FUNCTIONAL IONIC LIQUIDS FOR USE IN CRYSTAL ENGINEERING AND DRUG DELIVERY

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Abstract

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Functional ionic liquids in crystal engineering and drug delivery

Key words: Phosphonium ionic liquids, imidazolium ionic liquids, synthesis, pharmaceutical drugs, crystallisation, solubility, pharmaceuticals, API-ILs synthesis and drug release.

The objective of this research is to explore the use of ionic liquds in crystal engineering and drug delivery. Ionic liquids have a wide range of applications in pharmaceutical field due to their unique physicochemical propertie ssuch as chemical, thermal stability, low melting point, nonvolatility, nonflamability, low toxicity and recyclability which offer unique and interesting potential for pharmaceuitcal applications. Currently, many research groups are working on the development of ionic liquids to use in this field but there is need to develop systematic understanding about new techniques for synthesis and applications of ionic liquids to obtain new crystal form and potential of drug ionic salts.

The synthesis of fifteen phosphonium ionic liquids under microwave irradiation and their physicochemical properties was investigated. The reaction time was significantly reduced compared to conventional methods, and higher yields were reported. The crystallisation of pharmaceutical drugs such as sulfathiazole, chlorpropamide, phenobarbital and nifedipine were investigated using imidazolium ionic liquids. The supramolecular complex of sulfathiazole and phenobarbital with imidazolium ionic liquids and polymorphic change in

chlorpropamide was achieved. The ionic liquids provides unique environment for the crystallisation.

The imidazolium salts of ibuprofen and diclofenac were synthesised and evaluated for physicochemical properties and their pharmaceutical performances especially transdermal absorption. The investigation of physicochemcal properties and pharmaceutical performance of imidazolium drug salts indicated opportunity to optimise lipophilicity and other physicochemical properties such as molecular size, osmolality, viscosity to achieve desired skin deposition and permeation.

This study will provide a new approach to design of new drug salts develop using the interdisciplinary knowledge of chemical synthesis and drug delivery.

Dedicated To

Dr Babasaheb Ambedkar

Preface

This research work has carried out at the Centre of Pharmaceutical Engineering Science at the University of Bradford, Bradford, UK between April 2012 to March 2016 under the supervision of Professor Anant Paradkar, Professor Nazira Karodia and Dr Venu Vangala. The contents are original and reference has made to other work mentioned in this dissertation.

Presentation of research work in conferences

A part of the results from this dissertation were presented at the following conferences.

A. Oral Presentation

1. Understanding of the Antisolvent crystallisation using ionic liquids as solvent and water as antisolvent for polymorphic design of active pharmaceutical ingredient. UK Pharm Sci. 2012.

B. Poster presentation

2. Presented poster entitled “Crystallisation of pharmaceutical drugs using ionic liquids” in APS PharmSci 2012, held in University of Hertfordshire, Hatfield, UK (8^{th} - 10^{th} September, 2014).

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I would like to first say a very big thank you to my supervisor Professor Anant Paradkar for all the support and encouragement he gave me. His cordial cooperation, enthusiasm and keen interest helped me throughout research work. Without his guidance and constant feedback this PhD would not have been achievable.

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I gratefully acknowledge the funding received towards my PhD from the Social Justice Department, Government of Maharashtra, India. I am also grateful to the Royal Society of Chemistry for Conference Bursaries to attend the conferences.

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This work is possible because of immense support from my family members. I would like to say a heartfelt thank you to my Aai, Papa, and Sandip for always believing in me and encouraging me to follow my dreams. I cannot thank enough to my Uncle, Aunty, Gaurav and Sneha for having faith and helping me in whatever way they could during this challenging period. I am thankful for their blessings, constant encouragement and unconditional love.

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ABBREVIATIONS

RTIL	Room temperature ionic liquids
$[BF_4]$	Tetrafluoroborate
$[PF_6]$	Hexafluorophosphate
$[Br]^-$	Bromine ion
[BMIM]	1-Butyl-3-methylimidazolium
[HMIM]	1-hexyl-3-methyl imidazolium
[OMIM]	1-octyl-3-methyl imidazolium
[DMIM]	1-decyl-3-methylimidazolium
$[NTf_2]$	Bis(trifluromethylsulfonyl)imde
[DCA]	Dicyanamide
$[TfO]^-$	trifluoroacetate
API	Active pharmaceutical ingredient
FDA	Food and drug administration
ACV	acyclovir
NSAID	Non steroid anti-inflammatory drug
NMR	Nuclear magnetic resonance spectroscopy
TGA	Thermogravimetric analyser
IR	Infrared spectroscopy
DSC	Differential scanning calorimetry
PXRD	Powder X-ray diffractometer
SC-XRD	Single crystal X-ray diffractometer
HPLC	High performance liquid chromatography
FPD	Freezing point depression

SFT	Sulfathiazole
CPA	Chlorpropamide
PBB	Phenobarbital
NIF	Nifedipine
IBU	Ibuprofen
DIF	Diclofenac
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	multiplet
m.p.	Melting point
CAS	Chemical abstracts service registration number

Chapter 1. Introduction

Pharmaceutical industries are mainly dependents on pharmaceutical drugs and which get approved by the Food and Drug Administration (FDA). FDA approved drug on the basis of their biopharmaceutical performance such as solubility, chemical and physical stability. However, these properties can be variable because drugs can have different polymorphic forms which can also have significant impact on the manufacturing of drug products, storage and transport of the final product. So the commercial volumes of manufactured drug products can also depend on the final crystallisation product.

The isolation and purification of the final product of the drug is a critical step in industry and it can be carried out by chemical synthetic processes where organic or aqueous based solvents or mixtures can be used for the crystallisation of powders. At the commercial scale, it must be of high purity and the correct polymorphic form. However, it is difficult to ensure this occurs by crystallisation therefore the crystallisation process is conductive for isolation and subsequent downstream processing. This process requires large amounts of volatile organic solvents in which the availability of solvents are very limited and it is very difficult to assign a specific solvent for a specific crystallisation process. Therefore the use of volatile organic solvents can have significant impact on environmental factors and process costs.

The problems of obtaining pure drugs in the correct form, as discussed above, can be solved by the formation of stable liquid drugs from the solid crystalline form. Unfortunately, limited research is available on liquid drugs. Liquefaction of a drug could be achieved by the solubilisation of solid drugs by using various

drug delivery routes such as emulsions, suspensions, and liposomes. Thus, a new form of liquid drugs could reduce the problems associated with the solid-state.

In recent years, ionic liquids have been emerging as novel media in pharmaceuticals applications. Specifically in crystallisation and liquid drug conversion, ionic liquids could play a vital role due to their solvents properties such as such wide liquid range from -100 to 300 °C, good solvation power, almost zero vapour pressure, thermally stability up to 200 °C, recyclable, tuneability of cations and anions and easy preparation. In addition, the multifunctionality of ionic liquids can provide a unique opportunity to design a specific process which could potentially reduce the process cost and significant impact on environmental factors.

The present work focused on microwave assisted synthesis, crystallisation of pharmaceutical drugs using ionic liquids and drug-ionic liquid combination and investigates its pharmaceutical performances. A review of the literature showed that ionic liquids are used in many applications such areas as catalysis, electrochemistry, lubrication and solvents for synthetic chemistry but there are a limited number of publications on crystal engineering and drug delivery. Thus ionic liquids have enormous potential to be explored in these fields due to their unique properties. Hence the focus of this research was the investigation of some functional ionic liquids for use in crystal engineering and drug delivery.

1.1 Research objectives

The thesis begins with a review of the literature and the current stage of ionic liquids in crystal engineering and drug delivery, which is largely unexplored. The gaps in the research knowledge are examined and the background to ionic liquids is presented.

Specific objectives of this research were:

A. Solvent free synthesis of phosphonium ionic liquids

- To investigate a comparison study of conventional and microwave-assisted synthesis of a series of phosphonium ionic liquids;
- To investigate the thermophysical properties of the synthesised phosphonium ionic liquids.

B. Use of functional imidazolium ionic liquids in crystal engineering

- To investigate ionic liquids as crystallisation media: whether the ionic liquid can modify the molecular functionality and physical form of four selected pharmaceutical drugs;
- To address the solubility of selected drugs in ionic liquids at different temperature;
- To investigate what may be practically possible with this novel media and whether ionic liquids can be used in solubilisation and to change the physical form of drug.

C. Use of drug ionic liquids combination for pharmaceutical performances.

- To synthesise drug ionic liquid and evaluate their thermophysical properties;

- To study the diffusion, skin deposition and skin permeation study.

1.2 Thesis outline

Chapter 2 explains the background to the work and the literature review is divided into:

- Definition of ionic liquids, the different types and recent publications
- Brief history of ionic liquids; how ionic liquids were synthesised and the growth in application to date.
- The properties of ionic liquids are discussed, including; melting point, liquid range and thermal stability, viscosity and density, flammability, solubility and miscibility, polarity and solvation, conductivity and electrochemical window.
- Toxicity of ionic liquids: examples of environmental exposure.
- Synthesis and purification of ionic liquids: conventional, microwave and ultrasound methods.
- Introduction to crystallisation and its procedure
- Applications of ionic liquids; ionic liquids as solvents, crystallisation using ionic liquids, ionic liquids in drug delivery, active pharmaceutical ingredients based on ionic liquids,

Chapter 3 provides details of the materials and methods used in the current work. In Chapter 4, the first section gives an introduction to solvent free synthesis of ionic liquids and the next section is a discussion on phosphonium ionic liquids. In chapter 5, first section introduces the crystallisation of

pharmaceutical drugs from ionic liquids and in next section covers the result and discussion of the solubility crystallisation study.

In chapter 6, the first section provides an introduction on drug-ionic liquid salts and their synthesis in a detailed study. The next section explains the results and discusses the synthesised drug salt systems. Chapter 7 provides a global conclusion of the overall work presented in the thesis. Chapter 8 provides the conclusion and future work which is followed by a list of references cited for the current work and appendix sections.

Chapter 2. Background

In this section, a brief overview of ionic liquids is provided. It begins with the definition and is followed by history, properties, synthesis and purification methods and application of ionic liquids in different fields. However, in this work, pharmaceutical applications were discussed in brief and special attention has been given to applications such as solvents, crystallisation using ionic liquids, ionic liquids in drug delivery, active pharmaceutical ingredients based on ionic liquids.

2.1 Ionic liquids

Ionic liquids are organic salts which are composed entirely of ions rather than molecules. In general ionic liquids, also known as room temperature ionic liquids (RTIL), are defined as salts whose melting points or glass-transition temperatures are below 100 °C (Earle and Seddon, 2002, Welton, 2011). However, in traditional salts positively charged cations and negatively charged anions are held together by strong attracting forces which results in salts with very high melting points and this is not useful for many applications. For example, common table salt has a melting point of 800 °C which makes it unsuitable as an ionic liquid see Figure 2.1. In the 19th century, researchers discovered new salts which are liquid at room temperature and below. Generally they are thermally stable, have almost zero vapour pressure, are non-flammable, and can act as solvents. These are some of the attractive properties of these salts which make them useful as of ionic liquids.

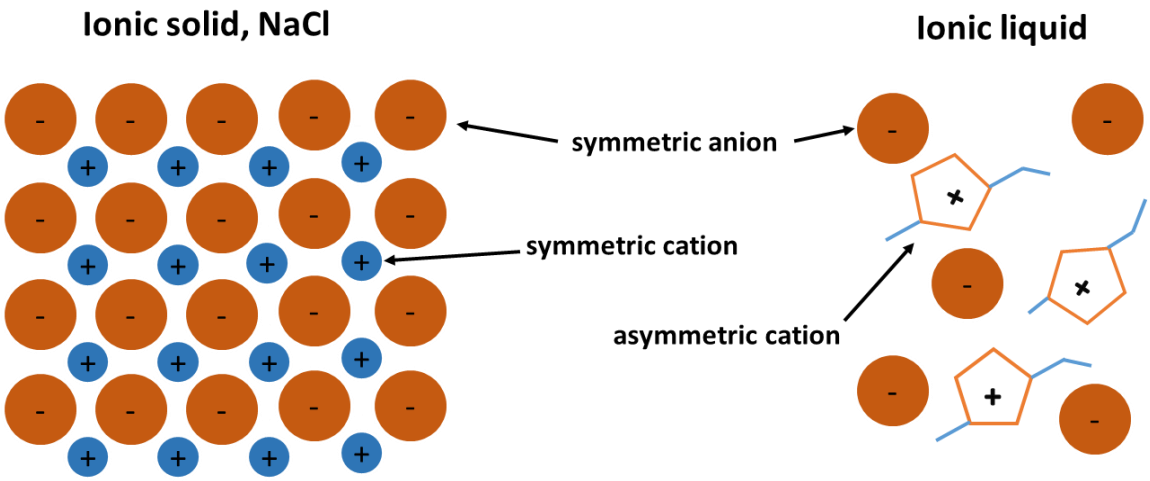


Figure 2.1 Crystal structure of ionic solids and ionic liquids

Ionic liquids are a mixture of organic salts or eutectic mixtures of an organic cation such as imidazolium, ammonium, pyridinium, pyrrolidinium and phosphonium and these are coupled with different types of inorganic or organic anions such as halides, nitrate, alkyl sulfates, tetrafluoroborate (BF_4) and hexafluorophosphate (PF_6), see Figure 2.2 and Figure 2.3. Ionic liquids have low melting points due to the large unsymmetrical cations which are responsible for their low lattice energies (Smith et al., 2011).

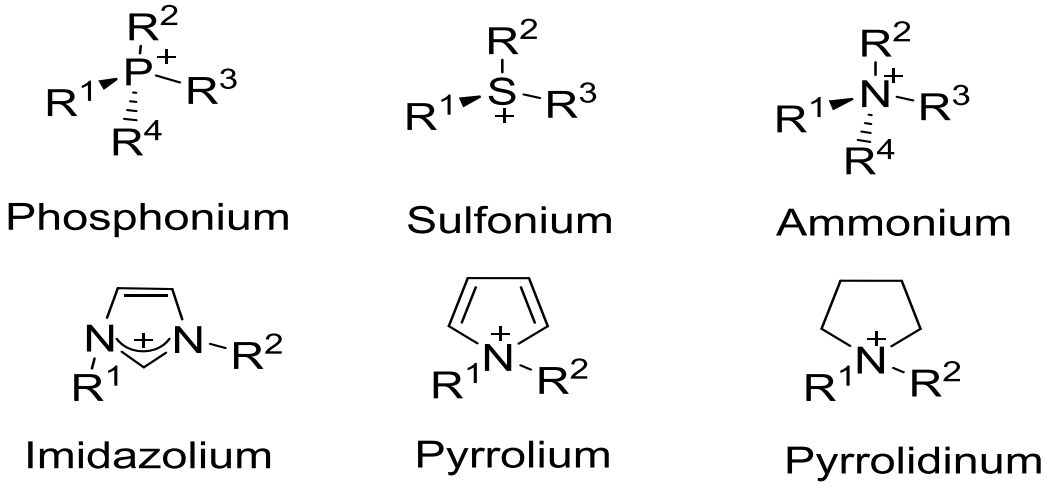


Figure 2.2. Examples of common cations in ionic liquids

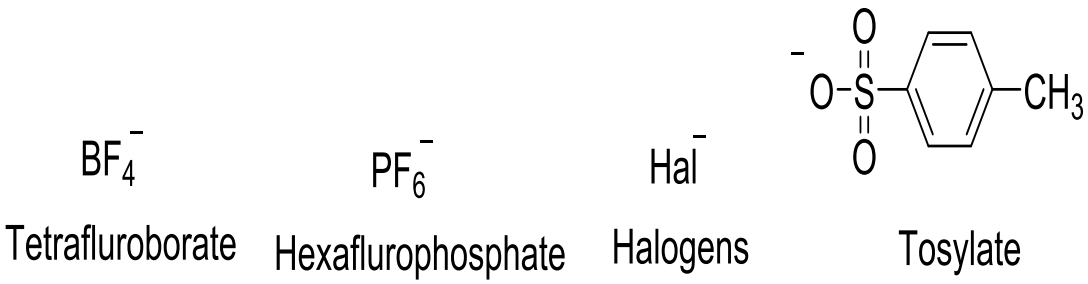


Figure 2.3 Examples of common anions in ionic liquids

In the late 19th century, ionic liquids had various synonyms such as low, room temperature and ambient molten salt, liquid organic salt and fused organic salt. During the 1980's and 1990's, there was limited research on the applications of ionic liquids. However, over the past decade, there has been an extraordinary advance in research on their applications such as electrochemistry (Lang et al., 2005, Bansal et al., 2005, Loupy, 2006), lubrications (Ye et al., 2001, Jiménez et al., 2006, Zhou et al., 2009), solvents for synthetic chemistry (Earle and Seddon, 2002, Ramnial et al., 2005, Carmichael et al., 1999), active pharmaceutical ingredients, functional materials (Ferraz et al., 2011, Dean et al., 2008, Mizuuchi et al., 2008, Smith et al., 2011) and solvents for the extraction of metal ions (Wei et al., 2003, Visser et al., 2001b). The ionic liquids consist of both cations and anions; however they possess dual functional characteristics. This is a distinctive feature of ionic liquids which separates them from molecular liquids or solvents.

Nowadays ionic liquids are extensively studied in a green chemistry context due to their notable and tuneable physicochemical properties such as high thermal stability (Tokuda et al., 2004, Brennecke and Maginn, 2001, Kosmulski et al., 2004, Austen Angell et al., 2012), high ionic conductivity (Tokuda et al., 2004, Bansal et al., 2005), negligible vapour pressure (Marsh et al., 2002, Rogers et

al., 2002), huge liquid range (Earle and Seddon, 2002, Marsh et al., 2002) and ability to strongly solvate compounds with different polarities (Zhang et al., 2006, Ab Rani et al., 2011). Ionic liquids are now recognized in green chemistry because they can be applied as cleaner and more sustainable solvents in chemistry and have been exploited as environmentally friendly solvents in organic synthesis and in catalytic processes (Earle and Seddon, 2002). Up to the 19th century there were few ionic liquids known. But in the current literature this picture has changed dramatically and to date over 900 ionic liquids are known with an extensive database of physical and chemical (IonicLiquidsTechnologies, 2015). Figure 2.4 shows the number of publications related to ionic liquids published from 1998–2013 with various applications and the number of papers and patents continue to increase.

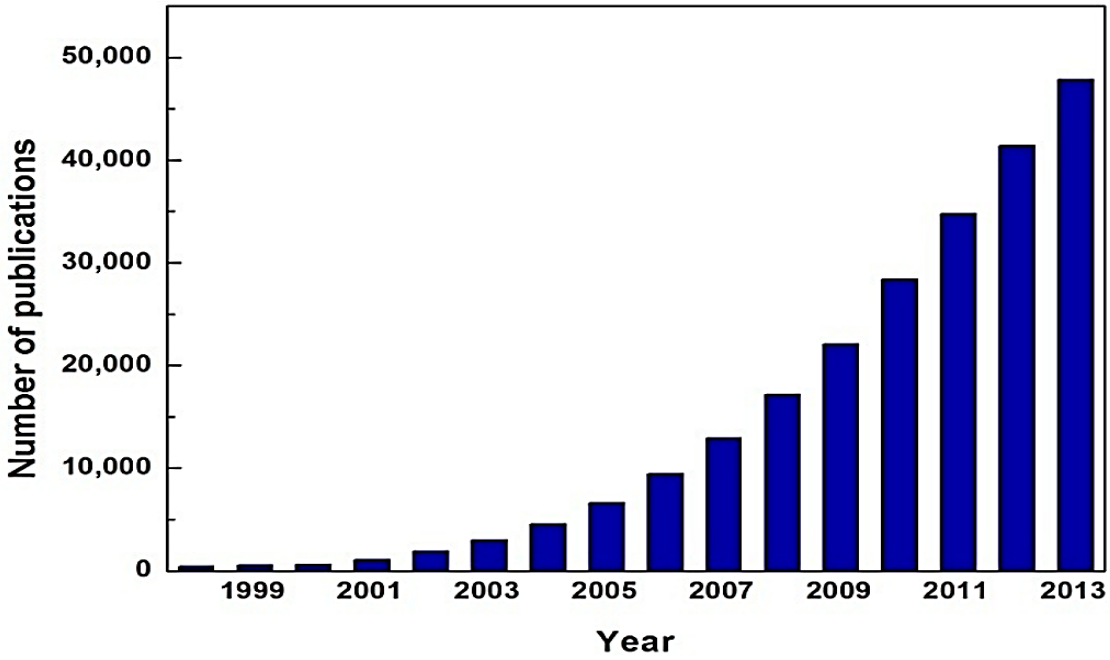


Figure 2.4 Number of publication from 1998 to 2013 (Park et al., 2014)

In traditional chemical processes huge amounts of organic solvents are used, which are incompatible with the aims of sustainable chemistry because they

have a high volatility, flammability and toxicity profile. According to the green chemistry perspective, an ideal solvent should have low volatility, be chemically and physically stable, easy to handle, recyclable and reusable (Wasserscheid and Keim, 2000). According to the green chemistry principles, ionic liquids possess excellent properties which contribute to green chemistry objectives. The main green chemistry goals are (Bradaric et al., 2003):

- Chemical processes that reduce or eradicate the use of and generation of hazardous substances;
- Generate less chemical wastage and pollution;
- Renewable resources are used instead of toxic, flammable volatile organic solvents;
- Improving the standard of human and environmental health;
- Solution for various environmental problems.

Most research on ionic liquids has focused on imidazolium ionic liquids which are particularly based on the 1-alkyl-3-methylimidazolim cations. There are fewer studies on phosphonium, pyridinium, pyrrolidinium, and sulfonium ionic liquids. Phosphonium ionic liquids are less common but a recent study showed that they possess advantageous properties (Fraser and MacFarlane, 2009).

2.1.1 History

The history of ionic liquids can be traced back to the second half of the 19th century when a chemist reported “red oil” during Friedel-Craft reactions. In the following century a Japanese scientist proved that the red oil was a mixture of

an alkylated aromatic ring cation and a chloroaluminate anion. This oil was considered an ionic liquid (Welton, 2011, Freemantle, 2009).

Ethanoaluminate nitrate, which has a melting point 12 °C, was first synthesized in 1914 by Paul Walden and this is one of the earliest known room temperature ionic liquids (Welton, 1999b). Interest in room temperature ionic liquids as a research field continued growing after the end of the nineteenth century. In 1895, Trowbridge and co-workers worked on the synthesis of molten salts which have melting points below 100 °C, for example, pyridine hydrochloride which he reported melts at 82 °C. But over the decades it was proved that pyridinium hydrochloride has a higher melting point (144 °C), making it a low melting salt instead of molten fused salt. However pyridinium hydrochloride has been used as a solvent (Prescott and Trowbridge, 1895). Initially in the 1970s and 1980s ionic liquids, which were based on alkyl substituted imidazolium and pyridinium cations, with halide anions, were used as electrolytes in battery applications (Ye et al., 2001). There has been enormous increase in research publications on ionic liquids as electrolytes over the past two decades.

This section has reviewed the definition, examples, green aspect and history of ionic liquids. The next section described the properties of ionic liquids with examples in detail.

2.1.2 Properties

Ionic liquids have significant and interesting physicochemical properties. Research on their physical, biological and chemical properties are very limited when compared with traditional organic solvents. Recently this field has been of great interest due to the fact that the physical, chemical and biological

properties of ionic liquids can be altered with specific requirements for various applications. This tunability of their physicochemical properties opens a new challenge in this research area. For example, the water solubility of ionic liquids depends upon the alkyl chain length. As the alkyl chain length of the cation increases then this decreases the water solubility by enhancing the hydrophobicity of the cation (Brennecke and Maginn, 2001). Quaternary ammonium salts have been available commercially for a long time and some are best known for their application as phase transfer catalysts.

Table 2.1 Comparison of organic solvents with ionic liquids

Property	Organic solvent	Ionic liquids
Vapour pressure	Very high	Negligible VP under normal condition
Flammability	Usually flammable	Usually non-flammable
Tuneability	Limited range of solvent available	Virtually unlimited range "designer solvent"
Viscosity (cP)	0.2 – 100	22 – 40,000
Density, g/cm3	0.6 - 1.7	0.8 – 3.3
No of solvents	> 1000	> 1,000,000
Applicability	Single function	Multifunction

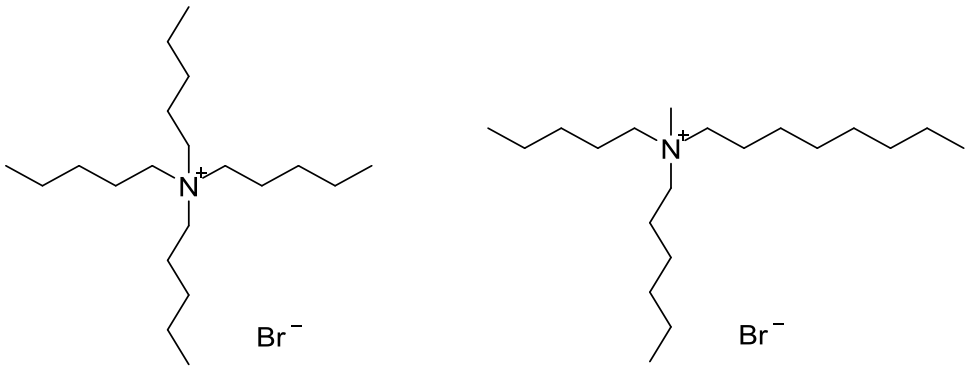
The most useful property of ionic liquids is the independent 'tunability' of the cations and anions, and this is the key feature of ionic liquids which gives them a wide range of properties (Table 2.1). For example, miscibility and immiscibility with water, acidic, basic and neutral nature of ionic liquids and toxicity and nontoxicity (Vineet and Sanjay, 2010). Over 1000 known ionic liquids have been synthesized but most of the ionic liquids with the data for their physicochemical

is not available or is incomplete. Ionic liquids are therefore also called “designer solvents”.

2.1.2.1 Melting points

The melting point of room-temperature ionic liquids depends upon the size or nature of the cation or anion. As the size of the cation or anion increases, the melting point of the ionic liquid tends to decrease. A slight change in alkyl chain length in a cation can also make a large difference in the melting point (Trohalaki and Pachter, 2005, Tokuda et al., 2004). Symmetry also plays an important role in determining the melting point. Some ionic liquids have low melting points due to their large unsymmetrical cations which results in low lattice energy (Brennecke and Maginn, 2001). For example, the ammonium bromide $[N_{5,5,5,5}]^+$ $[Br]^-$, which has four straight-chain pentyl groups, has a melting point of 101.3 °C while $[N_{1,5,6,8}]^+$ $[Br]^-$, which has four different alkyl groups (methyl and straight chain pentyl, hexyl and octyl groups), is liquid at room temperature (Figure 2.5).

The melting points of imidazolium, ammonium, and phosphonium salts can be influenced by introducing asymmetry on the cations. In imidazolium ionic liquids lower melting points are achieved by adding a larger alkyl group on one nitrogen, while keeping a smaller alkyl group (usually methyl) on the other nitrogen (Freemantle, 2009). This trend is also observed in the phosphonium analogues.

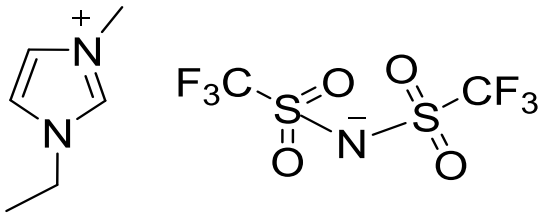


m.p. 101.3 °C **liquid at RT**

Figure 2.5 Influence of substitutent on melting point

2.1.2.2 Liquid range and thermal stability

Thermal stability of ionic liquids plays an important role in high temperature applications and there are extensive studies on this (Kosmulski et al., 2004, Cao and Mu, 2014, Bonhôte et al., 1996). Ionic liquids have much wider liquid ranges in comparison to molecular organic solvents. Liquidus range means the temperature range between melting point and boiling point temperatures. For example 1-ethy-l,3-methylimidazolium bis(trifloromethylsulfonyl)imide has a liquidus range of 471 °C, melting point at -15 °C and its thermal decomposition temperature is a 455 °C see (Figure 2.6) (Murugesan and Linhardt, 2005). This is important for industrial applications for processes which operate at high temperatures, e.g. over 100 °C (Fraser and MacFarlane, 2009). In addition, ionic liquids provide a wide liquid range of higher and lower temperatures for a process in a single solvent (Reichert et al., 2006). The phosphonium ionic liquids are generally more thermally stable than ammonium ionic liquids and thermogravimetric analysis studies have reported that most of these ionic liquids are thermally stable up to 300 °C.



liquid range up to 471°C

Figure 2.6 Examples of thermally stable ionic liquids

In 2013, Maton *et al*., reviewed thermal stability data of ionic liquids. In this paper, the thermal stability of imidazolium ionic liquids with the same cation, e.g. *n*-butyl-3-methylimidazolium with different anions such as Cl, I, DBS (*para*-dodecylbenzenesulfonate), BF_4, and trifluoromethanesulfonate were examined. They evaluated the maximum operating temperature, the speed of decomposition and the decomposition product (Maton et al., 2013) of this series of ionic liquids (Figure 2.7).

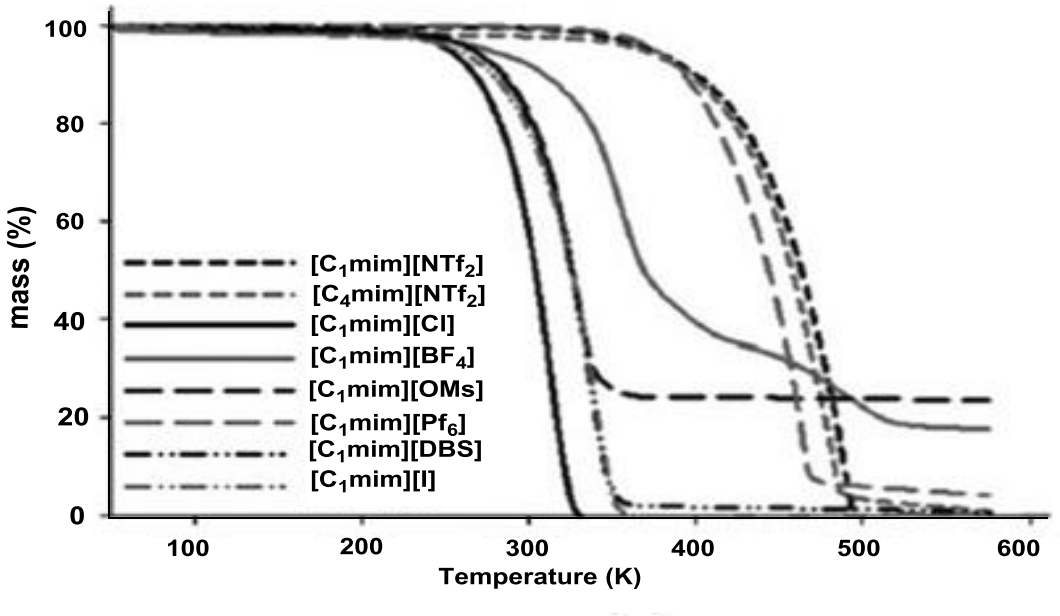


Figure 2.7 Ramped temperature TGA (20 °C min^{-1}) of imidazolium salts with different anions (Maton et al., 2013).

2.1.2.3 Flammability

Generally, ionic liquids are non-flammable and can be used in high temperature reactions and they are safe to use near flames or heat sources. For liquid flammability, this is well-defined and volatile liquids have their flash point below 37.8 °C while the ionic liquids have a flash point above this (Smiglak et al., 2006). The flammable properties of ionic liquids are as good as aliphatic hydrocarbon plastics, e.g. polyethylene and polyamide, and lesser than high boiling organic solvents such as the common solvent ethyl lactate and dimethyl sulfoxide (Fox et al., 2008). In 2003, Fox *et al*., reported on the flammability of 1, 2-dimethyl-3-propylimidazolium hexafluorophosphate and 1-butyl-2,3-dimethyl-3-propylimidazolium chloride ionic liquids. They observed that trialkylimidazolium ionic liquids are more thermally stable than the dialkyl imidazolium ionic liquids. In the case of trialkylimidazolium ionic liquids, they were unable to detect the flash point below 200 °C using high temperature flashpoint apparatus (Fox et al., 2003).

2.1.2.4 Vapour Pressure

Vapour pressure is the most interesting property of ionic liquids. They have negligible vapour pressure (Bier and Dietrich, 2010, Earle and Seddon, 2002). In 2011, the first report was published on ionic liquids which were subjected to high-accuracy measurement of volatility. In this study the imidazolium cation of the 1-alkyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide series ([$C_n$mim][Ntf2], where n = 2, 3, 4, 5, 6, 7, 8, 10, 12) were used. In their experiment the vapour pressures in the temperature range of 176.85 °C to 226.85 °C range were measured, and finally molar standard enthalpies,

entropies, and Gibbs energies of vaporisation were derived (Rocha et al., 2011) (Figure 2.8). This property contributes to green chemistry with respect to the reduction in air pollution and the elimination of hazardous volatile substances. The lack of vapour pressure at thermal decomposition temperatures is due to the strong coulombic interactions between the ions in the liquid (Fumino et al., 2008). Generally organic solvents used in a chemical process are toxic, have poor solubility of reactants, are not thermally stable and they contaminate the final products.

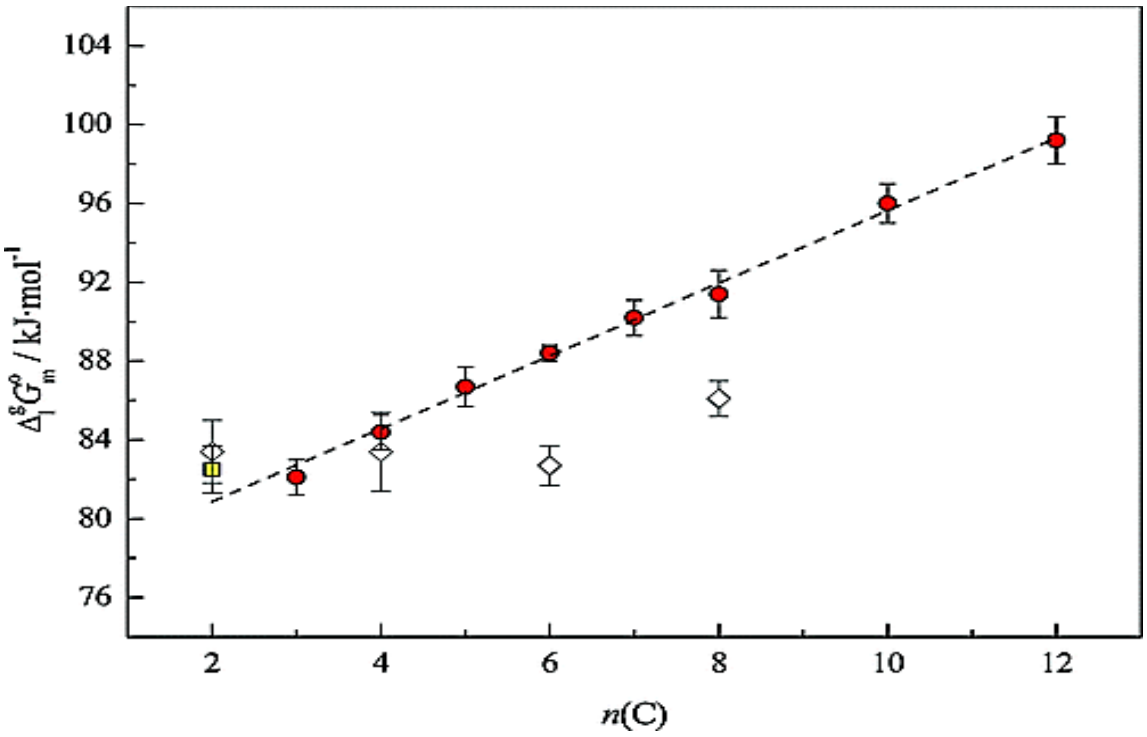
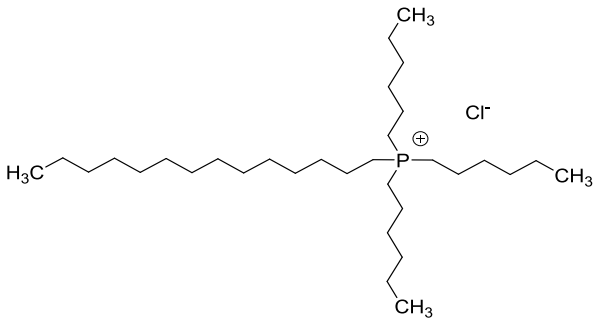


Figure 2.8 Vaporisation temperature of ionic liquids temperature as a function of the number of carbon atoms in the alkyl side chain of the cation (Rocha et al., 2011)

Phosphonium ionic liquids can also be designed with a wide range of properties such as a low volatility, low flammability, and low vapour pressure and strong thermal stability (Figure 2.9).



Viscous nature of $[P_{6\ 6\ 6\ 14}]$+[Cl]- at 40 °C - 70 Pa.S

Figure 2.9 Vapour pressure of phosphonium ionic liquid $[P_{6\ 6\ 6\ 14}]^+$ $[Cl]^-$ (Fraser et al., 2007)

2.1.2.5 Viscosity and density

In general, ionic liquids are more viscous compared to molecular solvents. Viscosity measures a liquid's resistance to flow. The viscosities of ionic liquids are generally correlated to the size of the cation and the viscosity of ionic liquids increase with increase in the size of the cation (alkyl chain length) (Marsh et al., 2002, Abbott, 2004). Ionic liquids with weakly coordinating anions, such as $[BF_4]$ and $[PF_6]$, have lower viscosities and those with strong coordinating anions have higher viscosities. The viscosity of ionic liquids depends upon temperature variants, and decreases with an increase in the temperature (Freemantle, 2010). Higher viscosities are not useful in bulk crystallisation, but can be useful in crystal engineering, where slow crystal growth from diffusing solvents is an advantage (Reichert et al., 2006). The presence of small amounts of impurities can also affect the viscosities of ionic liquids. The centipoise (cP) is the physical unit of viscosity.

Generally, phosphonium ionic liquids are less dense than water and imidazolium ionic liquids are denser than water. The density of ionic liquids decrease with increase in the alkyl chain length on the cations; this is due to the

van der Waals interactions of ions which are reduced with respect to temperature and that tends to lower the efficient packing of ions (Seddon Kenneth et al., 2002).

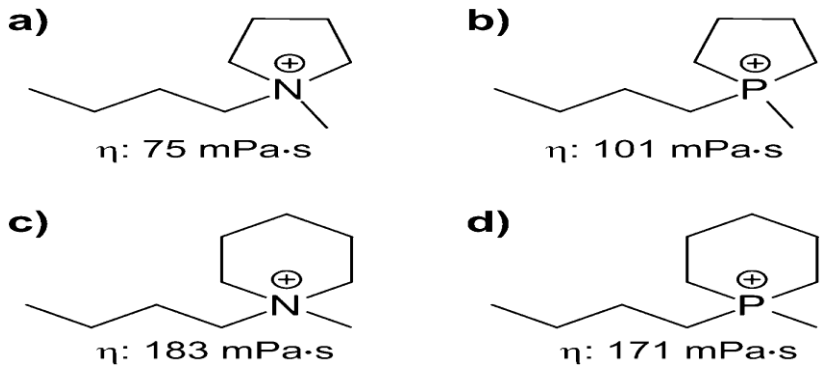


Figure 2.10 Viscosity of some ionic liquids (Scarbath-Evers et al., 2015)

In 2010, Abai and co-workers reported the change in density of *S*-alkylthiouronium salts (Abai et al., 2010). They worked on three *S*-ethylthiouronium ethylsulfate ionic liquids and temperature range 20-90 °C. They observed the linear decrease in density with increasing temperature which illustrate in figure 2.11.

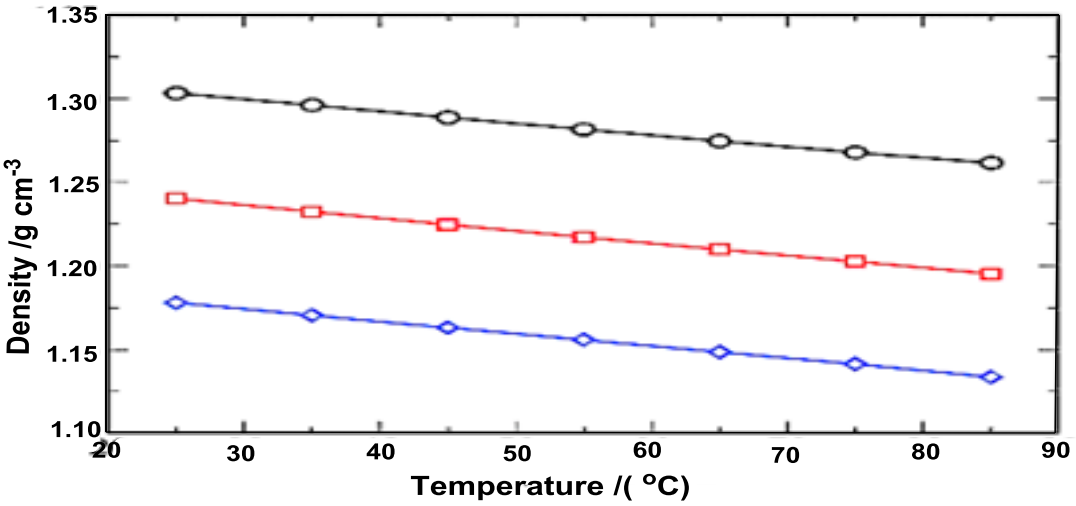


Figure 2.11 Change in density of ionic with temperature (Abai et al., 2010).

2.1.2.6 Solubility and miscibility

Solubility and miscibility are interesting properties of ionic liquids and they possess a wide variation in their solubility and miscibility properties. This also depends on the nature of the cations and anions. Different types of conditions, such as polarity or coordination ability of its ions, also have an effect on the solubility of ionic liquids (Cammarata et al., 2001). Both ionic and covalent compounds can dissolve in ionic liquids and this property plays a very important role in their applications as solvents for synthetic chemistry, separation from solutions and extraction of materials from mixtures (Brennecke and Maginn, 2001). Therefore this has opened new areas of chemistry where they are used as solvents and as catalysts (Freemantle, 2009). Ionic liquids can be tuned with different cation and anions which can be helpful in the dissolution study of organic and inorganic gases, liquids and solids.

2.1.2.7 Polarity and solvation

Ionic liquids are mostly used as solvents in chemical processes with great success. Therefore polarity is one of the most important properties in the study of solvents. However solvent polarity is defined as the potential behaviour of the solvent with respect to the solute (Ab Rani et al., 2011, Freemantle, 2009). Solvation occurs by the gathering of solvent molecules or ions with solute ions or molecules. Ionic liquids can dissolve both polar and nonpolar solutes and solvation studies show interactions such as solute-solvent interactions, which includes ionic, columbic and various dipole interactions, hydrogen bonding and van der Waals forces, and electron pair donor-acceptor interactions (Ab Rani et al., 2011). The solvent property can be changed by appropriate choice of

cations and anions. Thus, specific solvents can be used as a replacement or where unique solvation is needed. The solvent properties of ionic liquids is more structured compared to molecular organic solvents (Reichert et al., 2006). There are a number of different methods to determine solvent polarity. Dielectric constant or relative permittivity measures the polarity of a solvent or liquid. The liquid containing non-polar molecules, such as toluene, have low dielectric constants, whereas polar liquid molecules, for example methanol or acetone, have high dielectric constants. Hydrogen bonded liquids, also have high dielectric constants. Ionic liquids also conduct electricity. However, for determining the dielectric constant of ionic liquids, the indirect method known as microwave dielectric spectroscopy can be used (Wakai et al., 2005). These techniques are very useful tools for the study of solvation properties under conditions that approximate infinite dilution (Poole, 2004).

2.1.2.8 Conductivity and electrochemical window

Ionic liquids are interesting because of their use as non-aqueous electrolytes in electrochemical applications and conductivity is the key feature. Generally, mobility of charge carriers in electrolytes usually depends or correlates with their diffusion rate in the electrolyte. The viscosity of ionic liquids is generally higher than the other electrolytes and tends to decrease with increasing temperature however, contains more charge carriers.

In 2010, Zech *et al*., reported on the conductivity of imidazolium-based ionic liquids while varying their anionic nature and the temperature (248 K to 468 K) (Zech et al., 2010). They showed the effect of anions for e.g. dicyanamide, PF_6 and trifluoroacetate with 1-*n*-butyl-3-*n*-methylimidazolium as the cation. They

observed that conductivity decreases on order to [bmim][DCA] > [bmim][TA] > [bmim][TfO] > [bmim][PF_6] (Table 2.2).

Table 2.2 Conductivities of the imidazolium-based ionic liquids (Zech et al., 2010)

κ/S·m$^{-/}$				
***T*/K**	[bmim][DCA]	[bmim][PF_6]	[bmim][TfO]	[bmim][TA]
248.15	0.0483	-	-	0.00858
258.15	0.1180	-	-	0.0244
268.15	0.242	0.0164	0.0539	0.0569
278.15	0.433	0.0385	0.1038	0.1144
288.15	0.702	0.0792	0.1808	0.205
298.15	1.052	0.1465	0.290	0.333
308.15	1.483	0.248	0.436	0.504
318.15	1.991	0.390	0.621	0.723
328.15	2.57	0.578	0.848	0.988
338.15	3.22	0.815	1.117	1.301
348.15	3.93	1.102	1.426	1.658
358.15	4.69	1.440	1.775	2.06
368.15	5.41	1.825	2.16	2.50
378.15	6.34	2.26	2.60	-
388.15	7.26	2.74	3.04	-
398.15	8.19	3.25	3.52	-
408.15	9.15	3.81	4.03	-
418.15	10.12	4.39	4.56	-
428.15	11.12	5.01	5.12	-
438.15	12.10	5.65	5.69	-
448.15	13.09	6.31	6.28	-
458.15	13.75	7.00	6.88	-
468.15	14.54	7.69	7.50	-

2.1.3 Toxicity

Since the late 1990s, extensive research on ionic liquids has been done on their applications and as a result a huge number of novel ionic liquids were synthesized. To date the toxicity of only a few have been published.

Regarding the safety, health and environmental issues of ionic liquids and for future industrial uses, it is important to understand their toxicity, ecotoxicity and biodegradability. Recently, researchers working in the green chemistry field they have become more aware of the ionic liquids and now new research has highlighted that many regularly used ionic liquids have a certain level of toxicity.

Commonly, ionic liquids are synthesized or designed with large cation, such as imidazolium, pyridinium, pyrrolidinium and phosphonium, etc., with small or large alkyl chain length and with anions used like PF_6, BF_4, bis(trifluromethylsulfonyl)imide (Tf_2N), Cl, Br, and nitrite. Most of the starting materials for ionic liquids are labelled with many hazardous symbols e.g. 1-methylimidazole is corrosive, sodium dicyanamide is labelled as harmful and Li(Tf_2N) is toxic in nature, and one could possibly assume that the risk hazards of these precursors will be incorporated in their synthesised ionic liquids.

In 2002, the first paper appeared on the environmental exposure of ionic liquids. Jastorff and co-workers studied the hazardous nature of ionic liquids and their work continued by Zhao on toxicity of ionic liquids in 2007 (Zhao et al., 2007). They proposed a multidimensional risk analysis method for the environmental risk assessment of two ionic liquids, 1-butyl-3-methylimidazolium BF_4, and 1-decyl-3-methylimidazolium BF_4. In their study they used these two ionic liquids and acetone, a common organic solvent, as a reference. They considered five

ecotoxicological indicators: release (R), Spatiotemporal Range (S), Bioaccumulation (B), Biological activity (A), and Uncertainty (U). The risk indicator was scaled up from 1-4, where higher values mean higher risk. Compared to ionic liquids, acetone is a highly volatile solvent. The release of ionic liquids in environment through air can be very low (Value 2). Due to the lack of information on the decomposition residues and biodegradation of ionic liquids the uncertainty indicator information was kept high (value 4). Considering water solubility, biotic/abiotic transformation, and sorption to soil, there is very little information. Regarding the limited data, the author predicated the spatiotemporal range of ionic liquids and the risk was taken into account was rather high (value 3), while acetone also has the same value. In bio accumulation, both ionic liquids showed different risks, which depends upon alkyl chain length. 1-Decyl-3-methylimidazolium BF_4 has a higher bioaccumulation because of its molecular similarity to membrane lipids, and the risk is scored as 3 and 1-butyl-3-methylimidazolium tetrafluoroborate is scored 2. While biological activity is considered as a function of alkyl chain length, i.e., the higher alkyl chain length, the higher the toxicity so the biological activity value for 1-decyl-3-methylimidazolium BF_4 (value 3) is higher than for 1-butyl-3-methylimidazolium BF_4 (value 3). This study was based mainly on theoretical estimation. In 2007, the group followed their initials work with a comprehensive review of the ecotoxicological risk profiles of numerous ionic liquids.

Microorganisms play a vital role in the ecosystem and are considered as higher-order multicellular organisms (Zhao et al., 2007). They participate in the carbon cycle to nitrogen cycle in the ecosystem and are involved in recycling of their

organism. Therefore, toxicity of ionic liquids to microorganisms is an interesting concern in ionic liquid toxicity profile.

In 2006, Docherty and co-workers reported on the toxicity of imidazolium and pyridinium ionic liquids to *Vibro fischeri, V. fischeri bacterium*. These bacteria are bioluminescent and globally available in marine animals, e.g. bobtail squid. Ionic liquids with long alkyl chain length on cations show hydrophobicity which may induce toxicity. In this context, they tested $[C_4mim][BF_4]$ and $[C_4mim][PF_6]$ ionic liquids, to three microorganisms, *Escherichia coli, Pichia pastoris*, and *Bacillus cereus* and compared their study with commonly used industrial solvents such as phenol, toluene, and benzene. They concluded, that the octyl and hexyl substituent on the ionic liquids are more toxic and reported that the ionic liquids showed inhibitory effects on the growth of these microorganisms, similar to dimethyl sulfoxide (Ganske and Bornscheuer).

The toxicity of ionic liquids in animals is a very important consideration when using ionic liquid as drugs. Rogers and co-workers provided the first report on the toxicity of ionic liquids to animals (Swatloski et al., 2004). They carried out their experiment on *Caenorhabditis elegans*, a well-studied free-living soil roundworm, using $[C_4mim]Cl$, $[C_8mim]Cl$, and $[C_{14}mim]Cl$ and studied the survival of *C. elegans*. They concluded that $[C_4mim]Cl$ and $[C_8mim]Cl$ are not acutely toxic while $[C_{14}mim]Cl$ showed slight toxicity. They proved that the alkyl chain length on the cation was mainly responsible for increasing the toxicity of these ionic liquids.

In another example, Landry and co-workers tested ionic liquids for oral acute toxicity on Fischer 344 rats (Landry et al.). In their experiment, 175mg/kg of

[C_4mim]Cl dosage was consumed by rats and later they observed that there was no influence on their body weight, body activity and health over the two weeks periods. However, when they increased the ionic liquid dose to 550 mg/kg, most of the rats died; moreover death occurred within 1 day with 2000 mg /kg dose with hypoactivity and abnormal posture.

The possible release of ionic liquids into the environment is very low because of their negligible vapour pressure. If large amounts are used, e.g. in industrial applications, is it quite possible that they can enter to the surface water or ground water, by accidental release into waste water or, directly into soil which would contribute to environmental hazards.

The above sections described and discussed in details of ionic liquids property and toxicity. However, from this section it was assume that ionic liquids can provides unique environment to conduct this work. In the next section (Section 2.1.4) the mode of synthesis were discussed in details.

2.1.4 Synthesis and purification of ionic liquids

In this section the synthesis method and its purification were discussed

2.1.4.1 Synthesis

Until the 90s the availability of ionic liquids “were considered to be rare” according to Welton (Welton, 1999a). Nowadays ionic liquids are commercially and easily available. Non-chloroaluminate ionic liquids with dialkyl imidazolium cations were synthesised and reported in 1992 (Wilkes and Zaworotko, 1992) but their utility was not recognised for another five years.

Currently ionic liquids are synthesised on a large commercial scale as well in as for research and development purposes and these ionic liquids are synthesised by various methods. Some of the most general synthesis routes are outlined below.

2.1.4.1.1 Quaternisation Reactions

In general, quaternisation reactions are very simple and easy to conduct; the amines, e.g. pyridine (Gordon et al., 1998), 1-methylpyrrolidine (MacFarlane et al., 1999), trialkylamines (Sun et al., 1998), or phosphines are mixed with the desired amount of haloalkane, and the reaction mixture is then stirred for the desired time and at a specific temperature. Quaternisation reactions usually depend on the haloalkanes employed; thus temperature and time of reaction varies with reactivity of the haloalkanes. For example, heating of 1-methylimidazole with chloroalkanes at 80 °C and stirring for 2-3 days gives the final product in 95-100% conversion whereas, bromoalkanes requires 24 hrs and at lower temperatures (50-60 °C).

Generally, in quaternisation, different methodologies are available and reported, but mostly the round-bottomed flask/reflux condenser method is widely used. The reaction vessel is maintained under nitrogen or other inert gas to exclude water and oxygen during quaternisation process. This is particularly important with phosphines where oxidation readily occurs to give the phosphine oxides.

2.1.4.1.2 Anion exchange

Anion exchange follows ionic liquid synthesis usually by anion metathesis. In anion metathesis, generally, organic salts and inorganic anions are used. For

example, ethyltri-*n*-butylphosphonium tetrafluoroborate was prepared by reaction of an aqueous solution of sodium tetrafluoroborate [$NaBF_4$] with ethyl tri-*n*-butylphosphonium bromide.

2.1.4.1.3 Microwave and ultrasound-assisted synthesis

Microwave assisted synthesis is a convenient one pot reaction reported by Varma and Namboordiri in 2001. They point out that in the traditional method, preparation of dialkylimidazolium halides involves heating of 1-methyl imidazolium and large amount of the alkyl halide under reflux in an organic solvent such as toluene for several hours (Varma and Namboodiri, 2001). The authors eliminated this lengthy and tedious procedure by using microwave-assisted synthesis and they prepared a series of dialkylimidazolium halides within minutes of reaction time using a household microwave. This process did not require an organic solvent, although in some cases, the reaction required a minimum amount of solvent.

$$[C_4mim]\,Cl + [NH_4]\,[BF_4] \longrightarrow [C_4mim]\,[BF_4] + NH_4\,Cl$$

at 30 kHz for 1 h at 20-24 °C (cooling bath at 5 °C)

Figure 2.12 Example of microwave synthesis ionic liquid

In 2002, Leveque and co-workers reported on the use of an ultrasonic reactor for the synthesis of ionic liquids with increased yield up to 90%, dramatic time reduction and high purity of product. They prepared [C_4mim] [BF_4], [C_4mim] [PF_6] and related series of ionic liquids (Leveque et al., 2002).

2.1.4.2 Purification of ionic liquids

The desirable property of low vapour pressure becomes a disadvantage when high boiling point by-products are produced which cannot be separated by distillation or extraction. While carrying out chemical syntheses using ionic liquids, the purity of the ionic liquids has a great importance. Impurities in the ionic liquids may significantly affect the outcome of the reaction.

Purity of the ionic liquids is the most important factor which affects their physicochemical properties. Trace impurities in ionic liquids result in dramatic changes in their physicochemical properties. For example, traces of halide ions, non-ionic impurities e.g. water, acids and co-solvents in ionic liquids, can alter their physical, spectroscopic and chemical characteristics. In 2000, Seddon and co-workers reported on a systematic study of the effect of impurities and additives on the physical properties of ionic liquids (Seddon et al., 2000a). Ionic liquids containing halides create a problem because the halide content changes solvent property and its usefulness in a chemical process (Villagrán et al., 2004). A small amount of chloride impurities in ionic liquids dramatically increases their viscosities, whereas the presence of water, or other solvents, reduces the viscosity. In general, the addition of co-solvents in ionic liquids greatly reduces their viscosities (Seddon et al., 2000a).

Various purification techniques can be used, such as ion chromatography which is mostly used for removal of the halide impurities. In many cases ionic liquids show yellow or brown discoloration which is due to trace amounts of impurities present in the ionic liquids. This type of impurity is typically removed by passing the ionic liquids through activated charcoal and then passing through an

alumina column. The technique was developed reported by Clare and co-workers in 2008 (Clare et al., 2008).

In 2012, Fiene and co-workers reported the patented method for purification. In their invention, in first step the partial crystallisation of the ionic liquids was achieved from its melt and they separate the crystal from the residual melt (Fiene et al., 2012).

2.1.5 Summary

The ionic liquids section provides a review on its definition, history, properties synthesis mode and its purification methods. From the review it was found the unique properties can plays an important role in the pharmaceuticals applications and importantly ionic liquids are easy prepare with wide range of cations and anions. In addition, the microwave technique for synthesis is easy, solvent free, cost reduction, minimum impurities.

As explained in introduction, in this work chapter 5 was focused on crystallisation study of APIs using ionic liquids. So the next section described in details about and its crystallisation and its process, techniques and polymorphism in detail.

