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Research paper

Partitioning of drugs in micelles and effect on micellization: Physicochemical insights with tryptophan and diclofenac sodium

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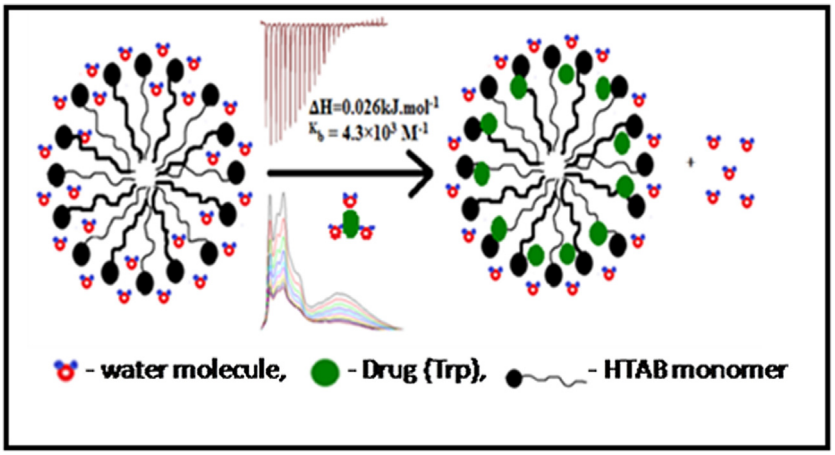
HIGHLIGHTS

- Interactions of Trp with HTAB, TX-100 and their mixed micelles are described.
- Partitioning of Trp. in HTAB micelles is exclusively mechanized.
- Balance of hydrophobic and hydrophilic interaction results in small $\Delta H_{saturation}$.
- Trp is partitioning in outer palisade layer of HTAB micelles.
- Diclofenac sodium partitions better in mixed micelles than individual.

GRAPHICAL ABSTRACT



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ABSTRACT

Rational drug design is undoubtedly an extremely important objective for chemists and biologists. As a step in this direction, quantitative understanding of physical chemistry underlying partitioning of drugs in drug delivery vehicles such as micelles provides guidelines to meet such an objective. Interactions of tryptophan (chosen as a model drug) and diclofenac sodium (nonsteroidal anti-inflammatory drug) have been studied with the micelles and monomers of cationic surfactant hexadecyltrimethylammonium bromide (HTAB), non-ionic surfactant triton X-100 (TX-100), and their mixture. This has been addressed in terms of changes in physicochemical properties such as standard molar enthalpy, entropy and Gibbs free energy of partitioning in combination with pyrene fluorescence emission and dynamic light scattering measurements. The mechanism of partitioning of the drugs in individual micelles, micellar mixture, and interaction behavior with the monomers has been discussed. The energetics of interaction of partitioning, correlated with the functional groups on a wide range of drugs can be very important in deriving guidelines for target oriented synthesis. The effect of drugs on micellization properties of HTAB, TX-100 and their mixture has also been addressed.

1. Introduction

Acquiring required solubility of hydrophobic drugs in aqueous environment has been a challenge [1]. Micelles have been used [2–5] as suitable drug delivery vehicles since they can incorporate

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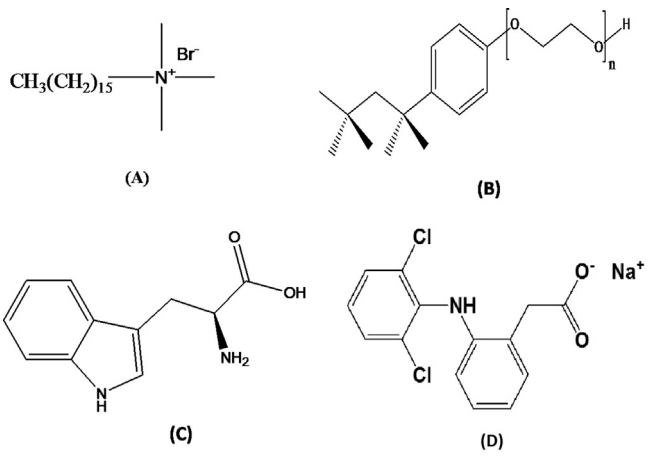

Fig. 1. Chemical structures of (A) hexadecyltrimethylammonium Bromide; (B) TritonX-100 and (C) Tryptophan (D) Diclofenac sodium.

hydrophobic molecules in the hydrophobic core or in the palisade layers, positioning of which depends upon the hydrophobic content of the drug. Further, the partitioning ability of molecules can be tuned in terms of their properties depending upon the desired delivery at the target. Quantitative insights into the partitioning phenomena in terms of thermodynamic parameters of interaction and their relationship with the functional groups on the drug molecules can provide guidelines for suitable modification of the drug and the partitioning medium.

