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Enhanced membrane transport of pharmaceutically active protic ionic liquids†

Jelena Stoimenovski* and Douglas R. MacFarlane

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We show that pharmaceutically active protic ionic liquids can be designed to rapidly transport through model membranes as neutral hydrogen bonded clusters.

Ionic liquids (ILs) are currently being investigated for use in a number of areas of science.[1] Some years ago, Rogers and co-workers proposed ILs based on active pharmaceutical ingredients (APIs), whereby the synthesised ILs not only retain pharmaceutical activity but also have the added benefits of existing in a liquid form.[2] Some of the benefits of the liquid state include improved solubility, stability, bioavailability and alternative delivery modes of the drug. Being amorphous, pharmaceutical ILs could be a possible solution to one of the more significant problems in the pharmaceutical industry – polymorphic inter-conversion, whereby one polymorph of a drug converts into another over time.[3] Given that the counter-ion chosen for the formation of the IL can have a significant influence on the pharmacokinetics of the drug candidate, the new salt form of the registered drug would need to be treated as a new chemical entity, meaning that it can be separately patented.[4] Hence, the formation of ILs of existing APIs could assist in the development of new forms of the API.

Since their emergence, pharmaceutically active ILs have been studied by a number of groups. Hough *et al.* and our group have reported on pharmaceutically active ILs containing cations/anions of various actives.[5] One of the compounds, lidocaine docusate, was shown to have enhanced analgesic effect compared to the parent lidocaine chloride salt.[5a] This is just one of the examples where combining two pharmaceutical/biocompatible ions results in compounds with characteristics superior to the parent drugs. Bica and co-workers have reported ILs based on analgesic, anti-pyretic and anti-inflammatory compounds, acetylsalicylic and salicylic acids,[6] while Cybulski *et al.* have synthesised and characterised ILs based on antiseptic/disinfectant cations and enzyme/amino acid anions and the resulting ILs were found to be very effective against bacteria and fungi.[7,8] A large number of drugs on the market are based on actives that are acids and bases (or simple salts thereof) and hence we have also recently reported on pharmaceutically active *protic* ILs (PILs), where we reacted pharmaceutically active acids with pharmaceutical/biocompatible bases to produce salts with dual activity, *e.g.* an analgesic/nasal decongestant dual activity PIL.[9]

However, it is a well-established fact that ionic drugs do not readily cross biological membranes and skin due to their lack of sufficient lipophilicity.[4] *Stratum corneum* is the main barrier for permeation of most drugs through the skin and only a small number of drug molecules have the optimal physicochemical characteristics to penetrate it sufficiently to exert their therapeutic effect. A number of strategies have been proposed to overcome skin impermeability. Wotton *et al.* suggest that an increase in the diffusion coefficient (D) or the partition coefficient (K) of the drug, or both, can result in a multiplicative effect on the flux of the permeant.[10] Penetration enhancement is most commonly achieved by incorporating solvents that promote transfer through the *stratum corneum*.[11]

Here we describe a series of attenuated total reflectance–Fourier transform infrared (ATR-FTIR) experiments designed to investigate the permeation of different types of PILs through a model membrane. We show that some of the PILs exhibit strongly enhanced permeation properties, probably due to the formation of hydrogen bonded complexes in the membrane. The results of this study will assist in the design of the most effective pharmaceutically active ILs.

The use of the ATR-FTIR spectroscopic technique to study the diffusion of permeants is well established in the pharmaceutical field.[12] The model membrane used for this study is a silicone membrane. Although the *stratum corneum* is a more complex molecular structure, the trends observed are thought to be similar to those seen in the silicone membrane and it is thus accepted as a useful model in this context.[12a] The synthetic procedures and characterisation data for the compounds investigated and the detailed experimental procedures are given in the supporting information. Following the work of Tantishaiyakul *et al.*,[12a] propylene glycol (PG) was used as the solvent for the control experiments. PG was found not to change the properties or diffusion barrier of the membrane.

The two types of PILs that were chosen for study were (i) those that have been shown to be proton transferred and fully dissociated[13] due a sufficiently large difference in pK_a between acid and base and (ii) those that are thought to be proton

School of Chemistry, Monash University, Clayton, Victoria 3800, Australia. E-mail: Jelena.Stoimenovski@monash.edu; Fax: +61 3 9905 4535; Tel: +61 3 9905 4540

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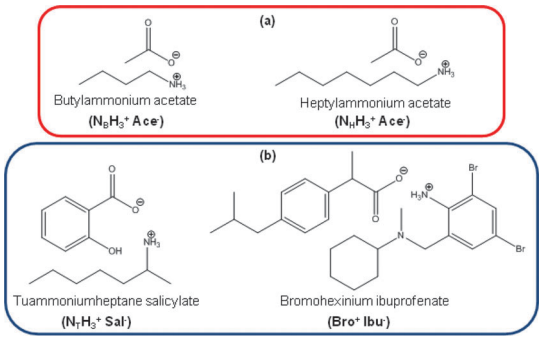

