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Design of controlled release systems for THEDES—Therapeutic deep eutectic solvents, using supercritical fluid technology

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ABSTRACT

Deep eutectic solvents (DES) can be formed by bioactive compounds or pharmaceutical ingredients. A therapeutic DES (THEDES) based on ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), and menthol was synthesized and its thermal behavior was analyzed by differential scanning calorimetry (DSC). A controlled drug delivery system was developed by impregnating a starch:poly-ε-caprolactone polymeric blend (SPCL 30:70) with the menthol:ibuprofen THEDES in different ratios (10 and 20 wt%), after supercritical fluid sintering at 20 MPa and 50 °C. The morphological characterization of SPCL matrices impregnated with THEDES was performed by scanning electron microscopy (SEM) and micro-computed tomography (micro-CT). Drug release studies were carried out in a phosphate buffered saline. The results obtained provide important clues for the development of carriers for the sustainable delivery of bioactive compounds.

1. Introduction

Deep eutectic solvents (DES) have been presented as alternative solvents for a variety of applications, similarly to the developments observed with ionic liquids (ILs) in the early 90's (Abbott et al., 2004; Paiva et al., 2014; Pena-Pereira and Namiesnik, 2014). DES present, however, two major advantages that overcome the limited applicability of ILs. DES, and particularly natural deep eutectic solvents (NADES), are produced from naturally occurring molecules and have therefore inherent low toxicity (Dai et al., 2013). Additionally they are formed by combining two or more compounds that are solid at room temperature, which upon mixing at a particular composition become liquid.

The development of therapeutic deep eutectic solvents (THEDES) is a field of research that has not been extensively explored. Stott and co-workers reported that ibuprofen formed eutectic mixtures with different terpenes that were shown to promote enhanced skin permeation. It has also been reported that DES can dissolve model drugs, increasing their solubility, permeation and absorption (Stott et al., 1998). The enhancement of the permeation of THEDES has been demonstrated by Wang et al. (2014). The permeation of the lidocaine:ibuprofen system can be finely tuned depending on the molar ratio of the two components, allowing the development of tailor-made, transdermal drug delivery systems (Wang et al., 2014). Tuntarawongsa and Phaechamud (2012a,b) reported on the preparation of a DES with therapeutic properties, consisting of a mixture of menthol and camphor with dissolved ibuprofen. DES dissolved considerable higher amounts of ibuprofen when compared to water. With the addition of a polymer, a polymeric eutectic drug delivery system was formed (Tuntarawongsa and Phaechamud, 2012b). The same behavior was observed by Morrison et al. (2009) who studied the solubilisation of benzoic acid, danazol, griseofulvin, AMG517 and itraconazole in urea:choline chloride and malonic acid:choline chloride DES. Bica et al. (2012) reported on the synthesis of new therapeutic ILs, namely tetrabutylphosphonium ibuprofenate and ephedrinium ibuprofenate and on the controlled release of these ILs from porous silica particles. The possibility to couple a THEDES with a second component, particularly a polymer, and to

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synthesize bioactive eutectic systems opens a broad spectrum of future developments in pharmaceutical and biomedical applications of these systems. The doping of biopolymers with THEDES is a new strategy for the delivery of the therapeutic agent. Biodegradable polymers made from renewable resources are an important innovation in materials science (Malafaya et al., 2007; Mano et al., 2007). Starch-based polymers in particular have been studied for a wide range of applications including the development of controlled drug delivery systems (Balmayor et al., 2009; Lu et al., 2009; Reis et al., 2008; Silva et al., 2004). Their natural origin, together with their mechanical properties and biocompatibility, are behind the potential of starch-based materials in the biomedical field (Marques et al., 2002).

The combination of THEDES, biodegradable natural based polymers, and supercritical carbon dioxide ($scCO_2$) is a viable alternative for the production of drug delivery systems. The use of $scCO_2$ for the development of enhanced biomaterials for pharmaceutical and/or biomedical applications has been reported in different reviews (Duarte et al., 2009a,b; Knez et al., 2011; Salerno and Pascual, 2015; Zhang et al., 2014). CO_2 is the most commonly used solvent at supercritical conditions due to its low critical parameters (T_c = 31.1 °C and P_c = 73.8 bar) and to the fact that it is environmentally benign, non-toxic, non-flammable, non-corrosive, readily available and inexpensive. Supercritical fluid sintering was proposed by Singh et al. (2010) for the preparation of highly porous and interconnected structures, under mild conditions. The supercritical sintering technique, similarly to supercritical fluid foaming, relies on the plasticizing effect of CO_2, which reduces the glass transition temperature (T_g) of the polymer. In the case of sintering, polymeric particles are softened and fused together creating a three dimensional (3D) structure (Alves et al., 2012). Supercritical fluid sintering is a technique which relies on the decrease of the T_g of the polymer (Duarte et al., 2013). The softening of the polymer under a CO_2 atmosphere allows the sintering of the particles, promoting their adhesion while leaving empty pores inside the formed structure. Supercritical fluid sintering has been described in the literature for the preparation of different scaffolds, particularly for tissue engineering, and it is particularly attractive due to the mild operating conditions, which allow the processing of thermolabile substances (Bhamidipati et al., 2013; Singh et al., 2010). The main objective of this work was the development of a controlled delivery system based on a starch polymer blend impregnated with menthol:ibuprofen THEDES, obtained by supercritical fluid sintering.

