

Green Chemistry and Sustainable Technology

Mara G. Freire *Editor*

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# Ionic-Liquid- Based Aqueous Biphasic Systems

Fundamentals and Applications

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# Chapter 12

## Toward the Recovery and Reuse of the ABS Phase-Forming Components

Sónia P.M. Ventura and João A.P. Coutinho

**Abstract** Ionic liquids (ILs) have attracted significant interest as solvents in the extraction and purification of diverse biomolecules. Despite the so many different applications of ILs as solvents or as phase forming components of aqueous biphasic systems (ABS), little is known about the economic impact and scale-up of these processes. In fact, for any process to be of industrial relevance while using ILs as solvents, it is crucial to study their effective recovery, removal, and recyclability. In this sense, this chapter intends to summarize the approaches and strategies of recycling and reuse of ILs as pure compounds, in aqueous solution, and as IL-rich phases.

**Keywords** Aqueous biphasic systems • Ionic liquids • Recycle • Reuse • Economic impact • Sustainability

### 12.1 Introduction

Ionic liquids (ILs) have been used in a wide range of applications in both organic environments and aqueous media. The crescent interest in these compounds is closely related with the recurrent identification of ILs as “tunable compounds” and “green” or even “biocompatible solvents” and their unique properties such as their high solvation ability for a wide range of organic and inorganic solutes, negligible vapor pressure, wide electrochemical window, and good chemical and thermal stabilities [1, 2]. In spite of the many applications reported using ILs, among which their use in the extraction/purification of biomolecules [3], the number of studies addressing the scale-up of extraction processes, including the recycling and reuse of ILs, is scarce, and those describing real industrial extraction applications are indeed inexistent, mainly because ILs continue to be considered fancy and expensive solvent chemicals, despite some efforts showing that this is not always correct [4].

The study of aqueous biphasic systems (ABS) based on ILs and salts is a decade old [5], and it has been extended to ABS combining ILs and other phase-forming

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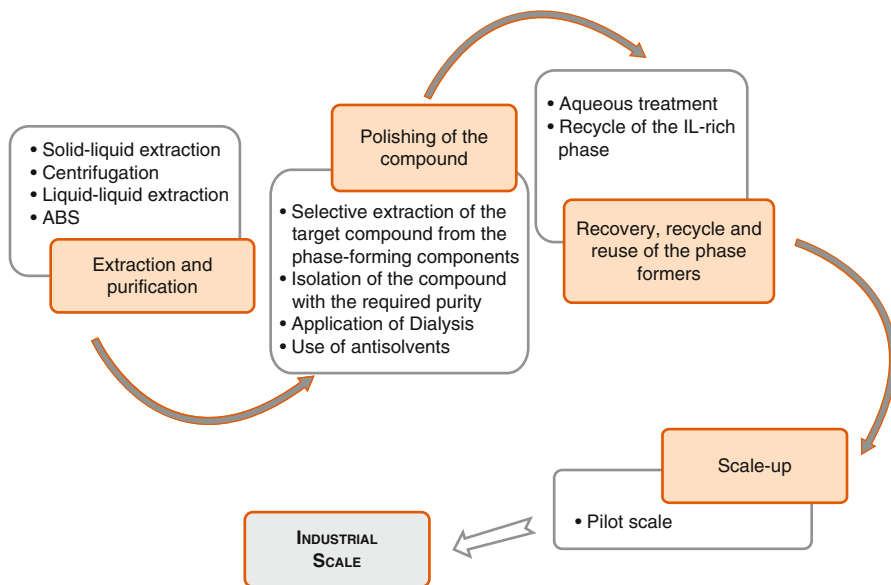
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components, namely, polymers, carbohydrates and amino acids [6], and, more recently, organic solvents [7] and surfactants [8]. Different authors have looked for the fundamentals and applications of this type of liquid–liquid extraction process [6], which promoted, in the last decade, a significant increase on their number of applications as recently reviewed [6]. ABS based on ILs can be used for multiple applications, as pointed by Rogers and co-workers on their seminal article [5], but up to present, they have been restricted to two major applications [6], namely, their use as liquid–liquid extraction/purification processes and as a route for the recovery or concentration of hydrophilic ILs from aqueous effluents or aqueous solutions. Actually, most works in literature deal with the use of IL-based ABS as separation and purification technologies, in which the extraction of alkaloids [9–11], pharmaceuticals [12–16], metals [17], amino acids [18, 19], proteins and enzymes [20–24], dyes [8, 25] and colorants [26], and aromatic and phenolic compounds [27, 28] was investigated. Several of these works highlight the potential of these processes to be scaled up; however, no relevant studies were yet developed on this direction, being this normally attributed to economic factors (high price of ILs), but also to the environmental footprint (toxicity [29–40], persistence [29–31, 41], and bioaccumulation [29–31, 37, 42], among others). If in one hand, the industry is still worried about the high costs of ILs, when compared with the prices of the conventional solvents, on the other hand, the number of processes capable to regenerate and recover ILs, allowing their recycling into the extraction system, is still scarce.

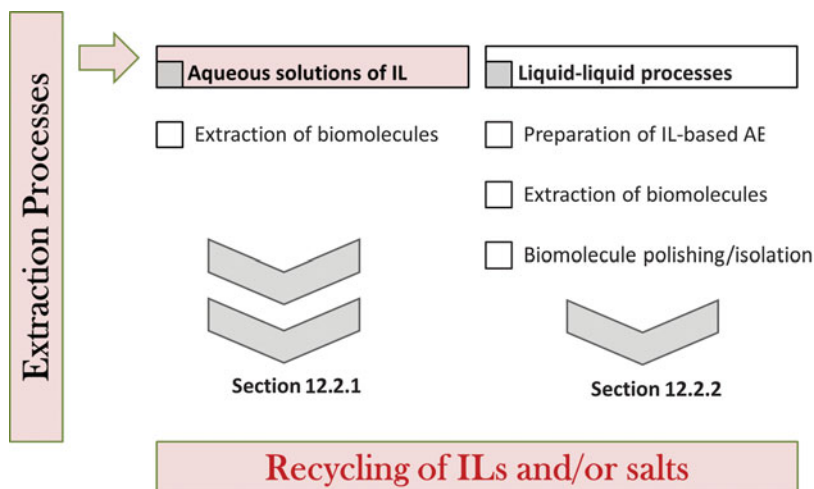
Despite the crescent number of publications focusing on IL-based ABS at laboratory scale (more than 380 publications reported in the *ISI Web of Knowledge* by March 2016), the scale-up of these technologies lagged behind. To minimize the environmental and economic impact of IL-based ABS, various conditions need to be investigated, but one aspect stands out: the necessity to recover and reuse the phase-forming components, principally the IL, which represents the most expensive solute. The number of methodologies published regarding the recycling of ILs from aqueous solutions, although scarce, is quite relevant, as recently described in different publications [43–45]. In this chapter, different techniques will be described and analyzed as depicted in Fig. 12.1. In this figure, the main steps on the development of an integrated process of extraction and purification, coupled to the IL recovery, and considering these systems' industrial application, are described. It should be noted that most studies addressing the use of ILs in the extraction and purification fields are focused in the two first steps and practically none in the final task.

## 12.2 State of the Art on the IL Recyclability

Despite the fact that the number of articles on IL-based ABS, considering not only their fundamental aspects, but also their application as extractive technologies is nowadays very large, the number of works addressing the recycle, recovery, and reuse of ILs, applied to ABS extractions, is still limited.



**Fig. 12.1** Schematic representation of the principal steps in the development of a scaled-up process for the extraction and purification of added-value compounds



**Fig. 12.2** Extraction processes considered in this chapter

The results summarized in this chapter are divided into two major sections. The first section (Sect. 12.2.1) presents the description of works dealing with the recovery, regeneration, removal, and reuse of ILs from aqueous solutions (or aqueous effluents), while the second section (Sect. 12.2.2) describes the studies regarding the recovery and reuse of the phase-forming components from IL-ABS, whose studies are depicted schematically in Fig. 12.2. The first section is

relevant in the context of IL-ABS because the techniques reported for the recovery of ILs in process streams or effluents can be extended to other processes and can provide new insights and directions on potential methodologies to be applied in the recyclability (recovery, removal, and reuse) of ILs used in ABS formation.

## 12.2.1 Recovery of ILs from Aqueous Solutions

This section deals with the recycling of pure ILs or IL aqueous solutions, since this information can be helpful in the implementation of IL-based ABS for extraction purposes.

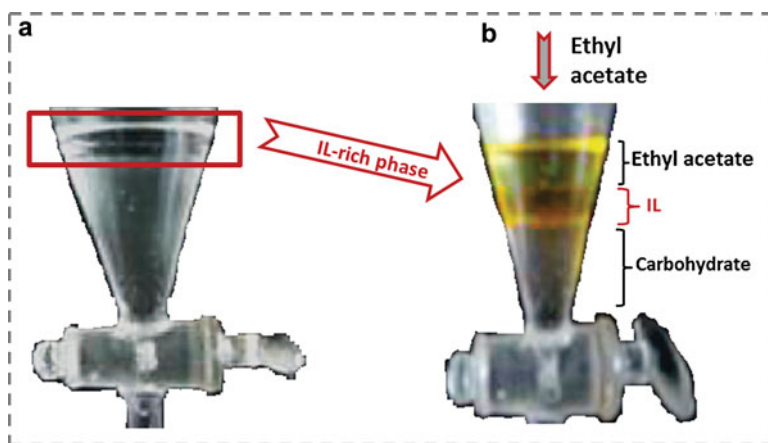
### 12.2.1.1 The Use of IL-Based ABS to Recover ILs

