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Green technologies for design of drug delivery systems for tuberculosis treatment

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PURPOSE OF THE ABSTRACT

Tuberculosis continues to be one of the top 10 causes of morbidity and mortality in worldwide and the treatment usually involves a combination of antibacterial drugs administered for several months.1,2,3 This airborne infectious disease is caused by Mycobacterium tuberculosis complex,2,3 and the World Health Organization estimated 10.4 million of new cases of tuberculosis, in 2016, and 1.7 million died from the disease.1

Therapeutic deep eutectic solvents (THEDESs) emerged as alternative solvents to organic solvents due to its non-toxicity, biodegradability, biocompatibility, low volatility and easy synthesis, with high yields and high purity. The THEDES are prepared by mixing the components at a certain molar ratio, until a clear liquid solution was formed. The components interact by hydrogen bonds and electrostatic interactions, presenting a lower melting point than the pure components.4,5 The use of THEDES in combination with supercritical fluid technology using CO2 to explore controlled drug delivery systems has been recently explored. The combination of supercritical CO2 technology and THEDES is very appealing for several application as they both fulfill green criteria. However, the scarce information in the literature regarding the fundamentals of DES and CO2 mixtures in terms of phase equilibrium is a limiting factor. The determination of vapor-liquid equilibrium (VLE) of these binary mixtures is crucial for its characterization. Moreover, it will allow to understand the impact of its thermodynamic state in the design of innovative systems, from the appropriate choice of starting materials, conditions and technique, to the required final product properties or application outcome.

In this study were developed THEDES systems based on anti-tuberculosis drugs ethambutol and L-arginine that were characterized by differential scanning calorimetry (DSC), polarized optical microscopy (POM), nuclear magnetic resonance spectroscopy (NMR) and rheometry. Furthermore, the bioavailability of the systems was evaluated through the determination of their solubility and permeability at 37ºC in phosphate saline buffered (PBS), to stimulate physiological conditions.6 Their cytotoxicity and IC50 was evaluated in Caco-2 cell line, to compare the cytotoxicity of the original drug and the cytotoxicity of our systems. To be able to design formulation processes, such as particles from gas saturated solutions (PGSS) it is important to determine the VLE of the pseudo-binary system DES + CO2. In this work, the VLE was studied by determining pressure bubble points of different THEDES:CO2 ratios, in isothermic conditions, using variable-volume view cell methodology. Results suggest that it is possible to formulate drug delivery systems using the THEDES herein described by PGSS process, without compromising the integrity of the system.

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FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

therapeutic deep eutectic solvents | tuberculosis | supercritical CO2

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