2. Materials and methods

2.1. Materials

The reagents used in the preparation of THEDES were menthol (≥98%, CAS 89-78-1, Sigma) and ibuprofen, which was obtained from ibuprofen sodium salt (98%, CAS 31121-93-4, Sigma). A 50 mg/mL solution of this compound in distilled water was prepared, and the pH was adjusted to 1-2 by adding small amounts of a solution of hydrochloric acid (1 M) (36.5-38%, CAS 764-01-0, Scharlau). The two compounds react, yielding ibuprofen in its acid form, and sodium chloride. Ibuprofen is extracted with dichloromethane (≥99.8%, CAS 75-09-2, Fluka) that is subsequently subjected to drying with sodium sulphate, filtration and evaporation of the solvent under reduced pressure until a fine white powder is obtained. The purity of the obtained ibuprofen was accessed by GC and NMR to a value of >98%. The polymer used in this work was a commercial blend of corn starch (70 wt%) with poly-ε-caprolactone (PCL; 30 wt%), henceforth designated SPCL, in granular form, obtained from Biocycle. Carbon dioxide (99.998 mol %) was supplied by Air Liquide. Phosphate buffered saline (PBS) was prepared from Phosphate buffered saline tablets (Sigma) as indicated. One tablet is dissolved in 200 mL of deionized water, yielding a 0.01 M phosphate buffer, 0.0027 M potassium chloride, 0.137 M sodium chloride, pH 7.4 solution, at 25 °C. All chemicals, with the exception of ibuprofen, were used without any further purification.

2.2. THEDES preparation

The menthol:ibuprofen THEDES was prepared according to previous reports (Carriazo et al., 2012; Russ and Konig, 2012; Stott et al., 1998), in a 3:1 molar ratio eutectic mixture. The compounds were weighted and mixed. The solid mixture was heated up to 40 °C until it became a clear liquid. Following the procedure of Stott et al., (1998), the mixture was stored at −20 °C until further use.

2.3. Characterization

2.3.1. Water content—Karl Fischer titration

The water content of the THEDES was determined by Karl Fischer titration, using an 831 KF Coulometer with generator electrode without diaphragm. The water content values given are an average of at least three measurements.

2.3.2. Thermal properties—differential scanning calorimetry (DSC)

DSC analysis was performed on a Q2000 isothermal differential calorimeter (TA Instruments, Tzero™ DSC technology). The samples were packed in a TA aluminum pan. For samples of menthol and ibuprofen, DSC data were collected between −90 °C and 120 °C, at a rate of 10 °C/min. In the case of the 3:1 menthol: ibuprofen mixture, the DSC analysis was performed between −10 °C and 120 °C, at a rate of 1 °C/min.

2.4. Dissolution studies

For the dissolution studies, approximately 65 mg of 3:1 menthol:ibuprofen was weighed and immersed in 20 mL of PBS. Samples of 0.5 mL were withdrawn at 5, 15, 20, 30, 45 60, 120 and 180 min, 5, 7 and 24 h, and each sample was replaced by an equal amount of fresh PBS. The dissolution tests were also carried out with ibuprofen in the solid form. The same mass of ibuprofen present in 65 mg of THEDES was used, which corresponded to approximately 20 mg. The samples dissolution was quantified by UV–vis spectroscopy at 265 nm in a microplate reader (BIO-TEK, SYNERGY HT). The results presented are an average of three measurements. The cumulative mass of drug released was determined taking into consideration the replacement of aliquots with fresh medium and the dilution derived from the addition of fresh buffer.

A calibration curve for ibuprofen (correlation coefficient of 0.99996) was obtained using standards prepared with the following concentrations: 0 (blank), 0.05, 0.1, 0.2, 0.5 and 1 mg/mL. A calibration curve for ibuprofen (correlation coefficient of 0.99999) was also built using the same concentrations of 3:1 menthol:ibuprofen.

2.5. Supercritical fluid sintering

SPCL in granular form was milled in an ultra-centrifugal mill (Retsch, ZM 200). Appropriate amounts of SPCL in powder form and of THEDES were weighed and mixed to yield SPCL mixtures with 10 and 20 wt.% of 3:1 menthol:ibuprofen. The mixtures were homogeneous. SPCL in the same amount as used to prepare SPCL-THEDES mixtures was used as control. Another control was prepared by mixing SPCL powder with ibuprofen also in powder form. In this case, the amount of ibuprofen was the same as used in