In the first work reporting IL-based ABS, Gutowski et al. [5] proposed the concept of recycling ILs from aqueous solutions by means of ABS formation. This allows the creation of an IL-rich phase from a diluted aqueous solution. Meanwhile, some authors have been working on the IL recovery from aqueous solutions along these lines [46–49]. Deng et al. [46] investigated the recovery of 1-allyl-3-methylimidazolium chloride, [aC<sub>1</sub>im]Cl, using three inorganic salts, namely, tripotassium phosphate, K<sub>3</sub>PO<sub>4</sub>; dipotassium phosphate, K<sub>2</sub>HPO<sub>4</sub>; and dipotassium carbonate, K<sub>2</sub>CO<sub>3</sub>. The authors [46] have determined the ABS phase diagrams of [aC<sub>1</sub>im]Cl with those three inorganic salts, followed by the proper characterization of the binodal curves and tie-lines and additional recovery tests. The results reported showed that it is possible to increase the recovery efficiency of ILs by increasing the “salting-out” strength, following the order K<sub>3</sub>PO<sub>4</sub> > K<sub>2</sub>HPO<sub>4</sub> > K<sub>2</sub>CO<sub>3</sub>, representative of the Hofmeister series [50]. Besides the ionic strength of the salt, higher concentrations also lead to an increase on the recovery efficiency of the IL. The best results were achieved using 46.48 wt% of K<sub>2</sub>HPO<sub>4</sub>, and the maximum recovery efficiency found was 97 % [46]. Li and coauthors [47] proposed the use of sodium salts, namely, sodium phosphate, Na<sub>3</sub>PO<sub>4</sub>; sodium carbonate, Na<sub>2</sub>CO<sub>3</sub>; sodium sulfate, Na<sub>2</sub>SO<sub>4</sub>; sodium phosphate monobasic, NaH<sub>2</sub>PO<sub>4</sub>; and sodium chloride, NaCl, to promote the recovery of 1-butyl-3-methylimidazolium tetrafluoroborate – [C<sub>4</sub>C<sub>1</sub>im][BF<sub>4</sub>] – from water or aqueous solutions. The binodal curves were experimentally described for different temperatures and the respective tie-lines calculated. The study of the IL recovery was performed considering the addition of a known mass fraction of salt to an IL aqueous solution of known concentration until the formation of the ABS (the system was placed for 5 min in a centrifuge at 2000 rpm) [47]. The sample was placed under controlled temperature until phase separation, and the concentration of the IL in the top phase was quantified by UV–vis spectroscopy at 211 nm (since an imidazolium-based IL was used). The percentage recovery efficiency (100R) was then calculated (for more details, see [47]). The results obtained suggest that

the recovery efficiency of  $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$  increases with the mass fraction of each salt (due to a “salting-out” effect). The authors [47] demonstrated that different salts have distinct effects on the recovery efficiency of this specific IL, following the order  $\text{Na}_3\text{PO}_4 > \text{Na}_2\text{CO}_3 > \text{Na}_2\text{SO}_4 > \text{NaH}_2\text{PO}_4 > \text{NaCl}$ . The best results regarding the IL recycling were achieved with  $\text{Na}_2\text{CO}_3$ , with a maximum recovery of 98.77 % [47].

Wu and collaborators [48] studied the removal of ILs from an aqueous solution by means of ABS formation using carbohydrates. The authors used xylose, sucrose, fructose, and mannose to promote the ABS formation with  $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$  in which the upper phase is rich in IL and the bottom phase is rich in carbohydrate (Fig. 12.3a). The ABS was prepared by the addition of specific compositions of carbohydrate to the IL in water. The top phase, richer in IL, was removed, and a known volume of ethyl acetate was added to the top phase, inducing the formation of a second phase rich in ethyl acetate (Fig. 12.3b). The authors [48] clarified that, when ethyl acetate is added to the IL-rich top phase, a third phase is originated in which the bottom phase is sugar rich; the intermediate phase is rich in IL and does not contain ethyl acetate due to their mutual immiscibility; and the top phase is concentrated in ethyl acetate (Fig. 12.3b).

Although it was found to be easy to separate this particular IL from water, after the process of regeneration/purification, the recovered IL (water content  $< 1\%$ ) was sugar-free (tests were performed to prove the absence of carbohydrates in the IL-rich phase). However, the recoveries of IL measured were not so satisfactory in the authors’ perspective (74 % for sucrose, 72 % for xylose, 64 % for fructose, and 61 % for glucose) [48]. In the same year, the same group of authors published an additional work focusing on the separation of ILs by using IL + sugars ABS [49]. In this work, the same idea was applied to other ILs, particularly 1-allyl-3-



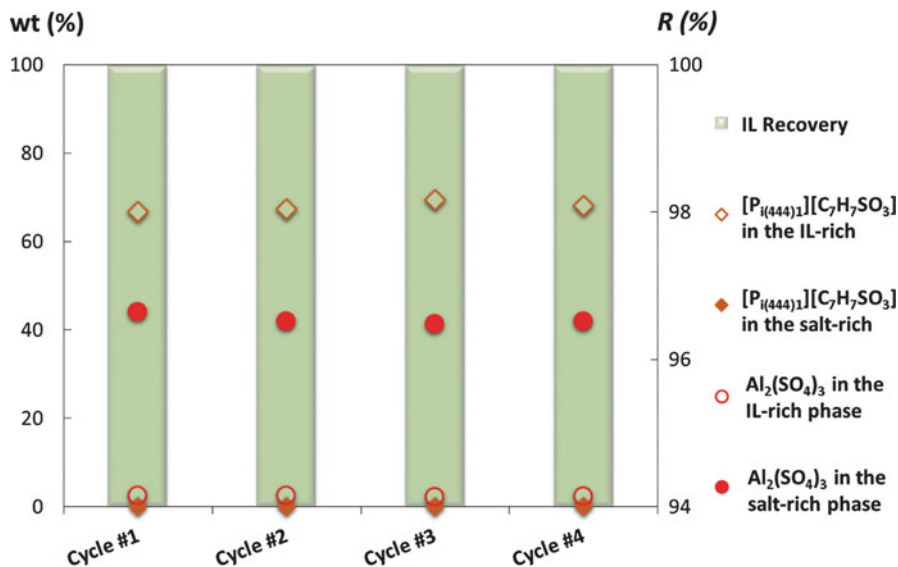
**Fig. 12.3** IL-carbohydrate-based ABS: (a)  $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$  + sucrose + water and (b) top phase of the system  $[\text{C}_4\text{C}_1\text{im}][\text{BF}_4]$  + sucrose + water + ethyl acetate (Adapted with permission from Ref. [48]. Copyright 2008 American Chemical Society)

methylimidazolium chloride, [aC<sub>1</sub>im]Cl; 1-allyl-3-methylimidazolium bromide, [aC<sub>1</sub>im]Br; and 1-butyl-3-methylimidazolium tetrafluoroborate, [C<sub>4</sub>C<sub>1</sub>mim][BF<sub>4</sub>]. The formation of ABS was again studied using sucrose. This study reported some effects of the IL structure on the phase equilibrium, being described the favorable effect promoted by the increase of the ILs' alkyl side chain length [49]. Regarding the anion effect, the authors concluded that the phase separation varies with the halogenated anions [49], being this behavior related with the decrease of the ILs' hydrophobicity as follows: [C<sub>4</sub>C<sub>1</sub>im][BF<sub>4</sub>] > [aC<sub>1</sub>im]Br > [aC<sub>1</sub>im]Cl. The same methodology previously described [48] was again applied with success [49], being the results regarding the recovery of the ILs around 74 % for [C<sub>4</sub>C<sub>1</sub>im][BF<sub>4</sub>], 65 % for [aC<sub>1</sub>im]Br, and 63 % for [aC<sub>1</sub>im]Cl. One year later, Wu and collaborators provided a mini-review [51] on the recycling of ILs focusing on the methods needed for the removal of ILs from different "working environments".

In 2010, Wu et al. [52] studied the "salting-out" effect of different ILs on the formation of ABS with poly(propylene glycol). They determined the respective phase diagrams, with the binodal curves for PPG400 + [aC<sub>1</sub>im]Cl or [C<sub>4</sub>C<sub>1</sub>im][CH<sub>3</sub>COO] or [C<sub>4</sub>C<sub>1</sub>im]Cl, and the respective tie-lines and tie-line lengths. The authors [52] described the use of these ABSs in the development of new methodologies to promote the recycling and/or enrichment of ILs from aqueous solutions; however, no data on this matter were provided [52].

Neves et al. [53] proposed the use of the aluminum salts, Al<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> and AlK(SO<sub>4</sub>)<sub>2</sub>·12 H<sub>2</sub>O, to concentrate and then eliminate imidazolium-, pyridinium-, and phosphonium-based ILs from aqueous solutions. The authors [53] justified the choice of these salts by their high "salting-out" aptitude to promote the formation of ABS [50] and by the fact that these salts are normally used in water treatment processes [54]. The phase diagrams with the different ILs conjugated with the two salts were determined, and some additional properties of the coexisting phases were addressed, namely, density, viscosity, conductivity, and pH values. The study of the ILs' reuse in various (removal/recovery) cycles was also performed to test the suitability of the proposed approach [53]. The main results showed the great ability of these salts to remove and recover ILs from aqueous solutions, being the recovery efficiency results achieved in the range of 96–100 %. The residual concentrations of ILs in the aqueous solution were between 0.01 and 6 wt%. Considering the recovery efficiencies obtained, four cycles of ILs' removal/recovery were tested with the IL tri(isobutyl)methylphosphonium tosylate, [P<sub>i(444)1</sub>][C<sub>7</sub>H<sub>7</sub>SO<sub>3</sub>]. The results obtained showed that for each cycle, the recovery was maintained at around 100 %, proving the recyclability of the IL as shown in Fig. 12.4.

The results obtained by Neves et al. [53] suggest that, as initially proposed by Gutowski et al. [6], ABS can indeed be used to reconcentrate and recover ILs from aqueous solutions (e.g., process streams or aqueous effluents). Given the mechanism of phase formation in IL-ABS, strongest salting-out-inducing salts should be used (phosphates, sulfates, and carbonates are thus recommended), and high concentrations also favor the IL recovery.



**Fig. 12.4** Recovery of a phosphonium-based IL in several cycles using the inorganic salt  $\text{Al}_2(\text{SO}_4)_3$ . The concentrations of both salt and IL in both aqueous phases at the end of each cycle are also depicted (Adapted from Ref. [53]. Reproduced with permission from the Royal Society of Chemistry)

### 12.2.1.2 Other Methodologies

In this section, other methodologies to remove ILs from aqueous effluents other than using salting-out agents are described. It is not our objective to present an exhaustive list and analysis of all methodologies and processes that can be used to recover ILs from water. Instead, we are concerned in the description of the most relevant IL recycling methodologies, namely, distillation [55–61], the use of membranes or resins [62], back-extraction with organic solvents [63], the use of precipitate agents [64], the application of salting-out agents to promote the preparation of ABS [65–67], and the thermoreversibility phenomenon [68].

