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The role of hydrogen bonding propensity in tuning the morphology of crystals obtained from imidazolium based ionic liquids

S. Karthika, T.K. Radhakrishnan *, P. Kalaichelvi

Department of Chemical Engineering, National Institute of Technology, Tiruchirappalli 620 015, Tamil Nadu, India

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ABSTRACT

The pharmaceutical crystallization is quite challenging in terms of the target properties like desired habit or morphology, size and the size distribution of the resultant crystals. Controlling the dimensions along the crystallographic axes, especially for the crystals with needle shape, is desired for operational flexibility. There has been a great interest in using Ionic Liquids (ILs) as a novel crystallization media, but inter molecular interaction between ILs and pharmaceutical solids are quite complex. Interactions in ionic media can be tuned to achieve target physical properties. In this study, ibuprofen is crystallized using imidazolium based IL with PF_6 anion, which produces needle shaped crystals with high aspect ratio. It is found that aspect ratio is significantly altered when a small quantity of organic solvents is added to the crystallizing media. These organic solvents prefer to interact with certain domain of IL and this interaction can be utilized in achieving the objective of reduction in aspect ratio. Use of methanol and 2-ethoxy ethyl acetate is found to provide a significant reduction in aspect ratio. The role of hydrogen bonding ability of C_2 hydrogen of imidazolium ionic liquid in steering the crystal shape is discussed.

1. Introduction

Ionic liquids (ILs) are the class of solvents having favorable solvating properties, low vapor pressure, tunability and good thermal stability which has recently attracted attention as potential solvents for the purification of pharmaceuticals by crystallization. Earlier attempts show that the antisolvent crystallization using Imidazolium (Im) based Ionic Liquids (ILs) as solvent and antisolvent could produce a new polymorph of the drug adefovir dipivoxil at temperatures below 50 °C [1]. The crystallization of pharmaceuticals with greater purity and improved yields could be possible by the use of low viscous IL, was also explored [2]. Hydrogen bond donating cosolvents can alter the solubility of a drug in the ILs containing acetate anions by disrupting the interaction between hydrogen bond donating phenol moiety on Acetaminophen and the IL, thereby manipulating the interaction which led to the crystallization yields greater than 88% at 25 °C [3]. Recently, form I of clopidogrel bisulphate, which is the industrially preferred form, has been studied to control the solvent mediated transformations from form I to form II using Ethanol/Im based IL as solvent and antisolvents [4].

Both the crystallization technique and the solvent influence the crystal habit or morphology there by affecting the dissolution properties of the drug. Physical properties like solubility, dissolution rate, melting point and micromeritic properties like tablet compressibility, mechanical strength and powder flow vary with respect to various forms of crystal habits. The ILs find applications in inorganic synthesis as a neutral solvent or templates and are known to crystallize wide range of substances with different morphologies. The Im based ILs have been tried as additives in protein crystallization to influence morphology. While the morphology of lysozymes crystals are plate like in the presence of 1-butyl-3-met hylimidazolium(Bmim) cations with BF_4, Cl and Br anions, a needle like morphology is obtained from 1,3-dimethyl imidazolium iodine ([dmim]I). Morphology also seems to be dependent on strength or concentration of ILs where the increased concentration of [dmim]I lead to the transition from a mixture of plate and needle like structure to thinner needles without plates. The IL influences the interaction between lysozyme molecules, alters the solubility and shifts the thermodynamic equilibrium. In the pharmaceutical crystallization, the cooling crystallization produced crystals of different morphology when acetaminophen was crystallized from Im based ILs [5]. The needle and plate like morphology with high aspect ratio was also observed when ibuprofen was crystallized from Bmim with PF_6 anion [6].

* Corresponding author.
E-mail address: radha@nitt.edu (T.K. Radhakrishnan).

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The objective of the present study is to investigate the role of hydrogen bonding in the Bmim PF_6 media in achieving a desired aspect ratio of ibuprofen crystals. The unique structure of Im ring is attributed to the presence of $N_1C_2N_3$ moiety, with positively charged C_2 and neutral C_4, C_5 carbon atoms (Fig. 1a). The hydrogen atom of C_2 is known to interact with solutes through hydrogen bonding [7]. To analyse its role in change of face growth rates, organic solvents which could alter the strength of hydrogen bonding interactions have been chosen for the study, each known to interact with different domains of ILs. The crystallization of ibuprofen from $BmimPF_6$, with four members of organic solvents (OS) viz., dimethyl sulphoxide (DMSO), 2-ethoxy ethyl acetate (EEA), methanol (MeOH) and n-hexane (n-hex) added in small quantities (Fig. 1b) is investigated for the change in aspect ratio, as quantitative descriptor of change in morphology.

