CRYSTALLISATION OF ACTIVE PHARMACEUTICAL INGREDIENTS USING IONIC LIQUIDS

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ABSTRACT

It is proposed that Ionic Liquids (ILs) offer a new opportunity for exploration into a novel medium for processing Active Pharmaceutical Ingredients (API), particularly with respect to habit control and polymorphic form. It is possible that due to the highly functional nature of these materials that they could offer a new route to manipulation of physical form, drug substance version and crystal structure during particle formation and growth. It is this basic hypothesis which the project aims to test.

A review of relevant literature relating to ionic liquids properties, commercial applications and current research has been summarised together with background into fundamental crystallisation theory.

Methods to establish the solubility of API in ILs was determined by using the common APIs paracetamol and ibuprofen in two common ionic liquids [bmim][PF_6] and [hmim][PF_6] and the data are fitted using two established solubility modelling equations. Crystallisations using thermal methods were employed at laboratory scale and the physical properties of the resultant powders were analysed and compared to commonly encountered crystal forms. The crystallisation work was extended by selecting a test set of ILs for further screening work. Practical issues in working with this medium were encountered during development and have been documented together with possible solutions.

It was shown that, for the systems studied, good solubility can be achieved and that the data can be modelled successfully using widely used models. For all the APIs studied in this work, cooling crystallisations were successfully used to crystallise material for characterisation. For

paracetamol it was found that the morphology of the crystals could be manipulated, producing in some cases, habits not reported for conventional organic solvent crystallisation. This was achieved through changing both the IL used and the saturation of the system whilst in all cases retaining the most stable polymorph. The same range of particle modification could not be repeated for ibuprofen whose morphology and form remained constant throughout. Studies on flufenamic acid showed that metastable forms can be isolated through changes in the IL and method employed. In general crystallisation from ILs followed the same fundamental principles as for other media. However there is potential for an ILs to be 'designed' for a given API but greater understanding of the interactions between IL and solute are required first.

Properties such as increased solvation power, thermal stability, liquidus range and low vapour pressure bring a number of advantages when designing industrial crystallisations. However ILs also have a number of disadvantages including phase separation problems. These may be solved through deploying other strategies such as use of co-solvents or potentially non-routine crystallisation methods such as Supercritical Fluid (SCF) crystallisation.

DEDICATION

I would like to dedicate this thesis to my wife Caroline and to my parents Brenda and Gordon for their patience, endless support and encouragement.

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
[bmim][BF_4]	1-butyl-3-methylimidazolium tetrafluoroborate
[bmim][CH_3COO]	1-butyl-3-methylimidazolium acetate
[bmim][$C_8H_{17}OSO_3$]	1-butyl-3-methylimidazolium octyl sulphate
[bmim][NTf_2]	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide
[bmim][PF_6]	1-butyl-3-methylimidazolium hexafluorophosphate
CAD	Charged Aerosol Detector
DCM	Dichloromethane
DSC	Differential Scanning Calorimetry
[emim][PF_6]	1-ethyl-3-methylimidazolium hexafluorophosphate
EtOAc	Ethyl Acetate
GAS	Gas Anti-Solvent
[hmim][PF_6]	1-hexyl-3-methylimidazolium hexafluorophosphate
IL	Ionic Liquid
IPA	2-Propanol
MeOH	Methanol
MSZW	MetaStable Zone Width
OM	Optical Microscopy
PSD	Particle Size Distribution
SCF	SuperCritical Fluid
SEM	Scanning Electron Microscopy
TGA	Thermal Gravimetric Analysis
XRD	X-Ray Diffraction

CHAPTER 1: INTRODUCTION

The mechanisms which govern the biopharmaceutical performance of an Active Pharmaceutical Ingredient (API) such as solubility, chemical and physical stability are intrinsically linked to the physical form of the API and can also impact the manufacturability of drug products. The final crystallisation of an API is therefore fundamental in delivering a safe, efficacious drug product which can be manufactured at commercial volumes.

Predominately APIs are purified and isolated from chemical synthetic process as powders by crystallisation from organic or aqueous based solvents or mixtures thereof. The final crystallisation step is critical to ensure that the API produced is of a high purity, the correct polymorphic form and the particle habit and size is conducive for isolation and subsequent downstream processing. The range of solvents available for these processes is limited and therefore the properties of the solvent are not always ideally suited to a given process. This can lead to the use of large quantities of volatile solvents which have a significant impact on both the process cost and environmental impact of such processes.

Is has been proposed that Ionic Liquids (ILs) may offer a new opportunity as novel media for processing API, particularly with respect to habit control and polymorphic form. ILs are unique solvents as it is possible to manipulate their properties by altering the cation, anion or substituent side chains. This means that they have the potential to be designed for a specific process or API. Common characteristics such as good solvation power, wide liquidus range, thermal stability and low vapour pressures means that they may also offer significant

advantages to reduce both the cost and environmental impact of pharmaceutical crystallisation processes.

The objectives of this work were firstly to examine the current literature and summarise: the background to ionic liquids, the current state of the art in crystallisation from ILs and gaps in current knowledge. Secondly, using well characterised ionic liquids and APIs to assess the practical implications of using ILs as crystallisation media by conducting laboratory scale experiments and where possible establish whether the additional molecular functionality of ILs can be exploited to modify physical form and beyond that whether a rationale can be developed to describe in qualitative or quantitative terms the underlying mechanisms for crystal growth and form modification.

Overall the thesis aims to help establish what may be practically possible with this novel media and whether they can be used to control the physical form of API.

CHAPTER 2: LITERATURE REVIEW

2.1 Definition of Ionic Liquid and Brief History

Ionic liquids (ILs) are liquids predominately composed of ions, they contain at least one organic cation and one anion and by definition are liquids at less than 100 °C (with many being liquids at room temperature). It is this low melting point, relative to molten salts, that has opened up the field to a wide range of potential applications.

As with many research areas it is difficult to define an exact date by which it is generally accepted that the field started. Wilkes (2002) suggests that the history of ILs can be traced back to the mid-19th century when chemists noted a 'red oil' produced from a side product of a Friedel-Crafts reaction. This 'red oil' was not of interest at the time but has since been proposed to be an ionic liquid based on a heptachlorodialuminate salt. However it wasn't until 1914 when the synthesis and physical properties of ethyl ammonium nitrate (EAN), which has a melting point of 12 °C, was documented by Walden (1914); many believe this marks the true start of IL research (Plechkova and Seddon, 2008).

Fundamental research into ILs began in earnest throughout the 1960s and 1970s when chloroaluminate salts for use in thermal batteries was investigated by the US Air Force Academy (US Patent 4122245, 1978) in collaboration with groups at the Colorado State University (Koch et al, 1976 and Gale et al, 1978). However many of the ILs discovered in this era were found to have melting points in excess of 40 °C and suffered from hydrolysis issues; this led to the search for more stable and lower melting ILs.

In the 1980s ILs based on imidazolium cations were investigated and published (Fannin et al, 1984). Using this cation a series of ILs were produced that were liquids at or around room temperature and it is this cation that the majority of research still carried out with. However a major drawback of the ILs used in this research was that the anions, which were based on chloroaluminate, were found to be reactive with water.

Synthesis of the imidazolium based cation was extended from chloroaluminates to ions such as tetrafluoroborate, hexafluorophosphate, nitrate, sulphate and acetate (Zaworotko and Wilkes, 1992) which were found to be stable with water (at ambient conditions).

The discovery of these air and water stable ILs provided the spark for research into numerous fields over the last two decades, as can be seen from the number of articles that have been published since 1980 as shown in Figure 2.1.

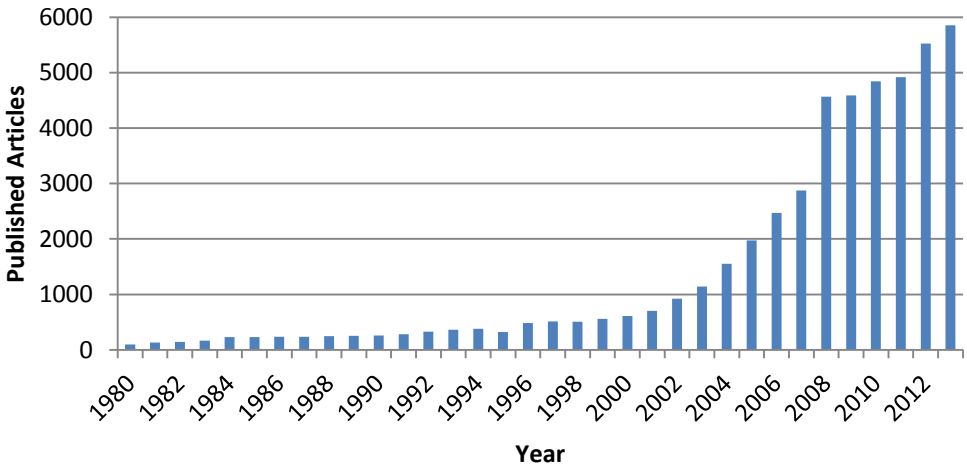

Figure 2.1: Ionic Liquid Publications 1992 to 2013

Although many areas of research were initiated using these newly found stable ILs the largest area of focus in the 1990s and early 2000s was their use in chemical reactions. Specifically, it was shown that they could be used as media in a large range of chemical

reactions while providing reaction rates that were either comparable or better than conventional organic solvents (Welton, 1999 and Seddon, 1996). Reactions studied include isomerisations, alkylations, Diels-Alder reactions, hydrogenations and Heck and Suzuki coupling reactions.

This work greatly expanded the demand for ILs and as such there are now a number of commercial suppliers providing an ever expanding range of ILs ready for use. This, coupled with the ever increasing drive to find ILs that are both chemically and biologically inert, whilst remaining liquid at room temperature, has now made their use in the pharmaceutical arena possible.

This brief development history brings ILs into the current age of research. Their use in the pharmaceutical industry is the focus of this thesis and a greater commentary of the current research in this area is detailed in later sections.

2.2 Properties

The number of potential number of ILs consisting of a single cation and anion (although more complex examples do exist) gives in the region of 10^6 possible combinations. To put this into context there are just approximately 600 conventional molecular solvents (Plechkova and Seddon, 2008). It is this potential choice that has facilitated much of the investigation into ILs as many researchers look to them as 'designer solvents' whose properties could potentially be tailored and refined for a specific process.

Given the large number of possible ILs it is not appropriate to generalise the properties, as such a large number of possible combinations means that exceptions to general 'rules of thumb' can almost always be found. Up to date physical properties of many ILs can be found on Ionic Liquids Database - ILThermo (v2.0) (2014) and there are also a number of reviews documenting the properties of many commonly used ILs (Weingarten, 2008, Zhang et al, 2006, Domanska, 2006 and Fredlake et al 2004).

While it is beyond the scope of this work to outline the full range of possible physicochemical properties available, a summary of properties of common ILs that are most pertinent to this work are described in Table 2.1. To highlight some of the major differences the properties are compared with three of the most commonly used organic solvents in the manufacture of APIs at GlaxoSmithKline (Constable et al, 2007).

	Ionic Liquids			Organic Solvent		
Property	**[bmim] [PF_6]**	**[bmim] [BF_4]**	**[bmim] [$C_2F_6NO_4S_2$]**	**MeOH**	**IPA**	**EtOAc**
Molar Mass g mol^{-1}	284.2	226	419.4	32.0	60.1	88.1
Melting Point K	283	202	272	176	184	190
Liquidus Range K	339	474	440	162	172	160
Relative Polarity	0.667	0.673	0.664	0.76	0.57	0.23
Density at 298 K Kg.m^{-3}	1350	1260	1430	792	786	897
Viscosity at 293 K Pa s (10^3)	450	154	69	0.59	1.96	0.426

Table 2.1: Comparison of Sub-set of ILs and Organic Solvents

The small subset of ILs and organic solvents shown here highlights some of the major differences between ILs and organic solvents. These properties are further analysed in the sections below.

2.2.1 Structure

Commercially available ILs are based on a relatively small number of core structures shown in Figures 2.2 and 2.3. The cations are generally single charged species where the charge is distributed across the entire structure avoiding strong coulomb interactions. They are large bulky asymmetric structures that prevent packing of the unit cell and hence crystallisation. The most widely researched ILs are based on the imidazolium cation as they are relatively easy to produce and are perceived to have good physical properties. Other commercially available cations are based on ammonium, phosphonium, pyridinium, pyrrolidinium and sulfonium.

The substituents on the cation are typically alkyl chains but can contain a variety of other functional groups such as fluroalkyl, alkeny and methoxy. Increasing the length of an alkyl chain tends to decrease water solubility by increasing the hydrophobicity of the cation.

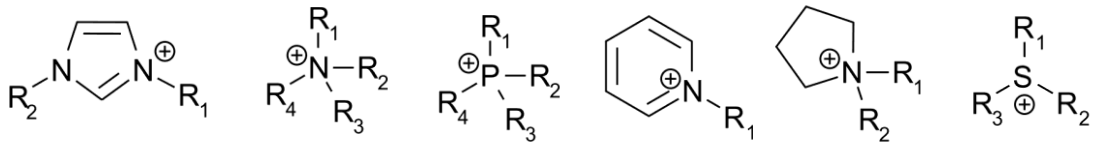

Figure 2.2: Common Cation Structures; Imidazolium, Ammonium, Phosphonium, Pyridinium, Pyrrolidinium and Sulfonium

The choice of anion also influences the chemical and physical properties of an ionic liquid. For example ionic liquids based on the imidazolium cation can be made to be totally miscible or immiscible with water through careful choice of anion (Rogers and Seddon, 2002).

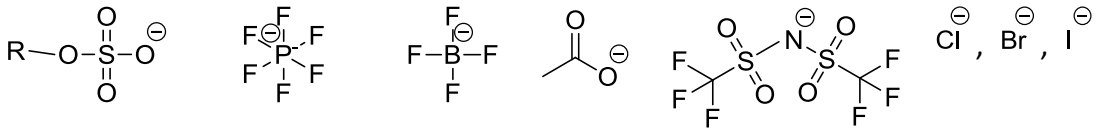

Figure 2.3: Common Anion Structures; Alkylsulfate, Hexafluorophosphate, Tetrafluoroborate, Acetate, Bis(trifluoromethylsulfonyl)imide, Halide

2.2.2 Melting Point and Liquidus Range

When looking to use ILs as crystallisation solvents it is key that the IL remains as a liquid during the separation of the solid product. While ILs are defined as having a melting point less than 100 °C melting temperatures at or below room temperature are more desirable from a processing perspective. All three major components of the IL (cation, side chains and anion) will have an impact on the melting point of an IL.

Large cations and increased asymmetric substitution results in a reduction of the melting point. Short side chains are more likely to form crystalline phases with comparatively high melting points whereas medium sized tend to have low melting points with a large liquidus range. The melting point of ILs with long side chains can be complicated as they can result in complex phase diagrams and are dependent on the anion and its ability to hydrogen bond.

Increasing the anion size has the impact of decreasing the Coloumb interactions in the crystal lattice, decreasing the melting point. For example the melting point of ILs containing halides tends to be much higher than ILs containing hexafluorophosphate or bis(trifluoromethylsulfonyl)imides (Zhang, 2006).

The melting points of ILs are considerably higher than organic solvents as the examples in Table 2.1 show. This will restrict the number of ILs that could be considered for use via conventional crystallisation methods and may be one of the drawbacks of ILs that has restricted their use as pharmaceutical solvents.

The temperature range over which ILs remain in the liquid state (liquidus range) are far superior to conventional organic solvents. Typically the liquidus range is the difference between the boiling and melting points, however as ILs have no discernible vapour pressure the liquidus range is determined by the difference between the decomposition temperature (as measured by Thermal Gravimetric Analysis, TGA) and the melting temperature.

Liquidus ranges in the region of 300 to 500 K are commonly found for ILs whereas typical liquidus range for organic solvent is typically in the region of 100 to 200 K. So while the melting temperature of many ILs may preclude them from conventional crystallisation methods the superior liquidus range offers an opportunity to work at a much greater range of temperatures than possible using conventional solvent systems.

2.2.3 Vapour Pressure and Thermal Stability

While for most applications ILs could be considered to have negligible vapour pressures it is false to claim that ILs have no vapour pressure as in some cases this has been measured

(Esperanca et al, 2010) and some ILs have even been designed to undergo distillation (Earle, 2006).

The thermal stability of ionic liquids is limited by the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds. It has been reported that ILs can be stable up to temperatures of 700 K. However such high temperatures can only be tolerated by ionic liquids for a short period as long time exposure at high temperatures leads to decomposition (Kosmulski et al, 2004).

The low vapour pressure means that ILs are not susceptible to evaporation which helps reduce emissions and also offers the possibility that ILs could be used at temperatures never possible using conventional solvents without the need for extensive changes to infrastructure. This could make ILs very efficient solvents for chemical processes such as API manufacture and crystallisation.

2.2.4 Polarity

Commonly used to describe the solvation capability of a solvent, polarity is important when considering a solvent for a particular application. For molecular solvents the relative dielectric permittivity or static dielectric constant, ε_s, can be measured directly. However because direct measurement requires a non-conducting medium the dielectric constant of ILs needs to be determined by measuring the frequency dependent dielectric permittivity and extrapolating to zero. Using this method ILs can be classified as moderately polar solvents. However it should be noted that generally the ε_s values tend to be lower than for other methods.

Another common empirical method used to measure the polarity of ILs is the use of solvatochromic or fluorescent dyes, where the change in absorption when the dye comes into contact with media of different polarity. One of the most common scales is the Dimroth–Reichardt $E_T(30)$ scale (Reichardt, 2005), based on the N-(4-oxidophenyl) pyridinium dye, where the difference in solvation of the dipolar zwitterionic ground state compared to the less polar first state is detected by a shift in λ_{max} from 453nm to 810nm. A polarity scale, $E_T(30)$, is used to scale solvent polarity. Increasing the value of $E_T(30)$ leads to a polarity increase; however values are often normalised to give a parameter E_T. Solvents are normalised to values between N = 0.0 (tetramethylsilane) and 1.0 (water).

For the examples used in this work shown in Table 2.1 the ILs are within the range 0.664 to 0.673 which would indicate that they have a similar polarity to methanol. The anion has been found to have little influence on the E_T values (Muldoon, 2001), hence the values shown for the ILs in Table 2.1 are very similar to each other. In the same study it was found the alkyl chain length also has little impact with a small decrease detected for increasing chain length, a similar effect also observed in short chain alcohols. The biggest influence is therefore from the cation. E_T values are known to be strongly influenced by the ability of a solvent to act as a hydrogen bond donor and it is this property of the cation that influences the polarity value for this dye.

It is unclear whether the concepts for rationalising the polarity of ILs this way are suitable given the complex nature of the bonding in these media. Further work is needed to understand these complex systems to determine the interplay between different bonding in ILs and how they interact with solutes.

2.2.5 Viscosity and Density

The viscosity of an IL is determined by the ability to form hydrogen bonds and Van der Waals interactions. ILs have viscosities that are orders of magnitude more viscous than most conventional solvents. Both the cation and anion can have significant effect, the magnitude of which is particular to the bonding ability of a given ion. For example, for some of the anions used in this work in a homologous series of cations, as shown in Table 2.1, the following trend occurs: $[(CF_3SO_2)_2N^-] < [BF_4] < [PF_6]$. The impact of alkyl chain length is less pronounced than changing either of the ions but increasing alkyl chain length will result in an increase in viscosity. The viscosities of ILs are also known to be highly temperature dependent and they can be extremely viscous at low temperatures.

In general ionic liquids have densities greater than water and organic solvents, with densities ranging from 1260 $kg.m^{-3}$ to 1430 $kg.m^{-3}$ for the examples shown in Table 2.1; as the side chain of the ionic liquid increases the density decreases. The densities are also affected by anion type.

The high viscosities and densities of ILs and their high temperature dependence compared to more conventional solvents would mean that careful attention would need to be given to the mixing conditions and any impact on the filtration processes.

2.3 Safety, Environmental, Regulatory and Cost

For any new chemical entity that is being considered for a pharmaceutical process it is important to also consider the process safety, environmental impact, regulatory implications and costs. A comparison of some of the indicators used to assess such details are summarised for the same solvents previously in Table 2.2.

	Ionic Liquids			Organic Solvent		
Property	**[bmim] [PF_6]**	**[bmim] [BF_4]**	**[bmim] [$C_2F_6NO_4S_2$]**	**MeOH**	**IPA**	**EtOAc**
Hazard Notations (Hazard Category) **Skin Irritant (SI), Skin Corrosion (SC), Eye Irritant (EI), Serious Eye Damage(SED), Specific Organ Toxicity (SOT), Acute Toxicity (AT), Flammable Liquid (FL)**	SI (2) EI (2A) SOT (3)	AT (3), SI (2) EI (2A),	AT (3) SC (1) SED (1) SOT (2)	FL (2) AT (3) SOT (1)	FL (2) EI (2) SOT (3)	FL (2) EI (2) SOT (3)
Environmental Notations **AQT = Acute Aquatic Toxicity ST = Slightly Toxicity**	AQT (2)	AQT (2)	AQT(2)	ST	n/a	n/a
Degradation **Not Readily Biodegradable (NRB) Readily Biodegradable (RB)**	NRB	NRB	NRB	RB	RB	RB
Safety Marker **LD 50 (rat)** in $mg.kg^{-1}$	300 - 500	> 50 - < 300	300	5630	5050	5620
Cost £/kg (July 2014)	448.00	486.84	1506.00	0.58	1.18	1.14

Table 2.2: Comparison of Safety, Environmental, Toxicity and Cost

2.3.1 Safety

The flammability of organic solvents means that significant controls are required to ensure safe handling, dispensing and chemical plant / equipment design. The low or negligible vapour pressure could bring advantages on how solvents are safely controlled in chemical processes by significantly reducing the flammability risk.

Despite these clear advantages the safety of ILs needs careful consideration, especially in chemical synthesis processes as ILs can be reactive (Chowdhury et al, 2007), so the compatibility with reaction mixtures would need to be assessed on a case by case basis. Many of the ILs have specific safety notations, as the examples in Table 2.2 show, which may require the user to have a greater level of protective equipment in order to prevent unexpected exposure.

The degradation products also need to be carefully monitored. For example it is known that hydrogen fluoride is formed when water is present in a number of fluorine containing ILs such as the commonly used PF_6 and BF_4 anions (Huddleston et al, 2001).

2.3.2 Environmental

One of the many perceived advantages of ILs is that they are 'green' solvents. This is primarily based on the reduction of volatile emissions that replacing organic solvents could bring (MacFarlane and Sneddon, 2007).

Any environmental impact needs to be considered as a whole rather than just the impact on emissions. While much research has gone on into the production of ILs and their applications, measurements of potential environmental impact is still to be fully detailed. It was recognised within the scientific community that a systematic approach to measuring, reporting and where possible predicting environmental impact was required. The Centre for Environmental Research and Sustainable Technology located in Bremen has now measured the environmental toxicology of over 300 ILs and their data, together with other literature data, provides a useful resource for evaluating the environmental toxicology of ILs (Thuy Pharm, 2010).

Their studies have shown that the biggest influence on the ecotoxicity has been found to come from the alkyl side chains, while generally the cation itself seems to have little influence (although noted that some pyridium and quinolinium head groups are found to be exceptions to this).

The environmental toxicity can be altered by changing the hydrophobicity of the IL, for example reducing the alkyl chain length or introducing polar functional groups can improve

the environmental toxicity. Most anions do not display significant environmental toxicity. The exceptions to this are hydrophobic anions which tend to be fluorinated which gives them specific environmental toxicity as shown in Table 2.2. As the use of ILs becomes wide spread there is increasing focus on what their long term environmental toxicity may be. Good reviews on the subject have been written by Thuy Pham et al (2010), Romero et al (2008) Frade and Afonso (2010).

Currently not much is known about the biodegradation of ILs. However some general rules are known. Cations based on pyridinium exhibit higher degrees of biodegradation than imidazolium based ILs. Also the larger the side chain, the better the biodegradation (trade off between biodegradability and environmental toxicity). For the anions, alkyl sulphates and salts of organic acids (e.g. acetate or lactate) are recommended, while fluorine containing ILs should be avoided.

2.3.3 Regulatory Status

Regarding regulatory status of ILs no guidance has yet been published from the relevant authorities. If ILs are to be used in the manufacture of APIs then more extensive research and justification for use will be required. Guidelines in place for conventional solvents require low values of solvent to be present and unless the ILs themselves are designed to be tolerable it should be expected that equally strict regulations would exist for these solvents.

The tolerability of ILs would need to be determined in safety studies to ensure that there would be no adverse toxicological risks passed onto patients if trace levels of IL remained. This would also require the development of sufficient analytical methods in order to determine trace levels of IL.

2.3.4 Cost

Currently ILs can be considered as niche solvents and the cost reflects this status although the purification of ILs can be problematic and they are likely to always have a higher initial cost compared to commonly used organic solvents. This cost could be offset if the IL can be sufficiently recycled from batch to batch; in this case over the lifecycle of the IL the increased cost may be negligible. The range of possible ILs means that it is not commercially viable to make large quantities for general purchasing. The approach taken by companies like BASF is to supply a limited range and once a suitable IL is identified a bespoke product can be negotiated. This would allow bespoke specifications to be determined to control attributes such as purity, by-products, halogen content, colour, viscosity etc. If the process required large volumes then this would also drive the cost of the IL down. The cost to manufacture API using current solvents provides by far the highest impact to the cost of the drug product. If a proposed process is to use an IL it must also be economically viable and not significantly impact the cost of goods.

Overall it is clear that ILs have some unique properties that make them stand out from conventional organic solvents as broadly summarised in Table 2.3. While some of these properties may provide technical solutions to a given problem, in order for successful implementation much more work is needed to understand the lifecycle impact of this potential new medium.

Property	Organic Solvent	Ionic Liquid
Number of Solvents	$> 10^3$	$> 10^6$
Flammability	Usually Flammable	Usually Non-Flammable
Operating Range	circa. 100 °C	circa. 300 °C
Viscosity	Low	High
Safety and Environment	Well understood	Emerging Data
Cost	Normally Cheap	Expensive

Table 2.3: Comparison of Organic Solvent and ILs

2.4 Applications

The rise in published articles on ILs in the last decade gives an indication as to the breadth of research that ILs currently spans. While they have found applications in diverse areas of research the sections below have concentrated on commercial applications and research that is focused on their use either in the delivery of APIs or as a medium for particle formation.

2.4.1 Industrial Applications

Chemical Processing

It is claimed (Maase and Massonne, 2005) that the first industrial application using ILs was the BASIL (Biphasic Acid Scavenging utilizing Ionic Liquids) process by BASF™. The process is used for the production of a generic photo-initiator. Using 1-methylimidazole as an acid scavenger an ionic liquid is formed, which is then separated and used for further reaction steps. The process has been in routine production since 2002 producing ILs on a multi-ton scale. Comparing to the previously used process the yield was increased from 50% to 98% allowing the process to be conducted using a much smaller reactor.

While the BASIL process was the first self proclaimed commercialised process, in fact the Eastman Chemical Company had been running a process involving an isomerisation that required a phosphonium based IL to act as a Lewis basic media. The process run by the Texas Eastman Division in a plant with a 1400 metric ton capacity operated from December 1996 through to 2004. The process was terminated due to decline in requirement for the product. (Plechkova and Seddon, 2008)

Other noteable processes that may be future commercial processes include: cellulose processing which was developed at University of Alabama by a group headed by Robin Rogers (Swatloski et al, 2002) and has now been licensed by BASF. Cellulose is the earth's most abundant natural organic resource, an important bio-renewable resource and the excellent solvation properties of ILs mean that dissolution of this biomass can be achieved and utilised for subsequent processing.

Petrochemical Industry

The petrochemical companies such as BP, ExxonMobil, Chevron have invested heavily in a number of areas including refining, extraction, waste processing and emulsification (Plechkova and Seddon, 2008). While they have been very active in the field it is not clear what the current stage of development these processes is. However, currently the largest commercial process is run by a petrochemical company. The PetroChina process which is a sulphuric acid alkylation process named Ionikylation produced 65,000 tonnes of product per year. The process was retrofitted to the existing plant and has improved the process yield such that an increase in the process capacity of 248 tonnes a day (40%) was achieved. Also in the petrochemical arena the Institut Français du Petrole (IFP) patented a process called Difasol, which is operated by a company called Axens. The process, which uses chloroaluminate ILs as solvents for nickel catalysed dimerisation reactions, has been shown to have a number of improvements over the existing Dimersol process such as improving selectivity, yield, catalyst use and reduced reactor size.

Other Industries

Electroplating processes such as BASF's aluminium plating process or the chromium plating process from Scionix have also been developed as commercial processes for electropolishing of stainless steel, meanwhile Degussa have used ionic liquids to improve the appearance and drying properties of their paints under the name TEGO Disps and the Pliolite range.

Summary

The above applications demonstrate that ILs can be and have been developed into viable commercial processes. The chemical processing and petrochemical industries have shown the greatest success in developing commercial processes. Many of the largest processes have been developed and implemented before the recent upsurge in IL research. As more and more applications are investigated the number of commercial applications is expected to rise and diversify into other industrial sectors.

2.4.2 Pharmaceutical Based Research

There has been much focus on the chemistry involved in the synthesis of APIs and good reviews in this field have been published already (Welton, 1999). The literature reviewed in the section below has been targeted to cover the areas relevant to the use of ILs in the pharmaceutical industry and particle engineering of materials using ionic liquids.

One emerging area of focus for ILs is their application in the production and delivery of Active Pharmaceutical Ingredients (API). The strategies employed can be broadly split into two approaches; use of ILs as drug delivery vehicles to dissolve and deliver API and the development of ILs that are designed to be the API.

Solubility of API in ILs

While their use in green chemical processes was of interest in the last ten years it is their unique solvation properties that have re-ignited interest in the industry. Research groups have shown (Mizuuchi et al, 2008) that the solubility of poorly water soluble drugs such as albendazole and danazol could be significantly increased (more than 10,000 times in the case of albendazole). The ILs used in this study were hydrophobic and immiscible in water; however it was demonstrated that the miscibility could be improved through addition of a second more miscible IL.

Recently a number of solubility studies have been published. For example Forte et al (2012) measured the solubility of anti-tubercular drugs in ILs based on the imidazolium cation and bis(trifluoromethylsulfonyl)amide and trifluoromethanesulfonate anions. They measured the solid-liquid equilibrium using thermal techniques and used six different correlation equations to provide a fit for the data. The work shows that, in terms of solubility, ILs provide a viable alternative to molecular solvents for pharmaceutical processing. Interestingly the correlation equations that are well established for molecular solvents was able to provide a reasonable fit to the experimental data. The solvation mechanisms involved in ILs are still largely unknown so as data continues to emerge relating to established correlations which may help to identify similarities and differences between ILs and molecular solvents as more data are published.

A feature from the published solubility work is that compounds that exhibit poor solubility in organic solvents can often be solubilised using ILs. The reason for the increased solvation properties in ILs has been debated in a number of journals. Using Flory-Huggins theory,

Areov et al (2006) proposed that the extra solvation power is due to the repulsive force created between the shells of the anion and cation. The only way to reduce this repulsive force is to dissolve the solute molecules to help shield this effect.

ILs as Drug Delivery Systems

The ability to dissolve poorly soluble API has been exploited by a number of authors, namely Jaitely et al (2008) who was one of the first to publish on the use of ILs in drug delivery, investigating the use of the hexafluorophosphate anion with imidazolium cation with differing alkyl chains. They showed that controlled release of solute into the aqueous phase was achieved and that the release profile could be manipulated by changing the alkyl chain length and hence the hydrophobicity of the IL. This impacts both the solubility of the solute but also the hydrophobicity of the IL and hence the partition co-efficient and release of the drug from the IL into the aqueous phase.

This approach has been taken forward by other authors such as Moniruzzaman (2010) who developed a microemulsion process to form thermodynamically stable emulsions that were found to have spherical micelles in the range of 8-34 nm.

The use of ILs as a drug delivery vehicle to deliver poorly soluble API has been investigated by a number of groups. For instance Williams et al (2014) have showed, through careful targeting of the IL, that the solubility of danazol and itraconazole could be significantly enhanced with a more prolonged exposure when compared to a lipid formulation.

Both of the above authors highlight that one of the great unknowns of these approaches is the toxicity of the IL being used to deliver the API. Both completed toxicity tests and showed that no significant toxicity was observed. While these results are encouraging much more

work is required to assess both the toxicity but also the persistence and the clearance of ILs *in-vivo*. Until this is addressed questions will always be raised when direct administration of ILs in formulations is proposed.

ILs as Active Pharmaceutical Ingredients

The concept of using ILs as the API was published by Hough et al (2007) where they propose that pure liquid salt forms of APIs should be considered and may be useful for overcoming commonly encountered problems in the solid form such as polymorphism, solubility and bioavailability. The concept was demonstrated by producing IL-APIs of Ranitidine Hydrochloride (Histamine H2-receptor, active ingredient in Zantac), lidocaine hydrochloride (pain reliever that is commonly delivered topically) and ibuprofen (common anti-inflammatory). Lidocaine (cation) was paired with docusate (anion) to produce lidocaine docusate which formed a clear colourless gel with a measured glass transition of 244 K. Biological testing was completed on this via topical application and it was found that release of the API was observed. However, compared to the conventional formulation the release was slower, indicating the mechanism of release was different, but this opens up the possibility of controlled release formulations. This initial work has been followed up with a position paper from Stoimenovski et al (2010) and more recently a review by Shamshina et al (2013).

There are a number of potential advantages that this approach could bring: firstly the authors highlight that as the material remains in liquid form no control over the polymorphism would be required, secondly, through careful selection of the counter ion it may be possible to control the solubility either to enhance it or to act as a controlled release

mechanism, thirdly it has been it has been demonstrated that it may be feasible to produce a dual active API where both ions are pharmaceutically active. This provides the possibility of delivering combination products in a manner where both actives would dissolve at exactly the same time as the each other (this is not true of co-administered salts).

There are a number of considerations that need to be researched before any of the above benefits could be realised. Firstly the pharmaceutical industry has historically always worked with solids and the regulations which govern the development and manufacture of pharmaceuticals have been developed accordingly, so if ILs were to be considered, control strategies would need to be carefully considered from both the pharmaceutical and the regulatory authorities. The delivery systems used to deliver these liquid APIs would also need to be considered, as current delivery technologies (such as softgel capsules) may not be compatible with these new materials. The same can also be said for the filling systems used in the manufacture; current infrastructure may not be viable, requiring significant investment from companies if the technology is to be implemented.

Published literature in this area also points out that little or nothing is known about the toxicological effects of the majority of commonly used ions, which would require safety studies to be conducted. The point is valid; however this should not preclude IL-APIs being investigated, as any API under development would be treated as a new chemical entity and would be subject to both safety and efficacy testing during its development. However many of the commonly used counter ions that have been used in IL research to date do have high toxicity and would not be suitable as pharmaceutical ingredients, this limitation will limit the flexibility of this approach.

Like conventional API salts, ILs which have been crystallised have been shown to demonstrate polymorphism. Cherukuvada and Nangia (2012) formed three polymorphs of the dibenzoate salt of the anti-tubercular drug ethambutol. However if the IL can be shown to remain in a liquid state throughout its lifecycle, then this strategy could be used to avoid the need to control polymorphic forms of API.

Crystallisation Using ILs

While the use of ILs for drug release or as the API may be some way off, given the present hurdles, they have undoubtedly been shown to be useful media for chemical reactions and for solubilising otherwise poorly soluble compounds, which suggests that ILs may be useful crystallisation media.

Given the vast amount of research that is conducted in ILs there are relatively few publications in this area. Many crystallisation practitioners would argue that ILs are not conducive to crystallisation. There are a number of reasons why this would be considered to be the case; the negligible vapour pressure means that inducing crystallisation by evaporation of the solvent cannot be used. Also ILs are very difficult to purify meaning that crystallisation from these solvents may be very difficult as even trace impurities either inhibit crystallisation or mean that robust crystallisation processes are difficult to design due to the inconsistency in impurities from batch to batch. Another consideration is the vast choice of ILs available and to date very little knowledge around the solvation mechanisms meaning that the choice of solvent for a given crystallisation may be difficult given the number of interactions between ions and solute that can occur.

However a number of researchers have recognised that while there are drawbacks to using these as media, with the correct strategies in place they could be overcome and the benefits of ILs may outweigh some of the perceived disadvantages (Reichert et al, 2006).

The largest area of crystallisation from ILs that has been conducted to date has been crystallisation of inorganic materials. ILs have been used to crystallise a wide range of inorganic materials and morphologies. For example Kowacz et al (2011) used ILs to precipitate barium sulphate crystals in a range of sizes while Hines et al (2008) used ILs as a basis for trapping unique polymorphs of $ErCl_3(OH_2)_4 \bullet 2([C_2mim]Cl)$. Since then a number of research groups have investigated the use of ILs in inorganic crystallisations. Ahmed et al (2012) reviews current progress in this area, including a wide range of crystallisation techniques such as ionothermal, solvothermal, hydrothermal, ultrasonic and microwave crystallisations alongside the traditional crystallisation methods. This variety of methods produced nano-, micro- and macroscopic crystals show that they are promising media for such crystallisations. Crystallisations of organic materials such as APIs will behave very differently. However it is promising that ILs have been successfully used as crystallisation media in this arena.

The use of ILs as crystallisation media for proteins has also been reported. Li et al (2008) reported the use of $[bmim][BF_4]$ to modify the crystallisation of lysozyme from aqueous based media where it was found that the presence of $[bmim][BF_4]$ both helped to induce crystallisation and produced larger crystals than conventional techniques that are more suited for single crystal determination. This promising work was followed up by the same author (Li et al, 2009) where the work was extended to include thaumatin. In this study they

found the ILs [bmim][PF_6] to be unsuitable for crystallisation but found that [bmim][BF_4] also produced large single crystals of thaumatin. The salting out ability of ILs in protein crystallisation is described by Kowacz et al (2012) using lysozyme and ribonuclease to demonstrate a rank order of ILs based on their hydration properties. ILs that have a large polarisable anion with low charge density were found to be the most suited for these types of crystallisation.

Interest in the use of ILs as pharmaceutical solvents was initially down to their proposed use as green solvents. This concept was demonstrated by Earle et al (2000) where synthesis of the anti-inflammatory and analgesic drug pravadoline was carried out in the ionic liquid [bmim][PF_6]. The process was designed such that the product (and by-products) could be then separated from the IL which could then be re-used in the next reaction. While this process is important in highlighting the potential for the reduction in process solvents, it should not be assumed that this could be a platform for production of many pharmaceuticals, as the molecule used for this demonstration was specifically targeted at this sequence of synthesis (regioselective nucleophilic displacement and Friedel-Craft reactions). The product and by-products still have to be isolated from the IL through distillation or extraction using organic solvent other API chemical processes are unlikely to provide the same efficiencies seen here and any new chemical route would need to be assessed on a case by case basis. In summary, this is not a platform for all new processes.

A range of possible crystallisation techniques was discussed by Reichert et al (2006). They suggest that while there are a number of challenges to be overcome, ILs may be useful

media to carry out crystallisation of organics. However since this publication there has been relatively limited progress when compared to inorganic and protein crystallisation.

In one study two new polymorphs of adefovir dipivoxil (An et al, 2010) were produced from an IL-water system. More recently particles <1 μm of rifamoicin were produced using a similar crystallisation technique (Viçosa et al, 2012). Using [emim][PF_6], amorphous particles in the region of 280-360 nm were isolated as a means to improve the bioavailability of this compound. 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 (Kroon et al, 2008).

Summary of Pharmaceutical Based Research

The uses of ILs in applications in the pharmaceutical industry have been suggested. However, to date much of the research into ILs has focussed on their use either as active ingredients or as drug delivery vehicles. Their use in crystallisation studies is limited, with most research carried out either in inorganic systems which are not directly relevant to organic molecules or as crystallisation aids to producing single protein crystals. The known barriers to using ILs as crystallisation media for small molecules, such as their difficulty to purify, may be limiting the research in this area. This work aims to investigate the practical aspects of performing API crystallisation in ILs to assess whether the suggested benefits and drawbacks are encountered.

2.5 Crystallisation Theory

In order to evaluate whether ILs can be used as media to crystallise APIs it is important to understand the solution-solute interactions and crystallisation mechanisms involved in the formation of crystalline material from a solution.

2.5.1 Solubility and Supersaturation

The choice of a suitable solvent for crystallisation can be complicated as the solvent must fulfil a number of criteria. One of the main criteria, especially using thermal methods to induce supersaturation, is that the API should have a good solubility at high temperatures but low solubility at low temperatures to ensure a good product yield.

If the solute and solvent can be considered to form an ideal solution then the solubility can be predicted from the van't Hoff equation (1903).

$$\ln x = \frac{\Delta H_f}{R}\left[\frac{1}{T_f} - \frac{1}{T}\right] \tag{2.1}$$

where x is the mole fraction of the solute in the solution, T is the solution temperature (K), T_f is the fusion temperature (melting point) of the solute (K), ΔH_f is the molal enthalpy of fusion of the solute ($J.mol^{-1}$) and R is the gas constant (8.314 $J.mol^{-1}K^{-1}$).

The equation can be written in the form

$$\ln x = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R} \tag{2.2}$$

For ideal solutions the a plot of ln x versus T^{-1} will give a straight line, with the intercept = $\Delta S_f/R$ and the slope = $-\Delta H_f/R$. However when the system is non-ideal the slope may differ

from $-\Delta H_f/R$. In such cases the entropy and entropy of mixing must be taken into account such that:

$$\ln x = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \tag{2.3}$$

There are various methods available for predicting the solubility that can range from relatively simple correlation equations to thermodynamic prediction approaches. If using correlation equations then the data set used must be suitable, and it so should not be attempted if there is a suspected phase change in the region that is being predicted. For example correlation and prediction of solubility data can be completed using a modified Apelblat equation (dual parameter equation).

$$lnx = a + \frac{b}{T} \tag{2.4}$$

where *x* is the mole fraction solubility, *T* is the absolute temperature *K* and *a* and *b* are empirical parameters obtained by least-squares fit from the experimental data. Buchowski et al (1980) described the behaviour of solid solubility in liquid as the Buchowski equation. This equation gave a good description for many solid – liquid systems using two adjustable parameters λ and h.

$$\ln\left(1 + \frac{1-x}{x}\right) = \lambda h \left(\frac{1}{T_m} - \frac{1}{T_m}\right) \tag{2.5}$$

While it is possible to describe the equilibrium thermodynamically it is possible to create supersaturated systems by, for example, cooling a saturated solution. Creating a

supersaturated solution is a requirement for forming crystals from a solution. In order to understand how a material forms crystals we must first understand the solution thermodynamics of the system by describing when the system is saturated (at equilibrium), unsaturated, metastable or supersaturated (labile).

A representation of the solubility – supersaturation relationship is shown in Figure 2.4. In the supersaturated (labile) zone, spontaneous crystallisation followed by crystallisation occurs, whereas material in the undersaturated zone will dissolve. The meta-stable zone width is the area between super-solubility and the solubility curve. In this region spontaneous crystallisation does not occur; however crystals may grow if the solution is seeded or a surface on which growth can occur is present.

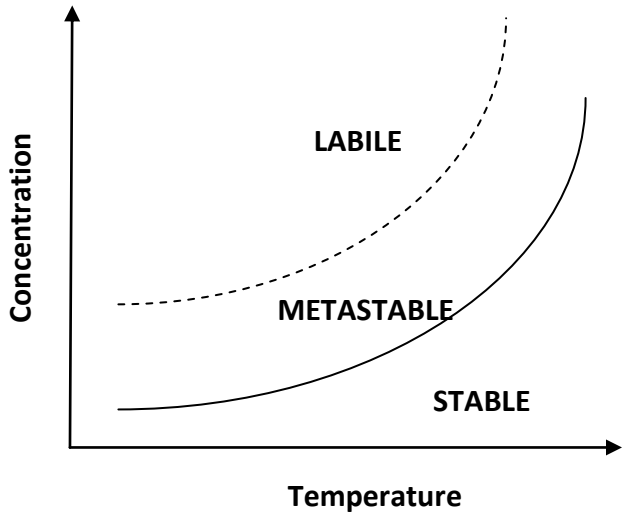

Figure 2.4: Representation of Stable, Metastable and Labile Regions

Crystals can only nucleate and grow if the solution is supersaturated; this is the driving force for crystallisation in a system. This can be defined as the difference in chemical potential

between a molecule in an equilibrium state, μ_{eq} and a molecule in its supersaturated state, μ_{ss}. This can be expressed as:

$$\frac{(\mu ss - \mu eq)}{kT} = ln\left(\frac{as}{aeq}\right) \approx ln\frac{xs}{xeq} = \ln S \tag{2.6}$$

where a_s and x_s is the activity and mole fraction respectively of the solute, a_s and x_{eq} are the activity and mole fraction respectively of the solute that is in equilibrium at temperature *T*, *k* is the Boltzmann constant and *S* the supersaturation ratio defined as:

$$S = \frac{c}{c*} \tag{2.7}$$

Where *c* is the solution concentration and *c** is the equilibrium concentration for a given temperature.

2.5.2 Nucleation and Growth

In order to form crystals from a saturated solution the initial formation of a centre of crystallisation (seeds, nuclei, dust etc) needs to be present. The nucleation event can be described as being primary or secondary. Primary nucleated systems are where there is no crystalline material present in the crystallisation and can be further described in terms of homogeneous and heterogeneous nucleation. Conversely secondary nucleation describes systems where nuclei grow in a system that already contains crystalline material.

Primary Nucleation - Homogeneous

Classical nucleation theory relies on the formation of molecular clusters combining to form a crystal nuclei. The theory is based on the condensation of a vapour to a liquid, the change in

the Gibbs free energy required to form a nucleus of radius r is given by the following equations, where γ is the interfacial tension.

$$\Delta G(r) = -(4\pi r^3/3\Omega)k_B T\ln(1+\sigma) + 4\pi r^2\gamma \quad (2.8)$$

ΔG passes through a maximum denoted as ΔG^*. Taking the derivative with respect to r and setting this equal to zero allows calculation of r_c, the critical cluster size.

$$r_c = (2\Omega\gamma) / (k_B\ln(1+\sigma) \quad (2.9)$$

Inserting this value of r_c into the original equation yields the activation energy necessary to form a nucleus of the critical size (ΔG^*). The process is depicted in Figure 2.5.

$$\Delta G^* = (16\pi\Omega^2\gamma^3)/3[k_B T\ln(1+\sigma)]^2 \quad (2.10)$$

As the supersaturation of a solution increases, both the barrier for the critical activation energy and the value of the critical size decrease. As the degree of supersaturation increases, the activation energy becomes so low that spontaneous and rapid nucleation occurs. These crystallisations require the system to be in high supersaturation and even then without a surface to grow on many materials will not nucleate.

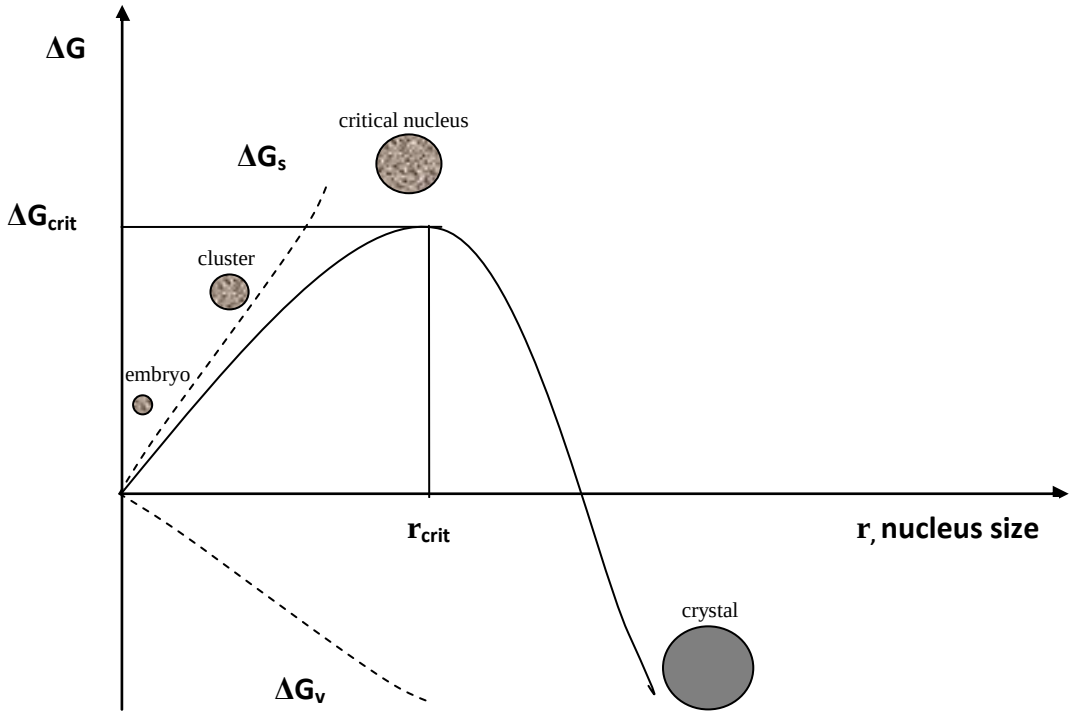

Figure 2.5: Gibbs Free Energy Change for Homogeneous Nucleation

Primary Nucleation - Heterogeneous

Heterogeneous nucleation is more common in industrial crystallisation than homogeneous nucleation. In this case, a foreign particle acts as a centre for nucleation by lowering the energy barrier required to form nuclei. The value of γ is lowered which lowers the value of ΔG^*.

Secondary Nucleation

This is used to describe systems where seed material is present. The seed acts as a centre for growth and means that the nucleation can occur at much lower supersaturations. This is a common techniques used in pharmaceutical production as a means to control either the crystal form and/or crystal habit.

While Classical Nucleation Theory (CNT) has proved to be a sufficient for describing the kinetics of the process, new theories on nucleation have focussed on the evolution of structure ,in particular, the competing nature of crystallisation in a polymorphic system. CNT suggests that the formed clusters reflects all possible polymorphs of the solute and the crystal nuclei have the same structure as a mature crystal. New proposed mechanisms of nucleation have been described, Vekilov (2010) describes a two step process in which crystalline order is preceded by the separation of a dense disordered liquid phase, as often observed in protein crystallisation (Tosi, 2011). Also Gebauer and Cofen (2011) reviewed evidence for 'pre-nucleation clusters' seen predominately in inorganic systems. This has led to non-classical theory in which the crystalline order is preceded by the separation of a dense, disordered liquid phase and fluctuations in density are disconnected from fluctuations in order. Initial clusters are liquid like and crystalline order appears overtime.

2.5.3 Crystal Growth

Once stable nuclei have been established they can grow into crystals. A number of theories and refinements have been proposed to explain the theory of crystal growth and they can be broadly categorised into three types: surface energy, adsorption and diffusion theories.

Surface energy theory suggested by Gibbs (1948) is based on crystals assuming a shape which gives a surface area minimum. Data to support this theory are lacking and it also fails to explain some known important effects such as supersaturation and solution movement on crystal growth. These drawbacks mean that currently surface energy theories are not generally used to explain crystal growth.

Adsorption layer theory was first introduced by Volmer in 1939. When solute molecules (growth units) arrive at the surface of a crystal they are loosely absorbed, free to migrate over the crystal surface, creating a dynamic equilibrium between this layer and the bulk solution. The absorbed growth units will attach into the lattice where the attractive forces are the strongest, where, under ideal conditions, a whole new plane face is completed. Once this plane has been fully formed in order for a new plane to begin, a new crystallisation centre must form. It was suggested that growth units form a monolayer island nucleus, other growth units then adding to this island to complete the next plane.

The mechanism as to how these growth units add into crystals has been refined by a number of researchers. They acknowledge that the crystals do not grow in the ideal layer by layer without imperfections occurring as described in Volmers model. The dislocations cause steps or kinks, acting as locations for growth units to add into. The mechanisms of how crystal growth occurs can be described in terms of continuous growth, surface nucleation and spiral growth.

Continuous growth assumes that the energy to form a step is low. Therefore the surface will be rough, containing many kink and step sites so material arriving at the surface easily finds a site to attach.

As the roughness of the interface decreases not all of the growth units will find a growth site. They will either return to the fluid phase or join other adsorbed growth units to form ‘surface islands’. These islands then act as step or kink sites where additional material can join and continue growth of the crystal.

If the surface is flat, growth can only occur if a step can be created. This occurs from lattice defects called dislocations where part of the crystal becomes misaligned with the rest of the crystal. Screw dislocations only extend over only part of the surface and during growth wind up into a spiral. The kinetic theory for this was developed by Burton, Cabrera and Franck (1951) and is more commonly referred to as the BCF theory.

Diffusion theory can be traced back to the work of Noyes and Whitney (1897) and is based on the understanding that crystal growth is driven by the difference in concentration of solid crystal surface and the bulk solution. The diffusion theory was refined by Berthoud (1912) and Valeton (1924) who suggest that there were two steps involved whereby the diffusion of solute molecules to the solid surface is followed by a first order reaction to arrange the molecules into the lattice. The diffusion step is widely believed to be linearly related to the concentration difference however the assumption of a first order reaction is not supported. Although it is recognised that diffusion theories have deficiencies, crystal growth rates are still measured and reported in diffusion terms.

The morphology (crystal habit) depends on the relative growth rates of the crystal faces. It is therefore the slowest growing faces that have the biggest influence on the morphology of a crystal.

2.5.4 Polymorphism

Understanding and delivering the correct form of an API is fundamental to the pharmaceutical industry for three main reasons: firstly different forms of API have different solubilities and hence can impact the bioavailability of a drug product; secondly it is important that the form of API produced is stable and does not interconvert to another form

during downstream processing, packaging and storage; and thirdly different forms of an API can be patented separately so that understanding the various forms for a given API is important for securing the intellectual property.

The form or polymorph of a substance is used to describe the unique packing order of the unit cell. Although chemically the same some substances can pack together in a different arrangement giving rise to polymorphism or different forms. Crystalline material is organised into a series of repeating units, these unit cells will form one of seven possible crystal systems; regular, tetragonal, orthorhombic, monoclinic, triclinic, trigonal and hexagonal are shown in Table 2.4.

System	Other Names	Angles between axis	Length of axis	Examples
Regular	Cubic Octahedral Isometric Tesseral	$\alpha = \beta = \gamma = 90°$	$x = y = z$	Sodium Chloride Potassium Chloride Alums Diamond
Tetragonal	Pyramidal Quadratic	$\alpha = \beta = \gamma = 90°$	$x = y \neq z$	Rutile Zircon Nickel Sulphate
Orthorhombic	Rhombic Prismatic Isoclinic Trimetric	$\alpha = \beta = \gamma = 90°$	$x \neq y \neq z$	Potassium Permanganate Silver Nitrate Iodine α- Sulphur
Monoclinic	Monosymmetric Clinorhombic Oblique	$\alpha = \beta = 90° \neq \gamma$	$x \neq y \neq z$	Potassium Chlorate Sucrose Oxalic Acid β - Sulphur
Triclinic	Anorthic Asymmetric	$\alpha \neq \beta \neq \gamma \neq 90°$	$x \neq y \neq z$	Potassium Dichromate Copper Sulphate
Trigonal	Rhombohedral	$\alpha = \beta = \gamma \neq 90°$	$x = y = z$	Sodium Nitrate Ruby Sapphire
Hexagonal	None	z axis is perpendicular to the x, y and u axes, which are inclined at 60°	$x = y = u \neq z$	Silver Iodide Graphite Water (ice) Potassium Nitrate

Table 2.4: The Seven Crystal Systems (re-created from Mullin)

More than 80% of crystalline elements and inorganic compounds are either regular or hexagonal. As molecules become more complex then orthorhombic and monoclinic systems are favoured.

