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The role of ionic vs. non-ionic excipients in APIs-based eutectic systems

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Abstract

Aiming to contribute to drug pre-formulation, new eutectic mixtures were developed. Thymol, coumarin, or quaternary ammonium chlorides as excipients, were combined with the active pharmaceutical ingredients (APIs) acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, or lidocaine. Their solid-liquid equilibrium (SLE) binary phase diagrams were measured to study eventual phase separation between the compounds, preventing manufacturing problems, and to study the molecular interactions between the APIs and ionic or non-ionic excipients. The Conductor-like Screening Model for Real Solvents (COSMO-RS) capability to predict the SLE of mixtures containing non-ionic excipients was further evaluated. COSMO-RS gives a good quantitative description of the experimental SLE being a tool with great potential in the screening of eutectic systems containing APIs and non-ionic excipients. While thymol presents strong interactions with the APIs, and consequently negative deviations to thermodynamic ideality, systems containing coumarin follow a quasi-ideal behavior. Regarding the ionic excipients, both choline chloride and the tetraalkylammonium chlorides are unable to establish relevant interactions with the APIs, and no significant negative deviations to ideality are observed. The liquefaction of the APIs here studied is favored by using non-ionic excipients, such as thymol, due to the strong interactions it can establish with the APIs.

Keywords: Drug formulation, thymol, quaternary ammonium chlorides, solid-liquid equilibrium, phase diagrams, COSMO-RS.

1. Introduction

Pharmaceuticals are an essential element in medicine, and due to their benefits to society, their demand increases every day. However, the development of new drugs is expensive and time-consuming. On average, around 10 years and more than 800 million dollars are required to design and test a new drug (Berg et al., 2010; Tiwari et al., 2012). Clinical development that comprises pre-clinical research and clinical trials are the main issues to be accounted for, but it is also important to consider the challenges with drug discovery or product development. The search for the best excipient is related to chemical instability, poor water solubility, crystallinity, and polymorphism (Strickley and Oliyai, 2007). More than 40% of the drugs under development are classified as poorly soluble, or even insoluble, and to improve their bioavailability they should be in the liquid state or sufficiently soluble in the gastric fluids at the absorption point (Kalepu and Nekkanti, 2015; Savjani et al., 2012). Regarding dermal drug delivery, problems arise from physicochemical restrictions imposed by the protective function of human skin. Key factors for a drug to be delivered passively via the skin are suitable lipophilicity and molecular weight (Brown et al., 2006). Thus, approaches that would increase the bioavailability of the compounds leading to lower dosages and decreasing the wastage would be of importance.

Improving the formulation of existing drugs is much simpler and faster than the development of new ones. Therefore, many attempts to find solutions for that particular challenge faced by the pharmaceutical industry have been followed (Kalepu and Nekkanti, 2015; Pedro et al., 2019). Examples comprise chemical modifications such as changing the solution pH, derivatization or the use of buffers, and/or physical changes such as particle size reduction, solid dispersions, and drug dispersion by eutectic formation (Savjani et al., 2012).

The formation of eutectic mixtures, and more recently *deep* eutectic mixtures or deep eutectic solvents (DES), has been proposed as a technique to increase active pharmaceutical ingredients (APIs) water solubility and bioavailability on the development of new drugs (Cherukuvada and Nangia, 2014; Gala et al., 2013; Martins et al., 2019; Pedro et al., 2019; Savjani et al., 2012). These mixtures are characterized by a decrease in the melting temperature of the system compared to the pure components melting temperatures, while

keeping the therapeutic integrity of the forming compounds. Eutectic mixtures are expected to have a significant role in the pharmaceutical industry if they are formed between APIs, between APIs and excipient, or between excipients, where excipients are defined as molecules with the ability to deliver the active ingredient to the active site (Gala et al., 2013; Kalasz and Antal, 2006). The choice of the appropriate excipients and APIs, and their respective ratios, are crucial during drug pre-formulation. Wrong choices either in terms of composition or temperature range at which mixtures are at a given physical state, may lead to the undesirable melting of a pharmaceutical tablet or even decomposition of the pure components (Gala et al., 2013; Pedro et al., 2019). Thus, it is essential to know the solid-liquid equilibria (SLE) phase diagrams of the mixtures in order to understand the range of temperatures and compositions at which these mixtures can be used and stored (Sangster, 1999).

