Chapter 21

Pharmaceutical Salts: Solids to Liquids by Using Ionic Liquid Design

Clarissa P. Frizzo, Izabelle M. Gindri, Aniele Z. Tier, Lilian Buriol, Dayse N. Moreira and Marcos A. P. Martins

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1. Introduction

Ionic liquids (ILs) have attracted increasing interest lately in several areas such as chemistry, physics, engineering, material science, molecular biochemistry, energy and fuels, among others. Scientific literature has been daily invaded by papers that show a variety of new ionic liquids and new applications. Furthermore, the range of ILs used has been broadened, and there has been a significant increase in the scope of both physical and chemical IL properties [1, 2]. ILs are defined as liquid organic salts composed entirely of ions, and a melting point criterion has been proposed to distinguish between molten salts and ionic liquids (mp< 100 °C) [3].

When ILs based on 1-alkyl-3-methylimidazolium salts were first reported in 1982 by Wilkes et al. as tetrachloroaluminates, they were called ILs of first generation [4]. Replacement of this moisture-sensitive anion by the tetrafluoroborate ion and other anions led, in 1992, to air- and water-stable ILs, called then second generation, [5] which have found increasing applications such as reaction media for various kinds of organic reactions. At the onset of the new millennium, the concept of task-specific ILs, called third generation was introduced by Davis [6] (Figure 1). These compounds are defined as ILs in which the anion, cation, or both covalently incorporate a functional group (designed to endow them with particular properties, such as physical, chemical or in terms of reactivity) as a part of the ion structure [6,7]. Simultaneously, Rogers et al. [8] proposed that the ILs can be grouped into three generations in according to their properties and applications (Figure 1). The use of these compounds as solvents characterized them as ILs of first generation due to a unique and accessible physical property set characterized by low or no volatility, thermal stability, or large liquid ranges. Second genera-

tion of ILs has potential application such as energetic materials, lubricants and scavenger materials. In these cases, ILs provide a platform where the properties of both cation and anion can be independently modified, permitting the design of new functional materials, while retaining the desired features of an IL. Third generation of ILs has been described as the one where the biological activity is a primary IL property. Thus, ILs are seen as active pharmacological ingredient (API).

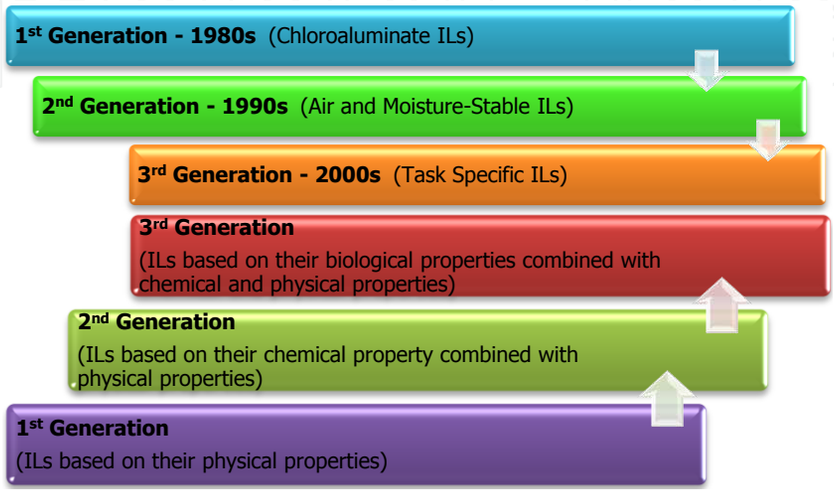

Figure 1. Historical evolution of ILs: chronological and useful development.

Potential pharmaceutical applications of ILs have been showed initially by studies of their toxicity and antimicrobial activity [9,10]. Currently, applications expanded to the use of pharmacologically active ions to develop novel ILs (3rd generation), the use in the formation of microemulsion droplets to transport and release of drugs, and as stabilizing agents of actives, additives and polymers in pharmaceutics [11]. One of the most import pharmaceutical applications is the use of pharmacologically active ions to develop novel liquid salts, since more than 50% of the drugs in the market today are sold as organic salts [12]. Hough and Rogers consider in their review [13] that the conversion of a drug into a salt is a crucial step in the drug development and can have a huge impact on its properties, including solubility, dissolution rate, hygroscopicity, stability, impurity profile and particle characteristics. Thus, the authors believe that an IL approach seems more than appropriate in the design of APIs, where a delicate balance exists between the exact chemical functionality needed for the desired effect in the absence of adverse side effects and the physical properties required for manufacturing, stability, solubility, transport and bioavailability [14,15]. Historically, the pharmaceutical industry depends mostly on crystalline APIs. However, many formulations fail during testing because of issues as, for example, delivery mechanisms such as dissolution, transport, and bioavailability or poor control over polymorphism which can dramatically change properties such as solubility [16,17,18]. In the context of APIs, the counter ions could be selected to synergistically enhance the desired effects or to neutralize unwanted side effects of the active entity. They could also be chosen to pharmacologically act independently [12,19] or to improve the pharmacokinetics properties [20] (Figure 2). Over the past few years, there have been three

