RSC Advances

RSC Publishing

PAPER

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Cite this: *RSC Advances*, 2013, **3**, 10019

Hydrophobic *vs.* hydrophilic ionic liquid separations strategies in support of continuous pharmaceutical manufacturing†

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Taking advantage of the dramatically different solvent properties of hydrophilic ionic liquids (ILs) when dry *vs.* when wet allows unique separations strategies compared to the use of hydrophobic ionic liquids. This is demonstrated here by comparing the separation of a water insoluble amide intermediate for aliskiren from its reactants, a water insoluble lactone, water soluble 3-amino-2,2-dimethylpropanamide, and the water soluble promoter 2-ethylhexanoic acid, using the hydrophobic ionic liquid 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[C_2mim][NTf_2]$) and the hydrophilic ionic liquid 1-ethyl-3-methylimidazolium acetate ($[C_2mim][OAc]$). Both the water soluble $[C_2mim][OAc]$, when dry, and water insoluble $[C_2mim][NTf_2]$ can dissolve the highly hydrophobic and hydrophilic compounds simultaneously, but the two ILs require different strategies to separate the mixtures of these compounds. Using the hydrophobic $[C_2mim][NTf_2]$, the hydrophobic compounds can be separated from the hydrophilic reactants by extraction and precipitation with water, however, the hydrophobic IL is more difficult to completely remove after the separations. In $[C_2mim][OAc]$, the most hydrophobic starting material can be extracted from the IL phase into ethyl acetate, and then water can be added to precipitate the hydrophobic amide product while at the same time removing the IL from the pharmaceuticals.

Received 5th March 2013,
Accepted 26th April 2013

DOI: 10.1039/c3ra41082j

www.rsc.org/advances

1. Introduction

Manufacturing in the pharmaceutical industry is presently governed by batch production[1,2] which allows quality verification of each batch from each process before further processing.[3] Today, however, it is becoming more difficult for pharmaceutical companies to make profits due to increasing research and development costs and competition from generics manufacturers.[4] In addition, the variety of equipment involved in a batch-based process is not always amenable to scale-up, a growing problem.[3] Fueled by a need to reduce costs and improve efficiencies, companies are considering continuous processing in their short- and long-term strategies. In a continuous manufacturing process, raw materials are injected into an automated system which is capable of carrying out reactions and quality analysis according to predetermined parameters.[5] These quality checks occur throughout the manufacturing process without interruptions. If the quality of the intermediates doesn't meet the standards, the intermediates will be rejected and sent back for reprocessing.

Efficient separations are critical for the continuous manufacturing of pharmaceuticals as the produced drugs can contain impurities, such as starting materials, intermediates, solvents, catalysts, byproducts, *etc*.[6] Ionic liquids (ILs), commonly defined as salts which melt below 100 °C,[7] have gained much attention as new solvent systems since the late 1990s as a result of the unique properties often obtainable with specific examples, such as low volatility, high thermal stability, wide electrochemical windows, *etc*. The study of ILs as solvents has naturally turned to their use in separations. For example, using ILs as mobile phase modifiers has improved liquid chromatography separations,[8,9] metal ions have been extracted from polluted environmental samples using ILs,[10,11] and the extraction of bioactive compounds from natural plants using ILs shows great promise.[12,13]

ILs also have the potential to be utilized in continuous separation processes because of their specific properties, *e.g.*, low volatility, high thermal stability, *etc*. Kim *et al.* reported the separation and recycling of SO_2 from a gaseous mixture using ILs, such as 1-butyl-3-methylimidazolium chloride ($[C_4mim]Cl$).[14] Conventional separation of SO_2 using amine-based absorbents often involves the contamination of SO_2 by

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† Electronic supplementary information (ESI) available: CCDC 934967. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra41082j

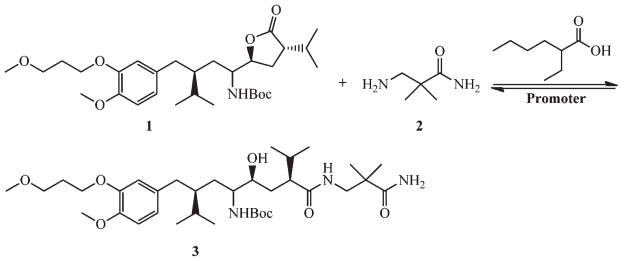
the amine compounds because of the high vapor pressure of these absorbents.[15] The use of ILs in this type of separation can overcome this shortcoming and enable continuous absorption and stripping of SO_2 even at high temperatures, thus enabling a reversible absorption of SO_2 without loss, decomposition, or degradation of the IL solvent.

The continuous cleaning of contaminated soils can be realized using ILs and supercritical CO_2 ($scCO_2$).[16] In this process, the model contaminated component, naphthalene, was extracted with 1-butyl-3-methylimidazolium hexafluorophosphate ($[C_4mim][PF_6]$) and then recovered with $scCO_2$ from the IL phase, which enables the recovery and reuse of the IL. The soil was cleaned near ambient conditions and allowed the continuous processing of $[C_4mim][PF_6]$-contaminant-$scCO_2$.

