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Review

Role of Ionic Liquids in Capillary Electrophoresis

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Abstract: Ionic liquids are a very important class of compounds due to their remarkable properties and wide range of applications. On the other hand, capillary electrophoresis is also gaining importance in separation science because of its fast speed and inexpensive nature. The use of ionic liquids in capillary electrophoresis is gaining importance continuously. The present review article describes the applications of ionic liquids in capillary electrophoresis. This article also describes the general aspects of ionic liquids and capillary electrophoresis. The use of ionic liquids in capillary electrophoresis, optimization of separation, mechanism of separation, and toxicity of ionic liquids, as well as their future perspectives, have also been discussed. It was observed that not much work has been performed in capillary electrophoresis using ionic liquids. It was also realized that the use of ionic liquids in capillary electrophoresis could revolutionize analytical science. Briefly, there is a great need for the use of ionic liquids in capillary electrophoresis for better and more effective separation.

Keywords: ionic liquids; capillary electrophoresis; optimization; separation mechanism; future perspectives

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1. Introduction

Among various branches of science, the discipline of separation is one of the most important ones due to its wide range of applications. All new compounds are either synthesized or extracted from natural resources. During these procedures, some impurities remain with the compounds of interest. This aspect becomes more important when dealing with medicinal products. Therefore, there is a great demand for good separation techniques. There are many separation techniques (TLC, HPLC, SFC, etc.) for separating compounds at the analytical and preparative levels. The separation at the analytical level is important because preparative scaling is carried out after achieving successful analytical separation. In the case of analytical science, capillary electrophoresis (CE) is the most important technique due to its fast and inexpensive nature [1]. Therefore, CE is gaining continuous attention nowadays. On the other hand, ionic liquids (ILs) are a special class of compounds and have been used widely for a wide range of applications [2–8]. Many drugs are ILs because the combination of an active anion and a cation leads to the formation of an active ionic fluid [9]. Other ionic liquids, including 1-alkylpyridinium chlorides, play important roles in cellulose dispersal [10]. The valorization of cellulose is achieved through the use of ionic liquids. Products representing glucose, esters, sorbitol, and alkylgycosides depend on ILs [11]. Ionic liquids are very important in the release of biofuel [12]. It is important to mention here that ILs have been used in CE for the separation of a variety of compounds. During the write-up of this article, interesting results were observed in various published papers [13–24] on the use of ILs in CE. Therefore, it was realized that there is a need for

one article describing the use of ILs in CE. It is important to mention here that no article is available in the literature on this topic. The present article describes the role of ILs in CE for separation.

2. Ionic Liquids

Ionic liquids (ILs) are naturally occurring compounds, which are present as liquids at temperatures below 100 °C with low vapor pressure. Ions and ion pairs are considered the main components of ionic liquids [25]. These are also called liquid electrolytes, ionic melts, mixtures of salt, liquid ions, and salts of liquid ions. These are also known as future solvents, lab-synthesized solvents, and green solvents. Ionic liquids are chemically stable and non-combustible with high ionic conductions and, hence, they are considered a future window of electrochemistry. ILs have also been investigated as co-catalysts in several reactions such as polymerization [5], organic catalysis, and biocatalysis [6]. Ionic liquids are also used as electrolytes, sealants, fluid batteries, etc. For the development of ILs, pyridinium and methylimidazolium ions have been used as pioneers. Throughout the study of chemistry, researchers have dedicated their attention to the progress of green as well as environmentally friendly processes and analyses. This is due to the growing number of natural contaminants due to global population progression and industrial growth. Ionic liquids have played important roles in such processes, making research more effective. Today, flexible organic compounds are considered outdated solvents in the industries. Researchers are interested in replacing these outdated solvents by using ILs to stop the release of organic pollutants, which are a major source of pollution. Ionic liquids were identified as "red oil" formed during the reaction of Friedel-Crafts acylation/alkylation [7]. BASF AG (Ludwigshafen, Germany) developed the first commercial system to extract acids using ionic liquids [7]. Ionic liquids may be hydrophilic as well as hydrophobic; it depends on the structures of the cations and anions [8].

In addition, the use of ionic liquids as agents in capturing carbon dioxide has also been suggested. Ionic liquids have numerous benefits over conventional solvents and other compounds. Protic-based, superbase-derived protic ionic liquids have also been used for CO_2 capturing [13]. The role of ILs in separation science is of great importance because they can be used as cellular phase extensions and phase fixers for all types of chromatography. The mixing nature of ILs with various solvents make them useful in capillary electrophoresis. Ionic liquids are naturally vicious and have been used as supplements in capillary electrophoresis and chromatography [14]. Capillary electrophoresis is a very important separation technique because of its fast speed and inexpensive nature. The use of CE is increasing continuously in various fields of separation science. The use of ILs in CE is described in the following subsections.

3. Capillary Electrophoresis

Capillary Electrophoresis is a technique of separation involving the movement of charged species or ions under an applied electric field. The compounds are separated because of their different electrophoretic mobilities. The charges of the compounds and the viscosity of the background electrolyte affect electrophoretic mobility. The applied potential is directly proportional to the mobility of the analytes. Capillary electrophoresis is a high-speed, high-sensitivity, low limit-of-detection and quantification technology with a low cost of experimentation [15–17]. Hjerten invented the first capillary electrophoresis apparatus in 1967 [18]. The current state of capillary electrophoresis is linked to Jorgenson and Lukacs's works [19–22]. The various aspects of CE such as silica capillaries, electrodes, buffer reservoirs, power supplies, and detectors were discussed in these papers.

Capillary electrophoresis is based on the divergence of molecules' electrophoretic and electro-osmotic mobilities. The separation of the analytes is based on these mobilities. The analytes' different migration velocities are due to different charge-size ratios. The greater the charge-size ratio, the greater the mobility and, as a result, the shorter the migration time. The analytes of various sizes are also responsible for their different migrations (steric effect).

