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Thermodynamic, interfacial and hydrodynamic aspects of interaction of cationic drug amitriptyline hydrochloride with anionic and nonionic polymers

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ABSTRACT

Interaction of amitriptyline hydrochloride (AMT), a tricyclic antidepressant amphiphilic drug, was seen with various polymers using conductometry, surface tensiometry and viscometry. Amphiphilic drug interacted with polymers in a surfactant like fashion. The plots of specific conductivity versus concentration of drug were nonlinear with three different linear regions and with two clear breaks. First break point, i.e., critical aggregation concentration (C_1), appeared well below the usual critical micelle concentration while polymer domain saturated at quite higher concentration (C_2). In case of surface tension measurements, the isotherms were composed of three identifiable points termed as T_1, T_2 and T_3. T_1 signaled the onset of the interaction, i.e., C_1, while T_2 is regarded as the saturation of the polymer backbone. For weakly interacting polymers the surface tension isotherms were different from the strongly interacting polymers. Viscosity measurements suggest the relative size of the polymer-drug complex which changes differently for each polymer according to their nature of interactions. Free energies of aggregation (ΔG_{agg}) and micellization (ΔG_{mic}) were computed with the help of degrees of micelle ionization obtained from the specific conductivity — [AMT] plots.

1. Introduction

Several drug molecules such as phenothiazine and benzodiazepine tranquilizers, analgesics, tricyclic antidepressants and non-steroidal anti-inflammatory drugs display amphiphilic behavior [1]. Owing to the characteristics of self aggregation, amphiphilic drugs are always the concerns of the pharmacists and scientists. They behave like surfactants and self aggregate above certain concentrations; known as critical micelle concentrations (cmc) [1–8]. Although the micellar aggregation numbers of these drugs are rather less as compared to the numbers observed for surfactants, the understanding of their aggregation behavior under various conditions is necessary in order to get some insight on their delivery and physiological action [9,10]. Though their therapeutic action might start well below the critical micelle concentration, the aggregation of these drugs as a result of accumulation and likely localized high concentration inside the human body is also possible. It is further of interest to see their interaction with career molecules such as polymers, nanomaterials, dendrimers, etc.

Polymers have been used extensively in the drug delivery formulations [11–15]. Several polymers like, poly ethylene glycol (PEG), polyvinylpyrrolidone (PVP), and cellulose ethers have recognized in many drug targeting applications due to their biodegradability, biocompatibility and very low or no toxicity. These polymers are important ingredients in many technological applications, particularly, in the pharmaceutical, cosmetics and medical fields where they are useful in various ways such as to regulate the rheology of a system and to control the release of the drug. These polymers possess an amphiphilic structure with mixed hydrophilic/hydrophobic segments that leads to an apparent surface activity and the magnitude of which depends on type and degree of substitution [16].

The interaction between polymers and surfactants in aqueous solution has attracted great interest during the several decades, and the topic has thoroughly been reviewed [17]. It has been shown that all types of surfactants (cationic, anioinic and nonionic) interacts with the polymers in a cooperative manner [18–20].

In our previous paper we have studied the effect of drug on the hydrodynamic size of the polymers [21]. The effect of surfactants and salts on the phase behavior of important cellulose ether hydroxypropylmethyl cellulose (HPMC) was also investigated [22,23]. Very recently, it was found that nonsteroidal anti-inflammatory drug ibuprofen interacts with polymers in a typical surfactant like manner, i.e., appearance of two types of aggregation phenomenon (i) critical aggregation concentration (C_1) at which the interaction of polymer and amphiphile begins and (ii) polymer saturation point or apparent critical micelle concentration (C_2) corresponding to the saturation of polymer domain with amphiphile and the onset of formation of independent micelles [24]. The interaction was dependent on both hydrophobicity as well as the charge of both the drug and polymers. The anionic drug interacted with cationic polymers more strongly as compared to the nonionic though anionic surfactants had shown the least interaction. From the observed results it was concluded that hydrophobicity plays an important role in the

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interaction as it overcomes the likely repulsion between the anionic drug and anionic polymers. All these previous studies motivated us to explore the effect of cationic drug with various polymers. Therefore, in this paper we have studied the effect of amitriptyline hydrochloride, AMT (Scheme 1), with various polymers like HPMC, dextran sulfate (DxS), sodium carboxymethyl cellulose (NaCMC), poly ethylene glycol (PEG) and polyvinylpyrrolidone (PVP) using conductometry, surface tensiometry and viscometry.

2. Materials and methods

2.1. Materials

The amphiphilic drug amitriptyline hydrochloride (AMT) (99%, Sigma, USA), neutral polymers, i.e., polyvinylpyrrolidone K 30 (Fluka, Switzerland), polyethylene glycol K 35 (Fluka, Germany), hydroxypropylmethyl cellulose (Sigma, USA), and anionic polymers, i.e., sodium carboxymethyl cellulose (Sigma, USA) and dextran sulfate (Merck, Germany), were used as received. Demineralized double-distilled water of specific conductivity $(1–2)\times10^{-6}$ S cm^{-1} was used to prepare the stock solutions of the drug and polymers.