In liquid–liquid separations using pure ILs reported to date, the vast majority of these have involved the use of hydrophobic ILs which phase separate with water. The main driver for interest in hydrophobic ILs has been the fact that aqueous solutions are the focus of many separations and decontamination studies, *e.g.*, separation of metal ions (Hg^{2+}, Cu^{2+}, Cd^{2+}, Ag^{+}) from aqueous solution,[17] recovery of butanol or hexanol from water,[18] *etc*. Hydrophobic ILs, such as 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[C_4mim][NTf_2]$) show promising prospects in these areas.[19–21]

Nonetheless, the majority of known ILs are water soluble and the number of water insoluble ILs is limited to a few cation/anion combinations.[22] Most of the hydrophobic ILs contain fluorinated anions (*e.g.*, $[PF_6]^-$, $[NTf_2]^-$), which are environmentally non-benign (for example, we have shown that $[PF_6]^-$ can decompose to dangerous HF gas in the presence of water[23]). Surprisingly, little attention has been paid to the use of water soluble ILs for extraction or separation of organic molecules, despite the advantage of being able to rinse away the IL with water. In addition, hydrophilic ILs (*e.g.*, $[C_4mim]Cl$), can form aqueous biphasic systems (ABS) with concentrated solutions of water-structuring salts, such as K_3PO_4 or K_2CO_3.[22] The ability to form salt–salt ABS allows hydrophilic ILs to be used in aqueous separation systems which can be finely tuned by simply changing the concentrations of the ions.[24] This feature of salt–salt ABS provides additional operational diversity to these systems compared to traditional liquid–liquid separations.

Continuous pharmaceutical manufacturing will need to separate a variety of water soluble and water insoluble components, often of close polarity and across a wide range of reaction temperatures. ILs have the advantage of being able to dissolve various kinds of compounds (organic and inorganic, hydrophobic and hydrophilic, polar and non-polar) if the ions are properly chosen. In addition, many ILs can be used at high temperatures because of their low volatility and high thermal stability. Moreover, ILs, either as the additive or co-solvent, can facilitate the isolation and purification of drugs.[25,26] However, in order for ILs to be used for separations in the continuous manufacturing of pharmaceuticals, more information is needed into the range of separations one might accomplish using the unique attributes of ILs.

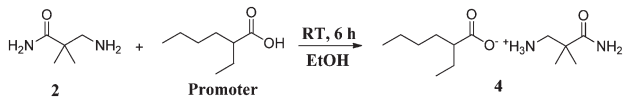


Scheme 1 Synthesis of amide **3** from lactone **1**.

Here, we will compare a prototypical water soluble and a water insoluble IL for the separation of a pharmaceutical intermediate from its starting materials. Amide **3** (Scheme 1, bottom) is an intermediate for the synthesis of aliskiren (Fig. S1, ESI†), the first orally available renin inhibitor approved by the Food and Drug Administration (FDA) for the treatment of hypertension.[27] Scheme 1 shows the common synthetic route for **3**, the ring-opening aminolysis reaction of lactone **1** with 3-amino-2,2-dimethylpropanamide (**2**) in the presence of the promoter, 2-ethylhexanoic acid.[27]

The reaction process in Scheme 1 doesn't proceed to the full conversion of the lactone, which leaves the desired product **3** mixed with the unreacted starting materials.[27] In order to obtain the desired pure amide **3** and recycle the expensive starting material **1**, **1** and **3** have to be efficiently separated from the final reaction mixture. The published separation starts with the addition of ethyl acetate (EtOAc) and H_2O immediately after the reaction to form a biphasic system.[27] The layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a white solid. Amide **3** was then isolated following flash chromatography. These separation procedures are quite complex and not amenable to continuous manufacturing, moreover, the presence of small amounts of water in EtOAc significantly influences the solubility of **3** in EtOAc.

To investigate whether ILs could provide an efficient separation strategy for this system, amenable to continuous manufacturing, two ILs were studied, the hydrophobic 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($[C_2mim][NTf_2]$) and the hydrophilic 1-ethyl-3-methylimidazolium acetate ($[C_2mim][OAc]$). A liquid–liquid extraction and precipitation strategy was explored for $[C_2mim][NTf_2]$-containing system. For $[C_2mim][OAc]$, we chose to combine an antisolvent addition strategy with liquid–liquid extraction based on our experience in the dissolution of the water insoluble cellulose[28–30] and chitin[31] using this IL, and their subsequent regeneration by adding water as an antisolvent. Herein we compare the separation strategies of these two distinct methods.



Scheme 2 Synthesis of **4**.

