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Crystallisation Control of Paracetamol from Ionic Liquids

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The crystallisation of Active Pharmaceutical Ingredients (API) from conventional organic solvents can yield undesirable crystal habits with poor physical properties that cause downstream processing problems. It has been proposed that ionic liquids (ILs) may offer an opportunity to perform controlled crystallisations from this media. Using paracetamol and the ionic liquids 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] and 1-hexyl-3-methylimidazolium hexafluorophosphate [hmim][PF_6] fundamental understanding of these systems was established by determining the Meta-stable Zone Width (MSZW) before completing a series of cooling crystallisations investigated across a temperature range between 20°C and 90°C. It has been shown that paracetamol can be crystallised from these systems to obtain the stable monoclinic form I and that the particle habit and size can be manipulated by changing the IL used, the solution concentration and the mechanism of crystal growth and in some cases crystal habits not commonly found from aqueous or organic solvents were produced. The results demonstrate that ILs may be a viable approach to manipulate crystal properties and should be explored more widely as a potential media for crystallisation of API.

Introduction

The ability to control polymorphic form and, where possible, the crystal habit of Active Pharmaceutical Ingredients (API) is fundamental to the pharmaceutical industry in developing drug products.[1] Each form can have different physicochemical properties and therefore can impact product performance. There are well documented examples where polymorphism has had a major impact on commercial pharmaceutical products that, in some cases, have resulted either in costly product recalls[2] or early entry of generic versions onto the market.[3] Manufacturing issues due to poor physical properties are still commonly encountered throughout the pharmaceutical industry.

Fundamentally it is the final API crystallisation and isolation that is the critical step in defining the physicochemical properties of the final solid. The choice of solvent used for crystallisation can have a significant impact on both the polymorphic form (if under kinetic control) and the crystal habit,[4,5] by altering the supersaturation or by changing the solvent-solute interactions.[6,7] There has been significant research into crystal engineering approaches with the aim of either improving the solubility or dissolution rate of poorly soluble materials[6] or to control the crystal habit to improve manufacturability.[8]

Ionic Liquids (ILs) are composed entirely of ions with many remaining as liquids at room temperature and below making them useable as solvents in the conventional sense. The low melting points of ILs are achieved through large unsymmetrical cations resulting in low lattice energies. The physicochemical properties of ILs depend on both the nature and size of the cation and anion. It is proposed that by careful selection of ionic components the solubility and supersaturation critical to the crystallisation process could be controlled. The solvation of poorly water soluble APIs in ionic liquids has already been demonstrated[9] and highlights their potential as solvents for manipulation of APIs.

In recent years ionic liquids have generated interest across a number of research fields due to their unique properties. One such area of interest is their potential use as crystallisation media.[10] In particular, a number of publications have emerged for their use in crystal engineering applications for inorganic molecules.[11] Initial research concerning API and ILs has focussed on their use as reaction media as a means of chemical synthesis[12] however recently research has progressed into their use as media for carrying out crystallisations and in some cases producing ILs as the API itself.[13] In this emerging area there are relatively few publications that have explored this avenue of research. The literature reports the use of ILs to crystallise proteins such as lysozyme using the hanging drop vapour diffusion method.[14] While this method works well for large

molecules, techniques such as anti-solvent or cooling crystallisations are more commonly used for small molecule APIs. The anti-solvent method was used to produce polymorphs of adefovir dipivoxil[15,16] and recently particles <1μm of rifamoicin were produced using this technique.[17] In addition, the organic compound methyl-(Z)-acetamido cinnamate (MAAC) was crystallised from the IL 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) using supercritical carbon dioxide as an antisolvent.[18]

The purpose of this paper is to report an initial feasibility of using ILs as media for crystal engineering of API. For this work paracetamol in commonly used ILs 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] and 1-hexyl-3 methylimidaxolium hexafluorophosphate [hmim][PF_6] were studied. In order to understand the operating space available for cooling crystallisation the meta-stable zone width (MSZW) for these systems was established by measuring the cloud point data and combining this with previously published equilibrium solubility data[19](extended up to 95°C). A series of cooling crystallisations were then completed to investigate the impact of supersaturation and nucleation mechanism on the precipitated particles investigated across a temperature range of 20°C to 90°C.

