SUSTAINABLE DEVELOPMENT OF BIOMATERIALS USING IONIC LIQUIDS

Cariny Polesca¹, Helena Passos¹, João A. P. Coutinho¹, Mara G. Freire¹*

¹ CICECO - Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
Corresponding author: maragfreire@ua.pt

Abstract

This review summarizes and critically addresses the advances achieved on the processing of biomaterials, namely films, scaffolds, and nanoparticles, using ionic liquids as alternative solvents. Biomaterials composed of proteins, polysaccharides, and their blends are here considered. Despite their relevance, the low solubility of these compounds in most solvents represents a major limitation on biomaterials processing. The use of ionic liquids as solvents allows to overcome this limitation towards the development of simpler, more efficient and sustainable processes for the processing of biomaterials with enhanced properties. Nevertheless, the used ionic liquids also have some disadvantages that need to be overcome when foreseeing the development of sustainable biomaterials processing, being discussed herein.

Keywords: ionic liquids, polysaccharides, proteins, biomaterials, sustainability.

Abbreviations

[C₁₂C₁im][C₁CO₂] 1-ethyl-3-methylimidazolium acetate
[C₁₂C₁im]Cl 1-ethyl-3-methylimidazolium chloride
[C₄C₁im][C₁CO₂] 1-butyl-3-methylimidazolium acetate
[C₄C₁im]Cl 1-butyl-3-methylimidazolium chloride
[C₄C₁im][HSO₄] 1-butyl-3-methylimidazolium hydrogensulfate
[N₁₁₁(2OH)][C₁CO₂] cholinium acetate
[TMG][C₁CO₂] 1,1,3,3-tetramethylguanidinium acetate
[TMG][C₂CO₂] 1,1,3,3-tetramethylguanidinium propionate
[TMG][HCO₂] 1,1,3,3-tetramethylguanidinium formate
DMSO dimethyl sulfoxide
SAIB sucrose acetate isobutyrate
PCL-nHAP-CNW polycaprolactone/nano-hydroxyapatite/chitin-nano-whisker
FTIR Fourier-Transform Infrared Spectroscopy
1. Introduction

Biomaterials are usually produced by the dissolution of natural polymers, such as polysaccharides, proteins or their blends in an appropriate solvent. In the past years, there has been an increasing interest in the development of biomaterials derived from renewable sources (e.g. silk, collagen, cellulose, and chitosan [1,2]) due to their low cost and biocompatibility [3,4]. These natural polymers have been used, pure or in blends, to prepare different types of biomaterials, including films [1,2,5–8], scaffolds [9–16], nanoparticles [17–21], among others [22]. Their main applications comprise wound dressing, drug delivery, pharmaceutical coating, and bone and tissue engineering [22,23].

The transformation of natural resources from their native form to a more usable form with adequate properties and purity creates however several challenges. The low solubility of some polysaccharides and fibrous proteins in water or organic solvents, resulting from strong intramolecular hydrogen bonding and hydrophobic interactions [13,24,25], is one of the biggest limitations found on biomaterials processing. To overcome this drawback, ionic liquids (ILs) have been proposed as alternative solvents to solubilize different types of biopolymers, such as cellulose, silk, collagen, chitosan, and chitin. ILs are composed of organic cations and organic or inorganic anions, having a low lattice energy and thus a low melting temperature, with the ability to establish a wide diversity of interactions not possible to occur in inorganic salts [26]. In addition to their low vapor pressure, these compounds are classified as designer solvents due to the possibility to tune their properties by the correct choice of different cation-anion combinations [27]. Their unique properties and advantages relevant to the dissolution of biopolymers and biomaterials processing, as well as their limitations, are summarized in Table 1. However, it should be remarked that these properties are not general to all ILs and that ILs can be fine-tuned by changes in their chemical structure.

