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Ionic liquid–based aqueous biphasic systems as sustainable extraction and separation techniques

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Owing to the growing emphasis on development of green and sustainable processes in extraction and separation technologies, interest in ionic liquid (IL)–based aqueous biphasic systems (ABSs) has significantly amplified for extraction and separation of value-added compounds. The ability of IL-based ABS to act as alternative solvents for non-biocompatible volatile organic compounds provided strength to green and sustainable aspect. The field of IL-based ABS has undergone much development over years with respect to phase constituting components, factors such as temperature and pH in extraction of wide variety of chemical compounds. This work provides an overview of recent developments of IL-based ABS and the mechanistic aspects of phase formation and extraction processes. Moreover, future prospects and challenges are highlighted as addressed for further expansion.

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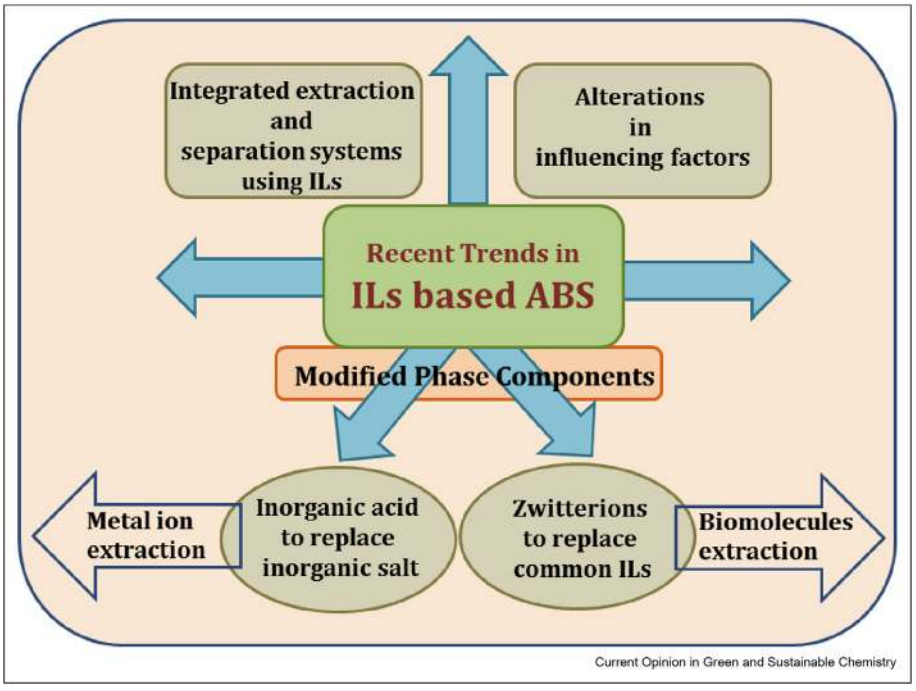
Introduction

Extraction, separation, and purification techniques are essential components in downstream processing and bio refineries beacuse these techniques are essential to obtain biomolecules from their sources in pure and valuable forms [1,2]. Most established methods such as membrane separation similar to ultrafiltration, chromatography, and solvent extraction used with harmful volatile solvents involve operation using complex multiple steps with high energy inputs and time-consuming methods. To develop efficient methods, it is vital to minimize energy inputs and operation time involved to ensure economic viability [3,4]. In the growing emphasis on development of green and sustainable techniques for the optimization, widespread awareness is noted as about adverse effects of volatile organic compounds (VOCs) and highlighted the inevitability to develop alternatively novel and efficient green solvents for these processes [5,6]. As a part of sustainable solvents, researchers proposed ionic liquid (IL)–based aqueous biphasic systems (ABSs) as plausible alternatives [7] to minimize the use of VOCs in conventional liquid–liquid extractions. The 'greenness' of ABS is attributed mainly to the presence of the most sustainable solvent i.e. water in major proportions and additional benefits including shorter equilibration time and potential scale up from laboratory to industry.

