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Drug specific, tuning of an ionic liquid's hydrophilic–lipophilic balance to improve water solubility of poorly soluble active pharmaceutical ingredients†

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Amphotericin B and itraconazole were used to demonstrate that ionic liquids can be designed or chosen to provide tunable hydrophilicity in one ion and lipophilicity in the other allowing one to match the structural requirements needed to solubilize poorly water soluble active pharmaceutical ingredients. These liquid, amphiphilic excipients could be used as both drug delivery systems and solubilization agents to improve the aqueous solubility of many drugs. The solubility in deionized water, simulated gastric fluid, simulated intestinal fluid, and phosphate buffer solution was greatly improved over current methods for drug delivery by utilizing designed ionic liquids as excipients.

Introduction

There has been great interest in developing strategies to solubilize poorly water soluble active pharmaceuticals ingredients (APIs) in order to establish better drug delivery systems.[1,2] Many of the methods that have been attempted involve manipulating the structure or environment of the drug, such as salt formation,[3–5] creating solid dispersions,[6,7] designing prodrugs,[8–10] crystal engineering to synthesize cocrystals,[11–14] or by utilizing surfactants to create micelles for a nano-scale delivery system.[15] Amphiphilic surfactants, when added to water, surround the drug leaving only the hydrophilic regions of the API in contact with the water, which helps to minimize hydrophobic effects and increase the water solubility of the drug.[16–19] However, these surfactants are typically added to the aqueous system independently of the API and are not specifically tuned for a given API, which limits their effectiveness for solid drugs that are prone to immediate, irreversible aggregation. Exacerbating these problems, lipophilic regions are now being incorporated into the structure of APIs to increase their potency as drugs,[20] but this also can lead to higher molecular weights, lower aqueous solubilities, and lower oral bioavailability due to the added hydrophobic character.[21] A simple, drug-specific, and tunable strategy that can increase the water solubility of amphiphilic drugs would be an extremely powerful technique, which would obviate the need to alter the chemical structure of the drug.[22]

Recently, we and others have proposed utilizing an ionic liquid (IL, a salt with a melting point below 100 °C, but here specifically below body temperature) strategy to transform solid drugs into liquids.[23–26] This approach can be useful in solving many of the deficiencies of solid drugs, such as elimination of polymorphism, controlling water solubility, or improving transdermal penetration.[27,28] However, the pK_a values for many APIs will not be sufficient to retain a charged state once dissolved in the body, in which case the drug may simply revert to a less soluble, neutral form.[29,30] There is clearly still a need for an excipient or carrier, which can help solubilize and deliver hard to dissolve pharmaceuticals. Here, we explore the use of carefully selected or designed ILs for this task.

The unique solvent capabilities of ILs are already being used to dissolve, extract, or stabilize cellulose,[31,32] chitin,[33] nanomaterials,[34–37] proteins,[38] natural products,[39] and even drugs.[40–43] However, in order to effectively solubilize APIs in water, the ILs must be designed to dissolve the drug and prevent aggregation in water. Previous work has employed ILs as drug delivery systems,[17,18,44] including developing IL micelles to stabilize drug molecules;[45] however, a micellular approach is not drug-specific, but utilizes a finite space to sequester the entire drug in water.

Here, we suggest carefully tuning the structure of an IL to maximize interactions with a targeted drug needed to both solubilize it and prevent aggregation in water. A truly designed IL-excipient would take advantage of the solvent capability of the IL, as well as its ability to prevent aqueous aggregation by