Table 1. Advantages and limitations of (some/most) ionic liquids in biomaterials processing.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designer solvents and tunable properties</td>
<td>Complex synthesis</td>
</tr>
<tr>
<td>Low volatility and low vapor pressure</td>
<td>High cost for large applications</td>
</tr>
<tr>
<td>Possibility of reuse</td>
<td>Challenging recovery</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>High chemical and thermal stability</td>
<td>High viscosity</td>
</tr>
<tr>
<td>High dissolution capability</td>
<td>Non-negligible toxicity</td>
</tr>
<tr>
<td>Simplification of biomaterials processing</td>
<td></td>
</tr>
</tbody>
</table>

In addition to their high capability to dissolve biopolymers, the use of ILs as solvents also allows the simplification of biomaterials processing. After the dissolution step, ILs enable the biomaterials regeneration by the simple addition of a coagulant agent, such as water – the greenest solvent, eliminating the need of dialysis or other steps required by conventional processing [11]. However, if not properly chosen, ILs also have some limitations that restrict their application in this field and at an industrial scale, including potential environmental concerns (which may be assessed by life cycle assessment analysis), high cost and high viscosity [28]. Despite their non-volatile nature and non-harmful effects to the atmosphere, the overall environmental impact of ILs has been questioned in the past years since most of them are water-soluble and can enter into aquatic systems [29]. This drawback emphasizes the need of the ILs removal from biomaterials followed by a proper recovery step. Although already attempted, the difficulty of complete removing ILs from biomaterials, as reported by Ribeiro et al. [8], highlights the need to improve the ILs removal process, which should be followed by their recovery and reuse towards the development of sustainable processes. At the same time, the high viscosity of most ILs difficult the solvent handling and dissolution capability, being required high temperatures in most of the reported studies [8,18]. Of particular interest are examples that overcome this issue using aqueous solutions of ILs instead of pure ILs, while decreasing the operating temperatures [17,20].

The most relevant results reported between 2020 and 2021 on the application of ILs as solvents on biomaterials processing are here described and critically reviewed. The following sections highlight how ILs influence the processing and properties of films, scaffolds, and nanoparticles.

2. Processing of biomaterials using ILs

The ILs nature has a pivotal role in biopolymers dissolution, with a major effect exerted by the IL anion [8–10]. Mostly, chloride- and acetate-based ILs have been successfully used to dissolve different biopolymers, including cellulose and silk, due to their strong hydrogen bonding accepting capability [2,6,7,17,18]. In addition to their dissolution capacity, ILs also have an influence on biomaterials properties. Usually,
[C$_2$C$_1$im][C$_1$CO$_2$] leads to higher crystallinity in the structure of silk-cellulose biomaterials compared with other ILs [6], while [C$_3$C$_1$im]Cl increases the surface area and decreases the average rupture strain of polycaprolactone scaffolds [14].

The processing of biomaterials (Figure 1) as films, scaffolds and nanoparticles using ILs as solvents is typically carried out in three steps: (i) biopolymer(s) dissolution in IL (pure or in solution) at temperatures up to 100 °C, followed by homogenization when blends are used; (ii) addition of a coagulant agent (e.g. water, methanol, ethanol or their mixtures), allowing the regeneration of the biomaterial and consequent separation from the IL solution; and (iii) biomaterial drying [7,9,19].

Figure 1. Schematic overview of the processing of biomaterials using ILs as solvents.

Table 2 summarizes the content of 18 articles published in 2020 and 2021 concerning the use of ILs on biomaterials processing, highlighting the type of biopolymer, solvent (IL, pure or in solution) and coagulant agent used, as well as the most relevant findings.
Table 2. Main conditions and findings in the preparation of films, scaffolds and nanoparticles using ILs.