2.2 Introduction to crystallisation

Crystallisation is the process of formation of solid crystals from a solution and it is a separation and purification technique commonly used in the chemical industry. In most of the pharmaceutical manufacturing processes, active pharmaceutical ingredients are formulated in solid dosage to achieve high purity and to produce the desired final crystal form (Figure 2.13). The crystallisation

process mainly depends on techniques such as filtration, drying, formulation, the product bioavailability and shelf-life (Mullin, 2001a)

In crystallisation processes, a number of different methods are used which involve solvent and non-solvent methods. It should be noted that the traditional crystallisation methods have not been able to deliver 100% polymorph screening (Mullin, 2001a)

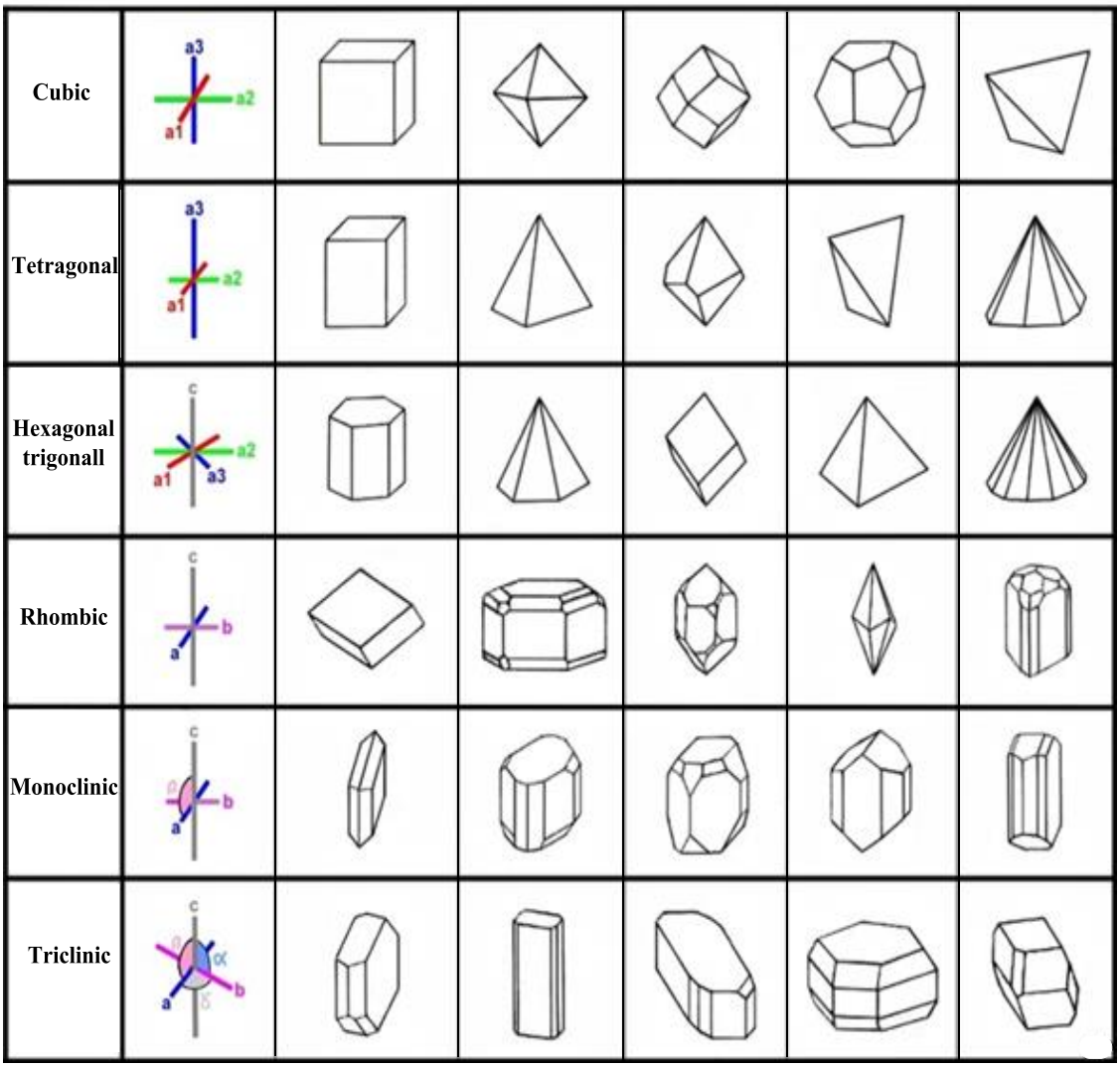


Figure 2.13: Crystal systems and examples (Mullin, 2001a)

Crystallisation is a two-step process, which includes the nucleation step and a growth step. In the nucleation step the liquid phase changes to liquid phase containing a solid, and which is obtained from the term “supersaturation” in the solution. Supersaturation is defined as a state in which the liquid (solvent) contains more dissolved solids (solute) than under normal circumstances. Crystallisation is a surface binding phenomenon which involves a process between the solute and solvent binding in solution. In this process the solute gets transferred from solution onto the surface of the crystal and then formation of bulk crystals that are provided by the solvation process.

For example, continuously adding table salt to boiling water whilst stirring until no more salt will dissolve, gives a saturated solution. The addition of more of salt at this stage will result in the salt not dissolving. The undissolved salt at the bottom of the pot provides a site for nucleation to occur. This is the first step of crystallisation and is called “nucleation” or primary nucleation for a new crystal growth start.

2.2.1 Crystallisation process

The following sections described the process of crystallisation in details.

2.2.1.1 Nucleation

The nucleation process is the formation of crystals from solution, a liquid or vapour. This process can be split into two main categories: Heterogeneous processes which occur at interfaces or surfaces, and may be induced by foreign particle and homogenous nucleation, which occurs spontaneously in bulk solution; and homogenous nucleation which forms the basis for classical

nucleation theory. The metastable zone widths, with respect to nucleation type, are schematically shown in Figure 2.14. The classical nucleation theory was originally derived for the condensation of vapour into liquid and has been extended to crystallisation from solutions.

Crystallisation in the pharmaceutical field assists in the development of new polymorphs. Polymorphs have the same elemental composition but there is a difference in physicochemical properties (Threlfall, 2000).

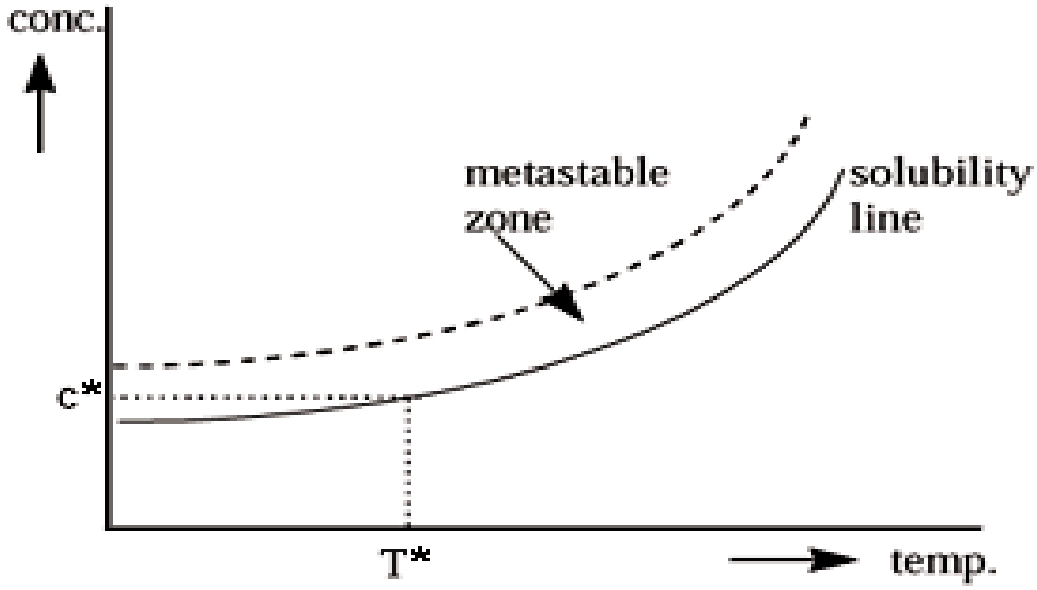


Figure 2.14: Schematic digram showing the metastable zone with respect to temperature (Giulietti et al., 2001)

2.2.1.2 Crystal growth

Crystal growth is a major process in crystallisation. Crystal growth consists of the addition of new atoms, ions or polymers into the characteristic arrangement of a crystalline lattice. Crystallisation is multistep process which includes 1) transport of a growth unit from or through the bulk solution to an impingement

site; 2) adsorption of the growth unit at the impingement site; (3) diffusion of the growth units from the impingement site to a growth site; and (4) incorporation into the crystal lattice. The relative importance of each step depends on the surface of the crystals and the properties of the solution (Rodríguez-hornedo and Murphy, 1999, Meenan et al., 2002) (Figure 2.15)

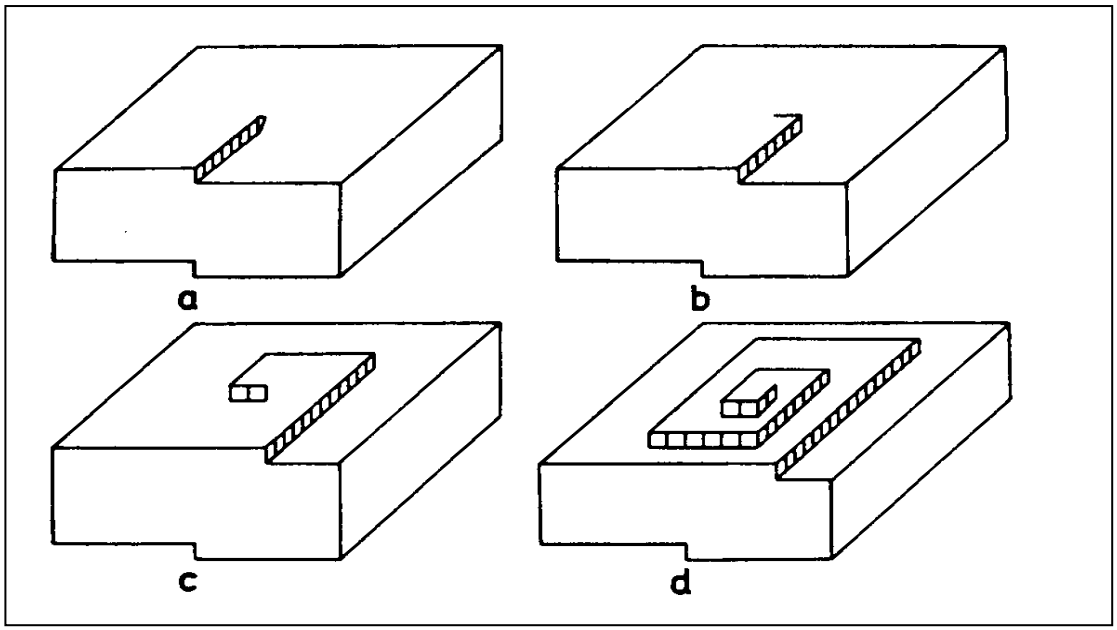


Figure 2.15: Schematic diagram showing crystal growth (Mullin, 2001b)

2.2.2 Crystallisation methods

There are various strategies reported on crystallisation techniques to obtained supersaturation required to crystallise API. Generally, cooling crystallisation and anti-solvent crystallisation techniques are usually applicable and discussed.

Cooling crystallisation generally used in less soluble compounds. In this method, a saturated solution is prepared, where the solvent is heated to just below the boiling point and then spontaneous crystallisation will occur while the solvents cool sufficiently. During cooling, the solution becomes supersaturated and crosses the metastable zone and is able to form crystals. The required

important factors during or while carrying out cooling crystallisation, is having a sufficiently high temperature for materials to dissolve into solution and having a low enough solubility to produce crystals from the process. The rate of cooling is also an important factor which may affect the crystal growth. For controlling the particle size and avoiding secondary nucleation through the cooling crystallisation, then slow cooling is an ideal technique over fast cooling technique.

Antisolvent crystallisation is another method for crystallisation and it is usually used where the solution containing the compound is mixed with a solvent where the solute has low solubility. In this technique the antisolvent is added slowly after minimising the higher supersaturation within the solution. Adding the antisolvent quickly into the solution may create problems, e.g., incorporation of impurities increase and also isolation of the kinetically favourable form.

2.2.3 Polymorphism

Polymorphism control of active pharmaceutical ingredients (APIs) is a very important factor in drug development and delivery (Sarma et al., 2011, An and Kim, 2012). Polymorphism is the ability of a solid material to exist in more than one form or crystal structure. Over the last few decades, many methods, including solution crystallisation from single or mixed solvent systems have been used to study polymorphism change (Teychené et al., 2004). The polymorphic nucleation also depends on the crystallisation temperature. The most popular method for the polymorphic design of APIs is solution crystallisation due to the variety of possible crystallisation methods and conditions. By using various organic solutions to create polymorphs of APIs, it

would appear that different solutions induce different interactions between API molecules, thereby generating different polymorphs in the crystallisation.

The polymorphic system of a substance is described as the unique packing order of the unit cell. In polymorphic state the substances are chemically same but packed in a different arrangement and gives rise to different form of substances and which is packed in a series of repeating units. These types of unit cells can be arranged in seven possible crystal systems: regular, tetragonal, orthorhombic, monoclinic, triclinic, trigonal and hexagonal as shown in Table 2.3.

Table 2.3 The Seven Crystal Systems (Mullin, 2001a)(reproduced from Mullin)

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

Thus the application of ionic liquids to influence polymorphic design also needs to be considered, as they might induce distinctive inter-molecular interactions compared to conventional organic solvents. Few studies have explored the use of ionic liquids for polymorphic design. Zhao *et al*. have used 1-butyl-3-methylimidazolium bromide and 1-dodecyl-3-methylimidazolium bromide as additives to produce polymorphic change in calcium carbonate (An and Kim, 2012, Zhao et al., 2009).

2.2.4 Summary

The above section well described the crystallisation, process, techniques and polymorphism. From this section it was found that the unique properties of ionic liquids could help the crystallisation process. In the next section, the applications of ionic liquids are discussed in detail but the main objective of this work was on the pharmaceutical applications. So in the following section the pharmaceutical applications were described in details rather than other applications.

2.3 Applications

In recent years, ionic liquids have received more attention on the basis of their wide range of applications (Figure 2.16). Generally, ionic liquids for electrochemical applications mainly depend upon their two features; one is their ionic conductivity and other is their electrochemical stability. Ionic liquids show intrinsic ionic conductivity as solvents in electrochemical applications. The electrochemical stability, stated as an electrochemical potential window, for ionic liquids is between 2.0 and 6.0 V. For example [C_2mim] [NTf_2] and [C_4mim] [PF_6] have windows of 4.5 and 4.2 V. The ionic conductivity and electrochemical

stability of ionic liquids makes them interesting as potential electrolytes for batteries (Holzapfel et al., 2005, Seki et al., 2006, Angell et al., 2007), solar cells (Wang et al., 2003a, Wang et al., 2003b, Wang et al., 2004), fuel cells (Belieres et al., 2006, Susan et al., 2003) and other electrochemical devices (Hurley and WIer, 1951, McEwen et al., 1999).

Figure 2.16 Applications of ionic liquid in various fields (Plechkova and Seddon, 2008)

In another application, ionic liquids have great potential in chemical analysis and it is generally interesting because ionic liquids can be easily handled and used in a wide variety of environments. Consequently, a variety of analytical applications of ionic liquids have started to emerge in various fields such as

chromatography (Armstrong et al., 1999, Berthod and Carda-Broch, 2004, Wang et al., 2009), as solvents for extraction (Visser et al., 2001a, Luo et al., 2004, Huddleston et al., 1998), electroanalytical chemistry (Wang et al., 2003b, Chen and Hussey, 2004) and spectrometry (Mank et al., 2004, Armstrong et al., 2001, Baker et al., 2003).

In this research programme the focus was on the application of ionic liquids in crystal engineering and drug delivery processes. The following section briefly reviews the application of ionic liquids in the development of pharmaceuticals.

2.3.1 Pharmaceutical applications

Over the past few decades, the pharmaceutical industry has been facing great challenges and huge pressure due to the environmental issues, long term and lengthening drug-development process and customer expectation as a cost constrained on the healthcare system. Nowadays, customers are also demanding new therapies which are more economical and clinically better than the existing old therapies. Thomas Huxley, a British biologist wrote that “The great tragedy of science – the slaying of a beautiful hypothesis by an ugly fact.” Meanwhile, this quote fits when the pharma market is analysed. According to researchers, pharma output becomes unstable as average cost per molecule goes on increasing year on year. For example, between 2002 and 2011, the pharma and biotech sectors invested nearly $ 1.1 trillion on research and development. Over the past ten years, the FDA launched and approved 308 new molecular entities (NMEs) and biologics. In other words, the pharma industry invested an annual average of $ 2.3 billion to $ 4.9 billon per approved

molecule. In addition, investment costs are still rising relentlessly (PricewaterhouseCoopers, 2012), see Figure 2.17.

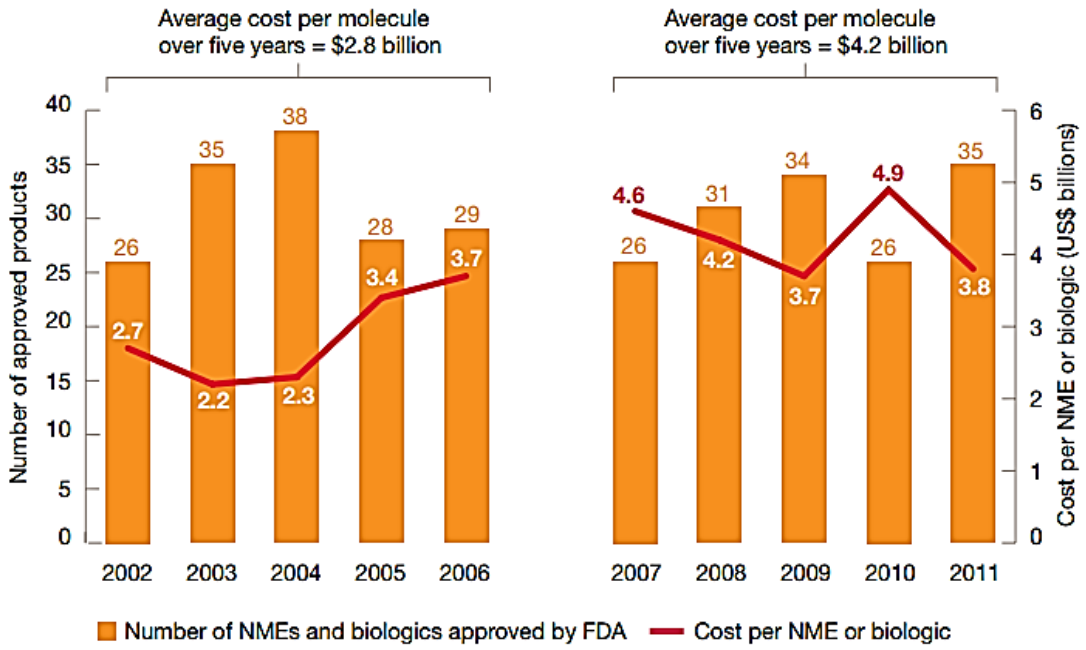


Figure 2.17 Average cost per molecule from 2002 to 2011 (PricewaterhouseCoopers, 2012)

However, the pharmaceutical industry is also facing challenges over the new drug formulations with their slow dissolution in biological fluids and clinical efficacy issues. To overcome these issues pharmaceutical companies are continuously developing new strategies to overcome these limitations. Overall these strategies include salt formation (Serajuddin, 2007), solid dispersion (Dhirendra et al., 2009) and prodrug strategies (Rautio et al., 2008) (Figure 2.18).

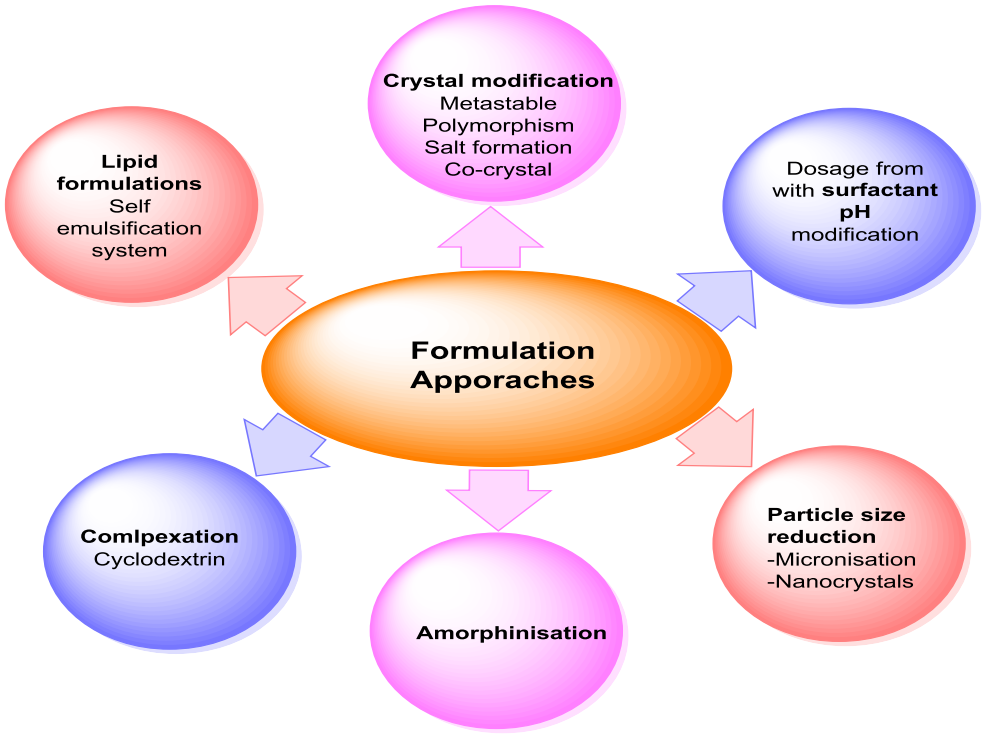


Figure 2.18 Overall strategy for poorly soluble drugs enhancement

According to the Biopharmaceutical Classification System (BCS), specific drug molecules are classified on the basis of their aqueous system and gastrointestinal permeability (FDA regulations). Drug molecules are further classified into four categories on the basis of their aqueous solubility and permeability. These four categories are classified into a class I where, the drug molecule is absorbed above 90% (it should not be less than 90%). In class II the drug molecules exhibits poor solubility and poor performance in the dissolution. The class III system shows exactly opposite characteristics to class II, highly soluble but challenges in permeability due to poor lipophilicity, and in the class IV system the drug molecules have complete neither solubility nor permeability for complete absorptions. Now this BCS classification is widely accepted by pharmaceutical industries and it is very useful for formulation strategy decisions.

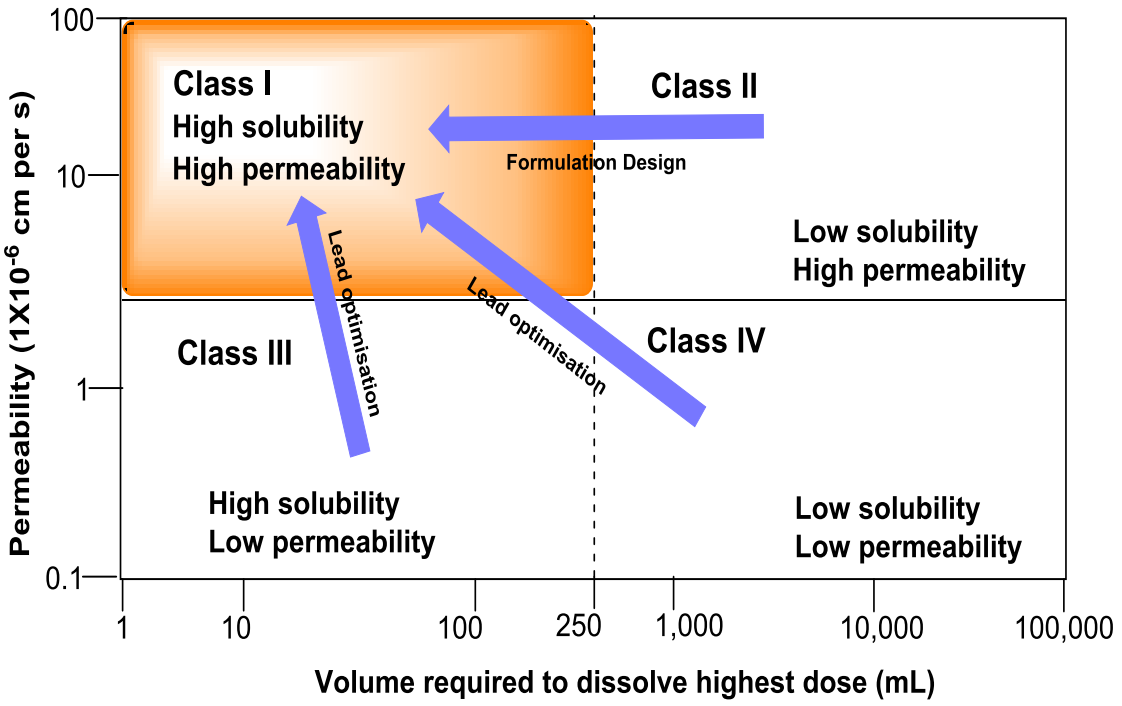


Figure 2.19 BCS classification of drugs (Rautio et al., 2008)

More recently, ionic liquids have received more attention in the pharmaceutical industry and some have gained interesting and commercial attention as alternative solvents and for the replacement of traditional volatile organic solvents for a variety of applications (Earle and Seddon, 2002). The interesting properties of ionic liquids which have been discussed previously and their wide range of applications promise to solve classical pharmaceutical problems.

Regarding green chemistry principles, the waste generation from the pharmaceutical manufacturing process is appalling. In 2008 Sheldon proposed the E-factor (Environmental) and defined it as kg waste/kg product. He further concluded that the pharmaceutical industry has the highest Sheldon E-factor (25-100), compared to the oil-refining (<0.1) and fine chemicals (5-50) industries (Sheldon, 2008). The ionic liquids used as green solvents possess properties such as negligible vapour pressure, non-volatility and thermal

stability which play an important role when considering replacing organic and toxic hazardous solvents. Furthermore, the tunability of cation and anion for a specific interaction with a specific entity helps solubilisation of complex molecules (Bouder, 2008, Siodmiak et al., 2012).

2.3.1.1 Ionic liquids as solvents

Recently, pharmaceutical drugs were synthesized by using ionic liquids as alternative reaction media instead of hazardous organic solvents. In pharmaceutical companies, or in research and development sectors, organic solvents are mostly used in synthetic processes, which impacts on the purification of the final product which can contain organic contamination and residual impurities. Siodmiak and co-workers explored alternative ionic liquid reaction media for the easiest and faster method for organic transformations and preparation of pharmaceutical drugs compared to traditional organic solvents (Siodmiak et al., 2012).

Earle et al. (2000) used ionic liquids as alternative solvent media for the synthesis of nonsteroidal anti-inflammatory drugs ($NSAID_S$), such as pravadoline, with excellent yield.

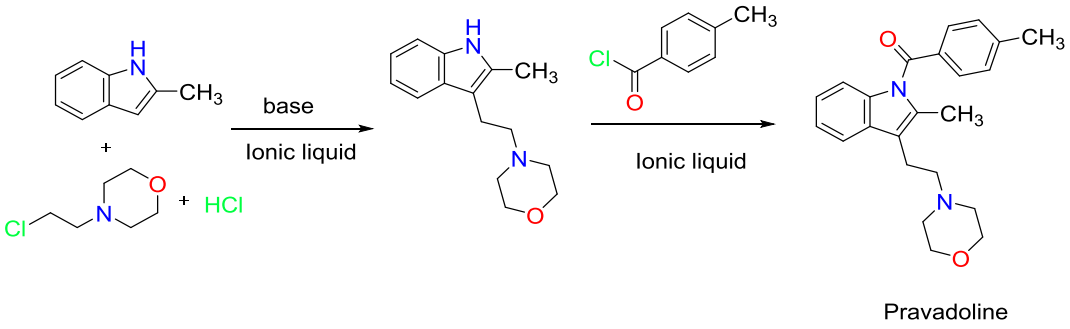


Figure 2.20 Synthesis of pravadoline in [bmim][PF_6]

Usually synthesis of pravadoline is carried out in DMSO or DMF solvent and sodium hydroxide or sodium hydride as base, which creates unpleasant smells, noxious in the case of DMSO and the remaining solvent impurity in the final product is difficult to remove. In contrast, for the ionic liquid as solvent, the final product separates out easily and the solvent was recycled after the process. In addition, the ionic liquid reaction did not need heating for a long time. In this context, Friedel-Craft reactions and nucleophilic displacement reactions were carried out with 2-methylindole and 1-(*N*-morpholino)-2-chloroethane hydrochloride in 1-butyl-3-methylimidazolium PF_6 at 150 °C, and overall the ionic liquid improved the product yield from 91 % to 95 % with consideration of environmental factors (Earle et al., 2000).

In 2008, Kumar *et al.* synthesised nucleoside-based antiviral drugs such as brivudine, trifluridine and stavudine using the ionic liquids 1-methoxyethyl-3-methylimidazolium methanesulfonate, 1-methoxyethyl-3-methylimidazolium trifluoroacetate and 1-butyl-3-methylimidazolium trifluoroacetate. In the case of stavudine the reaction was complete within 5 -10 min with 89 - 93 % yield along with an easy work up procedure. In the trifluridine case, interestingly, the desired product was obtained in a high yield (90-91%) and the reaction was complete in 20-25 min. The author concluded that using ionic liquids as a solvent resulted in a tenfold reduction in solvent use compared to the conventional reaction media (e.g., pyridine/DMAP/ acetonitrile/Et_3N/DMAP) and higher purity product was obtained (Kumar and Malhotra, 2008).

Zaidlewicz *et al.* (2003) synthesised the potential antitumor drug L-4-boronophenylalanine (L-BPA) which is a clinically approved drug. They reported

on the use of ionic liquids such as 1–butyl-3-methylimidazole as a cation and BF_4, PF_6 as the anions. In this context, the authors synthesised a drug for boron neutron capture therapy (BNCT) which targeted the tumour tissue (Figure 2.21).

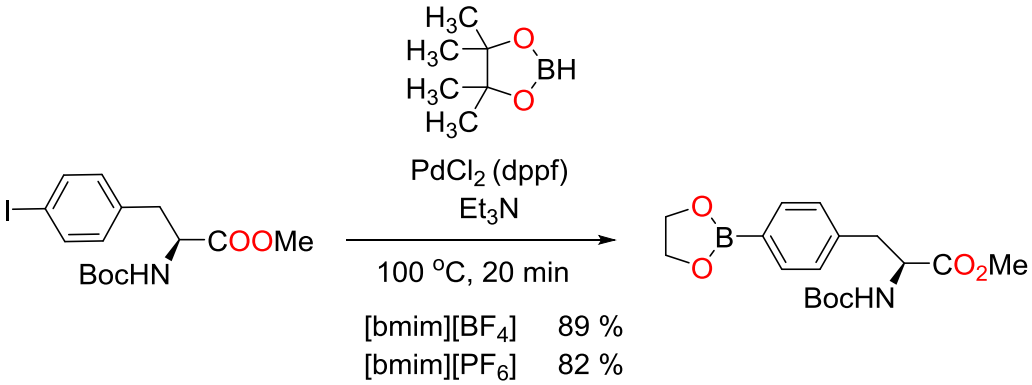


Figure 2.21 Synthesis of L-BPA in imidazolium-based ILs

The reaction was carried out by cross-coupling with pinacolborane with protected *p*-iodophenylalanine in bmim based ionic liquid as alternative solvent to give 82-89% yield within 20 minutes (Zaidlewicz *et al.*, 2004, Wolan and Zaidlewicz, 2003).

This section illustrated that ionic liquids can be used as alternative solvents for the synthesis of a variety of pharmaceutical drugs. In the near future, task-specific ionic liquids could replace all organic toxic molecular solvents and this could improve reaction conditions, purification, problematic reaction and isolation of specific products.

2.3.1.2 Ionic liquids in drug delivery

The main challenge in the use of solvents in the pharmaceutical industry is their potential toxicity. In the case of ionic liquids, there is a huge lack of knowledge on their toxicity profile. When considering EC_{50} values for the ionic liquids, there is very limited literature material available. In 2010, Frade published an

overview on the impact of ionic liquids on the environment and humans. He finally concluded that different test models for the same ionic liquid showed different or varying results. He also reported that the IPC-81 leukaemia cell line seemed to be the most vulnerable to the ionic liquids within the experiment and thus this model study could be used as a first stage for a preliminary screening (Frade and Afonso, 2010). In recent years, researchers successfully synthesized non-toxic ionic liquids by combining organic cations and inorganic anions which are biocompatible (Imperato et al., 2007).

Pharmaceutical industries have a great challenge in the transdermal administration of drugs which are poorly soluble in water as well as in most pharmaceutical organic liquids. This limitation can be addressed through the introduction of ionic liquids which can provide a wide range of solubility and they can increase the solubility of a sparingly soluble drug and enhance its topical and transdermal delivery. This has the potential to provide an efficient nano delivery system for insoluble or sparingly soluble drug systems (Moniruzzaman *et al.*, 2010a, Moniruzzaman *et al.*, 2010b), (Reichert *et al*., 2006).

In 2010, Moniruzzaman *et al*. used ionic liquids with pharmaceuticals such as acyclovir (ACV), methotrexate and 1-[(5-(*p*-nitrophenyl)furfurylidene) amino] hydantoin sodium (dantrolene sodium) in formulation applications. They reported a novel ionic liquid-in-oil micro emulsion which is able to dissolve pharmaceuticals that are insoluble or sparingly soluble in water and in organic liquids. The effect of various ionic liquids, such as $[C_1mim][(CH_3O)_2PO_2]$, on the formation of a micro emulsion for acyclovir stabilized by a blend of two non-ionic

surfactants, polyoxyethylene sorbitan monololeate (Tween-80) and sorbitan laurate (Span-20) in isopropyl myristate (IPM) was studied (Figure 2.22).

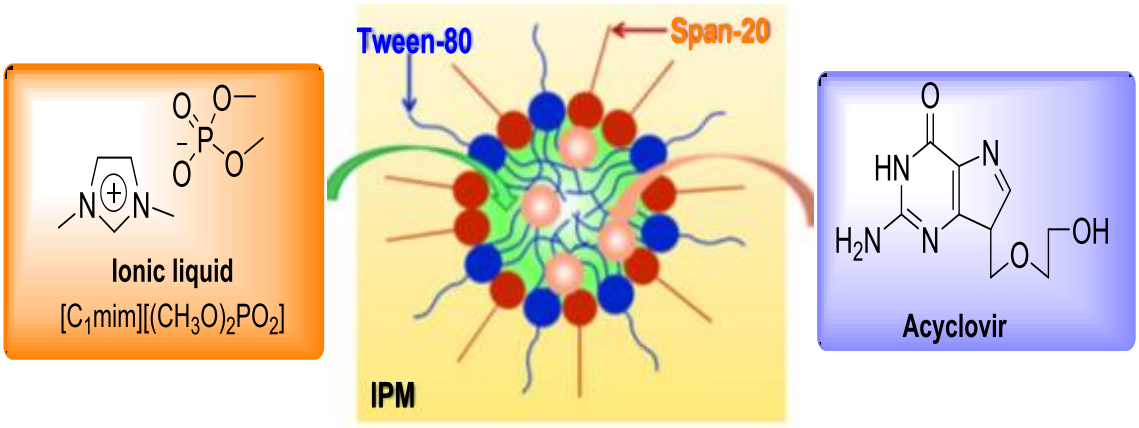


Figure 2.22 Ionic liquid-in-oil (IL/o) microemulsions containing drug molecules

For the study, samples were prepared by weight using polyoxyethylene sorbitan monololeate and sorbitan laurate in 2:3 ratios. An appropriate amount of IPM was added to produce surfactants at concentration of 20 wt. % in IPM, and the mixture was stirred and then titrated with the ionic liquid until it turned turbid to determine the maximum solubilisation. The result showed that hydrophilic ionic liquids containing co-ordinating anions can be solubilised in the Tween-80/Span-20/IPM micelles, whereas hydrophobic ionic liquids containing non-coordinating anions, was found to be very poorly soluble. Interestingly, ionic liquids possessing coordinating anions which are strong hydrogen bond acceptors were found to be very effective as a disperse phase in the bulk IPM stabilized by a mixture of Tween-80 and Span-20. Tween-80 and Span-20 both contain hydroxyl groups which can form hydrogen bonds with the anions of the ionic liquids (Fukaya et al., 2008). The solubility of the ionic liquid $[C_2mim][BF_4]$ in this system suggests that such electrostatic interaction is present because the anion (BF_4) has a very poor ability to form hydrogen bonds with surfactants

head groups. In contrast, the solubility of the ionic liquid $[C_1mim][(MeO)_2PO_2]$ was greater compared to the ionic liquid with BF_4 because this ionic liquid has dual interactions, hydrogen bonding and electrostatic interaction, with the surfactants head group. It was concluded that the ionic liquids acted as the "glue" to bond the surfactants head groups together, which was a driving force for the formation of stable micro emulsion droplets. Non-aqueous micro emulsions using ionic liquids therefore have potential applications as drug delivery carriers.

In 2008, Jaitely *et al.* reported on ionic liquids as versatile solvents in drug reservoirs for controlled release. They used analogues of fixed anion and increased or decreased alky chain length on the cation $[C_{4\text{-}8}MIM]$ as potential drug reservoirs or solvents for hydrophobic or hydrophilic drugs. The authors studied sucrose, dexametasone, progesterone, and penicillin V potassium and dehydroepiandrosterone drugs and investigated the physio-chemical properties of ionic liquids, such as viscosity, water uptake, partition coefficient and surface tension, to understand their effect on the drug release profile.

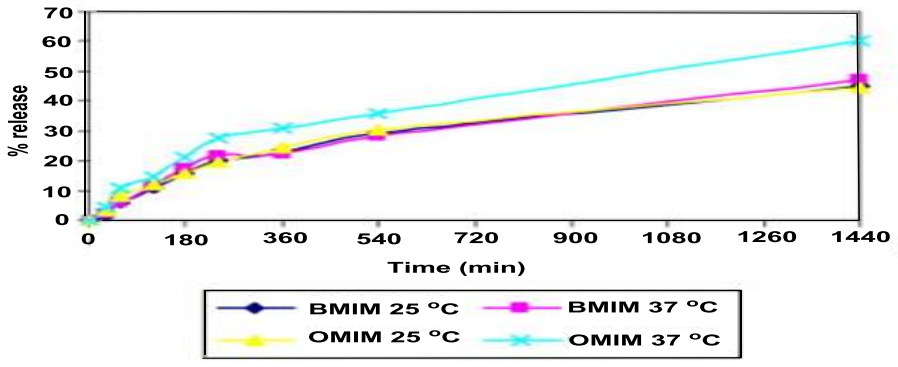


Figure 2.23 The release of dexametasone from ionic liquids as a function of time at 25 °C and 37 °C

Their investigation showed that there was a direct relationship between the hydrophilicity and lipophilicity on the partition of drugs in the ionic liquid/water system. In the case for dexamethasone, the partition coefficient was increased with respect to alkyl chain length of the cation, while there were no noteworthy changes in the other remaining sets of drugs. They also reported a cell line study on the caco-2 cell line for ionic liquid toxicity. The study showed that under exposure to ionic liquids in saturated solutions (0.1- 1% for [C_{4-6}MIM] [PF_6] and 0.1-0.3 % for [C_8MIM] [PF_6]), 90% of cell lines remained sustainable. The authors concluded that ionic liquids make interesting solvent reservoirs for controlled release because of their non-toxicity, counter ion combinations and range of properties (Jaitely *et al.*, 2008).

This section has reviewed the key aspects of ionic liquids in drug delivery. From the literature review it was found that the ionic liquids can be used in emulsion based product and controlled drug release system. The following section reviews the use of ionic liquids in crystallisation media.

2.3.1.3 Crystallisation using ionic liquids

In the crystallisation field, crystallisation of APIs from traditional organic solvents can change its crystal habit and can produce crystals with poor physical properties which result into downstream processing problems. In 2010 Smith *et al*. reported on the solubilities of pharmaceutical compounds in ionic liquids (Smith *et al.*, 2011). They investigated the use of ionic liquids as solvents to dissolve and deliver poorly soluble drugs transdermally. In this investigation the solubilities of paracetamol and ibuprofen were determined in two different ionic liquids at temperatures of 298.15 K, 308.15, 318.15 K, 328.15 K, and 338.15 K.

and the ionic liquids were 1-hexyl-3-methylimidazolium hexafluorophosphate, [HMIM][PF_6], and 1-butyl-methylimidazolium hexafluorophosphate, [HMIM][PF_6]. An excess of a drug was added to the ionic liquid in a sealed glass tube and it was stirred until saturation solubility was reached. Degradation occurred in [BMIM] [PF_6] and, in contrast, no degradation was observed in [HMIM][PF_6]. It was found that water (an impurity) in [BMIM][PF_6] was the reason for the degradation and this led to a decomposition reaction which produced HF (Visser *et al.*, 2000). The study highlighted that both ionic liquids were found to be good solvents for ibuprofen and paracetamol, indicating that significant amounts of drug-solvent interaction were taking place. The solubility of both solutes were greater in [HMIM][PF_6] than [BMIM][PF_6]. However, both ionic liquids showed sufficient solubility towards the drug compounds to make them suitable for crystallisation studies (Smith et al., 2011).

The Bogel-Lukasik group explored the solubility of APIs in ionic liquids. They examined the antibiotic drugs isoniazid and pyrazine-2-carboxamide in ionic liquids with imidazolium cations with different alkyl chain lengths and combined with the anions [NTf_2] and [CF_3SO_3]. They reported that the solubility of the drugs depended upon the nature of the ionic liquids where, both the drugs solubilities decreased with increasing alkyl chain length on imidazolium cation with [NTf_2] anion. It was found that [C_{10}MIM] [CF_3SO_3] was a good solvent for both drugs. The authors concluded that the cation and anion play important roles in the solubilisation of APIs (Forte et al., 2012, Lourenço et al., 2012). Again, by using the same drugs (isoniazid and pyrazine-2-carboxamide) the Bogel-Lukasik group repeated the study with ammonium based ionic liquids. In this study they worked with ionic liquids with one long alkyl chain

(didecyldimethylammonium anion) and one short alkyl chain [ethyl (2-hydroxyethyl)dimethylammonium] with NTf_2 and NO_3 anions. They reported that [$N_{111}C_2OH$] [NO_3] was a promising solvent for solubilisation of both drugs (Melo et al., 2013).

In 2015 Weber *et al*., reported on the purification of pharmaceutical drugs by using an ionic liquid system. They worked on 12 APIs [acetaminophen (AAP), fenofibrate (FF), ibuprofen (IBU), acetylsalicylic acid (ASA), itraconazole (ITR), griseofulvin (GSF), salicylic acid (SA), naproxen (NPX), amoxicillin (AMOX), etomidate (ETO), rufinamide (RUF), cyclosporine (CYC), 4-aminophenol (4-AP), 4-nitrophenol (4-NP), 4-chloroacetanilide (4-CA)] and 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([EMIM][NTf2]) as the cooling crystallisation solvent system. They measured the solubility curve for nine APIs and finally, cooling crystallisation was applied with common impurities as models and they achieved improved yields in control cooling and antisolvent crystallisations. In this context, they added excess solid samples in [EMIM][NTf_2] and the resultant suspension was stirred for 24 hrs at different temperatures and the solubility was measured. In crystallisations, the suspensions were heated above the specific temperature and cooled 1 °C per minute. Finally it was concluded that the purity of the crystallised product was greater than the crystallisations from organic solvents or antisolvent with improved yields (Weber et al., 2015).

Compared to other fields, there has been less research focussed on ionic liquids in crystallisation studies. There are several properties of ionic liquids which may be advantageous in a crystallisation process, for example, ionic

liquids provide thermal operating ranges above 200-300 °C which are not possible with conventional solvents (Smith et al., 2011). By selection of the appropriate ionic combination of salts with respect to its capability for solubilising specific solutes, the solvent can be designed to control solubility critical to a particular crystallisation process. Solvent properties of ionic liquids are also helpful in the crystallisation process because the solvent property can be altered or tuned by changing its cation and anion. Where unique solvation is needed, one can use ionic liquids by adjusting its solvent properties which can decrease or increase the interactions between the solvent and the solute. These unique physical and solvent properties of ionic liquid and the tunability of cations and anions make ionic liquids desirable solvents/additives in the crystallisation process (Murugesan and Linhardt, 2005, Reichert *et al.*, 2006).

The major challenge of using ionic liquids in crystallisation is their non-volatility under normal conditions. For the purification of products, evaporation of solvents is needed in most of the cases. However, their non-volatile property does not mean that ionic liquids cannot be used as crystallisation solvents. Perhaps a more challenging reason for the limited study of ionic liquids as crystallisation solvents is how crystallisation will occur in the ionic liquids and the choice of ionic liquid for a particular crystallisation process as their properties and behaviours are not well understood as yet. In crystallisation s processes, solute and ions may lead to many interactions which may result in very difficult or complicated crystal structures (Reichert et al., 2006).

Another consideration in crystallisation is the ion shape. Most of the ionic liquid ions are bulky and with low symmetry and this property induces low lattice

energy and low melting points. These ion properties on crystallisation are yet additional design advantages. Ionic liquids are also more advantageous over traditional solvents for high or low temperature processes. For example, in volatile solvents, high temperature solvothermal techniques are usually restricted because this technique creates high pressure under high temperature. In contrast ionic liquids have negligible vapour pressure and high thermally stability, such high temperature routes may not require pressure vessels, making this crystallisation technique more widely available and commercially viable.

This section has reviewed the key aspects for the use of ionic liquids as crystallisation media. From the literature review, it was found that the new developments examined which types of cations or anions of the ionic liquids could be exploited to solve the problem with polymorphic conversion, low solubility and also introduce new solvent in pharmaceutical industries. The following section reviews the use of ionic liquids as a combination with APIs.

2.3.1.4 Active pharmaceutical ingredients based on ionic liquids

To date the pharmaceutical industry's major focus is on solid dosage form such as tablets or powder form and thus liquid forms are neglected because of the shelf life, availability and cost issue. The solid dosage form research is usually struggling with their solubilisation issues and this is the reason that drugs fails during the drug development phase. This is mainly due to their non-effective release into the blood stream (Hauss, 2007).

Ionic liquids with their excellent physio-chemical properties could bypass these delivery problems (Stoimenovski *et al*., 2010). Worldwide most of the drugs are

sold in salt forms. Salts composed by ionic bonds which help to keep the mixture liquid at room temperature, could improve solubility, absorbability and stability (Shadid *et al*., 2015). Drug molecules converted into salts by combining basic or acidic drug molecules with counterions may also overcome the physio-chemical properties of the drug. The salt form of drugs may show several benefits over original neutral formulations which relate to their pharmaceuticals properties, such as permeability, bioavailability and drug delivery and in terms of physical properties, such as melting point, crystallinity, hygroscopicity, and dissolution rate. In the salt form the counterion plays a vital role in influencing the pharmacokinetics of drug candidates. Regarding the counterion tenability, the pharmacodynamics and toxicology profile can be changed or modified. Therefore the regulatory authorities consider the new salt form of drugs as new chemical entities which need to be registered.

From the above considerations the physio-chemical properties of ionic liquids open new pathway in drug delivery and API-ionic liquid systems may have an exciting future. In recent years, there has been lots of work going on in this field. For example, the non-steroidal anti-inflammatory drug (NSAID) salicylic acid was converted into a liquid salt by combining with procainium to give procaine salicylate. The new formulation could deliver the benefits of both compounds and opens new treatment options. Industry is looking for novel therapies which may are economically and clinically better than the old therapies (Shamshina, 2015) (Figure 2.24).

Figure 2.24 Ionic liquid pharmaceuticals face (Shamshina, 2015)

Recently Restolho *et al.* exploited the tunability of ionic liquids by using biological active cations and anions, commonly designed on active pharmaceutical ingredients. Lidocaine docosate (LD), ranitidine docosate (RD), and didecyldimethylammonim ibuprofen (DI), were selected for their study. They focused on the interfacial properties of LD, RD and DI, and measured the surface tension and the contact angles on both hydrophilic and hydrophobic surfaces within a wide temperature range. Based on the wettability data, the polarity fractions were estimated. For the three ionic liquid-APIs, liquid-liquid transition temperature occurred near ambient temperature. Near this transition they showed abnormal behaviour which was explained by the appearance of a mesophase between the isotropic and the vapour phase. The ionic liquid-APIs show low surface tension and low contact angles which was determined on both hydrophobic and hydrophilic surfaces. The relatively low polarity fractions confirm the smaller contribution of the coulomb forces when compared with the dispersive interaction for ionic liquids possessing larger ions (Restolho *et al.*, 2011).

The use of ionic liquids in the pharmaceutical industry could provide access to painkillers that also contain antibiotics or antimicrobials. According to Rogers *et al*., the painkiller aspirin (acetyl salicylate) which is normally used in tablet form or in solution, has some problems such as poor solubility, bitter taste and unpleasantly large tablets for required dosages. A liquid salt form of aspirin could solve these problems and provide new delivery routes. Anionic salts of the active component of aspirin or chemically similar to salicylic acid, paired with ammonium cations were studied. They also investigated one example of a phosphonium ionic liquid. Applications of ammonium or phosphonium anions as antibacterial or antimicrobial materials, is another option. Therefore ionic liquids could provide new techniques in drug development, design and delivery processes (Bica *et al*., 2010).

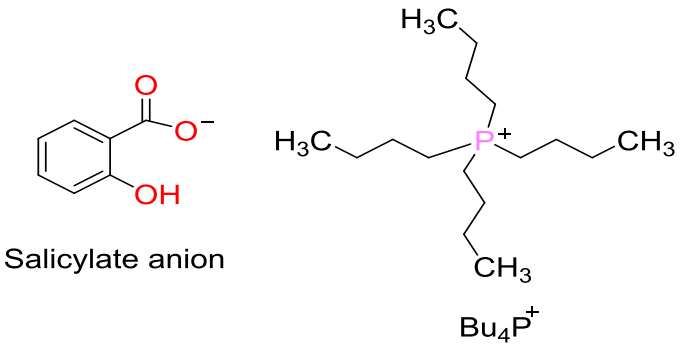


Figure 2.25 Drug-ionic liquid systems: antibacterial cations used in combination with the salicylate anion

Another strategy to improve the properties of APIs is by combining them with ionic liquids in order to improve the solubility, permeability and bioavailability of solid APIs with prodrugs. Prodrug ionic liquids present additional advantages such as controlled release of the APIs in simulated fluids. This provides an important strategy to improve the properties of APIs and drug delivery (Cojocaru et al., 2013) (Figure 2.26).

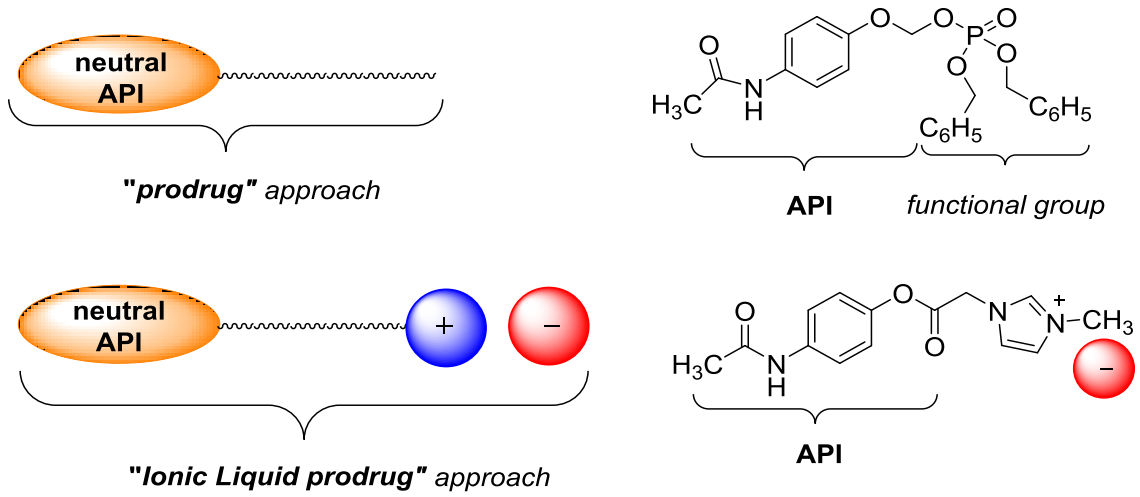


Figure 2.26 Ionic liquids as prodrugs (Cojocaru et al., 2013)

Zakrewsky *et al.* developed ionic liquids as a class of materials for transdermal delivery and pathogen neutralization. They used a series of ionic liquids tetraalkylphosphonium carboxylate, tetraalkylphosphonium hexanoate, choline bistriflimide (NTf_2), 1-butyl-1-methylpyrrolidinium NTf, benzethonium-ZnCl2-BMP-NTf_2, 1-hexyl-3-methylimidazolium chloride, and deep eutectic solvents such as choline carboxylate, choline-oleate, choline-hexanoate, choline geranate, choline-malonate and choline-urea for biofilm disruption and improved antibiotic delivery through skin layers. They reported their study on two biofilms-forming pathogens, *Pseudomonas aeruginosa* and another *Salmonella enterica*, for neutralisation effect. Furthermore, they extended their study to skin irritation, delivery of antibiotics through the skin, cytotoxicity and biofilms in a wound model. They examined the treatment on biofilms *S. enterica* and *P. aeruginosa* and choline geranate showed excellent activity compared to the other ionic liquids. Choline geranate displayed remarkable antimicrobial activity, minimum toxicity to epithelial cells as well as skin layer effective permeation enhancement for drug delivery. When compared to other ionic liquids, choline

geranate enhanced the cefadroxil delivery, by >16-fold, into deep tissue layers of the skin without tempting skin irritation. In the biofilm infected wound model study, the *vivo* efficacy of choline-geranate was validated whereas >95% bacterial death was observed after 2 hr of treatment. These ionic liquids provide an arsenal of material to effectively disrupt antibiotic-resistant bacterial biofilms, neutralise pathogens in skin and enhance antibiotic delivery in topical transdermal drug delivery (Zakrewsky *et al*., 2014). Figure 2.27 shows a model of cross section of skin layers along with stratum corneum, epidermis and dermis section and topical application of ionic liquids for fighting with a skin-borne bacterial infection.

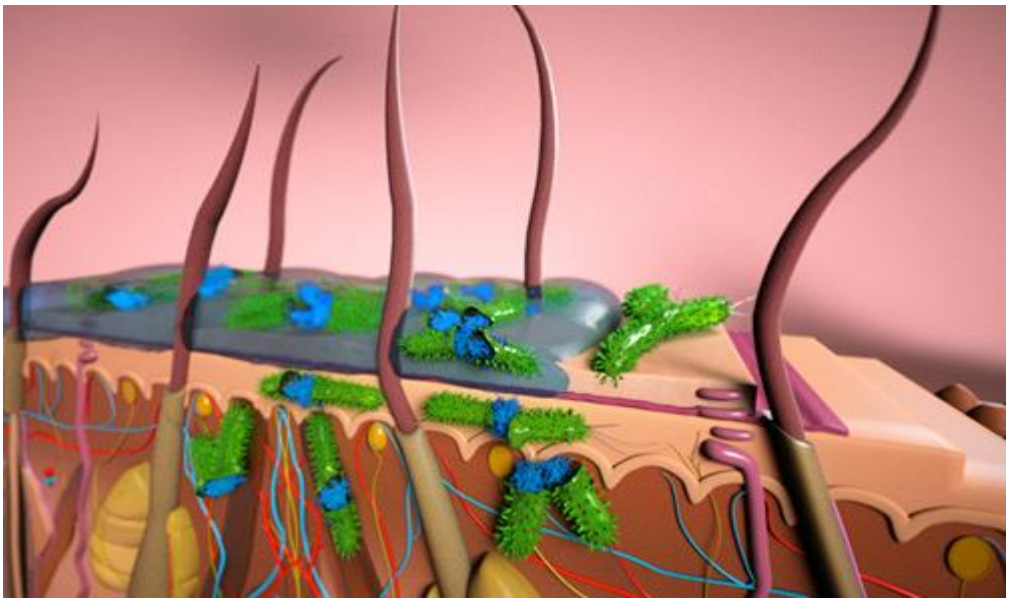


Figure 2.27 Diagram of a cross-section of skin layers showing an ionic liquid in transdermal drug delivery (Zakrewsky et al., 2014, Ambrosiano, 2014)

2.3.2 Summary

The background section summarised the properties, method of preparation and pharmaceutical applications of ionic liquids. It was found that there is a huge amount of research needed for understanding ionic liquids at the microscopic as

well as molecular level. There are a large and diverse number of cations and anions available for producing novel ionic liquids with selected properties. Most importantly, should the pharmaceutical industries involved in manufacturing solids and solid dosage forms explore the use of ionic liquid as liquid dosage form more intensely, ionic liquids could feature hugely in pharmaceuticals.

Chapter 3. Materials and methods

In this chapter, the material and methods used for the investigating the synthesis, crystallisation and drug delivery using ionic liquids are discussed in detail. The chapter is divided into three major sections; materials, methods and instrumentation. In the first section, all materials used are discussed, in second section, all methods which are used in this study are discussed and third section describes all instrumentation.