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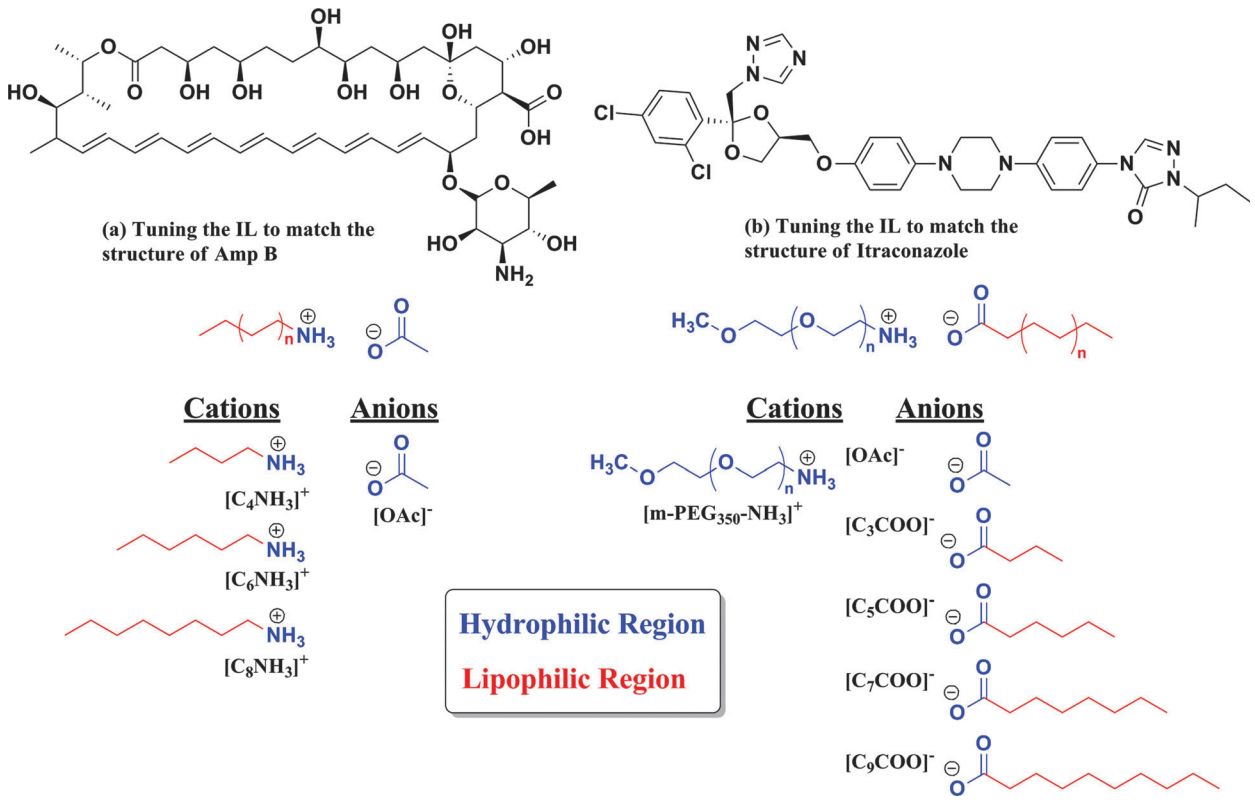

Fig. 1 (a) $[OAc]^-$ based ILs to dissolve Amp B by tuning cation hydrophobicity; (b) PEG-based ILs with a hydrophilic cation and tunable hydrophobicity in the anion to dissolve itraconazole.

preferentially interacting with each specific drug target *via* either or both of the IL ions. In this report, we demonstrate our approach with two complex, amphiphilic drugs, amphotericin B (Amp B, 0.2 μg mL^{-1} in water)[46] and itraconazole (1.0 ng mL^{-1} in water)[47] (Fig. 1), where a tailored approach must be utilized, since salt formation with a hydrophilic counterion is unlikely to control water solubility.

Experimental

Chemicals

N-Butylamine, *N*-hexylamine, *N*-octylamine, butanoic acid, hexanoic acid, octanoic acid, decanoic acid, *p*-toluenesulfonyl chloride, and 1-ethyl-3-methyl-imidazolium acetate ($[C_2mim][OAc]$) were purchased from Sigma-Aldrich (St. Louis, MO) and used as received. Triphenylphosphine, sodium azide, potassium carbonate, potassium hydroxide, and magnesium sulfate were purchased from Alfa Aesar (Ward Hill, MA). Glacial acetic acid and methylene chloride were purchased from Fischer Scientific (Hampton, NH) and used without any further purification. Oleic acid was purchased from Sigma-Aldrich (St. Louis, MO) as a technical grade, but was further purified by vacuum distillation. The distillate was stored under ambient conditions in a sealed container. CH_3-PEG_{350}-OH was purchased from Alfa-Aesar (Ward Hill, MA) and dried under high vacuum for 24 h prior to use. Amphotericin B (Amp B) was provided by Abbott Laboratories (Abbott Park, IL) as a dry orange powder and stored at 0 °C and covered to prevent light exposure. Itraconazole was provided by Abbott Laboratories as a white powder and used as received.