2. Experimental

2.1 Materials

The pharmaceutical compounds, **1**, **2**, **3**, and the reaction mixture used in this study were obtained from Massachusetts Institute of Technology (MIT) and used without further purification. 2-Ethylhexanoic acid was supplied by Sigma-Aldrich Inc. (St. Louis, MO). The ILs, $[C_2mim][NTf_2]$ and $[C_2mim][OAc]$, were purchased from Iolitec USA (Ionic Liquids Technologies Inc., Tuscaloosa, AL). Deuterated chloroform ($CDCl_3$) and DMSO (DMSO-d_6) were purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA). Deionized (DI) water was obtained from a commercial deionizer (Culligan, Northbrook, IL) with specific resistivity of 17.25 MΩ cm at 25 °C. All other organic solvents, such as ethanol, methanol, n-heptane, ethyl acetate, acetone, chloroform ($CHCl_3$), were obtained from Sigma–Aldrich (Milwaukee, WI) and used as received.

2.2 Synthesis of 3-amino-2,2-dimethyl-3-oxopropan-1-ammonium-2-ethylhexanoate

The reaction of **2** and the promoter 2-ethylhexanoic acid (Scheme 2) can lead to the formation of an ammonium salt, 3-amino-2,2-dimethyl-3-oxopropan-1-ammonium-2-ethylhexanoate (**4**),[27] which could interfere with a continuous flow operation if it crystallizes. To study this salt, equimolar amounts (0.1 mol) of **2** and the promoter were added to 50 mL ethanol, and the mixture was stirred at room temperature (RT) for 6 h. The ethanol solvent was removed by rotary evaporation, and the obtained white solid was dried at 60 °C for 48 h. (IR: 3160, 2958, 2929, 1670, 1536, 1479, 1400, 1226, 1112, 1032 cm^{-1}; melting point: 90.2 °C).

2.3 Solubility of organic solvents and H_2O in ILs

0.5 mL of the IL and 1.0 mL of the organic solvent or H_2O were loaded into a vial, and the mixture was stirred overnight at room temperature. If a clear solution was obtained, the IL and solvent were considered to be miscible with each other. If the solution was turbid, it was left to stand for 1 h to form a biphasic system. Concentration of the organics or water in the IL phase was determined by ^1H NMR based on the proton peak areas.[32]

Solubility was calculated using eqn (1):

$$\text{Solubility (mol/mol solvent)} = \frac{\text{Mole of solute}}{\text{Mole of solvent}} \quad (1)$$

where solvent represents the ionic liquid and solute is the organic solvent or water.

2.4 Solubility measurement of 1, 2, 3, and 4

The solubilities of **1**, **2**, **3**, and **4** in $[C_2mim][OAc]$, $[C_2mim][NTf_2]$, EtOAc, n-heptane, and H_2O were measured. 0.01 g of each compound was added to a vial loaded with 0.5 g solvent, and the mixture was stirred at the specified temperature. If all the added compound was dissolved, additional amounts were added until no more could dissolve and the solvent was saturated. For solubility measurement at room temperature (21 °C), the solution with suspended compound was centrifuged to separate the undissolved particles, and the concentration of the solute in the clear solution was analyzed. The solubilities of **1** and **3** were measured by ultraviolet-visible spectroscopy (UV-Vis) based on the absorbance at 280 nm and a predetermined calibration curve. As **2** and **4** have no UV absorption, their solubilities were determined by ^1H NMR based on the proton peak areas of the solutes and the solvents.[32] Solubility was calculated using eqn (1).

Solubility measurement in $[C_2mim][OAc]$ at 70 °C. Solutions of **1**, **2**, **3**, and **4** in $[C_2mim][OAc]$ became too viscous to stir when the concentrations reached a certain level. Therefore, it was not possible to observe an equilibrium between homogeneous solutions and undissolved solutes in $[C_2mim][OAc]$. Instead, we report the highest concentrations we were able to obtain with each of these solutes until the liquid could no longer be stirred.

Solubility measurement in n-heptane at 70 °C. After n-heptane was saturated by **2**, **3**, or **4**, the solutions were left standing at 70 °C to settle any undissolved particles. The concentration of the solute in the clear solution was analyzed by UV-Vis or ^1H NMR. The maximum solubility of **1** was not determined, as after 0.88 g **1** was added to 0.5 g n-heptane, the solution was still clear. No solubility measurements above this concentration were attempted as at this point we had shown that the solubility of **1** in n-heptane increased significantly when temperature was raised to 70 °C, while the solubilities of the other three compounds did not increase by a measurable amount.

