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Synthesis and Characterization of Flufenamic Ionic Liquids

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Abstract: Active Pharmaceutical Ingredients-Ionic Liquids (APIs-ILs), when compared to Active Pharmaceutical Ingredients Hydrochloride (APIs-HCl), exhibits modified solubility, increased thermal stability and significant enhancement in the efficiency of APIs. To produce and demonstrate application of green ionic liquid form of the APIs, we prepared ammonium, phosphonium and choline couple with flufenamic acid. Their physical properties such as thermal stability, melting points and solubility were studied. Flufenamic ionic liquids undoubtedly represent a promising group of ionic liquids. As these new ionic liquids are halogen–free, it is expected that such new compounds will prove useful in further studies centered on active pharmaceutical ingredients ionic liquids.

Key words: Active pharmaceutical ingredients, ionic liquids, flufenamic

INTRODUCTION

Solid and crystalline forms of APIs have been traditionally used in drug formulations because of their improved properties with respect to solubility, purity, thermal stability and bioavailability. Such forms of drugs are also desirable for ease of handling and lower production and storage cost. However, the solid form of many drugs has drawbacks that are mainly related to polymorphic conversion, low solubility and low bioavailability for crystalline solids and the tendency of amorphous form to spontaneously crystallized (Saadeh *et al*., 2009).

In 2007, researchers have discovered that ILs could be used as APIs with new and unique properties compare to solid pharmaceutical forms (Hough *et al*., 2007). They reported that hydrophobic Room Temperature Ionic Liquid (RTIL), lidocainium docusate (prepared from lidocaine hydrochloride) and sodium docusate showed modified solubility and increased thermal stability when compared to lidocaine hydrochloride.

Defined as salts that melt below 100°C with most liquid at room temperature, ILs has been known since the early 1900's (Walden, 1914). Recently, many researchers have recognized that ILs are actually customizable materials in which properties of the anions result in various ILs which can provide wide ranges of hydrophobicity/hydrophilicity, acidity/basidity, viscosities, solubilities, etc. (Wasserscheid and Welton, 2007).

In this study, APIs-ILs, ammonium and phosphonium based were synthesized. The H^1-NMR, FTIR and elemental analysis were used to confirm the structures of this compound. Physical properties were measured with differential scanning calorimetry to measure glass transition and melting points. While, the start and decomposition temperatures were measured at heating rate 5°C min^{-1}.

METHODOLOGY

Generally, tetramethylammonium hydroxide, tetrabuthylphosphonium hydroxide, tetrabuthylammonium hydroxide, choline hydroxide and flufenamic acid were dissolved in acetone or deionized water separately and the two solutions were slowly mixed and stirred at room temperature for 24 h. This method has an advantage since the by-product is only water, thus avoiding the use of metal salts and ion exchange. Therefore, in this study, halide contamination and extensive of purification procedures were avoided. Four flufenamic ILs was prepared; Tetrabuthylphosphonium flufenamate, Tetramethylammonium flufenamate Tetrabuthylammonium flufenamate and Choline

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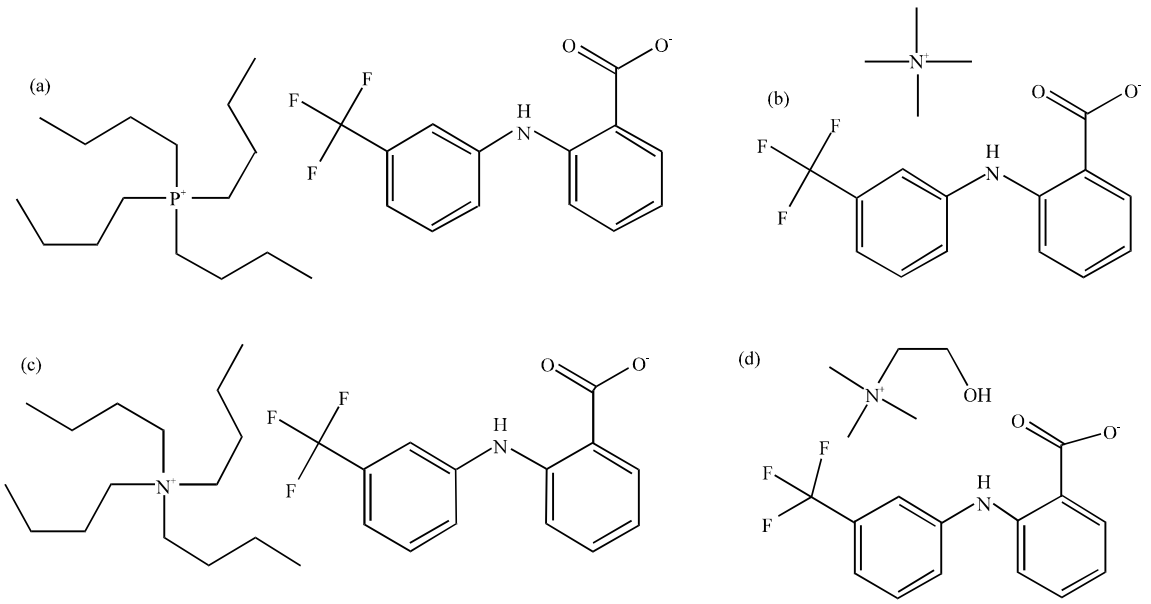

