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Tensiometric and conductometric studies of the effect of polymers on the aggregation behavior of cationic amphiphilic drugs IMP and PMT

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ABSTRACT

The present work is aimed at studying the interactions of two cationic amphiphilic drugs, viz. imipramine hydrochloride (IMP) and promethazine hydrochloride (PMT), with several polymers (cationic, nonionic, and anionic) in aqueous solutions by using tensiometric and conductivity measurements. The onset of interaction, the so-called critical aggregation concentration (CAC), decreases on increasing the polymer concentrations whereas the critical micelle concentration (CMC) of the drugs rises. The strength of interaction was found to be dependent upon the nature of the polymers. The interaction between the anionic polymer NaCMC and drugs was maximum while it was minimum in case of drug–cationic polymer HECEQ system. The interfacial parameters like Gibbs surface excess (Γ_{max}) and the minimum area occupied by the drug monomer (A_{min}) have been estimated. The free energies of adsorption (ΔG^0_{ad}), aggregation (ΔG^0_a), micellization (ΔG^0_m) and transfer (ΔG^0_t) associated with the interactions between the drugs and polymers have also been evaluated.

1. Introduction

Several drug molecules, e.g., tricyclic antidepressants [1,2], phenothiazines [3–5], benzodiazepine [6], analgesics [7], and non-steroidal anti-inflammatory drugs [8], are amphiphilic in nature. They tend to self-assemble in a typical surfactant-like manner to form aggregates above certain threshold concentration. However, unlike typical surfactant molecules, they do not form simple spherical micelles; instead, their aggregates are non-spherical [9]. Despite the fact that the aggregate formation in these drugs generally occurs at concentrations well above their therapeutic levels, a possibility of their accumulation at a particular site in human body still exists. This can cause a localized high concentration which may affect the drug's biological activity. To avoid such side effects, various vectors are used for drug delivery to target the required sites.

Advances in polymers, nanoparticles, surfactants, and liposomes have enabled to make advancement in designing carriers/vectors or protective agents for controlled release or delivery of drugs. In this context polymers have special importance due to availability of a variety of biocompatible and biodegradable polymers for pharmaceutical applications. It has been demonstrated that the polymer–amphiphile interactions depend on the polymer as well as on the amphiphile concentration [10]. Addition of an amphiphile into a polymer solution induces the onset of binding between the components at a given amphiphile concentration at which interaction between amphiphile and polymer starts (known as critical aggregation concentration, CAC), followed by the formation of aggregates bound to the polymer, and the formation of free micelles when the binding sites of polymer are saturated by the amphiphile monomers [11]. Contrary to this, there are reports that, in some cases, the free micelle formation can occur long before the polymer saturation [11,12]. Generally, the CAC does not depend on the polymer molecular weight; instead, it depends on the nature of polymer and the polymer saturation concentration [12,13]. The amphiphile–polymer interactions have many applications in various areas, but in the field of colloid chemistry it has become more important in view of their wide industrial applications [14]. In spite of lot of work devoted to this field, the aspect which still remains not fully understood is the complex nature of drug–polymer interactions.

In case of surfactant–polymer interactions, it is comparatively easier to understand the cationic polymer–anionic surfactant/anionic polymer–cationic surfactant interactions due to Coulombic attractions. In the case of neutral polymers, however, the situation demands consideration of factors such as the nature of the surfactant head group, the nature of the polar groups embedded in the polymer backbone, and polymer hydrophobicity [15]. Polymers and surfactants strongly interact with each other when they are present together either inherently or by design. This significant interaction is important in diverse areas like detergency, enhanced oil recovery, paint formulation, mineral and materials processing, chemical reactivity, etc. [16–20]. In continuation with our keen interest on drug–polymer [21–25] and analogous surfactant–polymer interactions [26–31], we have selected two cationic

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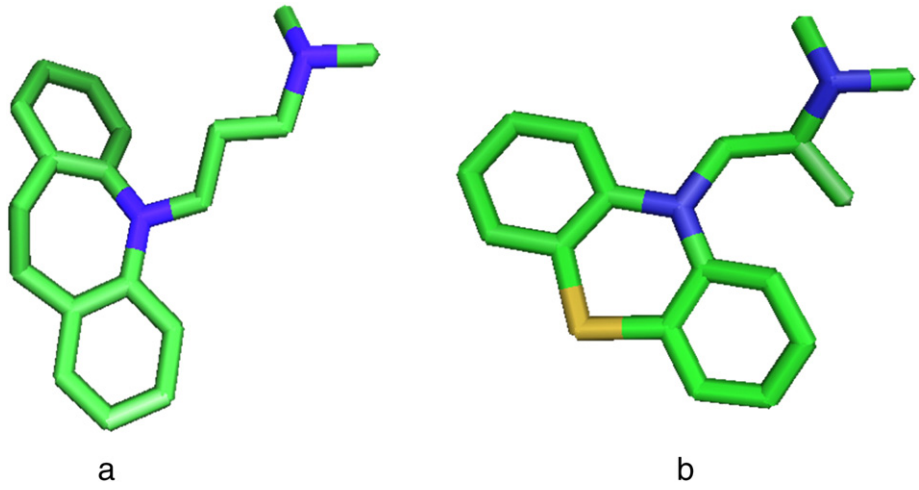

Fig. 1. Molecular structure of amphiphilic drugs (a) imipramine hydrochloride (IMP) and (b) promethazine hydrochloride (PMT).