In 2011, Bica and coauthors [58] suggested the use of aqueous solutions of ILs (in concentrations of 20–50 wt%) to extract and purify essential fragrance oils from orange peels. They reported a comparison between the IL-based and the conventional process, regarding their capacity to extract and isolate the fragrances. ILs (1-butyl-3-methylimidazolium chloride,  $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ ; 1-allyl-3-methylimidazolium chloride,  $[\text{aC}_1\text{im}]\text{Cl}$ ; and 1-ethyl-3-methylimidazolium acetate,  $[\text{C}_2\text{C}_1\text{im}][\text{CH}_3\text{COO}]$ ) were used as solvents to promote the dissolution of the biomass, thus allowing the extraction and separation of biopolymers and the essential oils found in the composition of the orange peels. After the dissolution of the biomass, the solution was distilled to separate the essential oils from the nonvolatile biopolymers and ILs. To this solution, water was added as anti-solvent to precipitate the



biopolymers, and then water was evaporated, allowing the IL regeneration. The IL regenerated was shown to be in a “spectroscopically pure form” but “dark in color” as described by the authors [58]. The “dark” IL recovered was passed through charcoal, reaching a purity level between 90 and 95 % that would allow it to be recycled into the process [58].

Ressmann and collaborators [60] studied a scalable integrated process focused in the isolation of betulin, a pharmaceutically active compound extracted from birch bark. In this study, the IL recycling was investigated due to its relevance in the scale-up strategy. The experimental approach applied to isolate betulin from the biomass followed three main steps: First, (1) ILs were added to the crude biomass, after dissolution methanol was used to precipitate biopolymers, and then (2) a centrifugation step was conducted allowing the fast separation of the solid biomass and the supernatant, in which the betulin is concentrated (ethanol can be added to precipitate undesired biopolymers, and an extra crystallization may be applied if a higher purity level of betulin is required). This integrated process culminated with the (3) IL recovery and recycling by the distillation of the ethanol/water azeotrope.

The authors [60] tested several ILs on the extraction of betulin from the biomass, namely, 1-ethyl-3-methylimidazolium acetate ( $[\text{C}_2\text{C}_1\text{im}][\text{CH}_3\text{COO}]$ ), 1-ethyl-3-methylimidazolium chloride ( $[\text{C}_2\text{C}_1\text{im}]\text{Cl}$ ), 1,3-dimethylimidazolium acetate ( $[\text{C}_1\text{C}_1\text{im}][\text{CH}_3\text{COO}]$ ), 1,3-dimethylimidazolium *n*-butyrate ( $[\text{C}_1\text{C}_1\text{im}][\text{C}_3\text{H}_7\text{CO}_2]$ ), 1-ethyl-3-methylimidazolium propionate ( $[\text{C}_2\text{C}_1\text{im}][\text{C}_2\text{H}_5\text{CO}_2]$ ), 1-ethyl-3-methylimidazolium *n*-butyrate ( $[\text{C}_2\text{C}_1\text{im}][\text{C}_3\text{H}_7\text{CO}_2]$ ), and 1-ethyl-3-methylimidazolium iso-butyrate ( $[\text{C}_1\text{C}_1\text{im}][\text{CH}(\text{CH}_3)_2\text{CO}_2]$ ). At the optimum dissolution and extraction conditions, the scale-up of the betulin isolation process was studied [60]. In the final step of purification of betulin, a filtrate stream, principally composed of water, ethanol, and IL, was obtained. This filtrate was evaporated and posteriorly dried under vacuum with stirring, at 80 °C for 24 h. As explained by the authors [60], the low content in water (20 vol.% in ethanol) was advantageous to the recovery and recycling of the IL, since through an azeotropic distillation of ethanol/water, the IL is automatically separated from the remaining solvents, with a recovery of 86–92 %. Summing up, an easier “energy-saving” recovery of the IL was achieved (the IL recovered was tested via  $^1\text{H}$  NMR spectroscopy and no impurities were detected), with the possibility to reuse the IL recovered without any additional purification step [60].

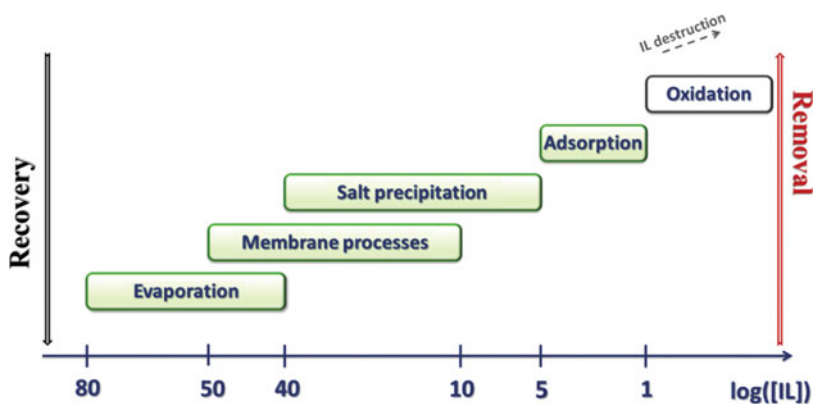
Four ILs, including 1-ethyl-3-methylimidazolium hexanoate ( $[\text{C}_2\text{C}_1\text{im}][\text{C}_5\text{H}_{11}\text{CO}_2]$ ), cholinium hexanoate ( $[\text{N}_{111}\text{C}_2\text{H}_4\text{OH}][\text{C}_5\text{H}_{11}\text{CO}_2]$ ), cholinium octanoate ( $[\text{N}_{111}\text{C}_2\text{H}_4\text{OH}][\text{C}_7\text{H}_{15}\text{CO}_2]$ ), and cholinium decanoate ( $[\text{N}_{111}\text{C}_2\text{H}_4\text{OH}][\text{C}_9\text{H}_{19}\text{CO}_2]$ ), were used to extract suberin from cork, a study conducted by Ferreira and coauthors [69]. A detailed description of the methodology used to extract suberin was presented, and an accurate characterization of the extracted material was reported. The authors [69] tested the influence of the anion alkyl chain length and the basicity of the IL on the suberin separation. Taking into account the best results, found for the cholinium hexanoate IL [69], the recyclability of this IL was studied. The IL recovery followed a simple methodology, which consists in the elimination of water (the main contaminant present in the IL effluent) through

evaporation under vacuum [69]. The study shows that the yield of cholinium hexanoate recovered by the methodology described was higher than 99%. Other works also apply processes based on distillation or evaporation of water to promote the recovery and recycling of ILs used as solvents in aqueous solution [55–57, 61].

Recently, Cláudio et al. [63] proposed a process to extract caffeine from guaraná (*Paullinia cupana*, Sapindaceae) seeds using aqueous solutions of ILs (imidazolium and pyrrolidinium cations combined with the chloride, acetate, and tosylate anions) as solvents. The IL recyclability was attempted using the back-extraction of caffeine from the IL aqueous solution by applying several nonmiscible organic solvents, namely, chloroform, ethyl acetate, hexane, diethyl ether, methylene chloride, toluene, butanol, dimethylfuran, and xylene. For that purpose, the best solvents identified were chloroform and methylene chloride, being chloroform capable of a complete extraction of caffeine from the IL aqueous solution. They also show that these organic solvents can be replaced by butanol, a more environmentally benign candidate to extract caffeine from the aqueous IL solution allowing its reutilization [63].

Various are the recovery and recyclability processes for ILs described by different authors [45], here summarized in Fig. 12.5. Some of the processes (evaporation, salt precipitation) described above are capable of recovering ILs from concentrated solutions, while others can do it only with diluted aqueous effluents, with low IL contents, as the adsorption using activated carbon [43, 45] discussed hereafter.

Recent reports by Palomar and coworkers [70–74] showed various approaches for the adsorption of ILs from aqueous effluents using activated carbon. In their first work [72], the authors carried a study on the use of a commercial activated carbon as adsorbent to recover 17 imidazolium-based ILs from aqueous solutions by adsorption. The adsorption isotherms of ILs on the activated carbon were determined at different temperatures and the effects of different cations and anions analyzed. The adsorption mechanism was investigated using various activated



**Fig. 12.5** Processes used to remove and recover ILs from aqueous effluents, taking into account the IL concentration to be treated

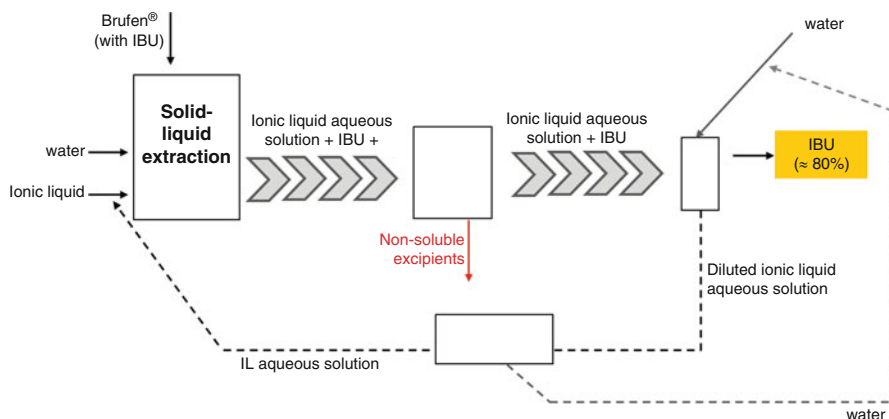
carbon adsorbents modified by oxidative and thermal treatments and by a computational study by COSMO-RS, which was developed to estimate molecular and thermodynamic properties of the solvent–adsorbate–adsorbent system [72]. The results obtained demonstrate that it is possible to use activated carbon to remove hydrophobic and hydrophilic ILs from water streams. They concluded that the adsorption of the hydrophilic ILs may be improved by the formation of more hydrogen-bonding interactions and by changing the number and nature of oxygen groups on the activated carbon surface [72]. Finally, the authors [72] proposed the use of acetone to regenerate the solid adsorbent. Later, they attempted at the development of heuristics for the choice of the activated carbon regarding the recovery of a given IL from aqueous media [73]. The conclusions suggested that the selection of a specific adsorbent is dependent on the physical and chemical properties of both IL and activated carbon. Microporous and/or narrow mesoporous activated carbons, i.e., with high amount of pores and of diameters lower than 8 nm, present the best adsorption capacities, with maximum values of 1 g of IL *per* gram of activated carbon. Moreover, the authors [73] concluded that the adsorption process was improved by the proper modification of the chemical surface of the adsorbent, in which the recovery of hydrophilic ILs is more efficient by applying activated carbons with a higher number of polar groups on their surface, and the hydrophobic ILs are more efficiently recovered from water when low polar materials are applied (such as the thermally treated adsorbents) [73]. Finally, the regeneration of the activated carbons was also successfully achieved by applying acetone as a solvent to remove the IL adsorbed. An additional evaporation was used to remove the acetone to complete the process of the IL recovery [73].