Experimental

Materials

1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (99%), S9587950/036 and 1-hexyl-3-methylimidazolium hexafluorophosphate [hmim][PF_6] (98%), lot: S5205765/922 were supplied from Merck with a 99% purity, UK. Paracetamol (99%) was supplied by Merck, UK. Iso-octane (>99%) from Sigma Aldrich was used for particle sizing. All chemicals were used without further purification. The paracetamol was analysed prior to use by X-ray diffraction, laser diffraction and microscopy. The as-received paracetamol was found to be concordant with monoclinic form I, particles had a plate habit and a wide particle size distribution with a span of 4.0 and a d50 of 47 μm.

Methods

The meta-stable zone width (MSZW) was determined by a polythermal technique using an Avantium Crystal 16™ which consists of four independently heated aluminium blocks with turbidity measurement on each vial using light transmission. It has an accuracy of (±0.1 °C). A known excess of paracetamol was added to 0.5 mL(±0.01 mL) IL to give a range of concentrations, the solutions were then heated under agitation (700 rpm) at a heating rate of 0.2, 0.5 or 1.0 °C /min to 90 °C in order to achieve full dissolution of the solid. The solutions were cooled at the same rate to 15 °C. The point at which crystals could be detected (the cloud point) was used in combination with the equilibrium solubility to determine the MSZW for the measured IL and paracetamol system.

To determine the impact of supersaturation on the crystal habit, crystals were nucleated and grown from a range of solution concentrations using a) non-seeded and b) seeded approaches. All crystallisations were carried out in a 60 mL glass vessel with overhead stirring (500 rpm); temperature and stirring were controlled using a Mettler Toledo Multimax™. For the non-seeded experiments, a desired mass of paracetamol was added to 20 mL(±0.5 mL) IL and heated to 90 °C in order to achieve full dissolution (confirmed both visually and using a turbidity probe), then cooled at 0.2 °C/min to 20 °C. Two additional rapid cooling experiments were also performed on the same equipment at a cooling rate of 10 °C/min. For the seeded experiments, the solutions were cooled to 60 °C, seeded with 20 mg of the as-received form I paracetamol, and held for 4 hours before cooling to 20 °C at 0.2 °C/min.

In all cases the precipitate was recovered by vacuum filtration (750 mbar). Information on the morphology and size of the crystals was obtained by scanning electron microscopy (Hitachi TM-1000) and laser diffraction (Malvern Mastersizer 2000) with iso-octane and 0.05 w/w% lecithin used as dispersant. Polymorphic form was obtained by X-ray diffraction (PANalytical Empyrean diffractometer) at a wavelength of Cu (Kα = 1.54060 Å, Kα2 = 1.54443) measured in transmission mode; samples presented in a 96 well plate.

Results and Discussion

The MSZW was determined for paracetamol in each of the ILs using turbidity to detect the cloud point. Although the MSZW is not as well defined as the equilibrium solubility, (as it is determined by kinetic rather than thermodynamic properties and therefore can be highly influenced by factors such as scale, equipment, agitation etc), it does give insight to how easily a system will produce crystals. It can also help determine regions where crystal growth is driven either by primary or secondary nucleation followed by crystal growth. The cloud point data were combined with previously published equilibrium solubility data[19] which has been extended to 95°C to obtain the meta-stable zone width for these systems as shown in Figures 1 and 2.

The MSZWs obtained show that high supersaturation concentrations can be generated. Where the supersaturation ratio ΔS is defined as being:

$$\Delta S = c/c^*$$

Where, c is the solution concentration and c* is the equilibrium solubility at a given temperature.