Fig. 1(a-d): Structure of flufenamic ILs, (a) Tetrabuthylphosphonium flufenamate, (b) Tetrabuthylammonium flufenamate, (c) Tetrabuthylammonium flufenamate and (d) Choline flufenamate

flufenamate. The structures of the synthesized ILs are shown in Fig. 1.

The structure and purity of each API-ILs was confirmed by ^{1}H (NMR), CHNS elemental analysis and Fourier Transform Infrared. All APIs-ILs was dried at 50°C for 4 h on a rotary evaporator under reduced pressure before the spectroscopic measurements were made. The water content of the APIs-ILs was checked with a coulometric Karl Fischer titrator.

Physical properties was measured with Differential Scanning Calorimetry (DSC) to measure glass transition (T_g), cold crystallization temperatures (T_{cc}) and melting points (T_m). Thermogravimetric analysis (TGA) is a useful tool for the investigation of material properties and was used for measurement of the decomposition temperature.

RESULTS AND DISCUSSION

The present flufenamic ILs were synthesized by the neutralization procedure. The structures of the synthesized ILs were confirmed using ^{1}H-NMR and FTIR analysis (Fig. 2). The analysis results are shown in Table 1, which also includes the product yields range from 90-68%. ^{1}H-NMR and elemental analysis data for the ILs.

The definition of ILs requires that they are in liquids form below 100°C and that RTILs are in liquid form at room temperature (Rogers and Seddon, 2003). Only three ILs synthesized in this study were RTILs when they dried under reduced pressure. ILs 3 was in white solid. However it's instantly absorbed H_2O after exposure to air to change transparent liquids like RTILs.

Table 2 shows the physical state, water content value and appearance for flufenamic ILs. The flufenamic ILs obtained is thermally stable around 200-340°C. The decomposition temperature of the ILs is shown in Table 3 and Fig. 3. It shows that phosphonium ILs is more stable than ammonium ILs.

Melting and glass transition temperature were measured using DSC. The results are presented in Table 3, showing the transition temperature where appropriate. Only three flufenamic IL, 1, 2 and 3 showed a glass transition temperature at -38, -23 and -8.99°C.

These behaviors are characterize by no true phase transitions but only the formation of an amorphous glass on melting temperature and glass cooling and reformation of the liquid on heating. These ILs have no melting or freezing points but only glass transition.

The solubility performance of flufenamic ILs, with water and other solvents, has been investigated as shown

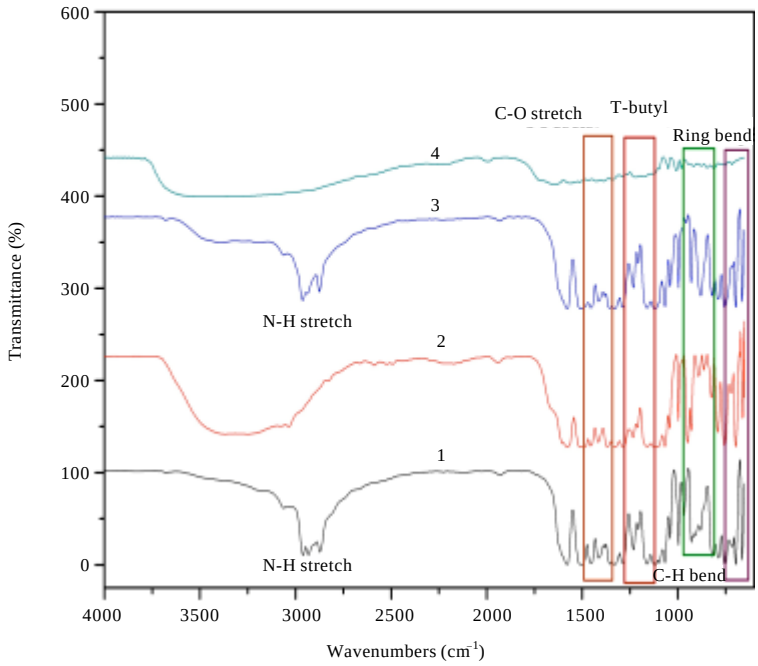

Fig. 2: FTIR curve for the ILs

Table 1: Characterization data for the Ionic Liquids (ILs)

