

# **Progress in Science**

## **Current Commentary**

### **Ionic liquids – pharmaceutical potential**

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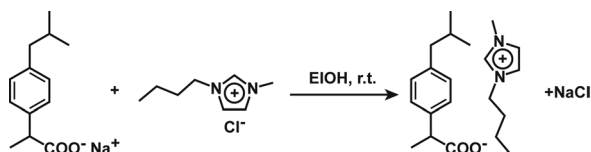
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#### **I. Nature and scope of bio-active ionic liquids**

Ionic liquids (ILs) are a recently developed class of materials with the property of being both fully ionic as in a conventional salt but also liquid rather than as the familiar crystalline solid. They have been the subject of much interest in the last year, being the subject of two major international conferences and a number of reviews. The latter have covered: (i) their potential as ‘green solvents’<sup>1</sup> (they have virtually zero vapour pressure) (ii) their thermochemistry<sup>2</sup>; and (iii) their development and applications<sup>3</sup>. One area not addressed in these otherwise very full treatments was the exciting prospects of ILs as agents in pharmacology, an area developing as rapidly as those many applications detailed in refs 1–3.

The basic strategy in applying the solvent properties of ILs in pharmaceutical materials has been to develop ILs which contain a pharmaceutically active component as one of the two component ions, i.e. the medication exists in a liquid rather than a solid form, thereby facilitating **more controllable and/or faster transport** within the subject receiving the medication; an early achievement in this field was that of Rogers *et al.*<sup>4</sup> who patented the concept of ‘Multi-functional ionic liquid compositions’. A further advantage of ILs as opposed to crystalline drugs is that the latter can be prone to polymorphic change on storage to give versions with differing solubilities. An illustrative example of an IL that incorporates pharmaceutical activity is that of 1-methyl-3-butylimidazolium ibuprofenate (BM1mlbu), synthesised as shown in Scheme 1<sup>5</sup>.



**Scheme 1** Synthesis of BMImbu<sup>5</sup>.

In this example, the pharmaceutically active component is present in the anion but it is also possible to place the activity in the cation, or even in both anion and cation as in lidocaine docusate<sup>6</sup> (Structure 1).



**Structure 1** Component ions of pharmaceutical IL lidocaine docusate<sup>6</sup>.

Lidocaine in its hydrochloride form is used as a local surface anaesthetic in dentistry whilst the docusate anion acts as an emollient.

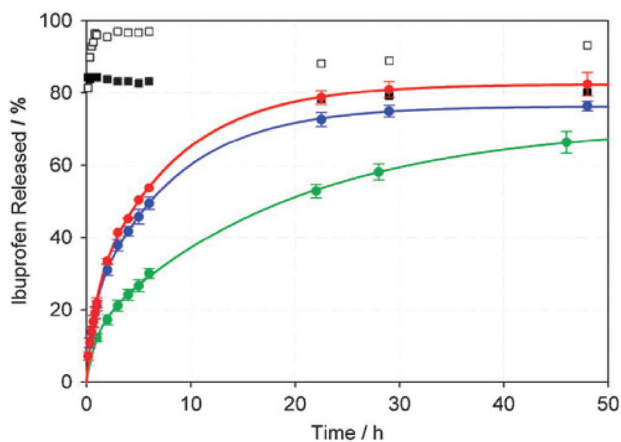
Combinations of different cations and anions provide a wide range of possible ILs, some such combinations being listed in refs 6 and 7; ILs containing biologically-active cations include antibacterials<sup>8</sup>, local anaesthetics, anticholinergics and antifungal agents<sup>9,10</sup>, while active anions furnish emollients, anti-acne agents, antibiotics, non-steroidal anti-inflammatory drugs and vitamins, among other materials<sup>6,7</sup>.

## 2. Aspects of drug delivery

One aim of developing bio-active ILs is to achieve enhanced drug delivery. It was demonstrated in an early paper<sup>6</sup> that lidocaine docusate, a hydrophobic IL, when compared with lidocaine hydrochloride, exhibited modified solubility, increased thermal stability and significant enhancement in the efficacy of topical analgesia in two different models of mouse antinociception; this was attributed not simply to changes in the delivery system but also to the induction of a different activity mechanism.

