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Research paper

A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: Solubility and permeability studies

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ABSTRACT

THEDES, so called therapeutic deep eutectic solvents are here defined as a mixture of two components, which at a particular molar composition become liquid at room temperature and in which one of them is an active pharmaceutical ingredient (API). In this work, THEDES based on menthol complexed with three different APIs, ibuprofen (ibu), BA (BA) and phenylacetic acid (PA), were prepared. The interactions between the components that constitute the THEDES were studied by NMR, confirming that the eutectic system is formed by H-bonds between menthol and the API. The mobility of the THEDES components was studied by PFGSE NMR spectroscopy. It was determined that the self-diffusion of the species followed the same behavior as observed previously for ionic liquids, in which the components migrate *via* jumping between voids in the suprastructure created by punctual thermal fluctuations. The solubility and permeability of the systems in an isotonic solution was evaluated and a comparison with the pure APIs was established through diffusion and permeability studies carried out in a Franz cell. The solubility of the APIs when in the THEDES system can be improved up to 12 fold, namely for the system containing ibu. Furthermore, for this system the permeability was calculated to be 14×10^{-5} cm/s representing a 3 fold increase in comparison with the pure API. With the exception of the systems containing PA an increase in the solubility, coupled with an increase in permeability was observed. In this work, we hence demonstrate the efficiency of THEDES as a new formulation for the enhancement of the bioavailability of APIs by changing the physical state of the molecules from a solid dosage to a liquid system.

1. Introduction

Pharmaceutical sciences face major challenges associated with drug solubility and permeability, which result in an inadequate pharmacokinetics and poor bioavailability of the active pharmaceutical ingredient (API) [1]. According to the biopharmaceutics classification system (BCS) the drugs can be categorized in four main groups based on their solubility and permeability [2] (Fig. 1):

This classification system is often related to the solubility in simulated body fluids and gastrointestinal permeability. Nonetheless, in vitro models have been adopted to determine the permeability of the drugs in synthetic membranes mimicking the effect of a tissue. To overcome the problem of low solubility and/or low permeability of drugs, often higher dosages are administered leading to potential systemic toxicity and severe side effects. Pharmaceutical innovations require either crystal engineering strategies coupled with new methods of administration and novel delivery systems able to provide a more effective and patient compliant therapy.

Crystal engineering has been the focus of different studies which aim is to promote the enhancement of solubility and/or permeability of APIs [3]. Various methods, namely the creation of metastable polymorphs, amorphization, salt formation or co-crystal formation have been proposed in order to manipulate the APIs properties, particularly their crystallinity and consequently their bioavailability [1,4]. On the other hand, the manipulation of the physical and/or morphological properties of the API itself, for instance micronization of the powders may also contribute to the enhancement of drug dissolution and permeability [5]. Other strategies involve the preparation of more complex systems, such as suitable delivery systems and the design of new carriers [6–8].

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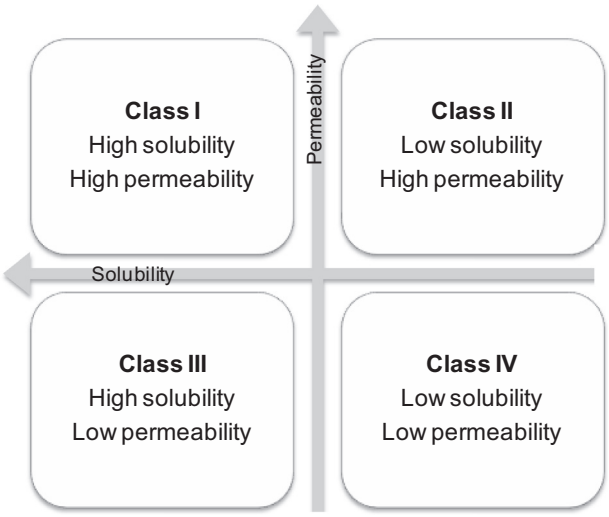

Fig. 1. Biopharmaceutics classification system of APIs.