Spectroscopy

All Nuclear Magnetic Resonance (NMR) spectra were recorded utilizing a Bruker Avance Spectrometer Bruker/Magnex UltraShield 500 MHz magnet (Madison, WI) or a Bruker Spectrospin DRX 360 MHz UltrashieldTM spectrometer (Madison, WI). ^1H (500 MHz) was collected using DMSO-d_6 or D_2O-d_2 as the solvent (or as a neat liquid in a sealed glass capillary) with TMS as the internal standard and shifts reported in δ (ppm).

Single crystal X-ray diffraction

Data were collected on a Bruker diffractometer with an Apex II CCD area detector equipped with a low-temperature device, using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were measured using a strategy of omega scans of 0.5° per frame. Data collection, integration, and absorption corrections were performed using the APEX2[48] software suite from Bruker and SADABS.[49] Structure solution and refinement were conducted using the SHELXTL[50] software package from Bruker. Packing diagrams for both structures were made using Mercury from the Cambridge Crystallographic Data Center.[51] The two structures were solved by direct methods. Non-hydrogen atoms in all structures were located from the difference map and refined anisotropically through least squares refinement against F^2. Hydrogen atoms were placed in calculated positions and allowed

to ride on the carrier atom. Hydrogen atoms on methyl groups were refined using a riding rotating model. CCDC 908843 and 908844.

General synthesis of ILs

The protic acid (10 mmol) was placed in a 20 mL vial. The vial was cooled using an ice water bath to 0 °C while stirring vigorously. Alkylamines or *m*-PEG_{350}-NH_2 (10 mmol) were added drop-wise while maintaining the temperature at 0 °C. Each reaction was immediately exothermic and turned a light yellow shade upon finishing the addition. The reactions were stirred overnight remaining in the water bath, but the temperature was allowed to slowly rise to ambient conditions. Detailed synthetic procedures and all applicable characterization data are available in the ESI.†

Preparation of simulated fluids

Phosphate buffer saline (PBS, pH = 7.4) solution was prepared from the commercially available tablets (Sigma-Aldrich, Saint Louis, MO) by dissolving 1 tablet in 200 mL DI-H_2O. Simulated intestinal fluid (SIF, pH = 6.8) without added pancreatin[52] was prepared by dissolving 0.6805 g KH_2PO_4 and 0.0896 g NaOH in a 100 mL volumetric flask and diluted with DI-H_2O. Simulated gastric fluid (SGF, pH = 1.2) without added pepsin[53] was prepared by dissolving 0.200 g NaCl, and 0.7 mL concentrated HCl (to adjust to pH = 1.2) in a 100 mL volumetric flask and diluted with DI-H_2O. SIF and SGF solutions (without the added enzymes) were prepared by following the United States Pharmacopeia (USP) guidelines.

Results and discussion

Ionic liquid design

Utilizing functional groups, such as amines and carboxylic acids, commonly found in APIs, we can carefully design the hydrophilic–lipophilic balance (HLB) of an IL while maintaining similar functionality and structural interactions with the API. The IL approach allows us to carefully segregate and balance the amphiphilic character of each IL ion (Fig. 1) to match our model APIs, Amp B and itraconazole. In theory, the scope of ion combinations capable of forming ILs should also allow one to choose ions already approved for internal consumption, *i.e.*, edible IL-excipients.

