Ionic Liquids in Pharmaceutical Applications

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Abstract

In the past several years, ionic liquids (ILs) have been at the cutting edge of the most promising science and technology. ILs not only have found applications in classical areas of knowledge but also are important candidates to solve classical problems within several societal challenges, such as clean and efficient energy, through the development of a broad swath of energy technologies, such as advanced batteries, dye-sensitized solar cells, double-layer capacitors, actuators, fuel cells, thermo-cells, and water splitting, essentially related to highly efficient carbon capture and storage technologies and resource efficiency to date. This review focuses on the application of IL methodologies to solve critical pharmaceutical problems, in particular, the low solubility and thus bioavailability of pharmaceutical compounds and the presence of polymorphs, which severely hamper the efficacy of important commercially available drugs. The development of strategies to use ILs as carriers of pharmaceutical active compounds is an extremely promising and wide avenue. Further, the synthesis of liquid salts through the discerning combination of cations and anions with several distinct pharmaceutical roles provides answers to some of today's pharmaceutical industrial challenges.

INTRODUCTION

The pharmaceutical industry is at a crossroads, facing growing pressure from a range of environmental issues, major losses of revenue owing to patent expirations, increasingly cost-constrained healthcare systems, lengthening of drug-development cycles, and more demanding regulatory requirements. Performance indicators reveal that pharmaceutical research and development (R&D) is focusing on fewer new molecular entities and at an increasing cost. However, the possibility of producing pharmaceutical materials "by design," that is, the knowledge of quantitative structure-activity relationships that enable the control of the biological and chemical properties by precise changes in the chemical structure, brought to pharmaceutical industry portfolios an increasing number of active pharmaceutical ingredients (APIs) possessing limited aqueous solubility (Biopharmaceutics Classification System class II drugs). The challenging aspects of new formulations of such drug molecules are associated with their slow dissolution in biological fluids, and thus insufficient and inconsistent systemic exposure and consequent suboptimal clinical efficacy. Pharmaceutical companies are pursuing strategies to overcome this limitation as the key to these challenges. Among the many strategies attempted are prodrugs (1, 2), salt formation (3–5), crystal engineering (6–8), solid dispersions (9, 10), and micellar systems (11).

In particular, ionic liquids (ILs) were found to play a special role in the pharmaceutical industry. ILs have been defined as compounds that consist quasi-exclusively of ions with a melting point below 100°C, and some have gained increasing attention as clean, multifunctional solvents for a variety of applications (12). This "neoteric" class of solvents (12) generally presents interesting properties, namely, negligible vapor pressure at relatively ambient conditions; high thermal, chemical, and electrochemical stability; and widely tunable properties with regard to polarity, hydrophobicity, and solvent miscibility (13). These properties result from a matchless combination of molecular characteristics of their constitutive ions. Moreover, many types of ILs can be regarded as nanosegregated fluids with polar networks permeated by apolar domains, which enables the understanding of their peculiar solvent behavior at a molecular level (14) and the numerous applications to solve classical problems addressing today's societal challenges (15–19).

A research topic that has deserved some attention from the scientific community is the use of ILs as extractants of pharmaceutical compounds from aqueous solutions. Efficient and cost-effective extraction/purification processes are in constant demand in the pharmaceutical industry, where 20–50% of the total production costs (20) are connected to these separation processes. Also, the detection of trace levels of very hydrophilic, biologically active compounds in biological samples becomes an important area of research that challenges the detection limits of currently available analytical techniques. However, numerous studies show that a wide variety of pharmaceuticals are present in wastewater effluents and are a matter of great concern for public health. Although wastewater treatment plants use advanced technologies for removal of pollutants/contaminants, none of these processes was specifically designed for APIs. The development of sophisticated analytical techniques, in particular very small detection limits and selective sorption of analytes, enables the study of chemically diverse chemicals, such as APIs. The interest in ILs in analytical chemistry has grown very quickly, and ILs have been used as solvents for extraction, as mobile-phase additives, and as modifiers of the sorbent or stationary phases. Excellent reviews have been published on this subject (21–24), and thus, this topic is not covered here. The development of these techniques also triggered the interest in the extraction of bioactive compounds with multiple therapeutic effects and pharmacological activities. Natural bioactive compounds are of interest in the pharmaceutical industry, and recent reviews covering this topic have been published (25, 26). For this reason, this subject is not developed further here. Protein stabilization and biopreservation in ILs are other very popular topics of interest for the pharmaceutical industry

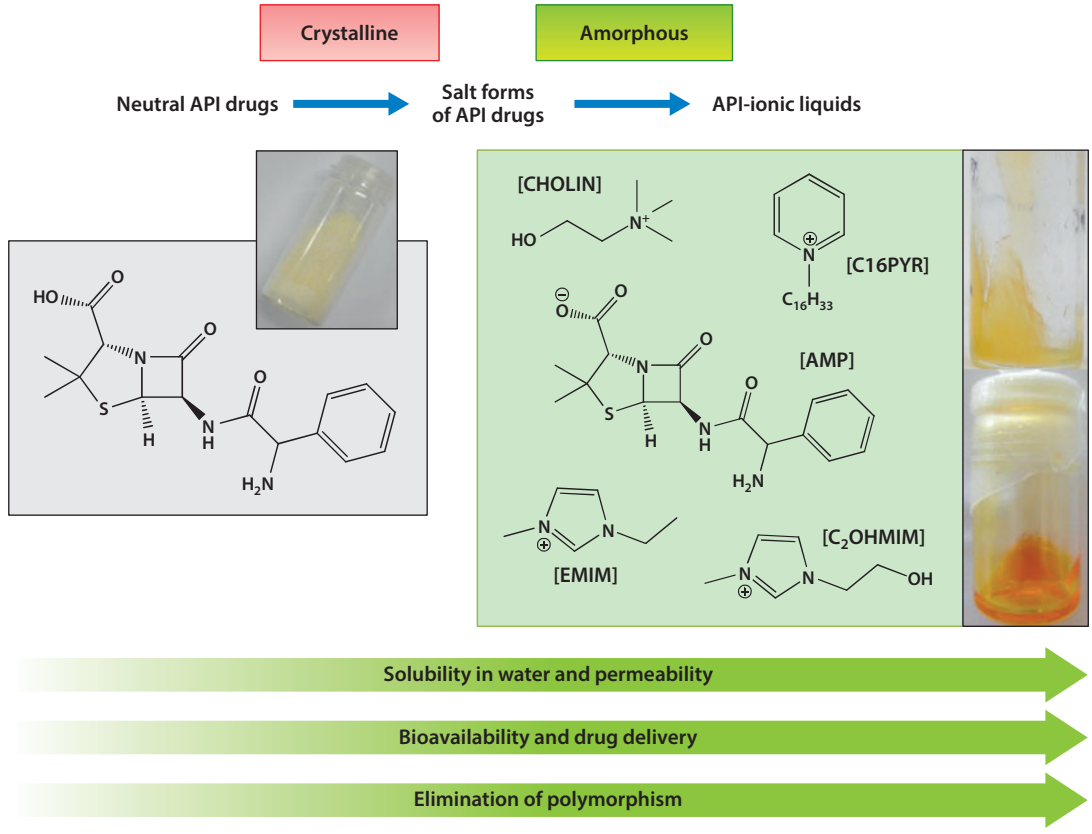


Figure 1

Schematic diagram of active pharmaceutical ingredient (API)–ionic liquids perspectives.

because the instability of proteins that have pharmaceutical potential is a limitation of some protein therapeutics. Again, excellent updated reviews (27–30) covering the rapid advancement of this field have been published; thus, it is not further developed here.

