Chapter

IONIC LIQUIDS: A PHARMACEUTICAL PERSPECTIVE

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ABSTRACT

In the last decades, ionic liquids (ILs) progressed from chemical curiosities to interesting biological compounds apprehending the attention of researchers of distinct areas, from chemistry to pharmacology.

Initially, ILs were explored as materials for diverse applications due to the possibility of synthesize compounds with targeted chemical properties combined with selected physical properties. More recently, the emergence of ILs with biological activity revolutionized the scientific focus of these compounds and opened interesting perspectives regarding their pharmaceutical application. From the pharmaceutical point of view, an IL approach, in the design of novel active pharmaceutical ingredients (APIs), appears to be appropriate as it enables the chemical manipulation of the compounds with specific objectives related with the manufacturing process, the stability of the formulation, bioavailability and eventual adverse effects. Furthermore, even though crystallinity confers advantages during isolation, processing and storage of the drug, it is known that solid forms of APIs often suffer from low solubility and polymorphic conversion which can influence negatively the bioavailability of the drug and ultimately its therapeutic effect.

On a distinct perspective, the possibility of engineering the properties of ILs by manipulating anion-cation combinations, in association with their solvent properties and in some cases water-miscibility, are considered promising characteristics regarding the applicability of ILs as solvents or carriers of pharmaceutical drugs.

In this chapter it is intended to expose the pharmaceutical potential of ILs through the discussion of their utilization either as APIs or solvents/carriers of pharmaceutical drugs. The discussion will be centered on the benefits of the IL approach for the development of novel drug candidates considering not only physico-chemical aspects but also the pharmaceutical profile of the developed active pharmaceutical ingredients with IL properties. Considering the utilization of ILs as solvents of drugs or as part of drug delivery systems, it is anticipated that the discussion will be focused on the efficiency and toxicity of the systems and on their influence on the pharmacokinetics and

pharmacodynamics of the vehiculated drugs. It is also planned to debate the motivations for the pharmaceutical usage of ILs as well as their peculiar properties that launched them in this context. Currently, the pharmaceutical utilization of ILs is one of the most relevant applications of these solvents, with impact on the safety and effectiveness of the involved processes and with benefits in terms of pharmaceutical formulations and pharmacological activity. It is our belief that this chapter is adequate for the book in project and can greatly enhance its acceptance and interest by readers in distinct research areas.

ABBREVIATIONS

Ionic Liquid(s)	IL(s)
Research and Development	R&D
GlaxoSmithKlein	GSK
Active pharmaceutical ingredient(s)	API(s)
Ethylammonium nitrate	$EtNH_3 [NO_3]$
1-butylpyridinium chloride-aluminum chloride	bmpy [Cl]-$AlCl_3$
Tetrafluoroborate	BF_4
Hexafluorophosphate	PF_6
Generally recognized as safe	GRAS
Volatile organic solvent(s)	VOCs
Food and Drug Administration	FDA
1-butyl-3-methylimidazolium tetrafluoroborate	bmim [BF_4]
NSAID(s)	non-steroidal anti-inflammatory drug(s)
Ring closing metathesis	RCM
Triethylammonium acetate	TEAA
Support ionic liquid phase	SILP
1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	bmim [NTf_2]
n-propyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide	dmim [[NTf_2]
DPEN	(R,R)-1,2 diphenylethylenediamine
1-hexyl-3-methylimidazolium tetrafluoroborate	hmim [BF_4]
1-ethyl-3-methylimidazolium tetrafluoroborate	emim [BF_4]
1-butyl-2,3-dimethylimidazolium hexafluorophosphate	dbmim [PF_6]
1-ethyl-3-methylimidazolium chloride-aluminum chloride	emim [Cl]-$AlCl_3$
1-butyl-3-methylimidazolium chloride-iron chloride	bmim [Cl]-$FeCl_3$
1-butyl-3-methylimidazolium chloride-aluminum chloride	bmim [Cl]-$AlCl_3$
1-butyl-3-methylimidazolium chloride-zinc chloride	bmim [Cl]-$ZnCl_2$
1-ethylpyridinium tetrafluoroborate-zinc chloride	etpy [BF_4]-$ZnCl_2$
1-butyl-3-methylimidazolium hexafluorophosphate	bmim [PF_6]
1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	emim [NTf_2]
methyltrioctylammonium bis(trifluoromethylsulfonyl)imide	moma [NTf_2]