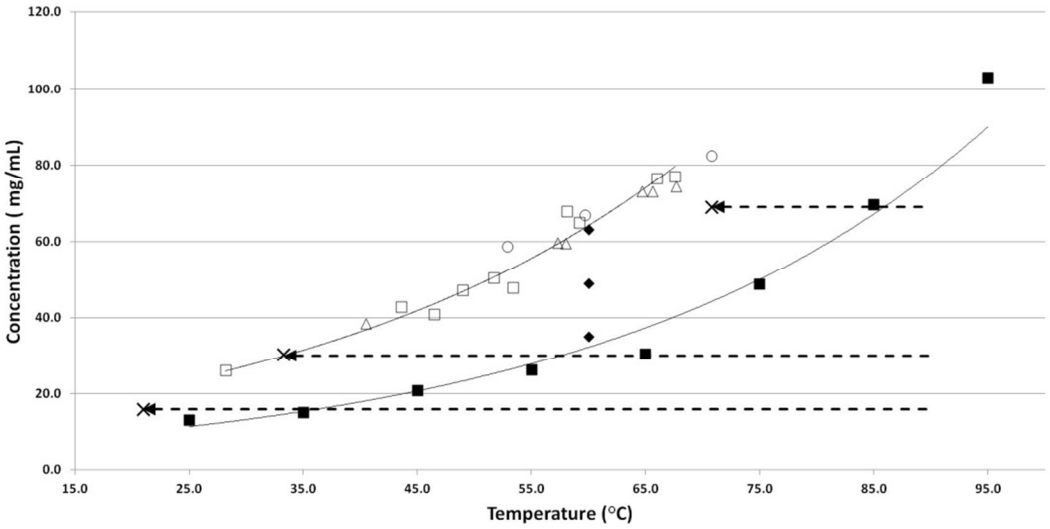


Fig 1: MSZW for Paracetamol in [hmim][PF_6] located between the two solid lines. Equilibrium solubility shown by ■ (ref 19). Point of nucleation obtained at cooling rates of □ 0.2 °C/min, Δ 0.5 °C/min and ○ 1.0 °C/min. Non-seeded crystallisation concentrations are shown by the dashed lines. Seeded crystallisations were seeded at 60 °C, initial concentrations are shown by ♦.

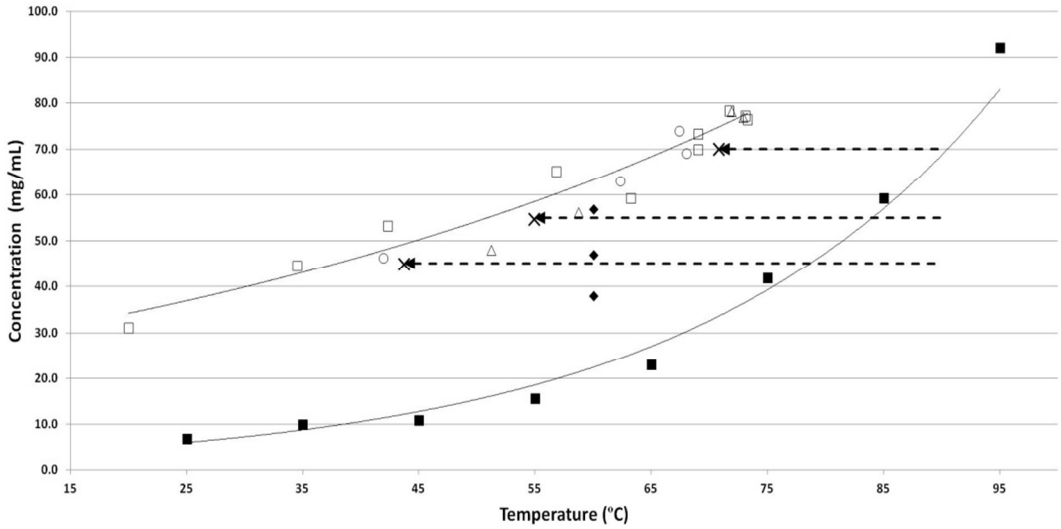


Fig 2: MSZW for Paracetamol in [bmim][PF_6] located between the two solid lines. Equilibrium solubility shown by ■ (ref 19). Point of nucleation obtained at cooling rates of □ 0.2 °C/min, Δ 0.5 °C/min and ○ 1.0 °C/min. Non-seeded crystallisation concentrations are shown by the dashed lines. Seeded crystallisations were seeded at 60 °C, initial concentrations are shown by ♦.

For example supersaturation ratios of 2.3 and 3.3 can be obtained in [hmim][PF_6] and [bmim][PF_6] respectively at 60°C indicating that crystals are not readily formed in these systems, however, this does lead to the availability of a wide operating window to manipulate using seeded crystallisation. Uncontrolled crystallisations resulting in primary nucleation and growth from such highly supersaturated solutions would result in large spontaneous crystallisations giving small particles. This would increase the possibility of isolating meta-stable forms of the paracetamol product. Despite the MSZW being driven by kinetic factors a reasonable correlation was obtained across the temperature range studied.

