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Regular Article

The interaction of a model active pharmaceutical with cationic surfactant and the subsequent design of drug based ionic liquid surfactants

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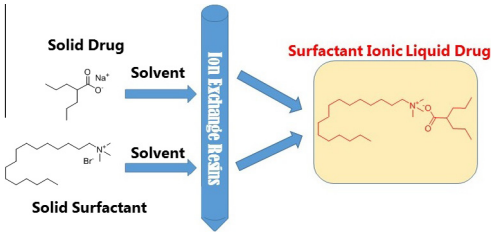
GRAPHICAL ABSTRACT



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ABSTRACT

Interactions of active pharmaceutical ingredients (API) with surfactants remain an important research area due to the need to improve drug delivery systems. In this study, UV–Visible spectrophotometry was used to investigate the interactions between a model low molecular weight hydrophilic drug sodium valproate (SV) and cationic surfactant cetyltrimethylammonium bromide (CTAB). Changes in the spectra of SV were observed in pre- and post-micellar concentrations of CTAB. The binding constant (K_b) values and the number of drug molecules encapsulated per micelle were calculated, which posed the possibility of mixed micelle formation and strong complexation between SV and CTAB. These results were compared to those of a novel room temperature surface active ionic liquid, which was synthesized by the removal of inorganic counterions from a 1:1 mixture of CTAB and SV. In this new compound the drug now constitutes a building block of the carrier and, as such, has considerably different surfactant properties to its building blocks. In addition, enhanced solubility in a range of solvents, including simulated gastric fluid, was observed. The study provides valuable experimental evidence concerning the performance of drug based surfactant ionic liquids and how their chemical manipulation, without altering the architecture of the API, leads to control of surfactant behavior and physicochemical properties. In turn, this should feed through to improved and controlled drug release rates and delivery mechanisms, and the prevention of precipitation or formation of polymorphs typical of crystalline form APIs.

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1. Introduction

The distribution of a drug in the body is primarily effected by molecular polarity. Non-polar drugs are lipophilic and distribute into adipose tissue as well as passing the brain blood barrier [1], whereas, polar drugs are hydrophilic and are mainly distributed in lean body tissue. Large, stable biomolecules can reach their destination easily but small biomolecules (with an upper molecular weight of approximately 900 g mol^{-1}), are not able to reach their target in effective concentrations because of dissociation in water/acid prior to reaching the lipophilic target due to their high hydrophilicity. Such unsuitable bio-distribution is seen for almost all small hydrophilic drugs [2,3]. One way around this delivery problem is to employ surfactants.

Surfactants have hydrophilic and hydrophobic moieties in their structures. Their basic function is to preferentially adsorb at interfaces and effect solubilization [4]. Assemblies of cationic surfactants have received much interest as carriers for chemotherapeutic agents and subsequent drug delivery [5]. The assemblies self-aggregate above a critical micelle concentration (cmc) forming micelles [6] thus allowing either for the partitioning of drug molecules into the lipidic microdomain of the micelle core or condensation on the surface. Some cationic surfactants are already in use in different drug formulations such as cetalkonium chloride used to retard the release of an ophthalmic drug [7], or benzalkonium chloride, which is used as a drug absorption enhancer [8–10]. More than a decade ago Paulsson and Edsman reported that surface active drugs could be mixed with cationic surfactants to form catanionic vesicles and micelles, which, when incorporated into gels, were useful in slowing release rates of the active pharmaceutical ingredient (API) [11]. Tourné-Péteilh et al. have called this approach elegant as "in contrast to the use of classical vesicles in which the drug is encapsulated, the drug constitutes a building block of the carrier" [12]. Their approach of creating ionic liquid surfactants has further improved on this [12].

