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Ionic Liquids Gelation with Polymeric Materials: The Ion Jelly Approach

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1. Introduction

The development of ionic liquids (ILs)-based materials is a promising field of research for the design of new advanced functional tailor made materials. In particular, ILs gelation induced by polymers originates quasi-solid materials commonly termed as ion gels which are very interesting, offering good mechanical strength and conductivity. (Torimoto et al., 2010) Indeed, ion gels hold both the processability and mechanical properties of polymers, but with added physico-chemical properties and although primarily developed as replacements for current solid-state polyelectrolytes (Delaney et al., 2010) several other applications are currently emerging as in biosensors and drug delivery applications.

2. From ILs towards new polymeric materials

Ionic liquids (ILs) are probably one of the most studied chemical compounds in the last decade. This is particularly motivated by ILs unique physical-chemical properties that enable their application in a broad range of scientific fields. ILs are comprised entirely by ions and most of them exhibit a negligible vapour pressure, ionic conductivity and a high thermal, chemical and electrochemical stability. (Fernicola et al., 2006; Galinski et al., 2006; Lu et al., 2002)

Nevertheless the tailor made design of ILs is probably the most fascinating and creative domain on ILs research. In fact the creative design of ILs has driven their application to completely different areas such as in physics or biology.

For the design, however is imperative to evaluate the fundamental physical-chemical properties before trying to evolve a given IL structure for a particular application. For instance, the type of molecular interaction between cation and anion is determinant for physical-chemical properties such as melting temperature, glass transition temperature or conductivity. (Yoshida et al., 2007) Thus, numerous works have published about the

understating of fundamental properties of ILs. Most of these studies have been directed towards the elucidation of the impact of both anion and cation on ILs physical-chemical properties.

When we think about IL applications two fields emerge immediately: solvents and electrolytes. In the first case ILs can be designed in order to become green solvents. A very large number of works have been done at this level, namely on the use of ILs on different extraction processes or as reaction media. The industrial application is however very limited. Until now the only example of an industrial process using ionic liquid is the BASIL™ (Biphasic Acid Scavenging utilizing Ionic Liquids) process. (BASF, 2007) This process is used for the production of alkoxyphenylphosphines. The original process for the production of alkoxyphenylphosphines, triethylamine is used to scavenge the acid produced during the reaction. Nevertheless this reaction produces a solid that leads to the formation of an insoluble paste and consequently affects all the downstream purification processes. The idea was to replace triethylamine by 1-methyl imidazole which leads to the formation of 1-methylimidazolium chloride which is an ionic liquid. The substitution of triethylamine by 1-methylimidazole leads to the formation of a new phase on the reaction mixture which makes the purification a more straightforward process when compare with conventional techniques.

The great ability to dissolve organic compounds have put ILs on the edge of the chemicals development for commercial applications. More recently the design of biocompatible IL has lead to the application of ILs as drug solvents for drug delivery systems. Some authors have showed that ILs could in fact dissolve and stabilized different therapeutic agents and also assist the controlled drug release. (Dobbs et al., 2009; Moniruzzaman et al., 2010; Park et al., 2010; Stoimenovski et al., 2010; Zhang et al., 2009)

A good example was brought by Moniruzzaman et al. which have used ionic liquid-in-oil (IL/o) microemulsions to enhance the topical and transdermal delivery of acyclovir (ACV). The microemulsion was composed by a blend of nonionic surfactants, namely polyoxyethylene sorbitan monooleate (Tween-80) and sorbitan laurate (Span-20), isopropyl myristate (IPM) as an oil phase, and IL $[C_1mim](CH_3O)_2PO_2$ (dimethylimidazolium dimethylphosphate) as a pseudophase. The solubility of ACV on the microemulsion system significatively increased in the presence of IL, which act as a drug reservoir during the process of delivery. Moreover the transdermal delivery was only achieved when the IL was present in the microemulsion mixture.

Following the same line different authors have been using the IL chemistry to develop ionic hydrid delivery systems. Note that in spite of the success of these two examples this area is still in its infancy and with the recent examples of ILs based on active pharmaceutical ingredients (API) a world of creative developments will emerge to address some of the pains and limitations of pharmaceutical industry.

As salts the most natural application of ILs is of course as electrolytes. In fact ILs are known for their high conductivity (10^{-4} to 10^{-2} S cm^{-1}), high electrochemical stability (4-5.7 V) and thermostability (up to 300 ^{o}C). This set of properties together with the fact that most of ILs are nonvolatile and nonflammable, has driven their application as electrolytes for different electrochemical devices, such as dye synthesized solar cells, double layer capacitors, fuel cells, electrochemical windows and of course lithium secondary batteries.(Byrne et al., 2005; Fernicola et al., 2006; Galinski et al., 2006; Lu et al., 2002; Stephan, 2006)

In fact the actual trend in electrochemical devices points to ILs as the most promising approach to develop safety and highly conductive electrolytes.

