Fluid Phase Equilibria 462 (2018) 100–110

Contents lists available at ScienceDirect

Fluid Phase Equilibria

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

Experimental determination and correlation of acetaminophen solubility in aqueous solutions of choline chloride based deep eutectic solvents at various temperatures

Hemayat Shekaari*, Mohammed Taghi Zafarani-Moattar, Masumeh Mokhtarpour

Department of Physical Chemistry, University of Tabriz, Tabriz, Iran

ARTICLE INFO

Article history:
Received 24 October 2017
Received in revised form
15 January 2018
Accepted 17 January 2018
Available online 31 January 2018

Keywords:
Deep eutectic solvent
Solubility
Acetaminophen
Activity coefficient model
Dissolution thermodynamic

ABSTRACT

The aqueous solubility of acetaminophen (ACP) in some choline chloride (ChCl) based deep eutectic solvents (DESs) with urea, oxalic acid and malonic acid as neoteric green solvents were measured up to 0.90 wt fraction of DESs at $T = (293.15–318.15)$ K and at atmospheric pressure. The solubility in these solvents increased more than forty–fold with increasing the weight fraction of DESs, especially in DES containing malonic acid. The solubility data were accurately correlated by the NRTL, Wilson and UNIQUAC activity coefficient models. Also, to describe the thermodynamic behavior of ACP in the aqueous DES solutions, the thermodynamic functions, Gibbs energy, enthalpy, and entropy of dissolution and mixing were obtained by using the van't Hoff and Gibbs equations. The results indicate that the main contribution to the solubility of ACP in the aqueous DES solutions is enthalpic.

1. Introduction

The solubility in pharmaceutical industry is an paramount parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Drugs that have low solubility in water often show low bioavailability. Currently, only 8% of new drugs have both high solubility and permeability [1]. Various methods have been developed to enhance the solubility and bioavailability of the drugs including addition of surface-active agents, cyclodextrins, co-solvents, and pH adjustment. It is well-known that the addition of an organic co-solvent to water can significantly change the solubility of drugs [2]. Traditionally, organic solvents [3–6] and then after, in recent years ionic liquids (ILs) [7–9] have been used as co-solvent to improve the solubility of drugs but these types of solvents have problems including toxicity, flammability and high prices [10,11]. Therefore, developing a simple synthetic and greener alternative solvent has very significant practical importance. Recently, to overcome the limitations of organic solvents and ILs, deep eutectic solvents (DESs) have been developed in this area [12]. These neoteric solvents have advantages such as a lower cost and desirable environmental impact rather than the ILs and organic solvents [13]. In addition, they can be also prepared from biodegradable and natural components, and it was found that their toxicity is much lower than ILs [14]. These types of solvents are liquid at room temperatures typically formed by mixing two safe and relatively inexpensive solid compounds, such as a quaternary ammonium salt as hydrogen bond acceptor (HBA) (e.g. choline chloride (ChCl)) and a hydrogen bond donor (HBD) (e.g. urea or a carboxylic acid) at their eutectic composition with melting point much lower than that of the individual components [12]. The properties of DESs can be easily controlled by changing the mixing ratio of the HBA and HBD.

Acetaminophen (ACP) is one of the most popular and most commonly used analgesic and antipyretic drugs around the world, available in mono- and multi-component preparations. The main issue with this drug is its low solubility in water ($14\,g\,L^{-1}$ at 298.15 K), ACP is specially indicated in the treatment of several minor diseases presented by pediatric patients [15]. To the best of our knowledge, a few researches have been reported about the solubility of drugs in DES systems, which show increase in the solubility at higher concentrations of DESs [16–18]. Lu and coworkers [18] studied several drugs as models to explore the possibility of DESs application to improve their solubility and stability for potential nonaqueous liquid administration. The results indicate

* Corresponding author.
E-mail address: hemayatt@yahoo.com (H. Shekaari).

https://doi.org/10.1016/j.fluid.2018.01.017
0378-3812/

noticeable increasing in the solubility of ACP in pure DES including ChCl/urea, ChCl/oxalic acid and ChCl/malonic acid. In continuation of our previous work [19] the purpose of this work is providing the aqueous solubility of ACP in the presence of some DESs based on ChCl as HBA and urea, malonic acid, oxalic acid, as HBD up to 0.90 wt fraction of DESs at $T = (293.15–318.15)$ K and at atmospheric pressure. To correlate the solubility data, different activity coefficient models are suggested in literature. The local composition activity models such as Wilson [20], NRTL [21], and UNIQUAC [22] have been used in this study. Also, to describe the thermodynamic behavior of ACP in the aqueous DES solutions, thermodynamic functions, Gibbs energy, enthalpy, and entropy of dissolution and of mixing were obtained from the solubility data by using the van't Hoff and Gibbs equations at temperatures ranging from 293.15 K to 318.15 K.