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reviews published in which ILs from APIs occupied a central theme [12,13,20]. In these reviews, the approach of ILs from APIs is discussed from different points of view: i) historical approach of ILs (from solvents to ILs from APIs), ii) focus on the use of ILs from APIs to solve the toxicity of ILs and polymorphism and iii) a good review where all these topics are shortly discussed. However, there is no concern with the issue of the synthesis and physical and chemical characterization of new salts like ILs. Thus, considering the lack of complete and deep survey about all questions (advantages and disadvantages) in the literature and in continuation of our research on ILs [21], we propose this chapter to show the application of IL approach to obtain liquid pharmaceutical salt. This denotes that the material to be covered here includes only papers where pharmaceutical activities (pharmacokinetic and pharmacological) are present at the cation or anion and there is focus on the obtainment of ILs from APIs (Table 1). Here, we consider biologically active the ILs whose components interact with any biological system, and pharmaceutically active the ILs that present any pharmacokinetics and/or pharmacological activities (Table 3). Thus, it was necessary to mention that papers describing ILs with only one of the biologically active components or with no pharmaceutically active were excluded. Thus, the ions alkyimidazolium, phosphoniun, derivatives of non-nutritive sugars, and N-trifluoromethanesulfonate were not included in the scope of this chapter. Another scope limitation of this chapter is about the use of mechanical or thermal methods to the liquefaction of a salt from APIs. This means that pharmacologically active salts such as the procainamide and verapamil hydrochloride that pass from a crystalline state to amorphous state through changes of conditions such as temperature and pressure were excluded [22,23].

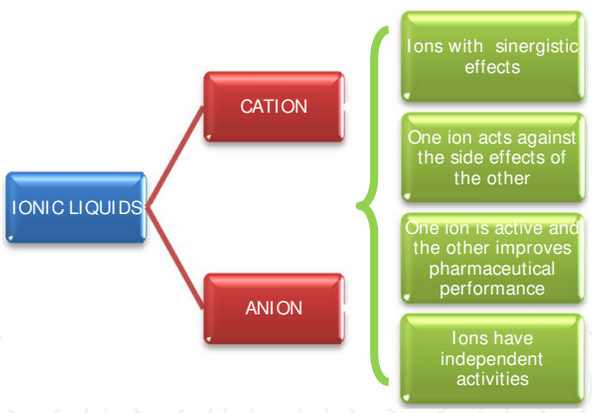

Figure 2. Cation and Anion combination in ILs from APIs and their activities.

Hence, in this chapter we will present the main problems of pharmaceutical industry in relation to solid salt APIs and how the proprieties as well as the limitations of the ILs affect the salification (i.e., salt formation) of APIs. The synthesis, the characterization of physical and chemical properties as well as the pharmaceutical performance of new ILs will be discussed. For this propose, we emphasize that the ILs selected to this chapter (Table 1) present in their structure at least one pharmacologically active entity, and the other (cation or anion) was introduced with the objective to increase the activity, reduce side effects or improve pharmaceutical performance by changing physical or chemical properties (Figure 2).

Compound	Name	Ref.
1	3-hydroxy-1-octyloxymethylpyridinium acesulfamate ([1-(OctOMe)-3-OH-Py][Ace])	[47]
2	3-hydroxy-1-octyloxymethylpyridinium Saccharinate ([1-(OctOMe)-3-OH-Py][Sac])	[47]
3	Benzalkonium Acesulfamate [BA][Ace]	[47]
4	Benzalkonium Saccharinate [BA][Sac]	[47]
5	Benzalkonium Salicylate [BA][Sal]	[37]
6	Benzethonium Acetylsalicylate [BE][Asp]	[37]
7	Benzethonium Aaccharinate[Ben][Sac]	[32]
8	Benzethonium Salicylate [BE][Sal]	[37]
9	Cetylpyridinium Acetylsalicylate [CetPy][Asp]	[37]
10	Cetylpyridinium Salicylate [CetPy][Sal]	[37]
11	Cetylpyridinium Ampicillin [C_{16}pyr][Amp]	[35]
12	Choline Ampicillin [Col][Amp]	[35]
13	Choline Phenytoin[Col][Phe]	[32]
14, 15, 16	Choline-derivative Acesulfamate [Col][Ace]	[46]
17	Didecyldimethylammonium Acesulfamate ([DDA][Ace])	[47]
18	Didecyldimethylammonium Ibuprofenate [DDA][Ibu]	[8]
19	Didecyl-dimethyl-ammonium Saccharinate ([DDA][Sac]	[47]
20	Hexadecylpyridinium Acesulfamate ([Hex][Ace])	[47]
21	Hexadecylpyridinium Aaccharinate ([Hex][Sac])	[47]
22	Hexetidinium Salicylate [Hext][Sal]	[37]
23	Lidocainium Acetylsalicylate [LID][Asp]	[37]
24	Lidocainium Docusate [Lid][Doc]	[8]
25	Lidocainium Salicylate [LID][Sal]	[37]
26	Mepenzolate Acesulfamate[Mep][Ace]	[32]
27	Mepenzolate Saccharinate[Mep][Sac]	[32]
28	Procainium Salicylate [Proc][Sal]	[37]
29	Procainium Amidesalicylate [PA][Sal]	[37]
30	Propantheline Acesulfamate[Pro][Ace]	[32]
31	Propantheline Cyclamate[Pro][Cyc]	[32]
32	Propantheline *p*-toluenesulfonate[Pro][pTO]	[32]
33	Propantheline Saccharinate[Pro][Sac]	[32]
34	Pyridostigmine Saccharinate[Pyr][Sac]	[32]
35	Ranitidine Docusate [Ran]Doc]	[8]

Compound	Name	Ref.
36	Tetrabutylphosphonium Salicylate [$P(BU)_4$][Sal]	[37]
37	Tetraethylammonium Ampicillin[TEA][Amp]	[35]
38	Tramadolium Acetyl-salicylate [Tram][Asp]	[37]
39	Tramadolium Salicylate [Tram][Sal]	[37]
40	Trihexyltetradecylphosphonium Ampicillin [$P_{6,6,6,14}$][Amp]	[35]

Table 1. ILs from active pharmaceutical ingredients found in this chapter.

