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Simultaneous membrane transport of two active pharmaceutical ingredients by charge assisted hydrogen bond complex formation†

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Using permeation through a model membrane in a Franz diffusion cell, we have demonstrated that acidic and basic active pharmaceutical ingredients (APIs) in deep eutectic 'liquid co-crystal' form can be held tightly together, even in solution, *via* strong hydrogen bonds or partially ionized interactions, providing simultaneous transport at rates much higher than solutions of their corresponding, commercially available crystalline salts, albeit at rates that are lower than the neutral forms of the individual molecules. It was also shown that the deep eutectic APIs do not have to be premade, but hydrogen-bonded complexes can be formed *in situ* by mixing the corresponding API–solvent solutions. To understand the behavior, we have extensively studied a range of nonstoichiometric mixtures of lidocaine and ibuprofen spectroscopically and *via* membrane transport. The data demonstrates the nature of the interactions between the acid and base and provides a route to tune the rate of membrane transport.

Introduction

The pharmaceutical industry relies predominantly on solid, primarily crystalline active pharmaceutical ingredients (APIs). Unfortunately, these solids frequently have problems related to low solubility, low bioavailability, poor control over polymorphism, *etc.*[1,2] Co-crystals, incorporating pharmaceutically acceptable guest molecules into a crystal lattice along with the API, are emerging as an attractive alternative to crystalline APIs.[3,4] Co-crystal pharmaceuticals do not affect the pharmacological activity of APIs, but can improve their physical properties, such as solubility, hygroscopicity, compaction behavior, *etc.*[5,6] However, co-crystals suffer from some of the same problems as any solid crystalline drug forms do, including polymorphism.[7]

The unique properties of ionic liquids (ILs, typically defined as salts melting below 100 °C,[8] but here referring to salts melting below body temperature[9]) led us to develop a strategy that applies IL properties to APIs (so-called API-ILs), to help overcome some of the shortcomings mentioned above.[10–12] The IL approach was initially exemplified by choosing alternative counterions that would lower the melting points of the salts, while potentially providing a second biological function.[10] For example, lidocaine docusate ([Lid][Doc]), a combination of a topical pain reliever and an emollient, was shown to have enhanced analgesic effect compared to the commercial lidocaine hydrochloride ([Lid][Cl]).[10] The data also suggested that this IL might be working through a different mode of action than [Lid][Cl], even though both were studied in solution.[10]

Transdermal drug delivery for analgesics is one of the most promising methods for drug application because this route offers several advantages over conventional dosage forms including extended duration of activity, minimization of pain, reduction of side effects, possible sustained drug release, *etc.*[13] Recently, MacFarlane *et al.* reported the transport of pharmaceutically active protic ILs, such as butylammonium acetate and tuammoniumheptane salicylate, through a silicone membrane by applying either the neat ILs or a propylene glycol solution of the IL onto the membrane.[14] They found that permeation of these ILs through the membrane depends on the nature of the components, and salts in general are less likely to permeate the skin-mimicking membrane from solution where each ion is individually solvated, in accordance with the observation that water soluble pharmaceuticals in salt form do not permeate these membranes readily.[15]

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In 2011, Rogers *et al.* demonstrated that not only salt formation, but also very strong, partially ionized hydrogen bond formation can be the driving force in the liquefaction of solid pharmaceuticals[16] in the form of deep eutectics.[17] For example, lidocaine free base in combination with fatty acids such as decanoic acid or oleic acid produced low viscosity deep eutectics with no observed crystallization events, only glass transition temperatures of *ca.* −50 °C. Spectroscopic data showed that these liquid mixtures were not as fully ionized *via* proton transfer as one would expect for such an acid–base mixture, but strongly hydrogen bonded, leading us to refer to these as 'liquid co-crystals' (*i.e.*, the liquid equivalent to pharmaceutical co-crystals).[16] In this context a liquid co-crystal can be thought of as a stoichiometric combination of two molecular components that has a set of properties distinctly different from those of the individual components.

Liquid co-crystals are very strongly hydrogen-bonded in a unique complex where the acidic proton is localized between the acidic and basic sites, in fast exchange between the possible low energy states. This results on average in a partially, but not completely, proton-transferred (or ionized) state for each of the acid and base in the complex.[9] Such liquid co-crystal type complexes could have advantages in the delivery of APIs transdermally, since the acidic and the basic moieties could both be APIs allowing simultaneous delivery, and the strong interactions through the acidic proton could prevent crystallization of the individual neutral components in the delivery device. A key unanswered question, however, is, are these liquid co-crystal moieties so strongly interacting that they remain intact in solution and thereby affect membrane transport? Here we provide evidence that, with appropriate choice of solvent, the liquid co-crystal can remain intact in solution providing simultaneous transport of both APIs.

