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Solubilities of Pharmaceutical Compounds in Ionic Liquids

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ABSTRACT: The solubilities of paracetamol and ibuprofen were determined in two different ionic liquids at temperatures of 298.15 K, 308.15 K, 318.15 K, 328.15 K, and 338.15 K. The ionic liquids selected were 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] and 1-hexyl-3-methylimidazolium hexafluorophosphate [HMIM][PF_6]. In addition, solubility data for paracetamol and ibuprofen in water are reported at the same temperatures extending the data commonly reported in pharmaceutical reference texts. For all solvents the concentration of drug in solution was determined by UV spectrophotometry.

INTRODUCTION

Unlike conventional solvents, ionic liquids (ILs) are composed entirely of ions rather than molecules, and the term is generally used to describe ionic substances that have a melting point below 373.15 K. The low melting point of ILs is achieved by having a large unsymmetrical cation which results in low lattice energies. They are generally composed of an organic cation and either an organic or inorganic anion.

The physicochemical properties of ILs depend on both the nature and the size of the cation and anion, and there is an enormous range of potential combinations of cation and anion that could be synthesized to produce an IL. For example, it has been reported that there are at least a million potential binary ILs and a possible 10^{18} ternary combinations of cation and anion;[1] this vast array of possibilities provides an opportunity to synthesize ILs for specific applications. Because of their ability to dissolve a wide range of organic and inorganic compounds, their relative nonvolatility, nonflammability, and thermal stability, ILs have been widely used as "green" solvents in chemical synthesis and separations[2] and as solvent media for homogeneous catalysis.[3]

An emerging research field of interest is the use of ILs in pharmaceutical applications. Their potential as pharmaceutical solvents to dissolve poorly soluble active pharmaceutical ingredients (APIs) has been investigated in a range of ILs.[4] Other research has investigated their use as drug delivery vehicles; for example, the use of ILs to form stable micro-emulsions as a vehicle to dissolve and deliver poorly soluble drugs transdermally has been reported.[5,6] The use of imidazoluium-based ILs as drug reservoirs for controlled release has also been reported.[7] Other researchers have taken a further step in developing ILs that are themselves the APIs.[8−10]

The crystallization of APIs from conventional organic solvents can yield undesirable crystal habits with poor physical properties that cause downstream processing problems. It has been proposed that ILs could be used as a novel media to carry out controlled crystallizations.[11] To date some crystallization work has been published such as the crystallization of lysozyme and thaumatin in the ILs [BMIM][PF_6], [BMIM][BF_4], and [BMIM][Cl] using a vapor diffusion method.[12,13] Also the organic compound methyl-(*Z*)-α-acetamido cinnamate (MAAC) was crystallized from the IL 1-butyl-3-methylimidazolium tetrafluoroborate ([$BMIM^+$][BF_4]) using supercritical carbon dioxide as an antisolvent.[14]

To develop well-understood controlled crystallizations by thermal methods from ILs, fundamental solubility data are required. The purpose of this paper is to show solubility data for ibuprofen and paracetamol in ILs as a precursor to evaluating the application of using ILs to influence crystallization habits of organic materials and produce, for example, novel drug particles. Paracetamol and ibuprofen were chosen as model compounds for the study. These two common pharmaceutical drugs were selected as they are from different classes of the Biopharmaceutical Classification System (BCS);[15] paracetamol is a class III compound[16] (low permeability in vivo, high aqueous solubility), whereas ibuprofen is a class II compound[17] (high in vivo permeability, low aqueous solubility).

The ILs selected were 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] and 1-hexyl-3-methylimidazolium hexafluorophosphate [HMIM][PF_6]. These ILs have been well-characterized in the literature and are known to be good solvents for a wide range of organic and inorganic compounds. The toxicity of these ILs and their degradation products has been documented in the literature; however, recently published data[7] have demonstrated that they were largely nontoxic toward caco-2 cells. Other potentially hazardous chemicals are routinely used during the manufacturing of APIs so this alone should not preclude their use as pharmaceutical solvents.

