Electronic Supporting Information

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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Table of Contents

I. Materials and Methods S2
II. Synthesis of IL Precursors S3
III. Synthesis of ILs S3
IV. Physical Properties S7
V. NMR of Dissolved APIs in ILs S8
VI. Solubility in Simulated Fluids S10
I. Materials and Methods

Differential Scanning Calorimetry

All experiments were done on a TA instruments Differential Scanning Calorimeter (DSC) 2920 Modulated DSC, TA Instruments, Inc. (New Castle, DE) cooled with a liquid nitrogen cryostat. The calorimeter was calibrated for temperature and cell constants using indium ($T_m = 156.61 \, ^\circ C; C = 28.71 \, J \, g^{-1}$). Samples were weighed and sealed in aluminum pans (5 – 15 mg) with a hole in the top to allow gases to escape and heated at a rate of 5 °C/min to 100 °C. Following the initial heating cycle the samples were cooled to -100 °C followed by a heating cycle to 100 °C at a rate of 5 °C/min. After each dynamic temperature ramp, a 5 min isotherm was employed to ensure equilibration of the temperature in the cell. The entire cycle was repeated a second time and the values for phase changes were analyzed. Each sample was referenced to an empty aluminum pan.

Thermal Gravimetric Analysis

Thermal experiments for all fatty amine based ILs were conducted with a Mettler-Toledo (Columbus, OH) TGA/DSC 1. The instrument’s internal temperature was calibrated by observing the melting point of Au, Zn, and In. Samples of 2-15 mg were analyzed on a 70 µL alumina pan under a stream of argon. Samples were heated from room temperature to 75 °C at 5 °C/min and with a 30 min isotherm at 75 °C in order to ensure excess volatiles or residual solvents were removed. Following the isotherm, samples were heated to 800 °C at 5 °C/min. Thermal experiments for m-PEG$_{350}$-NH$_2$ and [m-PEG$_{350}$-NH$_3$][Fatty Acid] ILs were conducted with a TA Instruments (New Castle, DE) model 2950 thermogravimetric analyzer (TGA). The instrument’s internal temperature was calibrated by observing the Curie point of Nickel (358.15 °C). In order to investigate the decomposition profile of the ILs, samples of 5-25 mg were analyzed on a platinum pan under a purge of argon and measured via dynamic heating. Samples were heated from room temperature to 75 °C at 5 °C/min and with a 30 min isotherm at 75 °C in order to ensure excess volatiles or residual solvents were removed. Following the isotherm, samples were heated to 800 °C at 5 °C/min. Decompositions temperatures are recorded from both machines as the onset to 5% weight mass loss ($T_{5\% \text{dec}}$).

Viscosity

Viscosity measurements were taken at approximately 37 °C (body temperature) with a Cambridge Viscosity (Medford, MA) Viscometer, VISCOlab 3000. Approximately 1 mL of IL was placed in the sample chamber. The correct sized piston corresponding to the expected viscosity range was added and the measurement was taken. The value for viscosity was not recorded until the error had averaged out to be less than 3%.
II. Synthesis of IL Precursors

Synthesis of Polyethylene Glycol Amine, m-PEG$_{350}$-NH$_2$

CH$_3$-O-PEG$_{350}$-OH (m-PEG$_{350}$-OH) (50 mmol, 17.50 g) was added to a 1000 mL beaker charged with K$_2$CO$_3$ (10.00 g) and stirred by hand for 5 min. Tosyl chloride (75 mmol, 14.30 g) was added piecewise while continuing manual stirring. KOH (250 mmol, 14.08 g) was ground and finally added and stirred until the reaction mixture thickened and turned to a yellow color. The yellow paste was cooled to room temperature by placing the beaker in a cold water bath. 200 mL of water and 200 mL of methylene chloride were added to the reaction. The bilayer was stirred for 10 min and the organic layer was separated, dried over MgSO$_4$, and removed under reduced pressure. m-PEG$_{350}$-OTs was isolated as an orange oil.