Results and discussion

Our study began with drug diffusion studies using compounds we had previously prepared to study supporting API-ILs on silica, tetrabutylphosphonium ibuprofenate ([P_{4444}][Ibu]) and a 1 : 1 liquid prepared by combining lidocaine and ibuprofen ([Lid][Ibu]),[18] and comparative studies with ephedrinium ibuprofenate ([Eph][Ibu]), the neutral forms of the APIs, and their commercially available salts ([Lid][Cl] and ibuprofen sodium ([Na][Ibu])). The neutral forms of lidocaine and ibuprofen (Fig. 1) are low melting solids with melting temperatures (T_m) 68–69 °C[19] and 75–77 °C,[20] respectively. The solid salt [Lid][Cl] has a relatively low melting temperature of 74–79 °C,[21] and [Na][Ibu] is a high melting crystalline solid with a melting temperature of 220 °C.[22] As prepared, [Lid][Ibu] and [P_{4444}][Ibu] are liquids at room temperature, with glass transition temperatures of −27 °C and −43 °C,[18] respectively, whereas [Eph][Ibu] (see ESI† for synthesis and characterization) is a solid at room temperature, with a melting temperature of 110 °C.[23]

Drug diffusion experiments were conducted at 37 °C following a literature procedure[24,25] using a model silicone membrane (0.01 in., Specialty Manufacturing Inc., Saginaw, MI, USA) and a Franz diffusion cell system shown in Fig. S1, ESI† (PermeGear, Inc., Hellertown, PA, USA) with 12.0 mL of degassed phosphate buffered saline (PBS, pH = 7.4) as the receiver solution to mimic body fluid. The silicone membrane was cut to the appropriate size and allowed to soak overnight in ethanol. The membrane was taken out, dried in air and then mounted between the donor and receiver chambers, which were sealed together using Parafilm (Fig. 2). The assembled Franz cell was placed into the diffusion system and allowed to equilibrate for 30 min before loading the donor solution. Parafilm was used to seal the donor chamber to minimize evaporation and water absorption.

Ethanol (95%) was chosen as the donor solvent since all compounds had good solubility in this solvent and because ethanol is known to be a good vehicle to enhance the permeation of drugs through membranes.[26,27] (Absolute ethanol did not provide sufficient solubility to conduct the studies; DMSO can also dissolve all of the compounds studied, however, this solvent deforms the membrane.) The donor phase usually consisted of 0.5 mL of 0.5 M ethanolic solution of each compound, however in one case 0.3 mL of neat [Lid][Ibu] was applied directly to the membrane in a thin layer. Samples (0.5 mL) were taken out through the sampling arm of the receiver compartment at specific time intervals and immediately replaced by an equal volume of degassed PBS at the appropriate temperature. Samples were sealed and stored at room temperature until analysis was performed. Ethanolic donor phases are known to transport through the membrane[26] and after 24 h, there was no ethanol left in the donor chamber.

In our first study using [Lid][Ibu], samples were analyzed by liquid chromatography-mass spectrometry (LC-MS) to determine the concentrations of lidocaine and ibuprofen independently (see Fig. S2, ESI† for typical LC chromatogram and Fig. S3, ESI† for calibration curves). The percentage of the applied dose transported across the membrane was calculated using eqn (1).

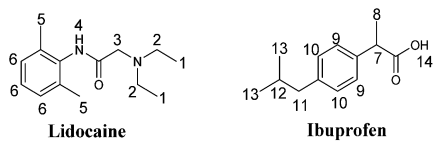

Fig. 1 Structures of lidocaine and ibuprofen.

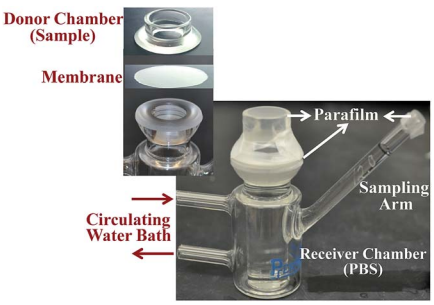

Fig. 2 Franz cell for membrane transport.

$$\text{Permeation}(\%\ \text{applied dose}) = \frac{C_i \times 12 + \sum_{j=1}^{i-1} C_j \times 0.5}{\text{moles API donor phase}} \times 100\% \quad (1)$$

where C, in mol mL^{-1}, is the concentration of the API in the receiver phase, i and j are sample numbers (#1: 0.5 h; #2: 1 h; #3: 2 h; #4: 3 h; #5: 5 h; #6: 7 h; #7: 9 h), 12 is the receiver chamber volume in mL, and 0.5 is the volume of the collected sample in mL. UV-Vis spectroscopy was subsequently used to confirm the results for [Lid][Ibu] and these values matched those obtained by LC-MS (Fig. S4, ESI†). Only UV-Vis was used in the following studies of [P_{4444}][Ibu] and [Eph][Ibu].

Repeatability of the membrane transport experiments were examined by determining the permeation of [Lid][Ibu]/EtOH three times and of lidocaine free base and ibuprofen free acid twice. The deviations were found to be in the range ±0.03% to ±0.30%. The membrane transport data for ethanolic solutions of lidocaine free base and ibuprofen free acid with error bars are shown in Fig. S5, ESI,† and for [Lid][Ibu]/EtOH in Fig. S6, ESI.†

Comparison of membrane transport of lidocaine and ibuprofen in different forms

Fig. 3 presents the membrane permeation data obtained for each form of lidocaine and ibuprofen studied. Neutral ibuprofen (●) transports at a slightly slower rate than lidocaine free base (●), probably because ibuprofen can exist as both monomer and hydrogen bonded dimer in ethanolic solution,[28] and the larger size of the dimer results in slower permeation. It is also clear from the data, and perhaps not so surprising, that the neutral forms of the APIs transit the membrane quite easily, compared to the salt forms (■-[Lid][Cl], □-[Na][Ibu], ⊠-[P_{4444}][Ibu]) which do not penetrate the membrane well. This is in agreement with the general observation that ionic compounds do not cross membranes as readily as neutral compounds.[15] The only slightly enhanced penetration rate of [Eph][Ibu] (+), as well as its 110 °C melting point, suggest this compound is also a salt.