When a solid crystallises from solution it can either be under thermodynamic or kinetic control. If it is thermodynamically controlled then the solvent used is immaterial. However if under kinetic control then in some cases the choice of solvent can influence the resultant crystal structure and hence crystallise meta-stable forms. If a form is meta-stable then it will covert in time to the thermodynamically stable polymorph; this process can take a matter of minutes to years.

This phenomenon can be described in Ostwald's rule of stages (Liesegang, 1911) where he stated that an unstable system will not directly convert to the most stable state but to a state that results in the smallest loss of free energy. Exceptions to this rule are known to exist but it provides an important consideration when crystallising molecules that are either known to or predicted to have multiple polymorphic forms.

2.5.5 Crystallisation Methods

There are various methods that can be employed to generate the supersaturation required to crystallise APIs. By far the two most common methods used to do this are cooling crystallisation or anti-solvent crystallisation.

In cooling crystallisation methods the temperature of the solution is lowered so that is below the saturation concentration of the solution. Spontaneous crystallisation will occur when the solution is cooled sufficiently that it becomes supersaturated to such an extent that it crosses the metastable zone and forms crystals as there is enough energy in the system to

form stable nucei. Alternatively once in the meta-stable zone width (MSZW) crystallisation can be initiated using seed crystals which grow as the solution becomes de-supersaturated. Factors to consider when designing a cooling crystallisation include: the solubility gradient such that at higher temperatures sufficient material can be dissolved in solution in order to design a process capable of being scaled into an appropriate reactor while having a low enough solubility at the isolation temperature to ensure commercially viable yield is obtained from the process. The rate of cooling also needs to be considered as it is more likely that kinetically favoured forms can be isolated when higher cooling rates are used whereas, in general, it is the thermodynamically favourable form that is usually desired. If trying to control the particle size through crystal growth then slow cool is preferred over fast to avoid any secondary nucleation events.

Evaporative crystallisation is also used to generate saturated solutions for crystallisation. This is achieved by heating a solution to its boiling point. As solvent evaporates the concentration of the solution increases. The surface from which the evaporation occurs becomes more supersaturated than the bulk solution, forming crystals at the surface. Crystals can then fall back into the bulk solution and grow. Although it has been shown that some ILs can be distilled (Earle et al, 2006) it is not practically possible to use the majority of ILs for such processes and this was not considered as a viable method for this work.

Antisolvent crystallisation is a commonly used method to induce crystallisation where the solution containing the compound is mixed with a solvent where the solute has low or negligible solubility. The mixed solvent system has a lower solubility and hence the possibility for generating supersaturated solutions. The technique can be especially useful

for materials where temperature has little impact on the solubility and materials that are unstable at high temperatures. To ensure that regions of higher saturation within the solution are minimised then the antisolvent should be added slowly under good mixing. Adding the antisolvent too quickly increases the risk of forming and isolating kinetically favourable forms but also increases the chance that impurities can be included into the crystal, which if uncontrolled can result in batches failing specification.

Reactive crystallisation works by adding one reactant to a solution of another causing a chemical reaction. The resulting product has a lower solubility and crystallises out of solution. Reactive crystallisations have been carried out in ILs but have not been considered as this work is more focussed on the physical control of API rather than formation through chemical synthesis. However this remains a possible method that could be used with ILs.

An alternative crystallisation method that may be suitable in combination with ionic liquids is the use of SuperCritical Fluids (SCF). The most applicable strategy to any potential IL crystallisation is commonly referred to as the Gas Anti-Solvent (GAS) process, where the supercritical fluid is used as the anti-solvent. A SCF is a substance, commonly CO_2, that is above its critical temperature and pressure. When in this physical state they possess unique properties that can give them the diffusivity of a gas but the solvation power of a liquid. When brought into contact with a solution containing API saturation point is rapidly reached promoting nucleation very quickly, which depending on the equipment set-up can produce small particles.

2.6 Summary

This review highlights that, compared to conventional solvents, ILs have unique properties which have been exploited by some industries to develop new chemical processes. While some potential applications for their use in the pharmaceutical industry have been reported little has been done to assess their suitability as a medium for crystallisation of API. This work looks to address this gap by establishing if the unique properties of ILs could provide any benefits to crystallising APIs and in particular if they could be used to modify physical properties.

The following chapters detail the work undertaken to establish this and includes details on the materials and methods used followed by studies conducted with paracetamol, ibuprofen and flufenamic acid and finishes by providing details of the practical issues encountered during this work. The conclusions from the work with thoughts as to further work in the field are provided at the end of this thesis.

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CHAPTER 3: MATERIALS AND METHODS

3.1 Introduction

This chapter introduces the materials and methods that were used throughout this work. It provides a rationale as to the selection of the materials used and baseline data on the specific materials used in this study such that any of the reported work could be repeated.

3.2 Materials

The nature and sourcing of materials used in this work are described in the following sections. A summary of all the materials used is provided in Tables 3.2 and 3.3.

3.2.1 Rationale for IL Selection

The primary aim of the thesis was to investigate the possibility of using ionic liquids as crystallisation media. It was decided therefore to source these materials from suppliers rather than to synthesise in the laboratory.

Given the large number of possible ionic liquids that could be used in this study a rationale for the selection was required. The criteria used were:

1. Needed to be commercially available
2. To be a liquid at or around room temperature
3. Have a purity >95%
4. Cost <£2 per g

There are a number of suppliers of ionic liquids that operate at a range of scales from gram to multi-ton and offer various ranges of products that, due to the nature of IL research, are ever changing and evolving. The suppliers assessed during this work were:

1. Merck Chemicals
2. BASF
3. Cytec
4. Scionix
5. IoLiTec
6. Sigma Aldrich

A traffic light system was used to assess the products from these suppliers against the required criteria; details are shown in Table 3.1.

From this assessment in order to complete as systematic a study as possible given the ILs currently commercially available, it was decided to base the studies on the 1,3-methylimidazolium cation. This cation is by the most researched cation in IL studies and fulfilled many of the criteria needed for this work. Anions were then selected to provide a range to assess the impact of the crystallisation of the model compounds. The ionic liquids used in this study are displayed in Table 3.2.

CATION	ANION	Melting Point <20 °C	Commercially Available (Purity >95%)	Cost < £2 per g	Suitable for Further Evaluation?
Ammonoium	Halides (Cl, Br, I)				
	Borate (inc. Tetrafluoroborate)				
	Amide (Dicyanoamide)				
	Imide (bis(trifluoromethylsulfonyl)imide))				
	Phosphate (inc. Hexafluorophosphate)				
	Acetate				
	Sulfates / Sulfonates				
	Nitrates				
Imidazolium	Halides (Cl, Br, I)				
	Borate (inc. Tetrafluoroborate)				
	Amide (Dicyanoamide)				
	Imide (bis(trifluoromethylsulfonyl)imide))				
	Phosphate (inc. Hexafluorophosphate)				
	Acetate				
	Sulfates / Sulfonates				
	Nitrates				
Pyridinium	Halides (Cl, Br, I)				
	Borate (inc. Tetrafluoroborate)				
	Amide (Dicyanoamide)				
	Imide (bis(trifluoromethylsulfonyl)imide))				
	Phosphate (inc. Hexafluorophosphate)				
	Acetate				
	Sulfates / Sulfonates				
	Nitrates				
Pyrrolidinium	Halides (Cl, Br, I)				
	Borate (inc. Tetrafluoroborate)				
	Amide (Dicyanoamide)				
	Imide (bis(trifluoromethylsulfonyl)imide))				
	Phosphate (inc. Hexafluorophosphate)				
	Acetate				
	Sulfates / Sulfonates				
	Nitrates				
Sulfonium	Halides (Cl, Br, I)				
	Borate (inc. Tetrafluoroborate)				
	Amide (Dicyanoamide)				
	Imide (bis(trifluoromethylsulfonyl)imide))				
	Phosphate (inc. Hexafluorophosphate)				
	Acetate				
	Sulfates / Sulfonates				
	Nitrates				
Phosphonium	Halides (Cl, Br, I)				
	Borate (inc. Tetrafluoroborate)				
	Amide (Dicyanoamide)				
	Imide (bis(trifluoromethylsulfonyl)imide))				
	Phosphate (inc. Hexafluorophosphate)				
	Acetate				
	Sulfates / Sulfonates				
	Nitrates				

Table 3.1: IL Selection Criteria

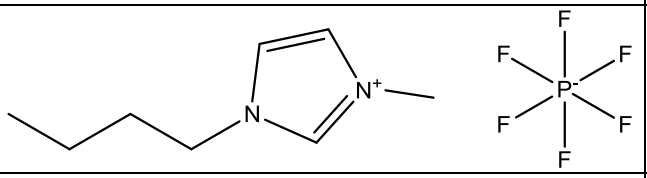
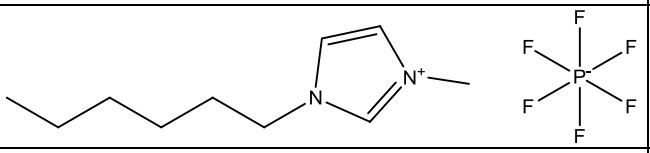
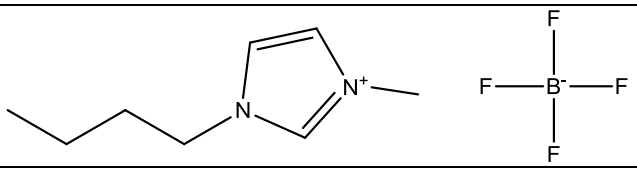
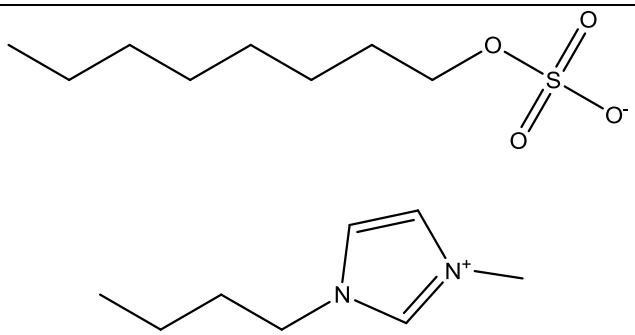
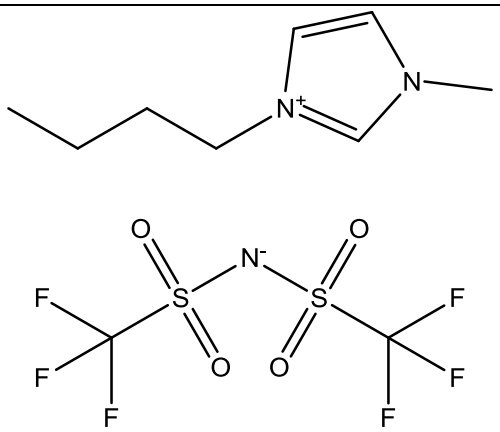
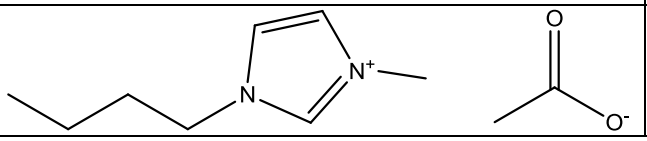
Material	Structure	Purity	Source	Batch
[bmim][PF_6]		99%	Merck	S9587950 917
[hmim][PF_6]		98%	Merck	S5205765 922
[bmim][BF_4]		>98%	BASF	BCBK6686V
[bmim] [$C_8H_{17}OSO_3$]		>95%	Sigma	BCBJ9526V
[bmim][NTf_2]		>98%	BASF	BCBJ5958V
[bmim] [CH_3COO]		>95%	BASF	STBC9122V

Table 3.2: Ionic liquids Used in Practical Work

3.2.2 Rationale for Model API Compounds

Three model compounds were selected for this investigation. They were acetaminophen (commonly known as paracetamol), ibuprofen and flufenamic acid.

Paracetamol is a well known active pharmaceutical ingredient used to treat pain that has been used in market products since 1953. It can be considered to be a polar molecule that is freely soluble in water. Ibuprofen is also a well established active pharmaceutical that has been marketed since 1969 for pain relief and to reduce swelling. Ibuprofen is less polar than paracetamol and as such is poorly soluble in water. Flufenamic acid is a potent anti-inflammatory API used in the treatment of osteoarthritis, rheumatoid arthritis and other painful musculosketal illnesses. Flufenamic acid is known to be highly polymorphic with eight polymorphs having been reported in the literature. These three molecules represent different scenarios when choosing a solvent for crystallisation and so were chosen as good model compounds for this study. A summary of the materials used their source and the grade or purity used is shown in Table 3.3.

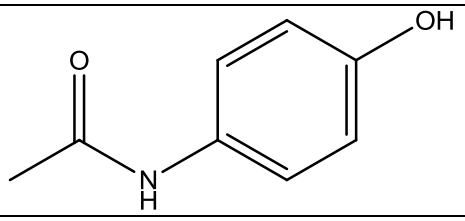
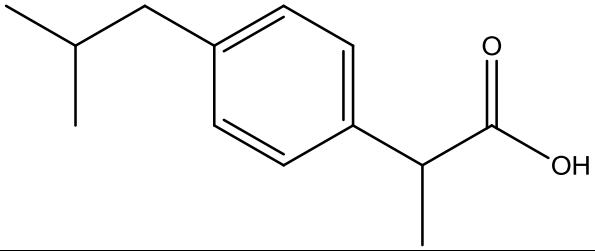
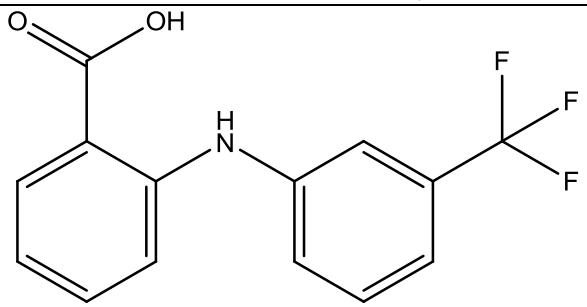
Material	Structure	Grade or Purity	Source	Batch
Paracetamol		>99%	Merck	S3876440 424
Ibuprofen		>98%	Sigma	SLBF2671V
Flufenamic Acid		>97%	Alfa Aesar	B23583

Table 3.3: Purity and Source of Materials Used

3.2.3 Model Compound Characterisation

Paracetamol

The paracetamol was used as supplied from Merck. Baseline analysis was completed on this material to determine: form, melting point, particle size and habit, were assessed by XRD, DSC, laser diffraction and microscopy. The diffraction pattern of the input material was concordant with the reference for monoclinic form I material (Haisa, 1975) as shown in Figure 3.1

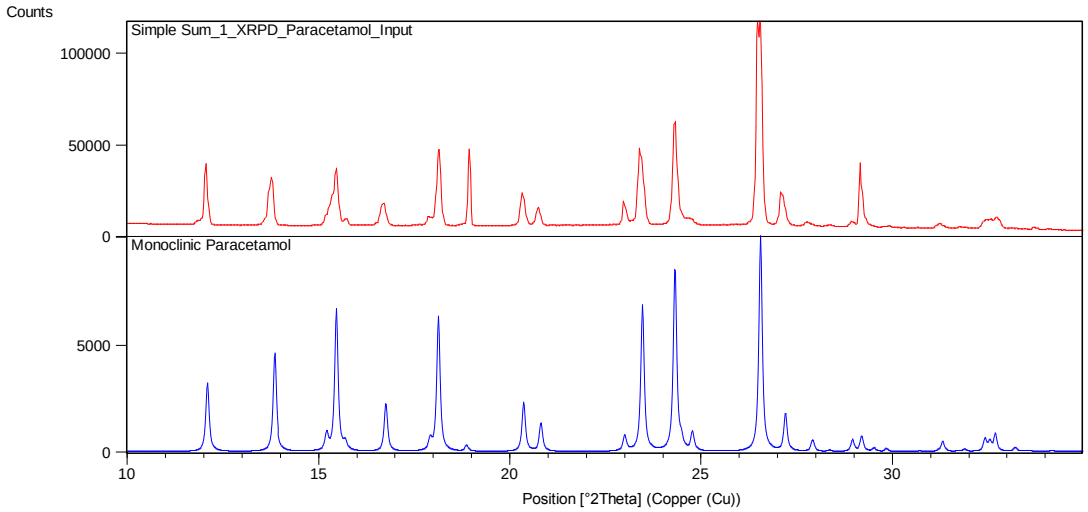


Figure 3.1: Overlay of Input Paracetamol (red) and Monoclinic Form I Reference (blue) (Haisa, 1975)

Thermal analysis by DSC, shown in Figure 3.2, shows an onset of melt at 169.01 °C with the melting point recorded at 169.78 °C which is consistent with literature data for this form. No other thermal events were observed.

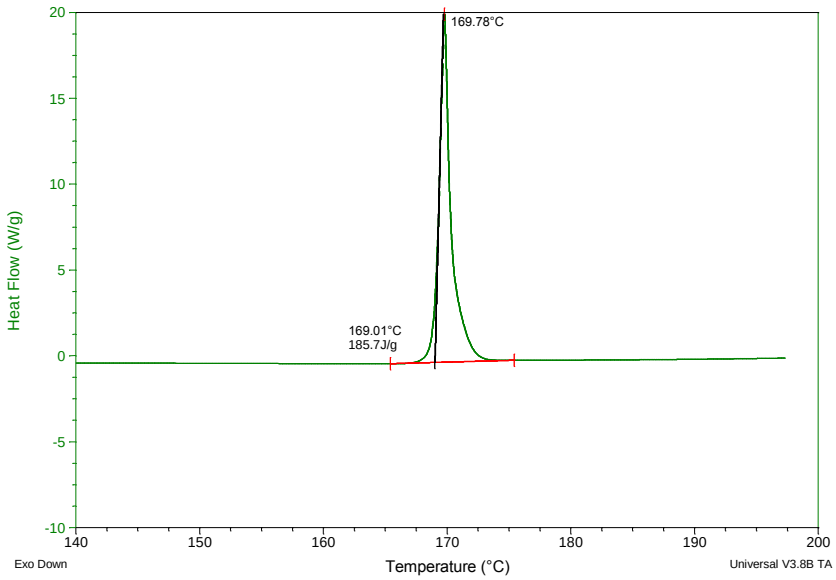


Figure 3.2: DSC Trace of Input Paracetamol

Particle habit was analysed by optical and scanning electron microscopy shown in Table 3.4. The images show the primary particles to have an irregular shape with a broad range of particle sizes observed in the sample.

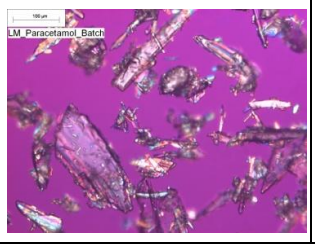
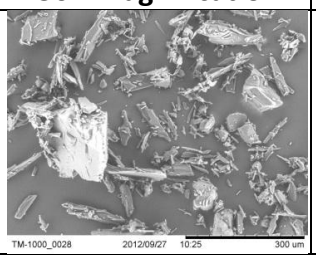
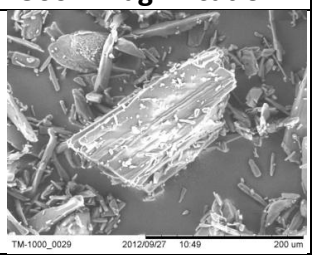
Optical Microscopy		Scanning Electron Microscopy	
50X Magnification	100X Magnification	250X Magnification	500X Magnification
			

Table 3.4: Optical and Scanning Electron Microscopy of Input Paracetamol

The particle size distribution shown in Figure 3.3 confirms the wide particle size range observed with the d_{10}, d_{50} and d_{90} values measured as 11 µm, 47 µm and 199 µm respectively. The distribution is multi-modal showing multiple populations of particles observed giving calculated span of 4.0.

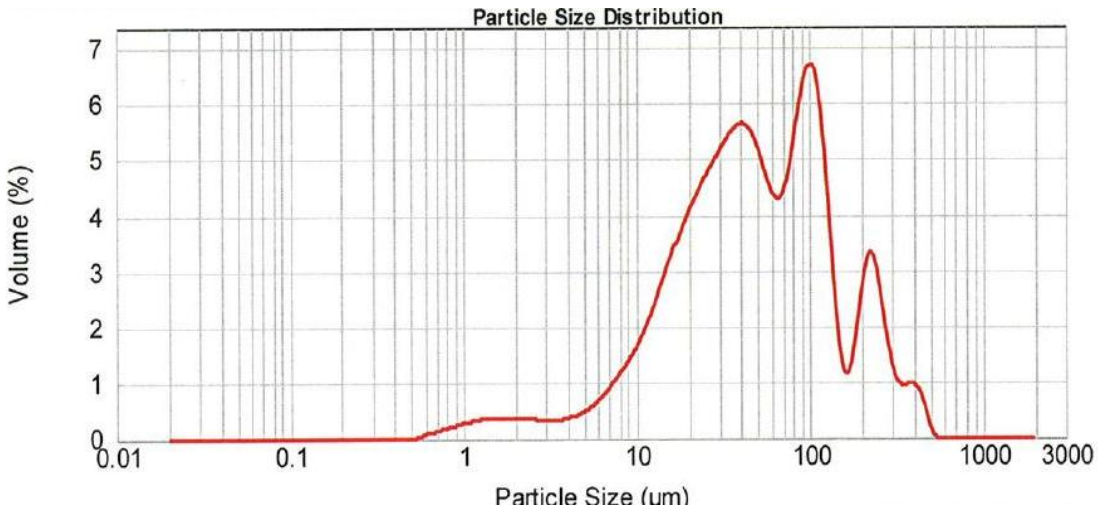


Figure 3.3: Particle Size Distribution of Input Paracetamol

Ibuprofen

Ibuprofen was used as supplied from Sigma Aldrich. The same analyses were completed to obtain baseline data for the input.

The diffraction pattern of the input was concordant with Form I material and is displayed in Figure 3.4.

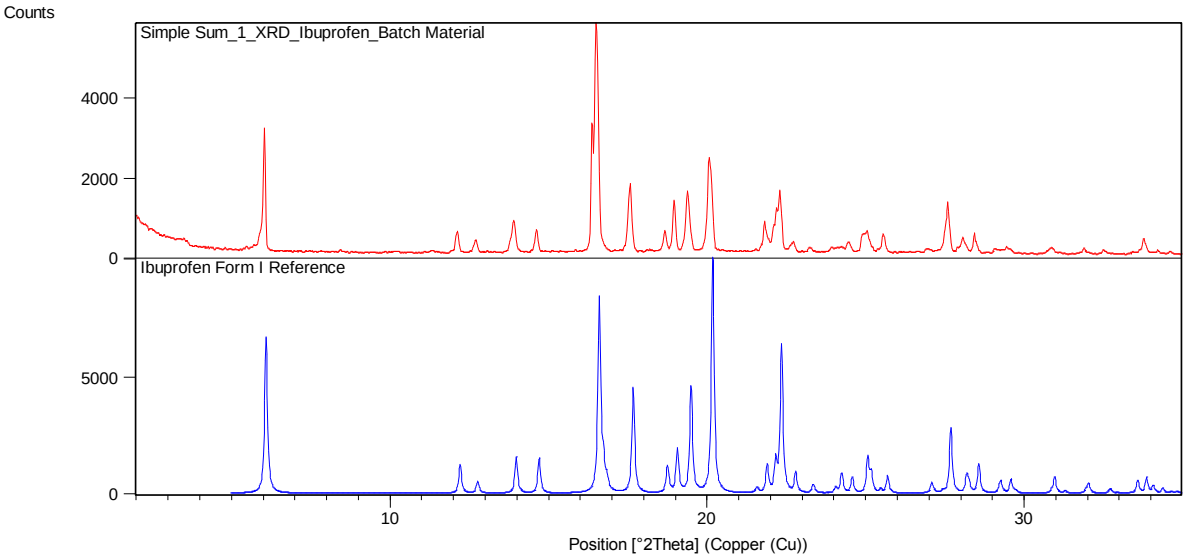


Figure 3.4: XRD Pattern of Input Ibuprofen (red) and Form I Reference (blue)

Thermal analysis by DSC shows an onset of melt at 74.04 °C with the melting point recorded at 76.74 °C which is consistent with literature data for this form. No other thermal events were observed. The obtained trace is shown in Figure 3.5.

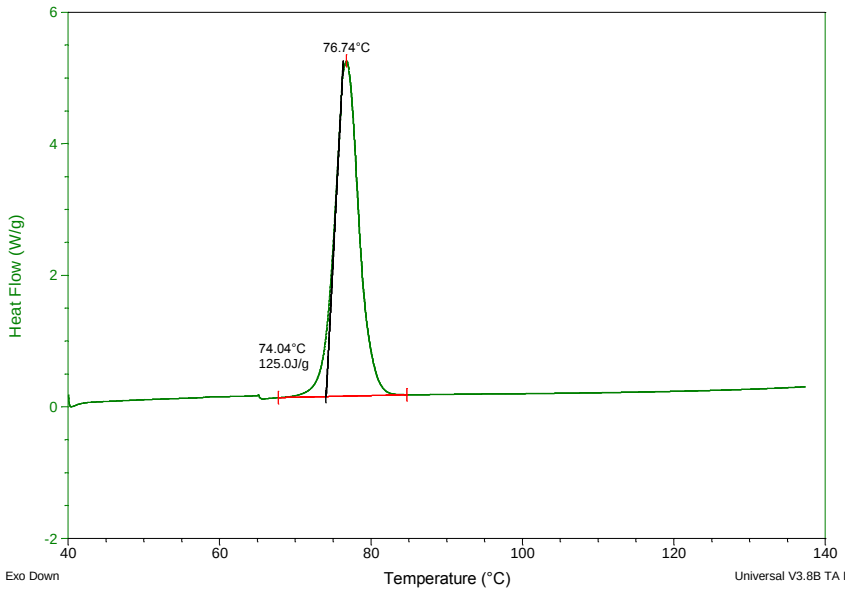


Figure 3.5: DSC Trace of Input Ibuprofen

Particle habit was as analysed by optical and scanning electron microscopy shown in Table 3.5. The images show the primary particles to plate shaped with broad range of particle sizes observed in the sample.

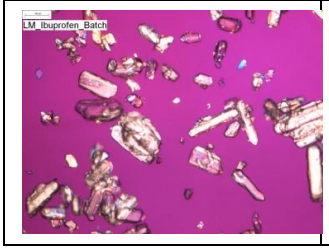
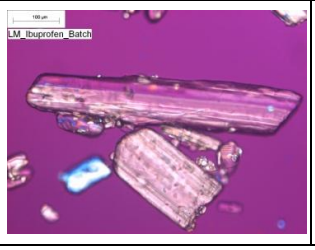
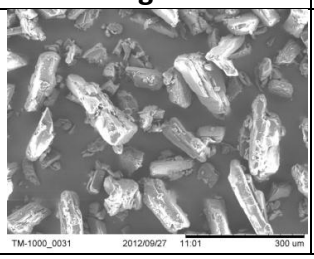
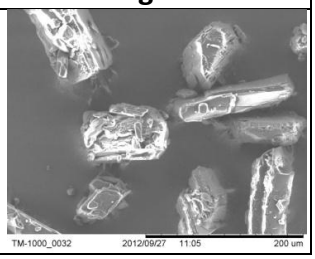
Optical Microscopy		Scanning Electron Microscopy	
50X Magnification	**100X Magnification**	**250X Magnification**	**500X Magnification**
			

Table 3.5: Optical and Scanning Electron Microscopy of Input Ibuprofen

The particle size distribution shown in Figure 3.6 shows a reasonable control of the particle size with the d_{10}, d_{50} and d_{90} values measured as 21 µm, 57 µm and 126 µm respectively. The span for the input ibuprofen was calculated as 1.8.

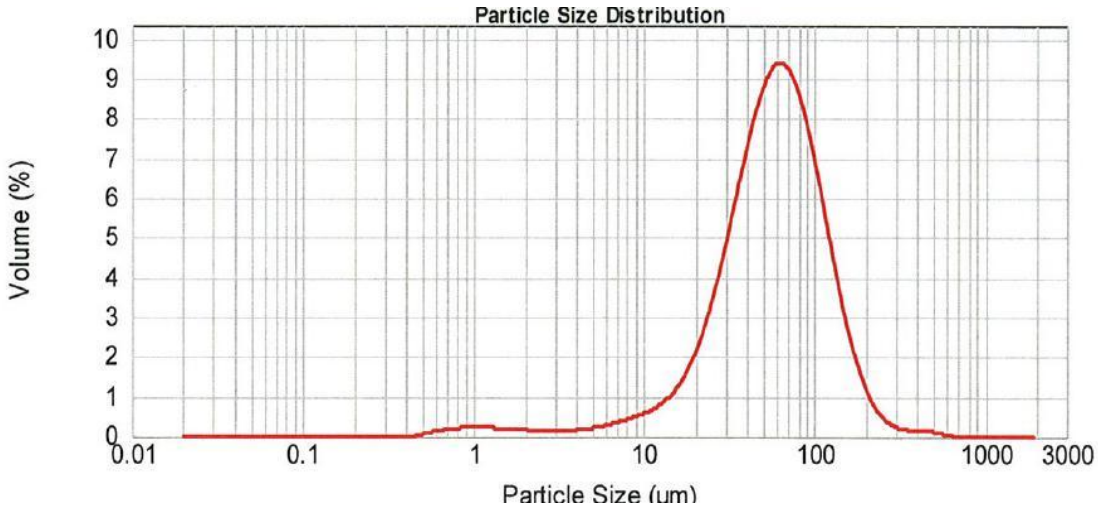


Figure 3.6: Particle Size Distribution of Input Ibuprofen

Flufenamic Acid

The input flufenamic acid was analysed by XRD, DSC and optical and scanning electron microscopy. The size of the input was not determined as particle size was not deemed relevant to the crystallisation studies.

For reference the XRD on the input batch was completed and the obtained diffraction pattern is shown in Figure 3.7.

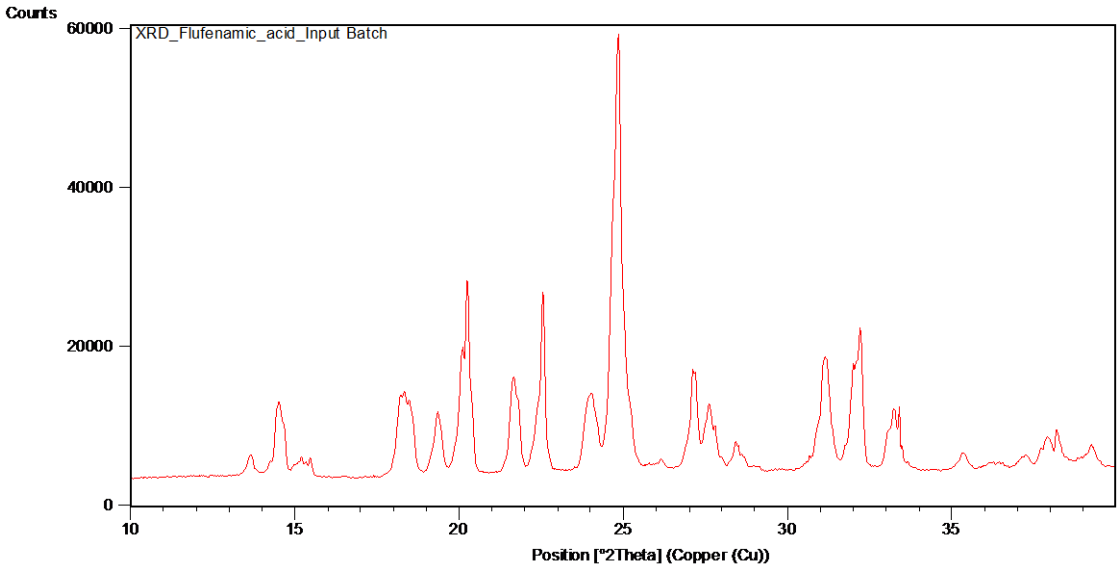


Figure 3.7: XRD Analysis of Input Flufenamic Acid

DSC analysis, Figure 3.8, shows the onset of melt of the material at 133.57 °C with the melting point recorded at 136.41 °C which is the melting temperature of form I. No exothermic transition was detected prior to the melt.

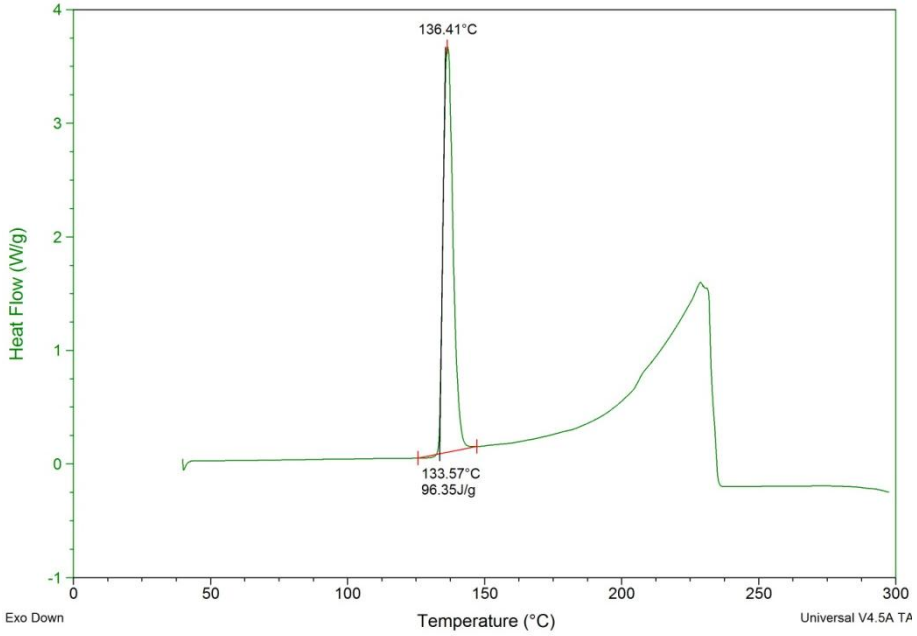


Figure 3.8: DSC Analysis of Input Flufenamic Acid

The images obtained from optical microscopy and SEM show large tabular crystals which are >300 µm are displayed in Table 3.6.

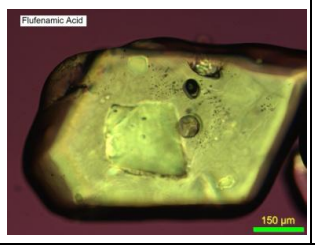
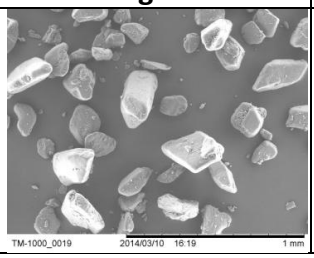
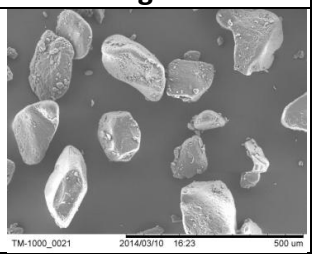
Optical Microscopy		Scanning Electron Microscopy	
50X Magnification	**100X Magnification**	**100X Magnification**	**200X Magnification**
			

Table 3.6: OM and SEM Images of Input Flufenamic Acid

3.3 Methods

Methods used to prepare and analyse materials used in this thesis are described in the following sections. This includes details on the development of a method to measure the equilibrium solubility of API in ILs. Followed by details of how the MSZW was established for the systems of interest. The equipment and methodology used to conduct various small scale crystallisations and how the resultant precipitated products were analysed are then provided.

3.3.1 Solubility

Paracetamol and Ibuprofen in [bmim][PF_6], [hmim][PF_6] and water

An excess of a compound was added to approximately 5 ml ionic liquid 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 hours 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 analysing the amount of solute dissolved by UV over time. Saturation was found to be reached after 22 hours, and consequently all samples were left for at least 24 hours.

At each temperature point an aliquot of the saturated solution was removed using an oven-heated (5 K above sample temperature) plastic syringe (2.5 ml syringe) fitted with a PTFE filter 0.5 ml (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 R2>0.996). Where necessary, further dilution was carried out to ensure that the measured absorbance was within the standard curve. The volume of ionic liquid and methanol or water was determined from the graduated scale of the syringe (±0.1mL) and was used as the volume in the solubility determination. For paracetamol solubility studies, data were obtained at λmax = 250 nm in [bmim][PF_6] and [hmim][PF_6], and λmax = 245 nm in water. For ibuprofen, data were obtained at λmax = 264 nm for [bmim][PF_6] and [hmim][PF_6] and λmax = 222 nm for water. Three independent samples were analysed for each temperature point and each sample was measured three times. The temperature–solubility profiles were then determined for ibuprofen and paracetamol in [bmim][PF_6], [hmim][PF_6] and water.

Solubility for Paracetamol and Flufenamic Acid Scoping work

A slurry sample was prepared in an HPLC vial fitted with a screw top; the slurry was heated to the desired temperature using a mini-reactor. The sample was held at the desired temperature for >24 hours 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. An aliquot of the sample was weighed into a HPLC vial by filtering through a PTFE filter (Whatman filter, 0.2 µm filter). The vial was diluted with methanol and re-weighed to calculate the dilution factor. Samples were run on an HPLC Linear gradient from 0 to 95% acetonitrile over 3 minutes at 60 °C and 1.5 mL/min on a Zorbax SB-C18 3x50 mm, 1.8 µm column (part number 884950-576). The concentration was determined from

pre-determined calibration curves in the same solvent. Each sample was run in duplicate with the average result reported.

3.3.2 Meta-Stable Zone Width

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 K). A known excess of model compound 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 $K.min^{-1}$ to 263 K in order to achieve full dissolution of the solid. The solutions were cooled at the same rate to 288 K. 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 the model compound system.

3.3.3 Cooling Crystallisations

All crystallisations were carried out in a 60 mL glass vessel with overhead stirring (500rpm); 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 >353 K in order to achieve full dissolution, then cooled at 0.2 $K.min^{-1}$ to 293 K. Crash cooling experiments were also performed on the same equipment at a cooling rate of 10 $K.min^{-1}$. For the seeded experiments, the solutions were cooled to 333 K, seeded with 20 mg of input seed, and held for 4 hours before cooling to 293 K at 0.2 $K.min^{-1}$. In all cases the precipitate was recovered by vacuum filtration (750 mbar).

3.3.4 Anti-Solvent Crystallisation

An anti-solvent crystallisation was performed on the same equipment to determine the impact of an additional solvent on the filtration time. In this case dichloromethane was added to a final ratio of 80:20 vol:vol using the multimax syringe pumps. A small condenser was attached to the vessel to reduce the loss of solvent as vapour.

3.3.5 SCF Crystallisation

Experiments were performed using a stainless steel pressure vessel equipped with a viewing port and a heating jacket with circulating silicon oil, Figure 3.9. The sample contained in a HPLC vial was lowered into the pressure vessel. After the sample vial was lowered, the vessel was sealed and the CO_2 was added to the required pressure. CO_2 entered the pressure vessel from a liquid withdrawal cylinder at 55 bar via stainless steel tubing. CO_2 was further pressurised using a manual pump. The manual pump worked like a piston and was covered with a coil containing circulating refrigerant to cool the CO_2 and ease pressurisation. The flow rate of CO_2 into the pressure vessel was controlled using valves V1, V2 and V3. At the end of the experiment CO_2 was vented to the atmosphere using valves V4 and V5.

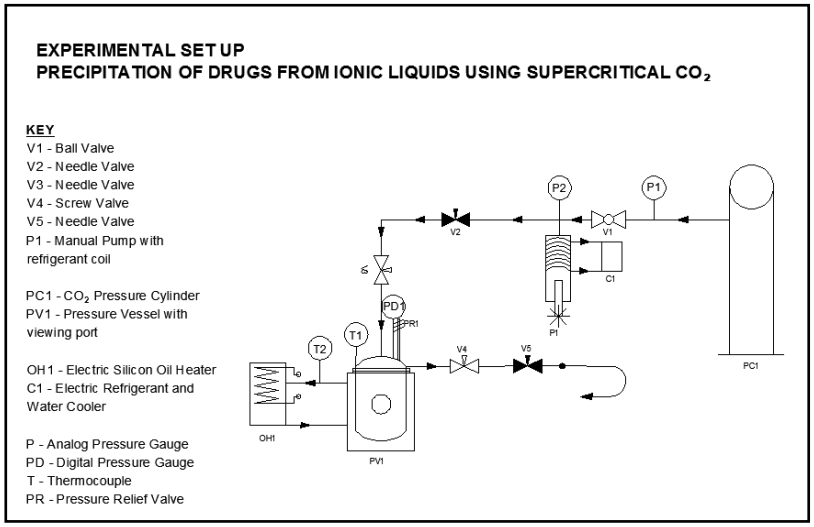


Figure 3.9: Equipment set-up for scCO2 Crystallisation

3.3.6 Analysis

Analysis of the crystallised products and the starting materials was carried out using the procedures below.

X-Ray Diffraction

Samples were prepared by adding approximately 25 mg of material into a single well in a 96 well plate. The samples were scanned three times and an average of the three scans taken. The diffraction patterns were obtained using a PANalytical Empyrean diffractometer in transmission mode using the following parameters:

Scan Axis:	2Theta only	Receiving Slit Size [mm]	0.1000
Start Position [°2Th.]	1.9975	Temperature [°C]	21.00
End Position [°2Th.]	34.9915	Anode Material	Cu
Step Size [°2Th.]	0.0260	K-Alpha1 [Å]	1.54060
Scan Step Time [s]	175.1850	K-Alpha2 [Å]	1.54443
Scan Type	Continuous	K-Beta [Å]	1.39225
Divergence Slit Type	Fixed	K-A2 / K-A1 Ratio	0.50000
Divergence Slit [°]	0.4354	Generator Settings	40 mA, 45 kV

Imaging Techniques

Particles were analysed by optical microscopy using a Olympus BX51 fitted with a CoolSNAP-Pro camera), using Image-Pro Plus software (Version 4.5). Samples were prepared by dispersing a small amount of material in oil with a glass slide placed on top of the sample.

Scanning electron microscopy was carried out using a Hitachi TM-1000. Using a adhesive carbon disc mounted on an aluminium stub. A small amount of sample was dispersed onto the carbon disc and the sample was then analysed using an accelerated voltage of 15000 Volts (note the sample was not coated).

Particle Size

Particle size was measured by laser diffraction using a Malvern Mastersizer 2000. The dispersants used for the model compounds were different: iso-octane with 0.05%w/w lecithin was used for paracetamol and water used for ibuprofen. To prepare the sample a small amount (approximately 100mg) of material was placed in 2mL of dispersant. The sample was sonicated for 30 seconds at 25% power. The Malvern was flushed with the diluents and, when clean, a background measurement was taken. The sample was then added to give a obscuration of between 2 and 10% before analysing the sample three times. An average of the three results was reported, along with the span of the distribution (d_{90}-d_{10}/d_{50}). It should be noted that the calculation of particle size was based on Fraunhofer theory and assumed particle sphericity which was not seen, nor expected, for the crystals obtained from any of the solvent systems.

Differential Scanning Calorimetry

When samples were analysed by differential scanning calorimetry the following procedure was used. Small amount of sample (1-5mg) was accurately weighed into an aluminium pan. An aluminium lid was placed on top of the pan and lightly crimped. The sample was analysed using a TA Q200. The pan was allowed to equilibrate at 298 K before a standard ramp of 10 $K.min^{-1}$ was started.

3.4 Conclusions

This chapter discussed how the selected materials were prepared and characterised. Detail on the experimental protocols and methods are give such that any of the work in the

following chapters could be repeated. The chapter has also reported the physical properties of the input API materials used for the study.

3.5 References

Haisa, M., Kasjino, S., Kawai, R., Maeda, H., (1975) The Monoclinic Form of *p*-Hydroxyacetanilide, **Acta Cryst**., B32, 1283

CHAPTER 4: STUDIES WITH PARACETAMOL

4.1 Introduction

This chapter is focussed on the experimental work completed on paracetamol. Starting first by outlining the methodology used to determine the solubility of paracetamol in the ILs [bmim][PF_6] and [hmim][PF_6] the results were then assessed using solubility correlations to understand if these models could be applicable to such systems.

Using these unique solvents a series of cooling crystallisations were designed and completed. The Meta-Stable Zone Width (MSZW) was established and combined with the solubility data to design a series of cooling crystallisations. The crystallisations assessed the impact that nucleation mechanism and concentration had on the crystal form, habit and size of the resultant crystals.

A protocol for screening further ILs was then developed and used to assess a homologous series of ILs to determine the impact of changing the anion on the physical form of crystallised material.

4.2 Solubility

4.2.1 Validation of Solubility Method – Solubility in Water

Before the solubility was determined in any ILs the methodology was established by analysing the solubility in water and comparing to literature values. Solubility data were determined between 298.15 K and 338.15 K in 10 K increments. For each measurement the overall mean from three experiments plus or minus the standard error of the mean were calculated for both the absorbance and solubility.

A summary of the data are shown below in Table 4.1. The raw data obtained from the UV spectrophotometer with corresponding solubility data in mg solute per mL water can be found in Appendix 1.

Temperature K	Absorbance $\sum_{abs} (\overline{x}/n)$	Solubility 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

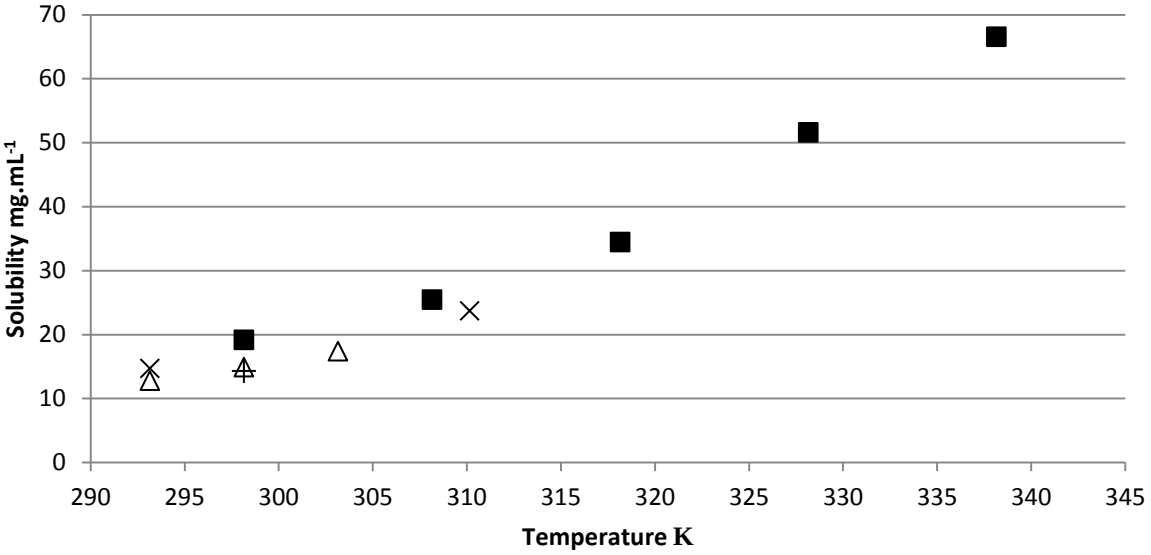
[a] **The absorbance values are out of line for 328.15 K and 338.15 K due to additional dilution of the samples.**

Table 4.1: Solubility of Paracetamol in Water

where solubility is the overall mean from three independent experiments ± the standard error of the mean

The solubility of paracetamol ranged from 19.16 mg.mL^{-1} to 66.55 mg.mL^{-1} across the temperature range studied which, according to the US Pharmacopeia definition (U.S. Pharmacopeia, Section 5.30), means that paracetamol can be described as being sparingly soluble to soluble. The standard errors of the mean obtained at these temperatures were all <2.14 mg.mL^{-1} showing that all the samples were in reasonable agreement.

Data obtained in this work were plotted against literature data (Etman, 1990), (Granberg, 1999) and (Garekani, 2003), Figure 4.1, to determine if the method used provided comparable results.



This work ■, Granberg et al Δ, Etman et al x and Garekani et al +

Figure 4.1: Solubility Data in Water as a Function of Temperature for Paracetamol

The solubility data for paracetamol data measured in this work are in good agreement with other laboratories and also extends to higher temperatures than has been reported in the literature. This gives confidence that the methodology used in this work is suitable for the purposes of establishing equilibrium solubility data for crystallisation development.

4.2.2 Solubility in Ionic Liquids

Using the same methodology the solubility of paracetamol was determined in the ILs [bmim][PF_6] and [hmim][PF_6] across the temperature range 298.15 K to 338.15 K at 10 K increments. A summary of the data is shown below in Tables 4.2 and 4.3 for [bmim][PF_6] and [hmim][PF_6] respectively. The raw data obtained from the UV spectrophotometer with corresponding solubility data in mg solute per mL can be found in Appendix 1.

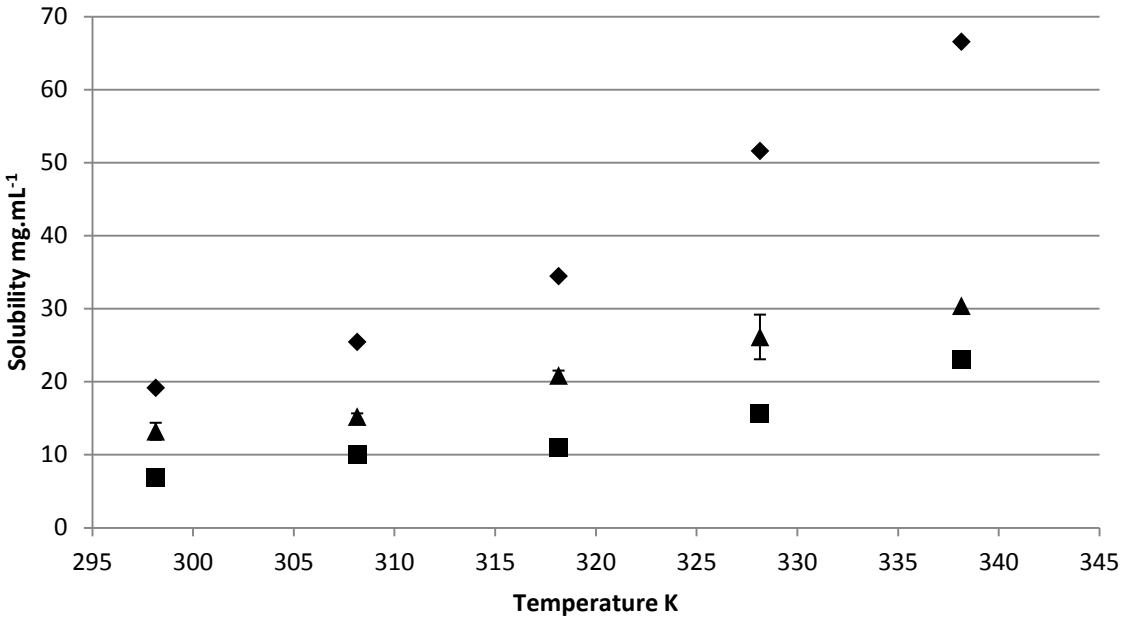
Temperature K	Absorbance $\sum_{abs}(\overline{x}/n)$	Solubility mg.mL^{-1}
298.15	0.579 ± 0.011	6.95 ± 0.14
308.15	0.829 ± 0.059	10.05 ± 0.73
318.15	0.907 ± 0.102	11.01 ± 1.26
328.15[a]	1.282 ± 0.009	15.67 ± 0.11
338.15[a]	1.880 ± 0.018	23.09 ± 0.23

Table 4.2: Solubility of Paracetamol in [bmim][PF_6] from T = 298.15 K to 338.15 K
where solubility is the overall mean from three independent experiments ± the standard error of the mean

Temperature K	Absorbance $\sum_{abs}(\overline{x}/n)$	Solubility 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[a]	1.931 ± 0.048	26.13 ± 0.67
338.15[a]	2.242 ± 0.223	30.40 ± 3.06

Table 4.3: Solubility of Paracetamol in [hmim][PF_6] from T = 298.15 K to 338.15 K.
where solubility is the overall mean from three independent experiments ± the standard error of the mean

Solubility values of 6.95 mg.mL^{-1} to 23.09 mg.mL^{-1} were obtained for [bmim][PF_6] and 26.38 mg.mL^{-1} to 120.41mg.mL^{-1} for [hmim][PF_6] across the same temperature range. This would rank paracetamol as ranging from slightly soluble to sparingly soluble in [bmim][PF_6] and sparingly soluble to freely soluble in [hmim][PF_6] across the temperature range studied. The samples were all in good agreement with standard error of the mean of <1.26 mg.mL^{-1} and <3.06 mg.mL^{-1} obtained for [bmim][PF_6] and [hmim][PF_6] respectively. The data were plotted together with the solubility data in Figure 4.2.



water ♦, [bmim][PF_6] ■ and [hmim][PF_6]▲

Figure 4.2: Paracetamol Equilibrium Solubility Data

Solubility as a function of temperature for Paracetamol. Each point represents the overall mean from three independent experiments ± the standard error of the mean.

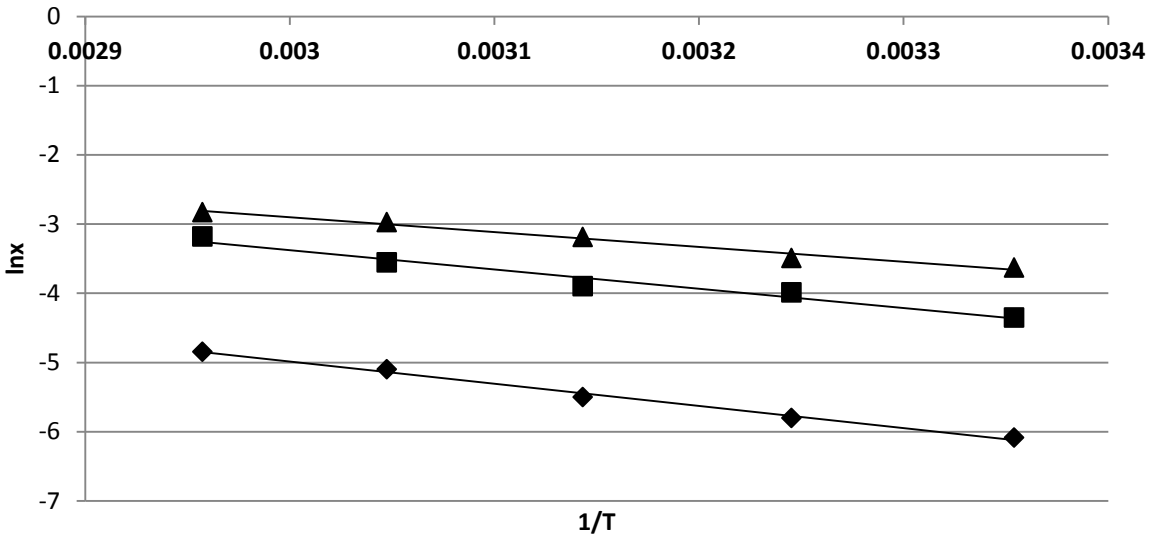
For all solvents tested the solubility was found to increase with temperature. Although paracetamol was found to have a reasonable solubility in both ILs, indicating drug-solute interactions, the solubility was less that in water. The O-H and N-H bond can form hydrogen bonds, giving paracetamol good solubility in polar and medium polar solvents (Granberg, 1999), whereas the hydrophobic PF_6 anion in these ILs makes solvation less favourable, reducing the solubility compared to water as expected. However the solubility in [hmim][PF_6] was found to be higher than [bmim][PF_6]. This was an unexpected result as the longer alkyl chain length makes [hmim][PF_6] more hydrophobic. The rationale as to the reason for this is not straightforward as the solvation mechanisms and drug-solute integrations of ILs are still relatively unknown. The increase in the alkyl chain length increased the hydrophobicity and viscosity but reduces the density and surface tension. However the purity of the IL should also not be overlooked. The [bmim][PF_6] used was

supplied with a purity 99% while the [hmim][PF_6] supplied was 98% pure. While this may be considered to be a relatively small difference in purity this may have a significant impact on the solubility of paracetamol.

