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Recent Advances of Ionic Liquids in Extarction of Biologically Active Compounds: A Review

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Abstract Regarding to green feature and interesting adjustable properties of ionic liquids, they have left their footprints in large number of science areas. In last few years they have been involved in extraction of bio-active substances as well. Here we have summarized recent experiments in case of extraction of biologically active compounds using ionic liquids. Some of these studies are novel and have been done for first time. Most of these extractions are conducted by Ionic Liquid Aqueous Biphasic System (ILABS) method, while some others have used ionic liquids as (co) solvents. Besides, solid-phase system is applied for caffeine and keratin extraction.

Keywords Ionic liquids, Extraction, Bio-molecules, Ionic liquid biphasic systems, Solid-phase extraction

1. Introduction

Ionic liquids (ILs) are a new group of organic salts generally composed of organic cation (e.g. imidazolium, pyrrolidinium, pyridinium tetraalkyl ammonium, or tetraalkyl phosphonium) and inorganic or organic anion (e.g. tetrafluoroborate, hexafluorophosphate, bromide) which are liquid below 100 °C. ILs have been widely recognized due to their unique properties. From the extended list of fascinating characteristics, we can name their high chemical and thermal stability, negligible vapor pressure, nonflammability, nonvolatility, tunable viscosity, high ionic conductivity, adjustable miscibility and polarity. Low volatility makes the able to easy separations of components (gases and volatile liquids) out of ILs. They have also been shown to have good solvation properties. Depending on their structure, they can dissolve polar and non-polar compounds. With these characteristics, they could be a greener replacement for volatile organic compounds (VOCs) in industrial processes [1-3].

ILs properties are strongly dependent on their cation and anion structures [1, 4]. Since high numbers of possible combinations provide so many ILs with various properties they are known as “designer solvents”. The specific aspect of an IL can be tailored by altering the cation and anion structure regarding to required application. For more information, readers are referred to some reported reviews about different cations and anions combinations in ILs and accordingly the different properties [5-7].

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ILs specific potential makes them a noticeable choice capable of wide applications. These new materials were successfully applied on gas chromatography (GC) [8], capillary electro chromatography [9] and liquid chromatography (LC) [10]. They have also used as sorbents in solid-phase microextraction (SPME) [7] and solid-phase extraction (SPE) [11, 12]. It should be mentioned that their application as a medium for reactions, such as oxidation, thermal fluids, lubricants in high temperature environment, and extraction solvents has been extensively investigated in last decades [5-7, 13, 14].

The present review is focused on recent advances of ILs in extraction of biologically active compounds. It is devoted to ionic liquid aqueous biphasic systems (ILABS), liquid-liquid extraction (LLE) and solid-phase extraction (SPE) techniques.

2. Recent Bio-Molecules Extraction Using ILs

Here, ILs application in bio molecules extraction is categorized due to applied method.

2.1. The Ionic Liquid Aqueous Biphasic System (ILABS) Based Extractions

Nowadays development of efficient, cost effective and environmentally friendly processes is the major industrial challenge. Regarding to recent investigations, it seems that liquid-liquid extraction (LLE) techniques offering the best gains such as higher yields, purities, capacity, and better selectivity between recovery and purification [15, 16]. Commonly in LLE processes, VOCs with toxic and denaturing characters are employed. For this reason LLE process may have some disadvantages with negative

environmental effect despite its benefits [15-19]. To overcome this issue, so many studies have been done [20-22] and as a result, regarding to ambient friendly thermo-physical properties of ionic liquids (ILs), using them as extraction media and their replacement with VOCs, is one of the best suggestions.

In biotechnological applications using of ILs in LLE process is mostly based on aqueous biphasic systems (ABS). ABS are usually formed by polymer-salt, polymer-polymer and salt-salt combinations in an aqueous solution. Firstly it was used for bio-molecules extraction and purification by Albertsson in 1958 [23]. Today it is known as a promising technique that provides a fast, economical and gentle recovery and purification of bio-based compounds [24] and has been extended to the separation of cells, viruses, proteins, membranes and other added-value bio-molecules [25].

