Chemicals

The investigated imipramine hydrochloride (3-(10,11-dichydro-5H-dibenzo[b,f]azepin-5-yl)-N,N-dimethylpropan-1-amine) and promethazine hydrochloride ((RS)-N,N-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine) of at least 98% purity were purchased from Sigma Chemical Co. (St. Louis, MO, USA). The nonionic surfactants polyoxyethylene(23)lauryl ether (Brij-35, $C_{12}H_{25}(OCH_2CH_2)_{23}OH$,) polyoxyethylene(10)cetyl ether (Brij-56, $C_{16}H_{31}(OCH_2CH_2)_{10}OH$), and polyoxyethylene(20)cetyl ether (Brij-58, $C_{16}H_{31}(OCH_2CH_2)_{20}OH$) were Merck (Germany) products.

2.2. Surface tension measurements

Surface tensions (γ) of the surfactant solutions were measured with a Du Noüy tensiometer model Krüss 11 MK 3 by the principle of detachment of a platinum ring. A Hamilton microsyringe was used to add the drug–surfactant mixture gradually into the water in the measuring vessel maintained at the required temperature (0.05 K) by circulating water from an ORBIT RS10S thermostat. The accuracy of measurements was 0.05 mN/m and tensions were measured at 288.15, 293.15, 298.15, and 303.15 K. The measurements were duplicated, and the mean value was recorded.

3. Results and discussion

3.1. Critical micelle concentration (cmc)

The cmc values of pure and binary mixtures of (IMP-Brijs and PMT-Brijs) at four different temperatures were determined from surface tension (γ) vs log[drug] plots (Fig. 1 presents representative plots for different mole fractions of IMP + Brij-35 mixtures at 293.15 K) and the values obtained are presented in Tables 1 and 2. The experimental cmc values are less than the ideal cmc values obtained by the use of the Clint equation [9] (details of which are given elsewhere [15]) indicating synergistic interaction. The cmc values of pure amphiphiles agree well with the literature values [16,17]. The data show that the increase in bulk mole fraction of Brijs in the mixed systems of both PMT and IMP results in the decrease in cmc values due to the enhancement of the hydrophobic environment in the mixed state resulting in onset of micellization at lower concentrations. The reduction in cmc is the manifestation of different ions and molecules present in the system.

Temperature plays a complex role in controlling the aggregational behavior of amphiphiles in aqueous solution. Increase in hydrophobic interactions is generally considered to be a favorable factor for micellization. Rise in temperature disrupts hydration of the hydrophilic groups making conditions suitable for micelle formation and also breaks down the structured water around the hydrophobic moieties and thereby opposing the micellization. Therefore, the temperature dependence of cmc is controlled by opposing effects. The display of the dominant factor decides the fate of cmc, whether to increase or decrease, over a specified range

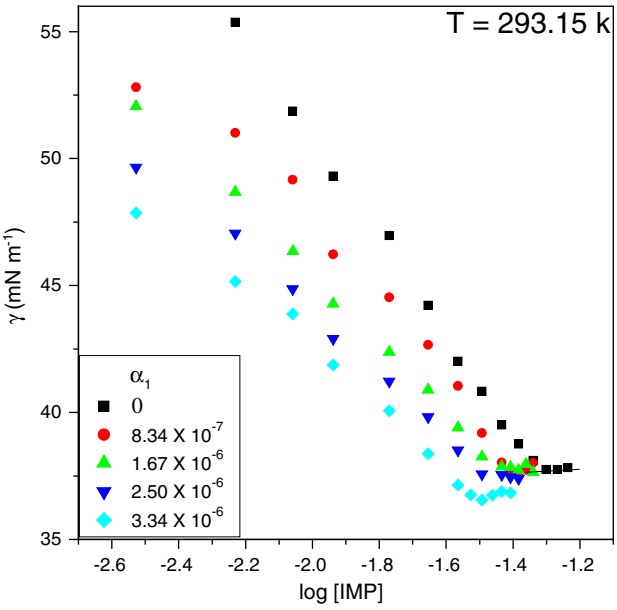

Fig. 1. Plot of surface tension vs [IMP] in the presence of different fixed mole fractions (α_1) of Brij-35.