4.2.3 Modelling Paracetamol Solubility Data

van't Hoff

If the solvent and solute are assumed to form an ideal solution then dissolution enthalpy (ΔH_d) and entropy (ΔS_d) can be predicted from the van't Hoff equation (equation 2.1). The van't Hoff plots are shown in Figure 4.3



Water ♦, [bmim][PF_6] ■ and [hmim][PF_6]▲

Figure 4.3: van't Hoff plot of Paracetamol

The dissolution entropy can be approximated by extrapolating the data while the entropy can be approximated from the slope of the trend line. The obtained values are shown in Table 4.4

Solvent	Water	[bmim][PF_6]	[hmim][PF_6]
ΔH_d $kJ.mol^{-1}$	26.65	41.47	17.76
ΔS_d $J.mol^{-1}.K^{-1}$	38.48	23.18	29.14

Table 4.4: Dissolution Enthalpy and Entropy Values from van't Hoff Plot

In each case values of $\Delta H_d > 0$ and thus the solvation process is endothermic indicating that the interactions between paracetamol and the solvents are not strong enough to break down the energy of attraction of the paracetamol molecules with each other and the electrostatic interactions of the IL cation and anion. Positive values of ΔS_d were also obtained indicating that the paracetamol-solvent system became increasingly disordered as temperature was increased.

Dual Parameter

A simplified dual parameter equation, $(\ln x = A + \frac{B}{T})$,was used to determine if the solubility results could be fitted using this. The values of A and B were obtained by least squares fit from the experimental data.

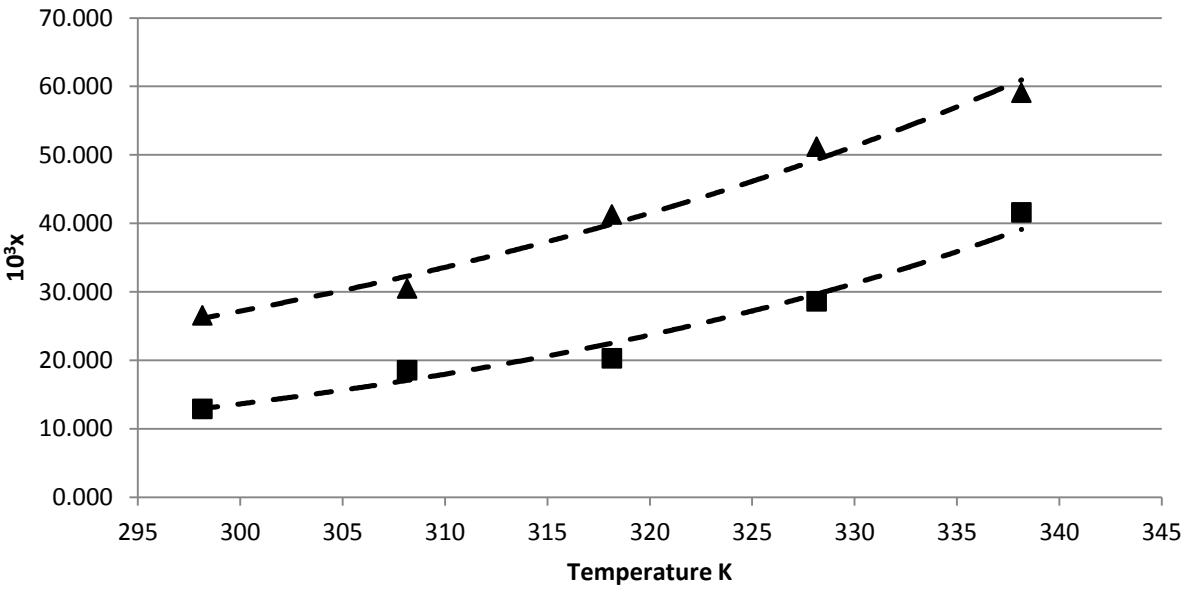
The calculated parameters for the dual parameter equation are displayed in Table 4.5 together with the root mean square deviation. Using the parameters the solubility was calculated using the dual parameter equation and are compared together in Table 4.6. The experimental data and calculated data were plotted together in Figure 4.4.

	Dual Parameter Equation		
IL	**A**	**B**	**10^3rmsd**
[bmim][PF_6]	4.989	-2788.8	2.006
[hmim][PF_6]	3.505	-2135.8	1.352

Table 4.5: Calculated A and B Parameters and Root Mean Square Deviation

T / K	$10^3 x^{exp}$	$10^3 x_1^{cal}$
[bmim][PF_6]		
298.15	12.893	12.718
308.15	18.543	17.229
318.15	20.285	22.898
328.15	28.611	29.910
338.15	41.596	38.456
[hmim][PF_6]		
298.15	26.559	25.775
308.15	30.485	32.520
318.15	41.297	40.436
328.15	51.199	49.615
338.15	59.083	60.145

Table 4.6: Comparison of Experimental Data and Calculated Values of Solubility



[bmim][PF_6] ■ and [hmim][PF_6]▲

Figure 4.4: Experimental data points (solid points) and fitted data (dotted line)

The calculated results from the dual parameter equation are in good agreement with the experimental values. While it is recognised that the solvation mechanisms of ILs are not fully understood the data shows that simplified correlations such as the ones used here could potentially be used as a tool to provide solubility trends of APIs in ILs.

Buchowski Equation

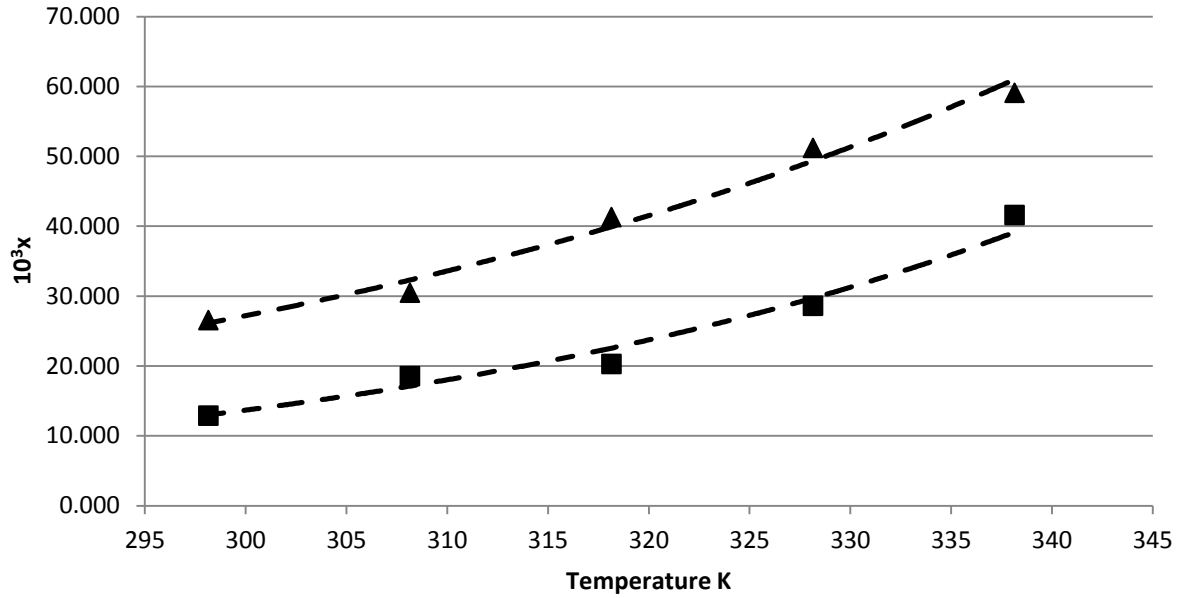
The relationship between mole fraction solubility and temperature on the solid-liquid phase equilibrium was also assessed using the λh (Buchowski) equation, $(\ln\left(1+\frac{1-x}{x}\right) = \lambda h\left(\frac{1}{T_m}-\frac{1}{T_m}\right))$. The values of λ and h were obtained from non-linear least squares fit. The values obtained are shown in Tables 4.7 and 4.8.

	λh Parameter Equation		
IL	**λ**	**h**	**10^3rmsd**
[bmim][PF_6]	0.19	13019	1.884
[hmim][PF_6]	0.15	11401	1.489

Table 4.7: Calculated λ and h Parameters and Root Mean Square Deviation

T / K	**10^3x^{exp}**	**$10^3x_1^{cal}$**
[bmim][PF_6]		
298.15	12.893	12.863
308.15	18.543	17.242
318.15	20.285	22.809
328.15	28.611	29.851
338.15	41.596	38.740
[hmim][PF_6]		
298.15	26.559	25.999
308.15	30.485	32.418
318.15	41.297	40.143
328.15	51.199	49.452
338.15	59.083	60.711

Table 4.8: Comparison of Experimental Data and Calculated Values of Solubility



[bmim][PF_6] ■ and [hmim][PF_6]▲

Figure 4.5: Experimental data points (solid points) plotted with trend line (dotted line) from calculated values from Buchowski Equation

Like the dual parameter equation the Buchowski equation also provided a good fit for the experimental data. The good correlation shown here was also observed in work by Ge et al (2013), where using the same modelling equation they found a close correlation for the solubility of aloe-emodin in five imidazolium based ILs. The results show that such correlations may be useful to help in the selection of ILs as fewer data points would be needed when selecting an IL to have a specific solubility for a given solute.

4.2.4 Paracetamol Solubility Conclusions

Methodology to measure the solubility of paracetamol was established and used to successfully measure the equilibrium solubility in [bmim][PF_6] and [hmim][PF_6]. Both were found to be good solvents for paracetamol. However, compared to water both gave lower solubilities over the temperature range measured. Given the hydrophobic nature of the ILs used here the lower solubility of this polar molecule was expected. However the increased

solubility seen for the more hydrophobic [hmim][PF_6] would lead to the assumption that small differences in impurities could have a significant impact on the solubility and further work is required to understand the solvation mechanisms of ILs and the relationship between the physical properties of solute and IL.

While further work is required to determine the solvation mechanisms and interactions it was shown that simple fits can be applied to the experimental data to correlate and predict the solubility of these systems. If this is true of most IL-solute systems then this provides a useful tool for designing onwards processing steps that involve dissolution. The data generated for these two systems also shows that that the solubility does vary with temperature meaning that using temperature to generate supersaturated solutions to investigate cooling crystallisations is possible.

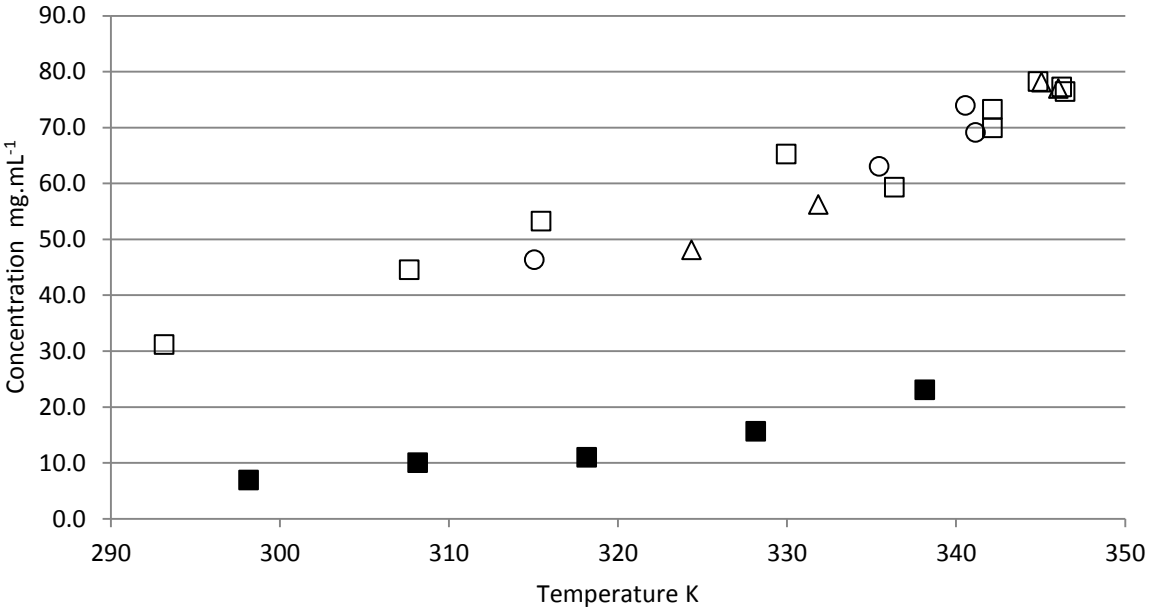
4.3 Cooling Crystallisations

4.3.1 Meta-Stable Zone Width Determination

Although the MSZW cannot be defined in absolute terms as is it is driven by kinetic rather than thermodynamic factors it is important to understand the degree of supersaturation that can occur in a particular system giving insight into how easily a system will produce crystals. The MSZW was determined for paracetamol in each of the ILs using turbidity to detect the cloud point. It can also help determine regions where crystal growth is driven either by primary or secondary nucleation followed by crystal growth.

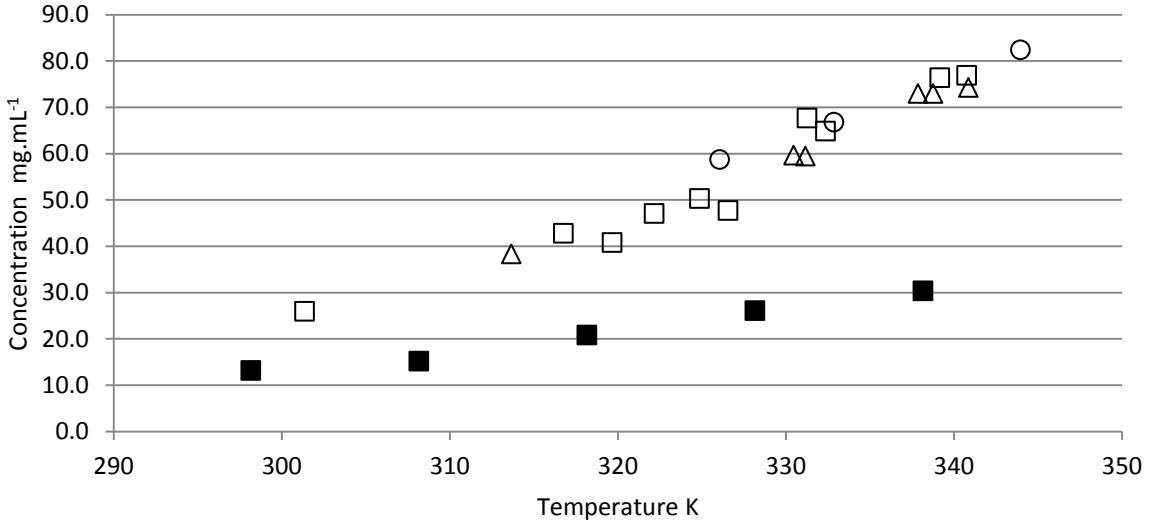
To determine if there is any significant effect of the rate of cooling, the MSZW was investigated at cooling rates of 0.2, 0.5 and 1.0 $K.min^{-1}$. The obtained nucleation points were

plotted with the solubility data obtained in Section 4.2.2 and are shown in Figures 4.6 and 4.7.



Equilibrium Solubility ■, cooling rate of 0.2 K.min^{-1} □, 0.5 K.min^{-1} Δ and 1.0 K.min^{-1} ○

Figure 4.6: Paracetamol Equilibrium Solubility and obtained MSZW in [bmim][PF_6]



Equilibrium Solubility ■, cooling rate of 0.2 K.min^{-1} □, 0.5 K.min^{-1} Δ and 1.0 K.min^{-1} ○

Figure 4.7: Paracetamol Equilibrium Solubility and obtained MSZW in [hmim][PF_6]

The MSZWs obtained show that high supersaturation concentrations can be generated. For example a supersaturation ratio of ΔS = 3.3 at 333.25 K would be possible 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.

The cooling rate was found to have an insignificant impact on the MSZW across the range of 0.2 to 1.0 $K.min^{-1}$. The data generated define the operating region for developing a cooling crystallisation.

4.3.2 Primary Nucleated Systems

Experiments were designed to cross the meta-stable zone width at different levels of supersaturation. These scoping experiments investigated the impact of concentration on resulting particle formation when the crystals are grown from a primary nucleation event and subsequent growth.

Process Conditions

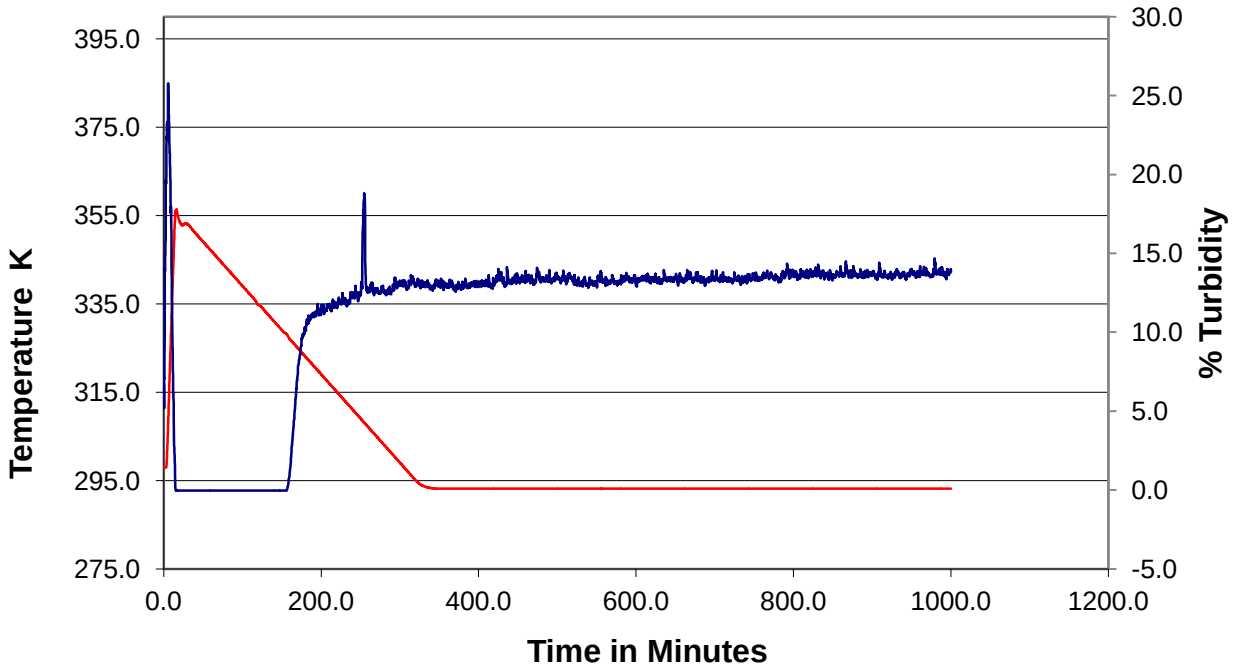
Crystallisations were completed to in order to understand the impact of crystallising from primary nucleation and subsequent growth. Conditions investigated are displayed in Table 4.9.

Ionic Liquid	Concentration $mg.mL^{-1}$
[bmim][PF_6]	44.82
[bmim][PF_6]	54.85
[bmim][PF_6]	70.09
[hmim][PF_6]	15.73
[hmim][PF_6]	30.21
[hmim][PF_6]	69.06

Table 4.9: Paracetamol Cooling Crystallisation Conditions (non-seeded)

Where possible the crystallisation was monitored by turbidity; a typical profile is displayed in Figure 4.9. In the profile a minimum in the turbidity is observed when dissolution of all the powder had occurred. The turbidity remains at this minimum as the solution is cooled until

the meta-stable zone width has been crossed and there is a rapid burst of nucleation and the material precipitates out of solution causing a dramatic rise in the turbidity.



The plot shows the temperature (red line) increase to 353 K as the input paracetamol is dissolved. At this temperature the % turbidity (blue line) reaches zero as there is a clear solution. As the solution is cooled to 293 K at 0.2 $K.min^{-1}$ a sudden rise in the turbidity is observed at 325 K due to the spontaneous nucleation of paracetamol. Note the turbidity event at 245 K was due to the probe being manual moved to conduct a visual observation.

Figure 4.8: Typical Turbidity Plot for non-seeded Paracetamol Crystallisation

Analysis

Form

As the MSZW showed, the systems can generate large supersaturations with the potential to crystallise a meta-stable form or to create small particles. There are two well known and characterised forms of paracetamol, the monoclinic form I and the orthorhombic form II. A third polymorph has also been proposed, which is extremely unstable, rapidly converting to one of the other forms. Form II is metastable although can be isolated under the right conditions; form I is the most stable form of paracetamol.

The form of the resultant crystals was determined by X-Ray Diffraction (XRD) and compared to both the calculated XRD pattern and against reference patterns in the literature. Reference pattern was obtained from the Cambridge Crystallographic Database (CCDC) are displayed in Appendix 2 which were used to confirm that the input material was also the monoclinic form I.

All samples produced XRD patterns consistent with the monoclinic form I material (Nichols, 1998). An example XRD is shown in Figure 4.9, XRD for the other samples are contained in Appendix 2 together with the pattern obtained for the starting material. The monoclinic form is most stable as the orthorhombic form; form II is metastable to form I at ambient temperature (Burger & Ramberger, 1979). Given the relatively low cooling rate, form I was the expected form from these experiments.

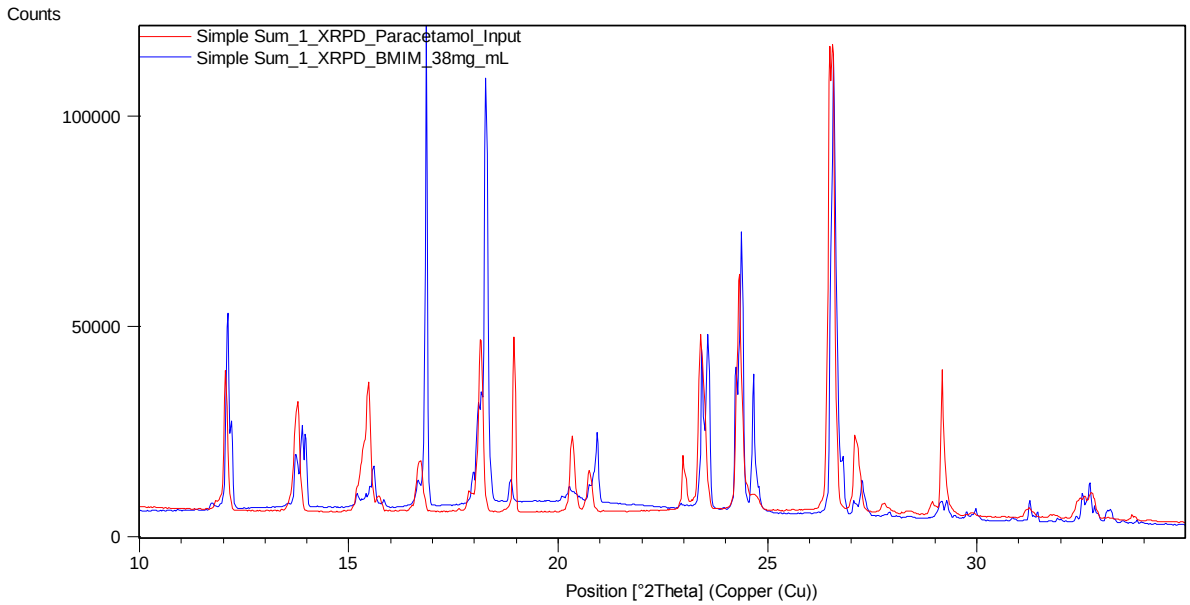


Figure 4.9: Example XRD pattern from [bmim][PF_6] cooling crystallisation (blue) with input paracetamol material (red) known to be Form I

To test this, two further crystallisations were completed at a higher cooling rate (10 $K.min^{-1}$) and high concentration 70 $mg.mL^{-1}$, 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 Table 4.10. This had the effect of agglomerating the crystals and was particularly seen for the smaller and more plate-like particles. As a result XRD patterns obtained for these particles had weaker signals 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.

Habit

The particle habit was assessed by optical and Scanning Electron Microscopy (SEM); the images are displayed in Tables 4.10 and 4.11.

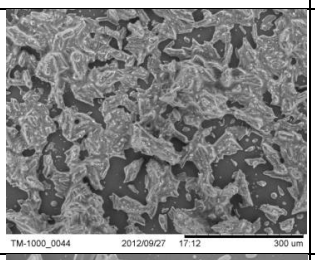
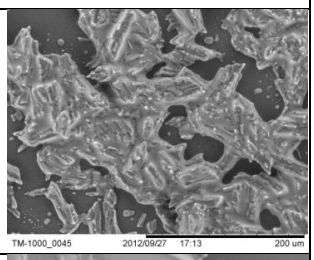
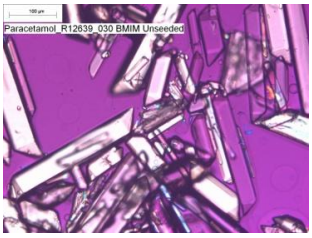
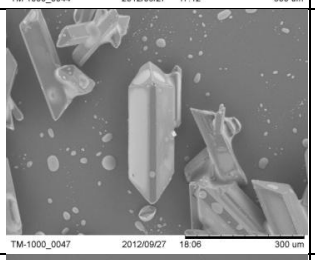
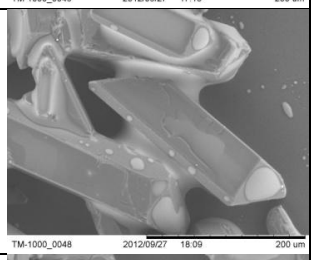
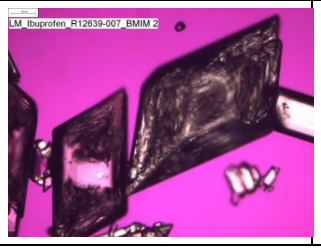
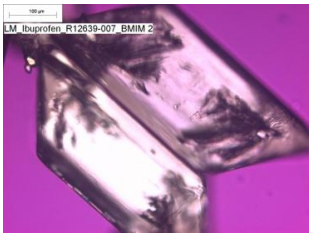
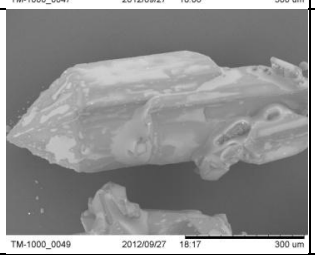
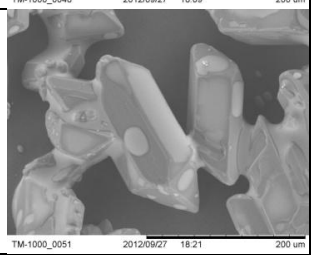
	Optical Microscopy		Scanning Electron Microscopy	
mg. mL^{-1}	50X Magnification	100X Magnification	250X Magnification	500X Magnification
45				
55				
69				

Table 4.10: OM and SEM Images of Paracetamol as crystallised from [bmim][PF_6]

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. The particle habits produced from [bmim][PF_6] displayed smaller plate-like particles at the lowest concentration (45 mg.mL^{-1}). Triangular prisms were formed when the concentration was increased to 55 mg.mL^{-1}, while predominantly elongated prism particles were obtained from 69 mg.mL^{-1} solutions.

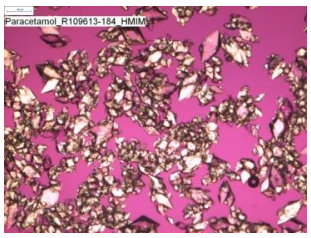
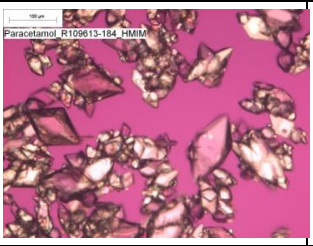
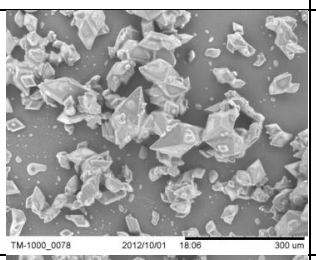
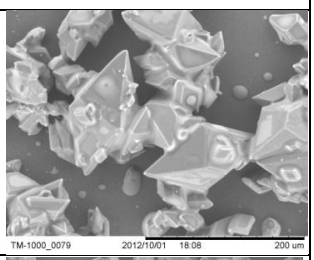
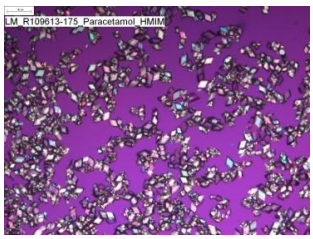
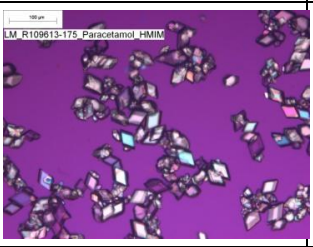
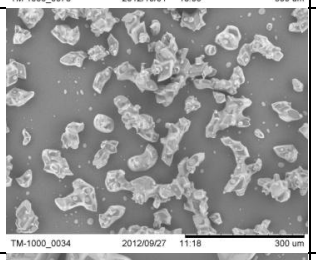
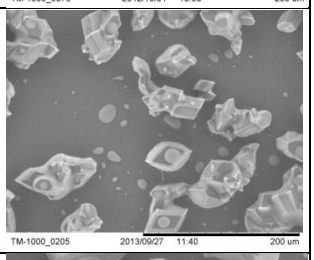
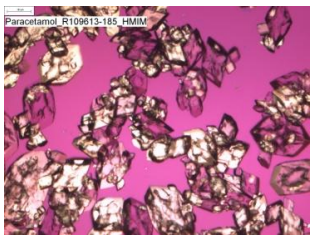
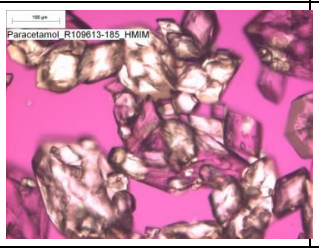
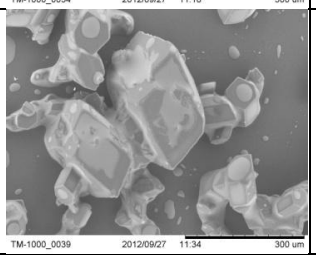
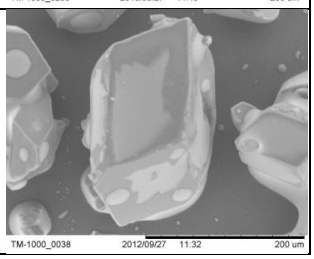
	Optical Microscopy		Scanning Electron Microscopy	
mg. mL^{-1}	50X Magnification	100X Magnification	250X Magnification	500X Magnification
16				
30				
69				

Table 4.11: OM and SEM Images of Paracetamol as crystallised from [hmim][PF_6]

When [hmim][PF_6] was used at the lowest concentration (16 mg.mL^{-1}) tetragonal bypyramids were formed, increasing the concentration (30 mg.mL^{-1}) small plate particles formed, whereas for the highest concentration (69 mg.mL^{-1}) larger more tabular structures were produced.

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 (Finnie, 1999) (Ristic, 2001). At high

supersaturations (ΔS>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.

Particle Size

The particle size of the resultant powders was measured by laser diffraction. A summary of the data is shown in Table 4.12. An example of a typical size distribution is shown in Figure 4.10 with all raw data in Appendix 3.

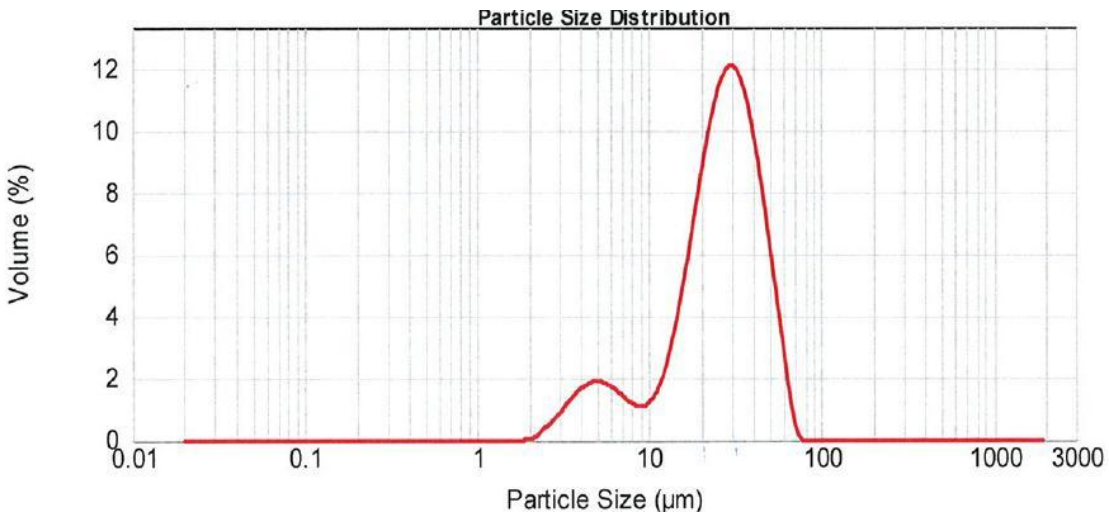


Figure 4.10: Paracetamol PSD from [hmim][PF_6] at 30 mg.ml^{-1}

			Particle Size				
Experiment Number	**Ionic Liquid**	**Concentration mg.mL^{-1}**	**d_{10}**	**d_{50}**	**d_{90}**	**Span**	**Distribution Description**
1	[bmim][PF_6]	44.8	6	23	56	2.2	Multi-Modal
2	[bmim][PF_6]	54.9	144	254	389	1.0	Multi-Modal
3	[bmim][PF_6]	70.1	44	277	621	2.1	Multi-Modal
4	[hmim][PF_6]	15.7	10	37	78	1.8	Tri-Modal
5	[hmim][PF_6]	30.2	7	26	46	1.5	Bi-Modal
6	[hmim][PF_6]	69.1	9	60	124	1.9	Bi-Modal

Table 4.12: Summary Particle Size Data for Non-Seeded Paracetamol

It would be expected that the particle size would decrease as the concentration increases. For samples crystallised from [bmim][PF_6] and [hmim][PF_6] it was found that the least concentrated solution produced the smallest particles while the highest concentrated solution gave the largest particles. However the experiment completed in [hmim][PF_6] at 30.2 $mg.mL^{-1}$ did not follow the expected trend. The result highlights that variable nature of conducting crystallisations via primary nucleated systems makes controlling the output particle size difficult to control from batch to batch. No samples produced mono-modal distributions (for example see Figure 4.10). No evidence of attrition was observed from the microscopy analysis so the bimodal distribution may result from residual IL that can be observed in Figure 4.11. This would account for the size population seen around 3 μm.

4.3.3 Secondary Nucleated

In order to control carry out crystallisations under more controlled conditions seed is commonly added to supersaturated solutions inducing growth onto the crystals. This is a common tactic used in the pharmaceutical industry to control form and habit but in particular the particle size of the resultant crystals.

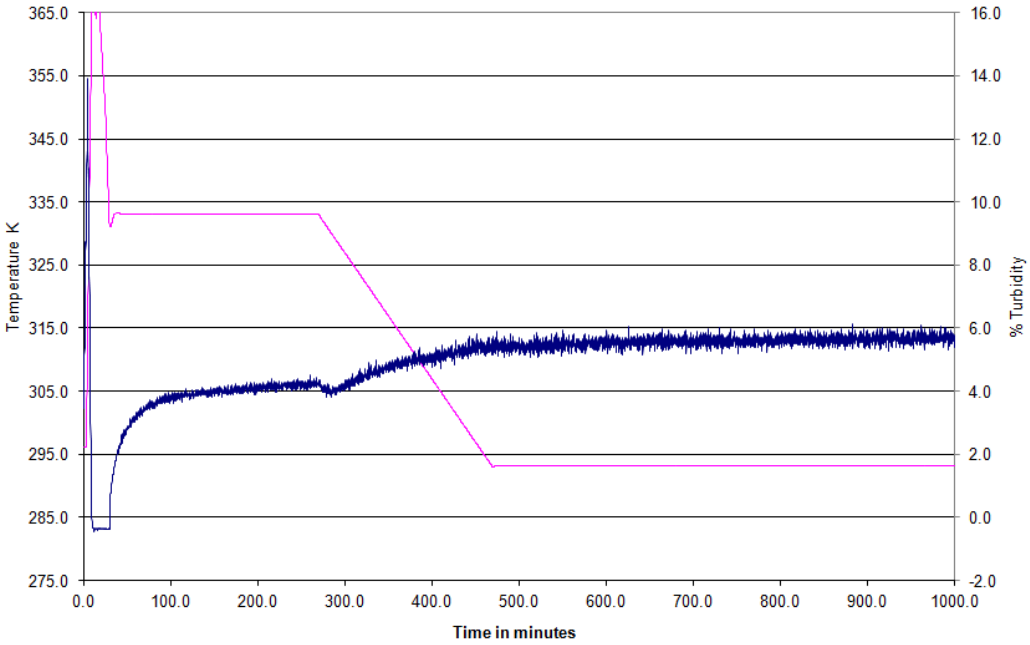
Process Conditions

A set of seeded experiments were conducted at different supersaturation ratios, defined at 333.15 K as indicated in Table 4.13. The wide MSZW curve at 333.15 K enabled a broad range of supersaturations to be investigated before spontaneous crystallisation occurred.

Ionic Liquid	Concentration mg.mL^{-1}	ΔS at 333.15 K
[bmim][PF_6]	38.1	2.0
[bmim][PF_6]	47.4	2.5
[bmim][PF_6]	57.0	3.0
[hmim][PF_6]	35.0	1.25
[hmim][PF_6]	49.0	2.00
[hmim][PF_6]	63.0	2.25

Table 4.13: Paracetamol Seeded Cooling Crystallisation Conditions

The crystallisations were also monitored where possible using turbidity. An example of a turbidity plot from the experiments is shown in Figure 4.11.



The plot shows the temperature (red line) increase to 365 K as the input paracetamol is dissolved. At this temperature the % turbidity (blue line) reaches zero as there is a clear solution. Following addition of the seed material at 333.15 K a steady increase is observed as material precipitates out of solution growing onto the seed crystals before reaching a plateau at equilibrium. Upon cooling there is another inflection in the turbidity as further material comes out of solution.

Figure 4.11: Temperature and Turbidity Profile from [hmim][PF_6] at 63 mg.mL^{-1}

Analysis

Form

All samples produced diffraction patterns that were consistent with the monoclinic form I material. Given that all the non-seeded samples also produced this stable form and that the seeds added to the crystallisations were also form I this was an expected result. The XRD data for all seeded samples are shown in Appendix 2 while Figure 4.12 shows an example XRD pattern together with the input form I material as a reference.

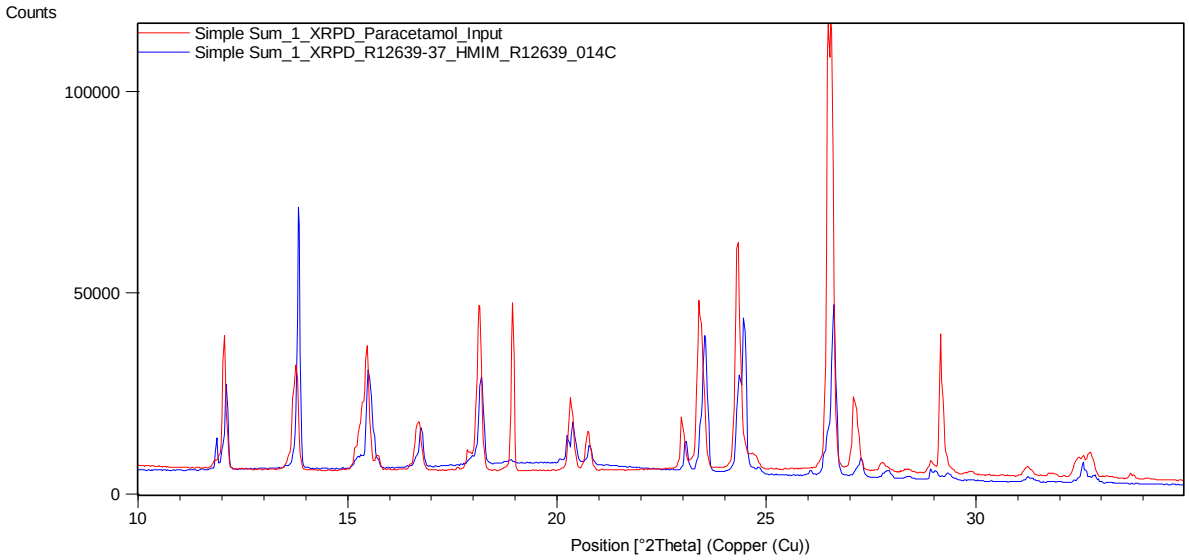


Figure 4.12: X-Ray Diffraction of Paracetamol from [hmim][PF_6] at 35 mg.mL^{-1} (Blue Trace) with input Paracetamol Form I (Red Trace)

Particle Habit

The particle habit was assessed by optical and Scanning Electron Microscopy (SEM) as shown in Tables 4.14 and 4.15.

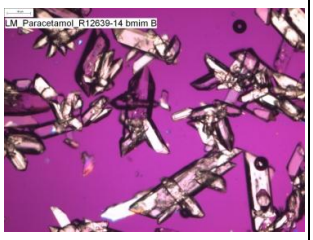
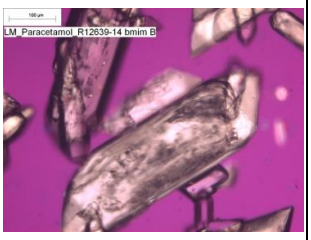
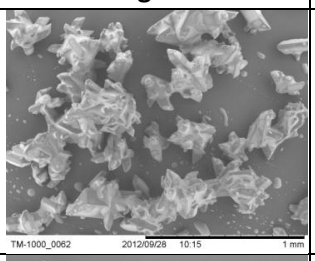
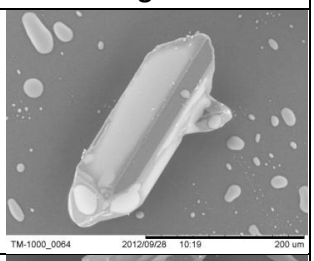
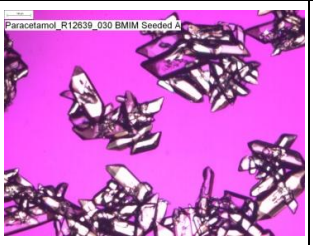
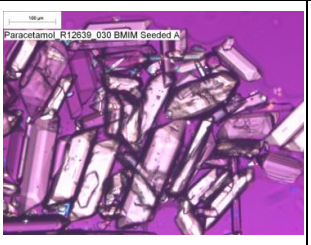
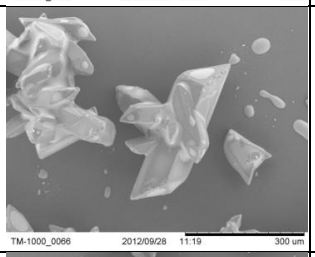
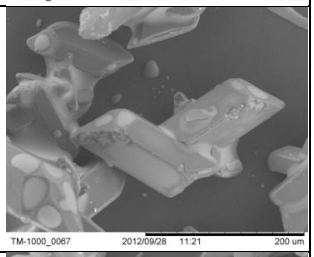
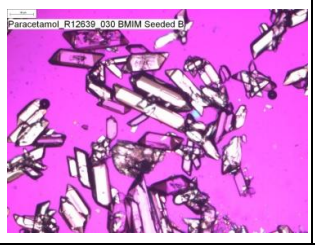
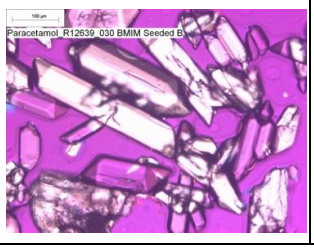
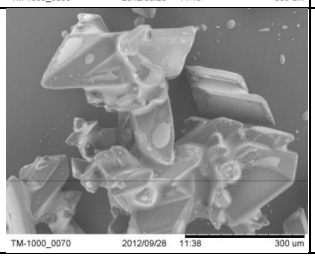
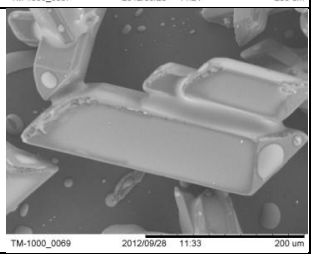
	Optical Microscopy		Scanning Electron Microscopy	
ΔS	**50X Magnification**	**100X Magnification**	**250X Magnification**	**500X Magnification**
2.0				
2.5				
3.0				

Table 4.14: Paracetamol OM and SEM Images from [bmim][PF_6] Seeded Crystallisation

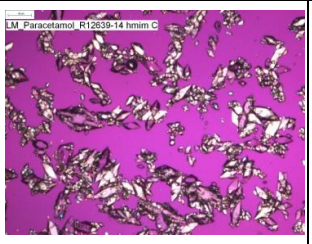
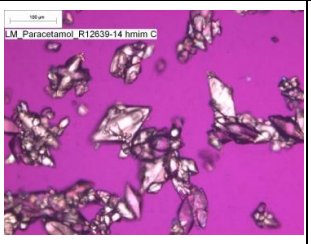
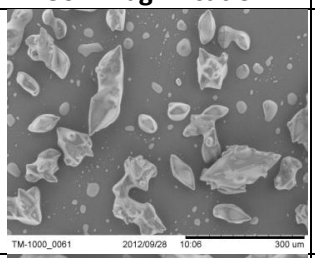
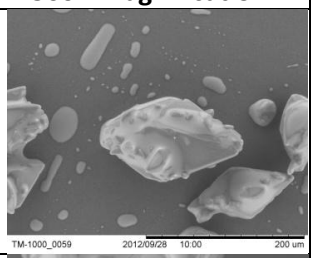
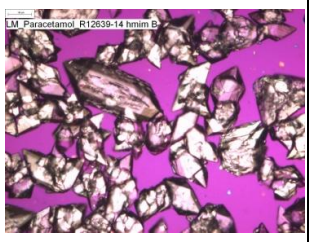
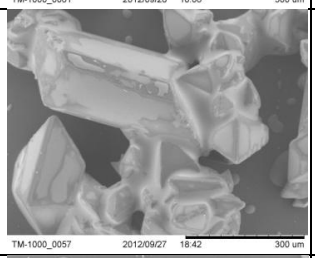
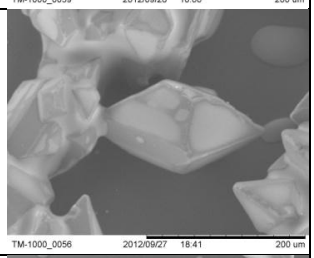
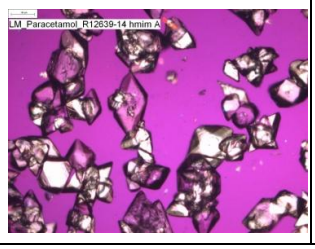
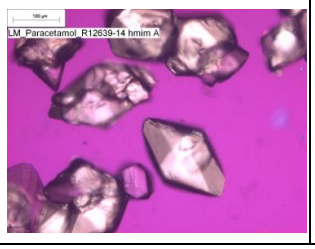
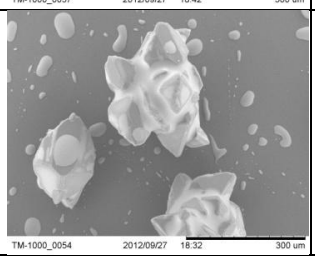
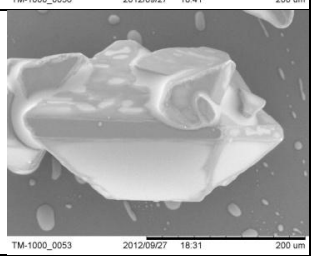
	Optical Microscopy		Scanning Electron Microscopy	
ΔS	**50X Magnification**	**100X Magnification**	**250X Magnification**	**500X Magnification**
1.25				
2.0				
2.25				

Table 4.15: Paracetamol OM and SEM Images from [hmim][PF_6] Seeded Crystallisation

Samples produced from [bmim][PF_6] produced long prisms while the samples grown from [hmim][PF_6] produced particles with a distinct tetragonal bipyramid habit. Results here indicate that it is possible to modify the particle habit in a seeded process through changing the alkyl chain length and hence the hydrophobicity of the IL. While these results are promising, further investigation would be required to make sure that the changes seen here are due to the change in interaction between solute and solvent and not as a result of different impurity profiles of the two ILs.

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

Particle Size

The particle size of the precipitates was measured by laser diffraction. A selection of the data is shown in Table 4.16. An example of a typical size distribution is shown in Figure 4.13 with all raw data in Appendix 3.

		Particle Size				
Ionic Liquid	**Supersaturation ΔS**	**d_{10}**	**d_{50}**	**d_{90}**	**Span**	**Distribution Description**
[bmim][PF_6]	2.0	112	212	323	2.1	Bi-Modal
[bmim][PF_6]	2.5	122	206	329	2.2	Bi-Modal
[bmim][PF_6]	3.0	104	205	349	2.2	Bi-Modal
[hmim][PF_6]	1.25	30	73	121	2.1	Multi-Modal
[hmim][PF_6]	2.00	40	173	314	2.0	Multi-Modal
[hmim][PF_6]	2.25	49	138	228	2.0	Bi-Modal

Table 4.16: Summary of Paracetamol Particle Size Data from Seeded Crystallisations

No trend was observed as the concentration was increased within a given IL. The particle size obtained for the [bmim][PF_6] produced a very consistent particle size range across the concentration range studied each with a bi-modal distribution.

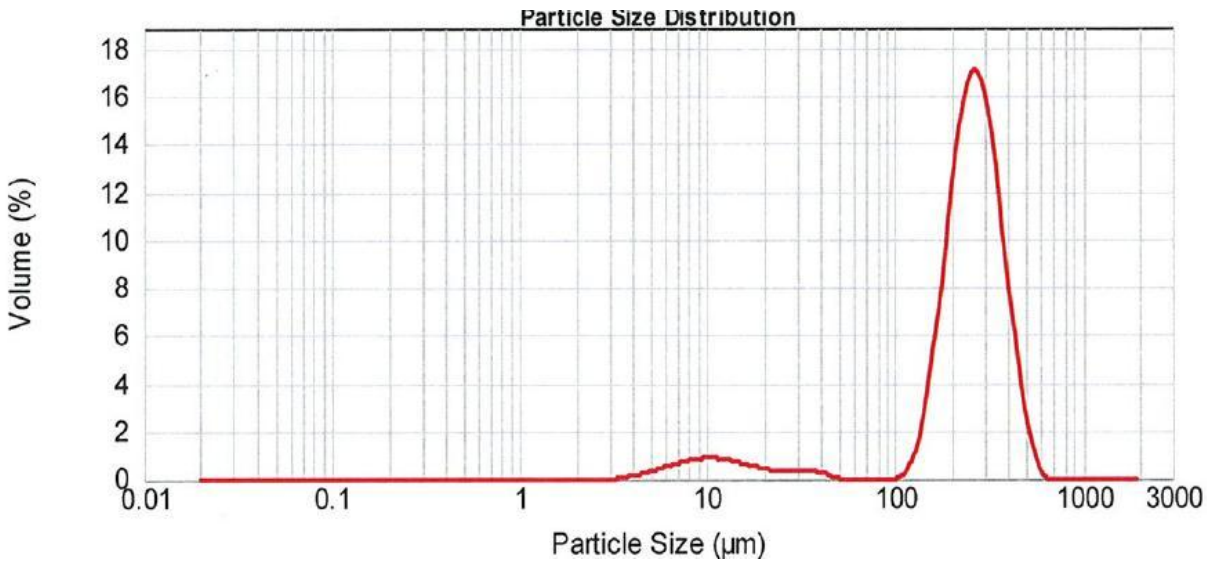


Figure 4.13: Paracetamol PSD from [bmim][PF_6] at ΔS 2.5

The span of the particle size distributions was consistent, distributions of 2.0 to 2.1 were obtained across the range of crystallisations in [bmim][PF_6] and [hmim][PF_6], while for the [hmim][PF_6] samples, although the span of the size distributions was consistent and similar to those obtained from [bmim][PF_6], the particle size obtained was not consistent and varied significantly between runs. The particle size obtained was also generally smaller from [hmim][PF_6] to those obtained from [bmim][PF_6].

4.3.4 Extension to Other ILs

The cooling results above show that ILs can be used as media to crystallise paracetamol. One of the main potential benefits of ILs is the range of ILs that potentially could be used. This section of the practical work aims to extend the above practical work by screening other ILs that may be suitable as crystallisation media. For this work it was decided to concentrate on

the same cation and vary the anion. The criteria used for selection are detailed in Section 3.2.2 methods section, such that the ILs were liquids at room temperature, the purity was >95% and the cost was <£2 per g. The ILs used for this screening study are outlined below in Table 4.17. To carry out the screen the solubility was measured at three temperatures and potential candidates then selected for further evaluation.

Temperature K	[bmim][BF_4] mg.mL^{-1}	[bmim][NTf_2] mg.mL^{-1}	[bmim][CH_3COO] mg.mL^{-1}	[bmim][$C_8H_{17}OSO_3$] mg.mL^{-1}
298.15	68.9	8.4	>277.0	>287.7
328.15	124.9	15.4	Not Measured	Not Measured
358.15	194.8	32.2	Not Measured	Not Measured

Note: the biggest error measured between duplicate results was 4 mg.mL^{-1}

Table 4.17: Paracetamol Solubility Measured during Screening Work

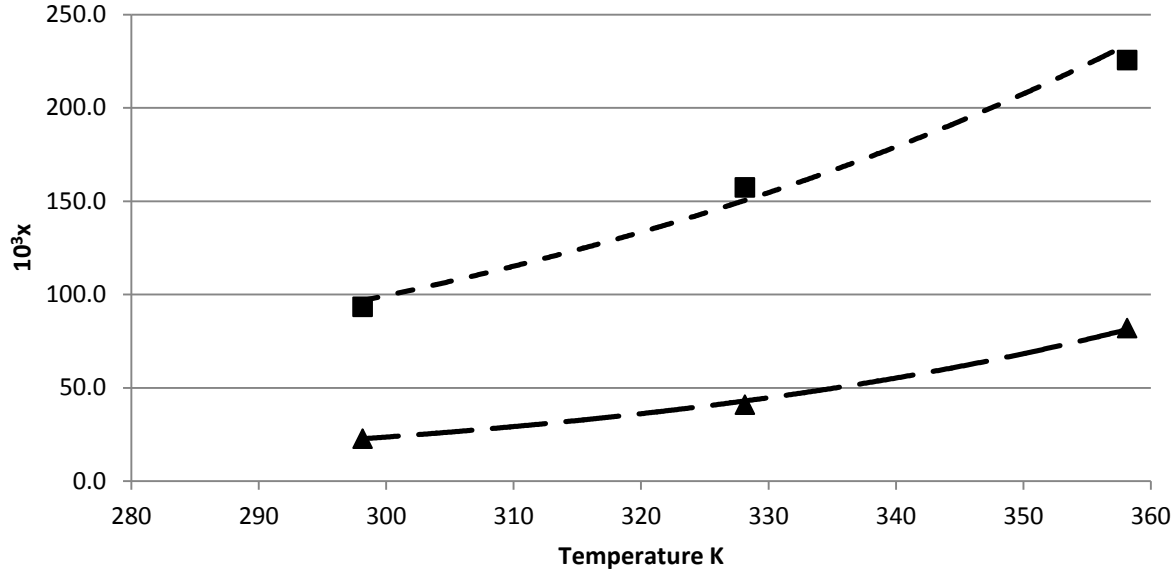
It was found that paracetamol was highly soluble in the ILs [bmim][CH_3COO] and [bmim][$C_8H_{17}OSO_3$] with a measured solubility of >277 mg.mL^{-1} were seen at 298.15 K. The solutions that were formed were also extremely viscous which could prove challenging to agitate and separate the liquid from any crystallised product. The ILs [bmim][BF_4] and [bmim][NTf_2] were selected for further evaluation and the dual parameter equation assessed in Section 4.2.3 was used to correlate the solubility data. The results from the parameters used with corresponding root mean square deviation are shown in Table 4.18 followed by the calculated values in Table 4.19 with the plotted data in Figure 4.14.