2. Fundamentals

In this section we will deal with some important points of ILs approach salification of APIs and the strategies used in the search and characterization of new ILs from APIs. The synthetic procedure as well as physical and chemical properties (main thermal properties) of ILs will also be discussed.

2.1. Salification of APIs

The physical form of a drug substance is of great importance since it directly affects the manner in which the material is formulated and presented to the consumer, as well as influence more fundamental characteristics such as solubility and dissolution rate, which, in turn, impact on bioavailability [8, 17, 18].

The drugs converted into salts were found to be more stable and water soluble in comparison to free bases or acid which qualifies them as the preferred forms to use as therapeutic agents [19, 24-26]. Such salts may offer advantages over the corresponding free drug in terms of physical properties such as melting point (thermal stability), crystallinity, hygroscopicity, dissolution rate, or solubility (bioavailability). From a pharmaceutical viewpoint the melting enthalpy, melting temperature and solubility are of particular importance, both because of their routine measurement and their influence on processing and bioavailability [19, 26]. Taking these advantages into account, the pharmaceutical industry relies predominantly on solid, primarily crystalline forms for the delivery of APIs, mainly for reasons of purity, thermal stability, manufacturability, and ease of handling [8, 17, 18]. However, solid forms of APIs often suffer from polymorphic conversion, low solubility, and a variety of factors which affect bioavailability associated with the final solid form [17, 18, 27]. Many phase II trials of new APIs end in failure due to their efficacy, often related to bioavailability and thus solubility [16-18]. These factors motivate the screening for novel solid forms, including salts, polymorphs, pseudopolymorphs (or solvates), and co-crystals (Figure 3).

Liquid drug formulations from salification are rarely found and are usually based on eutectic mixtures [24], however, salt drug generation can result in a liquid salt, known as ionic liquid. The main advantage of ILs in most of the cases is that their salt properties are retained in a

wide liquid range. This fundamental property of ILs is because ions are generally organic with low symmetry and diffuse charge. In addition, ILs have properties such as negligible vapor pressure resulting in reduced inhalatory exposure, absence of flammability, and their high variability concerning organic chemical structure in order to optimize technological features like solvation properties. This tunable solubility with several organic compounds, viscosity, conductivity, as well as thermal and electrochemical stability is ideal in terms of technical applicability [3]. The control of the properties of an IL is based on the manipulation of the interactions between the ions. The suppression of these interactions reduces lattice energies and the extreme suppression of these interactions leads to glass formation upon cooling, polymorphism, multiple phase transitions, and ion dissociation [28-31]. An understanding of the physical and chemical properties of ILs allows the proper selection of a specific IL for a given application. Thus, for example, by choosing ionic components capable of solubilizing specific solutes, one can control the critical solubility to crystallization processes [29].

Stoimenovski et al. [12] cited in their work that studies have been suggest that ILs do not dissolve as independent ions but keep a nanostructured organization in aqueous media. This fact, constitute other important advantage of the obtainment of an API as IL. Drugs that are highly ionic have difficulty crossing the membrane in order to reach their site of action. Ion-pair formation enhances the transport of various ionic drugs through the skin and across the absorbing membrane [12]. Therefore, highly ion-associated pharmaceutically active ILs would be highly beneficial forms of the original pharmaceutical active salts, as they could cross the membrane more rapidly [12]. Therefore, targeted alterations of a final drug form based on the various property sets obtainable through an IL approach may help to enhance efficacy, while retaining, improving or even introducing a second activity. The potential of this approach as a drug phase is to date poorly exploited [13, 13, 20].

Clearly, a salt that does not exhibit a crystalline phase will not present polymorphism, but there are further advantages to be realized and exploited in the delivery of the API [32]. In particular, a non-crystalline salt in a liquid or glassy phase will probably exhibit the enhanced solubility exhibited by amorphous phases [17, 18, 32]. This concept bears further discussion as it is potentially one of the most important advantages of the formulation of APIs as ionic liquid phase [32].

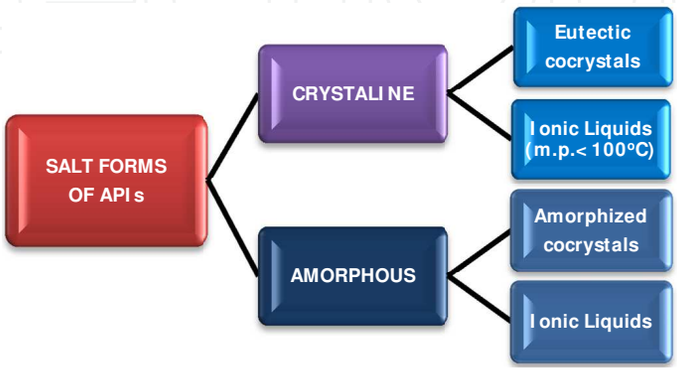

Figure 3. Salt forms of Active Pharmaceutical Ingredients (APIs).

2.2. Synthesis of ILs from APIs

The selection of pairs of ions to form ILs is carried out with candidate ions that have low symmetry and charge diffuse, traits that also characterize several typical APIs. Even the nitrogen-containing heterocycles, commonly used in ILs today, are frequently found in APIs or API precursors [8,33]. The process generally is a simple way to modify the properties of a drug with ionizable functional groups to overcome undesirable features of the parent drug [12].