Interestingly, however, [Lid][Ibu] in ethanol transports across the membrane much faster than the corresponding commercial salts, albeit more slowly than neutral lidocaine (●) or ibuprofen (●). Sarveiya *et al.* noted a higher transport of amine salts of ibuprofen (*e.g.*, triethylamine ibuprofen) than for [Na][Ibu] through a polydimethylsiloxane membrane and suggested ion-pairing was responsible.[29] However, we were intrigued by the data in Fig. 3 which suggests that *both lidocaine* (▲) *and ibuprofen* (▲) *in [Lid][Ibu] transport through the membrane simultaneously* since their transport rates are almost identical, in contrast to their neutral forms. This suggests that the lidocaine and ibuprofen (neutral, ionized, or partially ionized) are strongly interacting and passing through the membrane as a single entity. The increased size and mass of such a complex of these two APIs would account for the slower passage through the membrane than the individually solvated neutral molecules.[30]

To determine whether the [Lid][Ibu] complex would form spontaneously in the ethanolic solution, neutral lidocaine and neutral ibuprofen were individually dissolved in 95% ethanol to prepare 1.0 M solutions and equal volumes of each were combined and stirred for 1 h to obtain a solution 0.5 M in each API. When this solution was used as the donor phase, the results were essentially identical to those shown in Fig. 3 for [Lid][Ibu] (Fig. S7, ESI†), suggesting that *lidocaine and ibuprofen form a strong interaction in ethanolic solution whether preformed or not*. This could have important implications in treatments using both lidocaine and ibuprofen where the effective dose might be reduced due to these synergistic effects.

Membrane transport of neat [Lid][Ibu]

One major advantage of the APIs when liquid at or below body temperature is the ability to be directly applied on the skin, eliminating the need for additional excipients used to solubilize high melting APIs. Therefore we also studied the permeability of the neat liquid [Lid][Ibu] by coating the membrane with 0.3 mL of neat [Lid][Ibu], covering the entire membrane surface.

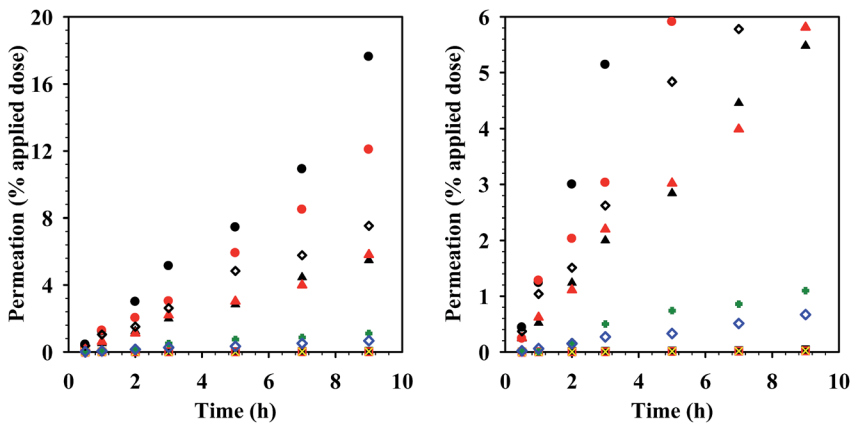

Fig. 3 Permeation as a percentage of applied dose in mol% *vs.* time from ethanolic donor solutions or neat [Lid][Ibu] to PBS (left – all data; right – expanded view of 0–6% permeation). Ethanolic solutions of: ●-lidocaine; ●-ibuprofen; ▲-lidocaine from [Lid][Ibu]; ▲-ibuprofen from [Lid][Ibu]; +-ibuprofen from [Eph][Ibu]; ■-[Lid][Cl]; □-[Na][Ibu] and ⊠-[P_{4444}][Ibu]. Neat liquids: ◇-lidocaine from neat [Lid][Ibu]; ◇-ibuprofen from neat [Lid][Ibu]. Note that the data from [Lid][Cl], [Na][Ibu], and [P_{4444}][Ibu] all overlap in the figures at essentially zero permeation.

The results (Fig. 3: ◊, ◊) indicated that lidocaine and ibuprofen did not transport simultaneously and that transport of lidocaine (◊) was much faster than ibuprofen (◊). The membrane transport of neat [Lid][Ibu] was faster than the commercial salts, but slower than the neutral APIs. The origins of these effects are explored further below.

Characterization of [P_{4444}][Ibu], [Eph][Ibu], and [Lid][Ibu]

Since the membrane transport data in ethanolic solution suggested that [Lid][Ibu] was more like a 'liquid co-crystal'[16] than a fully-ionized salt, we examined the level of ionization in [P_{4444}][Ibu], [Eph][Ibu], and [Lid][Ibu]. The ^{1}H NMR spectrum of [P_{4444}][Ibu] compared with that of ibuprofen in DMSO-d_6 (Fig. S8, ESI†) and the FT-IR C=O stretch in [P_{4444}][Ibu] at *ca.* 1583 cm^{-1} (Fig. S9, ESI†) confirm that [P_{4444}][Ibu] is pure and is fully ionized as expected by the formula. The same was observed for [Eph][Ibu], where upfield chemical shifts of the ibuprofen protons in [Eph][Ibu] (Fig. S10, ESI†) and the FT-IR C=O stretch at *ca.* 1557 cm^{-1} (Fig. S11, ESI†) indicated ionization.

