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Investigation on drug solubility enhancement using deep eutectic solvents and their derivatives

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ABSTRACT

Deep eutectic solvent (DES) is a room temperature liquid typically formed by mixing two solid compounds, such as a quaternary ammonium salt (QAS) (e.g. choline chloride) and a hydrogen bond donor (HBD) (e.g. urea or a carboxylic acid) at their eutectic composition. Very often, a range of room temperature liquids can also be obtained near the eutectic composition. Hence, it is more convenient to introduce a more general term deep eutectic solvent derivatives (DESDs) to describe a wide range of DES-like derivatives including those derived from ternary mixtures. The melting point of the mixture is lowered because the hydrogen bonding between DESD components reduces the lattice energy of components of the eutectic system. Based on the analysis of available data for 22 such choline chloride-based DES pairs, we found that the observed melting point depression can be statistically correlated with the difference between the hydrogen bonding contribution (δ_h) and the polar contribution (δ_p) to the solubility parameter of the hydrogen bond donor (HBD) component. The correlation was validated with a new DESD based on glycolic acid and choline chloride, which form DESDs at a molar ratio between 1:1 and 1:4 with DES-like properties. As a room temperature liquid, this DESD exhibits a wide range of solubility enhancement on several weakly basic poorly water-soluble drugs. For example, the solubility of itraconazole, piroxicam, lidocaine, and posaconazole has been observed to increase by 6700, 430, 28, and 6400-fold, respectively as compared to their aqueous solubility at room temperature. Furthermore, another new ternary DESD based on choline chloride, glycolic acid, and oxalic acid at a molar ratio of 1:1.6:0.4 is shown to further increase the solubility of itraconazole to a remarkable level of 5.36 mg/mL (a 53,600-fold increase!). Because the components of such DESDs can include those biodegradable ones that had previously been used in formulated human products, the potential applicability of suitable DESDs to drug delivery, especially in enhancing drug solubility for topical formulations could be very attractive.

1. Introduction

In the 1990s, room temperature ionic liquids (RTILs) emerged as a promising class of new solvents to replace some of the conventional volatile organic solvents in the fields of catalysis, synthesis, electrochemistry, and material chemistry because of RTILs unique ability to dissolve highly polar substrates, inertness to water, and negligible vapor pressure (Rogers and Seddon, 2003; Welton, 1999; Yang and Pan, 2005). However, industrial applications of RTILs were limited by the realization of their toxicity, poor biodegradability, impurities, and high cost of synthesis (Romero et al., 2008; Zhang et al., 2012). In the early 2000s, a new type of solvent called deep eutectic solvent (DES), typically formed by mixing a quaternary ammonium salt (QAS) (e.g. choline chloride) and a hydrogen bond donor (HBD) (e.g. urea or a carboxylic acid), was found to have comparable physicochemical properties of RTILs but without metal salt-associated drawbacks (Abbott et al., 2004). As a result, DESs have attracted growing recent interest in the fields of electrodeposition, biocatalysis, and organic synthesis (Díaz-Álvarez et al., 2011; Durand et al., 2013; Malaquias et al., 2013).

It is worth noting that the term DES has been used to refer to liquids close to the eutectic composition of a binary mixture (Smith et al., 2014). However, in many cases, similar room temperature liquids can be obtained at compositions close to but distinct from the eutectic composition. Besides, room temperature liquids can also be formed from ternary solid mixtures, although their eutectic points are more difficult to measure. Hence, we use the term, deep eutectic solvent derivatives (DESDs), to better describe such a wide range of DES-like room temperature liquid mixtures.

Pharmaceutical applications of eutectic mixtures can be traced back to the 1960s when sulfathiazole was mixed with urea to

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increase the drug solubility and its oral absorption rate (Sekiguchi and Obi, 1961). There are many known pharmaceutical eutectic mixtures, such as lidocaine/prilocaine (Buckley and Benfield, 1993), menthol/testosterone (Kaplun-Frischoff and Touitou, 1997), and ibuprofen/menthol (Aroso et al., 2015). Conventionally, the components of a pharmaceutical eutectic mixture consist of the active pharmaceutical ingredient (API) and a suitable excipient or another API. However, studies on the pharmaceutical applications of DESDs are very limited at this stage. Only very few reports have studied the feasibility of using DES or RTILs as a solvent to dissolve certain poorly water-soluble drugs (Morrison et al., 2009; McCrary et al., 2013). In this paper, the solubilizing behavior of several choline chloride-based DESDs towards poorly soluble drugs will be further investigated.