Subsequent approaches have included attempting to control the release of the drug by encapsulating the bio-active IL in the channels of a silica host using a one-step sol-gel process<sup>5</sup>. BMImbu (Scheme 1) was synthesised and then employed in sol-gel synthesis using either pure tetramethoxysilane (TMOS) or mixtures of TMOS and methyltrimethoxysilane (MTMOS) in 75/25 or 50/50 proportions in the presence of dilute HCl; the product was a monolithic ionogel. The loading of the drug in the ionogel was found to be *ca* 50% by

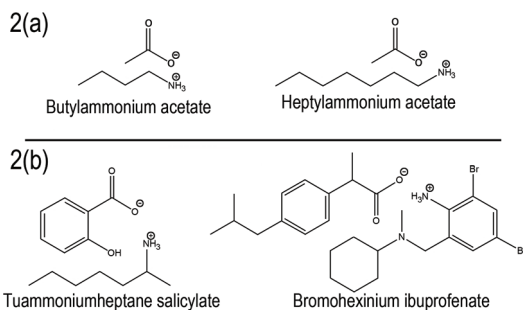
weight. The release kinetics of ibuprofen were determined by high performance liquid chromatography (HPLC) and the results are shown in Figure 1. Clearly the encapsulation of the IL form of the drug has a major influence on its release kinetics. The authors surmise that the slower release from the more methylated ionogel is related to the more hydrophobic nature of the cavity walls following the gelation.



**Figure 1** Release kinetics of (□) ibuprofen, (■) BMLmbu, (●) ionogel from TMOS, (●) from ionogel 75 TMOS:25 MTMOS, (●) from ionogel 50 TMOS:50 MTMOS<sup>5</sup>. Reproduced by permission of the Royal Society of Chemistry.

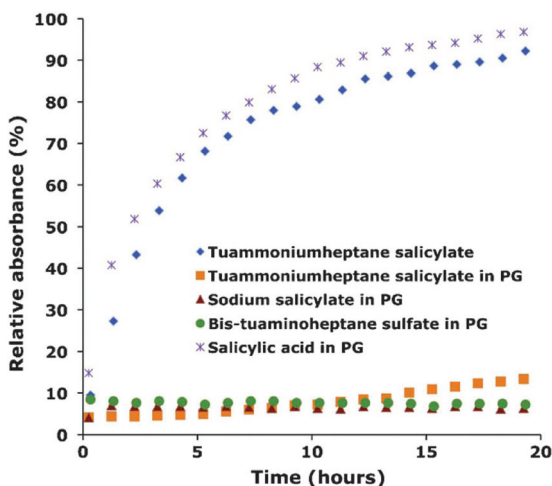
### 3. Protic ionic liquids

Another means of enhancing transport of ILs across membranes is to utilise protic ILs (or PILs)<sup>11–13</sup>; these fall into two types; one involves a fully transferred and fully dissociated proton [type (a) in Structure 2(a)]<sup>12</sup>, in the other, type (b), the proton is transferred but forms hydrogen-bonded clusters [Structure 2(b)]<sup>13</sup>.



**Structure 2** The types of protic ILs investigated 2(a) proton transferred and fully dissociated butylammonium acetate ( $N_4H_3^+Ace^-$ ) and heptylammonium acetate ( $N_7H_3^+Ace^-$ ); 2(b) proton transferred but forms hydrogen bonded clusters tuammoniumheptane salicylate ( $N_7H_3^+Sal^-$ ) and bromohexinium ibuprofenate ( $Bro^+Ibu^-$ )<sup>11</sup>.

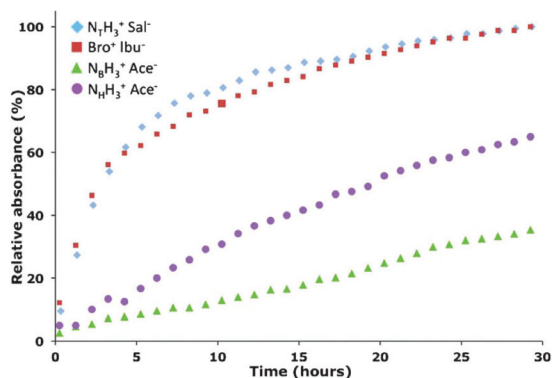
Figure 2 shows the relative absorbances as measured by attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy of the species crossing the silicone membrane over time for  $N_7H_3^+ Sal^-$ , either in the form of a pure liquid or as dissolved in propylene glycol (PG). Evidently this PIL permeates the model membrane very quickly, achieving saturation in *ca* 20 hours, while its permeation kinetics resemble those of (neutral) salicylic acid in PG (Figure 2). By contrast, the permeations of the membrane by (i) the PIL dissolved in a PG solution, and (ii) of the separate ions of the PIL in the form of simple salts, i.e. sodium salicylate and  $N_7H_3^+$  sulfate, are much slower. The authors propose that  $N_7H_3^+$  may exist as a cyclic, two ion-pair complex<sup>13</sup>, i.e. an electrically neutral species which can cross the membrane easily, whereas this complex ceases to exist in PG solution, dissociating into its individual ions, the penetration of which are limited.