2. Experimental

2.1. Chemical

The origin, CAS number and purity of the used chemicals are given in Table 1. The doubly distilled deionized water was used to prepare the solutions with a specific conductivity less than 1 μS cm^{-1}.

2.2. DES preparation

The purified compounds of ChCl as HBA and urea, oxalic acid and malonic acid as HBDs were mixed with the molar ratio 1:2, 1:1, 1:1, respectively. The eutectic mixtures were stirred at 353.15 K for 4 h until a homogeneous, colorless liquid formed. Some of the features of these solvents are given in Table 2 and compared with those values in literature. The density, *d*, and speed of sound, *u*, of samples were measured with a vibrating tube densimeter (Anton Para, DSA 5000 densimeter and speed of sound analyzer) and the device was calibrated by distilled water. Also, refractive indices, n_D, of the studied DESs were measured using a digital refractometer (ATAGO-DRA1, Japan). The apparatus was calibrated with doubly distilled water before each series of measurements. In addition, to ensure that the refractometer is working correctly, calibration was conducted with pure liquids of known refractive index such as hexane. The temperature was controlled using a circulating bath thermostat (Cooling Bath 490, Iran) with a thermal stability of ±0.1 K.

2.3. Solubility measurement

The binary solvent mixtures (DES + water) were prepared by mixing the appropriate amounts (in grams) of the solvents with an analytical balance with precision 1×10^{-4} g (AW 220, GR220, Shimadzu, Japan). There are different methods to measure the solubility in the literature [26]. Among them, the shake flask method has been employed in this work. Briefly, the sealed vials containing an excess amount of ACP powder in the solvent mixtures were mixed using a shaker (Behdad, Tehran, Iran) and placed in water bath thermostat that was equipped with a temperature-controlling system with the uncertainty of 0.1 K (ED, Julabo Co., Germany) for 3 days to reach an equilibrium, the comparative calibration method was used to calibrate the thermostat, this method is carried out by comparing the thermostat with a higher-quality reference thermometer. When a saturated solution was attained, the solid phase was removed by centrifugation using a

Table 1
Descriptions of the used chemicals.

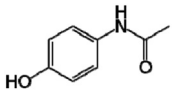
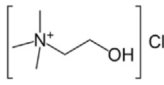
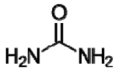
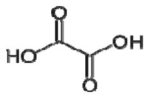
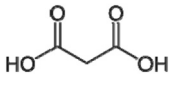
Chemical name	Provenance	CAS No.	Mass fraction (purity)	Structure
Acetaminophen	Merck	103-90-2	>0.98	
Choline Chloride	Merck	67-48-1	>0.99	
Urea	Merck	57-13-6	>0.98	
Oxalic Acid	Merck	144-62-7	>0.99	
Malonic Acid	Merck	141-82-2	>0.99	

Table 2
Common properties of DESs used in this work at 298.15 K and 0.0866 MPa.[a]

DES	Salt - HBD (molar ratio)	Melting Point (K)	M_{DES} (g mol^{-1})	$10^{-3}d$/(kg m^{-3})		u(m s^{-1})	nD	
				Exp	Lit		Exp	Lit
ChCl/urea	1:2	285.15 [23]	259.74	1.193926	1.1979 [24]	2062.27	1.5041	1.5044 [25]
ChCl/malonic acid	1:1	283.15 [23]	243.68	1.251470	1.2500 [16]	1962.69	1.4887	1.4871 [25]
ChCl/oxalic acid	1:1	307.15 [23]	229.65	1.210926	1.2200 [16]	1925.00	1.4809	1.4868 [25]

[a] Standard uncertainties for $u(d) = 0.006$ kg m^{-3}, $u(u) = 0.50$ m s^{-1}, $u(n_D) = 0.0002$, $u(T) = 0.1$ K and $u(P) = 0.0001$ MPa.