Liquid forms of pharmaceutical co-crystals: exploring the boundaries of salt formation†

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We present evidence of hydrogen bond formation, not salt formation, as the driving force in the liquefaction of a solid pharmaceutical in the form of a neutral acid–base complex, as exemplified by the liquid formed from a mixture of the local anesthetic lidocaine with fatty acids; these complexes exist at the boundary between simple eutectics and partially ionised ionic liquids.

The constant search for new drug forms and formulations to feed the pharmaceutical pipeline has raised tremendous interest in crystal engineering of pharmaceutical co-crystals formed between a molecular or ionic active pharmaceutical ingredient (API) and a co-crystal former that is a solid under ambient conditions.[1] The attractive features of a co-crystal composition typically arise as a result of specific supramolecular interactions (*e.g.*, hydrogen bonding) between the active ingredient and the co-former which crystallize together in a new solid state form without the need to make or break covalent bonds.[2]

As the name 'co-crystal' implies, the goal of this field is to produce new crystalline pharmaceuticals, in keeping with the long-standing reliance of the pharmaceutical industry and regulators on crystalline drug forms. However, co-crystals suffer from some of the same problems as any solid drug form, including polymorphism.[3] These same issues motivated us to explore whether liquid salt forms of pure drugs could be used as an additional strategy to improve the API performance. Such liquid salts form part of the large family of ionic liquids (ILs), being salts that melt below 100 °C; here specifically below room or body temperatures.[4,5]

Our search for new IL formulations of the local anesthetic drug lidocaine (Lid, **1**) incorporating lipophilic counterions such as fatty acids led us to study short (hexanoic acid, **2**), medium (decanoic acid, **3**), and long-chain (stearic acid, **4**) fatty acids, as well as mono (oleic acid, **5**), and double (linoleic acid, **6**) (*z*-)unsaturated acids (Fig. 1).[6] We observed

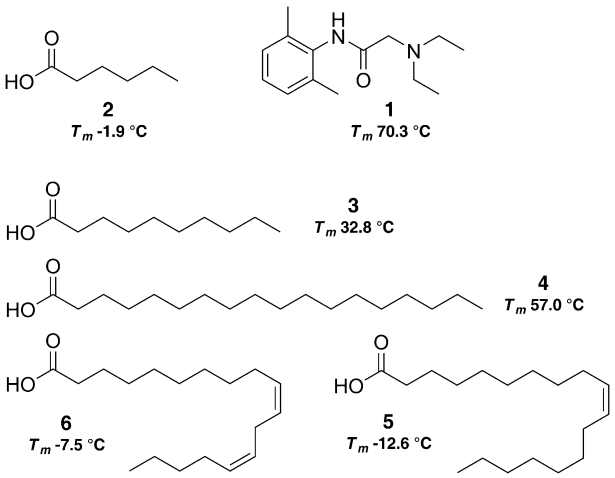

Fig. 1 Local anesthetic lidocaine **1** and fatty acids **2–6**.[7]

a phenomenon whereby liquefaction of solid acids and bases occurred due to hydrogen bonding and *not* proton transfer. The close analogy between this phenomenon and the field of co-crystals and the overlapping goals of that field with ours led us to examine the potential utility of 'liquid co-crystals' as another strategy to solve the numerous problems with modern pharmaceuticals.

Unlike an IL form of an API, which might be considered a new pharmaceutical entity, the approach we propose here combines molecules whose toxicity profiles are already well known and whose use in pharmaceutical applications is well accepted. In addition, these new liquid compositions can be prepared with variable stoichiometry in contrast to pharmaceutical co-crystals which are crystalline and of defined stoichiometry.

In order to develop straightforward syntheses for these new formulations without the risk of solvent-, halide-, or metal contamination, Lid as the free base was melted with a stoichiometric amount of the corresponding fatty acid until a clear liquid was formed. For stearic acid (**4**), a colorless solid crystallized after cooling with a melting point (T_m) of 42.8 °C (Fig. 2; Fig. S8, Table S1, ESI†).