The first report of combination of ILs, ABS and salt was in 2003 by Rogers [26]. Ionic liquid based aqueous biphasic systems (ILABS) create such a biocompatible media with negligible viscosity, quick phase separation, little emulsion formation, high extraction efficiency and free of VOCs environment [27]. A large amount of studies are done about phase behavior in ternary systems composed of {ILs + water + salt} which can be found in literatures [28-30]. These days, ILABS based extraction has found its platform as a potent method for bio-molecules separation and purification in a wide range [24]. It has been applied in extraction and purification of antibiotics, aminoacids, drugs, proteins, alkaloids and small organic molecules [29, 31-34]. Here we try to review the application of ILABS in bio-molecules extraction in recent years.

There is a report about the extraction of some specific bio-molecules using ILABS composed by hydrophilic ILs and aminoacids at 298K and atmospheric pressure [35]. In the studied systems, three different aminoacids: l-lysine, d,l-lysine HCl and l-proline were considered while ILs were the combination of 1-butyl-3-methylimidazolium cation with tetrafluoroborate, triflate, and dicyanamide anions – $[C_4mim][BF_4]$, $[C_4mim][CF_3SO_3]$, and $[C_4mim][N(CN)_2]$. In this work, ABS have been established based on an aqueous solution of each aminoacid and aqueous solution of different hydrophilic ILs and finally were evaluated through their capability in caffeine, ciprofloxacin and ciprofloxacin HCl bio-molecules extraction. Results show that [C4-mim]-based ILs are able to induce aqueous phase extraction in the presence of aminoacids by this order: $[BF_4]^- > [CF_3SO_3]^- > [N(CN)_2]^-$, inversely proportional to the hydrogen bond accepting strength of the IL anion. On the other hand, aminoacids potential to produce ABS follows this order: l-lysine≈d,l-lysine HCl > lproline.

An Iranian research team have done a relevant experimental work to show the excellent potential of ILABS in separation and purification of bio-molecules. They added a small amount of IL 1-butyl-3-methyl imidazolium bromide ($[C_4mim][Br]$) to the ABS based on Polyethylene Glycol {PEG400 + $K_3C_6H_5O_7$} to promote its applicability in hydrophobic bio-molecules extraction [36]. In this work, the LLE data are correlated using the NRTL model. They found that the ILABS has higher affinity for the hydrophobic PEG besides phase-forming capability promotes in compare to the ABS. The partition coefficient of L-tryptophanbio-molecule examined by this ILABS and the results represent extraction potential enhancement, up to twice caused by small quantity of $[C_4mim][Br]$.

Moreover, ILs effect on {polyethylene glycol (PEG) + Na_2SO_4} two phase system was studied in case of diverse antioxidants extraction [37]. Extraction efficiency was considered as a function of PEGs molecular weight and ILs chemical structures. It was found that all anti-oxidants preferentially partition for the PEG-rich phase while PEG molecular weight directly affect the two-phase formation ability. Improved extraction yield 80-99% was achieved in presence of IL in system which shows interesting advance application of ILs in biotechnological extraction and separation processes.

Proteins have also been extracted by ILs in last several years. Simultaneous extraction and purification of aleo polysaccharides (APS) and proteins is done in an ILABS in 2012 [38]. The {$[Bmim][BF_4]$ + NaH_2PO_4} ILATPS couples with dialysis membrane was selected as the media and effective parameters like, pH, temperature, type and etc, are studied in details. As results represent, the IL is highly selective toward proteins while, 95.85% proteins and 93.12% APS were respectively extracted into IL-rich phase and salt-rich phase. Proteins were simply separated by recycling the IL in a single step solvent (dichloromethane) extraction.

The application of ILs in extraction of lactoferrin; a high-added value protein from bovine whey has also been reported [39]. As results indicate, the activity coefficient is highly dependent on lactoferrin concentration and ionic strength. [Bmim][NTF2] and $BmimPF_6$ ILs found selective toward this protein and the highest yield achieved in low protein concentration (100 mg L_1), neutral pH (6.4–8.2) and low ionic strength (0.03 M). This study proves the ability of hydrophobic imidazolium based ILs in protein extraction.

Furthermore, guanidine based ILABS were studied for bovine serum albumin (SBA) extraction [40]. Guanidine ILs are green and superior in compare to imidazolium based. In this study, protein extraction efficiency was optimized through orthogonal experiment as a multifunction of IL mass, K_2HPO_4 and BAS mass, time and temperature. In conclusion, 99.6% achieved as process yield under the best condition. As results indicate, the protein conformation has been remained unchanged during the extraction. Due to promising reports, a wide perspective in large-scale separation and purification of bio-active ingredients opens up.