<table>
<thead>
<tr>
<th>Starting biopolymer</th>
<th>Biomaterial</th>
<th>Solvent</th>
<th>Coagulant</th>
<th>Relevant results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silk-cellulose</td>
<td>Film</td>
<td>[C$_2$C$_1$im][C$_2$CO$_2$]</td>
<td>Methanol</td>
<td>The IL presents good ability to dissolve both silk and cellulose, allowing the processing of blended films with benefits derived from each material; Films flexibility increases with the amount of cellulose used in the initial blend.</td>
<td>[1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>water:water:H$_2$O$_2$</td>
<td>Ethanol</td>
<td>The cellulose crystallinity can be influenced by the IL and the type of coagulant; Films developed by using H$_2$O$_2$ solutions as coagulant agent present high thermal stability. The use of lower percentages of silk in the initial blend confers a higher semicrystallinity to the produced films.</td>
<td>[6]</td>
</tr>
<tr>
<td>Silk-SAIB</td>
<td>Scaffolds</td>
<td>[C$_2$C$_1$im][C$_2$CO$_2$]</td>
<td>water:water:isopropanol</td>
<td>The structures obtained with the Cl-based IL present low stability due to the IL inferior dissolution power; Water:isopropanol was identified as the best coagulant agent; Silk-SAIB scaffolds showed a slightly higher water uptake compared to those composed of silk only.</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[C$_2$C$_1$im][C$_2$CO$_2$]</td>
<td>water:methanol</td>
<td>The blend was dissolved efficiently in [C$_2$C$_1$im][C$_2$CO$_2$]; Samples treated with methanol produced structures with good mechanical stability compared to those produced with ethanol.</td>
<td>[13]</td>
</tr>
<tr>
<td>Silk-chitin</td>
<td>Scaffolds</td>
<td>[C$_2$C$_1$im][C$_2$CO$_2$]</td>
<td>water:methanol</td>
<td>Water was used as a co-solvent to reduce the viscosity of the IL solution; NPs showed 7% decrease of β-sheet content compared to silk, probably due to an incomplete regeneration. NPs loaded with naringenin were evaluated as drug delivery systems; The initial release of NPs was around 82 - 86% of the total drug released in the first 2h. NPs loaded with curcumin were evaluated as drug delivery systems; The release occurred within the initial 5 h, reaching a maximum value of 35 % of the drug-loaded.</td>
<td>[17] [20] [21]</td>
</tr>
<tr>
<td>Silk</td>
<td>Nanoparticles</td>
<td>[C$_2$C$_1$im][C$_2$CO$_2$] (aqueous solutions)</td>
<td>methanol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Silk NPs showed a comparatively lower diameter than curcumin-silk NPs.

<table>
<thead>
<tr>
<th>Cellulose blended with silk, collagen, chitosan, gelatin, starch, lignin, agar, β-cyclodextrin, dextran, arabic gum, κ-carrageenan, gum xanthan gum, xylan agarose, tragacanth</th>
<th>Film</th>
<th>[C₂C₃im][C₄CO₂]</th>
<th>Ethanol</th>
<th>Starting materials show different solubility in [C₂C₃im][C₄CO₂]; The structure of the films (fibrous or smooth and dense) varies according to the blend used.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose (+citric acid)</td>
<td>Film</td>
<td>[C₂C₃im]Cl</td>
<td>Water</td>
<td>Materials were successfully dissolved in [C₂C₃im]Cl; The addition of citric acid (up to 10 wt%) decreases the film ability to uptake water, inducing the formation of more hydrophobic and strongest materials.</td>
</tr>
<tr>
<td></td>
<td>Film</td>
<td>[TMG][C₄CO₂]</td>
<td>Water</td>
<td>[TMG][HCO₂] was not able to dissolve cellulose; Films produced with [TMG][C₄CO₂] present a lower crystallinity; Films consistency largely depends on the washing regeneration process, namely on the amount of water and washing time.</td>
</tr>
<tr>
<td></td>
<td>Scaffolds</td>
<td>[C₂C₃im]Cl</td>
<td>Water</td>
<td>The addition of NaCl into the cellulose-IL solution resulted in porous scaffolds with larger pore sizes.</td>
</tr>
<tr>
<td>Cellulose</td>
<td>Nanoparticles</td>
<td>[C₂C₃im][C₄CO₂]</td>
<td>water</td>
<td>[C₂C₃im][C₄CO₂] is a non-derivatizing solvent for cellulose, as the chemical structure of cellulose remains unchanged after hydrolysis; IL was recovered with a yield of 86%; NPs were cylindrical-shaped fibrils with a smooth surface and refined fibrillar structure.</td>
</tr>
<tr>
<td></td>
<td>Nanoparticles</td>
<td>[C₂C₃im][HSO₄]</td>
<td>water</td>
<td>The use of high amounts of cellulose (&gt; 25 wt %) resulted in IL low solubilization efficiency, inducing the formation of large NPs with low uniformity when compared to those obtained with lower cellulose concentration (5 - 20 wt %); IL was recovered with a yield of 90%.</td>
</tr>
<tr>
<td>Polycaprolactone</td>
<td>Scaffolds</td>
<td>[C₂C₃im]Cl</td>
<td>Ethanol</td>
<td>IL induced the formation of thinner fibers than conventional solvents; The use of IL significantly decreased the mean tensile strength of samples; IL stays chemically attached to the scaffold (according to FTIR results).</td>
</tr>
<tr>
<td>PCL-nHAP-CNW</td>
<td>Scaffolds</td>
<td>[C₂C₃im]Cl</td>
<td>not mentioned</td>
<td>The increase of nHAP content improved the mechanical properties of the scaffolds;</td>
</tr>
</tbody>
</table>
CNW content improved both cell attachment and proliferation properties of the scaffold and increased the biodegradation rate.
2.1 Films