2.5 Partition coefficient measurements

The partition coefficients of **1**, **2**, **3**, and **4** in two biphasic systems, $[C_2mim][OAc]$/EtOAc and $[C_2mim][OAc]$/n-heptane, were determined. 8.5 mg **1**, 29.5 mg **2**, 41.4 mg **3**, or 20.6 mg **4** (corresponding to the amount of each in 100 mg of the standard reaction mixture described below) was added to each biphasic system containing 0.5 mL IL and 0.75 mL organic solvent, and the mixtures were stirred at the specific temperature for 6 h. The concentration of each component in each phase was determined by UV-Vis or ^1H NMR as discussed above. The partition coefficient (K_d) was calculated as the ratio of the molarity of the compound in the organic (upper) phase to its molarity in the IL (lower) phase, as shown in eqn (2):

$$K_d = \frac{\text{Molarity in the organic phase}}{\text{Molarity in the IL phase}} \quad (2)$$

2.6 Preparation of the standard mixture

In the preparation of the standard mixture, conversion of **1** was assumed to be 80% under the optimized reaction conditions: 1 eq. **1**, 5 eq. **2**, and 1 eq. promoter, 120 °C, 50 min (subsequently, conversion of **1** was optimized to be 84%[27]), thus the molar ratio of **1 : 2 : 3 : 4** in the standard mixture will be 0.2 : 3.2 : 0.8 : 1.0. A standard mixture containing **1**, **2**, **3**, and **4** was prepared by mixing each component based on the above molar ratio, and the mixture was melted and stirred at 120 °C for 10 min to make sure that all the components were well mixed.

2.7 Characterization

Crystal structure of 4. Single crystal X-ray diffraction data was collected on a Bruker diffractometer with a PLATFORM 3-circle goniometer and an APEX-2 CCD detector using graphite-monochromated Mo-Kα radiation. A hemisphere of data was collected through a series of omega scans with 0.5° frame widths. The crystal was cooled to −100 °C under a stream of cold nitrogen gas during collection. Unit cell determination, data collection, integration, absorption correction, and scaling were done using the Apex 2 software suite.[33] Space group determination, structure solution, and refinement were done using the SHELXTL software suite.[34]

The structure was solved by direct methods and refined by full matrix least squares refinement against F^2. Non-hydrogen atoms were located from the difference map and refined anisotropically. Hydrogen atoms bonded to strong hydrogen bond donors (N or O) were located from the difference map, and hydrogen atoms bound to carbon were placed in calculated positions. Hydrogen atom positions were allowed to refine freely while hydrogen atom thermal displacement parameters were constrained to ride on the carrier atom. The terminal four-carbon chain of 2-ethylhexanoate was found to be disordered across two conformations. Both parts were able to be fully refined anisotropically with occupancies fixed at a 41 : 59 ratio.

Crystal data. $C_{13}H_{28}N_2O_3$, M = 260.37, monoclinic, space group $P2_1/c$, a = 12.260(1), b = 12.729(1), c = 10.9082(9), β = 110.413(6), $\alpha = \gamma = 90°$, U = 1595.2(2) Å^3, Z = 4, T = 100 K, 18 524 reflections measured, 3288 unique (R_{int} = 0.1059). Final R factors were 0.0675 for observed reflections ($I > 2\sigma$) and 0.1278 for all reflections. Crystallographic information is available free of charge from the Cambridge Crystallographic Data Center (CCDC), deposition number 934967.

NMR. ^{1}H NMR and ^{13}C NMR spectra were analyzed using a Bruker Avance 500 MHz NMR spectrometer (Karlsruhe, Germany), 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. NMR spectra of pure **1**, **2**, **3**, **4**, [C_2mim][OAc], and [C_2mim][NTf_2] were collected using $CDCl_3$ as the solvent (although the solubility of [C_2mim][NTf_2] in $CHCl_3$ is limited, in order to compare the spectra, ^{1}H NMR of this IL was collected using a saturated [C_2mim][NTf_2]/$CDCl_3$ solution). Samples for solubility determination containing **2** or **4**/[C_2mim][NTf_2] were dissolved in DMSO-d_6 for analysis, while saturated solutions of **2** or **4**/[C_2mim][OAc], **2** or **4**/EtOAc, and **2** or **4**/n-heptane, were analyzed using $CDCl_3$ as the solvent.

^{19}F NMR spectrum was obtained on a Bruker Avance 360 MHz NMR spectrometer (Karlsruhe, Germany), using $CDCl_3$ as the solvent. No reference standard compound, *e.g.*, $CFCl_3$, was used as ^{19}F NMR was only used to confirm the presence of F.

Mass spectrum. High-resolution mass spectra (HRMS) of the regenerated **3** were recorded on a Waters AutoSpec-Ultima™ NT mass spectrometer (Milford, MA) operating in electronic ionization mode (70 eV).

FT-IR. Pure **1**, **2**, **3**, the synthesized **4**, and the regenerated **1** and **3** were characterized using neat samples by FT-IR using a Perkin–Elmer Spectrum 100 FT-IR spectrometer (Waltham, MA) with 4 scans at 2 cm^{-1} resolution.

