Fluid Phase Equilibria 397 (2015) 18–25

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Solubilities of pharmaceutical and bioactive compounds in trihexyl (tetradecyl)phosphonium chloride ionic liquid

Ricardo A. Faria, Ewa Bogel-Łukasik *

REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

ARTICLE INFO

Article history:
Received 5 February 2015
Received in revised form 28 March 2015
Accepted 30 March 2015
Available online 2 April 2015

Keywords:
Solubility
Solid–liquid equilibrium
Ionic liquid
Green solvent
Drugs

ABSTRACT

The solubility of pharmaceutical and bioactive compounds, such as *N*-acetyl-L-cysteine, isoniazid, pyrazine-2-carboxamide, coumarin, 4-hydroxycoumarin, 4′-isobutylacetophenone, ibuprofen and thymoquinone, was tested in trihexyl(tetradecyl)phosphonium chloride. Hydrophobicity/hydrophilicity feature and melting point affected the solubility of the solutes in $[P_{6,6,6,14}][Cl]$. 4′-Isobutylacetophenone, thymoquinone, coumarin and ibuprofen exhibited the best solubility in the IL due to their hydrophobicity. Then, *N*-acetyl-L-cysteine was found to be less soluble, and later on isoniazid, 4-hydroxycoumarin and pyrazinecarboxamide showed limited solubility in IL. The solid–liquid phase equilibria of all investigated systems were described using the six different correlation equations. Considering the correlation of the phase equilibrium data, the satisfactory results which revealed a good description with an acceptable standard deviation temperature range were collected for systems with: *N*-acetyl-L-cysteine, coumarin, thymoquinone and ibuprofen. The solubilities of the studied compounds were approximately 2 times higher in trihexyl(tetradecyl)phosphonium chloride than in trihexyl (tetradecyl)phosphonium bis[(trifluoromethyl)sulfonyl]amide ionic liquid.

1. Introduction

Volatile organic solvents used in chemical synthesis and pharmaceutical industries generate about 350 million tons of toxic waste per year. Ionic liquids, IL are considered as alternative media that are non-flammable, highly thermally stable [1] and non-volatile green solvents [2]. Ionic liquids properties can be tuned by changing the cation or the anion making them suitable for a specific application, [3–5] such as reaction media, [6–8] active pharmaceutical ingredients [9], catalysts [8] and separation media [10].

ILs have been recently proposed to be used in the pharmaceutical applications [5,11,12]. 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 [13]. For this reason, attention is focused on the development of pharmaceutical processes with waste minimization and 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. Considering the various toxicity of ionic liquids and the commonly used solvents in drug development, the advantageous use of IL comes from their inflammability in a way to be competitive to flammable solvents which use affects the engineering design, features of pharmaceutical facilities and process equipment [5]. It can be desirable to develop manufacturing processes with solvents that are generally identified as being "safer" [14] and suitable in pharmaceutical processing [11].

One of the most important feature of ionic liquids except their non-flammability and non-volatility, is their high solvating power [15] for organic, inorganic and organometallic compounds. Ionic liquids are used in solvent extraction as one of the major hydrometallurgical techniques for the separation and purification of metals [16]. For example, extraction system with trihexyl (tetradecyl)phosphonium chloride was applied in the separation of iron from neodymium and of cobalt from samarium [17] and of cobalt from nickel present in an aqueous phase. The IL's use was advantageous due to elimination of the volatile and flammable character of the extraction phase. These separations are relevant to recycling of rare earths from permanent magnets [18]. Moreover, trihexyl(tetradecyl)phosphonium chloride was reported to be applied in triphasic catalysis [19], and its use for classic solvent

* Corresponding author. Tel.: +351 212948500.
E-mail address: ewa.lukasik@fct.unl.pt (E. Bogel-Łukasik).

http://dx.doi.org/10.1016/j.fluid.2015.03.053
0378-3812/

Nomenclature

$[P_{6,6,6,14}]$	Trihexyl(tetradecyl)phosphonium
[Cl]	Chloride
$[NTf_2]$	Bis[(trifluoromethyl)sulfonyl]amide
DSC	Differential scanning calorimetry
SLE	Solid–liquid equilibrium
T	Temperature
g_{12}–g_{22},g_{21}–g_{11}	Adjustable parameters of Wilson
G^E	Gibbs excess energy
K	Association constant
l_i	Bulk factor
n	Number of experimental points
q	Pure component surface parameter
P_1, P_2	model parameters resulting from the minimization procedure
r	Pure component volume parameter
R	Ideal gas constant
SLE	Solid–liquid equilibrium
$T^{exp}{}_i$	Experimental equilibrium temperature
$T^{cal}{}_i$	Calculated equilibrium temperature
$T_{fus,1}$	Melting temperature of solute
T_g	Glass transition temperature
u	Standard uncertainty of measurement
V_m	Molar volume of pure compound at 298.15 K
x_1	Mole fraction of solute
Z	Coordination number
α	Constant of the NRTL, NRTL 1 and NRTL 2 equations
γ_1	Activity coefficient of solute
$\Delta C_{p,g}$	Heat capacity at glass transition temperature
$\Delta_{fus}C_p$	Heat capacity between the solid and liquid at the melting temperature
Δg_{12}, Δg_{21}	Adjustable parameters of NRTL, NRTL 1 and NRTL 2 equations
$\Delta_{fus}H_1$	Enthalpy of fusion of solute
Δh_h	Enthalpy of association
Δu_{12}, Δu_{21}	Adjustable parameters of UNIQUAC and UNIQUAC ASM equations
σ_T	Root-mean-square deviation of temperature
Ω	Objective function

extraction processes is justified from an economical point of view compared to the use of fluorinated ionic liquids [20].