Amp B, an amphiphilic molecule, contains a hydrophobic section of nearly 14 carbons, responsible for its low water solubility;[54] therefore, the IL must be designed to not only disrupt inter and intramolecular hydrogen bonding, but to balance sequestration of the hydrophobic region while still retaining adequate water solubility to act as a practical drug delivery system. Acetate ($[OAc]^-$) was chosen as the hydrophilic anion due to its ability to dissolve strongly hydrogen bonded and poorly water soluble polymers such as cellulose and chitin by breaking inter- and intramolecular hydrogen bonds.[31,32] With hydrophilicity and hydrogen bond acceptor ability provided in our anions, we choose to pair these with more hydrophobic cations to balance the overall HLB. Initially, we chose short-chain fatty amines (Fig. 1a) where the lipophilic character could be easily modified by increasing the alkyl chain length.

The acetate ILs were synthesized, with a slightly modified procedure from previously reported syntheses of lipophilic ammonium acetate ILs,[27,55] by the drop-wise addition of the appropriate length amine to a flask containing glacial acetic acid at 0 °C, which resulted in a dramatic increase in the viscosity of the mixture. In the case of the longer amines, $[C_6NH_3][OAc]$ (Fig. 2a) and $[C_8NH_3][OAc]$ (Fig. 2b), colorless single crystals formed when stirring was stopped and the composition of both salts was confirmed by single crystal X-ray diffraction. The remaining salts were confirmed to be fully ionized by neat ^1H NMR monitoring of the carboxylic acid peak (see ESI† for details). While two salts were obtained as crystalline solids, both $[C_6NH_3][OAc]$ (mp = 52 °C) and $[C_8NH_3][OAc]$ (mp = 48 °C) exhibited supercooled behavior at room temperature after melting allowing easy preparation of solutions. All other ILs were liquids at room temperature.

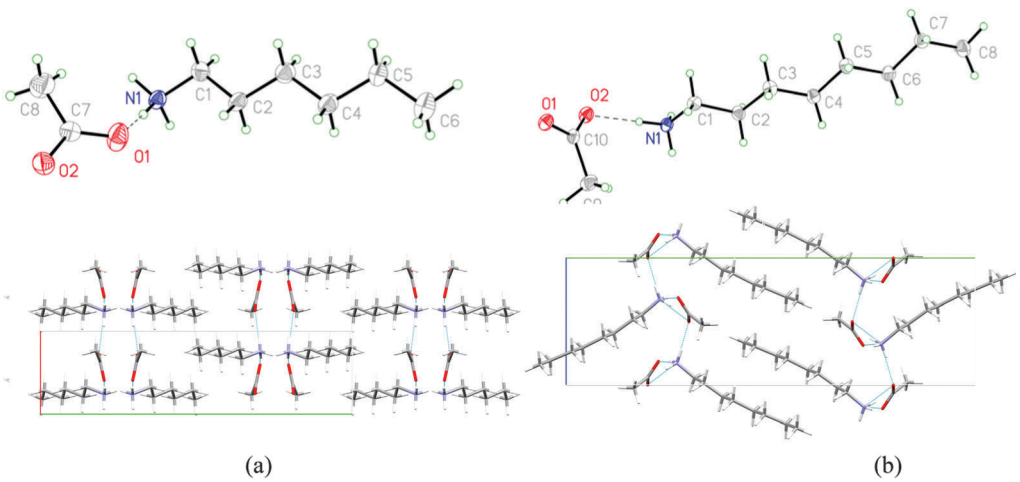

Fig. 2 (a) $[C_6NH_3][OAc]$: asymmetric unit with 50% probability ellipsoids (top) and packing viewed along the *c* axis (bottom) illustrating the separate hydrophilic and lipophilic regions; (b) $[C_8NH_3][OAc]$: asymmetric unit with 50% probability ellipsoids (top) and packing viewed along the *a* axis (bottom).

