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# Interfacial and micellar properties of mixed systems of tricyclic antidepressant drugs with polyoxyethylene alkyl ether surfactants

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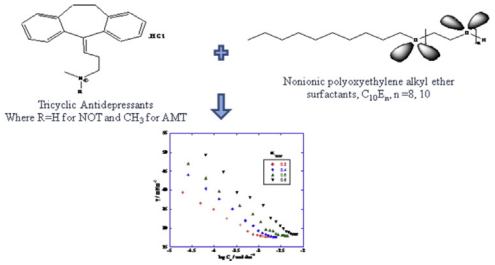
## HIGHLIGHTS

- Micellar and interfacial studies of amphiphilic drugs with nonionic surfactants.
- Drug-surfactant mixtures show improved surface active properties.
- Synergism is observed in all mixed systems.
- Hydrophobicity plays an important role in micellization.

## GRAPHICAL ABSTRACT

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## ABSTRACT

The aqueous mixed systems of tricyclic antidepressants: nortriptyline hydrochloride (NOT) and amitriptyline hydrochloride (AMT) with nonionic polyoxyethylene alkyl ether surfactants: $C_{10}E_8/C_{10}E_{10}$ have been studied to determine the micellar and interfacial behavior and various experimental techniques like surface tension, fluorescence and cloud point have been employed. The micellar, interfacial and thermodynamic parameters like critical micelle concentration (*cmc*), interaction parameter ($\beta$), maximum surface excess concentration ($\Gamma_{max}$), surface pressure at *cmc* ($\Pi_{cmc}$) and minimum area per molecule ($A_{min}$), aggregation number ($N_{agg}$), Gibb's free energy of micellization ($\Delta G_m$), Gibb's free energy of adsorption ($\Delta G_{ads}$), excess free energy of micellization ($\Delta G_{ex}$) have been evaluated. The negative values of interaction parameter obtained from regular solution theory suggest the synergistic interactions in all the proposed mixed systems. The negative values of $\Delta G_m$ and $\Delta G_{ads}$ show that micelle formation and adsorption at the air/water interface is energetically favorable. The higher values of aggregation number show the existence of hydrophobic interactions and supports synergism. The cloud point measurements have also depicted enhancement of hydrophobicity in the mixed micelles with an increase in concentration of nonionic surfactants.



## 1. Introduction

The amphiphilic drugs such as phenothiazine and benzodiazepine tranquillizers, analgesics, non-steroidal anti-inflammatory and tricyclic antidepressants have strong tendency to self-associate like surfactants [1–4]. Among these drugs, tricyclic antidepressants (TCA's) have been keystones of antidepressive therapy for over three decades. The selected TCA's namely nortriptyline hydrochloride (NOT) and amitriptyline hydrochloride (AMT) are the most widely used tricyclic antidepressants in the mental health care. These drugs constitute planar tricyclic ring system with a short hydrocarbon chain carrying a terminal charged nitrogen atom. A "surfactant-like" behavior exhibited by these drugs is conferred by the presence of the alkyl amine side chain [5–7]. An important relation between two drugs NOT and AMT is that NOT is the active metabolite of AMT which is methylated in the liver and both

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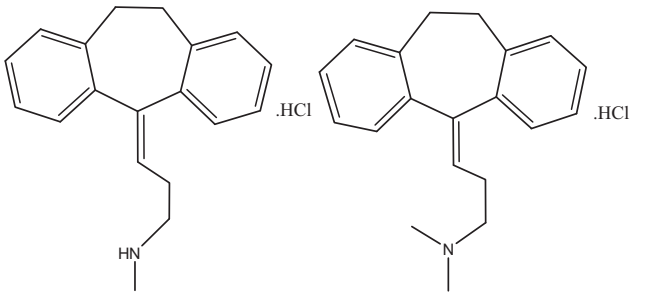
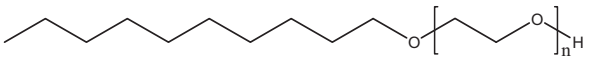
possess similar shortcomings such as seizures, tinnitus, cardiovascular, hypersensitivity, hypotension and mania side effects [8,9]. These undesirable side effects may be minimized if the drugs are properly targeted to the organ. Limited aqueous solubility of drug molecules poses a serious obstacle in designing their formulation, dosage form and the liberation of active components therefore; various vehicles such as cyclodextrins, mixed micelles and vesicles/liposomes have been employed as drug vectors [10–15].