Lemus et al. [70] described a systematic analysis of the influence of different IL alkyl chain lengths, head groups, and anions and also the presence of functional groups on their adsorption onto commercial activated carbons from water effluents. In this work, 21 ILs were studied, including imidazolium-, pyridinium-, pyrrolidinium-, piperidinium-, phosphonium-, and quaternary ammonium-based cations, those conjugated with several hydrophobic and hydrophilic anions. The range of ILs tested was here increased, and in this context, it was possible to improve the understanding of the adsorption mechanism of these IL structures. The results evidenced the significant effect of the IL cation (or family) on the adsorption phenomenon of ILs into the activated carbon. Increased uptakes were described considering the following tendency: quaternary ammonium > phosphonium > pyridinium > imidazolium > pyrrolidinium > piperidinium, promoted by van der Waals interactions between the IL and the surface of the adsorbent [70]. The increase of the alkyl chain length in the anion or cation and the inclusion of substituents can promote different and increased (in the case of the long alkyl side chains) adsorption coefficients, due to high number of interactions between the IL and the activated carbon. As the adsorption was more difficult for the hydrophilic ILs, the authors further proposed the use of a *salting-out* salt to enhance the adsorption of hydrophilic ILs onto activated carbon [71]. The effect of several concentrations of Na<sub>2</sub>SO<sub>4</sub> on the adsorption profile of five different ILs of imidazolium and pyridinium families

conjugated with hydrophilic and fluorinated anions was studied. The results suggest that the adsorption of the studied ILs onto activated carbon is increased 5.5 times with the addition of  $\text{Na}_2\text{SO}_4$  [71].

In 2016, e Silva and collaborators [64] aimed at the development of a process for the recovery of ibuprofen from pharmaceutical residues. The ibuprofen solid–liquid extraction and the drug polishing were the main tasks developed. Moreover, also the excipient elimination and the aqueous solution recycling were proposed. The optimization of the solid–liquid extraction and drug isolation tasks was assessed. Regarding the solid–liquid extraction of ibuprofen, different conditions were tested, namely the type of IL and the ratio of IL *versus* citrate buffer. From this particular study, the tetrabutylammonium chloride ( $[\text{N}_{4444}]\text{Cl}$ ) was selected for further process optimization. Moreover, through the results obtained for the IL/citrate buffer ratio, the mixture 45 wt% of  $[\text{N}_{4444}]\text{Cl}$  + 5 wt % of citrate buffer + 50 wt% of water was adopted as the most efficient extracting ibuprofen (extraction efficiency of around 98 %). The recovery of ibuprofen from aqueous media was evaluated by precipitation promoted by the addition of different amounts of KCl and water as precipitating agents. Different volumes of extract/volume ratios of an aqueous solution of KCl (25 wt% and proportions of 1:1, 1:2, 1:3, 1:4, and 1:5) and water were added. The recovery results suggested a significant influence of citrate buffer used in the solid–liquid extraction step, represented by higher recovery efficiencies of ibuprofen (around 97 % and 92 %) when using as precipitating agents KCl aqueous solutions (1:5) and water (1:3), respectively. However, the authors demonstrated that, when applying KCl or water in the same ratios, in the aqueous solutions with IL and 5 wt% of citrate buffer initially applied in the solid–liquid extraction, the precipitation of ibuprofen decreases for 88 % and 35 %, respectively. The authors justify that water has a great capacity to precipitate ibuprofen from the solutions free of citrate buffer due to the hydrophobicity of the drug [64]. Meanwhile, the authors explain that the ionic speciation of the drug in solution and the pH induced by the addition of KCl in the system decreased the main interactions between the drug and the components of the extractive solution, thus promoting its precipitation in aqueous solution. By applying these precipitation strategies, it was possible to obtain precipitates with high level of purity, at around 80 %, considering the IL as the main contaminant. Due to the presence of IL in the ibuprofen precipitate, extra steps were included in the integrated process defined in this work (Fig. 12.6), namely, a washing step with cold water eliminating the IL [64].

Another very recent strategy to recover and recycle some ILs is the use of thermosensitive polymers that, conjugated with aqueous solutions of some specific ILs, namely, the protic ones, can promote the two-phase formation by the exclusive effect of the temperature increase [68]. In this study, and despite the different aims of the authors, the thermoreversibility of the systems based in aqueous solutions of N,N-dimethyl-N-ethylammonium acetate,  $[\text{N}_{1120}][\text{C}_1\text{CO}_2]$ ; N,N-diethyl-N-methylammonium methane sulfonate,  $[\text{N}_{1220}][\text{C}_1\text{SO}_3]$ ; N,N-dimethyl-N-(N',N'dimethylaminoethyl)ammonium acetate,  $[\text{N}_{11[2(\text{N}_{110})_0]}][\text{C}_1\text{CO}_2]$ ; N,N-dimethyl-N-(N',N'dimethylaminoethyl)ammonium chloride,  $[\text{N}_{11}$



**Fig. 12.6** Process developed in Ref. [64] to recover and purify ibuprofen from pharmaceutical wastes by using aqueous solutions of different ILs and the citrate buffer

$[2_{(N_{110})_0}]Cl$ ; *N,N*-dimethyl-*N*-ethylammonium phenylacetate,  $[N_{1120}][C_7H_7CO_2]$ ; and *N,N*-dimethyl-*N*-(*N'*,*N'*-dimethylaminoethyl)ammonium octanoate,  $[N_{11}[2_{(N_{110})_0}][C_7CO_2]$  and polypropylene glycol (PPG) was studied. In general, this work allows to understand the region of thermoreversibility of these systems. Briefly, if aqueous solutions of these protic ILs are used to extract biomolecules from biomass or fermentation broth, the IL can be regenerated by adding PPG and increasing the temperature to a certain value, which will allow the formation of two phases, one rich in IL and the other richer in the PPG, thus promoting the regeneration of the IL-rich solution and allowing its reuse in other steps of purification.

### 12.2.2 Recovery and Recycle of ILs from IL-Based ABS Extraction Processes

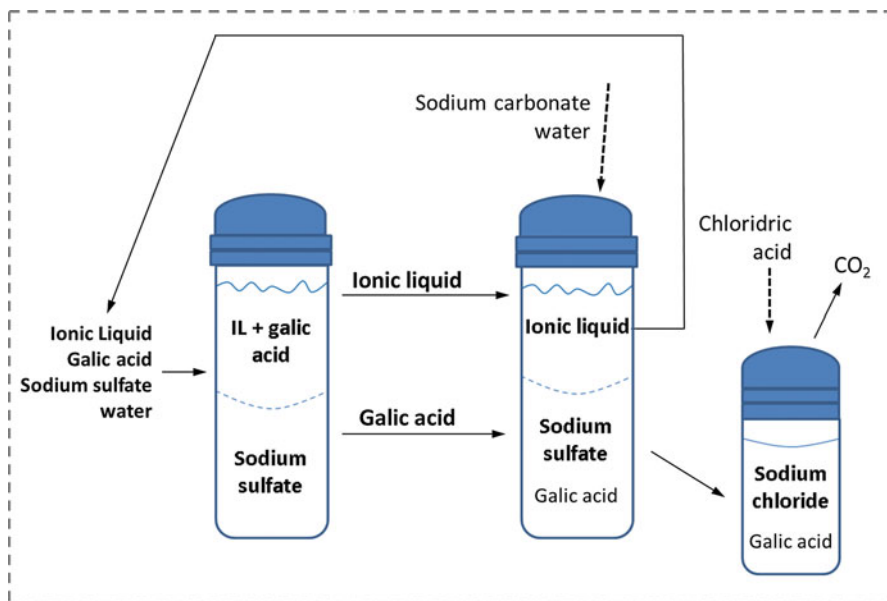
The application of ABS as extractive platforms for the extraction and/or purification of biomolecules has been extensively described and discussed [6]. However, the molecule polishing and the recycle of the phase-forming components are yet deficiently explored [6].

In 2012, Li and coauthors [23] developed a work focused on the use of ABS composed of cholinium-based ILs and polypropylene glycol 400 (PPG400) for the recovery of distinct proteins, namely, bovine serum albumin (BSA), trypsin, papain, and lysozyme. The phase diagrams were determined for various aqueous systems: PPG400 + tri-cholinium citrate, di-cholinium oxalate, cholinium glycolate, cholinium lactate, cholinium butyrate, cholinium formate, cholinium propionate, and cholinium acetate [23]. It was observed the protein preference for the IL-rich phase and extraction efficiencies between 86.4 % and 99.9 % were

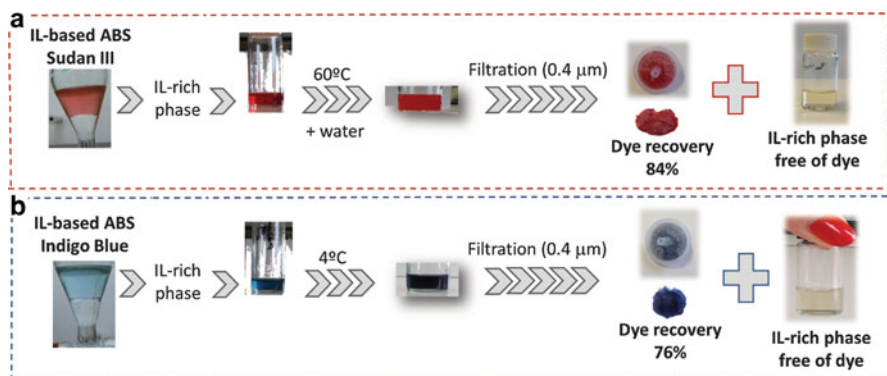
obtained. After the partition studies, the authors [23] investigated the recovery of the phase-forming agents, in particular the polymer recyclability. PPG, being a thermosensitive polymer, can be properly recovered by changing the temperature of the medium. Thus, and in order to investigate the recovery and reuse of PPG from aqueous solutions, different temperatures were tested, and the cloud point curves of PPG400 aqueous solutions were defined. With the cloud point curve of PPG at different temperatures, it was possible to determine the PPG400 lower critical solution temperature (LCST) to be approximately 46 °C that further decreases by about 20 °C in the presence of 2 % of IL (cholinium propionate) [23]. The temperature of 26.6 °C was then adopted to study the optimization of the recycling process. Aqueous solutions tested were exposed to different temperatures, above and below the critical temperature as the authors show. In the image shown in this work, the system becomes turbid at around 26.6 °C, and at 35 °C two distinct phases are already formed being the separation even more intense at 45 °C. The recycling process proposed is thus based on a temperature increase that drives the polymer from the aqueous solution of cholinium propionate + PPG400, promoting the concentration of PPG400 in the polymer-rich phase to circa 78 wt% at 35 °C and 90 wt % at 45 °C, finally allowing the recyclability of 90 % of PPG400 [23].

