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Liquid pharmaceuticals formulation by eutectic formation

Andrew P. Abbott [a, *], Essa I. Ahmed [a], Kamalesh Prasad [b], Idrees B. Qader [a], Karl S. Ryder [a]

[a] Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK
[b] Natural Products & Green Chemistry Division, CSIR-Central Salt & Marine Chemicals Research Institute, Bhavnagar, Gujarat 364002, India

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ABSTRACT

The amphiphilic nature of many pharmaceutical active ingredients often makes them difficult to solubilise and leads to significant wastage through non-optimal dosage. In this study it is shown that highly concentrated liquid formulations can be produced from pharmaceutical active ingredients which either contain a strong hydrogen bonding functionality e.g. -OH or -COOH or a quaternary ammonium moiety. These mixtures can overcome solubility issues in water as the eutectics prevent recrystallization of the active ingredient when dispersed in water. The depression of freezing point for these eutectic mixtures is modelled using the enthalpy of hydrogen bond formation which was calculated using calorimetric data. The study also demonstrates that complex drug molecules which exhibit polymorphism such as Adiphenine and Ranitidine can be formulated into a homogeneous liquid and the hydrogen bond donor can also be a pharmaceutical active ingredient e.g. aspirin.

1. Introduction

Many pharmaceutical active ingredients are polar or ionic to enable binding to the active site of the substrate. This often results in materials with high lattice energies and hence low solubilities in water. Complex compounds which display pharmaceutical activity also often have different crystalline polymorphs which can exhibit variable pharmacokinetics due primarily to different rates of solubility. To avoid this, co-crystals have been studied and have been thought of as a way of circumventing polymorphism. Recently, however it has been shown that polymorphism can also exist in co-crystals and result in different properties [1].

To overcome this issue there has been significant interest recently in developing liquid formulations. Rogers et al. has developed a range of pharmaceutical formulations based on ionic liquids with anionic and catatonic active ingredients [2]. Combinations of cations such as Lidocaine (used as a local anesthetic) together with anions such as docusate (a laxative) have been formulated into a liquid that has shown both curative effects. One of the issues with ionic liquids is that each new combination of anion and cation is a novel material and as such needs toxicological testing and registration. The topic of pharmaceutical ionic liquids has recently been reviewed [3,4].

In the current study the principle of making liquids via deep eutectic solvents (DES) is utilised. DESs are mixtures of quaternary ammonium salts with hydrogen bond donors (HBD) [5,6]. Mixtures of choline chloride with hydrogen bond donors such as urea and ethylene glycol have been used for applications such as metal deposition and metal oxide processing [7,8]. From a pharmaceutical perspective many active ingredients are either hydrogen bond donors or quaternary ammonium salts. In particular, many drugs have amine functionalities which are converted to the quaternary ammonium salts with HCl to aid solubility. Substituted phenols are commonly used pharmaceutical ingredients and used extensively for antioxidants and painkillers. Compounds such as paracetamol, aspirin and salicylic acid are notoriously insoluble in water. A DES has been used as a solvent for a pharmaceutical agent. It was shown that urea: choline chloride could dissolve benzoic acid, danazol, griseofulvin, and itraconazole [9]. Eutectic mixtures have also been made from two molecular components such as ibuprofen with a variety of terpenes [10] or menthol and ibuprofen [11].

In this study two types of DESs are shown; those where the pharmaceutical agent is a HBD and those where the active ingredient is a hydrogen bond acceptor (HBA) in this case in the form of a quaternary ammonium salt. It is shown that eutectic mixtures form readily with a variety of phenolic based HBDs with choline chloride. Choline chloride is chosen as it is a pro-vitamin which is already extensively used in food and other consumer products. These

* Corresponding author.
E-mail address: apa1@le.ac.uk (A.P. Abbott).

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formulations are liquid and can lead to highly concentrated formulations. It is also shown that solid quaternary ammonium compound which would normally exhibit a variety of polymorphs tend to form liquids or amorphous gels.

2. Methods

All chemicals were are shown in Table 1 and were used without further purification.

The DESs were formed by mixing the two components together and putting them in sealed sample tube in an oven at 50 °C for 24 h. After that a clear homogenous liquid was formed for mixtures of phenol, resorcinol, 4-methoxyphenol and o-cresol with ChCl. The other mixtures of hydrogen bond donors and acceptors were heated on a magnetic stirrer hotplate to approximately 90 °C until a clear homogenous liquid was formed. The water content of these liquids was quantified using thermogravimetry and found to be less than 1% in all cases. The melting points and glass transitions were measured by Differential Scanning Calorimetry (Mettler Toledo DSC1 STARe system) in the temperature range of 25 to −125 °C and −125 to 125 °C then from 125 to 25 °C. The samples were sealed in an aluminium pan and heated at a scan rate of 5.0 °C min^{-1} under a flow of dry nitrogen. Typical DSC curves for freezing points are shown in the supplementary information (Fig. S1). The heat capacities of the constituents and mixtures reported in Table S1 were calculated at 298 K and were also determined using DSC.