Nevertheless the large scale fabrication of the above electrochemical devices is following the printing trend due to large scale production impositions. To address this issue different authors have tried to develop solid/polymeric/composites based ion liquids.(He et al., 2007; Leys et al., 2008; Winther-Jensen et al., 2009; Tiyapiboonchaiya et al., 2003) In fact some of these systems have been very competitive in terms of ionic conductivity.
The development of solid/polymeric/composites based ion liquids have of course a special interest to electrochemical applications. However as mentioned before these materials could also play an important role to develop different bioapplications such as the drug delivery.

2.1 IL-based polymer gels: the ion jelly approach

In general, the methods to prepare IL-based polymer gels can be classified into three major types: gelation of ILs within polymers/biopolymers, in situ polymerization of vinyl monomers in ILs, and polymerization of ILs containing polymerizable groups (e.g vinyl groups).(He et al., 2007; Le Bideau et al., 2011; Tiyapiboonchaiya et al., 2003)
The introduction of polymerizable groups into the ionic liquid structure has been presented as a very interesting way to obtain good ionic conductivity without liquid components. These polymerized ionic liquids (PILs) have been developed for battery electrolyte and for other solid electrolyte applications.(Jiang et al., 2006; Ohno et al., 2004; Washiro et al., 2004; Winther-Jensen et al., 2009)
PIL have been investigated to be used on polymeric lithium batteries. In these batteries besides a good conductivity it is necessary that specific molecules like the lithium ion could be easily transport through the electrolyte. Combining these two factors on PILs is not a simple task since the variables, conductivity and ion transport, are related with several issues. One of the major factors that can affect simultaneously the lithium transport and conductivity is the type of cation used in PIL.
Ohno and co-workers have shown that the type of cation could enhance the lithium transport trough the PIL. (Ogihara et al., 2006) They found that cations with the piperidinium salt structure could be an advantage for lithium ion conduction.
The most simple and efficient approach is based on gelation which is a simple method that allow a good compromise between the retention of the IL and its fluidity inside the polymeric network. These so called ion gels are simpler than solid polymer electrolytes and exhibit improved conductivities. In fact ion gels hold both the processability and mechanical properties of polymers, but with added physico-chemical properties and were primary developed as replacements for current solid-state polyelectrolytes in energy devices, such as dye-sensitized solar cells, supercapacitors, lithium ion batteries, and fuel cells. (Fernicola et al., 2006; Galinski et al., 2006; Le Bideau et al., 2011; Lu et al., 2002; Mazille et al., 2005; Stephan, 2006)
For instance, He and co-workers have shown the potential of an ion gel formed by gelation of poly(styrene-block-ethylene oxideblock-styrene) (SOS) triblock copolymer in 1-butyl-3-methylimidazolium hexafluorophosphate.(He et al., 2006) This system has shown interesting conductivity values at room temperature (above 10^{-3} S/cm^{-1}).
Another good example was described by McFarlane and co-workers. In this case the authors develop a novel self-polymerised ionic liquid (IL) gel prepared at room temperature (RT), without light or heat or addition of initiator, using choline formate (CF), and 2-hydroxyethyl methacrylate (HEMA). (Winther-Jensen et al., 2009)
This field of research has been developed in order to create ILs based materials that can work as electrolytes in different electrochemical devices and be used either as printer substrates or printable “inks”.

Following this trend we recently reported Ion Jelly (IJ), a light flexible electrolyte that results from the combination of gelatin with an IL. This allows the production of gels that are extremely versatile conductive materials that can be molded into different shapes, using several techniques, and can be adapted to multiple surfaces. Moreover, on cooling, Ion Jelly can undergo a liquid-gel transition near room temperature (near 35ºC) which makes a promising solution to develop electrolyte "inks" for printed electrochemical devices.(Vidinha et al., 2008)

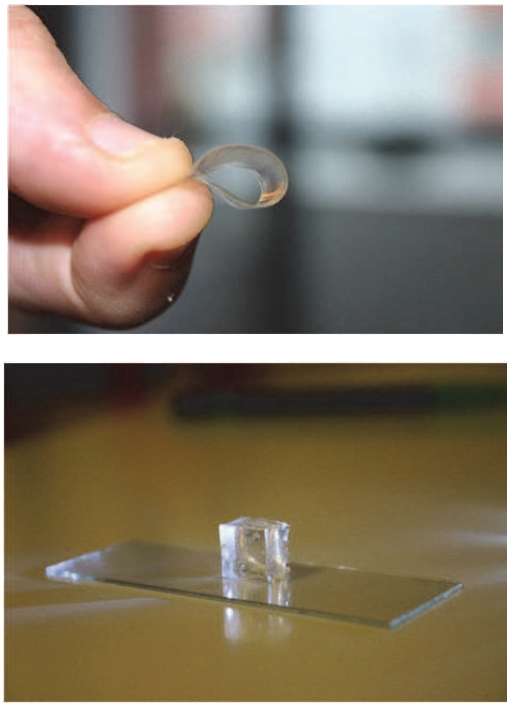

Fig. 1. Ion jelly materials.