Care must be taken when choosing appropriate IL-forming ion pairs. Many of the important APIs are not permanent ions, but rather are protonated or deprotonated to form the commonly used salts; thus suitable pKa differences need to be considered [8,34]. MacFarlane and Seddon [8,1] have recently proposed that protic ILs can only be considered ILs if the pKa difference is such that more than 99% of the salt exists in ionized form. For an API this distinction may not be needed, since having a balance between ionized and neutral forms may have advantages. There may be a significant advantage of drugs with low degree of ionisation over the fully ionised ones due to their ability to cross membranes more efficiently. An example of a partially ionized pharmaceutically active IL is 1-methylhexylammonium salicylate [12]. 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 and a ΔpKa of 7.52.

Most of the syntheses found in the papers selected to this chapter consist of metathesis reactions. The cation and anion in their available salt forms were separately dissolved in a solvent (e.g., water, methanol, ethanol, acetone) allowed to stir with heating to ca. 90 °C (if necessary) or at room temperature. Some alternative methods to methatesis reaction to specific ILs were also described. Ferraz et al. [35] used a method to change the anion using ion exchange resin described by Ohno et al. [36]. Ferraz et al. [35] employed Amberlite resin (in the OH form) in order to exchange 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. The organic cations were selected from salts which were first transformed into hydroxides by 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. In this case, pure ILs were obtained after eliminating the excess ammonia and/or β-lactam antibiotic by evaporation and crystallization, respectively. Bica et al. [37, 38] also showed an alternative synthesis in solvent-free conditions. The compounds **25** and **28** were also prepared by melting a stoichiometric mixture of base and salicylic acid at ~100 °C to obtain a liquid. Similarly, **22** was directly synthesized by the reaction of hexetidine with salicylic acid. This solvent-free preparation is clearly advantageous compared to conventional metathesis, since solvents and stoichiometric NaCl waste are prevented. Furthermore, ILs are obtained in high purity without halide, metal, or solvent impurities, as necessary for pharmaceutical applications. The isolation of the product occurred considering that usually the inorganic salt precipitates. Thus, in most of cases, the product was extracted by filtration of inorganic salt. The solvent was removed with a rotary evaporator. The resulting product was placed on a high vacuum line to remove any residual solvent. In

some cases, when inorganic salt is partially soluble, ILs had to undergo a process of extraction typically with chloroform or dichloromethane. Following that step, the organic phase was then washed with water to remove any inorganic salt (e.g., NaCl, which was monitored by a silver nitrate test), and solvent was removed with a rotary evaporator. The resulting product was placed on a high vacuum line to remove any residual solvent. In some cases, an extra purification was described, mainly to remove excess of halides.

2.3. ILs characterization

When searching for an IL from APIs, one has to care about its physical state and properties because it may not be an IL, but a crystalline solid (Figure 3). A significant number of drugs currently on the market are formulated as amorphous materials, and the most common means of preparing the amorphous phase is by quenching: rapid cooling from the melt; rapid precipitation from solution (for example on addition of an antisolvent); spray drying; flash evaporation; lyophilisation, in other words, methods that allow the disordered glassy phase to be "frozen in" before nucleation and growth that would lead to the appearance of crystals [32, 17, 18]. Dean et al. [32] have showed a schematic comparison of the accessible phases and the relative free energy of each phase. The authors highlight that in cases where a stable crystalline form exists at ambient temperature, $\Delta Gf°$ for the crystalline phase is lower than that for the amorphous material formed by quenching. In this manner, the quenching results in a form that is not the most thermodynamically stable phase at that temperature. The authors also emphasize that in this situation, any event that initiates nucleation may lead to growth of a crystalline phase at the expense of the amorphous glass. Such nucleation initiators may include heating (yielding a plastic phase that then crystallizes) or localized shock, such as that applied during size reduction (grinding) or formulation. In some cases, even the desired increased solubility leads immediately to the crystallization of a stable crystalline phase. In relation to the search by ILs, the authors emphasized that in the preparation of a salt that has an amorphous phase as its most thermodynamically stable form (in the temperature range of interest), a less preferred, but an effective form would be one with fusion temperature below the temperature of interest [32].