For the remaining mixtures, crystallisation was never observed and low viscosity liquid samples with glass transition temperatures (T_g) of ~−50 °C or below were obtained, even when solid Lid was mixed with the solid decanoic acid (**3**). The introduction of double bonds has a dramatic influence, for example comparing stearic (**4**) to oleic (**5**) acid, producing no observable T_m and further reduction of T_g after introduction of a second double bond. This behaviour is not totally

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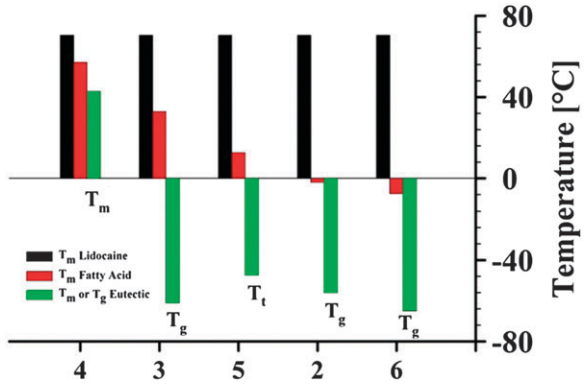

Fig. 2 Reduction or elimination of the melting point for 1 : 1 lidocaine : fatty acid mixtures.

unexpected, given that for the fatty acids themselves, the presence of a double bond results in a lower T_m.[8]

Interestingly, despite a $\Delta pK_a \approx 3$ between fatty acid and Lid, IR spectroscopy indicates no salt formation, although a ΔpK_a of ~ 3 would normally be sufficient to generate substantial proton transfer in aqueous solution.[9] In all cases, the C=O stretch of the fatty acid is in the range of ~ 1690 cm^{-1} rather than ~ 1560 cm^{-1}, as would be expected for the COO$^-$ anion.[10] The drastic reduction or elimination of T_m thus has to be explained by the presence of a non-ionic interaction between Lid and the various fatty acids. When we performed DSC analyses of the Lid : stearic acid formulations at different compositions, we observed the presence of 2 endothermic transitions, corresponding to the solidus (eutectic) and liquidus transitions of the mixture. A eutectic point was found to appear at a composition of Lid : stearic acid 2 : 1 (χ_{stea} 0.33) at 42.9 °C (Fig. 3).[11]

The eutectic transition is clearly observed between χ_{stea} 0.1 and χ_{stea} 0.8. The decrease in the transition temperature on either side of this range suggests solid solubility of the minor phase in the major phase and hence solidus behaviour.

However, the phase diagrams of the systems lidocaine : decanoic acid and lidocaine : oleic acid differ significantly. For both formulations, we observed the expected reduction of the melting point starting from the pure lidocaine or the pure acid, until a certain composition at which the sample does not crystallize at all, at the cooling and heating rates

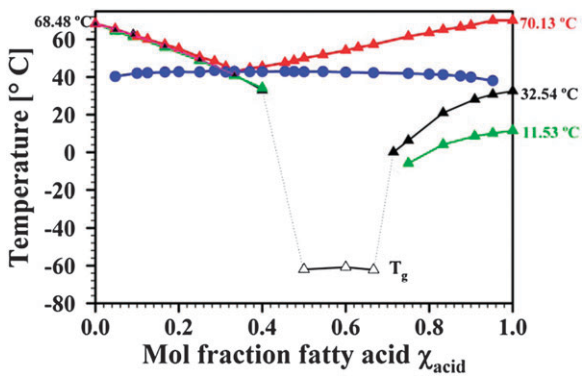

Fig. 3 Transition temperatures for lidocaine : stearic acid (liquidus line: red; solidus line: blue), lidocaine : decanoic acid (black), and lidocaine : oleic acid (green).

involved; only a glass transition was observed (Fig. 3; Fig. S4 and S5, ESI†). This is remarkably similar to the "Deep Eutectic Solvents" described by Abbot for aprotic quaternary ammonium salts in combination with strong hydrogen bond donors such as amines, amides, or carboxylic acids.[12] It was further noted that once lidocaine was present in excess ($\chi_{oleic} < 0.5$), the excess base can crystallize from the mixture, which was confirmed by single crystal and powder X-ray diffraction of the precipitate.