1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide	bmpyr [NTf$_2$]
1-hexyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide	hmpyr [NTf$_2$]
methyl *tert*-butyl ether	MTBE
1-methylimidazolium acetate	mim [OAc]
1-methoxyethyl-3-methylimidazolium methanesulfonate	moemim [Ms]
1-methoxyethyl-3-methylimidazolium trifluoroacetate	moemim [TFa]
1-butyl-3-methylimidazolium trifluoroacetate	bmim [TFa]
1-butyl-3-methylimidazolium methanesulfonate	bmim [Ms]
1-butyl-3-methylimidazolium hydroxide	bmim [OH]
dimethylimidazolium dimethylphosphate	dmim [(CH$_3$O)$_2$PO$_2$]
1-hexyl-3-methylimidazolium acetate	hmim [OAc]
1-ethyl-3-methylimidazolium acetate	emim [OAc]
1-methylimidazolium hydrogen sulfate	hmim [SO$_4$]
1-butylimidazolium tetrafluoroborate	hbim [BF$_4$]
1-hexyl-3-methylimidazolium hexafluorophosphate	hmim [PF$_6$]
1-octyl-3methylimidazolium hexafluorophosphate	omim [PF$_6$]
1-ethyl-3-methylimidazolium methanesulfonate	emim [Ms]
1-ethyl-3-methylimidazolium trifluoromethanesulfonate	emim [TfMs]
dimethylimidazolium dimethylphosphate	dmim [(CH$_3$O)$_2$PO$_2$]
1-hexyl-3-methylimidazolium chloride	hmim [Cl]
1-tetradecyl-3-methylimidazolium bromide	tmim [Br]
1-hexyl-3-methylimidazolium bromide	hmim [Br]
Ionic liquid(s) with pharmaceutical activity	IL-API(s)

1. INTRODUCTION

The pharmaceutical industry faces nowadays unprecedented challenges and amendments. Drug development became a question of millions of dollars and the emergence of generic drugs led to dramatic decreases on the sales of huge market successes [1]. With this, the investment on research and development (R&D) tends to decelerate since the risks associated with drug discovery seem to not be in accordance with the current economic demands. It is known that 95% of the experimental drugs that reach clinical trials fail to be both effective and safe. Before this, 40% of the novel drug candidates never reach this stage due to poor pharmaceutical properties such as reduced solubility or diminished permeation of the blood-brain barrier [2].

Additionally, the demands regarding the environmental impact of drug discovery are on the frontline of the guidelines of Green Chemistry [3].

In this scenario, the pharmaceutical industry has been struggling to keep the high standards of R&D whit the demands of preserving economically viability and integrate environmental sustainability. Novel approaches and management models have been implemented and at the same time the academic community started to invest on innovative pathways for the development and synthesis of novel drug candidates. Additionally, there has

been also investment on the reformulation of old synthetic and production processes to make them more adequate to the current economic and environmental demands. Some pharmaceutical companies are nowadays sensitive to this matter and are aware of the environmental consciousness of the general population. Companies like Pfizer and GlaxoSmithKlein (GSK) created internal guidelines (in accordance with the Green Chemistry principles) that aim, among others, the reduction of greenhouse emissions, the minimization of the impact of R&D (from drug discovery to usage and disposal) and the sustainable utilization of water. On the chemical perspective, one of the most obvious and intuitive approach is the search for greener alternative solvents in research, development, and manufacturing of novel active pharmaceutical ingredients (APIs) [4].

In this context, ionic liquids (ILs) emerged as a new class of compounds with properties that empower their pharmaceutical application in a variety of strands. In April 2000, industry and academia joined efforts and ideas on a NATO Advanced Research Workshop on the topic of "Green Industrial Applications of Ionic Liquids" opening interesting perspectives regarding the future utilization of these compounds.