Differential scanning calorimetry (DSC). The melting point of **4** was measured by DSC using a DSC 2920 Modulated DSC, TA Instruments, Inc. (New Castle, DE). Data were collected in nitrogen over a temperature range from room temperature to 120 °C with heating at a rate of 5 °C min^{-1} using a sample of 5 mg in an aluminum sample pan.

UV-Vis. Solubilities of **1** and **3** were determined by dissolving certain amounts of saturated **1** or **3**/solvent solution in ethanol and analyzed with a Cary 3C UV-Vis spectrophotometer (Varian Instruments, Palo Alto, CA). Concentrations were calculated based on the absorbance at 280 nm. Calibration curves for **1** and **3** were obtained using stock solutions with concentrations ranging from 0.03 × 10^{-3} mol L^{-1} to 0.30 × 10^{-3} mol L^{-1}.

3. Results and discussion

The reaction in Scheme 1 has been optimized to give an 84% conversion of the lactone under the reaction conditions: 1 eq. **1**, 5 eq. **2**, and 1 eq. promoter, 120 °C, 50 min,[27] with a 4 fold excess of **2** which acts as reactant and solvent. Byproduct formation was observed after 30 min.[27] In addition, reaction (Scheme 2) between **2** and the promoter can lead to the formation of a crystalline ammonium salt (**4**), and the crystal structure of **4** was determined (Fig. S2, ESI†; also see ESI† for crystal structure description).

The reaction in Scheme 1 was optimized at 120 °C. Since this is below the onset decomposition temperatures (150 °C for [C_2mim][OAc],[35] 400 °C for [C_2mim][NTf_2][36]) of the selected ILs, we had the option of conducting the separation at the reaction temperature. This is a relatively unexplored area of IL separations, but one which highlights the advantage of using a nonvolatile and thermally stable IL compared to low boiling volatile organic solvents, beyond the ability of ILs to dissolve compounds with such different polarities.

The initial separations we studied used a standard mixture containing both the product and remaining reactants. Utilizing the optimized conditions for separations developed with the standard mixture, studies were then conducted with the actual reaction mixture, which contains the product, reactants, and any byproducts.

The two ILs chosen have quite different miscibilities with water and organic solvents (Table S1, ESI†), despite sharing a common cation. They strongly differ in each anion's interactions, particularly hydrogen bond basicity. The acetate anion

in [C_2mim][OAc] is strongly basic and a very good hydrogen bond acceptor,[37] and thus this IL is water miscible. The bis(trifluoromethylsulfonyl)imide anion in [C_2mim][NTf_2] has very low hydrogen bonding acceptor ability and is generally weakly interacting, resulting in very low water solubility.

In the absence of water, the ions in [C_2mim][OAc] interact strongly with each other in contrast to [C_2mim][NTf_2]. We have shown that reaction of [C_2mim][OAc] with sulfur or selenium at room temperature leads to the corresponding imidazole-2-chalcogenones,[38] while bubbling CO_2 through this IL at room temperature and atmospheric pressure leads to crystallization of a neutral imidazolium carboxylate ([C_2mim^+–COO^-]) cocrystallized with a [C_2mim]$^+$ cation and acetic acid/acetate hydrogen bonded anion.[39] The acetate anion forms strong hydrogen bonds with the acidic proton of the imidazolium ring in [C_2mim][OAc][40] due to its strong hydrogen bond basicity, and we have suggested that some carbene exists in this pure IL.[39] However, [C_2mim][OAc] is miscible with water, and when water solvates the acetate anion, the solvent properties are completely changed.

In the absence of water, the [C_2mim]$^+$ cation of [C_2mim][OAc] is so strongly interacting with the basic acetate that the weaker hydrogen bond acceptor EtOAc cannot compete for hydrogen bonding with the imidazolium hydrogen. Thus, only 0.18 mole EtOAc is soluble in one mole of [C_2mim][OAc] (Table S1, ESI†).

By contrast, the interactions between the cations and anions of [C_2mim][NTf_2] are weak.[41] The [NTf_2]$^-$ anion is charge diffuse and has very low hydrogen bond basicity.[42] EtOAc is totally miscible with this IL, presumably by accepting weak hydrogen bonds from the cation. By contrast, water is immiscible with [C_2mim][NTf_2], with a water solubility of 0.45 mol/mol IL (*ca.* 2 wt%).

Nonpolar organics such as n-heptane are immiscible with both ILs. Taken together, these miscibility studies suggest several biphasic systems for exploration, including [C_2mim][OAc]/EtOAc, [C_2mim][OAc]/n-heptane, [C_2mim][NTf_2]/n-heptane, and [C_2mim][NTf_2]/H_2O. Here we will explore these systems for the separations of **1**, **2**, **3**, and **4**.

