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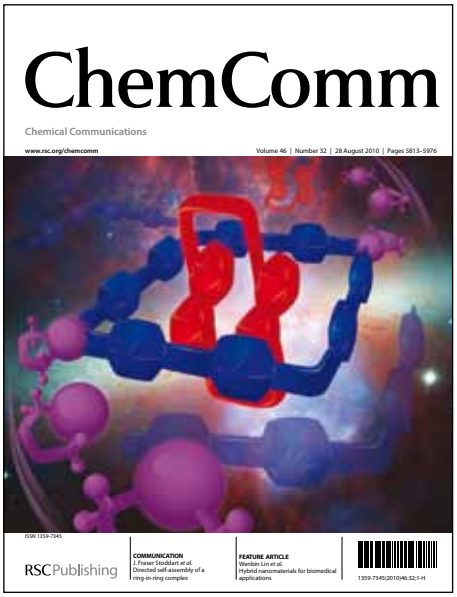

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Ionic Liquids Provide Unique Opportunities for Oral Drug Delivery: Structure Optimization and In Vivo Evidence of Utility

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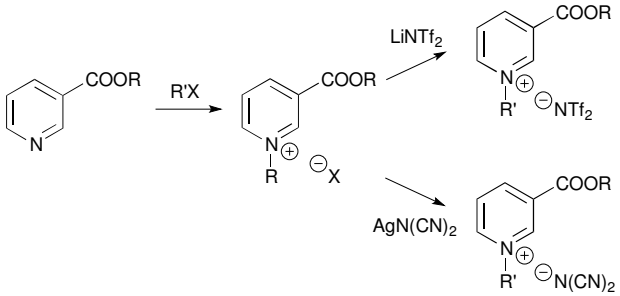
Ionic liquids (ILs) have been exploited to improve the absorption of poorly water-soluble drugs. Custom-made ILs solubilized very high quantities of the poorly water-soluble drugs, danazol and itraconazole, and maintained drug solubilization under simulated intestinal conditions. A danazol-containing self-emulsifying IL formulation gave rise to 4.3-fold higher exposure than the crystalline drug and prolonged exposure compared with a lipid formulation.

Ionic liquids (ILs) have generated considerable interest in fields as broad as catalysis,[1] extraction,[2] energy storage[3] and CO_2 capture.[4] The unique solvent properties of ILs are perhaps most well described[5] and form the basis of the use of ILs as potentially 'green' solvents in chemical synthesis.[6] Solubility properties are also a critical design feature of optimized drug delivery vehicles, and an area in which ILs might be expected to provide particular advantage. Although a number of interesting studies have demonstrated the capacity of ILs to dissolve active pharmaceutical ingredients,[7] in vivo application of ILs as enhanced oral drug delivery vectors has not been described. We describe here customized ILs to provide remarkable (20-500 fold) increases in drug solubility in oral formulations, and show for the first time that this provides a means to enhance and prolong absorption of drugs with intrinsically low solubility in water.

Poorly water-soluble drugs are a challenge in drug delivery since traditional formulations (tablets, capsules etc.) typically fail to provide for useful drug exposure after oral administration.[8] This reflects the fact that in almost all cases, drugs must be molecularly dispersed in aqueous solution in the gastro-intestinal (GI) fluids for absorption to occur. For poorly water-soluble drugs, dissolution is usually sufficiently slow that drug absorption is restricted. A common mechanism by which the absorption of such drugs can be enhanced is to pre-dissolve the drug in a non-aqueous vehicle, usually a lipid, and to 'piggy-back' into lipid digestion/absorption pathways. In this way drug solubilization is maintained by partition into the lipidic microdomains (micelles, vesicles etc.) that are produced by lipid digestion.[9] Notable examples of lipid-based formulations that have achieved commercial success include Neoral®, Agenerase® and Norvir SEC®. A limitation of this technology, however, is low drug solubility in most lipid vehicles. This reduces the prospective dose that can be administered. To address this technological limitation, we show here that ILs have the potential to provide a large increase in solvent capacity for model poorly water-soluble drugs when compared to commonly used lipidic excipients and also to promote and sustain drug absorption after oral administration.