Even though the industrial applications in this field are still scarce, the peculiar properties of ILs envision immense and successful possibilities illustrated by an increasing number of literature examples [5]. ILs are being explored as solvents or reagents in a variety of pharmaceutical processes and as reaction media for common synthetic routes of both known and novel drugs [6]. Additionally, ILs can be part of distinct drug delivery systems for drugs with reduced bioavailability [7-10].

Ultimately, the biological activity of ILs can be explored to form active pharmaceutical ingredients (APIs) with tunable physico-chemical and biological properties [11-14]. Still, changes at the industrial level demand a strict and rigid protocol in order to guarantee the safety and viability of the developed drugs.
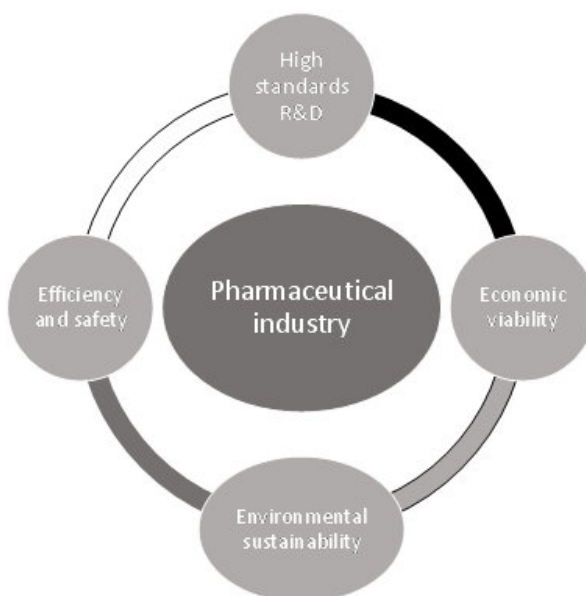

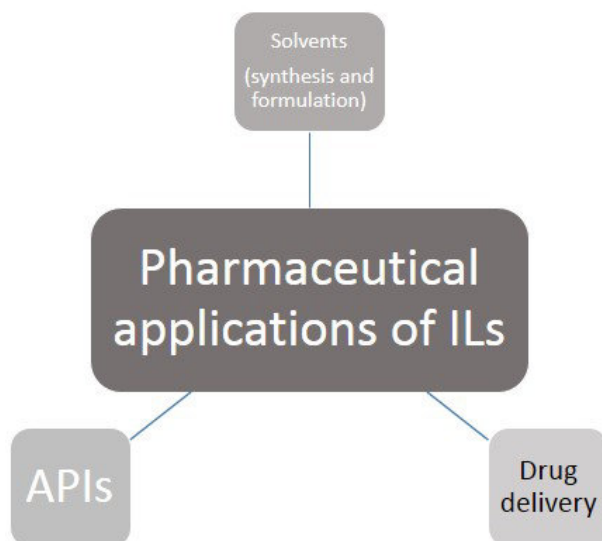Figure 1. Current demands of the pharmaceutical industry.

Figure 2. Pharmaceutical applications of ILs.

So, aspects like pharmaceutical profile, safety and human toxicity, environmental impact and biodegradability must be deeply addressed and explored to promote the acceptance of ILs by pharmaceutical industry.

The following discussion will be focused on the evolution of the IL concept to justify the pharmaceutical potential of these solvents. The main features and advantages of the abovementioned pharmaceutical possibilities will be emphasized and where possible, literature and industrial examples will be explored and debated.

2. HISTORICAL PERSPECTIVE OF ILS

Most documents focused of the history of ILs go back to the 19th century, to the "red oil" obtained from Friedel-Crafts reactions and to 1914 where the first IL of history, ethylammonium nitrate (EtNH$_3$ [NO$_3$]), was synthesized [15]. However, ILs as we know them today can find their origin in the 1960´s when U.S Air Force Academy started a project based on the replacement of LiCl-KCl molten salt electrolyte in thermal batteries [6]. By that time, the involved researchers managed to synthesize and characterize a totally ionic, non-aqueous solvent, 1-butylpyridinium chloride-aluminum chloride (bmpy [Cl]-AlCl$_3$), an alkyl-chloroaluminate that triggered the interest of chemists on ILs, especially those on the electrochemistry field. This was the first compound fitting the definition of IL that has been accepted for almost a century since Waldens´ studies in 1914: a salt which melts at or below 100ºC.