However, comparison of the ^{1}H NMR spectrum of [Lid][Ibu] with spectra of lidocaine free base and ibuprofen free acid in DMSO-d_6 (Fig. S12, ESI†) revealed no obvious chemical shift differences. In the FT-IR spectrum of neat [Lid][Ibu], the characteristic stretch of the lidocaine's ammonium NH$^+$ (located between 2600 to 2300 cm^{-1} in [Lid][Cl][31]) was not observed (Fig. S13 left, ESI†), indicating that full proton transfer did not occur. Additionally, the carbonyl C=O stretching absorption band of ibuprofen in [Lid][Ibu] was observed at *ca.* 1686 cm^{-1} (Fig. S13 right, ESI†), which would be expected for the unionized or at best partially ionized carboxylic acid functionality since this C=O stretch in the ibuprofen sodium salt typically appears around 1550 cm^{-1}. Conductivity measurements indicated that [Lid][Ibu] has low conductivity (*e.g.*, 0.006 S cm^2 mol^{-1} at 80 °C). Taken together, these data suggested that [Lid][Ibu] is liquid due to strong non- or partially-ionic interactions between lidocaine and ibuprofen, in accordance with the previously observed liquefaction behavior of lidocaine with fatty acids.[16]

This low degree of ionization (proton transfer) is consistent with previous observations[32] that in neat protic ionic liquids based on tertiary amines, proton transfer can be severely restricted because of the lack of a satisfactory hydrogen bonding solvation environment for the anionic species formed. Poor proton transfer thereby leaves a significant fraction of the free base in the mixture in equilibrium with the H-bonded complexes – in this case available to permeate the membrane. It has also been observed that dimeric and trimeric acid species can form under these circumstances, which have stronger acidity; but in the present context such large moieties will permeate the membrane more slowly as is observed for the ibuprofen component when applied to the membrane neat (◊) in Fig. 3.

Characterization of [Lid]$_m$[Ibu]$_n$

To further explore the nature of [Lid][Ibu], we prepared a series of [Lid]$_m$[Ibu]$_n$ mixtures by grinding lidocaine free base and ibuprofen free acid in various mole ratios (9 : 1, 4 : 1, 3 : 1, 2 : 1, 1.5 : 1, 1 : 1, 1 : 1.5, 1 : 2, 1 : 3, 1 : 4, 1 : 9) in a hot mortar (100 °C) until free-flowing clear liquids were obtained. After cooling to room temperature, [Lid]$_m$[Ibu]$_n$ with lidocaine to ibuprofen mole ratios of 9 : 1, 4 : 1, 3 : 1, 2 : 1, and 1 : 9 solidified, while the others remained liquid (Fig. S14, ESI†). DSC analyses (Fig. 4 and S15, ESI†) indicated the same deep eutectic behavior we have reported previously for lidocaine decanoic and oleic acid complexes:[16] reduction of the melting point starting from the pure lidocaine or pure ibuprofen, until a certain composition at which the sample does not crystallize at all, at the cooling and heating rates involved, and only a glass transition was observed. The glass transition temperatures (T_g) of [Lid]$_m$[Ibu]$_n$ first increased and then decreased with increasing ibuprofen mole fraction, reaching a maximum of −19.5 °C for [Lid]$_1$[Ibu]$_2$ and a minimum of −47.3 °C for [Lid]$_4$[Ibu]$_1$. It should be noted that [Lid]$_1$[Ibu]$_9$ only shows a melting point in the first cycle of the DSC run. After it was melted, it did not crystallize in the second and third cycles (Fig. S15(b), ESI†) under our conditions, indicating sluggish crystallization kinetics.

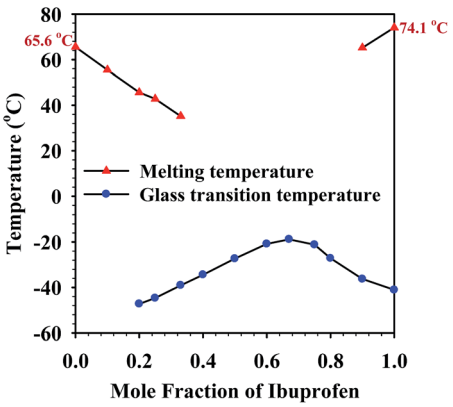

Fig. 4 Melting and glass transition temperatures of lidocaine free base, ibuprofen free acid, and [Lid]$_m$[Ibu]$_n$.

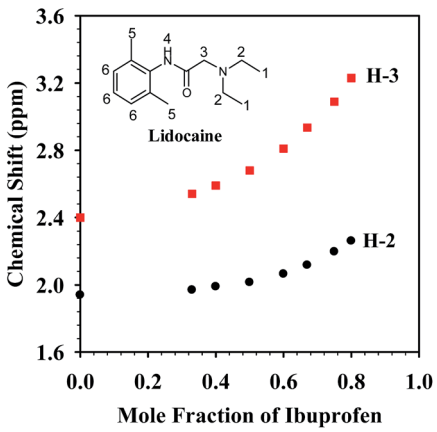

Fig. 5 ^{1}H NMR chemical shifts of lidocaine H-2 (●) and H-3 (■) protons as a function of mole fraction of ibuprofen.

