



A favourable solubility of isoniazid, an antitubercular antibiotic drug, in alternative solvents

Andreia Forte^a, Catarina I. Melo^a, Rafał Bogel-Łukasik^b, Ewa Bogel-Łukasik^{a,*}

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

^b Laboratório Nacional de Energia e Geologia, I.P., Unit of Bioenergy, Estrada do Paço do Lumiar 22, 1649-038 Lisboa, Portugal

ARTICLE INFO

Article history:

Received 9 December 2011

Received in revised form 13 January 2012

Accepted 18 January 2012

Available online 25 January 2012

Keywords:

Isoniazid

Ionic liquid

Solubility

Solid–liquid equilibria

Thermochemical properties

Drug

Antibiotic

ABSTRACT

The sufficient solubility of isoniazid in alternative solvents obtained in this work can open new perspectives in pharmaceutical processing. Solid–liquid equilibrium (SLE) measurements have been made using a dynamic (synthetic) method. The melting point and the enthalpy of fusion of isoniazid were acquired using differential scanning calorimetry (DSC). The solubility of isoniazid in bis(trifluoromethylsulfonyl)amide ionic liquids was found to be significantly lower than in the studied trifluoromethanesulfonate ionic liquid. The best solvent amongst studied for this common antibiotic against tuberculosis was discovered. The solid–liquid phase equilibria were described using the six different correlation equations which revealed relatively good description with the acceptable standard deviation temperature range.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction

According to the statistics of the World Health Organization, tuberculosis kills more people than any other infectious disease in the world. It causes more deaths than AIDS and malaria combined [1]. Tuberculosis is an infectious bacterial disease caused by *Mycobacterium tuberculosis* which most commonly affects the lungs [2]. Several drugs are needed to treat active tuberculosis. In normal treatment of tuberculosis, patients take the antibiotic drugs: isoniazid and rifampicin (the most effective tuberculosis drug available) for a few months. A drug called isoniazid can be used as a preventative therapy for those who are at high risk of becoming infected with tuberculosis. Isoniazid is available worldwide, as well as is inexpensive and generally well tolerated. Moreover, except being an antitubercular drug, isoniazid was one of the first antidepressants discovered. The Sheldon's *E*-factor, defined as the mass ratio of waste to desired product indicates the highest *E* factor of 25–100 [3] for pharmaceutical industry amongst oil refining, bulk or fine chemicals sectors. For this reason an attention should be focused on development in pharmaceutical industry with regard to waste minimisation and to assessing its current status in the broad context of green chemistry and sustainability. Particularly, the pharmaceutical industry should search for solutions to the problem of waste

generation in chemicals manufacture. Organic hazardous solvents can be substituted by green solvents which are advantageous especially in terms of volatility and flammability. Ionic liquids have proven their sustainable applications in reactions [4,5] and separations [5,6] mostly due to their unique tuneable properties, such as a thermal stability [7,8] and a solvent power [6,9–14]. In general, ILs with a short alkyl chain appended in the imidazolium cation and with hydrophilic anions have low toxicity [15,16]. The [C₄mim] and [C₆mim] cations were largely nontoxic towards Caco-2 cells [17], although a slightly higher toxicity was noticed for a surface active cation of [C₈mim]. Nevertheless, the toxicity of these ionic liquids did not prevent their use as pharmaceutical solvents as many pharmaceutical excipients such as the non-ionic surfactants (e.g. polysorbate 80) exhibit similar toxicities to many ILs [18]. In case of classical solvents in operations such as granulation, blending, compounding and drying, volatile liquids are used, and thus flammable or explosive atmospheres can be created. The flammable solvents' use has a direct impact on a specific engineering design, features of pharmaceutical facilities and process equipment [19]. Due to this it is desirable to improve manufacturing processes with solvents recognised as "safer" [19,20] and suitable in pharmaceutical processing [21,22].

This work is focused on screening of alternative solvents in order to open possibilities for the pharmaceutical processing by presenting the solubility data of isoniazid, a common antitubercular antibiotic drug, in bis(trifluoromethylsulfonyl)amide and trifluoromethanesulfonate ionic liquids. To the best of

* Corresponding author. Tel.: +351 212948353; fax: +351 212948550.
E-mail address: ewa.lukasik@fct.unl.pt (E. Bogel-Łukasik).