This IL constitutes the first element of the so called first generation of ILs that was mainly composed of dialkylimidazolium and alkylpyridinium cation derivatives combined with chloroaluminate and other metal halides anions. These compounds were largely studied by Osteryoung group [16, 17] and other researchers for their tunable and unique physical properties such as density, viscosity and thermal stability, among others. However, the

majority of these compounds are liquid only on a very narrow composition range and demand particular conditions of handling since chloroaluminates are water and oxygen sensitive. Additionally, the typical cations are very prone to reduction. Thus, these ILs are not suitable to be applied in biotransformations and not surprisingly the investigations on this field advanced to the synthesis of air and water stable compounds with wider liquid range. This was achieved initially through the combination of alkylimidazolium cations (less predisposed to reduction than the pyridinium ones) with water–stable anions like tetrafluoroborate (BF_4), hexafluorophosphate (PF_6) and acetate, among many others. These ILs gathered wide attention from the scientific community not only because of their low reactivity with water but also because of their large electrochemical window. These properties enabled the synthesis of novel ILs with tunable chemical properties combined with selected physical properties and that could be used as materials for diverse applications. These compounds constitute the second generation of ILs and are known for their lower melting points, negligible vapor pressure and moderate polarity. The boost on ILs research occurred between 1999 and 2000 after the emergence of this second generation, with an exponential increase of applications in a variety of fields from biocatalysis to nanotechnology. The major drawback of these ILs is still their toxicity that even though can be modulated is inherent to the majority of the compounds and can be similar to that of chlorinated and aromatic solvents.

As expected, the investigations followed the route to non-toxicity. This conducted to the utilization of stable, safe and biodegradable ions sometimes with biological activity and derived from materials generally recognized as safe (GRAS). The third generation of ILs is then composed of ILs with tunable chemical and physical properties and with reduced toxicity, like for instance ILs based on amino acids. Considering these particularities it is not unexpected that this new generation of ILs broadened the applicability of these compounds and triggered the investigation of their biotechnological and pharmaceutical potential. In this historical perspective it is important to highlight that even though the biological and pharmaceutical properties of ILs were explored before, namely through the investigation of antimicrobial, antifungal and anti-cancer activities of imidazolium, ammonium and phosphonium ILs [18-21], only at this stage this property was explored on purpose and recurring to selected materials.
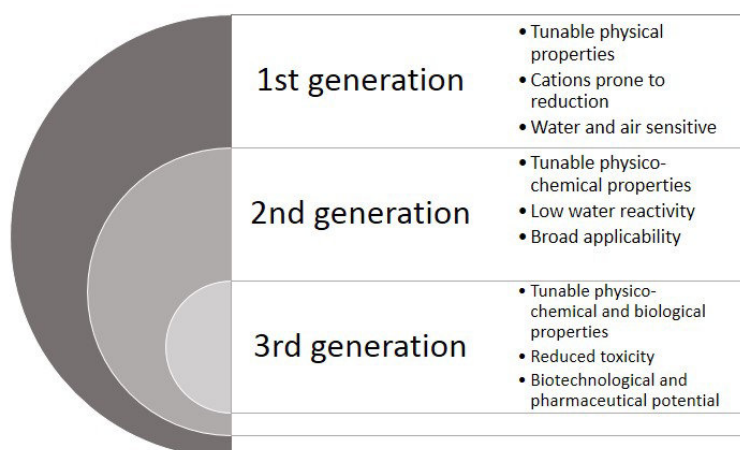

Figure 3. Historical perspective of the evolution of ILs according to their properties and applications.