Apart from the proteins, other bio-molecules have also been extracted by the use of ILs. For example in 2010 vanillin partition coefficient were determined in several ILABS [41]. In that study, IL structure, vanillin

concentration and temperature studied as three effective parameters, in partitioning. In conclusion, the maximum extraction efficiency for [C_4mim][CH_3SO_4], [C_7H_7mim][Cl] and [amim][Cl] obtained at 298.15K while the best yield for [C_4mim][Cl] achieved at 308.15K. Encouraging results declare that ILs can be further used in vanillin extraction and separation from various sources.

Likewise, there is a report in selectively extraction of vitamin B12 from urine by use of ILABS technique [42]. In this work, hydrophilic ionic liquid (IL) 1-hexyl-3-methylimidazolium chloride and K_2HPO_4, used to form the biphasic system while the temperature, pH and ATPS composition optimized to achieve the highest possible yield. Under the optimized condition average extraction efficiency was 97%. The suggesting method shows an effective, environmental friendly, fast and selective extraction for B12 extraction. In compare to multi step organic solvent consumption, ILABS presents easier and faster process with higher extraction efficiency.

ILs has considered in an ILASB for enzyme extraction purpose too. Two imidazolium based ILs paired with alkylsulfate and alkylsulfonate anions were used to extract lipase A from Candida Antarctica [43]. [C_2mim][C_6SO_3] and [C_2mim][C_4SO_4] were the investigated ILs and it was shown that 1-ethyl-3-methylimidazolium butyl sulfate ([C_2mim][C_4SO_4]) with ammonium sulfate could lead to 99% enzyme recovery. Enhanced process time, energy consumption and high extraction efficiency in mild condition and great potential of ILABS in lipase extraction obviously are shown in this job.

Separation of poly and disaccharides were considered in 2012 [44]. In this work, two biphasic systems based on hydrophilic [C_8mim][Cl] IL with K_2HPO_4 and hydrophobic [C_6mim][BF_4] IL with IPA were employed while xanthan and maltose used to show a charged (anionic) polysaccharide and a neutral disaccharide. Polysaccharide (xanthan) completely isolated in IL-rich phase in [C_8mim][Cl] system while in case of [C_6mim][BF_4] system, it is transferred to the aqueous coacervate phase. Therefore it is concluded that biphasic system {[C_6mim][BF_4] + water + IPA} is favorable in view of the polysaccharide complex. It found that ILABS have enormous capability in neutral and charged substances separation which can be more specifically investigate in future researches.

Besides, ILs potential in dairy products treatment was satisfactorily highlighted [45]. An IL aqueous two-phase system composed of 1-Butyl-3-methylimidazolium tetrafluoroborate and trisodium citrate dihydrate were used to extract six sulfonamides (SAs) in milk samples. Several parameters such as temperature, time, solution pH, type and amount of salt and IL were the optimizing factors. This fast, feasible and effective method found with a successful developed results under the optimized condition. In comparison to conventional LLE, this technique avoids organic solvents consumption while extraction, clean-up and pre-enrichment can be done in one-step.

2.2. Text Solid-Phase Extraction (SPE)

ILs have been involved even in case of bio-molecule solid sources. Here we address several studies about ILs application in solid-phase extraction (SPE) method employed for some bio-active agents. For example about feathers which are known as a rich source of keratin with significant applications in flocculants, biomedical, biomaterials and adhesive [46-49]. A great amount of feather produces in poultry industry discharges pollutant gas which can cause environmental problems if not treated in time [50]. Therefore, it is quite noticeable to find an effective method to extract keratin from poultry feather. Superheated water and strong acid, alkali or high concentrated salt solutions have been used to extract the keratin previously [51-53]. These methods are multi-steps and can cause the protein degradation. For this regard, a group of scientists selected a common imidazolium based IL; [Bmim][Cl] to dissolve poultry feather for keratin extraction [54]. Optimum conditions were studied whereas Na_2O_3 and water were used to improve the extraction yield. Under the optimized condition, dissolution rate of feather was 96.7% and the keratin extraction yield is 75.1%. This method considered as a highly efficient method in keratin recovery and feather treatment.

Caffeine (1,3,7-trimethylxanthine) from alkaloids family, a bio-active ingredient consuming by human. This valuable compound has pharmaceutical [55], antibacterial and antifungal features [56] as well as its application in food industry. In order to enhancing the traditional separation methods, a study is conducted in 2013 based on ILs performance in caffeine extraction from one of its richest sources, Guaraná seeds (Paullinia cupana, Sapindaceae) [57]. In this work, several combinations of imidazolium and pyrrolidinium based ILs were investigated in a solid-phase extraction process. Regarding to results, excellent extraction yield obtained that makes the aqueous solutions of ILs a well alternative in large scale extractions of bio-molecules.