As summarized in Table 2, the processing of films has been mainly carried out using silk and cellulose blends. Silk and cellulose are biocompatible materials; biomaterials derived from these compounds present improved properties induced by the strong interactions that typically occur in polysaccharides and proteins [7]. Furthermore, different blends and material ratios allow the development of tunable biomaterials through the optimization of their properties according to a required application, avoiding the need of chemical modifications of the final material [1,2,5–7]. These biomaterials properties also depend on the solvent, coagulant agent and other experimental conditions applied during their processing. Concerning the solvent influence, results obtained by Ribeiro et al. [8] revealed that cellulose films produced with [TMG][C$_1$CO$_2$] present higher resistance than films produced with [TMG][C$_2$CO$_2$] and [TMG][HCO$_2$]. On the other hand, Blessing et al. [7] reported some changes in the morphology of silk-cellulose films according to the coagulant concentration. Films coagulated with 1% v/v ethanol are not as smooth and uniform as films coagulated with 10% v/v ethanol [7]. In addition, Ribeiro et al. [8] observed that a shorter washing time results in sticky, yellowish and low consistency cellulose film, probably because this time was not enough to achieve the complete IL removal, causing a plasticizing effect. Longer washing times generate a brittle and whitish film, with no presence of IL. Love et al. [6] reported that the use of H$_2$O$_2$ in an aqueous solution as the coagulant agent significantly increases the thermal stability (~82 °C) of the silk-cellulose film in relation to that coagulated with pure water, highlighting the influence of the coagulant agent. According to the authors, films coagulated in H$_2$O$_2$ are more thermally stable due to fewer interfaces between polymer chains for all bio composites, being required a lower cohesive energy to break these interfaces compared to the actual disruption of the polymer chains themselves [6]. Rivera-Galletti et al. [1] and Soheilmoghaddam et al. [5] confirmed that the use of blends and mixtures (cellulose-silk and cellulose + citric acid, respectively) improve the properties of films, with the increase of cellulose content conferring more flexibility to the film [1]. In the same line, Park et al. [2] showed that different types of blends can influence the physicochemical properties of the biomaterials. For instance, the surfaces of cellulose-chitosan film have fibrous structure, whereas those composed of silk-cellulose are smooth and dense [2].
The IL and temperature used on raw material dissolution also influence the properties of the films. Ribeiro et al. [8] evaluated different [TMG]-based ILs and temperatures (90 - 130 °C) to process cellulose films. Films produced with [TMG][C\textsubscript{1}CO\textsubscript{2}] presented lower crystallinity; however, film crystallinity could be increased by increasing the dissolution temperature. On the other hand, temperature has no effect on films crystallinity when these are produced using [TMG][C\textsubscript{2}CO\textsubscript{2}]. When considering mechanical properties, films produced with [TMG][C\textsubscript{1}CO\textsubscript{2}] present higher resistance. According to FTIR results, an increase in temperature does not promote any changes in cellulose structure, while some IL is retained in the film's structure. Furthermore, results showed that the type of IL has no significant effect on the amount of retained IL. However, the increase in the dissolution temperature leads to an increase of the retained IL amount in the film [8]. Since some ILs can exhibit a certain level of toxicity, the IL removal from the biomaterial matrix must be considered, and citotoxicity studies need to be carried out to ensure the biomaterials safety.