At a cooling rate of 0.2 °C/min fitting the data by exponential regression gave values of R^2 0.9663 and 0.9466 respectively for [hmim][PF_6] and [bmim][PF_6]. The cooling rate was found to have an insignificant impact on the MSZW across the range of 0.2 – 1.0 °C/min. The data generated define the operating region for developing a cooling crystallisation.

A set of cooling crystallisations were completed at a range of concentrations from both unseeded and seeded solutions. The unseeded experiments were designed to cross the meta-stable zone width at different levels of supersaturation as indicated by the dotted lines in Figures 1 and 2. These scoping experiments investigated the impact of concentration (as indicated in Table 1) on resulting particle formation when the crystals are grown

from a primary nucleation event and subsequent growth. Following these experiments a set of seeded experiments were conducted at different supersaturation ratios (as indicated in Table 2).

The values of supersaturation were all defined at 60 °C. The wide MSZW curve at 60 °C enabled a broad range of supersaturations to be investigated before spontaneous crystallisation occurred. The seeding point for each of these experiments is also shown in Figures 1 and 2 (as indicated by the black solid diamonds). The objective of these experiments was to investigate the impact on secondary nucleation and growth on the habit, form and size of the particles.

Form

The form of the resultant crystals was determined by X-ray diffraction (XRD). All seeded and non-seeded samples produced XRD patterns concordant with the monoclinic form I material,[20] example XRDs are shown in Figure 3. The monoclinic form is the most stable form as the orthorhombic form; form II, is metastable[21] to form I at ambient temperature. Given the relatively low cooling rate, form I was the expected form from these experiments. To test this further two further crystallisations were completed at a faster cooling rate (10°C/min) and high concentration 70 mg/mL, in each of the ILs. The recovered crystals (data not shown) were also found to be form I.

The precipitated crystals were separated from the ionic liquid by vacuum. Residual IL remained on the surface of the crystals as can be seen in the SEM images shown in Tables 1 and 2. This had the effect of agglomerating the crystals and was particularly seen for the smaller and more plate-like particles (as observed in Table 1 for [bmim][PF_6] 45 mg/mL). As a result some XRD patterns obtained for these particles had less intense diffraction peaks (not shown) and showed signs of preferred orientation, which may have accounted for any observed differences in peak intensity. This demonstrates that while ILs can be used to precipitate APIs, in order for them to be considered as viable solvents the separation of the product from the IL should be the subject of further investigation.

Particle Habit

NON-SEEDED CRYSTALLISATIONS

The particle habit of the samples was assessed by scanning electron microscopy. Interestingly, it was found that the habit of the precipitated crystals can be modified through changes in both the IL selected and the starting solution concentration.

When [hmim][PF_6] was used at the lowest concentration (16 mg/mL) tetragonal bypyramids were formed, increasing the concentration (30 mg/mL) small plate particles formed, whereas for the highest concentration (69 mg/mL) larger more tabular structures were produced as a consequence of growth post spontaneous nucleation. The particle habits produced from [bmim][PF_6] displayed smaller plate-like particles at the lowest concentration (45 mg/mL). Triangular prisms were formed when the concentration was increased to 55 mg/mL, while predominantly elongated prism particles were obtained from 70 mg/mL solutions (see Table 1).