Figure 1 is self-drawn and depicts a schematic representation of capillary electrophoresis and its separation mechanism. During the migration time, the mixture of analytes moves in the capillary in the shape of separate zones. The separation happens in different zones. Figure 1 (a) shows the loading of the mixture components a, b, and c into the capillary, whereas Figure 1 (b) shows a partial separation of these three components. On the other hand, Figure 1 (c) depicts the distinct separation of analytes a, b, and c, which was identified by the detector and displayed in the form of peaks by the recorder (Figure 1 (d)).

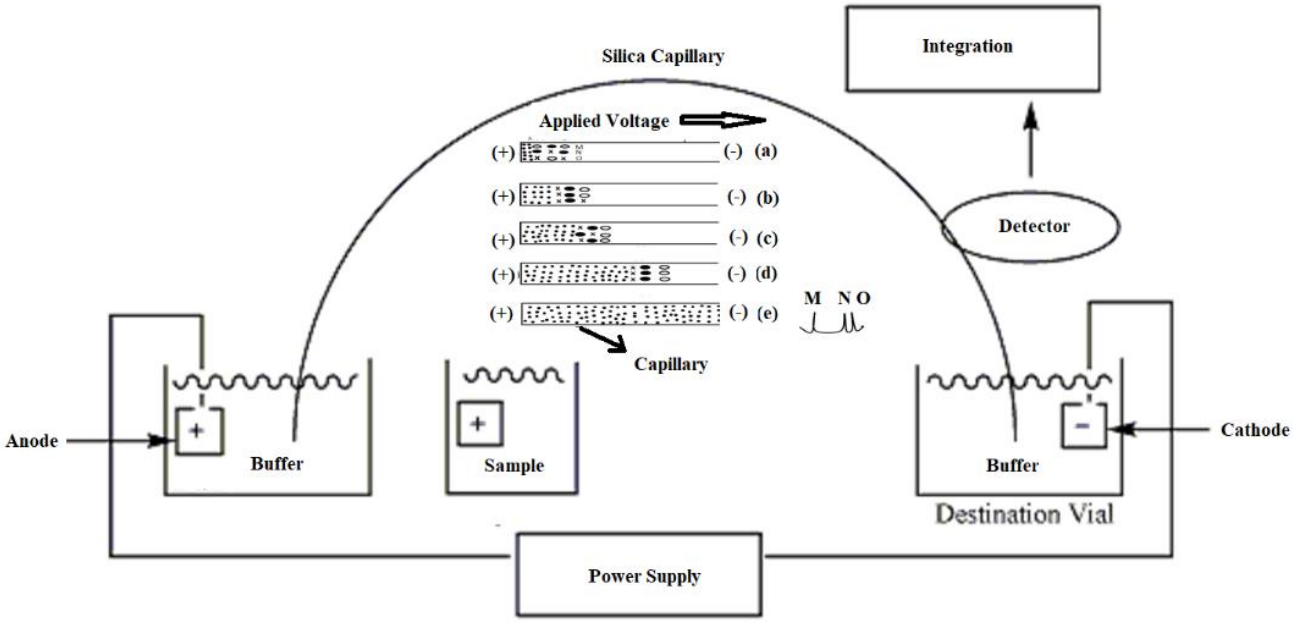

Figure 1. Schematic representation of capillary electrophoresis; a: loading of analytes, b: partial separation, c: some separation of analytes, d: complete separation of analytes and e: elution of analytes.

4. Applications of ILs in CE

In CE, molecular separation occurs through high voltages that produce an electro-osmotic and electrophoretic flow of buffer solution [23,24]. Fused-silica capillaries contain silanol groups that have a negative effect on the inner surface, leading to the formation of electro-osmotic fluid (EOF). There are many electrophoretic techniques for the separation of different compounds. The most widely used technique for the separation of ionic compounds is CE. This is due to the use of a small amount of buffer and the need for samples in low volumes. CE allows the separation of a wide variety of compounds, i.e., from charged ions to a complex array of large and small neutral molecules, with high efficiency and selectivity, as well as low throughput and sample use. CE is a special method of separation according to the differences in the electrophoretic flow of analytes using a background electrolyte. Some of the applications of ILs in CE are as follows.

4.1. Separation of Phytochemicals

Ionic liquids have also been used in the separation of many constituents found in plants (phytochemicals). Yanes et al. [24] used ILs in capillary electrophoresis for this purpose. 1-Alkyl-3-methylimidazolium was used as the main constituent of background electrolytes for the determination of polyphenols in grape seed extracts. 1-butyl-3-methylimidazolium (1B-3MI-TFB) ionic liquid was reported [26] as a background electrolyte in capillary-zone electrophoresis with β-cyclodextrin (β-CD) to separate the anthraquinone extracts of Chinese herbs. Chen and Qi [27] reviewed the use of 1B-3MI-TFB IL as a background electrolyte constituent for the separation and determination of eastside, cinnamic acid, and ferulic acid in *Euphrasia regelii.* It was found that the employed fused-silica capillary had a negatively charged surface due to the presence of silanol groups, which attracted the positively

charged sites of proteins. A negatively charged surface dynamically became coated on the capillary wall after the addition of 1-alkyl-3methylimidazolium (1A-3MI) ILs. This led to a surface charge reversal on the capillary wall and the running electrolyte solution became acidic (pH~6). Due to repulsion between positively charged proteins and positively charged surfaces, proteins were separated easily, which resulted in high efficiencies [28].