The solubilities of **1**, **2**, **3**, and **4** in the two ILs and three selected solvents were determined (Table 1). **1** and **3** are water insoluble, while **2** and **4** are water soluble. At room temperature (RT), **2** and **4** readily dissolved in [C_2mim][OAc], and their solubilities were much higher than that of **1** or **3**. When the temperature was increased to 70 °C, the solubilities of all four compounds in [C_2mim][OAc] increased significantly, suggesting that the entire reaction mixture could be dissolved in this IL at the reaction temperature (120 °C).

[C_2mim][NTf_2] can dissolve **2** to some extent, while the solubilities of **1**, **3**, and **4** in [C_2mim][NTf_2] are quite limited. The solubility of **1** in EtOAc is much higher than that of **2**, **3**, or **4** at RT, and in n-heptane, the solubility of **1** increased from 0.0016 mol/mol at RT to more than 0.32 mol/mol at 70 °C. Interestingly, no obvious increase in solubilities for **2**, **3**, or **4** in n-heptane was observed when the temperature was raised.

Table 1 Solubilities of **1**, **2**, **3**, and **4** in the investigated solvents

		Solubility (mol per mol solvent)			
Solvent	Temperature	**1**	**2**	**3**	**4**
[C_2mim][OAc]	RT	0.013	0.63	0.045	0.31
	70 °C	>0.27[a]	>1.25[a]	>0.18[a]	>0.56[a]
[C_2mim][NTf_2]	RT	0.05	0.19	0.0002	0.004
EtOAc	RT	0.107	0.031	0.002	0.005
n-Heptane	RT	0.0016	0.0009	0.0001	0.0004
	70 °C	>0.32	0.003	0.0002	0.002
H_2O	RT	0	0.37	0	0.22

[a] Solubilities in [C_2mim][OAc] at 70 °C were based on the amounts of **1**, **2**, **3**, and **4** added to the IL until the solutions were too viscous to stir.

Based on the solubility data, we initially decided to use the traditional approach of an IL/water biphasic system to separate the standard mixture since **2** and **4** were used together and water soluble, and thus might be obtained by extraction with water followed by evaporation. The separation procedure using biphasic [C_2mim][NTf_2]/H_2O is shown in Fig. 1.

A 200 mg portion of the standard mixture of all four compounds was added to 1.0 mL [C_2mim][NTf_2] at 120 °C. All the components dissolved in less than 5 min, resulting in a homogeneous clear solution, which remained clear after cooling to room temperature. Then 1.0 mL water was added to this solution and stirred, upon which a white suspension was formed in the bottom IL phase. The top water phase was separated from the bottom layer by a pipette, and H_2O was evaporated at room temperature to get A, which contained **2**, **4**, and [C_2mim]$^+$, as shown by ^{1}H NMR (Fig. S3, ESI†). The presence of the [NTf_2]$^-$ anion in A was confirmed by ^{19}F NMR (Fig. S4, ESI†).

The precipitated solid in the bottom layer was separated by filtration and dried in the oven. After drying, the solid was still wet, suggesting the presence of IL. ^{1}H NMR analysis in $CDCl_3$

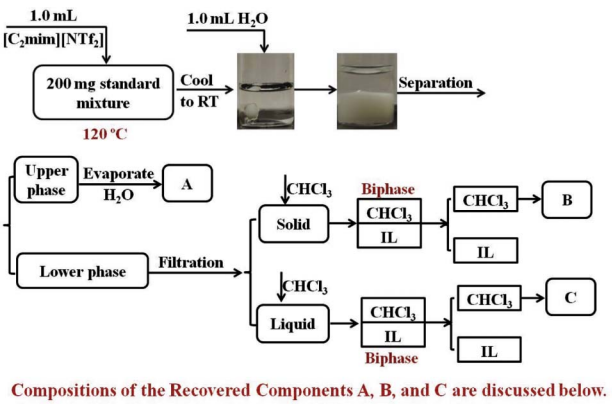


Fig. 1 Procedure for separation of the standard mixture using [C_2mim][NTf_2]/H_2O.

Table 2 Partition coefficients of **1**, **2**, **3**, **4** in biphasic systems

	[C_2mim][OAc]/EtOAc (RT)			[C_2mim][OAc]/n-heptane (70 °C)[a]		
Compound	Molarity in [C_2mim][OAc] (mol L^{-1})	Molarity in EtOAc (mol L^{-1})	Partition coefficient	Molarity in [C_2mim][OAc] (mol L^{-1})	Molarity in n-heptane (mol L^{-1})	Partition coefficient
1	0.0022	0.0198	9	0.0151	0.0099	0.6560
2	0.390	0.0011	0.0028	0.339	0	0
3	0.101	0.0018	0.0178	0.138	0.0011	0.0080
4	0.120	0.0010	0.0083	0.148	0	0

[a] This was carried out at 70 °C because of the significant increase of solubility of **1** in n-heptane at 70 °C.