m-PEG$_{350}$-OTs (50 mmol) was combined in 200 mL water with NaN$_3$ (250 mmol, 16.25 g) and stirred for 18 h at 80 °C. The solution was cooled to room temperature and extracted with 3 x 150 mL of methylene chloride. The organic layers were combined, dried over MgSO$_4$, and removed under reduced pressure to isolate a pale yellow m-PEG$_{350}$-N$_3$.

m-PEG$_{350}$-N$_3$ (48 mmol, 18.07 g) was combined neat with triphenylphosphine (52.8 mmol, 13.85 g) and stirred at 50 °C for 18 h. 100 mL of ice cold water was combined into the round-bottom flask and stirred in an ice water bath for 30 min. The reaction was filtered and water was evaporated under reduced pressure. The resulting liquid was dried under high vacuum for 1 day. The liquid was further purified by centrifugation to remove excess triphenylphosphine dissolved within the m-PEG$_{350}$-NH$_2$. 8.19 g was purified resulting in a 46.9% yield through three synthetic steps. TGA: $T_{5\text{% }}$ onset = 179 °C. DSC: $T_m$ = 14 °C on heating, $T_{cryst}$ = -2 °C on cooling. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ ppm: 3.52 (m, 22H), 3.44 (t, $J$ = 5.5 Hz, 4H), 3.37 (t, $J$ = 5.8 Hz, 2H), 3.25 (s, 3H), 2.65 (t, $J$ = 5.8 Hz, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ ppm: 73.52 (s), 72.86 (s), 71.78 (s), 70.33 (s), 70.04 (s), 60.71 (s), 58.50 (s), 41.84 (s). IR cm$^{-1}$: 2875 (s), 2362 (s), 2337 (m), 1458 (s), 1350 (s), 1296 (m), 1250 (s), 1198 (s), 1096 (s), 948 (s), 845 (s), 540 (s).

III. Synthesis of ILs

Synthesis of N-butylammonium acetate, [C$_4$NH$_3$][OAc]

Glacial acetic acid (10 mmol, 0.6005 g) was placed in a 20 mL vial. The vial was cooled using an ice water bath to 0 °C while stirring vigorously. N-butylamine (10 mmol, 0.7314 g) was added drop-wise while maintaining the temperature to be 0 °C. The reaction was immediately exothermic and turned a light yellow shade upon finishing the addition. It was stirred overnight remaining in the water bath, but the temperature was allowed to slowly rise to ambient conditions. A yellow viscous oil was observed with no mass loss for essentially a 100% yield. TGA: $T_{5\text{% }}$ onset = 106 °C. DSC: No thermal transitions were observed. $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ ppm: 8.236 (s, 3H, -NH$_3^+$), 2.667 (t, 2H, -CH$_2$-N, $J$ = 7.642 Hz), 1.693 (s, 3H, CH$_3$-COO$^-$), 1.492 (quintet, 2H, -CH$_2$-, $J$ = 7.443 Hz), 1.305 (sextet, 2H, -CH$_2$-, $J$ = 7.584 Hz), 0.864 (t, 3H, CH$_3$-, $J$ = 7.382 Hz).

Synthesis of N-butylammonium olate, [C$_4$NH$_3$][Oleate]