Micellar solubilization by employing surfactants as drug vector is the most effective method since it reduces the contact of drug with inactivating species like enzymes and thus, reduces the side effects of drugs. Interactions of drugs with surfactant micelles have been visualized as an approximation for their interactions with biological membranes so to rationalize materials for pharmaceutical development and thus, understanding of physicochemical aspect of drug-surfactant interactions is mandatory [16–18]. Among various surfactants, nonionic surfactants are chemically potent molecular species that are becoming increasingly important as excipients used in the pharmaceutical formulations, delivery of drugs and vaccines [19–21]. These are biodegradable, less toxic, stable and mild in nature. These surfactants form micelles in dilute solution and by using proper combination of oxyethylene and alkyl chain parts, their aqueous solubility and hydrophobic–lipophilic balance (HLB) value can be optimized. The interfacial tension produced by polyoxyethylated nonionic surfactants when they form aggregates is usually higher as compared to ionic surfactants, making the nonionic surfactants less destructive on cell membranes and thus, less irritating. They play essential role in wetting, emulsification, cancer research, formulations of paint and personal care products [22–25]. The polyoxyethylene alkyl ether surfactants used in the present study are free of counterion effects which have strong impact on self assembly in water and non aqueous solvents. These possess better solubilization properties and high surface activity. The aggregation of nonionic surfactants occurs due to three driving forces: hydrogen bonding, hydration and hydrophobic interactions. Among these, hydrophobic interactions provide large contribution. Recently, Kabir-ud-din et al. have studied the interactions between amphiphilic drugs imipramine hydrochloride (IMP) and promethazine hydrochloride (PMT) with nonionic polyoxyethylenes (Brij 35,56,58) using surface tension technique [33]. Our research group has investigated the interactions between amitriptyline hydrochloride (AMT) and a new series of cationic surface active ionic liquids based on DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) by employing conductivity and surface tension techniques [2].

Keeping in mind the importance of drug-surfactant mixed systems, the present work is focused on the on the micellar and interfacial interactional behavior of tricyclic antidepressants (TCA): nortriptyline hydrochloride (NOT) and amitriptyline hydrochloride (AMT) drugs with nonionic polyoxyethylene alkyl ether surfactants: octaoxyethylene glycol monodecyl ether ($C_{10}E_8$) and decaoxyethylene glycol monodecyl ether ($C_{10}E_{10}$) using surface tension, fluorescence and cloud point techniques. Surface tension measurements provide information about the interfacial properties of the mixed systems and interactions between them, while fluorescence measurements throw light on the variation of aggregation number of mixed systems. The various micellar and interfacial parameters like experimental *cmc*, interaction parameter ($\beta$), activity coefficients ($f_1$, $f_2$), micellar mole fraction of drug in the mixed state ($X_1$), maximum surface excess concentration at the air/water interface ($\Gamma_{max}$), minimum area per molecule ($A_{min}$), surface pressure at *cmc* ($\pi_{cmc}$) are evaluated using surface tension technique. Various thermodynamic parameters like Gibb's free energy of micellization ($\Delta G_m$), Gibb's free energy of adsorption ($\Delta G_{ads}$), excess free energy of mixed micellization ($\Delta G_{ex}$) have been calculated. Aggregation numbers ($N_{agg}$) of the pure and mixed systems are calculated using fluorescence quenching technique.




(a) Nortriptyline Hydrochloride (NOT) (b) Amitriptyline hydrochloride (AMT)




(c) Nonionic polyoxyethylene alkyl ether surfactants, $C_{10}E_n$, n =8, 10

**Fig. 1.** Chemical structures of tricyclic antidepressants: (a) Nortriptyline hydrochloride (NOT), (b) amitriptyline hydrochloride (AMT), and (c) nonionic polyoxyethylene alkyl ether surfactants, $C_{10}E_n$, $n = 8, 10$.

It is well known that in considering a nonionic surfactant system as a drug delivery vehicle, temperature variation can affect the drug-surfactant stability and can lead to precipitation of drug which may affect its therapeutic action. Therefore, to evaluate the stability of proposed drug-surfactant mixtures, phase behavior of drug-surfactant mixed system has also been studied along with a detailed evaluation of various micellar and interfacial parameters.

## 2. Experimental

### 2.1. Materials

Amphiphilic drugs: nortriptyline hydrochloride (NOT) and amitriptyline hydrochloride (AMT) with purity ≥98.0% were purchased from Sigma–Aldrich. Nonionic polyoxyethylene alkyl ether surfactants ($C_{10}E_8$, $C_{10}E_{10}$) of varying ethoxylate content with 99.0% purity were received from BASF as gift samples. Fig. 1 shows the structure of tricyclic antidepressants and nonionic polyoxyethylene alkyl ether surfactants. The fluorescence probe pyrene employed to perform fluorescence studies was obtained from Sigma–Aldrich. Hexadecylpyridinum chloride (HpyCl), a quencher with 98.0% purity was purchased from Lancaster Synthesis, UK. All products were used as received. All the solutions were prepared in double distilled water. A sartorius analytical balance with a precision of ±0.0001 g was used for weighing purpose.

### 2.2. Methods

#### 2.2.1. Surface tension measurements

Surface tension measurements were performed using ring detachment method on KRUSS Easy Dyne tensiometer (Hamburg, Germany) at room temperature. Tensiometer was calibrated with double distilled water before commencement of each experiment. The measured surface tension values were corrected according to the procedure of Harkins and Jordan inbuilt instrument software. The p*K*a values of the drugs lie between 9.1 and 9.4 and pH of solution is approximately 7. For the determination of critical micelle concentration, surfactant solution of concentration higher than its *cmc* value was added in small instalments and surface tension was noted after thorough mixing. The accuracy in the measurement of surface tension using a tensiometer was ±0.15 m $Nm^{-1}$.