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ORIGINAL ARTICLE

Influence of additives (inorganic/organic) on the clouding behavior of amphiphilic drug solutions: Some thermodynamic studies

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Abstract Herein we provide a detailed result about the effect of various additives, viz. inorganic salts, quaternary ammonium bromides (QABs) and amino acids on clouding behavior of amphiphilic drug amitriptyline hydrochloride (AMT). The continuous increase in the cloud point (*CP*) of drug by increase in inorganic salt concentration and the magnitude of increases rely upon the position of the salts in Hofmeister series and hydrated radii. The QABs also influence continuous increase in the *CP*, which is illustrated in terms of the alkyl chain length of peculiar QAB. The effect of amino acids on *CP* of the drug solution is dependent upon the characteristics (acidic, basic, polar or nonpolar) of particular amino acids. The overall behavior of additives has been analyzed and discussed on the basis of electrostatic repulsion or interaction, micellar growth, and mixed micelle formation between the ingredients. In addition to this, thermodynamic parameters are also evaluated.

1. Introduction

Like surfactant many amphiphilic drug molecules (analgesics, phenothiazines, tranquillizers, peptides, tricyclic antidepressants, antibiotics, etc.) also self-associate in aqueous solution to form small aggregates so called micelles (Taboada et al., 1999; Schreier et al., 2000; Krishnan et al., 2003; Mandal et al., 2010; Tiwary et al., 2011; James and Mandal, 2011; James et al., 2011). Micelle formation can be regarded as a choice mechanism to adsorption at the interfaces for dismissal of hydrophobic groups from contact with water, thereby diminishing the free energy of the systems. It is well known that amphiphilic molecules act differently when present in

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micelles than as free monomers in solution. As amphiphilic drug molecules bear an ionic or nonionic polar headgroup and a hydrophobic portion, their self-association powerfully depends on a number of parameters, involving (a) structure of amphiphile (b) presence of salt, cosolute, etc. and (d) temperature (Rosen, 2004). The concept of micelle solutions originates from their ability of becoming as functional molecular assemblies for use in many fields in pure and applied science. They can be used as template for various biochemical and pharmacological schemes and can solubilize water-insoluble materials (including particular medicines and drugs) in their hydrophobic cores (Barzykin and Tachiya, 1996). Although aggregation of the drugs could act as their own carriers and it has been also claimed that the drug vesicle formation is able to be carried out (Vaizoglu and Speiser, 1986), even though, most drugs are not lipophilic to sufficient degree to form vesicles so that they require drug delivery systems to implement them into the body. Therefore, over the years, micelles have been of interest to pharmacological scientists either as drug delivery or as targeting systems (Lawrence and Rees, 2000).

Nonionic surfactants are thought to be true to owe their solubility in water through hydrogen bonding; on heating, these weak hydrogen bonds break and by means of that turn down the surfactant solubility in water. Hence, cloud point (*CP*) phenomenon is usually observed in aqueous nonionic surfactant solutions when the temperature of the surfactant solution is elevated to a particular value (Al-Ghamdi and Nasr-El-Din, 1997; Gu and Galera-Gomez, 1999; Schott, 2001; Shigeto et al., 2001). The phase separation occurs within a temperature range that is moderately constant for surfactant concentrations within a narrow range (Nakagawa and Shinoda, 1963). The phases that come into view are composed of an almost micelle-free dilute solution of the nonionic surfactant and a surfactant-rich micellar phase. The phase separation is reversible and, on cooling, the two phases merge to form a clear solution. In what way, for ionic surfactants, occurring of the clouding phenomenon is unusual because electrostatic repulsions among charged micelles impede occurrence of phase separation. In these systems, the happening of clouding (under unique situations) is illustrated, in terms of charge neutralization and raised hydrophobic interactions (Kumar et al., 2000, 2002, 2003).