This review is then divided into two main parts, of which the first highlights the many uses of ILs as solvents in the synthesis of APIs, providing novel drug-delivery options and serving as a solution for polymorphic molecules. The second describes the use of APIs as cations or anions combined with counterions from the IL toolbox, so that liquid APIs can be obtained and their bioavailability-related properties evaluated. Interestingly, in chronological terms, this last part was the first to be developed, owing to the vast pharmaceutical industry knowledge of salts formulations and the vision of some members of the IL community, as illustrated in **Figure 1**.

IONIC LIQUIDS AS SOLVENTS

In the late 1980s, Sheldon proposed the introduction of the E(nviromental)-factor, defined as kg waste/kg product, to assess the environmental impact of waste generation in manufacturing processes. This parameter has played a major role in focusing the attention of the chemical industry worldwide, and particularly the pharmaceutical industry, to waste minimization. The pharmaceutical industry has the highest Sheldon E-factor (25–100), as compared with oil-refining (<0.1) and

bulk (<1–5) or fine chemicals (5–50) (31). For this reason, the improvement of waste minimization in pharmaceutical industry is mandatory so that its status in the broad context of green chemistry and sustainability can be revised. Organic hazardous solvents should be replaced by greener solvents showing lower volatility and flammability. In this context, ILs are especially useful because they present, in most cases, negligible vapor pressure. Further, the rigorous choice of cations and anions can provide special interactions with specific groups of the solute, which are essential in the solubilization of complex molecules, such as APIs and their precursors.

Synthesis of Pharmaceutical Drugs Using Ionic Liquids as Alternative Media

Industrial synthesis of pharmaceutical compounds frequently involves the use of organic solvents that are responsible for organic contamination of the final product and, many times, contain residual impurities (32). ILs have been explored as alternative and sustainable reaction media for several organic transformations, including the preparation of pharmaceutical drugs (33). Reactions in ILs are often faster and easier to carry out compared to those in conventional organic solvents and usually require no special apparatus or methodologies (34). Despite the large array of different cations and anions available today in the IL toolbox, the [C_4MIM] cations combined with the [BF_4], [PF_6], or [NTf_2] anions have been used most often as solvents in the synthesis of APIs.

Recent publications showed the possibility of performing the synthesis of nucleoside-based antiviral drugs (brivudine, stavudine, trifluridine) using ILs such as 1-methoxyethyl-3-methylimidazolium methanesulfonate, 1-methoxyethyl-3-methylimidazolium trifluoroacetate, and 1-butyl-3-methylimidazolium trifluoroacetate as reaction media (35, 36). For instance, trifluridine (5-trifluoromethyl-2′-deoxyuridine) (see **Figure 2**) was produced, in high yield (90–91%) and short reaction time (20–25 min), as a single product using these ILs as reaction media. Importantly, the IL methodology resulted in a higher-purity product as well as a tenfold decrease

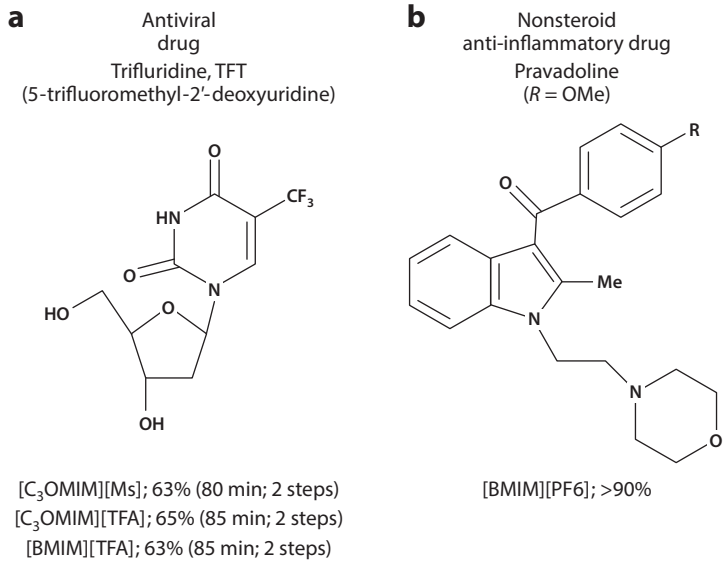


Figure 2

Use of ionic liquids as alternative and efficient solvents for the synthesis of (*a*) trifluridine (TFT) as an antiviral drug and (*b*) pravalodine as a nonsteroid anti-inflammatory drug.

in solvent consumption compared with the standard reaction media (e.g., pyridine/DMAP or acetonitrile/Et_3N/DMAP). For example, Shaabani et al. (37) used 1-butyl-3-methylimidazolium bromide for the synthesis of side-chain-modified imidazo[1,2-α]pyridinic derivatives.

Fan et al. (38) developed a green efficient synthesis of hybrid compounds based on pyrimidine nucleosides combined with pyrano[3,2-c]pyridines and pyrimidine nucleosides combined with pyrano[4,3-c]pyranes as potential antiviral and antileishmanial agents, using 1-butyl-3-methylimidazolium tetrafluoroborate ([C_4MIM][BF_4]) as a reaction medium. This reaction was carried out without any catalyst and achieved higher yields compared with other reported methods; additionally, the possibility of easy recovery and reuse of the solvent was demonstrated in some of the previous examples. Zhang et al. (39) synthesized pyrimidine nucleoside-thiazolini-4-one hybrids as potential antiparasitic drugs, using 1-butyl-3-methylimidazolium hexafluorophosphate ([C_4MIM][PF_6]) as the reaction medium.

ILs have also been applied in the synthesis of drugs with promising antitumor potential. Zaidlewicz et al. (40, 41) used ILs [C_4MIM][*X*] (*X* = BF_4 or PF_6) in the synthesis of L-4-boronophenylalanine (L-BPA), a clinically approved drug in boron-neutron capture therapy. Cross-coupling reaction with pinacol borane using protected p-iodophenylalanine was performed in [C_4MIM][BF_4], enabling the synthesis of L-BPA and its analogs in good yields (82–89%) after 20 min. Kurata et al. (42) developed a novel, efficient biocatalytic procedure providing several caffeic acid phenethyl ester (CAPE) analogs with potential antiproliferative effects on human tumor cells. The authors used *Candida antarctica* lipase B (Novozyme 435) in 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide as media and obtained a conversion yield of 92%, which is comparable to that obtained when CAPE was synthesized in isooctane.