4.2. Separation of Pharmaceutical Drugs

A long-acting ionic fluid based on imidazole (1-dodecyl-3-methylimidazolium chloride and 1-cetyl-3-methylimidazolium chloride) is used in online sample concentration techniques. It has been used for enhanced sample packaging, head-sample packaging column field-amplified, and sweeping of catecholamines followed by capillary electrophoresis analysis. The use of a high-resolution sample matrix in the sweep was found to be significant for increasing the efficiency of analyte analysis up to 2×10^6 plates per meter and significantly reduced the catecholamine uptake limits up to 50 ng/mL. This method was revealed to be effective in determining trace levels of catecholamines in biological samples [29]. The work of research group, [30], developed two analytical methodologies based on the combined use of hydroxypropyl-β-cyclodextrin and two different amino acid-based chiral ionic liquids (tetrabutylammonium-L-lysine or tetrabutylammonium-L-glutamic acid) in electrokinetic chromatography to perform the enantioselective determination of econazole and sulconazole in pharmaceutical formulations. The work of another research group, [31], investigated the enantiomeric separation of ivabradine with the help of electrokinetic chromatography (EKC) using different anionic and neutral cyclodextrins (CDs) and amino acid-based chiral ionic liquids (CILs) as sole chiral selectors. Baseline separation was only achieved with sulfated-γ-CD. Another group [32] introduced graphene quantum dots (GQDs) and ionic liquid (IL) modified screen-printed carbon electrodes (GQDs/IL-SPCE) for the simultaneous determination of ascorbic acid (AA), dopamine (DA), and uric acid (UA). GQDs were synthesized by directly pyrolyzing citric acid and then dropped onto the surface of ILSPCE, which was prepared by screen-printing the mixture of IL and carbon ink on a portable substrate. Two new chiral ionic liquids based on the ester of the non-protein amino acid carnitine (as cationic counterpart) were synthesized, characterized, and evaluated [33] as chiral selectors for the enantiomeric separation of homocysteine and cysteine derivatized with 9-fluorenyl-methoxycarbonyl chloride by electrokinetic chromatography. The use of both ionic liquids, L-carnitine methyl ester bis(trifluoromethane)-sulfonimide and L-carnitine methylester L-(+)-lactate (as sole chiral selectors in the separation buffer) did not allow the enantiomeric separation of the studied amino acids. However, the combined use of L-carnitine methyl ester bis-(trifluoromethane) sulfonamide ionic liquid with γ-CD (forming a dual system) led to the enantiomeric separation of both analytes and showed the existence of a strong synergistic effect. Six novel mono- and di-tetraalkylammonium l-tartrate ILs (TAA-l-TTs) with different alkane chain lengths were evaluated as sole chiral selectors in capillary electrophoresis (CE) [34]. In comparison with conventional l-tartaric acid (l-TT) chiral selectors, these IL-type chiral selectors exhibited remarkably improved enantio-separation performance, which was even better than most previously reported TT ester-type chiral selectors.

4.3. Separation of Chiral Compounds

Chiral compounds have also been separated using ionic liquids with capillary electrophoresis. The compounds separated successfully were propranolol, atenolol, indoprofen, warfarin, ketoprofen, ibuprofen, and flurbiprofen. The separation was reported based on amino-acid-based chiral ILs, such as tetramethylammonium-L-hydroxyproline [N_{1111}][L-Hyp] [35], [C_2C_1Im][L-Lac] [36], and tetrabutylammonium-L-asparagine [N_{4444}][L-Asp] [37]. Using an IL-based chiral selector and β-CD, an effective green CE method for separation and detection was developed for the quantification of underivatized amino acids (DL-tryptophan and DL-phenylalanine). The reported method was suitable for the quality control of amino acids. By combining [N_{4444}][L-Asp] with HP-β-CD in the ammonium

acetate background electrolyte (BGE), the separation of Cinchona alkaloids (quinine, quinidine, cinchonine, cinchonidine) was achieved successfully [38]. An ephedrine-based IL was used as the chiral selector for the separation of omeprazole and rabeprazole [39]. It was found that the primary separation mechanism was due to ion–pair interactions and hydrogen bonding. It was also noted that $[S(CHTA)^+(Tf_2N)^-]$ chiral IL could be used as not only an electrolyte but also a chiral selector in separation based on capillary electrophoresis [40]. The used molecules were indoprofen, propranolol, atenolol, ketoprofen, warfarin, flurbiprofen, and ibuprofen. In the case of ibuprofen, the second type of chiral selector. namely chiral anion (sodium cholate), was required to separate the chiral drugs. For flurbiprofen, in addition to $[S\text{-}(CHTA)^+(Tf_2N)^-]$ and sodium cholate, a third and neutral chiral extract, 1-S-octyl-b-D-thioglucopyranoside (OTG), was also used.

Achiral ionic liquids improve the common chiral classification system. The common chiral ionic liquids used in CE for chiral separation include alkylimidazolium, tetraalkylammonium, and alkylpyridinium. Inorganic anions (e.g., OH^-, Br^-, $[BF_4]^-$, $[PF_6]^-$) usually act as anionic partners [41]. Achiral ionic liquids can improve the normal chiral differentiation system and this method is usually caused by the following factors:

(1) the ionic potential of the active buffer, which can be altered by the addition of chiral ionic liquids, and these differences may affect the electroosmotic flow rate (EOF) and current strength, thus causing changes in migration times and efficiency of separation [42];
(2) cation adsorption within the area of the capillary can diminish or reverse EOF to contribute to differentiation [42];
(3) the tail height of some basic enantiomers may be partially suppressed by competition for advertising IL cations on the inner wall of capillary [43]; and
(4) some achiral ionic liquids may be involved in the enantio-recognition process, especially if cyclodextrins or their derivatives are used as chiral selectors (e.g., by influencing the formation of complex compounds [44].

It was found that tetraalkylammonium based ionic liquids appear to be the best choice in most of the cases, mainly for the following two reasons:

(1) tetraalkylammonium based ionic liquids are almost hydrophilic and less likely to take the chirrup hydrophobic cavity of selectors (e.g., cyclodextrins or their derivatives); and
(2) tetraalkylammonium derived ionic liquids are relatively incompatible and exhibit UV exposure to wavelengths where enantiomers are commonly found.