In the light of the extensive literature on crystalline drug forms, currently supported by crystal engineering [39,40] by using supramolecular synthons [41] concept and considering the abovementioned data, their benefits are clear to develop strategies for increasing solubility of drug compounds [42] and to chose co-crystal formers [43] for poorly soluble drugs [44]. Therefore, combining an understanding of the effect of robust supramolecular synthons on the process of crystallization, with concepts involving IL, Dean et al. [32] proposed the development of an "anti-crystal engineering" approach to the synthesis of ILs from APIs. This would comprise identifying and intentionally avoiding the pairing of cations and anions that might yield common supramolecular synthons, with the goal of decreasing the likelihood of crystallization of salt. This "anti-crystal engineering" approach is postulated as a means of narrowing the search for ILs from API to cation and anion pairs that have a higher likelihood of not crystallizing. Dean et al. [32] illustrated this approach by preparing and analyzing a series of API salts; some of which crystallized readily, while 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, the authors studied the possibility of cations and anions form supramolecular synthons mainly from interactions of hydrogen that usually considered imparting a tendency toward crystallization that should be avoided in the quest for ILs from APIs. As a result, they observed that all cation/anion combinations bearing both hydrogen bond donor and acceptor groups yield crystalline salts (**13**, **26**, **27** and **31**) [32]. For example, **13** (Table 1 and 2) which might be predicted to form the greatest number of strong, directional hydrogen bonds between different ions yields the salt with the highest melting point. Of greater interest, however, are those salts that are crystalline solids and even do not (at first examination of individual ions) exhibit the capability to form hydrogen bonded synthons (**33** and **34**), but have some energy stabilization resulting in crystallization. On the other hand, some salts were observed as salt without a crystalline phase (or with a sub-ambient melting point) indicating that they are in the most thermodynamically stable phase as a liquid or glass at ambient temperature. Thus, these salts (**7**, **30** and **32**) are considered ILs by the authors [32]. In another work in search by ILs from APIs, Bica et al. [38] found that generating oligomeric ions from tautomer's protons has a tremendous influence on physical properties that allow the expansion of the liquid ranges of some salts. They proposed that for this type of liquid salt formulation, the term ionic liquids might be controversial. They suppose (say) this based on initial experiments and further investigation concerning ionicity and simple eutectic behavior are currently ongoing in their laboratories. The authors define oligomeric ions as those that enable liquefaction of solid ILs (or other salts) by simply changing the stoichiometry or complexity of the ions. They highlight that the strategy does not need to employ the parent of the anion or cation in use and that this can be particularly useful for pharmaceutically active salts or ILs. According to the authors, another advantage of the oligomeric ions strategy is that the design of pharmaceutical IL may benefit since it is permitted to modify the physical properties of a given salt form once obtained [38].

Therefore, considering the "anti-crystal strategy" proposed by Dean et al. [32] and the "oligomeric ions" proposed by Bica et al. [38] in the search for ILs from API, the possibility of formation of solid crystals (eutectics), amorphous, or liquid phase is a fundamental question (Figure 3). Thus, one cannot imagine the search for new ILs from API without performing a complete calorimetric characterization of what an IL may be. Currently, unfortunately, in most of the cases, the ions are selected by facility from synthesis or purification routes rather than rational choice or screening.

The calorimetric data reported in papers collected to this chapter showed that most of the salts synthesized can be classified as ILs, while the remaining were crystalline salts. Those who were characterized as IL can be shared in three general types of behavior. The first group of ILs exhibits just melting points below 100 °C, allowing their classification as ILs (**1**, **2**, **4**, **9**, **10**, **14**, **16** and **21**). The second type of behavior is characterized by formation of an amorphous glass. These ILs have no melting, but only glass-transition (**6-8**, **17**, **18**, **23-25, 28-30**, **32-35** and **38**). The third group of ILs is characterized by compounds that have melting points and glass transition (**2**, **5**, **11**, **12**, **15**, **19**, **20**, **34**, **36** and **37**)). Compounds **13**, **22**, **26**, **27, 31, 33** and **39** were found to have high melting not fitting the definition of ILs (Table 2). Other physical and

chemical properties also should be evaluated to characterize an organic salt as an IL. Considering the scope of this chapter, some of the properties were found in a few papers (Table 2). These properties were density, solubility and thermal stability (Table 2). Viscosity is an important physical property to characterize an IL. The viscosity of ionic liquids is essentially determined by their tendency to form hydrogen bonding and by the strength of their van der Waals interactions. The structure of the cation strongly influences the viscosity of the IL. However, this property was not reported in any of the selected papers. Density was reported only for two ILs (**14**, **15**). These ILs were denser than water thus the density of comparable ILs decreases as the bulkiness of the organic cation increases. It is evident that the density of such compounds increases with increasing molecular weight of the anion which confirms the results shown by Fredlake et al [45]. Density reported to ILs from APIs in the selected papers to this chapter is characteristic of ILs[3]. At room temperature, the ILs from API reported in this chapter were grouped into miscible in water and other polar organic solvents (hydrophilic) and partially miscible or immiscible in water and hexane (hydrophobic). Water miscible ILs were choline derivatives, ampilicin, saccharinate and water imiscible were choline, ammoniun and pyridiniun derivatives. IL choline derivatives were present in both groups on dependence of anion. Solubility data of other IL derivatives of other cations and anions were not reported by the authors. The thermal stability of ILs is limited by the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds, respectively [3]. The ILs **9**, **14**, **15** and **23** showed a lower thermal stability (115.14-126.5 °C) while **1-6**, **8**, **10-12**, **17-22**, **24**, **25**, **28**, **29** and **35-40** have shown more stable (154.22-307.94 °C).

Compound	Thermal Data (°C) and Density at 25°C (g.mL-1)	Ref.
1	m.p = 79-81[d], TGA = 267	[47]
2	m.p = 95-98[d], TGA = 301	[47]
3	m.p = 90, Tg = -36[a], TGA = 187/249/394[c]	[47]
4	m.p = 74, TGA = 204	[47]
5	m.p = 96.02, Tg = 51.01, TGA = 171.95[b]	[37]
6	Tg =2.84, TGA = 154.22[b]	[37]
7	Tg = -4	[32]
8	Tg = -13.72, TGA = 167.76[b]	[37]
9	m.p = 61.31, TGA = 115.14[b]	[37]
10	m.p = 73.97, TGA = 205.61[b]	[37]
11	m.p = 86.0, Tg = -19.64, TGA = 269.39	[35]
12	m.p = 58.0, Tg = -20.12, TGA = 221.29	[35]
13	m.p = 215 – 217	[32]

