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Research Paper

Dissolution enhancement of active pharmaceutical ingredients by therapeutic deep eutectic systems

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ABSTRACT

A therapeutic deep eutectic system (THEDES) is here defined as a deep eutectic solvent (DES) having an active pharmaceutical ingredient (API) as one of the components. In this work, THEDESs are proposed as enhanced transporters and delivery vehicles for bioactive molecules. THEDESs based on choline chloride (ChCl) or menthol conjugated with three different APIs, namely acetylsalicylic acid (AA), benzoic acid (BA) and phenylacetic acid (PA), were synthesized and characterized for thermal behaviour, structural features, dissolution rate and antibacterial activity. Differential scanning calorimetry and polarized optical microscopy showed that ChCl:PA (1:1), ChCl:AA (1:1), menthol:AA (3:1), menthol:BA (3:1), menthol:PA (2:1) and menthol:PA (3:1) were liquid at room temperature. Dissolution studies in PBS led to increased dissolution rates for the APIs when in the form of THEDES, compared to the API alone. The increase in dissolution rate was particularly noticeable for menthol-based THEDES. Antibacterial activity was assessed using both Gram-positive and Gram-negative model organisms. The results show that all the THEDESs retain the antibacterial activity of the API. Overall, our results highlight the great potential of THEDES as dissolution enhancers in the development of novel and more effective drug delivery systems.

1. Introduction

Increasing concern with health care worldwide has been the driver for pursuing new pharmaceutical formulations. Ageing populations, worried about the quality of life in the senior years, are actively seeking new, more effective and patient-compliant drug delivery devices. It has long been recognized that pills of injections may not be suitable methods of administration for certain active compounds. These medications present several problems and/or limitations, such as poor drug solubility and thus bioavailability, limited pharmacokinetics and systemic toxicity. A recent review highlights the potential use of eutectics as improved pharmaceutical materials [1]. Until now, limited data have been obtained for these systems, which are often mistaken for unstable cocrystals or solid solutions.

A deep eutectic solvent (DES) is defined as a mixture of two or more compounds that are typically solid at room temperature, but when combined at a particular molar ratio, presents a significant melting point depression, often becoming liquid at room temperature [2–4]. The ability to form a DES with an active pharmaceutical ingredient (API) and the possibility to develop drug delivery devices, for transdermal drug delivery in particular, were demonstrated for the first time in 1998, by Stott and coworkers [5]. In this work, the authors describe mixtures of an API with different terpenes as enhancers of skin permeation. It is reported that the DES formulation can increase the solubility, permeation and absorption of the API. Similarly, Morrison and coworkers reported on the solubility of benzoic acid, danazol, griseofulvin and itraconazole in urea-choline chloride and malonic acid-choline chloride DES [6]. The solubility of these molecules increases, in

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some cases, 5–22,000-fold when compared with their solubility in water. Tuntarawongsa and Phaechamud have reported on the preparation of a DES solution with therapeutic properties made from menthol and camphor, and dissolved ibuprofen [7,8].

A similar approach has been developed using ionic liquids. Bica and co-workers have reported on the development of pharmaceutical ionic liquids, namely tetrabutylphosphonium ibuprofenate supported in a solid formulation [9]. The developed system had enhanced thermal stability and ensured a fast release of the API. Also dos Santos et al. have reported on the production of antimicrobial ionic gel fibres with chloride mandelate [10].

A major difference between ionic liquid-based and DES-based systems is the fact that the preparation of ionic liquids requires chemical reactions, rather than simple physical mixture of the two components, increasing the complexity of the synthesis. The development of bioactive eutectic systems containing an API as one of the DES components further increases the potential of these systems and opens a broad spectrum for future developments on pharmaceuticals and biomedical applications. The API-based DES systems are hereafter defined as therapeutic deep eutectic systems – THEDESs.