ABS are variants of aqueous two-phase systems formed when two water soluble components are minimized with such polymers, salts, ILs, and sugars as mixed in water at certain concentrations [8–11]. The inherent benefits of ABS can be combined with biocompatibility and favorable characteristics of ILs such as tunability, wide solubility for polar and non-polar compounds. This has led to extensive research on IL-based ABS since their first report by Rogers et al. [12]. In following years, ILs with varied combinations such as inorganic, organic salts, alcohols, carbohydrates, and polymers were reported to form ABS. Most studies were dedicated for exploring multiple combinations of phase forming components and analyzing physical or chemical interactions that led to phase splitting [13,14]. The properties of such density, viscosity, and surface tension of ILs appreciably influenced the phase behavior in various studies on analyzing this aspect of ABS [15,16]. In parallel, some studies were dedicated to explore the potential of these systems for extraction, separation and the enrichment of variable classes of compounds including but not limited to biomolecules, metal ions, pharmaceutical compounds, and dyes [17–21]. For deeper understanding of dynamics of aqueous–aqueous interfaces has led to expansion of ABS into biotechnology and biomedical fields including cell micropatterning and 3D bioprinting [22,23] recently.

Despite the persistent increase in the amounts of studies over the years, there are new aspects of ABS that are intriguing from academic, as well as industrial point of view. Many research groups have continued efforts in exploring the relatively newer and intriguing aspects of ABS that remain unexplored until now. In this brief report, we attempt to provide an overview of hot research topics and recent breakthroughs in the field of

Figure 1



Schematic diagram representing various recent developments of ABS. ABS, aqueous biphasic system.

ABS using ILs and the assisting expansion to applications. Figure 1 depicts pictorial overview of recent advancements in the field of IL-based ABS.

Recent developments in IL-based acidic ABSs

Amongst various chemical techniques used for metal ion extractions, hydrometallurgy is considered as advantageous method with its better precision, control and relatively greener approach [24]. The traditional approach involves acid leaching using inorganic acids such as HCl, H_2SO_4, or HNO_3, these systems have poor leaching selectivity in successive steps. Thus, it is necessary to develop sustainable techniques for extraction of metal ions. In this context, use of ILs as relatively novel and unique class of solvents was proposed in solvent extraction processes for rare earth elements in the form of either pure ILs, nonfunctional or functional ILs with extractants [25]. Ability of ILs to solvate both charged and neutral metal complexes assisted metal ion extractions unlike organic solvents. This also feasible to tune the selectively of ILs for specific metal ion by deliberately modifying cation and anion combinations. For example, the direct application of ILs having fluorinated ions for metal ion extraction was limited as hurdles for the application due to certain constraints since the counter ions were adverse in the characteristics such as hydrophobic nature, higher cost, higher toxicity, and difficulty in viscosity adjustment especially in the case of longer alkyl chains. These hurdles could be overcome through use of new type of ABS in terms of acidic aqueous biphasic systems (AcABSs) having acidic group, instead of inorganic salts in the systems [26–29]. The very first report on AcABS involving hydrophilic IL of tributyltetradecyl phosphonium chloride ($[P_{44414}][Cl]$) was based in concentrated HCl and water resulting upper IL-rich phase and lower phase rich in HCl [26**]. The proposed AcABS was used to extract Fe(III), Pt(IV), Co(II), and Ni(II) ions as well as single step separation of Co(II) and Ni(II) from HCl leachates of NiMH batteries. Because the already existing leachate solution itself acted as the salting-out agent, this process practically turned out to be a single step or 'one-pot' in practice. The thermotropic behavior additionally was shown in these systems as benefit to overcome kinetic limitations and to develop the recycling, and extraction of metal ions.

Further, the clear understanding of formation mechanisms would be helpful in expanding their applications. The detailed screening of range of ILs suggested that driving force for their applicability is the charge shielding of ILs' cation [27*]. The computational approach was used to compared with experimental results and evaluate the role of both cation of IL and acid in AcABS. In out of various classes of ILs, only quaternary ammonium and phosphonium cations were capable of forming AcABS and the cation's apparent charge density attributed to its solvent-accessibility at the charge surface, while heterocyclic chemical structure of

ILs such as imidazolium, pyridinium, and piperidinium was not capable of forming ABS. The tunability of [P44414]Cl—based AcABS was also verified with respect to temperature as shown by strong thermomorphic properties with lower critical solution temperature (LCST). Remarkably, the distinct LCST behavior was traditionally associated with polymers and nonionic surfactants. In AcABS formed by [P44414]Cl with structural similarity to ionic surfactants comparison of experimental results with computational ones was made of understanding the LCST mechanism indicating difference in conventional ABS due to the presence of hydronium ion. This was due to promoted micelle—micelle interaction for favored aggregation [27]. Thus to compile, the properties of the shielded cationic charges, relatively apolar surface area, dispersion forces and entropic effects were favorable factors for phase separation in AcABS.