The solubilities of ibuprofen and paracetamol in 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] and 1-hexyl-3-methylimidazoliumhexafluoro phosphate [HMIM][PF_6] are presented at temperatures of 298.15 K, 308.15 K, 318.15 K, 328.15 K, and 338.15 K. In addition, the solubilities of ibuprofen and paracetamol are reported in water at 298.15 K, 308.15 K, 318.15 K, 328.153 K, and 338.15 K, extending the data reported in pharmaceutical references. The existing literature reports aqueous solubility data for paracetamol between (268.15 and 310.15) K[18−20] and at 373.15 K.[21] For ibuprofen, solubilities

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Table 1. Solubility of Ibuprofen in [BMIM][PF_6] from T = (298.15 to 338.15) K, Where the Final Calculated Solubility Is the Overall Mean from Three Independent Experiments ± the Standard Error of the Mean

	1		2		3			
		S		S		S		$\Sigma(\bar{x}/n)S$
	abs	mg·mL^{-1}	abs	mg·mL^{-1}	abs	mg·mL^{-1}	$\Sigma_{abs}(\bar{x}/n)$	mg·mL^{-1}
				298.15 K				
	0.6984	12.036	0.7225	12.496	0.6996	12.059		
	0.6961	11.992	0.7209	12.464	0.6969	12.006		
	0.6979	12.026	0.7232	12.509	0.6961	11.992		
$\bar{x}$	0.6975	12.018	0.7222	12.490	0.6976	12.019	0.706 ± 0.014	12.18 ± 0.27
				308.15 K				
	1.1586	20.816	1.1196	20.072	1.1111	19.910		
	1.1618	20.877	1.1184	20.049	1.1116	19.919		
	1.1625	20.890	1.1230	20.137	1.1106	19.900		
$\bar{x}$	1.1610	20.861	1.1203	20.086	1.1111	19.910	1.131 ± 0.027	20.27 ± 0.48
				318.15 K				
	1.6351	29.908	1.7479	32.060	1.7723	32.525		
	1.6445	30.087	1.7387	31.884	1.7692	32.466		
	1.6518	30.226	1.7424	31.955	1.7780	32.634		
$\bar{x}$	1.6438	30.074	1.7430	31.966	1.7732	32.542	1.720 ± 0.068	31.53 ± 1.29
				328.15 K				
	2.6332	35.721	2.6530	36.001	2.6016	35.272		
	2.7533	37.424	2.6328	35.715	2.7151	36.882		
	2.7451	37.308	2.7561	37.464	2.6701	36.244		
$\bar{x}$	2.7105	36.817	2.6806	36.393	2.6623	36.133	2.685 ± 0.024	36.45 ± 0.35
				338.15 K				
	2.9031	57.125	2.7834	54.673	2.8436	55.907		
	2.8040	55.095	2.8825	56.703	2.9839	58.781		
	2.9421	57.924	2.9774	58.647	2.8674	56.394		
$\bar{x}$	2.8831	56.715	2.8811	56.675	2.8983	57.027	2.888 ± 0.009	56.81 ± 0.19

are currently reported in aqueous systems between (293.15 and 313.15) K.[17,22−24]

EXPERIMENTAL SECTION

Materials. 1-Butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6] (99 %), lot: 99/871, and 1-hexyl-3-methylimidazolium hexafluorophosphate [HMIM][PF_6] (98 %), lot: 99/774, were supplied from Merck. Ibuprofen (USP grade), lot: 045K1124, was supplied by Sigma-Aldrich, UK. Paracetamol (99 %) was supplied by Merck, UK. Methanol, high-performance liquid chromatography (HPLC) grade, batch: 0610514, and water, Chromasolv Plus HPLC grade, batch: 0623453, were supplied by Fisher Scientific. All chemicals were used without further purification.

Methods. An excess of a compound was added to approximately 5 mL of IL or water in a sealed glass vial. The vial was loaded into the heater block of a ReactArray unit (AnaChem, UK). The sample was held at the desired temperature for > 24 h under agitation (magnetic flea at 900 rpm) to ensure that the saturation solubility was reached. The temperature of the block was measured using an independent, calibrated type K thermocouple (± 0.1 K) to ensure that the sample was held at the desired temperature. The solution was stirred until saturation of the drug in solution was achieved, which was shown by analyzing the amount of solute dissolved by UV over time. Saturation was found to be reached after 22 h, and consequently all samples were left for at least 24 h.