As itraconazole is structurally quite different from Amp B, a separate design strategy was formulated. Based on previous work using polyethylene glycol (PEG) as a surfactant and excipient to increase the water solubility of itraconazole,[47,56–58] we developed a series of PEG-350 (MW *ca.* 350 g mol^{-1}) ILs based on the PEG-ammonium cation ([*m*-PEG$_{350}$-NH$_3$]$^+$) combined with a fatty acid anion, allowing us to add or subtract alkyl units to properly control the HLB of the overall IL (Fig. 1b). *m*-PEG$_{350}$-NH$_2$ was synthesized from *m*-PEG$_{350}$-OH by functionalization of the alcohol group to a tosylate intermediate.[59] The *m*-PEG$_{350}$-OTs was then converted to *m*-PEG$_{350}$-N$_3$ through an S$_N$2 reaction with sodium azide. The *m*-PEG$_{350}$-N$_3$ intermediate was then reduced with triphenylphosphine to yield *m*-PEG$_{350}$-NH$_2$ in a neat reaction[60] (see ESI† for details).

In order to control the HLB, the ([*m*-PEG$_{350}$-NH$_3$]$^+$) cations were paired with fatty acid anions through neat, drop-wise addition reactions with fatty acids from acetic acid to decanoic acid. In the case of [*m*-PEG$_{350}$-NH$_3$][C$_9$COO], decanoic acid was first melted before it was drop-wise added to *m*-PEG$_{350}$-NH$_2$. These protic ILs were characterized and determined to be ionized through neat ^{1}H NMR on the basis of the disappearance of the carboxylic acid peak and the appearance of the newly formed $-NH_3^+$ peak.

API solubility in ionic liquids

In order to determine the effectiveness of these designed ILs as drug delivery systems, we first had to test how well the ILs could dissolve the APIs. To test solubility in the ILs, each API was added portion-wise (in 5 mg increments up to 30 mg) to 1 mL of the selected IL and placed in a Branson 5510 bath sonicator for up to 7 consecutive 99 min cycles until aggregation was no longer visible along the bottom of the vial. (Vortex mixing was unable to dissolve the APIs and thus sonication was chosen to overcome the surface tension of the ILs and allow adequate mixing.) Solubility was evaluated by assessing the visual turbidity and aggregation present in the resulting mixture. Incremental addition of the API was ended when a cloudy yellow or white suspension was observed which led to visible aggregated solid on the bottom of the vial. Completely dissolved samples were characterized by a clear colored (red for Amp B and yellow for itraconazole) solution with increasing darkness observed upon addition of subsequent portions of API. All of the prepared solutions were stable for months without any visible sedimentation. In addition, no degradation of either API was observed spectroscopically by ^{1}H or ^{13}C NMR.

The solubility studies of Amp B revealed that this API was soluble in those ILs containing the strongly basic, hydrogen bond acceptor [OAc]$^-$ anion (Table 1), but not soluble in any of the fatty acid-based ILs. A maximum Amp B solubility of 85 mg mL^{-1} was observed in 1-ethyl-3-methylimidazolium acetate ([C$_2$mim][OAc]); the same IL known for strongly solvating natural biopolymers such as cellulose, lignin, and chitin.[31–33]

In our study of Amp B, fatty amines were investigated to add lipophilicity to the IL cations. Both [C$_4$NH$_3$][OAc] and [C$_6$NH$_3$][OAc] solubilized Amp B up to 30 mg mL^{-1}, however, once the chain length was increased to [C$_8$NH$_3$][OAc], the solubility decreased to 20 mg mL^{-1}. It should be noted that if these cations are oriented tail to tail, allowing for the maximum nonpolar interactions, both [C$_4$NH$_3$]$^+$ and [C$_6$NH$_3$]$^+$ would fit under the 14 carbon hydrophobic region present in Amp B, while [C$_8$NH$_3$]$^+$ would not. In addition, ILs with too much added lipophilicity will be dominated by interchain interactions, which could lead to lower API solubilities. For example the packing in [C$_8$NH$_3$][OAc] (Fig. 2b) suggests a higher degree of interchain interactions than in [C$_6$NH$_3$][OAc] (Fig. 2a) where the alkyl groups are more segregated.