Freshly distilled oleic acid (10 mmol, 2.8246 g) was placed in a 20 mL vial. The vial was cooled using an ice water bath to 0 °C while stirring vigorously. N-butylamine (10 mmol, 0.7314 g) was added drop-wise while maintaining the temperature to be 0 °C. The reaction was
immediately exothermic and turned a bright yellow shade upon finishing the addition. It was stirred overnight remaining in the water bath, but the temperature was allowed to slowly rise to ambient conditions. A yellow viscous oil was observed with no mass loss for essentially a 100% yield. TGA: \( T_{5\% \text{ onset}} = 110 \, ^\circ\text{C}. \) DSC: On heating, \( T_{\text{cryst}} = -32 \, ^\circ\text{C}, T_m = -24 \, ^\circ\text{C}. \) \(^1\)H NMR (360 MHz, DMSO-\(d_6\)) \( \delta \) ppm: 5.322 (t, 2H, -CH=CH-, \( J = 4.777 \, \text{Hz} \)), 4.304 (s, 3H, -NH\(^3\)), 2.619 (t, 2H, -CH\(_2\)-N, \( J = 7.361 \, \text{Hz} \)), 2.011 (m, 5H), 1.429 (m, 4H), 1.291 (m, 20H), 0.868 (m, 6H).

**Synthesis of N-hexylammonium acetate, \([C_6\text{NH}_3]\)[OAc]**

Glacial acetic acid (10 mmol, 0.6005 g) was placed in a 20 mL vial. The vial was cooled using an ice water bath to 0 °C while stirring vigorously. N-hexylamine (10 mmol, 1.012 g) was added drop-wise while maintaining the temperature to be 0 °C. The reaction was immediately exothermic upon finishing the addition. It was stirred overnight remaining in the water bath, but the temperature was allowed to slowly rise to ambient conditions. A clear crystalline solid was observed with no mass loss for essentially a 100% yield. TGA: \( T_{5\% \text{ onset}} = 94 \, ^\circ\text{C}. \) DSC: On heating, \( T_{\text{cryst}} = -18 \, ^\circ\text{C}, T_m = 52 \, ^\circ\text{C}. \) \(^1\)H NMR (360 MHz, DMSO-\(d_6\)) \( \delta \) ppm: 7.800 (s, 3H, -NH\(^3\)), 2.656 (t, 2H, -CH\(_2\)-N, \( J = 7.565 \, \text{Hz} \)), 1.715 (s, 3H, CH\(_3\)-COO\(^-\)), 1.489 (m, 2H), 1.268 (m, 6H), 0.878 (t, 3H, CH\(_3\)-, \( J = 7.098 \, \text{Hz} \)).

**Synthesis of N-octylammonium acetate, \([C_8\text{NH}_3]\)[OAc]**

Glacial acetic acid (10 mmol, 0.6005 g) was placed in a 20 mL vial. The vial was cooled using an ice water bath to 0 °C while stirring vigorously. N-octylamine (10 mmol, 1.292 g) was added drop-wise while maintaining the temperature to be 0 °C. The reaction was immediately exothermic and turned cloudy upon finishing the addition. It was stirred overnight remaining in the water bath, but the temperature was allowed to slowly rise to ambient conditions. A clear crystalline solid was observed with no mass loss for essentially a 100% yield. TGA: \( T_{5\% \text{ onset}} = 117 \, ^\circ\text{C}. \) DSC: No thermal transitions were observed. \(^1\)H NMR (360 MHz, DMSO-\(d_6\)) \( \delta \) ppm: 9.038 (s), 5.324 (t), 5.162 (s), 2.606 (t), 2.033 (m), 1.982 (m), 1.861 (m), 1.440 (m), 1.243 (m), 1.138 (m), 0.866 (m).