Compound	Thermal Data (°C) and Density at 25°C (g.mL-1)	Ref.
14	m.p. = 31-36 and82-84 TGA = 126.5, density = 1.103 - 1.277	[46]
15	m.p. = 85-86,Tg = -49, TGA = 122, density = 1.041-1.270	[46]
16	m.p.= 87-88	[46]
17	Tg = -53, TGA = 232/426[c]	[47]
18	Tg = -73, TGA = 168[b]	[8]
19	m.p = 16, Tg = -33, TGA = 214	[47]
20	m.p = 57, Tg = -11, TGA = 267/494[c]	[47]
21	m.p = 66, TGA = 253/412[c]	[47]
22	m.p = 106.81, TGA = 182.14[b]	[37]
23	Tg = -13.97, TGA = 120.71[b]	[37]
24	Tg = -29, TGA = 222 [b]	[8]
25	Tg = 19.78, TGA = 158.46[b]	[37]
26	m.p = 135 – 137, Tg = 34	[32]
27	m.p = 187 – 189, Tg = 53	[32]
28	Tg = 13.87, TGA = 187.33[b]	[37]
29	Tg = 19.87, TGA = 159.21[b]	[37]
30	Tg = -20	[32]
31	m.p = 133 – 137, Tg = 20	[32]
32	Tg = 7	[32]
33	m.p = 133 – 135, Tg = 18	[32]
34	m.p = 94 – 96, Tg = 4	[32]
35	Tg = -12, TGA = 249	[8]
36	m.p = 57.32, Tg = -56.47, TGA = 307.94[b]	[37]
37	m.p = 79.0, Tg = -18.64, TGA = 214.75	[35]
38	Tg = 13.78, TGA = 169.64[b]	[37]
39	m.p = 176.17, TGA = 177.16[b]	[37]
40	TGA = 297.65	[35]

[a]Solid-solid transition.[b]$T_{onset\ 5\%}$.[c]Multiple decomposition steps. [d]Visual melting point range *via* hot-plate apparatus.

Table 2. Physical and Chemical Properties of some ILs from APIs.

3. Pharmaceutical activity assessment

In view of the objective of our chapter, it is important to evaluate the pharmaceutical profile of ILs from API. Pharmaceutical profile includes changes on the pharmacokinetics and/or pharmacological behavior of the salts when they turn into liquids by changing their cation or/anion.

No specific pharmacokinetic property was evaluated. However important observation reporting by Hough et al [8] and related in a review by Stoimenovski et al [12] is that strongly hydrophilic ionic actives often possess insufficient ability to penetrate biological membranes. Combining such an active ion with another of a more lipophilic character may offer a solution to this problem. For example, lidocaine docusate [Lid][Doc], an IL form of the local surface anaesthetic lidocaine, combines the relatively hydrophobic lidocaine cation with a hydrophobic anion, docusate (an emollient), to produce a hydrophobic IL, which exhibits reduced or controlled water solubility (Figure 2) and thus should exhibit extended residence time on the skin [8].

From the selected papers to this chapter, only three of them bring evaluation of pharmaceutical properties of new API (IL). Pharmacological activities were evaluated in four papers. Pharmacological activity evaluated were antinociception [8], suppression of PC12 neuritic outgrowth [8], antibactericidal [46, 47] and antifungal [46, 47] activities and skin irritation [47]. Antinociception activity [8] was assessed using a modification of the tail-withdrawal procedure. Two antinociceptive models were used: warm water tail-withdrawal from 49 °C water in intact mice, and warm water tail-withdrawal from a 47 °C bath, following tail injury. In this test it was observed that [Lid][Doc] produced a longer duration of antinociceptive effect than lidocaine hydrochloride [Lid][HCl]. The authors suggest that the high hydrophobicity for [Lid][Doc] in relation to [Lid][HCl] account for the increased duration of [Lid][Doc] over [Lid][HCl] observed *in vivo* models. Also, this may constitute a slow-release mechanism unique to any hydrophobic IL [8].

In the same paper [8], the evaluation of the suppression of PC12 neuritic outgrowth by [Lid][Doc] and [Lid][HCl] was evaluated. The suppression of PC12 neuritic outgrowth is related to the local anesthetic effects. These anesthetics suppress nerve growth factor (NGF) mediated neuronal differentiation in rat pheochromocytoma (PC12) cells. This was used as a bioassay for detecting that killed PC12 cells treated with [Lid][HCl] was higher than [Lid][Doc]. Authors suggest that the PC12-NGF data indicate potential differences between [Lid][Doc] and [Lid][HCl] at the cellular level and showed a mechanism of action entirely different for [Lid][Doc] than that for [Lid][HCl]. Docusate may enhance membrane permeability which may suggest at least one mechanism associated with the apparent increase in [Lid][Docl] efficacy *in vivo*. However, while an increase in permeability may enhance transdermal transport and account for the longer duration and greater efficacy of [Lid][Doc]*in vivo*, the longer duration of [Lid][Doc] on the mouse tail-withdrawal indicates an alternative mechanism.