^{1}H NMR, ^{15}N NMR, and FT-IR spectroscopy were used to analyze the interactions. ^{1}H NMR spectra of neat $[Lid]_m[Ibu]_n$ at 70 °C are shown in Fig. S16, ESI† and the chemical shifts of H-2 and H-3 as a function of mole fraction of ibuprofen are presented in Fig. 5. The signals of the two protons adjacent to the tertiary nitrogen in lidocaine (H-2, H-3) shift downfield with increase of ibuprofen content, indicating increasing COO–H···N (amine) hydrogen bonding,[33] similar to the behavior we have reported previously for complexes of lidocaine with fatty acids.[16] This conclusion was also supported by ^{15}N 2D HMBC data (Table S1, ESI†), where the amine nitrogen shifts downfield as ibuprofen mole fraction increases.

FT-IR spectra (Fig. 6 and S17, ESI†) show that the carbonyl stretch (C=O) of $[Lid]_m[Ibu]_n$ appears in the region from 1660 to 1740 cm^{-1}, as expected for the non-/not fully-ionized COOH, however, the C=O peak splits into three bands (Fig. 6). When the lidocaine to ibuprofen mole ratio is less than 9 : 1, a band (marked by the black solid line) appears as a shoulder *ca.* 1733 cm^{-1}, which is at higher wavenumber compared to the carbonyl peak in ibuprofen free acid (1710 cm^{-1}), and might be attributable to disruption of intermolecular interactions in the ibuprofen hydrogen bonded dimer as lidocaine–ibuprofen hydrogen bonds form.[34,35] The middle band (marked by the black dashed line) at *ca.* 1686 cm^{-1} suggests a partially ionized carbonyl peak in ibuprofen. The band at *ca.* 1701 cm^{-1} in $[Lid]_1[Ibu]_4$ and $[Lid]_1[Ibu]_9$ is the carbonyl stretch found in ibuprofen free acid due to the large excess of ibuprofen.

The right most peak in this region at *ca.* 1655 cm^{-1} (marked by the red solid line), can be attributed to the carbonyl stretch of lidocaine's amide group. When compared to the corresponding stretch in lidocaine free base and formulations with a large excess of lidocaine (*e.g.*, $[Lid]_9[Ibu]_1$, $[Lid]_4[Ibu]_1$, and $[Lid]_3[Ibu]_1$), this C=O stretch in lidocaine shifts to lower wavenumber (1655 cm^{-1} *vs.* 1660 cm^{-1}) as the amount of lidocaine decreases. Since this C=O group in lidocaine can also participate in hydrogen bonding,[36] there is a redshift of this band as hydrogen bonding increases.

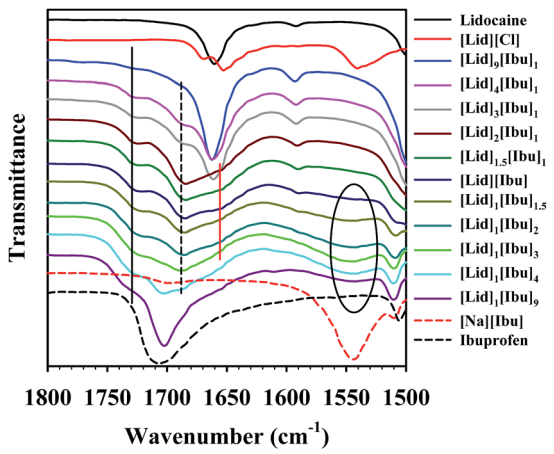

Fig. 6 FT-IR spectra (C=O region) of lidocaine free base, [Lid][Cl], $[Lid]_m[Ibu]_n$, [Na][Ibu], and ibuprofen free acid.

The C=O stretch characteristic of the anion of ibuprofen shows up at *ca.* 1550 cm^{-1} (marked by the black circle in Fig. 6) in the spectra of $[Lid]_m[Ibu]_n$ with excess of ibuprofen ($m < n$). Also when $m < n$, the characteristic protonated lidocaine NH^+ vibration at *ca.* 2600 to 2300 cm^{-1} appears (Fig. S17(b), ESI†). Thus when ibuprofen is in excess, the ionization of $[Lid]_m[Ibu]_n$ is higher than that with an excess of lidocaine, perhaps due to oligomeric ion formation.[37] These observations are also supported by mass spectroscopy (MS), where the relative intensity of the ibuprofen dimer peak ($m/z = 411$) to the monomer peak ($m/z = 205$) was found to be higher in $[Lid]_1[Ibu]_4$ than in [Lid][Ibu] or $[Lid]_4[Ibu]_1$ (Fig. S18, ESI†).

To distinguish between purely hydrogen bonded *vs.* partially ionized states, Walden plots were determined for the series of $[Lid]_m[Ibu]_n$ (Fig. 7). All of the data points lie well below the ideal line, indicating poor proton transfer and/or strong hydrogen bonding in ion-pairs (*i.e.*, low ionicity in either case[38,39]) between lidocaine and ibuprofen. The Walden plot data also suggests, however, that the degree of ionization of $[Lid]_m[Ibu]_n$ with excess ibuprofen is a little higher, in accordance with the FT-IR data above. Nonetheless, the ionicity is still quite low, even at the highest acid content.