3. Results

Fig. 1 shows the freezing points as a function of composition determined from differential scanning calorimetry measurements for a variety of substituted phenols with ChCl. It can be seen that compounds which only have one HBD such as 2, 4, 6- trimethyl phenol and 3, 4 xylenol have a eutectic composition at a molar ratio of 1 ChCl: 2HBD whereas those with two HBD functional groups have a eutectic composition at a molar ratio of 1 ChCl:1HBD. This is the same finding as that found previously with carboxylic acids [7].

Table 2 shows the freezing points of eutectic mixtures of choline chloride with phenol and various substituted phenols together with the depression of freezing point. To understand the interaction between the two components it is necessary to quantify the depression of freezing point at the eutectic composition. To create a reference point a theoretical freezing temperature for an ideal mixture was calculated by interpolating between the values for the two pure components (T_m (ChCl) = 301 °C) and calculating the value at the eutectic composition. The depression of freezing point will depend upon the interaction between the two components.

Phenol forms a free-flowing liquid at ambient temperature with a eutectic molar ratio of 1 choline chloride: 2 phenol. The mixture does not give a crystalline solid on cooling so does not show a distinct melting point but rather it forms a glass at −97 °C. This is quite common for many ionic liquids and DESs. The dihydroxybenzene isomers form eutectic mixture at a 1:1 mol ratio with choline chloride. The concentration of phenol in the eutectic mixture is 67 wt% compared to the saturated concentration in water which is 8 wt%. In these mixtures IR and NMR analysis shows that there are no new covalent bonds formed although hydrogen bonding clearly occurs between the HBD and the anion of the quaternary ammonium salt.

The three isomers of dihydroxybenzene have very different phase behaviours the *o*- and *m*-derivatives form eutectics with a melting point which correlates with this solubility in water. Catechol forms a eutectic with ChCl which has a freezing point of 50 °C but it will form a super-cooled liquid which is stable for greater than one month before eventually solidifying. Fig. 2 shows a photograph of some of the examples from Table 2.

Examining the alkyl substituted phenols in Table 2 it can be seen that 2 mol equivalents of the HBD are required for the eutectic composition. The depression of freezing point is related to the position and size of the functional substituent. When the alkyl groups are not adjacent to the −OH group a larger depression of freezing point is observed. Thymol has an *iso*-propyl group in the 2-position hindering hydrogen bonding and this demonstrates the lowest depression of freezing point. The sterically hindered 2,6-di-*tert*-butyl-4-methylphenol does not form a DES showing that the *tert*-butyl groups disrupts hydrogen bond formation.

The same trends are noted for the polar substituted phenols.

Table 1
Sources and purity (by mass) of chemicals used in this study.

Chemicals	Source	Purity %
Phenol	Sigma-Aldrich	≥99.5
4-methoxyphenol	Sigma-Aldrich	99
2,4,6-trimmethyl phenol	Sigma-Aldrich	≥99
3,4-Dimethylphenol	Laboratory (BDH) Reagent	99
Glycerol	Fischer	98
Resorcinol	Sigma-Aldrich	99
Choline chloride	Sigma-Aldrich	≥98
Hydroquinone	Sigma-Aldrich	99
Aspirin	Sigma-Aldrich	≥99
Paracetamol	Sigma-Aldrich	98
2,6-di-tert-butyl-4-methylphenol	Sigma-Aldrich	≥99
Benzoic acid	Analar (analytical reagent)	99.8
Salicylic acid	Sigma-Aldrich	≥99
Thymol	Laboratory (BDH) Reagent	99.5
Catechol	Sigma-Aldrich	≥99
2-methylphenol	Sigma-Aldrich	≥99
4-Chlorophenol	Sigma-Aldrich	≥99
Urea	Alfa Aesar	≥98
Adiphenine hydrochloride	Sigma-Aldrich	≥99
Phenformin hydrochloride	Sigma-Aldrich	analytical standard
Ticlopidine hydrochloride	Sigma-Aldrich	≥99
Tetracycline hydrochloride	Sigma-Aldrich	≥95