**Synthesis of N-octylammonium oleate, \([C_8\text{NH}_3]\)[Oleate]**

Freshly distilled oleic acid (10 mmol, 2.8246 g) was placed in a 20 mL vial. The vial was cooled using an ice water bath to 0 °C while stirring vigorously. N-octylamine (10 mmol, 2.246 g) was added drop-wise while maintaining the temperature to be 0 °C. The reaction was immediately exothermic and turned a bright yellow shade upon finishing the addition. It was stirred overnight remaining in the water bath, but the temperature was allowed to slowly rise to ambient conditions. A yellow viscous oil was observed with no mass loss for essentially a 100% yield. TGA: \( T_{5\% \text{ onset}} = 104 \, ^\circ\text{C}. \) DSC: On cooling, \( T_{\text{cryst}} = -12 \, ^\circ\text{C}, T_m = 48 \, ^\circ\text{C}. \) \(^1\)H NMR (360 MHz, DMSO-\(d_6\)) \( \delta \) ppm: 7.160 (s, 3H, -NH\(^3\)), 2.637 (t, 2H, -CH\(_2\)-N, \( J = 7.493 \, \text{Hz} \)), 1.733 (s, 3H, CH\(_3\)-COO\(^-\)), 1.463 (m, 2H), 1.246 (m, 8H), 0.877 (t, 3H, 6.973 Hz).
to ambient conditions. A orange viscous oil was observed with no mass loss for essentially a 100% yield. TGA: $T_{5\% \text{ onset}} = 112^\circ C$. DSC: No thermal transitions were observed. $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ ppm: 9.038 (s), 5.324 (t), 5.162 (s), 2.606 (t), 2.033 (m), 1.982 (m), 1.861 (m), 1.440 (m), 1.243 (m), 1.138 (m), 0.866 (m).

**Synthesis of m-PEG$_{350}$-ammonium acetate, [m-PEG$_{350}$-NH$_3$][OAc]**

m-PEG$_{350}$-NH$_2$ (m-PEG$_{350}$-NH$_2$, 5 mmol, 1.695 g) was stirred at room temperature in a commercial vial. Glacial acetic acid (5 mmol, 0.30025 g) was added drop-wise to the stirred solution of m-PEG$_{350}$-NH$_2$. The reaction was immediately exothermic and turned a slightly brighter yellow shade upon addition. The reaction was stirred for 24 h to obtain a yellow, viscous oil. The resulting liquid was obtained with no mass loss for essentially a 100% yield. TGA: $T_{5\% \text{ onset}} = <75^\circ C$. DSC: On cooling, $T_{\text{cryst}} = $ -0.4 $^\circ C$; $T_m = 40^\circ C$, 46 $^\circ C$. $^{13}$C NMR (125 MHz, neat with an exterior DMSO-$d_6$ aliquot as seen in Figure S3) $\delta$ ppm: 174.766 (s), 71.571 (2) 70.104 (s), 66.974 (s), 58.047 (s), 38.945 (s), 22.135 (s); $^1$H NMR (500 MHz, neat with an exterior DMSO-$d_6$ aliquot as seen in Figure S3) $\delta$ ppm: 8.776 (s), 3.304 (m), 3.199 (t), 3.024 (s), 2.846 (t), 1.620 (s).

**Synthesis of m-PEG$_{350}$-ammonium butanoate, [m-PEG$_{350}$-NH$_3$][C$_3$COO]**

m-PEG$_{350}$-NH$_2$ (5 mmol, 1.695 g) was stirred at room temperature in a commercial vial. Butanoic Acid (5 mmol, 0.44055 g) was added drop-wise to the stirred solution of m-PEG$_{350}$-NH$_2$. The resulting reaction was immediately exothermic and turned a slightly brighter yellow shade upon addition. The reaction was stirred for 24 h to obtain a yellow, viscous oil. The resulting liquid was obtained with no mass loss for essentially a 100% yield. TGA: $T_{5\% \text{ onset}} = <75^\circ C$. DSC: On cooling $T_{\text{cryst}} = $ -19 $^\circ C$; $T_m = 19^\circ C$. $^{13}$C NMR (125 MHz, neat with an exterior DMSO-$d_6$ aliquot) $\delta$ ppm: 176.830 (s), 71.559 (s), 70.089 (s), 66.939 (s), 58.009 (s), 38.766 (s), 37.368 (s), 18.630 (s), 16.537 (s); $^1$H NMR (500 MHz, neat with an exterior DMSO-$d_6$ aliquot) $\delta$ ppm: 8.033 (s), 3.245 (t), 3.289 (m), 3.181 (t), 3.006 (s), 2.841 (t), 1.869 (t), 1.272 (q), 0.618 (t).