ILs	Formula	Molecular weight	Yield (%)	IR (cm^{-1})	^{1}H-NMR	Elemental analysis (%) Experimental	Calculated
1	$C_{30}H_{45}F_3NO_2P$	539.65	76	2960, 2932, 2873, 1578, 1503, 1455, 1413, 1330, 1288, 1232, 1206, 1161, 1119, 1067, 996, 880, 787, 715, 663	δ0.91 (12H, t, CH3), 1.3-1.4 (16H, m, CH_2), 6.7 (8H, m, CH_2), 6.7 (1H, m, CH), 7.1-7.4 (6H, m, CH), 7.9 (1H, m, CH)	C 63.19 H 6.90 N 2.98	C 66.77 H 8.40 N 2.60
2	$C_{18}H_{21}F_3N_2O_2$	354.37	90	3367, 1579, 1501, 1457, 1416, 1368, 1285, 1114, 1043, 996, 824, 752, 660	δ3.1 (12H, s, CH_3), 6.7 (1H, m, CH), 7.1-7.4 (7H, m, CH), 7.9 (1H, m, CH)	C 54.75 H 5.96 N 7.42	C 61.01 H 5.97 N 7.91
3	$C_{30}H_{45}F_3N_2O_2$	522.69	68	2962, 2875, 1578, 1507, 1455, 1413, 1330, 1289, 1232, 1206, 1161, 119, 1067, 995, 879, 788, 663	δ0.9 (12H, t, CH_3), 1.2-1.3 (8H, m, CH_2), (1.5-1.6 (8H, m, CH_2), 3.3 (8H, s, CH_2), 6.7 (1H, m, CH), 7.1-7.4 (6H, m, CH), 7.9 (1H, m, CH)	C 67.01 H 6.30 N 5.54	C 68.94 H 8.68 N 10.90
4	$C_{19}H_{23}F_3N_2O_3$	384.39	90	3240, 1929, 1582, 1417, 1335, 1163, 756, 699	δ3.3 (9H, s, CH_3), 3.4 (2H, s, CH_2), 6.7-7.9 (8H, m, CH), 12.2 (1H, s, NH)	C 56.22 H 4.902 N 6.782	C 59.37 H 6.03 N 7.29

Table 2: Physical State for the Ionic Liquids (ILs)

ILs	Physical state (25°C)	Appearance	Water content (%)
1	Liquid	Bronze	2.52
2	Liquid	Bronze	1.05
3	Solid	White	-
4	Liquid	Bronze	1.06

Table 3: Physical properties for the Ionic Liquids (ILs)

ILs	T_g	T_m	T_d
1	-38.70	-	342
2	-23.43	-	207
3	-	-	201
4	-8.99	-	218

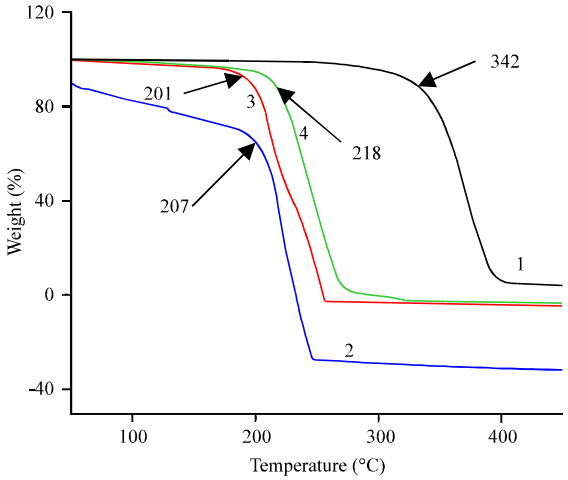

Fig. 3: TGA curve for flufenamate ILs

Table 4: Solubility for ILs

IL	DMSO	H_2O	Acetone	Methanol	Toluene
1	√	×	√	√	√
2	√	×	√	√	√
3	√	×	√	√	√
4	√	×	√	√	√

in Table 4. It was discovered that all flufenamate ILs are not soluble in water. Additionally, flufenamate ILs also soluble with low polarity solvents such as acetone, methanol and toluene.

CONCLUSION

Four ILs based on flufenamate were synthesized and prepared by coupling with ammonium, phosphonium and choline to demonstrated the APIs-ILs. These ILs undoubtedly represent a promising group of ILs. As these new IL are halogen-free, it is expected that such new compounds will prove useful in further studies centered on APIs-IL.

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