At each temperature point an aliquot of the saturated solution was removed using an oven-heated (5 °C above sample temperature) plastic syringe (2.5 mL syringe) fitted with a 0.5 mL PTFE filter (Whatman filter, 0.4 μm filter). The heated syringe was necessary to avoid precipitation of the solute due to temperature fluctuation during sampling. The sample was then diluted with 2.5 mL methanol and the drug content determined by UV spectrophotometry using a diode array spectrophotometer (HP 8452A) against a standard curve for the compound in solution (for all curves $R^2 > 0.996$). Where necessary, further dilution was carried out to ensure that the measured absorbance was within the standard curve. The volume of IL and methanol or water was determined from the graduated scale of the syringe (± 0.1 mL) and was used as the volume in the solubility determination. For paracetamol solubility studies, data were obtained at λ_{max} = 250 nm in [BMIM][PF_6] and [HMIM][PF_6], and λ_{max} = 245 nm in water. For ibuprofen, data were obtained at λ_{max} = 264 nm for [BMIM][PF_6] and [HMIM][PF_6] and λ_{max} = 222 nm for water. Three independent samples were analyzed for each temperature point, and each sample was measured three

Table 2. Solubility of Paracetamol in [BMIM][PF_6] from (298.15 to 338.15) K, Where the Solubility Is the Overall Mean from Three Independent Experiments ± the Standard Error of the Mean

temperature		$\Sigma(\bar{x}/n)S$
K	$\Sigma_{abs}(\bar{x}/n)$	mg·mL^{-1}
298.15	0.579 ± 0.011	6.95 ± 0.14
308.15	0.829 ± 0.059	10.05 ± 0.73
318.15	0.907 ± 0.102	11.01 ± 1.26
328.15	1.282 ± 0.009	15.67 ± 0.11
338.15	1.880 ± 0.018	23.09 ± 0.23

Table 3. Solubility of Ibuprofen in [HMIM][PF_6] from T = (298.15 to 338.15) K, Where the Solubility Is the Overall Mean from Three Independent Experiments ± the Standard Error of the Mean

temperature		$\Sigma(\bar{x}/n)S$
K	$\Sigma_{abs}(\bar{x}/n)$	mg·mL^{-1}
298.15	1.254 ± 0.095	26.38 ± 2.08
308.15	1.749 ± 0.113	37.20 ± 2.47
318.15	2.139 ± 0.113	50.76 ± 2.67
328.15[a]	2.005 ± 0.033	65.88 ± 1.08
338.15[a]	1.371 ± 0.048	120.41 ± 4.15

[a] The absorbance values are out of trend for (328.15 and 338.15) K due to additional dilution of the samples.

Table 4. Solubility of Paracetamol in [HMIM][PF_6] from T = (298.15 to 338.15) K, Where the Solubility Is the Overall Mean from Three Independent Experiments ± the Standard Error of the Mean

temperature		$\Sigma(\bar{x}/n)S$
K	$\Sigma_{abs}(\bar{x}/n)$	mg·mL^{-1}
298.15	0.991 ± 0.085	13.21 ± 1.17
308.15	1.138 ± 0.032	15.22 ± 0.44
318.15	1.547 ± 0.100	20.86 ± 1.38
328.15	1.931 ± 0.048	26.13 ± 0.67
338.15	2.242 ± 0.223	30.40 ± 3.06

times. The temperature−solubility profiles were then determined for ibuprofen and paracetamol in [BMIM][PF_6], [HMIM][PF_6], and water.

RESULTS AND DISCUSSION

Solubility data for ibuprofen and paracetamol in [BMIM][PF_6], [HMIM][PF_6] and water were determined between (298.15 to 338.15) K at 10 K increments. The data obtained are shown in Tables 1 to 6 where both the absorbance (abs) values obtained from the UV spectrophotometer and the corresponding solubility (S) data in mg of solute per mL of IL or water are given. The numbers in Table 1 are representative of the raw data obtained from the experimental procedure, while Tables 2 to 6 present the data in a concise format. For each condition the overall mean from three independent experiments plus or minus the standard

Table 5. Solubility of Ibuprofen in Water from T = (298.15 to 338.15) K, Where the Solubility Is the Overall Mean from Three Independent Experiments ± the Standard Error of the Mean

temperature		$\Sigma(\bar{x}/n)S$
K	$\Sigma_{abs}(\bar{x}/n)$	mg·mL^{-1}
298.15	0.213 ± 0.008	0.124 ± 0.004
308.15	0.313 ± 0.036	0.179 ± 0.020
318.15	0.489 ± 0.140	0.276 ± 0.077
328.15	0.669 ± 0.126	0.376 ± 0.070
338.15	0.935 ± 0.148	0.523 ± 0.082