Micelles are highly ordered aggregates formed by association of surfactant monomers. Usually micelles are spherical in shape with internal hydrophobic region and hydrophilic head groups [6]. With change in solution conditions and concentration of surfactant, micelles have turned into ellipsoidal, cylindrical and bilayer structures [7–9]. Such unique structures of micelles offer different extent of partitioning depending upon the properties of incoming molecules. For example, increased hydrophobic content of the molecule can lead to its greater partitioning into the palisade layers of the micelle. Micelles mediated drug delivery has been reported to be effective in the release of drugs at the sites having low pH, such as carcinoma [10], the condition under which it demicellizes thereby releasing the drug molecules.

With the availability of high sensitivity of isothermal titration calorimetry (ITC), it has now become possible to address systems in which weak interactions play a dominate role. Although ITC has been extensively used in addressing binding of drugs to transport proteins from a very low affinity to tightly bound systems, its use in addressing drug partitioning has only been recent [11].

In order to obtain quantitative insights into drug partitioning phenomena in self assemblies, we need to have information on such systems comprising of very simple and small to complex and large drug molecules. In this work we have chosen tryptophan (Trp) and diclofenac sodium (DCF) drugs (Fig. 1). Trp is an essential amino acid of human diet and has been used in the treatment of several diseases such as depression [12], mood disorders, insomnia, and hypertension [13]. Another advantage of choosing Trp is its small size and simple functionalities which will enable a clear correlation between structure and energetics, thus serving as one of the steps toward understanding of partitioning and delivery of complex molecules. The anti inflammatory DCF is widely used to relieve swelling and joint stiffness caused by arthritis [14] and has comparable results with naproxen, ibuprofen, sulindac and diflunisal in osteoarthritis treatment. It has also been used to reduce pain resulting from minor surgery, trauma and dysmenorrhoea [15]. The surfactants chosen for the present work are cationic, nonionic and their mixture in the monomeric and the micellar forms. Hexadecyltrimethyl-ammonium bromide (HTAB) ($(C_{16}H_{33})N(CH_3)_3Br$ (Fig. 1), is an amine-based cationic surfactant with the quaternary ammonium group at corona of the micelle. It is one of the components of the topical antiseptic cetrimide[16]. The cetrimonium (or hexadecyltrimethylammonium) cation is an effective antiseptic agent against bacteria and fungi [16]. Triton X-100 ($C_{14}H_{22}O(C_2H_4O)_n$) (Fig. 1) is a nonionic surfactant having hydrophilic polyethylene oxide chain usually with n = 9–10 and an aromatic hydrocarbon group with a 4-(1,1,3,3-tetramethylbutyl)-phenyl group. Its use as an ingredient in influenza vaccine has also been reported [17].

Binary mixtures of surfactants are advantageous over the single surfactant as their properties are complementary [18]. In general, mixture of ionic-nonionic surfactant is of great importance compared to ionic-ionic and nonionic-nonionic as the former exhibits non-ideal behavior. Reduction in repulsion between charged head groups of ionic surfactants facilitates the micellization process thereby lowering the CMC values, improved solubilisation and high surface tension [18,19]. Therefore, in order to explore modification in the partitioning behavior of the drug, its partitioning in the mixture of surfactants both in the micellar and monomeric forms was also studied.

We have employed a combination of isothermal titration calorimetry (ITC), pyrene fluorescence emission and dynamic light scattering (DLS) to address the energetics of interaction and structural changes in the micelles. ITC is an established technique to study the energetics of interaction ranging from weak to sufficiently strong association in a variety of biomolecular recognition processes [11,20]. Pyrene fluorescence and DLS methods have been used as complementary techniques for fundamental understanding of molecular structure of drug-micelle aggregates [21–24]. We believe that such studies will provide a quantitative understanding of partitioning of drug molecules in self assemblies which forms an essential step in the correlation of structure properties and energetics for improvements in rational drug design.

2. Experimental

2.1. Materials

Hexadecyltrimethylammonium bromide (HTAB) (M_r = 364.5 g mol^{-1}, Sigma Aldrich), TritonX-100(Average M_r = 625 g mol^{-1}, Sigma Aldrich), L-Tryptophan (M_r = 204.23 g mol^{-1}, Sisco research laboratory, Mumbai) and diclofenac sodium (M_r = 318.13 g mol^{-1}, Sigma Aldrich) were purchased with a minimum mass fraction purity of 0.99 and used without further purification. All solutions were prepared in water which was doubly distilled, deionized and degassed over Branstead Thermolyne degassing unit. All the mass determinations were done on a Sartorius BP 211D digital balance which has a least count of 0.01 mg.

2.2. Isothermal titration calorimetry

A Nano ITC procured from TA Instruments (New Castle, DE, USA) was used for studying the interaction of Trp with the micelles and monomers of the chosen surfactant. Aliquots of 200 μL aqueous titrant (Trp) solution were injected sequentially by a computer controlled syringe (25 injections of 8 μL each injection) into 940 μL sample cell containing the surfactant solution of interest with an interval of 300 s between the successive injections. The concentration of Trp in the syringe (50 mM) was optimized such that it was sufficient to saturate the micelles. VP-ITC from Microcal LLC (Northampton, MA, USA) was used for the interaction studies of DCF with individual and mixed micelles. For this the volume of