Clouding happens in many amphiphilic drug solutions too. As additives change solution properties, their presence have an affinity to effect the clouding. Many workers have deliberated the effect of various additives on the cloud point of amphiphilic drugs recently (Kim and Shah, 2002, 2003; Alam et al., 2010a,b,c,d, 2011; Kabir-ud-Din et al., 2010a,b; Naqvi et al., 2011). In the present study, amitriptyline hydrochloride (AMT – a tricyclic antidepressant) was considered as a model drug. It contains a tricyclic ring and alkyl amine side chain (Fig. 1). The tricyclic part of AMT molecule is hydrophobic and alkyl amine part is hydrophilic. The pharmacological undertaking of these drugs comes into view at low concentrations where aggregation is insignificant (Attwood, 1995). However, the agglomeration of drug can occur at particular site of organism after long period of administration, giving rise to making of aggregates that are lacking ability to pass by way of membranes; decreasing transport rate and, as a result, leading to hostile effect on health. Thus, the study of physico-chemical properties of an amphiphilic drug is significant from physical, chemical, biological and pharmaceutical outlook for their implication. AMT feel pain from distinct drawbacks such as anticholinergic, cardiovascular and antiarrhythmic side effects. These side effects may be lessened if the drug is properly targeted to the organism. Here, we give an account the effect of various additives like inorganic salts, quaternary ammonium salts, and amino acids, on *CP* behavior of AMT solution prepared in 2.5 mM CTAB + 10 mM sodium phosphate (SP) buffer solution (pH = 6.7).

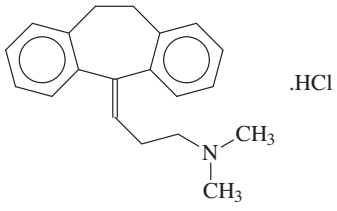

Figure 1 Molecular structure of amitriptyline hydrochloride (AMT).

2. Materials and methods

AMT (⩾98%, CAS Registry No. 113-52-0, Sigma, USA), lithium chloride, LiCl (98%, Loba Chemie, India), lithium bromide, LiBr (99.4%, Riedel–deHaen, Germany), sodium fluoride, NaF (97%, BDH, England), sodium chloride, NaCl (99.9%, BDH, England), potassium chloride, KCl (99.8%, BDH, India), sodium bromide, NaBr (99.8%, Loba Chemie, India), potassium bromide, KBr (99%, Merck, India), ammonium chloride, NH_4Cl (99%, Merck, India), ammonium bromide, NH_4Br (99%, Loba Chemie, India), tetramethylammonium bromide, TMeAB (⩾97%), tetraethylammonium bromide, TEtAB (⩾98%), tetra-*n*-propylammonium bromide, TPrAB (⩾98%), tetra-*n*-butylammonium bromide, TBuAB (⩾99%), tetra-*n*-pentylammonium bromide, TPeAB (⩾99%), (all Fluka, Switzerland), aspartic acid (⩾99.0%), glutamic acid (⩾99.0%), glycine (⩾99.5%), phenylalanine (⩾99.0%), alanine (⩾99.0%), (all SISCO, India), leucine (⩾99.9%, E. Merck, Germany), asparagine (⩾99.0%, Reanal, Hungary), threonine (⩾98.5%, BDH, England), lysine monohydrochloride (⩾99.0%, s.d. fine, India), arginine monohydrochloride (99.0%, Loba Chemie, India), were used as received without any further purifications. Trisodium phosphate dodecahydrate (TSP) and sodium dihydrogen phosphate monohydrate (SDP) were of reagent grade procured from Merck, India.

All the solutions were prepared in double-distilled water with specific conductivity: $(1–2) \times 10^{-6}$ S cm^{-1} at 30 °C. Combination of TSP and SDP were used to fix the pH of the sample solutions (Britton, 1942). The drug solutions were prepared in cetyltrimethylammonium bromide (CTAB) and sodium phosphate (SP) buffer solutions (pH = 6.7).

For determining the *CP*, the sample solution was taken in a Pyrex glass tube, which was then stoppered and put in a controlled heating set-up. The temperature was elevated slowly, at the rate of 0.5 °C/min near the *CP*, and the beginning of surprising clouding in the solution was noted. The temperature was subsequently lowered until the sample became clear again. The temperature was cycled (twice) in this way to get the mean *CP*. Uncertainty in *CP* measurements was ±0.5 °C. Unless referred to under other circumstances, the pH and drug