The Im based ionic liquids are likely to interact differently when mixed with the different OS as solutes and is shown in Fig. 2. In general, some solutes interact strongly with the polar network of ILs. The interaction of imidazolium ILs and methanol is dominated by hydrogen bonding between the —OH group of methanol and fluorine of the PF_6 anion [8,9]. Also, there exists some interaction, although weak, between oxygen of methanol and the hydrogen of Im cation. Another type of interaction also exist in DMSO, in which hydrogen bonds are formed between Im C_2—H and oxygen of DMSO, whereas C_4—H, C_5—H interaction with oxygen of DMSO are insignificant [10,11]. In the case of non-polar solutes like n-hex, weak interaction is observed between n-hex and both the anion and the cation of ILs and the strong interaction exist between methyl group of n-hex and end alkyl side chain of Im cation [12,13]. The hydrogen on the C_2 position is known to bind with the solutes. So, if a solvent is able to compete for the hydrogen bond at C_2, the interaction of C_2—H with the solute is likely to get reduced. In the presence of solvents, which can hydrogen bond with the IL, the interaction of the cation with specific face of the solute can be sufficiently altered, thereby resulting in a significant change in the aspect ratio of resultant crystals and this has been concluded from the present study.

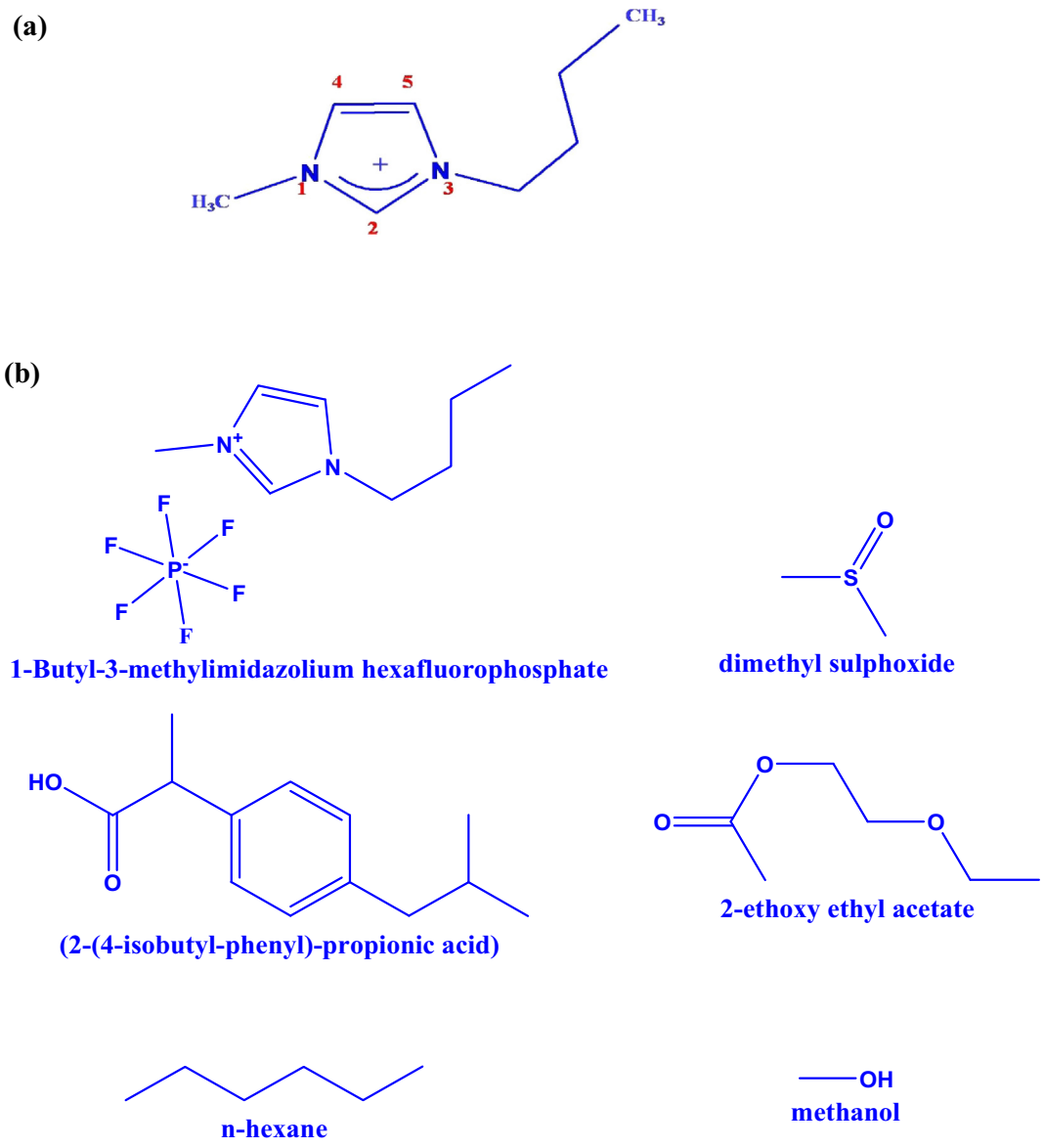

Fig. 1. (a) Structure of imidazolium cation of $BmimPF_6$. (b) Chemical structures of compounds used in the present study.