(Fig. S5, ESI† the bottom spectrum) shows that the main component of this wet solid was **3**, but peaks of [C_2mim][NTf_2] were also detected. This wet solid was then dissolved in $CHCl_3$, and a biphase was formed, with the IL at the bottom. (The amount of IL coated on **3** was sufficient to form a biphase with $CHCl_3$, partially because [C_2mim][NTf_2] is able to dissolve a large amount of $CHCl_3$ without fully mixing (Table S1, ESI†), which would increase the volume of the IL containing phase). The top $CHCl_3$ layer was separated, and $CHCl_3$ was evaporated at RT to obtain B (mainly **3**). However, ^{1}H NMR (the green spectrum in Fig. S5, ESI†) shows that the regenerated **3** washed by $CHCl_3$ still contains a minor amount of [C_2mim][NTf_2], which is difficult to completely remove because of the measurable (0.01 mol/mol $CHCl_3$) solubility of this IL in $CHCl_3$.

Since we proved that **2** and **4** mainly existed in the water phase, and **3** precipitated with the addition of water, **1** should remain in the [C_2mim][NTf_2] phase. After filtration of the precipitated solid, $CHCl_3$ was added to the IL solution to extract the remaining compound. The top $CHCl_3$ phase was separated from the IL phase, and after evaporating $CHCl_3$, C was obtained. ^{1}H NMR spectra (Fig. S6, ESI†) showed that C contains mainly **1**, but again a minor amount of [C_2mim][NTf_2] was detected.

Overall the results suggest that using the hydrophobic IL, **1** or **3** cannot be obtained with high purity as it is difficult to completely remove the hydrophobic IL. However, removing a water soluble IL from the hydrophobic **1** and **3** should be relative easy by washing the final compounds with water. We therefore turned our attention to the water soluble [C_2mim][OAc] for further study.

To explore the use of the water miscible IL in combination with EtOAc, n-heptane, and water, partition coefficients for each compound were measured (Table 2). The results indicated that for the [C_2mim][OAc]/EtOAc system at RT, the partition coefficient of the most hydrophobic **1** between the organic layer and the IL phase is 9, while, those of **2**, **3**, and **4** are all well below 1. Thus, EtOAc could theoretically extract **1** from the mixture/[C_2mim][OAc] solution, while leaving the other three compounds in the IL. Partition coefficients of the compounds for the [C_2mim][OAc]/n-heptane system suggested that n-heptane would not be able to extract any of the pharmaceuticals from [C_2mim][OAc], and this system was not considered further. All subsequent studies reported here utilized the [C_2mim][OAc]/EtOAc system for the separation of the pharmaceutical compounds.

The separation procedure investigated using [C_2mim][OAc]/EtOAc is shown in Fig. 2. A 200 mg portion of the standard mixture of **1**, **2**, **3**, and **4** readily dissolved in 1.0 mL of [C_2mim][OAc] at 120 °C. After cooling to RT, the solution was homogeneous and clear, and 1.5 mL EtOAc was then added to the solution. The whole mixture was stirred at RT for 6 h, and a biphasic system was formed upon standing for 1 h.

Based on the partition coefficients, the top layer was expected to be **1**/EtOAc solution, and the bottom phase was expected to contain **2**, **3**, **4**, and the IL. To ensure that all of **1** was extracted, the two phases were separated using a pipette and another 1.5 mL EtOAc was added to the [C_2mim][OAc] solution for further extraction, followed by separation. The EtOAc solutions were combined and EtOAc was evaporated at RT, leaving **1**, which was washed with water to remove [C_2mim][OAc].

Water was added to the lower IL phase to precipitate **3**, which was separated by filtration and then washed twice with water. The obtained **1** and **3** were dried overnight in an oven at 70 °C.

The regenerated **1** and **3** were analyzed by ^{1}H NMR, ^{13}C NMR, FT-IR, and high resolution mass spectroscopy. Comparison of the ^{1}H NMR spectrum of recovered **1** with those of pure **1** and **3** (Fig. S7, ESI†) shows that the separated **1**

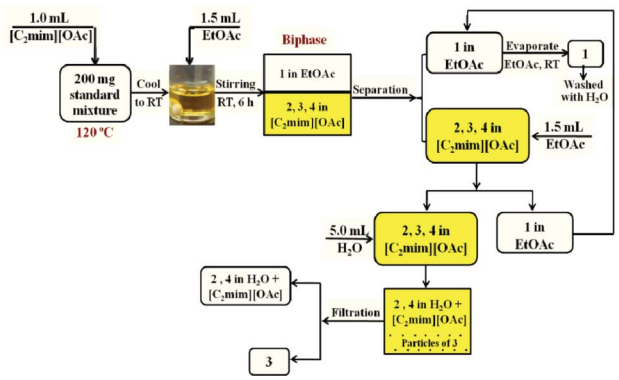


Fig. 2 Procedure for separation of the standard mixture using [C_2mim][OAc]/EtOAc.

contains a minor amount of **3**. ^{1}H NMR and ^{13}C NMR spectra (Fig. S8 and S9, ESI†) of the regenerated **3** match the spectra of pure **3**, with no evidence of **1**. No IL was detected in **1** or **3**, indicating that water could completely remove [C_2mim][OAc] from the pharmaceuticals. FT-IR data (Fig. S10, ESI†) illustrate that the lactone peak of **1** at around 1773 cm^{-1} is not present in the spectrum of regenerated **3**, indicating that the separated **3** does not contain **1**.