Table 1 Loading[a] of Amp B and itraconazole in tested ILs

Ionic liquid	Amp B (mg mL^{-1})	Itraconazole (mg mL^{-1})
[C$_2$mim][OAc]	85	<5
[C$_4$NH$_3$][OAc]	30	<5
[C$_6$NH$_3$][OAc]	30	<5
[C$_8$NH$_3$][OAc]	20	<5
[C$_4$NH$_3$][Oleate]	<5	<5
[C$_6$NH$_3$][Oleate]	<5	<5
[C$_8$NH$_3$][Oleate]	<5	<5
[*m*-PEG$_{350}$-NH$_3$][OAc]	5.1	5.3
[*m*-PEG$_{350}$-NH$_3$][C$_3$COO]	<5	5.2
[*m*-PEG$_{350}$-NH$_3$][C$_5$COO]	<5	5.4
[*m*-PEG$_{350}$-NH$_3$][C$_7$COO]	<5	5.3
[*m*-PEG$_{350}$-NH$_3$][C$_9$COO]	<5	5.4
[*m*-PEG$_{350}$-NH$_3$][Oleate]	<5	<5

[a] Loading as determined by incremental addition of 5 mg of API to 1 mL of IL until the API no longer completely dissolved.

In order to determine the mechanism for solubility, Amp B dissolved in [C$_6$NH$_3$][OAc] at 10 mg mL^{-1} was placed in a sealed capillary (with DMSO-d_6 in an external tube for locking) and the interactions between the IL excipient and the drug were monitored by ^{1}H NMR. Compared to the IL alone, for the solution of Amp B, the quaternary ammonium peak at 7.8 ppm shifted further upfield to 7.5 ppm due to an increased shielding effect (See ESI† for NMR spectra). In addition, the resulting peak was broadened, corresponding to the ammonium functional group hydrogen bonding to any of the many hydrogen bond acceptor sites in the drug molecule.

The solubility results with Amp B suggested that it is possible to design or choose an IL excipient to contain complementary functional groups to the drug molecule and to create proper HLB such that the API will readily dissolve. To further test this hypothesis, we studied a structurally quite different API, itraconazole, which is characterized by rigidity and aromatic moieties rather than Amp B's conjugated double bonds and hydroxyl groups. As predicted, itraconazole was not soluble in any of the ILs based on the lipophilic ammonium cation. However, itraconazole was soluble at 5.2–5.4 mg mL^{-1} in each of the five linear [*m*-PEG$_{350}$-NH$_3$][Fatty Acid] ILs with no significant differences seen based on the length of the alkyl chain in the anion.

Neat NMR studies of a 5.3 mg mL^{-1} solution of itraconazole in [*m*-PEG$_{350}$-NH$_3$][OAc] demonstrated an upfield shift of the quaternary ammonium peak, but without any broadening of the quaternary ammonium peak. This suggests less hydrogen bonding between the itraconazole molecule and the IL structure when compared to the system used to dissolve Amp B.

Table 2 Concentration of Amp B in water loaded from different stock solutions of $[C_6NH_3][OAc]$

	Stock solutions of [Amp B] in $[C_6NH_3][OAc]$			
[Amp B] in H_2O	5 mg mL^{-1} Solution stability	10 mg mL^{-1} Solution stability	20 mg mL^{-1} Solution stability	30 mg mL^{-1} Solution stability
1 mg mL^{-1}	Insoluble[a]	Insoluble[a]	Insoluble[a]	Insoluble[a]
0.50 mg mL^{-1}	5 m[b]	1 m[b]	Insoluble[a]	Insoluble[a]
0.25 mg mL^{-1}	24 h[b]	12 h[b]	12 h[b]	12 h[b]
0.10 mg mL^{-1}	~3 mo[c]	7 d[c]	7 d[c]	7 d[c]
0.01 mg mL^{-1}	∞[c]	∞[c]	14 d[c]	14 d[c]

[a] Addition of Amp B in $[C_6NH_3][OAc]$ resulted in immediate and irreversible precipitation. [b] Addition of Amp B in $[C_6NH_3][OAc]$ resulted in a turbid, but stable dispersions. [c] Addition of Amp B in $[C_6NH_3][OAc]$ resulted in clear solutions.

As itraconazole does not contain a large number of alcohol groups in its structure (Fig. 1b), disrupting inter- and intramolecular hydrogen bonding is less important for solubilization.