**Figure 2** Membrane transport of  $N_7H_3^+ Sal^-$  (pure and as a saturated PG solution) and its starting materials as saturated PG solutions<sup>11</sup>.  
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In Figure 3 are shown the permeation kinetics of three other PILs together with  $N_7H_3^+$ , namely  $Bro^+Ibu^-$ ,  $N_8H_3^+Ace^-$  and  $N_4H_3^+Ace^-$ .  $Bro^+Ibu^-$  shows evidence for ion pairing and the IR data indicate full proton transfer; this PIL shows the same permeation trends as  $N_7H_3^+$ , and also achieves saturation in *ca* 20 hours. The two acetates are both highly ionised PILs but sit closer to the ideal line on the Walden plot, indicating a lesser tendency to form associated species. These two ILs undergo permeation at reasonable rates but which are significantly slower than the associated PILs. The authors were able to offer a quantitative interpretation of the permeation kinetics using a previously reported diffusive flux equation which required the use of two diffusion

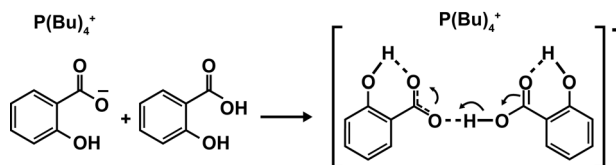
coefficients, one referring to the ‘normal’ diffusion process, and the second to diffusion through a membrane already swollen by the permeant. It was concluded that the very low diffusion rate of some species related to a very low solubility in the membrane rather than a low diffusion coefficient *per se*.



**Figure 3** Membrane diffusion of the various types of protic ILs<sup>11</sup>.  
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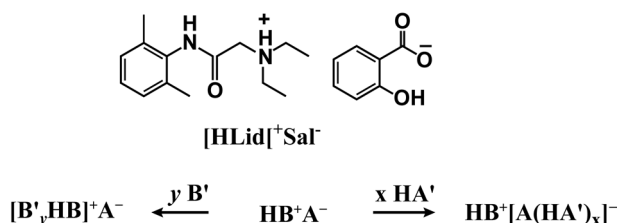
#### 4. Oligomeric ionic liquids

A large number of ILs is available commercially, thus Merck lists over 100<sup>14</sup>. However, it has been shown possible to enhance the scope and applicability of ILs by extending their liquid range. Bica and Rogers<sup>15</sup> have demonstrated that in preparing oligomeric pharmaceutical anions and cations they could obtain ILs with extended liquid ranges. Thus the grinding together of solid tetrabutylphosphonium salicylate with solid salicylic acid in appropriate proportions yielded a free-flowing liquid. This phenomenon is attributed to the association of further salicylic acid molecules to the 1:1 complex as a result of hydrogen bonding to the salicylate ion component (Scheme 2). Further salicylic acid could be added while maintaining the liquid state until a saturation level was reached at a composition of  $P(Bu)_4Sal_3H_2$ .



**Scheme 2** Proposed formation of oligomeric ions based on salicylate/salicylic acid<sup>15</sup>.

Addition of either excess acid or base to lidocainium salicylate had the effect of extending the liquid range as a result of oligomerisation (Scheme 3).



**Scheme 3** Proposed oligomeric ion approach for lidocaine HB<sup>+</sup> salicylate A<sup>-15</sup>.

## 5 Conclusions

In summary, it has proved possible to create a substantial range of ionic liquids with pharmaceutically active properties, based on the known activity of one or both components of the IL. These offer the potential for devising superior means of dosing the active ingredient and of avoiding any of the deterioration on storage of the solid counterparts due to polymorphic changes. As far as I am aware, noting the position paper from one of the most active groups working in this area<sup>16</sup>, the stage of clinical trials has yet to be reached. However, it should be noted that Carson *et al.*<sup>17</sup> have shown that a series of ILs, namely 1-alkyl-3-methylimidazolium chlorides, displayed potent, broad spectrum antibiofilm activity towards a variety of microorganisms, including clinical isolates of MRSA.

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