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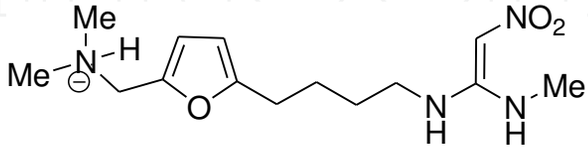
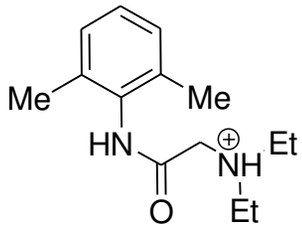
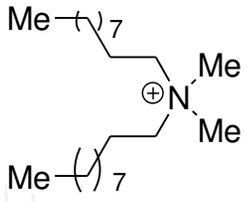
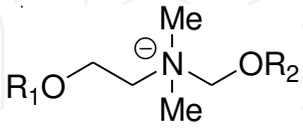
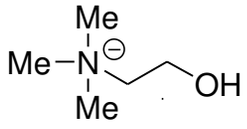
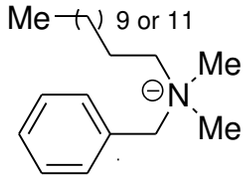
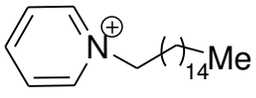
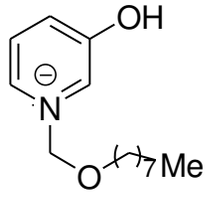
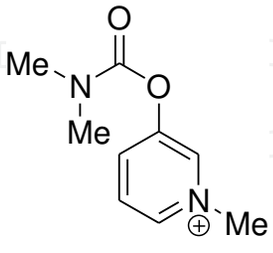
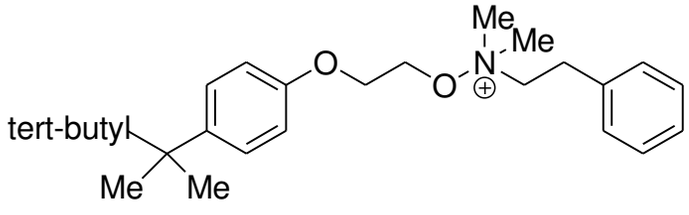
Antimicrobial, antifungical and antibactericidal activities were evaluated to ILs **14** and **15** [46], **3**, **4**, **17** and **19** [47]. Results were expressed in terms of mean minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). The efficacies of **14** and **15** were low (but still high enough to be effective) in comparison with that of the widely used benzalkonium chloride. No MIC and MBC values could be established for the [Ace] salts **16**, because of their hydrophobic characters. Salts **3**, **4**, **17** and **19** were also evaluated; benzalkonium and didecyl-methylamonnium chloride which inherently exhibit anti-microbial, anti-bacterial and anti-fungal activities were used as standard for comparison. ILs activities are similar to those of commercially available, although the ILs were not found to be limited to a specific class of bacteria or fungi. Skin irritation of salts **17** and **19** [47] was also determined. Each IL was tested on 3 male New Zealand albino rabbits, where the fur was previously removed from the back of the rabbit. Half a milliliter of the ILs (100%, pure) was distributed on two 6 cm^3 sites of the same animal. The application site was then covered with a porous gauze dressing and secured in place with tape. After a 4h exposure, the dressing was removed and the application site was gently washed with water. Observations were then conducted at 1, 24, 48, and 72 h, where the test sites were evaluated for erythema and edema using a prescribed scale. The skin irritation of these ILs is defined as category 4 (the highest) by standard organization for economic co-operation and development (OECD) grading.

Finally, the acute oral toxicities of salts **17** and **19** were determined. The toxicity was tested according to the method of acute toxic class. Wistar rats male and female were used for each IL tested. Results indicated the acute toxicity range for both ILs was between 300–2000 mg/kg in male and female rats. Thus, these ILs would be classified as category 4 (harmful) toxins according to standard organization for economic co-operation and development (OECD) grading. Table 3 depicted the cation and anion covered in this review. Structures and pharmacological activities of each of them are also showed.

Structure	Name	Activity
	Ranitidine [Ran]	Histamine H2- receptor antagonist
	Lidocainum [Lid]	local anesthetic,

Structure	Name	Activity
	Didecylmethylammonium [DDA]	antibacterial
  R^1=H, R^2=from Et to $C_{14}H_{29}$ and $C_{12}H_{23}$(4) R^1=Ac, R^2=from Et to $C_{14}H_{29}$ and $C_{12}H_{23}$(5) R^1 =C_9H_{19},R^2 = from Etto $C_{12}H_{25}$ and $C_{12}H_{23}$(6)[a]	Cholinederivatives[Col]	acetylcholine precursor
	Benzalkonium [BA]	antibacterial
	Hexadecylpyridinium [Hex]	antibacterial
	3-Hydroxy-1-octyloxymethylpyridinium [1-(OctOMe)-3-OH-Py]	antimicrobial
	Pyridostigmine [Pyr]	reversible acethylcholinesteterase inhibitor
	Benzethonium[Ben]	antibacterial