Our results suggest that the Lid : decanoic acid and Lid : oleic acid systems might be best described as "deep eutectics", with strong interactions of acid and base present in a certain range resulting in a sudden drop in T_m. An NMR study of the neat mixtures revealed that as χ_{oleic} increased, a gradual shift of the α-CH–N protons of Lid towards a lower field was observed, indicating that the amine becomes involved in a COO–H···N hydrogen bond. This is in agreement with ^{15}N HMBC spectroscopy, where the ^{15}N chemical shift increases as χ_{oleic} increases, with a maximum shift difference for χ_{oleic} 0.33–0.6, indicating the strongest hydrogen bonding in the deep eutectic region. Additionally, a sharp drop in viscosity was observed in this region of composition. Finally, IR spectra also revealed the changes in the compositional range χ_{oleic} 0.3–0.5 where a broad new peak at 1690 cm^{-1} was observed only for these compositions (Fig. 4).

Considering ionicity and the research focus on protic ILs, the systems observed here seem to mark an unrecognized state of proton interaction between acid and base in pure, solvent-free mixtures. Previously a low degree of proton transfer had been identified as producing "poor ILs" as a result of their position in the Walden plot, meaning that, in fact they were mixtures of the parent acid and base plus rather small amounts of the salt.[13] However, not all acid/base combinations having a low degree of proton transfer exhibit the behavior observed here; in fact at the other extreme, some acid/base combinations are not even miscible when the hydrogen bond is not sufficiently strong. Hence we envisage proton interaction/transfer increasing in the order: immiscible mixtures < eutectics < deep eutectics < partially ionized ILs < fully ionized ILs. Thus, stronger proton interactions produce the deeper eutectic that consequently merges into partial ionization creating a 4 component mixture deepening the eutectic

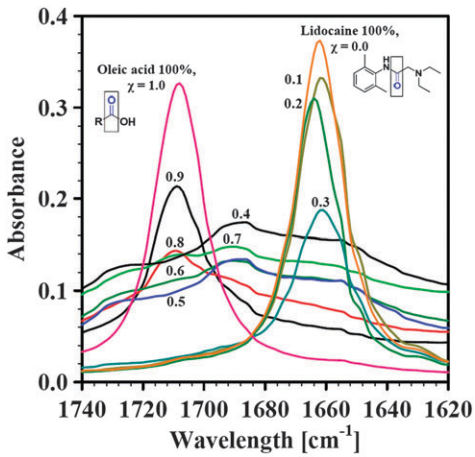

Fig. 4 IR spectra of lidocaine : oleic acid mixtures.

still further. Liquid samples were only obtained for the intermediates between the eutectic and fully ionized salt, indicating that the hydrogen bond interaction rather than proton transfer reduces the T_m, an effect that we have previously observed in oligomeric ILs.[14]

In summary, we have presented new liquid formulations of the local anesthetic lidocaine with various fatty acids that, based on their hydrogen-bonded nature, can be considered as liquid equivalents to pharmaceutical co-crystals. It is important to note that, in contrast to our previous work with ionic liquids composed of pharmaceutically active ingredients, these liquids are prepared from known compounds of known toxicity and in current clinical use. Furthermore, the low ionicity observed here in comparison to fully ionized salts provides the possibility for these liquids to penetrate membranes more efficiently and for a possible future use in transdermal drug delivery and local anaesthesia.

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