In order to determine if lidocaine and ibuprofen remain complexed when dissolved in ethanol, ^{1}H NMR spectra of $[Lid]_m[Ibu]_n$/EtOH solutions (0.5 M; 0.5*m* M lidocaine + 0.5*n* M ibuprofen) were collected by loading the solutions in capillaries using DMSO-d_6 as external lock. The H-3 protons (see Fig. 1 for proton numbers) adjacent to the tertiary nitrogen in lidocaine gradually shifted downfield with increasing ibuprofen mole fraction (Fig. S19, ESI†), suggesting that lidocaine and ibuprofen still hydrogen bond in EtOH. With increasing ibuprofen content, the H-2 protons shifted downfield until the mole ratio of lidocaine to ibuprofen reached 1 : 2, then shifted slightly upfield. The H-3 protons are acidic because they are located between lidocaine's amide carbonyl amino group and can form intramolecular hydrogen bonds which result in greater shifts than observed for the H-2 protons. As the amount of ibuprofen increases, the number of acidic sites that can hydrogen bond to EtOH increases and H-2 becomes even less preferred, resulting in its slight upfield shift. Overall, these results suggest that, in EtOH solution, lidocaine and ibuprofen are hydrogen bonded together.

Membrane transport of $[Lid]_2[Ibu]_1$ and $[Lid]_1[Ibu]_2$

Finally, membrane transport data were collected for 0.5 M ethanolic solutions of $[Lid]_2[Ibu]_1$ and $[Lid]_1[Ibu]_2$ using the same conditions noted earlier (Fig. 8). Interestingly, for the $[Lid]_2[Ibu]_1$ system (equivalent to 1.0 M lidocaine and 0.5 M ibuprofen), the permeation of lidocaine through the membrane at any given time (⬢) was essentially equal to the average (★) of the permeation data for lidocaine from 0.5 M [Lid][Ibu] (▲) and that of 0.5 M lidocaine free base (●), while the permeation of ibuprofen through the membrane (⬢) was essentially equal to that of 0.5 M [Lid][Ibu] (▲). This suggests that in ethanol solution, $[Lid]_2[Ibu]_1$ exists as [Lid][Ibu] (0.5 M) and excess lidocaine free base (0.5 M) which transport the membrane independently.

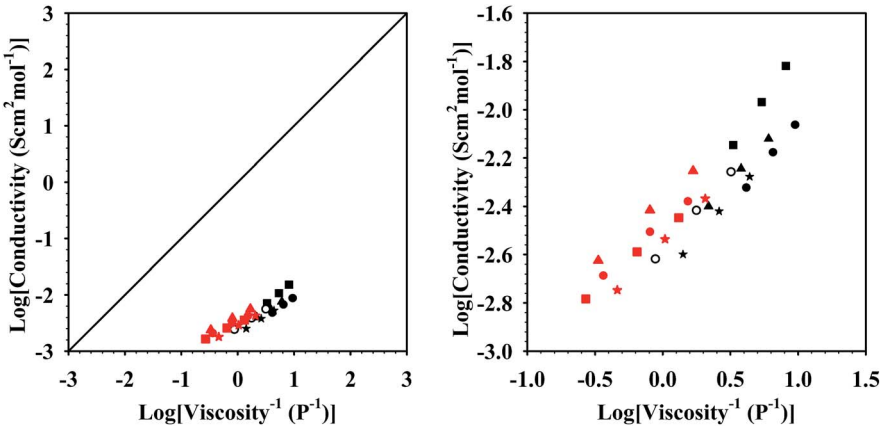

Fig. 7 Walden plot of $[Lid]_m[Ibu]_n$ (●-$[Lid]_4[Ibu]_1$; ■-$[Lid]_3[Ibu]_1$; ▲-$[Lid]_2[Ibu]_1$; ★-$[Lid]_{1.5}[Ibu]_1$; ○-[Lid][Ibu]; ★-$[Lid]_1[Ibu]_{1.5}$; ▲-$[Lid]_1[Ibu]_2$; ■-$[Lid]_1[Ibu]_3$; ●-$[Lid]_1[Ibu]_4$).