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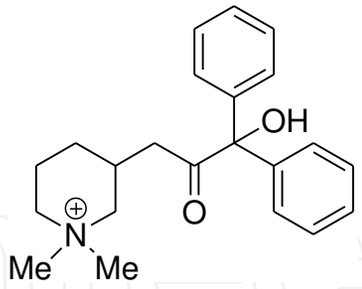
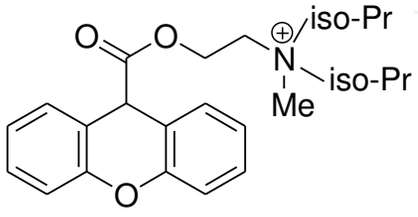
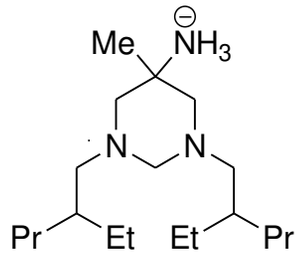
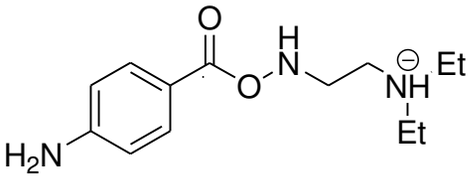
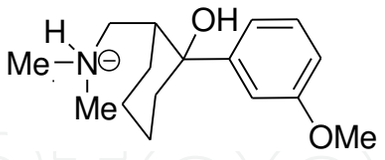
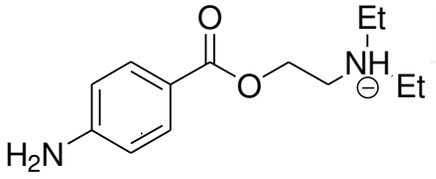
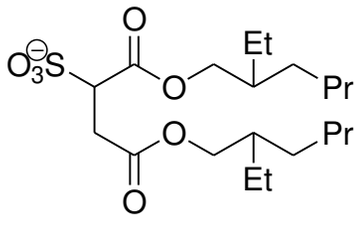
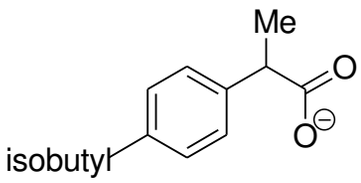
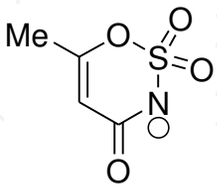
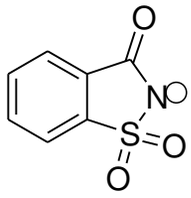
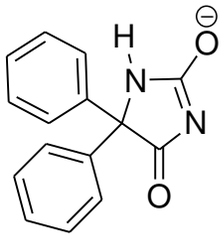
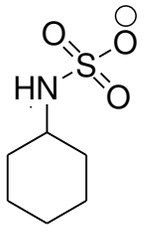
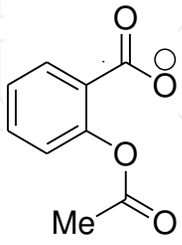
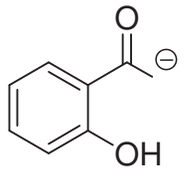
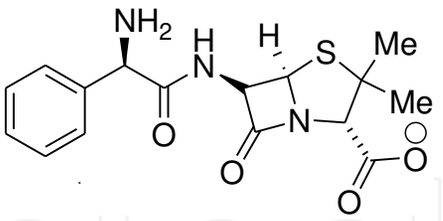
Structure	Name	Activity
	Mepenzolate[Mep]	skeletalmusclerelaxant
	Propantheline[Pro]	antimuscarinic
	Hexetidinium[Hext]	antibacterial
	Procainiunamide[PA]	antiarrhythmic
	Tramadolium[Tram]	analgesic
	Procainiun [Proc]	localanesthesic
	Docusate [Doc]	emolient

Structure	Name	Activity
	Ibuprofenate [Ibu]	anti-inflammatory
	Acesulfamate [Ace]	noncaloric sugar
	Saccharinate[Sac]	noncaloric sugar
	Phenytoin[Phe]	antiepileptic
	Cyclamate [Cyc]	noncaloric sugar
 and 	Acetylsalicylate [Asp] salicylate [Sal]	anti-inflammatory, analgesic, anti-pyretic

Structure	Name	Activity
	Ampicillin [Amp]	antibacterial

[a]Number **4**, **5** and **6** are of the ILs formed from these cations (See Table 1).

Table 3. Structure and activity of ions found in this chapter.

4. Conclusion

After having examined the literature in ILs from APIs it is possible to conclude that: *(i)* this is a research area developed by few groups; *(ii)* a complete and elaborated work including synthesis, physical and chemical properties studies and pharmacological activity estimation is necessary to produce significant results in this area (some groups have already performed more elaborated works); *(iii)* evaluation of physical and chemical properties, main thermal behavior is fundamental to develop new liquid APIs from IL approach; *(iv)* modification in the physical state of an API can result in modification or modulation of pharmaceutical properties of drugs. For example, co-formation of two separate solid actives in a solid dosage form significantly differ from a dual functional IL formulation. The ions in an IL dissolve in the body fluids exactly the same way—since one ion cannot dissolve without the other; this is not true to separate solid forms administered at the same time since each may dissolve at quite different rates. In addition, increase in solubility and bioavailability can enable a new formulation and/or a new doseage. Consequently, pharmacokinetic and pharmacological profiles studies necessarily lead to a potential patent protection for each of new forms of drugs [12].

In this chapter, we hope to have given a clear idea of the use of IL approach in the obtainment of liquid or amorphous API. We would like to conclude with an optimistic view for the future expansion of the development of new drug profiles. This positive view comes from the certainty that the results reported here are the beginning of a great advance in this promising field in the near future.

List of Abbreviations

API – Active Pharmacological Ingredient

IL –Ionic Liquid

MBC - Minimum Bactericidal Concentration

MIC - Minimum Inhibitory Concentration

NGF - Nerve Growth Factor

OECD - Organization Economic Co-operation and Development

PC12 - Pheochromocytoma Cells

ΔGf°– Free Energy of Fusion

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Author details

Clarissa P. Frizzo*, Izabelle M. Gindri, Aniele Z. Tier, Lilian Buriol, Dayse N. Moreira and Marcos A. P. Martins

*Address all correspondence to: clarissa.frizzo@yahoo.com.br

Department of Chemistry, NUQUIMHE, Federal University of Santa Maria, Santa Maria, RS, Brazil

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