In the above tests, a flexible, hydrophobic alkyl chain in either ion was utilized to closely associate with the nonpolar regions of the drug molecules. In order to test the importance of the hydrophobic interactions on solubilizing the drug, the flexible alkyl lipophilic tail was substituted with a rigid, nonpolar hydrophobic anion containing a *cis* alkene functional group ($[Oleate]^-$), which would prevent close associations with the drug molecule due to its shape. In all cases, neither itraconazole nor Amp B were soluble in the $[Oleate]^-$ based ILs (Table 1) suggesting that the flexible lipophilic region was necessary for the solubilization of either IL.

Enhanced API solubility in water

Having successfully prepared several ILs that could solubilize each API, we turned our attention to determining under what the conditions these IL–API solutions would stabilize the API in aqueous solutions; where the ILs must preferentially interact with drug and prevent precipitation and aggregation. In order to test this concept, stock solutions of the APIs in the ILs were added drop-wise to deionized (DI) water (pH = 7), PBS (pH = 7.4), SIF (pH = 6.8), and SGF (pH = 1.2) in known volumes to determine the IL's ability to enhance water solubility.

Despite the high solubility of Amp B in $[C_2mim][OAc]$, Amp B immediately precipitated when a solution of Amp B in $[C_2mim][OAc]$ was added drop-wise to water. This is similar to the coagulation of dissolved biopolymers in this IL where the biopolymers freely dissolve in the dry IL through a hydrogen bonding network with the anion, but water, once added, acts as an anti-solvent, solvating the IL ions and resulting in coagulation of the biopolymers.[61,62]

Of the remaining ILs that solubilize Amp B, $[C_6NH_3][OAc]$ was chosen for water solubility studies due to the relative non-toxicity of its cation (*n*-hexylamine, LD_{50} = 240 mg kg^{-1} in rats),[63] its full miscibility with water, and its ability to dissolve Amp B. While $[C_6NH_3][OAc]$ is a crystalline solid at room temperature, once melted, it exhibits supercooled behavior at room temperature and does not crystallize until −18 °C making it easy to work with at room temperature.

Aliquots (0.2 μL to 200 μL) of Amp B–$[C_6NH_3][OAc]$ stock solutions (5 mg mL^{-1} to 30 mg mL^{-1}) were added drop-wise to vials containing DI water and dissolved *via* vortex mixing for 3–5 min. Initially, the drop of $[C_6NH_3][OAc]$ containing Amp B simply fell to the bottom of the vial; however, upon vortex mixing, the droplet of IL created a clear orange solution with turbidity visible in highly concentrated samples. Three different types of mixtures were obtained (Table 2): (i) insoluble samples, which resulted in immediate and irreversible aggregation (at attempted Amp B concentrations in water of 0.50–1 mg mL^{-1}), (ii) stable dispersions with visual turbidity and limited stability (at Amp B concentrations in water of 0.25–0.50 mg mL^{-1}), and (iii) clear solutions, which demonstrated fully soluble Amp B in water (up to 0.10 mg mL^{-1}). The solubilities of Amp B achieved here (up to 0.10 mg mL^{-1} in water) are more than three times higher than concentrations achieved using surfactants, nano dispersions, or micellular delivery at pH 7 (0.03 mg mL^{-1}).[64]

In several cases, the soluble samples precipitated Amp B over a period of days to months, but each of these samples was easily redissolved with no visual turbidity by simply shaking the vial. In the dispersed samples, Amp B settled from the dispersions over a shorter time, but could be easily redispersed upon simple shaking or stirring by hand. All solutions and dispersions exhibited the same stability whether freshly prepared or redissolved and redispersed.

Since the highest concentration of Amp B in water we achieved was only stable for 3 months after which sedimentation was visible along the bottom of the vial, further study was undertaken to probe this behavior. By varying the concentration of Amp B in the IL prior to dissolution in water, it became apparent, that more stable solutions of Amp B in water were achieved when loading from lower concentrations of Amp B in IL; that is more IL was needed in order to increase the stability of Amp B in water. A concentration of 0.10 mg mL^{-1} (0.11 mM) in water, loaded from a stock solution of 5 mg mL^{-1} in $[C_6NH][OAc]$, was stable for several months, while an Amp B concentration of 0.10 mg mL^{-1} (0.11 mM) in water, loaded from a stock solution of 10 mg mL^{-1} was stable for only 7 days.