It is well accepted that DES has a lower melting point than each of its components because hydrogen bond formation reduces the lattice energy of the components of the eutectic system (Abbott et al., 2004; Smith et al., 2014). Therefore one of the objectives of this study is to relate the ability of a HBD to form hydrogen bonding directly to the degree of melting point depression of the resulting binary DES. Since the number of reported DES is still small, a correlating equation that can estimate the melting point depression will be extremely useful to the search for new binary DESDs components. In this study, such a correlating equation will be first established and applied to the estimation of melting point depression of new DESDs based on choline chloride/glycolic acid, the ability of which to dissolve several poorly water-soluble drugs will be subsequently demonstrated.

2. Methods and materials

2.1. Materials

Choline chloride, citric acid, and α-ketoglutaric acid were purchased from BioShop Canada. Glutaric acid, glycolic acid, malonic acid, oxalic acid, piroxicam, and lidocaine were purchased from Sigma–Aldrich Canada. Itraconazole was generously provided by Albemarle Corporation, USA. Posaconazole was purchased from API Vanguard USA. Choline chloride was vacuum dried at 110 °C for 24 h before use. All other chemicals and solvents were reagent grade obtained commercially and used as received.

2.2. Preparation of deep eutectic solvent derivatives

To prepare a DESD, choline chloride and selected carboxylic acids were mixed at different molar ratios. The mixtures were sealed in vials and heated in an oven at 75 °C until homogenous solutions were formed. Subsequently, these samples were stored at room temperature and only those samples that remained liquid were tested as room-temperature solvents for model poorly soluble drugs.

2.3. Drug solubilization

Itraconazole, posaconazole, lidocaine, and piroxicam were selected as model drugs for solubility experiment due to their poor aqueous solubility. To determine the drug solubility in DESDs, an excess amount of drug was added to a blank DESD solvent followed by vigorous vortexing until the excess solid remained undissolved. The resulting solution containing excess drug was left standing for 24 h to ensure equilibrium was attained. Before the solubility was measured, the solution containing excess drug was filtered through a Millex PES syringe filter unit with a 0.22 μm membrane. The drug concentration in the filtered DESD supernatant was determined spectrophotometrically on a Cary 50 UV–Vis spectrophotometer (Varian, ON, Canada). The absorbance of posaconazole was measured at 263 nm by diluting the filtered aliquots in methanol. The absorbance of itraconazole, lidocaine, and piroxicam was measured at 260 nm, 264 nm, and 326 nm, respectively, by diluting the filtered DESD in equal volumes of anhydrous ethyl alcohol and dichloromethane.

2.4. Solubility parameter calculation

The calculation of the three components of Hansen solubility parameter (HSP) was based on the well-established group contribution method of Hoftyzer and van Krevelen (Van Krevelen and Te Nijenhuis, 2009).

$$\delta_d = \frac{\sum F_{di}}{V} \quad (1)$$

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad (2)$$

$$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}} \quad (3)$$

where δ_d, δ_p, and δ_h are the dispersion, polar, and hydrogen bonding components of the HSP, respectively, F_{di}, F_{pi}, and E_{hi} are the group contributions to δ_d, δ_p, and δ_h, respectively, and V is the molar volume of the molecule.

2.5. Melting point depression of hydrogen bond donors

ΔMP_{HBD} refers to the difference between the melting point of a pure HBD and that of its choline chloride-based binary DES at the eutectic composition. The melting point difference between choline chloride and the eutectic mixture is not calculated because choline chloride decomposes at 302 °C before it melts. Since choline chloride is used across all the reported eutectic pairs in Table 1, the correlation being developed here describes how the molecular properties of different hydrogen bond donors affect the melting point of the resulting eutectic mixture. Because the eutectic composition of different mixtures may vary, ΔMP_{HBD} is normalized to ΔT_n with respect to the molar ratio of choline chloride to HBD at the eutectic composition (Eq. (4)), realizing that the concentration of ChCl proportionally contributes to the melting point depression of the HBD.

$$\Delta T_n = \frac{n_{ChCl}}{n_{HBD}} \times \Delta MP_{HBD} \quad (4)$$

2.6. Statistical regression

An IBM statistical software package, SPSS (v21), was used to analyze the correlation between molecular properties of a HBD and the observed melting point depression in its resulting choline chloride-based DES. The significance level of relevant compound properties including molecular weight, enthalpy of fusion, entropy of fusion, and the three components of HSPs were assessed by multiple linear regression analyses. The selection of descriptors was performed in a stepwise fashion by eliminating the least significant descriptor one at a time until all remaining factors became significant (i.e. $p < 0.05$). The correlations evaluated included both linear and non-linear forms, and the coefficient of correlation was determined by the least squares analysis using the SPSS software. Whenever possible, available experimental HSP data were used in the analysis. For cases where experimental data are not available, HSP values were calculated by using the group contribution method of Hoftyzer and van Krevelen. Table 1 includes 22 eutectic pairs for which the HSP of the HBD component can be obtained by one of these two approaches.