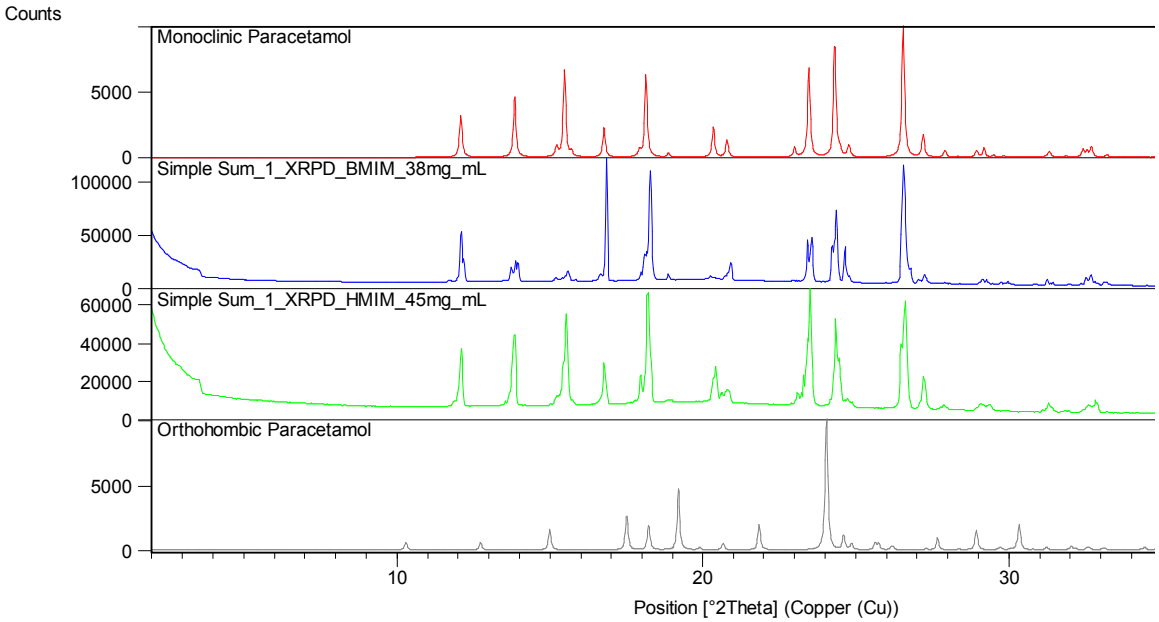


Fig 3: XRD patterns of Paracetamol from (a) Monoclinic Form I Reference (red) (b) [bmim][PF6] (blue) (c) [hmim][PF6] (green) and (d) Orthorhombic Form II Reference (grey)

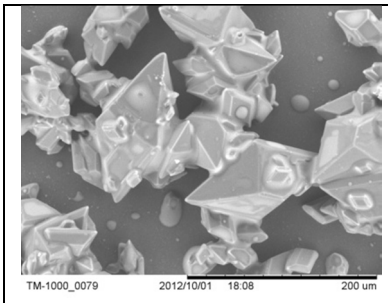
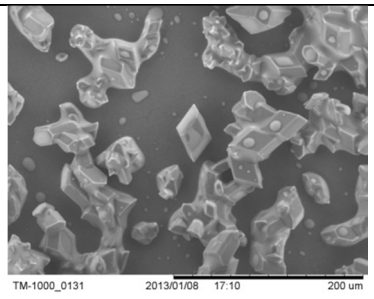
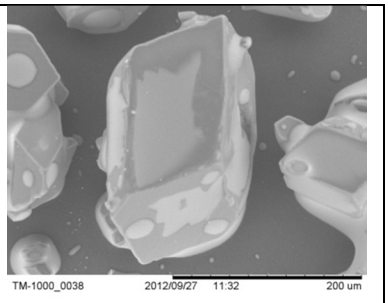
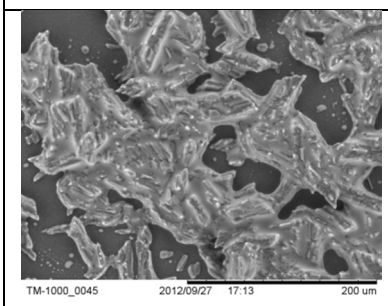
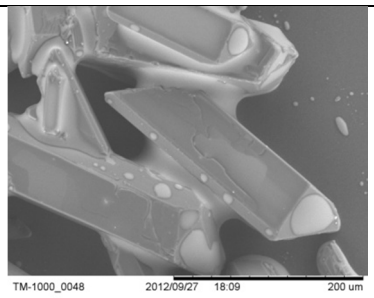
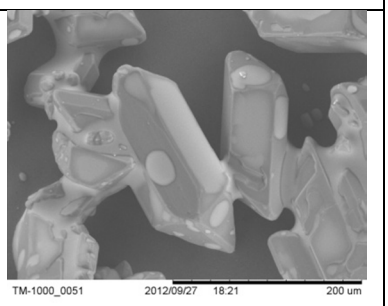
		
[hmim][PF_6] 16 mg/mL	[hmim][PF_6] 30 mg/mL	[hmim][PF_6] 69 mg/mL
		
[bmim][PF_6] 45 mg/mL	[bmim][PF_6] 55 mg/mL	[bmim][PF_6] 70 mg/mL

Table 1: SEM images of paracetamol produced from unseeded cooling crystallisations at range of starting concentrations. All SEM images are shown with a 200 µm scale bar.