In the reported literature, the presence of achiral ionic liquids was found to be significant. It may be possible to increase the enantiomeric resolution to some extent through the conversion of achiral ionic liquids.

4.4. Other Applications in CE

Some other applications of ILs in CE can also be included. Ionic liquids are very important for the separation of gases, e.g., 1-butyl-3-methylimidazolium chloride was used for the separation of H_2 and H_3NBH_3 [3]. Phenols and nucleoside monophosphates were separated using $[(C_4mim)(BF_4)]$ IL [45]. Separation based on CE methods was found to be good when ionic liquids were used as background electrolytes [24]. In addition, the capillary wall was also repaired by ionic liquids [25]. The use of ionic liquids in CE classification was reviewed [46]. The authors have shown that ILs play key roles in transforming separation based on electrophoresis. Typical buffer requirements include a wide range of fluids, high clearance compared to analysts, low resistance to flow, low molar volume, noble solvent anion and cation analytes, low air pressure, high chemical resistance, and low eco-toxicity. Tetraethylammonium tetrafluoroborate was used as a background electrolyte due to some of the above-mentioned features [47].

In addition, alkylimidazolium cations combined with anion variants, such as the posterior electrolyte, were used to separate constituents from grape seed extracts [25]. The researchers noted that the pH of the background electrolyte was below seven to confirm

that the analysts were in their unbiased state. The researchers also used capillaries coated with ionic liquids for compound separation. This work was like that of Yanes et al. [24], excluding the higher electro-osmotic flow of the same concentration. The researchers noted that the abolished charge of [(C_2mim)(BF_4)] with [(N_{2222})(BF_4)] produced lower cohesive constants, which were responsible for higher ion migration. The authors also described the phenomenon as a combination of polyphenolic compounds and free cations of ionic liquids that were more potent compared to adsorbed cations in the capillary walls. Active migration of chemical compounds was observed with an increasing concentration of [(C_2mim)(BF_4)]. The polyphenolic compound separation was enhanced by the diversity of the alkyl chain from $–C_2H_5$ to $–C_4H_9$. This might be because of the effect of the barrier created by the length of the alkyl chain. Ionic liquids also play an important role in the detection of 1-butyl-3-methylimidazolium chloride (nuclear fuel). 1-butyl-3-methylimidazolium chloride is known as non-liquid electrolyte media, which is of great importance in the detection of radioactive substances [48].

Flavonoid extracts obtained from Chinese medicines were examined using $(C_n\text{mim})^+$ as an additive of ILs [49]. The researchers explained that the hydrogen bonds between the phenolic compounds and the C-2 proton of the imidazolium cation were accountable for the separation. The researchers also noted that differentiation was enhanced by increasing the alkyl chain length of the imidazolium cation [(C_4mim)(NTf_2)] (from C_2 to C_4) [50]. The experiments were carried out to distinguish many chiral drugs. The authors explained that the electro-osmotic flow of background electrolytes and the electrophoretic flow of carprofen, suprofen, ketoprofen, and naproxen reduced significantly. According to the authors, it was because of the illumination of the cationic IL on the capillary wall; it caused the flexible adhesion of the IL [50]. In addition, the authors stated that IL is attracted to the wall of the capillary (at low levels) and worked as a standing phase that was responsible for increasing migration times. In addition, the wall of the capillary was entirely covered with a high IL concentration. As a result, the ion pair interaction between 2-arylpropanoic acid and ions of ILs was ruled out [50]. Due to their sole activities and infinite structural combinations, the abundant use of organic salt is getting much attention. The presented work aimed to shed light on the effects of ILs based on amidinium- and phosphonium ions. A relatively novel and modest method was developed to seal large vesicles in two separated hydrophilic compounds made up of TiO_2 and Si_3N_4 nanolayers [51]. Among the previously treated surroundings, attachment of vesicles to both substrates was attained by 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer in the presence of NaOH. Additionally, the presence of $CaCl_2$ was also involved. In order to understand how ILs interact with strong vesicles or lipid bilayers some ionic liquids, such as 1,5-diazabicyclo-(4.3.0)-non-5-enium acetate ([DBNH][OAc]), tributyl (tetradecyl) phosphonium acetate ([P_{14444}][OAc]), and tributylmethylphosphonium acetate ([P_{4441}][OAc]), were utilized in the biomimetics system [51]. Only a small effect was observed when [(P_{4441})(OAc)] was used at very high concentrations. In general, these effects led to a new understanding of the effects of ionic liquids on phospholipid vesicles, which is crucial in the overall understanding of IL damage in biomimicking and biomembrane systems [51]. In addition, this work highlighted the important role of the indirect biosensing process that is critical in assessing and differentiating the integrity and composition of phospholipid vesicles in the range of nanoscale range [51]. Some important applications of ILs in CE are summarized in Table 1.

Table 1. Applications of ILs in CE.