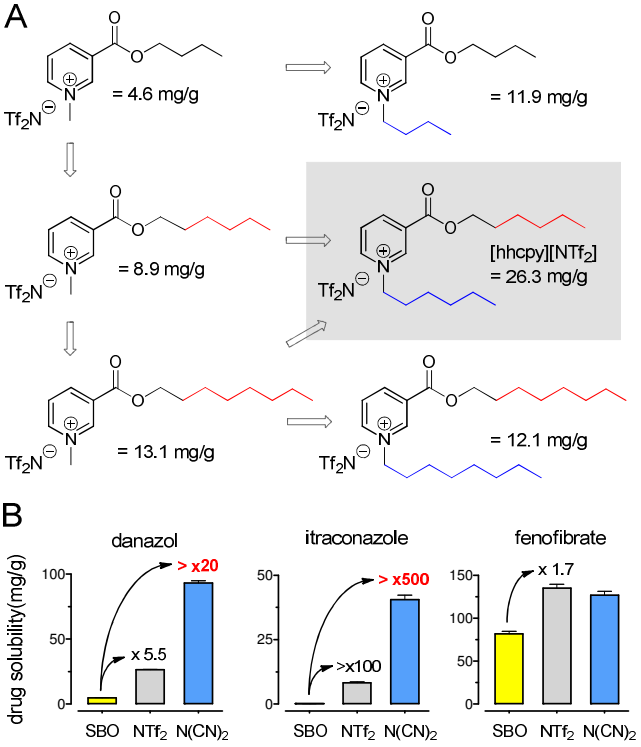
Our initial series of ILs were based on a nicotinic acid and its metabolite, trigonelline (*N*-methylnictonic acid). Nicotinic acid is a dietary component with low toxicity, while trigonelline is the second most abundant alkaloid in roasted coffee beans and is found in a range of plants and in some animals.[10,11] Nicotinic acid/trigonelline based ILs also show good biodegradability.[12] Water-immiscible ILs were targeted since, like lipids, water-immiscible ILs were expected to retain solvent properties on mixing with the GI fluids. Accordingly, nicotinic acid-based cations were paired in the first instance with the hydrophobic bis(trifluoromethylsulfonyl)imide ([NTf_2]) anion (Scheme 1).



Scheme 1. Preparation of nicotinicate ester ILs (where R = butyl, hexyl, octyl and R' = methyl, butyl, hexyl, octyl).

To probe the solvent properties of the ILs, danazol was initially used as a model drug. Danazol has low aqueous solubility (~1μg.ml^{-1})[13] and this limits exposure after oral administration.[14] Similar to many poorly water-soluble drugs, danazol has low solubility in lipids (< 5-10 mg.g^{-1} in triglycerides),[15] precluding the use of lipid based formulations as a means to enhance oral bioavailability. Danazol therefore provides an excellent example of a drug for which lipid formulations may be beneficial, but where low solubility in commonly used excipients limits utility. 3-

Butoxycarbonyl-1-methylpyridinium triflimide (Figure 1A), was initially evaluated following extensive study in previous work.[12a] Increasing the alkyl chain length of the pyridinium cation led to increases in danazol solubility, likely as a result of increases in hydrophobic van der Waals (dispersive) solute-solvent interactions

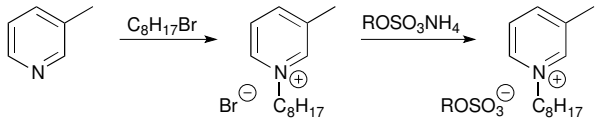


that promote solute dissolution.[16]

Fig. 1 A: A: Fine tuning the IL cation structure to optimize danazol solubility. [hhcpy][NTf_2] (shaded grey) was selected for further study. B: Solubility of danazol, itraconazole and fenofibrate in IL comprising the [hhcpy]$^+$ cation and triflimide [NTf_2]$^-$ or dicyanamide [$N(CN)_2$]$^-$ anions in comparison to solubility in soybean oil (SBO). Values in A are expressed as means (n = 3), and in B, as means (n = 3) ±1 SD.