Conventional nonsteroid anti-inflammatory drugs (NSAIDs) have also been prepared using ILs as alternative media. In this context, the synthesis of pravadoline (see **Figure 2**) was performed in imidazolium-based ILs by combined Friedel-Crafts reaction and nucleophilic displacement reaction (43). Alkylation of 2-methylindole with 1-(*N*-morpholino)-2-chloroethane was achieved in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate with 99% of yield, whereas the best yield of Friedel-Crafts acylation of the product from the nucleophilic displacement reaction was obtained in [C_4MIM][PF_6] at 150°C. No catalysts or strictly anhydrous conditions are required in the reactions performed in ILs as reaction media (44). Another NSAID, (*S*)-naproxen, was synthetized using Ru-BINAP catalyst precursors immobilized in IL [C_4MIM][BF_4] and had optical yields similar to those of the homogeneous reaction (45). Contesini et al. (46) reported the effect of commercially available lipases and two native lipases from *Aspergillus niger* and *Aspergillus terrus* on the kinetic resolution of (*R*,*S*)-ibuprofen in systems containing [C_4MIM][PF_6] and [C_4MIM][BF_4].

ILs clearly can be advantageously used as alternative solvents for the preparation of different pharmaceutical drugs. The replacement of the organic toxic solvents by ILs can often provide better reaction conditions, accelerating some more problematic reactions, as well as facilitating the purification and isolation of the desired product. From the pharmaceutical industrial point of view, ILs can be an excellent choice of solvent for some specific drug synthesis. Furthermore, the possibility of IL recycling opens a greater economical perspective to produce APIs in IL milieu at the industrial scale.

Ionic Liquids in Drug Delivery

To use a solvent for pharmaceutical processing of an API, a solubility greater than 1 mg/ml must be attained. Toxicity is another relevant factor for any chemical to be used in medicine and biomedicine, and the wide use of ILs in biology-related areas has been hampered by the lack of

accurate knowledge of their toxicity. However, the ability to finely adjust the physical chemical properties by simply changing their anion/cation combination can also be used to generate nontoxic and/or biocompatible ILs (47, 48). Fortunately, in recent years, nontoxic ILs have been synthesized by selecting biocompatible organic cations and inorganic anions (49). In addition, even by changing the side chains appended in the IL cations, biocompatible ILs can be attained. Very recently, the incorporation of ether groups into the ester side chain of the IL cation was proven to significantly reduce the toxicity compared with that of alkyl derivatives (50). The literature is still insufficient and often presents very disperse EC50 values for the same IL. For example, Dobler et al. (51) reported EC50 values of 5 and 7 mmol/L for $[C_6MIM]Cl$ and $[C_4MIM][PF_6]$. These values were determined using human keratinocyte cells. Using IPC-81 leukemia cells, Ranke et al. (52) found that EC50 values for $[C_6MIM]Cl$ range between 661 and 933 μm/L, comparable to those of conventional organic solvents. For $[C_4MIM][PF_6]$, larger discrepancies were also observed: 1,250 μm/L (52) and 13,900 μm/L (53) using IPC-81 leukemia and HeLa cells, respectively. These differences are probably related to the different sensitivities of the various cell lines. Very recently, Frade & Afonso (54) published a concise review on the impact of ILs in the environment and humans; they concluded that because IPC-81 leukemia cells seemed to be the most vulnerable to ILs within the experimented cell line models, these cells should be used at a first stage in a preliminary screening. In a debate on ILs to be used as solvents for the pharmaceutical industry, it is worth mentioning that many useful and necessary chemicals are toxic: Many pharmaceutical excipients, such as dimethylsulfoxide and nonionic surfactants (e.g., polysorbate 80), display toxicities similar to those observed in many ILs. Hence, the toxicity of ILs does not preclude their use as pharmaceutical solvents. In addition to low toxicity, ILs should exhibit good biodegradability, in an attempt to decrease the high E-factor of the pharmaceutical industry. In the end, there will always remain a balance between the benefit of producing a highly effective drug and the environmental and public health issues derived from its production (55).

EC50: effective concentration scale based on a 50% response; a measure of the effectiveness of a substance in inhibiting a specific biological or biochemical function

Kow: octanol/water partition coefficient related to water solubility, soil/sediment adsorption, and bioconcentration

Despite their well-known properties as solvation media, the use of ILs as carriers of poorly water soluble APIs has been weakly explored. Jaitely et al. (56) introduced the use of ILs as pharmaceutical solvents in 2008. Regardless of the undeniable interest in having tunable solvents for specific drugs, very few ILs have been tested until now. Again, the majority of the ILs used for this purpose are the classic ILs based on the imidazolium cation combined with $[BF_4]$, $[PF_6]$, and $[NTf_2]$ anions, probably because these were among the first anions to be proposed in IL chemistry and thus are the most studied in terms of thermophysical properties, hydrophobicity, and polarity. Recently, a wide variety of anions based on natural compounds, such as organic acids, aminoacids, and other functional groups, for example, nitrile, became commercially available. Jaitely et al. (56) used a set of ILs with fixed anion and increased the alkyl chain length of the same cation, $[C_{4-8}MIM][PF_6]$, as drug solvents or reservoirs of hydrophobic/hydrophilic, polar/nonpolar drugs where sucrose, penicillin V potassium, dexamethasone dehydroepiandrosterone, and progesterone were used. The authors also investigated relevant physical and chemical properties of the ILs, such as water uptake, viscosity, and surface tension, to understand their effect on the drug solvation and release profile. They observed that the partition of drugs in the studied ILs/water systems was directly related to their hydrophylic/lipophilic balance, described by the Kow, octanol-water partition coefficient, values. This result was expected because only hydrophobic ILs were used in this study. Only in the case of dexamethasone did they observe an increase of the partition coefficients with the alkyl side chain of the imidazolium cation. No significant changes were found for the other four APIs. This indicates that both cation and anion might play a relevant role in API solubility. The toxicity of these ILs was also addressed using Caco-2 cell lines, showing that 90% of these cell lines remained viable after being exposed to saturated solutions (0.1–1% for $[C_{4-6}MIM][PF_6]$ and 0.1–0.3% for $[C_8MIM][PF_6]$) of the used ILs, indicating that, despite the fact that these

[PF_6]-based ILs are considered toxic, their very low solubility in water (and thus in biological fluids) reduces this problem (57). However, the authors are cautious about [C_8MIM][PF_6] owing to its surfactant nature and possible membrane activity (56). The encouraging results of these toxicological studies triggered the development of ILs for biomedical applications.