The ILs toxicity depends on several factors, including their chemical structures, concentration and specific organisms and methods used to address such property. Flieger and Flieger [30] published a review manuscript highlighting the effect of different ILs on the environment, which is useful to provide insights on the design of ILs according to the required application. Overall, the toxicity determination of newly synthesized ILs should be a mandatory task. Furthermore, when envisaging IL industrial applications nowadays, it is required to address the use of computational tools to improve properties and processes performance, such as the use of machine learning tools as recently discussed by Welton and co-workers [31], which may result in time and costs saving.

Although scarcely considered in the published works (cf. Table 2), the IL recovery and reuse have a positive impact on the process feasibility from an economical and sustainable point of view, and should be a mandatory aspect in all related studies. Due to their non-volatile nature, the volatile compounds of the solution containing the IL and coagulant agent can be simple removed by evaporation [18–20]. Still, the energy cost associated to the IL recovery step, as well as equipment handling, are topics that need to be evaluated in a technical-economical evaluation before their industrial application can be foreseen.

### 2.2 Scaffolds
The use of blends can improve and allow to tune the final properties of biomaterials [9,10,15]. This is demonstrated by the results of Oliveira and co-workers [9,10], who developed SAIB-based scaffolds from chitin or silk. Results of structure characterization showed the influence of blend processing on the parameters evaluated according to the starting biopolymer used. In addition, these results reported some differences in structure characterization according to each biopolymer (silk or chitin). The presence of SAIB increased the adhesive strength of the scaffolds by almost four times compared to pure chitin scaffolds [9], while SAIB-silk scaffolds showed a slightly higher water uptake than pure silk-based ones [10]. These authors also evaluated the use of different coagulants (cf. Table 2) [9,10], finding that water is a better coagulant to SAIB-chitin samples, whereas for SAIB-silk the use of water results in scaffolds with lower strength. For these, isopropanol:water (1:1, v:v) solution was identified as the best coagulant. On the other hand, results reported by Gomes et al. [12] and Silva et al. [13] indicate that the use of methanol as coagulation agent leads to biomaterials with higher stability and firmness, probably due to its high polarity. However, from a sustainable point of view, the use of methanol is not the best option and water should be considered whenever possible.

Concerning the IL nature effect, preliminary results obtained by Oliveira and co-workers [9,10] revealed that SAIB does not dissolve in [C₄C¹im]Cl and does not form gels alone (without chitin) when dissolved in [C₄C¹im][C¹CO₂]. Furthermore, the use of [C₄C¹im]Cl to the processing of SAIB-silk scaffolds results in biomaterials with low stability, which may be related with the low dissolution power of this IL when compared to the acetate-based IL [10]. These results highlight the significant influence that ILs anions have on biomaterials processing and on their final properties.

Silva et al. [14] compared the influence of an IL – [C₄C¹im]Cl – and a conventional solvent – trichloromethane (CHCl₃) – on the processing of scaffolds. The use of the IL allowed to decrease the fibers diameter and consequently increase the surface area and the stretching resistance. The scaffolds obtained when using the IL as a solvent presented minor variations of mechanical properties, indicating a robust mechanical behavior. The cytotoxicity of the obtained scaffolds was determined by direct contact tests in L929 cells, showing that cells adhered and proliferated on both samples. Scaffolds processing in the IL have enhanced adhesion and activity when compared with those obtained with CHCl₃ [14].
Gomes et al. [12] reported the use of a cholinium-based IL to develop chitin scaffolds. This type of ILs, if properly designed, is well known by their lower toxicities when compared to their imidazolium counterparts, being thus more promising and safer for biomedical applications. The use of [N_{111(2OH)}][C_1CO_2] promoted a decrease in the pore size, improved the mechanical properties, and increased the resistance to thermal degradation. Furthermore, the presence of [N_{111(2OH)}][C_1CO_2] did not induce a negative impact on the L929 cell viability, with a positive effect on the human adipose stem cells biological behavior [12]. These results demonstrate that depending on the ILs used, it is possible to consider the processing of biomaterials in which ILs may be retained or be part of the blends, while improving their properties and possibility of biomaterials application.