The highest solubility was achieved using a 1-hexyl-3-hexyloxycarbonylpyridinium cation ([hhcpy]$^+$) (shaded in Fig. 1A). The [NTf_2] anion was subsequently substituted for the more hydrophilic dicyanamide [$N(CN)_2$] anion to explore the possibility of attaining higher solvent capacity using a more polar anion. Using the [hhcpy] cation and [$N(CN)_2$] anion, danazol solubility increased 3.6-fold from 26.3 mg.g^{-1} to over 95 mg.g^{-1} (Fig. 1B). This represents a 20-fold increase in solubility over soybean oil, and a level of solvency that exceeds that provided by many widely used co-solvents such as ethanol and PEG. The solvent properties of [hhcpy][NTf_2] and [hhcpy][$N(CN)_2$] were also evaluated for itraconazole (another drug showing poor water and lipid solubility[16]) and itraconazole solubility was >100-fold and ~500-fold higher, respectively, than that of soybean oil in these ILs (although absolute solubility was somewhat lower than danazol). The solvation benefit provided by ILs appears to be highest for drugs that exhibit poorer solvation in traditional lipids (e.g. danazol, itraconazole), since the ILs showed little solvent benefit over soybean oil for a more lipophilic drug, fenofibrate, where lipid solubility was already high.

Further studies were subsequently conducted to identify more amphiphilic ILs with improved miscibility properties with a range of lipid-based drug delivery systems. These '2nd generation' ILs were based on a 3-methylpyridinium core that is structurally similar to nicotinic acid, but allows for simpler synthesis and more facile scale-up for *in vivo* evaluation. A series of derivatives of the 3-methylpyridinium cation were synthesized, and the data obtained for the 1-octyl-3-methylpyridinium cation ([C_8mβpy]$^+$) (Scheme 2) are described in detail here. Alkyl sulfate anions were explored since the hydrogen bond acceptor sites on the sulfate moiety were expected to complement the hydrogen bond donor site on danazol, and the long alkyl chain was expected to increase the potential for favorable van der Waals interactions between the IL and non-polar drugs, and limit the water-miscibility of the IL (since IL miscibility with water was expected to increase the risk of drug precipitation on dispersion *in vivo*). Alkyl sulfate anions therefore possessed the combined qualities of [$N(CN)_2$] (i.e. hydrogen bonding) and [NTf_2] (i.e. hydrophobicity) anions. The melting temperature of the ILs containing longer chain anions [$C_{10}SO_4$]$^-$ and [$C_{18}SO_4$]$^-$ were higher than the 1st generation ILs, and as such, it was not possible to accurately measure drug solubility at room temperature. However, danazol solubility in the [C_6SO_4]$^-$ derivative, which was liquid at 37°C, was high (88.9 mg.g^{-1}) and similar to that of the 1st generation ILs containing [$N(CN)_2$]$^-$.



Scheme 2. Preparation of 1-methyl-3-octylpyridinum alkyl sulfate ILs (abbreviated as [C_8mβpy][$C_n$$SO_4$]). R = hexyl, decyl, octadecyl (details of the synthesis method are in the supporting information).

[hhcpy][[NTf_2] and [hhcpy][[$N(CN)_2$] from the 1st generation series and [C_8mβpy][$C_{10}SO_4$] and [C_8mβpy][$C_{18}SO_4$] from the 2nd generation ILs were progressed into *in vitro* studies to assess their potential as components of oral drug delivery systems. ILs were incorporated into formulations modeled on contemporary lipid formulations that emulsify spontaneously on contact with the GI fluids (so called *s*elf-*e*mulsifying *d*rug *d*elivery *s*ystems or SEDDS) and improve the oral bioavailability of many poorly water-soluble drugs.[17] Formulations (described in Table S1, Supporting Information) were loaded with danazol, and the respective solubilization properties assessed after dispersion in simulated gastric and intestinal fluids. With the exception of $SEDDS_{N(CN)2}$ (the dispersion of which resulted in drug crystallization), the other IL-SEDDS were highly effective in maintaining danazol in a solubilized form *in vitro*. Danazol absorption in rats was therefore assessed after administration of SEDDS based on ILs comprising [hhcpy][[NTf_2] and [C_8mβpy][$C_{10}SO_4$] and [C_8mβpy][$C_{18}SO_4$] ($SEDDS_{NTf2}$, $SEDDS_{C10SO4}$, $SEDDS_{C18SO4}$). A 'gold standard' lipid-based formulation ($SEDDS_{lipid}$) was also explored as was a crystalline danazol suspension. The plasma concentration profiles for danazol after administration of each formulation are shown in Figure 2A and total danazol exposure (the area under the plasma concentration curves) in Figure 2B (see Supporting Information, Table S2 for all pharmacokinetic results). The $SEDDS_{lipid}$ resulted in danazol exposure of 498.3 ± 149.8 ng.h.mL^{-1} over 8 h, whereas the suspension provided only a fraction (<25%) of this exposure, highlighting the benefit of administering a poorly water-soluble drug in a lipid formulation. Danazol plasma concentrations after administration of $SEDDS_{NTf2}$, and $SEDDS_{C10SO4}$, were also low despite these formulations containing drug in the pre-dissolved form. The exposure obtained for $SEDDS_{C18SO4}$, however, was much improved, and consistent with that of the $SEDDS_{lipid}$ but with noteworthy evidence of sustained plasma concentrations and the prospect of controlled drug release and absorption.