One of the main advantages of Ion Jelly is using gelatin which is a widely available, inexpensive and well studied biopolymer. Gelatin is prepared through the thermal denaturation of collagen, after acid or alkaline pre-treatment. Basically gelatin is a heterogeneous mixture of left-handed proline helix polypeptides and amino acid strands, with a typical sequence of -Ala-Gly-Pro-Arg-Gly-Glu-4Hyp-Gly-Pro. Dissolution of gelatin in water occurs at 30–35 ºC, at which these polypeptide strands undergo a coil-helix transition.(Bigi et al., 2004) The presence of the hydroxyproline residue favors compactness of the quaternary structure due to the formation of hydrogen bonds between hydroxyl and carbonyl groups of the main chain helices. The physical properties of gelatin and collagen are influenced by this interaction.(Powel &Boyce, 2009)

Although inexpensive, biocompatible and biodegradable, the gelatin molecule only interacts strongly with molecules that are very soluble in aqueous media. The combination of gelatin with ionic liquids can tremendously increase the scope of the gelatin application, since ILs

can confer upon this polymer different physical-chemical properties and also change the gelatin microenvironment. The latter can in fact address one of gelatin's limitations which is related with the entrapment of poorly water soluble molecules.

The formation of an Ion Jelly should occur in much the same way as the formation of a water-based gelatin gel. Both gelatin and ILs have ionic character and this leads to strong interactions between the two species, and a high solubility of gelatin. During the renaturing or annealing process, the polypeptide strands will have a tendency to rearrange into the most thermodynamically favourable structure. X-ray diffraction experiments have shown important differences between the water-based gelatin and Ion Jelly films indicating a pronounced modification in the conformation of the gelatin left-hand helix. These results clearly show that Ion Jelly molecular structure is completely different from gelatin.

Due to the nature of ionic interaction between gelatin and ILs we also verify that hydrogen bonding played an important role on the mechanism of interaction between IL and gelatin. In fact Table 1 shows a selection of cation/anion combinations that provided the formation of either Ion Jelly or solid structures, 1-ethyl-3-methyl-imidazolium [emim], 1-butyl-3-methyl-imidazolium [bmim], 1-butyl-3-methyl-imidazolium [bdmim], 1-decyl-3-methyl-imidazolium [C_{10}mim] and tri-n-octyl-methylammonium (Aliquat336®).

Cation	Anion	Il:gelatin ratio (w/w)	Water-miscible	Type of material formed
		1:1	YES	Solid Transparent films
[bmim]	[N (CN)$_2$]	3:1	YES	Solid Transparent films
		6:1	YES	Liquid gel
[omim]	[N (CN)$_2$]	1:1	YES	Solid Transparent films
		1:3	YES	Solid Transparent films
Aliquat 336®	[N (CN)$_2$]	1:1	NO	No Ion Jelly formation
[Him]	[Cl]	1:1	YES	Solid Transparent films
[Him]	[Cl]	1:3	YES	Solid Transparent films
[Hmim]	[Cl]	1:1	YES	Solid Transparent films
		1:3	YES	Solid Transparent films
[bmim]	[Cl]	1:1	YES	Solid Transparent films
		1:3	YES	Solid Transparent films
[omim]	[Cl]	1:1	YES	Solid Transparent films.
		1:3	YES	Solid Transparent films.
[C_{10}mim]	[Cl]	1:1	YES	Solid Transparent films
[bdim]	[Cl]	1:1	YES	Solid Transparent films
		1:3	YES	Solid Transparent films
Aliquat 336®	[Cl]	1:1	NO	No Ion Jelly formation
[bmim]	[saccharin]	1:1	YES	Solid Transparent films
		1:3	YES	Solid Transparent films
Aliquat 336®	[saccharin]	1:1	NO	No Ion Jelly formation
[bmim]	[PF_6]	1:1	NO	No Ion Jelly formation

Table 1. Selected cation and anion combinations that led to the formation of an Ion Jelly.

The hydrophilicity of the IL correlates broadly with its ability to form Ion Jelly structures. This is well illustrated by the results obtained with the [bmim] series. The result for [bmim] BF_4, which is water-miscible but still does not form an Ion Jelly structure, may be due to the weak coordination ability of the BF_4 ion. More recently we have shown that 1-(2-hydroxyethyl)-3-methyl-imidazolium tetrafluoroborate ([C_2OHmim]BF_4) is able to form Ion Jelly materials. In fact Holbrey and co-workers found that the physico-chemical properties of ILs containing a hydroxyl group in the alkyl side-chain were substantially different from common N,N-dialkyimidazolium ILs. The presence of a hydroxyl group in the alkyl chain increases the polarity of the latter, leading to a stronger hydrogen bonding ability with surrounding groups. This reinforces the above idea that stronger hydrogen bonding between the ILs and gelatin is an essential requisite for forming Ion Jelly materials.
Moreover we also verify that the IL/gelatin ratio is an important feature to obtain IJ materials. For instance when using the ratio (6:1) we were unable to obtain IJ materials this may be related with the limited availability of sites on the gelatin molecules for hydrogen bonding with the IL, higher proportions of the latter decreasing the internal cohesion of the material formed.
With this we have tried to develop different applications for Ion Jelly. Our approach aims for scoping the advantages of gelatin and IL combination. Those applications were explored in three different fields: electrolytes, drug delivery and biosensing.