In a subsequent study, Mizuuchi et al. (58), using the same set of ILs, showed that the solubility of danazole and albendazole in [C_4MIM][PF_6] increased by more than 10,000 and 1,000 times, respectively, compared with that of water. To circumvent the fact that [C_4MIM][PF_6] is poorly soluble in water, the authors showed that this problem can be minimized by the addition of a second water-miscible IL, such as [C_6MIM]Br. In fact, these authors explored the use of IL mixtures as drug reservoirs, in which one IL is used to solubilize the drug while the other improves the water solubility of the mixture. Despite this excellent idea, the authors did not fully address the question of how IL mixtures can be used to tune API solubility, because neither the solubility of the APIs in the IL mixtures nor the effect of water on API solubility in the IL mixtures was reported. The extra degree of freedom in the fine tuning of properties, such as water solubility, provided by the use of IL mixtures has been successfully explored in other IL applications, such as, for example, carbon dioxide separation (59).

The Bogel-Łukasik group (60, 61) reported a series of studies on the solubility of APIs in ILs. The solid-liquid equilibria of the antibiotic drugs isoniazid and pyrazine-2-carboxamide in [C_{2-10}MIM] combined with the anions [NTf_2] and [CF_3SO_3] were investigated. The solubility of both drugs at room temperature is very low in all the studied ILs. Despite the fact that the solubility of both drugs decreases with the increase of the alkyl chain for ILs containing the [NTf_2] anion, [C_{10}MIM][CF_3SO_3] was the best solvent for both APIs, highlighting the fact that both cation and anion play a relevant role in the solubilization of APIs. The authors also compared the measured solubility data with the calculated ideal solubility and concluded that because very large deviations were obtained, it is extremely important to accurately measure this type of thermodynamic information. A similar conclusion was taken by Manic & Najdanovic-Visak (62), who studied the solubility of erythromycin, another common antibiotic drug, in a variety of ILs. Recently, these authors also proposed the use of ammonium-based ILs as green solvents for the same drugs (63). The ILs chosen include ammonium anions with long (didecyldimethylammonium anion) and short [ethyl(2-hydroxyethyl)dimethylammonium] alkyl chains, combined with [NTf_2] and [NO_3] anions. Solid-liquid equilibria studies, performed at atmospheric pressure and in temperatures up to 420 K, indicate that [$N_{111C2OH}$][NO_3] is the best solvent for both drugs. Apart from their low environmental impact, in comparison with pyridinium- and pyrrolidinium-based ILs (64), judiciously chosen ammonium-based ILs were found to have interesting properties, such as antibacterial effects and bioactivity. When practical applications and production costs were considered, ammonium-based ILs combined with the [NO_3] anion were found to be the most promising because they are cheap, hydrophobic, and multifunctional (65).

Rogers and coworkers (66, p. 2196) developed a "truly designed IL-excipient" that maximized interactions needed to increase water solubility and simultaneously prevented drug aggregation in water. The high solubility of ampicillin B (0.10 mg/ml) and itraconazole (0.25 mg/ml) in water is achieved by providing the proper hydrophilic/lipophilic balance in either one or both of the ions of the IL-excipient.

Still to be mentioned is one interesting study on the use of current flow (1–5 mA) to stimulate the release of dexamethasone in [C_{4-8}MIM][PF_6] (67). A threefold increase of the release rate of dexamethasone from the IL phase to the water phase was observed under certain conditions. Preliminary studies on transdermal penetration using a Franz cell with rat skin as membrane showed a very fast release from [C_8MIM][PF_6] phase using 5 mA of current flow, which dramatically decreases if the field is removed.

In 2010, Moniruzzaman et al. (68) reported the development of IL-in-oil microemulsions for the delivery of sparingly water-soluble drugs. This is the first work to address the use of IL-based microemulsions as drug-delivery devices. The solubility of acyclovir, a poor water- and organic solvents–soluble antiviral, in [C_1-C_4MIM]-based ILs combined with a variety of anions was measured. It was observed that acyclovir is soluble only in ILs possessing coordinating anions that are strong hydrogen bond acceptors, such as acetate and dimethylphosphate. In fact, this is the first work to include the use of such sustainable anions, reflecting the evolution of available cations and anions for ILs preparation. However, no transport of acyclovir in these ILs through the skin was observed when using a Franz diffusion cell with Yucatan hairless micropig skin, thus requiring other strategies for effective delivery. Consequently, IL-in-oil microemulsions, using isopropyl myristate as continuous phase, [C_1MIM][$(CH_3O)_2PO_2$] as dispersed phase, and Tween-80 and Span-20 as surfactants, were prepared and tested. Skin permeability of acyclovir was increased by several orders of magnitude compared with the results obtained for the cream currently available on the market. Cytotoxicity tests performed on the reconstructed human epidermal model show that 80% of cell viability was attained with this microemulsion (containing 4% of IL) compared with the control experiment. However, the use of pure [C_1MIM][$(CH_3O)_2PO_2$] shows a remarkable decrease in cell viability. Other drug molecules were studied in two subsequent articles (69, 70), along with several other relevant parameters, such as the emulsion properties, phase diagram at 25°C, droplet diameter, emulsion stability, drug uptake, and cytotoxicity. Dobler et al. (51) recently reported the formulation of water-in-oil and oil-in-water microemulsions using two ILs, one hydrophilic IL, [C_6MIM]Cl, and one hydrophobic IL, [C_4MIM][PF_6]. Interestingly, owing to its specific properties, [C_4MIM][PF_6] can replace different phases of the emulsion: It can be used as the oil (71) or water (72) phase. Cytotoxicity effects of both ILs were evaluated using human keratinocyte cell line, and the EC50 values obtained corresponded to low toxicity for both [C_6MIM]Cl and [C_4MIM][PF_6] ILs.

Other techniques have also been used to enhance API bioavailability, namely iongels and high–surface area inert carriers, such as porous ceramic and synthetic zeolites (73) and silica gels (74). Viau et al. (75) discussed the possibility of using iongels as a drug-delivery device for ibuprofen. For that purpose, and because ibuprofen is insoluble in many ILs, the authors synthesized [C_4MIM][ibuprofenate], which was used in sol-gel synthesis using tetramethoxysiloxane and mixtures of tetramethoxysiloxane and methyltrimethoxysiloxane. A high loading was obtained: 0.8 g of ibuprofen per g of dried silica. The release kinetics was found to be slower than that of ibuprofen and [C_4MIM][ibuprofenate]. Rogers and coworkers (76) studied the sorption, stability, and release properties of [P_{4444}][ibuprofenate] and [lidocainium][ibuprofenate] from a silica-supported phase. Mesoporous silica-based materials have been used successfully owing to their high surface area, uniform porous structure, nontoxicity, and biocompatibility. However, the prepared materials did not provide release-tuning capacity, showing only enhanced thermal stability.