Furthermore, advanced approach was proposed as synergistic ABS-AcABS system, where selective separation of cobalt from nickel and manganese was pertinent to recycling of nickel metal hydride and was applied to lithium ion batteries [28*]. In this approach, the acid HCl partially substituted by certain amount of NaCl thereby providing relatively eco-friendly operating conditions with retaining metal extraction efficiency of AcABS. Because of the acid reduction of the acid concentration required for the phase separation in the ILs' rich phase. 'one-pot' process was advantageous integrated method for sequential leaching, solvent extraction, and electrodeposition of metals [29].

Chemical structural modification of phase forming components

The journey of ABS over many years involved variable range of phase forming components including polymers, inorganic and organic salts, ILs, alcohols, and carbohydrates [9,11,30,31]. Though many combinations of phase forming components have been tested for ABS formation and extractions, the search for better phase forming components has been an ongoing process. With a motive to propose a newer class of compounds, it is important to retain the chemical structure as advantages of ILs for ABS but also to provide an improvement for IL-based ABS having a set of zwitterions (ZIs) [32—34]. Here, ZIs are compounds with covalently bonded cationic and anionic parts as shown in Figure 2. The anticipated benefits of ZIs include plausible structural and functional group modifications as similar to ILs and play significant role in designing ABS systems. ZIs typed ABS were reported to be used as additives for hydrophobic-IL water systems to improve their water content [33] and paved its way into liquid—liquid extractions. Ferreira et al. [32*], firstly reported ABS formed by ammonium based ZIs with potassium salts in the temperature dependent of the phase transitions. These systems were found to be efficient in single step separation of aromatic and aliphatic amino acids. Further studies [34*] explored ABS formed by water-soluble ZIs such as imidazolium, pyridinium, and pyrrolidinium in the point of view of the effect of structural and temperature changes on phase behavior presenting effective for partitioning of alkaloids and amino acids.

Quantum mechanical studies using density functional theory (DFT) and Conductor-like Screening MOdel-Real Solvents supported to understand solvent properties of ZIs. Further studies revealed that higher polarity of ZIs with favorable interactions to polar solutes and lower miscibility with non-polar compounds [35**] envisaging the expansion of ZIs applications in separation processes.

Blesic et al. [36] proposed a new class of zwitterionic salts which are hybrid materials in ILs consisting cation and anion in addition of a zwitterionic moiety. Because the cationic and anionic materials could preserve potential advantages of ILs high hydrophilicity domains interfaced at the extended polar ones they seemed to be suitable solvents in extraction and separation processes.

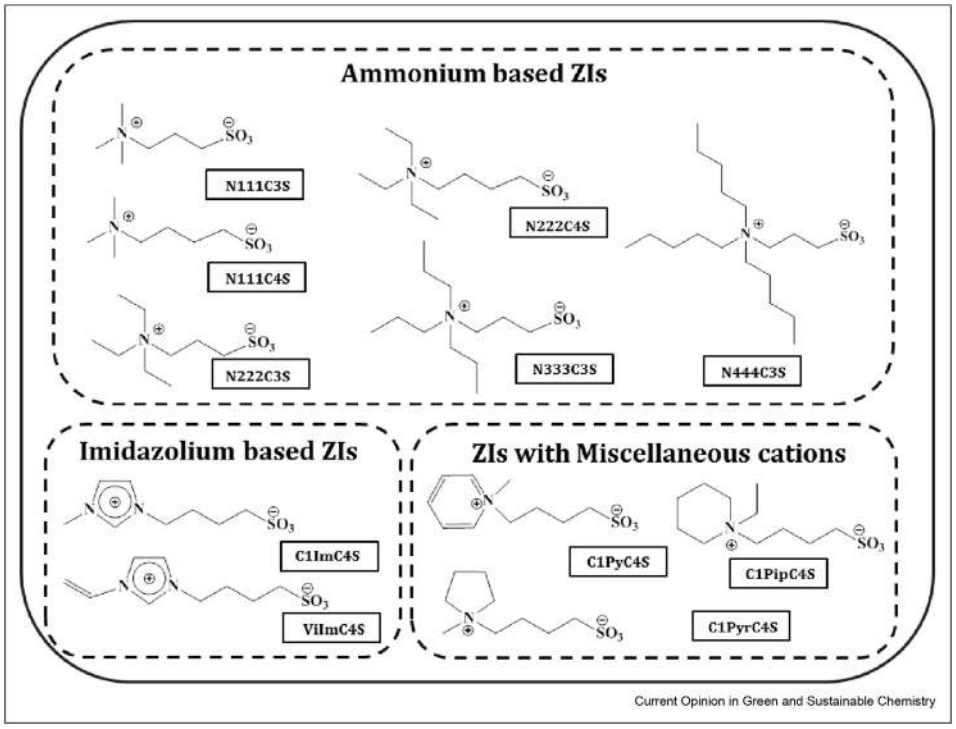
Another was dicationic ILs as explored for their application in formation of ABS. Gardas et al. [37*] reported ABS formed by dicationic ILs having variable cationic groups of ammonium, imidazolium, morpholinium, and pyrrolidinium. Their systematic comparison was made in structural similarity with mono cationic ILs. The designed ABS were efficient in extracting a compound of pharmaceutical compounds, for example, in of diclofenac sodium. Thus recent studies opened up the possibility of proposing newer variety of compounds that could effectively form ABS and extract value-added compounds.