2.3. Extractions by Use of Ionic Liquids as (Co)-Solvents

Using solvents have always been a common method for extraction purposes. Beside the environmental issues, denaturing in bio-molecules is a disturbing point of organic solvents usage. To detract side effects, ILs replaced with common organic solvents recently and presented impressive results in some bio-molecules extraction cases. IL solutions, have significant recoverability and contamination reduction. In addition, in almost all processes chemical bonds of target extract remain unchanged.

Twenty one various ILs solutions applied to direct extraction of yeast proteins in order to reduce the process costs and energy for first time in 2010 [58]. Proteins were easily separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDSPAGE) and 2-dimensional gel electrophoresis (2-DE). As results indicate, chemical properties of target proteins were stable

during the process and3-(dimethylamino)-1-propylaminium formate ([DMAPA][FA]) found as the most effective IL solution for protein extraction.

Moreover, application of six different ILs as solvent is reported in dispersive liquid–liquid micro extraction (DLLME) of deoxyribonucleic acid (DNA); the main biomolecule containing the genetic information necessary for the viability of virtually every organism [59]. 1-(1,2-dihydroxypropyl)-3-hexadecylimidazolium bromide [C_{16}POHIM][Br] and N,N-didecyl-N-methyl-d-glucaminium bromide [$(C_{10})_2$NMDG][Br] represented the best results: remarkable extraction efficiency (97%) achieved by small amount (0.50 mg) of ILs. In conclusion ILs obtained obvious advantage in DLLME method and DNA extraction. They can be favorable alternatives for purification and extraction goals in larger scales.

Plus, a new synthesized ammonium-based IL [trialkylmethylammoniumbis-(2,4,4-trimethylpentyl)phosphinate] applied to extract Butyric Acid (BA) 0.724 Kmol/m3 solution in dodecane [60]. The reported distribution coefficient of BA in this ILs is over 80 in low concentrations of BA at aqueous phase. Regarding to results, the new ammonium based IL is a very efficient choice for BA extraction since multiple molecules of BA are formed BA-IL complexes with it in chain. Shown equilibrium data for BA indicate that this IL has highly promising characteristic in carboxylic acids extraction.

ILs have considerable application in biomass field as well. In biodiesel productions, jatropha is famous as a beneficial source. Previously the phorbol esters in jatropha oil reduced by strong bases and bleaching agents but this treatment didn't diminish their amounts to the non-toxic level [61]. In 2013, a co-solvent mixture of IL with methanol was used to extract and solubilize the jatropha phorbol esters simultaneously [62]. It was the first time for such an IL co-solvent system application in a single step phorbol esters and bio-oil extraction from jatropha. Under the optimized conditions, 30 wt% [C_2mim][$MeSO_4$] and 70 wt% methanol concluded to nearly complete auto-partition and extraction of bio-oil and almost 98% extraction of phorbol esters from original biomass. These encouraging data makes a wide perspective of ILs advantages for their further prosperous performance in industrial fields, specifically bio-science area.

3. Conclusions

Ionic liquids (ILs) have been noticed in last decades due to their specific properties and wide application in different industrial cases. Their green applications in various fields such as, reaction medium, thermal fluids, extraction solvent and etc, have been noticeable in last decades. Due to the ILs green and environmental friendly behaviour, replacing them with organic solvents is one of proposed developing techniques which declares promising results.

One of the concerning processes is bio-molecules extraction which so many studies conducted in case of their improvement and minimizing their environmental risks as small as possible. According to wide ability of ILs in different areas, scientists have tried to investigate ILs potential in bio-molecules extraction too. Here in this work, we tried to show the recent enormous ability ILs in biomolecules separation, extraction and purification. The promising results of mentioned studies show that ILs have left their effect on this area successfully and provide a new perspective in case of bio-chemical treatments.

The represented jobs are categorized based on the applied methods like ionic liquid biphasic systems (ILABS), solid-phase extraction (SPE) and solvent consumption. We tent to clarify this new achievement and have a deep look in recent advances of ILs applications. Mentioned progresses present novel methods in bio-molecules treatment and highlight their ability. Hope to extend this capability in different fields in near future.

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