Another promising application is the use of polycationic ILs, in particular [poly(3-butyl-1 vinylimidazolium) L-prolinate], as gene-delivery vectors (77). Nonviral gene-delivery vectors are usually positively charged, chemically synthetic vectors that strongly interact with both the negatively charged DNA and the negatively charged cell membranes. Pyridinium and quaternary ammonium compounds have been used for a variety of clinical purposes, such as preoperative disinfection of unbroken skin, application to mucous membranes, and disinfection of noncritical surfaces. In addition, several members of these families of compounds have antimicrobial properties and are membrane active agents (11). The chosen polyIL assembles the negatively charged DNA molecules, forming a stable complex with a diameter of approximately 330 nm. In vitro transfection experiments of these complexes show that 6.8% of the cells expressed green fluorescent protein, at an N/P ratio of 16/1, against 0% to naked DNA control. Furthermore, [poly(3-butyl-1

vinylimidazolium) L-prolinate] showed only marginal toxic effects toward the cells and could carry a reporter gene into HeLa cells and successfully mediate the gene expression without the aid of an exogenous agent.

Very recently, Azevedo et al. (78) addressed the effect of using ILs as cosolvents (1%) on parameters that determine the pharmacodynamics and pharmacokinetics of nimesulide. Three ILs ([C_2MIM][BF_4], [C_2MIM][CH_3SO_3], and [C_2MIM][CF_3SO_3]) were chosen, and the nimesulide behavior was analyzed through the study of albumin, in human albumin serum, binding and interaction with hexadecylphosphocholine (HDPC) micelles. Since albumin is the most abundant protein in human plasma and the major target for endogenous and exogenous compounds, interacting reversibly with a broad spectrum of therapeutic agents (79), it is usually used as a model protein for studying drug-protein interaction. This article (78) shows that the incorporation of nimesulide in an IL-based system increased the binding affinity between nimesulide and albumine (dissociation constant, Kd = 7.24, 10.96, 74.35, and 17.82 μmol L^{-1} without IL and using 1% [C_2MIM][BF_4], [C_2MIM][CH_3SO_3], and [C_2MIM][CF_3SO_3], respectively). Regarding lipophylicity, a significant increase in the partition coefficient between the serum and HDPC micelles, Kp, was observed (Kp = 501, 1,759, 1,476, and 1,262 M^{-1} without IL and using 1% [C_2MIM][BF_4], [C_2MIM][CH_3SO_3], and [C_2MIM][CF_3SO_3], respectively), indicating a more favorable interaction of the drug with the biological membranes when small amounts of IL are used.

In conclusion, most of the studies on the application of ILs as drug-delivery devices are research ILs from the so-called first generation, where fluorinated anions are used. Recently, isolated studies of other more benign, modern ILs with tuned properties have been pursued, owing not only to their availability but also to recently published citotoxicity studies. Nevertheless, the results discussed here show that ILs can play an important role as solvents and cosolvents in the pharmaceutical industry. Also, the array of new IL-based drug-delivery strategies, such as microemulsions, iongels, functionalized silica, and polymeric ILs, provide interesting perspectives of the use of ILs in the pharmaceutical industry.

Solutions for Pharmaceutical Drug Polymorphism Problems

The development of salts of targeted active compounds is a suitable and well-known approach to overcome polymorphism phenomena, the tendency of APIs to crystallize. In spite of this, cocrystals, amorphous forms, and polymer-embedded pharmaceuticals have been tested to overcome or circumvent classical problems, such as spontaneous polymorphic transformation of crystalline drug forms. These strategies might lead to significant problems for drug designers because they can convert an effective dose into a lethal dose by altering the solubility of the active ingredient (80).

Pure compounds, salts, and all kinds of pharmaceuticals and drug candidates can suffer polymorphism. Despite recent efforts toward a better understanding of crystal polymorphism in pharmaceutical compounds, there are no means to predict this phenomenon for any specific compound (81, 82). Sertraline hydrochloride (an antidepressant), indinavir sulphate ethanolate (a protease inhibitor used to treat HIV infection), and itraconazole succinic acid cocrystal (an antifungal agent) are examples of crystal forms of pharmaceutical compounds with polymorphism problems (83). The cost of a pharmaceutical product is directly dependent on crystal polymorphism and solvation state. This situation has been illustrated by costly product failures and protracted patent litigation. One of the best examples is the ritonavir capsule product failure in 1998, which was recounted and rationalized by solving the crystal structures of the ritonavir polymorphs (84). An unexpected metastable form of 5-fluorouracil (a well-known antitumor drug) was described as a new polymorphic structure (85). Drug companies mainly rely on solid, primarily crystalline forms for the delivery of APIs for reasons of purity, thermal stability, manufacturability, and ease of handling.

Polymorphism: tendency of a compound to undergo structural transformations between distinct crystalline forms; one of the great problems of solid drugs

In contrast, liquid drug formulations are much less common and are usually based on eutectic mixtures (86, 87). The use of an active drug in liquid form can avoid some of the polymorphism problems associated with solids. Other similar approaches have been developed with liquid drug formulations prepared as eutectic mixtures (88), but these can dilute the APIs owing to large quantities of inactive ballast in the formulation. Along these lines, the possibility of solubilizing APIs in biocompatible ILs can provide new perspectives for drug delivery and treatment approaches. From the point of view of the pharmaceutical industry, the use of liquid salts, preferably those with melting points below room temperature, is relevant. Some synthetic strategies can be developed to decrease the melting point of salts, including selection of cations with a low tendency to crystallize or ions with a more diffuse charge. For example, 1-ethyl-3-methylimidazolium chloride is an organic salt with a melting point of 77–79°C, which can be lowered to −21°C simply by replacing the chloride with a dicyanamide anion (89). In conclusion, the preparation of API-ILs, or even the simple dissolution of APIs in biocompatible ILs, has been reported as a novel, efficient approach for elimination of polymorphism and thus to enhance drug efficacy.

NOVEL ACTIVE PHARMACEUTICAL INGREDIENTS BASED ON IONIC LIQUIDS

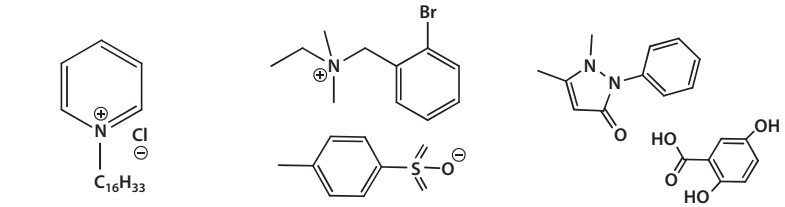
Synthesis of Pharmaceutical Salts Ionic Liquids (API-ILs)

The number of reported examples of pharmaceutical active compounds in the cationic or anionic form combined with inert or biocompatible counterions is growing (90). Nowadays, half of all drug molecules used in medicine are administered as salts, and the formation and formulation of a suitable salt as a drug candidate are recognized as essential steps in the preclinical phase of modern drug development (5, 91).