Fig. 1 The types of protic ILs investigated: (a) proton transferred and fully dissociated;[13] (b) proton transferred but form hydrogen bonded clusters.[9]

transferred, but form hydrogen bonded clusters[9] (Fig. 1). The PILs in (ii) are dual active PILs, with both the cation and anion pharmaceutically active. This is the first report of the pharmaceutical IL bromohexinium ibuprofenate; we have previously described the preparation and properties of the other compounds.[9,13] In that previous work, the IR spectroscopy and Walden plot analysis of the transport properties were used to assess the extent of proton transfer; proton transfer was found to be high in all cases. However, as discussed in more detail below, the existence of ion pairs and clusters was identified, supported by a crystal structure analysis of analogous compounds.[9]

Fig. 2 shows the relative absorbances of the species crossing the membrane over time for $N_TH_3^+$ Sal^- (as a pure liquid and as a PG solution) and its starting materials (in PG). ATR-FTIR spectroscopy allows the concurrent measurement of the diffusional parameters of both the primary permeant and its formulation solvent, if both species diffuse into the membrane under study (and their absorbance bands are distinct from each other).[12b] In the case of the salicylate compounds we monitored the carboxylate asymmetrical stretching band at 1570 cm^{-1}, whereas in salicylic acid the C=O stretching at 1665 cm^{-1} was analysed. Internal hydrogen bonding present in salicylic acid reduces the frequency of the carbonyl stretching absorption, which is normally observed at 1760 cm^{-1}.[20] Fig. 2 clearly illustrates that $N_TH_3^+$ Sal^- permeates the model membrane very rapidly, achieving saturation (100% relative absorbance) in ~20 h. However, when this compound is

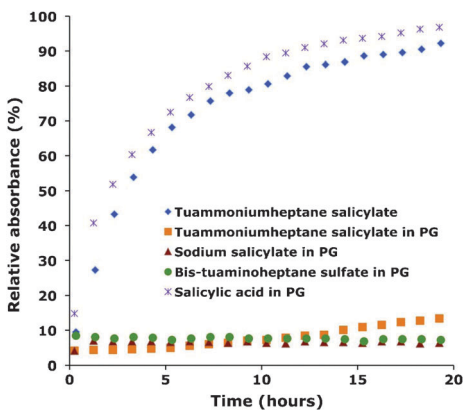

Fig. 2 Membrane transport of $N_TH_3^+$ Sal^- (pure and as a saturated PG solution) and its starting materials as saturated PG solutions.

present as a PG solution a very different behaviour is observed; it permeates slowly through the membrane, achieving only 15% of saturation in 20 h. The two pure salt starting materials for this PIL, sodium salicylate and $N_TH_3^+$ sulphate, when dissolved in PG, permeate < 10% in a 20 h period. Thus the IL form is significantly more permeable than either of the inorganic salt forms of the actives.

Salicylic acid (SalH) in PG was also examined in order to determine how the permeation of a neutral compound would compare to the ionic species. The salicylic acid was found to permeate about as rapidly as the salicylate-containing IL. Since the two starting materials, which are simple salts, do not cross the membrane, whereas the pure acid form does, it appears that neutral species are the most rapidly permeable in this type of membrane. This is in accord with the general observation that ionic compounds do not cross the membrane as readily as neutral compounds. The behaviour of the IL may therefore appear paradoxical. However, our previous studies[9] have suggested, on the basis of crystallographic analysis of analogous compounds and gas phase *ab initio* structure calculations, that $N_TH_3^+$ Sal^- may exist as a cyclic, two ion-pair complex.[9] Thus, as this neutral complex, the PIL can cross the membrane as rapidly as unionised neutral species. Furthermore, it is likely that the cyclic complex ceases to exist in the PG solution, dissociating into individual ions and hence limiting the permeability. The fact that some level of permeation is observed, as shown in Fig. 2, may relate to the presence of a small equilibrium fraction of neutral species being present, or formed at the membrane interface. As these are removed by permeation from the membrane's outer surface, their concentration is maintained by the equilibrium process in the liquid.

Thus, it appears that the permeation of salt forms of actives can be enhanced by formation of a PIL in which there is significant association present in the form of neutral species. In the case of $N_TH_3^+$ Sal^-, the permeation of both ions is strongly enhanced. Fig. 3 summarises the extent of permeation over time for two types of PILs. Like $N_TH_3^+$ Sal^-, Bro^+ Ibu^- shows evidence of ion pairing; the IR data suggests full proton transfer, but it sits well below the ideal line on the Walden plot. It shows the same permeation trends as $N_TH_3^+$ Sal^-, achieving saturation in ~20 h.