3. APPLICABILITY OF ILs IN THE PHARMACEUTICAL FIELD

As stated before, the peculiar properties of ILs make them suitable for distinct pharmaceutical applications and only their toxicity has hindered major developments in earlier years. Still, there are several situations in which toxicity can be modulated and others where toxicity can be a desirable property. With the forthcoming of the 3rd generation of ILs novel possibilities arose.

This chapter will focus on the major possible applications of ILs in the pharmaceutical perspective: reaction media for the synthesis of APIs, as vehicles of drugs (solvents and drug delivery) and as APIs themselves.

3.1. Synthesis of Pharmaceutical Drugs in IL Media

In the pharmaceutical industry the use of volatile organic solvents (VOCs) is common and most of the times these solvents are an important part of the whole process from synthesis of APIs (or intermediates) to manufacturing operations like granulation and extraction [22, 23].

Considering that solvent use is about 80-90% of mass utilization in a typical pharmaceutical industry, the use of VOCs becomes a serious concern either from the human or environmental perspective as the toxicity of the production process is largely dependent on the nature of the selected solvents [24]. Moreover, the final formulations will unavoidably contain residual amounts of solvent. Even though there are strict rules and residual solvents limits improved by Food and Drug Administration (FDA) and other organizations and Pharmacopoeias, the risks and adverse effects of VOCs on human health are well known [25, 26]. It is then desirable that novel approaches could be implemented, as it has been already stated on the introduction section.

The current concerns of both academia and industry resulted already on several attempts to substitute VOCs by ILs in drug´s synthetic procedures [27, 28]. This approach is based on the demonstrated ability of ILs to drastically change the rate and selectivity of organic chemical reactions [6]. Currently, it is demonstrated that behind the environmental and safety issues, ILs can have also impact on the reactivity of the species involved in organic synthesis due to a fine balance of entropic and enthalpic contributions that involve the interactions inside the IL and between the ions and dissolved species. In fact, ILs can interact with solutes through dipolar and dispersion forces and act as strong hydrogen-bond acceptors [6]. The most important properties that set ILs apart from other solvents include:

- existing as molten salts, in many cases even below room temperature
- highly polar
- negligable vapor pressure
- nonflammable
- wide liquid range (typically > 300 °C grade)
- electrically conducting
- noteworthy dissolution properties (of both organic and inorganic compounds)
- high thermostability.

Table 1. Synthesized compounds with pharmaceutical interest through the implementation of organic reaction in IL

Synthesized Compound	Biological activity	Reaction	Ionic Liquid	Ref
Isoxazoline derivatives	Antimicrobial	Diels-Alder	bmim [BF$_4$]	[32]
Pyrrole-fused polycyclic heterocycles (alkaloyds)	Alkaloids	Diels-Alder	bmim [BF$_4$]	[33]
Pyrano/Thiopyrano fused polycyclic heterocycles	Bactericide	Diels-Alder	TEAA	[34]
Regioselective arylated products	Pharmaceutical intermediates	Palladium catalyzed	bmim [PF$_6$] bmim [BF$_4$]	[35]
Arylboronates	Pharmaceutical intermediates Anti-tumoral	Palladium catalyzed	bmim [PF$_6$] bmim [BF$_4$] hmim [BF$_4$] emim [BF$_4$]	[30]
(S)-Naproxen	NSAID	RCM	bmim [BF$_4$]	[36]
Hydrogenated aromatic ketones	Pharmaceutical intermediates	RCM	Imidazolium ILs	[37]
Pravadoline	NSAID	Friedel-Crafts	Imidazolium (PF$_6$ and chloroaluminate) catalysts	[38]
Substituted indoles	Pharmaceutical intermediates	Friedel-Crafts	Imidazolium chloroaluminate catalysts	[39]
Benzophenone derivatives	Pharmaceutical intermediates Sunscreens components	Friedel-Crafts	Imidazolium chloroaluminate catalysts	[40]
Benzophenone derivatives	Pharmaceutical intermediates Sunscreens components	Friedel-Crafts	Imidazolium chloroindate(III) catalysts	[41]
Coenzyme Q10	Antioxidant	Friedel-Crafts	Pyridinium chloroaluminate catalysts	[42]
Kinetic resolution of ibuprofen	NSAID	Biocatalysis (*Candida rugosa* lipase)	bmim [PF$_6$] bmim [BF$_4$] bmim [MeSO$_4$] mmim [MeSO$_4$] bmim [OctylSO$_4$] (C$_6$H$_{13}$)$_3$C$_{14}$H$_{29}$PN$_3$ (C$_4$H$_9$)$_3$CH$_3$PTOs	[43]
Kinetic resolution of ibuprofen	NSAID	Biocatalysis (lipases from *Aspergillus niger AC-54, Candida antarctica, Candida rugosa, Rhizomucor miehei* and *Thermomyces lanuginose*	bmim [PF$_6$] bmim [BF$_4$]	[44]
Caffeic acid phenethyl ester analogues	Anti-tumoral	Biocatalysis (*Candida antarctica* lipase)	bmim [NTf$_2$]	[45]
(R)-1-(4-chlorophenyl)ethanol	Pharmaceutical intermediate	Whole cell biocatalysis (*Lactobacillus kefir*)	bmim [PF$_6$] bmim [NTf$_2$] moma [NTf$_2$]	[46]
(R)-1-(4-chlorophenyl)ethanol	Pharmaceutical intermediate	*Escherichia coli Saccharomyces cerevisiae*	bmim [PF$_6$] bmim [NTf$_2$] moma [NTf$_2$] hmim [PF$_6$] hmim [NTf$_2$]	[47, 48]