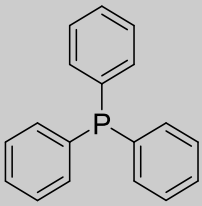
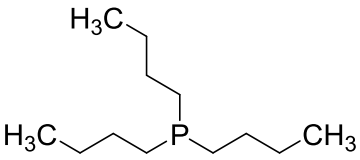
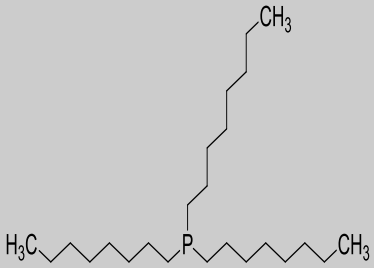
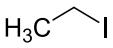
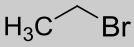
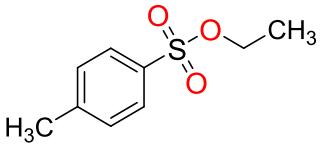
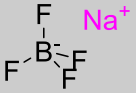
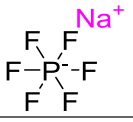
3.1 Materials

The sourcing of materials used in this work is described in the following sections.

3.1.1 Chemicals for synthesis of phosphonium ionic liquids and drug ionic liquids

The details of chemicals used in this study as shown in Table 2.5

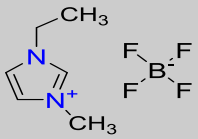
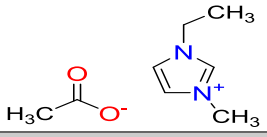
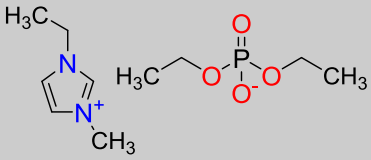
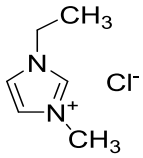
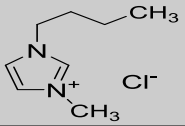
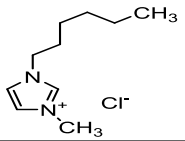
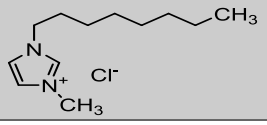
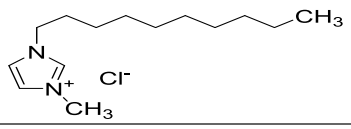
Table 3.1: phosphonium ionic liquids for synthesis

Name	Structure	Purity	Source	CAS no.
Triphenylphosphine		97	Sigma	603-35-0
Tributylphosphine		97	Sigma	998-40-3
Trioctylphosphine		98	Sigma	4731-53-7
Iodoethane		98	Sigma	75-03-6
Bromoethane		95	Sigma	74-96-4
Ethyl tosylate		97	Sigma	80-40-0
Sodium tetrafluoroborate		98	Sigma	13755-29-8
Sodium hexafluorophosphate		98	Sigma	21324-39-0

3.1.2 Imidazolium ionic liquids used in crystallisation and drug ionic liquids.

The details of imidazolium ionic liquids are given below

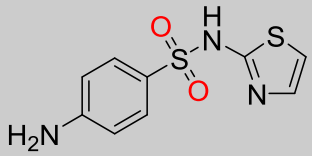
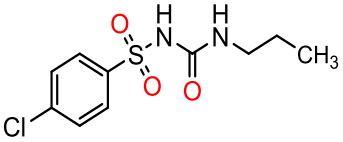
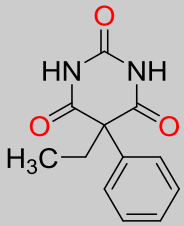
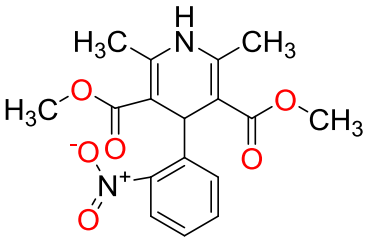
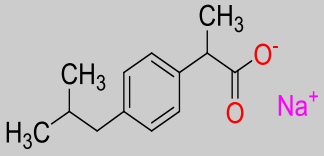
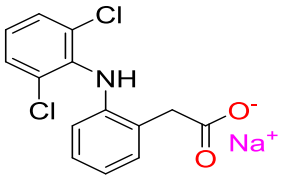
Table 3.2 Details of imidazolium ionic liquids

Name	Structure	Purity (%)	Source	CAS no
[EMIM] [BF4]		97	Sigma	143314-16-3
[EMIM][acetate]		97	Sigma	143314-17-4
[EMIM][DEP]		98	Sigma	848641-69-0
[EMIM][Cl]		98	Sigma	65039-09-0
[BMIM][Cl]		98	Sigma	79917-90-1
[HMIM][Cl]		98	Sigma	171058-17-6
[OMIM][Cl]		97	Sigma	64697-40-1
[DMIM][Cl]		98	Sigma	171058-18-7

3.1.3 Active Pharmaceutical Ingredients (APIs)

The drugs molecules for crystallisation and drug ionic liquid study are given below table (Table 2.7)

Table 3.3 Details of drugs used in crystallisation and drug ionic liquid.

Name	Structure	Purity (%)	Source	CAS number
Sulfathiazole		97	Sigma	72-14-0
Chloropropamide		97	Sigma	94-20-2
Phenobarbital		98	Sigma	50-06-6
Nifedipine		97	Sigma	21829-25-4
Sodium ibuprofen		98	Sigma	31121-93-4
Sodium diclofenac		97	VWR	15307-79-6

In the Materials section the ionic liquid and APIs were described in the following section, the methods used in this work are discussed in detail.

3.1.4 Chemicals for analysis

I. De-ionised water: De-ionised water used for experiments was collected from ELGA purelab ultra system providing water with purity of 18.2 MΩ/cm.

II. Deuterated chloroform (molecular sieves): CAS number 64-17-5 was purchased from Cambridge Isotope Laboratories for NMR analysis.

III. Ethanol (HPLC grade): CAS number 64-17-5 was purchased from Sigma Aldrich.

IV. Methanol (HPLC grade): CAS number 67-56-1 was purchased from Sigma Aldrich.

3.1.5 Instruments

No.	Instrument	Made
1	Nuclear magnetic resonance spectroscopy (NMR)	Bruker-Spectrospin 400 Ultra shield
2	Differential scanning calorimetry (DSC)	TA Q2000
3	Thermogravimetric analyser (TGA)	TA Q5000
4	Infrared spectroscopy (IR)	Jascov-630
5	Powder X-ray diffractometer (PXRD)	Bruker D 8 diffractometer
6	Single crystal X-ray diffractometer (SC-XRD)	Bruker APEX 8
7	High performance liquid chromatography (HPLC)	Waters e-2695)
8	Osmometer	Advanced instrument. Inc. Model 3320

3.1.6 Other consumables and supportive equipment

Description of other consumables and supportive equipment are provided below,

i. Water radleys manifold was used for heating and refluxing reaction mixtures.
ii. A vacuum filter assembly of 1 L capacity glass flask with side arm (Pyrex) and vacuum pump (Greiffenberger Antriebstechnik); whatman filter papers (55mm diameter) was used for solvent filtration.
iii. Vortex machine (Clifton cyclone) used for vortexing solutions for calibration studies.
iv. Centrifugation (Hettich centrifuges) was used in SPE studies to centrifuge samples at 1000rpm for 1 minute for partition coefficient study.
v. Magnetic stirrer (IKA WERKE RT 15 power) used for crystallisation study
vi. Cellulose sac used for diffusion study

3.2 Methods

In this section various methods were used for the work, however this section divided into three subsections i) preparation of ionic liquids ii) crystallisation of drug from ionic liquids iii) pharmaceutical performance of drug imidazolium ionic liquids and all these subsections includes methods and characterisations. This section describes as shown in schematic figure 2.28

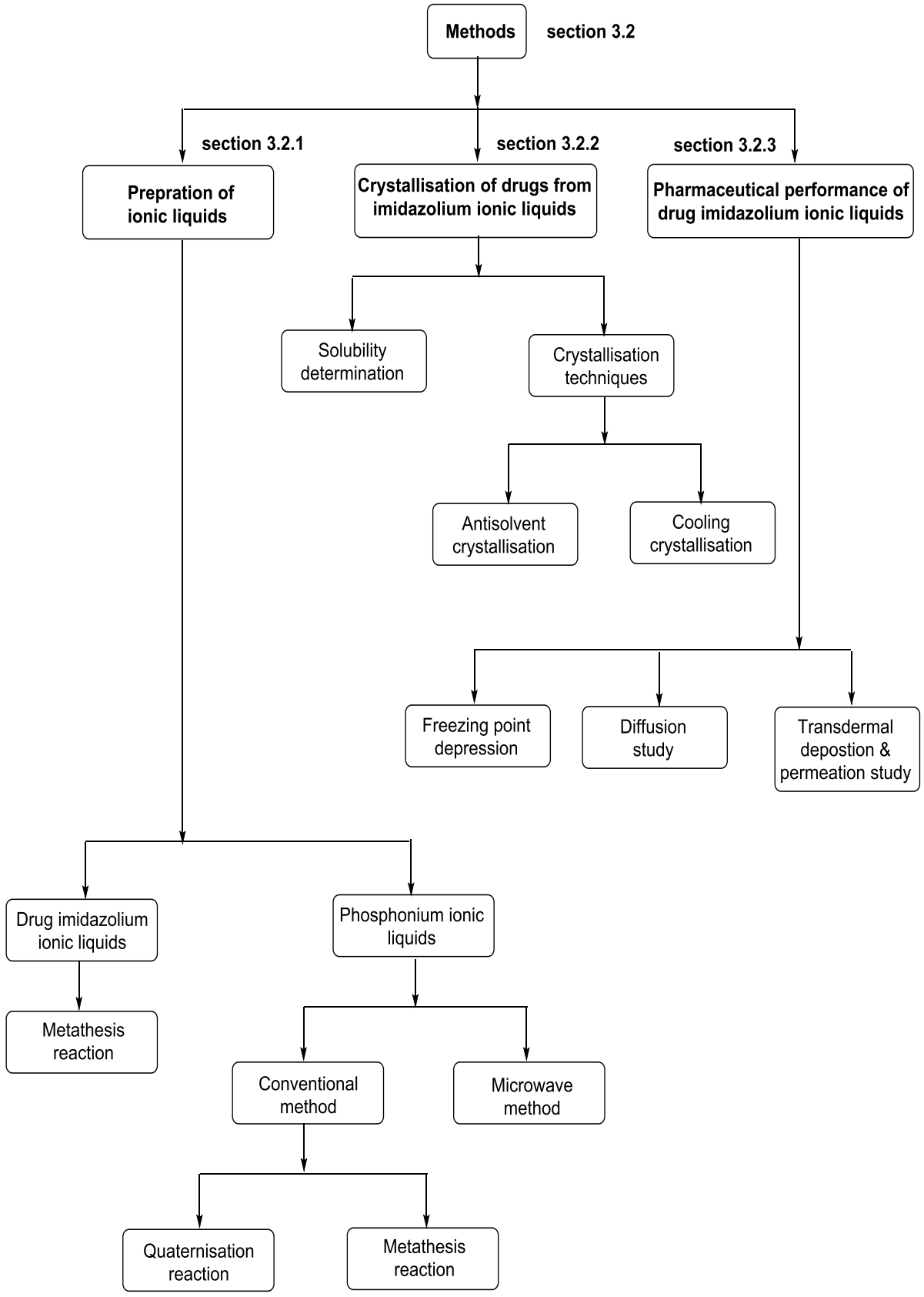


Figure 3.1 Schematic digram for methods used in work.

3.2.1 Preparation of ionic liquids

In this section methods used in the preparation of phosphonium and drug imidazolium ionic liquids were describes in details. This section also describes the NMR and IR results and for the details method for sample preparation was discussed in the section 3.2.2.2 and 3.2.2.4 respectively**.**

3.2.1.1 Preparation of phosphonium ionic liquids

This section describes the preparation of phosphonium ionic liquids using both conventional and microwave method.

3.2.1.1.1 Preparation of phosphonium ionic liquids by conventional method

In this section the preparation of phosphonium ionic liquids by conventional method is described. In the preparation methods for ionic liquids contains three anions which include tosylate, phosphonium halides, BF4 and PF_6 anions.

A Preparation of phosphonium ionic liquids by quaternisation method

The phosphonium tosylates and halides were prepared according to the method by Ludley (Ludley and Karodia, 2001) which was based on a modification of the method of Klamann and Weyerstahl (Klamann and Weyerstahl, 1964). A solution of phosphine (1 equiv.) and alkyl tosylates/alkyl halide (1 equiv.) in dry toluene was heated under reflux for the appropriate time. The reaction mixture was cooled to room temperature, the solvent was evaporated under vacuum and the product washed with ether, and the residual ether was removed under vacuum.

I. Preparation of ethyltriphenylphosphonium tosylate

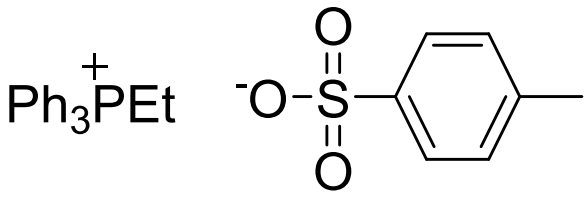


Figure 3.2 Structure of ethyltriphenylphosphonium tosylate

Ethyltriphenylphosphonium tosylate (Figure 3.2) was prepared by heating a solution of triphenylphosphine (13.13 g, 50 mmol) and ethyl tosylate (10.01 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product as a white solid (72%), mp: 134-137 °C (lit.135-138 °C) (Ludley and Karodia, 2001).Molecular formula: $C_{25}H_{22}O_3PS$. IR $\upsilon_{max}(cm^{-1})$: 1437, 3082, 2912, 1113, 985. ^{1}HNMR (δppm; $CDCl_3$): 1.32-1.40 (3H, dt, J_{P-H} 12, J_{H-H} 8, C$\underline{H}_3$CH$_2$P) 3.68 (2H, dq, J_{P-H} 16, J_{H-H}8, CH$_3$C$\underline{H}_2$P), 2.32 (3H, s, C$\underline{H}_3$C), 7.12 (2H,d, *J* 8, H-3 & 3; tolyl), 7.68-7.82 (17H, m, ArP, tolyl); ^{13}C NMR (δ, ppm, $CDCl_3$): 6.74 (d, *J* 5, $\underline{C}$H$_3$CH$_2$P), 16.38 (d, *J* 52, CH$_3\underline{C}$H$_2$P), 21.28 ($\underline{C}$H$_3$C), 117.89 (d, *J* 86 $\underline{C}$1 Ph-P), 126.18 (C-3 and 3 of tolyl), 128.32 ($\underline{C}$-2 and 2 of tolyl) 130.50 (d, *J* 12, $\underline{C}$-2 and 2' of Ph-P), 133.67 (d, *J* 3, $\underline{C}$-4 of Ph-P) 138.55 ($\underline{C}$-4 of tolyl), 144.37 (C-1 of tolyl); ^{31}P NMR (δ, ppm, $CDCl_3$): + 26.41.

II. Preparation of ethyltri-n-butylphosphonium tosylate

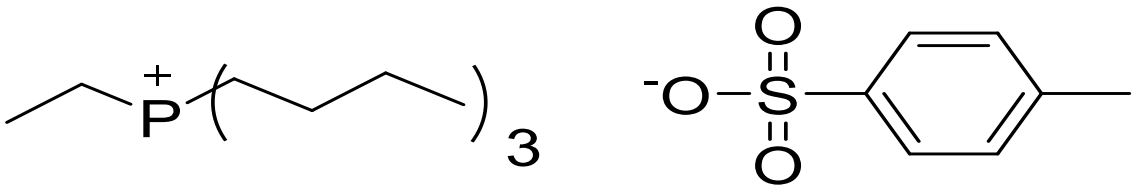


Figure 3.3 Structure of ethyltri-*n*-butylphosphonium tosylate

Ethyltri-*n*-butylphosphonium tosylate (Figure 3.3) was prepared by heating a solution of tributylphosphine (10.16 g, 50 mmol) and ethyl tosylate (10.01 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (69%)as a waxy solid, m.p.87-89 $^{\circ}$C, (lit.,73-76 °C) (Ludley and Karodia, 2001).Molecular formula: $[C_{14}H_{32}P]^{+}[C_7H_7SO_3]^{-}$. IR$\upsilon_{max}$($cm^{-1}$): 1465, 2932, 2931, 1116, 985. ^{1}HNMR (δ, ppm, $CDCl_3$): 0.93 (t, 9H, J_{H-H}8, (C$\underline{H}_3(CH_2)_3P$), 1.21 (dt, 3H, J_{P-H} 12, J_{H-H} 8, C$\underline{H}_3CH_2P$), 1.46 (m, 12H, $(CH_3C_2\underline{H}_4CH_2)_3P$), 2.27 (m, 6H, $(CH_3C_2H_4C\underline{H}_2)_3P$), 2.32 (s, 3H, CC$\underline{H}_3$) 2.37 (m, 2H, $(CH_3\text{-}C_2H_4\text{-}C\underline{H}_2)_3P$), 7.12 (2H, d, *J* 8, H-3 & 3; tolyl), 7.77 (2H, d, *J* 8, H-2 & 2' tolyl). ^{13}C NMR (δppm; $CDCl_3$): 6.0 (d, *J*6, $\underline{C}H_3CH_2P$), 12.36 (d, *J* 50, $CH_3\underline{C}H_2P$), 13.43 (d, *J* 7 $\underline{C}H_3CH_2$ CH_2CH_2P), 18.02 (d, *J* 47, $CH_3(CH_2)_2\underline{C}H_2P$), 21.26 ($\underline{C}H_3C_6H_4$), 23.84 ($\underline{C}H_2CH_2CH_2P$), 24.10 ($\underline{C}H_2CH_2P$), 126.06 (C-3 3' tolyl) 128.41 (C-2 & 2' of tolyl) 138.96 (C-4 of tolyl) 143.94 (C-1 of tolyl); ^{31}P NMR (δ, ppm, $CDCl_3$): +34.67.

III. Preparation of ethyltri-n-octylphosphonium tosylate

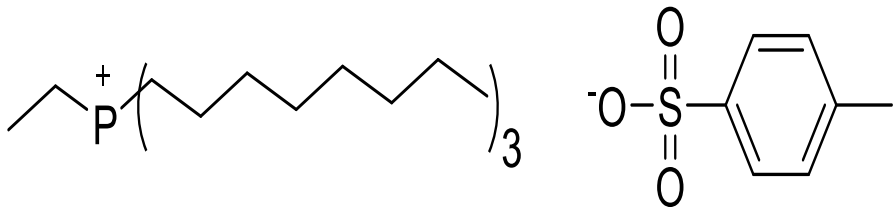


Figure 3.4 Structure of ethyltri-*n*-octylphosphonium tosylate

Ethyltri-*n*-octylphosphonium tosylate (Figure 3.4) was prepared by heating a solution of trioctylphosphine (18.53 g, 50 mmol) and ethyl tosylate (10.01 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (90%)as a white solid, oil. mp: 68-70 °C (lit. 72-76 °C) (Ludley and Karodia, 2001).Molecular formula: $[C_{26}H_{56}P]^{+}[C_7H_7SO_3]^{-}$. IR υ_{max}(cm^{-1}): 1463, 2925, 1120, 985. ^{1}H NMR

(δ, ppm, $CDCl_3$): 0.99 (t, 9H, J_{P-H} 12, J_{H-H} 8, ($C\underline{H}_3$-C_7H_{14})$_3$P), 1.07 (dt, 3H, $C\underline{H}_3CH_2P$), 1.29-1.70 (m, 30H, ($CH_3C_5\underline{H}_{10}C_2H_4$)$_3$P), 2.19 (m, 6H, ($CH_3$-$C_5H_{10}C\underline{H}_2CH_2$)$_3$P), 2.35 (s, 3H, $CC\underline{H}_3$) 2.33 (m, 6H, ($CH_3C_5H_{10}CH_2C\underline{H}_2$)$_3$P), 2.49 (dq, 2H,$J_{P-H}$ 16, J_{H-H} 8, $CH_3C\underline{H}_2P$), 7.28 (d, 2H,-$C\underline{H}$=C(SO_3)-$C\underline{H}$=) 7.81 (d, 2H, -$C\underline{H}$=C(CH_3)-$C\underline{H}$=). ^{13}C NMR (δ, ppm, $CDCl_3$): 6.07 (d, *J* 6, $\underline{C}H_3CH_2P$), 13.06 (d, *J* 50, $CH_3\underline{C}H_2P$), 14.05 ($\underline{C}H_3(CH_2)_7P$), 18.89 (d, *J* 47, $CH_3(CH_2)_6\underline{C}H_2P$), 21.30 ($C\underline{C}H_3P$), 21.82 (d, *J* 4, $\underline{C}H_2CH_2CH_2CH_2P$), 22.59 ($CH_3(CH_2)_2\underline{C}H_2(CH_2)_4P$), 30.88 (d, *J* 15, $\underline{C}H_2CH_2CH_2P$), 31.78 ($CH_3CH_2\underline{C}H_2(CH_2)_5P$), 126.14 (C3 & 3' tolyl) 128.60 (2 & 2' of tolyl) 139.74 (C-4 of tolyl) 142.43 (C-1 of tolyl); ^{31}P NMR (δ, ppm, $CDCl_3$): +34.41.

IV. Preparation of ethyltriphenylphosphonium iodide

Figure 3.5 Structure of ethyltriphenylphosphonium iodide

Ethyltriphenylphosphonium iodide (Figure 3.5) was prepared by heating a solution of triphenylphosphine (13.13 g, 50 mmol) and ethyl Iodide (7.79 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (76%) as a white solid, mp: 152-155 °C (lit.,164-165 °C) (McComsey and Maryanoff, 2001).Molecular formula: $C_{20}H_{20}IP$. IR υ_{max}(cm^{-1}): 1457, 2932. ^{1}HNMR (δppm; $CDCl_3$): 1.41 (3H, dt, J_{P-H} 16, J_{H-H} 8, $C\underline{H}_3CH_2P$), 3.79 (2H, dq, J_{P-H} 16, J_{H-H}8, $CH_3C\underline{H}_2P$), 7.84 (m, 15H, ArP) ; ^{13}C NMR (δ, ppm, $CDCl_3$): 6.84 (d, *J* 5, $\underline{C}H_3CH_2P$), 16.99 (d, *J* 52, $CH_3\underline{C}H_2P$), 117.80 (d, *J* 86 $\underline{C}$1 of Ph-P), 130.38 (d, *J* 12, $\underline{C}$-2 of Ph-P), 133.79 (d, *J* 3, $\underline{C}$-3 of Ph-P) 134.9 ($\underline{C}$-4 of Ph-P); ^{31}P NMR (δ, ppm, $CDCl_3$): + 26.35.

V. Preparation of ethyltriphenylphosphonium bromide

Figure 3.6 Structure of ethyltriphenylphosphonium bromide

Ethyltriphenylphosphonium bromide (Figure 3.6) was prepared by heating a solution of triphenylphosphine (13.13 g, 50 mmol) and ethyl bromide (5.44 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (78%) as a white solid, mp: 187-189 °C (lit.,209-210 °C) (McComsey and Maryanoff, 2001). Molecular formula: $C_{20}H_{20}PBr$. IR $\upsilon_{max}(cm^{-1})$: 1431, 3020, 2909. ^{1}HNMR (δppm; $CDCl_3$): 1.41 (3H, dt, J_{P-H} 16, J_{H-H} 8, C$\underline{H}_3$CH$_2$P), 3.95 (2H, dq, J_{P-H} 16, J_{H-H}8, CH$_3$C$\underline{H}_2$P), 7.45 (m, 15H, ArP) ; ^{13}C NMR (δ, ppm, $CDCl_3$): 6.84 (d, *J* 5, $\underline{C}$H$_3$CH$_2$P), 16.99 (d, *J* 52, CH$_3\underline{C}$H$_2$P), 117.75 (d, *J* 86 $\underline{C}$1 Ph-P), 130.38 (d, *J* 12, $\underline{C}$-2 of Ph-P), 133.67 (d, *J* 3, $\underline{C}$-3 of Ph-P) 134.9 ($\underline{C}$-4 of Ph-P); ^{31}P NMR (δ, ppm, $CDCl_3$): + 26.48.

VI. Preparation of ethyltri-*n*-butylphosphonium bromide

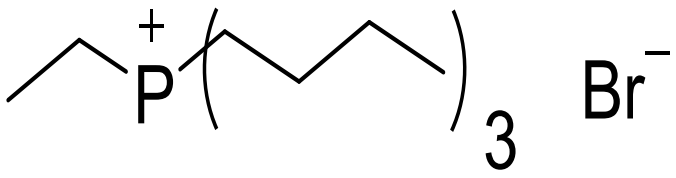


Figure 3.7 Structure of ethyltri-*n*-butylphosphonium bromide

Ethyltri-*n*-butylphosphonium bromide (Figure 3.7) was prepared by heating a solution of tri-*n*-butylphosphine (10.16 g, 50 mmol) and ethyl bromide (5.44 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (66%) as a waxy

solid. mp: 70-72 °C. Molecular formula: $[C_{14}H_{32}P]^{+}[Br]^{-}$. IR $\upsilon_{max}(cm^{-1})$: 1465, 2932. ^{1}HNMR (δ, ppm, $CDCl_3$): 0.92 (t, 9H, J_{H-H}8, ($C\underline{H}_3(CH_2)_3P$), 1.17 (dt, 3H, J_{P-H} 18, J_{H-H} 8, $C\underline{H}_3CH_2P$), 1.55 (m, 12H, ($CH_3C_2\underline{H}_4CH_2)_3P$), 2.20-2.43 (m, 6H, ($CH_3C_2H_4C\underline{H}_2)_3P$), 2.38 (dt, J_{P-H} 13, J_{H-H} 8, 2H, $CH_3C\underline{H}_2P$). ^{13}C NMR (δ, ppm, $CDCl_3$): 6.2 (d, *J*6, $\underline{C}H_3CH_2P$), 13.00 (d, *J* 50, $CH_3\underline{C}H_2P$), 13.50 (d, *J* 7 $\underline{C}H_3CH_2CH_2P$), 18.95 (d, *J* 47, $CH_3(CH_2)_2\underline{C}H_2P$), 23.80 ($\underline{C}H_2CH_2P$), 27.10 ($\underline{C}H_2CH_2CH_2P$); ^{31}P NMR (δ, ppm, $CDCl_3$): + 34.56.

VII. Preparation of ethyltri-*n*-butylphosphonium iodide

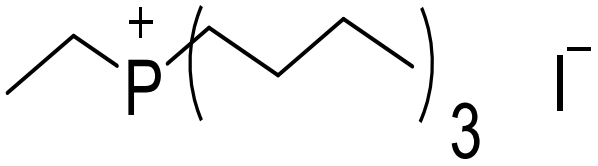


Figure 3.8 Structure of ethyltri-*n*-butylphosphonium iodide

Ethyltri-*n*-butylphosphonium iodide (Figure 3.8) was prepared by heating a solution of tributyl-*n*-phosphine (10.16 g, 50 mmol) and ethyl Iodide (7.79 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (62%) as a waxy solid. m.p. 48-50 °C, mp: 150-152 °C. Molecular formula: $[C_{14}H_{32}P]^{+}[I]^{-}$. IR $\upsilon_{max}(cm^{-1})$: 1457, 2952. ^{1}HNMR (δppm; $CDCl_3$): 0.92 (t, 9H, J_{H-H}12, ($C\underline{H}_3(CH_2)_3P$), 1.17 (dt, 3H, J_{P-H} 18, J_{H-H} 8, $C\underline{H}_3CH_2P$), 1.42 (m, 12H, ($CH_3C_2\underline{H}_4CH_2)_3P$), 2.29 (m, 6H, ($CH_3C_2H_4C\underline{H}_2)_3P$), 2.39 (dt, J_{P-H} 13, J_{H-H} 8, 2H, $CH_3C\underline{H}_2P$). ^{13}C NMR (δ, ppm, $CDCl_3$): 6.1 (d, *J*6, $\underline{C}H_3CH_2P$), 13.10 (d, *J* 50, $CH_3\underline{C}H_2P$), 13.55 (d, *J*7 $\underline{C}H_3CH_2CH_2CH_2P$), 19.24 (d, *J* 47, $CH_3(CH_2)_2\underline{C}H_2P$), 23.70 ($\underline{C}H_2CH_2P$), 24.07 ($\underline{C}H_2CH_2CH_2P$); ^{31}P NMR (δ, ppm, $CDCl_3$): + 34.48.

VIII. Preparation of ethyltri-*n*-octylphosphonium bromide

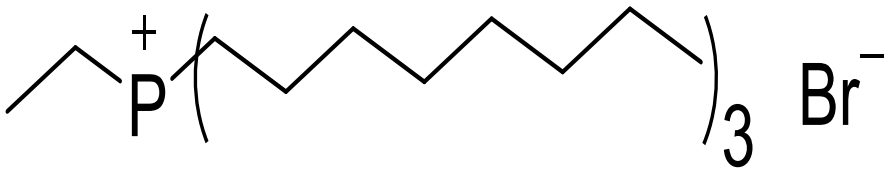


Figure 3.9 Structure of ethyltri-*n*-octylphosphonium bromide

Ethyltri-*n*-octylphosphonium bromide (Figure 3.9) was prepared by heating a solution of trioctylphosphine (18.53 g, 50 mmol) and ethyl bromide (5.44 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (96%) as a waxy solid. m.p. 50-54 ^{o}C. Irradiation time: 90 s. Yield: 98 %; mp: 85-87 °C. Molecular formula: $[C_{26}H_{56}P]^{+}[Br]^{-}$. IR υ_{max} (cm^{-1}): 1464, 2952. ^{1}HNMR ($CDCl_3$): 0.89 (t, 9H, J_{P-H} 12, J_{H-H} 8, $(C\underline{H}_3C_7H_{14})_3P$), 1.25 (dt, 3H, J_{P-H} 18, J_{H-H} 8, $C\underline{H}_3(CH_2)_7P$), 1.30-1.70 (m, 30H, $(CH_3C_5\underline{H}_{10}C_2H_4)_3P$), 2.20 (m, 6H, $(CH_3C_5H_{10}C\underline{H}_2CH_2)_3P$), 2.35 (m, 6H, $CH_3(C_6H_{12}C\underline{H}_2)_3P$), 2.52 (dq, 2H, J_{P-H} 20, J_{H-H} 8, $CH_3C\underline{H}_2P$); ^{13}C NMR (δ, ppm, $CDCl_3$): 6.12 (d, *J* 6, $\underline{C}H_3CH_2P$), 12.98 (d, *J* 50, $CH_3\underline{C}H_2P$), 14.1 ($\underline{C}H_3(CH_2)_7P$), 18.46 (d, *J* 6, $CH_3(CH_2)_7P$), 21.6 (d, *J* 4 $\underline{C}H_2CH_2CH_2CH_2P$), 22.7 ($CH_3(CH_2)_2\underline{C}H_2(CH_2)_4P$), 28.88 (d, *J* 15, $\underline{C}H_2CH_2CH_2P$), 31.1 (d, *J* 15, $CH_2CH_2CH_2P$), 31.8 ($CH_3CH_2\underline{C}H_2(CH_2)_5P$); ^{31}P NMR (δ, ppm, $CDCl_3$): +34.48.

IX. Preparation of ethyltri-*n*-octylphosphonium iodide

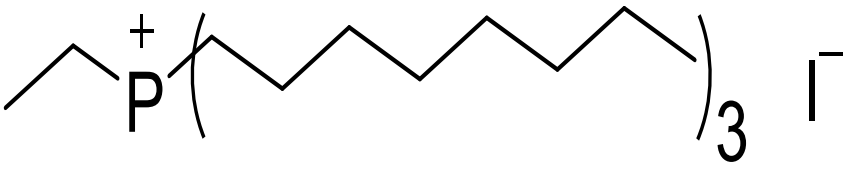


Figure 3.10 Structure of ethyltri-*n*-octylphosphonium iodide

Ethyltri-*n*-octylphosphonium iodide (Figure 3.10) was prepared by heating a solution of trioctyl-phosphine (18.53 g, 50 mmol) and ethyl iodide (7.79 g, 50 mmol) in dry toluene (40ml) for 40 hrs to furnish the product (92%) as a waxy solid, mp: 60-62 °C. Molecular formula: $[C26H56P]^{+}[I]^{-}$. IR υ_{max} (cm^{-1}): 1464, 2952. ^{1}H NMR (δ, ppm, $CDCl_3$): 0.92 (t, 9H, J_{P-H} 12, J_{H-H} 8, $(CH_3C_7H_{14})_3P$), 1.07 (dt, 3H, J_{P-H} 18, J_{H-H} 8, $CH_3(CH_2)_7P$), 1.30-1.70 (m, 30H, (CH_3C5H10C2H4)3P), 2.24 (m, 6H, ($CH_3C_5H_{10}$CH2CH2)3P), 2.32 (m, 6H, CH3(C6H12CH2)3P), 2.49 (dq, 2H, J_{P-H} 20, J_{H-H} 8, CH3CH2P); ^{13}C NMR (δ, ppm, CDCl3): 6.18 (d, J 6, CH3CH2P), 13.72 (d, J 50, CH3CH2P), 14.59 (CH3(CH2)7P), 18.85 (d, J 6, CH3(CH2)7P), 21.74 (d, J 4 CH2CH2CH2CH2P), 22.68 (CH3(CH2)2CH3(CH2)4P), 28.86 (d, J 15, CH2CH2CH2P), 29.86 (d, J 15, CH2CH2CH2P), 31.47 (CH3CH2CH2(CH2)5P); ^{31}P NMR (δ, ppm, CDCl3): +34.48.

B Preparation of phosphonium ionic liquids by metathesis method

A solution of anion in water was added slowly to a cold, rapidly solution of ionic liquid in water and acetone. The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane. The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%), and then with

water. The mixture was dried over $MgSO_4$, and then solvent was removed under vacuum to yield.

I. Preparation ethyltri-*n*-octylphosphonium tetrafluoroborate

Figure 3.11 Structure of ethyltri-*n*-octylphosphonium tetrafluoroborate

A solution of sodium tetrafluoroborate (10.97 g, 2 equivalents) in water (40 ml) was added slowly to a cold, rapidly stirring solution of ethyltri-*n*-octylphosphonium bromide (23.98 g, 50 mmol) in water (20 ml) and acetone (20 ml). The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane (2 x 50 ml). The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%, 2 x 20 ml), and then with water. The mixture was dried over $MgSO_4$, and then solvent was removed under vacuum to yield oil (89%).Molecular formula: $[C_{26}H_{56}P]^+[BF_4]^-$. IR υ_{max} (cm^{-1}): 1466, 2925, 1282. ^{1}HNMR (δ, ppm, $CDCl_3$): 0.90 (t, 9H, $J_{P\text{-}H}$ 12, $J_{H\text{-}H}$ 8, ($C\underline{H}_3C_7H_{14})_3P$), 1.05 (dt, 3H, $J_{P\text{-}H}$ 18, $J_{H\text{-}H}$ 8, $C\underline{H}_3(CH_2P)$, 1.31-1.67 (m, 30H, ($CH_3C_5\underline{H}_{10}C_2H_4)_3P$), 2.23 (m, 6H, ($CH_3C_5H_{10}C\underline{H}_2CH_2)_3P$), 2.32 (m, 6H, CH_3-($C_6H_{12}C\underline{H}_2)_3P$), 2.52 (dq, 2H, $J_{P\text{-}H}$ 20, $J_{H\text{-}H}$ 8, $CH_3C\underline{H}_2P$); ^{13}C NMR (δ, ppm, $CDCl_3$): 6.05 (d, *J* 6, $\underline{C}H_3CH_2P$), 13.08 (d, *J* 50, $CH_3\underline{C}H_2P$), 13.68 ($\underline{C}H_3(CH_2)_7P$), 17.89 (d, *J* 6, $CH_3(CH_2)_7P$), 21.74 (d, *J* 4 $\underline{C}H_2CH_2CH_2CH_2P$), 22.48 ($CH_3(CH_2)_2\underline{C}H_3(CH_2)_4P$), 27.86 (d, *J* 15, $\underline{C}H_2CH_2CH_2P$), 38.8 (d, *J* 15, $CH_2CH_2CH_2P$), 32.47 ($CH_3CH_2\underline{C}H_2(CH_2)_5P$); ^{31}P NMR (δ, ppm, $CDCl_3$): + 34.58.

II. Preparation of ethyltri-*n*-octylphosphonium hexafluorophosphate

Figure 3.12 Structure of ethyltri-*n*-octylphosphonium hexafluorophosphate

A solution of sodium hexafluorophosphate (16.75 g, 2 equivalents) in water (40 ml) was added slowly to a cold, rapidly stirring solution of in tri-*n*-octylphosphonium bromide (23.98 g, 50 mmol) in water (20 ml) and acetone (20 ml). The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane (2 x 50 ml). The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%, 2 x 20 ml), and then with water. The mixture was dried over $MgSo_4$, and then solvent was removed under vacuum to yield oil (90%). Molecular formula: $[C_{26}H_{56}P]^{+}[PF_6]^{-}$. IR $v_{max}(cm^{-1})$: 1489, 2925, 831. ^{1}HNMR (δ, ppm, $CDCl_3$): 0.90 (t, 9H, $J_{P\text{-}H}$ 12, $J_{H\text{-}H}$ 8, $(C\underline{H}_3C_7H_{14})_3P$), 1.05 (dt, 3H, $J_{P\text{-}H}$ 18, $J_{H\text{-}H}$ 8, $C\underline{H}_3(CH_2)_7P$), 1.29-1.70 (m, 30H, $(CH_3C_5\underline{H}_{10}C_2H_4)_3P$), 2.18 (m, 6H, $(CH_3\text{-}C_5H_{10}C\underline{H}_2CH_2)_3P$), 2.35 (m, 6H, $CH_3(C_6H_{12}C\underline{H}_2)_3P$), 2.54 (dq, 2H, $J_{P\text{-}H}$ 20, $J_{H\text{-}H}$ 8, $CH_3C\underline{H}_2P$); ^{13}C NMR (δ, ppm, $CDCl_3$): 6.12 (d, *J* 6, $\underline{C}H_3CH_2P$), 13.07 (d, *J* 50, $CH_3\underline{C}H_2P$), 15.1 ($\underline{C}H_3(CH_2)_7P$), 19.42 (d, *J* 6, $CH_3(CH_2)_7P$), 21.8 (d, *J* 4 $\underline{C}H_2CH_2CH_2CH_2P$), 22.5 $(CH_3(CH_2)_2\underline{C}H_3(CH_2)_4P)$, 28.09 (d, *J* 15, $\underline{C}H_2CH_2CH_2P$), 31.8 (d, *J* 15, $CH_2CH_2CH_2P$), 32.7 $(CH_3CH_2\underline{C}H_2(CH_2)_5P)$; ^{31}P NMR (δ, ppm, $CDCl_3$): + 34.58.

III. Preparation of ethyltri-*n*-butylphosphonium tetrafluoroborate

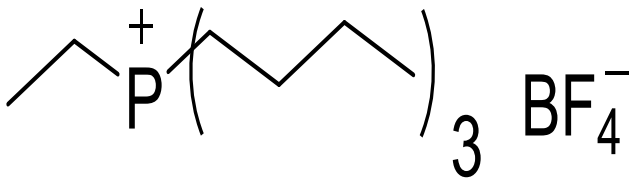


Figure 3.13 Structure of ethyltri-*n*-butylphosphonium tetrafluoroborate

A solution of sodium tetrafluoroborate (10.97 g, 2 equivalents) in water (40 ml) was added slowly to a cold, rapidly stirring solution of ethyltri-*n*-butylphosphonium bromide (15.60 g, 50 mmol) in water (20 ml) and acetone (20 ml). The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane (2 x 50 ml). The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%, 2 x 20 ml), and then with water. The mixture was dried over $MgSo_4$, and then solvent was removed under vacuum to yield as a white solid. (90%).mp: 153-155 °C, Molecular formula: $[C_{14}H_{32}P]^+[BF_4]^-$. IR υ_{max} (cm^{-1}): 1465, 2962, 1283. ^{1}HNMR (δ, ppm, $CDCl_3$); 0.96 (t, 9H, $J_{H\text{-}H}$8, ($C\underline{H}_3(CH_2)_3P$), 1.16 (dt, 3H, $J_{P\text{-}H}$ 18, $J_{H\text{-}H}$ 8, $C\underline{H}_3CH_2P$), 1.44 (m, 12H, ($CH_3C_2\underline{H}_4\text{-}CH_2)_3P$), 2.32 (m, 6H, ($CH_3C_2H_4C\underline{H}_2)_3P$), 2.39 (q, $J_{P\text{-}H}$ 20, $J_{H\text{-}H}$ 8, 2H, $CH_3C\underline{H}_2P$). ^{13}C NMR (δ, ppm, $CDCl_3$): 5.9 (d, *J*6, $\underline{C}H_3CH_2P$), 12.9 (d, *J* 50, $CH_3\underline{C}H_2P$), 13.44-13.67 (d, *J* 7 $\underline{C}H_3CH_2CH_2P$), 18.90 (d, *J* 47, $CH_3(CH_2)_2\underline{C}H_2P$), 23.70 ($\underline{C}H_2CH_2P$), 26.07 ($\underline{C}H_2CH_2CH_2P$); ^{31}P NMR (δ, ppm, $CDCl_3$): + 34.42.

IV. Preparation of ethyltri-*n*-butylphosphonium hexafluorophosphate

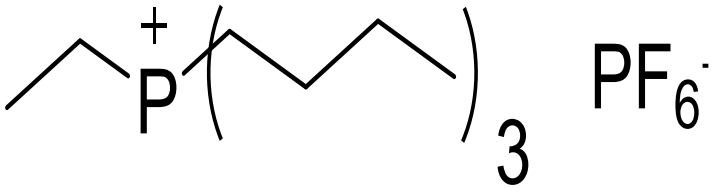


Figure 3.14 Structure of ethyltri-n-butylphosphonium hexafluorophosphate

A solution of sodium hexafluorophosphate (16.75 g, 2 equivalents) in water (40 ml) was added slowly to a cold, rapidly stirring solution of ethyltributylphosphonium bromide (15.60 g, 50 mmol) in water (20 ml) and acetone (20 ml). The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane (2 x 50 ml). The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%, 2 x 20 ml), and then with water. The mixture was dried over $MgSO_4$, and then solvent was removed under vacuum to yield as a white solid. (85%), mp: 145-147 °C, Molecular formula: $[C_{14}H_{32}P]^+[PF_6]^-$. IR $v_{max}(cm^{-1})$: 1465, 2958, 852. ^{1}HNMR (δ, ppm, $CDCl_3$); 0.98 (t, 9H, J_{H-H}8, (C$\underline{H}_3(CH_2)_3$P), 1.17 (dt, 3H, J_{P-H} 18, J_{H-H} 8, C$\underline{H}_3CH_2$P), 1.44 (m, 12H, (CH_3-$C_2\underline{H}_4$-CH_2)$_3$P), 2.26 (m, 6H, ($CH_3C_2H_4C\underline{H}_2$)$_3$P), 2.36 (dt, J_{P-H} 13, J_{H-H} 8, 2H, $CH_3C\underline{H}_2$P). ^{13}C NMR (δ, ppm, $CDCl_3$): 5.6 (d, *J*6, $\underline{C}H_3CH_2$P), 12.40 (d, *J* 50, $CH_3\underline{C}H_2$P), 13.67 (d, *J* 7 $\underline{C}H_3CH_2CH_2$P), 18.90 (d, *J* 47, $CH_3(CH_2)_2\underline{C}H_2$P), 23.70 ($\underline{C}H_2CH_2$P), 24.07 ($\underline{C}H_2CH_2CH_2$P); ^{31}P NMR (δ, ppm, $CDCl_3$): + 34.32.

V. Preparation of ethyltriphenylphosphonium tetrafluoroborate

Figure 3.15 Structure of ethyltriphenylphosphonium tetrafluoroborate

A solution of sodium tetrafluoroborate (10.97 g, 2 equivalents) in water (40 ml) was added slowly to a cold, rapidly stirring solution of ethyltriphenylphosphonium bromide (18.58 g, 50 mmol) in water (20 ml) and acetone (20 ml). The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane (2 x 50 ml). The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%, 2 x 20 ml), and then with water. The mixture was dried over $MgSO_4$, and then solvent was removed under vacuum to yield as a white solid (78%). mp: 138-140 °C, Molecular formula: $C_{20}H_{20}PBF_4$. IR $v_{max}(cm^{-1})$: 1436, 3057, 2958, 1283. ^{1}HNMR (δppm; $CDCl_3$):1.40 (3H, dt, J_{P-H} 16, J_{H-H} 8, C*H*$_3$CH$_2$P), 3.26 (2H, dq, J_{P-H} 16, J_{H-H}8, CH$_3$C*H*$_2$P), 7.73-7.83 (m, 15H, ArP) ; ^{13}C NMR (δ, ppm, $CDCl_3$): 6.80 (d, *J* 5, *C*H$_3$CH$_2$P), 16.78 (d, *J* 52, CH$_3$*C*H$_2$P), 117.32 (d, *J* 86 *C*1 of Ph-P), 130 (d, *J* 12, *C*-2 of Ph-P), 133.98 (d, *J* 3, *C*-3 of Ph-P) 135.72 (*C*-4 of Ph-P); ^{31}P NMR (δ, ppm, $CDCl_3$): + 25.67.

VI. Preparation of ethyltriphenylphosphonium hexafluorophosphate

Figure 3.16 Structure of ethyltriphenylphosphonium hexafluorophosphate

A solution of sodium hexafluorophosphate (16.75 g, 2 equivalents) in water (40 ml) was added slowly to a cold, rapidly stirring solution of in triphenylphosphonium bromide (18.58 g, 50 mmol) in water (20 ml) and acetone (20 ml). The reaction mix was stirred at RT for 36 h, and then was extracted with dichloromethane (2 x 50 ml). The combined organic phase as washed with cold aqueous sodium hydroxide solution (1%, 2 x 20 ml), and then with water. The mixture was dried over $MgSO_4$, and then solvent was removed under vacuum to yield as a white solid (88%), Mp: 168-170 °C, Molecular formula: $C_{20}H_{20}P_2F_6$ .IR υ_{max} (cm^{-1}): 1439, 3057, 2958, 830. ^{1}HNMR (δppm; $CDCl_3$): 1.41 (3H, dt, J_{P-H} 16, J_{H-H} 8, C<u>*H*</u>$_3$CH$_2$P), 3.27 (2H, dq, J_{P-H} 16, J_{H-H}8, CH$_3$C<u>*H*</u>$_2$P), 7.71-7.84 (m, 15H, ArP) ; ^{13}C NMR (δ, ppm, $CDCl_3$): 6.60 (d, *J* 5, <u>*C*</u>H$_3$CH$_2$P), 16.77 (d, *J* 52, CH$_3$<u>*C*</u>H$_2$P), 117.39 (d, *J* 86 <u>*C*</u>1 of Ph-P), 130.8 (d, *J* 12, <u>*C*</u>-2 of Ph-P), 133.98 (d, *J* 3, <u>*C*</u>-3 of Ph-P) 135.62 (<u>*C*</u>-4 of Ph-P); ^{31}P NMR (δ, ppm, $CDCl_3$): + 26.78.

3.2.1.1.2 Preparation of phosphonium ionic liquids by microwave-mediated synthesis

This section described the preparation of phosphonium ionic liquids by microwave method.

Figure 3.17 Microwave (monowave 300)

A General method for preparation of phosphonium ionic liquids by microwave

To a 30 cm^3 microwave vial was added the phosphine (1 eq) and tosyl ester or alkyl halide (1 eq). The vial was then placed in the microwave and the reaction was performed at 80°C and hold time was 30 s. The heat to time method was selected from the entry. The optimum reaction time was monitored by ^{31}P NMR spectroscopy which showed when the reaction was complete and the spectra matched those obtained from the traditional method. The data matches with section 3.2.2.

I. Preparation of ethyltri-*n*-butylphosphonium bromide

Ethyltri-*n*-butylphosphonium bromide was prepared by heating a solution of tri-*n*-butylphosphine (5.06g, 25 mmol) and iodoethane (3.9g, 25 mmol).The vial

was then place in the microwave and the reaction was performed at 80°C and hold time was for 60 s to furnish the pure product (100%).

II. Preparation of ethyltri-*n*-butylphosphonium tosylate

Ethyltri-*n*-butylphosphonium tosylate was prepared by heating a solution of tri-*n*-butylphosphine (5.06g, 25 mmol) and ethyltosylate (5.0 g, 25 mmol). The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 60 s to furnish the pure product (100%).

III. Preparation of ethyltri-*n*-butylphosphonium iodide

Ethyltri-*n*-butylphosphonium iodide was prepared by heating a solution of tri-*n*-butylphosphine (5.06g 25 mmol) and iodoethane (3.9g, 25 mmol).The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 60 s to furnish the pure product (100%).

IV. Preparation of ethyltriphenylphosphonium bromide

Ethyltriphenylphosphonium bromide was prepared by heating a solution of triphenylphosphine (6.6g, 25 mmol) and bromoethane 2.72g, 25 mmol).The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 30 s to furnish the pure product (100%).

V. Preparation of ethyltriphenylphosphonium iodide

Ethyltriphenylphosphonium iodide was prepared by heating a solution of Triphenylphosphine (6.6 g, 25 mmol) and iodoethane (3.9g, 25 mmol).The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 90 sec. The reaction was monitored by ^{31}P NMR spectroscopy which showed that the reaction was complete (100%).

VI. Preparation of ethyltriphenylphosphonium tosylate

Ethyltriphenylphosphonium tosylate was prepared by heating a solution of Triphenylphosphine (6.6 g, 25 mmol) and ethyl tosylate (3.9g, 25 mmol).The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 90 s. The reaction was monitored by ^{31}P NMR spectroscopy which showed that the reaction was complete (100%).

VII. Preparation of ethyl-tri-*n*-octylphosphonium bromide

Tri-*n*-octylethylphosphonium bromide was prepared by heating a solution of tri-*n*-octylphopshine (9.2g, 25 mmol) and bromoethane (2.72, 25 mmol).The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 30 s (100%).

VIII. Preparation of ethyl-tri-*n*-octylphosphonium iodide

Tri-*n*-octylethylphosphonium iodide was prepared by heating a solution of tri-*n*-octylphopshine (9.2g, 25 mmol) and iodoethane (3.9g, 25 mmol). The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 90 s. The reaction was monitored by ^{31}P NMR spectroscopy which showed that the reaction was complete (100%).

IX. Preparation of ethyltri-*n*-octylphosphonium tosylate

Ethyltri-*n*-octylphosphonium tosylate was prepared by heating a solution of tri-*n*-octylphopshine (9.2 g, 25 mmol) and ethyltosylate (5.00g, 25 mmol).The vial was then place in the microwave and the reaction was performed at 80°C and hold time was for 90 s. The reaction was monitored by ^{31}P NMR spectroscopy which showed that the reaction was complete (100%).

This section successfully evaluated the preparation of phosphonium ionic liquids by both conventional and microwave method.

In the next section the preparation of drug salt using imidazolium ionic liquids were describes in detail.

3.2.1.2 Preparation drug-imidazolium ionic liquids

In this section preparation of drug imidazolium ionic liquids were carried out by metathesis reaction which was described in detail.

3.2.1.2.1 General synthesis method

Ibuprofen sodium salt was dissolved in water and sodium diclofenac in 25 mL water: ethanol mixture (1:1 v/v ratio). This was added to warm aqueous solutions containing of [EMIM] [Cl], [BMIM] [Cl, [OMIM] [Cl], and [HMIM] [Cl], [DMIM] [Cl] ionic liquids in 25 mL ethanol: water mixture (1:1 v/v ratio). The mixtures were stirred at 30 °C for 24 hours and then cooled to room temperature. The water from the mixture was removed under vacuum to give the ionic liquid-drug and NaCl. Further, the removal of NaCl, extra ethanol was used to dissolve the ionic liquid and precipitated NaCl was removed through filtration. This process carried out at least three times using ethanol (3 X 50 mL). The ethanol was removed layer from the reaction mixture under the vacuum (175 mbar) at temperature 50 °C for 4 hrs. Further, obtained drug ionic liquids dried under the vacuum at temperature 60 °C for 8 hrs. A clear yellow and yellow brown colour of ibuprofen and diclofenac ionic liquids obtained respectively and ^{1}H NMR and ^{13}C NMR was carried out and describes in the following

I. 1-ethyl-3-methylimidazolium ibuprofen [RB-01]

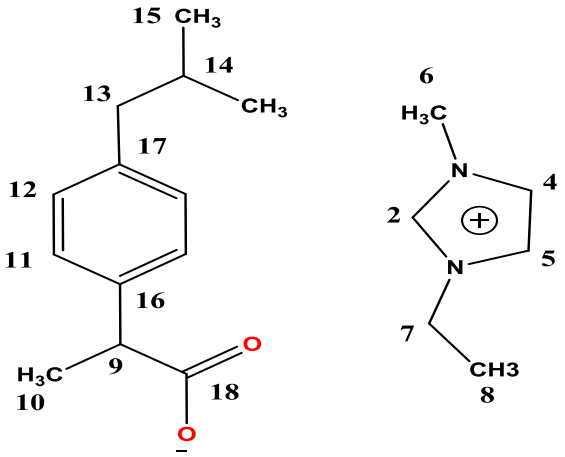


Figure 3.18 Structure of 1-ethyl-3-methylimidazolium ibuprofen

1-ethyl-3-methylimidazolium Ibuprofen (Figure 3.18) was obtained as a clear yellow gel: yield 88%^{1}H NMR (400 MHz, CDCl3) : δ =11.24 (1H, s, -N=C*H*-N-), 7.33-7.35 (2H, d, *J* = 8 Hz, =CH-CH=C*H*-CH=), 7.05-7.03 (1H, m, -N=C*H*-CH=N-), 7.05-7.03 (1H, m, -N=CH-C*H*=N-), 6.99-7.01 (2H, d, *J* = 8 Hz, =CH-C*H*=CH-CH=), 4.17 (2H, t, *J* = 16 Hz, ,-N-CH_2-), 3.90 (3H, s, CH_3-N-), 3.68-3.73 (1H, q, *J* = 20 Hz, CH3-C*H*-COO$^-$ H11), 2.39 (2H, d, *J* = 8 Hz, ,=CH-CH-CH_2-CH-), 1.80 (3H, m, CH_3-C-CH_3 H16), 1.49 (3H, d, *J* = 4 Hz, CH_3-CH-COO-), 1.23 (3H, t, *J* = 12 Hz, -N-CH_2-CH_3), 0.89 (3H, d, *J* = 16 Hz, ,CH_3-C-CH_3).

II. 1-butyl-3-methylimidazolium ibuprofen [RB 02]

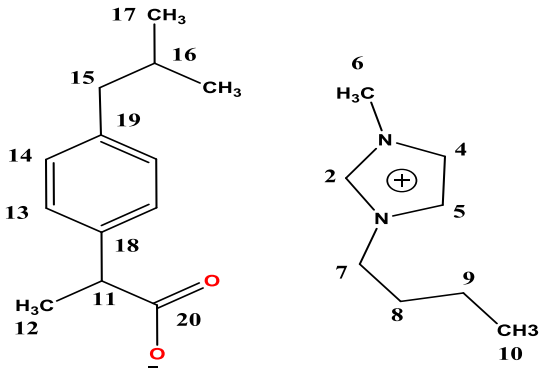


Figure 3.19 Structure of 1-butyl-3-methylimidazolium ibuprofen

1-butyl-3-methylimidazolium ibuprofen was obtained as a yellow clear gel. yield 91%. ^{1}H NMR (400 MHz, CDCl3) : δ =11.08 (1H, s, -N=C*H*-N-), 7.33-7.35 (2H, d, J = 8 Hz, =CH-CH=C*H*-CH=), 7.08-7.13 (1H, m, -N=C*H*-CH=N-H5,H4), 7.08-7.13 (1H, m, -N=CH-C*H*=N-), 6.98-7.00 (2H, d, J = 8 Hz, =CH-C*H*=CH-CH=H13), 4.15-4.18 (2H, t, J = 12 Hz,-N-CH_2- H7), 3.91 (3H, s, CH_3-N-H6), 3.66-3.71 (1H, q, J = 20 Hz, CH3-C*H*-COO^-H11), 2.38-2.39 (2H, d, J = 4Hz,=CH-CH-CH_2-CH- H15), 1.80 (2H, m, -N-CH2-C*H*2-CH_2-CH_3H8, H16),1.80 (3H, m, CH3-C-C*H*3 H16),1.47-1.49 (3H, d, J = 8 Hz, C*H*3-CH-COO^-H12), 1.25-1.28 (2H, m, H8, -N-(CH2)2-C*H*2-CH3 H9), 1.22 (3H, t, J = 12 Hz, -N-$(CH_2)_3$-CH_3H10), 0.89 (3H, d, J = 16 Hz,-CH2-CH-CH_3)H17).