The physicochemical or biopharmaceutical properties of a drug can be overcome by pairing a basic or acidic drug molecule with a counterion to create a salt-drug. Such salts may offer several advantages compared with the correspondent original neutral formulations in terms of physical properties, such as melting point, crystallinity, hygroscopicity, and dissolution rate, as well as pharmaceutical properties, such as bioavailability, permeability, and drug delivery. Salt forms of drugs have a large effect on quality, safety, and drug performance. The selected counterion can significantly influence the pharmacokinetics of a drug candidate, in particular its absorption or membrane-transfer process. As a result, the time course of its pharmacodynamic and toxicological effects may undergo a modification or modulation. This fact can significantly assist chemists and formulators in various aspects of drug discovery and development (92), and it is the main reason why regulatory authorities have considered new salts of a registered drug as new chemical entities (93).

In general, the synthetic process is a simple way to modify the properties of a drug with ionizable functional groups in order to overcome undesirable features of the parent drug (94). The selection of ion pairs to form ILs is carried out with candidate ions that have low symmetry and diffuse charge, parameters that also characterize several typical APIs. Even the nitrogen-containing heterocycles, commonly used in ILs today, are frequently found in APIs or API precursors (95, 96).

In the past century, many examples of organic pharmaceutical salts have been developed to change physicochemical or biopharmaceutical properties of a neutral original drug (91). Examples of several organic pharmaceutical drugs that can be defined as ILs are presented in **Figure 3**. This class of pharmaceutical salt pairs (i.e., containing both cation and anion as active ingredients and showing IL properties) has long been known in the literature. Cetylpyridinium chloride as an antiseptic drug (97) (melting point, mp 77°C, 1981); bretylium as an antifibrillatory and antiarrhythmic agent (98) (mp 86°C, 1978); and phenazone gentisate as an analgesic, anti-inflammatory,



Cetylpyridinium chloride (mp 77°C)
Antiseptic drug

Bretylium tosylate (mp 85–86°C)
Antiarrhythmic drug

Phenazone gentisate (mp 87–88°C)
Analgesic and antipyretic drug

Figure 3

Some examples of pharmaceutical salts with one component as active drugs that can be classified as active pharmaceutical ingredient–ionic liquids.

antipyretic drug (99) (mp 88°C, 1951) are some examples that can be classified as API-ILs. However, the connection between the organic pharmaceutical salt and APIs as ILs (API-ILs) appeared in only 2007 (100). Rogers et al. (100) described the synthesis of didecyldimethylammonium ibuprofenate (an anti-inflammatory), lidocainium docusate (a local anesthetic and antiarrhythmic), and ranitidine docusate (a histamine H2 receptor antagonist) as examples of API-ILs through simple metathesis reactions (see **Figure 4**).

Most of the syntheses of API-ILs reported in the literature are related to metathesis reactions. The cation and anion in their commercially available salt forms are separately dissolved in a selected solvent (e.g., water, methanol, ethanol, acetone), and the solution is stirred at room temperature or heated until 50°C to 100°C (if necessary). This synthetic methodology presents some limitations in terms of final purity of the API-ILs, owing to the presence of inorganic salts (e.g., NaCl), which can be eliminated through adequate solvent choice or by using additional purification methods (101). When the inorganic salt is partially soluble in organic solvents, an extraction process with apolar solvents, such as chloroform or dichloromethane, is used for the API-IL purification; the organic phase is then washed with water to remove the inorganic salt (e.g., NaCl, which can be checked by a silver nitrate test), and the solvent is removed using a rotary evaporator. In the final step, the resulting product is placed on a high vacuum line to remove any residual solvent. In some cases, an extra purification is described, mainly to remove excess halides.

The contamination of API-ILs prepared by metathesis reactions with residual impurities dramatically influences their physical, chemical, and thermal properties, as well as biological properties. The search for more efficient and sustainable synthetic strategies is crucial for the development of novel API-ILs. In this context, our group adapted an already-described anion-exchange resin method for the synthesis of API-ILs based on ampicillin anions ([Cation][Amp]) (102). Amberlite resin (in the OH form) was used to transform halides (bromide or chloride) to the hydroxide form, and then this basic solution was neutralized by the addition of an adequate acid solution. The acid–base reaction yielded the desired IL. Organic cations, such as cholinium [$N_{1,1,1,C2OH}$], cetylpyridinium [C_{16}PYR], 1-ethanol-3-methylimidazolium [C_2OHMIM], 1-ethyl-3-methylimidazolium [C_2MIM], trihexyltetradecylphosphonium [$P_{6,6,6,14}$], and tetraethylammonium [$N_{2,2,2,2}$], were selected from salts, which were first transformed into hydroxides through the use of an ionic exchange column (Amberlite IRA-400 OH) in methanol. Next, the β-lactam antibiotic previously dissolved in a moderately basic ammonia solution was used to neutralize the selected cations. Pure API-ILs were obtained after eliminating the excess ammonia and/or β-lactam antibiotic by evaporation and crystallization, respectively (see **Figure 4**). Some of the prepared ampicillin-ILs showed no