Once the maximum solubility was obtained in DI water, further tests were completed in order to determine if the solubility increases were also observable under physiological conditions. As described above, known volumes of stock solutions of Amp B in $[C_6NH_3][OAc]$ were added to vials containing each of the three body fluids in order to obtain a concentration of 0.25 mg of Amp B per mL of simulated fluid. Each mixture

Table 3 Loading of itraconazole in water utilizing 5 mg mL^{-1} stock solution of itraconazole in [*m*-PEG_{350}-NH_3][Fatty Acids]

IL-excipient	[Itraconazole] (mg mL^{-1} H_2O)
[*m*-PEG_{350}-NH_3][OAc]	0.01
[*m*-PEG_{350}-NH_3][C_3COO]	0.10
[*m*-PEG_{350}-NH_3][C_5COO]	0.25
[*m*-PEG_{350}-NH_3][C_7COO]	0.01
[*m*-PEG_{350}-NH_3][C_9COO]	Insoluble

was then vortex mixed and left standing to assess solubility. In all cases tested, Amp B was soluble after the initial mixing with a slight level of turbidity present. While Amp B was only soluble at 0.10 mg mL^{-1} in DI water, in each of the simulated body fluids a turbid suspension was stable for up to 5 days at 0.25 mg mL^{-1}.

It was also evident that the Amp B must first be dissolved into the IL and then this solution added to water in order to achieve the solubilities and stabilities reported in Table 2. Adding Amp B to water followed by adding the IL or adding Amp B to solutions of [C_6NH][OAc] in water led to no appreciable increase in Amp B aqueous solubility.

Itraconazole was soluble in water when loaded from any of the [*m*-PEG_{350}-NH_3][Fatty Acid] IL excipients for up to 72 h, and could be easily redissolved by simple stirring or vortex mixing. The maximum concentration achieved, however, was highly dependent on the original IL used to solubilize the drug (Table 3). [*m*-PEG_{350}-NH_3][C_5COO] was the most proficient at solubilizing itraconazole in water (0.25 mg mL^{-1}), and itraconazole's solubility in water decreased by either adding or subtracting hydrophobic character from the IL (*e.g.*, with [*m*-PEG_{350}-NH_3]-[C_4COO] only 0.10 mg mL^{-1} was achievable and only 0.01 mg mL^{-1} when using [*m*-PEG_{350}-NH_3][C_7COO]). Thus, for itraconazole at least, it appears that the HLB balance of the IL-excipient is highly important.

Conclusions

The research presented here has demonstrated a design strategy to solubilize amphiphilic and hard to dissolve APIs by selectively choosing complementary functionality in one or both ions of an IL excipient and providing HLB balance in either or both ions independently. This approach can not only be utilized to dissolve the API into the IL excipient, but to effectively solubilize and maintain the API in water. Utilizing this strategy both Amp B (30 mg mL^{-1}) and itraconazole (5 mg mL^{-1}) could be dissolved into specific ILs at relatively high concentrations. These API–IL solutions could then be introduced into water (pH = 7) to provide a stabilizing structure to retain aqueous solubility at high concentrations (Amp B, 0.10 mg mL^{-1}; itraconazole, 0.25 mg mL^{-1}) provided the amount of IL relative to the API was sufficient. Even when the APIs precipitated, they could readily be redissolved or redispersed and retained their original solution stability in all cases where solubility or dispersability was originally obtained. In PBS, SIF, and SGF, Amp B formed stable suspensions at up to 0.25 mg of API per mL of simulated fluid for up to 5 days. Additionally, the API had to be dissolved in the IL before incorporation into water in order to obtain the reported solubilities. Overall the results presented here suggest that with proper knowledge of the structural requirements of the drug molecule and of IL chemistry, nearly any drug can be dissolved and effectively solubilized into water by correctly designing in the correct HLB while maintaining the desired properties of the IL.

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