Table 6. Solubility of Paracetamol in Water from T = (298.15 to 338.15) K, Where the Solubility Is the Overall Mean from Three Independent Experiments ± the Standard Error of the Mean

temperature		$\Sigma(\bar{x}/n)S$
K	$\Sigma_{abs}(\bar{x}/n)$	mg·mL^{-1}
298.15	1.130 ± 0.018	19.16 ± 0.31
308.15	1.497 ± 0.052	25.45 ± 0.88
318.15	2.023 ± 0.072	34.45 ± 1.23
328.15[a]	1.533 ± 0.063	51.60 ± 2.14
338.15[a]	1.974 ± 0.055	66.55 ± 1.85

[a] The absorbance values are out of line for (328.15 and 338.15) K due to additional dilution of the samples.

error of the mean were calculated for both absorbance and solubility. Solubility data for ibuprofen in [BMIM][PF_6] at (328.15 and 338.15) K (Table 1) should be treated with a degree of caution. At these temperatures there was evidence of degradation observed through an onset of color change. The temperatures studied are below the melting point of ibuprofen,[22] (348.15 to 351.15) K, and no evidence of degradation was observed for ibuprofen in either [HMIM][PF_6] or water. The water content of [BMIM][PF_6] measured by Karl Fischer was found to be 0.15 % (w/w). It is known that the presence of water in [PF_6] ILs has been reported to lead to decomposition reactions producing HF.[25] The samples were held at elevated temperatures for extended periods of time and were in contact with the atmosphere; these factors are the likely cause of the discolouration seen in the IL. Caution should therefore be taken when working with ILs containing this anion by ensuring that the ILs are dry and their exposure to the atmosphere is kept to a minimum. Note that the water content of [HMIM][PF_6] was 0.05 % (w/w).

The solubility data for paracetamol and ibuprofen for all solvents are shown in Figures 1 and 2 where solubility can be seen to increase with temperature. Both ILs were found to be good solvents for ibuprofen and paracetamol, indicating that a significant amount of drug-solvent interactions are taking place for dissolution to occur. The solubilities of both solutes were greater in [HMIM][PF_6] than [BMIM][PF_6] over the conditions studied. Analyzing the structures and functional groups of ibuprofen and paracetamol, it should be expected that ibuprofen is more likely to favor solvents of lower relative permittivity. (The relative permittivities of [BMIM][PF_6] and [HMIM][PF_6] are 11.8[26] and 8.9,[27] respectively.) However, on the basis of the

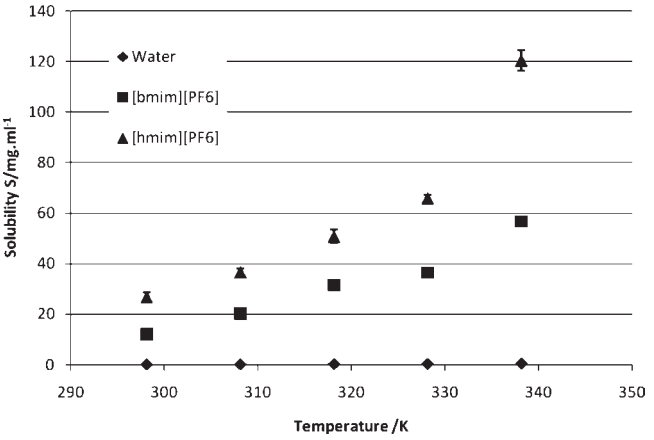

Figure 1. Solubility data in water, [BMIM][PF_6], and [HMIM][PF_6] as a function of temperature for ibuprofen. Each point represents the overall mean from three independent experiments ± the standard error of the mean.

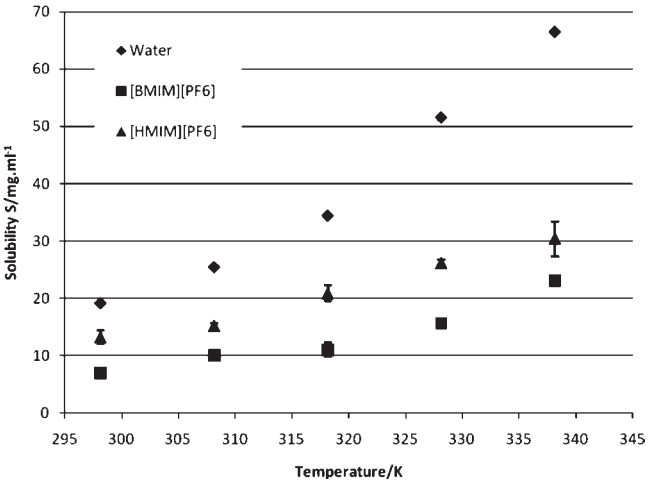

Figure 2. Solubility data in water, [BMIM][PF_6], and [HMIM][PF_6] as a function of temperature for paracetamol. Each point represents the overall mean from three independent experiments ± the standard error of the mean.