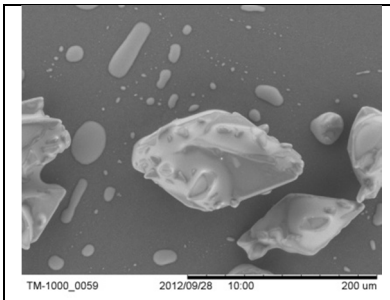
The crystal habit is dependent on the relative growth rate of the different crystallographic faces. The faces that grow rapidly have little or no effect on the particle habit whereas the slowest growing faces have most influence. For the crystals produced here, it is likely that this change in particle habit is being driven by the change in solution concentration. It has been observed in conventional solvents that the growth rate of the crystal faces {001} and {110} changes when the supersaturation changes. [22,23] At high supersaturations ($\Delta S>1.15$), the growth rate of face {110} decreases making these faces more dominant, resulting in more elongated crystals at low supersaturations compared to those grown at high supersaturations which produced crystals with a flat tabular morphology.

Seeded Crystallisations

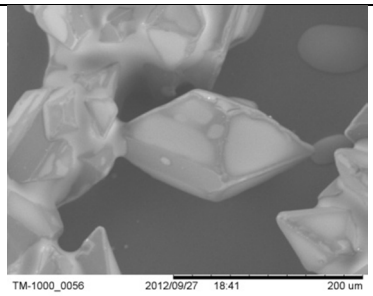
Crystals grown from the seeded crystallisations showed less variation in particle habit within each IL system, but did show differences between the two ILs studied. Crystals grown from [hmim][PF_6] formed bipyramids, when seeded at 60 °C across a supersaturation range of 1.25 to 2.25 ΔS. Triagonal bipyramid crystals were formed in [bmim][PF_6] samples when seeded at the same temperature across a supersaturation range of 2.0 to 3.0 ΔS.

The impact of ΔS had little impact on the crystal habit at the ranges studied. The supersaturation ratios used here were all greater than $\Delta S>1.25$ which are likely to be outside the region where changes in habit were observed in aqueous solutions as mentioned previously. [22, 23.]

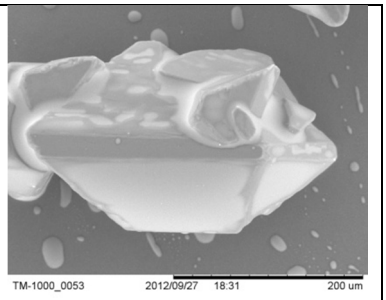
There have been numerous studies in the literature studying the crystallisation of paracetamol from conventional solvents. Finnie et al[24] detailed habit changes for aqueous solutions producing particles ranging from plate-like habits to larger tabular structures at high saturations. Similar larger tabular particle habits were produced by Yu et al[25] from aqueous systems using acetone as an anti-solvent. These two habits were also produced when paracetamol was crystallised from ethanol[26] and from benzyl alcohol[20]. Lee et al[27] crystallised paracetamol from thirteen pure solvents and found that plate-like crystals were formed from benzyl alcohol, n-butyl alcohol and water, while acetonitrile, 1,4 dioxane, isopropyl alcohol, methanol, methyl ethyl ketone, and tetrahydrofuran gave prism-like habits.



