European Journal of Pharmaceutical Sciences 111 (2018) 270–277

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Studying of drug solubility in water and alcohols using drug-ammonium ionic liquid-compounds

Mohammad Halayqa[a], Aneta Pobudkowska[a], Urszula Domańska[b,c,*], Maciej Zawadzki[a]

[a] Warsaw University of Technology, Faculty of Chemistry, Department of Physical Chemistry, Noakowskiego 3, 00-664 Warsaw, Poland
[b] Industrial Chemistry Research Institute, Rydygiera 8, 01-793 Warsaw, Poland
[c] Thermodynamic Research Unit, School of Engineering, University of KwaZulu-Natal, Howard College Campus, King George V Avenue, Durban 4041, South Africa

ARTICLE INFO

Keywords:
Synthesis MEF-IL-compounds
DSC data
Experimental solubility
MEF + water, ethanol, 1-octanol
Thermodynamic correlation

ABSTRACT

Synthesis of three mefenamic acid (MEF) derivatives - ionic liquid compounds composed of MEF in an anionic form and ammonium cation (choline, MEF1), or {di(2-hydroxyethyl)dimethyl ammonium (MEF2)}, or {tri(2-hydroxyethyl)methyl ammonium compound (MEF3)} is presented. The basic thermal properties of pure compounds i.e. fusion temperatures, and the enthalpy of fusion of these compounds have been measured with differential scanning microcalorimetry technique (DSC). Molar volumes have been calculated with the Barton group contribution method. The solubilities of MEF1, MEF2 and MEF3 using the dynamic method were measured at constant pH in a range of temperature from (290 to 370) K in three solvents: water, ethanol and 1-octanol. The experimental solubility data have been correlated by means of three commonly known G^E equations: the Wilson, NRTL and UNIQUAC with the assumption that the systems studied here present simple eutectic behaviour. The activity coefficients of pharmaceuticals at saturated solutions in each binary mixture were calculated from the experimental data. The formation of MEF-ionic liquid compounds greatly increases the solubility in water in comparison with pure MEF or complexes with 2-hydroxypropyl-β-cyclodextrin. The development of these compounds formulations will assist in medication taking into account oral solid or gel medicines.

1. Introduction

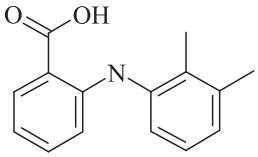
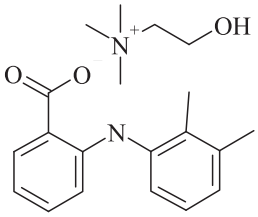
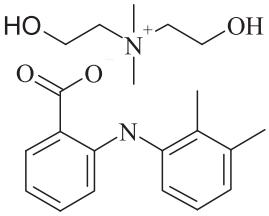
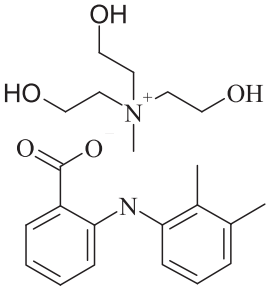
Solubility of drugs is dependent on material purity, thermophysical properties as melting temperature and the melting enthalpy, by polymorphism, salt formation, pressure and of pH. The solubility of sparingly-soluble ionisable pharmaceuticals (Phs) and methods of measurements was presented in reviews (Avdeef, 2003; Avdeef, 2007). Solubility can be influenced by co-solvents such as ethanol, propylene glycol, polyethylene glycol 400, 1-methyl-2-pyrrolidone as well as of presence of surfactants such as sodium lauryl sulfate, bile salts, mixed micelles, eutectic mixtures, solid dispersion (Gumaste et al., 2016), or complexing agents, such as cyclodextrins (Popović and Čakar, 2004). New strategies have been proposed to solubilize water insoluble pharmaceutical ingredients in order to get better delivery systems. Recently, new methods, such as formation of polymer-Phs, or ionic liquid (IL)-Phs compounds, which minimize hydrophobic effects and increase the water solubility of the Phs have been presented (McCrary et al., 2013; Viau et al., 2010). This strategy transforms very often solid Phs into liquids, thus eliminating polymorphism, increases the polarity of Phs, decreases their melting temperature ended in better solubility in water (Hough and Rogers, 2007; Hough et al., 2007; Stoimenovski et al., 2012), or improving trans-dermal penetration (Stoimenovski and MacFarlane, 2011). The high solvation properties and dissolution power of ILs provides to new methods of Phs delivery. Water solubility may be improved by designing Phs specific molecules with ILs to change hydrophilic-lipophilic balance (McCrary et al., 2013). The main challenges in the field are to develop less toxic and more biodegradable types of ILs with high solubilisation capacity (Park et al., 2008; Hough and Rogers, 2007). The new Phs-IL-polymer composites in form of nanoparticles or solid dispersions are proposed as new materials for poor soluble Phs (Mahkam et al., 2016).