2.3 Nanoparticles

Considering the works described in Table 2, nanoparticles (NPs) are typically produced using a single raw material, i.e. without blends, being usually silk or cellulose. As observed with films and scaffolds, the process conditions significantly influence the biomaterials' final properties. Samsudin et al. [18] showed that NPs present a porous structure when the dissolution temperature is higher than 100 °C. The optimum temperature was established to be 80 °C, based on the higher crystallinity and thermal stability of the NPs [18]. Low et al. [19] reported that a higher time of dissolution results in smaller NPs with higher crystallinity. Moreover, the increase of cellulose mass above 20 wt% leads to a drop in crystallinity index. The higher crystallinity index and the lowest crystalline size were achieved with 15 wt% of cellulose [19]. Crystallinity results reported by Samsudin et al. [18] and Low et al. [19] are presented in Table 3. Low et al. [19] also reported that the IL high viscosity limited the dissolution step performance, being a limitation in the mass transfer phenomenon.

Table 3. Crystallinity index and crystallinity size of microcrystalline cellulose and nanoparticles.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Crystallinity index, CrI (%)</th>
<th>Crystallinity size, D_{XRD} (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose</td>
<td>78.0</td>
<td>25.3</td>
</tr>
<tr>
<td>Nanoparticles*, 70 °C</td>
<td>59.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Nanoparticles*, 80 °C</td>
<td>78.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Nanoparticles\(^a\), 90 °C  & 58.6 & 2.7  
Nanoparticles\(^a\), 100 °C  & 45.5 & 2.7  
Nanoparticles\(^a\), 110 °C  & 39.2 & 2.9  
Nanoparticles\(^b\), 5 wt%  & 86.6 & 5.4  
Nanoparticles\(^b\), 10 wt%  & 89.5 & 5.3  
Nanoparticles\(^b\), 15 wt%  & 92.2 & 4.8  
Nanoparticles\(^b\), 20 wt%  & 85.8 & 5.1  
Nanoparticles\(^b\), 25 wt%  & 80.7 & 5.2

\(^a\) nanoparticles obtained as a function of synthesis temperature; \(^b\) nanoparticles obtained with different concentrations of microcrystalline cellulose.

Due to the unique properties of NPs, including their small size and high surface area, Fuster et al. [20] and Zhang et al. [21] developed silk-NPs and evaluated them as drug delivery systems. Silk was dissolved in \([\text{C}_2\text{C}_1\text{im}][\text{C}_1\text{CO}_2]\) under ultrasound conditions and regenerated in methanol, followed by the adsorption of naringenin or curcumin. The NPs loaded with naringenin reached 82-86% of the bio-compound release in the first 2 h [20], while the NPs loaded with curcumin released 35% in the initial 5 h [21]. These correspond to examples of scarce works reinforcing the potential of biomaterials processed by ILs to be used in biomedical applications.

### 3. Future perspectives and conclusions

Considering the low solubility of most starting biopolymers (e.g. cellulose, chitin, silk) in water and traditional organic solvents, the use of ILs on the processing of biomaterials appears as a remarkable alternative due their high dissolution capability (if properly designed and selected). Based on the works discussed on the advances in the field in the past years, it is clear that the use of ILs can simplify and improve the efficiency of biomaterials production processes and enhance the biomaterials properties. Among imidazolium-based ILs, \([\text{C}_2\text{C}_1\text{im}][\text{C}_1\text{CO}_2]\) has been highlighted in several studies, not only due to its low melting point and high dissolution capability for biopolymers [32], but also because this IL is approved by the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH). Still, there is a wide range of bio-based ILs that can overcome the concerns associated to most imidazolium-based ILs. Although the synthesis of bio-based ILs has been increasing in the literature in the past few years [33,34], they are still not properly investigated in biomaterials processing (cf Table 2). The promising results reported by Gomes et al. [12] should be an incentive...
for other researchers, especially when dealing with applications in the biomedical area. Other types of bio-based ILs [33,35], with low eco/citotoxicity and high biodegradability need to be further evaluated in biomaterials processing.