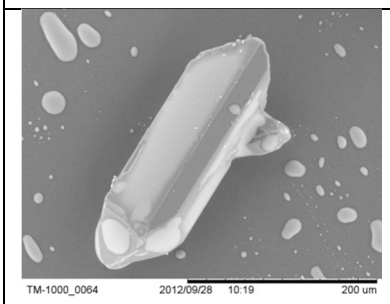
[hmim][PF_6] 1.25ΔS



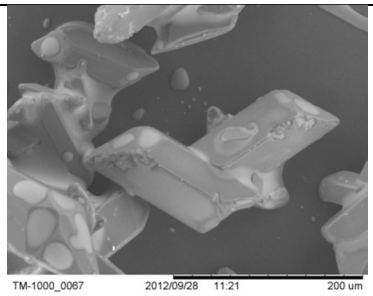
[hmim][PF_6] 1.75ΔS



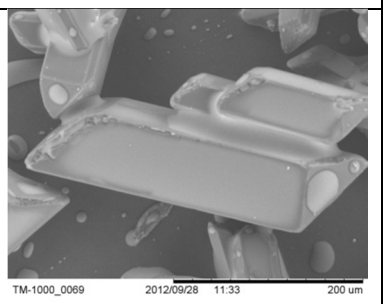
[hmim][PF_6]2.25ΔS



[bmim][PF_6] 2.0ΔS



[bmim][PF_6] 2.5ΔS



[bmim][PF_6]3.0ΔS

Table 2: SEM images of paracetamol produced from seeded cooling crystallisations at range supersaturation ratios ΔS. All SEM images are shown with a 200 μm scale bar.

Even though ΔS has little impact on crystal habit the triganol bypyramids formed from [hmim][PF_6] and elongated prisms formed from [bmim][PF_6] appear to be unique habits compared to those formed from conventional solvents. It is thought that the ILs used interact differently with the faces of paracetamol in comparison to aqueous or organic solvents previously reported in the literature. In order to understand the mechanism of crystal growth, crystal indexing is required and will form part of future work.

Particle Size

The particle size of the precipitates was measured by laser diffraction, a selection of the data are shown in Table 3. An example size distribution is shown in Figure 4. The particle size and size distribution followed the expected trend with larger particle sizes and narrower distributions obtained for samples grown from secondary nucleation than those formed from primary nucleation and growth (note the similar starting concentrations).

Ionic Liquid	Concentration (mg/mL)	Seeded (Y/N)	Particle size (μm) d_{10}	d_{50}	d_{90}	Span	Distribution
[hmim][PF_6]	69	N	9	60	124	1.92	Bi-modal
[hmim][PF_6]	63	Y	49	138	228	1.30	Bi-modal
[bmim][PF_6]	45	N	6	23	56	2.17	Multi-modal
[bmim][PF_6]	47	Y	112	206	329	1.05	Bi-modal

Table 3: Selected particle size data obtained from seeded and unseeded experiments at similar starting concentrations

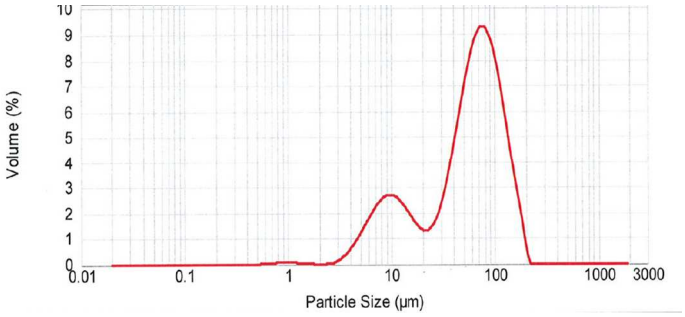


Fig 4: Paracetamol PSD from [hmim][PF_6] at 69 mg/mL

This is evidenced by an increase in the measured d_{50} from 60 µm to 138 µm and a reduction in the distribution span from 1.92 to 1.30 for paracetamol grown from [hmim][PF_6] when comparing samples with similar starting concentrations. The same observation was also seen for the two similar starting concentrations of [bmim][PF_6] with an increase in d_{50} of 23 µm to 206 µm and a reduction in the span from 2.17 to 1.05. These data demonstrate cooling crystallisations in ILs follow the same fundamental mechanisms as conventional solvents and methods such as seeding can be employed to control the particle size. As demonstrated in figure 4 it was found that the seeded crystallisations produced bi-modal distributions. No evidence of attrition was observed during the microscopy analysis and particles in this size population were seen indicating that this was a result of secondary nucleation. Further optimisation would be required to identify the required seed loading and cooling rate for these systems to produce a robust cooling crystallisation process capable of delivering a mono-modal size distribution.

Conclusions

The ability to manipulate the crystal form and habit of an API are crucial to the pharmaceutical industry. Given the highly functional nature of ionic liquids they may offer an opportunity to achieve these aims. It has been shown that paracetamol can be successfully crystallised from [hmim][PF6] and [bmim][PF6] using cooling crystallisation. Furthermore, the crystal habit and size of produced crystals can be modified through choice of solvent, concentration and method of crystal growth. It was found that cooling crystallisations from these systems followed the same rules for conventional organic solvents however crystal habits uncommon to conventional solvents were obtained indicating potential for crystal engineering applications . Building on these data a wider range of ionic liquids and APIs can now be explored in order to examine these solvents as alternative media for crystallisation of APIs and their impact on crystal growth.