III. 1-octyl-3-methylimidazolium ibuprofen [RB 04]

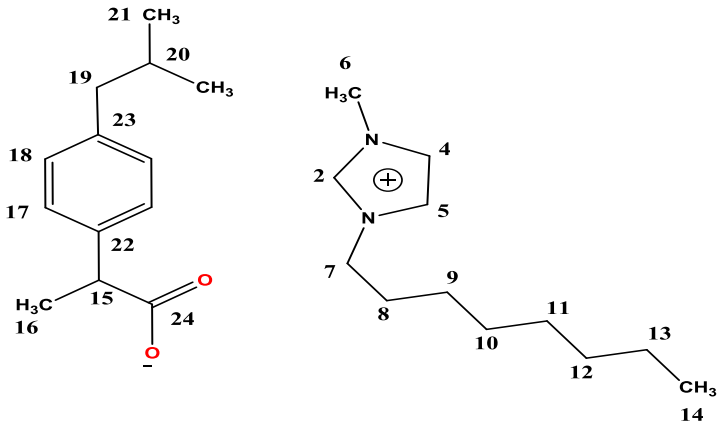


Figure 3.20 Structure of 1-octyl-3-methylimidazolium ibuprofen

1-octyl-3-methylimidazolium ibuprofen was obtained as a yellow clear gel; yield 78%: ^{1}H NMR (400 MHz, CDCl3) : δ =11.32 (1H, s, -N=C*H*-N-), 7.35-7.37 (2H, d, *J* = 8 Hz, =CH-CH=C*H*-CH=), 7.03-7.06 (1H, m, -N=C*H*-CH=N-), 7.03-7.06 (1H, m, -N=CH-C*H*=N-), 6.98-7.00 (2H, d, *J* = 8 Hz, =CH-C*H*=CH-CH=), 4.13-4.17 (2H, t, *J* = 16 Hz,-N-CH_2-), 3.89 (3H, s,CH_3-N-), 3.66-3.71 (1H, q, *J* = 20 Hz,CH_3-C*H*-COO^-), 2.38-2.40 (2H, d, *J* = 8Hz, =CH-CH-CH_2-CH-),1.80 (2H, m, -N-CH_2-CH_2-$(CH_2)_5$-CH_3),1.80 (3H, m, CH_3-CH-CH_3), 1.48-1.50 (3H, d, *J* = 8 Hz, CH_3-CH-COO^-), 1.28-1.31 (2H, m,-N-CH2-CH_2-CH_2-$(CH_2)_4$-CH_3), 1.28-1.31 (2H, m,-N-$(CH_2)_3$- CH_2-$(CH_2)_3$-CH_3), 1.28-1.31 (2H, m,-N-$(CH_2)_4$- CH_2-$(CH_2)_2$-CH_3), 1.28-1.31 (2H, m, -N-$(CH_2)_5$-CH_2-CH_2-CH_3),1.28-1.31 (2H, m, -N-$(CH2)_6$-CH_2-CH_3), 1.21 (3H, t, *J* = 12 Hz,-N-$(CH2)_6$-CH_2-CH_3) ; 0.88 (3H, d, *J* = 16 Hz, -CH_2-C-CH_3).

IV. 1-hexyl-3-methylimidazolium ibuprofen [RB 03]

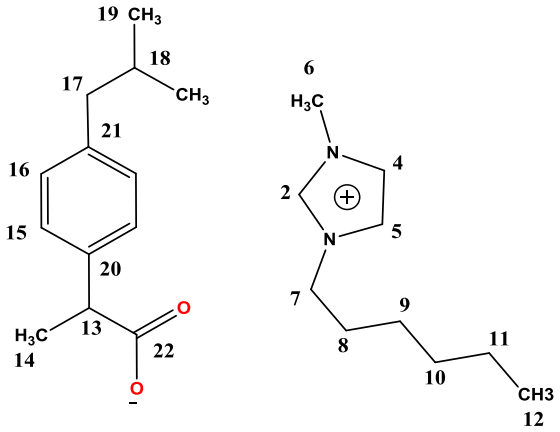


Figure 3.21 Structure of 1-hexyl-3-methylimidazolium ibuprofen

Yellow clear gel; yield 82%: 1H NMR, (400 MHz, $CDCl_3$) : δ =11.17 (1H, s, -N=C*H*-N-), 7.28-7.31 (2H, d, *J* = 12 Hz, =CH-CH=C*H*-CH=), 6.88-7.01 (1H, m, -N=C*H*-CH=N-), 6.88-7.01 (1H, m, -N=CH-C*H*=N-), 6.44-6.46 (2H, d, *J* = 8 Hz, =CH-C*H*=CH-CH=), 4.13 (2H, t, J = 16 Hz, H7), 3.89 (3H, s, -N-CH_2-), 3.69-3.74 (1H, q, *J* = 20 Hz, CH_3-C*H*-COO^-), 2.38-2.40 (2H, d, J = 8Hz, =CH-CH-CH_2-CH-),1.80 (2H, m, -N-CH_2-CH_2-$(CH_2)_3$-CH_3), 1.80 (3H, m, CH_3-CH-CH_3), 1.48-1.50 (3H, d, J = 8 Hz, CH_3-CH-COO^-),1.28-1.31 (2H, m,-N-CH_2-CH_2-CH_2-$(CH_2)_2$-CH_3), 1.28-1.31 (2H, m,-N-$(CH_2)_3$-CH_2-CH_2-CH_3), 1.28-1.31 (2H, m,-N-$(CH_2)_4$-CH_2-CH_3), 1.21 (3H, t, *J* = 12 Hz,-N-(CH2)$_4$-CH_2-CH_3) ; 0.86 (3H, d, *J* = 16 Hz, -CH_2-C-CH_3).

V. 1-decyl-3-methylimidazolium ibuprofen [RB 05]

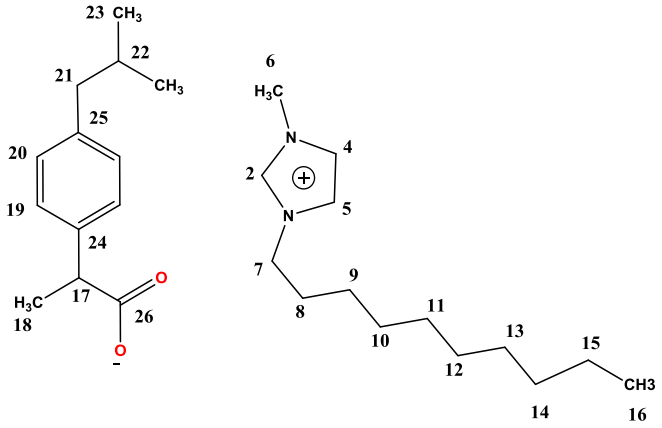


Figure 3.22 Structure of 1-decyl-3-methylimidazolium ibuprofen

Yellow clear gel; yield 82%: 1H NMR (400 MHz, CDCl3) : δ =11.31 (1H, s, -N=C*H*-N-), 7.35-7.37 (2H, d, *J* = 8 Hz, =CH-CH=C*H*-CH=), 7.03-7.06 (1H, m, -N=C*H*-CH=N-), 7.03-7.06 (1H, m, -N=CH-C*H*=N-), 6.98-7.00 (2H, d, *J* = 8 Hz, =CH-C*H*=CH-CH=), 4.13-4.17 (2H, t, *J* = 16 Hz,-N-CH_2-), 3.89 (3H, s,CH_3-N-), 3.66-3.71 (1H, q, *J* = 20 Hz,CH_3-C*H*-COO^-), 2.38-2.40 (2H, d, *J* = 8Hz, =CH-CH-CH_2-CH-),1.80 (2H, m, -N-CH_2-CH_2-$(CH_2)_7$-CH_3),1.80 (3H, m, CH_3-CH-CH_3), 1.48-1.50 (3H, d, *J* = 8 Hz, CH_3-CH-COO^-), 1.25-1.32 (2H, m,-N-CH2-CH_2-CH_2-$(CH_2)_6$-CH_3), 1.28-1.31 (2H, m,-N-$(CH_2)_3$-CH_2-$(CH_2)_5$-CH_3), 1.25-1.32 (2H, m,-N-$(CH_2)_4$-CH_2-$(CH_2)_4$-CH_3), 1.25-1.32 (2H, m, -N-$(CH_2)_5$-CH_2-$(CH_2)_3$-CH_3),1.25-1.32 (2H, m, -N-$(CH_2)_6$-CH_2-$(CH_2)_2$-CH_3),1.25-1.32 (2H, m, -N-$(CH2)_7$-CH_2-CH_2-CH_3), 1.25-1.32 (2H, m, -N-$(CH2)_7$-CH_2-CH_2-CH_3), 1.22 (3H, t, *J* = 12 Hz,-N-$(CH2)_8$-CH_2-CH_3) ; 0.84 (3H, d, *J* = 16 Hz, -CH_2-C-CH_3).

VI. 1-ethyl-3-methylimidazolium diclofenac [RB 06]

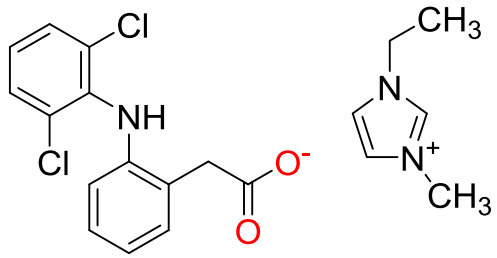


Figure 3.23 structure of 1-ethyl-3-methylimidazolium diclofenac

Yellow brownish clear gel; yield 72%: 1H NMR (400 MHz, CDCl3) : δ = 11.02 (1H, s, -C-N*H*-C-), 9.56 (1H, s, -N-C*H*-N-), 7.28 (1H, m, -Cl-C=CH-CH=C*H*-Cl-), 7.24 (1H, m, CH3-N-CH=C*H*-N-), 7.22 (1H, m, CH3-N-C*H*=CH-N-), 7.00 (1H, d, =CH-C*H*=CH-COO^-), 6.97 (1H, t, *J*=16 Hz, -Cl-CH=CH-C*H*=CH-CH-), 6.90 (1H, t, , J=16 Hz, -NH-C=CH-C*H*=CH-), 6.78 (1H, t, , J=12 Hz, -NH-C=CH-CH=C*H*-CH-), 6.44 (1H, d, *J*= 8 Hz, -NH-C=C*H*-CH=CH-), 4.16 (2H, qt, J=20 Hz, -N-C*H*$_2$ -CH_3), 3.85 (3H, s, -N-C*H*$_3$), 2.35 (1H, s, -CH=C*H*-COO^-), 1.24 (3H, t, J=12 Hz, -N-CH_2-C*H*$_3$).

VII. 1-butyl-3-methylimidazolium diclofenac [RB 07]

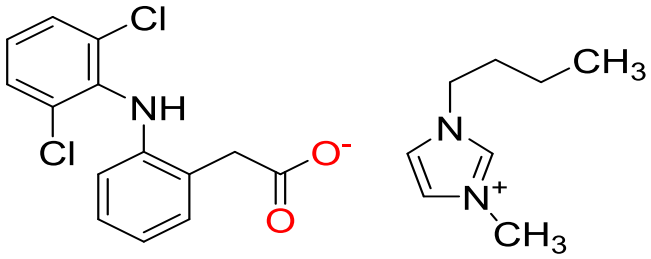


Figure 3.24 Structure of 1-butyl-3-methylimidazolium diclofenac

Yellow brownish clear gel; yield 78%: 1H NMR (400 MHz, CDCl3) : δ =10.98 (1H, S, -C-N*H*-C-), 9.53 (1H, s, -N=C*H*-N-), 7.29 (1H, m, -Cl-C=CH-CH=C*H*-Cl-), 7.25 (1H, m, CH3-N-CH=C*H*-N-), 7.23 (1H, m, CH_3-N-C*H*=CH-N-), 7.00 (2H,

d, =CH-C*H*=CH-COO$^-$), 6.98 (2H, m, -Cl-CH2-C*H*2-CH2-Cl-), 6.90 (1H, t, , J=16 Hz, -NH-C=CH-C*H*=CH-), 6.80 (1H, t, , J=16 Hz, -NH-C=CH-CH=C*H*-CH-), 6.47 (1H, m, -NH-C=C*H*-CH=CH-), 4.13 (2H, t, J=16 Hz, -N-CH_2 -$(CH_2)_2$-CH_3), 3.87 (3H, s, -N-CH_3), 2.33 (1H, s, -CH=C*H*-COO$^-$), 1.74 (2H, m, -N-CH_2-CH_2-CH_2-CH_3), 1.26 (2H, m, -N-$(CH_2)_2$-CH_2-CH_3), 0.89 (3H, t, J=16 Hz, -N-$(CH_2)_3$-CH_3).

VIII. 1-hexyl-3-methylimidazolium diclofenac [RB 08]

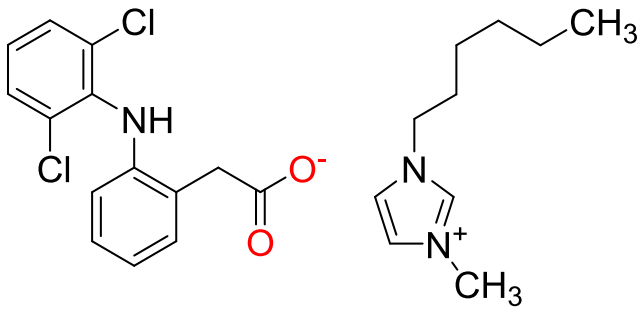


Figure 3.25 Structure of 1-hexyl-3-methylimidazolium diclofenac

Yellow brownish clear gel; yield 68%: 1H NMR (400 MHz, CDCl3) : δ = 11.40 (1H, S, -C-N*H*-C-), 9.56 (1H, s, -N-C*H*-N-), 7.28 (1H, m, -Cl-C=CH-CH=C*H*-Cl-), 7.24 (1H, m, CH_3NCHC*H*N), 7.22 (1H, m, CH_3NC*H*CHN), 7.00 (1H, d, =CH-C*H*=CH-COO$^-$), 6.97 (1H, t, *J*=16 Hz, -Cl-CH=CH-C*H*=CH-CH-), 6.90 (1H, t, , J=16 Hz, -NH-C=CH-C*H*=CH-), 6.78 (1H, t, , J=12 Hz, -NH-C=CH-CH=C*H*-CH-), 6.44 (1H, d,*J*= 8 Hz, -NH-C=C*H*-CH=CH-), 4.16 (2H, qt, J=20 Hz, NCH_2 -CH_3), 3.85 (3H, s, NCH_3), 3.73 (2H,qt, 20 J=20 Hz, N-C*H*2-CH3) 2.35 (1H, s, -CH=C*H*-COO$^-$), 1.24 (3H, t, J=12 Hz, N-CH_2-CH_3).

IX. 1-octyl-3-methylimidazolium diclofenac [RB 09]

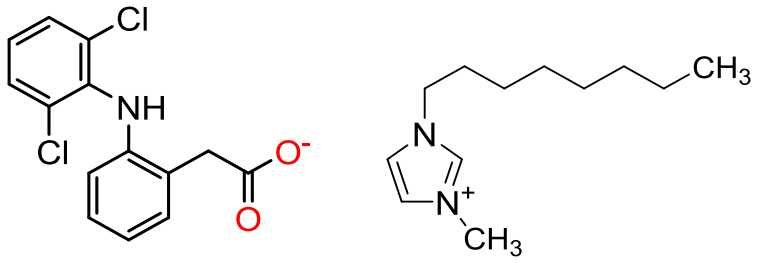


Figure 3.26 Structure 1-Octyl-3-methylimidazolium diclofenac

Yellow brownish clear gel; yield 72%: 1H NMR (400 MHz, CDCl3) : δ = 10.83(1H, S, -C-N*H*-C-), 9.46 (1H, s, -N=C*H*-N-), 7.29 (1H, m, Cl-C=CH-CH=C*H*-Cl), 7.25-7.27 (1H, m, CH3-N-CH=C*H*-N-), 7.22-7.24 (1H, d, *J*=8 Hz, CH_3-N=C*H*-CH=N-), 7.05 (1H, t, =CH-C*H*=CH-COO^-), 7.01-7.03 (1H, t, *J*=12 Hz, Cl-CH=CH-C*H*=CH-), 6.89-6.93 (1H, t, , J=12 Hz, -NH-C=CH-C*H*=CH-), 6.78-6.82 (1H, t, , J=16 Hz, -NH-C=CH-CH=C*H*-CH-), 6.45-6.47 (1H, d, *J*= 8 Hz, -NH-C=C*H*-CH=CH-), 4.12-4.15 (2H, t, *J*=16 Hz, -N-CH_2-$(CH_2)_7$), 3.91 (3H, s, -N-CH_3), 3.69-3.74 (2H, m, -N-CH_2-CH_2-$(CH_2)_6$), 2.65 (1H, s, -CH=C*H*-COO^-), 1.75-1.78 (2H, m, -N-CH_2-CH_2-CH_2-$(CH_2)_5$), 1.22-1.30 (2H, m, -N-$(CH_2)_3$-CH_2-$(CH_2)_4$), 1.22-1.30 (2H, m, -N-$(CH_2)_4$-CH_2-(CH2)$_3$), 1.22-1.30 (2H, m, -N-$(CH_2)_5$-CH_2-$(CH_2)_2$), 1.22-1.30 (2H, m, -N-$(CH_2)_6$-CH_2-CH_3), 0.86-0.89 (3H, t, *J*= 12 Hz, -N-$(CH_2)_6$-CH2-CH_3).

X. 1-decyl-3-methylimidazolium diclofenac [RB 10]

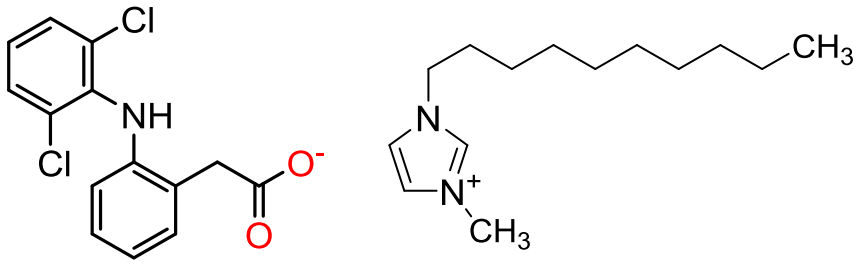


Figure 3.27 Structure of 1-decyl-3-methylimidazolium diclofenac

Yellow brownish clear gel; yield 68%: 1H NMR (400 MHz, CDCl3) : δ = 10.48 (1H, S, -C-N*H*-C-), 9.28 (1H, s, -N=C*H*-N-), 7.28 (1H, m, Cl-C=CH-CH=C*H*-Cl), 7.25 (1H, m, CH3-N-CH=C*H*-N-), 7.18-7.20 (1H, d, *J*=8 Hz, CH_3-N=C*H*-CH=N-), 6.95 (1H, d, =CH-C*H*=CH-COO^-), 6.92-6.95 (1H, t, *J*=12 Hz, Cl-CH=CH-C*H*=CH-), 6.84-6.87 (1H, t, , J=12 Hz, -NH-C=CH-C*H*=CH-), 6.73-6.76 (1H, t, , J=12 Hz, -NH-C=CH-CH=C*H*-CH-), 6.41-6.43 (1H, d, *J*= 8 Hz, -NH-C=C*H*-CH=CH-), 3.99-4.03 (2H, t, *J*=16Hz, -N-CH_2-$(CH_2)_9$), 3.68-3.75 (2H, m, -N-CH_2-CH_2-$(CH_2)_8$), 3.68 (3H, s, -N-CH_3), 2.65 (1H, s, -CH=C*H*-COO^-), 1.62-1.70 (2H, m, -N-CH_2-CH_2-CH_2-$(CH_2)_7$), 1.14-1.32 (2H, m, -N-$(CH_2)_3$-CH_2-$(CH_2)_6$), 1.14-1.32 (2H, m, -N-$(CH_2)_4$-CH_2-$(CH2)_5$),1.14-1.32 (2H, m, -N-$(CH_2)_5$-C*H*2-$(CH2)_4$), 1.14-1.32 (2H, m, -N-$(CH_2)_6$-C*H*2-$(CH2)_3$), 1.14-1.32 (2H, m, -N-$(CH_2)_7$-CH_2-CH_2-CH_3), 1.14-1.32 (2H, m, -N-$(CH_2)_8$-CH_2-CH_3), 0.87-0.91 (3H, t, *J*= 16 Hz, -N-$(CH_2)_8$-CH2-CH_3).

In the preparation of ionic liquids section, drug imidazolium ionic liquids were successfully prepared using metathesis reaction.

The next section describes various methods used for the characterisation of ionic liquids

3.2.2 Characterisation of ionic liquids

In this section characterisations techniques were describes which were used in preparation of ionic liquids.

3.2.2.1 Melting point

These were obtained using an electronic melting point apparatus (Gallenkamp, Germany) and are uncorrected.

3.2.2.2 Nuclear magnetic spectroscopy (NMR)

All NMR spectra were obtained using a Bruker DPX400 spectrometer. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. Tetramethylsilane was used internal standard. The ^{1}H NMR spectra were recorded in the range of 0-20 ppm from 16-20 scans at 270 MHz and 20-32 scans at 600 MHz. Coupling constants are quoted in Hertz (Hz). In general the sample size was 20 mg and 0.7 ml deuterated chloroform was used.

^{13}C NMR spectra were recorded in the range of 0-250 ppm from 500-2000 scans at 68 MHz and 128-234 scans at 151 MHz. In general the sample size was 50 mg and 0.7 ml deuterated chloroform was used. The ^{31}P NMR was recorded in the range of -200ppm to 250ppm from 64-128 scans. The ^{19}F NMR spectra were recorded in the range of -150 ppm to -50 ppm from 4 scans. In general the sample size was 20 mg and 0.7 ml deuterated chloroform was used

3.2.2.3 Infra-Red (IR) spectroscopy

All IR spectra were obtained on a Pelkin FTIR in range 4000-400 cm^{-1} Nicolet. IR spectra for solid as well as liquid were obtained by putting very small amount of sample on sample holder and data analysed by Grams software.

3.2.2.4 Thermogravimetric analysis (TGA)

Weight loss measurements were carried out using a TA Instruments Q5000. The TGA system was controlled by Universal Analysis V4.5A software for data acquisition and analysis. In data plots, the weight loss is expressed as a percentage of the initial sample weight and plotted vs. temperature. The temperature calibration of the TGA instrument was checked with a NIST SRM2232 indium. The onset melting point of indium is 156.60°C, while the measured value is 155.48°C. A sample weighing approximately 3-5 mg was loaded into the TGA. The sample was ramped from RT to 400 °C at 10°C/min, then isothermal for 50 minutes in nitrogen atmosphere at a flow rate of 50 ml/min.

3.2.2.5 Differential scanning calorimeter (DSC)

The DSC analysis was carried out using a TA Instruments Q2000 differential scanning calorimeter. The DSC was calibrated with indium and zinc standards. Approximately 3-5 mg of each sample was weighed into an aluminium pan with a lid hermetically sealed on the pan. The temperature range for all the samples was selected within 25 °C- 300°C range. A heating rate of 10 °C/min was used and the nitrogen flow rate was 50mL/min to maintain inert environment.

3.2.2.6 Determination of partition coefficient

The octanol-water partition coefficient of ionic liquids was determined (Zakrewsky et al., 2014). A 250 mL of n-octanol was shaken with 100 mL of distilled water and left for 12 hrs. The saturated octanol was used to prepare 0.01 M solutions of each ionic liquid in 5-mL volumetric flasks, as well as 0.01-M solutions in water. Absorption was measured and maxima observed between 205 nm and 215 nm. A 4-mL portion of the ionic liquid solution was shaken with 4 mL of distilled water and followed gentle centrifugation (800 rpm, (1,000 rpm, Hettich zentrifugen LBA centrifuge, 6-hole fixed angle rotor 804SF) to obtain clean separation of the two layers. The absorption of the octanol layer and water layers was measured and compared with the absorbance of the stock solutions. Measurements were repeated three times, and the distribution coefficients were reported as the average. The percentage of ionic liquid in octanol was calculated as the absorbance of the octanol layer after extraction divided by the absorbance of ionic liquid in octanol before extraction. The water/octanol distribution coefficient was calculated as of the percentage of IL in octanol divided by the percentage of ionic liquid in water.

Characterisation of ionic liquids section described details of methods used in the preparation of ionic liquids.

The next section describes various methods used in crystallisation of drugs from imidazolium ionic liquids study.

3.2.3 Crystallisation of drugs from imidazolium ionic liquids

Crystallisation of sulfathiazole, chlorpropamide, phenobarbital and nifedipine were carried out with various imidazolium ionic liquids. The imidazolium ionic liquids used include [EMIM][acetate], [EMIM][DEP] and [EMIM][BF_4]. For which both antisolvent and cooling crystallisation methods were employed. Solubility of drugs in the ionic liquids at different temperatures was determined. Subsequently, crystallisation experiments were performed. The crystals obtained were thoroughly characterised using Powder X-ray diffractometer (PXRD), Single crystal X-ray diffractometer (SC-XRD) and thermal studies.

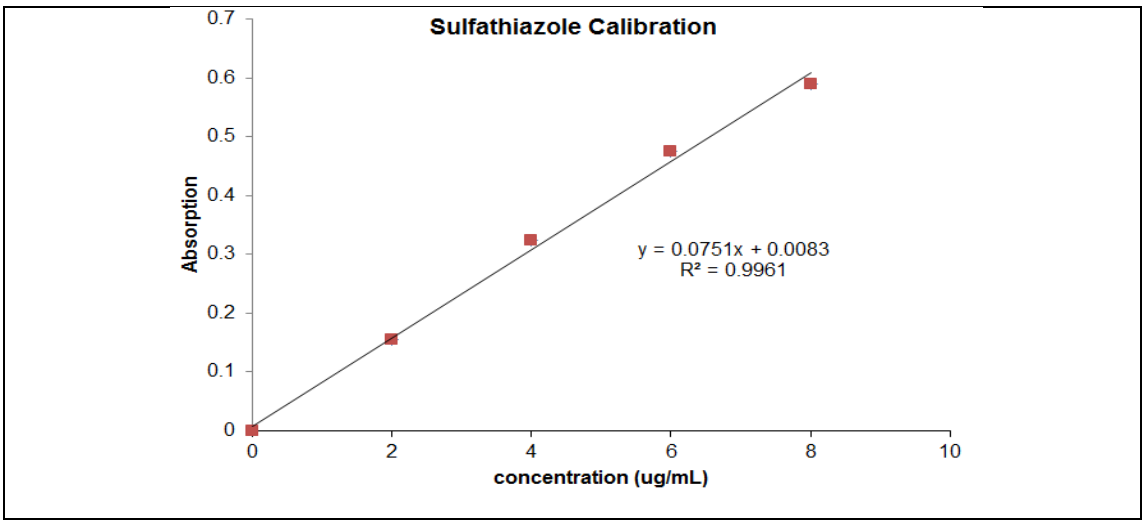
3.2.3.1 Solubility determination

An excess of a compound was added to the ionic liquid (approximately, 1 ml) in a 10 mL glass vial. The vial was loaded onto heating plate and sample was heated to below 100 °C for ~24 hours under agitation (magnetic flea at 100 rpm) to ensure that the saturation solubility was achieved, which was determined by using UV. Saturation was found to be reached in ~24 hours. The solubilities were performed in three different temperatures (50, 75 and 90 °C). At each temperature point an aliquot of the saturated solution was removed using an overheated (5 °C) 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 fluctuations during sampling. The sample was then diluted with the 10 mL methanol and the drug content was determined by UV spectra against a standard curve for the compound in solution (for all curves R^2 = ~0.95). As applicable, dilutions were carried out to ensure that the measured absorbance

was within the standard curve. The volume of ionic liquid and methanol was determined from the graduated scale of the syringe (±0.1ml) and was used as the volume in the solubility determination. However, the measurements at each temperature point were carried out in triplicate.

3.2.3.2 Preparation of calibration

10 mg drug was taken in a 100 ml volumetric flask and the volume was made up with water to give stock solution of, concentration 0.1 mg/ml. From the above solution 0.2, 0.4, 0.6, 0.8, 1, 1.5 and 2 ml was taken in 10ml volumetric flask and made up the volume to give concentration of 2, 4, 6, 8, 10, 15 and 20µg/ml. The absorbance of the samples was recorded for drugs. The average values of absorbance were plotted against respective concentrations. The absorption maximums (λ_{max}) used were the following for the various drugs: sulfathiazole (264 nm), chlorpropamide (233 nm), phenobarbital (264 nm) and nifedipine (237 nm). See in the following section



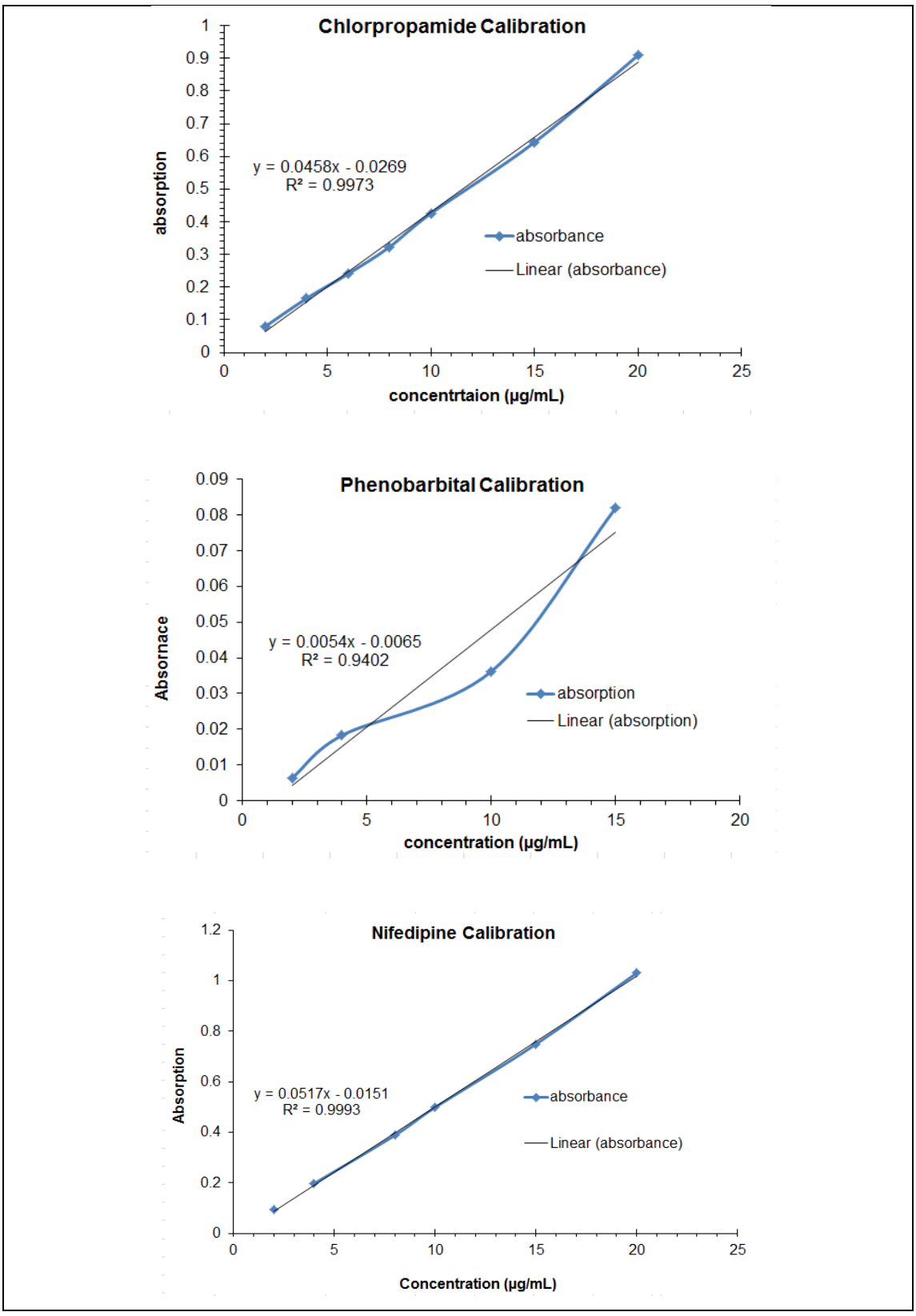


Figure 3.28 Calibration curve for sulfathiazole, chlorpropamide, phenobarbital and nifedipine.

3.2.3.3 Crystallisation techniques

The antisolvent and cooling crystallisation were carried out as shown schematic diagram (Figure 2.56)

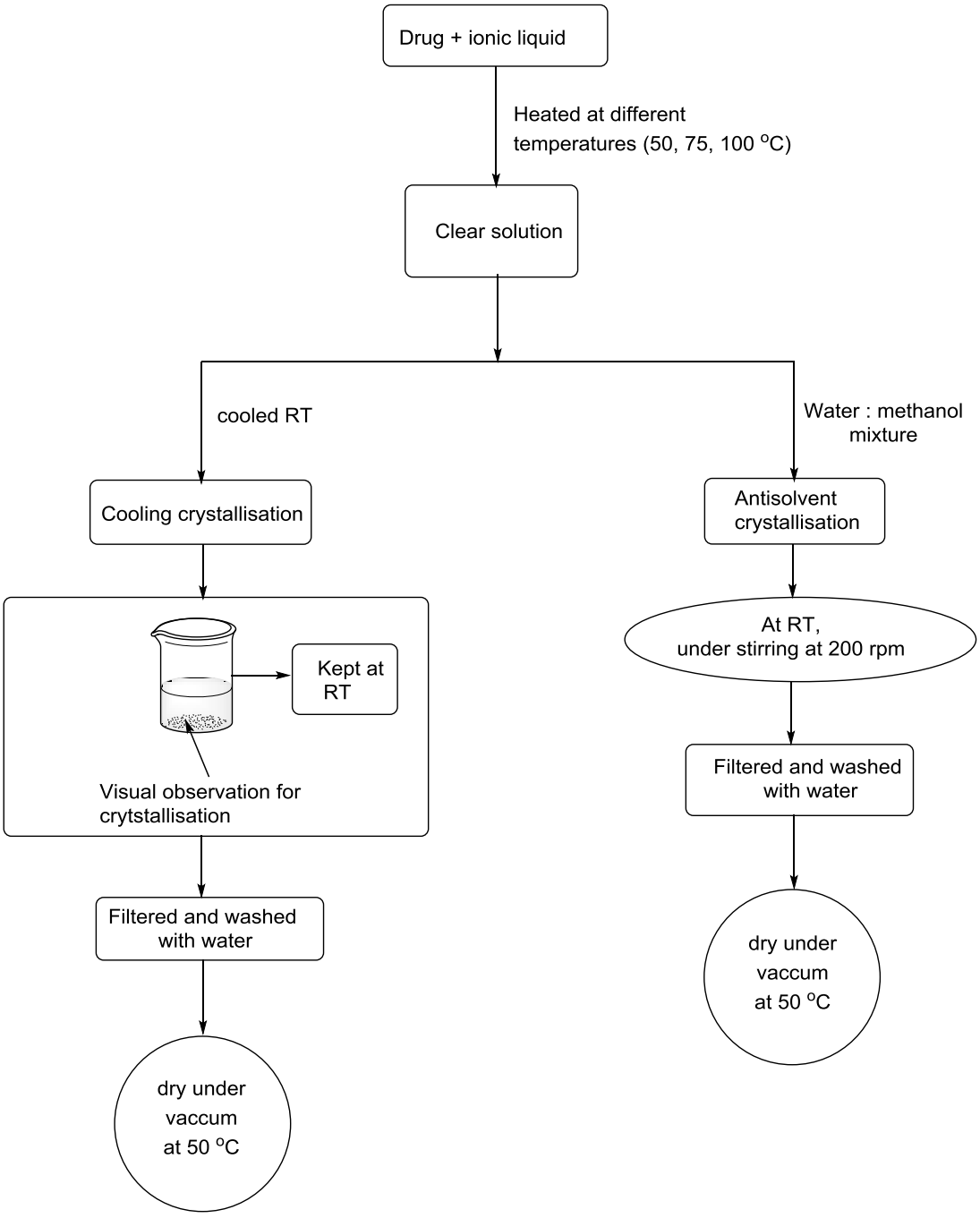


Figure 3.29 Schematic representation of crystallisation work.

Table 3.4 Details of cooling crystallisation study

Expt No.	Drug	Ionic liquid (1 mL)	Temperature (°C)	Crystallisation
1	Sulfathiazole	[EMIM][acetate]	75	Yes
2		[EMIM][DEP]		Yes
3		[EMIM][BF_4]		Yes
4	Chlorpramide	[EMIM][acetate]	75	No
5		[EMIM][DEP]		No
6		[EMIM][BF_4]		Yes
7	Phenobarbital	[EMIM][acetate]	75	Yes
8		[EMIM][DEP]		Yes
9		[EMIM][BF_4]		No
10	Nifedipine	[EMIM][acetate]	75	Degradation
11		[EMIM][DEP]		No
12		[EMIM][BF_4]		No

Table 3.5 Details of antisolvent crystallisation work

Expt No.	Drug	Ionic liquid (1 mL)	Antisolvent (mL)		Temp. (°C)	Crystallisation
			Water	Methanol		
1	Sulfathiazole	[EMIM][acetate]	5	-	75	Yes
2		[EMIM][DEP]	5	-		No
3		[EMIM][BF_4]	5	-		Yes
4	Chlorpramide	[EMIM][acetate]	7	3	75	No
5		[EMIM][DEP]	7	3		No
6		[EMIM][BF_4]	7	3		Yes
7	Phenobarbital	[EMIM][acetate]	7	3	75	Yes
8		[EMIM][DEP]	7	3		Yes
9		[EMIM][BF_4]	7	3		No
10	Nifedipine	[EMIM][acetate]	-	-	75	Degradation
11		[EMIM][DEP]	7	3		No
12		[EMIM][BF_4]	7	3		No

3.2.3.4 Characterisation for crystallisation study

In this section characterisation techniques were describes which were used in the crystallisation study which includes powder x-ray diffraction (PXRD), single crystal x-ray diffractometer (SC-XRD) and ultra-violet (UV) spectroscopy. DSC technique also used in this section and which was detailed describes in the section 3.2.2.6**.**

I. Powder X-ray diffraction (PXRD)

PXRD patterns of pharmaceutical drugs for crystallisation study using a PXRD instrument (Bruker D8 diffractometer, Madison, USA) having X-ray wavelength 0.154 nm and a 40 KV CU source with filament emission 40 mA All samples were scanned from 2 to 30° (2θ) using, a 0.01° step width and 1 s time count. A scatter slit and receiving slit were 0.2° and 1°,

II. Single crystal X-ray diffraction

A good quality single crystal of either sulfathiazole•1-ethyl,3-methyl-imidazole-[BF_4]or phenobarbital•1-ethyl,3-mehyl-imidazole-acetate was chosen under a Leica microscope and placed on a fibre needle which was then mounted on the goniometer of the X-ray diffractometer. The crystal was purged with a nitrogen gas stream at 173 K throughout the data collection. X-ray reflections were collected on a Bruker APEX X8 single crystal X-ray diffractometer with monochromatic Mo-Kα radiation (λ = 0.71073 Å). The crystal structure was solved and refined by direct methods and SHELX-TL was used for structure solution and least-squares refinement. Hydrogen atoms were treated by a mixture of independent and constrained refinements.

III. Ultra violet spectroscopy (UV)

JASCO V-630 UV-Visible spectrophotometer with intelligent remote (module iRM) and 'Spectra Manager' software was used for analysis. Light sources are two-deuterium lamp (190-350nm) and halogen lamp (330-1100 nm) with silicon photodiode detector. Wavelength range is from 190nm-1100nm. Wavelength accuracy is ± 0.2nm

3.2.4 Pharmaceutical performance of drug ionic liquids study

The drug ionic liquids were prepared and characterised as described in section 3.2.2 and Transdermal absorption was carried out by our collaborator Dr Maha Nsar at Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Egypt.

3.2.4.1 Osmolality

Prepared 1 mL solution a series of 2 M, 0.25 M, 0.025 M, 0.0025 M and 0.00025 M of drug ionic liquid in distilled water. A 20μL sample was purged into ohmmeter by sample plunger. Osmolality was measured in in mOsm/Kg.

Figure 3.30 Osmometer

3.2.4.2 Diffusion study

Drug-salt (200 mg) were placed in a dialysis bag, suspended in 200 mL of water as the external medium and maintained at 37 °C and stirred at 300 rpm. Samples (5 mL) were withdrawn periodically and the determined drug release by UV spectroscopy. An equivalent amount of water (5 mL) was replaced in the release medium to maintain sink conditions. Experiments were run in triplicate. At appropriate time intervals, 5 ml samples were withdrawn and refilled with the same volume of distilled water.

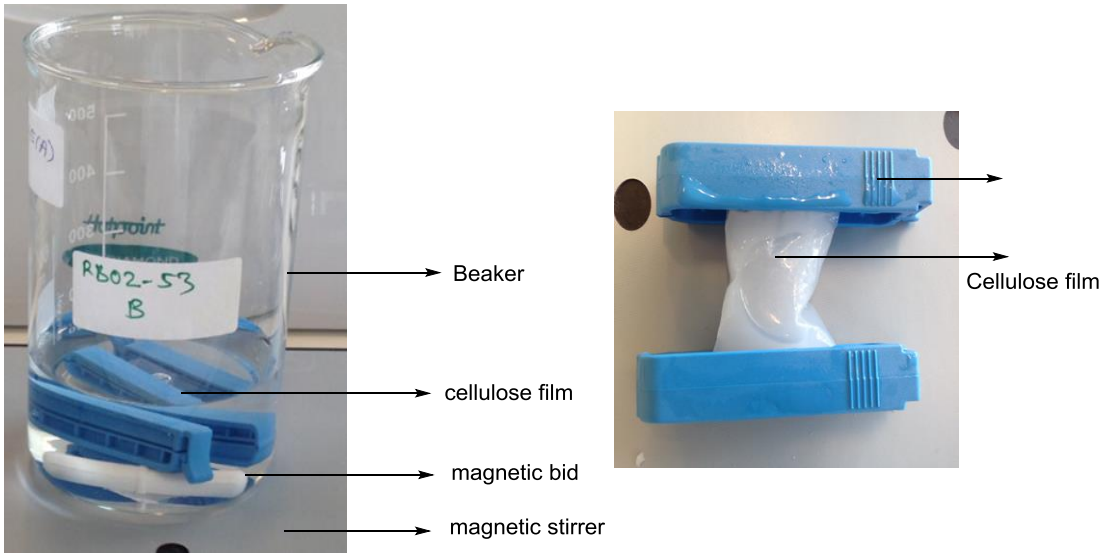


Figure 3.31 image of diffusion apparatus

3.2.4.3 Transdermal deposition and permeation study

Rat skin was carefully cleaned under cold running water and stored at -20ºC before use. At the day of the experiment, the skin was defrosted, cut into square pieces, and mounted with the stratum corneum uppermost in Franz-type diffusion apparatus. The area of the skin was 1.77cm^2. The receptor medium was composed of 7.5 ml phosphate buffer pH 7.4 containing 0.5% tween 80, which was constantly stirred with a magnetic bar, and maintained at 37ºC using

a circulating water jacket. An amount of 100 mg of the ionic liquid samples were placed in donor compartments (n=5). Samples were withdrawn at time intervals (15 min, 30 min, 1hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 5 hr) from the receptor compartment, and replaced with fresh medium. After the 5 hours, the skin samples were washed five times with distilled water and dried with filter paper to remove any excess formula. Tape stripping of the skin was performed with an adhesive tape, in which twenty pieces of adhesive tape were firmly pressed on the skin surface and rapidly pulled off with fluent strokes. The dermis was separated from the epidermal layer in each skin sample using a scalpel, and the tape strips, dermis and epidermis were individually placed in beakers containing 10 ml methanol each for extraction of the drugs, after placing them in a sonicate for 2 hours. All samples were filtered using a membrane filter of pore size 220 nm before injection into HPLC column to be analysed for the drug contents. The amounts of drugs accumulating in the different skin layers and permeated through the skin were expressed as percentage of the total amount of active ingredient applied on the skin. The following figure (Figure 3.32) describes the transdermal deposition and permeation of drug ionic liquid through the skin.

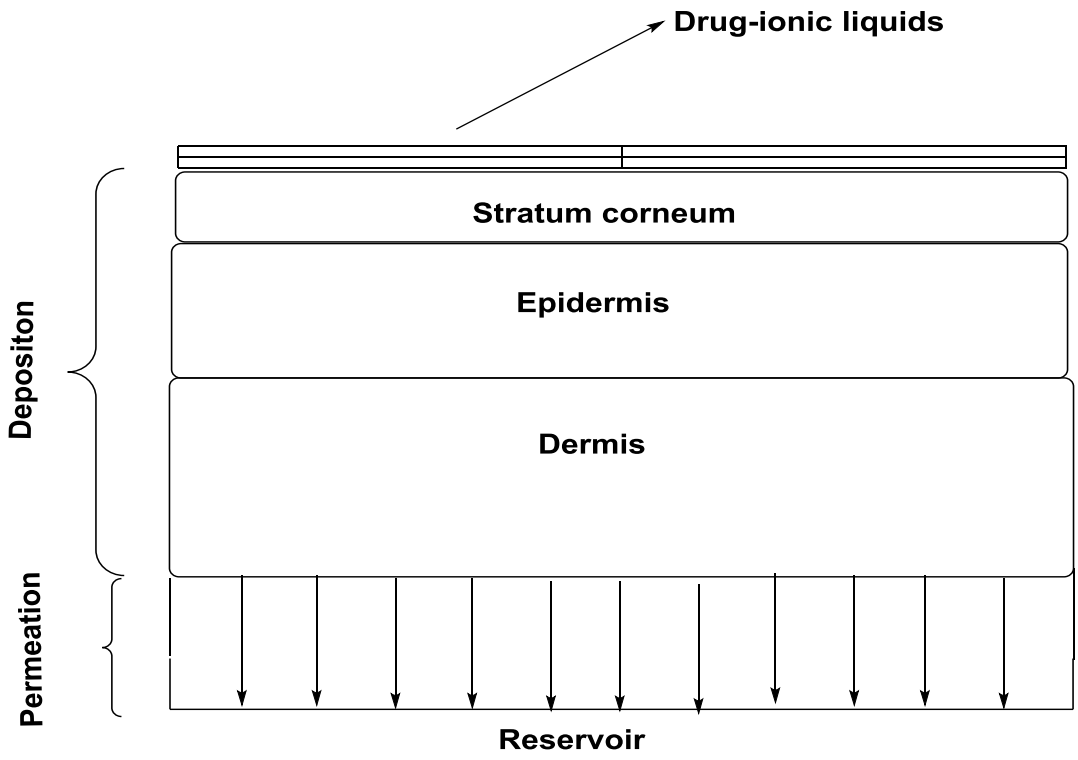


Figure 3.32 Transdermal deposition and permeation of drug ionic liquid through the skin.

3.2.4.4 Determination of drug content

The ionic liquid-drug sample (10 mg) was accurately weighed and dissolved in distilled water (20 ml) and mixed thoroughly. The solutions were filtered, diluted with distilled water, and analysed for the content of ibuprofen and diclofenac using UV-visible spectrophotometer at 221nm and 276nm respectively.

3.2.4.5 Preparation of standard calibration curve for ibuprofen and diclofenac in water

Ibuprofen (10 mg) or diclofenac (10 mg) was taken in a 100 ml volumetric flask and the volume was made up with water to give stock solution of, concentration 0.1 mg/ml. From the above solution 0.2, 0.4, 0.6, 0.8, 1, 1.5 and 2 ml was taken

in 10ml volumetric flask and made up the volume to give concentration of 2, 4, 6, 8, 10, 15 and 20 µg/ml. The absorbance of the samples was recorded 221nm and 276nm for ibuprofen and diclofenac respectively. The average values of absorbance were plotted against respective concentrations.

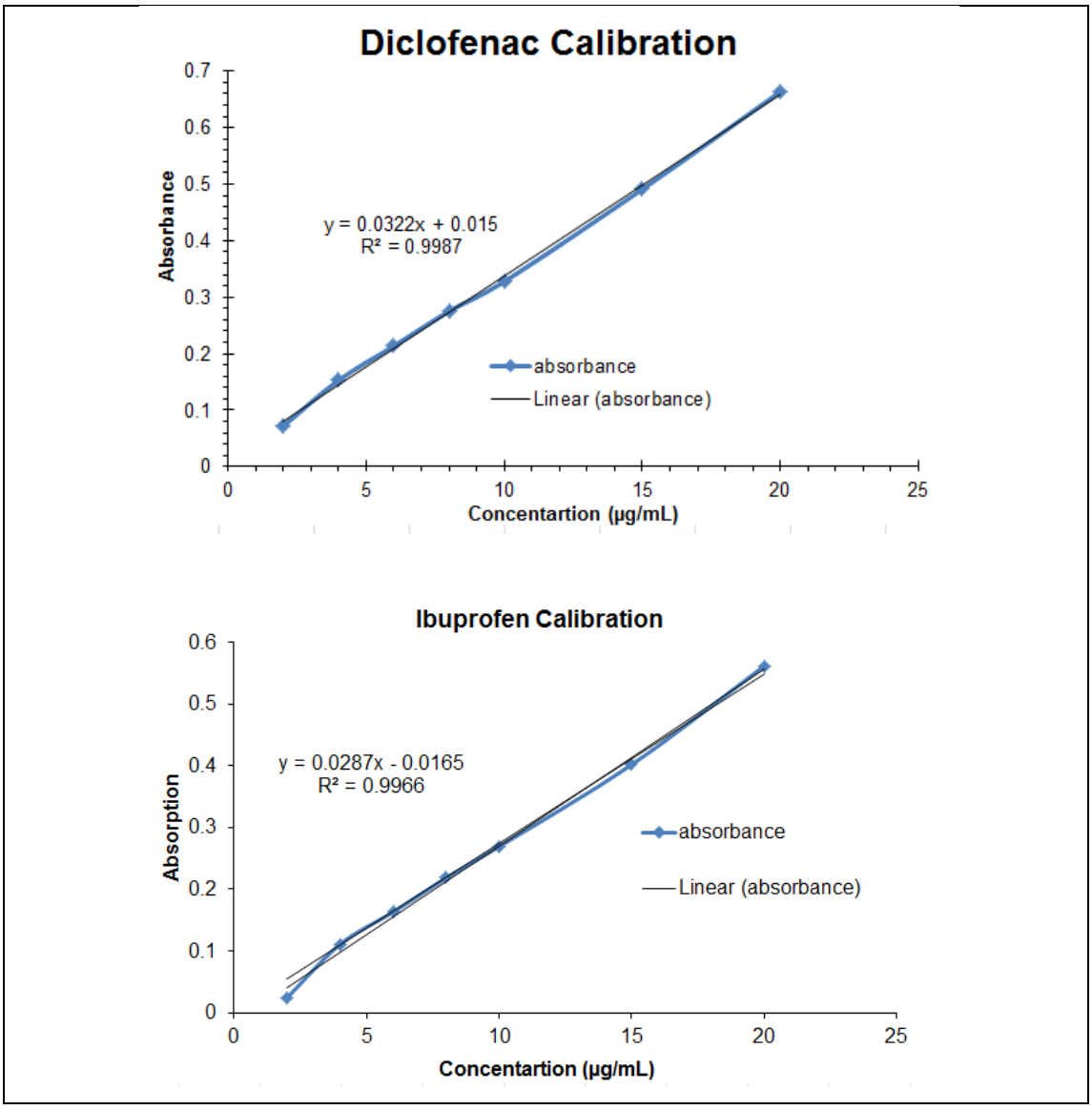


Figure 3.33 Calibration curve for ibuprofen and diclofenac

Chapter 4. Synthesis of phosphonium ionic liquids by microwave and conventional methods

In this chapter, fifteen phosphonium ionic liquids were synthesised and thoroughly investigated the thermophysical properties and partition coefficient.

4.1 Introduction

The synthesis phosphonium-based ionic liquids are the focus of this chapter and only this class of ionic liquids is reviewed. Similar techniques can be used for preparing ammonium-based ionic liquids. The phosphonium cation contains four substituents such as hydrocarbons (alkyl chains are most common) with various combinations and a variety of anions which result in a large number of different ionic liquids with different properties (Figure 4.1)

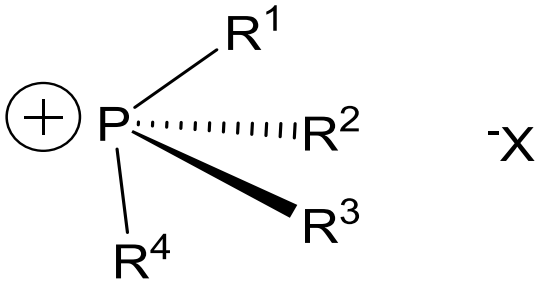


Figure 4.1: Generic formula for phosphonium ionic liquids

In fact not all phosphonium salts are liquid at room temperature, but the appropriate selection of alkyl and aryl group with appropriate anions give salts which fall within the general definition of ionic liquids if they possess low melting points which are less than 100 °C (Ermolaev et al., 2010).

The phosphorus analogues of amines are called phosphines. The chemistry of phosphines is related to their strong nucleophilicity and reducing character. The

nucleophilicity of trivalent phosphorus results in the formation of phosphonium salts when such compounds are treated with reactive alkyl halides which result in phosphonium cations. The first phosphonium salts were available as the chloride and bromide salts (Freemantle, 2009). Phosphorus is NMR active. Due to the downfield resonance shift from phosphine to phosphonium oxidation, ^{31}P NMR is commonly employed to monitor phosphonium synthesis from precursor phosphines. Initial reports related to phosphonium ionic liquids were published in the 1970's by Parshall using stannate and germinate salts, and by Knifton *et al*. (Fraser and MacFarlane, 2009).

Generally, phosphonium ionic liquids can be prepared in two ways; in the first method a phosphorus-containing compound is reacted with an alkyl halide to obtain a quaternary phosphorus halide salt; and the second route, the ion exchange method is used for halide ion exchanged with a suitable anion to obtain a low melting phosphorus salt (Zhou et al., 2004). In general, it is the phosphonium cations possessing longer alkyl chains which have the ability to dissolve nonpolar organic compounds. This is the common route employed in the synthesis of imidazolium-based ionic liquids since the starting ionic liquids are readily available commercially.

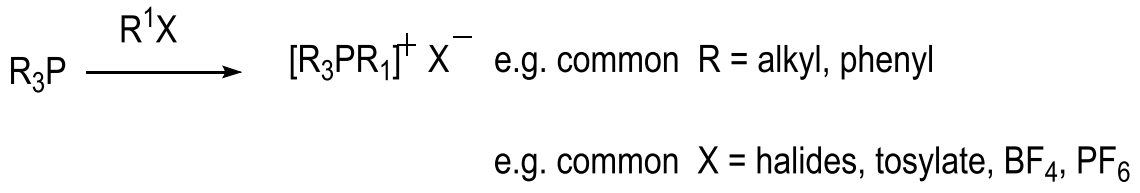


Figure 4.2 Quaternisation of tertiary phosphines

In fact, phosphonium-based ionic liquids can be differentiated from the ammonium and imidazolium based ionic liquids due their complementary properties. The most important properties of phosphonium ionic liquids are their greater thermal stability as compared to the corresponding ammonium and imidazolium salts. And this valuable property is very useful in processes which involve temperatures above 100 °C. Phosphonium salts do not contain an acidic proton in contrast to imidazolium cations which contain protons which are not entirely inert. This can result in unwanted side reactions (Fraser and MacFarlane, 2009). In past years the main reason for the lower interest in phosphonium-based ionic liquids was their poor availability and cost of starting materials. Nowadays, they are produced on a large commercial scale by companies such as Cytec Industries and Inc. who are experienced in manufacturing quaternary phosphonium salts and have thus filled this gap.

During World War II Randoll and Booth discovered microwave radiation frequency. In 1946 Raytheon Company filed a patent for the first dielectric heating oven which was used in a Boston restaurant. Microwave ovens are inexpensive, reliable and easy to operate. The general phenomenon of microwave heating is the dielectric heating effect and in ionic conduction in dielectric heating, the molecular dipole in the entire bulk tends to align with the electric field of the microwave and rotate or oscillate to follow the changing field. This movement of molecules results in the collision and friction between molecules and the kinetic energy is lost as thermal energy. In ionic conduction, a charged particle (ions) oscillates under the influence of oscillating electric field of microwaves and they collide with other molecules and atoms. The kinetic energy of ions is lost in the form of heat (Namboodiri and Varma, 2002). In

microwave dielectric heating, the microwave energy source is obtained remote switches and this energy source passes to the reaction vessel. The microwave radiations pass through the walls of the vessel and the microwaves heat the reactants and solvents and temperature will increase throughout the mixture (Lidström et al., 2001).

Microwave assisted synthesis of ionic liquids is a cleaner method and there is a greater emphasis on green chemistry. In traditional synthetic methods, large amounts of volatile organic solvents are used which can produce by-products. In addition, conventional heating under reflux using molecular solvents require several hours and have an effect on product yields which can create economic and environmental problems (Varma and Namboodiri, 2001, Deetlefs and Seddon, 2010). Microwave assisted synthesis of ionic liquids under solvent free conditions is an efficient and simple technique which uses simple glass vials in a microwave. This type of reaction requires only a few minutes in contrast to several hours and continuous heating conditions in the conventional method. For example, quarterisation of 1, 3-dialkylimidazolium salts with alkyl halides (Figure 4.3) has been established using a continuous microwave device (Lidström et al., 2001, Hoffmann et al., 2003).