Synthesized Compound	Biological activity	Reaction	Ionic Liquid	Ref
			bmpyr [NTf$_2$] hmpyr [NTf$_2$]	
Chiral alcohols	Pharmaceutical intermediate		[PF$_6$], [NTf$_2$] and [FAP] based hydrophobic ILs	[49]
(S)-3-chloro-1-phenyl-1-propanol	Pharmaceutical intermediate	E. coli	bmim [PF$_6$] bmim [NTf$_2$] emim [BF$_4$] mmim [MeSO$_4$]	[50]
Nucleosides derivatives	Pharmaceutical intermediates		momim [Ms] momim [TFa] bmim [TFa] bmim [Ms]	[51, 52] [53, 54]
2,3-Disubstituted-1,3-thiazolinin-4-one derivatives	Antiparasitic	Three component condensation (aldehyde, amine and mercaptoacetic acid)	bmim [BF$_4$] bmim [PF$_6$]	[55]
2-Aryl-4,5-diphenyl imidazoles, pyrazole derivatives, oximes	Pharmaceutical intermediates	Sonochemical organic synthesis	bmim [OH] emim [OAc] hmim [SO$_4$]	[56-58]
Quinoline derivatives		Sonochemical organic synthesis	hbmim [BF$_4$]	[59]

The possibility of developing tailor-made ILs for particular purposes offers exciting opportunities in the organic chemistry field enabling the creation of tasks specific compounds. Moreover, ILs can often form biphasic systems with classic VOCs which allows the simple isolation of reaction products by extraction of the ionic liquid layer. Their ionic nature enables immobilisation and recycling of many transition metal catalysts.

Many organic reactions have been studied in IL media sometimes with remarkable results [6, 29]. In a small number of cases the registered differences were small, not meeting anticipated high expectations or justifying extra expense. Herein we intend to focus on chemical reactions that can have significant utility at the pharmaceutical level and that in fundamental literature studies are not always immediately linked to that type of application. The selected reactions were: Dies-Alder, transition metal catalysed (including Heck reaction and ring-closing metathesis), Friedel-Crafts reactions not forgetting enzyme catalysed synthesis. Some examples of successful attempts to perform synthesis of APIs in ILs will be presented and discussed.