Most studies on IL-based ABS deal with impact of functional groups on alkyl side chains on cation and/or anions sites of ILs. The influence of positional isomers was reported for functional groups of pyridinium-based ILs on the ABS [38]. Three positional isomers of methyl pyridine that were ortho, meta, and para isomers based on the presence of methyl group on the cation core of IL. The modification of function groups and positional isomers altered the affinity of the pyridinium ILs for water. In turn, the salting-in behavior of ILs was affected and the experimental and computational studies also supported this inference.

Advanced extraction and separation techniques

Mostly, the fields of extraction, separation, and purification of biomolecules anticipated their application as components in downstream processing as alternative

Figure 2



Chemical structures of various ZIs for forming aqueous biphasic systems.

solvents for VOCs. Owing to complex of physical and chemical interactions of ABS with target compounds such as alkaloids, amino acids, proteins, and phenolic compounds in the liquid phase constituting ILs, and salts, there is always enough scope for improving the existing conditions and new findings in extraction and separation processes [3] with the efficiency for various valuable compounds. Furthermore, most initial studies were performed using representative biomolecules such as tryptophan for amino acids, caffeine for alkaloids, and gallic acid for phenolic compounds. There were few aspects that could provide an edge over most existing extraction techniques and those include: (i) the extraction of useful compounds followed by possible separation of components from mixture, and (ii) extraction from real matrix samples instead of using model bioactive compounds. Such advanced studies were focused on the separation of components from extracted mixture and applied for real matrix samples in analysis. For the possible separation of aliphatic and aromatic amino acids [39], the ability of aliphatic amino acids was implemented by ABS with tetraalkylammonium and tetraalkyl phosphonium ILs. Although amino acids formed ABS in combination with ILs, only ILs having both low hydrogen bonding basicity and highly hydrophilic aliphatic amino acids could generate ABS while aromatic amino acids were unable to form. This knowledge provided design approaching suitable platform for separation of aliphatic and aromatic amino acids from their mixture and trends in extraction efficiencies were related to salting-out aptitude of aliphatic amino acids.

Neves et al. [40**], reported the simultaneous separation of antioxidants and carbohydrates from food wastes of vanilla pudding by using ABS of cholinium bistriflimide ILs containing carbohydrates in mono, disaccharides, and polyols such as D-glucose, D-mannose, D-maltose, and D-sucrose, D-maltitol, and D-sorbitol. These were used for separation and recovery of antioxidants and carbohydrates from real food waste sample. The extra biocompatibility of choline ILs supported cytotoxicity assay toward human intestinal epithelial cells. In the top phase rich in carbohydrates, the antioxidants were extracted into bottom IL-rich phase and then were later recovered through solid-phase extractions. In nonaromatic and nonflourinated ILs such as tetraalkylammonium and tetraalkylphosphonium, those based ILs formed ABS with carbohydrates and the properties of high biodegradability, lower toxicity, and lower cost were reported [41]. These systems showed excellent extraction capabilities for antioxidants/phenolic compounds including vanillic, gallic, and syringic acids and later IL-rich phase used for recovering the extract through solid-phase extraction in effective cartridges.