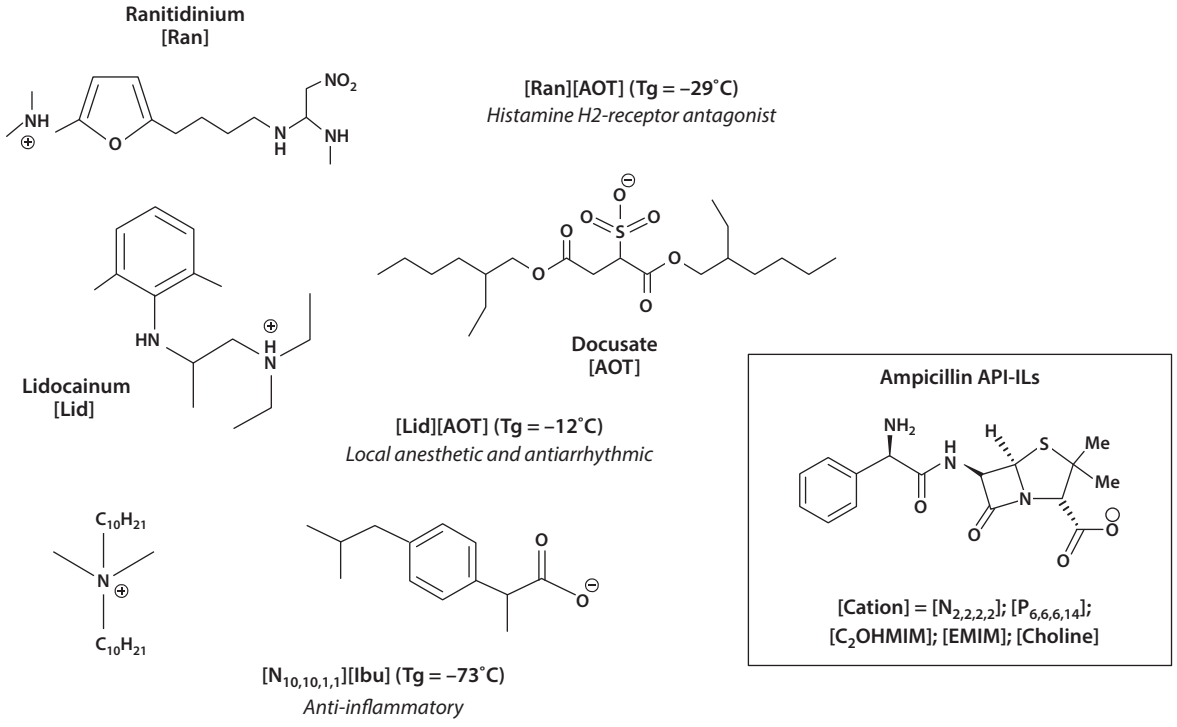


Figure 4

Some examples of novel active pharmaceutical ingredient–ionic liquids (API-ILs) based on ranitidine docusate, [Ran][AOT]; lidocaine docusate, [Lid][AOT]; didecylmethylammonium ibuprofenate, [$N_{10,10,1,1}$][Ibu]; and ampicillin API-ILs, [Cation][Amp].

polymorphism, as well as improved water solubility and bioavailability, when combined with adequate counterions (103). Additionally, ampicillin-ILs showed growth inhibition and efficient bactericidal properties against resistant Gram-negative strains of *Escherichia coli*, as well as relevant discriminative and strong antiproliferative activity against four different human cancer cell lines (liver, breast, prostate, and colon) (R. Rerraz, J.C. Rodrigues, M.H. Fernandes, I.M. Marrucho, L.P.N. Rebelo, C. Prudêncio, J.P.N. Noronha, Z. Petrovski, L.C. Branco, unpublished results).

To explore the advantages of transforming APIs into ILs (or organic salts) in avoiding polymorphism, we recently synthesized API-ILs using ibuprofen and naproxen as anti-inflammatory anion drugs. These compounds initially present no polymorphism evidence when properly combined with biocompatible cations (e.g., [C_{16}PYR][Ibu]) without any additional manipulation. Our laboratory is also working with fluoroquinolones (antibiotic drugs) and valproates (antiepileptic drugs), both of which can be developed as novel API-ILs that are more efficient and less toxic for medical therapeutics.

Bica et al. (104, 105) also reported an alternative synthesis of API-ILs in solvent-free conditions. These authors prepared API-ILs such as lidocainium acetylsalicylate ([Lid][Asp], glass temperature, Tg = 19.78°C), procainium acetylsalicylate ([Proc][Asp], Tg = −13.97°C), and procainium salicylate ([Proc][Sal], Tg = 13.87°C) by melting a stoichiometric mixture of base and salicylic acid derivatives at ∼100°C to obtain a liquid (see **Figure 5**). Similarly, hexetidinium

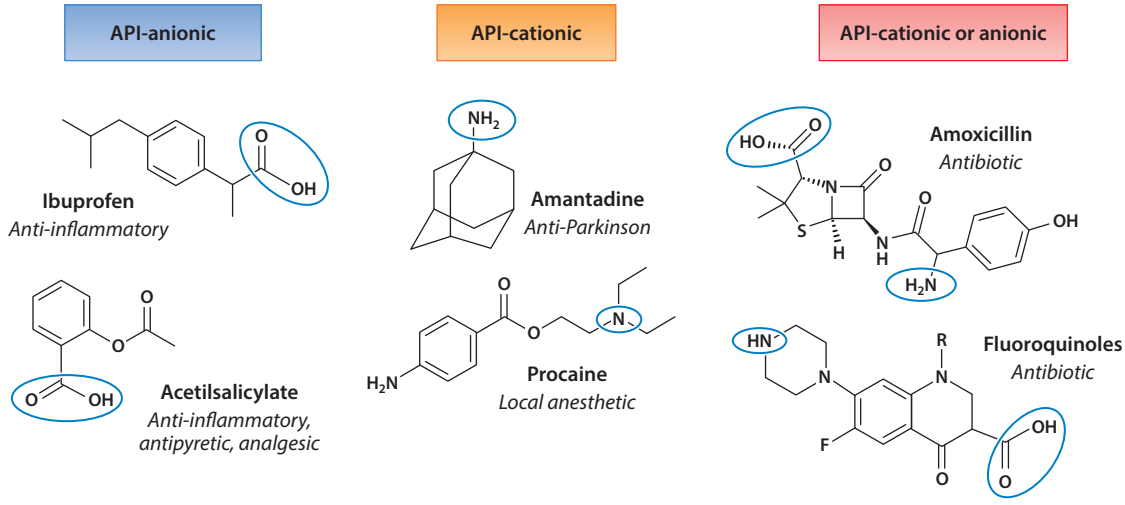


Figure 5

Examples of active pharmaceutical ingredient (API) ionizable functional drugs already developed as API–ionic liquids.

salicylate was directly synthesized by the reaction of hexetidine with salicylic acid. This solvent-free synthetic methodology presents advantages compared with conventional metathesis, because organic solvents, inorganic salts, halide, metal, or solvent impurities are avoided, as required for pharmaceutical applications. The isolation of the product occurred because the inorganic salt usually precipitates, and the product was extracted through filtration of inorganic salt and complete elimination of the solvent. Bica et al. (104, 105) also showed the preparation of other API-ILs, such as benzalkonium salicylate, benzethonium acetylsalicylate, benzethonium salicylate, cetylpyridinium salicylate, cetylpyridinium acetylsalicylate, trihexyltetradecylphosphonium salicylate, tramadolium acetylsalicylate, and tramadolium salicylate, using similar experimental protocols (**Figure 5**).

Other authors prepared API-ILs with potential antimicrobial, antifungal, and antibacterial activities (106) by combining common IL cations, such as 3-hydroxy-1-octyloxymethylpyridinium, benzalkonium, didecyldimethylammonium, hexadecylpyridinium, and cholinium-derived cations, with acesulfamate and saccharinate anions.