2.1.1 Electrolytes

Our primary approach was to develop Ion Jelly electrolyte materials. To this respect our first step was to evaluate the conductivity of Ion Jelly materials obtained with different ionic liquids in order to evaluate the impact of gelatin on the IL conductivity, Figure 2.
As we expected the conductivity of the Ion Jelly materials was affected by the type of IL used, since the type of interaction between IL and gelatin will be different in each case. Thus, in order to elucidate about the impact of gelatin on IL conductive properties we proceed to the physical chemical characterization of Ion Jelly materials. To accomplish this goal we have performed a dielectric relaxation spectroscopy characterization (DRS).
Basically, DRS spectra reproduce the set of molecular motions of all dipolar species present in the media. In ionic liquids these motions are highly correlated with the multiplicity of interaction between the different charged species present in the media, which makes it impossible to address a specific motion to a well defined dipole. In fact on ILs the molecular motions reflect the kinetics of the network rearrangement. (Aliaga et al., 2007; MacFarlane et al., 2001)
On the other hand, the Ion Jelly network is settled by the interaction between two polyelectrolyte molecules (gelatin and IL) creating a complex network with multiple interaction sites that can lead to a great variety of dipolar aggregates. Thus a comprehensive and detailed analysis of IL relaxation behavior inside gelatin matrix can result in important data about the crucial mechanisms implicated on the Ion Jelly conductivity. To conduct this study we have chosen the Ion Jelly materials based on 1-butyl-3-methyl imidazolium dicyanamide ([bmim]DCA). The dicyanamide (DCA) compounds are liquid at room temperature and characterized by their low viscosity, water miscibility, high thermo (over 100ºC) and electrochemical stability (over 3.5 V). (Aliaga et al., 2007; MacFarlane et al., 2001)
Moreover, the dicyanamide ion is an anionic bridge ligand that has Lewis base attributes, which makes it particularly attractive to synthesize ionic liquids with very specific

properties. Compared to common anions such PF_6 or BF_4, DCA has a permanent dipole and thus facilitates the research of IL dynamics through dielectric spectroscopy.(Sangoro et al., 2008)

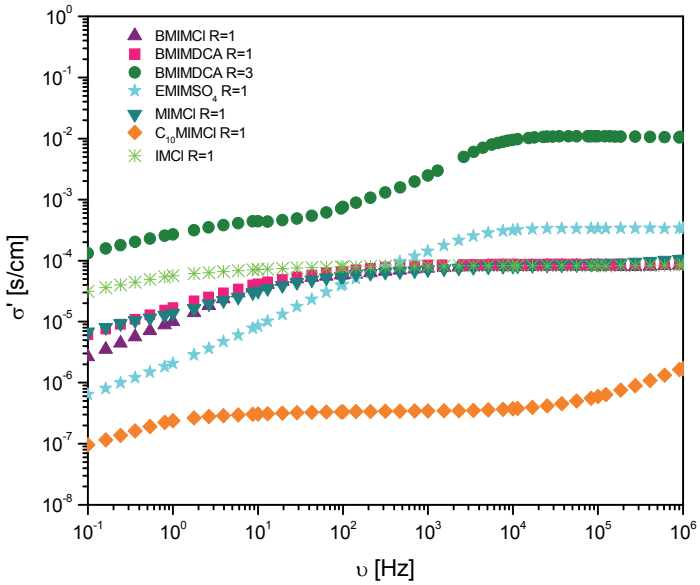

Fig. 2. Frequency dependent ionic conductivity was measured at 25º. C. R= IL/gelatin (w/w).

Our aim in this study was to evaluate the impact of gelatin on IL diffusion. For that purpose we have used a correlation to separate the mobility, μ, and the effective number density of charge carriers, n, from conductivity (σ_0) obtained from the dielectric measurements, allowing also to estimate the diffusion coefficient of migrating charges, D, which is done by considering the following Einstein-Smoluchowski equation:

$$\sigma_0 = nq\mu = \frac{nq^2}{k_B T} D \tag{1}$$

In figure 3 the obtained D and μ values are displayed for the ionic liquid and Ion Jelly; the inset shows the plot of the number density of charge carriers as a function of the reciprocal temperature.

Surprisingly, the diffusion coefficients and mobility of charge carriers in IJ3 are close to those in the pure [bmim]DCA. This means that the solid-like material retains a similar ability for charge transport as the ionic liquid. The same is not true in IJ1 due to the low ratio [bmim]DCA /gelatin. The difference in the temperature range where these quantities are able to be estimated is determined by the glass transition temperature that, which is nearly the same for IJ3 (174,3 K) and [bmim]DCA (174,6 K) and ~30K higher for IJ1 (204,1 K) .