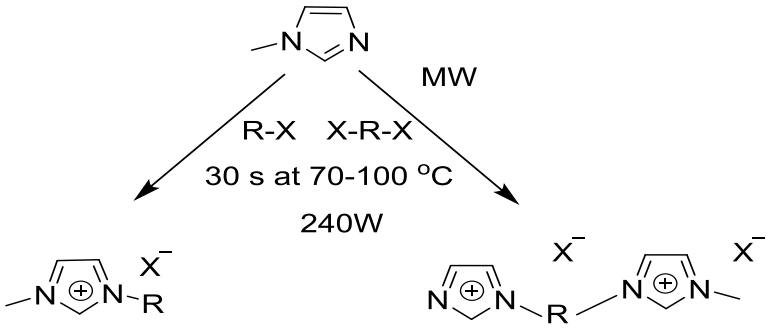


Figure 4.3: Synthesis ionic liquids by microwave (Varma and Namboodiri, 2001)

Applications of phosphonium ionic liquids are expanding in the field as alternative solvents and co-catalysts (Bonnet and Kariuki, 2006, Badri and Brunet, 1992, Kumar and Malhotra, 2009). They have also shown anti-cancer potential. Some phosphonium salts have anti-microbial activity and anti-electrostatic properties. It was found that both cation structure and type of anion have an effect on their biological properties and the ionic liquids showed high anti-electrostatic effect (Cieniecka-Roslonkiewicz et al., 2005). While phosphonium based ionic liquids have been used as phase transfer-catalysts, (Carmichael et al., 1999, Bradaric et al., 2003) as a solvents for synthesis (Ramnial et al., 2005) and electrochemistry (Tsunashima and Sugiya, 2007).

Before the use of microwaves for ionic liquids synthesis, the first reports were published on the application of microwave ovens for quick organic synthesis (Gedye et al., 1986) and later this method was noted for the reduction in reaction time and increased product yields (Deshayes et al., 1999).

4.2 Results and Discussion

This section evaluated the thermophysical properties, and time consuming data by microwave and conventional methods.

4.2.1 Microwave synthesis of phosphonium based ionic liquids

Due to the lengthy reaction times and the difficulty in removing solvents after the quaternisation reaction had occurred, alternative methods were investigated. Microwave mediated synthesis offered the best option for a green approach which also included solvent free synthesis. The optimum conditions for each ionic liquid were established by monitoring the reactions by ^{31}P NMR spectroscopy. Reactions were conducted at 30 s, 60 s and 90 s at 80 °C. For most of the substrates 90 s was the optimum time for 100% conversion (Table 3.5).

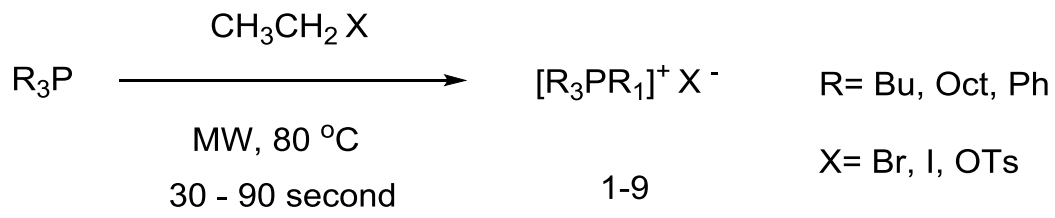


Figure 4.4: Microwave-mediated synthesis of phosphonium ionic liquids

Table 4.1: Microwave mediated synthesis of phosphonium ionic liquids.

Entry	R	R^1	X	Time (s)	Temp (°C)	^{31}P NMR
1	Ph	Et	Br^-	90	80	+26.48
2	Ph	Et	I^-	90	80	+26.35
3[a]	Ph	Et	TsO^-	60	80	+26.41
3	Ph	Et	TsO^-	90	80	+26.41
4	*n*-Bu	Et	Br^-	60	80	+34.56
5	*n*-Bu	Et	I^-	60	80	+34.48
6	*n*-Bu	Et	TsO^-	60	80	+34.67
7	*n*-Oct	Et	Br^-	90	80	+34.48
8	*n*-Oct	Et	I^-	90	80	+34.40
9	*n*-Oct	Et	TsO^-	90	80	+34.41

The advantages of the microwave method over the traditional method can clearly be seen in in the data presented in Table 4.2. The microwave method superior and more environmental friendly compared to method.

Table 4.2: Comparative study phosphonium ionic liquids prepared by microwave and traditional synthetic routes.

Entry	R	R^1	X	Reaction time	
				Microwave (sec)	Traditional (Hours)
1	Ph	Et	Br^-	90	36
2	Ph	Et	I^-	90	36
3	Ph	Et	TsO^-	60	36
4	*n*-Bu	Et	Br^-	60	24
5	*n*-Bu	Et	I^-	60	24
6	*n*-Bu	Et	TsO^-	60	36
7	*n*-Oct	Et	Br^-	90	36
8	*n*-Oct	Et	I^-	90	36
9	*n*-Oct	Et	TsO^-	90	36

4.2.2 Conventional synthesis of phosphonium ionic liquids

Based on the previous work within the group, 15 phosphonium ionic liquids were selected for synthesis in order for a systematic study to be conducted on their application as solvents for crystallisation of pharmaceutical drugs (Ludley and Karodia, 2001). The series of 15 phosphonium ionic liquids were synthesised in this project based on readily available phosphine precursors tri-*n*-butylphosphine, triphenylphosphine and tri-*n*-octylphosphine as the cationionic centres while the anions were derived from bromoethane, iodoethane and ethyl tosylate. The BF_4 and PF_6 analogues were obtained by ion exchange. These starting materials are readily available, cheap and easy to handle. In the conventional method developed by Ludley (Ludley and Karodia, 2001) the ionic liquids were easily prepared by heating the tertiary phosphine together with the alkyl halide/tosylate, in an inert, dry solvent and under nitrogen atmosphere for 24-48 h. The solvent was removed under vacuum. This method was used to prepare nine phosphonium ionic liquids in good to excellent yield.

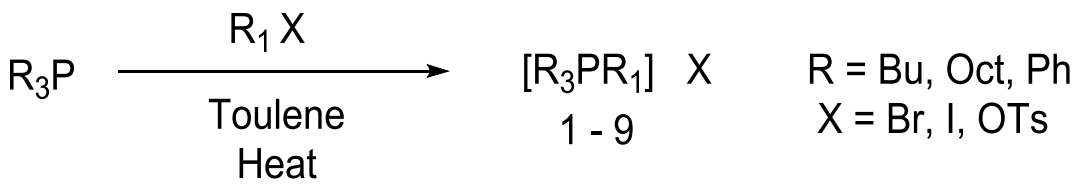


Figure 4.5: Conventional synthesis of phosphonium ionic liquids by quaternisation method.

The phosphonium ionic liquids with BF_4 and PF_6 anions were prepared by an anion metathesis method. A solution of halide phosphonium ionic liquids was dissolved in acetone and the sodium salt of the required anion was then added. The mixture was stirred at room temperature for 24 hrs which resulted in a

precipitate. Dichloromethane was added and this caused further precipitation. The mixture was filtered and the filtered evaporated to give the desired products in 70 - 90% yield.

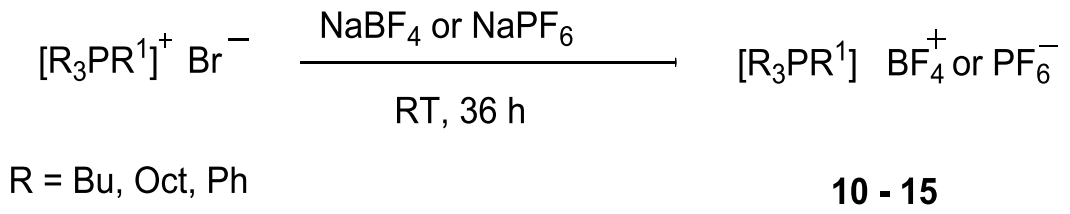


Figure 4.6: Metathesis reactions to prepare BF_4 and PF_6 phosphonium ionic liquids

The bromine and iodine content of these phosphonium ionic liquids was determined using the silver nitrate test. The ^{31}P chemical shifts of the starting ionic liquids change after the metastasis reaction.

4.2.2.1 Melting point

As can be seen from the Introduction (Chapter 1), the melting points of phosphonium ionic liquids are unusual. The melting points depend on the chain-length of the alkyl groups on the phosphorus atom and melting point decreases with increase in the alkyl chain length and this is illustrated by the series of phosphonium ionic liquids synthesised by Ludley *et al.* (Ludley and Karodia, 2001). For example, ethyltriphenylphosphonium ionic liquids are solid, with melting point range 100-140 °C and the octyl triphenylphosphonium ionic liquids are low melting solid or liquid at room temperature. (Table 4.3) The trioctylphosohonium ionic liquids display significantly lower melting points and many are liquids at room temperature. The same observation is made for the series of ionic liquids synthesised in this project where the triphenyl, tri-*n*-butyl

and tri-*n*-octyl follow the side chain rule. In comparison, BF_4 and PF_6 anions in the triphenyl and tri-*n*-butyl analogues increase the melting range.

The properties of phosphonium ionic liquids changes with the choice of cation and anion; essentially the melting point of the phosphonium ionic liquid were decreases as the anion size increases (Br < BF_4 < PF_6 < OTs). The melting point of BF_4 and PF_6 ionic liquids are higher than the others; this may be affected by the ratio of cation or anion radius which is good for forming a crystal lattice. The symmetry also has an effect on the melting point, for example, symmetry decreases with anions like the tosylate and this is accompanied by the decrease in melting point.

4.2.2.2 Spectral analysis of phosphonium ionic liquids

The final products were characterised by a number of techniques. The novel ionic liquids were also analysed using IR spectroscopy, which confirmed the presence of the functional groups. These experiments show exact interpretation of the ^{1}H, ^{13}C and ^{31}P spectra.

4.2.2.2.1 ^{31}P NMR Analysis

^{31}P NMR spectroscopy is the best way to monitor the reaction of the quarterisation of the tertiary phosphine to give phosphonium ionic liquids. The ^{31}P NMR spectra of tri-*n*-butylphosphine, triphenylphosphine, tri-*n*-octyl phosphonium ionic liquids were recorded prior to reaction and they are very different from the products (Table 4.7). The signal for tri-*n*-butylphosphine appears at -30.1 ppm, and at -4.8 ppm for triphenylphosphine. The positions of these

signals are very different to the products. Therefore in the ^{31}P NMR spectra a maximum of two signals were expected to determine whether the reaction had gone to completion or not. For example, the ^{31}P NMR spectrum of ethyltri-*n*-butylphosphonium bromide showed only one peak at +34.16 ppm, (Figure 4.7) this confirmed that the reaction was complete. When the PF_6 or BF_4 anions were present, the ^{19}F and ^{31}P atoms adjacent to each other caused the expected P-F coupling, and there were additional peaks at +144.42 ppm, corresponding to PF_6, which appeared as a heptet. When the reaction is exposed to oxygen, the phosphine oxide or [$O=PR_3$] can be formed, and peaks corresponding to these by-products are observed at +49.0 ppm and +58.1 respectively. None of these peaks were observed.

In the reaction the phosphines are quarternised, and this shows strong downfield shifts in the ^{31}P NMR spectra. According to the shielding effect the lone pair on the phosphorus is removed. The signals appear in a narrow range, +19 ppm to + 36 ppm, in which simple saturated alkyl and aryl derivatives resonate. Replacement of alkyl or aryl causes up field shifts. In the triphenylphosphonium salts, the chemical shifts appear between +26.30 to +26.50 ppm whereas the trialkylphosphonium salts shows downfield shift with chemical shift values between +34.40 to +34.80 ppm. These results confirm that the phosphorus atom is shielded more by phenyl rings than by alkyl groups.

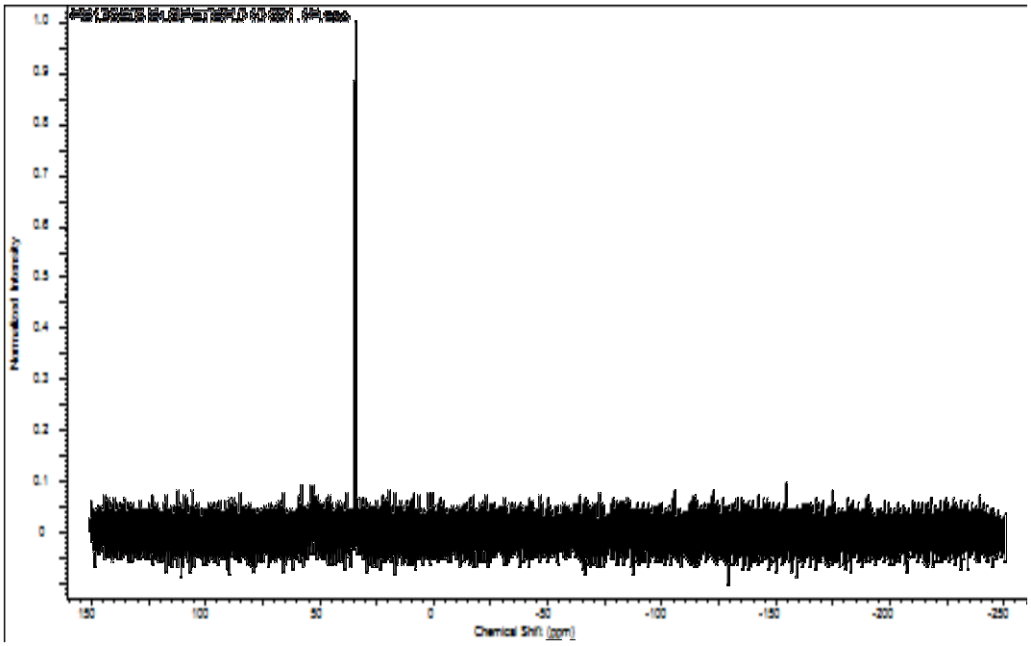


Figure 4.7: ^{31}P NMR of Ethyl-*n*-butylphosphonium bromide

Table 4.3 Yield, melting point and ^{31}P NMR data of ionic liquids $[R^1PR_3]^+ [X]^-$

Entry	R	R^1	X^-	Yield [%]	m.p. [°C]	^{31}P NMR
1	Ph	Et	Br	78	95-100	+26.48
2	Ph	Et	I	76	98-101	+26.35
3	Ph	Et	TsO	72	134-137	+26.38
3	Ph	Et	BF_4	78	131-133	+26.90
4	Ph	Et	PF_6	88	135-138	+26.0
6	*n*-Bu	Et	Br	66	Oil	+34.56
7	*n*-Bu	Et	I	62	48-50	+34.48
8	*n*-Bu	Et	TsO	69	87-89	+34.67
9	*n*-Bu	Et	BF_4	90	119-125	+34.52
10	*n*-Bu	Et	PF_6	85	128-131	+34.60
11	*n*-Oct	Et	Br	96	50-54	+34.48
12	*n*-Oct	Et	I	92	56-58	+34.40
13	*n*-Oct	Et	TsO	90	oil	+34.41
14	*n*-Oct	Et	BF_4	89	oil	+34.58
15	*n*-Oct	Et	PF_6	90	oil	+34.50

4.2.2.2.2 ^{1}H NMR Spectroscopy

The ^{1}H NMR spectra of the phosphonium ionic liquids were as expected and confirmed their structures. Due to the presence of phosphorus in the compound, P-H coupling is observed for some hydrogen atoms 2 and 3 bonds away as shown in Table 4.4. This is illustrated in Figure 4.8 and 4.9 using ethyltriphenylphosphonium bromide as an example.

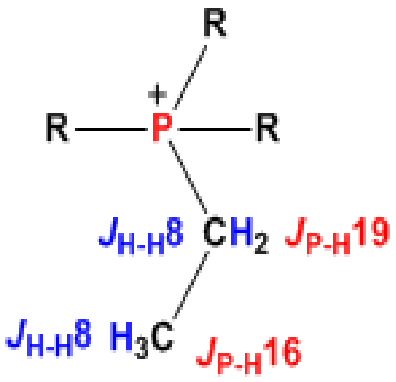


Figure 4.8: Phosphorus-hydrogen coupling and hydrogen-hydrogen coupling

Similarly, all the signals for the ethyltri-*n*-octylphosphonium series were identified. The triphenyl derivatives were clearly identified by the multiplet at 7.79 ppm which corresponded to the 15 aromatic hydrogens. The signals for the tosylate group were also evident and appeared as 2 doublets in the aromatic which corresponded to the four aromatic hydrogens. This is more clearly seen in the tri-*n*-butyl and tri-*n*-octyl series.

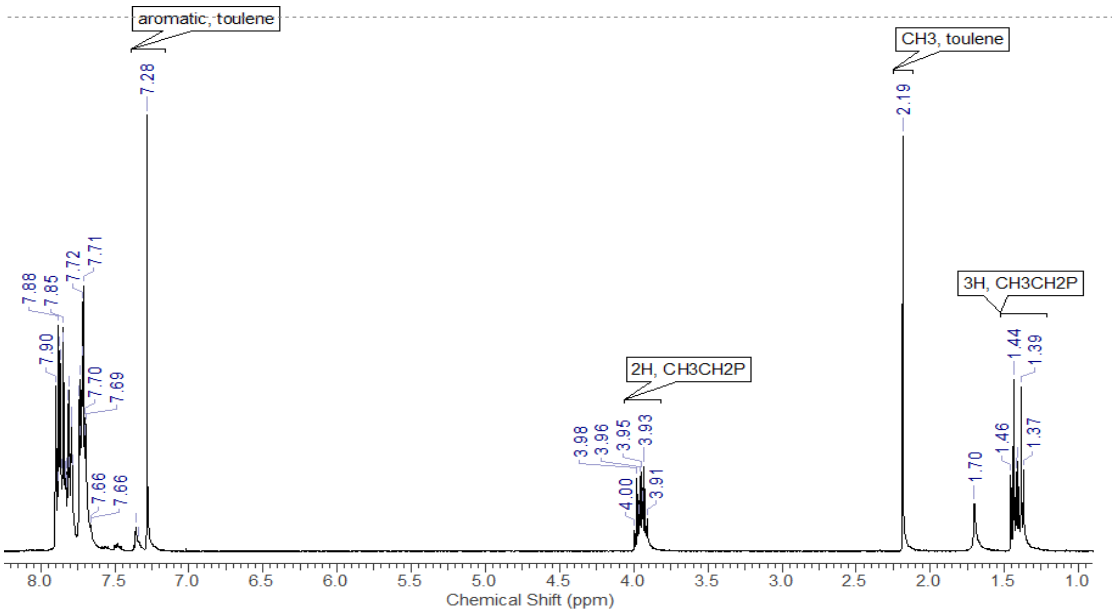


Figure 4.9: ^{1}H NMR of ethyltriphenylphosphonium bromide

Table 4.4: ^{1}H NMR data for phosphonium ionic liquids

Entry	R	R^1	X	$\delta_{H(ppm)}$ R	$\delta_{H(ppm)}$ R^1	OTs
1	Ph	Et	Br^-	7.79 (m)	1.41 (dt, 16, 8), 3.95 (dq, 12, 8)	
2	Ph	Et	I^-	7.84 (m)	1.41 (dt, 16, 8), 3.79 (dq, 16, 8)	
3	Ph	Et	Ts^-	7.12 (m)	1.36-1.42 (dt, 12, 8), 3.95 (dq, 16, 8)	7.12 (d, 8), 7.69-7.81(m)
4	Ph	Et	BF_4^-	7.73 (m)	1.40 (dt, 16, 8), 3.95 (dq, 12, 8)	
5	Ph	Et	PF_6	7.71-7.84 (m)	1.42 (dt, 16, 8), 3.95 (dq, 12, 4)	
6	*n*-Bu	Et	Br^-	0.97 (t, 16), 1.55 (m), 2.47-2.60 (m)	1.17 (dt, 16,8), 3.70-3.99 (dq, 19, 8)	
7	*n*-Bu	Et	I^-	0.98 (t, 16), 1.33-1.55 (m), 2.52 (m)	1.18 (dt, 16,8), 3.99 (dq, 19, 8)	
8	*n*-Bu	Et	Ts^-	0.97 (t, 16), 1.55 (m), 2.43 (m)	1.14 (dt, 16,8), 4.12 (dq, 19, 8)	7.15 (d,8), 7.80 (d, 8)
9	*n*-Bu	Et	BF_4^-	0.97 (t, 16), 1.54 (m), 2.43(m)	1.18 (dt, 16,8), 4.12 (dq, 19, 8)	
10	*n*-Bu	Et	PF_6^-	0.97 (t, 16), 1.55 (m), 2.47 (m)	1.17 (dt, 16,8), 4.13 (dq, 19, 8)	
11	*n*-Oct	Et	Br^-	0.90 (t, 12), 1.30-1.70 (m), 2.45-2.58 (m), 3.20 (m)	1.10 (dt, 18, 8), 3.96 (dq, 20, 8)	
12	*n*-Oct	Et	I^-	0.90 (t, 12), 1.32-1.68 (m), 2.47-2.58 (m), 3.43 (m)	1.07 (dt, 18, 8), 3.65-3.95 (m)	
13	*n*-Oct	Et	Ts^-	0.90 (t, 12), 1.29-1.70 (m), 2.35-2.50 (dq, 16, 8, m), 3.42-3.73 (m)	1.06 (dt, 18, 8), 4.13 (dq, 16,)	7.28 (d, 8), 7.81 (d, 8)
14	*n*-Oct	Et	BF_4	0.90 (t, 12), 1.31-1.67 (m), 2.25-2.33 (dq, 16, 8, m), 3.43-3.68 (m)	1.07 (dt, 18, 8), 3.96-4.11 (dq, 16, 8, m)	
15	*n*-Oct	Et	PF_6	0.90 (t, 12), 1.29-1.70 (m), 2.18 (dq, 12, 8, m), 3.41-3.68 (m)	1.05 (dt, 18, 8), 3.96-4.13 (dq, 16, 8, m)	

4.2.2.2.3 ^{13}C NMR Spectroscopy

The ^{13}C NMR data for the phosphonium ionic liquids are summarised in Table 4.5 As expected there is clear difference between the alkyltriphenyl- and tetraalkyl salts in the ^{13}C NMR spectra. When comparing the chemical shifts of ethyltriphenyl-, tri-*n*-butyl- and tri-*n*-octyl (entries 1-15), as expected that the values for C-1 of the alkyl groups are identical for the two ionic liquids, whereas the chemical shift for the triphenyl series appears in the upfield region. The signal for the phenyl rings are observed in the upfield region due to de-shielding (Figure 4.10). The tosylate group signals are found in the characteristic pattern of 4 signals. The chemical shifts of the carbon attached to phosphorus were affected slightly by the electronegativity of the anions. More electronegative anions lead to the chemical shift of C-P and C-C moving upfield.

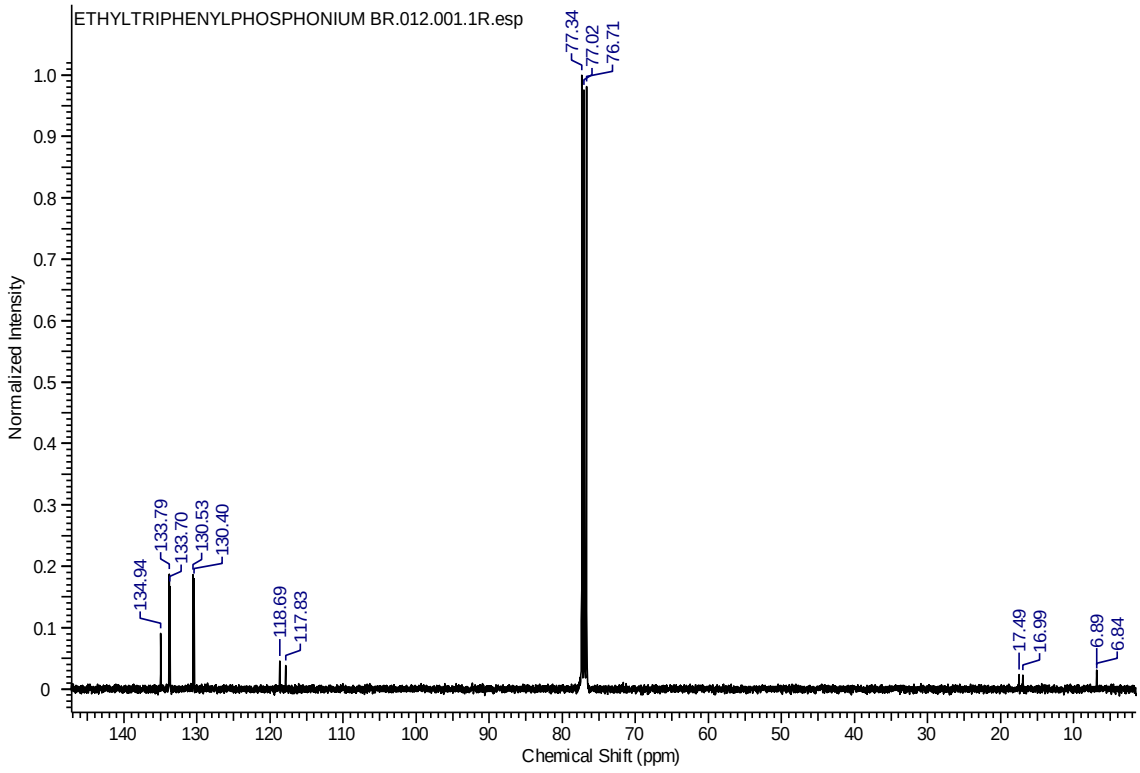


Figure 4.10: ^{13}C NMR of ethyltriphenylphosphonium bromide

As expected, P-C coupling is observed up to 4 bonds away in the triphenyl series (Figure 4.11) and 3 bonds away for the tri-*n*-butyl series and 2 bonds away for the tri-*n*-octyl series.

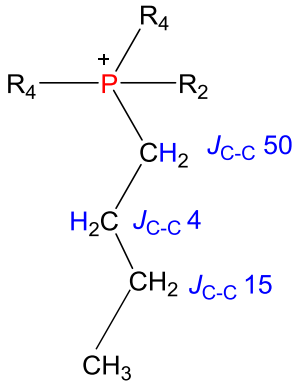


Figure 4.11: Structure and P-C coupling of phosphonium ionic liquids

Table 4.5: ^{13}C NMR data for phosphonium ionic liquids

Entry	R	R^1	X	P-C1 (R)	P-C1 (R^1)	R (*J*, Hz)	R^1	TsO
1	Ph	Et	Br^-	117.8 (*J* 86)	16.99 (*J* 52)	130.0 (12, 2C), 133.79 (11), 134.9 (3)	6.84 (*J* 5)	
2	Ph	Et	I^-	117.8 (*J* 86)	16.99 (*J* 52)	130.0 (12, 2C), 133.79 (11), 134.9 (3)	6.84 (*J* 5)	
3	Ph	Et	Ts^-	117.7 (*J* 86)	16.36 (*J* 52)	130.4 (12, 2C), 133.6 (11), 134.8 (3)	6.72 (*J* 5)	144.6,126, 137.4, 128.2
4	Ph	Et	BF_4	117.3 (*J* 86)	16.36 (*J* 52)	130 (12,2c), 133.98 (11), 135.72 (3)	6.80 (*J* 5)	
5	Ph	Et	PF_6	117.8 (*J* 86)	16.36 (*J* 52)	130.8 (12,2c), 133.98(11), 135.62 (3)	6.84 (*J* 5)	
6	*n*-Bu	Et	Br^-	18.5-19.5 (*J* 47)	13.0 (*J* 52)	13.49-13.62, 23.8, 27.36-28	6.2 (*J* 5)	
7	*n*-Bu	Et	I^-	18.4 (*J* 47)	13.1 (*J* 50)	13.50-13.66, 23.7, 27.34-28	6.0 (*J* 5)	
8	*n*-Bu	Et	Ts^-	18.5 (*J* 47)	13.0 (*J* 50)	13.5-13.62, 23.8, 27.36-28	6.2 (*J* 5)	125.4,129.4, 139, 145.1
9	*n*-Bu	Et	BF_4	18.1-18.9 (*J* 47)	12.9 (*J* 50)	13.4-13.67, 23.7, 27.34-28	5.9 (*J* 5)	
10	*n*-Bu	Et	PF_6	18.1-18.9 (*J* 47)	12.4 (*J* 50)	13.67, 23.7, 27.56	5.6 (*J* 5)	
11	*n*-Oct	Et	Br^-	18.5 (*J* 47)	12.96 (*J* 52)	14.1, 21.6, 22.7, 28.34, 29.0, 31.1, 31.8	6.12 (*J* 6)	
12	*n*-Oct	Et	I^-	18.9 (*J* 47)	13.72 (*J* 52)	14.59, 21.74, 22.68, 28.86, 29.4, 31.1, 31.8	6.18 (*J* 6)	
13	*n*-Oct	Et	Ts^-	18.4 (*J* 47)	13.06 (*J* 52)	14.1, 21.8, 22.5, 28.09, 29.0, 30.8, 31.7	6.18(*J* 6)	125.1, 129, 139,144.6
14	*n*-Oct	Et	BF_4	17.89 (*J* 47)	13.08 (*J* 52)	13.68, 21.74, 22.48, 27.86, 28.8, 31.4, 32.47	6.05 (*J* 6)	
15	*n*-Oct	Et	PF_6	19.42 (*J* 47)	13.08 (*J* 52)	15.1, 21.8, 22.5, 28.00, 28.09, 31.8, 32.7	6.12 (*J* 6)	

4.2.2.3 IR Spectroscopy of phosphonium ionic liquids

The IR spectra were obtained from the pure compounds using FTIR spectroscopy (Figure 4.12). The key signals expected were present in the spectra. For the triphenyl series, the IR characterisation of the phosphonium ionic liquids displayed a strong absorption band characteristic for the P-C stretching. The phenyl groups (entries 1-5) show a band around 1431-1440 cm-1 corresponds. However the tri-n-butyl and tri-*n*-octyl shows a band around 1440-1480 cm-1 (entries 6-15). The B-F stretch in the phosphonium ionic liquids is seen at 1280 cm-1 (entry 4, 9, 14) and the P-F signal is around 830 cm-1 (entries 5, 10, 15). For the tosylate group, the S=O stretching bands lies around 1110-1120 $cm^{-}1$ (entry 3, 8, 13) which correlates to the sulfonate group (1200-1145 cm^{-1}).

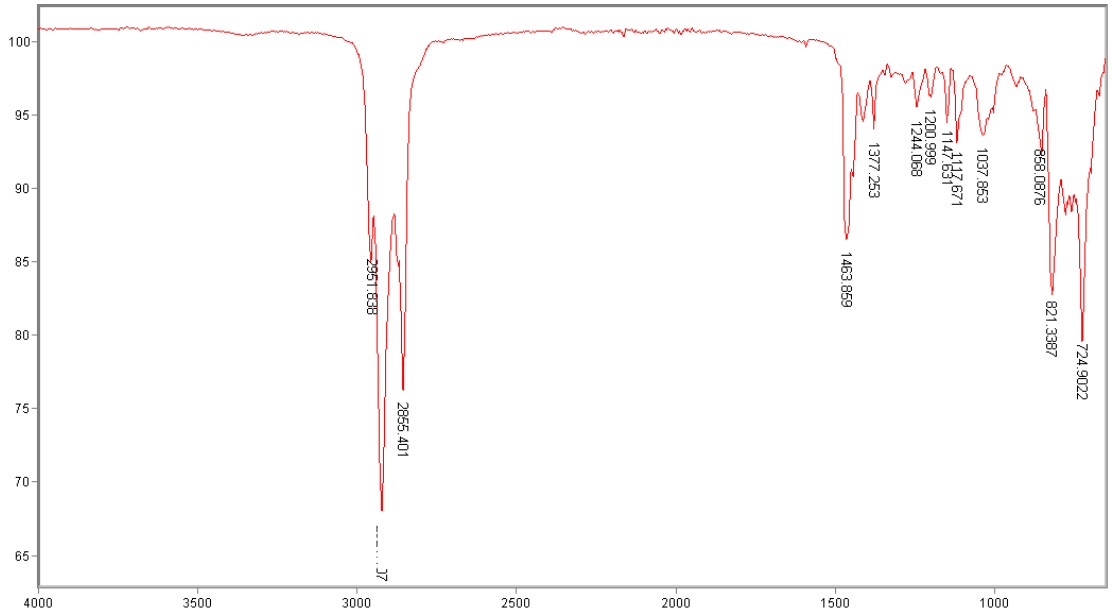


Figure 4.12: IR spectrum of ethyltri-*n*-butylphosphonium bromide

Table 4.6: IR Speactral analysis of $[R^1+PR_3]^+ [X]^-$ phosphonium ionic liquids

Entry	R	R^2	X^-	P-C stretch	Other stretches	Anion stretch (cm^{-1})
1	Ph	Et	B^-	1431	C=C (3020), C-H (2909)	-
2	Ph	Et	I	1435	C=C (3016), C-H (2863)	-
3	Ph	Et	OTs	1437	C=C (3082), C-H (2912)	(S=O) 1113, (S-O) 985
4	Ph	Et	BF_4	1436	C=C (3057), C-H (2958)	(B-F) 1283
5	Ph	Et	PF_6	1439	C=C (3057), C-H (2958)	(P-F) 830
6	*n*-Bu	Et	Br	1465	C-H (2932)	-
7	*n*-Bu	Et	I	1457	C-H (2932)	-
8	*n*-Bu	Et	OTs^-	1465	C-H (2931)	(S=O) 1116, (S-O) 985
9	*n*-Bu	Et	BF_4	1465	C-H (2962)	(B-F) 1283
10	*n*-Bu	Et	PF_6	1465	C-H (2958)	(P-F) 852
11	*n*Oct	Et	Br	1464	C-H (2952)	-
12	*n*-Oct	Et	I	1463	C-H (2952)	-
13	*n*-Oct	Et	Ts	1463	C-H (2925)	(S=O) 1120, (S-O) 985
14	*n*-Oct	Et	BF_4	1466	C-H (2925)	(B-F) 1282
15	*n*-Oct	Et	PF_6	1489	C-H (2925)	(P-F) 831

4.2.2.4 Thermogravimetric analysis (TGA)

The thermal stability of phosphonium ionic liquids was studied using thermogravimetric analysis (TGA). Generally, the thermal stability parameter is very important, especially for the reactions and crystallisation were carried out at high temperatures. In this section, TGA data, in which weight loss are reported for phosphonium ionic liquids that are heated at 10 °C/min rates and up to 400, are shown in figures 4.13, 4.14 and 4.15. Data from the TGA showed that the thermal stability of the ionic liquids is dependent on the cation/anion nature. Generally the phosphonium ionic liquids are stable to 300 °C or even higher (Fraser and MacFarlane, 2009). See Table 4.7.

Table 4.7 Thermal stability data of syntheised PILs

No.	PILs (code)	Molecular weight	Thermal stability (°C)
1	1	418.26	312
2	2	371.26	320
3	3	462.54	376
4	4	378.09	304
5	5	436.25	338
6	6	312.97	365
7	7	359.97	335
8	8	404.25	332
9	9	319.80	294
10	10	377.96	306
11	11	479.6	315
12	12	526.6	350
13	13	570.88	330
14	14	486.43	297
15	15	544.59	282

All the tributylphosphonium ionic liquids (5-10) were stable beyond 300-350 °C, and the best thermal stability was exhibited by ethyltri-*n*-butylphosphonium iodide at 350 °C (Figure 4.14). The trioctyl phosphonium ionic liquids (10-15) were less thermally stable than the tributylphosphonium ionic liquids. In the trioctyl series, the phosphonium ionic liquids lost weight from 150 °C - 200 °C (Figure 4.15). In case of the triphenyl analogues (1-5), they were more thermally stable than both series and loss of weight occurred from 300 °C-350 °C (Figure 4.13). The sequence of thermal stability was up to 350 °C. In addition, the phosphonium ionic liquids with the same anions and different cations had different thermal stability.

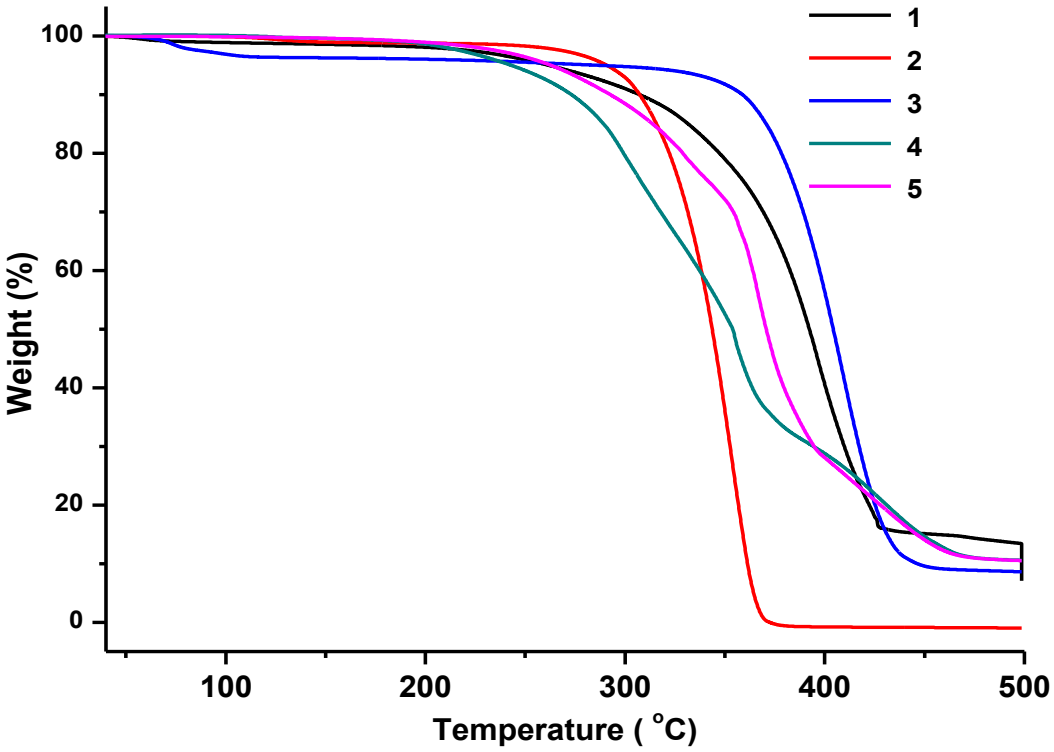


Figure 4.13 TGA analysis of phenyl series of phosphonium ionic liquids

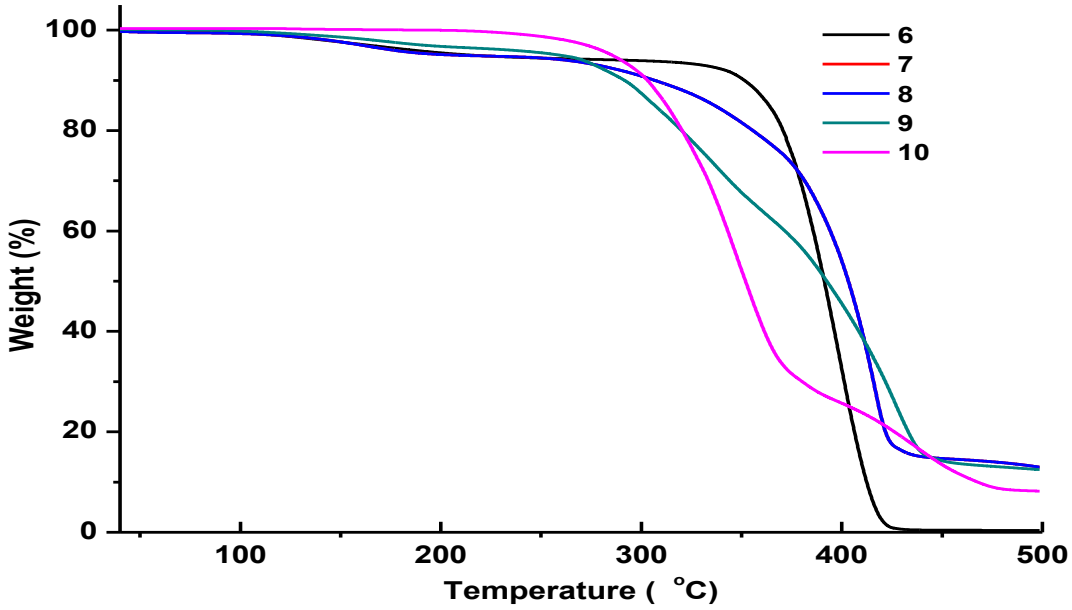


Figure 4.14 TGA analysis of butyl series of phosphonium ionic liquids.

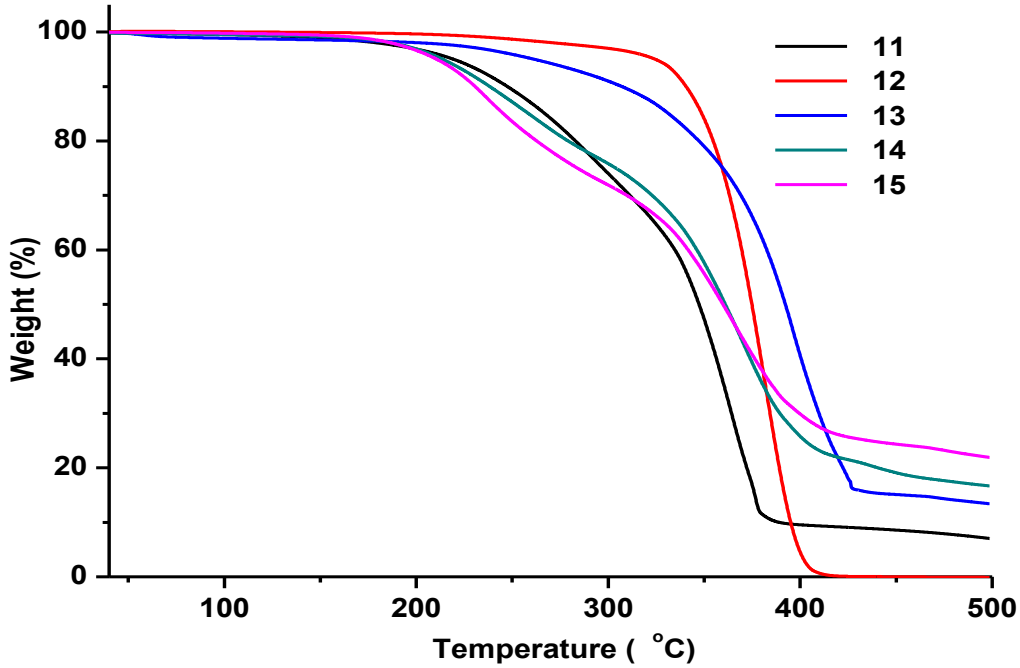


Figure 4.15 TGA analysis of octyl series of phoshphonium ionic liquids.

4.2.2.5 Octanol-water partition coefficient

Regarding the application of ionic liquids in the drug delivery system, the ionic liquid system could deliver medical benefits more efficiently and economically and could open new treatment options compared to the conventional methods. But considering the ionic liquid system in drug delivery, it may also have negative impact when exposed to the environment. Therefore, a simple thermodynamic octanol-water partition coefficient (K_{ow}) property plays an extremely important role in describing the hydrophobicity or hydrophilicity of the material and gives an understanding of the how ionic liquid or ionic liquid-drug system influences the aquatic ecosystems, bioaccumulation and toxicity in fish. In general, more lipophilic compounds have higher Log P values, and where drugs with higher values absorbed by cells easily and elimination from body it is less, and vice versa.

Partition coefficient of fifteen synthesised phosphonium ionic liquids (Table 4.8) was determined**.** From the values obtained it was observed that the entire partition coefficient values range below 1. In the case of tosylate, the partition coefficient values observed were above 1 and the bromide, iodide, PF_6, and BF_4 gave values below zero. The values obtained are in agreement with the molecular size. Considering the molecular weight in the following phosphonium ionic liquids, it was observed that as the molecular size increased partition coefficient increased.

Table 4.8 Ocatanol-water partion coefficient of PILs and their molecular weight

Sr. no.	PILs	Molecular weight	Partition coefficient
1	1	418.26	0.27
2	2	371.26	0.38
3	3	462.54	1.97
4	4	378.09	0.32
5	5	436.25	0.91
6	6	312.97	0.62
7	7	359.97	0.75
8	8	404.25	0.83
9	9	319.80	0.37
10	10	377.96	0.87
11	11	479.6	0.32
12	12	526.6	0.49
13	13	570.88	1.82
14	14	486.43	0.50
15	15	544.59	0.97

4.2.3 Summary

This chapter investigated the synthesis of the phosphonium ionic liquids using the microwave method. It was observed that the microwave-mediated synthesis complies with most of the green chemistry principles due to the environmental and economic benefits, coupled with higher yields (quantitative yields) and purer products compared to conventional synthesis methods.

The thermal properties of the phosphonium ionic liquids showed higher thermal stability when compared to nitrogen-based ionic liquids wherein, the triphenyl

series of the ionic liquids are more thermally stable than tributyl and trioctyl series. These thermal properties may be applicable for high temperature reactions as solvent media. The observed partition coefficient values of the synthesised ionic liquids were observed below 1. This means they will be less absorbed by cells and elimination of those drugs from body will be less.

Phosphonium ionic liquids were used in initial crystallisation study. In initial experimental findings phosphonium ionic liquids did not showed any crystallisation, however due to very limited availability in liquid form the study continued with the imidazolium ionic liquids

In this work, chapter 4 introduced the preparation methods of ionic liquids and investigated the easy preparation method of ionic liquids. In this study, the second objective was to investigate the possibility of crystallisation of APIs using ionic liquids as crystallisation media. The next chapter evaluated the solubility crystallisation of selected pharmaceutical drugs using imidazolium ionic liquids.

Chapter 5. Crystallisation of pharmaceutical drugs from ionic liquids

This chapter investigated the crystallisation of drugs using imidazolium ionic liquids and it is divided into two sections; introduction and results and discussion.

5.1 Introduction

The main objective of this chapter is to evaluate the possibility of using ionic liquids as solvent media for crystal engineering of drugs.

Recently a number of publications on the use of ionic liquids in crystal engineering have emerged (An and Kim, 2012, Weber et al., 2015, An et al., 2016, Smith et al., 2014, Pusey et al., 2007, Smith et al., 2011, dos Santos et al., 2013) due to their unique properties which were discussed in section 2.1.2 and 2.3.1.3. From literature it was suggested that one or both the ions of ionic liquids can be considered to generate the unique interionic (or intermolecular) interactions and to create a suitable environment for the solute (drugs) which may allow tailored solubility and novel crystallisation approaches (Reichert et al., 2006, Seddon et al., 2000b). The detailed applications were explained in section 2.3.1.3

After a literature review, it was decided to include a systematic study using imidazolium ionic liquids since 1,3-dialkylimidazolium cation is the most researched cation in the ionic liquid studies and fulfils many of the criteria needed for this work. Different anions were then selected to investigate its impact on the solubility and the crystallisation of the model compounds.

The model drugs chosen for this investigation includes sulfathiazole, chlorpropamide, phenobarbital and nifedipine as these actives belong to biopharmaceutical classification system (BCS) class II drugs. These drugs have very low water solubility and high permeability and each of these drugs exists in two or more polymorphic forms which are structurally very different from each other for a model drug.

5.2 Results and Discussion

The results were discussed as per each of the drug which includes sulfathiazole, chlorpropamide, phenobarbital and nifedipine. The methods used in this section were discussed in details in section 3.2.3.

5.2.1 Sulfathiazole [SFT]

SFT is an organosulfur compound which is used as an oral and topical antimicrobial agent. SFT is nonpolar and BCS class II drug having very low water solubility, 373 mg/L at 25 °C, it is sparingly soluble in ethanol, slightly soluble in dimethyl sulfoxide and practically insoluble in chloroform and diethyl ether (National Center for Biotechnology Information, 2016). SFT has four well characterised polymorphs (Blagden et al., 1998, Abu Bakar et al., 2008, Aaltonen, 2002) but most of the time the desired polymorph contain impurities of the other three polymorphs and it is difficult to produce a pure polymorphic form (Abu Bakar et al., 2008). For all the solubility and crystallisation studies, commercial form of sulfathiazole (Form III) has been used.

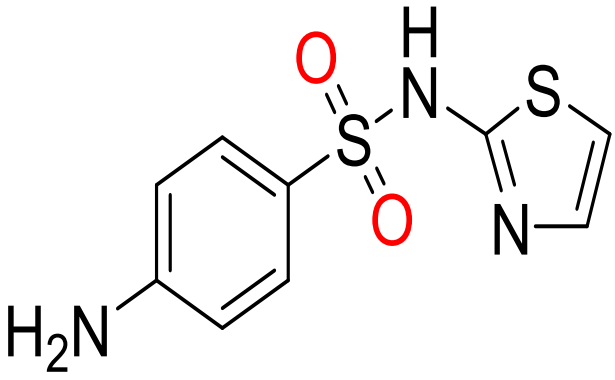


Figure 5.1 Chemical structure of sulfathiazole

5.2.1.1 Solubility determination

To understands controlled crystallisation, a fundamental solubility data required. For this, the solubility of SFT in [EMIM][acetate], [EMIM][DEP] and [EMIM][BF_4] were determined at various temperatures such as 50, 75 and 90 °C at 15 °C increment. In addition solubility of SFT was determined in water at 50, 75 and 90 °C temperatures (Figure 5.2). The solubility data can be seen to increase with increase in temperature. The solubility of SFT was higher in [EMIM][BF_4] than [EMIM][DEP] and [EMIM][acetate]. Analysing the chemical structure and functional groups of SFT it can be ascribed that was assumed that SFT will soluble in relatively lower dielectric constant (ε) (The dielectric constant of [EMIM][DEP]: 16.9, [EMIM][BF_4]: 13.9 (Singh and Kumar, 2008) and [EMIM][acetate]: 30 (Shi et al., 2013). In the experimental findings, it was observed that the solubility values were inversely proportional to the dielectric constant values of ionic liquids meaning, the [EMIM][BF_4] showed higher solubility with lower dielectric constant and similarly for the other two ionic liquids. The decreasing order of solubility is in the following order: [EMIM][BF4] > [EMIM][DEP] > [EMIM][acetate].

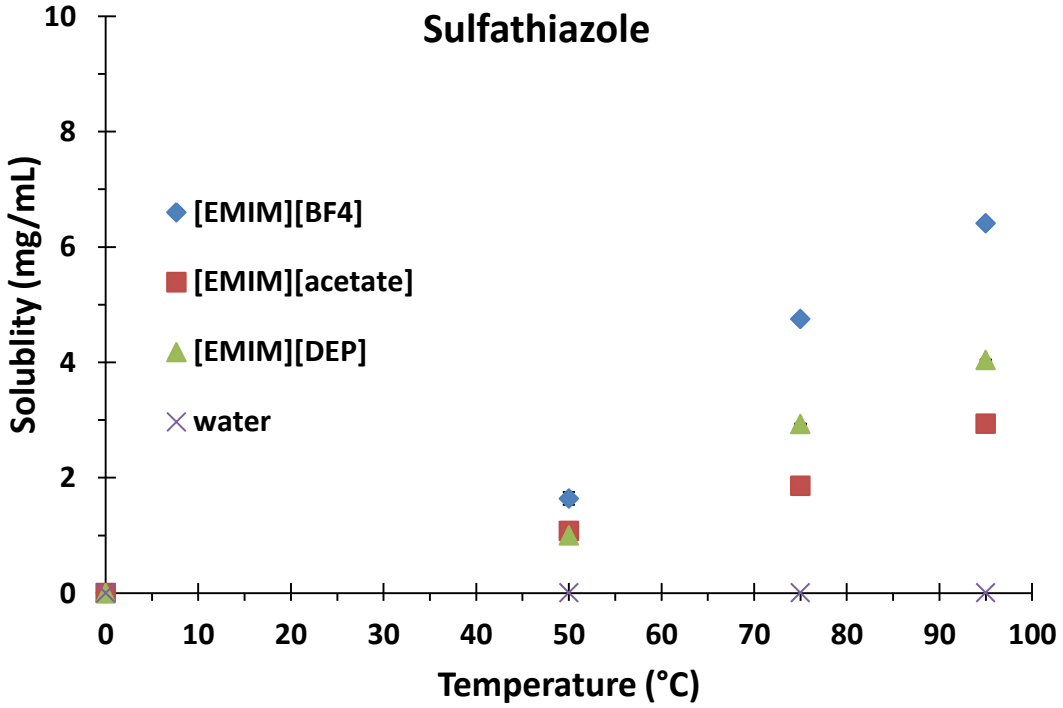


Figure 5.2 Solubility data in [EMIM][BF_4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for sulfathiazole.

Due to the high dielectric constant of water (ε: 80) the SFT molecule (nonpolar) did not show any solubility at various temperature. The ionic liquids solubility data showed significant higher values as compared to water solubility due to lower dielectric constant. Here the solute solvent interaction plays an important role to increase the solubility. However, the solvation mechanisms of ionic liquids are mostly unknown so it is difficult to predict the solute solubility (Mizuuchi et al., 2008). Overall, the solubility of SFT significantly enhances in the ionic liquids.

5.2.1.2 Crystallisation study

To understand the solute-solvent interactions, crystallisation studies of SFT with various ionic liquids were performed using cooling and antisolvent crystallisations. In cooling crystallisation, saturated solution of SFT with ionic

liquid at 75 °C was prepared and the solution was allowed to cool and crystallise at the ambient conditions. After 3 days, colourless good quality crystals were obtained with [EMIM] [BF_4]. The resulting novel crystals were analysed thoroughly using PXRD, DSC and SC-XRD. However, SFT with [EMIM][acetate] or [EMIM][DEP] did not show any crystallisation but it remained as a clear solution even after 30 days.

Next, antisolvent crystallisations of SFT-ionic liquids were also carried out using the green solvent, distilled water (5 mL) to gain further understanding on solute-solvent interactions. Firstly, a clear solution of SFT-ionic liquid was achieved by heating at 75 °C and it was transferred into the water. The colourless solid masses were obtained with all three ionic liquids. The respective product phases were filtered, dried in an oven at 60 °C for 4 hrs and analysed by PXRD and DSC.

5.2.1.3 PXRD and DSC analysis

The resultant materials from both cooling and antisolvent crystallisation were analysed by PXRD, which are shown in Figure 5.3. These were compared with pure commercial SFT (Form III) and simulated powder patterns obtained from the reported single crystal X-ray diffraction data sets for the SFT polymorphs (Forms I through IV).

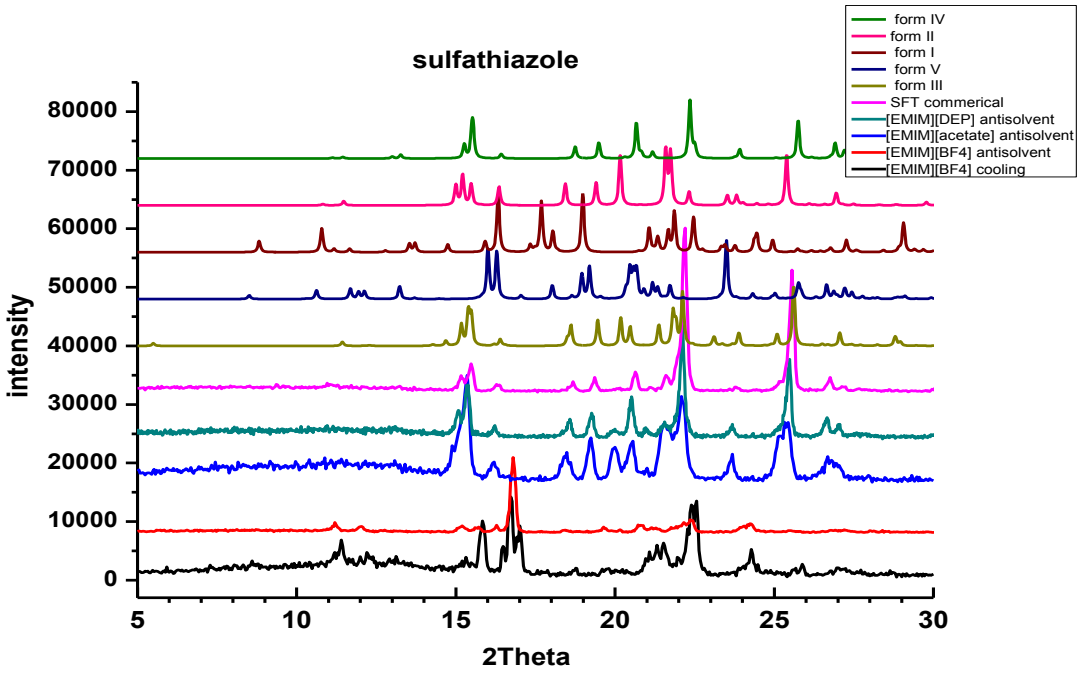


Figure 5.3 PXRD patterns for the sulfathiazole-ionic liquid product phases obtained from both cooling and antisolvent crystallisations. For a comparison, simulated powder patterns sulfathiazole polymorphs (Forms I – IV) from reported structures were also considered.

The results were interesting that good quality crystals obtained from SFT-[EMIM] [BF_4] showed unique powder patterns to that of all the polymorphs of SFT that include commercial SFT (Form III). It indicates a new solid form was obtained. Further analyses of this new phase have been conducted using DSC and SC-XRD. On the other hand, PXRD results of solid mass obtained from antisolvent crystallisation suggest the appearance of new phase with [EMIM] [BF_4], which was matching to that of cooling crystallisation result for the SFT-[EMIM] [BF_4] whereas with other two ionic liquids, no other new phase has been delineated but generation of SFT (Form III) was noted.

According to DSC thermograms, it was found that the product phases of SFT involving [EMIM][BF_4] from both cooling and antisolvent crystallisations showed the unique major endotherm at 100 and 98 °C, respectively (Figure 5.3). In the

case of antisolvent crystallisations of SFT using [EMIM][acetate] and [EMIM][DEP] produced the DSC profiles similar to SFT (Form III). Overall, the DSC results further confirm the PXRD results meaning both cooling and antisolvent crystallisations of SFT-[EMIM] [BF_4] produced a new phase, which was further analysed by SC-XRD.