Aiming to increase the solubility and bioavailability of APIs, terpenes, and in particular menthol and thymol, have been used as excipients in a variety of works involving eutectics in the pharmaceutical industry (Cherukuvada and Nangia, 2014; Gala et al., 2013; Mohammadi-Samani et al., 2014; Stott et al., 1998) giving rise to some patents (Jun and Kang, 1999; Schwarz and Weisspapir, 2005). Stott et al. (1998) studied mixtures between ibuprofen, a well-known anti-inflammatory drug, and terpenes such as L-menthol or thymol. The authors reported that the eutectic temperature of thymol and ibuprofen was 305.15 K for 40:60 % w/w and that the solubility of this mixture is enhanced by 12.7-fold over the saturated aqueous solution of ibuprofen (Stott et al., 1998). The observed melting point depression led to a faster transdermal penetration. A similar effect was observed for the mixture of meloxicam and thymol, where the terpenoid is a skin permeation enhancer that increases the meloxicam skin absorption (Mohammadi-Samani et al., 2014). Other authors (Abbott et al., 2017; Aroso et al., 2016; Duarte et al., 2017) combined menthol and/or choline chloride, [Ch]Cl, with different APIs such as ibuprofen, acetaminophen, or acetylsalicylic acid. These combinations were reported to liquefy close to body temperature (310.15 K), improving the API bioavailability (Aroso et al., 2016; Duarte et al., 2017). Abranches et al. (2019a) used the COSMO-RS model to predict the SLE of systems composed by [Ch]Cl and APIs obtaining a reasonable description of the systems studied.

Choline chloride is widely used to prepare *deep* eutectic systems, i.e., eutectic mixtures that present negative deviations to ideality due to strong intermolecular interactions established between their components (Martins et al., 2019). However, the ability of [Ch]Cl to form mixtures with sharp melting temperature depressions (sometimes even liquid at room temperature) is mainly due to its low melting enthalpy, and not particularly due to strong interactions with other compounds (Fernandez et al., 2017). Moreover, its generalized use is due to its price, low toxicity, biocompatibility and biodegradability, and it was also studied as a possible pharmaceutical ingredient (Abbott et al., 2017; Abranches et al., 2019a). Recently, we have also investigated other quaternary ammonium chlorides (Abranches et al., 2020; Pontes et al., 2017) and surprisingly found them as equally successful, or even better ionic liquefying agents, to use in the design of eutectic mixtures (Abranches et al., 2020).

Thymol and coumarin were selected as non-ionic excipients (structures available in Figure 1) due to their characteristics: while thymol is a stronger than usual hydrogen bond donor (and a weaker than usual hydrogen bond acceptor), coumarin is a simple hydrogen bond acceptor (Abranches et al., 2019b; Abranches et al., 2020), providing an interesting contrast in terms of interactions with the APIs. According to Abranches et al. (2019b) these non-ionic mixtures can form type V DES, a new class considering the original classification of DES proposed by Abbott and co-workers (Smith et al., 2014). Three quaternary ammonium salts were chosen as ionic excipients due to their proven success as liquefying agents (Abranches et al., 2020). Choline chloride, tetramethylammonium chloride, and tetrabutylammonium chloride were selected to study both the effect of the choline hydroxyl group and the increase of the alkyl chain length of the ammonium cation that leads to a substantial decrease in the compound melting point. Mixtures of APIs and quaternary ammonium salts are classified as type III DES: quaternary ammonium salt + hydrogen bond donor (Smith et al., 2014).

Aiming to contribute to the development of new drug formulations, binary eutectic mixtures involving thymol, coumarin, [Ch]Cl, tetramethylammonium chloride ($[N_{1111}]Cl$) or tetrabutylammonium chloride ($[N_{4444}]Cl$) and one API among acetylsalicylic acid, ibuprofen, ketoprofen, lidocaine or acetaminophen are here investigated. The choice of the APIs was

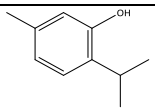
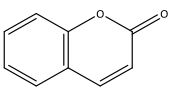
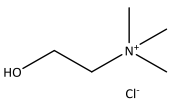
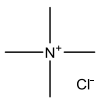
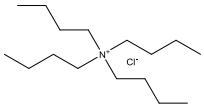
based on their use in the pharmaceutical industry, functional groups diversity and number, low melting temperatures, and no decomposition upon melting. The solid-liquid phase diagrams were measured to characterize these mixtures, and the main goal was to explore the impact of the excipient nature (ionic or non-ionic) on the eutectic formation of the mixtures containing APIs. The ability of the conductor-like screening model for real solvents – COSMO-RS to describe the SLE phase diagrams of mixtures involving non-ionic excipients was also evaluated.