Class	Compounds Separated	ILs/BGEs Used	Refs.
Phytochemicals	Polyphenols	1E-3MI-TFB	[25]
	Anthraquinones	1B-3MI-TFB	[26]
	Eastside, cinnamic acid, and ferulic acid	1B-3MI-TFB	[27]
	Proteins	1A-3MI	[28]
Pharmaceutical drugs	Catecholamines	1-dodecyl-3-methylimidazolium chloride and 1-cetyl-3-methylimidazolium chloride	[29]
Racemates	Brompheniramine, chlorphenamine, dioxopromethazine, zopiclone, repaglinide, etc.	[EMIM][L-lactate] (1-ethyl-3-methylimidazolium-L-lactate)	[36]
	Citalopram, chlorphenamine, propranolol, nefopam	[TMA-L-Hyp] (tetramethylammonium-L-hydroxyproline)	[35]
	DL-tryptophan, DL-phenylalanine	[TBA-L-Asp] (tetrabutylammonium-L-aspartic acid)	[37]
	Quinidine, cinchonidine, cinchonine, quinine	[TBA-L-Asp] (tetrabutylammonium-L-aspartic acid)	[38]
	Omeprazole and rabeprazole	Ephedrine-based IL	[39]
	Indoprofen propranol, atenolol, ketoprofen, warfarin, flurbiprofen and ibuprofen]	S-(CHTA)$^+$ (Tf_2N)$^-$	[40]
	Furbiprofen	1-S-octyl-b-D-thioglucopyranoside (OTG)	[45]
	Flavonoid extracts	($C_n$mim)$^+$	[49]
	Carprofen, suprofen, ketoprofen and naproxen	(C_4mim) (NTf_2)	[50]
	Propranolol, ofloxacin, liarozole, dioxopromethazine, chlorpheniramine, isoprenaline, etc.	1-ethyl-3-methylimidazolium-L-lactate ([EMIM][L-lactate])	[52]
	Duloxetine, amlodipine, propranolol, nefopam, tropicamide	1-butyl-3-methylimidazolium(T-4)-bis[(aS)-a-(hydroxy-kO)-4-methyl-benzeneacetato-kO]borate (BMImBSMB_); 1-butyl-3-methylimidazolium(T-4)-bis[(2S)-2-(hydroxykO)-3-methyl-butanoato-kO]borate (BMImBLHvB)	[53]
	Ibuprofen, indoprofen, naproxen, ketoprofen, fenoprofen, carprofen, flurbiprofen	L-alanine tert butyl ester lactate (L-AlaC4Lac)	[54]
	Nefopam, amlodipine, propranolol, duloxetine	[TMA-L-Hyp] (tetramethylammonium-L-hydroxyproline) [TMA-L-Ile] (tetramethylammonium-L-isoleucine); [TMA-L-Arg] (tetramethylammonium-L-arginine)	[55]
	Carprofen, ketoprofen, suprofen, naproxen, ibuprofen, indoprofen	Phenylcholinebis (trifluoromethylsulfonyl); imide Ethyl-bis(trifluoromethylsulfonyl)imide	[56]
	Warfarin, pranoprofen, naproxen	[L-AlaC4NTf2] (L-alanine tert butyl ester bis (trifluoromethane)sulfonamide; [L-ValC4NTf2] (L-valine tert butyl ester bis (trifluoromethane) sulfonamide)	[57]
	Ephedrine, methylephedrine, pseudoephedrine	[TBA-L-Arg] (tetrabutylammonium-L-arginine).	[58]
	Coumachlor, huperzine A, warfarin	[D-AlaC4Lac] (D-Alanine tert butyl ester lactate)	[59]

Table 1. *Cont.*

Class	Compounds Separated	ILs/BGEs Used	Refs.
	Nefopam, duloxetine, citalopram	[TMA-L-Arg] (tetramethylammonium-L-arginine); [TMA-L-Asp] (tetramethylammonium-L-aspartic acid)	[60]
	Econazole, ketoconazole, nefopam, voriconazole	[TMA-D-QUI] (tertramethylammonium-D-quinate); [TMA-D-PAN] (tertramethylammonium-D-pantothenate)	[61]
	Duloxetine, nefopam, cetirizine, citalopram, ketoconazole	[TMA-L-Asp] (tetramethylammonium-L-aspartic acid); [TMA-L-Arg] (tetramethylammonium-L-arginine)	[62]

5. Optimization in the Separation

Of course, during the development of the method, there were many important parameters for optimization, but the most important ones included the selection of the static phase (the segmentation of the analysts) and the composition of the ingredient used in the background electrolytes. When analysts showed excessive column presenting, an electrophoretic peak tail occurred and its diameter was improper [63]. By chance, when selecting a mobile phase, difficulties might occur with gaining isolated peaks for compounds, low efficiency, and a long analysis too [64]. Kiszkiel et al. [65] tested LLE ionic fluid [(C_4MIM)([PF_6)] and [(C_4MIM)(Nf_2T)] for their capabilities to differentiate nizatidine and ranitidine selectively from different types of water. Based on initial studies, IL with a different anion was designated for each analyst. [C_4MIM][PF_6] was used for the extraction of nizatidine, while [C_4MIM][Nf_2T] was used for the extraction of ranitidine. Their use allowed methanol intake to be reduced. During development, the appropriate IL amount was selected and the effect of additional factors, such as mixing time and pH, were measured. The recently developed and proven method allowed for more than 100% acquisition, a wide range of linearity, and low LOD values to be obtained from both analysts.

Optimization in Chiral Separation

Due to the use of low samples and rapid analysis, CE is gaining importance in enantioseparation continuously. However, chiral selectors known to be active in CE are much smaller than in the CSPs found in GC and HPLC [66,67]. As a result, the search for new chiral candidates is a major point in CE classification. Many chiral selectors, such as macrocyclic glycopeptide antibiotics, polysaccharides, CDs, proteins, chiral micelles, crown ethers, and metal complexes with chiral ligands, may be used in CE. Tactlessly, these selectors cannot distribute adequate selection and adjustment if they are used without any other additives. In many cases, various chiral selectors are required to separate enantiomers. Hence, in the last few years, efforts were made to find novel chiral selectors, which offer superior selection and refinement of the CE output. Chiral ionic liquids provide an attractive solution to this problem, acting as an electrolyte. S-[3-(chloro-2-hydroxypropyl)-trimethylammonium]-[bis-((trifluoromethyl)sulfonyl)amide] (S-[CHTA][Tf_2N]) was used as a chiral IL as well as a chiral selector [40]. Chiral ionic fluid was tested as an additive along with CD for the enantiomeric separation by CE [56]. Research has been performed on 2-arylpropionic acids (an anti-inflammatory drug) as model compounds. The consequences presented that these chiral ionic liquids did not display direct enantio-selectivity with respect to model analysts. The effect of chiral ionic liquids on background electrolytes was deliberated in the occurrence of older chiral selectivity. Although no common tendency could be recognized, growth in separation and adjustment options was perceived in many cases; this suggested synergistic properties. Amino acids with Zwitterionic structures are also used as ILs [60] or antibiotics [35]. An important point to note is that the structure and properties of the chiral component have a significant impact on the separation process, which is possibly due to the interactions of hydrogen bonding between basic analysts and ionic fluids. Although these chiral ionic liquid-based amino acids are used primarily to differentiate the chiral of the model drugs, they have been shown to be sufficient in calculat-

ing the amount of phenylalanine and tryptophan that has not been properly incorporated into the amino acid injections [37].