The abovementioned reactions have been extensively studied in IL media [6, 27, 29-31]. Considering that nowadays drug synthesis can be based on the concept of convergent synthesis, according to which several fragments are prepared in parallel paths and combined at the end of the process, the informations collected from those reactions if not totally adequate to a whole synthesis process can be important in one of those parallel paths.
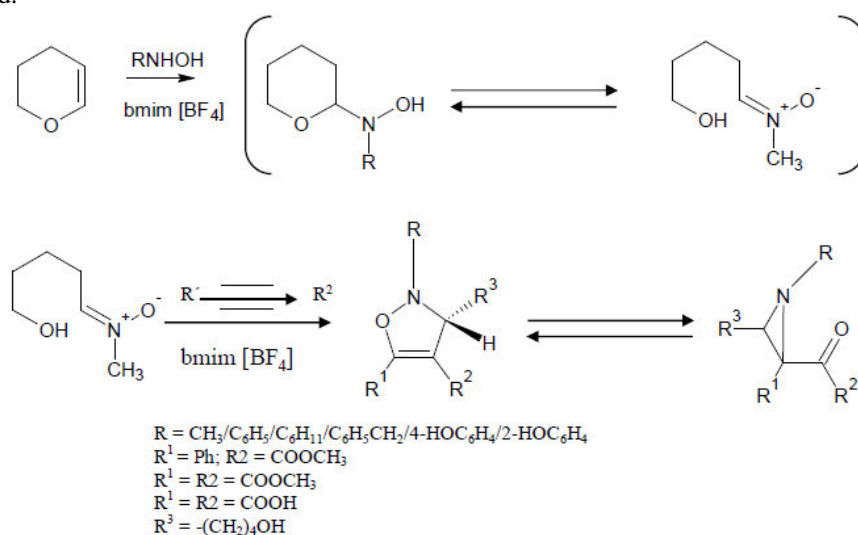
The most important achievements in this field are compiled in Table 1.

3.1.1. Diels-Alder Reaction

The Diels-Alders reaction is an organic chemical reaction, more specifically, a cycloaddition, between a conjugated diene and a substituted alkene to form a substituted cyclohexene system [60]. This reaction enables the synthesis of complex polycyclic molecules with adequate control of stereochemistry. Even though this type of reaction accounts for only 5 to 11 % of C-C bond-forming reactions performed under Good Manufacturing Practice in the pharmaceutical industry [61], it is largely explored by scientists in academic drug development and thus deserves a special attention on this chapter. Among

the most important drugs synthesized recurring to Diels-Alder cycloaddition reaction, it is important to highlight several types of vitamins, prostaglandins and steroids [60]. Generically, the Diels-Alder reaction applied to organic synthesis exhibits higher reaction rates in water than in organic solvents, but the need to work with moisture sensitive substrate hinders the industrial implementation of the reaction in aqueous media [27]. This explains the extensive investigation of this reaction in ILs as alternative reaction media [6, 27, 28]. From the available studies it is important to highlight that the majority of the tested ILs incorporate Lewis acidic anions and conduct to a general increase of both reactivity and selectivity of the studied reactions, in less drastic conditions [62-65]. Besides the advanced knowledge on Diels-Alder reaction in IL media with interest for drug development, it is also possible to find recent concrete examples of the synthesis of pharmaceutical drugs or intermediates in ILs [32-34].

The synthesis of isoxazoline derivatives can be performed in 1-butyl-3-methylimidazolium tetrafluoroborate (bmim [BF$_4$]) with enhanced reaction rates, improved yields, and high selectivity. The IL can be recycled and reused without loss of reactivity or selectivity. The synthesized isoxazoline derivatives are precursors of peptides with activity against gram positive and gram negative organisms and can constitute the basis for the development of new broad spectrum antimicrobial agent [32]. The same IL was used for the synthesis of pyrrole-fused polycyclic heterocycles through intramolecular 1,3-dipolar cycloaddition with higher rates and yields than in conventional organic solvents [33]. Along with the reutilization of the IL, the reaction products can also be readily separated by extraction. The synthesized compounds are of great interest since they are chemically related with well-known alkaloids such as myrmicarin and polyavolensin offering promising perspectives regarding the synthetic approach to natural products. Triethylammonium acetate (TEAA) was applied as greener solvent on a domino reaction based on the Diels Alder approach for the synthesis of pyrano and thiopyrano fused heterocycles thiopyrano fused heterocycles with bactericide activity [34]. Higher yields and shorter reaction times were attained.