Another approach to recover ILs from ABS was proposed by Cláudio et al. [65] for systems based on carbonate and sulfate salts. The authors [65] used ABS composed of imidazolium-based ILs and two distinct salts, Na<sub>2</sub>CO<sub>3</sub> and Na<sub>2</sub>SO<sub>4</sub>, being those applied on the extraction of gallic acid [65]. They developed a sequential two-step cycle of product extraction and IL recyclability. The first task consisted of the extraction of gallic acid in IL-ABS formed with sodium sulfate. Based on an extensive study on different ILs, the best results were obtained with [C<sub>4</sub>C<sub>1</sub>im][CF<sub>3</sub>SO<sub>3</sub>] and [C<sub>4</sub>C<sub>1</sub>im][N(CN)<sub>2</sub>]. The gallic acid concentrated in the IL-rich phase was then back-extracted into a saline solution using sodium carbonate [65]. The overall process is depicted in Fig. 12.7. Following the back-extraction, the IL-rich phase, without gallic acid, can be recycled into the process. The IL recovery efficiencies obtained were of about 95 %.

Still in 2014, Ferreira and collaborators have described a new methodology to recover textile dyes from aqueous media, based in the use of IL-based ABS [75]. In this work, the extraction efficiency and the partition of three common textile dyes, chloranilic acid, indigo blue, and Sudan III, were investigated regarding the use of ABS based in phosphonium and imidazolium ILs and the salts aluminum sulfate and potassium citrate. Conditions like the IL chemical structure, the nature of the salt, and the pH of the aqueous medium were investigated. The results achieved in this work revealed that with the adequate selection of the IL structure and salt, it is possible to obtain the complete extraction toward the IL-rich phase. Moreover, the dye recovery was also studied, taking into account, more than the recovery of the dyes, the recycling and reuse of the IL-rich phase, since the IL is the most expensive solvent used. These tests were done using the ABS based in the tributylmethylphosphonium methylsulfate [P<sub>4441</sub>][CH<sub>3</sub>SO<sub>4</sub>] and the potassium citrate salt. After the complete recovery for the IL layer of both Sudan III and indigo blue dyes, each phase of the ABS was carefully separated, being the IL-rich layer



**Fig. 12.7** Process diagram representing the integrated extraction and back-extraction of gallic acid and the IL recovery and reuse developed in Ref. [65]



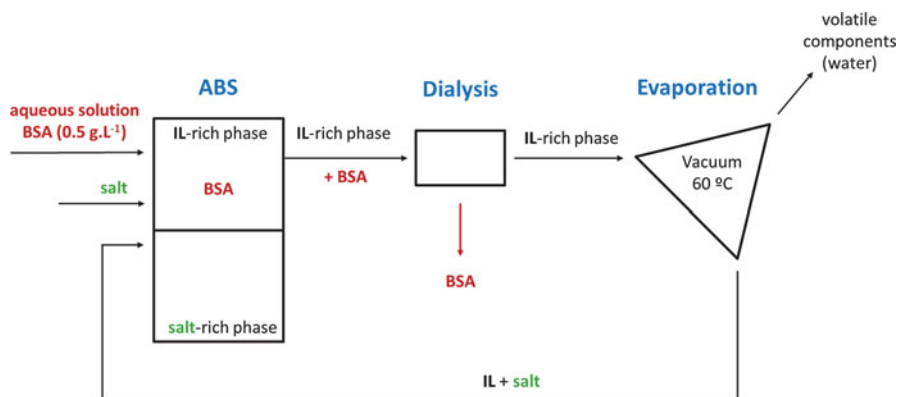
**Fig. 12.8** Schematic representation of the process developed in [75] to recover the dyes and to reuse the IL-rich phase

then used to precipitate the dyes. For each dye a specific via of precipitation was applied, for (i) Sudan III a slow process of water evaporation at  $60^\circ\text{C}$  was used, and for the recovery of (ii) indigo blue, a decrease in temperature until  $4^\circ\text{C}$  was defined (Fig. 12.8). After the temperature strategy was applied, each solution was filtered and each dye recovered as a solid. Then, the removal of each dye was quantified in the IL-rich phase proving the IL solution regeneration (i.e., the IL

phase is free of dye). As the authors mentioned, aiming at the development of a cost-effective and sustainable process, the possibility to reuse the IL-rich phase was also checked, by means of the identification of the saturation limit of the IL-rich layer and the number of cycles in which this phase can be used. Thus, in the method defined for Sudan III, after the dye filtration, water was added in the IL-rich phase to regenerate it. Since the saturation limit of the IL-rich phase was defined as being well above the saturation limit of each dye in water, the authors concluded that the IL-rich layer may be several times reused, at least up to 800 times without reaching saturation [75].

One year after in 2015, ABSs based in phosphonium (tetrabutylphosphonium bromide,  $[P_{4444}]Br$ ; tetrabutylphosphonium chloride,  $[P_{4444}]Cl$ ; tri(isobutyl) methylphosphonium tosylate,  $[P_{i(444)1}][C_7H_7SO_3]$ ; tributylmethylphosphonium methylsulfate,  $[P_{4441}][MeSO_4]$ ) and ammonium (tetrabutylammonium chloride,  $[N_{4444}]Cl$ ) families combined with the potassium citrate buffer at pH 7.0 were explored in the extraction of bovine serum albumin (BSA) [76]. The phase diagrams of the five IL-based ABSs were determined including the tie-lines and tie-line length assessment, and then the partition of BSA through the two aqueous phases was tested. The main results have shown that the majority of the systems under study allowed the complete extraction of BSA for the IL-rich phase in just one single step of extraction, being  $[P_{4444}]Br$  the only exception. In this case, the BSA precipitated due to the hydrophobic nature of the IL. Other conditions were tested considering the BSA partition to the IL-rich layer, namely, the influence of the (i) IL and citrate salt content aiming at the reduction of the costs associated with the amount of phase components used to form the ABS and (ii) the protein content. These conditions were tested for the system composed of  $[P_{i(444)1}][C_7H_7SO_3]$  (20–30 wt%) + citrate buffer (20–30 wt%) + water with concentrations of BSA varying from 0.5 to 10.0  $g\cdot L^{-1}$ . The main results suggested the possibility to decrease both the amounts of IL and salt and still maintain the complete extraction efficiency of the protein up to 10  $g\cdot L^{-1}$ . As a final step, the authors assessed the recovery of the protein and the IL-rich phase recycle, being this used to perform a second cycle of extraction (sequential ABSs were prepared) to infer about the possibility to perform sequential extractions of BSA using the same IL-rich phase. This allows the definition of a more sustainable process, in which not only its economic impact is decreased but also the environmental impact is lowered. In this context, three steps of sequential extractions were carried considering the system based in 30 wt% of  $[P_{i(444)1}][C_7H_7SO_3]$  + 30 wt% of citrate buffer and 40 wt% of an aqueous solution containing BSA at 0.5  $g\cdot L^{-1}$ . In this work, BSA was removed for the IL-rich phase by dialysis. Then, the IL-rich phase was cleaned through the same treatment for each cycle of extraction. First, the IL-rich phase was dried under vacuum conditions and at 60 °C to remove water (the volatile component); then, both salt and IL components were reintroduced in the system to form a new ABS. In this last step, specific amounts of salt and BSA (aqueous solution at 0.5  $g\cdot L^{-1}$ ) were added to prepare exactly the same systems defined in the first step of extraction. This procedure was repeated to perform the three cycles of extraction. The final results regarding the isolation of BSA and the recycle of IL and salt





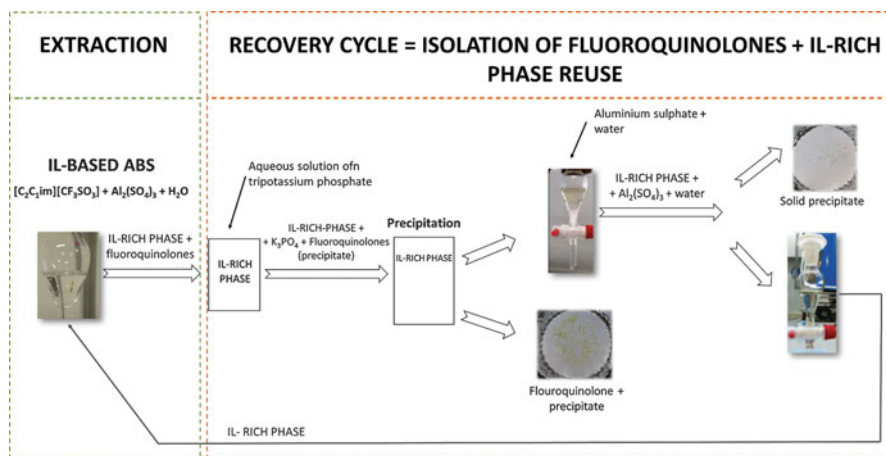
**Fig. 12.9** Integrated process developed in Ref. [76] to fractionate and isolate BSA and to reuse the IL-rich phase

(described schematically in Fig. 12.9) indicated the complete recovery of BSA from the IL-rich phase. Moreover, and considering the overall results obtained for the various steps of extraction, it was confirmed the complete extraction of BSA with its structure integrity was maintained, in all cycles, consequently indicating the potential reuse of the IL, however, with small losses of 1.74 wt% [ $P_{i(444)1}$ ] [ $C_7H_7SO_3$ ] *per* cycle, in a total of 9.96 wt% of IL loss regarding the entire process [76].