Zhang and co-workers [38] described the ammonium acetate (pH 5.0) effect in BGE on the enantiomeric resolution of cinchona alkaloids. The authors used 10 to 30 mM concentrations. The results are shown in Figure 2. The migration time was augmented by increasing the amount of ammonium acetate. It was observed that 25 mM was the best amount to obtain successful resolution. The same authors studied the effect of BGE pH (3.5–5.5) and the results are given in Figure 3. The mobility of the racemates was found to be reduced with an upsurge in pH, while the EOF augmented. Consequently, 5.0 pH gave the best and most successful resolution. In the same paper, the effect of the amount of ionic liquid [TBA][L-ASP] was studied from 1.0 to 20.0 mM and the results are given in Figure 4. The migration times were augmented from 3.4 to 4.3 s with the augmented amount of IL from 1 to 16 mM. Yujiao and co-workers [37] used 5, 10, and 15 kV voltage for the best separation. It was observed that 10 kV applied voltage was found to be the best one. A further upsurge in voltage could not give better separation.

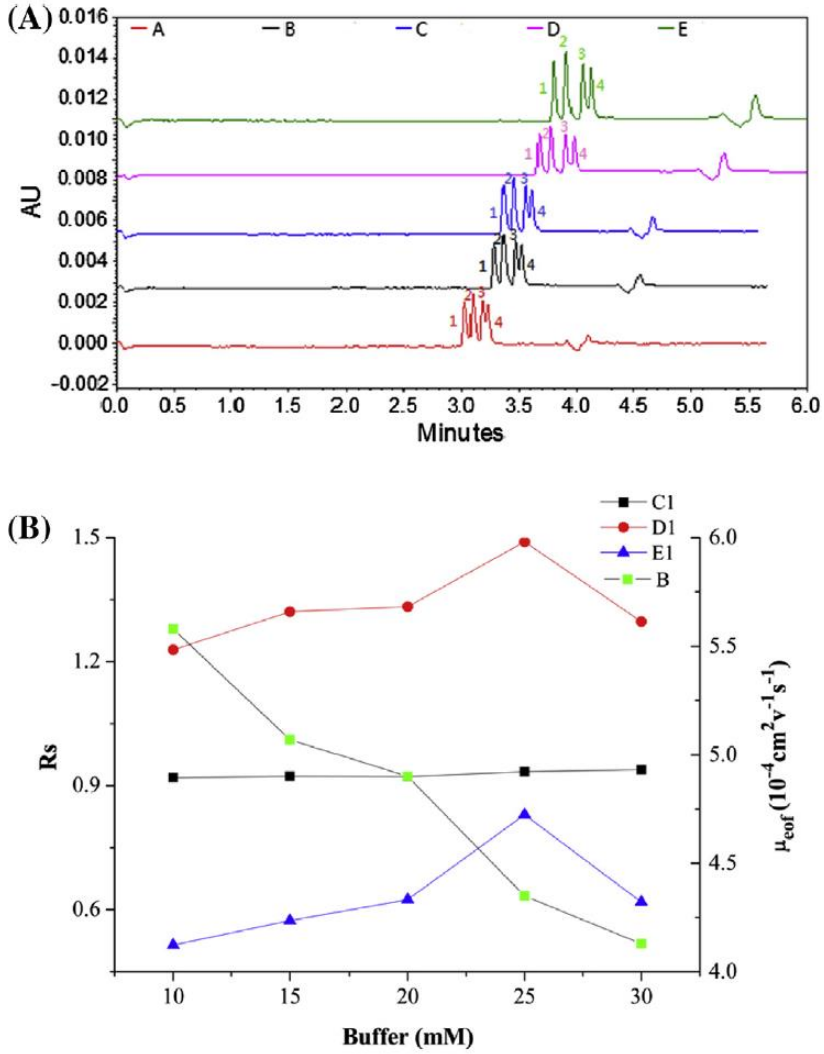

Figure 2. Effect of ammonium acetate amount (**A**), the separation phenomenon, and (**B**) resolution factors of the stereoisomers: cinchonidine (1), quinine (2), cinchonine (3), quinidine (4). (A) 10 mM, (B) 15 mM, (C) 20 mM, (D) 25 mM, (E) 30 mM. (C1)—cinchonidine/quinine, (D1)—quinine/cinchonine, (E1)—cinchonine/quinidine), and (B)—μ_{eof} of the diastereomers. Reprinted with permission from Ref. [38].