In another study, immunoglobulin G and human serum albumin were simultaneously separated from unused clinical transfusion plasma [42**]. Because human plasma is a complex matrix and usually requires multiple steps for isolation of targeted proteins, two-phase systems containing aqueous nonionic micellar systems such as Triton X-114 and Tergitol 15-S-7 were used as actual medium. Here, long alkyl chain containing types of surface active ILs was used as cosurfactant for optimized process plasma and surfactant concentrations and, pH. The combination of Tergitol 15-S-7 with $[P_{4,4,4,14}]Cl$ at pH 8 showed the selected purification factor of 1.14 folds for immunoglobulin G in the surfactant-poor phase and 1.36 folds of human serum albumin in the surfactant-rich phase. Although the obtained factors were not so much high, the followed method led to the enrichment of two different proteins in top and bottom phases in a single step.

ABS formed by a special class of functional chiral ILs provided an insight into their enantio separation aptitude [43**] and enabled as simple and fast operation with low cost. The chiral ILs acted as chiral selectors meaning that chiral recognition was performed through discriminatively intermolecular interactions thus without the selectors. The ABS resolved racemic mixture of mandelic acids optimized conditions like temperature, mandelic acid content, tie line length, and salt phase weight ratio was reported for S-mandelic acid in the IL-rich phase, while R-mandelic acid was present in salt rich phase. In another study of double protic ILs, ABS was formed with acetonitrile used for selective extraction of estrogen hormones [44]. This method emphasized the necessity to develop efficient extraction methods for recovery of hormones such as estrogen. As compared with protic ILs, double protic ILs were better in separation process of selected hormones into two pairs.

Apart from traditional applications of ABS including downstream processing at biotechnological and relevant extraction systems, recently ABS were proposed as powerful platforms for the separation processes also explored nonconventional applications in cell micropatterning, microtissue engineering, and microfluidic devices [45]. These included ABS innovative approaches in bioseparation and electrochemical field.

Conclusions and opportunities

This review provides overview of recent advancements and further challenges of IL-based ABS. The recent developments including modified phase forming components, plausible applications, and other advancements are highlighted as potential tools in extraction, separation, and purification processes. Although IL-based ABS show the efficient extraction performance, still there are certain bottle necks that need to be addressed. Further, analysis of these drawbacks is essential in the planning extension of ILs based ABS from an academic interest to the industrial implementation. Attempts can be made to overcome such drawback by developing techniques or recycling and reusing of ILs for economic advantage.

Although the mechanisms involved in ILs based extractions and separations are complex, the research recently shifts in focused for development of integrated techniques with positive extension of these systems to industry scale. Thus, IL-based ABS provide cost-effective, sustainable, and extraction systems as efficient platforms for integrated separation and recovery processes.

Declaration of competing interest

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

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** of outstanding interest

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This work is the first report on new type of acidic aqueous biphasic systems where tetrabutylphosphonium chloride was found to form ABS with acid. The reported systems exhibited thermomorphic behavior and efficiently carried out otherwise difficult separation of Co (II) from Ni(II). These systems facilitated to bridge the gap between ABS and metallic ion extraction in acidic phases.

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This study focuses on the versatility of acidic ABS as well as hybrid acidic ABS and the fundamental driving forces for phase formation in these systems. The presence of bulky and polar groups in the cationic portion of ILs is considered as determining structural factor. The weak salting-out ability of the acid i.e. HCl is affirmed through experimental and computational approach.

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In this study ABS based on relatively new class of ILs namely dicationic ILs is proposed and compared with the ABS formed by structurally similar monocationic ILs. This study is the first to report the formation of ABS by dicationic ILs and the application of such systems for extraction studies of pharmaceutically active compound namely diclofenac sodium. The possibility to explore newer classes of compounds with structural and functional similarity to ILs for formation of ABS and also in extraction processes.

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The simultaneous separation of two proteins immunoglobulin G and human serum albumin was performed from unused human plasma with the use of aqueous micellar two phase systems where ILs with surface active character act as cosurfactant. These two proteins were separated in opposite phases with appreciable separating factor. Unlike the conventional methods of separation which involve multiple complex recovery steps, the current method only involves a single step. This worked paved the path for future fractionation techniques for value added compounds from natural complex matrices.

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