IL	A	B	10^3rmsd
[bmim][BF_4]	2.919	-1573.7	3.161
[bmim][NTf_2]	3.791	2268.2	2.658

Table 4.18: Paracetamol Extension Calculated Dual Equation Parameters

	[bmim][BF_4]		[bmim][NTf_2]	
Temperature K	10^3x^{exp}	10^3x^{cal}	10^3x^{exp}	10^3x^{cal}
298.15	93.395	94.54	22.772	22.02
328.15	157.358	153.18	40.971	44.13
358.15	225.560	228.90	82.002	78.74

Table 4.19: Paracetamol Extension Calculated Solubility Values



[bmim][BF_4]■ and [bmim][NTf_2]▲

Figure 4.14: Paracetamol Extension Experimental Data (solid points) with Trend Line from Dual Parameter (dotted line)

Again a good correlation was obtained using this method. The solubility curves produced from this correlation were then used as a basis for preliminary crystallisation studies from these ILs.

Two cooling crystallisations were performed in each IL, a non-seeded crystallisation using the concentration at 358.15 K followed by a seeded crystallisation at the same concentration. As the metastable zone width has not been fully established for these systems the seed point used was determined using the data from the estimated solubility curve and the point of nucleation of the non-seeded crystallisation.

Analysis

Form

Samples all samples from these crystallisations produced material that was consistent with the stable form I material. The obtained diffraction patterns are shown in Appendix 2 with an example shown in Figure 4.15.

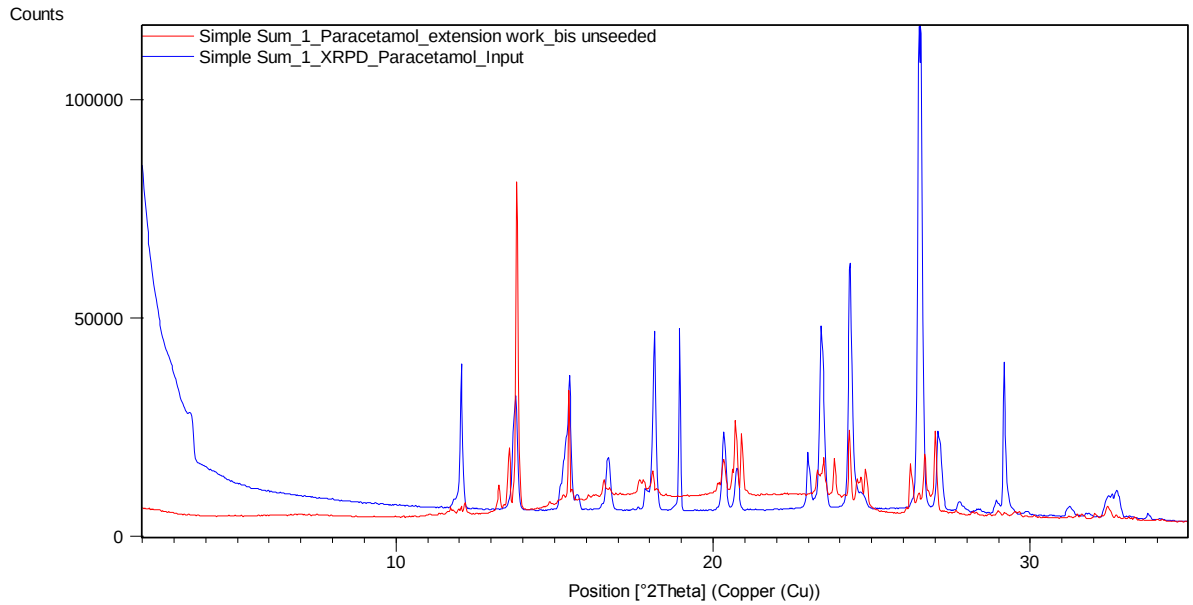


Figure 4.15: Paracetamol XRD from non-seeded [bmim][NTf_2] Crystallisation

Particle Habit

Optical and scanning electron microscopy was carried on cooling crystallisation samples, images are shown in Table 4.20

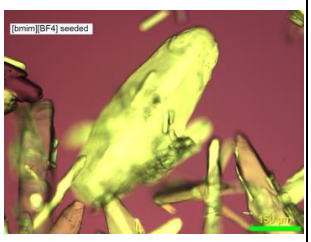
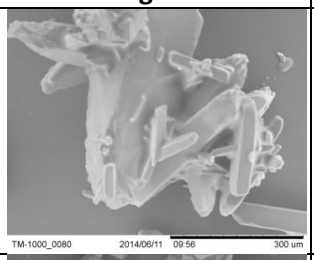
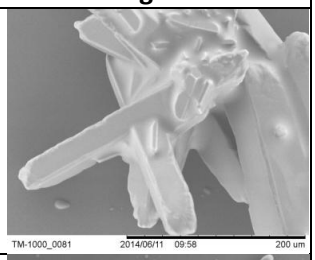
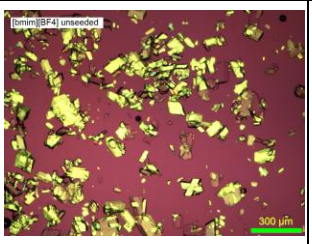
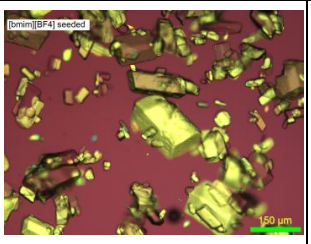
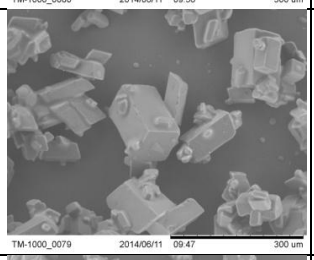
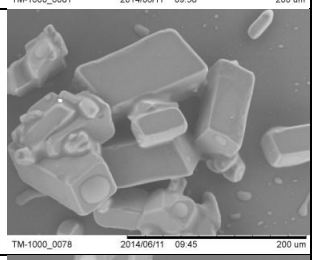
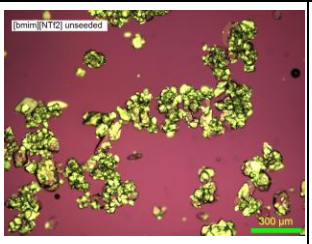
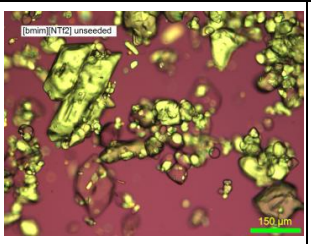
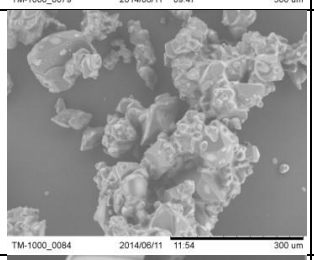
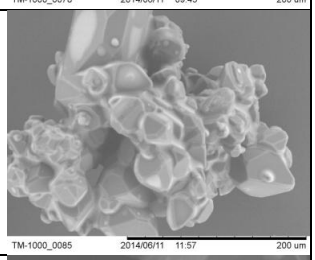
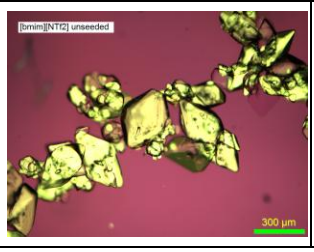
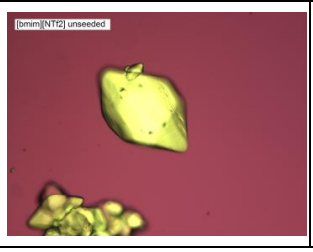
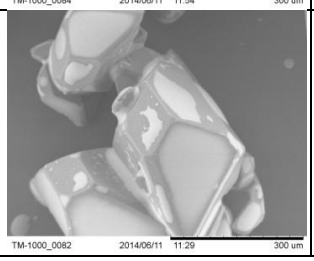
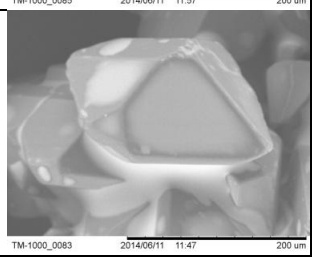
	Optical Microscopy		Scanning Electron Microscopy	
	50X Magnification	100X Magnification	250X Magnification	500X Magnification
[bmim][BF_4] Non-Seeded				
[bmim][BF_4] Seeded				
[bmim][NTf_2] Non-Seeded				
[bmim][NTf_2] Seeded				

Table 4.20: Paracetamol Images from cooling crystallisation extension experiments

There have been numerous studies in the literature studying the crystallisation of paracetamol from conventional solvents. The work by Finnie et al (1999) where the habit changes were described used aqueous solutions to conduct their studies and produced particles ranging from plate material to larger more tabular structures at high saturations. This larger tabular particle habit was produced by Yu et al (2005) from aqueous systems using acetone as an anti-solvent. These two habits were also produced when crystallised from ethanol (Ristic et al, 2001) and from benzyl alcohol (Nichols and Frampton, 1998). In a study by Lee et al (2006) paracetamol was crystallised from thirteen pure solvents. Their

study found that plate-like crystals were formed from benzyl alcohol, n-butyl alcohol and water. The solvents acetonitrile, 1,4 dioxane, isopropyl alcohol, methanol, methyl ethyl ketone, and tetrahydrofuran gave prism like habits.

Interestingly no evidence of cubic paracetamol particles was found, like those formed from [bmim][BF_4]. In order to determine which faces are being influenced from this IL further work will be needed to index the crystal.

4.4 Summary

In order to firstly understand if the API paracetamol can be crystallised from ionic liquids a detailed study was conducted using the [bmim][PF_6] and [hmim][PF_6]. The MSZW determined for these systems showed that, at small scale, large supersaturations could be generated, increasing the potential risk of meta-stable forms being produced and recovered. Another feature of the MSZW obtained for these systems was that at low temperatures the increased viscosity of the IL may slow down the crystallisation process as this is kinetically driven. Despite the wide meta-stable zone width the obtained results were very consistent, even at a range of cooling rates, whereas for conventional crystallisations it would be expected that the obtained MSZW would be much more variable.

A series of crystallisations designed to cross the MSZW at a range of increasing concentrations was carried out to determine the impact on the form, habit and size of the crystallised particles. Despite the large supersaturations that were generated, the systems all crystallised as the stable monoclinic form I. The particle habit produced from these crystallisation showed that different habits could be produced by changing both the length of the alkyl chain length and the concentration of the crystallising solution. The particle size

did not follow the expected trend, with large particles formed from highly concentrated solutions, which indicates a significant amount of growth occurring in the systems following the spontaneous nucleation, and the much increased viscosity of ILs compared to conventional molecular solvents may be the reason for this.

Crystallisations were also conducted using seed to act as secondary nuclei. These systems generally behaved as expected with much larger particles being produced compared to primary nucleated crystallisations. Variation of the supersaturation ratio at point of seeding had little impact on the habit of the particles produced.

The impact of changing the anion was assessed by completing a series of scoping experiments on different ILs. The results show that the different morphologies can be produced while still maintaining the most stable form.

Some practical issues with working with ionic liquids were encountered during the studies. One of these was that the viscosity of the ILs used, particularly at isolation temperatures, makes it difficult to obtain reliable solubility data and MSZW data. Where the API is freely soluble, the sample becomes so viscous that in some instances it can form a gel that cannot be sufficiently agitated. Secondary to this is that high viscosity can cause issues during the separation of the crystals from the IL liquor.

4.5 References

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CHAPTER 5: STUDIES WITH IBUPROFEN

5.1 Introduction

This chapter is focussed on the experimental work completed on ibuprofen. Starting first by outlining the methodology used to determine the solubility of ibuprofen in the ILs [bmim][PF_6] and [hmim][PF_6], the results were then assessed using solubility correlations to understand if these models could be applicable to such systems.

Using these unique solvents a series of cooling crystallisations were designed and completed. The Meta-Stable Zone Width (MSZW) was established and combined with the solubility data to design a series of cooling crystallisations. The crystallisations assessed the impact of nucleation mechanism and concentration on the crystal form, habit and size of the resultant crystals.

5.2 Solubility

5.2.1 Validation of Solubility Method – Solubility in Water

Before the solubility of Ibuprofen in ILs was measured the solubility was measured in water to validate that the method used in this work was fit for purpose. Solubility data were determined between 298.15 K and 338.15 K in 10 K increments. For each measurement the overall mean from the three experiments, plus or minus the standard error of the mean, were calculated for both the absorbance and solubility.

A summary of the data is shown below in Table 5.1. The raw data obtained from the UV spectrophotometer with corresponding solubility data in mg solute per mL water can be found in Appendix 4.

Temperature K	Absorbance $\sum_{abs} (\overline{x}/n)$	Solubility 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 5.1: Solubility of Ibuprofen in Water

where solubility is the overall mean from three independent experiments ± the standard error of the mean

The US Pharmacopeia lists Ibuprofen having a solubility less than 1 mg.mL^{-1} at 298.15 K, meaning that it is only very slightly soluble in water at room temperature. This definition matches the data measured here with solubilities in the range of 0.124 mg.mL^{-1} to 0.523 mg.mL^{-1} determined across the temperature range. Ibuprofen only has one polar group, the

carboxylic acid functional group making it less soluble in polar solvents like water compared to paracetamol.

The data was were plotted against previously published data (Potthast, 2005), (Garzon, 2004), (Higgins, 2004) and (Stippler, 2004) shown in Figure 5.1.

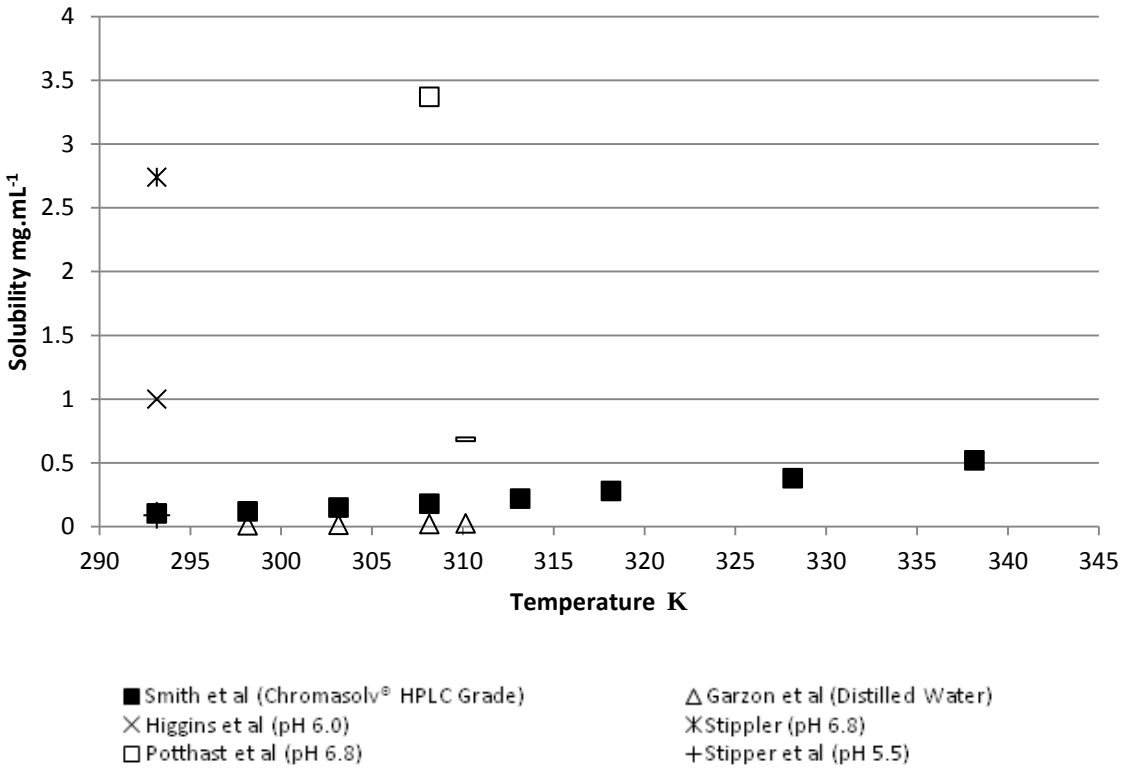


Figure 5.1: Solubility Data in Water as a Function of Temperature for Ibuprofen.

The data published for Ibuprofen are more variable as the solubility of Ibuprofen varies with pH; also the low solubility (<3.5 $mg.mL^{-1}$) would be sensitive to techniques used. The data in this work were obtained using analytical grade water (pH 7.4). While the data measured in this work fit within the range of the available data it is clear that the measured solubility for ibuprofen is highly dependent on the conditions used for the study.

5.2.2 Solubility in Ionic Liquids

Using the same method, the solubility of ibuprofen was determine in the ILs [bmim][PF_6] and [hmim][PF_6] across the temperature range 298.15 K to 338.15 K at 10 K increments. A summary of the data is shown below in tables 5.2 and 5.3 for [bmim][PF_6] and [hmim][PF_6] respectively. The raw data obtained from the UV spectrophotometer with corresponding solubility data in mg solute per mL water can be found in Appendix 4.

Temperature K	**Absorbance** $\sum_{abs}(\overline{x}/n)$	**Solubility mg.mL^{-1}**
298.15	0.706 ± 0.014	12.18 ± 0.27
308.15	1.131 ± 0.027	20.27 ± 0.48
318.15	1.720 ± 0.068	31.53 ± 1.29
328.15	2.685 ± 0.024	36.45 ± 0.35
338.15	2.888 ± 0.009	56.81 ± 0.19

Table 5.2: Solubility of Ibuprofen in [bmim][PF_6] from T = 298.15 K to 338.15 K

where solubility is the overall mean from three independent experiments ± the standard error of the mean

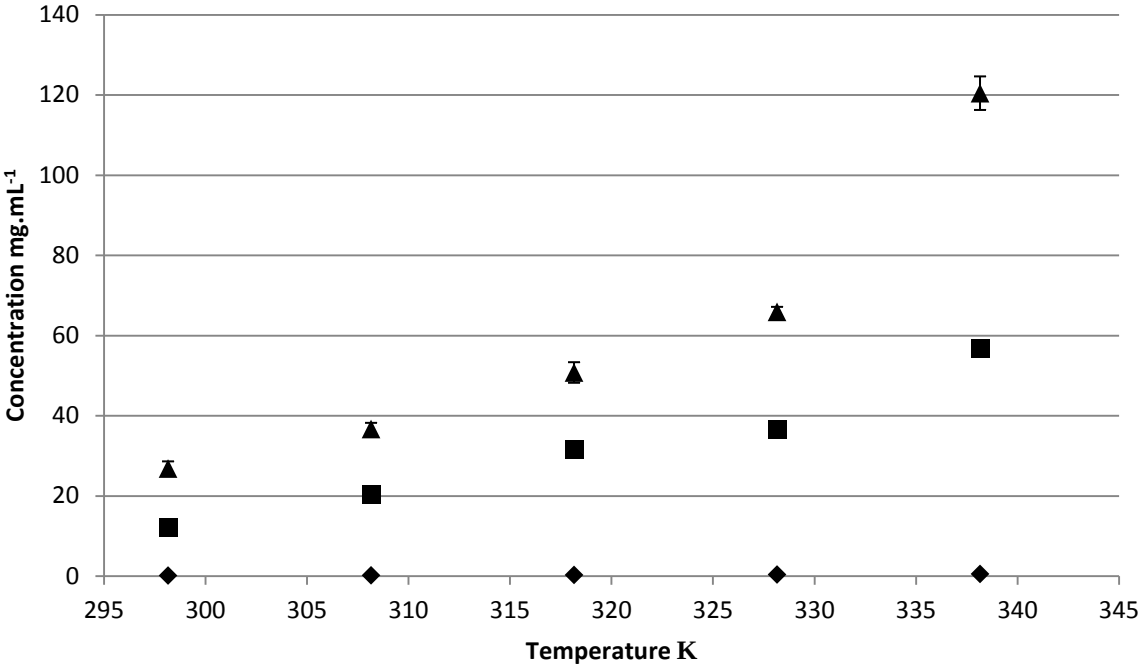
Temperature K	**Absorbance** $\sum_{abs}(\overline{x}/n)$	**Solubility mg.mL^{-1}**
298.15	1.254 ± 0.095	26.38 ± 2.08
308.15	1.749 ± 0.113	37.20 ± 2.47
318.15	2.139 ± 0.113	50.76 ± 2.67
328.15[a]	2.005 ± 0.033	65.88 ± 1.08
338.15[a]	1.371 ± 0.048	120.41 ± 4.15

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

Table 5.3: Solubility of Ibuprofen in [hmim][PF_6] from T = 298.15 K to 338.15 K,
where solubility is the overall mean from three independent experiments ± the standard error of the mean

Both ILs were found to be good solvents with solubility values of 12.18 mg.ml^{-1} to 56.81 mg.mL^{-1} obtained for [bmim][PF_6] and 26.38 mg.mL^{-1} to 120.41 mg.mL^{-1} for [hmim][PF_6]

across the temperature range studied. This would rank ibuprofen as ranging from sparingly soluble to soluble in [bmim][PF_6] and sparingly soluble to freely soluble in [hmim][PF_6]. The data was plotted together with the water solubility data obtained previously in Figure 5.2.



water ♦, [bmim][PF_6] ■ and [hmim][PF_6]▲. Solubility as a function of temperature for Ibuprofen. Each point represents the overall mean from three independent experiments ± the standard error of the mean

Figure 5.2: Ibuprofen Equilibrium Solubility Data

The solubility was greater in [hmim][PF_6] than [bmim][PF_6]. Based on the structure of the molecule this result would be expected as ibuprofen is likely to favour solvents of lower relative polarity.

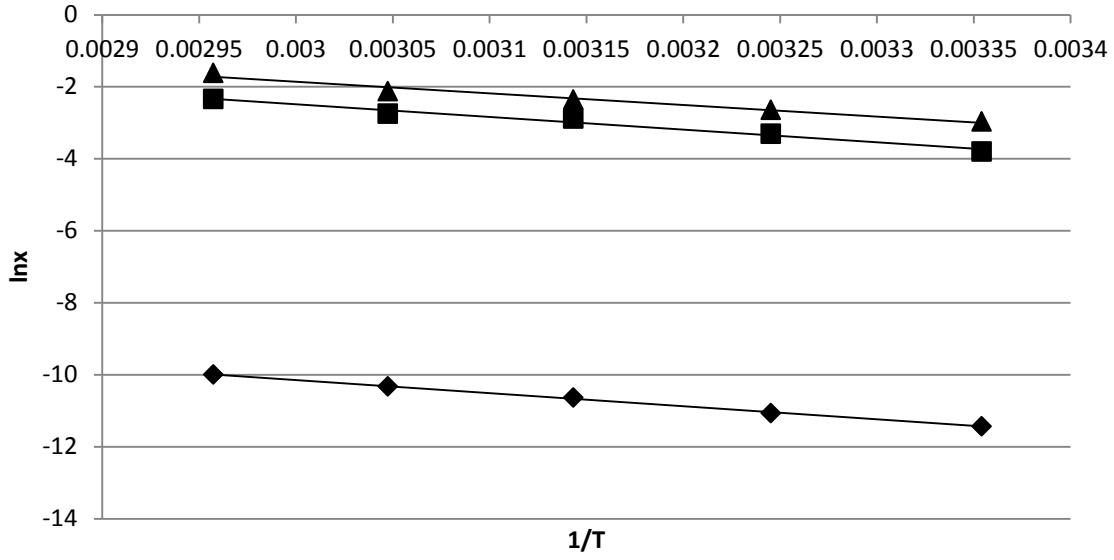
The solubility data at 328.15 K and 338.15 K for [bmim][PF_6] should be treated with a degree of caution as there was evidence of degradation observed through the onset of colour change which was not observed in either water or [hmim][PF_6]. The water content was measured by Karl Fischer and found to be 0.15 % (w/w). It is known that in the presence of water ILs containing fluorinated species such as [PF_6] can produce hydrogen fluoride,

especially at elevated temperatures, so catalysing the degradation of the ibuprofen. Caution should be taken when working with this anion at elevated temperatures ensuring that the ILs are dry and exposure to the atmosphere is kept to a minimum. It should be noted that the water content of [hmim][PF_6] was measured at 0.05 % (w/w).

5.2.3 Modelling Ibuprofen Solubility Data in ILs

van't Hoff plots

If the solvent and solute are assumed to form an ideal solution then dissolution enthalpy (ΔH_d) and entropy (ΔS_d) can be predicted from the van't Hoff equation (Equation 2.1). The van't Hoff plots are shown in Figure 5.3 with extrapolated values in Table 5.4.



Water ♦, [bmim][PF_6] ■ and [hmim][PF_6] ▲

Figure 5.3: van't Hoff plot of Ibuprofen

Solvent	Water	[bmim][PF_6]	[hmim][PF_6]
ΔH_d kJ.mol^{-1}	30.38	20.27	26.86
ΔS_d J.mol^{-1}.K^{-1}	6.79	67.13	65.15

Table 5.4: Dissolution Enthalpy and Entropy Values from van't Hoff Plot

In each case values of ΔH_d > 0 and thus the solvation process is endothermic, indicating that the interactions between ibuprofen and the solvents are not strong enough to break down the energy of attraction of the ibuprofen molecules with each other and the electrostatic interactions of the IL cation and anion. Positive values of ΔS_d were also obtained indicating that the Ibuprofen-solvent system became increasingly disordered as temperature was increased.

Dual Parameter

A simplified dual parameter equation, $(\ln x = A + \frac{B}{T})$, was used to determine if the solubility results could be fitted in this way. The values of A and B were obtained by least squares fit from the experimental data.

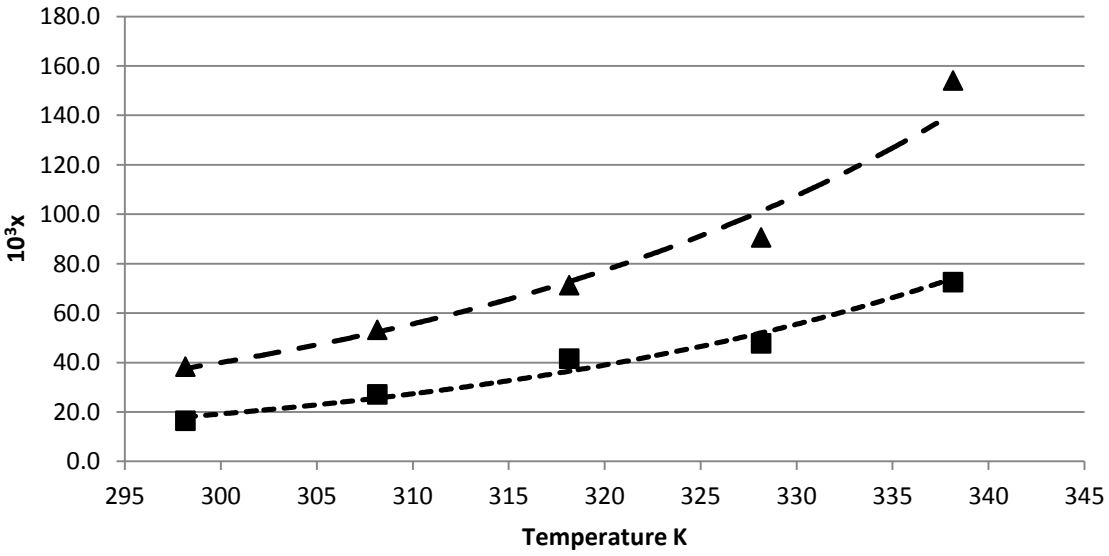
The calculated parameters are displayed in Table 5.5 with the root mean square deviation. The dual parameter and calculated values are compared together in Table 5.6. The experimental data and calculated data were plotted together in Figure 5.4.

	Dual Parameter Equation		
IL	**A**	**B**	**10^3rmsd**
[bmim][PF_6]	7.929	-3568.8	2.950
[hmim][PF_6]	7.852	-3325.2	9.042

Table 5.5: Calculated A and B Parameters and root mean square deviation

T / °K	**$10^3 x^{exp}$**	**$10^3 x_1^{cal}$**
[bmim][PF_6]		
298.15	16.502	17.584
308.15	27.165	25.931
318.15	41.627	37.318
328.15	47.812	52.526
338.15	72.580	72.452
[hmim][PF_6]		
298.15	38.396	36.854
308.15	53.304	52.926
318.15	71.348	74.297
328.15	90.674	102.164
338.15	154.157	137.860

Table 5.6: Comparison of experimental data and fitted values of solubility



[bmim][PF_6] ■ and [hmim][PF_6] ▲

Figure 5.4: Experimental data points (solid points) and fitted data (dotted line)

The obtained fit from the dual parameter equation is in good agreement for the [bmim][PF_6] system. However, more deviation was observed in the [hmim][PF_6]–ibuprofen system especially at the higher temperatures. The calculated data could still be used to describe the

trend of solubility but may not be an accurate predictor at high temperatures; the possibility of degradation should also be considered.

Buchowski Equation

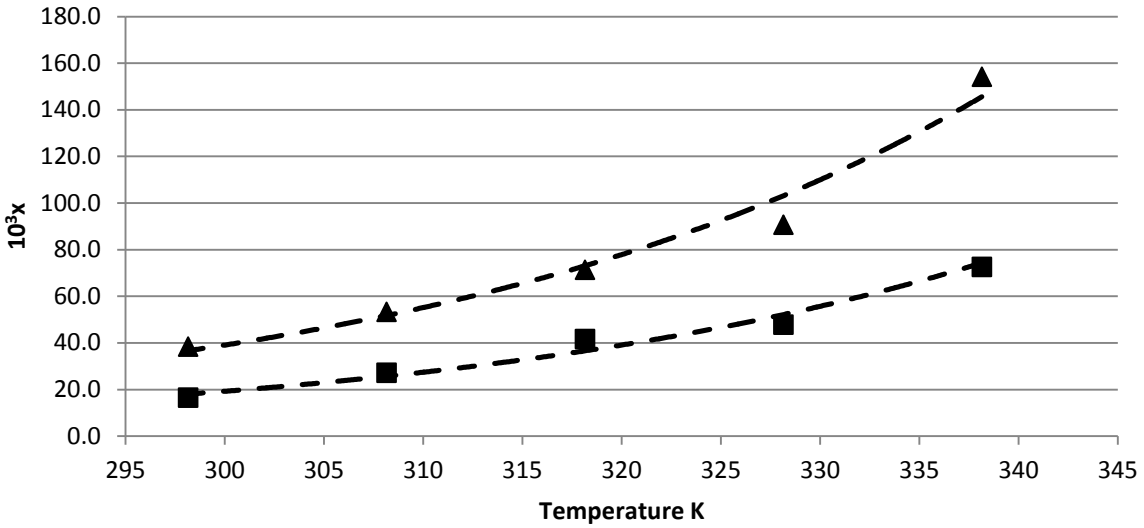
The relationship between mole fraction solubility and temperature on the solid-liquid phase equilibrium was also assessed using the λh (Buchowski) equation ($\ln\left(1+\frac{1-x}{x}\right) = \lambda h\left(\frac{1}{T_m}-\frac{1}{T_m}\right)$). The values of λ and h were obtained from non-linear least squares fit.

	λh Parameter Equation		
IL	**λ**	**h**	**10^3rmsd**
[bmim][PF_6]	0.85	4187	2.975
[hmim][PF_6]	1.87	1931	8.493

Table 5.7: Calculated λ and h Parameters and root mean square deviation

T /K	**$10^3 x^{exp}$**	**$10^3 x_1^{cal}$**
[bmim][PF_6]		
298.15	16.502	17.641
308.15	27.165	25.993
318.15	41.627	37.402
328.15	47.627	52.680
338.15	72.580	72.784
[hmim][PF_6]		
298.15	38.396	35.720
308.15	53.304	52.475
318.15	71.348	74.998
328.15	90.674	104.445
338.15	154.157	141.916

Table 5.8: Comparison of experimental data and calculated values of solubility



[bmim][PF_6] ■ and [hmim][PF_6]▲

Figure 5.5: Experimental data points (solid points) plotted with trend line (dotted line) from calculated values from Buchowski Equation

A reasonable correlation was found using both the dual parameter and the Buchowski equation with both approaches giving very similar fits to one another. The errors associated with the fit are greater than was observed for the studies in paracetamol due to the greater deviation between correlated data and experimental data at high temperatures, particularly for [hmim][PF_6] where larger errors were recorded for the high temperature data (cf. comment on degradation in dual parameter discussion).

5.2.4 Ibuprofen Solubility Conclusions

Methodology to measure the solubility of Ibuprofen was established and used to successfully measure the equilibrium solubility in [bmim][PF_6] and [hmim][PF_6]. The methodology highlighted the care needed when conducting such measurements as small changes in pH can have a significant impact. Compared to water, ILs were found to be good solvents for ibuprofen over the temperature range measured. Ibuprofen is more hydrophobic than paracetamol, meaning that it has more favourable solubility in the

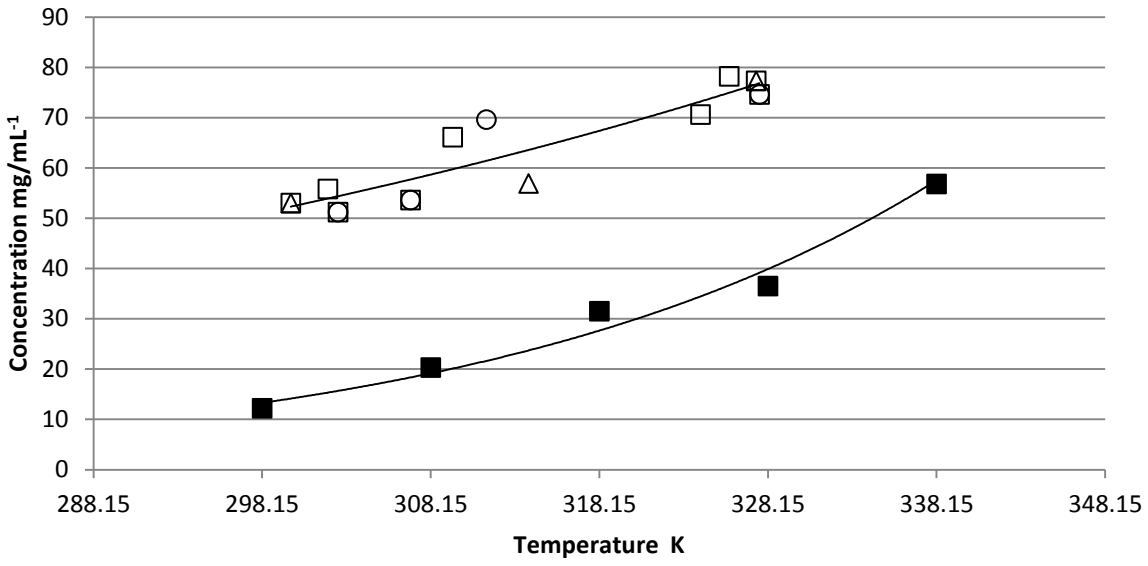
hydrophobic ILs. The models used showed good correlation at lower temperatures. However for high temperatures where the solubility is greater, the errors between the experimental and calculated were more significant.

The data generated for these two systems also shows that that the solubility does vary with temperature, meaning that using temperature to generate supersaturated solutions to investigate cooling crystallisations is possible.

5.3 Cooling Crystallisations

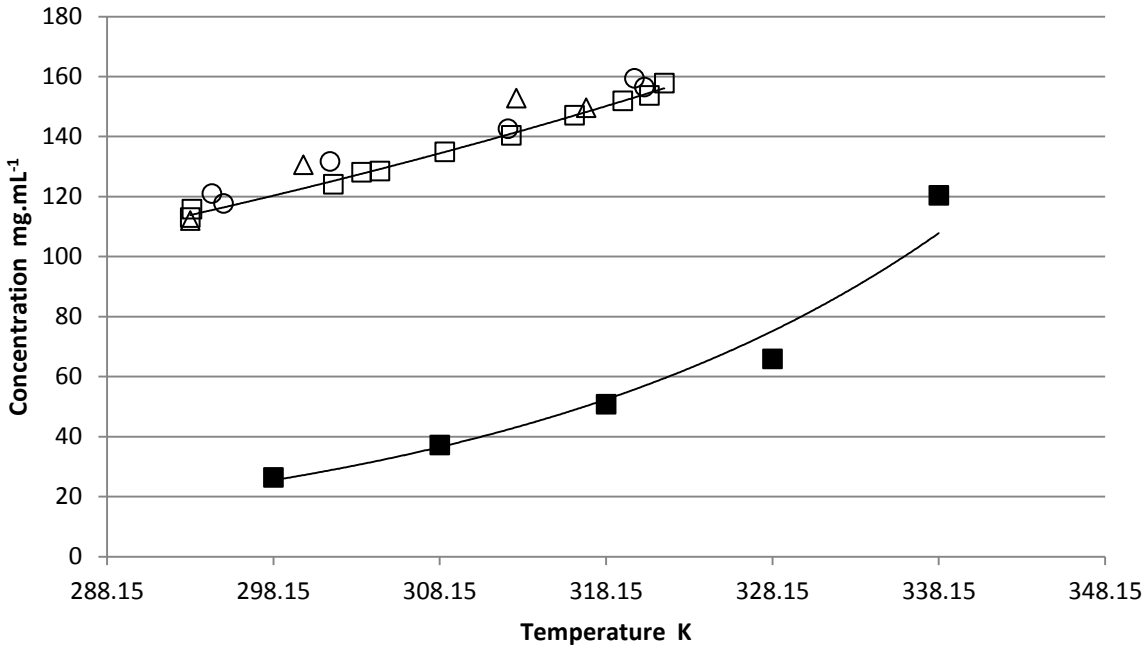
5.3.1 Meta-Stable Zone Width Determination

Using the same methodology used for during the Paracetamol investigation (see Chapter 4 Section 4.3.1) the MSZW was defined and the corresponding data shown in Figures 5.6 and 5.7.



Equilibrium Solubility ■, cooling rate of 0.2 K.min^{-1} □, 0.5 K.min^{-1} Δ and 1.0 K.min^{-1} ○

Figure 5.6: Ibuprofen Equilibrium Solubility and obtained MSZW in [bmim][PF_6]



Equilibrium Solubility ■, cooling rate of 0.2 K.min^{-1} □, 0.5 K.min^{-1} Δ and 1.0 K.min^{-1} ○

Figure 5.7: Ibuprofen Equilibrium Solubility and obtained MSZW in [hmim][PF_6]

The MSZWs obtained here are extremely high, especially in the case of [hmim][PF_6]. The MSZWs obtained show that high supersaturation concentrations can be generated, for example a supersaturation ratio of ΔS = 5.8 at 293.15 K would be possible 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.

The cooling rate was found to have an insignificant impact on the MSZW across the range of 0.2 to 1.0 K.min^{-1}. The data generated define the operating region for developing a cooling crystallisation.

5.3.2 Primary Nucleated Systems

The unseeded experiments were designed to cross the meta-stable zone width at different levels of supersaturation. These scoping experiments investigated the impact of concentration on resulting particle formation when the crystals are grown from a primary

nucleation event. Following these experiments a set of seeded experiments was conducted at different supersaturation ratios.

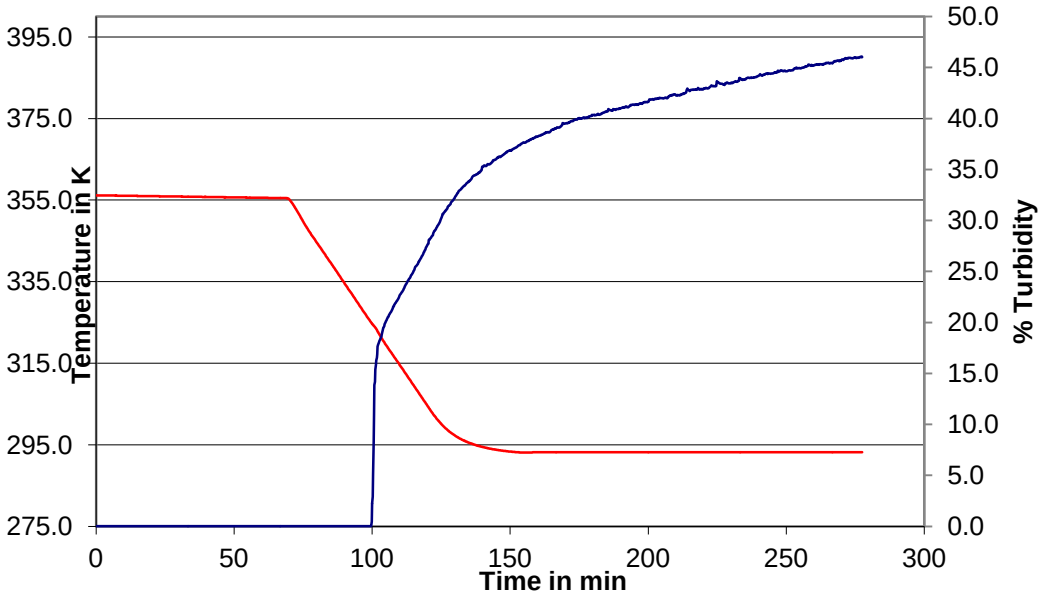
5.3.2.1 Process Conditions

A number of unseeded crystallisations were completed to in order to understand the impact of crystallising from primary nucleation and subsequent growth. Conditions investigated are displayed in Table 5.9.

Ionic Liquid	Concentration $mg.mL^{-1}$
[bmim][PF_6]	28
[bmim][PF_6]	57
[bmim][PF_6]	83
[hmim][PF_6]	79
[hmim][PF_6]	120
[hmim][PF_6]	155

Table 5.9: Ibuprofen Cooling Crystallisation Conditions (non-seeded)

Where possible the crystallisation was monitored by turbidity, a typical profile being displayed in Figure 5.8. In the profile a minimum in the turbidity is observed when dissolution of all the powder had occurred. The turbidity remains at this minimum as the solution is cooled until the meta-stable zone width has been crossed and there is a rapid burst of nucleation and the material precipitates out of solution causing a rise in the turbidity.



The plot shows the temperature (red line) 355 K as the input ibuprofen is dissolved. At this temperature the % turbidity (blue line) is zero as it is a clear solution. As the solution is cooled to 293 K at 0.2 K.min^{-1} a sudden rise in the turbidity is observed at 325 K due to spontaneous nucleation.

Figure 5.8: Typical Turbidity Plot for non-seeded Ibuprofen Crystallisation

Analysis

Form

As the MSZW showed, the systems can generate large supersaturations, increasing the potential either to crystallise a meta-stable form. However there is only one well known and characterised form of ibuprofen; another form has been proposed in the literature but is very unlikely to form.

The form of the resultant crystals was determined by X-Ray Diffraction (XRD) and compared to both the calculated XRD pattern and against published literature. All samples produced XRD patterns consistent with the form I material and are shown in Appendix 5 with an example trace shown in Figure 5.9.

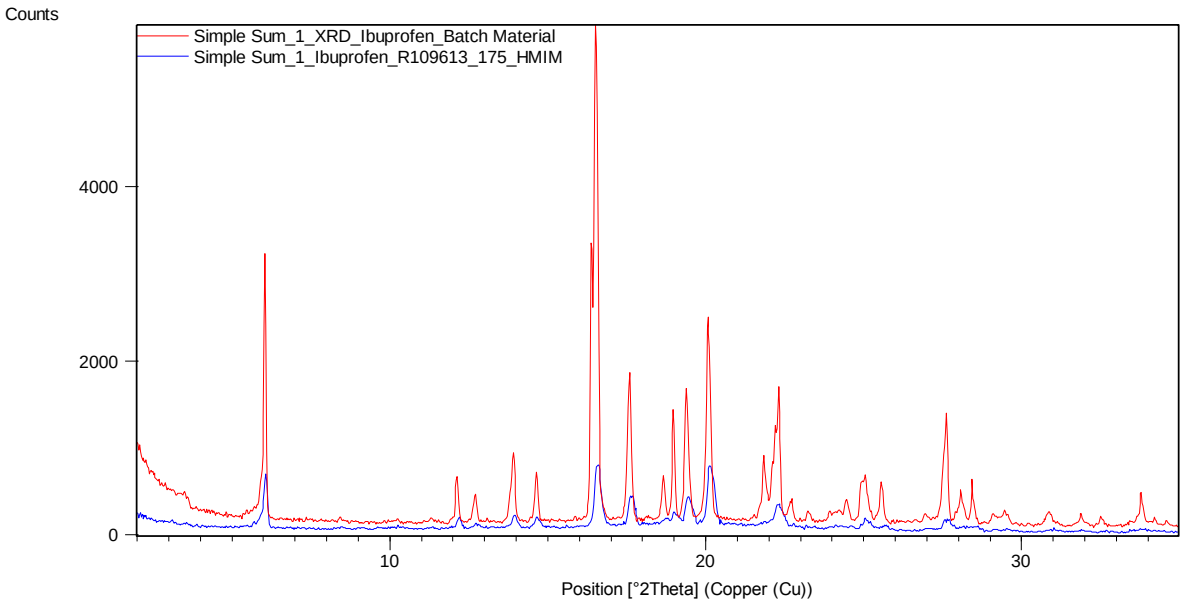


Figure 5.9: Example XRD pattern from [hmim][PF_6] cooling crystallisation (blue) with input ibuprofen material (red) known to be Form I

As was found with the paracetamol work, when the precipitated crystals were separated from the IL, residual liquid remained on the surface of the crystals as can be seen in the SEM images shown in Table 5.8 and 5.9. This had the effect of agglomerating the crystals and was particularly seen for the smaller and more plate-like particles. As a result XRD patterns obtained for these particles had weaker signals 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.

Habit

The particle habit was assessed by optical microscopy and SEM; images for the obtained powders are shown in Tables 5.10 and 5.11.

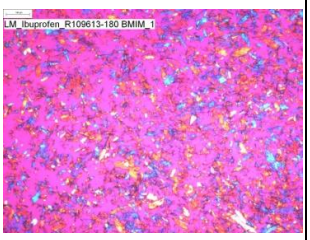
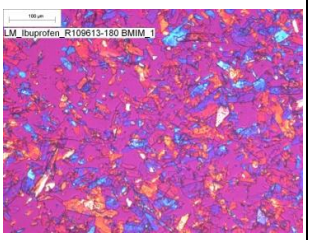
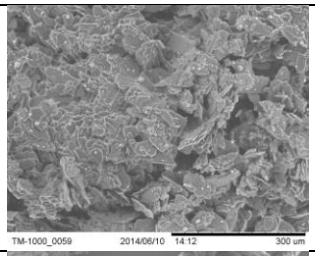
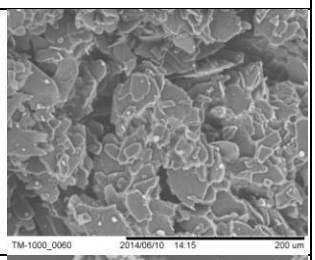
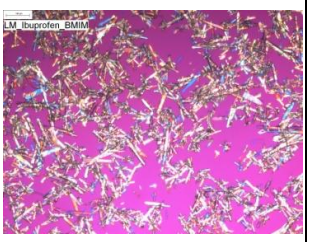
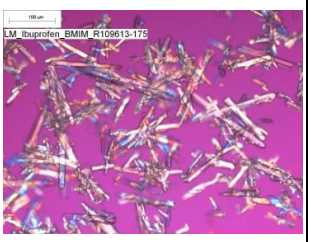
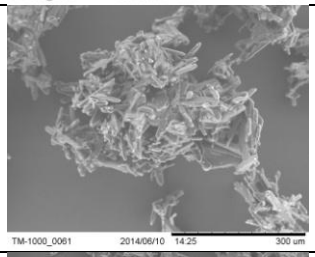
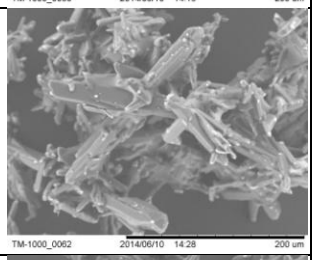
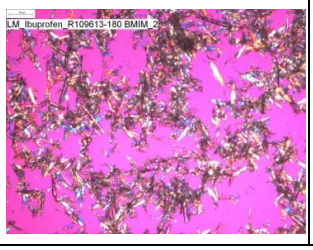
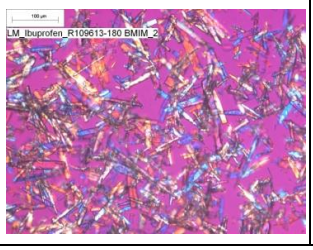
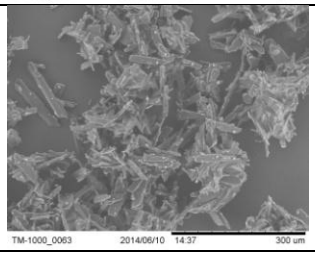
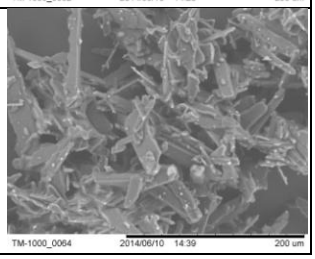
	Optical Microscopy		SEM	
mg. mL^{-1}	50X Magnification	100X Magnification	250X Magnification	500X Magnification
28				
57				
83				

Table 5.10: OM and SEM images of Ibuprofen from [bmim][PF_6]

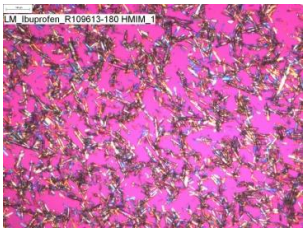
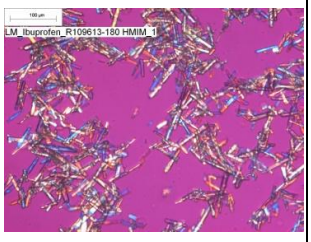
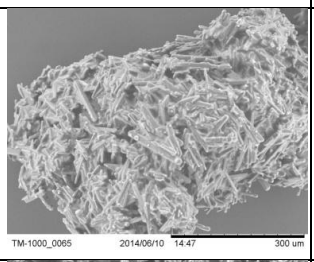
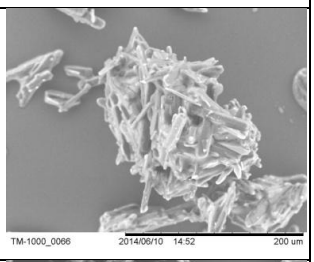
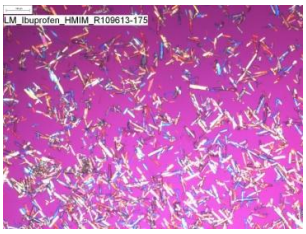
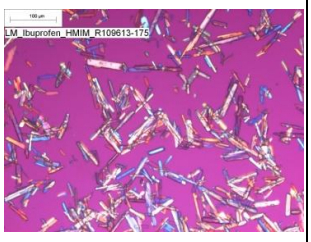
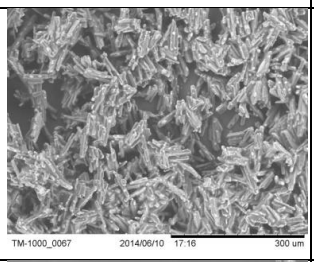
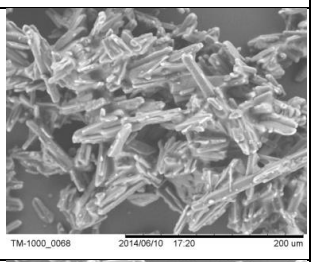
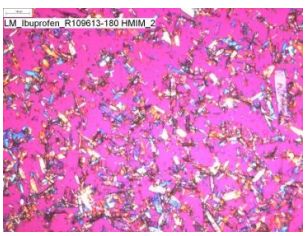
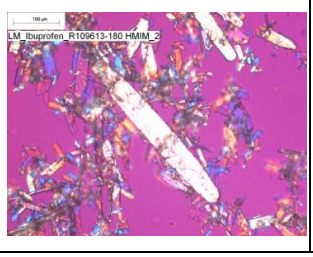
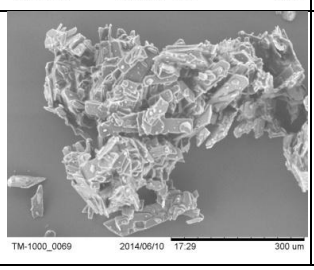
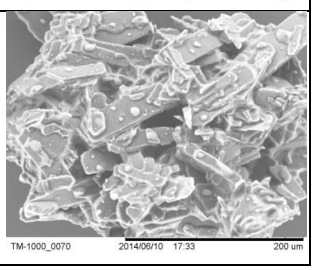
	Optical Microscopy		SEM	
mg .mL^{-1}	50X Magnification	100X Magnification	250X Magnification	500X Magnification
79				
120				
155				

Table 5.11: OM and SEM images of Ibuprofen from [hmim][PF_6]

The predominant habit produced was acicular or small plate-like particles, though some larger plates were observed in the highest concentrated sample. Unlike paracetamol it was found that concentration and modification of the alkyl chain length from butyl to hexyl had little impact on the habit produced.

Particle Size

The particle size of the resultant powders was measured by laser diffraction. A summary of the data is shown in Table 5.12. An example of a typical size distribution is shown in Figure 5.10 with all raw data in Appendix 6.