The study on possible recovery of pharmaceutical agents from ionic liquid solvent would be very interesting to perform basing on promising ionic liquid based aqueous biphasic systems as a versatile tool for recovery of antioxidants compounds [21], and of paracetamol from pharmaceutical waste [22]. Supercritical carbon dioxide extraction [23] and pervaporation [24] have been proposed as "green" methods to recover and purify solutes from ILs. There are several pharmaceutical and bioactive agents, that solubilities in ionic liquids were provided, concluding that the ionic liquids are sufficient solvents for the drugs and can be suitable for the pharmaceutical processing [20]. One of them is *N*-acetyl-L-cysteine (NAC), that is a natural intracellular antioxidant agent important in treatment of HIV infection, cancer, heart diseases, mental illnesses [25]. Two others are antibiotic drugs (isoniazid and pyrazinecarboxamide) [26] used to treat tuberculosis that causes more deaths than AIDS and malaria together. Others are coumarins that found application in pharmaceutical and cosmetic industries. Coumarin based derivatives exhibit anticoagulant, carcinogenic and antibiotic properties. Coumarin can be useful in the antitumour therapy [29], and 4- hydroxycoumarin is an intermediate toward other pharmaceutical compounds, Dicoumarol [27–29]. The other is thymoquinone, an antibiotic and anti-cancerous agent [30–32], and ibuprofen, a non-steroidal anti-inflammatory drug that lowers risk of Parkinson disease. The list closes 4′-isobutylacetophenone that is a precursor in ibuprofen synthesis [33–35]. Solvent screening studies are essential to optimize solvent dependency (solubility, polymorphism, crystallinity and crystal habit of pharmaceutical compounds) [4,11,36]. Solubilities of above stated that solutes have been studied in imidazolium [37–40] and ammonium ILs [41] and phosphonium bis(trifluoromethylsulfonyl) imide [42] proposing them to be alternative solvents to organic toxic solvents routinely used in pharmaceutical industries [35,36,39].

Considering drawback of the price of phosphonium bis (trifluoromethylsulfonyl) imide, and advantageous use of the corresponding chloride ionic liquid as the ionic liquid can easily be generated after extraction in the industrial application [16], we aim to investigate solubilities of eight pharmaceutical or bioactive agents of pharmaceutical and bioactive compounds in chloride IL. The aim of this work is to provide solubility data of isoniazid (IUPAC name: isonicotinohydrazide), pyrazinecarboxamide (IUPAC name: pyrazine-2-carboxamide), *N*-acetyl-L-cysteine, coumarin, 4-hydroxycoumarin, thymoquinone (IUPAC name: 2-isopropyl-5-methylbenzo-1,4-quinone), ibuprofen (IUPAC name: 2-(4-isobutylphenyl) propionic acid) and 4′-isobutylacetophenone in trihexyl (tetradecyl)phosphonium chloride, $[P_{6,6,6,14}][Cl]$.

2. Materials and methods

2.1. Chemicals

The chemical structures of solutes and the solvent used in this research are illustrated in Fig. 1. The sample table is depicted in Table 1.

2.2. Methods

2.2.1. Solid–liquid equilibria measurement

Solid–liquid equilibria (SLE) of studied systems were obtained at the ambient pressure of 0.1 MPa and at temperature ranging from 275.12 K to 410.26 K using a dynamic (synthetic) method. Experiments were performed in a Pyrex glass cell. The cell could be opened/closed by a Teflon valve at the end of a long, capillary-thin (inner diameter of 0.1 mm) neck. It allowed the cell to be deeply immersed in a temperature-controlled bath, while, at the same time, diminishing losses due to evaporation. The solutions were prepared by weighing the pure components with an accuracy of 10^{-4} g. The mixture of solute and solvent was heated very slowly (with maximum heating rate of 2 K h^{-1} near the equilibrium temperature), with continuous stirring. The measurement cell was placed in a thermostatic bath with water (293–333 K) or silicon (333–416 K). The last crystal disappearance temperatures, detected visually, were measured with a calibrated DOSTMANN electronic P600 thermometer equipped in a Pt 100 probe totally immersed in the thermostatic liquid. The uncertainty of the temperature measurements was ±0.03 K and that of the mole fraction did not exceed ±0.0005.

2.2.2. Differential scanning calorimetry

Glass transition temperature, T_g and heat capacity at glass transition temperature, $\Delta C_{p,g}$, of (trihexyl(tetradecyl)