In order to further confirm the purity of the regenerated **3**, we also analyzed it by high resolution mass spectrometry (HRMS). The mass spectrum shows a peak with high intensity at *m*/*z* 651.4435, which is within 5 ppm error compared to the expected molecular weight (651.4459) of **3**. None of the HRMS peaks of the regenerated **3** are attributable to the presence of **1**. Thus, the [C_2mim][OAc]/EtOAc biphasic system could efficiently separate **1** and **3** from the standard mixture, and the separated **3** has high purity.

1 and **3** can be successfully separated from the standard mixture, however, **2** and **4** would be lost in the water/IL mixture. If there is a need to recover all the starting materials, **2** and **4** could be recovered by washing the standard mixture with water. The mixture/water solution was stirred at room temperature for 2 h, and the undissolved particles (mixture of **1** and **3**) were filtered and dried, which can be separated using the procedure in Fig. 2. Water in the filtrate was evaporated at RT, leaving **2** and **4**, which was confirmed by ^{1}H NMR (Fig. S11, ESI†).

[C_2mim][OAc]/EtOAc, with high efficiency in separation of the standard mixture, was also used to separate **1**, **2**, **3**, and **4** from the actual reaction mixture, which contains the product, reactants, as well as some byproducts. The separation procedure followed what is described in Fig. 2. Briefly, 200 mg of the reaction mixture was added to a vial containing 1.0 mL [C_2mim][OAc], and it was found that the reaction mixture could be dissolved in this IL at 120 °C in a few minutes. After cooling to RT, 1.5 mL EtOAc was added to the homogeneous and clear solution. The whole mixture was stirred at RT for 6 h. The mixture phase separated upon standing. The top EtOAc phase was separated, and the IL phase was extracted with another 1.5 mL EtOAc, followed by separation. The EtOAc solutions were combined and EtOAc was evaporated at RT, leaving **1**, which was washed with water to remove the IL. Water was added to the [C_2mim][OAc] phase to precipitate **3**, which was separated by filtration and then washed twice with water. The obtained **1** and **3** were dried overnight in an oven at 70 °C. **3** was further washed with n-heptane as analysis indicated that **3** obtained in the above procedure contained some impurities (n-heptane was chosen here because it is a solvent widely used in the pharmaceutical area.[43]). Characterization of the separated **1** (Fig. S12, ESI†) and **3** (Fig. S13–S15, ESI†) indicated that the regenerated **1** contains a minor amount of **3**, while the regenerated **3** has high purity. Again, **2** and **4** (Fig. S16, ESI†) can be recovered by washing the reaction mixture with water, followed by solvent evaporation.

The differences in results for the standard mixture *vs.* the actual reaction mixture appear to arise from the presence of residual byproducts. Any of these residual byproducts that are carried through with the isolation of **3** from antisolvent addition to [C_2mim][OAc] solution could be removed by further washing the recovered **3** with n-heptane.

4. Conclusions

We utilized the dramatically different solvent properties of the hydrophilic ionic liquid [C_2mim][OAc] when dry *vs.* when wet to separate hydrophobic pharmaceuticals with similar structures and compared it to the use of the hydrophobic IL [C_2mim][NTf_2]. Both ILs studied here can be used at the reaction temperature (120 °C), with no volatilization or emission of toxic chemicals, because of their low volatility and high thermal stability. However, the water solubility of [C_2mim][OAc] provides a ready mechanism (washing with water) to purify the final separated compounds. When dry, [C_2mim][OAc] can dissolve highly hydrophobic and hydrophilic compounds simultaneously, and the most hydrophobic compound can be extracted from the IL phase into EtOAc. Water can then be used as an antisolvent to change the solvent property and precipitate any remaining hydrophobic solutes, while at the same time removing the IL from the pharmaceutical product.

The hydrophobic [C_2mim][NTf_2] can also be used to separate the pharmaceuticals by using a biphasic system with water, however, this IL is more difficult to be completely removed from the pharmaceutical compounds. Therefore, for this specific pharmaceutical separation the hydrophilic IL is superior to the hydrophobic IL. Undoubtedly there will be other separations where the hydrophobic IL strategy will be advantageous (*e.g.*, the formation of a biphasic system with H_2O, easy recycling of the IL, *etc.*), but the larger range of hydrophilic ILs should be added to the separations scientist's tool box.

Acknowledgements

We thank the Novartis-Massachusetts Institute of Technology (MIT) Center for Continuous Manufacturing (CCM) for financial support.

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