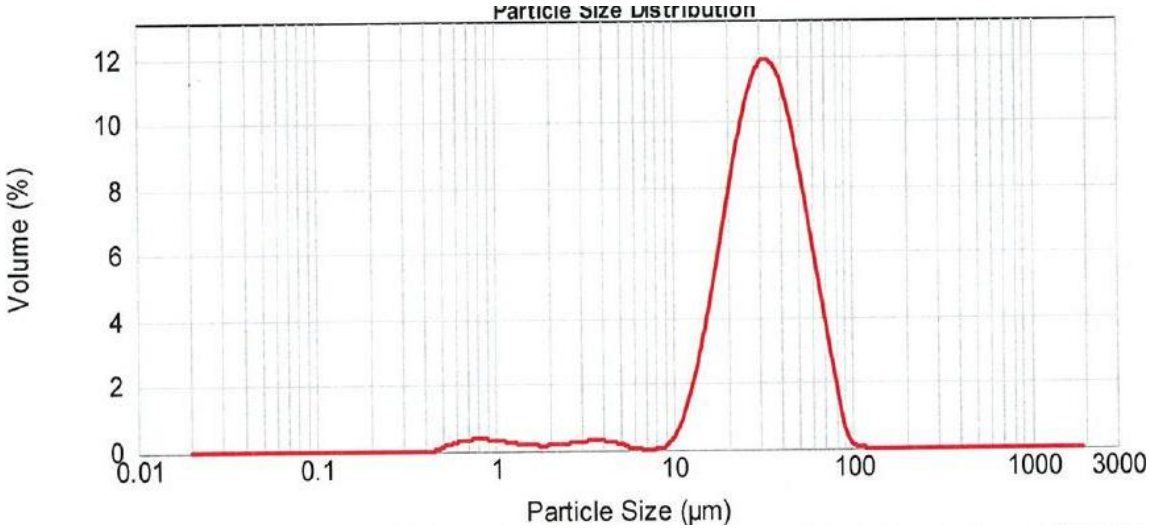


Figure 5.10: Ibuprofen PSD from [hmim][PF_6] at 120 mg.ml^{-1}

				Particle Size		
Ionic Liquid	**Concentration mg.mL^{-1}**	**d_{10}**	**d_{50}**	**d_{90}**	**Span**	**Distribution Description**
[bmim][PF_6]	28	4	17	44	2.4	Tri-Modal
[bmim][PF_6]	57	9	24	50	1.9	Tri-Modal
[bmim][PF_6]	83	15	36	79	1.8	Bi-Modal
[hmim][PF_6]	79	5	15	34	1.9	Tri -Modal
[hmim][PF_6]	120	16	32	58	1.3	Tri -Modal
[hmim][PF_6]	155	11	27	56	1.7	Tri-Modal

Table 5.12: Summary Particle Size Data for Ibuprofen

Particle data for the experiments showed no obvious trends. It would be expected that the particle size would decrease as the concentration increases. For samples crystallised from [bmim][PF_6] and [hmim][PF_6], it was found that the least concentrated solution produced the smallest particles while the highest concentrated solution gave the largest particles. These data are similar to the particle size observations for the paracetamol work. The highest concentrated samples cross the MSZW much earlier, these crystals are then able to go through a significant growth phase as the crystallisation slowly cools down to ambient temperature. For the lowest solubility samples, the temperature at which nucleation occurs is much closer to the isolation temperature, meaning that there is less material (and time) for the crystals to undergo as much growth.

5.3.3 Secondary Nucleated Systems

In order to carry out crystallisations under more controlled conditions seed is commonly added to supersaturated solutions inducing growth onto the crystals. This is a common tactic used in the pharmaceutical industry to control form and habit but in particular the particle size of the resultant crystals.

Process Conditions

A set of seeded experiments were conducted at different supersaturation ratios, defined at 333.15 K as indicated in Table 5.13. The wide MSZW curve at 333.15 K enabled a broad range of supersaturations to be investigated before spontaneous crystallisation occurred.

Ionic Liquid	Concentration mg.mL^{-1}	ΔS at 333.15 K
[bmim][PF_6]	61	1.28
[bmim][PF_6]	72	1.50
[bmim][PF_6]	84	1.75
[hmim][PF_6]	113	1.25
[hmim][PF_6]	136	1.51
[hmim][PF_6]	158	1.75

Table 5.13 : Ibuprofen Seeded Cooling Crystallisation Conditions

Reactions here were also monitored where possible using turbidity (refer to Chapter 4, Figure 4.11 for details of typical profile). Following addition of the seed material at 333.15 K, a steady increase is observed as material precipitates out of solution, growing onto the seed crystals.

Analysis

Form

All samples produced XRD patterns that were consistent with form I material. Given that all the non-seeded samples also produced this stable form and that the seeds added to the crystallisations were also form I this was an expected result. The raw data for all seeded samples are shown in Appendix 5 while Figure 5.11 shows an example.

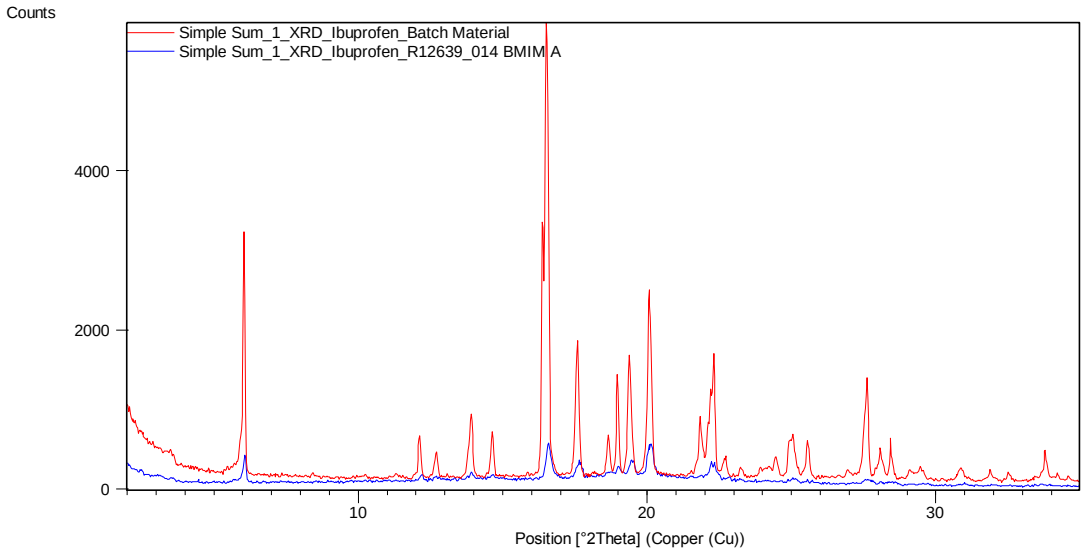


Figure 5.11: X-Ray Diffraction of Ibuprofen from [bmim][PF_6] (Blue Trace) with input Ibuprofen Form I (Red Trace)

Particle Habit

The particle habit was assessed by optical microscopy and SEM, as shown in Tables 5.14 and 5.15. ΔS had little impact on the crystal habit at the ranges studied, with plate-like particles forming in all the samples. Compared to the primary nucleated systems the particles were less acicular showing that growth onto the seed crystals had occurred.

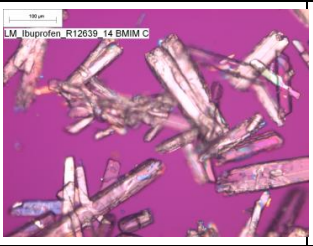
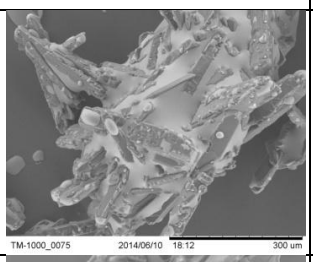
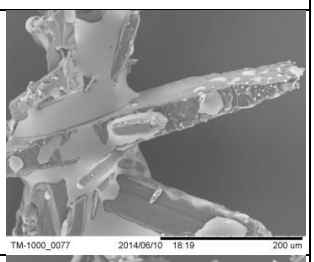
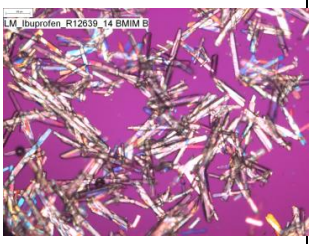
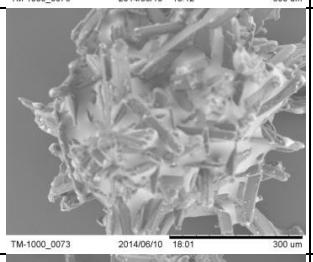
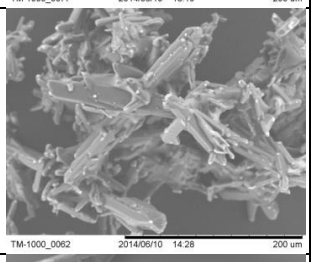
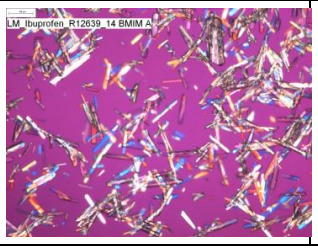
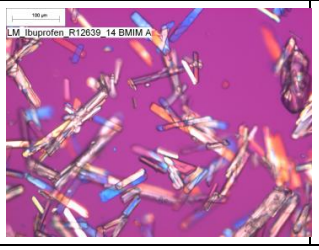
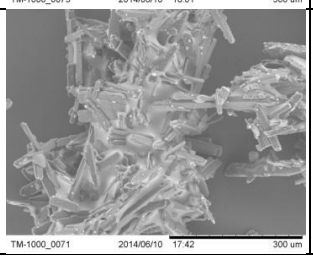
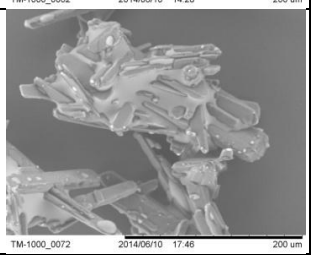
	Optical Microscopy		SEM	
ΔS	50X Magnification	100X Magnification	250X Magnification	500X Magnification
1.28				
1.50				
1.75				

Table 5.14: Ibuprofen OM Images of Ibuprofen from [bmim][PF_6]

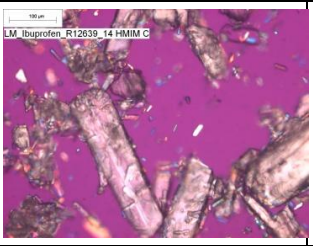
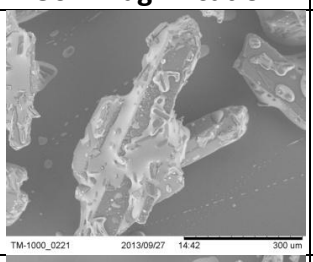
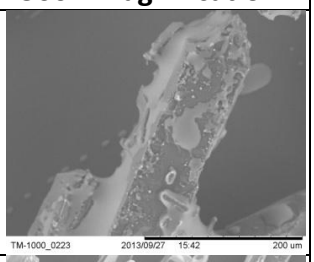
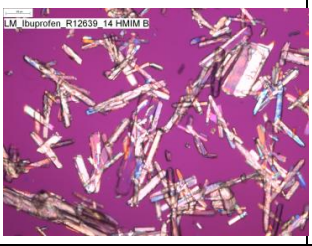
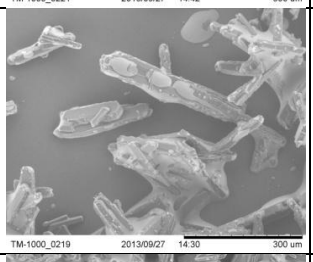
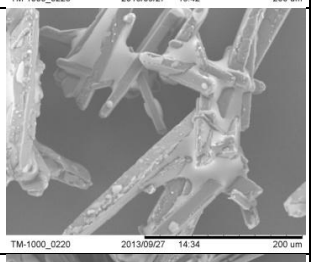
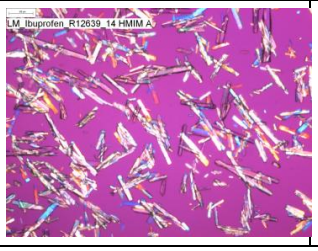
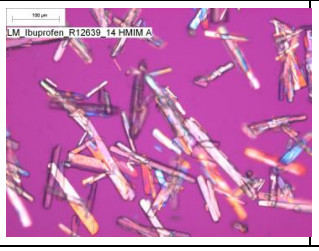
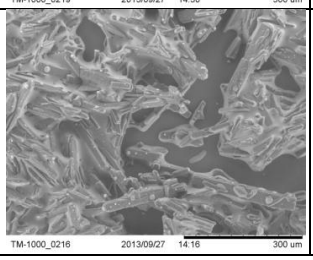
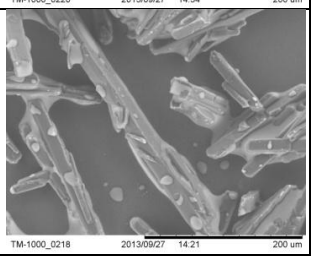
	Optical Microscopy		Scanning Electron Microscopy	
ΔS	50X Magnification	100X Magnification	250X Magnification	500X Magnification
1.25				
1.51				
1.75				

Table 5.15: Ibuprofen OM and SEM Images of Ibuprofen from [hmim][PF_6]

Comparison to organic solvents

Comparing the habits produced here to those obtained from other published data on conventional solvents it was observed that the majority of solvent systems produced thin plates or acicular habits. Rasenack and Muller (2002) crystallised ibuprofen using a number of techniques by using water as an anti-solvent. They found that material crystallised using a similar cooling crystallisation process, forming similar needle-like particles from acetone, diethyl ether and hexane. A change in habit was seen for samples crystallised from a cooling dichloromethane solution, where more cubic particles were observed. Cano et al (2001) conducted crystallisation studies into the impact of ethanol and ethyl acetate on the growth of single crystals. They found that the growth rate of the faces in ethanol was of the same order of magnitude, resulting in a relatively isomeric crystal whereas the crystals grown from ethyl acetate resulted in thin elongated particles, indicating that the ethyl acetate does impact the growth of the (1 0 0) face. When looking at the molecular arrangement of this face it is composed of successive layers that exhibit either polar or non-polar functional groups. The polar carboxylic acid groups project out from the surface, allowing them to form strong hydrogen bonds. The imidazolium cation can hydrogen bond from the C2 position, meaning that this is also likely to interact with the (1 0 0) face, leading to the acicular material.

Particle Size

The particle size of the precipitates was measured by laser diffraction; a selection of the data are shown in Table 5.16. An example of a typical size distribution is shown in Figure 5.12 with all raw data in Appendix 6.

		Particle Size				
Ionic Liquid	**ΔS**	**d_{10}**	**d_{50}**	**d_{90}**	**Span**	**Distribution Description**
[bmim][PF_6]	1.28	27	79	185	2.0	Bi-Modal
[bmim][PF_6]	1.50	17	40	88	1.8	Multi-Modal
[bmim][PF_6]	1.75	11	29	67	1.9	Multi-Modal
[hmim][PF_6]	1.25	28	133	352	2.4	Tri-Modal
[hmim][PF_6]	1.51	24	62	146	2.0	Bi-Modal
[hmim][PF_6]	1.75	14	40	120	2.7	Tri-Modal

Table 5.16: Summary of Ibuprofen Particle Size Data from Seeded Crystallisations

The particle sizes obtained from the seeded crystallisation studies are larger than those produced from the primary nucleated systems. A decrease in the particle size was observed as supersaturation was increased. This was coupled with the either a bi-modal, tri-modal or multimodal distribution indicating that two modes of nucleation are occurring in the system, with growth of the crystals and spontaneous nucleation, or that the particles produced from the more highly concentrated samples are more prone to attrition by breaking into smaller particles. The possibility that remaining IL on the surface contributes to the size distribution should also be considered (cf. as considered in Section 4.3.2).

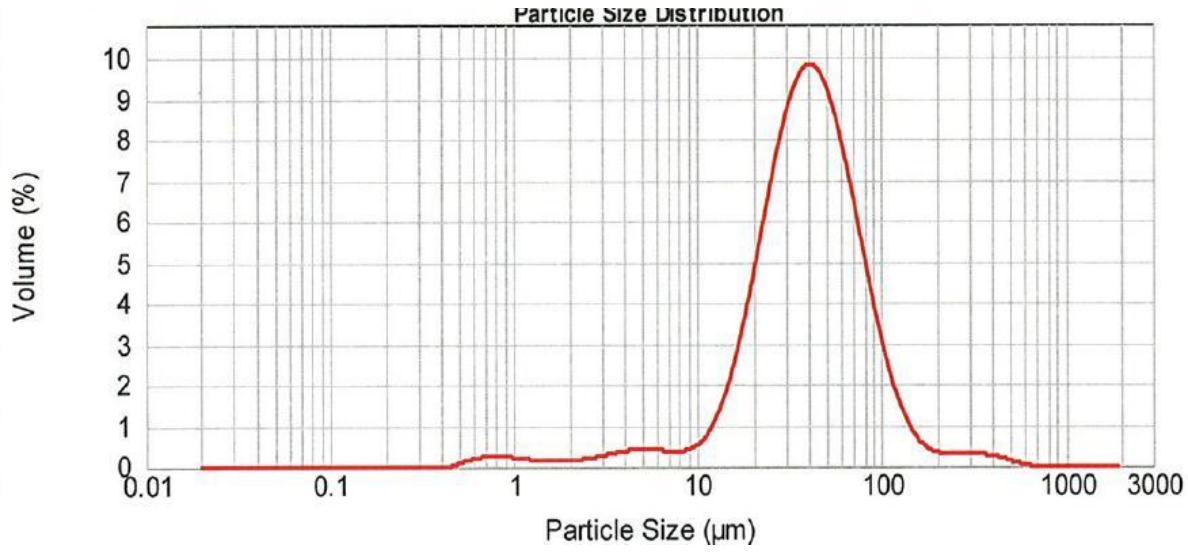


Figure 5.12: Ibuprofen PSD from [bmim][PF_6] at ΔS 1.5

5.4 Summary

It has been shown that ibuprofen can be successfully crystallised from [hmim][PF_6] and [bmim][PF_6] using cooling crystallisation. However, unlike paracetamol there was no change in the particle habit resulting from changing either the IL or the concentration, as it is likely that the cation may interact with the (1 0 0) resulting in elongated particles. No significant benefit to crystallising from the ILs used here or those selected as part of the test set over conventional organic solvents could be identified so no further investigation was carried out. It is possible that other ILs containing different cations may be selected to produce a more isomeric crystal but fundamental changes in habit are not anticipated.

5.5 References

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Potthast, H., Dressman, J.B., Junginger, H.E., Midha, K.K., Oeser, H., Shah, V.P., Vogelpoel, H., Barends, D.M. (2005) Biowaiver monographs for immediate release solid oral dosage forms: Ibuprofen, **Journal of Pharmaceutical Sciences**, 94, 2121-2131

Rasenack, N., Müller, B.W. (2002) Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs, **Pharmaceutical Research**, 19 ,1894-1900

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CHAPTER 6: STUDIES WITH FLUFENAMIC ACID

6.1 Introduction

This chapter is focussed on the experimental work completed on flufenamic acid, which is a potent anti-inflammatory API used in the treatment of osteoarthritis, rheumatoid arthritis and other painful musculosketal illnesses. Flufenamic acid is known to be highly polymorphic with eight polymorphs having been reported in the literature. The screening methodology established in previous chapters was applied to assess if ILs could be used to crystallise this compound and whether the polymorphic form of the API could be controlled through choice of IL. Where possible the results are compared to literature data for conventional organic solvents.

6.2 Solubility

6.2.1 Solubility of Flufenamic Acid in Water and ILs

Using the screening methods established during the studies on paracetamol and ibuprofen, the same methodology was applied to Flufenamic acid. Where practically possible a three point solubility curve was established in each of the chosen IL test sets.

In order to determine if the method and materials used gave a suitable measurement of the solubility, the solubility was measured in water and compared to literature values at 298.15 K. Other data at elevated temperatures could not be found, hence the single point comparison for this compound as shown in Table 6.1.

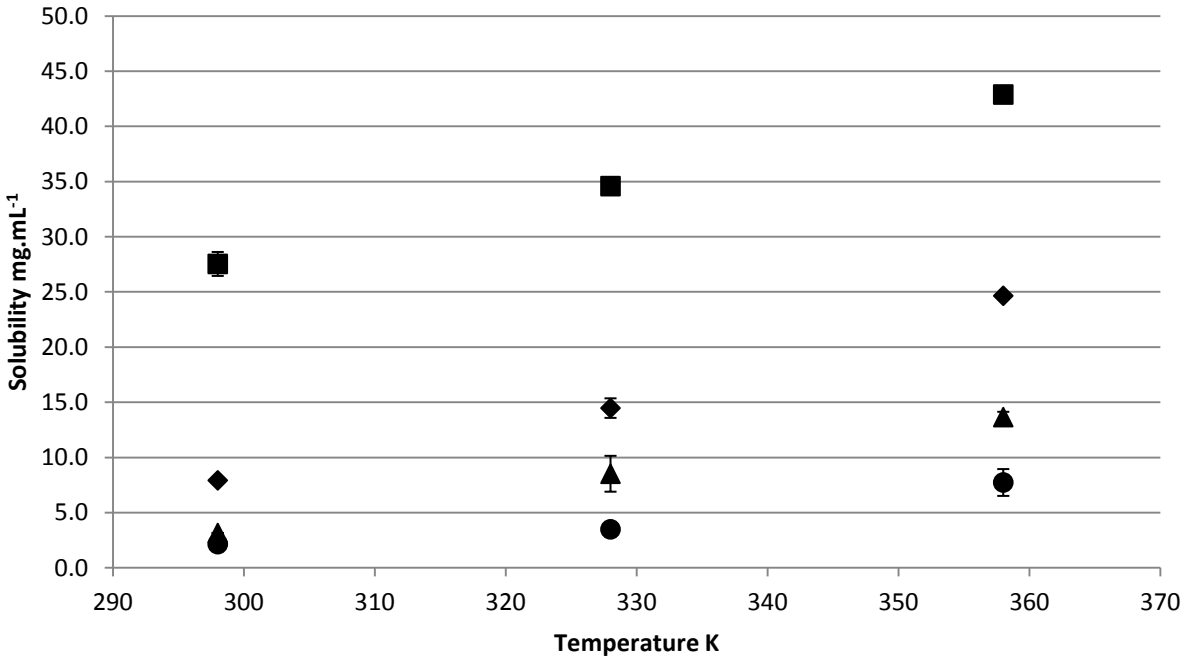
Temperature K	Solubility [a] $mg.mL^{-1}$	Solubility [b] $mg.mL^{-1}$
298.15	0.01 ± 0.018	0.01

Table 6.1: Flufenamic Acid Solubility in H_2O for this Work[a] and Domańska et al[b]

The measured solubility at 298.15 K was in good agreement with the work of Domańska et al (2011) giving confidence that suitably accurate results could be obtained. Solubility data were then determined as 298.15 K, 328.15 K and 358.15 K for each of the ILs selected as the test set for this study. For each measurement, the mean from duplicate experiments plus or minus the standard error of the mean were calculated. This is intended as a screening method for establishing fit for purpose data that would allow for suitable solvent selection. It is recognised that if a crystallisation process was to be developed further then further more detailed studies would be required to fully establish equilibrium solubility. The solubility results are shown in Table 6.2 and Figure 6.1.

Temperature K	[bmim][BF_4] mg.mL^{-1}	[bmim][NTf_2] mg.mL^{-1}	[bmim][CH_3COO] mg.mL^{-1}	[bmim][$C_8H_{17}OSO_3$] mg.mL^{-1}	[bmim][PF_6] mg.mL^{-1}	[hmim][PF_6] mg.mL^{-1}
298.15	7.94 ± 0.03	2.16 ± 0.02	130.49 ± 0.92	100.97 ± 1.61	27.55 ± 1.08	3.17 ± 0.01
328.15	14.49 ± 0.88	3.50 ± 0.03	Not Measured	Not Measured	34.60 ± 0.39	8.54 ± 1.63
358.15	24.66 ± 0.19	7.75 ± 1.22	Not Measured	Not Measured	42.90 ± 0.20	13.67 ± 0.48

Table 6.2: Solubility Results Screen for Flufenamic Acid



[bmim][BF_4] ♦, [bmim][PF_6] ■, [hmim][PF_6] ▲ and [bmim][NTf_2] ●

Figure 6.1: Solubility Data for Flufenamic Acid obtained from 298.15 K to 358.15 K

No further measurements beyond 298.15 K were obtained for the samples from [bmim][CH_3OO] and [bmim][$C_8H_{17}OSO_3$] for two reasons. Firstly, the solubility at the modest temperature of 298.15 K meant that large amounts of flufenamic acid would be needed to develop a crystallisation as large amounts of material would remain in solution on isolation. Secondly, the large amount of dissolved material also meant that the solutions were highly viscous and formed a gel-like consistency which makes separation more problematic.

A range of solubilities was observed from the IL test set. For the anions test, solubilities fell between those published in the literature for water and alcohols (Domańska et al 2011) with solubilities between 2.16 $mg.mL^{-1}$ and 130.49 $mg.mL^{-1}$ measured at 298.15 K. The anion was found to have a significant impact on the solubility of Flufenamic Acid.

When comparing the two $[PF_6]^-$ containing ILs it was found that increasing the alkyl chain length from butyl to hexyl and hence increasing the hydrophobicity caused the solubility to decrease. The same trend is observed in the organic solvents ethanol and 1-octanol. At 298.15 K ,using the same [bmim] cation the solubility was found to follow the following order $NTf_2 < BF_4 < PF_6 < C_8H_{17}OSO_3 < CH_3COO$.

Before the solubility data are reported it is necessary to scrutinise the reliability of the obtained data for this compound. The compound is known to be highly polymorphic and as solubility is intrinsically linked to the polymorphic form it is necessary to determine if any polymorphic changes were occurring during the solubility determination. An example of the XRD trace for $[bmim][BF_4]$ is shown below in Figure 6.2; the remaining XRD traces are shown in Appendix 7.

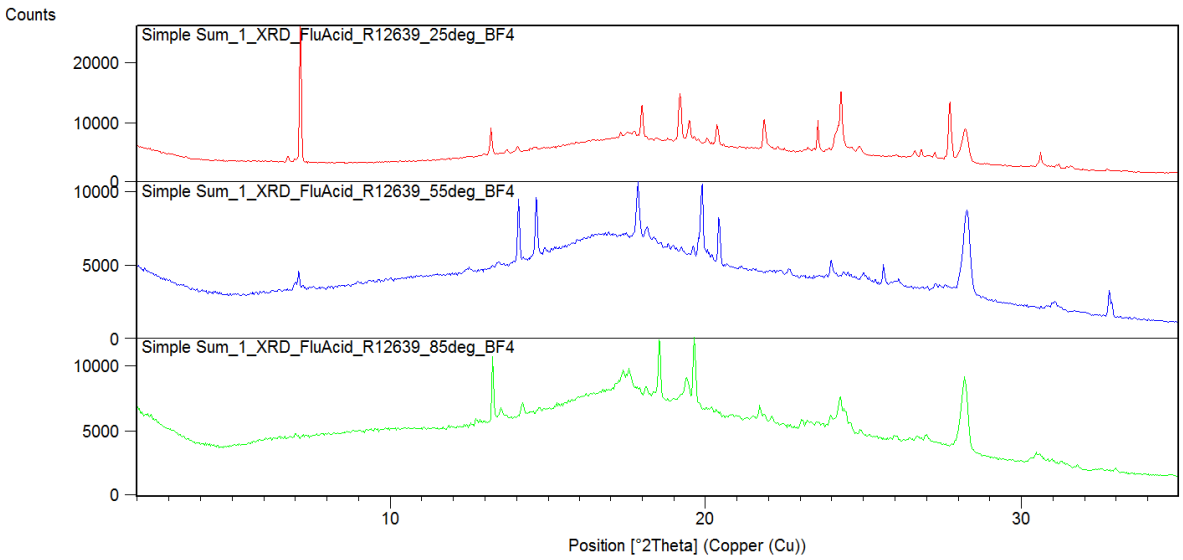


Figure 6.2: XRD patterns for slurry samples in [bmim][BF_4] at 298.15 K (red), 328.15 K (blue) and 358.15 K (green).

For all cases a change in the polymorphic form of the slurry samples was measured across the temperature range investigated. Hu et al (2005) found that Flufenamic Acid has a form transition from form III to form I around 318.15 K which accounts for the change in form seen here between 298.15 K and 328.15 K.

The solubility is intrinsically linked to how the unit cell packs. The impact of form on the solubility will be dependent on the compound and the specific forms being compared. Pudipeddi and Serajuddin (2005) compared the ratio of different forms of drug substances and show that, in general, the ratio is typically less than 2 fold. In the same research they determined the ratio of flufenamic Acid polymorphs using calculated ideal solubilites and using the Hoffman equation showed that the ratios at 303.15 K to be <1.9 but is unclear which forms are being compared.

The collected solubility data therefore cannot be considered as true equilibrium solubility data due to the change in form across the temperature range studied and as such no

modelling work was performed on this data set. The obtained solubility data were used only as a guideline to the dissolution point at high temperatures.

6.3 Cooling Crystallisations

6.3.1 Rapid Cooling Crystallisation

In order to determine the impact that the solvent may have on the crystal form of the material the four ILs were taken forward for further scoping studies. Using the solubility data obtained at 358.15 K, a flufenamic acid solution was dissolved at this concentration by taking the solution to 363.15 K to ensure full dissolution. The resulting solutions were then crash cooled to room temperature at a rate of 10 $K.min^{-1}$. No XRD data are reported for these samples as the resultant crystals produced poor x-ray diffraction patterns due to excess IL on the surface of the crystals.

The samples were analysed by optical and SEM as shown in Table 6.3. Samples from [bmim][PF_6] and [bmim][NTf_2] produced yellow needle-like crystals indicative of form III while samples from [hmim][PF6] and [bmim][BF4] produced white plate-like crystals indicative for form I (López-Mejías et al, 2012).

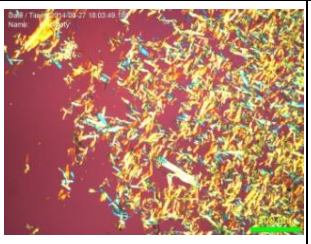
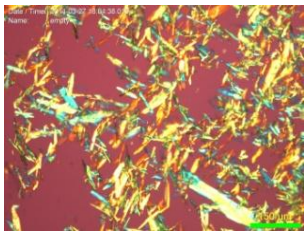
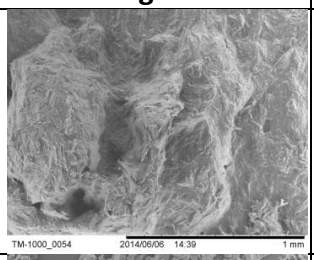
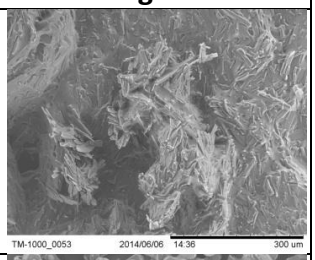
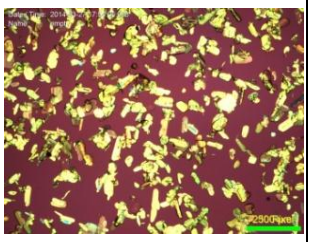
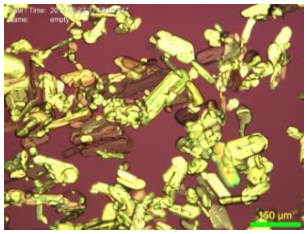
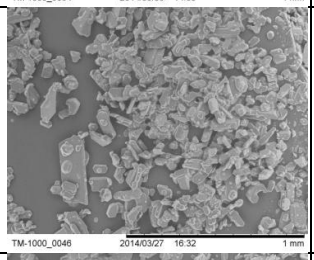
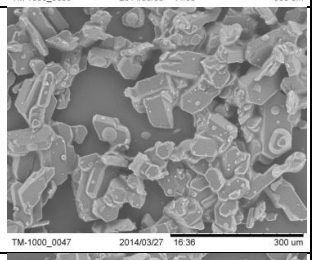
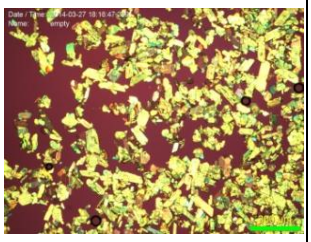
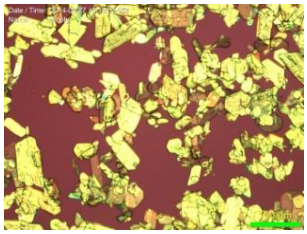
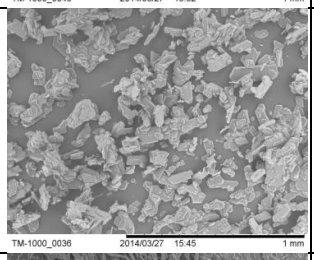
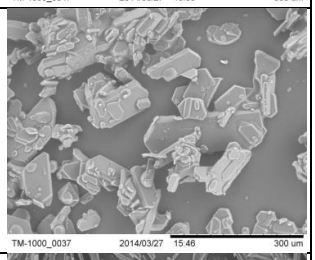
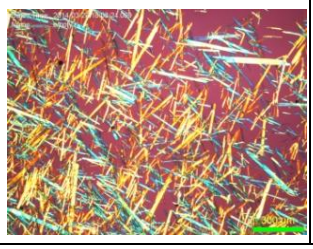
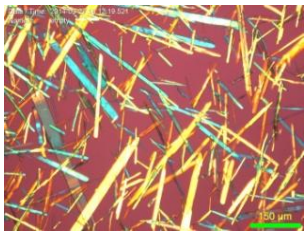
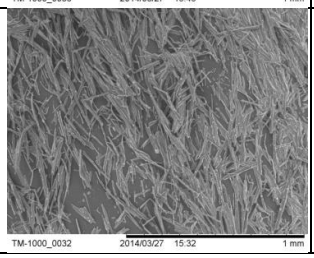
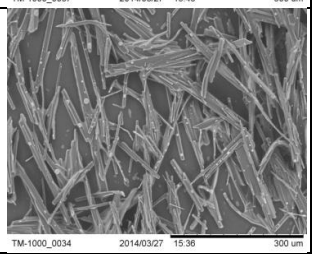
Ionic Liquid	Optical Microscopy		Scanning Electron Microscopy	
	50X Magnification	100X Magnification	100X Magnification	250X Magnification
[bmim][PF_6]				
[hmim][PF_6]				
[bmim][BF_4]				
[bmim][NTf_2]				

Table 6.3: Microscopy Images of Flufenamic Acid

6.3.2 Primary and Secondary Nucleated Systems

The ILs [bmim][PF_6] and [bmim][BF_4] were taken forward for further studies due to the higher achievable solubility in these solvents. To establish if a controlled crystallisation could be conducted using these solvents two ILs that gave differing polymorphic forms during the crystallisation were selected for further investigation. A further cooling crystallisation was conducted at a slower cooling rate at a concentration equal to the concentration at 358 K. The nucleation point from this crystallisation was used to determine the point at which spontaneous crystallisation would occur. Using this knowledge a second seeded crystallisation was then performed seeding at 5 K above the point of nucleation from the

primary nucleated system. A summary of the form as determined by XRD is shown in Table 6.4 with the raw data in Appendix 7.

Crystallisation	XRD
[bmim][PF_6] (non-seeded)	Mixture of Form I and III
[bmim][PF_6] (seeded with form III)	Form III
[bmim][BF_4] (non-seed)	Form I
[bmim][BF_4] (seeded with form I)	Form I

Table 6.4: Summary of Flufenamic Acid Form Results

A mixture of forms was produced from the non-seeded [bmim][PF_6] experiment, though when seeded with form III a pure sample of form III was produced. The particle habit matched the findings from the XRD as shown in Table 6.5.

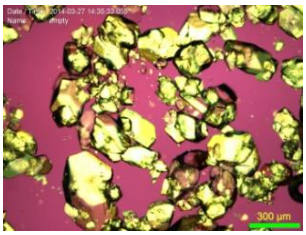
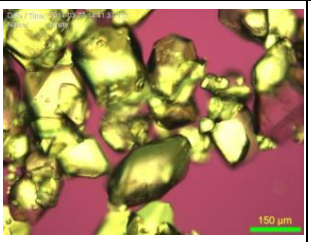
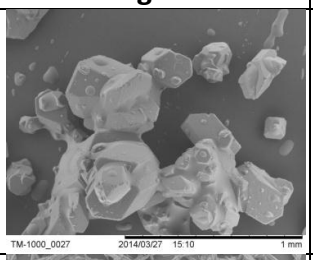
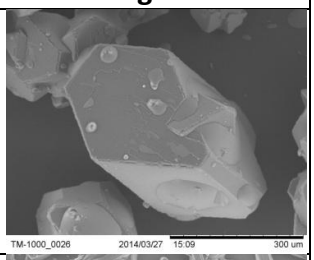
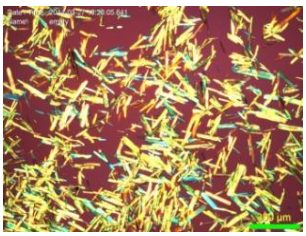
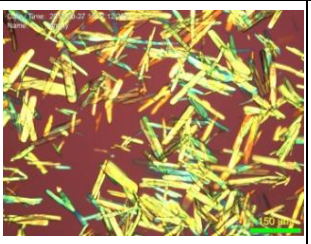
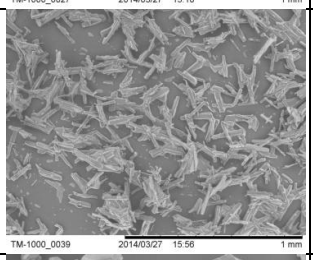
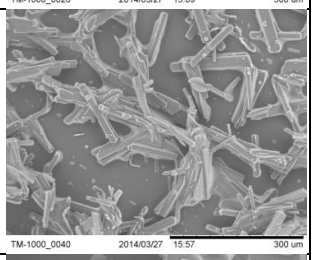
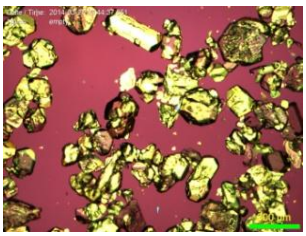
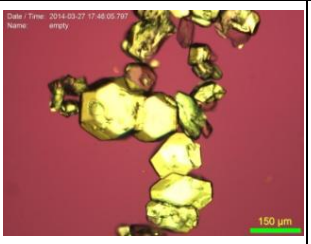
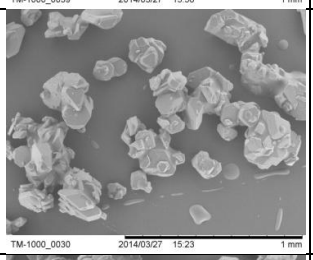
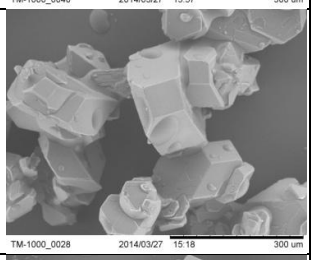
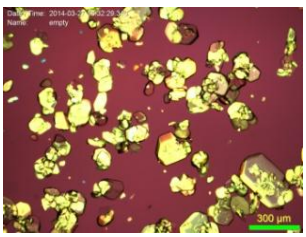
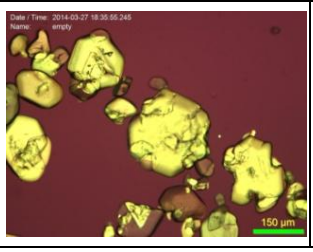
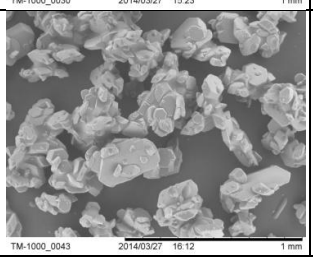
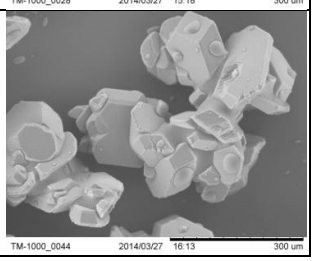
Ionic Liquid	Optical Microscopy		Scanning Electron Microscopy	
	50X Magnification	100X Magnification	100X Magnification	250X Magnification
[bmim][PF_6] unseeded				
[bmim][PF_6] seeded				
[bmim][BF_4] unseeded				
[bmim][BF_4] seed				

Table 6.5: OM and SEM Images of Crystallised Flufenamic Acid

Typical methods used to produce flufenamic acid include crystallisation from hot toluene (Li et al, 2010) and hot mixed xylene (Delaney et al, 2014) to produce form I; the same authors were also able to produce form III from methanol. In a similar light López-Mejías et al (2012) used polymers as heteronulcei to produce a range of forms from ethanol. The short scoping work applied here shows that, as with conventional solvents, in some cases metastable forms of flufenamic acid can be obtained by choosing a solvent that has different hydrogen bonding propensity.

6.4 Summary

The scoping work here has shown that different forms of flufenamic acid can be isolated though changing the IL used and the method of crystallisation. The polymorphs identified here are similar to those isolated at similar conditions in the literature. ILs do offer the opportunity to work at temperatures beyond those possible with organic solvents. Therefore for future work it would be prudent to investigate extremes of temperature to try and identify any new polymorphs, though this may lead to experimental difficulties due to the formation of gel-like systems.

6.5 References

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CHAPTER 7: PROBLEMS AND SOLUTIONS

7.1 Introduction

The purpose of this chapter is to document some of the issues encountered during the development of solubility and crystallisation practical work. They include well known problems that were anticipated at the outset of the work but also some problems that were encountered during development.

The work focussed on two main areas; methods to measure solubility and improving the filtration time. Hopefully future research will be able to build on any lessons learnt in this work so that similar problems are easily resolved.

7.2 Solubility Determination Methods

The first method commonly used with organic or aqueous-based systems is a gravimetric method where a saturated solution is weighed before evaporating off the solvent and weighing the remaining solid. This method obviously is not possible given the negligible vapour pressure of ILs. The choice of method available is limited to those that rely either on confirmation of dissolution of a known weight of API into a known volume or weight of solvent or by spectroscopic methods.

While confirmation of dissolution can provide a gross estimation of solubility, significant errors may be encountered when working with ILs in this manner. Particularly at low temperatures the viscosity of the ILs can increase significantly especially as solute is dissolved. Efficient mixing of the viscous slurries can prove challenging. If the dissolution point is being detected by a probe, care must be taken to ensure the proper point of dissolution is correctly recorded. If the assessment is conducted by eye, significant human

error may also occur. Many of the ILs are coloured making point of dissolution more difficult to determine.

This leaves spectroscopic methods such as the one used in this thesis. The most common method would be detection via Ultra Violet (UV) spectroscopy. However for this to be possible then the solute must have a chromophore. Other methods such as Charged Aerosol Detectors (CAD) are unlikely to be compatible with ILs as are likely to interfere with detection of the solute.

From a practical point of view there are also other factors that need to be considered. ILs can operate in temperature windows far outside those for conventional solvents. When developing data for process development, researchers have never had to operate outside these tight temperature ranges and as such much of the equipment used is not capable of exploiting this full range. Also it can be difficult to deal accurately with slurry mixtures that are at the extremes of temperature, not just from a method accuracy view point but also from the point of view of the safety of the operator. Another perhaps overlooked point is that if using weight to determine the solubility then steps need to be taken to avoid contaminating gloves when handling vials. As the IL is non-volatile any contamination could be passed onto outside of the vial and impact the accuracy of any weight measurements.

In order to be able to exploit the range of temperatures that ILs can operate at, using probes to give an online assessment of the solution concentration may be a viable option, so reducing the exposure to the operator and the error associated with sampling at extremes of temperature. Although the online readings will vary with changes in temperature, calibration curves can be determined to account for this.

7.3 Filtration

The high viscosity of ILs could result in a number of manufacturing problems. For example an important practical consideration when using ILs as pharmaceutical solvents is whether the product can be efficiently separated from the crystallisation liquor. In most pharmaceutical processes this is achieved using simple filtration through a mesh to leave a cake of material on the filter bed. The cake is then commonly washed with clean solvent before drying to remove any excess solvent. Working with ILs this provides a problem as all residual will need to be removed prior to any drying process. This could be achieved by displacing the ILs using a miscible solvent that is a poor solvent for the solute being crystallised.

7.3.1 Anti-solvent Crystallisation to Improve Filtration

To assess the issue a crystallisation of paracetamol was completed in the IL [bmim][$C_8H_{17}OSO_3$] which was found to be highly viscous when conducting the solubility studies in previous chapters. Three crystallisations were completed: a non-seeded cooling crystallisation, a seed crystallisation and an anti-solvent crystallisation. The aim was to determine the filtration performance for a highly viscous IL and the impact of adding a second solvent to reduce the viscosity.

To assess the filtration performance, a modified Darcy's equation was used which assumes a constant pressure cake filtration process (Ghosh, 2006). The constant pressure equation to used here to describe filtration performance is derived from Darcy's Law is shown below.

$$\frac{t}{V} = \frac{\bar{\alpha}\mu c}{2A^2P}V + \frac{R\mu}{AP}$$

where, $\bar{\alpha}$ is the average cake resistance in m.kg^{-1}, A is the filtration area in m^2, c is the solids concentration kg.m^{-3}, ΔP is the pressure differential in Pa (Pa), R is the resistance of the filter medium in m^{-1}, t is the elapsed filtration time in s, μ is the dynamic viscosity of the filtrate and V is the volume in m^3.

To make the comparison it was assumed that the filter resistance was negligible and the temperature was 293.15 K (to which all experiments had been cooled). Dynamic viscosity for [bmim][$C_8H_{17}OSO_3$] was taken from data in the literature (Wasserscheid and Hal, 2002). For the anti-solvent system, the presence of [bmim][$C_8H_{17}OSO_3$] was neglected because of its small volume and data for pure dichloromethane (DCM) was used (Yaws 2012). The results are shown in Table 7.1

Crystallisation Type	Cake Resistance m.Kg^{-1}
Cooling (non-seed)	3.9E+12
Cooling Seeded	1.4E+12
Anti-Solvent	6.8E+09

Table 7.1: Measured cake resistance for [bmim][$C_8H_{17}OSO_3$] Paracetamol Crystallisations

This cake resistance value can be plotted to give an indication in order to generalise the filtration performance as shown in Figure 7.1. The data obtained here demonstrate the poor filtration of the highly viscous IL. Employing seeding to increase the particle size improved the filtration but it can still be considered to be slow. The use of an anti-solvent to dilute the system improved the filtration significantly as this sample performed well.

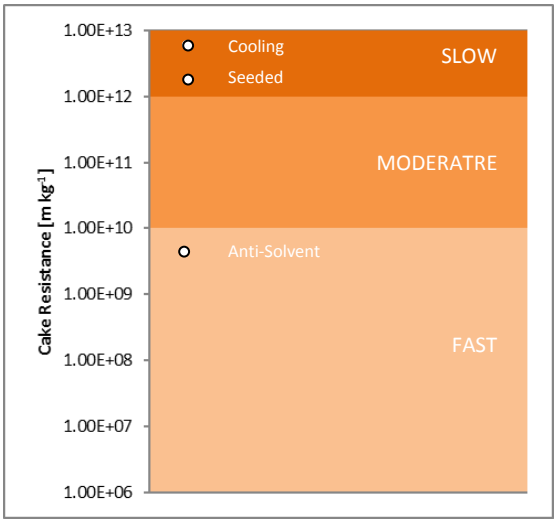


Figure 7.1: Calculated Cake Resistance for [bmim][$C_8H_{17}OSO_3$]

For comparison to previously crystallised material the output was analysed in-line with the previous paracetamol samples. The form of the material was consistent with the previously crystallised samples, form I. The images for the particles are shown in Table 7.2.

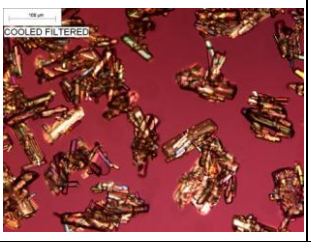
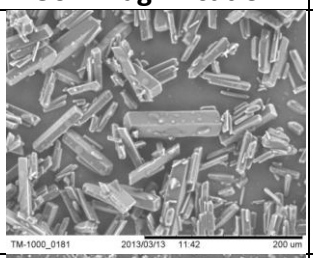
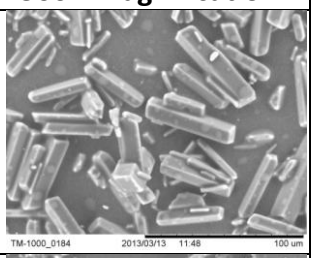
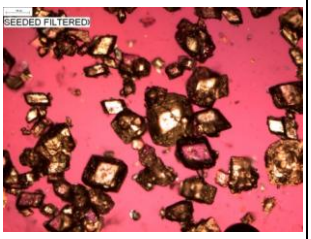
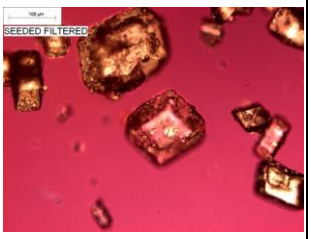
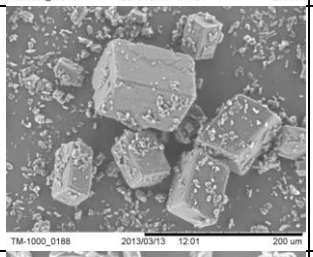
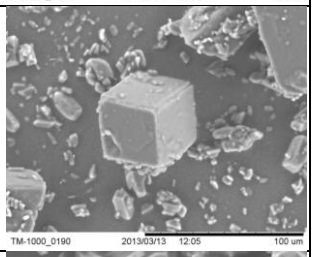
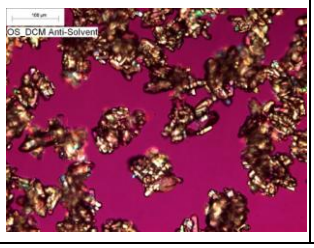
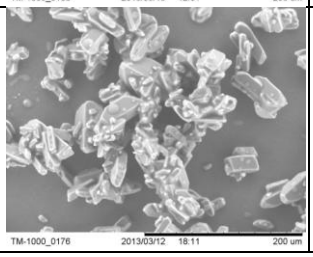
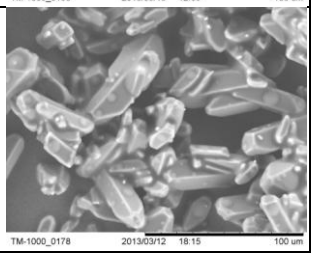
	Optical Microscopy		Scanning Electron Microscopy	
	50X Magnification	100X Magnification	250X Magnification	500X Magnification
[bmim] [$C_8H_{17}OSO_3$] unseeded				
[bmim] [$C_8H_{17}OSO_3$] Seeded				
[bmim] [$C_8H_{17}OSO_3$] DCM				

Table 7.2: Paracetamol Images from [bmim][$C_8H_{17}OSO_3$] Crystallisations

The images show that particle habit of paracetamol can be modified through changing the anion used for crystallisation. From [bmim][$C_8H_{17}OSO_3$] primary nucleation produced a columnar particle habit with primary particle size in the region of 100 µm by 20 µm in size. The seeded samples produced much larger particles with a distinctive cube or cuboid shape with primary particles in the region of 100 µm by 70 µm by 70 µm. Although crystallisation was initiated prior to the addition of the DCM the addition of the anti-solvent did impact the particle habit and size. The particle shape is less well defined and in general the particle size is smaller with typical particles around by 50 µm by 10 µm.

The experiment shows one potential solution to improving the filtration rate of highly viscous ILs. This solution also means that ILs where the solubility of the solute was deemed to be too high to develop a commercially viable process could be considered if combined with a suitable anti-solvent to ensure a satisfactory yield.

The disadvantage of this approach is that the introduction of anti-solvent means that any possible benefit from a green chemistry aspect is lost and this approach also restricts the temperatures at which the material can be isolated. Also recycling of ILs may be required to make any process commercially viable and addition of a second solvent would require additional separation process to re-purify the IL.

7.3.2 Anti-solvent Crystallisation to Improve Filtration

A possible solution to the above disadvantages would be to use a CO_2 as an anti-solvent. Some scoping experiments were carried out to determine the feasibility of this approach by completing some small scale experiments using scCO_2 as anti-solvent. Crystals were formed, Figure 7.2, that show that this approach may be viable and worthy of future investigation.

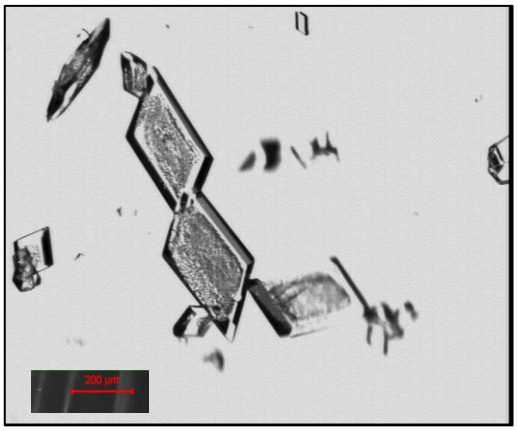


Figure 7.2: SCF crystallised Paracetamol from [hmim][PF_6]

7.4 References

Ghosh, R. (2006). Filtration. Principles of Bioseparations Engineering, World Scientific Publishing Co. Pte. Ltd.

Wasserscheid, P., R. V. Hal, et al. (2002). 1-n-Butyl-3-methylimidazolium ([bmim]) octylsulfate an even greener ionic liquid. Green Chemistry(4): 400-404.

Yaws, C. L. (2012). Yaws' Critical Property Data for Chemical Engineers and Chemists, Knovel.

CHAPTER 8: CONCLUSIONS AND FURTHER WORK

8.1 Conclusions

Ionic liquids have unique properties that, when compared to organic solvent, have been investigated by various industries a means to improve chemical processes. To date, little work has been conducted on their potential use in the pharmaceutical industry. The work that has been carried out had mainly focussed on either their use as drug delivery vehicles or as an Active Pharmaceutical Ingredients (APIs). Assessing their applicability as media to carry out crystallisations has not been extensively reported particularly for small molecules and it was this gap that the thesis looked to address.

To investigate this a set of criteria to select suitable ILs for this work is provided. Using these ILs and model API compounds a study was conducted to try and help address this current gap in the literature.

Methodology to determine the equilibrium solubility of API in ILs was established and successfully used to measure the solubility of paracetamol and ibuprofen in the ILs [bmim][PF_6] and [hmim][PF_6]. These ILs were found to be good solvents for both paracetamol and ibuprofen and the data have now been published for the first time (Smith et al, 2011).

In the literature it is debated as to whether, like conventional solvents, polarity could be used as a measure to describe the solvation capability of a solvent. The data reported here show that, when compared to water, the ILs follow the expected trend when considering their relative polarity against water.

Further to this it was shown, using the Dual parameter and Buchowski equations, that good correlations to the experimental data were obtained for the systems studied. Such data fits may aid the selection of an IL by allowing fewer data points to be generated when screening an IL for a given process.

Building on these data the Meta-Stable Zone Width (MSZW) for both paracetamol and ibuprofen in [bmim][PF_6] and [hmim][PF_6] were determined. A feature of the systems studied was that large supersaturations could be generated increasing the potential risk of meta-stable forms crystallising if left uncontrolled. A series of cooling crystallisations designed to determine the impact of supersaturation both with and without seeding were carried out to determine the impact on the physical form.

Despite the range of supersaturations investigated no meta-stable forms of either paracetamol or ibuprofen were obtained even at fast cooling rates. However it was found that the particle habit of paracetamol could be altered by changing either the concentration or the length of the alkyl chain. Particularly for samples that were allowed to form through spontaneous nucleation. The wide MSZW obtained meant that seeding could be used be used as a possible strategy to facilitate crystal growth. Less variation in the particle habit was observed for the seeded samples, but it shows seeding can be successfully in employed to grow crystals in ILs to produce much larger particles.

Using the criteria established at the start of the thesis the crystallisation work was extended to a homologous series of ILs with the aim of determining the effect that the anion had on the crystallisation of paracetamol. A screening method to assess potential ILs as crystallisation solvents is described and could be used as a basis for future screening work.