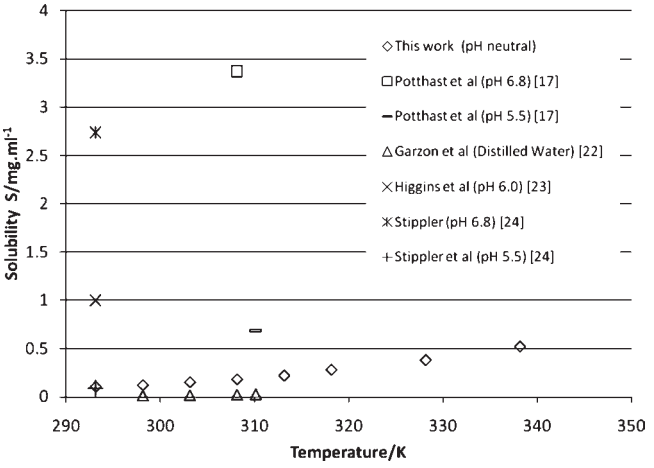

Figure 3. Solubility data in water as a function of temperature for ibuprofen.

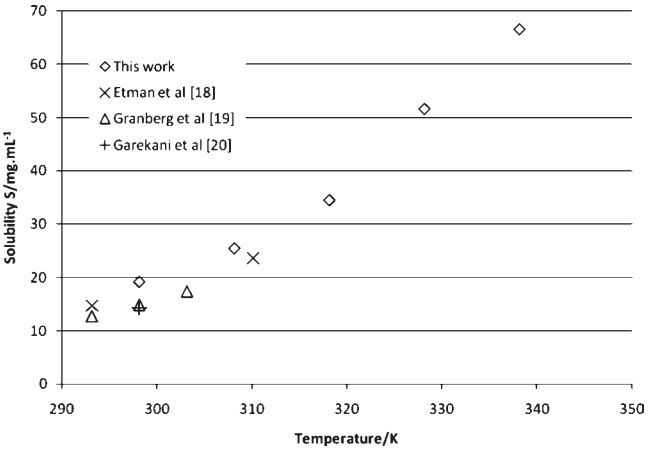

Figure 4. Solubility data in water as a function of temperature for paracetamol.

relative permittivity values, it could be expected that the solubility of paracetamol in [HMIM][PF_6] would be lower than [BMIM][PF_6], which is not the case. It has been hypothesized by Huang et al.[28] that the solubility of CO_2 in [BMIM][PF_6] was influenced by the existence of cavities in which the CO_2 dissolved. This would infer that [HMIM][PF_6] may have a larger population of cavities within which paracetamol dissolved leading to the observed higher solubility. However, these results highlight the difficulty predicting solute solubility especially when the solvation mechanisms of ILs are largely unknown,[4] and until these mechanisms have been elucidated, comparisons with conventional solvents should be made with caution.

Literature values shown in Figure 3 for ibuprofen in aqueous media vary depending on pH. The low solubility values (< 3.5 $mg \cdot mL^{-1}$) would also be sensitive to the techniques employed. The data measured in this work were recorded at neutral pH and fit within the available data[17,22−24] and also extend to higher temperatures. Comparing the paracetamol solubility data with other laboratories[18−20] (Figure 4), our results are in good agreement and again extend the data to higher temperatures. As expected, the polar paracetamol exhibits a greater solubility in water than the less polar ibuprofen.

CONCLUSIONS

Reliable solubility data were determined for paracetamol and ibuprofen in two ILs and water through analysis of saturated solutions using UV spectrophotometry. Both ILs showed sufficient solubility toward the drug compounds to make them suitable for further crystallization studies. It is reported that a solvent is sufficient for pharmaceutical processing when the solubility exceeds 1 $mg \cdot mL^{-1}$.[29] Solubility data of paracetamol and ibuprofen in aqueous systems have been extended to temperatures up to 338.15 K.

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