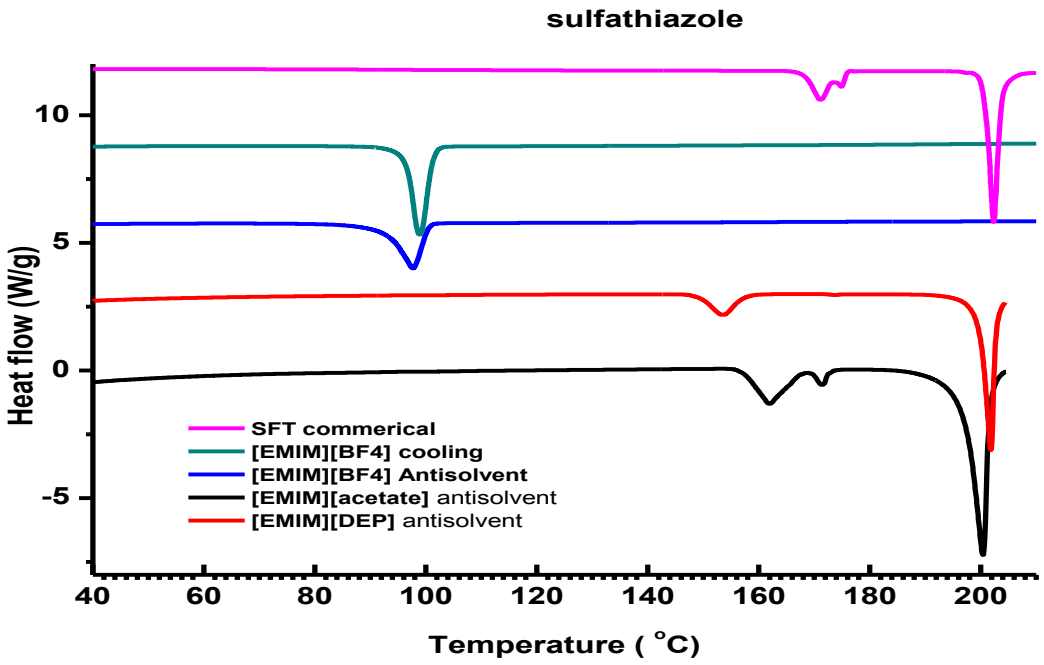


Figure 5.4 DSC analysis on product phases for sulfathiazole with various ionic liquids using cooling and antisolvent crystallisations were performed. For a comparison, DSC trace of commercial sulfathiazole (Form III) was also considered.

5.2.1.4 Single crystal X-ray diffraction (SC-XRD)

SC-XRD performed on the new phase obtained from cooling crystallisation of SFT and [EMIM][BF_4]. The crystallographic data is presented in the Table 5.1. It has crystallised in the triclinic $P^{-}1$ crystal system. Interestingly, the crystal structure analysis revealed the formation of a supramolecular complex (Golovanov et al., 2005) consist of one molecule each of SFT and [EMIM][BF_4]

(Figure 5.5). The quality of crystal data was found to be reasonable with the R-factor of ~6.8%.

Table 5.1 Crystal data collected from SC-XRD

Empirical formula	**$(C_9H_9N_3O_2S_2)\cdot(C_6H_{11}N_2)\cdot(BF_4)$**
Formula weight	481.34
Crystal system	Triclinic
Space group	$P\bar{1}$
T [K]	173(2)
***a* [Å]**	8.3439(5)
***b* [Å]**	8.6409(5)
***c* [Å]**	15.8505(9)
α [°]	90.985(3)
β [°]	93.152(3)
γ [°]	106.747(2)
Z	2
***V* [Å^3]**	1092.02(11)
D_{calc} [g cm^{-3}]	1.464
μ [mm^{-1}]	2.745
Reflections used	9989
Unique reflections	3575
Observed reflections	3382
Parameters	331
R1[I > 2σ(I)]	0.0679
wR_2 [all]	0.1878
GOF	1.055
Crystal shape	Needle

The crystal structure reveals that the SFT molecules self-assemble through N–H···N dimers (Figure 5.6 and Table 5.4). The detailed crystal packing shows the key interactions between SFT and ionic liquid are through the N–H···F and C–H···F hydrogen bonds. In the supramolecular organisation, the BF_4 ion plays

an anchor role meaning it connects both imidazolium cation and SFT molecules through intermolecular interactions.

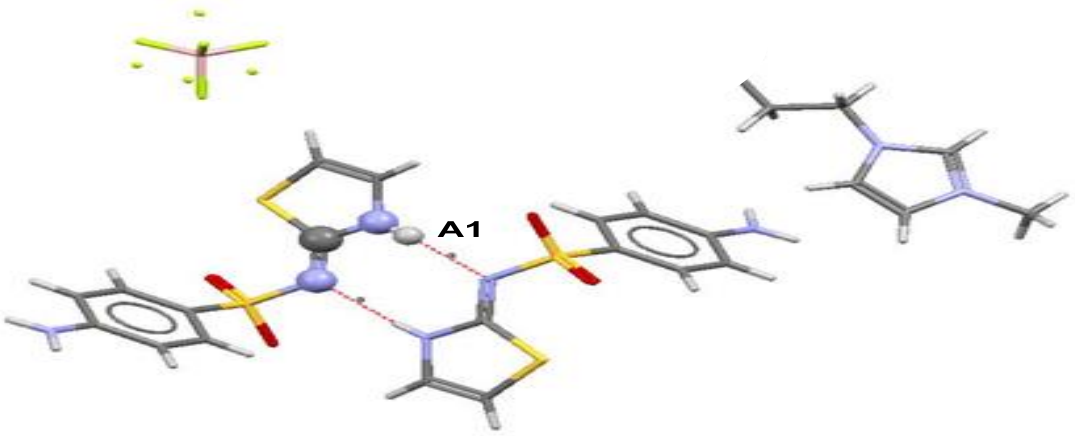


Figure 5.5 Crystal structure of sulfathiazole•[EMIM] [BF4] complex. Notice the N–H···N dimer hydrogen bonds between sulfathiazole molecules.

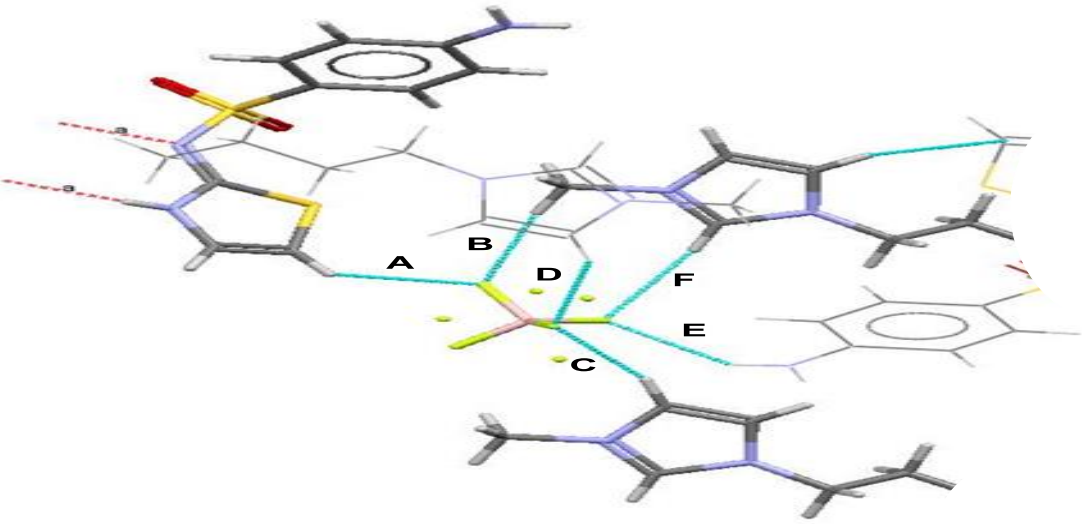


Figure 5.6 Crystal packing of sulfathiazole and [EMIM] [BF_4] complex where BF_4 anion connects imidazolium cation and sulfathiazole through N–H···F and C–H···F hydrogen bonds.

Table 5.4 Details of interactions of SFT and [EMIM][BF4].

No	Code	Interactions	Distance (Å)	Angle (θ)
1	A1	N–H···N	2.09	171.29
2	A	C–H···F	2.38	130
2	B	C–H···F	2.55	148
3	C	C–H···F	2.55	130
4	D	C–H···F	2.44	148
5	E	N–H···F	2.32	139
6	F	N–H···F	2.65	160

5.2.2 Chlorpropamide (CPA)

Chlorpropamide (CPA) (4-chloro-*N*-(propylcarbamoyl)benzenesulfonamide) belongs to the sulfonylurea class of compounds and it is used for the treatment of type II diabetic patients. CPA is nonpolar and excellent example of the BCS class II drug. CPA is commonly used as a model drug system for polymorphism study, the functional groups of which are capable of forming intermolecular hydrogen bonds and with very complex thermodynamic relationships (Ayala et al., 2012, Ueda et al., 1984, Simmons et al., 1973). CPA is practically insoluble in water (258 mg/L at 37 °C), sparingly soluble in organic solvents (National Center for Biotechnology Information, 2016). Some attempts have been made by researchers to increase the dissolution rate of CPA using solid dispersion and coprecipitation methods (Ford and Rubinstein, 1977, Dubois and Ford, 1985) and these techniques were shown to improve the drug bioavailability and absorption (Deshpande and Agrawal, 1985). For all the solubility and

crystallisation studies, commercial form of chlorpropamide (alpha form) has been used.

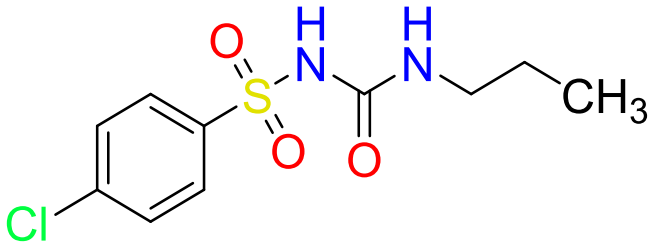


Figure 5.7 Chemical structure of chlorpropamide.

5.2.2.1 Solubility determination

The solubility of CPA was determined in the ionic liquids [EMIM][BF4], [EMIM][acetate] and [EMIM][DEP] at 50, 75 and 100 °C. In addition CPA solubility in water at the same temperatures was determined. The Figure 5.8 showed the solubility profiles for CPA-ionic liquids and water where the solubility can be seen to increase with the increase in temperature.

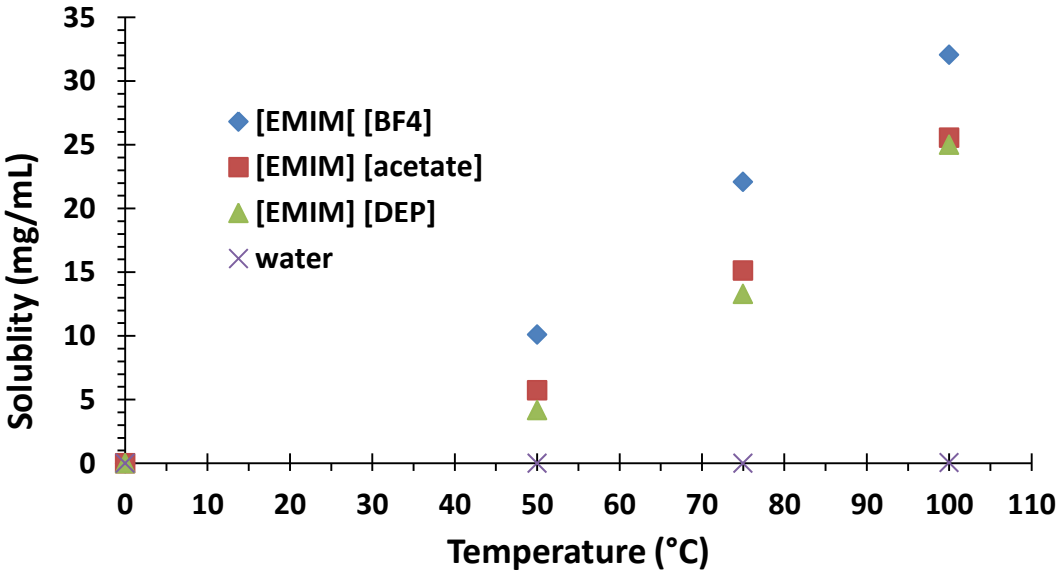


Figure 5.8 Solubility data in [EMIM][BF_4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for chlorpropamide.

In the experimental findings, it was observed that the [EMIM][BF_4] showed higher solubility as expected with its low agreeing with the dielectric constant, but in case of [EMIM][DEP] and [EMIM][acetate] the solubility behaviour did not correlate directly with respective dielectric constant values meaning [EMIM][acetate] showed higher solubility to that of [EMIM][DEP]. However, as discussed in SFT section the solvation mechanisms of ionic liquids are mostly unknown so it is difficult to predict the solute solubility. A sample of chlorpropamide was insoluble in water at various temperatures so it was difficult to ascribe on the graph. However, the solubility values in ionic liquids are significantly higher than the water solubility.

5.2.2.2 Crystallisation

To understand the solute-solvent interactions, crystallisation studies of CPA with various ionic liquids were carried out using cooling and antisolvent crystallisations. In cooling crystallisation, saturated solution of CPA with ionic liquids at 75 °C was prepared and solution was allowed to cool and crystallise at ambient conditions. After 20 days, colourless solid mass was obtained from [EMIM][BF_4]. The resulting solid mass was analysed thoroughly using PXRD and DSC. However, CPA with [EMIM][DEP] and [EMIM][acetate] did not show any crystallisation but it remained as clear solution even after one month.

In antisolvent crystallisations, water: methanol mixture (70%:30%, 10 mL) was used because water alone could produce highly viscous sticky mass. The colourless solid mass was obtained for CPA with ionic liquids except for [EMIM][BF_4]. In the case of [EMIM][BF_4], a sticky mass was observed. The resulting solid masses were analysed by PXRD and DSC.

5.2.2.3 PXRD and DSC analyses

The resultant solid mass obtained from cooling crystallisation was analysed by PXRD, which is shown in Figure 5.9. This was compared with pure commercial CPA (alpha form) and simulated powder patterns obtained from the reported single crystal X-ray diffraction data sets for the CPA polymorphs (alpha, beta, gamma and epsilon). The result was interesting that solid mass obtained from CPA–[EMIM][BF_4] showed different powder patterns compared to commercial CPA (alpha form). Detailed analyses suggest that this solid mass was matched with that of a metastable epsilon form of CPA (Figure 5.9). This result is interesting because in general, epsilon form could be obtained under specific crystallisation conditions such as hot solutions of solvents (Drebushchak et al., 2009), however, preparation of an epsilon form using ionic liquid was found to be reproducible and straightforward. This result suggests that ionic liquid – drug crystallisations will have a great potential in the controlled crystallisation of drugs.

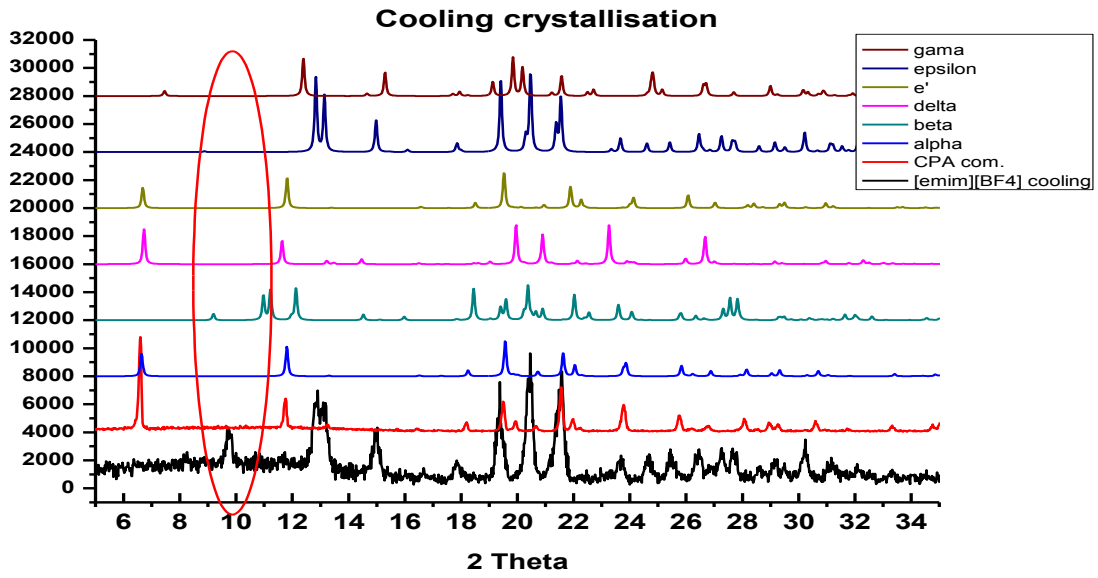


Figure 5.9: PXRD patterns for chlorpropamide solid mass obtained from cooling crystallisation. For a comparison, simulated powder patterns of chlorpropamide polymorphs (forms alpha to gamma) from reported structures were also considered.

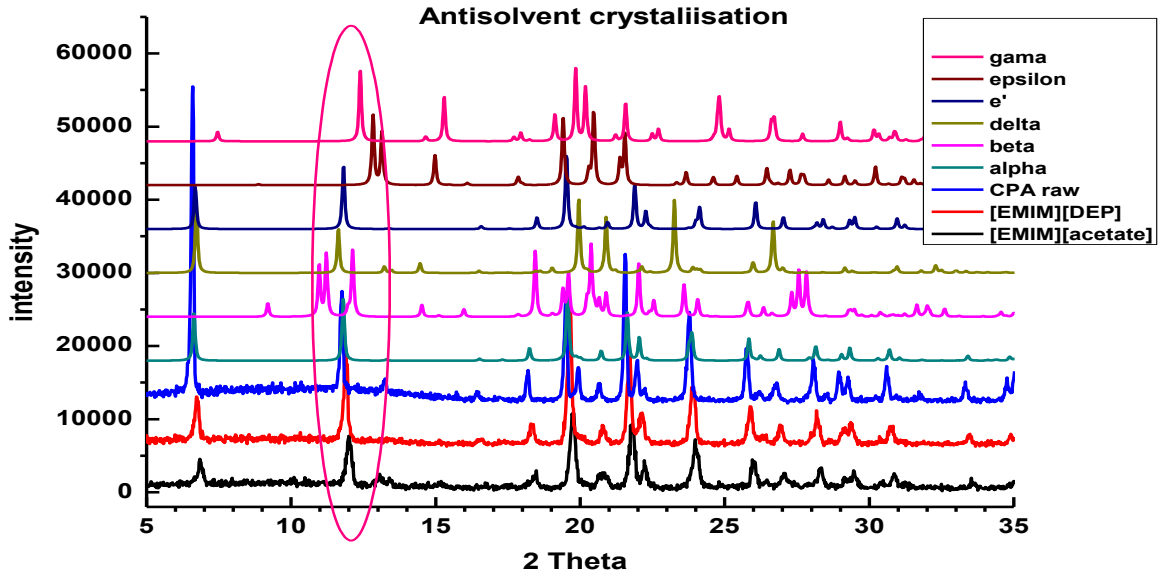


Figure 5.10 PXRD patterns for chlorpropamide solid mass obtained from antisolvent crystallisation. For a comparison, simulated powder patterns chlorpramide polymorphs (forms alpha to gamma) from reported structures were also considered.

Antisolvent crystallisation results are summarised in Figure. 5.10. The powder patterns of solid masses from [EMIM][acetate] and [EMIM][DEP] matches with that of commercial CPA (alpha form). It should be mentioned that antisolvent crystallisation did not yield any new phase but alpha form has precipitated out.

According to DSC thermograms, it was found that the obtained solid mass from cooling crystallisation in [EMIM][BF_4] showed a unique endotherm at 119.2 °C (Figure 5.11). From analysis it was observed that obtained endotherm did not match with the commercial CPA (126 °C) endotherm. From a detailed PXRD and DSC results it was confirmed that the alpha form of CPA converted into the metastable epsilon form.

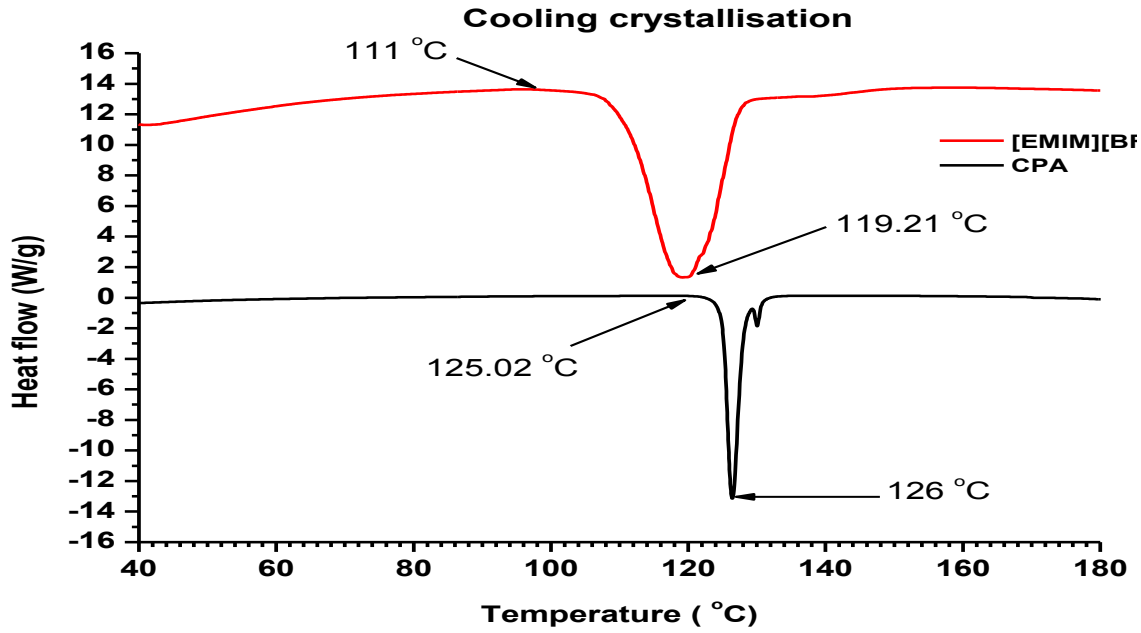


Figure 5.11 DSC analysis of obtained solid mass for CPA in cooling crystallisation was performed. For a comparison, DSCtrace of commerical chlorprpamide (alpha form) was also considered.

DSC thermograms of antisolvent crystallisation as shown in Figure 5.12 solid mass obtained from [EMIM][acetate] and [EMIM][DEP] displays endotherms at

127 °C and 122 °C respectively. These DSC endotherms match with the commercial alpha form of CPA (127 °C)

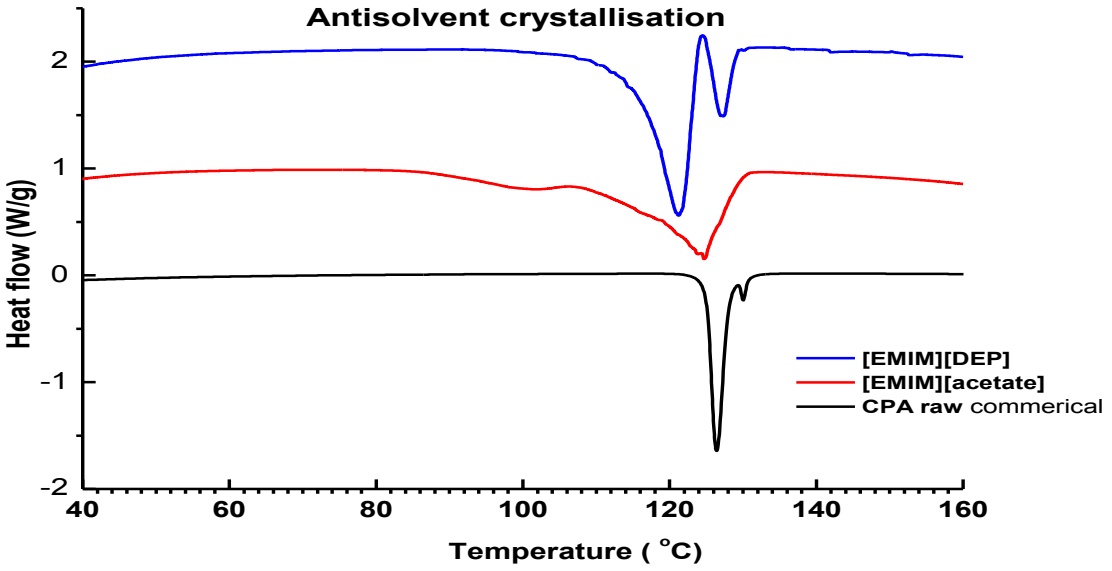


Figure 5.12 DSC analysis of obtained solid mass for CPA in antisolvent crystallisation was performed. For a comparison, DSC trace of commerical chlorpropamide (alpha form) was also considered.

From the above analysis, the cooling crystallisation in [EMIM][BF_4] provides the favourable condition for the formation of the metastable polymorph. In contrast, during the antisolvent crystallisation, the stable alpha form has been retained.

5.2.3 Phenobarbital (PBB)

Phenobarbital (PBB) is a sedative, hypnotic and anti-epileptic drug, which helps patients to relax before surgery or to sleep. PBB is supplied in an oral solid dosage form. Generally, PBB is a hydrophobic drug and it has very low water solubility (1 mg/mL), 1 g soluble in 8 mL alcohol; 40 mL chloroform; 12 mL ether; about 700 mL benzene. It is thus soluble in alcohol, ether, chloroform and essentially insoluble in benzene (National Center for Biotechnology Information,

2016). To increase the solubility of PBB water-miscible solvents are added. Therefore, to increase the solubility of PBB, ethanol is more often used as a co-solvent. PBB is well characterised by different analytical techniques and it has six polymorphs (PBB forms -I, II, III, IV, V, VI). The thermodynamic stability of PBB at 20 °C was confirmed as I > II > III > IV > V > VI (Zencirci et al., 2010). Here, for all the crystallisation and solubility studies, the commercial form of phenobarbital (triclinic form II) has been used.

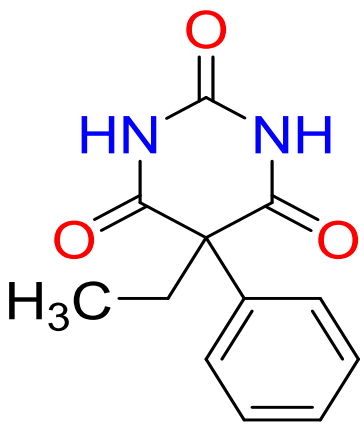


Figure 5.13 Chemical structure of phenobarbital

5.2.3.1 Solubility determination

The solubility of PBB was reported in the three different ionic liquids [EMIM][BF_4], [EMIM][acetate] [EMIM][DEP] and water at 50, 75 and 100 °C. Form the data (Figure 5.14) it was observed that the overall solubility of PBB was higher in [EMIM][DEP] compared to [EMIM][BF_4] and [EMIM][acetate].

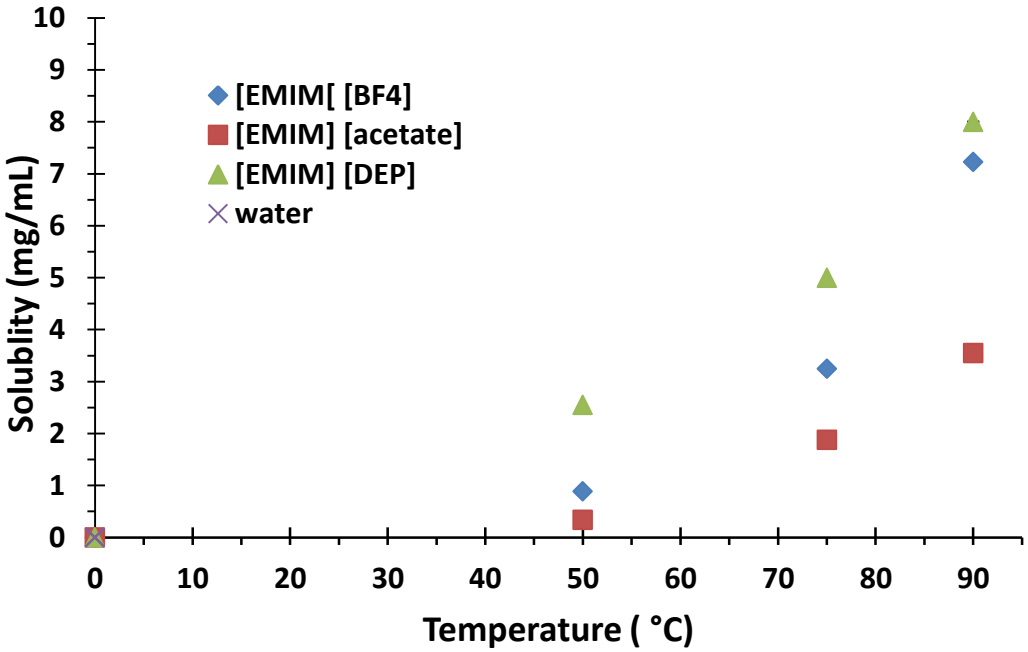


Figure 5.14 Solubility data in [EMIM][BF4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for phenobarbital.

In the case of [EMIM][DEP] (ε : 16.9) the PBB solubility observed higher than the [EMIM][BF_4] (ε : 13.9). Comparing the dielectric constant values [EMIM][DEP] and [EMIM][BF_4] there is not much difference between them. However, these results could be expected. Furthermore, due to nonpolar nature of molecule, PBB did not showed solubility in water (ε : 80). The ionic liquid solubility of PBB showed significant increase compared to water solubility.

5.2.3.2 Crystallisation

In sulfathiazole the supramolecular complexation with ionic liquid and in chlorpropamide polymorphic transition was investigated. To understand these events further, phenobarbital was selected and investigated to understand the solute-solvent interactions, In this study cooling and antisolvent crystallisation were performed with various ionic liquids at 75 °C. In cooling crystallisation, saturated solution of PBB with ionic liquids at 75 °C was prepared and the

solution was allowed to cool at ambient conditions. After 4 days, colourless good quality crystals were obtained with [EMIM][acetate]. The resulting crystals were analysed thoroughly using PXRD, DSC and SC-XRD. However, PBB with [EMIM][BF_4] and [EMIM][DEP] did not show any crystallisation but it remained as a clear solution even after 30 days.

In antisolvent crystallisations of PBB-ionic liquids were carried out using water: methanol (70%: 30%) 10 mL to gain further understanding on solute solvent interactions. In the experimental findings, a clear solution of PBB-ionic liquid was achieved by heating at 75 °C and the clear hot solution was decanted into water. Colourless solid masses have been obtained with [EMIM][DEP] and [EMIM][acetate]. The respective product phases were filtered, dried in an oven at 60 °C for 4 hrs and analysed by PXRD and DSC.

5.2.3.3 PXRD and DSC analyses

The resultant material obtained from the cooling crystallisation was analysed by PXRD, which was shown in Figure 5.15. These were compared with pure commercial PBB (triclinic form II) and with the simulated powder patterns obtained from the reported single crystal X-ray diffraction data sets for the PBB polymorphs (monoclinic form I, triclinic form II, monoclinic form III).

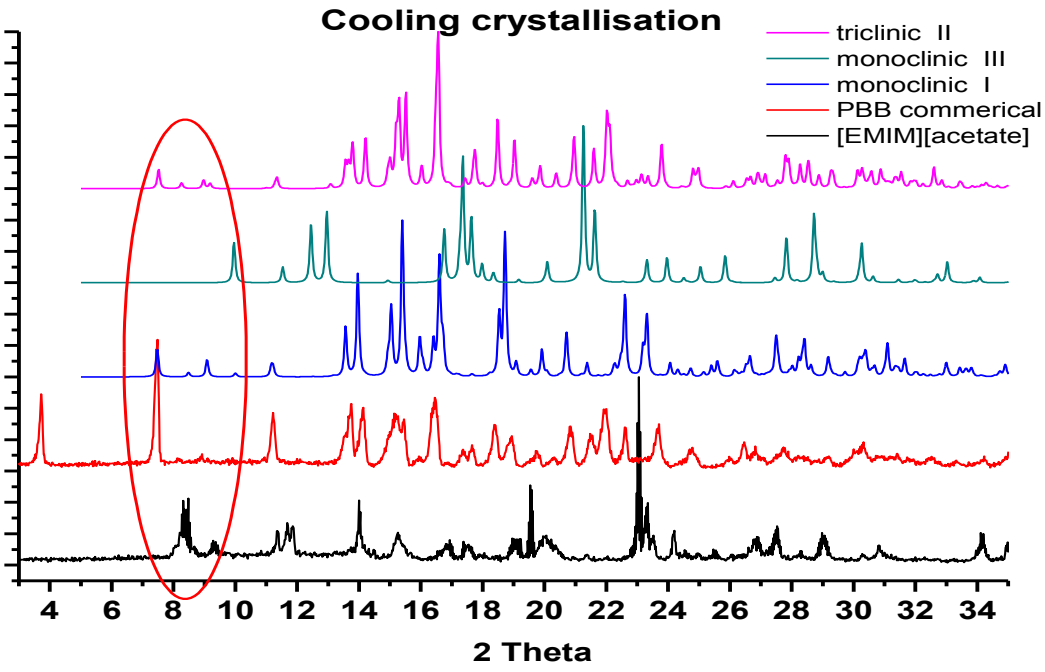


Figure 5.15 PXRD analysis of product phases for phenobarbital with ionic iquids using cooling crystallisation were performed. For comparison, simulated powder patterns of phenobarbital polymorphs (monolinic form I, triclinic form II and monoclinic form Iii) from reported structures were also considered.

The results were interesting that good quality crystals obtained from [EMIM][acetate] showed unique powder patterns to that of all the polymorphs of PBB that include commercial triclinic form II. It indicates a new solid form was obtained. Further analyses of this new phase have been conducted using DSC and SC-XRD. On the other hand, antisolvent crystallisation of solid masses which were obtained from [EMIM][DEP] and [EMIM][acetate] summarised in Figure. 5.16. The powder patterns of solid masses matches with that of commercial PBB (triclinic form II). It should be mentioned that antisolvent crystallisation did not yield any new phase but commercial triclinic form II has precipitated out. In present graph (Figure 5.16) the fact that the peak intensity of

obtained resultant masses is depressed may be due to the ionic liquid not being washed out appropriately.

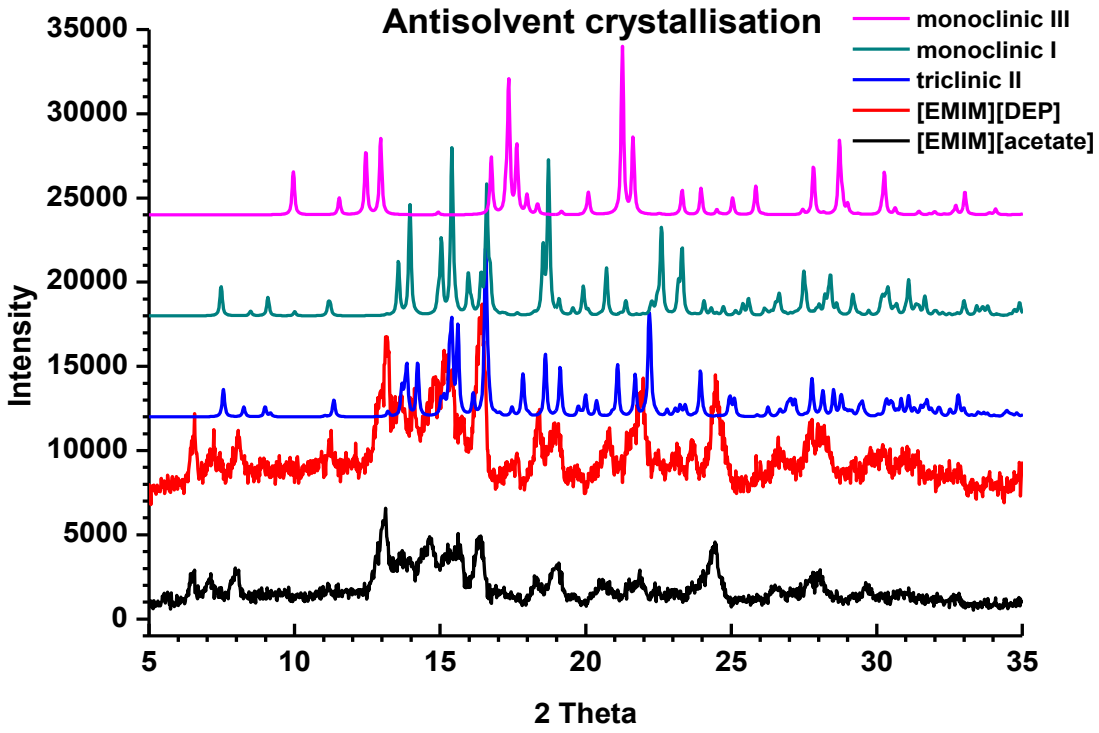


Figure 5.16 PXRD analysis of product phases for phenobarbital with variuos ionicl iquids using antisolvent crystallisation were performed. For comparison, simulated powder patterns of phenobarbital polymorphs (monolinic form I, triclinic form II and monoclinic form Iii) from reported structures were also considered.

The obtained crystals from cooling crystallisation ([EMIM][acetate]) was further analysed by DSC (Figure 5.17) and it showed a unique endotherm at 159 °C. Where, the commercial PBB (triclinic form II) showed endotherm at 176 °C. From this analysis it was observed that there was a significance difference between commercial and obtained endothermic peak. Overall DSC results further confirms the PXRD results meaning PBB-[EMIM][acetate} produced a new phase, which was further analysed by SC-XRD.

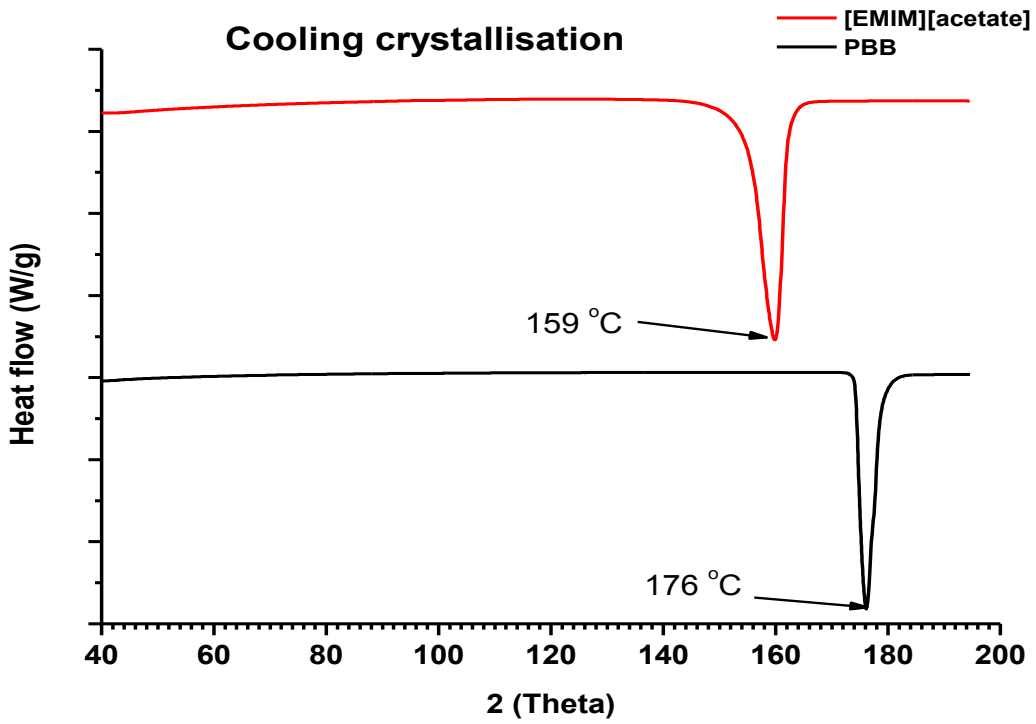


Figure 5.17 DSC analysis on product phase obtained for phenobarbital with [EMIM][acetate] using cooling crtystallisation was performed. For a comparison DSC trace of commerical phenobarbital (triclinic form II) was also considered.

A DSC thermograms of antisolvent crystallisation, (Figure 5.18) solid mass obtained from [EMIM][acetate] and [EMIM][DEP] showed endotherm at 174 and 176 °C. These DSC endotherms match with the commercial triclinic form II of PBB (176 °C)

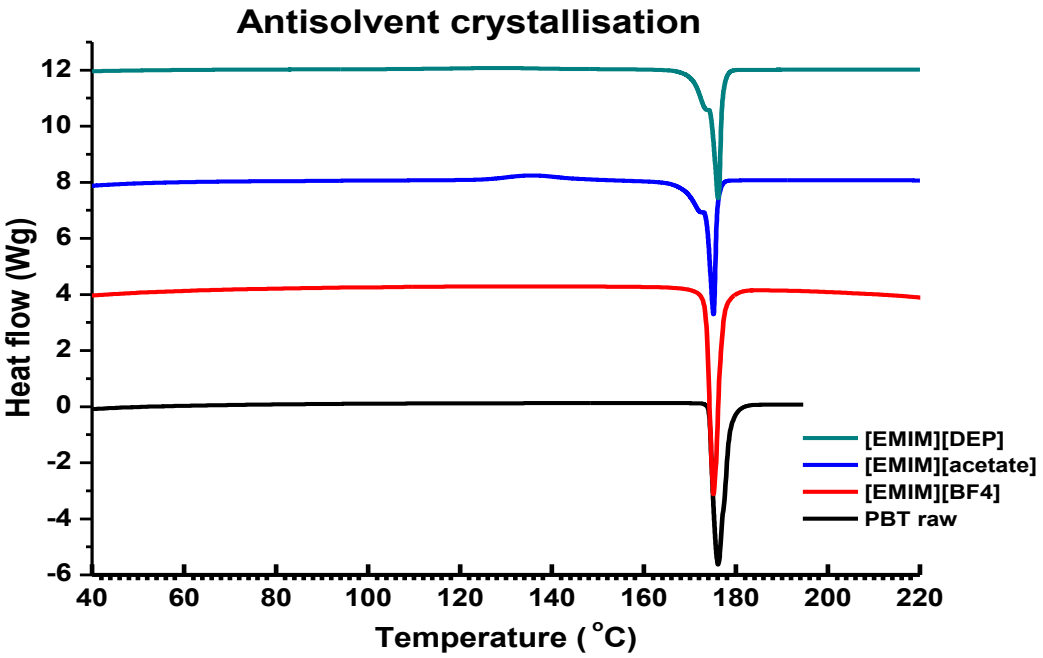


Figure 5.18 DSC analysis of phenobarbital obtained with various ionic liquid solvent and and water : methanol (70:30) as antisolvent mixtures. DSC curves obtained at heating rate 10 °C/min.

5.2.3.4 Single crystal X-ray diffraction (SC-XRD)

SC-XRD was performed on the new phase obtained from cooling crystallisation of PBB and [EMIM][acetate]. The crystallographic data was presented in the Table 5.2. It has crystallised in the triclinic $P\bar{1}$ crystal system. Interestingly, the crystal structure analysis revealed the formation of a supramolecular complex consist of one molecule each of PBB and [EMIM][acetae] (Figure 5.19). There was a disorder around acetate moiety. However, the quality of crystal data was found to be reasonable with the R-factor of 5.7%.

Table 5.2 Crystallographic parameters of phenobarbital and [EMIM][acetae] complex

Empirical formula	$(C_{12}H_{11}N_2NaO_3)\cdot(C_8H_{14}N_2O_2)$
Formula weight	402.43
Crystal system	Triclinic
Space group	$P\bar{1}$
T [K]	173(2)
***a* [Å]**	8.9597(4)
***b* [Å]**	9.7265(4)
***c* [Å]**	11.0346(5)
α **[°]**	95.815(3)
β **[°]**	104.696(3)
γ **[°]**	108.855(3)
Z	2
***V* [Å^3]**	862.443
D_{calc} **[g cm^{-3}]**	1.322
μ **[mm^{-1}]**	0.751
Reflections used	8363
Unique reflections	2877
Observed reflections	2457
Parameters	105
R1[I > 2σ(I)]	0.0567
wR_2 [all]	0.3007
GOF	0.12
Crystal shape	Needle

The crystal structure reveals that the PBB molecules self-assemble through N–H···O dimers (Figure 5.19 and Table 5.3). The detailed crystal packing shows the key interactions between PBB and imidazoliumion.

Table 5.3 Details of interactions of phenobarbital and [EMIM][acetate] complex

Sr No	Code	Interactions	Distance (Å)	Angle (θ)
1	A	N–H···0	-	175

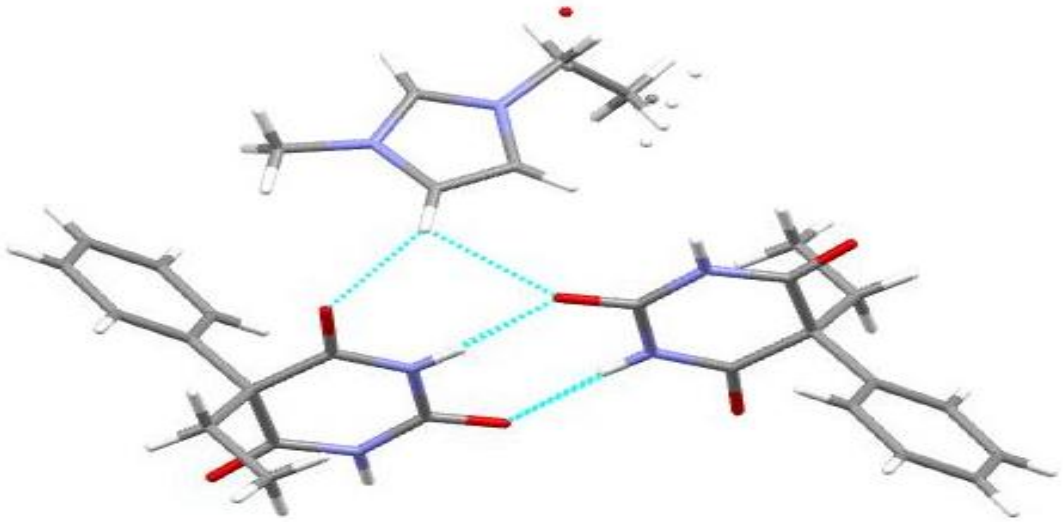


Figure 5.19 Single crystal structure of PBB and [EMIM][acetae]

From SC-XRD analysis it was confirmed that the formation of supramolecular complex of phenobarbital with [EMIM][acetate].

5.2.4 Nifedipine (NIF)

Nifedipine is a calcium channel blocking agent, broadly used in the treatment of hypertension and angina (chest pain). Its IUPAC name is 3,5-dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5 dicarboxylate. According to biopharmaceutical classification system NIF is a class II drug and practically insoluble in water ((5−6 μg·mL−1 at 298.2 K) (Yalkowsky et al., 2010) and solubility in some organic solvents. Solubility at 20 deg C (g/L): acetone 250, methylene chloride 160, chloroform 140, ethyl acetate 50, methanol 26, ethanol 17. In drug discovery and development processes, solubility plays a vital role for large areas like crystallisation, drug formulation and separation. Thus, the selection of solvent and its solubilisation effect have massive impact on these processes. NIF's equilibrium solubility in different co-solvent mixtures were

reported with water, ethanol and propylene glycol. In addition, drug solubility as a function of composition and temperature was reported using the Jouyban-Acree model (Sardari and Jouyban, 2013). For all the solubility and crystallisation studies, commercial nifedipine (form II) has been used.

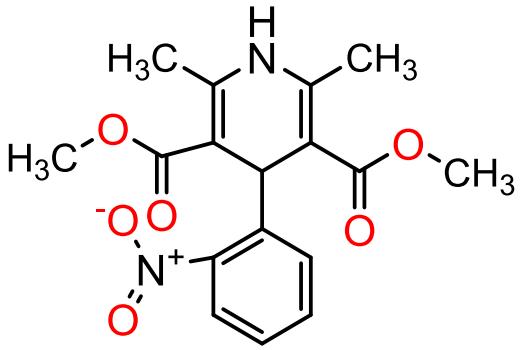


Figure 5.20 Chemical structure of nefidipine

5.2.4.1 Solubility determination

The solubility for NIF was conducted with [EMIM][BF_4], [EMIM][DEP] and water at 50, 75 and 100 °C. Due to the degradation of NIF in [EMIM][acetate] study did not continued with this ionic liquid. As shown in the graph Figure 5.21, the solubility increases with temperature, whereas the [EMIM][DEP] showed higher values than [EMIM][BF_4] as function of temperature.

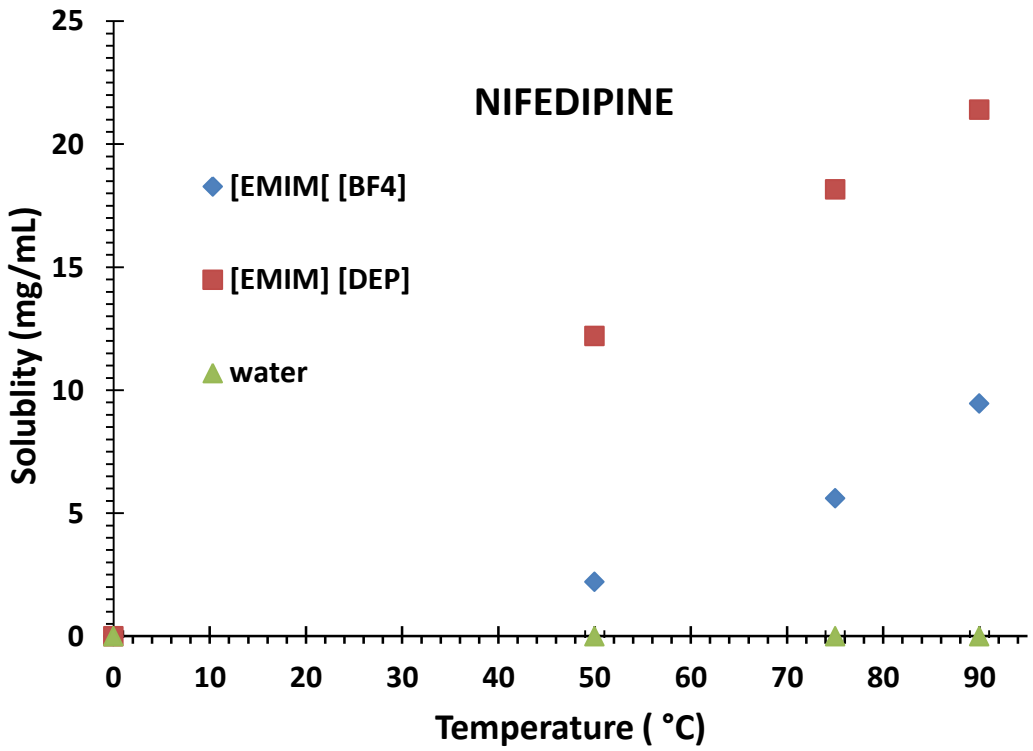


Figure 5.21 Solubility data in [EMIM][BF_4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for nifedipine.

In the experimental findings the same observation was repeated which was observed in the PBB. Here, [EMIM][DEP] (ε : 16.9) showed higher values as compared to [EMIM][BF_4] (ε : 13.9) which was contrast with the dielectric permittivity values. The solubility of NIF in ionic liquids was significantly higher than the water solubility. The water solubility of NIF showed negligible at various temperatures. A strong solute solvent was attributed in [EMIM][DEP] which results in the higher solubilisation of NIF molecule.

From the solubility results it was observed that the most important factors are the interactions between solute-solvent. The interesting results were obtained however, and to analyse the solute solvent interactions a computational approach needed to give a fundamental understanding of the interactions between the solute and solvent.

5.2.4.2 Crystallisation

From above three drugs investigation the nifedipine was used to understand the solute solvent interactions in various ionic liquids. For this study cooling and antisolvent crystallisation were performed with [EMIM[[DEP], [EMIM][acetate] and [EMIM][BF_4]. In cooling crystallisation a saturated solution of NIF with ionic liquids were prepared at 75 °C and cooled at ambient conditions but no crystallisation of NIF was observed. The nifedipine in [EMIM][acetate] ionic liquid degradation was observed.

5.2.4.3 PXRD and DSC analysis

The obtained crystals of NIF by antisolvent crystallisation were examined using PXRD shown in Figure 5.22. These were compared with pure commercial NIF (form II) and simulated powder patterns obtained from the reported single crystal X-ray diffraction data sets for the NIF polymorphs (Figure 5.22).

The powder patterns of solid masses from [EMIM][DEP] and [EMIM][BF_4] matches with that of commercial NIF (form II). It should be mentioned that antisolvent crystallisation did not yield any new phase but the alpha form has precipitated out.

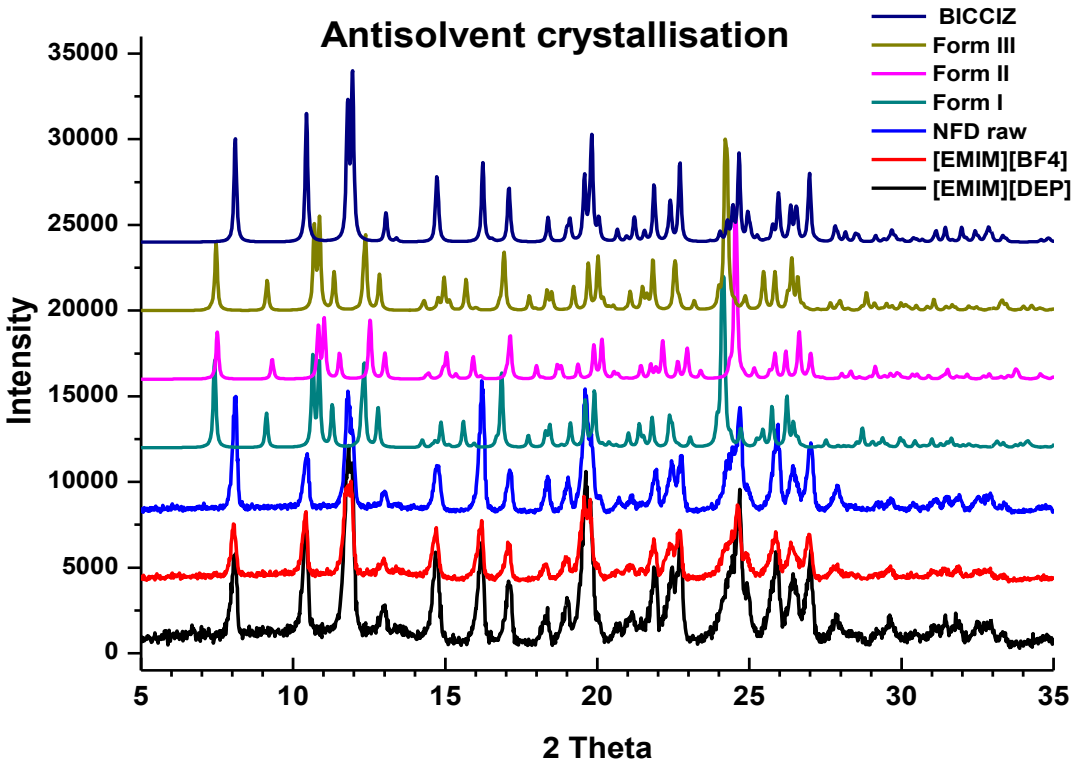


Figure 5.22 PXRD analysis of product phases for nifedipine with ionic liquids using antisolvent crystallisation were performed. For comparison, simulated powder patterns of nifedipine polymorphs (form I, form II and form Iii) from repored structures were also considered.

The NIF crystals recovered were further analysed by DSC at a heating rate of 10 °C/min. DSC scanning found that the NIF crystal exhibited nearly the same endotherm when compared to the commercial CPA crystals.

A comparison of DSC thermograms of antisolvent crystallisation products, (Figure 5.23) solid mass obtained from [EMIM][DEP] and [EMIM][BF_4] showed endotherm at 174 °C and 170 °C respectively. These DSC endotherms showed shift of melting point but according to PSRD pattern of solid masses it was confirmed that the commercial form of NIF (176 °C) was isolated.