Interestingly it was found that further particle habits of paracetamol were produced including cubic shaped particles that have not been reported before whilst remaining as the most stable form. This is potentially an exciting finding as manipulation of the physical habit could provide advantages for the manufacturability of API to help avoid common issues such as poor powder flow.

For the crystallisation studies involving ibuprofen the material formed was typical of that reported for conventional organic solvents. Highlighting that ILs may not be a platform for manipulation of all APIs, but will be dependent on whether the IL can sufficiently interact with the API to influence the relative growth rates of the crystal faces.

The screening method established during the paracetamol work was then successfully used to assess the crystallisation of the highly polymorphic flufenamic acid. Through this screen two different polymorphs of flufenamic acid were produced by changing the anion of the IL.

During these investigations the practical problems encountered with these solvent/solute media were reported and where possible practical solutions investigated. The majority of issues encountered relate to either the ability to conduct analysis on the IL-API system or the ability to separate the IL from the API after crystallisation.

At the outset of the thesis the main aim was to investigate whether ionic liquids could be viable media to crystallise API and given the highly functional nature of these materials if they offer a new route to manipulation of the physical form. It has been shown here using well characterised ionic liquids and APIs that crystallisations can successfully be carried out in these media and the physical form of the API can be manipulated, such as crystal habit for paracetamol and polymorphic form of flufenamic acid.

However, further understanding is required to determine the interaction between IL and solute if ILs are ever to fulfil their potential as designer solvents. From this work there are a number of areas that would be suitable for further investigation these are outlined in the section below.

8.2 Suggested Further Work

It would be beneficial to develop the selection criteria used here further to include more physical property factors, such as viscosity, to ensure that a more targeted approach could be taken in the selection of a suitable IL and to ensure that potential manufacturability issues such as filtration can be avoided. Also, methods for providing an efficient and complete removal of the IL from isolated solid need to be explored.

One of the major findings from this work was the manipulation of the particle habit of paracetamol which, in some cases, produced unique habits. By indexing crystals formed from these systems it will be possible to determine what faces are impacted during crystal growth and establish which anions are responsible for altering particle habit and the crystal faces they interact with.

This work only looked at a small sub-set of possible ILs by investigating modest changes to the alkyl side chain and the impact of changing the anion whilst retaining the same $[bmim]^+$ cation. It would therefore be interesting to carry out a similar study to determine the impact of the cation has on crystallisation by using similar methodology employed in this work.

It was shown here that at least two polymorphs of flufenamic acid can be isolated from ILs. It may be possible to isolate further polymorphs through operating at temperatures outside the normal range of organic solvents. If successful, such methodology could be expanded to

determine if this property should be considered by the pharmaceutical industry when screening for all possible polymorphs of an API.

One current disadvantage to the use of ILs in the pharmaceutical industry is the high cost when compared to commonly used organic solvent. Given the lack of volatility in ILs it may be feasible to re-cycle ILs and thus a cost model should be established to determine the economic viability of ILs in commercial use.

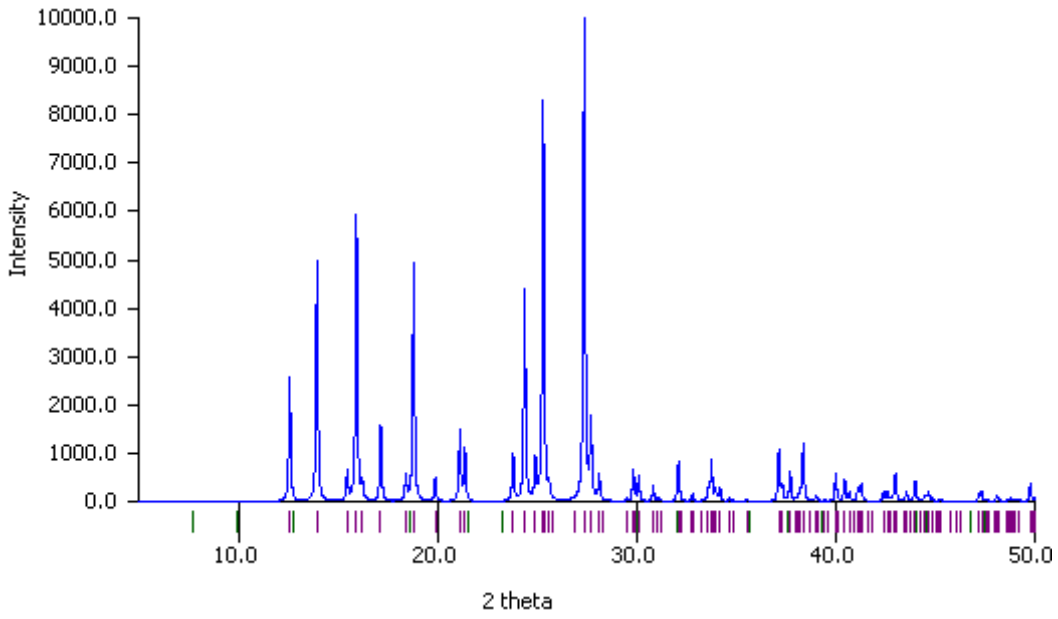
Appendix 1: UV and Corresponding Solubility Data for Paracetamol in [bmim][PF_6], [hmim][PF_6] and Water

Solubility of Paracetamol [bmim][PF_6]								
298.15 K								
	Sample 1		Sample 2		Sample 3		$\sum$abs$(\overline{x}/n)$	$\sum(\overline{x}/n)$
	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}
	0.5836	7.010	0.5669	6.803	0.5870	7.051		
	0.5840	7.014	0.5650	6.778	0.5870	7.051		
	0.5832	7.004	0.5653	6.783	0.5860	7.040		
$\bar{x}$	0.5836	7.009	0.5657	6.788	0.5867	7.047	0.579 ± 0.011	6.95 ± 0.14
308.15 K								
	0.8413	10.205	0.8777	10.656	0.7628	9.232		
	0.8439	10.237	0.8798	10.682	0.7625	9.228		
	0.8407	10.198	0.8829	10.720	0.7677	9.292		
$\bar{x}$	0.8420	10.213	0.8801	10.686	0.7644	9.251	0.829 ± 0.059	10.05 ± 0.73
318.15 K								
	0.8591	10.425	1.0219	12.444	0.8406	10.196		
	0.8582	10.414	1.0241	12.471	0.8360	10.139		
	0.8549	10.374	1.0243	12.474	0.8400	10.189		
$\bar{x}$	0.8574	10.404	1.0234	12.463	0.8389	10.175	0.907 ± 0.102	11.01 ± 1.26
328.15 K								
	1.2921	15.794	1.2711	15.534	1.2806	15.652		
	1.2848	15.704	1.2718	15.543	1.2826	15.677		
	1.2922	15.796	1.2739	15.569	1.2879	15.742		
$\bar{x}$	1.2897	15.765	1.2723	15.549	1.2837	15.690	1.282 ± 0.009	15.67 ± 0.11
338.15 K								
	1.8928	23.243	1.8741	23.011	1.8860	23.159		
	1.8694	22.953	1.8620	22.861	1.8980	23.307		
	1.8912	23.223	1.8448	22.648	1.9039	23.380		
$\bar{x}$	1.8845	23.139	1.8603	22.840	1.8960	23.282	1.880 ± 0.018	23.09 ± 0.23

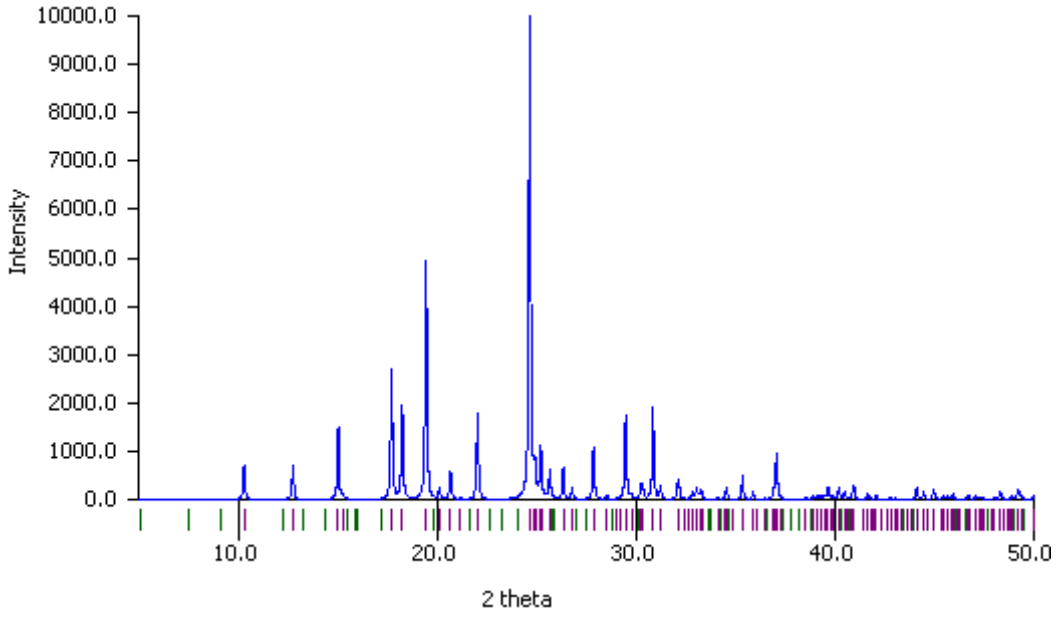
Solubility of Paracetamol [hmim][PF_6]								
298.15 K								
	Sample 1		Sample 2		Sample 3		$\sum abs(\overline{x}/n)$	$\sum(\overline{x}/n)$
	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}
	1.0586	14.137	0.9240	12.287	0.9921	13.222		
	1.0529	14.059	0.9010	11.971	0.9769	13.014		
	1.1243	15.040	0.9032	12.001	0.9866	13.147		
$\bar{x}$	1.0786	14.412	0.9094	12.086	0.9852	13.128	0.991 ± 0.085	13.21 ± 1.17
308.15 K								
	1.0969	14.663	1.1535	15.441	1.1324	15.151		
	1.1105	14.850	1.1359	15.199	1.1431	15.298		
	1.0985	14.685	1.1528	15.432	1.2153	16.291		
$\bar{x}$	1.1020	14.733	1.1474	15.357	1.1636	15.580	1.138 ± 0.032	15.22 ± 0.44
318.15 K								
	1.7519	23.665	1.5291	20.603	1.5215	20.499		
	1.5533	20.936	1.4566	19.607	1.4878	20.036		
	1.6814	22.696	1.5215	20.499	1.4233	19.149		
$\bar{x}$	1.6622	22.433	1.5024	20.236	1.4775	19.895	1.547 ± 0.100	20.86 ± 1.38
328.15 K								
	1.9636	26.575	2.0446	27.688	2.0140	27.268		
	1.9802	26.803	1.7765	24.004	1.9426	26.286		
	2.0153	27.286	1.8713	25.306	1.7699	23.913		
$\bar{x}$	1.9864	26.888	1.8975	25.666	1.9088	25.822	1.931 ± 0.048	26.13 ± 0.67
338.15 K								
	2.0919	28.338	2.6430	35.913	2.2619	30.675		
	2.7377	37.214	2.3552	31.957	1.6741	22.596		
	2.3482	31.861	2.0428	27.663	2.0230	27.391		
$\bar{x}$	2.3926	32.471	2.3470	31.844	1.9863	26.887	2.242 ± 0.223	30.40 ± 3.06

Solubility of Paracetamol Water								
298.15 K								
	Sample 1		Sample 2		Sample 3		$\sum \text{abs}(\overline{x}/n)$	$\sum(\overline{x}/n)$
	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}
	1.1484	19.467	1.1100	18.809	1.1316	19.179		
	1.1479	19.458	1.1129	18.858	1.1328	19.199		
	1.1458	19.422	1.1116	18.836	1.1330	19.203		
$\bar{x}$	1.1474	19.449	1.1115	18.834	1.1325	19.194	1.130 ± 0.018	19.16 ± 0.31
308.15 K								
	1.4496	24.628	1.4993	25.479	1.5496	26.341		
	1.4445	24.540	1.4998	25.488	1.5504	26.355		
	1.4433	24.520	1.4932	25.375	1.5468	26.293		
$\bar{x}$	1.4458	24.562	1.4974	25.447	1.5489	26.330	1.497 ± 0.052	25.42 ± 0.88
318.15 K								
	2.0890	35.583	1.9437	33.094	2.0178	34.363		
	2.0829	35.479	1.9557	33.299	2.0306	34.583		
	2.1095	35.935	1.9516	33.229	2.0262	34.507		
$\bar{x}$	2.0938	35.666	1.9503	33.207	2.0249	34.485	2.023 ± 0.072	34.45 ± 1.23
328.15 K								
	1.4636	49.247	1.5803	53.207	1.5634	52.634		
	1.4610	49.159	1.5692	52.831	1.5615	52.569		
	1.4562	48.996	1.5766	53.082	1.5635	52.637		
$\bar{x}$	1.4603	49.134	1.5754	53.040	1.5628	52.614	1.533 ± 0.063	51.60 ± 2.14
338.15 K								
	1.9296	65.060	2.0389	68.769	1.9755	66.618		
	1.9149	64.561	2.0322	68.542	1.9567	65.980		
	1.9299	65.070	2.0260	68.331	1.9584	66.038		
$\bar{x}$	1.9248	64.897	2.0324	68.547	1.9635	66.212	1.974 ± 0.055	66.55 ± 1.85

Appendix 2: X-Ray Diffraction Patterns for Paracetamol

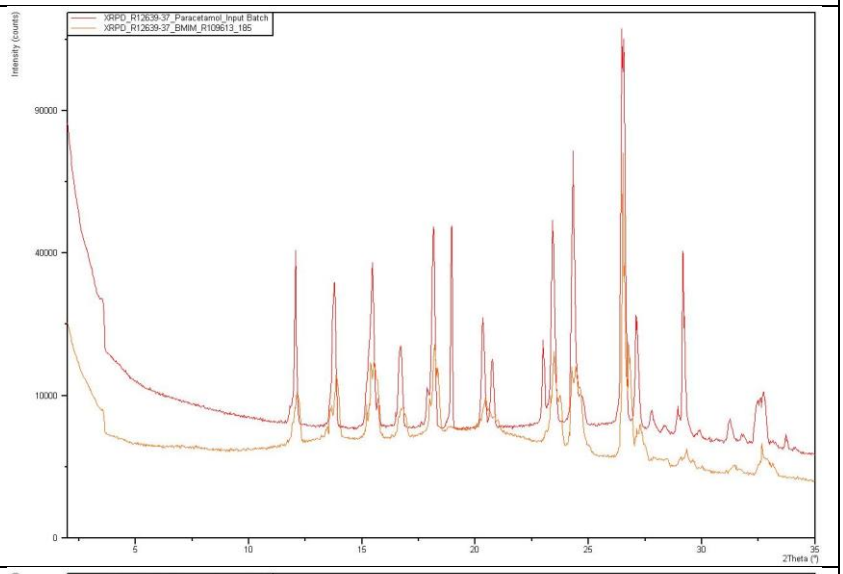
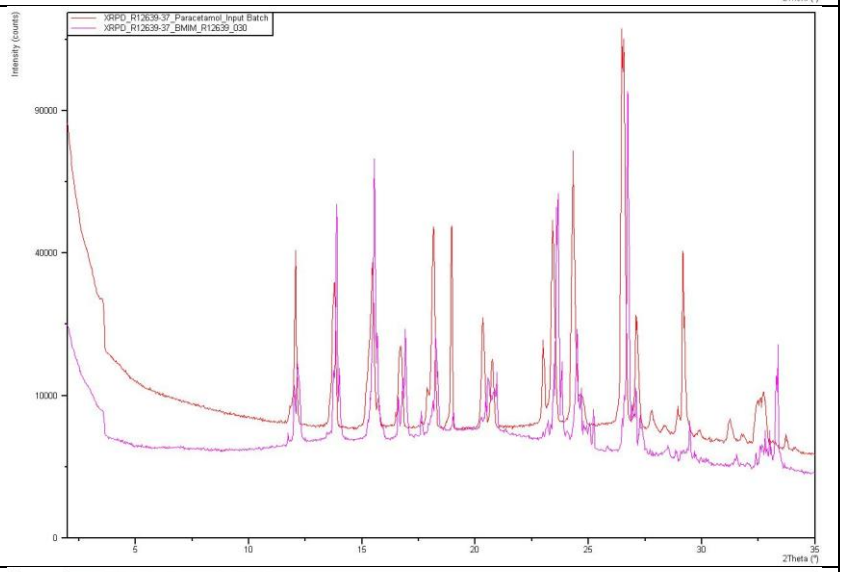
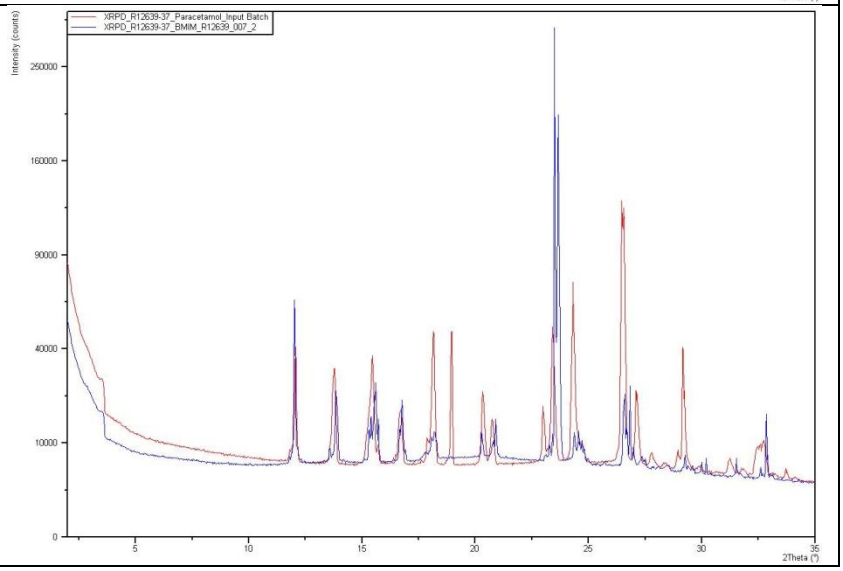


Paracetamol Monoclinic Form I X-Ray Pattern

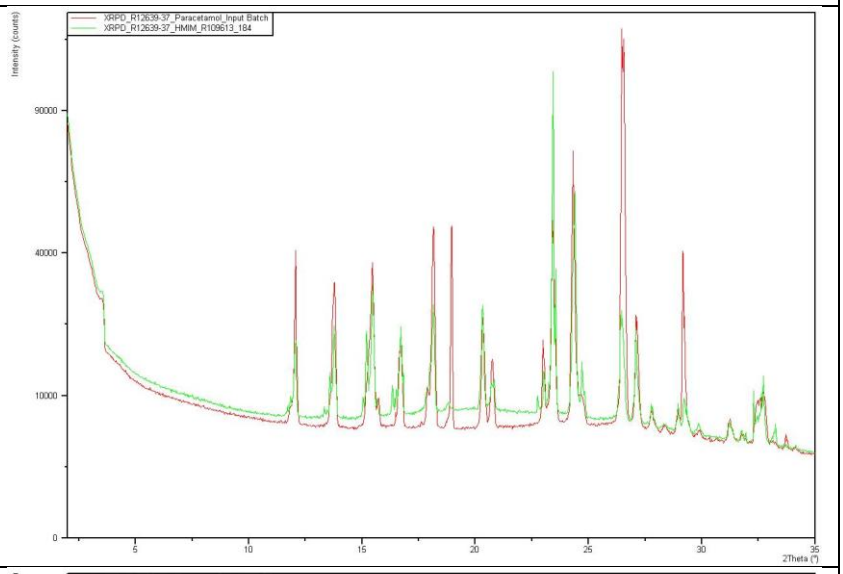
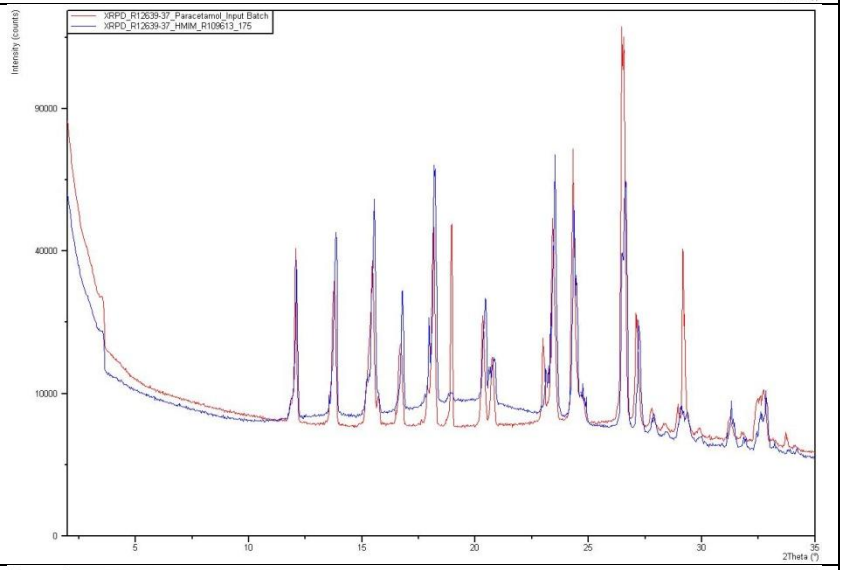
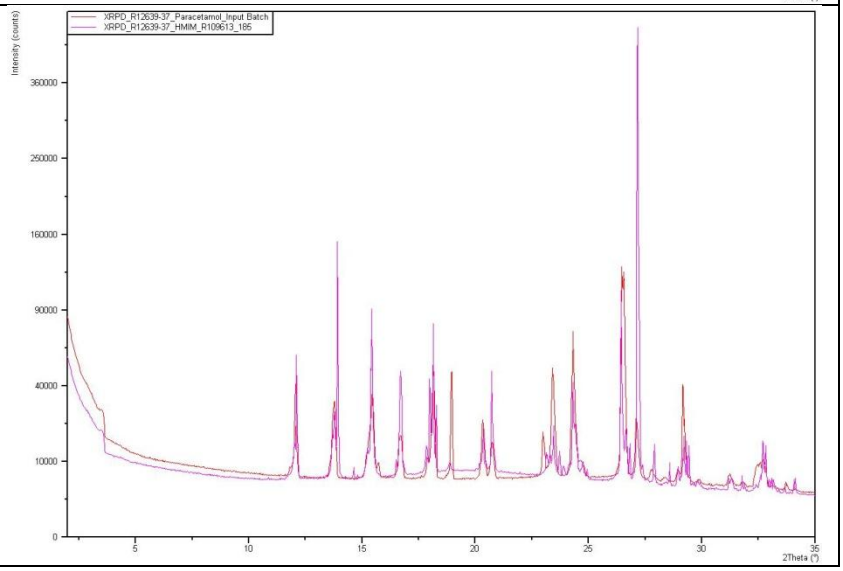


Paracetamol Orthorhombic Form II X-Ray Pattern

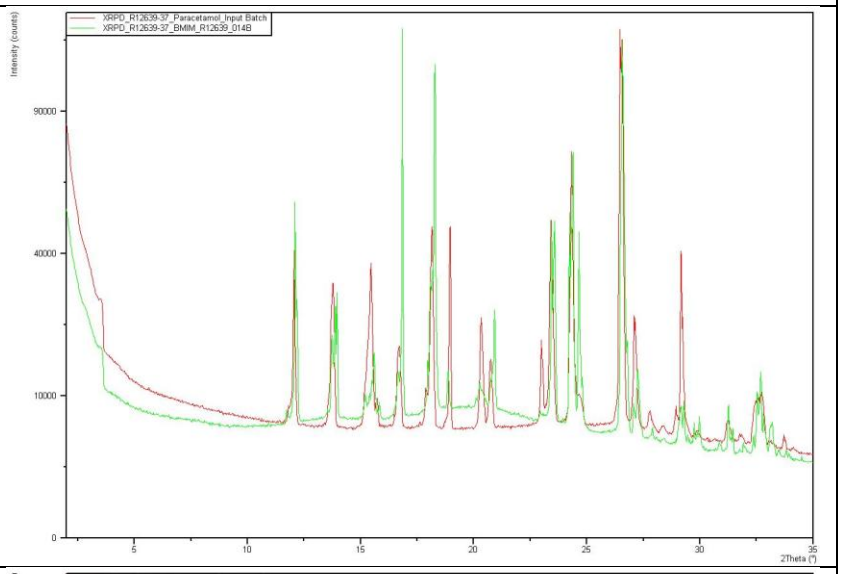
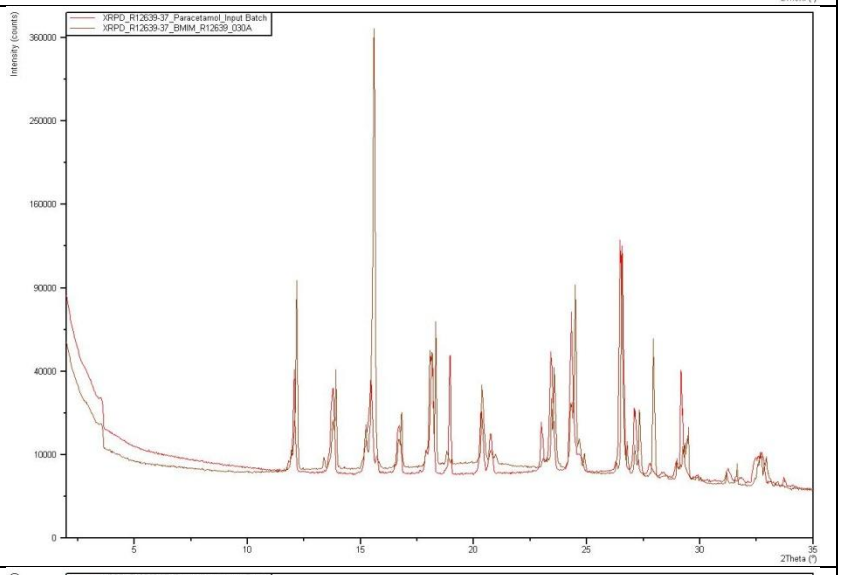
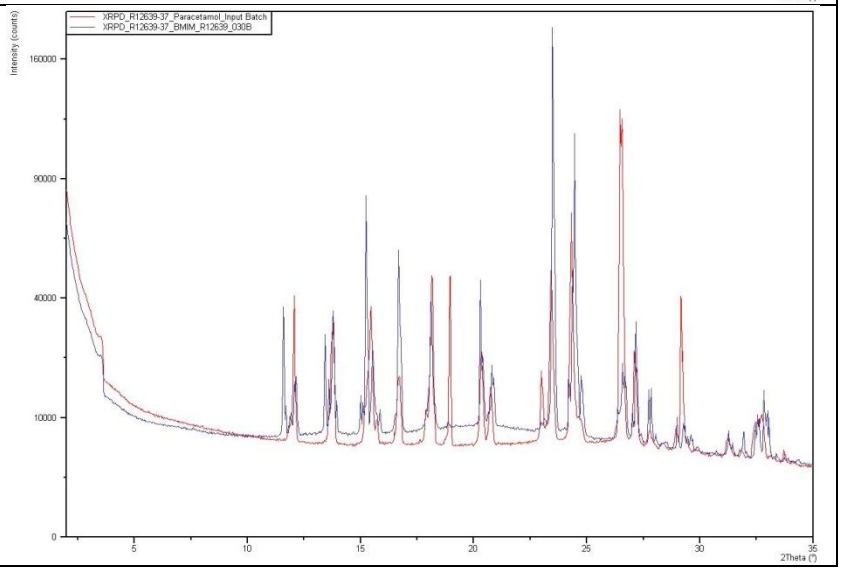
Paracetamol [bmim][PF_6] (non-seeded)

mg.mL^{-1}	XRD Trace
44.82	
54.85	
70.09	

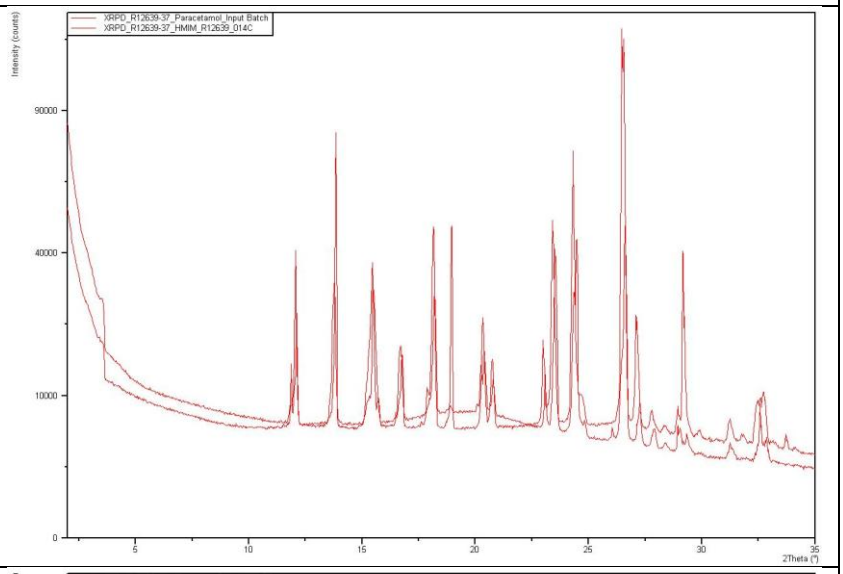
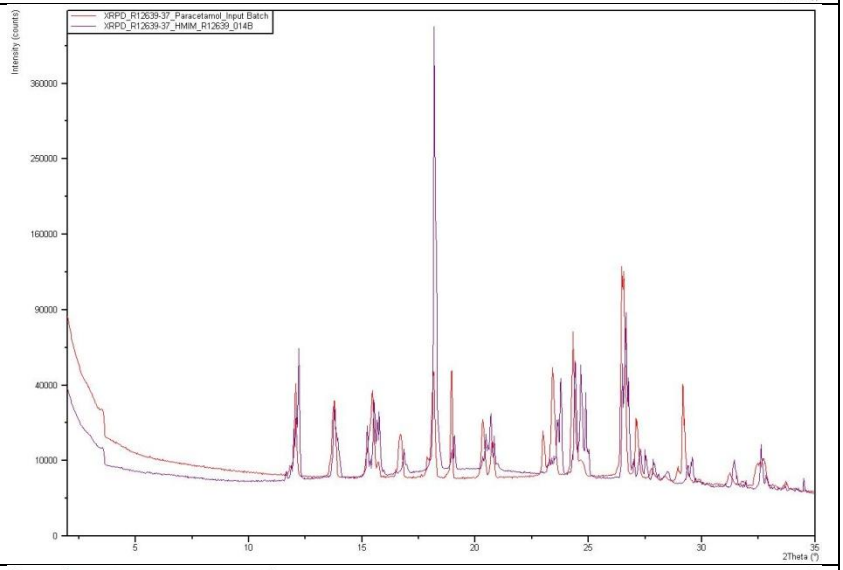
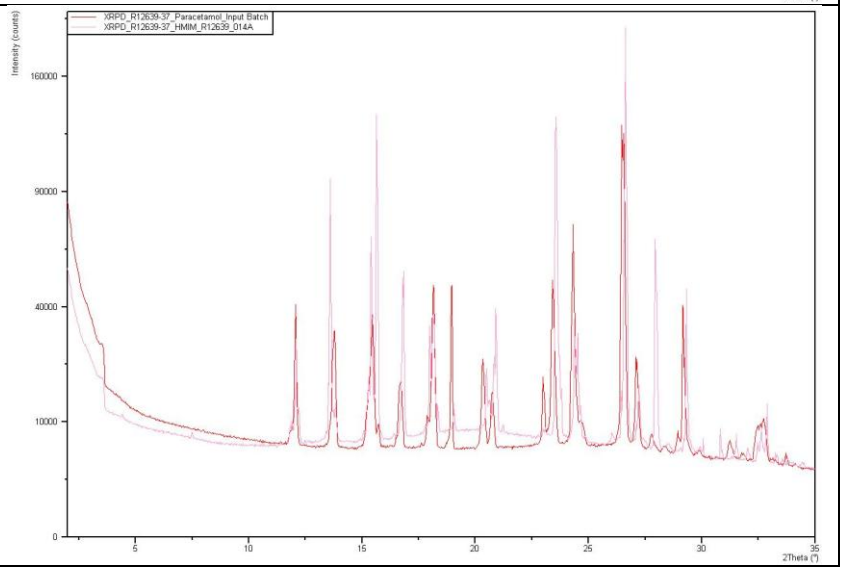
Paracetamol [hmim][PF_6] (non-seeded)

mg.mL^{-1}	XRD Trace
15.73	
30.21	
69.06	

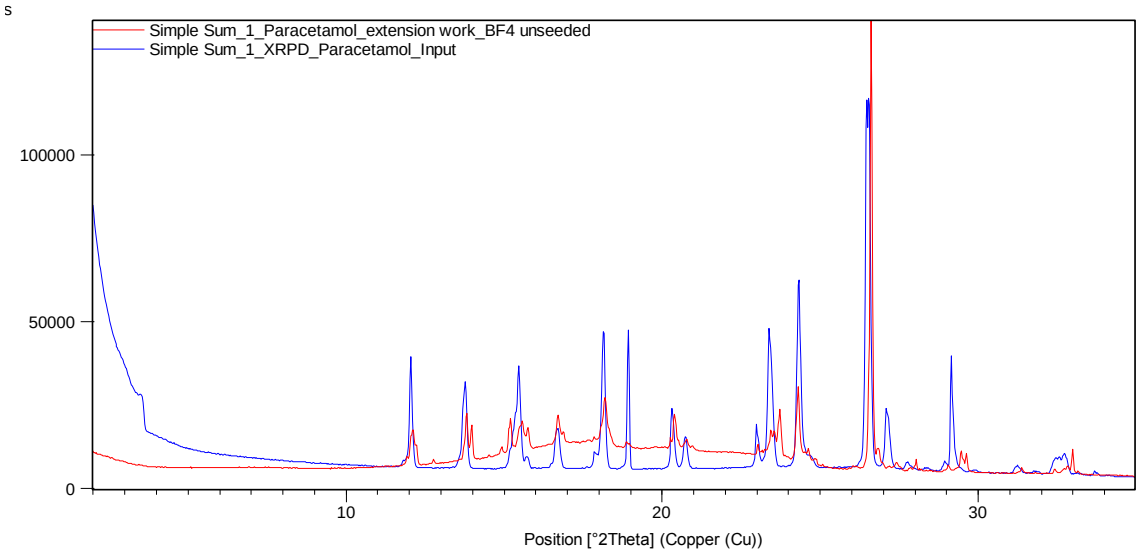
Paracetamol [bmim][PF_6] (seeded)

mg.mL^{-1}	XRD Trace
38.1	
47.4	
57.0	

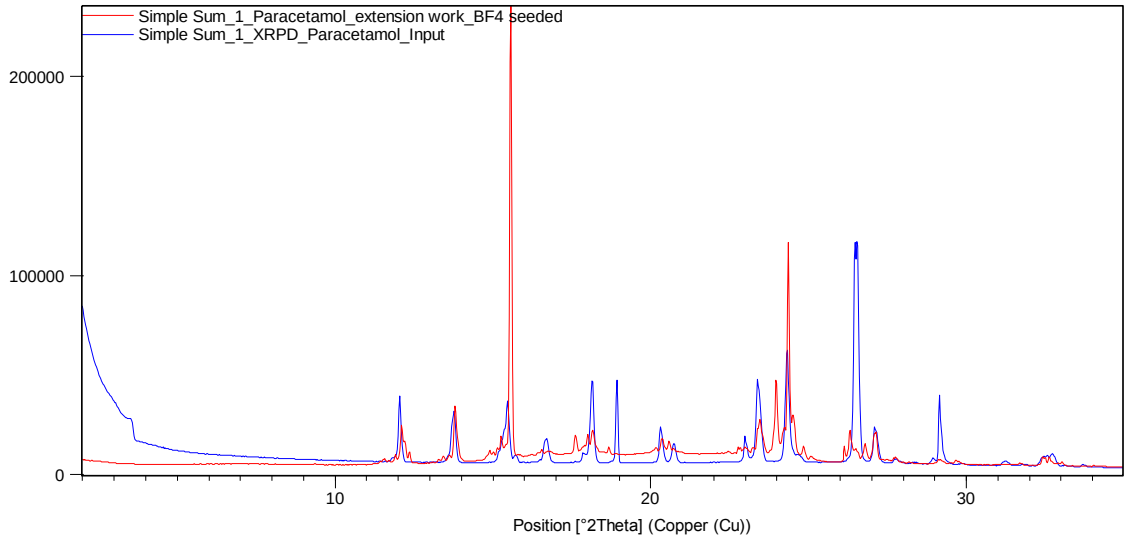
Paracetamol [hmim][PF_6] (seeded)

mg.mL^{-1}	XRD Trace
35.0	
49.0	
63.0	

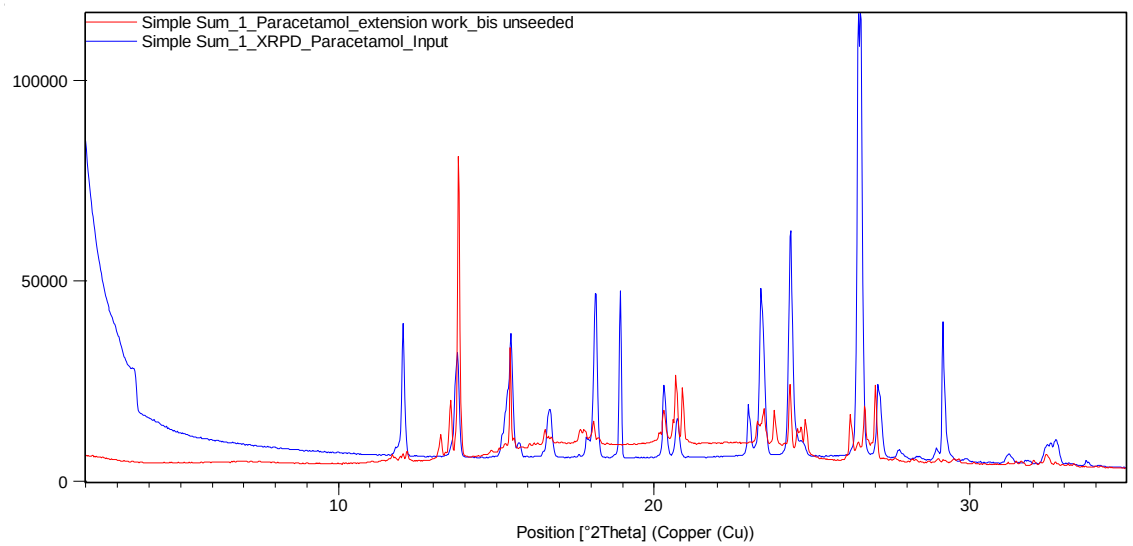
Paracetamol [bmim][BF_4] Non-Seeded



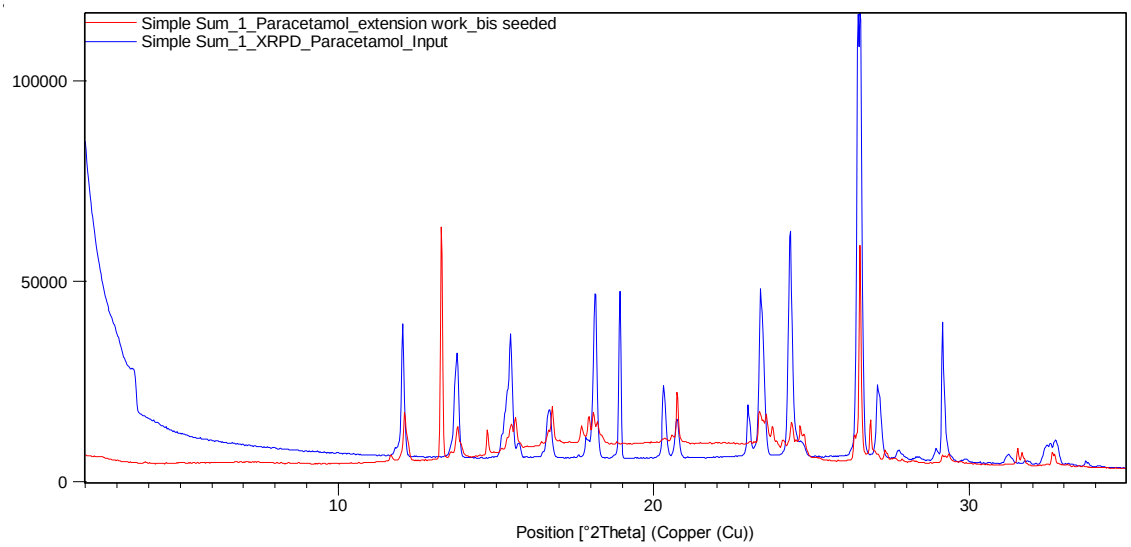
Paracetamol [bmim][BF_4] Seeded



Paracetamol [bmim][NTf_2] (non-seeded)



Paracetamol [bmim][NTf_2] (seeded)



Appendix 3: Paracetamol Sizing Data

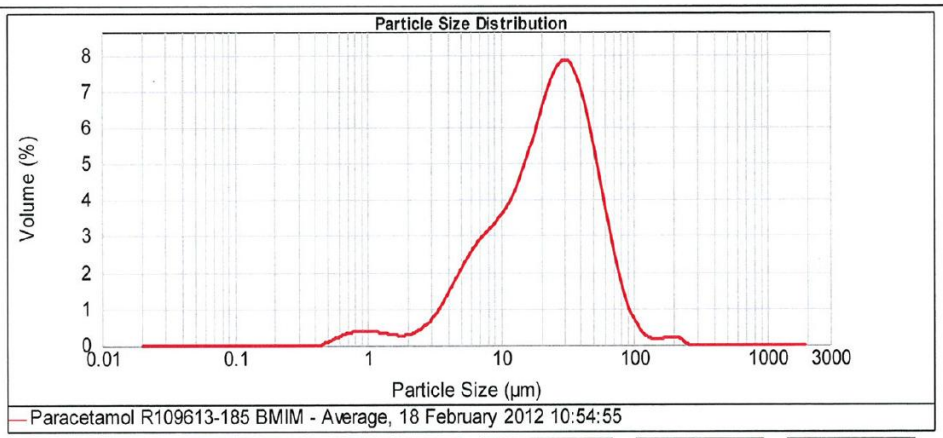
[bmim][PF_6] 45 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R109613-185 BMIM -	**SOP Name:**	**Measured:** 18 February 2012 10:54:55	
Sample Source & type: R109613-185	**Measured by:** kbs23436	**Analysed:** 18 February 2012 10:54:56	
Sample bulk lot ref: BMIM	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.07 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 1.244 %	**Result Emulation:** Off
Concentration: 0089 %Vol	**Span :** 2.179	**Uniformity:** 0.711	**Result units:** Volume
Specific Surface Area: 0.565 m²/g	**Surface Weighted Mean D[3,2]:** 10.625 um	**Vol. Weighted Mean D[4,3]:** 28.484 um	

d(0.1): 5.595 um **d(0.5):** 23.329 um **d(0.9):** 56.428 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.32	11.482	3.70	120.226	0.17	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.28	13.183	4.19	138.038	0.13	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.25	15.136	4.80	158.489	0.16	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.23	17.378	5.50	181.970	0.18	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.25	19.953	6.18	208.930	0.15	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.32	22.909	6.73	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.47	26.303	7.04	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.69	30.200	7.04	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.98	34.674	6.68	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	1.33	39.811	6.01	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	1.70	45.709	5.10	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.10	5.012	2.06	52.481	4.06	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.19	5.754	2.38	60.256	3.02	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.27	6.607	2.65	69.183	2.07	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.32	7.586	2.87	79.433	1.19	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.35	8.710	3.09	90.000	0.80	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.34	10.000	3.35	104.713	0.34	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 Trimethylpentane +0.5%Lecithin 2000rpm*

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R109613_18Feb2012
Record Number: 24
25 Feb 2012 12:13:12

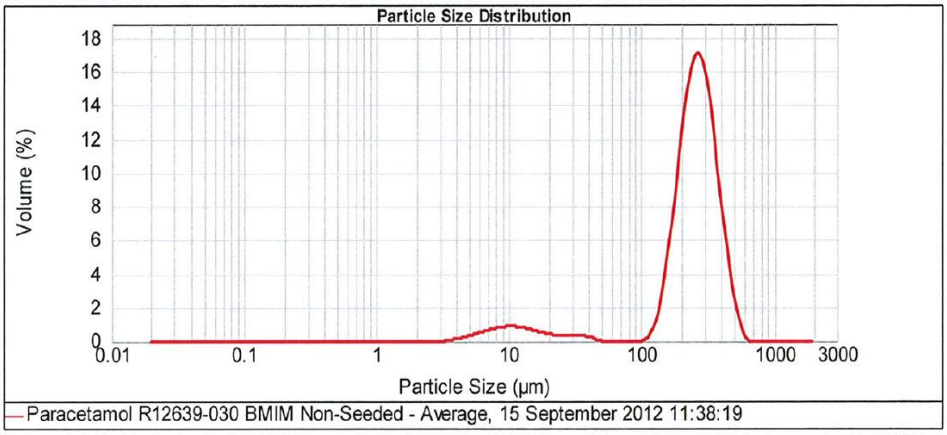
[bmim][PF_6] 55 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-030 BMIM	**SOP Name:**	**Measured:** 15 September 2012 11:38:19	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 15 September 2012 11:38:20	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.01 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.726 %	**Result Emulation:** Off
Concentration: 726 %Vol	**Span :** 0.968	**Uniformity:** 0.322	**Result units:** Volume
Specific Surface Area: 0.0684 m²/g	**Surface Weighted Mean D[3,2]:** 87.673 um	**Vol. Weighted Mean D[4,3]:** 254.821 um	

d(0.1): 143.500 um **d(0.5): 253.901 um** **d(0.9): 389.182 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.73	120.226	1.15	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.64	138.038	3.48	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.53	158.489	6.41	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.42	181.970	10.65	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.33	208.930	13.84	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.29	239.883	15.45	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.28	275.423	14.64	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.27	316.228	11.96	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.05	34.674	0.26	363.078	7.69	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.12	39.811	0.17	416.869	4.49	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.23	45.709	0.00	478.630	1.75	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.34	52.481	0.00	549.541	0.30	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.47	60.256	0.00	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.60	69.183	0.00	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.71	79.433	0.00	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.77	90.000	-0.00	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.77	104.713	0.23	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.77	120.226	0.23	1258.925	0.00		

Operator notes: *2,2,4 trimethylpentane + 0.05%w/w lecithin*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_030
Record Number: 8
02 Oct 2012 17:59:11

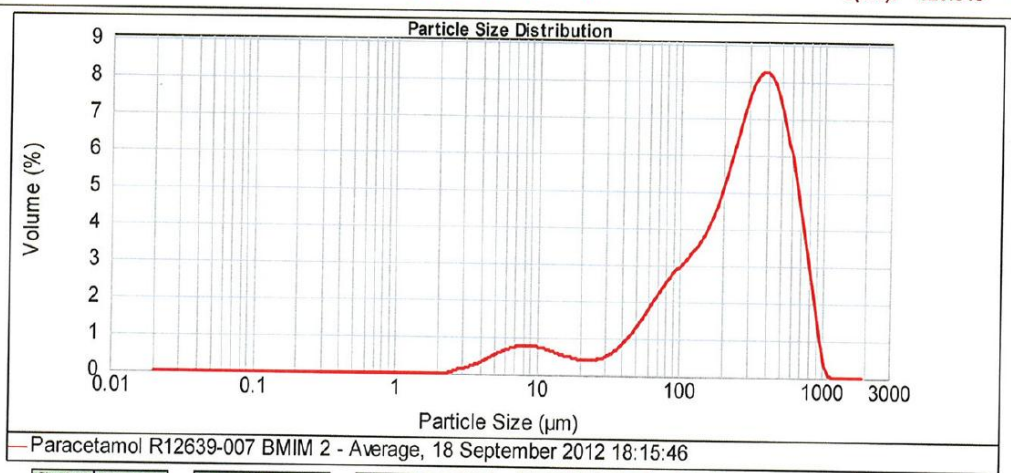
[bmim][PF_6] 75 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-007 BMIM 2 -	**SOP Name:**	**Measured:** 18 September 2012 18:15:46	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 18 September 2012 18:15:47	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.41 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.941 %	**Result Emulation:** Off
Concentration: 0.0718 %Vol	**Span :** 2.071	**Uniformity:** 0.644	**Result units:** Volume
Specific Surface Area: 0.0859 m²/g	**Surface Weighted Mean D[3,2]:** 69.883 um	**Vol. Weighted Mean D[4,3]:** 308.297 um	

d(0.1): 47.324 um **d(0.5):** 276.728 um **d(0.9):** 620.543 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.58	120.226	3.10	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.50	138.038	3.42	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.43	158.489	3.85	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.38	181.970	4.43	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.34	208.930	5.15	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.35	239.883	5.93	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.39	275.423	6.67	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.05	30.200	0.49	316.228	7.22	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.12	34.674	0.64	363.078	7.45	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.20	39.811	0.85	416.869	7.25	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.29	45.709	1.11	478.630	6.62	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.40	52.481	1.41	549.541	3.71	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.50	60.256	1.74	600.000	6.26	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.59	69.183	2.06	724.436	3.02	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.65	79.433	2.12	831.764	1.65	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.68	90.000	2.65	954.993	0.36	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.68	104.713	2.85	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.64	120.226	2.85	1258.925	0.00		

Operator notes: *2,2,4 Trimethylpetane + 0.05% Lecithin 2000rpm sonicated 30sec*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_007
Record Number: 8
18 Sep 2012 18:25:14

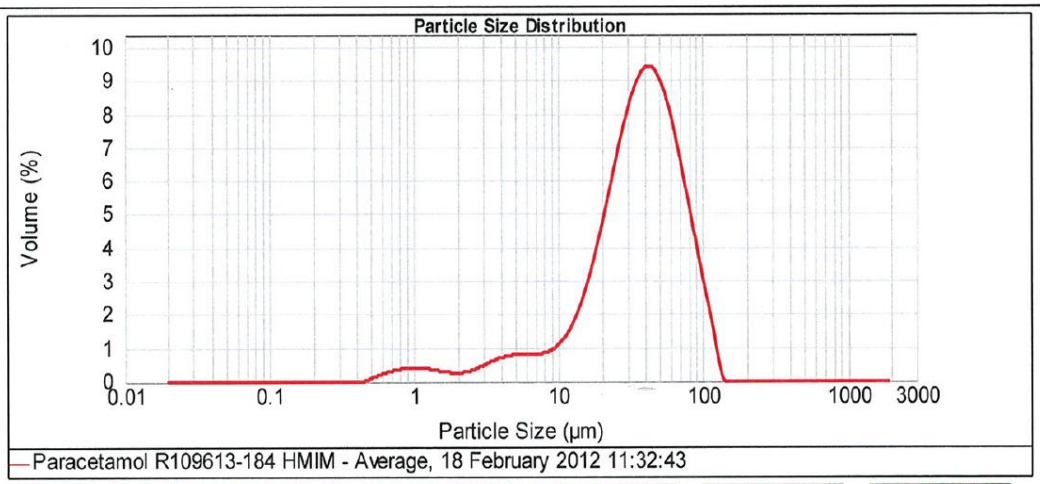
[hmim][PF_6] 16 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R109613-184 HMIM -	**SOP Name:**	**Measured:** 18 February 2012 11:32:43	
Sample Source & type: R109613-184	**Measured by:** kbs23436	**Analysed:** 18 February 2012 11:32:44	
Sample bulk lot ref: HMIM	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 1.73 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 1.585 %	**Result Emulation:** Off
Concentration: 0033 %Vol	**Span :** 1.820	**Uniformity:** 0.548	**Result units:** Volume
Specific Surface Area: 0.421 m²/g	**Surface Weighted Mean D[3,2]:** 14.247 um	**Vol. Weighted Mean D[4,3]:** 41.113 um	

d(0.1): 10.417 um **d(0.5):** 36.881 um **d(0.9):** 77.534 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.35	11.482	1.50	120.226	0.40	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.31	13.183	2.06	138.038	0.00	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.27	15.136	2.80	158.489	0.00	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.23	17.378	3.74	181.970	0.00	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.22	19.953	4.79	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.26	22.909	5.89	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.34	26.303	6.94	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.44	30.200	7.79	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.55	34.674	8.34	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.64	39.811	8.50	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.70	45.709	8.22	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.09	5.012	0.72	52.481	7.55	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.17	5.754	0.72	60.256	6.56	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.26	6.607	0.73	69.183	5.36	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.31	7.586	0.77	79.433	3.79	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.35	8.710	0.88	90.000	3.24	954.993	0.00	10000.000	
0.091	0.00	0.955	0.36	10.000	1.12	104.713	1.72	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 Trimethylpentane +0.05%Lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R109613_18Feb2012
Record Number: 36
25 Feb 2012 11:56:28

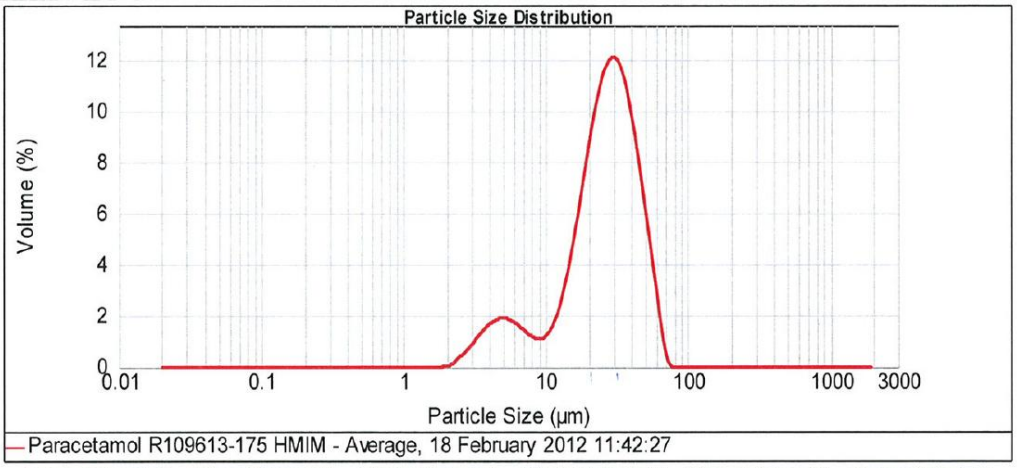
[hmim][PF_6] 30 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R109613-175 HMIM -	**SOP Name:**	**Measured:** 18 February 2012 11:42:27	
Sample Source & type: R109613-175	**Measured by:** kbs23436	**Analysed:** 18 February 2012 11:42:28	
Sample bulk lot ref: HMIM	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 2.66 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 1.589 %	**Result Emulation:** Off
Concentration: 060 %Vol	**Span :** 1.493	**Uniformity:** 0.427	**Result units:** Volume
Specific Surface Area: 0.361 m^2/g	**Surface Weighted Mean D[3,2]:** 16.603 um	**Vol. Weighted Mean D[4,3]:** 27.261 um	

d(0.1): 7.134 um **d(0.5):** 26.294 um **d(0.9):** 46.392 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	2.06	120.226	0.00	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	3.33	138.038	0.00	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	5.00	158.489	0.00	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	6.90	181.970	0.00	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.02	19.953	8.72	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.22	22.909	10.15	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.52	26.303	10.88	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.86	30.200	10.73	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	1.23	34.674	9.70	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	1.52	39.811	7.94	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	1.69	45.709	5.77	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	1.68	52.481	3.59	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	1.52	60.256	1.31	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	1.27	69.183	0.06	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	1.04	79.433	0.00	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	1.00	90.000	0.00	954.993	0.00	10000.000	
0.091	0.00	0.955	0.00	10.000	1.30	104.713	0.00	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482		120.226	0.00	1258.925	0.00		