The development of a lidocaine:ibuprofen THEDES has recently been described by Wang et al. who report on the permeability of the API through a porous membrane. The results demonstrate that there are differences between the dissolution and permeation of the active compounds, and depending on the formulation, this can be finely tuned towards the development of new transdermal delivery systems [11]. The combination of a THEDES with natural based biodegradable polymers and supercritical carbon dioxide ($scCO_2$) was recently demonstrated for the production of drug delivery systems and other biomedical applications [12]. Subjecting a THEDES-doped biopolymer to $scCO_2$ resulted in foaming, with increasing matrix porosity and creation of a lightweight, high surface area material [13]. The resulting construct offers the advantage of delivery of bioactive molecules of low aqueous solubility. The release of Ibuprofen from a doped polymer structure shows enhanced performance compared to the dissolution of the pure compound, which may be beneficial for specific applications [14].

In this work we have developed new THEDESs based on choline chloride and menthol, combined with three APIs, acetylsalicylic acid, benzoic acid and phenylacetic acid. The preparation of THEDES by itself is a major contribution beyond the state of the art as the ability to form a liquid formulation of an API may enhance the bioavailability and rate of delivery of the drug and reduce its toxicity.

2. Materials and methods

2.1. Materials

The reagents used in the preparation of THEDES were menthol (99% purity, CAS 89-78-1, Sigma), choline chloride (CAS 67-48-1, Sigma), acetylsalicylic acid (>99% purity, CAS 50-78-2, Sigma), benzoic acid (>99.5% purity, CAS 65-85-0, Sigma) and phenylacetic acid (99% purity, CAS 103-82-2, Sigma). All chemicals were used without any further purification.

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.

2.2. THEDES preparation

THEDESs were prepared by mixing the two components at a given molar ratio. The mixture was heated to 40 °C, under constant stirring, until a clear liquid solution was formed. Typically the liquid solution is obtained after a few hours. For the systems for which the formation of a liquid was not observed, the preparation process was deemed complete after 24 h, irrespective of the final state of the system. The different mixtures tested are described in Table 1.

2.3. Characterization

2.3.1. Thermal properties – differential scanning calorimetry (DSC)

The DSC experiments were performed using a DSC Q100 apparatus from TA Instruments Inc., USA, operating in the Heat Flow T4P option [15]. Standard calibrations were performed using indium leads. The measurements were performed under dry nitrogen atmosphere, at a flow rate of 50 mL min^{-1}. Approximately 5 mg of each sample was placed in aluminium pans covered with lids. The samples were equilibrated at 40 °C for 5 min, followed by cooling to −40 °C, an isothermal period of 5 min, and heating to the assay end temperature, at a heating rate of 5 °C/min.

2.3.2. Polarized optical microscopy (POM)

A droplet of THEDES was deposited on a microscope slide for observation. Optical characterization of the THEDES samples was carried out at 22 °C by POM using an Olympus transmission microscope coupled with a Leica digital camera and Leica Application Suite Software.

Table 1
Summary of the different THEDES prepared.

Component A	Component B	Mole ratio	Abbreviation	Observations/visual aspect
Choline chloride (ChCl)	Acetylsalicylic Acid (AA)	1:1	ChCl:AA (1:1)	Transparent viscous liquid at RT
Choline chloride (ChCl)	Phenylacetic Acid (PA)	1:1	ChCl:PA (1:1)	Transparent liquid at RT
Menthol	Benzoic Acid (BA)	1:1	Menthol:BA (1:1)	White solid at RT
		2:1	Menthol:BA (2:1)	White solid at RT
		3:1	Menthol:BA (3:1)	Transparent liquid at RT
Menthol	Acetylsalicylic Acid (AA)	1:1	Menthol:AA (1:1)	White solid at RT with some liquid
		2:1	Menthol:AA (2:1)	White solid at RT with some liquid
		3:1	Menthol:AA (3:1)	Transparent liquid at RT
Menthol	Phenylacetic Acid (PA)	1:1	Menthol:PA (1:1)	Transparent highly viscous liquid at RT
		2:1	Menthol:PA (2:1)	Transparent liquid at RT
		3:1	Menthol:PA (3:1)	Transparent liquid at RT

The ChCl:BA system did not form liquid mixtures for the tested molar ratios, 1:1; 2:1 and 1:2.