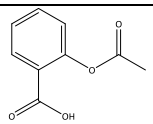
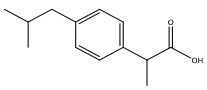
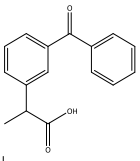
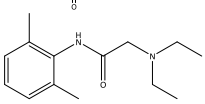
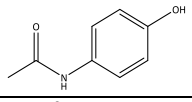
2. Experimental

2.1 Chemicals

Table 1 summarizes the information of the compounds investigated alongside with their structures. It also includes the melting temperatures and enthalpies measured in this work or obtained from the literature. All chemicals were used as received from the supplier without any further purification excepting the quaternary ammonium salts that were dried under vacuum (0.1 Pa and 298.15 K) for at least 72 h. The water content of all compounds was measured using a Metrohm 831 Karl-Fischer coulometer, with the analyte Hydranal®–Coulomat AG from Riedel-de Haën, and is reported in Table 1.

Table 1. List of the studied compounds, chemical structures and melting properties (melting temperature - T_m and enthalpy - $\Delta_m H$).

Compound	Chemical Structure	$T_{m,\,literature}$ K	$T_{m,\,this\ work}$ K[c]	$\Delta_m H_{literature}$ kJ·mol^{-1}	Reference
Thymol (CAS: 89-83-8; *wt%* > 99[a]; *w*[b] = 22 ppm) Acquired from TCI		323.5	-	19.65	Martins et al., 2018
Coumarin (CAS: 91-64-5; *wt%* = 99[a]; *w*[b] = 258 ppm) Acquired from Sigma-Aldrich		342.3	342.3 ± 0.1	18.63	Matos et al., 2009
Choline chloride, [Ch]Cl (CAS: 67-48-1; *wt%* = 98[a]; *w*[b] = 600 ppm) Acquired from Acros Organics		597	-	4.3	Fernandez et al., 2017
Tetramethylammonium chloride, [N_{1111}]Cl (CAS: 75-57-0; *wt%* = 97[a]; *w*[b] = 2957 ppm) Acquired from Sigma-Aldrich		612.9	-	20.49	Pontes et al., 2017
Tetrabutylammonium chloride, [N_{4444}]Cl (CAS: 1112-67-0; *wt%* = 97[a]; *w*[b] = 5758 ppm) Acquired from Sigma-Aldrich		344.0	-	14.69	Abranches et al., 2019c

Acetylsalicylic acid (CAS: 50-78-2; *wt%* > 99[a]; w^b = 162 ppm) Acquired from Sigma-Aldrich		414.0	407.3 ± 0.1	29.80	Kirklin, 2000
Ibuprofen[d] (CAS: 15687-27-1; *wt%* = 99[a]; w^b = 17 ppm) Acquired from Alfa Aesar		347.6	349.1 ± 0.2	26.4	Maxwell and Chickos, 2012
Ketoprofen (CAS: 22071-15-4; *wt%* > 98[a]; w^b = 192 ppm) Acquired from TCI		368.0	367.9 ± 0.1	37.30	Wassvik et al., 2006
Lidocaine (CAS: 137-58-6; *wt%* > 99[a]; w^b = 2982 ppm) Acquired from Sigma-Aldrich		340.7	341.1 ± 0.1	16.40	Lazerges et al., 2010
Acetaminophen (CAS: 103-90-2; *wt%* > 99[a]; w^b = 22 ppm) Acquired from Sigma-Aldrich		443.2	443.5 ± 0.1	27.60	Mota et al., 2009

[a]As reported by the supplier; [b]Water content; [c]Measured in this work using a glass capillary visual method; [d]Racemic form.

2.2 Phase Diagrams Measurements

Binary mixtures between excipients and APIs were prepared in different proportions covering the full compositions range (at mole fraction intervals of 0.1) by weighting the proper amounts of each pure substance using an analytic balance Mettler Toledo XP205 (repeatability of 0.015 mg). Mixtures involving ionic excipients were prepared inside a dry-argon glove-box using an analytical balance (model ALS 220-4 N from Kern, with a repeatability of 0.2 mg).

Mixtures comprising thymol + acetylsalicylic acid, ibuprofen, ketoprofen, or acetaminophen and coumarin + ibuprofen were prepared by homogenizing the mixture of API and excipient with a mortar and pestle. Remaining mixtures were heated under stirring in closed vials till a homogeneous liquid was formed and left under stirring for around 15 minutes. As a final preparation step, the flasks were left at room temperature for 2-3 days in order to check for possible phase separation, indicating incompatibilities between the compounds. Depending on the physical state of the final mixture obtained (solid, past-like consistency, or liquid), the eutectic and melting temperatures, i.e., the solidus and the liquidus lines were determined using a melting point apparatus, differential scanning calorimetry, or both techniques as described below.

Credit Author Statement

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Graphical Abstract