Operator notes: *2,2,4 Trimethylpentane +0.05%Lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R109613_18Feb2012
Record Number: 40
25 Feb 2012 11:56:28

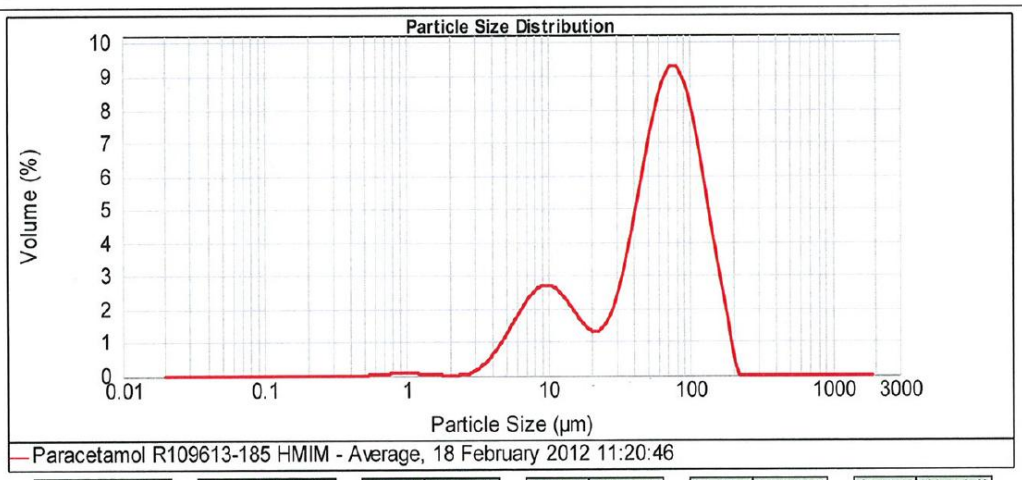
[hmim][PF_6] 69 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R109613-185 HMIM -	**SOP Name:**	**Measured:** 18 February 2012 11:20:46	
Sample Source & type: R109613-185	**Measured by:** kbs23436	**Analysed:** 18 February 2012 11:20:47	
Sample bulk lot ref: HMIM	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.31 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.462 %	**Result Emulation:** Off
Concentration: ^.0177 %Vol	**Span :** 1.927	**Uniformity:** 0.587	**Result units:** Volume
Specific Surface Area: 0.249 m²/g	**Surface Weighted Mean D[3,2]:** 24.094 um	**Vol. Weighted Mean D[4,3]:** 64.035 um	

d(0.1): 8.885 um **d(0.5):** 59.979 um **d(0.9):** 124.463 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.05	11.482	2.20	120.226	4.91	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.04	13.183	1.89	138.038	3.48	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.02	15.136	1.55	158.489	2.19	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	1.28	181.970	0.79	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	1.18	208.930	0.00	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	1.33	239.883	0.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.02	26.303	1.79	275.423	0.00	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.13	30.200	2.58	316.228	0.00	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.32	34.674	3.65	363.078	0.00	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.58	39.811	4.89	416.869	0.00	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.91	45.709	6.16	478.630	0.00	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	1.30	52.481	7.27	549.541	0.00	5754.399	0.00
0.052	0.00	0.550	0.02	5.754	1.70	60.256	8.07	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.04	6.607	2.05	69.183	8.39	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.05	7.586	2.32	79.433	7.42	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.05	8.710	2.44	90.000	8.21	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.05	10.000	2.39	104.713	6.29	1096.478	0.00		
0.105	0.00	1.096	0.05	11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 Trimethylpentane +0.05%Lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R109613_18Feb2012
Record Number: 32
25 Feb 2012 12:13:12

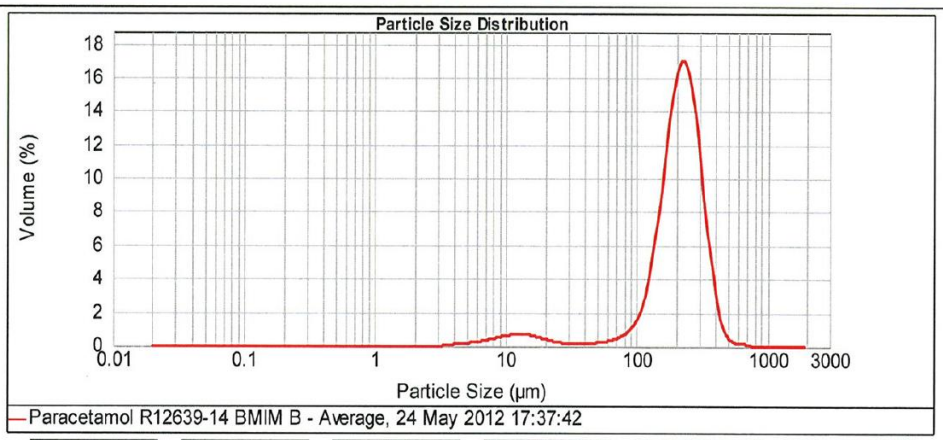
[bmim][PF_6] 38 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-14 BMIM B -	**SOP Name:**	**Measured:** 24 May 2012 17:37:42	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 24 May 2012 17:37:43	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** Single narrow mode (spherical)	**Sensitivity:** Enhanced
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 3.42 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.751 %	**Result Emulation:** Off
Concentration: 0.0464 %Vol	**Span :** 0.999	**Uniformity:** 0.325	**Result units:** Volume
Specific Surface Area: 0.06 m²/g	**Surface Weighted Mean D[3,2]:** 99.937 um	**Vol. Weighted Mean D[4,3]:** 213.753 um	

d(0.1): 111.894 um **d(0.5):** 211.611 um **d(0.9):** 323.285 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.00	11.482	0.64	120.226	4.55	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.00	13.183	0.62	138.038	7.28	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.00	15.136	0.54	158.489	11.21	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.00	17.378	0.42	181.970	14.16	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.00	19.953	0.30	208.930	15.37	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.00	22.909	0.21	239.883	14.00	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.00	26.303	0.15	275.423	10.80	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.00	30.200	0.12	316.228	6.31	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.03	34.674	0.12	363.078	3.32	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.09	39.811	0.14	416.869	1.07	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.12	45.709	0.17	478.630	0.32	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.18	52.481	0.22	549.541	0.08	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.24	60.256	0.32	600.000	0.12	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.32	69.183	0.49	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.00	7.586	0.41	79.433	0.67	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.00	8.710	0.51	90.000	1.40	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.00	10.000	0.60	104.713	2.36	1096.478	0.00		
0.105	0.00	1.096	0.00	11.482	0.80	120.226		1258.925	0.00		

Operator notes: *i-Octane + 0.05%lecthin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R109613_28Jun2012
Record Number: 148
10 Sep 2012 18:20:08

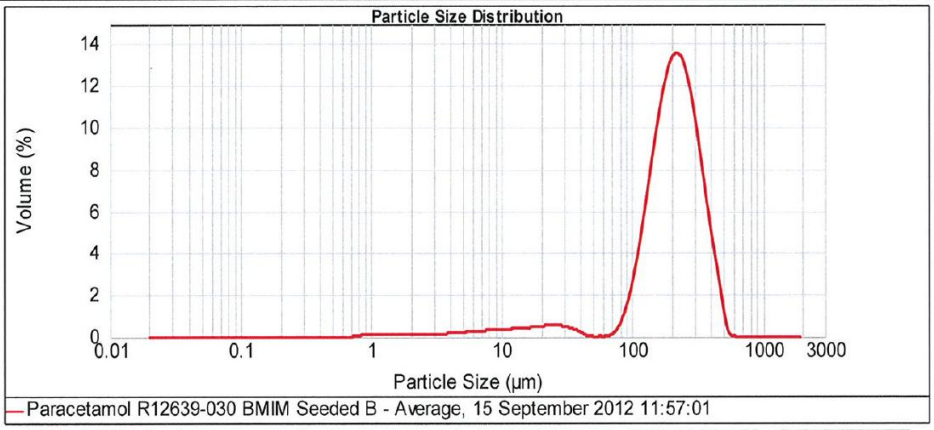
[bmim][PF_6] 47 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-030 BMIM	**SOP Name:**	**Measured:** 15 September 2012 11:57:01	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 15 September 2012 11:57:02	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.43 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.546 %	**Result Emulation:** Off
Concentration: 0.0669 %Vol	**Span :** 1.191	**Uniformity:** 0.384	**Result units:** Volume
Specific Surface Area: 0.0924 m²/g	**Surface Weighted Mean D[3,2]:** 64.902 um	**Vol. Weighted Mean D[4,3]:** 214.437 um	

d(0.1): 104.125 um **d(0.5):** 205.918 um **d(0.9):** 349.467 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.06	11.482	0.34	120.226	6.17	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.06	13.183	0.37	138.038	8.54	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.06	15.136	0.40	158.489	10.58	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.07	17.378	0.44	181.970	11.92	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.08	19.953	0.48	208.930	12.21	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.08	22.909	0.49	239.883	11.38	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.08	26.303	0.48	275.423	9.61	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.09	30.200	0.41	316.228	7.28	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.11	34.674	0.28	363.078	4.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.13	39.811	0.11	416.869	2.75	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.15	45.709	0.00	478.630	0.60	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.18	52.481	0.00	549.541	0.02	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.21	60.256	0.00	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.23	69.183	0.02	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.04	7.586	0.26	79.433	0.27	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.07	8.710	0.28	91.201	0.81	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.08	10.000	0.30	104.713	2.30	1096.478	0.00		
0.105	0.00	1.096	0.08	11.482	0.32	120.226	3.96	1258.925	0.00		

Operator notes: *2,2,4 trimethylpentane + 0.05%w/w lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_030
Record Number: 16
02 Oct 2012 16:06:44

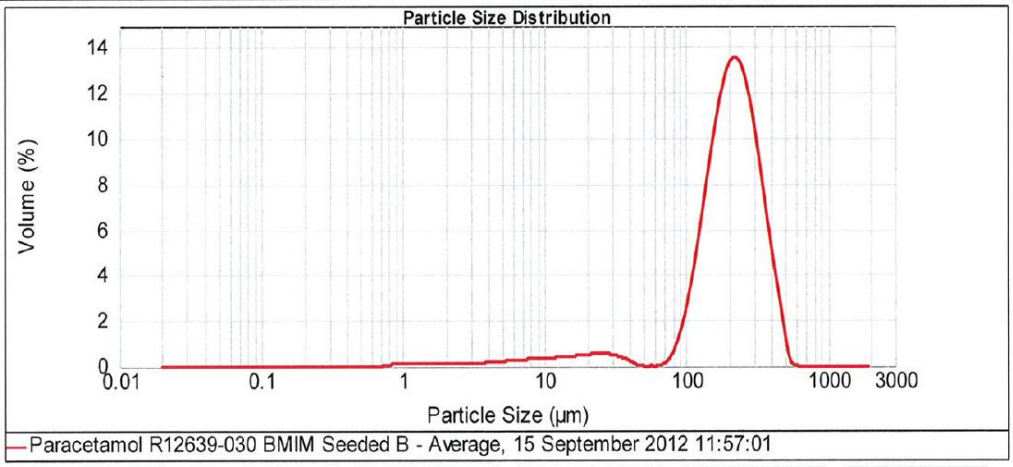
[bmim][PF_6] 57 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-030 BMIM	**SOP Name:**	**Measured:** 15 September 2012 11:57:01	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 15 September 2012 11:57:02	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.43 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.546 %	**Result Emulation:** Off
Concentration: 0669 %Vol	**Span :** 1.191	**Uniformity:** 0.384	**Result units:** Volume
Specific Surface Area: 0.0924 m²/g	**Surface Weighted Mean D[3,2]:** 64.902 um	**Vol. Weighted Mean D[4,3]:** 214.437 um	

d(0.1): 104.125 um **d(0.5):** 205.918 um **d(0.9):** 349.467 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.08	11.482	0.34	120.226	6.17	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.08	13.183	0.37	138.038	8.54	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.08	15.136	0.40	158.489	10.58	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.07	17.378	0.44	181.970	11.92	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.08	19.953	0.48	208.930	12.21	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.08	22.909	0.49	239.883	11.38	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.09	26.303	0.48	275.423	9.61	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	0.41	316.228	7.28	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.13	34.674	0.28	363.078	4.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.15	39.811	0.11	416.869	2.75	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.18	45.709	0.00	478.630	0.60	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.21	52.481	0.00	549.541	0.02	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.23	60.256	0.02	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.26	69.183	0.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.04	7.586	0.28	79.433	0.81	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.07	8.710	0.30	90.000	2.30	954.993	0.00	10000.000	
0.091	0.00	0.955	0.08	10.000	0.32	104.713	3.96	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 trimethylpentane + 0.05%w/w lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_030
Record Number: 16
15 Sep 2012 12:06:03

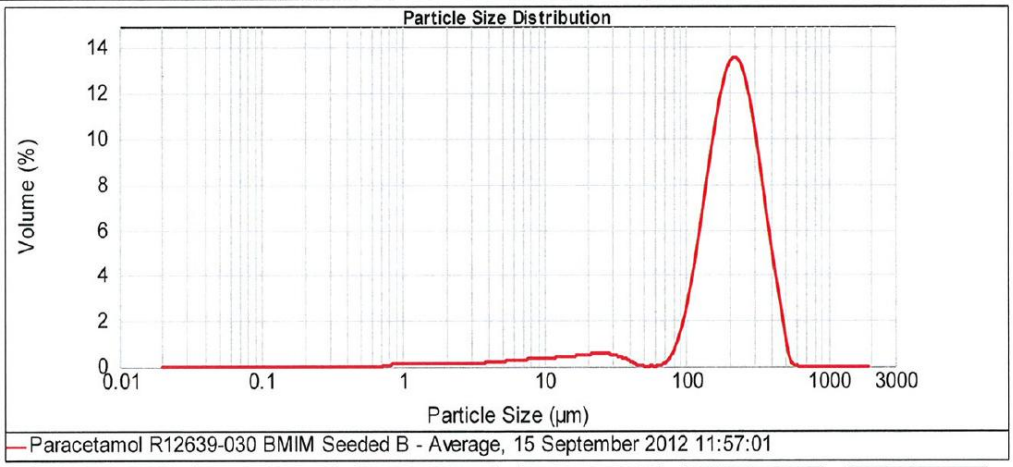
[hmim][PF_6] 35 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-030 BMIM	**SOP Name:**	**Measured:** 15 September 2012 11:57:01	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 15 September 2012 11:57:02	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.43 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.546 %	**Result Emulation:** Off
Concentration: 0669 %Vol	**Span :** 1.191	**Uniformity:** 0.384	**Result units:** Volume
Specific Surface Area: 0.0924 m²/g	**Surface Weighted Mean D[3,2]:** 64.902 um	**Vol. Weighted Mean D[4,3]:** 214.437 um	

d(0.1): 104.125 um **d(0.5):** 205.918 um **d(0.9):** 349.467 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.08	11.482	0.34	120.226	6.17	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.08	13.183	0.37	138.038	8.54	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.08	15.136	0.40	158.489	10.58	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.07	17.378	0.44	181.970	11.92	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.08	19.953	0.48	208.930	12.21	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.08	22.909	0.49	239.883	11.38	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.09	26.303	0.48	275.423	9.61	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	0.41	316.228	7.28	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.13	34.674	0.28	363.078	4.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.15	39.811	0.11	416.869	2.75	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.18	45.709	0.00	478.630	0.60	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.21	52.481	0.00	549.541	0.02	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.23	60.256	0.02	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.26	69.183	0.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.04	7.586	0.28	79.433	0.81	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.07	8.710	0.30	90.000	2.30	954.993	0.00	10000.000	
0.091	0.00	0.955	0.08	10.000	0.32	104.713	3.96	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 trimethylpentane + 0.05%w/w lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_030
Record Number: 16
15 Sep 2012 12:06:03

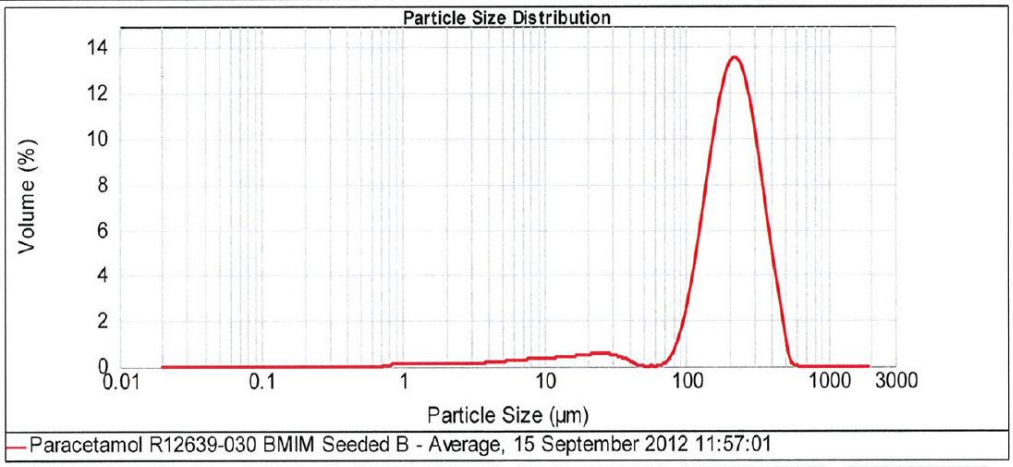
[hmim][PF_6] 49 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-030 BMIM	**SOP Name:**	**Measured:** 15 September 2012 11:57:01	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 15 September 2012 11:57:02	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.43 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.546 %	**Result Emulation:** Off
Concentration: 0669 %Vol	**Span :** 1.191	**Uniformity:** 0.384	**Result units:** Volume
Specific Surface Area: 0.0924 m²/g	**Surface Weighted Mean D[3,2]:** 64.902 um	**Vol. Weighted Mean D[4,3]:** 214.437 um	

d(0.1): 104.125 um **d(0.5):** 205.918 um **d(0.9):** 349.467 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.08	11.482	0.34	120.226	6.17	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.08	13.183	0.37	138.038	8.54	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.08	15.136	0.40	158.489	10.58	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.07	17.378	0.44	181.970	11.92	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.08	19.953	0.48	208.930	12.21	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.08	22.909	0.49	239.883	11.38	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.09	26.303	0.48	275.423	9.61	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	0.41	316.228	7.28	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.13	34.674	0.28	363.078	4.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.15	39.811	0.11	416.869	2.75	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.18	45.709	0.00	478.630	0.60	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.21	52.481	0.00	549.541	0.02	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.23	60.256	0.02	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.26	69.183	0.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.04	7.586	0.28	79.433	0.81	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.07	8.710	0.30	90.000	2.30	954.993	0.00	10000.000	
0.091	0.00	0.955	0.08	10.000	0.32	104.713	3.96	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 trimethylpentane + 0.05%w/w lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_030
Record Number: 16
15 Sep 2012 12:06:03

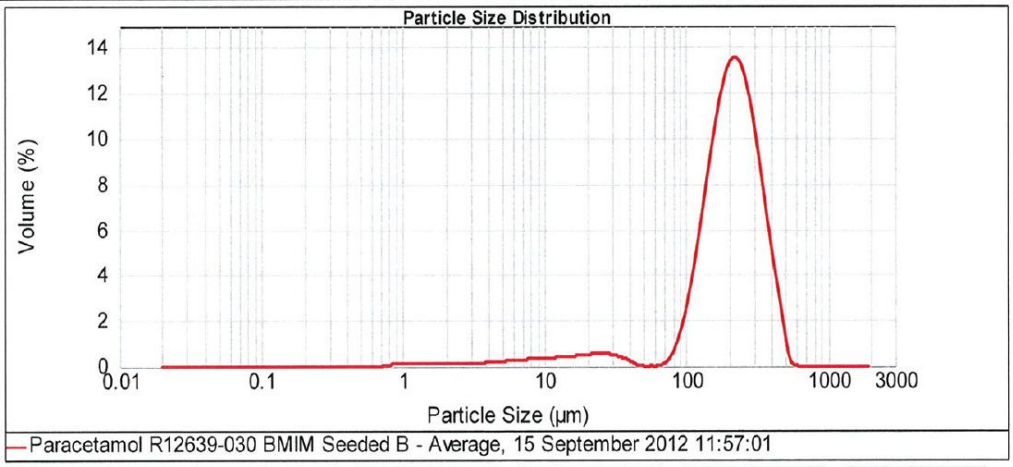
[hmim][PF_6] 63 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Paracetamol R12639-030 BMIM	**SOP Name:**	**Measured:** 15 September 2012 11:57:01	
Sample Source & type:	**Measured by:** kbs23436	**Analysed:** 15 September 2012 11:57:02	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 7.43 %
Dispersant Name: 2-2-4 trimethyl pentane	**Dispersant RI:** 1.391	**Weighted Residual:** 0.546 %	**Result Emulation:** Off
Concentration: 0669 %Vol	**Span :** 1.191	**Uniformity:** 0.384	**Result units:** Volume
Specific Surface Area: 0.0924 m²/g	**Surface Weighted Mean D[3,2]:** 64.902 um	**Vol. Weighted Mean D[4,3]:** 214.437 um	

d(0.1): 104.125 um **d(0.5):** 205.918 um **d(0.9):** 349.467 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.08	11.482	0.34	120.226	6.17	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.08	13.183	0.37	138.038	8.54	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.08	15.136	0.40	158.489	10.58	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.07	17.378	0.44	181.970	11.92	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.08	19.953	0.48	208.930	12.21	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.08	22.909	0.49	239.883	11.38	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.09	26.303	0.48	275.423	9.61	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.11	30.200	0.41	316.228	7.28	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.13	34.674	0.28	363.078	4.87	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.15	39.811	0.11	416.869	2.75	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.18	45.709	0.00	478.630	0.60	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.21	52.481	0.00	549.541	0.02	5754.399	0.00
0.052	0.00	0.550	0.00	5.754	0.23	60.256	0.02	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.00	6.607	0.26	69.183	0.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.04	7.586	0.28	79.433	0.81	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.07	8.710	0.30	90.000	2.30	954.993	0.00	10000.000	
0.091	0.00	0.955	0.08	10.000	0.32	104.713	3.96	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes: *2,2,4 trimethylpentane + 0.05%w/w lecithin 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R12639_030
Record Number: 16
15 Sep 2012 12:06:03

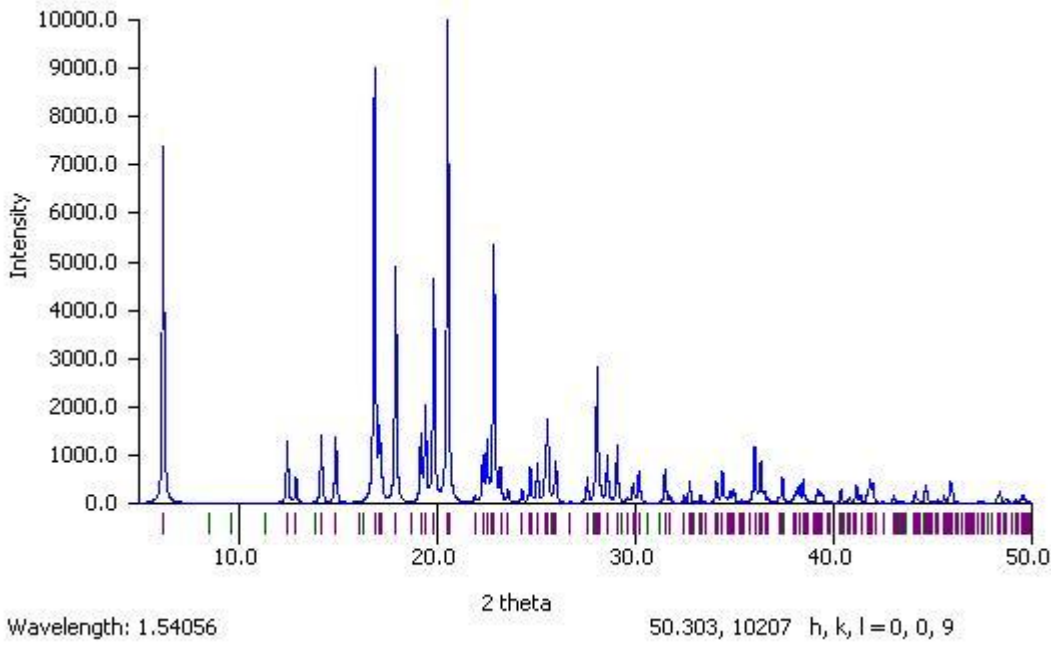
Appendix 4: UV and Corresponding Solubility Data for Ibuprofen in [bmim][PF_6], [hmim][PF_6] and Water

Solubility of Ibuprofen [bmim][PF_6]								
298.15 K								
	Sample 1		Sample 2		Sample 3		$\sum$abs$(\overline{x}/n)$	$\sum(\overline{x}/n)$
	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}
	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

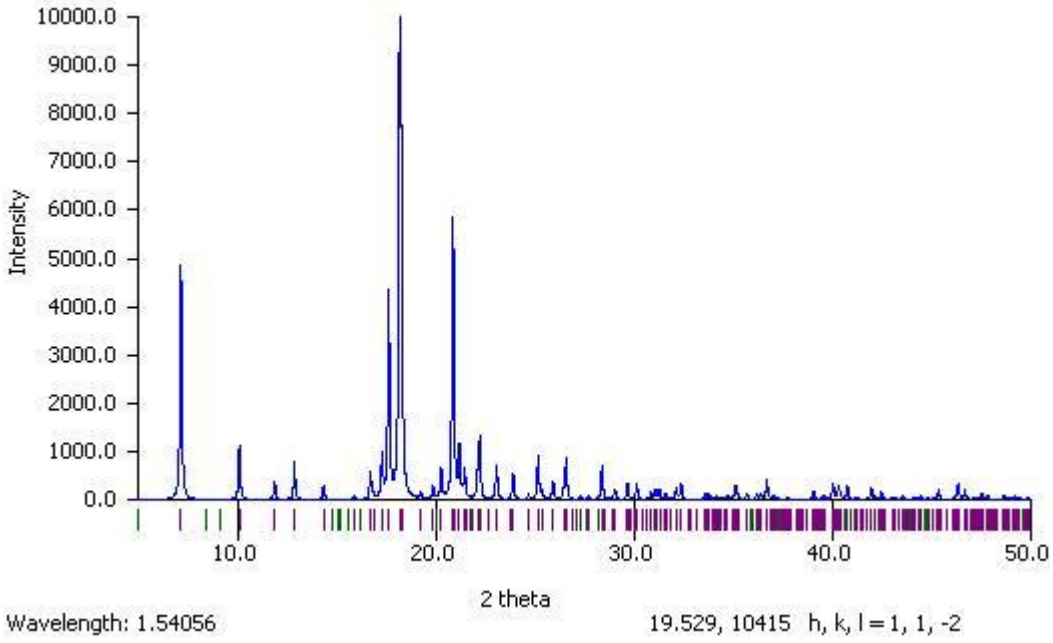
Solubility of Ibuprofen [hmim][PF_6]								
298.15 K								
	Sample 1		Sample 2		Sample 3		$\sum abs(\overline{x}/n)$	$\sum(\overline{x}/n)$
	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}
	1.1889	24.963	1.3726	28.975	1.2135	25.500		
	1.1949	25.094	1.3521	28.527	1.2137	25.504		
	1.1981	25.164	1.3669	28.850	1.1851	24.880		
$\bar{x}$	1.1940	25.073	1.3639	28.784	1.2041	25.295	1.254 ± 0.095	26.38 ± 2.08
308.15 K								
	1.6187	34.349	1.7179	36.516	1.7719	37.695		
	1.6312	34.622	1.8077	38.477	1.8282	38.925		
	1.6440	34.902	1.7524	37.269	1.9703	42.028		
$\bar{x}$	1.6313	34.624	1.7593	37.421	1.8568	39.549	1.749 ± 0.113	37.20 ± 2.47
318.15 K								
	2.2271	52.836	1.9970	47.403	2.1606	51.266		
	2.1217	50.347	2.0132	47.786	2.2754	53.976		
	2.2624	53.669	2.0162	47.856	2.1801	51.726		
$\bar{x}$	2.2037	52.284	2.0088	47.682	2.2054	52.323	2.139 ± 0.113	50.76 ± 2.67
328.15 K								
	2.0340	66.845	1.9737	64.873	1.9816	65.131		
	2.0561	67.567	2.0020	65.798	2.0042	65.870		
	2.0378	66.969	1.9756	64.935	1.9760	64.948		
$\bar{x}$	2.0426	67.127	1.9838	65.202	1.9873	65.317	2.005 ± 0.003	65.88 ± 1.08
338.15 K								
	1.4135	124.158	1.3190	115.920	1.3697	120.340		
	1.4239	125.065	1.3257	116.504	1.3667	120.078		
	1.4182	124.568	1.3257	116.504	1.3724	120.575		
$\bar{x}$	1.4185	124.597	1.3235	116.309	1.3696	120.331	1.371 ± 0.048	120.41 ± 4.15

Solubility of Ibuprofen Water								
298.15 K								
	Sample 1		Sample 2		Sample 3		$\sum \text{abs}(\overline{x}/n)$	$\sum(\overline{x}/n)$
	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}	abs	mg.mL^{-1}
	0.2217	0.128	0.2103	0.122	0.2075	0.121		
	0.2218	0.129	0.2112	0.123	0.2076	0.121		
	0.2220	0.129	0.2101	0.122	0.2074	0.121		
$\bar{x}$	0.2218	0.129	0.2105	0.122	0.2075	0.121	0.213 ± 0.008	0.124 ± 0.004
308.15 K								
	0.2829	0.162	0.3042	0.174	0.3522	0.201		
	0.2829	0.162	0.3042	0.174	0.3524	0.201		
	0.2828	0.162	0.3036	0.174	0.3522	0.201		
$\bar{x}$	0.2829	0.162	0.3040	0.174	0.3523	0.201	0.313 ± 0.036	0.179 ± 0.020
318.15 K								
	0.3570	0.203	0.4758	0.269	0.6351	0.357		
	0.3558	0.203	0.4755	0.269	0.6345	0.357		
	0.3563	0.203	0.4760	0.269	0.6351	0.357		
$\bar{x}$	0.3564	0.203	0.4758	0.269	0.6349	0.357	0.489 ± 0.140	0.276 ± 0.077
328.15 K								
	0.5533	0.312	0.6468	0.363	0.8037	0.450		
	0.5551	0.313	0.6468	0.363	0.8044	0.451		
	0.5553	0.313	0.6484	0.364	0.8054	0.451		
$\bar{x}$	0.5546	0.312	0.6473	0.364	0.8045	0.451	0.669 ± 0.126	0.376 ± 0.070
338.15 K								
	0.8284	0.464	1.1082	0.618	0.8709	0.487		
	0.8284	0.464	1.0930	0.610	0.8714	0.488		
	0.8303	0.465	1.1103	0.620	0.8717	0.488		
$\bar{x}$	0.8290	0.464	1.1038	0.616	0.8713	0.487	0.935 ± 0.148	0.523 ± 0.082

Appendix 5: X-Ray Diffraction Patterns for Ibuprofen

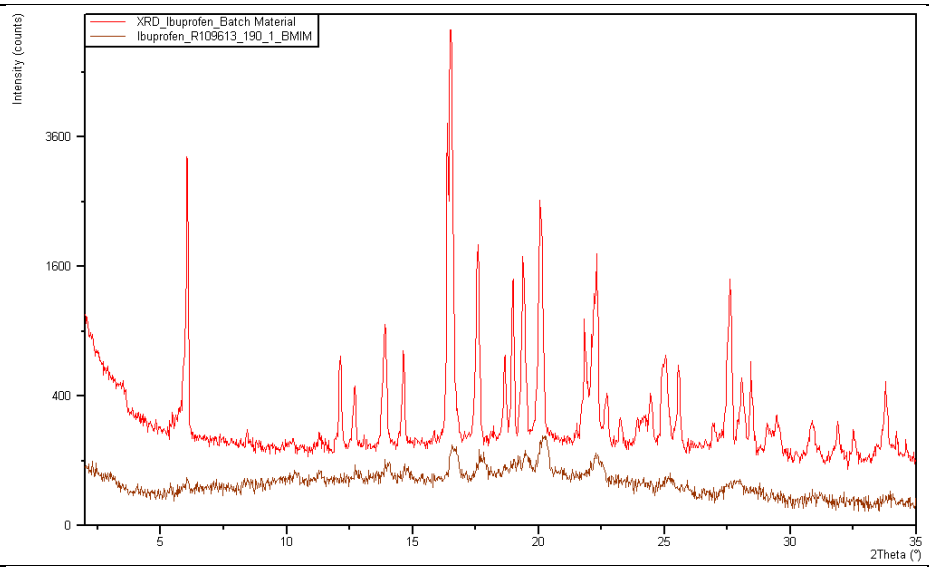
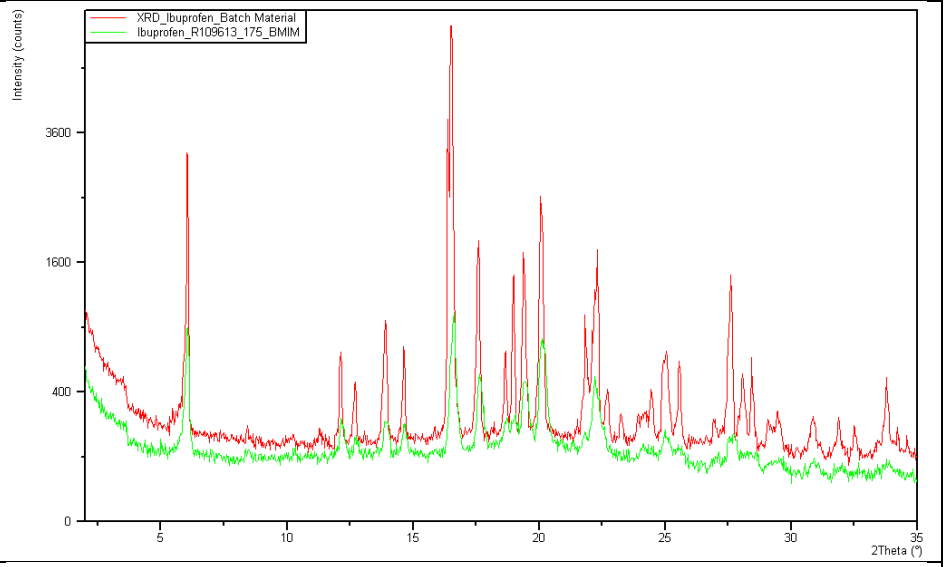
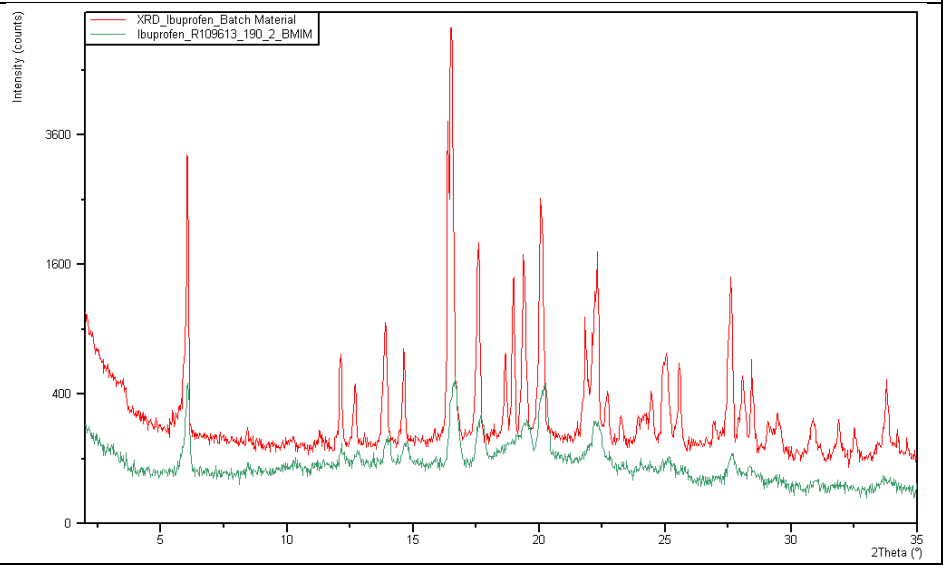


Ibuprofen Form I X-Ray Pattern

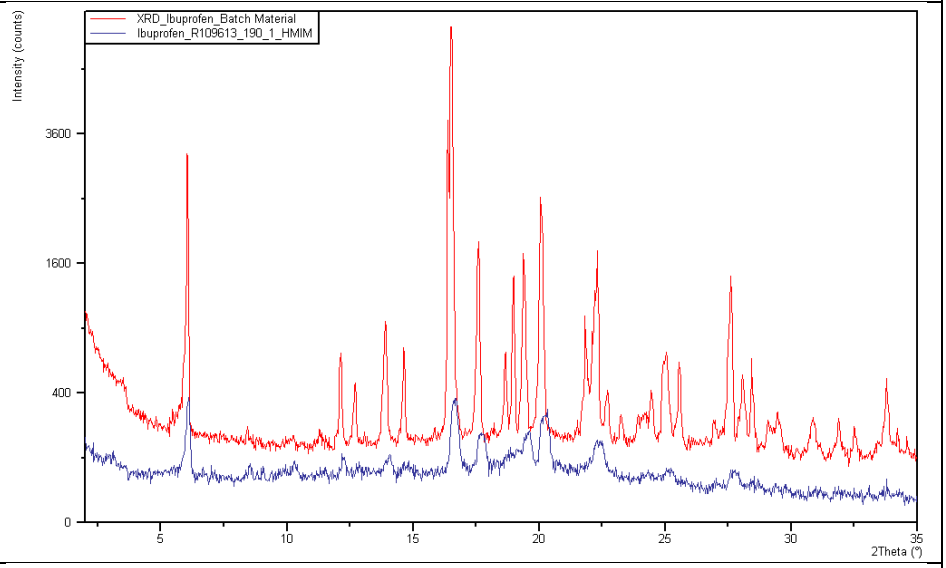
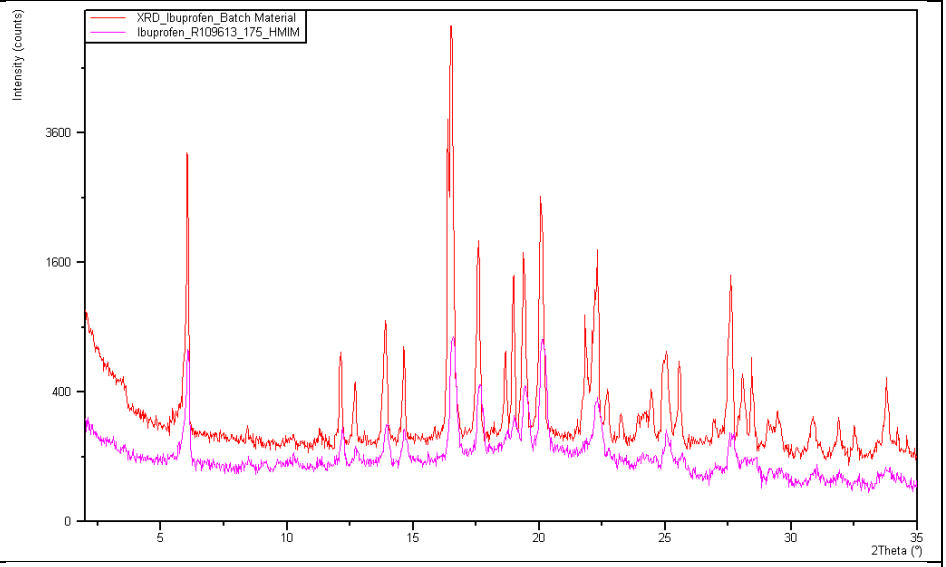
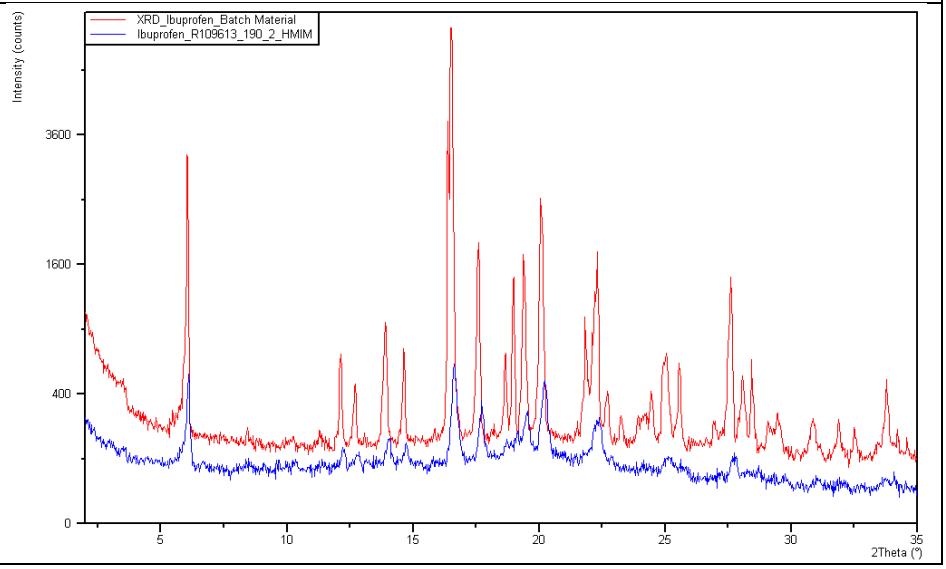


Ibuprofen Form II X-Ray Pattern

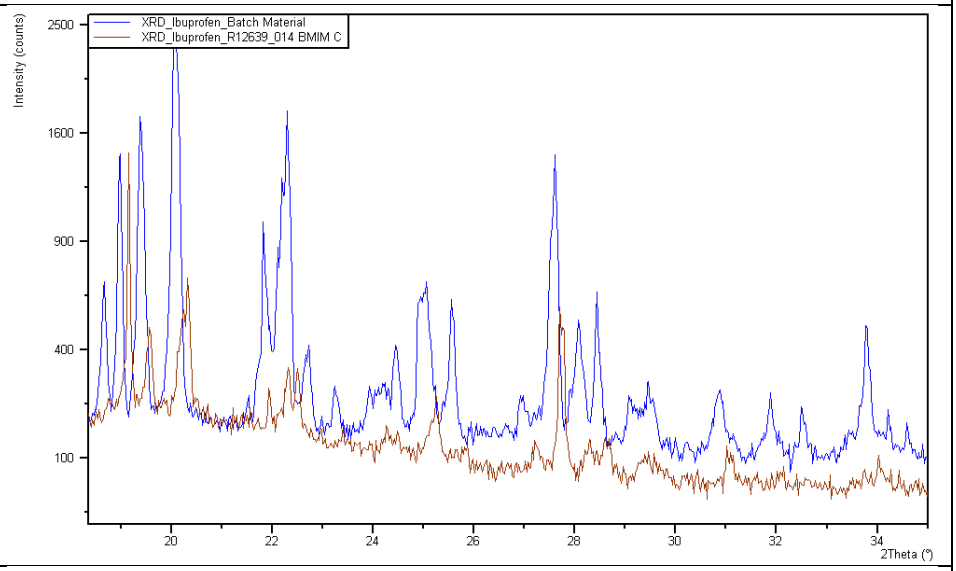
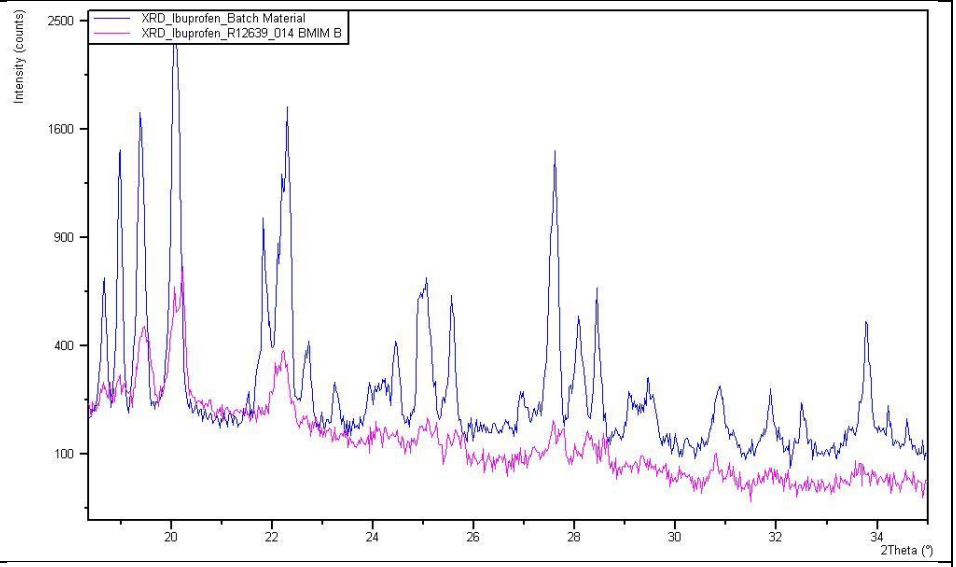
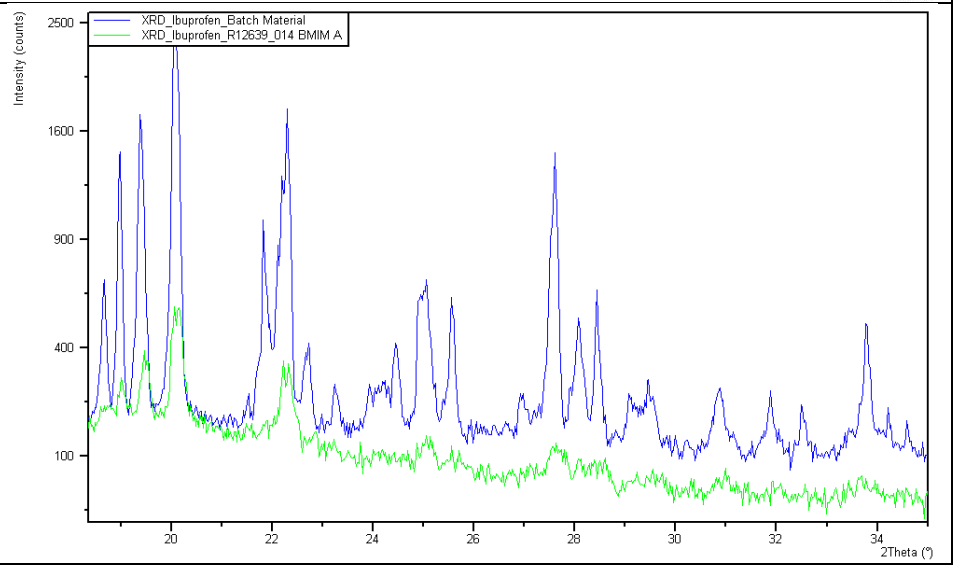
Ibuprofen [bmim][PF_6] (non-seeded)

mg.mL^{-1}	XRD Trace
28	
57	
83	

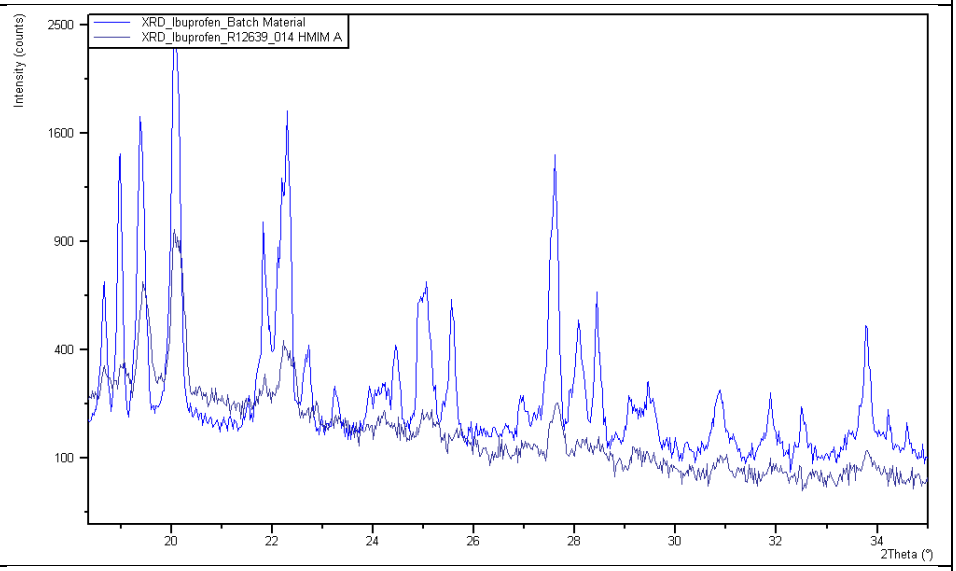
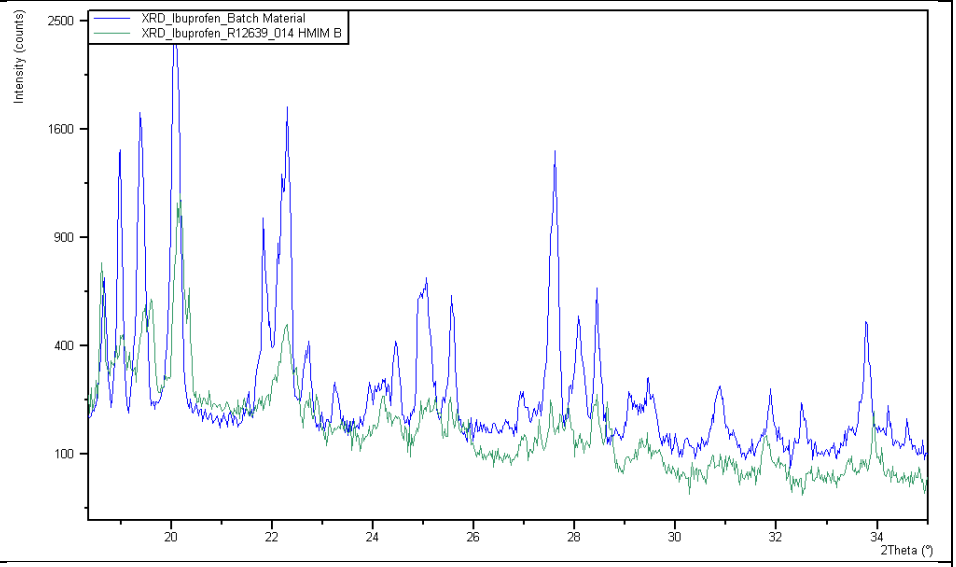
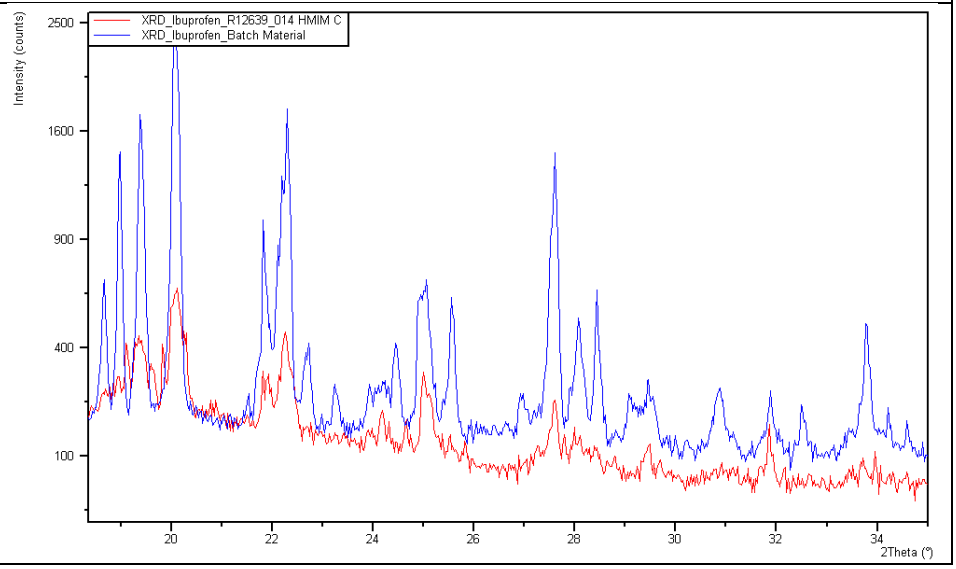
Ibuprofen[hmim][PF_6] (non-seeded)

mg.mL^{-1}	XRD Trace
79	
120	
155	

Ibuprofen [bmim][PF_6] (seeded)

mg.mL^{-1}	XRD Trace
61	
72	
84	

Ibuprofen [hmim][PF_6] (seeded)

mg.mL^{-1}	XRD Trace
113	
136	
158	

Appendix 6: Ibuprofen Sizing Data

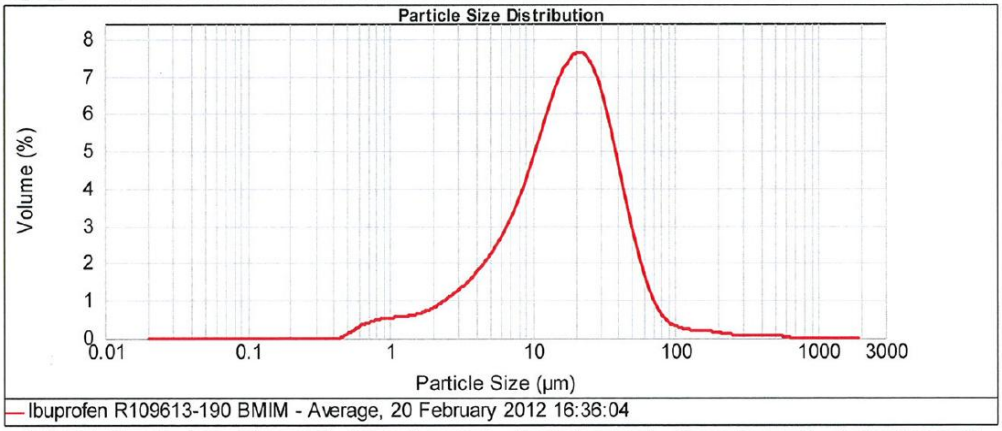
[bmim][PF_6] 28 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R109613-190 BMIM -	**SOP Name:**	**Measured:** 20 February 2012 16:36:04	
Sample Source & type: R109613-190	**Measured by:** kbs23436	**Analysed:** 20 February 2012 16:36:05	
Sample bulk lot ref: BMIM	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 1.13 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.267 %	**Result Emulation:** Off
Concentration: 0.0012 %Vol	**Span :** 2.306	**Uniformity:** 0.837	**Result units:** Volume
Specific Surface Area: 0.746 m²/g	**Surface Weighted Mean D[3,2]:** 8.044 um	**Vol. Weighted Mean D[4,3]:** 23.390 um	

d(0.1): 3.956 um **d(0.5):** 17.281 um **d(0.9):** 43.808 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.50	11.482	5.27	120.226	0.19	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.53	13.183	5.90	138.038	0.19	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.57	15.136	6.43	158.489	0.16	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.64	17.378	6.78	181.970	0.13	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.74	19.953	6.90	208.930	0.10	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.86	22.909	6.74	239.883	0.07	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	1.02	26.303	6.29	275.423	0.05	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	1.20	30.200	5.59	316.228	0.05	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	1.39	34.674	4.72	363.078	0.05	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	1.62	39.811	3.75	416.869	0.06	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	1.87	45.709	2.80	478.630	0.07	5011.872	0.00
0.046	0.00	0.479	0.13	5.012	2.16	52.481	1.96	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.25	5.754	2.51	60.256	1.27	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.36	6.607	2.93	69.183	0.79	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.42	7.586	3.42	79.433	0.43	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.46	8.710	3.98	90.000	0.34	954.993	0.00	10000.000	
0.091	0.00	0.955	0.49	10.000	4.62	104.713	0.22	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925			