In 2016, some progresses have been carried out. Almeida and collaborators [77] have shown the feasibility of several IL-based ABSs in the recovery of quinolones from the aqueous media. They have selected ABS based in imidazolium and phosphonium families conjugated with the aluminum-based salt, a salt commonly used in the water treatment plants. The one-step extraction approach was applied in the extraction of six fluoroquinolones (ciprofloxacin, enrofloxacin, moxifloxacin, norfloxacin, ofloxacin, and sarafloxacin), being the extraction efficiency data achieved up to 98 %. In addition to the extraction study, the authors also performed studies considering the recyclability and reusability of the solvents. To accomplish that, the example of the ciprofloxacin was taken and its precipitation studied, considering the alteration of the pH of the IL-rich phase, the layer in which the fluoroquinolone was concentrated. The authors used the alteration of the pH of the system to induce the precipitation of this fluoroquinolone. At pH 7.2 (the pH of the system), the acidic dissociation constants of ciprofloxacin are neutral or in its zwitterionic form. The authors explain that, because these species are nonionic, the fluoroquinolone precipitation from the IL-rich phase is possible to occur, a phenomenon justified by the decrease of its solubility in aqueous media for the non-charged species. In this sense, this fluoroquinolone was initially dissolved in an aqueous solution in which HCl and then NaOH were added to change the pH of the solution from 5 to 9. The results obtained have shown that the maximum precipitation of the ciprofloxacin occurred at pH 7.2, being this condition selected for further studies. The authors showed that the percentage of fluoroquinolone

precipitated increased from pH 5.23 to 7.23 (the compound is in its neutral form), but decreased in the pH range of 7.23–9.53, due to the presence of its zwitterionic and neutral forms. A second study was done aiming at the recycling of the IL and the isolation of the fluoroquinolone. In this step, the same precipitation procedure was tested but this time in an aqueous solution of the salt used in the ABS formation,  $\text{Al}_2(\text{SO}_4)_3$ . Three distinct salts were investigated regarding their capacity to precipitate ciprofloxacin by changing the pH of the saline solution to an alkaline solution, KOH,  $\text{K}_3\text{PO}_4$ , and  $\text{K}_2\text{CO}_3$ . As anticipated,  $\text{K}_3\text{PO}_4$  was the most efficient ( $96.97 \pm 0.35$  of compound precipitated) salt promoting the ciprofloxacin precipitation, not only because the fixation of the pH around 7.2 but also due to its higher salting-out capacity. Moreover, the authors identify also the formation of another crystal,  $\text{AlPO}_4$ , precipitating together with the ciprofloxacin, and according to the authors it corresponds to the white crystals [77]. Considering all the process details discussed, Almeida and collaborators developed a process diagram in which each step is evidenced, namely, the fractionation of the fluoroquinolones from the aqueous to the IL-rich phase and the treatment of this phase enclosing both steps of ciprofloxacin isolation and IL recycling, as described in Fig. 12.10. Finally, aiming to evaluate the viability of the process developed, consecutive cycles of fluoroquinolone isolation and IL recycling and reuse were tested, being the results indicating that the capacity of  $[\text{C}_2\text{C}_1\text{im}][\text{CF}_3\text{SO}_3]$  to remove fluoroquinolones from water and concentrate them in the IL-rich phase is maintained during the four cycles with low cross contamination of the phases and low losses of IL between the four cycles of extraction.

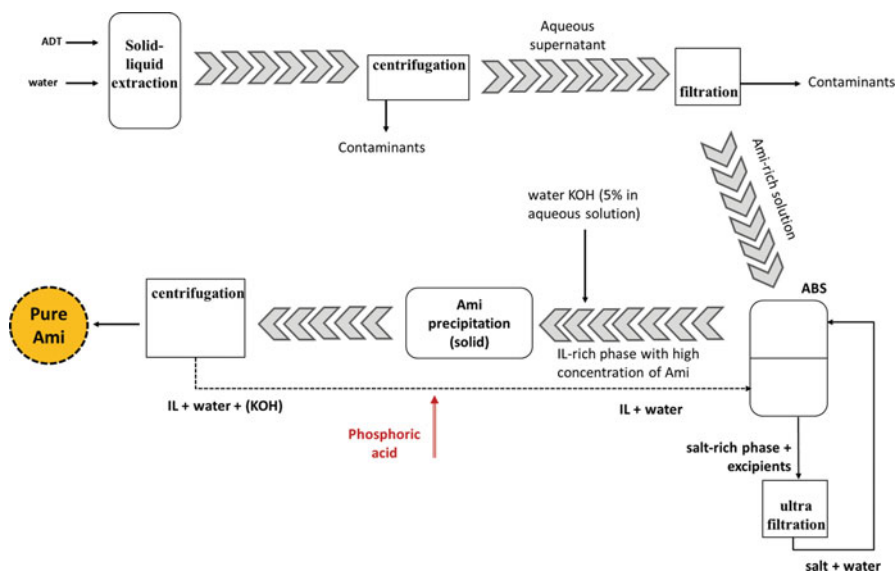
Recently, Zawadzki and collaborators [78] have developed a process for the recovery of the antidepressant drug amitriptyline hydrochloride from their pharmaceutical residues by applying ABSs based in five ILs, these belonging to the phosphonium and ammonium families. In this study, the removal of the excipients



**Fig. 12.10** Schematic representation of the process developed in Ref. [77] to recover fluoroquinolones and recover and reuse the IL-rich phase regarding various cycles

used in the antidepressant formulation was attained. The systems under study were based in the ILs, tetrabutylammonium bromide ( $[N_{4444}]\text{Br}$ ), tetrabutylammonium chloride ( $[N_{4444}]\text{Cl}$ ), tetrabutylphosphonium bromide ( $[P_{4444}]\text{Br}$ ), tributylmethylphosphonium methylsulfate ( $[P_{4441}][\text{CH}_3\text{SO}_4]$ ), and tri(isobutyl)methylphosphonium tosylate ( $[P_{i(444)1}][\text{C}_7\text{H}_7\text{SO}_3]$ ), and salts, the potassium phosphate tribasic ( $\text{K}_3\text{PO}_4$ ), potassium phosphate monobasic ( $\text{KH}_2\text{PO}_4$ ), and potassium phosphate buffer (prepared with  $\text{KH}_2\text{PO}_4$  and potassium phosphate dibasic –  $\text{K}_2\text{HPO}_4$ ). The experimental study started with the optimization of the main conditions associated with the use of ABS as purification platforms using the commercial standard of the antidepressant. The effects of various conditions of the process of purification, namely, the IL type, the pH of the system, and the composition of the mixture applied in the extraction step, were evaluated and then used in the process optimization, aiming to maximize the extraction of the antidepressant drug. The main results obtained by the application of IL-based ABS indicated the high capacity of these ABSs to concentrate the amitriptyline toward the IL-rich phase (the most hydrophobic layer), a conclusion represented by logarithmic functions of the partition coefficients higher than 2.5 and extraction efficiencies between  $93\% \pm 3\%$  and  $100\%$ . Then, the pH of the systems and different mixture points (meaning distinct compositions of the ABS) were tested and the best systems and conditions adopted in the development of the integrated process considering the purification of the antidepressant from the real pharmaceutical residue.

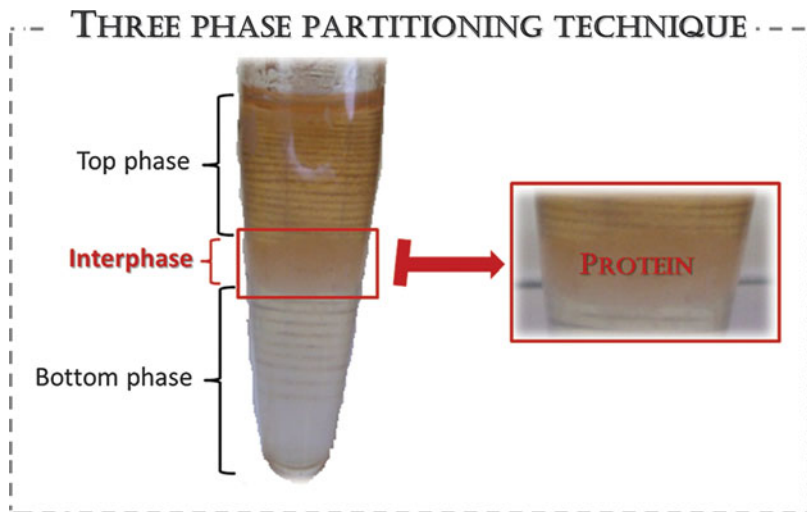
The three-step process was proposed [78] including the solid–liquid extraction of amitriptyline hydrochloride from ADT 25 pills, a purification step using the IL-based ABS with high purification performance defined in the optimization study, and finally the polishing or isolation of the drug by precipitation with anti-solvent (Fig. 12.11). Water was used as solvent in the solid–liquid extraction step, resulting in an aqueous extract rich in amitriptyline hydrochloride. This extract was centrifuged and filtrated aiming at the removal of the insoluble excipients present, the final amount of target antidepressant measured, and the most efficient IL-based ABS prepared using, as basis, the drug-rich aqueous extract. In general, the results of partition coefficients obtained in this second step were similar to those achieved in the optimization step. Then, the isolation of the target antidepressant from the IL layer was investigated by changing the pH of the system, promoting the appearance of the uncharged form of amitriptyline, which consequently decreased its solubility in water/aqueous media. For that purpose, an aqueous solution of KOH was added to the IL-rich phase considering the ABS based in the potassium phosphate buffer (pH 6.6) and only water in the  $\text{K}_3\text{PO}_4$ -based ABS (the neutral form of the drug is guaranteed in the characteristic pH of ABS based in this salt). The step of precipitation was performed at low temperature ( $277 \pm 1\text{ K}$ ), again to decrease even more the drug's solubility. The results evidenced that higher precipitations were achieved ( $95\% \pm 2\%$ ) for the ABS constituted by  $[N_{4444}]\text{Br} + \text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$  and  $[N_{4444}]\text{Cl} + \text{K}_3\text{PO}_4$ . As a final step, the authors proposed the two phases of recycling. The IL-rich phase should be neutralized by the addition of phosphoric acid, and the salt-rich phase should pass by an ultrafiltration to remove the high molecular weight excipients present.