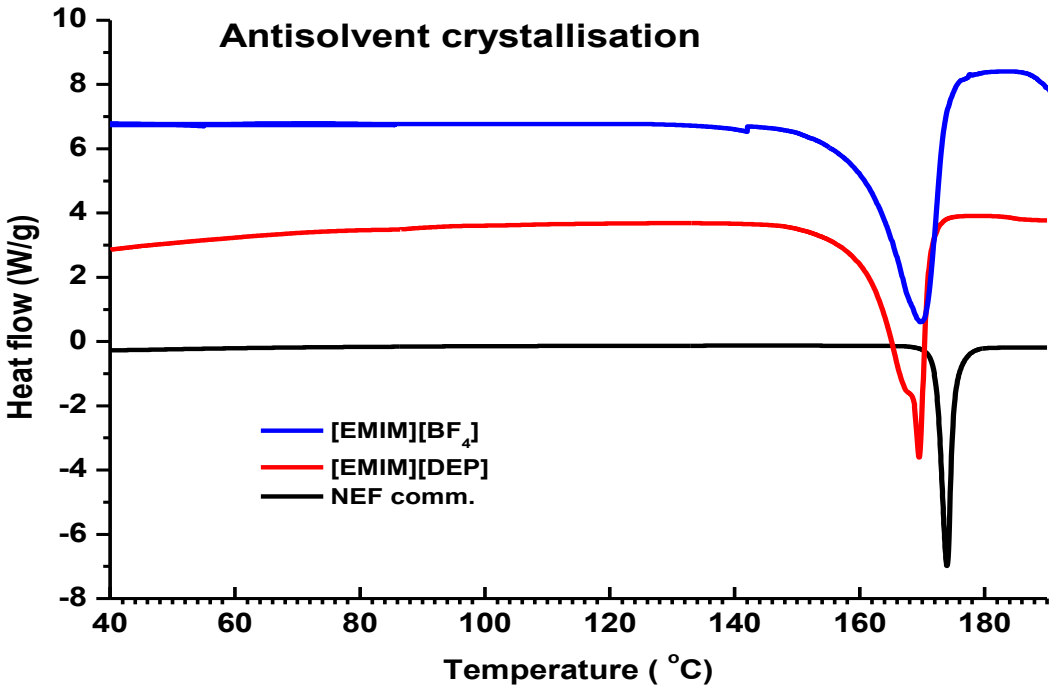


Figure 5.23: DSC analysis of nifedipine obtained with various ionic liquid solvent and and water : methanol (70:30) as antisolvent mixtures. DSC curves obtained at heating rate 10 °C/min

5.2.5 Summary

Solubility of pharmaceutical drugs using ionic liquids was evaluated and experimental findings suggested that, drug solubility in ionic liquids is difficult to predict on the basis of dielectric constant values. However, the solute solvent interactions play an important role and it is difficult to predict solvation mechanism of solute solubility, especially when the solvation mechanism of ionic liquids is largely unknown. To understand the solubilisation effect, needed a computational study to provide deep understanding on aq molecular basis.

In crystallisation study, the cooling crystallisation technique was investigated more significantly to obtained new crystal form. In the selected drugs sulfathiazole showed unique supramolecular organisation. In case of

EMIM][BF_4] supramolecular formation with [BF_4] moiety and in the phenobarbital imidazolium moiety forms supramolecular complex with imidazolium moiety. However, phenobarbital-[EMIM][acetate] the disorder attributed around the acetate group. Chlorpropamide showed polymorphic change in [EMIM][BF_4] ionic liquids where, kinetically stable alpha form transformed into metastable form. From the overall study can be concluded that ionic liquids can play an important role in the solubilisation of poorly water soluble drugs and can affect polymorphic changes.

The next chapter study focuses on the synthesis of drug-salt systems with different alkyl chain length of imidazolium cation and further evaluates for the pharmaceutical performances such as diffusion and transdermal study.

Chapter 6. Pharmaceutical performance of drug imidazolium ionic liquids

This chapter provides understanding about various physicochemical properties of imidazolium salts of ibuprofen and diclofenac and their potential in oral and topical drug delivery. The chapter will provide brief introduction including profiles of ibuprofen and diclofenac drugs and results obtained. Attempt has been made to provide comparative performance of ionic liquids of two drugs with objective to achieve better understanding.

6.1 Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) are commonly used all over the world with anti-inflammatory, analgesic and antipyretic properties and have been prescribed at least 2500 years ago (Pereira-Leite et al., 2013).

Pharmaceutical industries have great challenges with drug formulation and indeed huge amount of money and effort are to develop new drug delivery systems. In oral drug delivery, the main difficultly is to control the drug physicochemical properties that could hinder the effectiveness of the drug delivery (Hörter and Dressman, 2001). Therefore, to overcome the issue of oral drug delivery, it suggested that transdermal technology is expected to make significant impact on the quality of patient care due to this reason the huge pressure on the pharmaceutical industry to produce transdermal formulation. Essentially, the main reason is the crucial benefits of delivering drugs across the skin; this avoids gastrointestinal tract complications triggered by the enzymes and drug interactions with food during absorption. A single application

which is long lasting for multi-day therapy capacity is attractive. The advantages of delivering drugs across the skin, transdermal drug delivery have now become one of the fastest growing areas in drug development. Today, it is estimated that nearly more than one billon are currently manufactured each year.

Although there are many advantages using transdermal formulations, there are some disadvantages. These include the challenges in getting the active ingredients through the skin. The outer layer of the skin consists of non-polar molecules while the inner layer consists of polar ones. For example, ibuprofen as a non-polar compound will have difficulty penetrating through the polar inner and effective permeation through skin is a challenge.

Ionic liquids recently entered the pharmaceutical field, as explained in the introduction chapter in section 2.3.1, due to their unique properties which have been discussed in section 2.1.2. The ionic liquid salt combination with APIs was suggested by Roger *et.al*. 2010 where they successfully prepared ionic liquid with a dual functional liquid salt from of aspirin. They also used antibacterial, analgesic, local anaesthetic and antiarrhythmic drugs in combination with acetylsalicylic acid and reported stability issues with aspirinate ionic liquids (Bica et al., 2010). Overall, these results support the view that further investigation is needed in this area.

The approach taken in this study is novel and completely independent from their work and focuses on studying the effect of alkyl chain length on the imidazolium ionic liquids, on the drug release profile and skin penetration. The findings from this research would provide a good contribution to the published work in this area which includes a recent article published in *Nature International weekly*

journal of science (2015). Shamshina and colleagues described the application of ionic liquids in combination with pharmaceutical drugs and FDA and regulatory attitude towards ionic liquids. The interesting news is that the designing of ionic liquids based on pharmaceutical drugs is approved by the FDA and is a good place to start. A patent, on ionic liquid the combinations of the NSAID etodolac and the pain-reliever lidocaine which would be used as a patch treating for lower back pain and has finished phase III clinical trials (MEDRx USA, 2012).

For this study, model drugs ibuprofen sodium salt and diclofenac sodium salt were reacted with a series of imidazolium ionic liquids salts. On the basis of the two drug system, this chapter is divided into two main sections, each of which presents the results relating to the findings.

6.2 Ibuprofen imidazolium ionic liquid

As discussed in Section 6.1, ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), easily available in a wide range of forms including tablets, chewable tablets, oral suspension (liquid), gels and sprays. However, the oral administration of ibuprofen can cause a number of side effects due to the inhibition of prostaglandin synthesis which creates problems in the gastrointestinal tract (Hawkey, 2000), to overcome the side effects of oral administration, topical administration of ibuprofen have been accepted which helps in faster pain relief and decreases the side effects due its lower plasma concentrations (Tegeder et al., 1999). In general, Ibuprofen gel is used as a topical administration and there has been different techniques available for its preparation (Chen et al., 2006, Carter, 2012, King-smith, 2012). King-Smith *et.*

al., used a series of hydroalcoholic-based solvent, a C1-4 alcohol ester of citric acid, and a surfactant and showed that this composition had 2 to 4 times greater flux than the available standard ibuprofen topical formulations (King-smith, 2012). Later, in the same year, Carter *et. al*. topical formulation of ibuprofen in the free acid form. In their experiment, the formulation was prepared by using pharmaceutically accepted solvents, e.g. Pyrrolidone or dimethylacetamide, and dissolved the free acid form of ibuprofen in it. The findings from these studies suggest that ibuprofen composition was therapeutically effective in the locally affected region (Carter, 2012).

The ionic liquids in pharmaceutical applications were discussed in section 2.3.1. To overcome the limitations of topical formulations of ibuprofen in 2010, Viau *et al*. synthesised ionogels of ibuprofenate using imidazolium ionic liquids and showed an effective drug release profile with kinetics controlled by the nature of the silica wall. They reported the study with 1-methyl-3-butylimidazolium chloride ionic liquid (Viau et al., 2010). Recently, in 2015 Park *et al.*, synthesised a topical formulation of lidocaine-ibuprofen and their findings were that the lidocaine-ibuprofen ionic liquid increased absorption of lidocaine into the skin due to the high lidocaine concentration in the ionic liquid and due to interactions between the ionic liquid and the skin to increase skin permeability (Park and Prausnitz, 2015). Both the Park *et al*. and Viau *et al*. studies on skin permeability and ionogels used ionic liquids, but they had chosen a single cation for their studies.

For this study, model drugs ibuprofen sodium salt and diclofenac sodium salt were reacted with a series of imidazolium ionic liquids salts.

6.3 Result and Discussion

In this section results were discussed on ibuprofen imidazolium ionic liquids and divided into subsections which include synthesis, freezing point depression, thermal properties, partition coefficient, diffusion study and transdermal deposition and permeation study. The methods used in this section were discussed in details section 3.2.4.

6.3.1 Synthesis

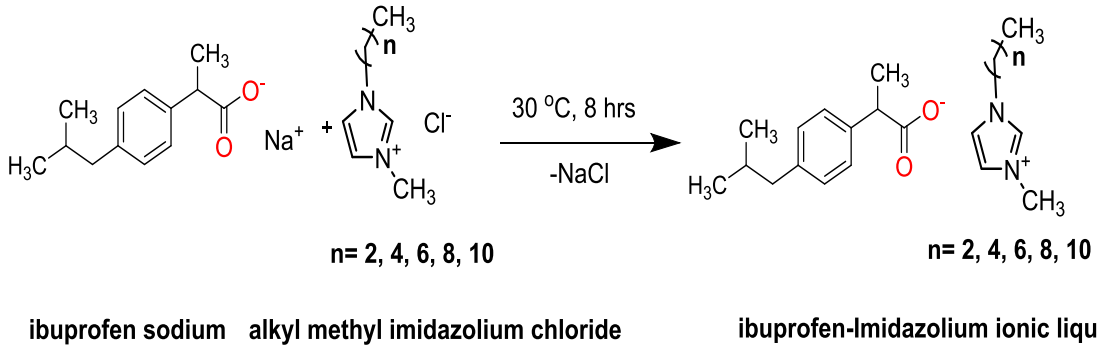


Figure 6.1 Syntheis procedure of [C$_n$mim] [IBU].

1-Ethyl-3-methylimidazolium ibuprofen [EMIM][IBU], 1-butyl-3-methylimidazolium ibuprofen [BMIM][IBU], 1-octyl-3-methylimidazolium ibuprofen [OMIM] [IBU], 1-hexyl-3-methylimidazolium ibuprofen [HMIM] [IBU] and 1-decyl-3-methylimidazolium ibuprofen [DMIM] [IBU] were synthesised using 1:1 stoichiometric metathesis reaction in ethanol to give good yields (70-90%)(Figure 6.1). The ibuprofen assay in [C$_n$mim] [IBU] was determined by using UV spectroscopy (Table 6.1**).** In addition, it was observed that the longer alkyl chain length on the imidazolium cation increased the hydrophobic nature of the compound. All the synthesised [$C_n$mim] [IBU] ionic liquids were obtained as yellow gels at room temperature.

Table 6.1. Ibuprofen assay in [$C_n$mim] [IBU]

Sr. no.	Code	Name	Assay (g)	Sodium Ibuprofen (g)
1	RB 01	[EMIM][IBU]	4.41	5
2	RB 02	[BMIM][IBU]	3.73	5
3	RB 03	[HMIM][IBU]	3.92	5
4	RB 04	[OMIM][IBU]	4.36	5
5	RB 05	[DMIM][IBU]	3.9	5

6.3.2 Freezing point depression

Freezing point depression (FPD) is a colligative property which will provide information about how the ionic entity interferes with the attractive forces of water molecules and thereby depress freezing point. The FPD (ΔT_f) is calculated using following equation

$$\Delta Tf = m\,x\,Kf$$

Where, m is molality (mOsm/Kg or Osm/Kg) and K_f is freezing point constant (1.853 °C Kg per mol for water).

As ΔT_f is directly proportional to m for convenience data is presented as molality in mOsm/Kg. The molality of 0.025 and 0.25 M solutions of different ibuprofen imidazolium salts are shown in Figure 6.2. The osmolality values with strength less than 0.025 M could not be measured as readings were 0 for all the solutions. The solutions stronger than 2 M could not be measured due to measurements limitation of instrument (2500 mOsm/Kg).

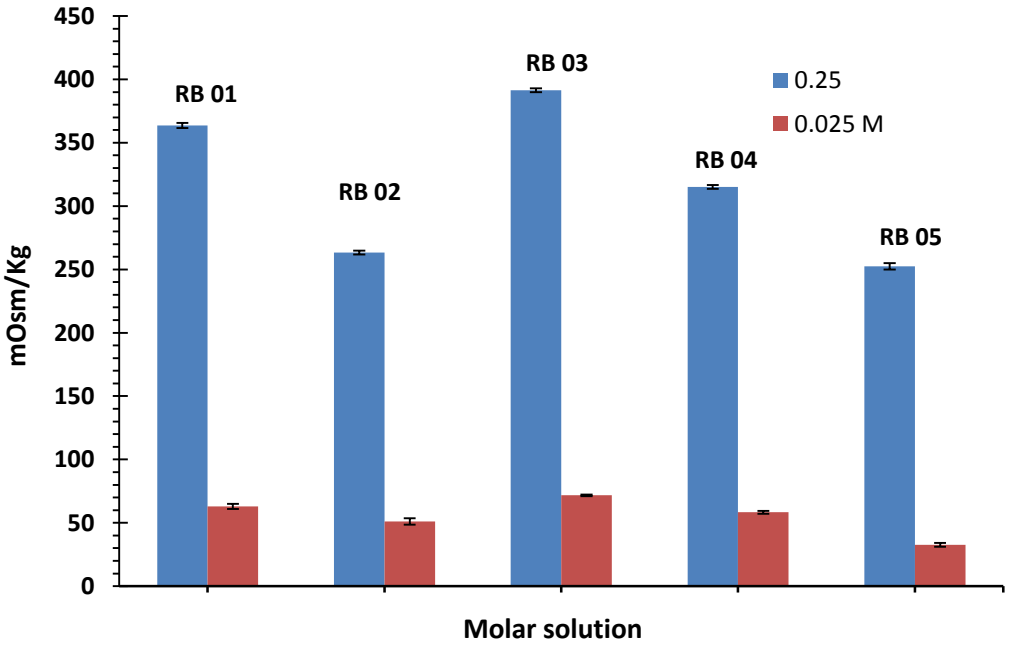


Figure 6.2: Osmolality of ibuprofen imidazolium ionic liquids

There is significant difference in the osmalilaity of solutions of different ionic liquids (t-test $p < 0.05$). The osmolality of imidazolium ibuprofen can be ranked as hexyl > ethyl > octyl > butyl > decyl which indicates ability of the salt to disturb water structure. Additional computational data about chemistry of these new molecules is currently being investigation in collaboration with Department of Pharmaceutical Chemistry at Nagpur University, India to understand this anomalous behaviour of these salts.

6.3.3 Thermal analysis

All [$C_n$mim] [IBU] liquids was observed in liquid form. Generally, Ibuprofen melts at 72 °C and has a glass transition (Tg) at -42 °C. In the experimental findings, DSC analysis did not show any Tg temperature and melting endotherm (Figure 6.3). This suggests that they were stable in the molten state. In addition, the

experiment could not be performed below -70 °C as this was the lowest that could be achieved on the instrument used.

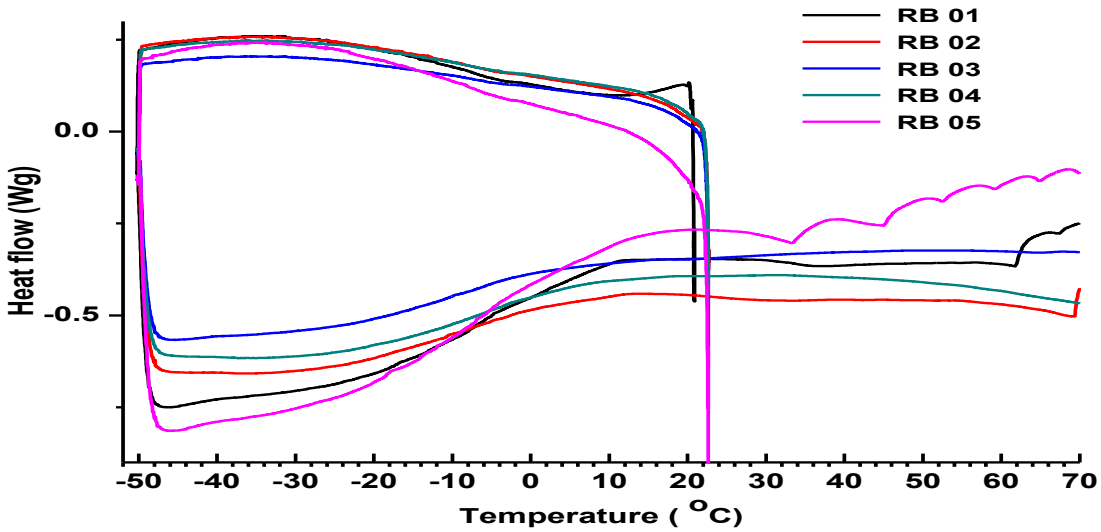


Figure 6.3: DSC thermogram of [$C_n$mim] [IBU] ionic liquids. DSC curves obtained at cooling rate 5 °C/min C and heating rate 10 °C/min.

Table 6.2 DSC and TGA data analysis of [$C_n$mim] [IBU] and starting imidazolium chloride

[$C_n$mim] [IBU]	Tg (°C)	Tm (°C)	Onset Degradation temp. (°C)
[EMIM] [IBU]	-	-	192
[EMIM] [Cl]	-	77-80	243
[BMIM] [IBU]	-	-	186
[BMIM] [Cl]	−74	70-73	226
[HMIM] [IBU]	-	-	193
[HMIM] [Cl]	-85	-	220
[OMIM] [IBU]	-	-	190
[OMIM] [Cl]	-	12	210
[DMIM] [IBU]	-	-	200
[DMIM] [Cl]	-14	24	206

Tg - glass transition temperature; Tm - melting point on heating. Decomposition temperatures were determined by TGA, heating at 5 °C min-1 under air atmosphere and are reported as degradation temperature

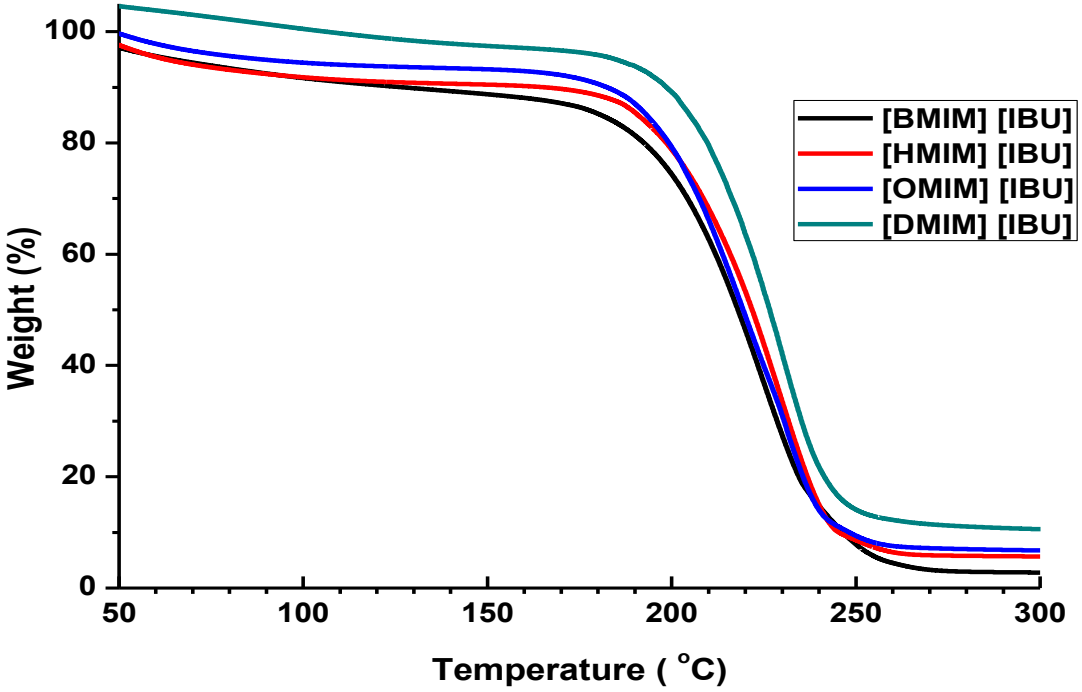


Figure 6.4 TGA analysis of [$C_n$mim] [IBU] ionic liquids at 10 °C per minute.

In the TGA analysis, the overall thermal stability of [$C_n$mim] [IBU] liquids ranges between 192 °C to 200 °C (Figure 6.4). There were no periodic changes such as increased or decreased in thermal stability observed with respect to alkyl chain length. As shown in Table 6.2 it can be seen that the thermal stability of imidazolium chloride ionic liquids increased with decreased alkyl chain length. It was concluded that the thermal stability of the starting precursor ionic liquids depends upon the alkyl chain length of the imidazolium cation. When these results were compared to [$C_n$mim] [IBU] liquids, it was observed that there was no correlation with the alkyl chain length in [$C_n$mim] [IBU] liquids. One more thing that was observed was that when the ibuprofen salt ion exchanged with the imidazolium cation, there was a decrease in the thermal stability of [$C_n$mim] [IBU] when compared to the starting imidazolium precursors (Table 6.2 and Figure 6.5)

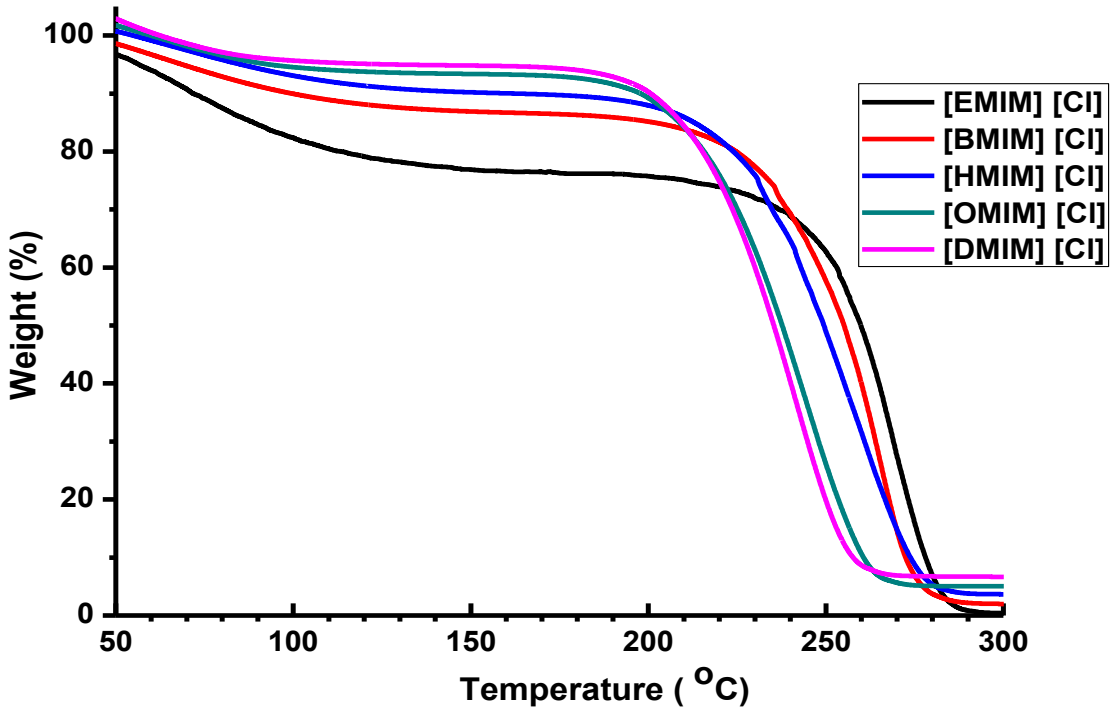


Figure 6.5 TGA anlysis of starting precursors of imidazolium chloride at 10 °C per minute.

In addition, when the starting imidazolium salt precursors were compared to the [$C_n$mim] [IBU] liquids, there was an interesting trend; as the alkyl chain length decreased, the thermal stability gap increased the between the starting salt precursors and [$C_n$mim] [IBU] liquids (Table 6.2) For example, [EMIM] [IBU] shows thermal stability upto 192 °C, while the starting precursor [EMIM] [Cl] shows stability upto 243 °C and the observed gap between both was 50 °C. In further the cases, the thermal stability of [DMIM] [IBU] is upto 200 °C while the starting precursor [DMIM] [Cl] is stable upto 206 °C so the thermal stability gap is 6 °C. This trend is followed by rest of the ionic liquids.

6.3.4 FTIR analysis

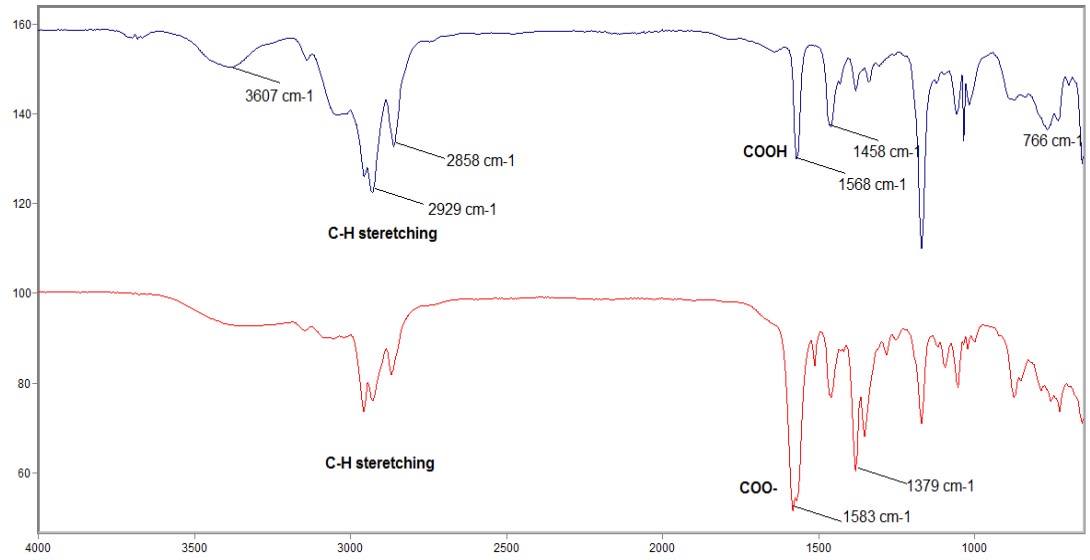


Figure 6.6 Comparioson of IR spectra of [HMIM][IBU]with Ibuprofen and [HMIM][Cl]

The IR spectral analysis of [Cnmim] [IBU] ionic liquids was similar to each other. For example, the spectrum of [HMIM] [IBU] exhibit signals at 2929 cm^{-1} and 2858 cm^{-1} which correspond to the aliphatic asymmetric and symmetric (C–H) stretching vibration due to methyl groups. A broad peak in the range 3197–3607 cm^{-1} is due to the quaternary amine salt formation with chlorine. Signals at 1568 cm^{-1} and 1458 cm^{-1} are due to C=C and C=N vibrations and the signal at 766 cm^{-1} is due to C–N stretching vibration (Figure 6.6). Based on the FTIR analysis, it was observed that the synthesized ionic liquid was [HMIM] Cl. It was concluded that no protonation occurred during the process and this was confirmed by ^{1}H NMR analysis. The FTIR spectrum of [BMIM] [IBU] presented the characteristic bands of carboxylate function at 1583 and 1379 cm^{-1} whereas no band at 1706 cm^{-1}, associated with a carboxylic group, was observed (Table 6.3).

Table 6.3 Comaprative IR analysis [$C_n$mim] [IBU] and starting precursors. where n = 2, 4, 6, 8, 10 (number of carbon on imidazolium cation).

Sr. No	C-H stretching (cm^{-1})	C-N stretching (cm^{-1})	Quaternary amine salt formation with chlorine (cm^{-1})	C=C and C=N stretching (cm^{-1})	Carboxylate (cm^{-1})
[EMIM][IBU]	2955, 2927 and 2867	866	3557-3244	-	1580 and 1379
[EMIM] Cl	2924 and 2854	766	3533–3368	1579 and 1323	-
[BMIM][IBU]	2923 and 2857	864	3577-3224	-	1580 and 1377
[BMIM] Cl	2929 and 2834	764	3672-3204	1560 and 1349	-
[HMIM][IBU]	2955, 2926 and 2867	870	3539-3349	-	1583 and 1379
[HMIM] Cl	2929 and 2858	766	3607-3197	1568 and 1458	-
[OMIM][IBU]	2855, 2925 and 2857	871	3370-3249	-	1580 and 1380
[OMIM] Cl	2924 and 2824	767	3527-3300	1639 and 1569	-
[DMIM][IBU]	2855, 2924 and 2857	871	3504-3349	-	1580 and 1380
[DMIM] Cl	2922, 2924 and 2857	871	3504-3349	1637 and 1570	-

This IR data, presented in the Table, confirmed the structure of the NSAID drug combined with the imidazolium cation.

6.3.5 Partition coefficient

In this section, partition coefficient values of the synthesised imidazolium ionic liquid-drug system were determined and detailed procedure was discussed in the section 3.2.2.7. The partition coefficient values measured are shown in Figure 6.7. The partition coefficient values for ibuprofen ionic liquids in the range of 0.39 to 9.8. As excepted the partition coefficient values increased with increase in molecular weight.

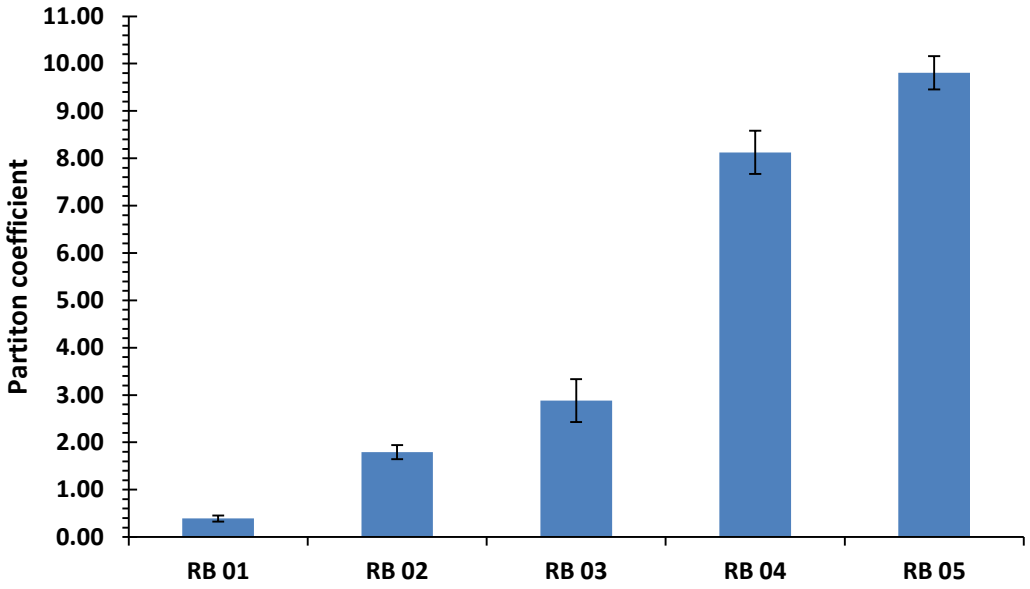


Figure 6.7 Partition coffecient of [C*n*mim] [IBU] where n = 2, 4, 6, 8, 10 (number of carbon on imidazolium cation).

6.3.6 Diffusion study

This section reports on the drug release profile of the ibuprofen-imidazolium liquid with different alkyl chain lengths and detailed procedure was described in the section 3.2.4.2.

The release profiles are shown in figure 6.8. The percent drug release from different ibuprofen ionic liquids in the range from 6.73 to 46.79, 0.52 to 42.25, 1.15 to 39.57, 2.86 to 32.92 and 1.84 to 12.39 for RB 01, RB 02, RB 03, RB 04 and RB 05 respectively. Drug release was highest for ethyl imidazolium and decyl imidazolium. There was no significant difference was observed in drug release butyl and hexyl imidazolium salts.

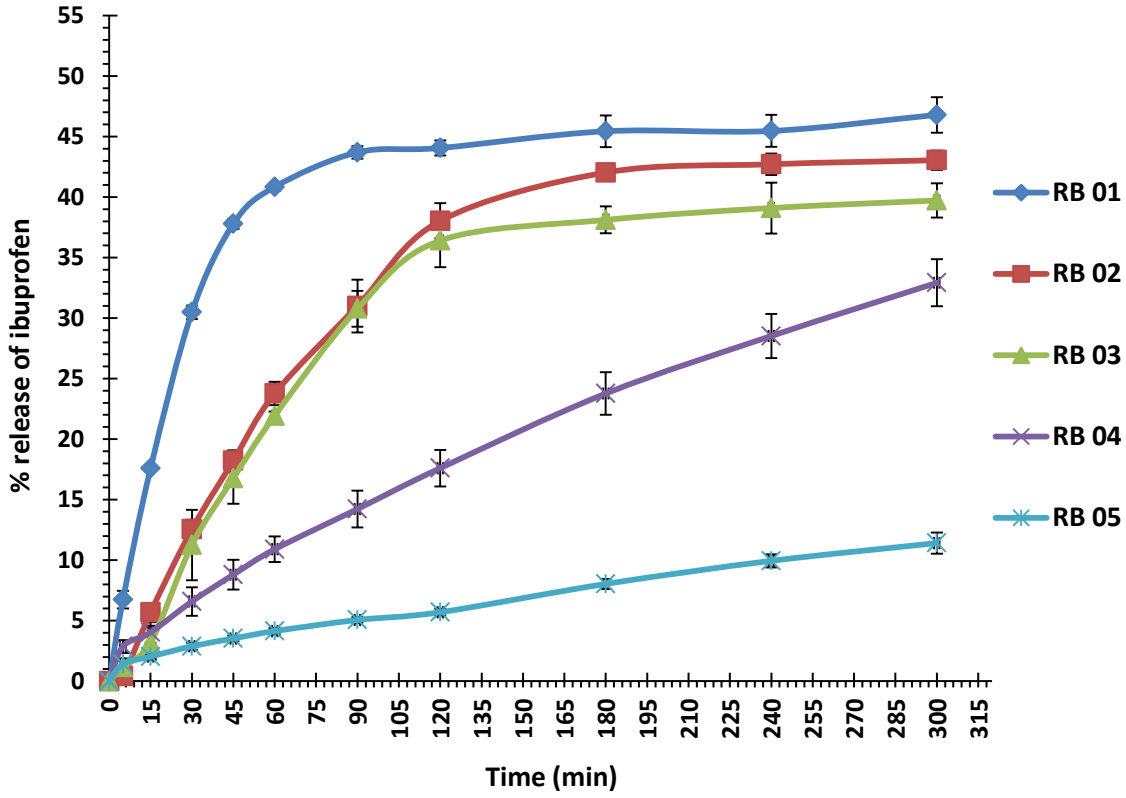


Figure 6.8 Percentage release profile of ibuprofen with different alkyl chain length.

To obtain the trend of initial and final drug release percent drug release in 30 minutes and 5 hrs was compared for different imidazolium salts (Fig 6.8). The trend remains similar at both time periods, in general drug release decreases with increase in carbon chain length but there is no significant difference in butyl and hexyl imidazolium salts.

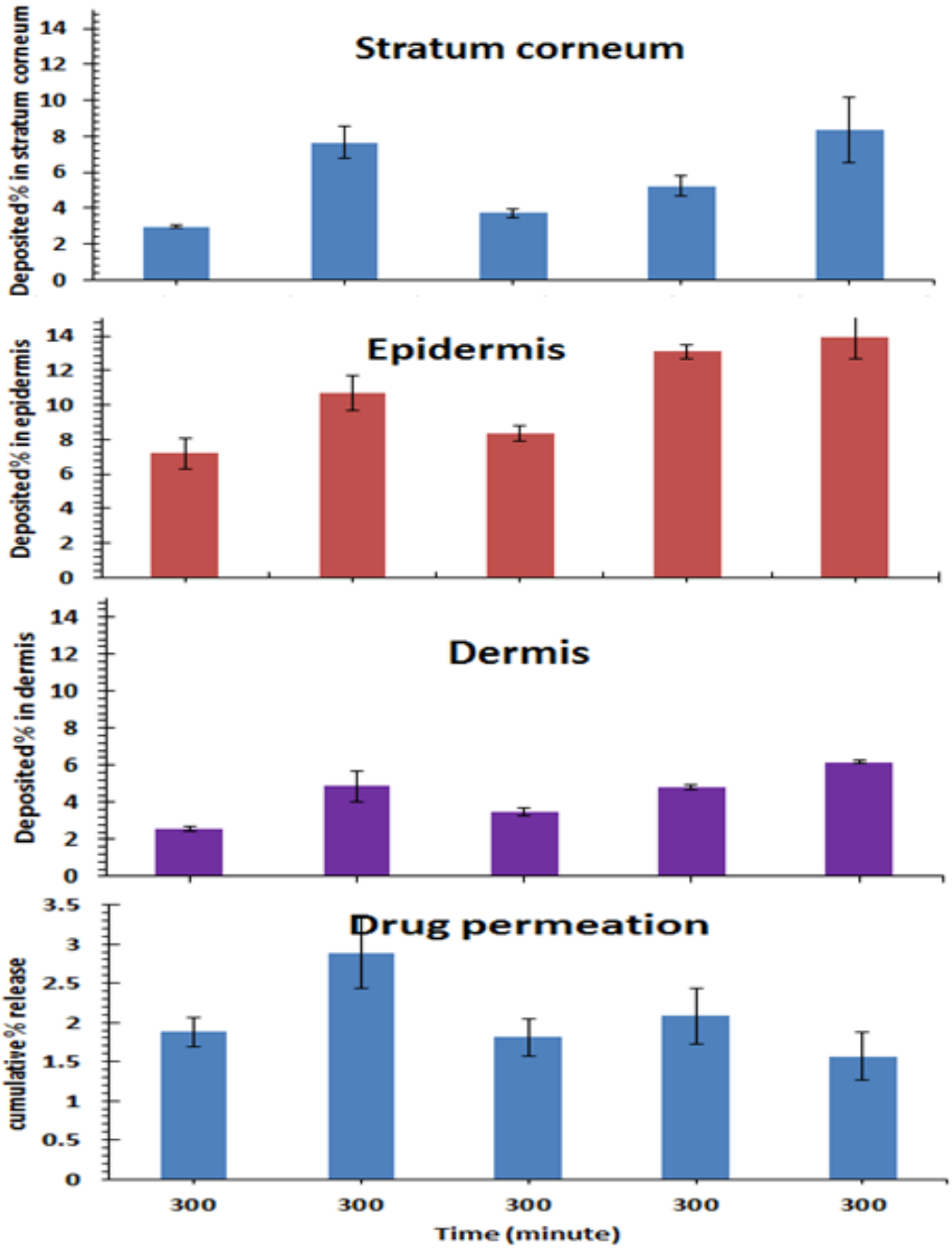
6.3.7 Transdermal deposition and permeation study

The skin deposition and permeation data provides major understanding about potential of use of drug in topical and transdermal drug delivery. The comparative deposition data generated after application of ibuprofen ionic liquids is shown in Figure 6.9. The percent deposition of ibuprofen in stratum corneum, epidermis and dermis layer, in the range of 3 to 8.4 %, 7.2 to 14 % and 2.6 to 6.2 % respectively. The percent ibuprofen deposited in each layer showed a typical trend, ethyl < butyl > hexyl < octyl < decyl. The major deposition of ibuprofen has occurred in epidermis for all the ibuprofen imidazolium salts.

The skin layers have significant difference in terms thickness, lipid content and moisture level. Stratum corneum which is the outermost epidermal layer is about 10 to 20 µm thick and comprises of dehydrated keratinised cells surrounded by lipid matrix. Stratum corneum contents about 75 to 80 % proteins, 5 to 15 % lipid and relatively little water. Epidermis is around 600 to 1500 µm. Epidermis contains different types of cells with different stages of keratinisation, mostly denucleated with cholesterol, free fatty acids and ceramides presents at matrix the water content is low but better than the stratum corneum. Dermis is about 3 to 5 mm thick and contains 70 % water and fibrous proteins such as collagen and elastin. There is extensive lymphatic and nervous supply in dermal region. The blood vessels are also presents in the dermal region.

Therefore deposition and permeation is dependent on molecular size, partition coefficient and solubility of the drug molecule. The major deposition in the

epidermal region indicates that slower transfer of the salt from epidermal layer. Comparison of osmolality of equimolar solution has been carried out as an indicator of dissociation of the salts. Osmolality has shown trend similar to % deposition in the skin layer amount deposited. The relation between osmolality and amount deposited was established using linear regression analysis. The trend lines and regression equations are shown in figure 6.10. It showed best correlation for drug deposited in the stratum corneum. This can be attributed to the dissociation tendency of the salt. The salt in undissociated is more non polar it becomes and higher is the deposition in the epidermis. Though correlation is not significant for other two layers overall trend remains same, and correlation is possibly significant for deposition in dermis. Surprisingly no correlation was observed between amounts deposited in the skin with partition coefficient which indicates significance of other factors which plan to investigate using computational techniques.



	RB 01	RB 02	RB 03	RB 04	RB 05
Molecular weight	375.35	402.93	430.93	458.73	486.99
Partition coefficient	0.39	1.79	2.88	8.12	9.8

Figure 6.9 Percent deposition of ibuprofen imidazolium ionic liquids in skin layers and cumulative percent release against partition coefficient values and molecular weight.

The amount of drug permitted after application of different drug salt did not correlate with osmolality or partition coefficient because molecular size and water solubility will have confounding effect with partitioning and dissociation of the molecule. It was observed that the ethyl imidazolium salt has low skin deposition but higher permeation due to smaller molecular size, low partition coefficient and better water solubility. The butyl imidazolium salt has shown best performance as it higher skin deposition and higher skin release.

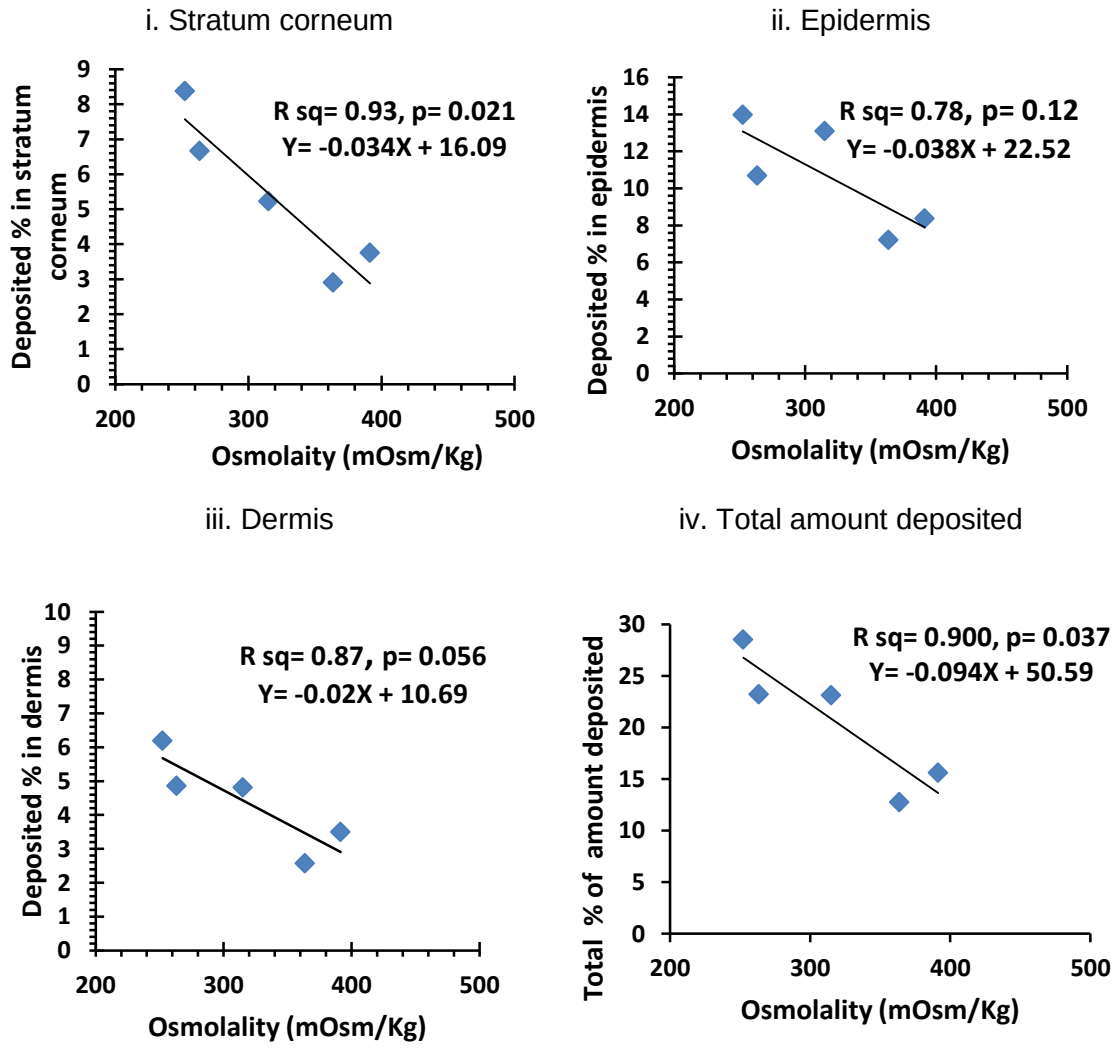


Figure 6.10 Regression values of ibuprofen imidazolium ionic liquids.

From above regression values it was observed that there was no correlation between them (figure 6.10).

The cumulative percent release compared for 60 min and 300 min (Figure 6.11) against the partition coefficient values. The cumulative release for ibuprofen showed consistency after 60 and 300 min.

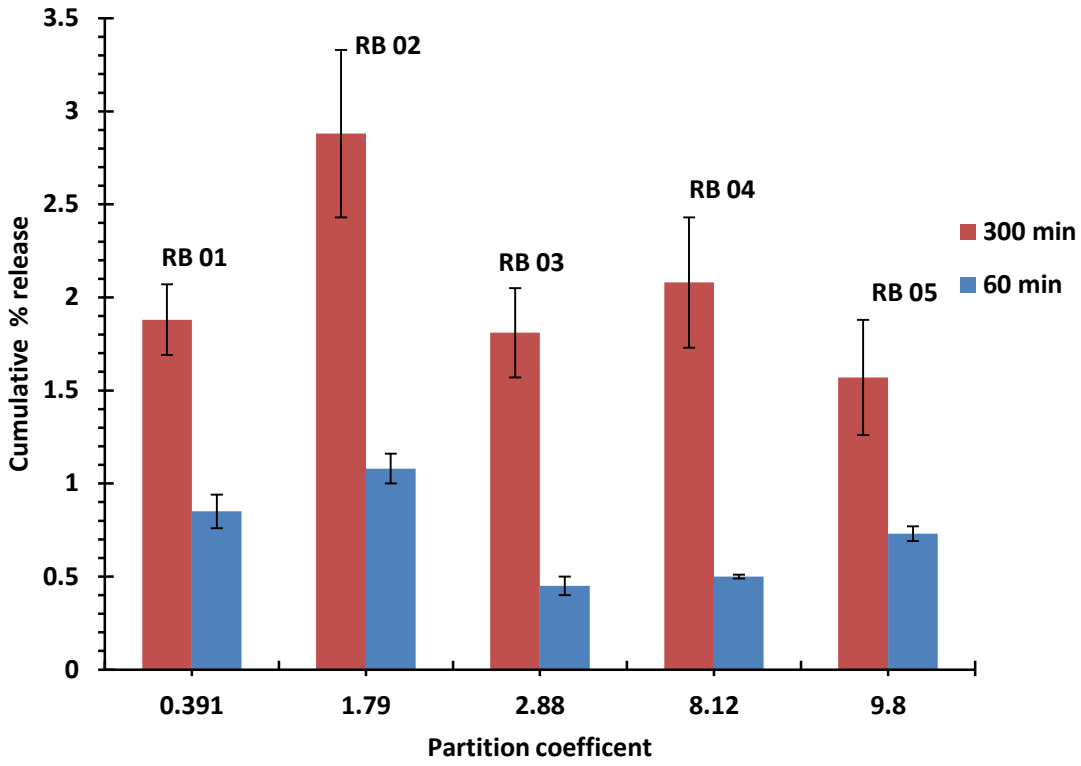


Figure 6.11 Cumulative precentage release at 60 and 300 min plotted against partion coefficient values of ibuprofen imidazolium ionic lqiuids.

6.4 Diclofenac imidazolium ionic liquids

In addition to the synthesis of ibuprofen containing ionic liquids, another anion diclofenac, was selected for combination with imidazolium cations. A number of different diclofenac-containing drug products have been developed including enteric coated products which are swallowed whole with liquid; immediate-release, extended or modified-release tablets; liquid-filled capsules and powder for oral solution and IV administration. Worldwide diclofenac has a huge market;

in the USA there are more than 10 million diclofenac drug products dispensed in 2015.

Diclofenac inhibits COX-1 COX-2 enzymes and binding of diclofenac to COX isozymes inhibits the synthesis of prostaglandin PGE2, PGD2, PGF2, prostacyclin (PGI2), and thromboxane (TX) A2 (Ku et al., 1986, Altman et al., 2015). In inflammation conditions, PGE2 is the main prostanoid produced. The mechanism of action of NSAIDs is to inhibit the synthesis of prostanoid and act as a potent analgesic and anti-inflammatory agent (Patrono et al., 2001, Altman et al., 2015).

In the oral dosage form, diclofenac shows adverse side effects such as an increased risk of serious dose-related gastrointestinal (GI) effects, cardiovascular and renal side effects (Brater, 2002, McGettigan and Henry, 2011, Altman et al., 2015). High dose of diclofenac is associated with GI toxicity and it is related to COX-1 enzymes (Altman et al., 2015). Liquid-Filled soft gelatin capsules of diclofenac potassium were developed and patented (ZIPSOR®, Depomed, Inc.). In their method, potassium diclofenac liquid formulation is combined with solubilizing and dispersing agents to increase the absorption rate in the stomach. The major side effects in this formulation are nausea, headache, vomiting, and constipation (Riff et al., 2009, Altman et al., 2015). Later, topical diclofenac sodium was developed for local pain or inflammation and with minimal side effects during treatment. The study reported that diclofenac has excellent transdermal penetration properties capable of penetrating through cell membranes, including the synovial lining of diarthrodial joints and the skin (Altman et al., 2015, Cordero et al., 1997, Cordero et al.,

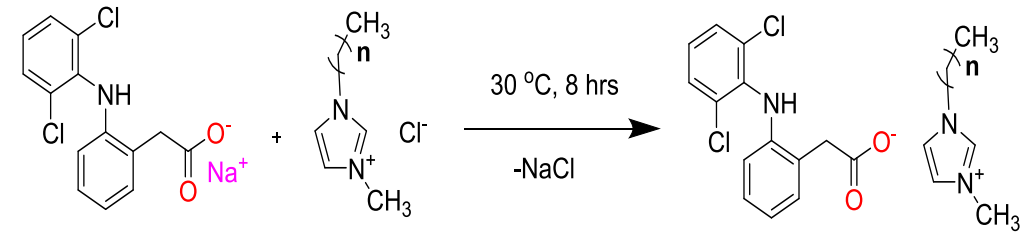
2001). Topical diclofenac sodium salt shows strong inhibition of PGE2 synthesis and excellent permeation property. Overall, topically applied diclofenac may overcome the adverse side effects of the oral delivery route. Today, in the market, there were several transdermal diclofenac formulations available including diclofenac sodium gels, diclofenac sodium topical solutions, and a diclofenac epolamine patch (Goh and Lane, 2014) and these also have side effects such as severe allergic reactions like rash, itching, tightness in the chest and peeling skin.

To overcome these disadvantages of the diclofenac gel, in 2015 Park *et al*. tried diclofenac in combination with lidocaine, but in their experiment, they did not form an ionic liquid (Park and Prausnitz, 2015). Recently, no other publications were available on diclofenac ionic liquid combination. This section discusses the effect of alkyl chain on drug release and skin penetration and attempts to fill the gap in the field.

6.5 Result and discussion

In this section results are discussed on diclofenac imidazolium ionic liquids and divided into subsections which include synthesis, freezing point depression, thermal properties, partition coefficient, diffusion study and transdermal deposition and permeation study. The methods used in this section were discussed in detail section 3.2.4.

6.5.1 Synthesis



n= 2, 4, 6, 8, 10

n= 2, 4, 6, 8, 10

sodium diclofenac

alkyl methyl imidazolium chloride

diclofenac-Imidazolium ionic liquids

Figure 6.12 Syntheis procedure of [C$_n$mim] [DIF]

1-Ethyl-3-methylimidazolium diclofenac [EMIM] [DIF], 1-butyl-3-methylimidazolium diclofenac [BMIM] [DIF], 1-hexyl-3-methylimidazolium diclofenac [HMIM] [DIF], 1-octyl-3-methylimidazolium diclofenac [OMIM] [DIF], and 1-decyl-3-methylimidazolium diclofenac [DMIM] [DIF] were synthesised (Figure 6.12) using 1:1 stoichiometric metathesis reaction. Here, ethanol was used to dissolve the ionic liquid and NaCl, which precipitated out, was removed. The diclofenac assay of [C$_n$mim] [DIF] was done using a UV spectrometer (see Table 6.4).

Table 6.4 Diclofenac drug assay in [C$_n$mim] [DIF] ionic liquids

Sr. no.	Code	API-IL	Diclofenac (g)	Sodium diclofenac (g)
1	RB 06	[EMIM] [DIF]	3.48	5
2	RB 07	[BMIM] [DIF]	3.63	5
3	RB 08	[HMIM] [DIF]	2.66	5
4	RB 09	[OMIM] [DIF]	3.55	5
5	RB 10	[DMIM] [DIF]	3.48	5

Here, it was observed that the longer alkyl chain on the imidazolium cation, influenced the hydrophobicity. All synthesised [$C_n$mim] [DIF] liquids were isolated as yellow brownish gels at room temperature and were highly viscous when compared to the [$C_n$mim] [IBU] ionic liquids.

6.5.2 Freezing point depression

As ΔT_f is directly proportional to m for convenience data is presented as molality in mOsm/Kg. The molality of 0.025 and 0.25 M solutions of different diclofenac imidazolium salts are shown in figure 6.13. The osmolality values with strength less than 0.025 M could not be measured as readings were 0 for all the solutions. The solutions stronger than 2 M could not be measured due to measurements limitation of instrument (2500 mOsm/Kg).

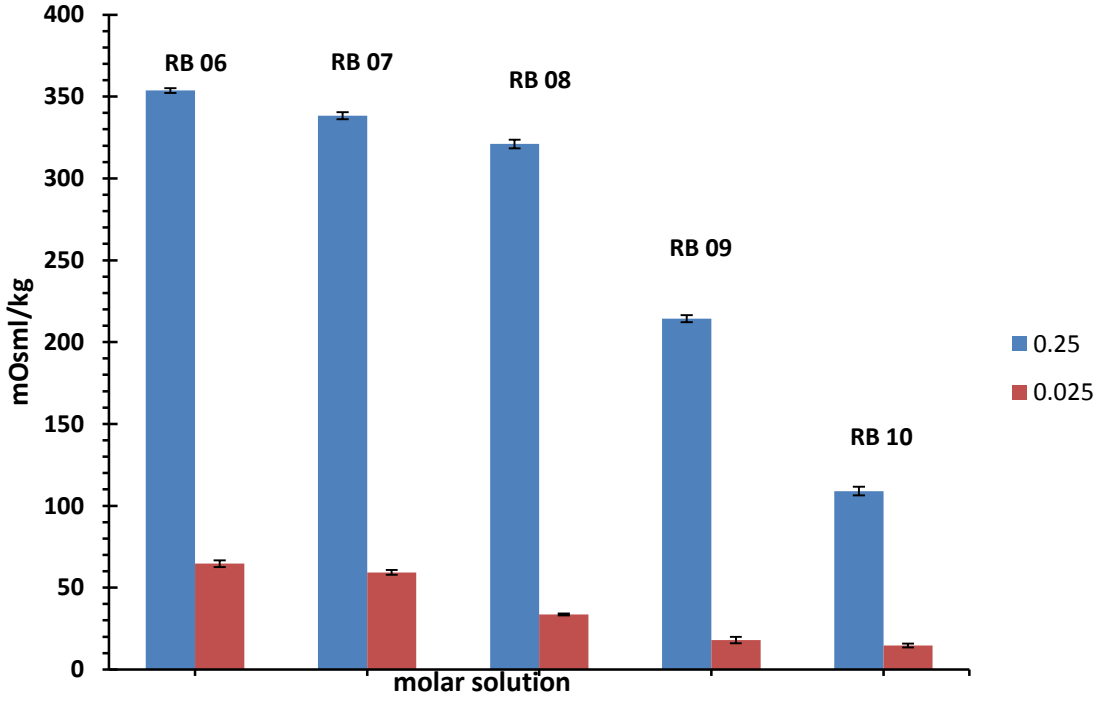


Figure 6.13 Osmolality of ibuprofen imidazolium ionic liquids at 0.25 and 0.025 M solution

There is significant difference in the osmolality of solutions of different ionic liquids (t-test $p < 0.05$). The osmolality of imidazolium diclofenac can be ranked as ethyl > butyl > hexyl > octyl > decyl which indicates ability of the salt to disturb water structure.