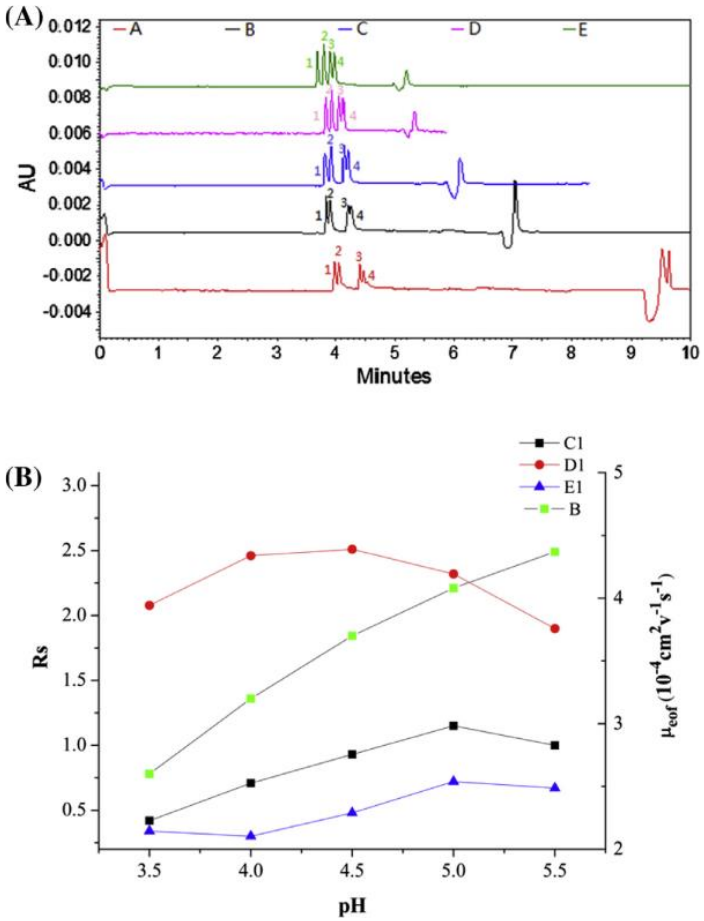

Figure 3. Effect of pH on (**A**), the separation phenomenon, and (**B**) resolution factors of the stereoisomers: cinchonidine (1), quinine (2); cinchonine (3); quinidine (4). (A) pH 3.5, (B) pH 4.0, (C) pH 4.5, (D) pH 5.0, (E) pH 5.5. (C1)—cinchonidine/quinine, (D1)–quinine/cinchonine, (E1)–cinchonine/quinidine), and (B)—μ_{eof} of the diastereomers Reprinted with permission from Ref. [38].

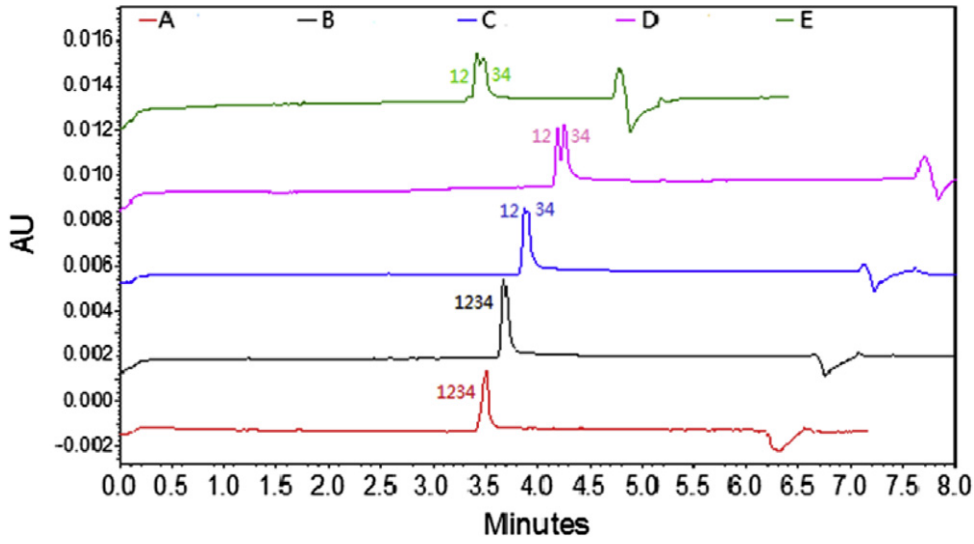

Figure 4. Ionic liquid [TBA][L-ASP] concentration effect. Peaks: cinchonidine (1), quinine (2), cinchonine (3), quinidine (4). (A) 1 mM, (B) 4 mM, (C) 8 mM, (D) 16 mM, (E) 20 mM. Reprinted with permission from Ref. [38].

6. Separation Mechanism

The separation mechanism determination is essential in CE when using ILs in BGE. In this section, we discuss the separation mechanism of compounds in CE using ILs. Generally, the inclusion complexes are formed among the molecules to be separated and the ILs. Wang and co-workers [68] described that the hydrophilic/hydrophobic properties of ILs are responsible for inclusion complex formation. A rise in complex formation is obtained by growing hydrophobicity [69–71]. Yang and co-workers [61] applied a simulation approach to establish the separation mechanism. These authors described multi-interactions among stereoisomers and ionic liquids. The authors reported hydrogen bonding, dipole-dipole, π–π, host–guest charge–charge, etc., interactions. The obtained negative values confirmed more stable interactions. Zhang and co-workers [53] also used a simulation study to determine the chiral separation mechanism. The authors described many exchanges for the separation mechanism. The authors reported hydrogen bondings, dipole-dipole interactions, π-π interactions, charge–charge, host–guest inclusions, hydrophobic interactions, etc. Huang and co-workers [42] enantio-separated β-agonist stereoisomers by utilizing N-butylpyridinium hexafluorophosphate and β-cyclodextrin. It was described that the stereoisomers formed inclusion complexes with β-cyclodextrin, following the association of butyl pyridinium groups and [PF_6] having positive and negative charges, respectively. The authors described different types of interactions for the separation mechanism. Concisely, the dissimilar motilities of the complex compounds formed in CE were accountable for the separation [72]. In general, ILs covered the capillary walls and made their layer. These ILs interacted with the molecules to be analyzed. The ILs combined with the molecules to be analyzed via various bondings. The important interactions were π-π, hydrogen bonding, dipole induced dipole interactions, van der Wall's forces, etc. A schematic representation of the mechanism was prepared and shown in Figure 5.