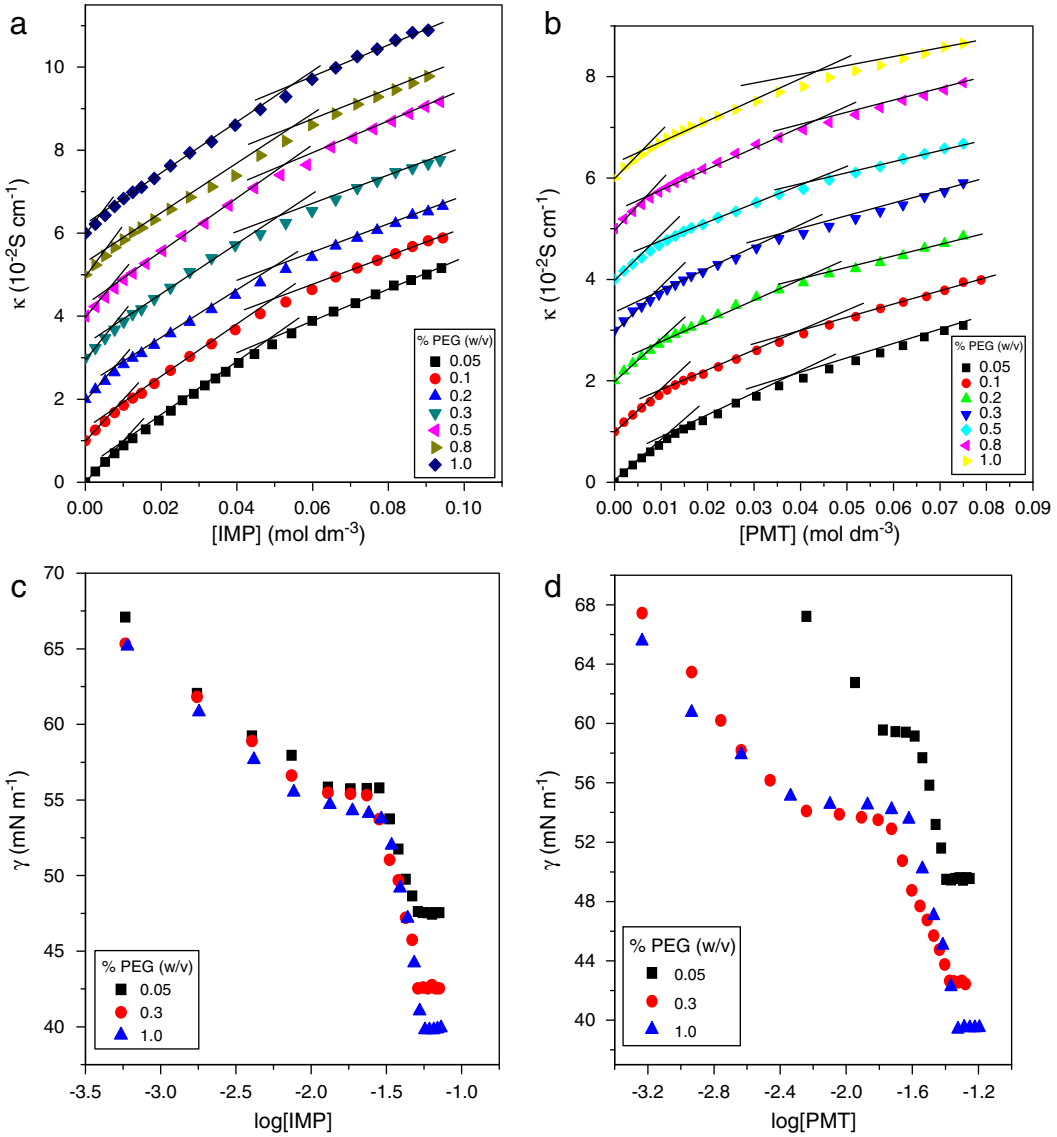

Fig. 2. Conductance (a, b) and surface tension (c, d) plots versus [drug]. The scale shown in (a) and (b) is for plot denoted as (■) whereas the other plots have been shifted upwards by 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 scale units (1×10^{-2} S cm^{-1}), respectively.