**Synthesis of m-PEG$_{350}$-ammonium hexanoate, [m-PEG$_{350}$-NH$_3$][C$_7$COO]**

m-PEG$_{350}$-NH$_2$ (5 mmol, 1.695 g) was stirred at room temperature in a commercial vial. Hexanoic Acid (5 mmol, 0.5808 g) was added drop-wise to the stirred solution of m-PEG$_{350}$-NH$_2$. The resulting reaction was immediately exothermic and turned a slightly brighter yellow shade upon addition. The reaction was stirred for 24 h to obtain a yellow, viscous oil. The resulting liquid was obtained with no mass loss for essentially a 100% yield. TGA: $T_{5\% \text{ onset}} = <75^\circ C$. DSC: On cooling $T_{\text{cryst}} = $ -9 $^\circ C$; $T_g = 0^\circ C$; $T_m = 18^\circ C$. $^{13}$C NMR (125 MHz, neat with an exterior DMSO-$d_6$ aliquot) $\delta$ ppm: 176.812 (s), 71.586 (s), 70.118 (s), 66.951 (s), 58.024 (s), 39.093 (s), 35.272 (s), 31.356 (s), 24.995 (s), 22.135 (s); $^1$H NMR (500 MHz, neat with an exterior DMSO-$d_6$ aliquot) $\delta$ ppm: 7.711 (s), 3.429 (t), 3.421 (m), 3.186 (t), 3.012 (s), 2.850 (t), 1.889 (t), 1.268 (t), 1.018 (m), 0.608 (t).

**Synthesis of m-PEG$_{350}$-ammonium octanoate, [m-PEG$_{350}$-NH$_3$][C$_7$COO]**

m-PEG$_{350}$-NH$_2$ (5 mmol, 1.695 g) was stirred at room temperature in a commercial vial. Octanoic Acid (5 mmol, 0.72105 g) was added drop-wise to the stirred solution of m-PEG$_{350}$-
NH₂. The resulting reaction was immediately exothermic and turned a slightly brighter yellow shade upon addition. The reaction was stirred for 24 h to obtain a yellow, viscous oil. The resulting liquid was obtained with no mass loss for essentially a 100%. TGA: $T_{5\%\,\text{onset}} = 118$ °C. DSC: On cooling, $T_{crys} = -12$ °C; $T_m = 22$ °C. $^{13}$C NMR (125 MHz, neat with an exterior DMSO-d₆ aliquot) δ ppm: 177.005 (s), 71.567 (s), 70.083 (s), 66.945 (s), 58.022 (s), 39.036 (s), 35.444 (s), 31.574 (s), 29.160 (s), 28.910 (s), 25.378 (s), 22.344 (s); $^1$H NMR (500 MHz, neat with an exterior DMSO-d₆ aliquot) δ ppm: 6.676 (s), 3.418 (t), 3.289 (m), 3.180 (t), 3.005 (s), 2.839 (s), 1.874 (t), 1.254 (m), 0.995 (m), 0.596 (t).

**Synthesis of m-PEG₃₅₀-ammonium decanoate, [m-PEG₃₅₀-NH₃][C₉COO]**

m-PEG₃₅₀-NH₂ (5 mmol, 1.695 g) was stirred at room temperature in a commercial vial. Decanoic Acid (5 mmol, 0.8613 g) was initially heated to its melting point and then added drop-wise to the stirred solution of m-PEG₃₅₀-NH₂. The resulting reaction was immediately exothermic and turned a slightly brighter yellow shade upon addition. The reaction was stirred for 24 h to obtain a yellow, viscous oil. The resulting liquid was obtained with no mass loss for essentially a 100% yield. TGA: $T_{5\%\,\text{onset}} = 130$ °C. DSC: On cooling, $T_{crys} = -12$ °C; $T_m = 20$ °C. $^{13}$C NMR (125 MHz, neat with an exterior DMSO-d₆ aliquot) δ ppm: 176.554 (s), 71.541 (s), 70.058 (s), 58.013 (s), 38.801 (s), 35.050 (s), 31.664 (s), 29.341 (s), 29.260 (s), 29.166 (s), 29.108 (s), 29.108 (s), 25.234 (s), 22.362 (s), 13.655 (s); $^1$H NMR (500 MHz, neat with an exterior DMSO-d₆ aliquot) δ ppm: 6.108 (s), 3.416 (t), 3.286 (m), 3.178 (t), 3.001 (s), 2.858 (t), 1.251 (m), 0.985 (m), 0.589 (t).