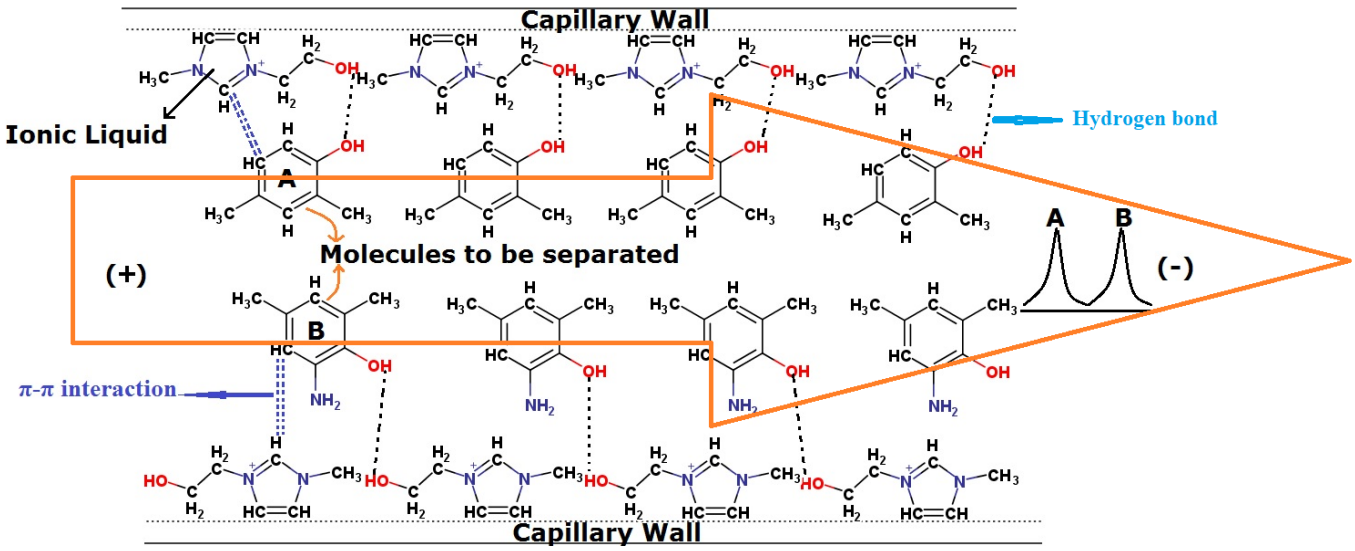

Figure 5. Schematic representation of separation in capillary electrophoresis with ionic liquids, A and B are analytes.

7. Toxicity

The moderate poisonousness of ionic liquids to microorganisms and other animals has been reported [73]. The toxic effects of ionic liquids were studied [74] on *Vibrio fischeri*, *Daphnia magna*, zebrafish *Danio rerio*, and *Pseudokirchneriella subcapitata*. The researchers concluded that ionic liquids were partially lethal to most microorganisms. In addition, the researchers described hydrophobicity as a direct relationship between toxicity and ionic liquids [75,76]. Other authors also reported the poisoning of ionic liquids. The toxicity of (BMIM)(PF_6) IL was defined [77] in *E. coli* at a low concentration, such as 0.5% (*v/v*). The

(BMIM)(PF_6) ionic liquid was also found to be toxic to *S. cerevisiae* [78]. Only very few papers are available on ionic liquid toxicity. There are no papers on the toxicity of ILs in human beings. Overall, no severe toxicity of ILs has been observed because there are no papers available on severe toxicity; however, there is a need to study the toxicity of ILs in detail.

8. Advantages and Disadvantages of ILs in CE

A background electrolyte that has ionic liquids might be used for a long time for running various experiments. This is due to the strong chemical stability of ionic liquids. Additionally, they do not catch fire like organic solvents and may be considered safe constituents of background electrolytes. Moreover, their solutions conduct electricity; hence, they can participate in augmenting the electrophoretic flow of background electrolytes. Contrarily, their hydrophobicity shows a disadvantage during their use. Due to their hydrophobic nature, they are fatal to many living organisms, including the operator of capillary electrophoresis.

9. Future Perspectives

As discussed above, ILs have the remarkable property of mixing with water and most solvents. In this way, ILs might be a good choice for making background electrolytes in CE. Chiral ILs may be synthesized and used as chiral selectors in CE. The tuning of ILs is very easy and chiral ILs may be prepared as per the requirements, i.e., by critical evolution of the racemates to be separated. ILs are ionic in nature and that is why they are the ideal molecule to be used in CE. ILs may be used to make ionic pairs with organic and inorganic species. In this way, ILs may be a module to separate a wide range of chemical compounds and ions. Additionally, ILs may be used as additives for background electrolytes and chemicals for covering walls of capillaries. The non-volatile nature of ILs make them eco-friendly solvents in CE applications. The applications of ILs in CE are not fully developed and need more attention. New ILs should be prepared so that they could be used in the simple and chiral separation and metal ion speciation. A combination of ILs and CE will revolutionize separation science. Along with the use of ILs in CE, it is also necessary to mention that the toxicity of ILs should be determined, especially for human beings. The reason is that there is no concrete evidence of the toxicity of ILs. In brief, it was realized that there is an excessive demand for IL applications in CE. Certainly, more advanced research on the use of ILs in CE will revolutionize analytical science.

10. Conclusions

ILs are a remarkable class of compounds with varied physico-chemical properties. They can be modified and tuned easily as per the requirements. During the write-up of this article, it was realized that only a few papers are available describing the use of ILs in simple and chiral separations of CE. The results of these papers were remarkable and it is hoped that ILs could be the choice in CE for separating a wide range of organic and inorganic species [79–82]. There is a great demand to synthesize new ILs for separating simple molecules, chiral compounds, and metal ions. This research area is not fully developed and is in the development stage. There is a great need to work with ILs in CE. Certainly, the use of ILs in CE will be revolutionary in separation science because both ILs and CE have remarkable features. Finally, it was concluded that there is a great need to develop new ILs to use in CE.

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