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Notes and references

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[b] School of Chemical Engineering, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.

1 J. Lu, S. Rohani, *Curr. Med. Chem.*, 2009, **16**, 884
2 J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter, J. Morris, *Pharm. Res.*, 2001, **18**, 859
3 M. L. Peterson, M. B. Hickey, M. J. Zaworotko, O. Almarsson, *J. Pharm. Pharmaceut. Sci.*, 2006, **9**, 317
4 Y. Ueda, Y. Lida, H. Manabe, M. Kitamura, *Chem. Eng. Res. Des.*, 2007, **85**, 406
5 I. Weissbuch, M. Lahav, L. Leiserowitz, *Cryst. Growth Des.*, 2003, **3**, 125
6 N. Blagden, M. Matas, P. T. Gavan, P. York, *Adv. Drug Delivery Rev.*, 2007, **59**, 617
7 X. M. Zeng, G. P. Martin, C. Marriott, J. Pritchard, *J. Pharm. Pharmacol.*, 2000, **52**, 633
8 E. Kougoulos, I. Smales, H. M. Verrier, *AAPS PharmSciTech*, 2011, **12**, 287
9 H. Mizuuchi, V. Jaitely, S. Murdan, A. T. Florence, *Eur. J. Pharm. Sci.*, 2008, **33**, 326
10 W. M. Reichert, J. D. Holbrey, K. B. Vigour, T. D. Morgan, G. A. Broker, R. D. Rogers, *Chem. Commun*., 2006, 4767
11 E. Ahmed, J. Breternitz, M. F. Groh, M. Ruck, *CrystEngComm*, 2012, **14,** 4874
12 M. J. Earle, P. B. McCormac, K. R. Seddon, *Green Chem.*, 2000, **2**, 261
13 K. Bica, H. Rodriguez, G. Gurau, O. A. Cojocaru, A. Riisager, R. Fehrmann, R. D. Rogers, *Chem. Commun.*, 2012, **48**, 5422
14 X. Chen, Y. Ji, J. Wang, *Analyst*, 2010, **135**, 2241
15 J. H. An, J. M. Kim, S. M. Chang, W. S. Sik, *Cryst. Growth Des.*, 2010, **10**, 3044
16 J.H. An, W.S. Kim, *Cryst. Growth Des.*, 2013, **13**, 31
17 A. Vicosa, J. J. Letourneau, F. Espitalier, M. I. Re, *J. Cryst. Growth*, 2012, **342**. 80
18 M. C. Kroon, V. A. Toussaint, A. Shariati, L. J. Florusse, J. Spronsen, G. J. Witkamp, C. J. Peters, *Green Chem.*, 2008, **10**, 333
19 K. B. Smith, R. H. Bridson, G. A. Leeke, *J. Chem. Eng. Data*, 2011, **56**, 2039
20 G. Nichols, C. S. Frampton, *J. Pharm. Sci.*, 1998, **87**, 684
21 A. Burger, R. Ramberger, *Mikrochim. Acta*, 1979, 273
22 S. D. Finnie, R. I. Ristic, J. N. Sherwood, A. M. Zikic, *J. Cryst. Growth*, 1999, **207**, 308
23 R. I. Ristic, S. Finnie, D. B. Sheen, J. N. Sherwood, *J. Phys. Chem. B*, 2001, **105**, 9057
24 S.D. Finnie, R.I. Ristic, J.N. Sherwood, A.M. Zikic, *J. Cryst. Growth*, 1999, **207**, 308
25 Z.Q. Yu, R.B.H. Tan, P.S. Chow, *J. Cryst. Growth*, 2005, **279**, 477
26 R.I. Ristic, S. Finnie, D.B. Sheen, J.N. Sherwood, *J. Phys. Chem. B*, 2001, **105**, 9057
27 T. Lee, C.S. Kuo, Y.H. Chen, *Pharm. Tech*., 2006, **30**, 72

Table of Contents

The use of ionic liquids as a novel media for crystallisation and potential suitability for particle habit manipulation of paracetamol.