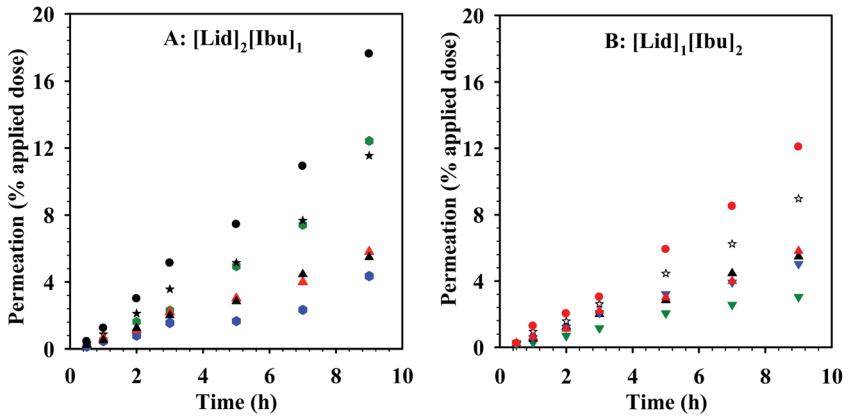

Fig. 8 Permeation as a percentage of applied dose in mol% *vs.* time from ethanolic donor solutions to PBS of $[Lid]_2[Ibu]_1$ (A, left) and $[Lid]_1[Ibu]_2$ (B, right): ●-lidocaine free base; ●-ibuprofen free acid; ▲-lidocaine from [Lid][Ibu]; ▲-ibuprofen from [Lid][Ibu]; ⬢-lidocaine from $[Lid]_2[Ibu]_1$; ⬢-ibuprofen from $[Lid]_2[Ibu]_1$; ★-calculated permeation of lidocaine across the membrane assuming that [Lid][Ibu] (0.5 M) and lidocaine free base (0.5 M) transport independently; ▼-lidocaine from $[Lid]_1[Ibu]_2$; ▼-ibuprofen from $[Lid]_1[Ibu]_2$; ☆-calculated permeation of ibuprofen across the membrane assuming that [Lid][Ibu] (0.5 M) and ibuprofen free acid (0.5 M) transport independently.

The results for membrane transport of $[Lid]_1[Ibu]_2$ from ethanolic solution (0.5 M: equivalent to 0.5 M lidocaine and 1.0 M ibuprofen), however, are quite different as presented in Fig. 8B. Comparing the permeation of ibuprofen (▼) through the membrane to the average (☆) of the permeation data for ibuprofen from 0.5 M [Lid][Ibu] (▲) and that from 0.5 M ibuprofen free acid (●), reveals that less ibuprofen permeated the membrane than predicted from the assumption that 0.5 M [Lid][Ibu] and 0.5 M ibuprofen free acid would transport independently in $[Lid]_1[Ibu]_2$. In addition, the permeation of lidocaine (▼) transported through the membrane was even slightly lower than found for 0.5 M [Lid][Ibu] (▲).

Taken together and considering the spectroscopic and Walden plot data reported above, the lower membrane transport ability of $[Lid]_1[Ibu]_2$ might be attributed to higher ionization of lidocaine and hydrogen bonded dimers[28] of neutral and ionized ibuprofen. As discussed above in the context of the neat system, such dimers have been shown to account for a higher degree of proton transfer, and therefore ionicity, in methylpyrrolidine–acetic acid systems.[32] Any ionized form of lidocaine would transport more slowly than the neutral form as shown in Fig. 3, as would a heavier $[Ibu\cdots H\cdots Ibu]^-$ complex whether neutral or charged. What is particularly notable and important here is that this type of behavior, as previously observed in the neat ILs, is maintained in the ethanolic solution.

Conclusions

In summary, this work has demonstrated that lidocaine and ibuprofen dissolved together in ethanol, either as a preformed complex or individually, have strong intermolecular hydrogen bonding even in solution, allowing simultaneous membrane transport of the APIs with much higher transport rates than their corresponding commercial crystalline salts, albeit lower than their neutral forms. In addition, the stoichiometries of the two APIs can be tuned, with the following considerations. In the presence of an excess of lidocaine ($[Lid]_m[Ibu]_n$ $m > n$), ibuprofen will transport the membrane as a [Lid][Ibu] complex, while

lidocaine will transport as [Lid][Ibu] and free lidocaine. In the presence of an excess of ibuprofen ($[Lid]_m[Ibu]_n$ $m < n$), lidocaine will be more strongly ionized and transport more slowly than [Lid][Ibu] or free lidocaine, while ibuprofen will also transport the membrane more slowly.

It continues to appear that the choice of APIs designed to produce a low melting or liquid salt, can be used as a design feature to change even the solution properties of the APIs by leading to increased pairing interactions even when dissolved. This should lead to a range of transdermal treatment options where two strongly interacting APIs can be combined to synergistically influence membrane transport and provide simultaneous delivery to the blood. We would suggest closer attention be paid not only to pharmaceutical properties controlling their solid state, but also to API properties which can be used to control their liquid state.

Competing financial interests

Dr Robin D. Rogers has partial ownership of 525 Solutions and is a named inventor on related patent applications. Drs Douglas R. MacFarlane and James H. Davis, Jr. are named inventors on related patent applications. Drs Gabriela Gurau and Julia Shamshina are part-time employees of 525 Solutions. The University of Alabama maintains approved Conflict Of Interest Management Plans.