Overall, it is essential to consider the pros and cons that ILs have in the processing of biomaterials, especially regarding human health and environment, since life cycle assessment studies have shown questionable toxicity for some ILs [28]. Considering that the complete removal of IL from the biomaterial is not always achieved, the ILs and biomaterials eco/citotoxicity nature need to be characterized when envisioning their applications. Due to their non-volatile nature, the volatile compounds of the solution containing the IL and coagulant agent can be simple removed by evaporation as shown by some authors [18–20]. Still, the energy cost associated to the IL recovery step, as well as equipment handling, are topics needing to be addressed before their industrial application can be foreseen. Furthermore, to be more competitive, ILs need to be produced at relatively low cost and at a large scale, without discarding the development of cost-efficient IL recovery techniques in this field. Water has been the most used coagulant agent, which is an advantage since it is safe and poses no risks for human health, while avoiding the need of extra steps for the biomaterials recovery after dissolution.

There is still a gap in the literature in what concerns the application of biomaterials obtained using ILs. Most studies reported the processing and characterization of biomaterials, but without addressing their final application. Moreover, the influence of ILs possibly retained in biomaterials must be considered. Literature demonstrates that blended biomaterials present, most of the times, better and more interesting properties than those based on single raw material. Blends allow tuning biomaterials properties by adjusting the raw materials ratio according to the requirements of a specific application. However, the balance between an enhanced structure and the functional properties of a biomaterial is still a challenge to achieve. Given the high number of natural polymers available, other protein-polysaccharide blends (in addition to the widely studied silk-cellulose blend) should be evaluated.

Accomplishments achieved so far include the evaluation of IL as a solvent to improve the efficiency of biomaterials production, investigation of the use of silk-cellulose blends in biomaterial properties, and analysis of the influence of different dissolution conditions and coagulant agents. On the other hand, the recovery and reuse of ILs did not attract sufficient attention and needs to be implemented in a routine way.
Furthermore, the investigation on the use of bio-based ILs, processing of new protein-polysaccharide blends, evaluation of the final application of biomaterials and analysis of the process at a large scale, are also important topics that need to be addressed in future works.

Nowadays, when envisaging IL industrial applications nowadays, it is required to address the use of computational tools to improve properties and processes performance, such as the use of machine learning tools recently highlighted by Welton and co-workers [32], which may result in time and costs saving.

Although there is still a long path ahead to completely disclose their full potential, evidences up to date show that greener solvents (ILs) coupled with simple coagulant agents (water) in the processing of renewable biopolymers (natural polysaccharides and proteins) can be used to produce biomaterials with relevant properties in different fields.

Author contributions
Writing - original draft preparation, C.P.; writing - review and editing, H.P., M.G.F. and J.A.P.C.; supervision, H.P. and M.G.F. All authors have read and agreed to the published version of the manuscript.

Funding
This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020, UIDP/50011/2020 & LA/P/0006/2020, financed by national funds through the FCT/MCTES (PIDDAC). This work was funded by FEDER, through COMPETE2020—Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES, from the project POCI-01-0145-FEDER-031106 (IonCytDevice). C. Polesca acknowledges FCT- Fundação para a Ciência e a Tecnologia for the Ph.D. grant with the reference UI/BD/151282/2021. H. Passos acknowledges FCT, I.P., for the researcher contract CEECIND/00831/2017, under the Scientific Employment Stimulus-Individual Call, 2017.

Declaration of competing interest
The authors declare that they have no know competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

References

* The structure and physical properties of the silk-cellulose blends films were characterized.


SAIB-chitin scaffolds, ACS Sustainable Chemistry and Engineering. 8 (2020) 3986–3994. https://doi.org/10.1021/acssuschemeng.0c00385.


* ILs with reduced toxicity and different solvents as coagulant agents were evaluated in scaffolds development.


* Development of biomaterials for biomedical application using ILs was reviewed.


Ionic liquids are efficient solvents to dissolve biopolymers.

Dissolution conditions and type of coagulants influence the biomaterial properties.

Silk-cellulose is the mostly used blend in biomaterials processing.

Blended biomaterials present better properties than those based on a single biopolymer.

Biomaterials processed from ionic liquid solutions display improved properties.
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.