Moreover we have obtained similar N values for all the three situations. Since N is the effective number density of charge carriers, this means that even in the Ion Jelly materials

the number of charge carriers per volume is comparable to the one existing in the pure ionic liquid. This result clearly shows that the differences obtained in the transport properties do not arise from different magnitudes of N. These results were in fact quite promising since were able to obtain identical conductive properties between the pure IL and the Ion Jelly. In fact the diffusion and mobility of ionic species are identical on Ion Jelly and [bmim]DCA, meaning that the ionic conductivity is not significantly affected by the presence of gelatin. Thus Ion Jelly appears as a very promising solution to design different electrochemical devices.

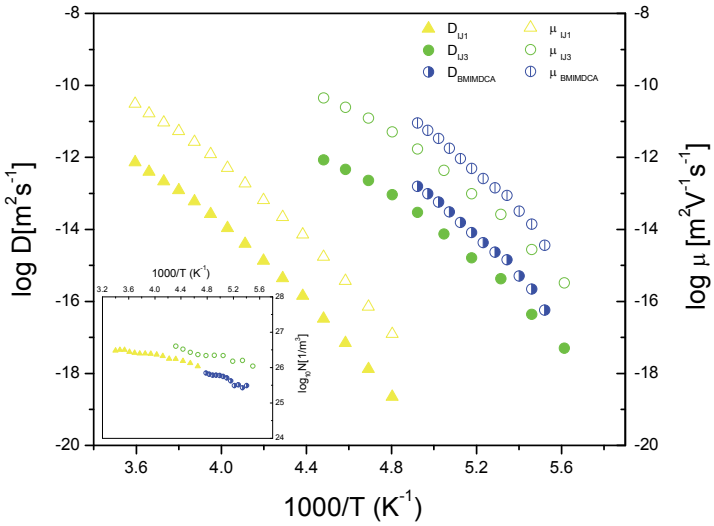

Fig. 3. Thermal activation plot for diffusion coefficients, D, and mobilities, μ,. (a) diffusion coeffiecents. (b) mobility. The inset shows the temperature dependence of N, the effective number of charge carriers. IJ1 – Ion Jelly with a IL/gelatin ratio (w/w) = 1 ; IJ3 – Ion Jelly with a IL/gelatin ratio (w/w) = 3.

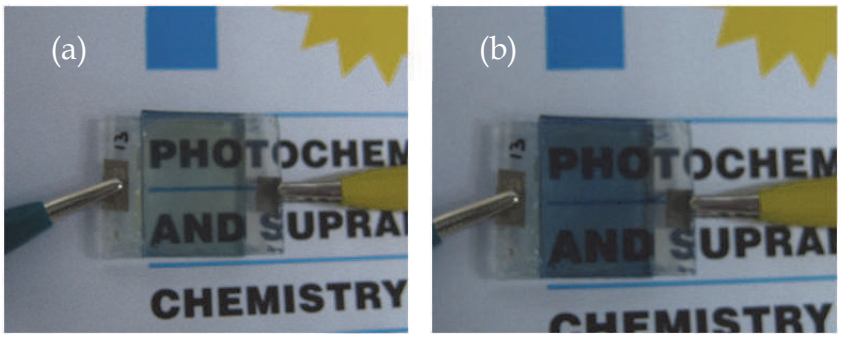

Fig. 4. Ion Jelly electrochromic window. Glass-ITO/PEDOT/Ion Jelly/PB/ITO-Glass. (a)– Colored state; (b) – Bleached state.

In order to test this possibility, we built an electrochromic window based on Prussian blue (PB) and poly(3-4-ethylenedioxy thiophene (PEDOT) as electrochromic layers and we coated one of the electrode surface with a thin film of Ion Jelly based on [bmim]DCA (figure 4). This electrochromic window built performed reasonably well in what concerns contrast and stability (figure 5). Nevertheless further optimization of this concept should be performed in order to improve the switching velocity. (Vidinha et al., 2008)

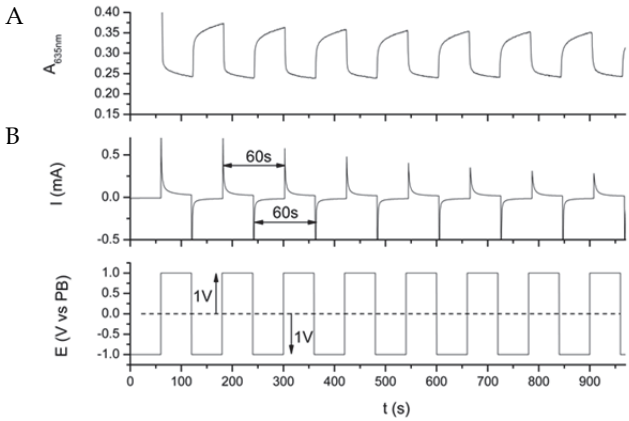

Fig. 5. In situ spectroelectrochemical cycling data for Glass-ITO/PEDOT/Ion Jelly/PB/ITO-Glass. A - Chronoabsorptometry recorded at 700nm; B - Square-wave switching between -1V (step duration 60 s) and +1, V (step duration 60 s) (vs. PB);

2.1.2 Biosensing

Another area that we have pursuing is biosensing. In this particular we are trying to develop biosensors based on the immobilization of different oxidoreductases in Ion Jelly matrices. This concept is based on the fact that enzyme exhibit an enhanced stability and activity in ILs.(Moniruzzaman et al., 2010) Thus, the possibility to tailor-make sensitive and specific enzyme-IL-polymeric materials is perceived as a great advantage, and is motivating extensive research.