6.5.3 Thermal analysis

The series of [$C_n$mim] [DIF] ionic liquids were analysed by by TGA and DSC so as to understand their thermal properties. It was observed that, the [$C_n$mim] [DIF] ionic liquids were more vicious than the starting imidazolium chloride ionic liquids. In the series, all the Tg were observed in the range between -30 to -35 °C (Figure 6.14),

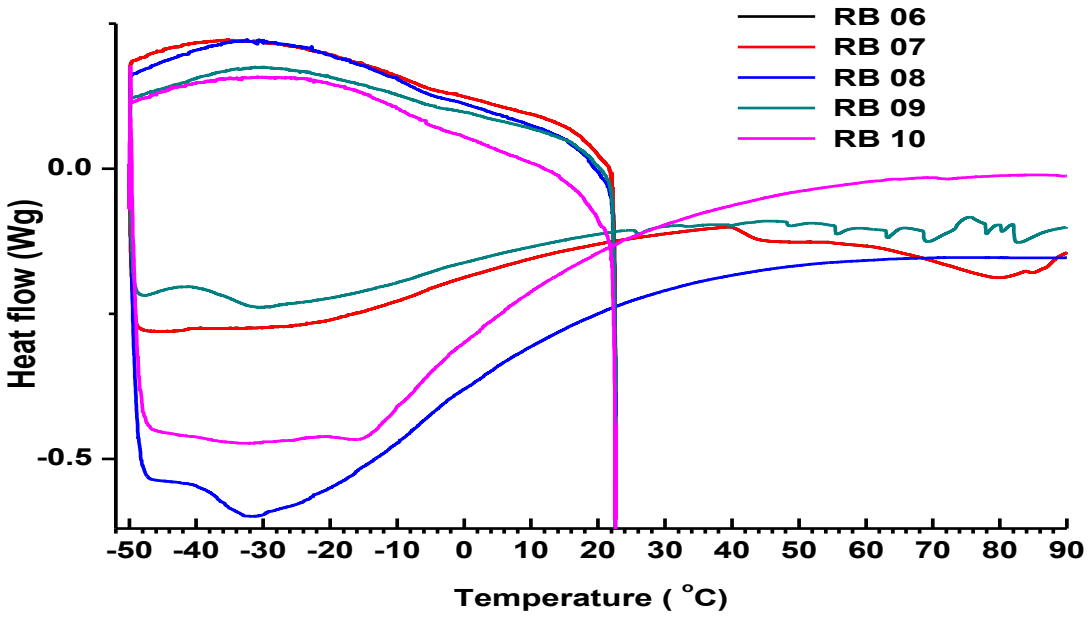


Figure 6.14: DSC analysis of synthesised [C$_n$mim] [DIF] ionic liquids

In all cases for the [C$_n$mim] [DIF] liquids, there was no melting point observed, as only Tgs were seen (Table 6.5).

Table 6.5: Comparative analysis of DSC and TGA for [C$_n$mim] [DIF] and starting imidazolium chloride ionic lquids.

Sr. no.	[C$_n$mim] [DIF]	Tg (°C)	Tm (°C)	Onset degradation temp. (°C)
2	[EMIM] [DIF]	-34.22	-	204.66
3	[EMIM] [Cl]	-	77-80	243
4	[BMIM] [DIF]	-33.85	-	203.30
5	[BMIM] [Cl]	-	70-73	226
6	[HMIM] [DIF]	-33.85	-	204.65
7	[HMIM] [Cl]	-85	-	220
8	[OMIM] [DIF]	-31.29	-	206.15
9	[OMIM] [Cl]	-	12	210
10	[DMIM] [DIF]	-34.35	-	194.89
11	[DMIM] [Cl]	-14	24	206

Tg - glass transition temperature; Tm - melting point on heating. Decomposition temperatures were determined by TGA, heating at 10 °C min-1 under air atmosphere and are reported as degradation temperature

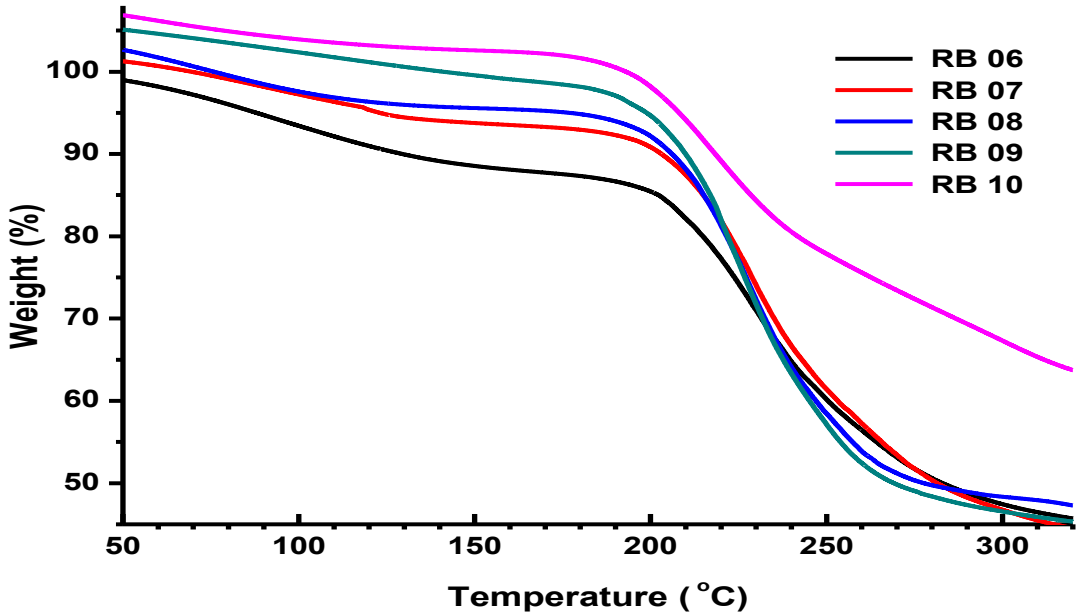


Figure 6.15: TGA analysis of [C$_n$mim] [DIF] ionic liquids.

The thermal stability analysis of [C$_n$mim] [DIF] is shown in Figure 6.15. All [C$_n$mim] [DIF] liquids showed thermal stability in the range of 204 to 206. A slight decrease was seen for thermal stability when compared to the starting imidazolium chloride ionic liquids (Table 6.5). Thermal stability of imidazolium chloride ionic liquids increased with decreasing alkyl chain length. But this pattern did not observed in drug imidazolium ionic liquids.

6.5.4 FTIR analysis

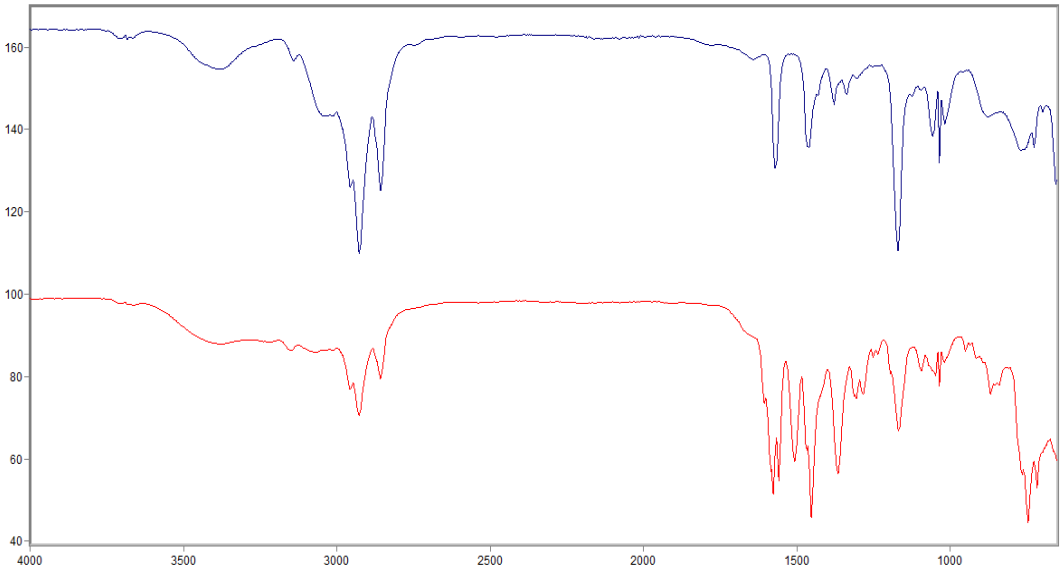


Figure 6.16: FTIR analysis of [HMIM] [DIF with [HMIM] [Cl]

The FTIR spectra of the [HMIM] [DIF] analogues were compared with the precursor ionic liquid [HMIM] Cl (Figure 6.16). This confirmed that no protonation occurred during the metathesis process. The expected signals for [HMIM] [IBU] were observed and the characteristic bands of carboxylate function occurred at 1571^{-1} and 1448 cm^{-1} (Table 6.6).

Table 6.6: IR analysis [$C_n$mim] [DIF]ionic liquids and starting precursors

API-IIs	C-H stretching (cm^{-1})	C-N stretching (cm^{-1})	Quaternary amine salt formation with chlorine (cm^{-1})	C=C and C=N stretching (cm^{-1})	Carboxylatestretching (cm^{-1})
[EMIM][DIF]	2955 and 2845	867	3558-3234	-	1571 and 1451
[EMIM] [Cl]	2924 and 2854	766	3533–3368	1579 and 1323	-
[BMIM][DIF]	2934 and 2865	862	3545-3304	-	1572 and 1450
[BMIM] [Cl]	2929 and 2834	764	3672-3204	1560 and 1349	-
[HMIM][DIF]	2956 and 2859	870	3486-3213	-	1571 and 1448
[HMIM] [Cl]	2929 and 2858	766	3607-3197	1568 and 1458	-
[OMIM][DIF]	2955 and 2856	865	3554-3372	-	1575 and 1450
[OMIM] [Cl]	2924 and 2824	767	3527-3300	1639 and 1569	-
[DMIM][DIF]	2923 and 2854	866	3584-3204	-	1575 and 1450
[DMIM] [Cl]	2922, 2924 and 2857	871	3504-3349	1637 and 1570	-

6.5.5 Octanol-water partition coefficient

In this section, partition coefficient values of the synthesised imidazolium ionic liquid-diclofenac system, [EMIM] [DIF], [BMIM] [DIF], [OMIM] [DIF], [HMIM] [DIF] and [DMIM] [DIF] were determined and detailed procedure was discussed in the section 3.2.2.7. The partition coefficient values measured are shown in Fig 6.17. The partition coefficient values for diclofenac ionic liquids in the range of 1.33 to 11.58. As excepted the partition coefficient values increased with increase in molecular weight.

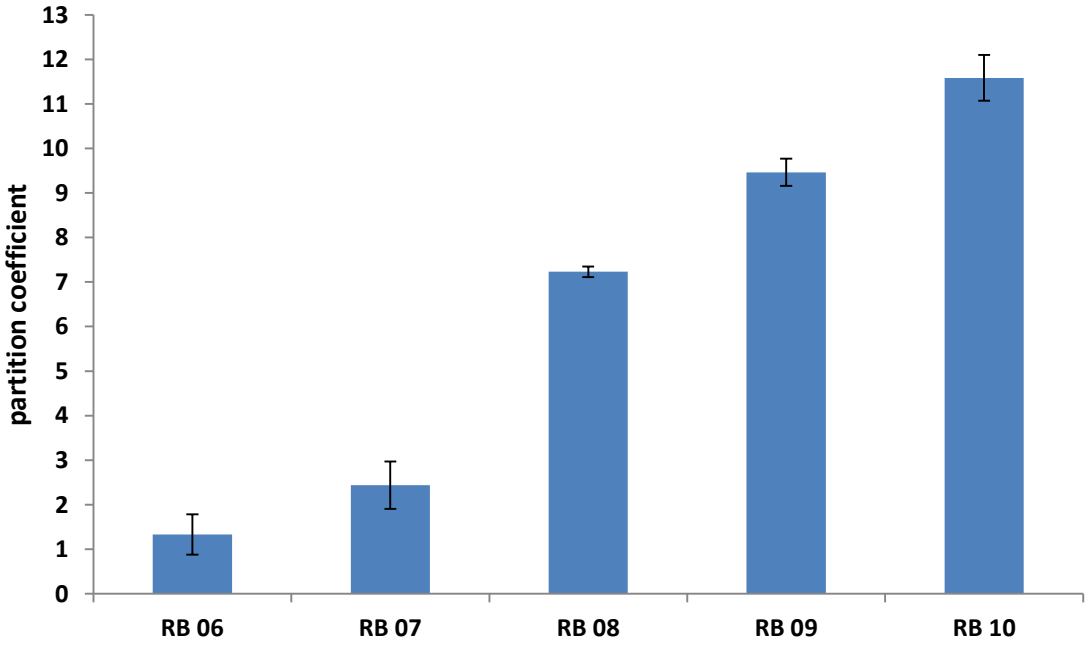


Figure 6.17 Ocatnol-water partion coffecient of [$C_n$mim] [IBU] ionic liquids

Studies by Domemanska *et al. (2005)* and Ropel *et al*. (2005) concluded that partition coefficient values increase with increasing alkyl chain length on the imidazolium cation, which was consistent with the values obtained for the drug-ionic liquids in this study (Ropel et al., 2005, Domańska et al., 2003). From the above data, some correlation can be made regarding the bioaccumulation and bioconcentration of the drug-ionic liquids. The bioconcentration process is

defined as the concentration of a chemical in aquatic organism due to the contact of the chemical with water. Basically, chemicals dissolved in water and absorbed through the skin and the respiratory organs of the organism, and chemicals ingested via food processing, this process is called biomagnification. The bioaccumulation factor (BAF) and bioconcentartion factor (BCF) is related to the partitioning of the chemical between the biota and the water:

$$\mathbf{BAF/BCF} = \frac{C_b}{C_w}$$

Where C_b is the concentration of the chemical in the biota and C_w is the concentration of the chemical in the water. For estimation of BCF from K_{ow} many correlation methods have been developed (Mackay, 1982, Meylan et al., 1999, Ropel et al., 2005).

Finally, it can be concluded that the octanol-water partition coefficients of both ibuprofen and diclofenac drug-ionic liquid systems were observed in the range of 0 to 11 at room temperature. Form these vales the hydrophilicity and hydrophobicity of the drug-ionic liquid systems can be correlated. The main findings were that, partition coefficient values increase with increasing alkyl chain length on imidazolium cation of the drug-ionic liquid compounds. These values are very important as they can indicate the potential impact on the environment, aquatic ecosystem and sorption to soils and sediments.

6.5.6 Diffusion study

This section reports on the drug release profile of the diclofenac-imidazolium liquid with different alkyl chain lengths and detailed procedure was described in the section 3.2.4.2.

The release profiles are shown in figure 6.18. The percent drug release from different diclofenac ionic liquids in the range of 16 to 107. Drug release was highest for ethyl imidazolium. There was significant difference observed in drug release of butyl and hexyl imidazolium salts. While in there was no such major difference observed in hexyl, octyl and decyl imidazolium salts and same pattern was observed for butyl and ethyl imidazolium salts. The percentage release of diclofenac can be ranked as ethyl > butyl > hexyl > octyl > decyl.

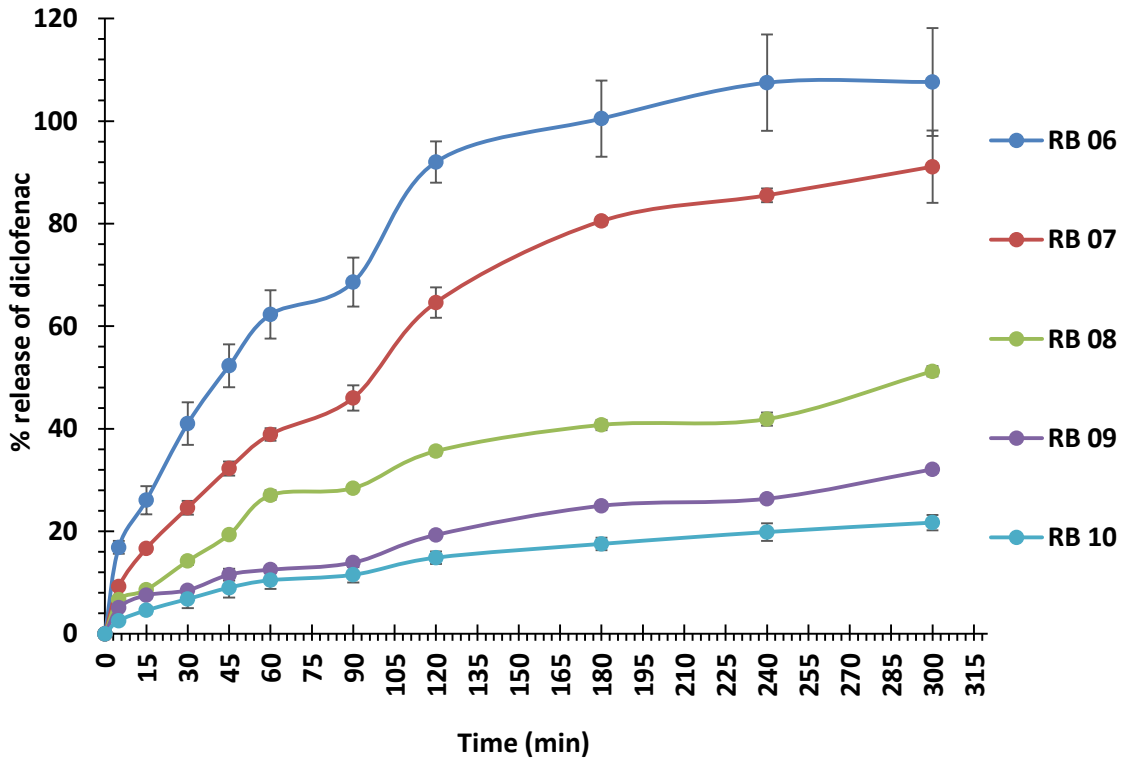
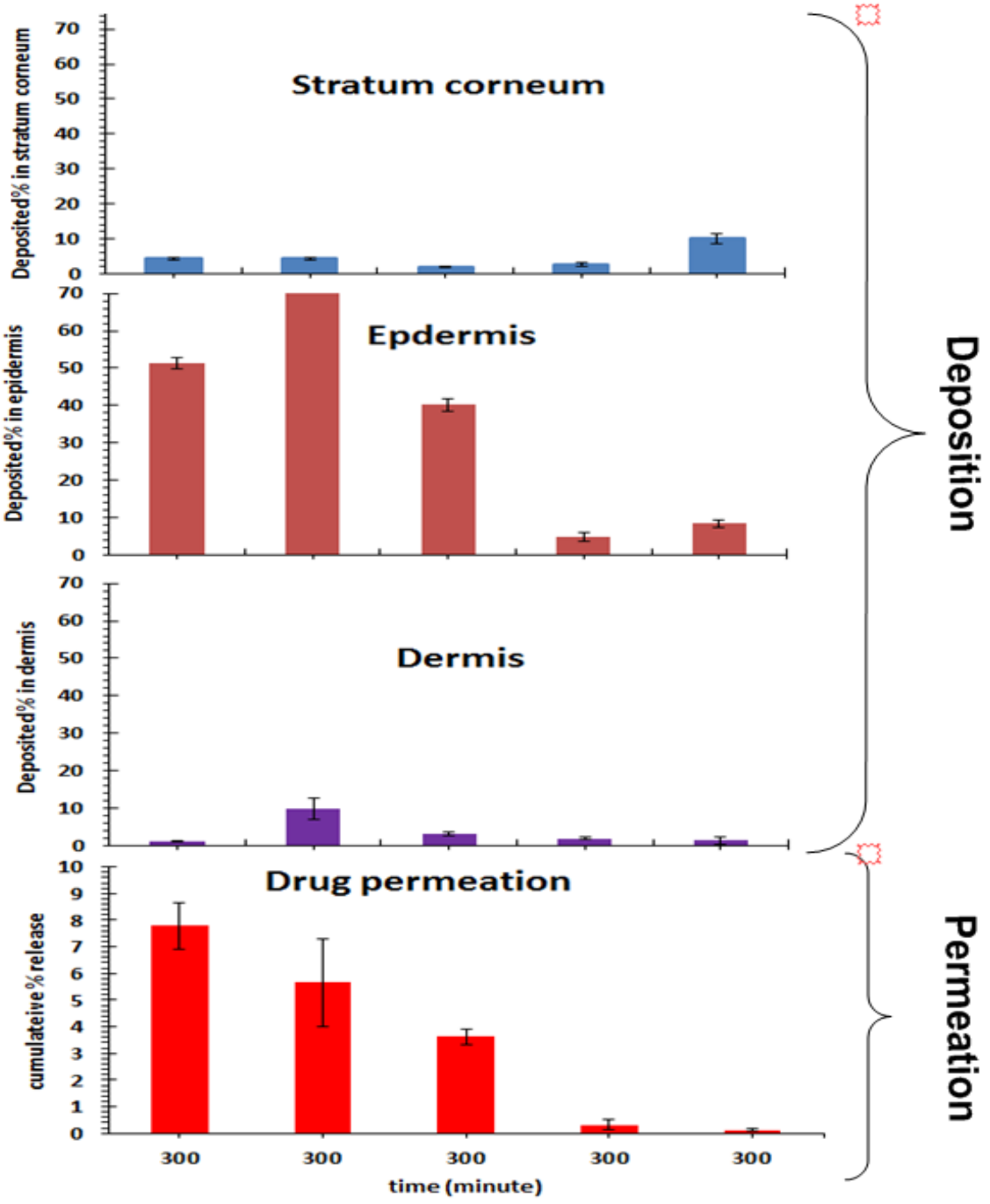


Figure 6.18 Percentage release profile of diclofenac ionic liquid in water at 37 °C.

6.5.7 Transdermal deposition and permeation study

This section gives potential information of diclofenac imidazolium salt interactions with skin profile. The key findings after application of diclofenac imidazolium salt is shown in figure 6.19. The percent deposition in the stratum corneum, epidermis and dermis layer where in the range of 4.22 to 9.96 %, 51.22 to 8.38 % and 1.08 to 1.26 % respectively. There is no such significant difference in deposition of diclofenac imidazolium salt in stratum corneum and dermis. Large proportion of salt is deposited in epidermis which can be ranked as butyl > ethyl > hexyl > decyl > octyl.

Molecular size, partition coefficient and solubility of drug molecule plays major role in deposition and permeation of drug molecule. The findings illustrate the major deposition of diclofenac imidazolium salt in epidermal part but the lower deposition in dermis allows diclofenac imidazolium salt to permeate. The permeation profiles of diclofenac imidazolium salt can be ranked in the following order ethyl > butyl > hexyl > octyl. > decyl.



	RB 06	RB 07	RB 08	RB 09	RB 10
Molecular weight	407.31	435.36	463.4	490.48	519.51
Partiton coefficient	1.33	2.43	7.23	9.46	11.58

Figure 6.19 Percentage of Skin deposition and skin permeation of diclofenac imidazolium ionic liquids

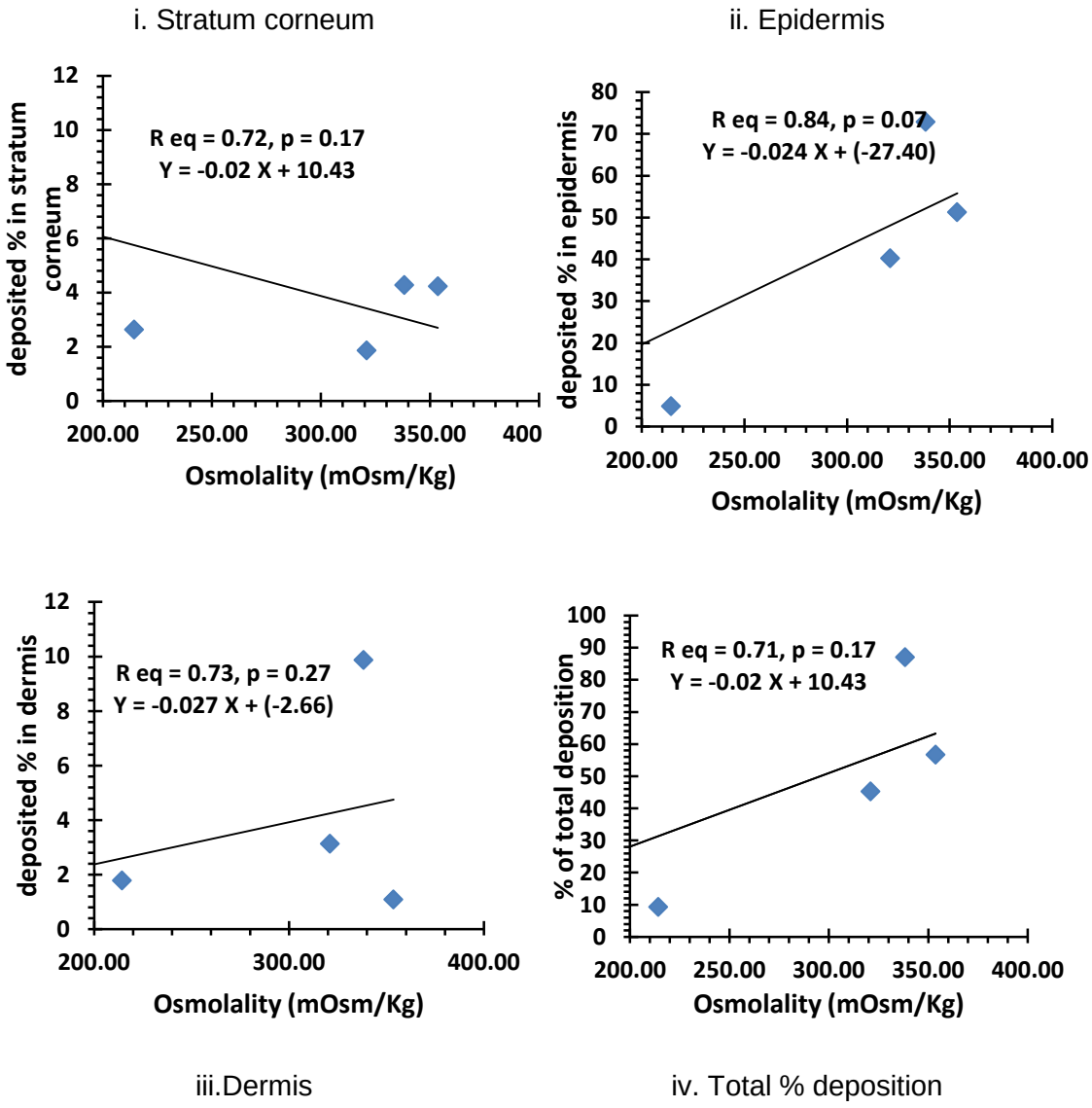


Figure 6.20 Regression of diclofenac ionic liquid

From above regression graph (Figure 6.20) it was observed that there were significance in calculated value.

The cumulative percent release is compared for 60 min and 300 min (Figure 6.21) against the partition coefficient values. As discussed above butyl showed higher release at 300 min. In 30 min the cumulative percent release was below 1 %.

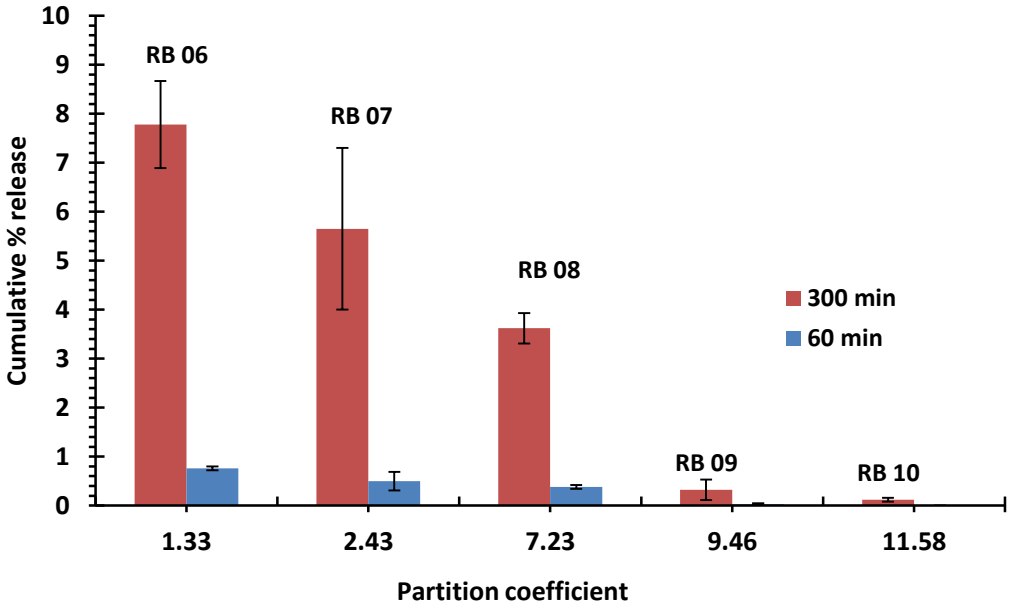


Figure 6.21 Cumulative % release at 60 and 300 min plotted against the partition coefficient of diclofeanc ionic liquids drug

Comparison of imidazolium salts of ibuprofen and diclofenac has shown significant differences. The partition coefficients of diclofenac ionic liquids (1.33 to 11.58) are significantly higher than that of ibuprofen ionic liquids (Figure 6.22).

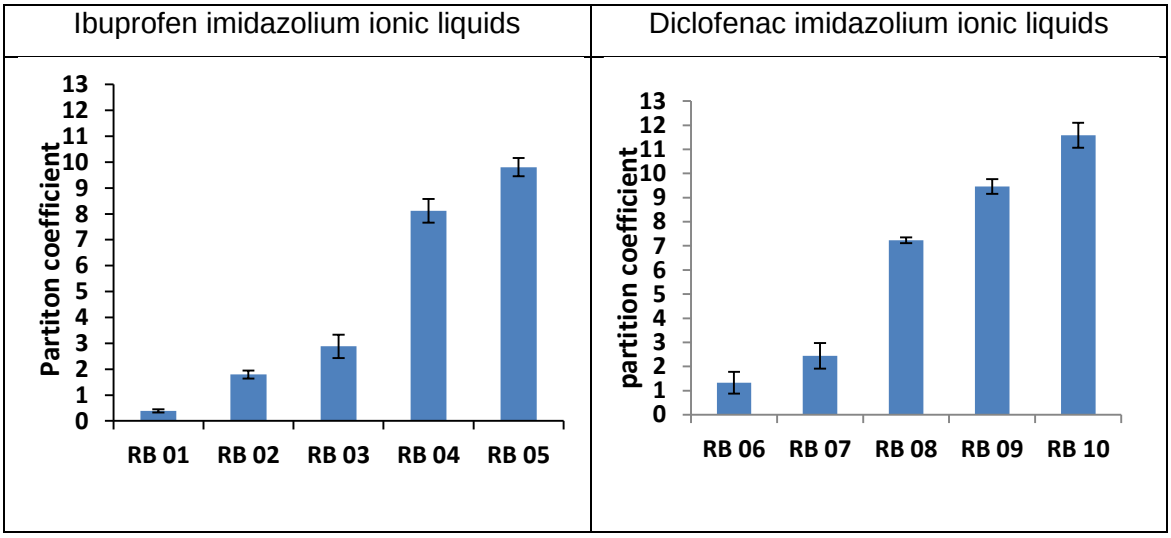


Figure 6.22 Comparision of partion coefficient values in ibuprofen and diclofeanc imidazolium ionic liquids.

The molecular properties such as pKa, Log P, molecular size and water solubility for ibuprofen (pKa: 4.91, Log P: 3.97, molecular weight: 206.29 g/mol and water solubility 21mg/L) and diclofenac (pKa: 4.15, Log P: 4.51, molecular weight: 296.148 g/mol and water solubility: 2.37 mg/L) are not significantly different. The ionic interaction between the two ions will determine degree of dissociation and internal partition coefficients of the salts. Hence osmolality of the equimolar salts of imidazolium solution of ibuprofen and diclofenac are compared (figure 6.23).

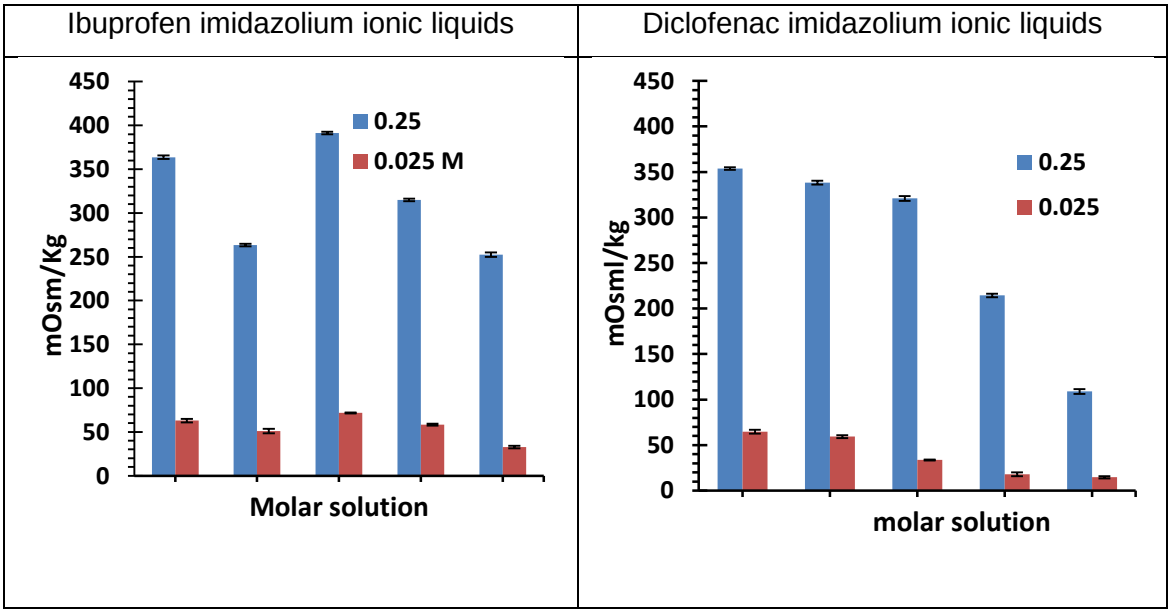


Figure 6.23 Comparision of osmolaity (mOsm/Kg) in ibuprofen and diclofenac imidazolium ionic liquids.

Overall diclofenac salts showed higher dissociation compared to respective to ibuprofen salts which contradicts the partition coefficient observations. Though relative comparison of physicochemical parameters provided some observations which could not be co related the more lipophilic diclofenac salts showed higher epidermal deposition compared to respective less lipophilic ibuprofen imidazolium salts (Figure 6.24).

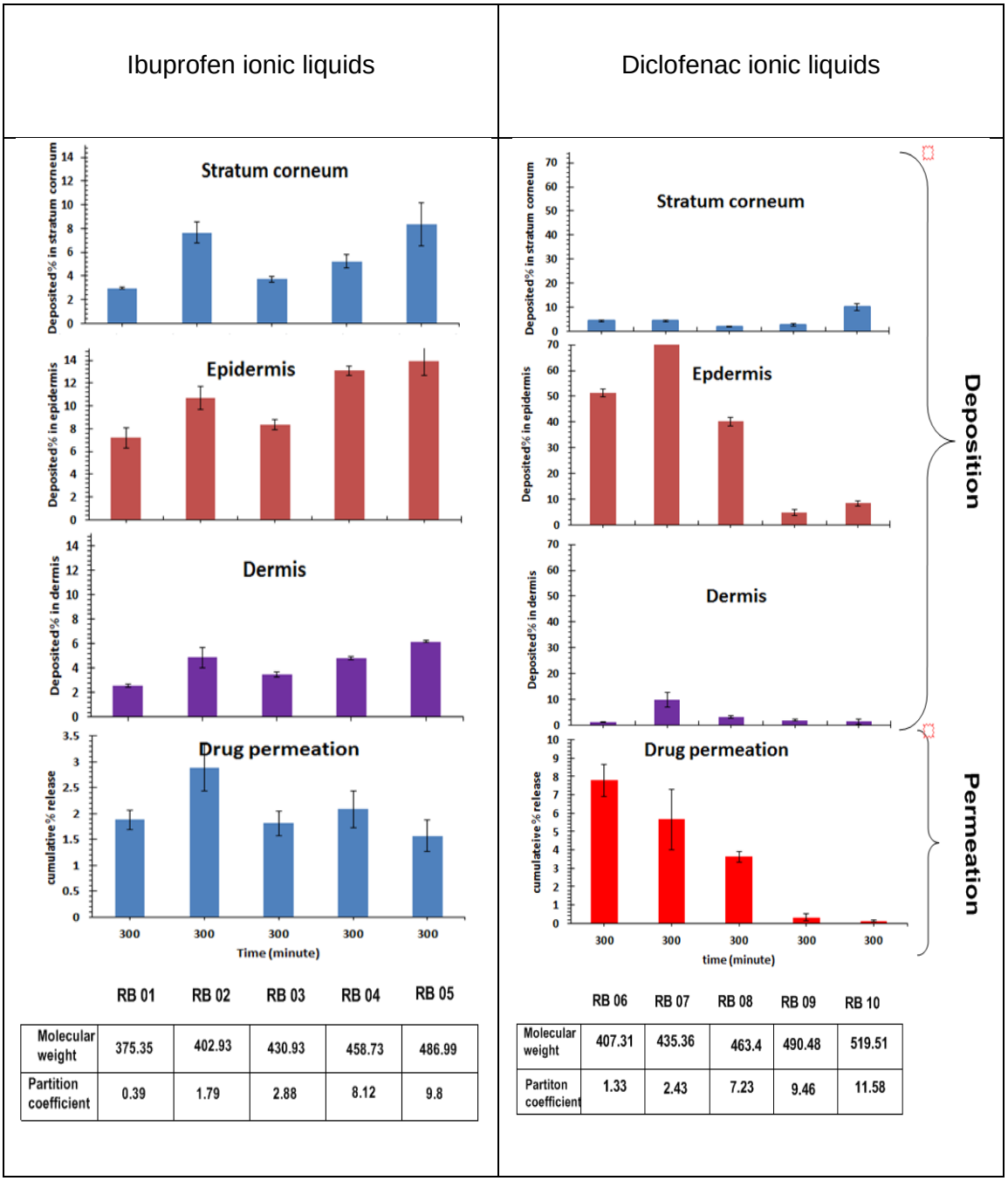


Figure 6.24 Compariative of skin deposition and skin permeation of ibuprofen and diclofenac imidazolium ionc liquids

This study clearly indicates potential of imidazolium ionic liquids to manipulate lipophilicity and other physicochemical properties such as molecular size, osmolality, viscosity to achieve desired skin deposition and permeation. The higher skin deposition of drug can act as reservoir providing slow drug permeation or can be restricted to skin layer for topical activity.

Chapter 7. Global conclusions

Ionic liquid were synthesised and characterised in good to excellent yields for different applications. A series of 15 PILs possessing three different cations with varying alkyl chain length (tri-*n*-butyl, tri-*n*-octyl, and triphenyl) were coupled with five different anions (Br, I, tosylate, tetrafluoroborate and hexafluorophosphate). All the compounds were characterised to confirm their structures using ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy. Phosphonium ionic liquids clearly offer, in some cases, several advantages over other types of ionic liquid, and this includes higher thermal stability, lower viscosity which is advantageous in high temperature reactions.

A green and efficient solvent free method using microwaves was developed to give these ionic liquids in quantitative yield. Therefore careful monitoring had to be established to produce this series of ionic liquids. The solvent free MW-assisted mediated synthesis that precluded the usage of volatile organic solvents was much faster, more economical and efficient and eco-friendly.

The thermal stability of these PILs was studied; they are generally stable upto 300 °C or even higher. This means that these PILs can be used as reaction media under a wide range of reaction temperature. These ionic liquids were found to be not appropriate for the crystallisation of APIs so imidazolium ionic liquids were investigated for this application.

Chapter 4 mainly focused on the crystal engineering using imidazolium ionic liquids. To date organic solvents are mainly used in the crystal engineering field as solvent media for pharmaceutical drugs. Nowadays, there is some literature

available on the crystallisation of drugs using ionic liquids but it is very limited and this was the gap that the chapter 4 looked to address. To fill this gap the study mainly focused on imidazolium ionic liquids due to their liquid form, easy availability and the accessibility of their physio-chemical properties. Using imidazolium ionic liquids and model APIs a study was conducted to try and to address this current gap in the literature.

The study focused on poorly water soluble drugs such as SFA, CPA, PBB and NIF. In the experimental findings interesting results were obtained, In the case of solubility, generally dielectric constant plays an important role on solubility but for ionic liquids this is difficult to predict. CPA, PBB and NIF showed opposite trend of solubility when compared to dielectric constant values. However, the solute solvent interactions plays an important role in the solubilisation and at this stage it is difficult to predict solubility of drugs in ionic liquids due to the largely unknown information of solvation mechanism of ionic liquids. Overall, CPA showed excellent solubility in the three ionic liquids compared to other model drugs. Where, CPA is practically insoluble in water and sparingly soluble in organic solvents.

For the crystallisation study, cooling and antisolvent methods were applied and the results were evaluated on the basis of the crystal structures obtained. In the cooling crystallisation, interestingly, polymorphic change was observed. For example, in the case of CPA, using the [EMIM][BF_4] ionic liquid final product of CPA converted thermally stable alpha to metastable epsilon form from. Where, the [acetate] and [DEP] anions did not show any polymorphic change. In another example, the [acetate] anionic environment, PBB was isolated in the

supramolecular organisation of with [EMIM][acetate] which was confirmed by SC-XRD. Interestingly, SFA drug, the solvent molecule [EMIM][BF_4] which was incorporated with the SFA molecule and formed supra molecular organisation which was further confirmed by SC-XRD. For the antisolvent crystallisation studies using the selected three ionic liquids with the model drugs, only SFA showed supramolecular organisation with [EMIM][BF_4] ionic liquids and for the other drugs same form was isolated as was initially used.

The main finding of this chapter is that good quality crystals were isolated which were directly analysed by SC-XRD. The polymorphic change was observed for one drug and supramolecular organisation for two drugs with ionic liquids which is a very interesting finding. However, this chapter provides supporting data to fill the gap in the use of ionic liquids in crystal engineering.

In recent years the application of ionic liquids in the pharmaceutical industry has started to increase. For example, the ionic liquid combination of the NSAID etodolac and the pain-reliever lidocaine which is used as patch to treat to lower back pain has finished phase III clinical trials. In this context, the combination of ionic liquids with drugs required much more knowledge to determine, how and which combination of ions affects, not only the physical properties, but also the biological activity. Chapter 6 focused on ibuprofen and diclofenac combination with the ionic liquids with different alky group. In fact, many researchers are working on the drug ionic liquids combination with its oral and transdermal activity, but in this project the main focus was on the effect of alkyl chain length of imidazolium cation on diffusion and transdermal study. Therefore, the study concisely focused on the effect of ethyl, butyl, octyl and hexyl alky group on the

imidazolium cation. The ionic liquid-drug combination synthesis was carried out by the simple metathesis method which gave a stable liquid form in excellent yield. The compounds produced were further analysed by TGA and DSC for thermal properties. The main advantage of this method is simple, cheap and eco-friendly. For ibuprofen, it was concluded that the alkyl group altered the thermal, as well as drug delivery properties. As a result the liquid salts showed excellent thermal stability in which the DSC did not show any Tg temperature and crystallisation during heating upto 100 °C. In addition the partition coefficient values were investigated. Partition coefficient values increased with increase in the alkyl chain length.

In comparison results, imidazolium salts of ibuprofen and diclofenac have shown significant differences. The partition coefficients of diclofenac ionic liquids (1.33 to 11.58) are significantly higher than that of ibuprofen ionic liquids. Overall diclofenac salts showed higher dissociation compared to respective to ibuprofen salts which contradicts the partition coefficient observations. Though relative comparison of physicochemical parameters provided some observations which could not be co related the more lipophilic diclofenac salts showed higher epidermal deposition compared to respective less lipophilic ibuprofen imidazolium salts

This study clearly indicates potential of imidazolium ionic liquids to manipulate lipophilicity and other physicochemical properties such as molecular size, osmolality, viscosity to achieve desired skin deposition and permeation. The higher skin deposition of drug can act as reservoir providing slow drug permeation or can be restricted to skin layer for topical activity.

Chapter 8. Conclusion and future work

This section presented the conclusion and future work in details

8.1 Conclusion

I. The synthesis of fifteen phosphonium ionic liquids under microwave irradiationand its physciochemical properties was investigated. The reaction time was significantly reduced compared to conventioanl methods, and higher yields were reported.

II. The crystallisation of pharmaceutical drugs such as sulfathiazole, chloropropamide, phenobarbital and nifedipine were investigated using imidazolium ionic liquids. The supramolecular complex of sulfathiazole and phenobarbital with imidazolium ionic liquids and polymorphic change in chlorpropamide was achieved. The ionic liquids provide unique enviorment for the crystallisation.

III. The imidazolium salts of ibuprofen and diclofenac were synthesised and evaluated for physicochemical properties and their pharmaceutical performances espically transdermal absorption. The investigation of physicochemcal properties and pharmaceutical performance of imidazolium drug salts indicated opportunity to optimise lipophilicity and other physicochemical properties such as molecular size, osmolality, viscosity to achieve desired skin deposition and permeation.

8.2 Future work

I. Use of ionic liquids to obtain metastable polymorphs or new crystal forms of drugs will be interesting area

II. Effect of alkyl chain length on drug solubility at various temperatures.

III. Computational approach to understand the solute-ionic liquid interactions.

IV. The challenges in measurement of physicochemical properties, especially concentration solution of the salt can be addressed using conductivity measurement and other techniques for colligative properties such as conductivity.

V. Computational approach to understand the changes in molecular properties of drug ionic liquids.

VI. Similar approach can be used for design of dual drugs and controlled release drug delivery system using skin as reservoir.

Chapter 9. REFERENCES

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Chapter 10. Appendix

A. Crystallisation of pharmaceutical drugs from ionic liquids

Table A.1 Solubility data in [EMIM][BF4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for sulfathiazole.

Temperature (°C)	solubility (1 ml)			
	[EMIM[[BF4]	[EMIM][acetate]	[EMIM] [DEP]	Water
	Solubility (mg)			
0	0	0	0	0
50 °C	1.64 ± 0.11	1.08 ± 0.010	1 ± 0.014	0
70 °C	4.75 ± 0.006	1.86 ± 0.008	2.93 ± 0.007	0
100 °C	6.41 ±0.007	2.94 ± 0.008	7.04 ± 0.016	0

Table A.2 Solubility data in [EMIM][BF4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for chlorpropamide.

Temperature (°C)	Ionic liquids (1 mL)			
	[EMIM[[BF4]	[EMIM] [acetate]	[EMIM] [DEP]	Water
	Solubility (mg)			
50	14.1 ± 0.02	5.71 ± 0.014	4.17 ± 0.011	0
75	28.07 ± 0.104	24.12 ± 0.038	13.29 ± 0.02	0
100	39.06 ± 0.015	40.54 ± 0.031	36 ± 0.100	0

Table A.1 Solubility data in [EMIM][BF4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for phenobarbital.

Temperature (°C)	Ionic liquids (1 mL)			
	[EMIM[[BF4]	[EMIM] [acetate]	[EMIM] [DEP]	Water
	Solubility (mg)			
0	**0**	**0**	**0**	**0**
50	0.89 ± 0.005	0.34 ± 0.008	2.55 ± 0.003	0
75	3.25 ± 0.008	1.88 ± 0.001	5.4 ± 0.004	0
100	7.23 ± 0.004	3.55 ± 0.002	8.06 ± 0.004	0

Table A.1 Solubility data in [EMIM][BF4], [EMIM][acetate], [EMIM][DEP] and water as a function of temperature for nifedipine.

Temperature (°C)	Ionic liquids (1 mL)		
	[EMIM[[BF4]	[EMIM] [DEP]	water
0	**0**	**0**	**0**
50	2.21 ± 0.016	12.21 ± 0.022	0
75	5.61 ± 0.007	18.17 ± 0.022	0.00026
90	9.46 ± 0.008	21.41 ± 0.005	0.00064

B Pharmaceutical performance of drug imidazolium ionic liquids

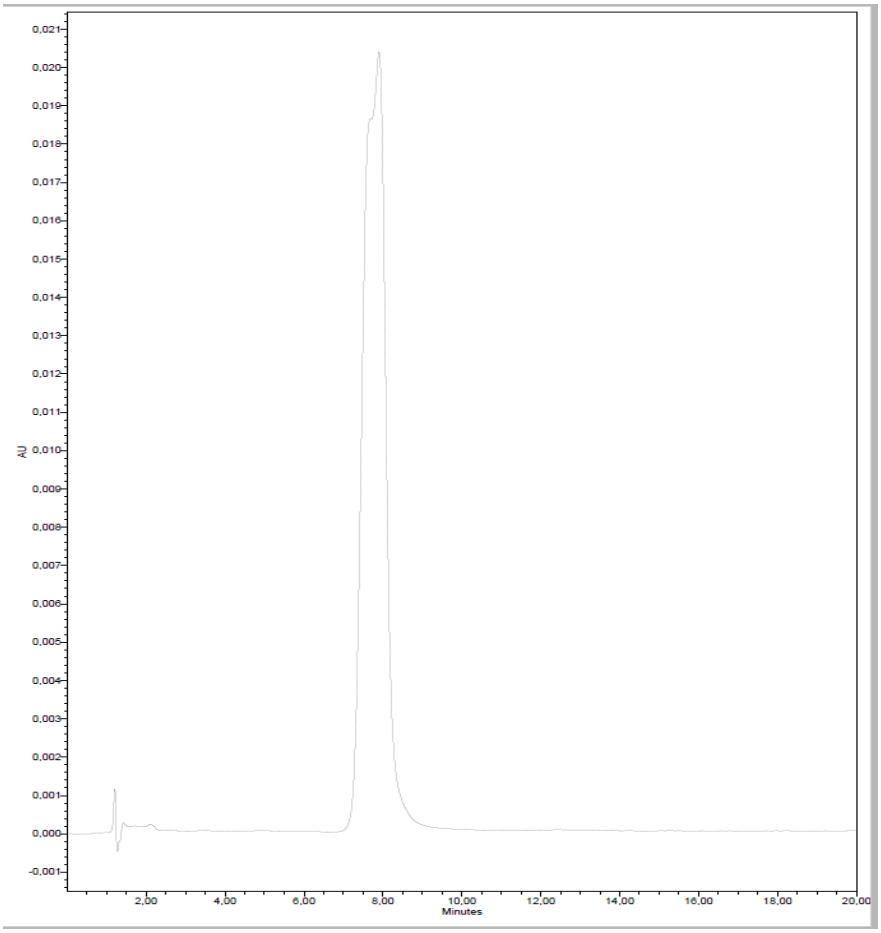

Figure B.1 HPLC calibration for diclofenac

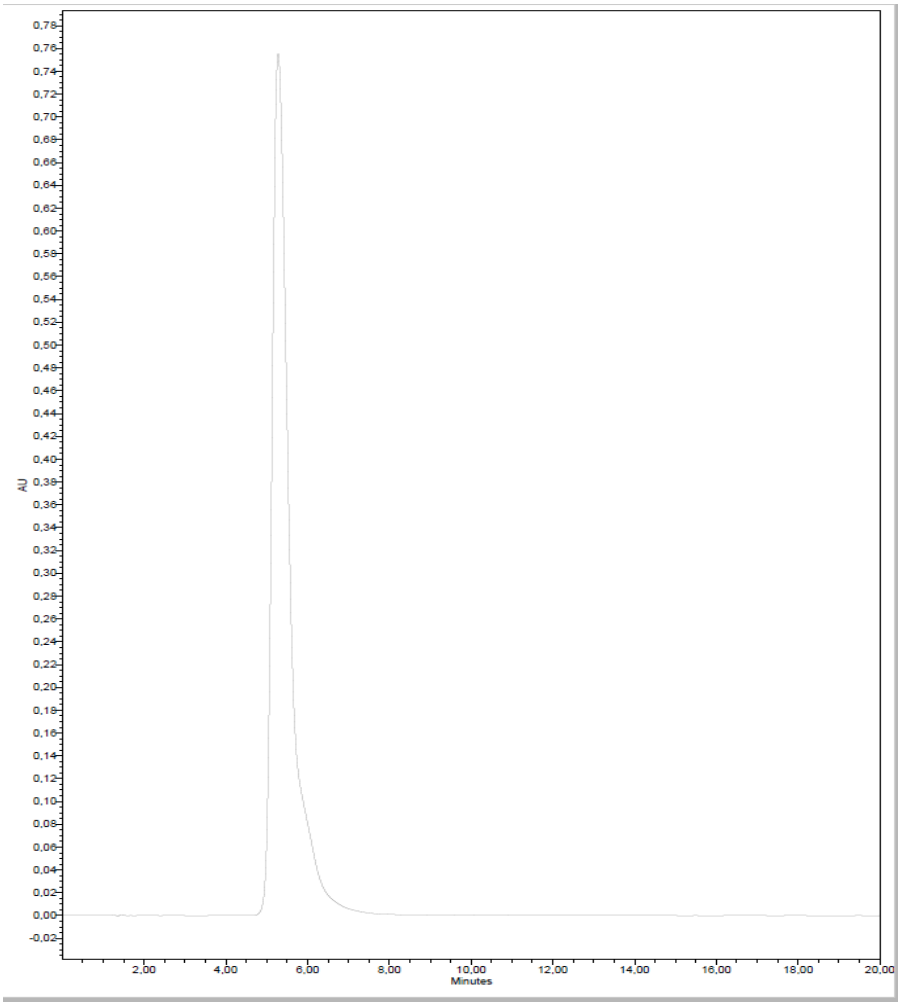

Figure B.2 HPLC calibration for diclofenac

Table B.1 Partition coffecient of [$C_n$mim] [IBU]

Sr. no.	Drug ionic liquid	Alkyl chain length (n)	Molecular weight	Partition coefficient(mean and SD)
1	RB 01	2	375.35	0.39± 0.064
2	RB 02	4	402.93	1.79 ± 0.15
3	RB 03	6	430.98	2.88 ± 0.45
4	RB 04	8	458.73	8.12 ± 0.46
5	RB 05	10	486.99	9.80 ± 0.35

Table B.1 Partition coffecient of [$C_n$mim] [DIF]

Sr. no.	Drug-ionic liquid	Alkyl chain length	Molecular weight	Log P (mean and STDEV)
1	[RB06]	2	407.31	1.33 ± 0.45
2	[RB07]	4	435.36	2.43 ± 0.53
3	[RB08]	6	463.4	7.23 ± 0.11
4	[RB09]	8	490.48	9.46 ± 0.51
5	[RB10]	10	519.51	11.58 ± 0.51

Table B.2 Skin deposition study drug ionic liquid

Sample code	Deposited % in stratum corneum layer	Deposited % in epidermis	Deposited % in dermis
RB01	2.99%±0.11	7.19%±0.86	2.57%±0.09
RB02	7.66%±0.88	10.69%±0.99	4.86%±0.82
RB03	3.75%±0.24	8.36%±0.45	3.5%±0.22
RB04	5.23%±0.57	13.08%±0.39	4.81%±0.11
RB05	8.37%±1.8	13.96%±1.29	6.19%±0.1
RB06	4.22%±0.26	51.22%±15.24	1.08%±0.06
RB07	4.27%±0.42	72.8%±13.59	9.86%±2.95
RB08	1.86%±0.22	40.17%±6.95	3.13%±0.37
RB09	2.62%±0.58	4.84%±1.64	1.78%±0.33
RB10	9.96%±1.47	8.38%±1.07	1.26%±1.07

Table B.3 Skin permeation of diclofenac imidazolium ionic liquids.

Time interval	RB06	RB07	RB08	RB09	RB10
	Cumulative % release				
15 min	0.33%±0.06	0.09%±0.1	0.25%±0.02	0%	0%
30 min	0.57%±0.15	0.25%±0.06	0.34%±0.05	0%	0%
1 hr	0.76%±0.04	0.5%±0.19	0.38%±0.04	0.03%±0.02	0%
1.5 hr	1.36%±0.11	0.93%±0.69	0.65%±0.13	0.04%±0.03	0%
2 hr	1.55%±0.2	1.74%±0.91	0.91%±0.2	0.06%±0.05	0%
3 hr	3.7%±1.46	3.06%±0.68	1.48%±0.24	0.14%±0.13	0%
4 hr	4.67%±1.33	3.65%±0.15	2.54%±0.14	0.23%±0.12	0.05%±0.04
5 hr	7.78%±0.89	5.65%±1.65	3.62%±0.31	0.32%±0.21	0.12%±0.04

Table B.4 Skin permeation of diclofenac imidazolium ionic liquids.

Time interval	RB01	RB02	RB03	RB04	RB05
	Cumulative % release				
15 min	0.46%±0.2	0.43%±0.11	0.35%±0.05	0.17%±0.01	0.67%±0.05
30 min	0.41%±0.02	0.86%±0.18	0.38%±0.009	0.21%±0.02	0.79%±0.05
1 hr	0.85%±0.09	1.08%±0.08	0.45%±0.05	0.5%±0.01	0.73%±0.04
1.5 hr	1.09%±0.13	1.45%±0.03	0.73%±0.15	0.99%±0.06	0.97%±0.31
2 hr	1.2%±0.28	1.67%±0.05	1.04%±0.1	1.14%±0.19	0.98%±0.11
3 hr	1.49%±0.26	1.94%±0.25	1.3%±0.17	1.46%±0.19	1.4%±0.18
4 hr	1.77%±0.31	2.43%±0.21	1.39%±0.31	1.67%±0.11	1.47%±0.44
5 hr	1.88%±0.19	2.88%±0.45	1.81%±0.24	2.08%±0.35	1.57%±0.31