**Synthesis of m-PEG₃₅₀-ammonium oleate, [m-PEG₃₅₀-NH₃][Oleate]**

m-PEG₃₅₀-NH₂ (5 mmol, 1.695 g) was stirred at room temperature in a commercial vial. Oleic Acid (5 mmol, 1.4123 g) was added drop-wise to the stirred solution of m-PEG₃₅₀-NH₂. The resulting reaction was immediately exothermic and turned a slightly brighter orange shade upon addition. The reaction was stirred for 24 h to obtain an orange, viscous oil. The resulting liquid was obtained with no mass loss for essentially a 100% yield as the liquid was never transferred out of the original vial. TGA: $T_{5\%\,\text{onset}} = 204$ °C. DSC: On cooling, $T_{crys} = -7$ °C; $T_m = 23$ °C. $^{13}$C NMR (125 MHz, neat with an exterior DMSO-d₆ aliquot) δ ppm: 176.793 (s), 129.435 (s), 129.289 (s), 71.646 (s), 70.023 (s), 58.070 (s), 39.010 (s), 35.368 (s), 31.699 (s), 29.575 (s), 29.518 (s), 29.329 (s), 29.256 (s), 29.128 (s), 29.087 (s), 29.057 (s), 26.956 (s), 25.887 (s), 25.389 (s), 22.415 (s), 13.718 (s); $^1$H NMR (500 MHz, neat with an exterior DMSO-d₆ aliquot) δ ppm: 7.798 (s), 5.037 (dd), 3.423 (t), 3.288 (m), 3.177 (t), 3.001 (s), 2.858 (t), 1.884 (t), 1.251 (m), 0.985 (m), 0.589 (t).
IV. Physical Properties

Table S1. Viscosities of Edible ILs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Viscosity (cP) @ 37 °C</th>
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<tr>
<td>[C₄NH₃][OAc]</td>
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</tr>
<tr>
<td>[C₆NH₃][OAc]</td>
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<tr>
<td>[C₈NH₃][OAc]</td>
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<tr>
<td>[C₄NH₃][Oleate]</td>
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<tr>
<td>[C₈NH₃][Oleate]</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>[m-PEG₃₅₀-NH₃][Oleate]</td>
<td>43.30</td>
</tr>
</tbody>
</table>

⁹Supercooled liquid; bWould not retain supercooled state long enough to complete viscosity test at 37 °C.
V. NMR of Dissolved APIs in ILs

Figure S1. Demonstration of the line broadening and shielding effect visible when Amp B was solubilized in [C₆NH₃][OAc]
Figure S2. Less line broadening apparent in the case of the addition of itraconazole to [m-PEG\textsubscript{350}-NH\textsubscript{3}][OAc].
VI. Solubility in Simulated Fluids

<table>
<thead>
<tr>
<th>[Amp B] in H₂O</th>
<th>[Amp B] in [C₆NH₃][OAc] 5 mg/mL</th>
<th>[Amp B] in [C₆NH₃][OAc] 10 mg/mL</th>
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</thead>
<tbody>
<tr>
<td>Solution Stability</td>
<td>Solution Stability</td>
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<tr>
<td>0.25 mg/mL</td>
<td>5 days(^b)</td>
<td>5 days(^b)</td>
</tr>
</tbody>
</table>

\(^b\): Indicates stability for 5 days.