Oxidoreductases, namely glucose oxidase (GOD) and horseradish peroxidase (HRP) have been used as model enzymes on the development of new enzyme-IL-polymeric materials. Most of the examples concern the use of these systems take advantage of the intrinsic IL electrochemical properties allowing a direct electron transfer. For example, the potential applications of several sol-gel–[bmim]BF_4 composite systems and the direct electrochemistry of HRP immobilized in such composites have been reported. (Liu et al., 2005) Another good example is the entrapment of GOD in nanogold-N,N-dimethylformamide-IL composite films on a glassy carbon electrode. The authors showed that ILs can affect the electron transfer through interactions with GOD. The influence of the IL on the thermal stability and catalytic activity of GOD entrapped in the composite was also demonstrated. (Li et al., 2007) HRP was also immobilized on a composite material based on the IL N-butylpyridinium hexafluorophosphate, as well as sodium alginate and graphite. The material allowed the determination of H_2O_2 with a detection limit of 0.5 μM.(Ding et al., 2008)

We have recently purpose the application of enzyme-IL-polymeric materials on biosensing, namely, colorimetric detection of glucose based on Ion Jelly materials. (Lourenço et al., 2011) Taking advantage of the preparation method of the Ion Jelly, which is a liquid material at temperatures above 35ºC, it was possible to prepare glucose paper test strips by physical deposition of gelatin-[emim]$EtSO_4$ containing GOD and HRP as well as color-generating precursors – in this case, phenol-4-sulfonic acid (PSA) and 4-aminoantipyrine (4-AAP) as reducing substrates:

$$\text{Glucose} + O_2 \xrightarrow{GOD} \text{Gluconic acid} + H_2O_2$$

$$2\,H_2O_2 + \text{PSA} + \text{4-AAP} \xrightarrow{HRP} \text{quinoneimine dye} + 3\,H_2O + NaHSO_4$$

The GOD entrapment on the gelatin-[emim]EtSO4 polymeric material showed a activity decrease of about 16 times comparing with the free enzyme, however with excellent storage stability at 4ºC for a period of two weeks, where it retains 70% of initial activity. Concerning HRP, this loses around 13 times activity but again with excellent storage stability, where it is retain 91% of initial activity. While free HRP loses activity rapidly above substrate concentrations of about 0,15 mM, the gelatin-[emim]$EtSO_4$ materials can protect the enzyme from immediate deactivation, making it possible to use much higher H_2O_2-concentration (110 mM), 1 thousand times higher concentration of H_2O_2 in relation to free enzyme.
The co-immobilization of phenol-4-sulfonic acid and 4-aminoantipyrine, as color-generating precursors, together with both enzymes (GOD, HRP) in gelatin-[emim]$EtSO_4$ demonstrate a positive effect on the enzymatic activity of both enzymes. (Figure 6)
Taking advantage of the observed positive effects on GOD-HRP activity and stability, a possible application of this enzyme-IL-polymeric materials was demonstrated on the colorimetric determination of glucose. In Figure 7 it is demonstrated the detection of glucose solutions at different concentrations 0.1- 15 g/L with a paper test strip that was prepared with the drop casting deposition of 110 µl of gelatin-[emim]$EtSO_4$ with the dye-components 4-AAP and PSA co-immobilized. The result of the glucose determination can be obtained in less than one minute.
The morphological and functional stability of these paper test strips was evaluated in a physiologic solution at 37 ºC. These experiments reveal good stability for a period of one hour. For a longer period of time it is observed the dissolution of the gelatin-[emim]$EtSO_4$ functional polymers. The simplicity of paper test strip preparation allied to the straightforward detection can open new opportunities for new biosensing platforms or other deposition types, such as screen printing or even ink-jet printing.

2.1.3 Drug delivery and biomedical applications

Recent research has shown that IL-based polymer gel materials can be used as drug delivery systems which is envisaged as a very promising field of application. The search for new drug delivery systems is of major importance in drug development, and research studies in this area have grown enormously. (Gil et al., 2002) In order to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability, various drug delivery systems are currently under development (Kita & Dittrich 2011). Furthermore, as new therapeutic agents emerge, for example from studies in biotechnology, such as proteins and genes, there is an increasing need for the development of new technologies and new materials with improved properties (Ghandehari, 2008). Indeed, polymers are used in a wide range of medical applications which they were not specifically designed for, often