Digestion of $SEDDS_{lipid}$ in the intestine allows the incorporated drug to 'piggyback' the lipid absorption pathway resulting in transfer of digested lipids (and drug) into intestinal mixed-micelles for efficient transport to the intestinal wall.[8] In contrast, IL-based SEDDS are not digested. Poor drug absorption from these formulations is therefore likely attributable to inefficient transfer to the intestinal wall of the relatively large colloidal droplets formed by dispersion of the IL formulations in the GI fluids. The improved absorption of danazol from $SEDDS_{C18SO4}$ suggests that this IL system allowed for more effective interaction with endogenous bile salt micelles resulting in the generation of highly dispersed species with improved access to the absorptive surface. Interestingly, the structure of this IL-based micellar species appears to be sufficiently different to that of lipid-bile salt mixed-micelles to allow for controlled drug release, and therefore, sustained drug absorption. Segments of gastric and intestinal mucosa from $SEDDS_{lipid}$ and $SEDDSC_{18}SO_4$ administered rats were isolated 24 h post-dose for histological analysis (see Supporting Information, Fig. S1 & S2). The results show that $SEDDS_{lipid}$ did not cause any detectable histological injury. In half of the animals administered $SEDDS_{C18SO4}$, no histological damage was evident, however in two animals there was some evidence of submucosal inflammation in the non-glandular region of the stomach, suggesting the possibility of some local irritancy.

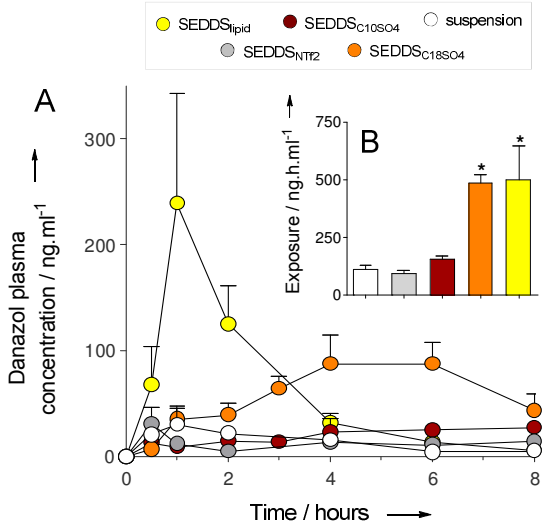


Fig. 2 Ionic liquids enhance and sustain drug absorption. A. Danazol plasma concentrations after oral administration of 25 mg.kg^{-1} danazol to rats in IL- or lipid-containing SEDDS or as a suspension formulation. Mean ($n \geq 4$) ± SEM. B: Total danazol exposure (AUC) over 8 h. Mean ($n \geq 4$) ± SEM. ✶ statistically significant ($p < 0.05$) relative to the suspension. Total exposure of danazol after administration in the $SEDDS_{C18CO4}$ IL formulation was similar to that of the 'gold standard' SEDDS lipid formulation, but with pronounced evidence of sustained plasma concentrations.

In summary, custom-made ILs have been synthesized that show great promise as improved drug delivery vehicles for poorly water-soluble drugs. IL-based SEDDS have many potential advantages including high drug loading capacity, facile dispersion in GI fluids, insensitivity to GI digestive processes and in some cases the ability to increase and extend drug absorption profiles. The flexibility of the IL synthetic platform provides particular attraction and subsequent studies will explore the potential for individually tailored drug delivery systems for drugs with widely differing, but problematic, physicochemical properties.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental methods, ionic liquid synthesis, Tables S1-S2 Figures S1-S4.

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