2.2. Conductivity measurements

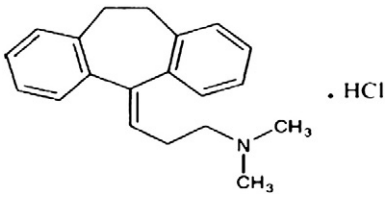
The conductivity measurements were executed on an ELICO (type CM 82 T) bridge equipped with platinized electrodes (cell constant = 1.02 cm^{-1}). The conductivity runs were carried out by adding gradually concentrated AMT stock solution into the thermostated solvent or solvent including polymer at temperature 25 °C. The critical micellar concentration of the pure AMT used was obtained from the plots of specific conductivity (κ) as a function of the drug concentration. The cmc values were taken from the intersection of the two straight lines drawn before and after the intersection point in the plots (Fig. 1). As in case of the polymer-drug mixtures the plots of κ versus [drug] showed two breaks (Figs. 2–6), the C_1 was determined by the intersection of first and second linear parts and the C_2 in this case was the intersection point of the second and third linear parts.

2.3. Surface tension measurements

Surface tension measurements were carried out by using S. D. Hardson tensiometer (Kolkata, India). In case of pure drug, the equilibration time was 15 min, whereas the drug-polymer solutions were equilibrated at least for 30 min. Thus, the values of surface tension (γ) were noted when it did not vary with time. The average values of equilibrium γ were obtained by repeating the measurement three times. The C_1 and C_2 values were estimated by the intersection between the two linear portions of γ–log [drug] isotherms.

2.4. Viscosity measurements

The viscosities were measured using an Ubbelhode suspended level capillary viscometer. The viscometer was always suspended vertically in a thermostat with a temperature stability of ±0.1 K in the investigated region. The requisite amount of drug was added in polymer solution. These solutions were used as stock solutions to see the effect of drug concentration. A high concentration solution was prepared for a typical drug, and further lower concentrations were made by dilution from above stock. Viscosities of such solutions under Newtonian flow conditions were obtained as described elsewhere [25]. Density corrections were not made since these were found negligible [26].



Scheme 1. Structure of amitriptyline hydrochloride.

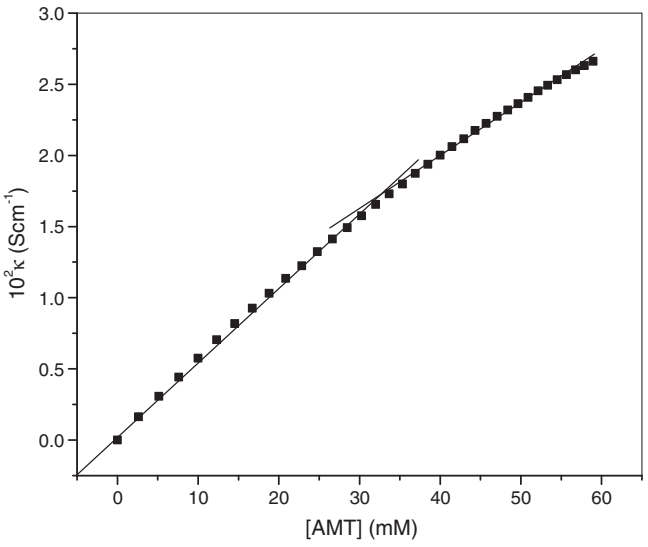


Fig. 1. Plot of specific conductivity (κ) versus [AMT] at 25 °C.

3. Results and discussion

3.1. Conductivity measurements

For the titration of AMT into pure water, the conductivity below the cmc is due to the contribution of drug's head-groups and counterions. Above the cmc, the rate of the conductivity is smaller because micelles have rather lower mobility and a fraction of counterions is ion-paired with the micelles [27]. According to observed break in the

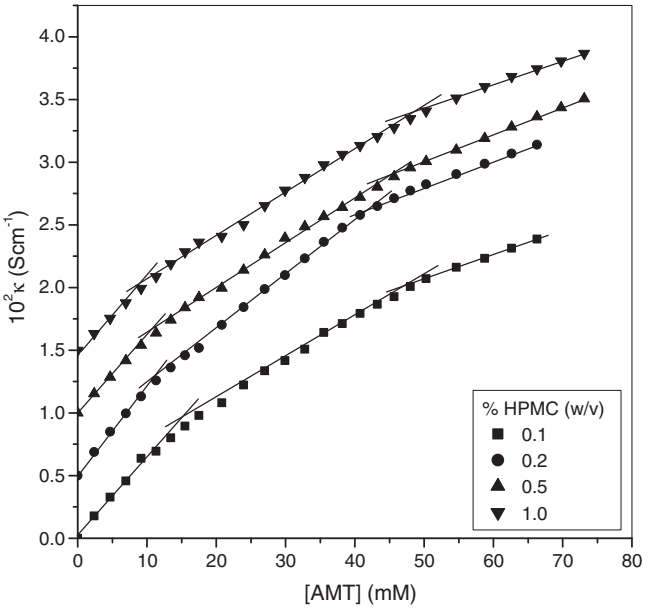


Fig. 2. Plots of specific conductivity (κ) versus AMT concentration at different concentrations of HPMC. The scale shown is for the plot denoted as (●). Other plots have been shifted upwards by 0.5, 1.0, and 1.5 scale units (1×10^{-2}Scm^{-1}), respectively.