Ionic liquids (ILs) are like any other salts but because at least one moiety is organic, asymmetric and bulky, the lattice energy, and therefore the melting point of the system, is lowered to produce a liquid salt with unusual solvent properties. Traditionally, they have been generated from an organic cation and a small halide anion. However, more recently, efforts have been made to move away from halides to create environmentally friendly, non-toxic ILs, where both cation and anion are bulky organic molecules [13]. The unique solvent properties of ILs have been exploited to optimize dissolution of various APIs, and have since started to gain significant attention and even been classed as "designer solvents" due to their easily tunable physicochemical properties. However, it is also possible to include the drug as an integral part of the IL itself, with some surprising results. One of the first drug-based ILs utilized the common local anesthetic lidocaine [14–16]. Lidocaine is usually used in pharmaceutical formulations as the solid hydrochloride salt, lidocaine hydrochloride, but by changing the anion from hydrochloride to docusate a room temperature ionic liquid was formed. Compared to lidocaine hydrochloride, it was found that the drug delivered longer lasting pain relief, suggesting that an entirely new but beneficial slow-release mechanism of drug delivery was active. Importantly, the structure of the API is not altered. This discovery presented a new paradigm as a drug delivery platform. One of the main advantages of drug-based ILs is that compared to most conventional drugs they do not crystallize and therefore exhibit no polymorphs nor do they precipitate at high loadings, allowing for simplified manufacture and ease of delivery.

With the sheer amount of cation anion pairs available, desired solubility and pharmacokinetics may be achieved without altering the synthetic route to the API. The surface active IL based on 1-dodecyl-3-methylimidazolium presented by Tourné-Péteilh et al. [12] may help with drug delivery due to unique partitioning at various lipid and biomolecule interfaces [3]. In particular, DNA has been known to be the cellular target for many cytotoxic anticancer agents for several decades and understanding how drug molecules interact with DNA is an active research area [17,18]. The ability to deliver drugs with surfactant counterions may allow for lower doses with equivalent efficacy. The surfactant properties of novel drug-based ionic liquids may also lead to the development of improved hydrogel, microemulsion and emulsion formulations and more sophisticated approaches to drug delivery.

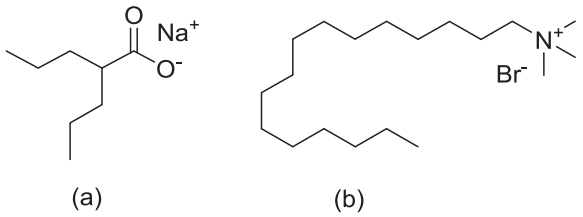

Fig. 1. The chemical structure of (a) sodium valproate and (b) CTAB.

In this work, we study sodium valproate (SV); a small hydrophilic drug (Fig. 1a) with medicinal uses including the treatment of epileptic patients [19], various cancers and HIV channels. Sodium valproate is crystalline (up to eight polymorphs) [20] but there is difficulty in its manipulation because of its hygroscopic nature [21]. Sodium valproate has a high solubility in water and is practically insoluble in organic solvents such is ether, chloroform, benzene, n-heptane [22].

We investigate how the drug partitions into cetyltrimethylammonium bromide (CTAB) (Fig. 1b) micelles using UV–visible spectroscopy and directly compare this to an analogous surfactant based IL (CTAVal) generated by removing the inorganic counterions of the drug and the surfactant. This provides a facile and universal method for drug delivery investigations. To the best of our knowledge, this system has not been studied before and this is vital because cationic surfactants and ionic liquids (ILs) are already being used in some drug formulations for sustained release purposes [7–9,23] and, most importantly, available data in literature on the interactions of small hydrophilic model drugs with surfactants is scarce. We have used the modified form of the Benesi-Hildebrand equation for the determination of the binding constant K_b. Moreover, the number of molecules per micelle (n), was also calculated.

2. Materials and methods

Cetyltrimethylammonium bromide (CTAB, ⩾99%), and sodium valproate (SV, ⩾98%) were bought from Sigma Aldrich and used without further purification. Simulated Gastric Fluid (SGF) was prepared using 7.0 mL hydrochloric acid, 3.2 g pepsin (from porcine gastric mucosa, Sigma) and 2.0 g sodium chloride, and making it up to 1000 mL in distilled water. The pH of the prepared SGF was 1.62.

2.1. Synthesis of cetyltrimethylammonium valproate (CTAVal) Ionic liquid

The preparation and analysis of CTAVal is identical to that of other ionic liquids reported in literature [13,24]. In brief, 1 eq. of CTAB (~80 mmol) was dissolved in EtOH/H_2O (1:1 v/v) and passed through a column (30 cm × 1 cm^2) of prewashed strongly basic ion exchange resin (Dowex 550A) to exchange halide for hydroxide.