Dean et al. (7) proposed the development of an anticrystal engineering approach to synthesize API-ILs. This anticrystal engineering approach can be achieved by preparing a salt that presents an amorphous phase as its most thermodynamically stable form (in the temperature range of interest); a less-preferred but also effective form would have a melting temperature below the temperature of interest. To illustrate this concept, the authors (7) prepared a series of API salts, some of which crystallized readily, whereas others were characterized as ILs and remained in an amorphous glass or liquid form in spite of vigorous attempts to bring about crystallization. To achieve the combination, they also studied the possibility of cations and anions forming supramolecular synthons, mainly through the establishment of hydrogen bonds. It was observed that such crystalline salts were obtained in the case of cation/anion combinations bearing both hydrogen bond donor and acceptor groups. Other salts that are crystalline solids, such as propantheline saccharinate (melting point, mp 133–135°C, Tg = 18°C; antimuscarinic) and pyridostigmine saccharinate (mp 94–96°C, Tg = 2°C; cholinergic being a reversible cholinesterase inhibitor), do not exhibit

the capability to form hydrogen-bonded synthons but have some energy stabilization resulting in crystallization. Some salts considered as API-ILs, such as benzethonium saccharinate (Tg = −4°C, antiseptic), propantheline acesulfamate (Tg = −26°C, antimuscarinic), and propantheline *p*-toluenesulfonate (Tg = 7°C, antimuscarinic), showed no crystalline phase (or subambient melting point), indicating that this liquid or glass phase is the most thermodynamically stable phase at room temperature.

In the next few years, it is expected that the number of novel API-ILs will greatly increase owing to the interest in the topic as well as the significant advantages of having pharmaceutical drugs as organic salts or ILs in terms of bioavailability, drug delivery, stability, permeability, and elimination of polymorphisms or drug side effects. To the best of the authors' knowledge, no API-IL formulations are being industrially produced currently, owing to the lack of detailed knowledge on their effects in terms of biological and pharmaceutical properties, which must be further evaluated.

Protic pharmaceutical salts. Another attractive synthetic strategy is related to the direct protonation or deprotonation of original drugs, taking advantage of their specific functional groups, such as primary and secondary amines or carboxylic and sulfonic acids. Many important APIs are not permanent ions but rather are protonated or deprotonated to form the commonly used salts, with suitable pKa differences (107, 108). There is some debate about the definition of protic ILs. Some authors (109) proposed that protic ILs can be considered ILs only if the pKa difference is such that more than 99% of the salt exists in ionized form. This distinction is not required for an API. In fact, drugs with low degrees of ionization have important advantages over fully ionized ones, in particular their ability to cross membranes more efficiently. An example of a partially ionized, pharmaceutically active IL is 1-methylhexylammonium salicylate (87). Salicylic acid, an analgesic with a pKa value of 2.98, was reacted with 1-methylhexylamine, a nasal decongestant with a pKa value of 10.5, to produce a liquid at room temperature with a glass transition at −40°C (ΔpKa = 7.52). MacFarlane et al. (110) presented examples of salts prepared by proton transfer for different pharmaceutically active acids and bases. For the purposes of a systematic study, a series of acids and bases were selected with slight structural variations and physicochemical properties, with the objective of understanding the factors controlling melting point, H-bonding, and proton transfer. A library of nine compounds and four oligomeric protic ILs was synthesized and characterized. Benzoic, salicylic, and gentisic acid were chosen, as these are frequently encountered in pharmaceutical compounds/formulations. Benzoic acid, a common preservative and pharmaceutical (antifungal) aid, is used in a range of products on the market, including ointments, mouthwashes, and cosmetics. A derivative of benzoic acid, salicylic acid, is a widely recognized and used keratolytic that also possesses anti-inflammatory, analgesic, and antipyretic properties, as a sodium salt. Gentisic acid, another benzoic acid derivative, is used in the pharmaceutical industry as an analgesic and anti-inflammatory (111). Two other pharmaceutical bases were also chosen according to their pKa values and structures. Tuaminoheptane, a primary amine base with a pKa value of 10.50, is used as a nasal decongestant. Amantadine, also a primary amine base with a pKa value of 10.10, is an antiviral/anti-Parkinsonian drug (see **Figure 5**). Of the thirteen compounds synthesized, nine satisfy the definition of an IL by having melting points below 100°C (five of them are room-temperature ILs). All salts containing the amantadine base possess high melting points. All ILs containing the $[(EtOH)PYRH]^+$ have melting points below 100°C, whereas those based on the $[NTH_3]^+$ cation have no obvious trends among their melting points. For each case, thermal and chemical stability should be evaluated to understand the potential of protic ILs in pharmaceutical applications.

Evaluation of API-IL Enhanced Properties

Despite the great interest that the IL synthetic platform has aroused, as well as its undeniable success as a tool to prepare liquid forms of pharmaceutical compounds, the efficacy of these API-ILs has seldom been tested. In particular, the bioavailability, expressed in terms of the drug's solubility in water or in biological fluids, and the interaction with membranes, where Kow or liposome-water partition coefficients are used, are rarely addressed. Rogers and coworkers (100) showed not only that lidocaine properties, water solubility, thermal stability, and efficacy of topical anesthesia can be modulated but also that the cellular-level mechanism of the new drug is different. This unexpected change in the drug mechanism clearly stresses the importance of the evaluation of API-IL properties. Cole et al. (112) reported increased water solubility and antibacterial activity for pyridinium-based ampicillin-ILs. Our groups (39, 40, 113) also published several studies on tetracycline and ampicillin with tuned properties regarding water and biological fluid solubility and Kow and liposome-water partition coefficients. Interestingly, there is always a balance between optimal solubility and the optimal Kow or liposome-water partition coefficient. Stoimenovski et al. (87) discussed the effect of the proton-transfer effect in protic ILs composed of pharmaceutically active anions in model membrane transport. Viau et al. (75) showed that it is possible to control the kinetics of release of ibuprofen-based ILs using iongels as a drug-delivery system. Some publications reported the stability of the ionic formulation of the acid pharmaceutical drugs as a problematic issue (76, 80). Overall, despite the fast pace of the development of this thematic, much remains to be done mainly in terms of the evaluation of the specific properties of API-ILs.

FUTURE PERSPECTIVES

The development of pharmaceutical applications using IL-based methodologies requires a deep understanding of ILs both in terms of their macroscopic properties and also at the molecular level, because structural aspects have been shown to play a crucial and unexpected role in a large number of situations. Despite the fact that ILs can no longer be considered a new field, the large diversity of combinations of cations and anions producing novel ILs with new specific properties is astonishing.

The examples used in this review nicely illustrate the great potential of ILs in the pharmaceutical field, and how little explored it is. Most of the examples shown here are still proofs of concept, and no significant efforts have been made to bring them from laboratory to bench scale. Despite the fact that the conventional pharmaceutical industry is based on solids and solids processing, the use of ILs should be pushed forward because it might recycle many of the drugs that have been put on hold owing to their limited aqueous solubility or polymorphic conversion, thus bringing a new market value for these products.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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