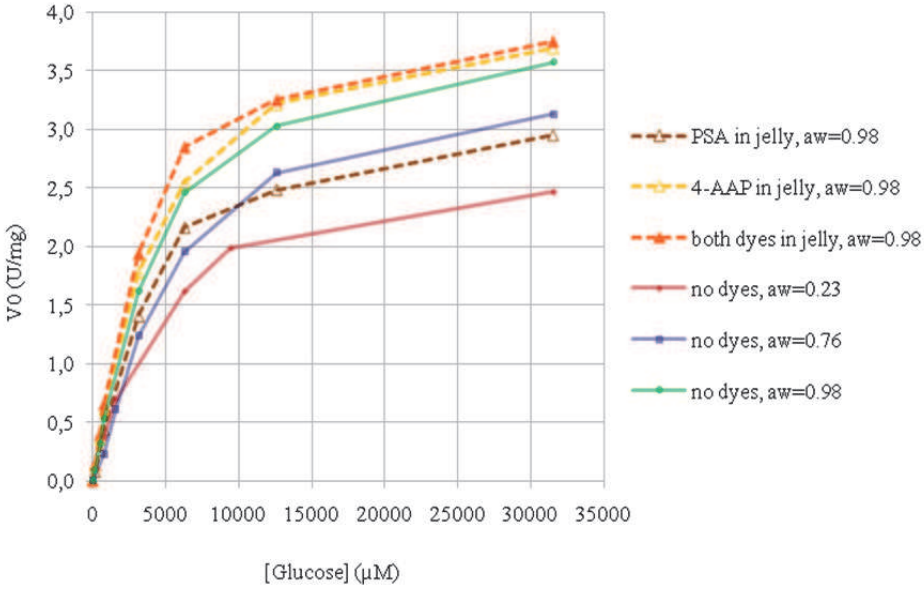

Fig. 6. Effect of the incorporation of the phenol-4-sulfonic acid and 4-aminoantipyrine, as color-generating precursors and water activity on the initial activity of GOD in gelatin-[emim]$EtSO_4$ functional polymers.

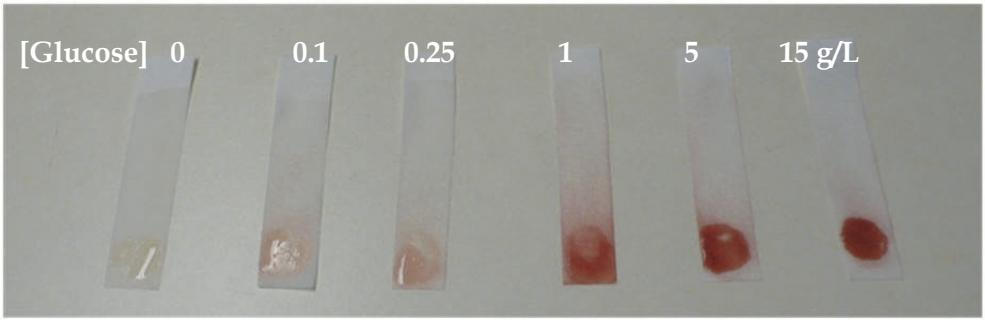

Fig. 7. GOD-HRP Paper Test Strip for glucose determination, from left to right: Control (50 µL MilliQ water) detection of 50µL of glucose solutions with different concentrations (0.1-15g/L).

presenting several problems such as "unsatisfactory entrapment efficiency"; poor stability; unacceptable delivery primarily to the liver and spleen; poor plasma pharmacokinetics and rapid dissociation of active agent. (Frokjaer & Otzen, 2005) What IL-based polymer gels offer is the opportunity of hybridized polymers properties with those of ILs, which can be further tuned by the appropriate choice of the anion-cation pair opening therefore millions of possibilities. These new hybrid materials are expected to present properties derived from both components, greatly increasing polymers performances and applicability.

In fact IL-based polymer gels hold several properties that make them adequate for drug delivery and other biomedical applications, for example due to IL tunable physico-chemical properties these materials can be tailored to respond to a number of stimuli e.g temperature, pH, electrical field. They can be design with different swelling capabilities, to be more or less stable and to have a controlled degradation rate. IL-based polymer gels may exhibit different bioadhesion degrees to facilitate drug targeting, especially through mucus membranes, delivering API for local or systemic effect and in this manner enhance bioavailability by avoiding or minimizing effects such as enzymatic or hepatic degradation. (Andrews et al., 2009) In addition, ion gels enjoy good mechanical strength and electrical conductivity which can be explored for more specialized applications as electrically stimulated controlled release devices (e.g iontophoresis) or artificial muscles as well as for cardiac and/or neuronal tissue engineering applications. (Guiseppi-Elie, 2010; Ravichandran et al., 2010) Finally, the versatility of sol-gel in shaping allows easy adaptations to a wide range of drug delivery applications. (Le Bideau et al., 2011)

Functionalization of IL-based polymer gels can be achieved using essentially two different strategies, by the incorporation of the active principle in the solid matrix or exploring the IL as the active principle ingredient, in which a specific biological activity is introduced through one or both of the ions. (Le Bideau et al., 2011) This latter strategy was recently reported by Vioux and co-workers in order to encapsulate ibuprofen in porous functionalized silica. (Viau et al., 2010) The authors synthesized a new ionic liquid based on ibuprofenate drug and imidazolium type cation and have further tested the ability of IL-silica gels to act as new drug delivery systems. The release kinetics were found to be slower with the gels than for both crystalline ibuprofen and pure ibuprofenate ionic liquid. The authors also reported that the release was governed by the inner and the outer surface of the IL-silica gel, as well as the chemical nature of the surface. They concluded that IL-silica gels act as drug reservoirs for controlled delivery and added that these gels are easily shaped and do not need any further processing to achieve a final pharmaceutical form.