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Notes and references

1 S. Datta and D. J. W. Grant, *Nat. Rev. Drug Discovery*, 2004, **3**, 42–57.
2 J. A. Foster, M. O. M. Piepenbrock, G. O. Lloyd, N. Clarke, J. A. K. Howard and J. W. Steed, *Nat. Chem.*, 2010, **2**, 1037–1043.
3 D. R. Weyna, T. Shattock, P. Vishweshwar and M. J. Zaworotko, *Cryst. Growth Des.*, 2009, **9**, 1106–1123.
4 M. Khan, V. Enkelmann and G. Brunklaus, *J. Am. Chem. Soc.*, 2010, **132**, 5254–5263.
5 W. Jones, W. D. S. Motherwell and A. V. Trask, *MRS Bull.*, 2006, **31**, 875–879.
6 H. D. Clarke, M. B. Hickey, B. Moulton, J. A. Perman, M. L. Peterson, Ł. Wojtas, Ö. Almarsson and M. J. Zaworotko, *Cryst. Growth Des.*, 2012, **12**, 4194–4201.
7 P. H. Karpinski, *Chem. Eng. Technol.*, 2006, **29**, 233–237.
8 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792–793.
9 S. P. Kelley, A. Narita, J. D. Holbrey, K. D. Green, W. M. Reichert and R. D. Rogers, *Cryst. Growth Des.*, 2013, **13**, 965–975.
10 W. L. Hough, M. Smiglak, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis Jr. and R. D. Rogers, *New J. Chem.*, 2007, **31**, 1429–1436.
11 W. L. Hough and R. D. Rogers, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 2262–2269.
12 J. Stoimenovski, D. R. MacFarlane, K. Bica and R. D. Rogers, *Pharm. Res.*, 2010, **27**, 521–526.
13 M. R. Prausnitz and R. Langer, *Nat. Biotechnol.*, 2008, **26**, 1261–1268.
14 J. Stoimenovski and D. R. MacFarlane, *Chem. Commun.*, 2011, **47**, 11429–11431.
15 P. Tyle, *Pharm. Res.*, 1986, **3**, 318–326.
16 K. Bica, J. Shamshina, W. L. Hough, D. R. MacFarlane and R. D. Rogers, *Chem. Commun.*, 2011, **47**, 2267–2269.
17 A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142–9147.
18 K. Bica, H. Rodríguez, G. Gurau, O. A. Cojocaru, A. Riisager, R. Fehrmann and R. D. Rogers, *Chem. Commun.*, 2012, **48**, 5422–5424.
19 M. J. O'Neil, *The Merck index: An encyclopedia of chemicals, drugs, and biological*, 14th edn, 2006, p. 950.
20 M. J. O'Neil, *The Merck index: An encyclopedia of chemicals, drugs, and biological*, 14th edn, 2006, p. 847.
21 C. Aitken-Nichol, F. Zhang and J. W. McGinity, *Pharm. Res.*, 1996, **13**, 804–808.
22 A. Martín, K. Scholle, F. Mattea, D. Meterc and M. J. Cocero, *Cryst. Growth Des.*, 2009, **9**, 2504–2511.
23 R. D. Rogers, D. T. Daly, D. R. MacFarlane, J. L. Scott, K. R. Seddon, G. Gurau, K. Bica, J. Turanjanin and P. M. Dean, *PCT Int. Appl.* US 2012/0046244 A1, 2012.
24 M. Moddaresi, M. B. Brown, S. Tamburic and S. A. Jones, *J. Pharm. Pharmacol.*, 2010, **62**, 762–769.
25 J. H. Oh, H. H. Park, K. Y. Do, M. Han, D. H. Hyun, C. G. Kim, C. H. Kim, S. S. Lee, S. J. Hwang, S. C. Shin and C. W. Cho, *Eur. J. Pharm. Biopharm.*, 2008, **69**, 1040–1045.
26 G. Oliveira, J. Hadgraft and M. E. Lane, *Int. J. Pharm.*, 2012, **435**, 38–49.
27 L. E. Bromberg and A. M. Klibanov, *Proc. Natl. Acad. Sci. U. S. A.*, 1995, **92**, 1262–1266.
28 R. M. Watkinson, C. Herkenne, R. H. Guy, J. Hadgraft, G. Oliveira and M. E. Lane, *Skin Pharmacol. Physiol.*, 2009, **22**, 15–21.
29 V. Sarveiya, J. F. Templeton and H. A. E. Benson, *J. Pharm. Pharmacol.*, 2004, **56**, 717–724.
30 Pharmacology for Anaesthesia and Intensive Care, *Section I Drug passage across the cell membrane*, ed. T. Peck, S. Hill and M. Williams, Cambridge University Press, Third edn, 2008.
31 N. V. S. Rodrigues, E. M. Cardoso, M. V. O. Andrade, C. L. Donnici and M. M. Sena, *J. Braz. Chem. Soc.*, 2013, **24**, 507–517.
32 K. M. Johansson, E. I. Izgorodina, M. Forsyth, D. R. MacFarlane and K. R. Seddon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 2972–2978.
33 M. Wierzejewska-Hnat, Z. Mielke and H. Ratajczak, *J. Chem. Soc., Faraday Trans. 2*, 1980, **76**, 834–843.
34 W. Ali, A. C. Williams and C. F. Rawlinson, *Int. J. Pharm.*, 2010, **391**, 162–168.
35 T. Ozeki, H. Yuasa and Y. Kanaya, *Int. J. Pharm.*, 1997, **155**, 209–217.

36 W. H. James III, C. W. Müller, E. G. Buchanan, M. G. D. Nix, L. Guo, L. Roskop, M. S. Gordon, L. V. Slipchenko, S. H. Gellman and T. S. Zwier, *J. Am. Chem. Soc.*, 2009, **131**, 14243–14245.
37 K. Bica and R. D. Rogers, *Chem. Commun.*, 2010, **46**, 1215–1217.
38 D. R. MacFarlane, M. Forsyth, E. I. Izgorodina, A. P. Abbott, G. Annat and K. Fraser, *Phys. Chem. Chem. Phys.*, 2009, **11**, 4962–4967.
39 J. Stoimenovski, P. M. Dean, E. I. Izgorodina and D. R. MacFarlane, *Faraday Discuss.*, 2012, **154**, 335–352.