Operator notes: *Water 2000rpm*

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Paracetamol_R109613_18Feb2012
Record Number: 68
25 Feb 2012 11:56:29

[bmim][PF_6] 57 mg.mL^{-1}

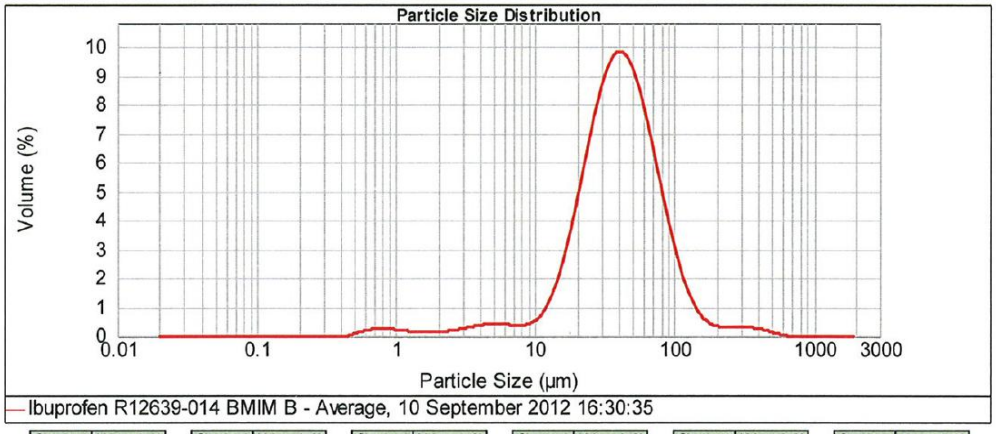
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: 0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.95	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.26	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.08	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.14	5.754	0.35	60.256	6.51	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.20	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.21	7.586	0.33	79.433	3.69	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.33	90.000	3.22	954.993	0.00	10000.000	
0.091	0.00	0.955	0.18	10.000	0.40	104.713	1.93	1096.478	0.00		
0.105	0.00	1.096		11.482	0.61	120.226		1258.925			

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

[bmim][PF_6] 83 mg.mL^{-1}

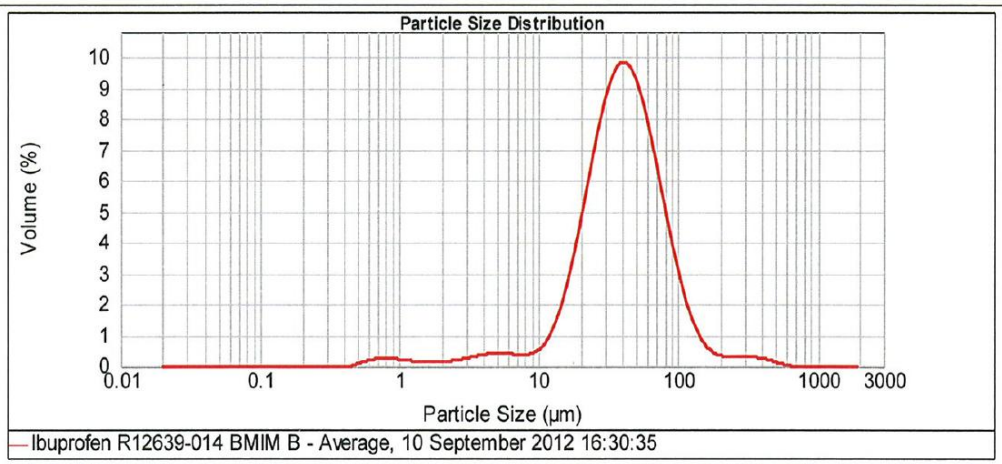
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: 0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.95	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.26	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.08	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.14	5.754	0.35	60.256	6.51	600.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.20	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.21	7.586	0.33	79.433	3.69	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.40	90.000	3.22	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.18	10.000	0.61	104.713	1.93	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925			

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

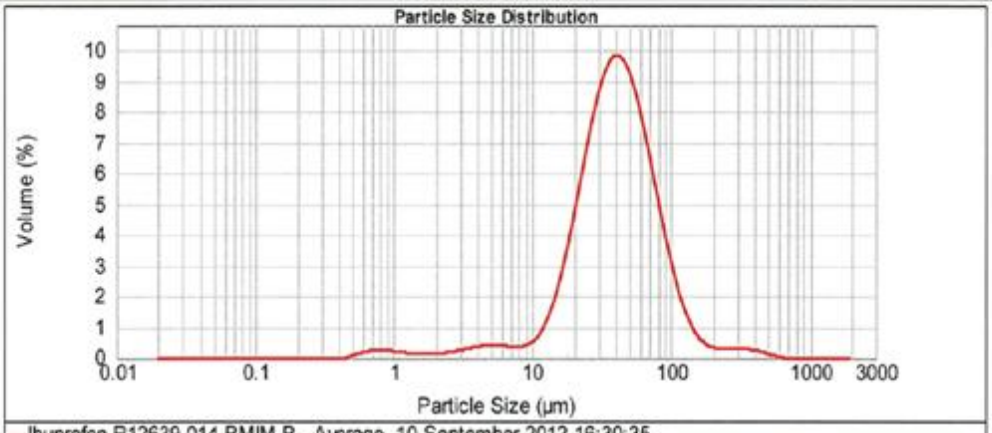
[hmim][PF_6] 79 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: 0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.96	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.26	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.08	5.754	0.35	60.256	6.51	630.957	0.00	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.20	7.586	0.33	79.433	3.89	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.40	91.200	3.22	954.993	0.00	10000.000	
0.091	0.00	0.955	0.21	10.000	0.61	104.713	1.99	1096.478	0.00		
0.105	0.00	1.096	0.18	11.482		120.226		1258.925			

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

[hmim][PF_6] 120 mg.mL^{-1}

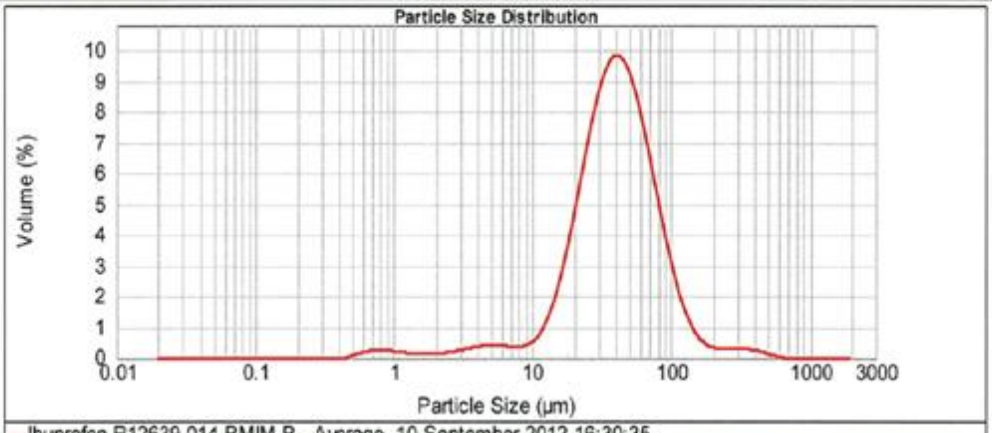
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: 0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.96	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.26	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.08	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.14	5.754	0.35	60.256	6.51	630.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.20	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.21	7.586	0.33	79.433	3.89	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.40	90.000	3.22	954.993	0.00	10000.000	
0.091	0.00	0.955	0.18	10.000	0.61	104.713	1.99	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925			

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

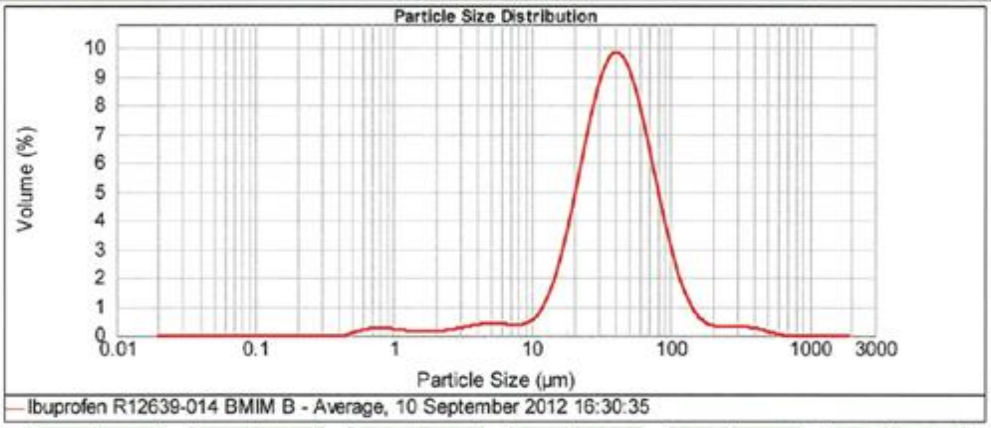
[hmim][PF_6] 155 mg.mL^{-1}

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: 0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %	Size (µm)	Volume in %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.95	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.20	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.08	5.754	0.35	60.256	6.51	630.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.20	7.586	0.33	79.433	3.89	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.40	90.000	3.22	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.21	10.000	0.61	104.713	1.99	1096.478	0.00		
0.105	0.00	1.096	0.18	11.482		120.226		1258.925	0.00		

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

[bmim][PF_6] 61 mg.mL^{-1}

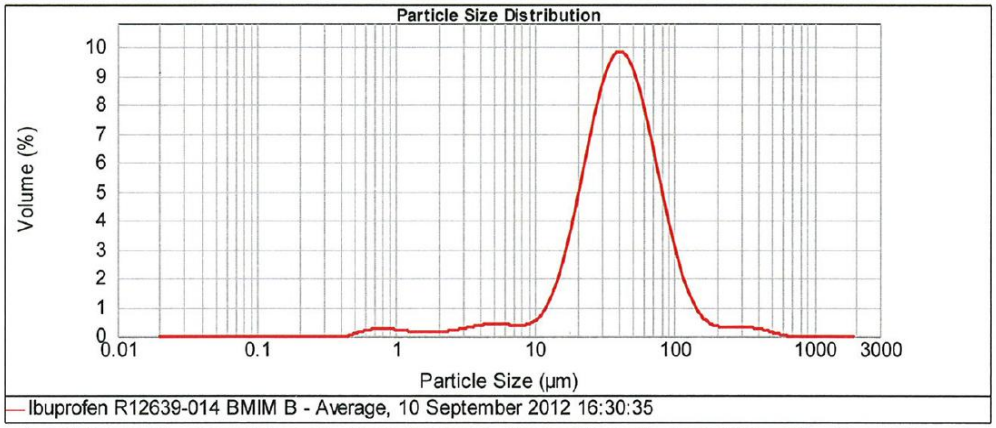
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: 0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.95	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.26	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.08	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.14	5.754	0.35	60.256	6.51	630.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.20	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.21	7.586	0.33	79.433	3.69	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.33	90.000	3.22	954.993	0.00	10000.000	
0.091	0.00	0.955	0.18	10.000	0.40	104.713	1.93	1096.478	0.00		
0.105	0.00	1.096		11.482	0.61	120.226		1258.925			

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

[bmim][PF_6] 72 mg.mL^{-1}

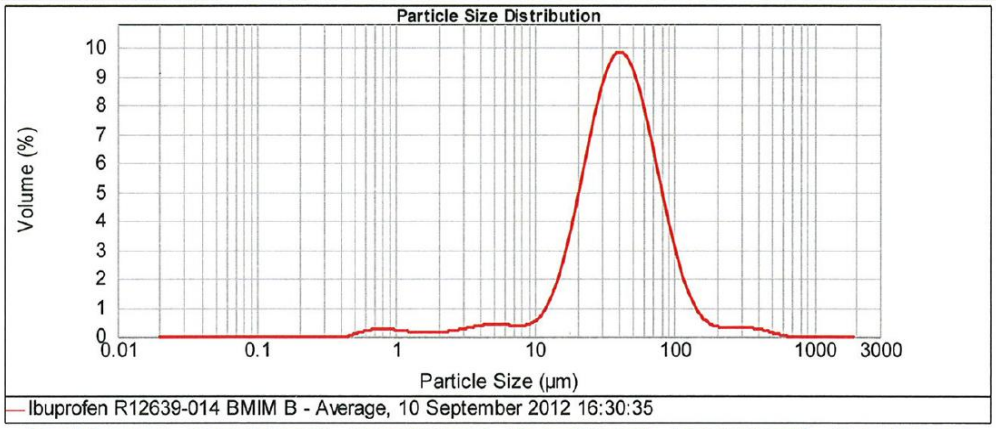
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 BMIM B -	**SOP Name:**	**Measured:** 10 September 2012 16:30:35	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:30:36	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.86 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.210 %	**Result Emulation:** Off
Concentration: .0157 %Vol	**Span :** 1.797	**Uniformity:** 0.649	**Result units:** Volume
Specific Surface Area: 0.309 m²/g	**Surface Weighted Mean D[3,2]:** 19.423 um	**Vol. Weighted Mean D[4,3]:** 50.339 um	

d(0.1): 16.762 um **d(0.5):** 39.670 um **d(0.9):** 88.068 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.15	11.482	1.01	120.226	1.21	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.13	13.183	1.65	138.038	0.72	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.11	15.136	2.54	158.489	0.44	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.10	17.378	3.68	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.12	19.953	4.95	208.930	0.27	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.14	22.909	6.26	239.883	0.27	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.19	26.303	7.43	275.423	0.27	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.24	30.200	8.32	316.228	0.26	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.29	34.674	8.82	363.078	0.22	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.33	39.811	8.85	416.869	0.18	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.36	45.709	8.42	478.630	0.09	5011.872	0.00
0.046	0.00	0.479	0.08	5.012	0.37	52.481	7.60	549.541	0.03	5754.399	0.00
0.052	0.00	0.550	0.14	5.754	0.35	60.256	6.51	630.000	0.00	6606.934	0.00
0.060	0.00	0.631	0.20	6.607	0.33	69.183	5.27	724.436	0.00	7585.776	0.00
0.069	0.00	0.724	0.21	7.586	0.33	79.433	3.69	831.764	0.00	8709.636	0.00
0.079	0.00	0.832	0.21	8.710	0.40	90.000	3.22	954.993	0.00	10000.000	
0.091	0.00	0.955	0.18	10.000	0.61	104.713	1.93	1096.478	0.00		
0.105		1.096		11.482		120.226		1258.925			

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 16
10 Sep 2012 17:29:03

[bmim][PF_6] 84 mg.mL^{-1}

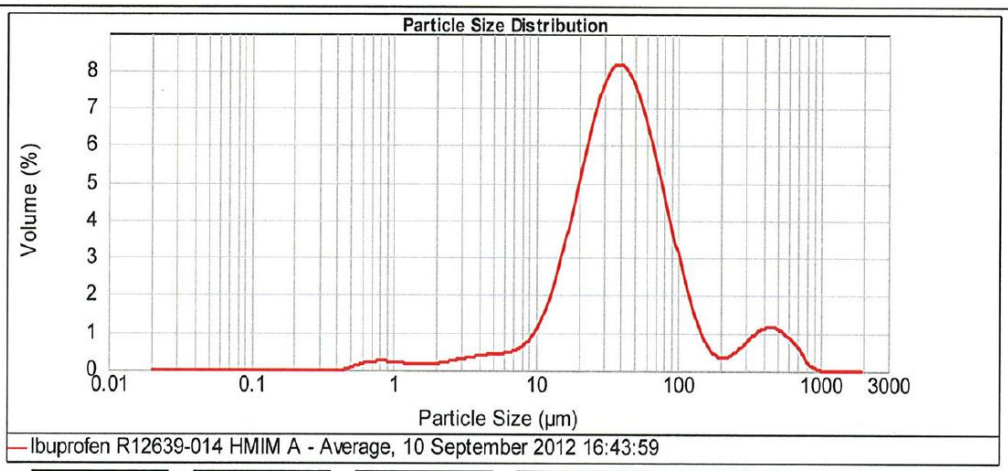
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 HMIM A -	**SOP Name:**	**Measured:** 10 September 2012 16:43:59	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:44:00	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.43 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.228 %	**Result Emulation:** Off
Concentration: 0.0167 %Vol	**Span :** 2.664	**Uniformity:** 1.27	**Result units:** Volume
Specific Surface Area: 0.319 m^2/g	**Surface Weighted Mean D[3,2]:** 18.811 um	**Vol. Weighted Mean D[4,3]:** 73.419 um	

d(0.1): 14.260 um **d(0.5): 39.737 um** **d(0.9): 120.136 um**



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.16	11.482	1.61	120.226	1.38	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.14	13.183	2.28	138.038	0.82	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.13	15.136	3.09	158.489	0.47	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.14	17.378	4.02	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.16	19.953	4.97	208.930	0.32	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.19	22.909	5.87	239.883	0.45	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.23	26.303	6.61	275.423	0.64	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.27	30.200	7.12	316.228	0.84	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.31	34.674	7.35	363.078	0.98	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.35	39.811	7.29	416.869	1.04	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.37	45.709	6.95	478.630	0.99	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.39	52.481	6.38	549.541	0.55	5754.399	0.00
0.052	0.00	0.550	0.08	5.754	0.41	60.256	5.63	630.957	0.87	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.47	69.183	4.77	724.436	0.27	7585.776	0.00
0.069	0.00	0.724	0.19	7.586	0.58	79.433	3.53	831.764	0.06	8709.636	0.00
0.079	0.00	0.832	0.20	8.710	0.78	90.000	3.28	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.20	10.000	1.12	104.713	2.10	1096.478	0.00		
0.105	0.00	1.096	0.19	11.482		120.226		1258.925	0.00		

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 20
10 Sep 2012 17:29:03

[hmim][PF_6] 113 mg.mL^{-1}

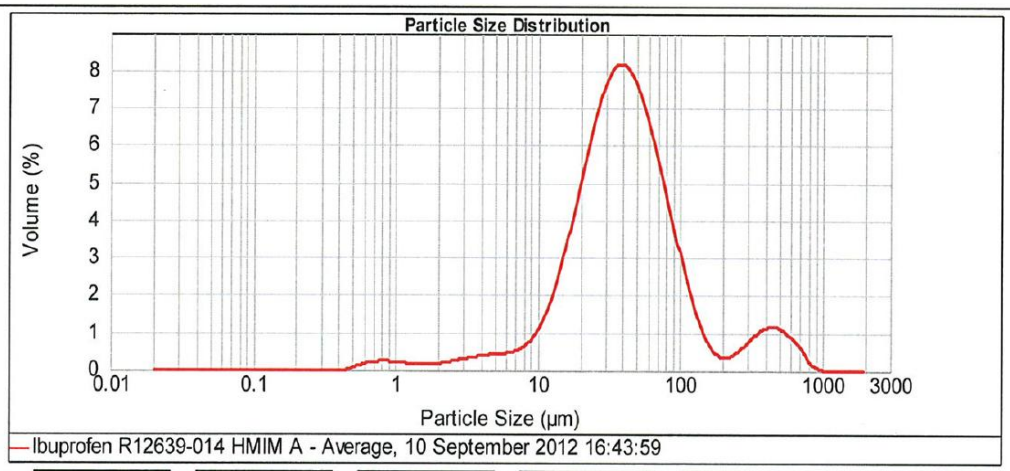
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 HMIM A -	**SOP Name:**	**Measured:** 10 September 2012 16:43:59	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:44:00	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.43 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.228 %	**Result Emulation:** Off
Concentration: 0.0167 %Vol	**Span :** 2.664	**Uniformity:** 1.27	**Result units:** Volume
Specific Surface Area: 0.319 m²/g	**Surface Weighted Mean D[3,2]:** 18.811 um	**Vol. Weighted Mean D[4,3]:** 73.419 um	

d(0.1): 14.260 um **d(0.5):** 39.737 um **d(0.9):** 120.136 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.16	11.482	1.61	120.226	1.38	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.14	13.183	2.28	138.038	0.82	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.13	15.136	3.09	158.489	0.47	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.14	17.378	4.02	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.16	19.953	4.97	208.930	0.32	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.19	22.909	5.87	239.883	0.45	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.23	26.303	6.61	275.423	0.64	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.27	30.200	7.12	316.228	0.84	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.31	34.674	7.35	363.078	0.98	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.35	39.811	7.29	416.869	1.04	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.37	45.709	6.95	478.630	0.99	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.39	52.481	6.38	549.541	0.55	5754.399	0.00
0.052	0.00	0.550	0.08	5.754	0.41	60.256	5.63	600.000	0.87	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.47	69.183	4.77	724.436	0.27	7585.776	0.00
0.069	0.00	0.724	0.19	7.586	0.58	79.433	3.53	831.764	0.06	8709.636	0.00
0.079	0.00	0.832	0.20	8.710	0.78	90.000	3.28	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.20	10.000	1.12	104.713	2.10	1096.478	0.00		
0.105	0.00	1.096	0.19	11.482		120.226		1258.925	0.00		

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 20
10 Sep 2012 17:29:03

[hmim][PF_6] 136 mg.mL^{-1}

MASTERSIZER 2000

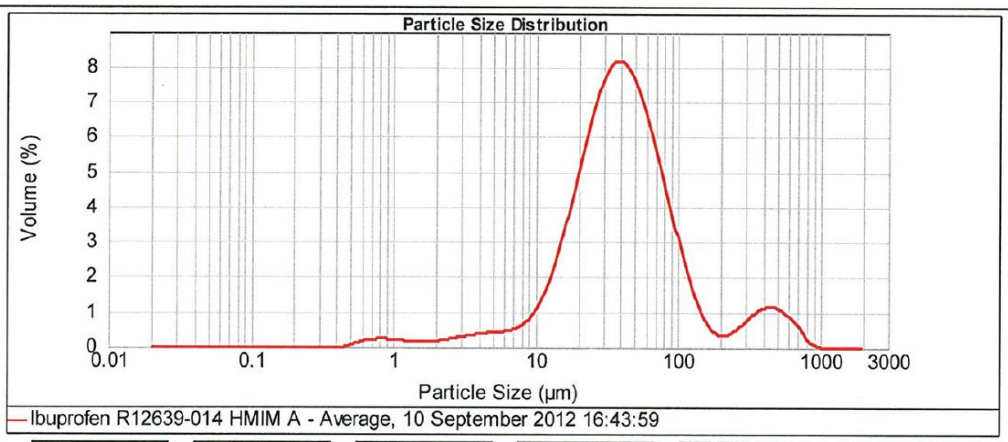
Result Analysis Report

Sample Name: Ibuprofen R12639-014 HMIM A -	**SOP Name:**	**Measured:** 10 September 2012 16:43:59
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:44:00
Sample bulk lot ref:	**Result Source:** Averaged	

Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.43 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.228 %	**Result Emulation:** Off

Concentration: 0.0167 %Vol	**Span :** 2.664	**Uniformity:** 1.27	**Result units:** Volume
Specific Surface Area: 0.319 m²/g	**Surface Weighted Mean D[3,2]:** 18.811 um	**Vol. Weighted Mean D[4,3]:** 73.419 um	

d(0.1): 14.260 um **d(0.5):** 39.737 um **d(0.9):** 120.136 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.16	11.482	1.61	120.226	1.38	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.14	13.183	2.28	138.038	0.82	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.13	15.136	3.09	158.489	0.47	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.14	17.378	4.02	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.16	19.953	4.97	208.930	0.32	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.19	22.909	5.87	239.883	0.45	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.23	26.303	6.61	275.423	0.64	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.27	30.200	7.12	316.228	0.84	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.31	34.674	7.35	363.078	0.98	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.35	39.811	7.29	416.869	1.04	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.37	45.709	6.95	478.630	0.99	5011.872	0.00
0.046	0.00	0.479	0.08	5.012	0.39	52.481	6.38	549.541	0.55	5754.399	0.00
0.052	0.00	0.550	0.14	5.754	0.41	60.256	5.63	631.000	0.87	6606.934	0.00
0.060	0.00	0.631	0.19	6.607	0.47	69.183	4.77	724.436	0.27	7585.776	0.00
0.069	0.00	0.724	0.20	7.586	0.58	79.433	3.53	831.764	0.06	8709.636	0.00
0.079	0.00	0.832	0.20	8.710	0.78	90.000	3.28	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.19	10.000	1.12	104.713	2.10	1096.478	0.00		
0.105	0.00	1.096		11.482		120.226		1258.925	0.00		

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 20
10 Sep 2012 17:29:03

[hmim][PF_6] 158 mg.mL^{-1}

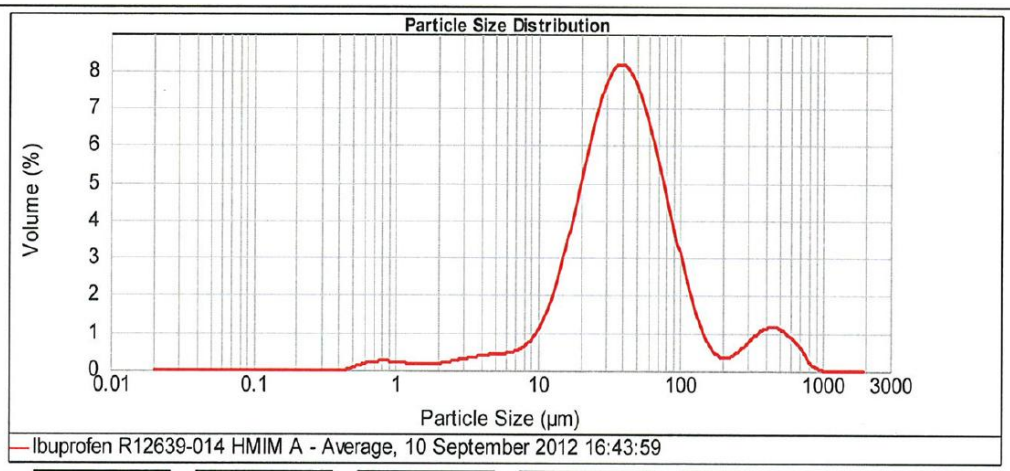
MALVERN INSTRUMENTS

MASTERSIZER 2000

Result Analysis Report

Sample Name: Ibuprofen R12639-014 HMIM A -	**SOP Name:**	**Measured:** 10 September 2012 16:43:59	
Sample Source & type: R12639-014	**Measured by:** kbs23436	**Analysed:** 10 September 2012 16:44:00	
Sample bulk lot ref:	**Result Source:** Averaged		
Particle Name: Fraunhofer	**Accessory Name:** Hydro 2000S+ (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 0.000	**Absorption:** 0	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 6.43 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 0.228 %	**Result Emulation:** Off
Concentration: 0.0167 %Vol	**Span :** 2.664	**Uniformity:** 1.27	**Result units:** Volume
Specific Surface Area: 0.319 m²/g	**Surface Weighted Mean D[3,2]:** 18.811 um	**Vol. Weighted Mean D[4,3]:** 73.419 um	

d(0.1): 14.260 um **d(0.5):** 39.737 um **d(0.9):** 120.136 um



Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %	Size (µm)	Volume In %
0.010	0.00	0.105	0.00	1.096	0.16	11.482	1.61	120.226	1.38	1258.925	0.00
0.011	0.00	0.120	0.00	1.259	0.14	13.183	2.28	138.038	0.82	1445.440	0.00
0.013	0.00	0.138	0.00	1.445	0.13	15.136	3.09	158.489	0.47	1659.587	0.00
0.015	0.00	0.158	0.00	1.660	0.14	17.378	4.02	181.970	0.31	1905.461	0.00
0.017	0.00	0.182	0.00	1.905	0.16	19.953	4.97	208.930	0.32	2187.762	0.00
0.020	0.00	0.209	0.00	2.188	0.19	22.909	5.87	239.883	0.45	2511.886	0.00
0.023	0.00	0.240	0.00	2.512	0.23	26.303	6.61	275.423	0.64	2884.032	0.00
0.026	0.00	0.275	0.00	2.884	0.27	30.200	7.12	316.228	0.84	3311.311	0.00
0.030	0.00	0.316	0.00	3.311	0.31	34.674	7.35	363.078	0.98	3801.894	0.00
0.035	0.00	0.363	0.00	3.802	0.35	39.811	7.29	416.869	1.04	4365.158	0.00
0.040	0.00	0.417	0.00	4.365	0.37	45.709	6.95	478.630	0.99	5011.872	0.00
0.046	0.00	0.479	0.00	5.012	0.39	52.481	6.38	549.541	0.55	5754.399	0.00
0.052	0.00	0.550	0.08	5.754	0.41	60.256	5.63	631.000	0.87	6606.934	0.00
0.060	0.00	0.631	0.14	6.607	0.47	69.183	4.77	724.436	0.27	7585.776	0.00
0.069	0.00	0.724	0.19	7.586	0.58	79.433	3.53	831.764	0.06	8709.636	0.00
0.079	0.00	0.832	0.20	8.710	0.78	90.000	3.28	954.993	0.00	10000.000	0.00
0.091	0.00	0.955	0.20	10.000	1.12	104.713	2.10	1096.478	0.00		
0.105	0.00	1.096	0.19	11.482		120.226		1258.925	0.00		

Operator notes: *1500rpm*
Water + 0.05%w/w Tween 80
sonicated 30s @25%power

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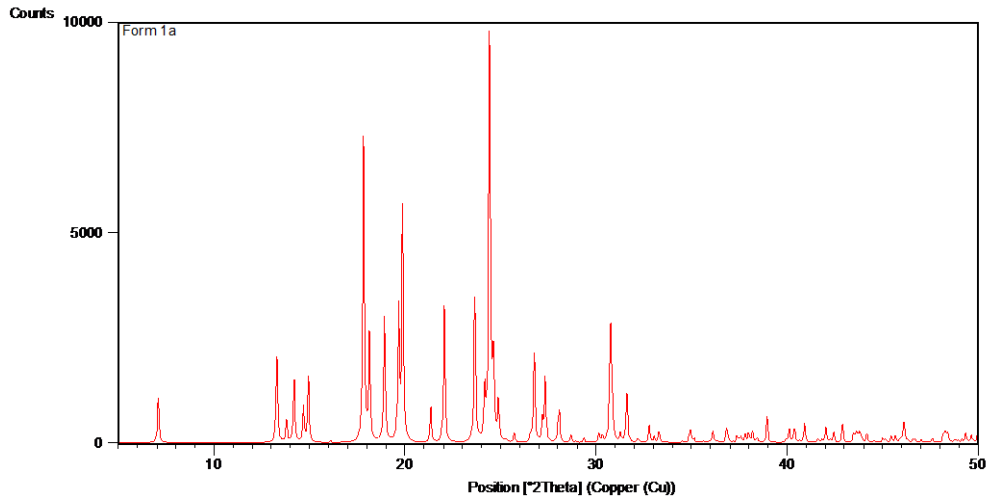
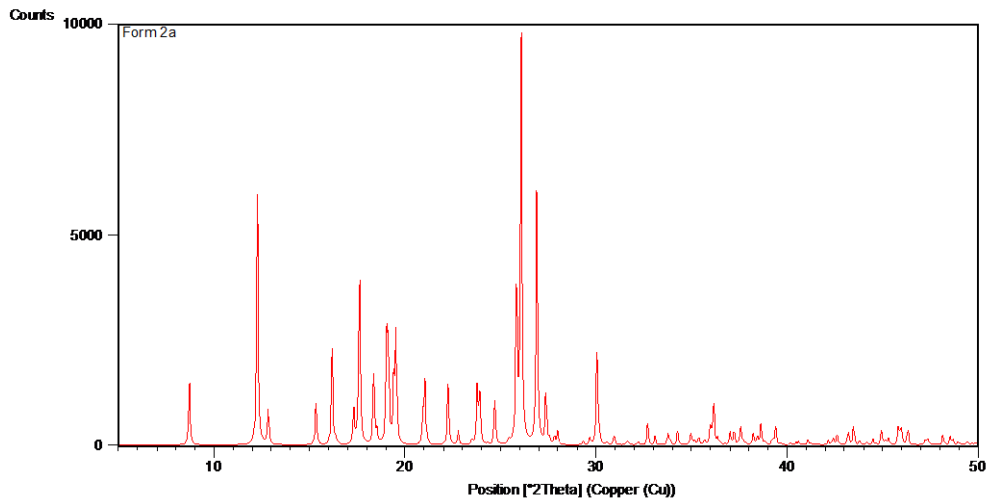
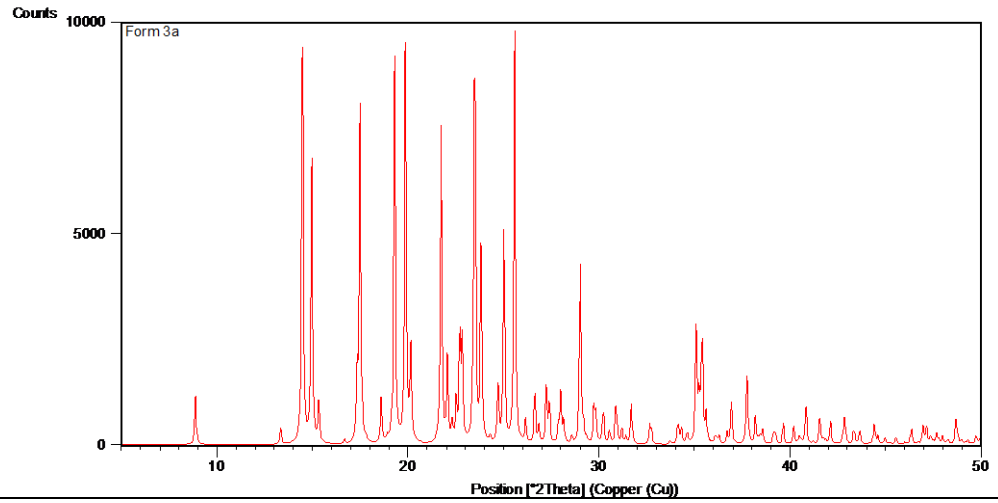
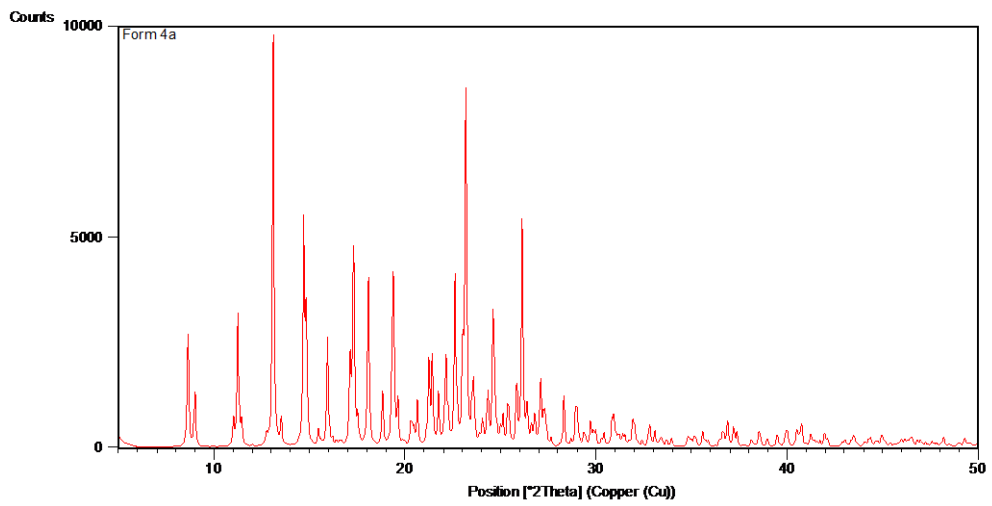
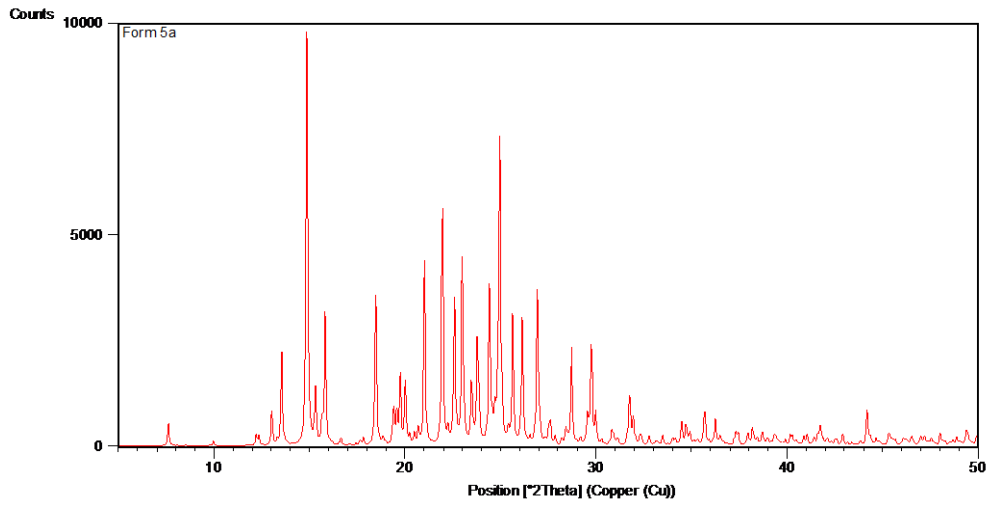
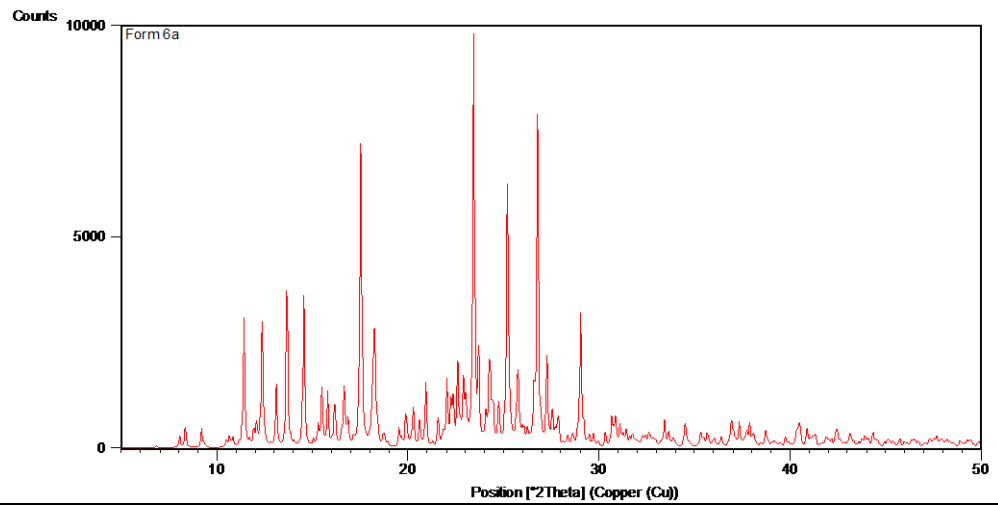
Mastersizer 2000 Ver. 5.40
Serial Number : MAL102037

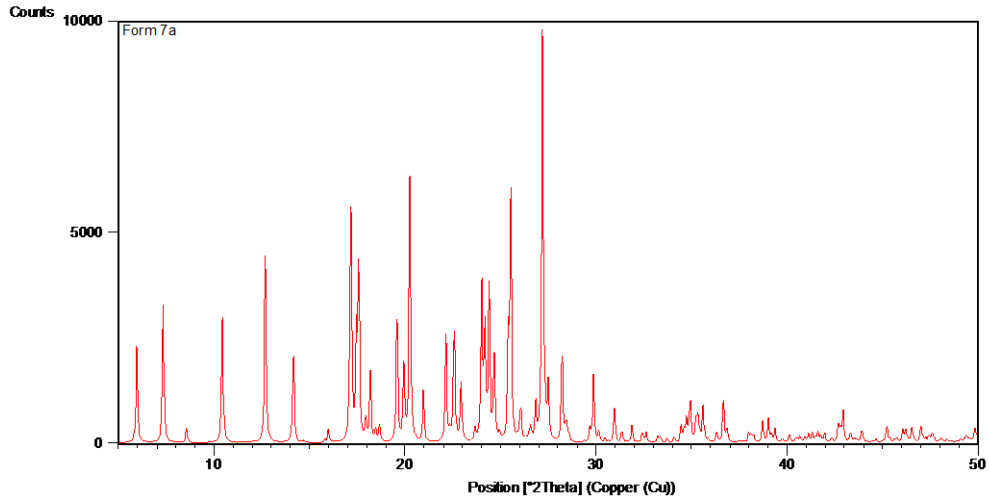
File name: PhD_Ibuprofen_R12639_014 Ibuprofen
Record Number: 20
10 Sep 2012 17:29:03

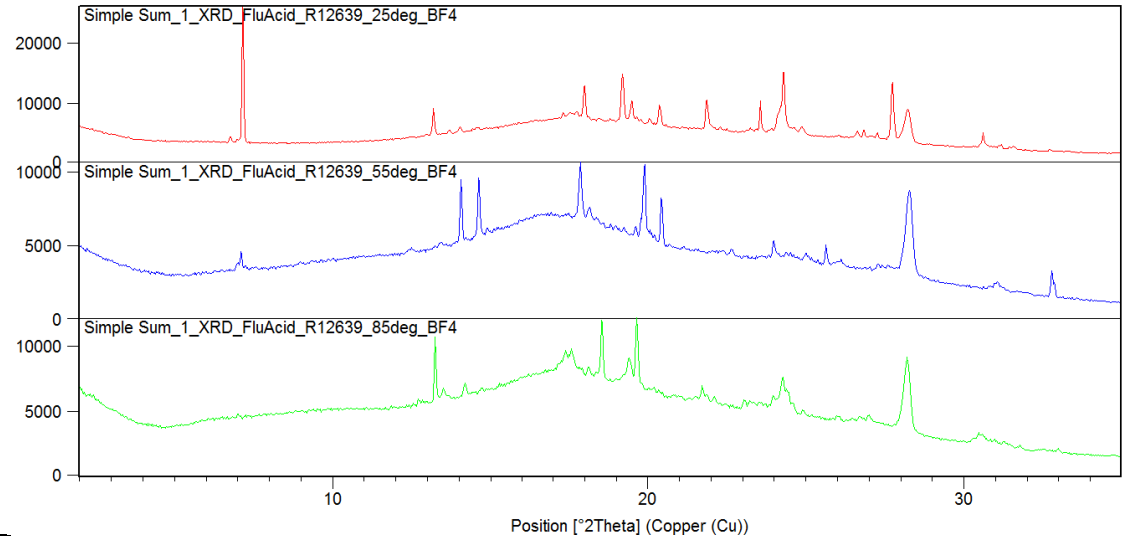
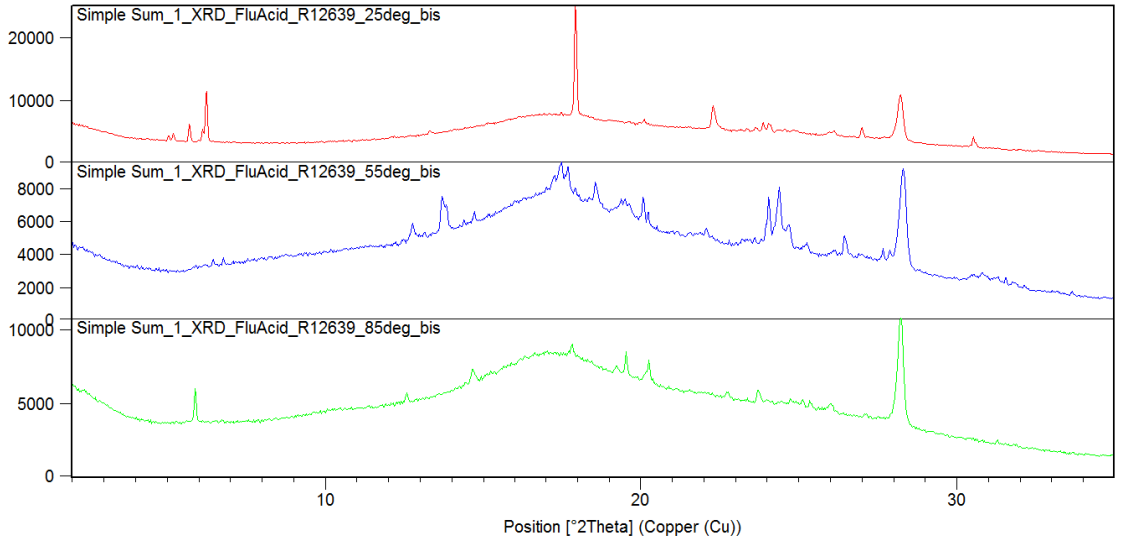
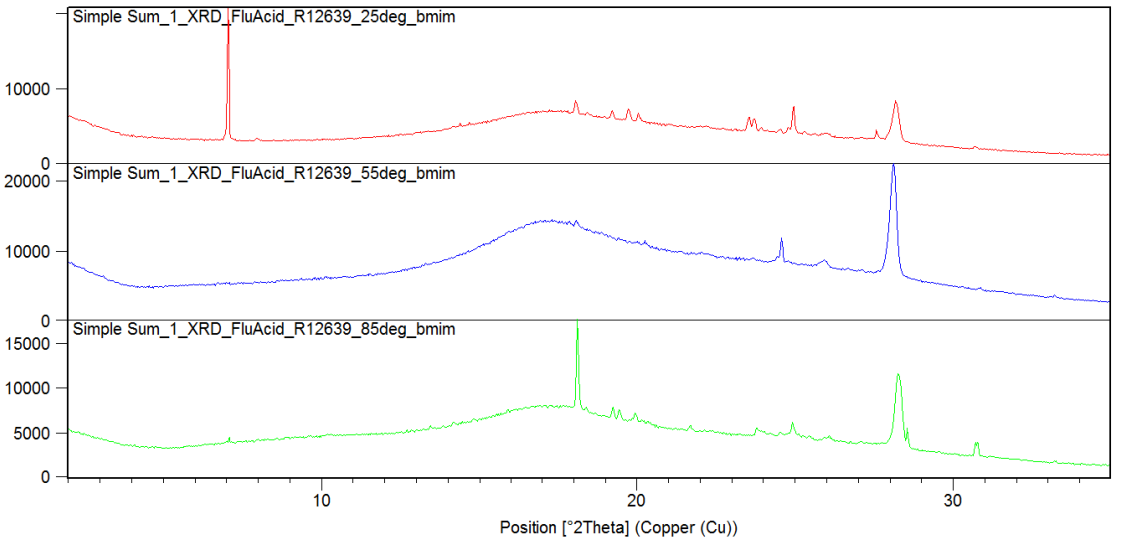
Appendix 7: X-Ray Diffraction Patterns for Flufenamic Acid

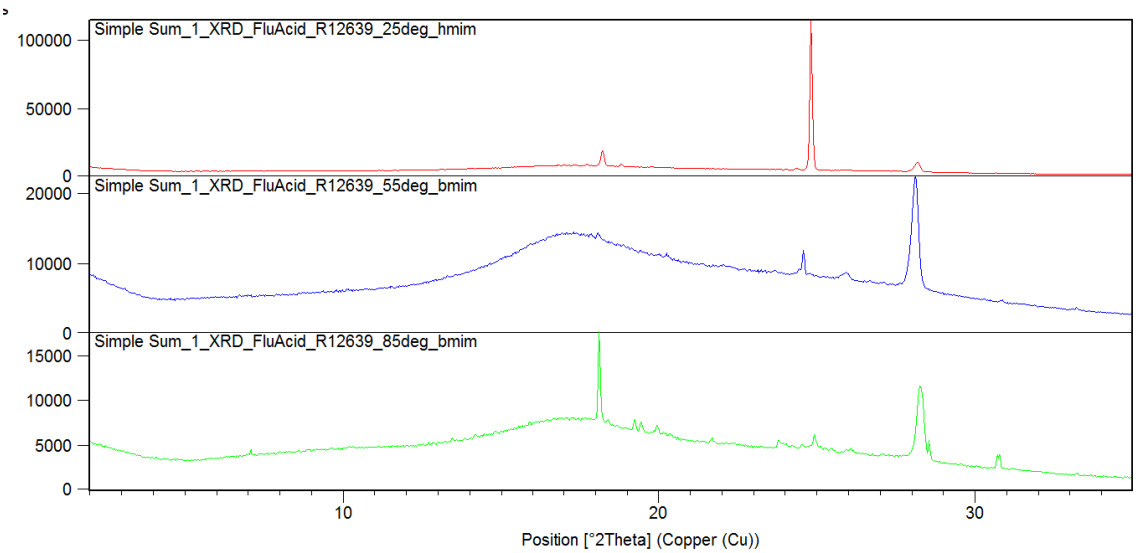
Reference XRD Patterns

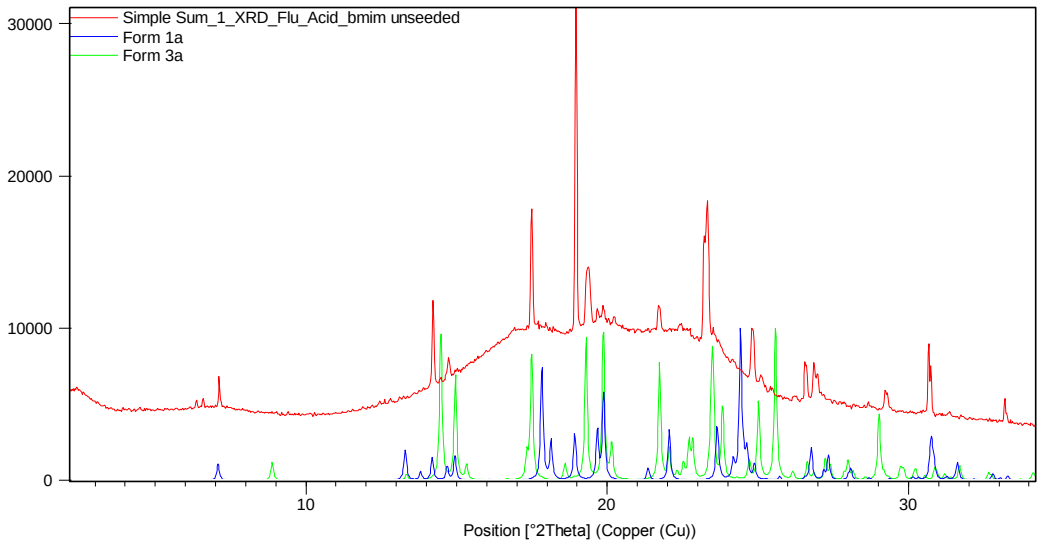
Form	XRD Trace
I	
II	
III	

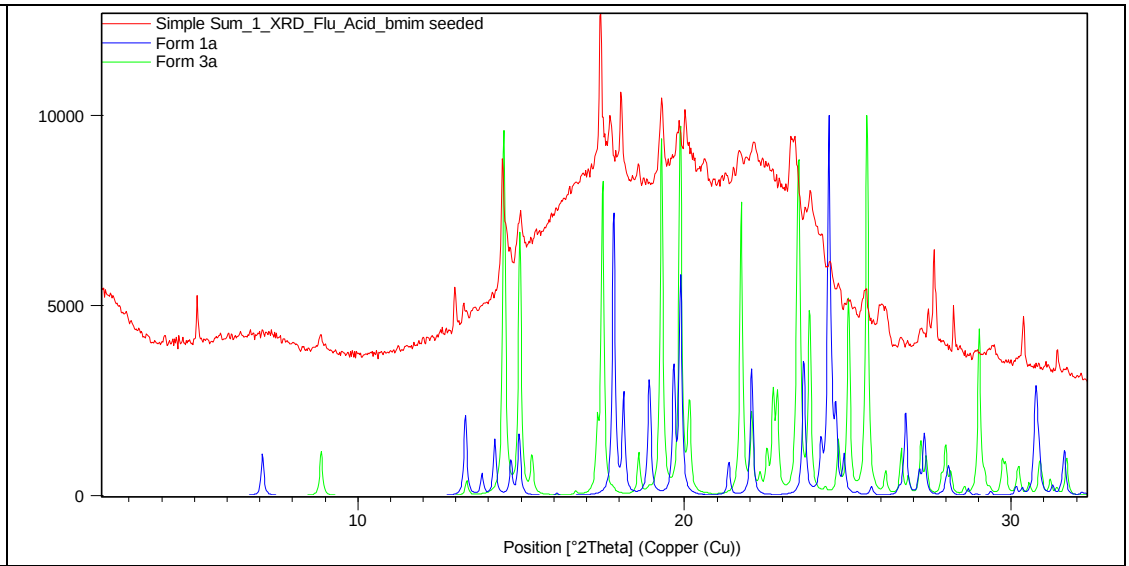
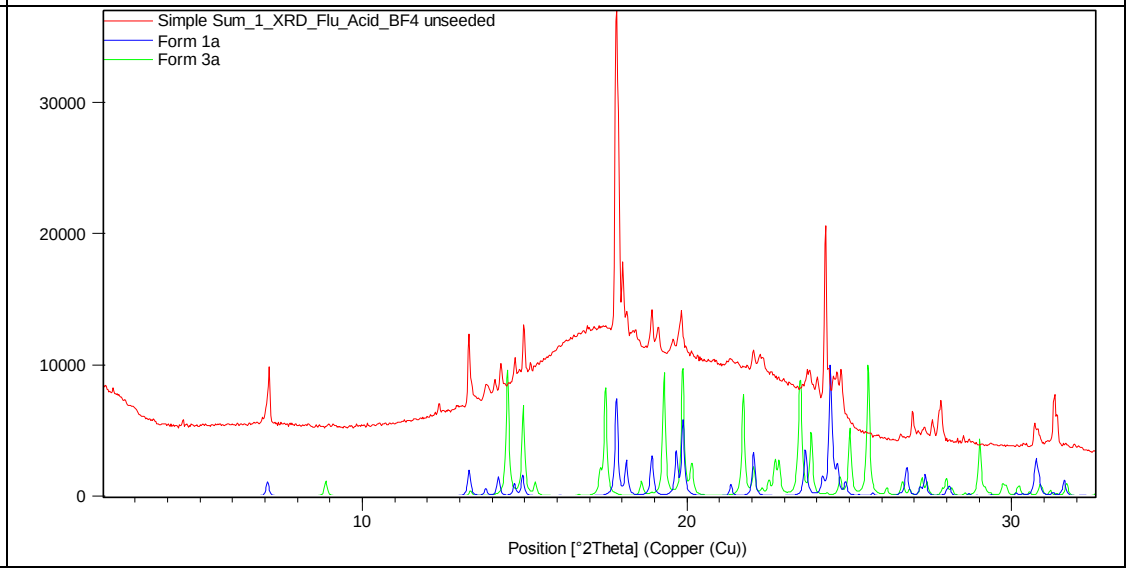
IV	 Counts 10000 5000 0 Form 4a 10 20 30 40 50 Position [°2Theta] (Copper (Cu))
V	 Counts 10000 5000 0 Form 5a 10 20 30 40 50 Position [°2Theta] (Copper (Cu))
VI	 Counts 10000 5000 0 Form 6a 10 20 30 40 50 Position [°2Theta] (Copper (Cu))

VII	 Counts 10000 5000 0 Form 7a 10 20 30 40 50 Position [°2Theta] (Copper (Cu))

Slurry Sample	XRD Trace
[bmim][BF_4]	
[bmim][NTf_2]	
[bmim][PF_6]	

[hmim][PF_6]	

Slurry Sample	XRD Trace
[bmim][PF_6] (non-seeded)	

[bmim][PF_6] (seeded with form III)	
[bmim][BF_4] (non-seed)	
[bmim][BF_4] (seeded with form I)