For drug delivery purposes, the biocompatibility of the material and thus IL toxicity is a crucial issue to be addressed. Indeed the toxicity of ILs has been one of the most debated topics in the field, and several different approaches have been used in order to decrease the level of toxicology. A very interesting ion that can be used for this purpose is a quaternary ammonium ion, namely choline (Nockemann et al., 2007). Recently ILs composed solely of biomaterials were developed. In particular the combination of a choline cation with propionate, tiglate, hydrogen succinate and hydrogen maleate, yielded room temperature ionic liquids with strong hydrogen bonding characteristics (Fukaya et al., 2007). Another strategy was reported, based on the chemical modification of the alkyl side chain of ions that present a certain level of toxicity (Gathergood et al., 2004). Duarte and co-workers has performed toxicity measurements with different ionic liquids. Results showed that the presence of a carboxylic group at the end of the alkyl chain greatly decreases toxicity, and that by further changing the carboxylic group to an ester, an increase in the toxicity was observed. (Frade et al., 2007) This inherent tuneability was recently highlighted as a key feature that is entirely appropriate and applicable to the field of pharmaceuticals (Hough et al., 2007).

In this context, one good example of a biocompatible IL-based polymer gel was given by Sehgal and co-workers. (Vijayaraghavan et al., 2010) The authors have used choline salts, some of which can be described as ionic liquids, as crosslinking agents for collagen in order

to replace commonly used glutaraldehyde, which is poorly biocompatible. In the reported work, the authors have hibridized collagen properties with those of ILs by actually synthesizing IL-collagen gels in order to improve collagen mechanical properties and above all to decrease collagen degradation rate, which is the main factor limiting it application for long-term biomedical implants. The materials prepared were found to be biocompatible and stable in water after 6 months of continuous immersion.

Along the same line, Ion Jelly is expected to improve gelatine properties and significantly increase it range of applications. An on-going research project supported by Fundação para a Ciência e Tecnologia, Portugal, is exploring the interesting features that result from the combination of the chemical versatility of an IL with the morphological flexibility, biocompatibility and bioavailabitity of gelatin, regarding an application in drug delivery systems. Gelatin is a very popular drug delivery vehicle, mainly because of its excellent biocompatibility and degradability to non-toxic products. The main limitations of gelatin are its extensive swelling, rapid dissolution and drug release. (Young et al., 2005) In this way, ILs can be used to replace chemical crosslinking in order to form relatively non-soluble networks and significantly expand gelatine applications. Furthermore also the possibility of introducing a determined biological activity in the immobilized IL phase will allow for the development of an entirely new concept of gelatine-based drug delivery systems

3. Conclusion

Ionic liquids are making in-roads in the development of new tailor-made and highly functional polymer-based materials. The hybridization between ILs and polymers allows taking advantage of ILs unique properties in the solid state, circumventing therefore some drawbacks related with liquids processability and opening for new ILs applications. On the other hand, as it was shown for the case of gelatine, widely known and already in use polymers can also see their applications greatly extended, as well as increase their performances by mixing with the right cation-anion pair. The multitude of possibilities, besides allowing for unlimited opportunities, may actually turn the choice of the best material to mix with the right IL a difficult task for researchers in the field. Close collaboration between engineers and chemists in this area will certainly open for new advancements and new materials with superior performances.

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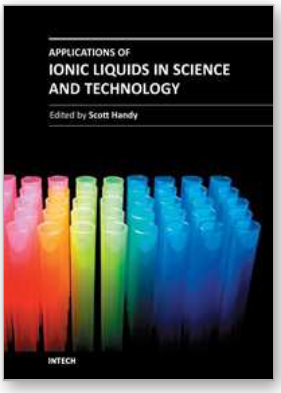

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This volume, of a two volume set on ionic liquids, focuses on the applications of ionic liquids in a growing range of areas. Throughout the 1990s, it seemed that most of the attention in the area of ionic liquids applications was directed toward their use as solvents for organic and transition-metal-catalyzed reactions. Certainly, this interest continues on to the present date, but the most innovative uses of ionic liquids span a much more diverse field than just synthesis. Some of the main topics of coverage include the application of RTILs in various electronic applications (batteries, capacitors, and light-emitting materials), polymers (synthesis and functionalization), nanomaterials (synthesis and stabilization), and separations. More unusual applications can be noted in the fields of biomass utilization, spectroscopy, optics, lubricants, fuels, and refrigerants. It is hoped that the diversity of this volume will serve as an inspiration for even further advances in the use of RTILs.

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