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Solubility of pharmaceutical compounds in ionic liquids

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ABSTRACT

The solubility of N-acetyl-L-cysteine, coumarin and 4-hydroxycoumarin in alternative solvents was studied in this work. The solid–liquid equilibrium (SLE) measurements have been performed using a dynamic (synthetic) method. Melting points and enthalpies of fusion of the pharmaceutical compounds were acquired using a differential scanning calorimetry (DSC). The solubility of N-acetyl-L-cysteine and 4-hydroxycoumarin in trifluoromethanesulfonate ionic liquids was found to be significantly higher than in the studied bis(trifluoromethylsulfonyl)amide ionic liquids while coumarin exhibited the opposite behaviour.

The solid–liquid phase equilibria were described using the six different correlation equations which revealed a good description with an acceptable standard deviation temperature range.

Moreover, the solubility data were used to calculate the 1-octanol/water partition coefficients of the studied drugs. Coumarin has a high partition coefficient, which is considered to be favourable for a rapid absorption of compounds once they are in an aqueous solution. N-acetyl-L-cysteine showed opposite results for the system with 1-octanol/water.

1. Introduction

Pharmaceutical compounds are chemical substances characterised by the specific properties towards a human body. The production of these particular compounds usually generates high quantities of residues. Sheldon's *E*-factor, defined as the mass ratio of waste to desired product, typically reaches *E* factors of 25–100 for the pharmaceutical industry, the highest among the oil refining, and the bulk or fine chemicals sectors [1]. For this reason, attention is focused in the development of pharmaceutical processes in waste minimisation and in assessing its current status in the broad context of green chemistry and sustainability. Particularly, the pharmaceutical industry is seeking for solutions to the problem of waste generation in chemicals' manufacture. Hazardous organic solvents may be replaced by green solvents, which are advantageous especially in terms of volatility and flammability. Ionic liquids (ILs) have proven their sustainable applications in reactions [2,3] and separations [4] mostly due to their unique tuneable properties, and due to their thermal stability [5] and solvent power [6,7]. Furthermore, they were successfully used in the formation of emulsions in ionic liquid-in-oil systems for drug processing [8–10]. The formation of emulsions is the method guiding to the reduction of ILs' toxicity against microorganisms [10].

In this work, N-acetyl-L-cysteine (NAC), coumarin and 4-hydroxycoumarin are used as examples of interesting pharmaceuticals. NAC may be used in preventing or treating the acetaminophen poisoning, angina, chronic bronchitis and chronic obstructive pulmonary disease, influenza, Acute Respiratory Distress Syndrome and HIV/AIDS [11]. Animal and human studies showed an NAC to be a powerful antioxidant and potential therapeutic agent in the treatment of cancer and myoclonus epilepsy [12]. Recently, NAC was reported to be used in the treatment of Parkinson's disease [13].

Coumarins (coumarin and 4-hydroxycoumarin) demonstrate the biological activities and are used as pharmaceuticals. They have anti-HIV, anti-tumour, anti-hypertension, anti-arrhythmia, anti-inflammatory, anti-osteoporosis, antiseptic, and analgesic activities [14]. Coumarin is also used in the treatment of asthma [14]. Coumarin derivatives are used widely as anticoagulants for the treatment of excessive or undesirable blood clotting due to their competitive binding to vitamin K reductase and vitamin K epoxide reductase, which are necessary for blood clotting [14]. 4-Hydroxycoumarin is used as a useful intermediate for the synthesis of anticoagulants, herbicides, and anticancer agents.

The present work is a continuation of our systematic study on the solubility of drugs in ionic liquids [15–17]. This work is focused on screening of several ionic liquids as alternative

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