The most popular, choline chloride is the *N*,*N*,*N*-trimethyl-hydroxyethyl-ammonium chloride, [N_{1112}OH][Cl] salt is non-toxic and biodegradable since it is naturally occurring in several biological functions. The data on choline chloride derivatives physicochemical properties and solubility in alcohols, water, ethers and many other solvents were presented in the literature (Domańska and Bogel-Łukasik, 2005; Costa et al., 2012; Costa et al., 2013; Nockemann et al., 2009; Domańska et al., 2014). Choline-based ILs are known as less toxic and better biodegradable ILs in comparison to popular imidazolium-, or

* Corresponding author at: Industrial Chemistry Research Institute, Rydygiera 8, 01-793 Warsaw, Poland.
E-mail address: Ula@ch.pw.edu.pl (U. Domańska).

http://dx.doi.org/10.1016/j.ejps.2017.09.052
Received 26 August 2017; Received in revised form 30 September 2017; Accepted 30 September 2017
Available online 03 October 2017
0928-0987/

Table 1
Investigated compounds: name, abbreviation, structure, molar mass, source, purification method, analysis method, mass fraction purity and water content in mass fraction.

Name of compound	Structural formula	M/(g·mol^{-1})	Source	Purif. method	Analys. method	Mass fraction purity/water content (mass fraction)
Mefenamic acid (MEF)		241.29	Sigma Aldrich	Low pressure, 24 h, 350 K	^{1}H NMR DSC water content	> 0.98 (given by supplier)
MEF1		344.45	Synth.	Low pressure, 24 h, 350 K	^{1}H NMR DSC water content	> 0.97/0.036
MEF2		375.24	Synth	Low pressure, 24 h, 350 K	^{1}H NMR DSC water content	> 0.963/0.012
MEF3		404.48	Synth	Low pressure, 24 h, 350 K	^{1}H NMR DSC water content	> 0.96/0.027

pyridinium-based ILs (Weaver et al., 2010; Petkovic et al., 2010). The special attention has been taken in recent years to study the choline-derivatives for pharmaceutical applications ILs (Weaver et al., 2010).

Solubility of Phs in water depends on the chemical structure, number of aromatic rings and of polar groups such as (−COOH), (−OH) or (−NH) group. The ionization state of each functional group plays a crucial role into therapeutic target and in the interaction with the specific receptor binding sites.

In our laboratory, we have undertaken various studies on factors influencing the solubility of different Phs in water and alcohols (Domańska et al., 2011b), the influence of cyclodextrin (Domańska et al., 2011a) and poly(DL-lactide-*co*-glycolide (PLGA) nanoparticles (Halayqa and Domańska, 2014).

The solubility of mefenamic acid (MEF) and few other Phs in water, ethanol and 1-octanol at constant pH was recently published by us (Domańska et al., 2010). MEF is an anthranilic and indole acetic-type acid, known as anti-inflammatory and analgesic drug. MEF reveals very small solubility, especially in water. The solubility predicted by us by the ALGOPS 2.1. software designed by VCCLabs (Tetko, 2010; Tetko et al., 2001) at T = 298.15 K was on a level 1.03 × 10^{-6} in mole fraction (Domańska et al., 2010). The aqueous solubility of MEF was described in open literature at T = 298 K on a level 1.27 × 10^{-7} in mole fraction (Rytting et al., 2005) or as 2.98 × 10^{-6} in mole fraction at T = 298.15 K and pH 7.1, and 7.97 × 10^{-6} at T = 310.15 K and pH 7.1 (TenHoor et al., 1991). An interesting analysis was provided for the solubility of MEF in water at T = 298.15 K influenced by the different excipients (Avdeef, 2007; Avdeef et al., 2007). The excipient-free aqueous solubility of MEF was about 1.57 × 10^{-9} in mole fraction at T = 298.15 K and pH between 3 and 6 (Avdeef et al., 2007). In conclusion it was stated that MEF forms in water anionic dimers and trimers, which in our opinion form larger molecules of higher melting temperature and lower solubility.

The objective of the current study was to investigate the influence of created new MEF-ammonium IL compounds on solubility in water, ethanol and octanol to improve the solubility of poorly soluble MEF. Synthesis of three mefenamic acid-ammonium ionic liquids, namely choline, or di(2-hydroxyethyl)dimethylammonium, or tri(2-hydroxyethyl)methyl ammonium compounds MEF1, MEF2 and MEF3 is presented. The basic thermal properties of pure compounds i.e. fusion temperature and enthalpy of MEF and new compounds have been measured with differential scanning microcalorimetry technique (DSC).

2. Materials and methods

2.1. Materials

Studied mefenamic acid was obtained from Sigma Aldrich, (CAS Registry No. 61-68-7). The substance was used without further purification and was used as a powder for the synthesis. Water used as a solvent was twice distilled, degassed and filtered with Milipore Elix 3. Other solvents i.e. ethanol and 1-octanol, were also obtained from Sigma Aldrich with a > 0.998 mass fraction purity. They were stored under freshly activated molecular sieves of type 4 Å. All solutes were filtrated twice with Schott funnel with 4 μm pores. The densities of solvents were measured using an Anton Paar GmbH 4500 vibrating-tube densimeter (Graz, Austria), thermostated at different