$N_BH_3^+$ Ace^- and $N_HH_3^+$ Ace^- are both highly ionised PILs but, in contrast to those discussed above, they sit closer to the ideal line on the Walden plot,[13] indicating a lesser tendency to form associated species. These PILs also permeate through the model membrane, but significantly slower than the associated PILs. As before, our hypothesis is that this arises from the transport of neutral species through the membrane, but in these less associated PILs this process is slower because the concentration of the neutral species is considerably lower. To put this on a more quantitative basis, Table 1 summarises the time for these compounds to permeate to 50% saturation (t_{50}). There is a clear distinction between the associated and less associated PILs.

A molecule will permeate the membrane well if it is highly soluble in the membrane and if it diffuses rapidly within it. Further analysis of these factors for the two types of PILs studied assists in understanding their different permeation behaviour. Experimental values of relative absorbance intensities

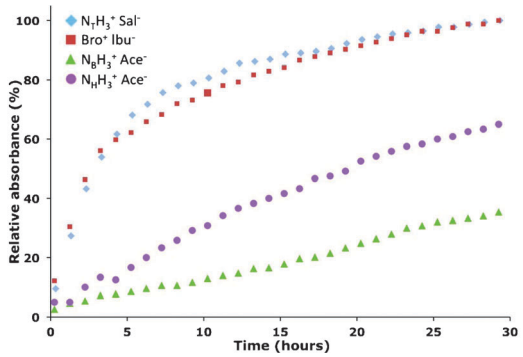

Fig. 3 Membrane diffusion of the various types of Protic ILs.

against time were fitted using a previously reported membrane diffusive flux equation:[12a,b]

$$\frac{A}{A_\infty} = 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1} \times \exp\left(\frac{-D(2n+1)^2\pi^2 t}{4h^2}\right) \qquad (1)$$

where A is the absorbance intensity at time t, D the permeant diffusion coefficient, h the film thickness and A_∞ the intensity of the permeant peak corresponding to the saturation of the membrane. Table 1 summarises the diffusion values obtained from a fit of eqn (1) for the compounds studied. A single diffusion coefficient did not provide an adequate fit to the data (including up to an $n = 3$ fit), except for the $N_BH_3^+$ Ace$^-$ case. However, introducing a second component, involving a second diffusion coefficient, provided a very good fit to the data (see ESI), as also observed by Dias *et al.*[14] It appears therefore that there are two processes contributing to the diffusion of these compounds (D_1 and D_2, Table 1), one approximately an order of magnitude slower than the other. In the work of Dias *et al.*, it was suggested that the second process arose from diffusion through a membrane already swollen by the permeant. It is interesting to note that the diffusion processes being observed here are relatively rapid, in some cases only two orders of magnitude slower than typical diffusion coefficients of ions in water.

From Fick's equation the overall flux, F, of molecules through the membrane is determined by $F = P.C_{IL}$ where P is the permeation coefficient given by $P = DK/h$ and C_{IL} is the concentration of the IL, K the partition coefficient of the species between the liquid phase and the membrane and h is the thickness of the membrane. The appearance of the partition coefficient in these relationships indicates the role of the intrinsic solubility of the permeant in the membrane. It is likely that the very low permeability of some species in Fig. 2 and 3 relate primarily to a very low solubility, rather than a low diffusion coefficient. An IL form of the actives does not necessarily address the solubility factor *per se*, other than the fact that the active ions are presented at very high concentrations. However, in cases where neutral species are present in the IL, the solubility in a membrane such as that used here would be enhanced. Solubility measurements in model membranes such as these would allow determination of the relationship between permeability and structure to be understood more fully and thus enable IL design. However, such measurements are difficult to achieve accurately.

Table 1 Membrane diffusion coefficients and t_{50} values for PILs

	R[a]	D_1 Fraction	$D_1 \times 10^{-8}$ (cm^2 s^{-1})	$D_2 \times 10^{-8}$ (cm^2 s^{-1})	t_{50} (hours)
$N_TH_3^+$ Sal$^-$	0.9982	0.69 ± 0.03	1.3 ± 0.1	10.1 ± 1.7	~2
Bro$^+$ Ibu$^-$	0.9933	0.50 ± 0.02	0.5 ± 0.1	6.1 ± 0.9	~2
$N_HH_3^+$ Ace$^-$	0.9977	0.74 ± 0.03	0.17 ± 0.01	1.5 ± 0.2	~20
$N_BH_3^+$ Ace$^-$	0.9981	—	0.097 ± 0.003	—	~50
SalH in PG	0.9993	0.58 ± 0.01	1.11 ± 0.02	15.6 ± 0.8	~2

In summary, we have shown that protic pharmaceutically active ILs are, in some cases, rapidly transported through a model membrane, most likely as hydrogen bonded complexes. We hypothesize that these paired compounds behave more like "neutral" species and hence cross the membrane faster than the more "ionic" drugs. It is interesting to note that hydrogen bonded complexes of un-ionised acid–base mixtures have also been found to display unusual properties recently.[15] One of the advantages of this protic IL approach is that active formulations can be designed that will be more membrane diffusive in a way that is not otherwise possible.

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