**Fig. 12.11** Representation of the integrated process developed in Ref. [78] to recover amitriptyline from pharmaceutical residues

Ionic liquid three-phase partitioning (ILTPP) systems were recently developed by Alvarez-Guerra et al. [66, 67, 79], considered as a new type of extraction/separation technology for proteins. The three-phase partitioning (TPP) systems represent an emerging technique for protein separation/extraction, involving the accumulation of the target protein at the liquid–liquid interface created between two liquid phases, as depicted in Fig. 12.12.

TPP can be applied to purify and/or concentrate proteins, commonly used as a one-step purification methodology, and it stands out for being simple, inexpensive, scalable, and rapid procedure that may lead to high purification factors (>100-fold) and great final purity levels (between 70 % and 85 %) [80, 81]. Some benefits emerge from the ILTPP, namely, the combination of the advantages of IL-based ABS and the TPP technique. The authors applied this technique to extract lactoferrin, a bovine whey protein with recognized biological properties [82], purified at industrial scale by means of cation exchange chromatography techniques, suffering from high costs and relatively low yields [83]. They tested different combinations of ILs and salts to prepare the ILTPP systems as well as the conventional system based in *t*-butanol, for comparative terms. The system based on 1-butyl-3-methylimidazolium trifluoromethanesulfonate, [C<sub>4</sub>C<sub>1</sub>im][CF<sub>3</sub>SO<sub>3</sub>], at moderate acidic conditions, leads to high protein accumulation in the interphase and high lactoferrin–BSA selectivity. The authors have also addressed the IL recovery and recycling [66], considering the use of various alternatives [67]. The first approach considered the thermodynamic characterization of the ILTPP systems of interest, based on the use of [C<sub>4</sub>C<sub>1</sub>im][CF<sub>3</sub>SO<sub>3</sub>] and

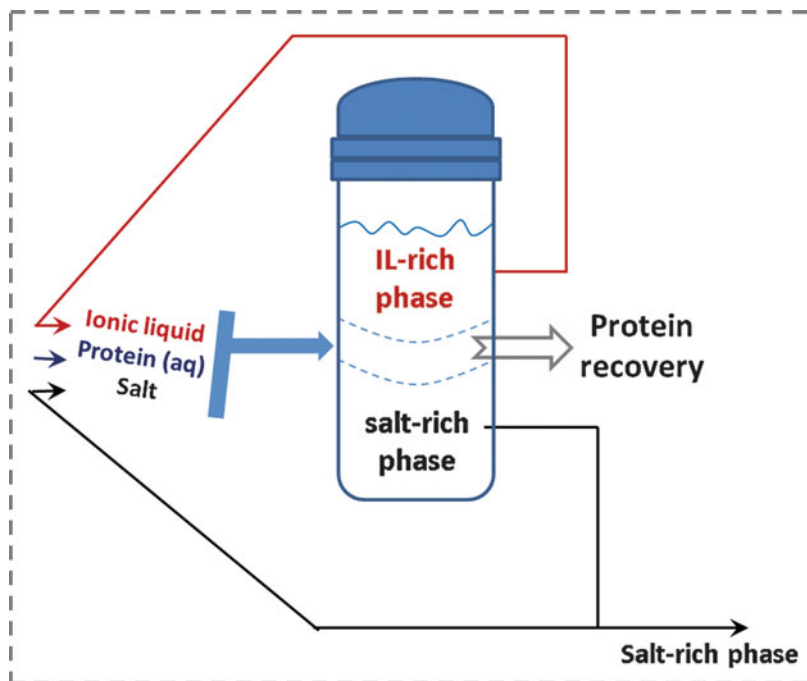


**Fig. 12.12** Schematic representation of the three-phase partitioning technique applied to the extraction of proteins

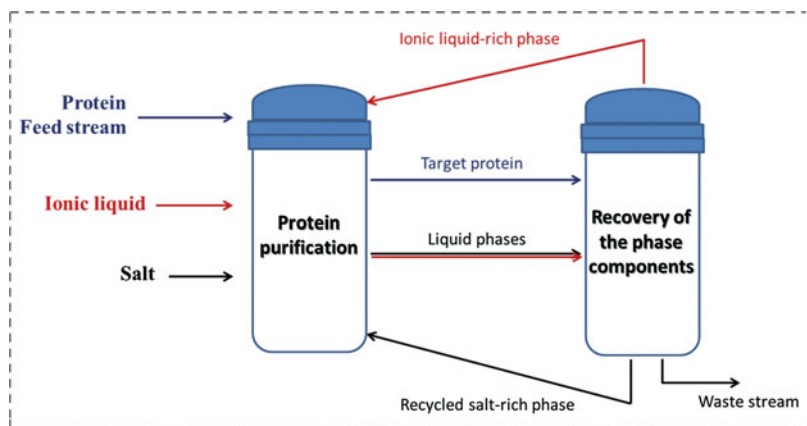
$\text{NaH}_2\text{PO}_4$ . The fraction of IL in the salt-rich phase, impossible to recycle to the ILTPP process, was determined as well as the influence of the amount of protein treated in the ILTPP systems studied. In contrast to previous studies on the recovery of the IL from IL-ABS based only on experimental data of the thermodynamic equilibrium [5, 46, 47, 53], here the ILTPP was modeled, allowing the operational variables and constraint characteristic of the process to be taken into account in the analysis and optimization of the operating conditions, able to minimize the IL losses in the overall process. The determination of the IL fraction possible to be recycled was described by the parameter  $R$ . After the thermodynamic analysis, some simplifications were taken into account, namely, the capacity to recycle the entire IL-rich phase, meaning the high IL recovery, since most of it was present in the top phase (richer in IL) – Fig. 12.13 – and that, in this case, only a fraction of the salt-rich phase is possible to be recovered and reused, being this dependent on the concentration of lactoferrin present in the initial feed and the salt added to prepare each new cycle of extraction.

In general, it was noticed that the distribution coefficient of the IL between the two phases decreases with the amount of salt introduced in the system, favoring the IL recyclability with the maximum  $R$  obtained being around 99 % [66].

For the ILTPP systems studied, the fraction of IL that is not possible to be recycled ( $1-R$ ) was monitored in each cycle of extraction, taking into account different lactoferrin loads [66]. It was concluded that this parameter varied from almost 5 %, at low protein concentrations in the feed stream, to values around 0.8 %, when high protein mass fractions were considered [66]. It was finally demonstrated that the ILTPP process can lead to a potential reuse of more than 99 % of the IL. Later, Alvarez-Guerra et al. [67] have proposed two other alternatives to maximize the fraction of IL being recycled. Figure 12.14 depicts the block



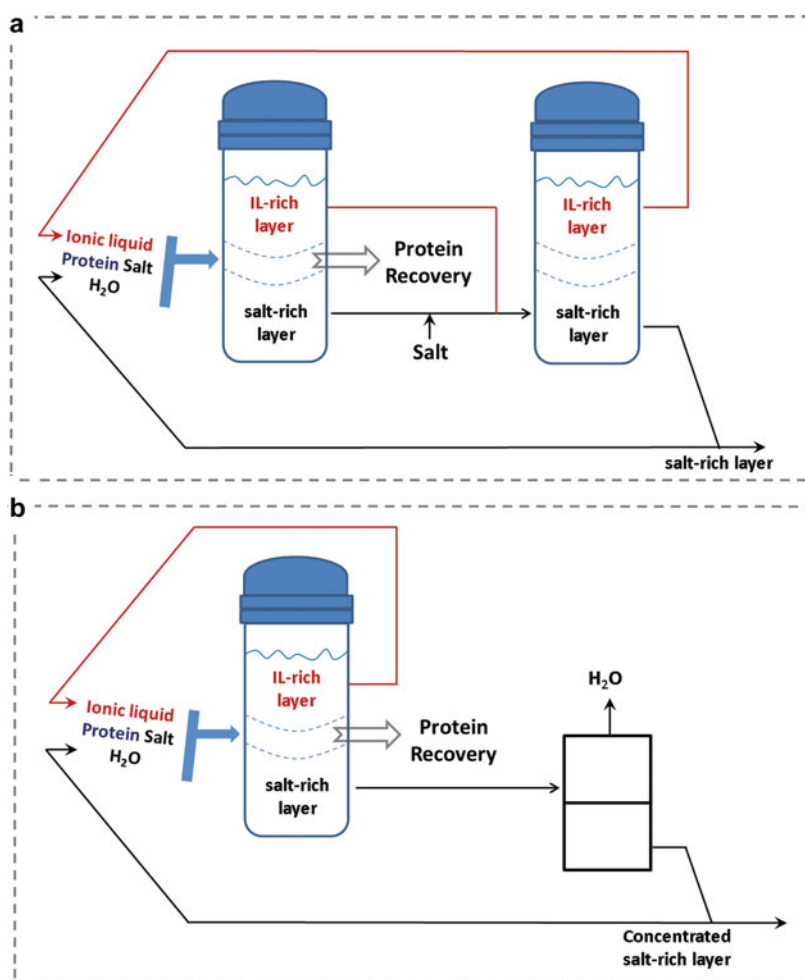
**Fig. 12.13** Schematic diagram of the IL recycling approach developed in [66] considering the use of  $[\text{C}_4\text{C}_1\text{im}][\text{CF}_3\text{SO}_3]$  TPP system to recover lactoferrin



**Fig. 12.14** Representation of the block diagram of the ILTPP process proposed in [67] in which an additional step of recovery to reduce the fraction of IL loss in the process is presented

diagram of the ILTPP process based on the  $[C_4C_1im][CF_3SO_3] + NaH_2PO_4$  and  $[C_4C_1im][CF_3SO_3] + NaH_2PO_4/Na_2HPO_4$ , in which the additional recovery step to reduce the IL mass fraction loss investigated by the authors is presented [67].