Cherukuvada and coworkers reviewed the potential use of eutectics as improved pharmaceutical formulations [9]. However, up to date limited information has been published or reported for these systems, which are often mistaken for unstable cocrystals. The major difference between eutectics and cocrystals relies on the interactions and the type of components present in the system. An eutectic system is a mixture of two components which interact trough hydrogen bonding and lead to an overall decrease in the melting temperature of the system. When the decrease in the melting temperature is such that the systems become liquid at room temperature they are so-called deep eutectic solvents (DES). THEDES – therapeutic deep eutectic solvents have, hence, been defined as a bioactive eutectic system containing an API as one of the DES components [10]. Stott and coworkers have described for the first time a THEDES system composed of menthol and ibuprofen (Ibu) [11]. The main purpose was the enhancement of skin permeation and development of transdermal delivery systems. Similarly, Morrison and coworkers reported a 5–22,000-fold increase on the solubility of BA (BA), danazol, griseofulvin and itraconazole in urea-choline chloride and malonic acid-choline chloride DES [12]. Wang et al. have reported the development of an eutectic system of lidocaine:ibu. The results of this study highlight the differences between the dissolution and permeation of the active compounds, which can be finely tuned towards the development of transdermal delivery systems [13].

The design of new THEDES systems is not easy and lack of knowledge on the type of interactions and associations established between the molecules which constitute the THEDES is still hindering the development of new systems. Nonetheless, this approach is, due to its simplicity, of utmost relevance in the pharmaceutical field. The preparation of the THEDES systems yields a 100% pure product, with no losses during production and no need for subsequent purification steps [14]. Furthermore, the scale-up of the process is relatively straightforward, which is highly important for the pharmaceutical industry [15].

In a previous work we have reported the development of novel THEDES based on choline chloride and menthol, combined with three APIs, namely acetylsalicylic acid, BA and phenylacetic acid (PA) [16]. It was herein demonstrated that the dissolution rate of the APIs is greatly enhanced by these systems, particularly in the case of menthol-based THEDES. The interest in terpenes and particularly in menthol is mostly due to its effectiveness as permeation enhancer, which has been reported in the literature [17]. The characterization of the systems in terms of dissolution rate, solubility and permeability are most relevant to the determination of the suitable dosage and form of administration. For this reason, in this work, we have further explored the menthol-based systems: menthol:ibu; menthol:BA and menthol:PA and evaluated the solubility and permeability of the APIs present in the systems. In the particular case of the systems studied the envisaged route of administration is the transdermal way. The systems prepared could be embedded in a patch, providing a more effective delivery of the API in a local delivery approach.

2. Materials and methods

2.1. Materials

The reagents used in the preparation of THEDES were menthol (99% purity, CAS 89-78-1, Sigma), ibu (>98% purity, CAS 15687-27-1, Sigma), BA (>99.5% purity, CAS 65-85-0, Sigma) and PA (99% purity, CAS 103-82-2, Sigma). Fig. 2 presents the chemical formulas of the reagents used. All chemicals were used without any further purification.

Phosphate buffered saline (PBS) was prepared from phosphate buffered saline tablets (Sigma), as indicated. One tablet was 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.

2.2. THEDES preparation

THEDES systems prepared were menthol:Ibu (3:1); menthol:BA (3:1); menthol:PA (2:1) and menthol:PA (3:1). The systems were prepared by mixing the two components at the given molar ratio [16]. The mixture was heated to 40 °C, under constant stirring, until a clear liquid solution was formed. Typically the liquid solution was obtained after a few hours.

2.3. Characterization

2.3.1. NMR studies

All the NMR experiments were carried out in a Bruker Avance 400 spectrometer, equipped with a BBO probe capable of producing magnetic field gradient pulses up to 53.5 G cm^{-1} in the *z*-direction, with a BCUextreme temperature control unit. The THEDES samples were placed in a 5 mm NMR tube and left for 15 min at the desired temperature (±0.1 °C) in order to reach thermal equilibrium. All chemical shifts were referred using tetramethylsilane (TMS) as internal reference and the shim was performed using a sealed C6D6 capillary tube.

2.3.2. Pulsed-field gradient (PFG) NMR

The diffusion measurements were performed using the stimulated echo sequence using bipolar sine gradient pulses and eddy current delay before the detection [18]. For each PFGSE experiment 16 spectra of 64 K data points were collected, with a relaxation delay of 2 s, in which the duration of the magnetic field gradient (τ) was 2–4 ms, the diffusion times was 80 ms (for the diluted samples) and 800 ms (for the neat samples) and the gradient recovery was 200 μs. The sine shaped gradient (g) was incremented from 5 to 95% of the maximum gradient strength in a linear ramp (2.68–50.83 G cm^{-1}).

To determine the self-diffusion coefficients, the spectra were first processed in the F2 dimension by standard Fourier transform and baseline correction with the Bruker Topspin software package (version 3.2). The self-diffusion coefficients were calculated by exponential fitting of the data belonging to individual columns of the 2D matrix using the Origin 9.0 data software program. In a PFG NMR experiment the spin echo attenuation decay, I, is related