Two alternatives were investigated through modeling, aiming at increasing the IL recyclability: (1) the addition of extra amounts of salt increasing its concentration (Fig. 12.15a) and (2) the concentration of the salt-rich phase by evaporation of some water, as depicted in Fig. 12.15b. Considering the first approach, two sequential separation units were considered, the first representing the lactoferrin recovery and the second the IL recycling.



**Fig. 12.15** Schematic representation of the two processual approaches developed in [67] regarding the IL recyclability: (a) represents the addition of extra amounts of salt and (b) represents the concentration of the salt-rich phase by means of vacuum evaporation of some of the water content

The introduction of the lactoferrin feed corresponds to the addition of significant amounts of water to the process, which is very relevant in the process of recyclability of the phase promoters. This water prevents the complete recycling of the salt-rich phase, due to the fact that, if the salt-rich phase is directly recirculated, the extra amounts of water will be changing the individual composition of each component. However, if the same amount of water included in the lactoferrin feed and introduced in the system is previously removed by evaporation from the salt-rich phase, IL and salt can be easily recycled, without any change in the composition of the ILTPP system [67]. It was also demonstrated that the salt concentration increase has a limited effect on the recovery of lactoferrin for high protein concentrations, while the application of evaporation of water could promote the IL's and salt's complete recycling [67].

As suggested by the authors [67], the conclusions of this work can be extended to IL-ABS, with the required development of specific strategies for the recovery of the solute, since ILTPP and IL-based ABS are based on the same thermodynamic systems and rules.

Despite the absence of experimental results describing and analyzing the strategies of IL recycling and isolation of the target biomolecules, other works [7, 84, 85] are applying IL-based ABS in the purification or extraction of various biomolecules using distinct extractive approaches and identifying theoretical possibilities for the recycling and reuse of the main components. Souza and co-workers [84], for example, have shown the application of polymer+salt ABS based in different imidazolium ILs used as adjuvants. Adjuvants are compounds used in small amounts, for example, 5 wt% as used in this work, to promote the alteration of the physicochemical properties of the original ABS, which normally are described by increases in the purification and extraction performances of various biomolecules. In this work, the authors applied these systems to promote the purification of an enzyme produced by submerged fermentation by *Bacillus* sp. ITP-001. The first optimization step was performed using the commercial lipase B from *Candida antarctica* (CaLB), in which a purification factor of  $5.22 \pm 0.65$  is much better than the result (purification factor of  $3.25 \pm 0.65$ ) obtained for the common polymeric ABS (without IL). After a careful optimization of the pretreatment task (salt precipitation and dialysis) and the ABS type and operational conditions, a purification factor of 245 for the lipase from *Bacillus* sp. ITP-001 was obtained using the system PEG 1500+phosphate buffer+1-hexyl-3-methylimidazolium chloride ([C<sub>6</sub>C<sub>1</sub>im]Cl) at pH 7. In this work [84], the authors explain that the use of the IL as adjuvant is promoting the manipulation of the contaminant proteins' migration to the opposite phase in which the lipase is concentrated, allowing the concentration of the lipase in the salt (phosphate buffer)-rich phase. The authors close this work describing a potential strategy to isolate the enzyme and contaminant proteins, from the salt- and polymer-rich phases, respectively, by using a dialysis process in each phase. According to their description, after the dialysis of both layers, the contaminant proteins and lipase can be collected in their most pure state and each phase reintroduced in the system to promote new cycles of purification [84].



Still in the purification of macromolecules appeared the work of Lee and coauthors [85]. Briefly, a new set of self-buffering ILs based in Good's buffer anions were synthesized, applied in the formation of different ABSs composed by these GB-ILs and potassium citrate and found to be significantly selective for the partition of the lipolytic enzyme from *Pseudomonas cepacia* toward the GB-IL-rich phase. The results allowed the development of a sustainable integrated catalytic process in which the self-buffer nature of GB-ILs and their capacity to maintain the enzyme stable are conjugated. In this sense, the authors meant that because the enzyme participating as a catalyst in the reaction is concentrated in the GB-IL-rich phase (with buffer properties), if the product formed in the reaction is hypothetically concentrated in the saline-rich phase, it will be possible to promote the reaction and the removal of the product in real time and as simultaneous steps, being the enzyme always pure and free to continue its catalytic action. Summing up, the authors attest that the process will allow the recovery and reuse of the top phase enriched in GB-ILs which will diminish the economic and environmental effects of the process [85].

Later in 2016, Santos and collaborators [7] studied the extraction and purification of capsaicin from pepper *Capsicum frutescens*, by applying various ABSs composed of acetonitrile and three cholinium-based ILs (cholinium chloride, cholinium bitartrate, and cholinium dihydrogenocitrate). The phase diagrams were prepared and the partition of capsaicin optimized considering the cholinium anion, the composition of the system, and the temperature of fractionation. After a careful optimization of the process of partition, and with a simple and more sustainable technology, capsaicin was extracted from pepper and purified through the application of acetonitrile + cholinium IL-based ABS, being defined an extraction efficiency of 90% and a purification factor of 3.26, considering as main contaminants the phenolic compounds extracted from the fresh biomass. Again, experimental tests were not performed, but the authors suggest a methodology to isolate capsaicin from the acetonitrile-rich phase and the phenolic compounds from the cholinium-rich phase, allowing thus the reutilization of the main phase formers. In this context, an evaporation step is described for the recovery of acetonitrile and isolation of capsaicin. In what concerns the recycle of the cholinium-rich phase contaminated with the phenolic compounds, an acidic precipitation step using HCl was defined to precipitate the contaminants, followed by the neutralization (NaOH) of the cholinium-rich phase to be reincorporated in the process [7].

## 12.3 Conclusions

Much attention has been given to ILs and their applications as solvents in different fields [6, 86]. The crescent number of works evidencing the use of ILs as solvents [86], and in particular as phase formers of ABS, is evident [6]; however, the number of studies reporting the scale-up of these processes is indeed very limited. The limited industrial impact of this technique results from a limited knowledge

about the market and industry needs by the academic groups working on this field. These techniques, based on special solvents, can only be economically applied to the extraction of molecules or compounds with high value. The use of ILs for the extraction and purification of compounds of low cost that can be obtained from synthetic pathways, or molecules with low economic/industrial value, is not recommendable [86]. Another aspect is the extraction of compounds that are only needed in a small scale and that can be purified by chromatographic techniques and for which the use and application of ABS does not make sense, since these processes are by far more efficient regarding their purification capacities; however, compounds, for which chromatographic techniques are not adequate, are improved candidates to be purified with alternative techniques such as ABS. Taking these factors into account and focusing on both economic and environmental problems/benefits still strongly associated with ILs, it is crucial to study the ILs' effective recovery, removal, and recyclability [6, 45, 86] and to encourage the use of ILs in separation processes. Until today, and taking into account the studies reviewed in this chapter, the evaporation of water or other organic solvents used in the back-extraction for the isolation of the target compounds extracted, or their precipitation by anti-solvents, is the process most used. The results reported indicate that it is possible to regenerate and reintroduce in new cycles of extraction the IL or IL-rich phase recovered while maintaining the IL integrity, the compound integrity, and the initial efficient extractions. However, the number of works studying the recyclability of the phase components is only occasional, and we are now limited, principally when ILs are part of an ABS used to purify a specific compound, to a few examples in which the purification of one enzyme [66, 67, 84, 85], four proteins [23, 76], three antioxidants [65], two dyes [75], and four active pharmaceutical ingredients [77, 78] was attempted. The need for more studies contemplating the purification of a variety of other (bio)compounds from a diversity of relevant raw materials integrated with studies regarding the recyclability of ILs and phase-forming components in general is apparent.

## 12.4 Critical Analysis and Future Perspectives

The use of ILs in technologies of purification is often criticized due to their high cost, when compared with other and more traditional solvents. It is thus mandatory to perform studies in which several variables are taken into account, namely:

- The cost of the target product, consumables, equipment, human resources, and licensing
- The purity required for the target product since the price of each technology will increase with the purity level required
- The number of potential molecules to be extracted, since the higher the number of compounds recovered, the higher the economic return of the entire process

- The study of processes with industrial importance, i.e., processes planned to purify compounds with real industrial relevance
- The possibility to recover and reuse the phase-forming components to decrease the environmental impact and to increase the viability and sustainability of IL-based ABS

As mentioned, there are some processes/strategies that can be applied to reduce the overall cost of a process of purification by the use of IL-based ABS. Among these, only nondestructive processes can be used, while there are some good strategies to remove ILs in low concentration, and while others are excellent to be applied in the recovery of ILs present in high concentrations in aqueous media. Still, there is much more open space to explore and develop novel strategies for the recovery of ILs while envisaging their use in scaled-up technologies.

This review, while still not very common, shows that some authors have started looking into the recovery and recycling of ILs applied in extraction steps, which is not surprising since they are normally the most expensive components used. However, the effect of impurities (both from contaminants and from IL degradation) is not addressed neither is their accumulation on the system that may be very important for cyclic processes. The recovery of other phase-forming compounds is also seldom addressed. The idea conveyed in most works that IL-based ABS display superior extraction performance is only supported by a limited number of extraction/recyclability cycles that do not allow to satisfactorily conclude about the success of the actual extraction process in the long run. To soundly establish ABS as sustainable technologies, the study of a higher number of cycles of extraction and recyclability must be carried out as this is the only way to understand the viability and sustainability of any extraction process. Other important issues to be focused in future publications are a set of properties of ILs, namely, purity, stability, biodegradability, and toxicity, since the control and deeper understanding of these properties can be determinant in the sustainability nature of IL-based separation processes. A life cycle assessment should eventually be carried out to the phase-forming components used in IL-based ABS to understand the impact of each individual component used in the purification processes.

There are other conditions that can be considered to design more cost-efficient and sustainable extraction strategies, namely, the design of purification processes with a lower number of separation steps, which can be translated into less components to be removed and less amounts of aqueous effluents to be treated and recycled, which finally can be translated into a reduced waste content and a lower environmental footprint.

Summing up, in order to replace conventional extraction approaches by a process using ILs, it is mandatory to initially evaluate its costs, environmental impact, and scale-up viability.

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