R = CH$_3$/C$_6$H$_5$/C$_6$H$_{11}$/C$_6$H$_5$CH$_2$/4-HOC$_6$H$_4$/2-HOC$_6$H$_4$
R^1 = Ph; R2 = COOCH$_3$
R^1 = R2 = COOCH$_3$
R^1 = R2 = COOH
R^3 = -(CH$_2$)$_4$OH

Scheme 1. Synthesis of isoxazoline derivatives by Diels-Alder reaction in the presence of bmim [BF$_4$] [32].

3.1.2. Transition Metal Catalysed Reactions

Transition metal catalysed reactions have been widely used for decades in the pharmaceutical industry for the synthesis of drugs or intermediates. Specifically, palladium catalyzed reactions, including Heck reaction, represented, in 2005, about 60% of the C-C bond forming reactions in medicinal chemistry [61]. This is partially explained by the fact that the implementation of convergent synthesis demands final coupling steps compatible with a wide variety of functional groups. The palladium technology is in accordance with these demands and at the same time avoids the excessive use of protective groups. However, in the pharmaceutical field, this technique poses problems associated with the contamination of the synthesized APIs with palladium, demanding specific removal strategies. This problem can be circumvented recurring to heterogeneous catalysis or removal strategies like nanofiltration or scavenging methods [66].

In the group of transition metal catalysed organic reaction, the Heck reaction and ring closing metathesis (RCM) will be highlighted due to their importance and available information. The Heck reaction is a classic example of a palladium catalyzed carbon-carbon bond formation process recognized as a good method to attach olefins to (hetero)aromatic compounds [67, 68]. In normal reaction conditions, the Heck reaction is not totally regioselective and the palladium catalysts are not stable, leading to high catalyst consumption and difficulties in the implementation of the reaction. In this context, ILs were applied as solvents for the Heck reaction for the first time in 1996. There are several aspects that justify the massive application of ILs in metal catalysed organic reactions. Firstly, besides the environmental and safety issues, the use of a non-volatile solvent simplifies the work set-up for distillation and avoids the problems related to the formation of azeotropic mixtures, typical of VOCs. Additionally, metal catalysts are either soluble or can be immobilized in ILs. In the latter case, the resulting solution can be immobilized into a solid support resulting on a support ionic liquid phase (SILP) catalysts that combines the advantages of both homogeneous and heterogeneous catalysis making this approach very sensitive process technologies.

Many researchers explored this strategy sometimes with slightly different approaches [68] providing important information for future developments in the pharmaceutical field.

Also on the pharmaceutical field, palladium catalyzed reactions have been already implemented in IL media with positive results. The arylation of allylic alcohols by aryl bromides was comparatively studied in imidazolium ILs (1-butyl-3-methylimidazolium - bmim [PF_6], bmim [BF_4] and 1-butyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl)imide bmim [NTf_2]) and molecular solvents [35]. The regioselectivity of the reaction is highly affected by the nature of the solvent, with ILs being the best option for the formation of branched arylated products with the best β/α ratios reported till that time. Amongst the tested ILs, bmim [PF_6] is the most favorable compound in terms of catalyst activity. This reaction conducts to the formation of substituted allylic alcohols with regiocontrol that constitute useful intermediates for pharmaceutical synthesis. The utilization of ILs overcomes deficient regioselectivity, the major problem of this kind of arylation. The synthesis of arylboronates by palladium catalyzed cross-coupling can be performed in alkylimidazolium ILs incorporating BF_4 or PF_6 anions [30]. Catalyst decomposition is however observed with ILs incorporating the PF_6 anion as well as with emim [BF_4]. From the tested ILs, bmim [BF_4] and 1-hexyl-3-methylimidazolium tetrafluoroborate (hmim [BF_4]) are the most appropriate solvents, with increased catalyst stability in the case of bmim [BF_4]. Furthermore, with this IL

the reaction time is shorter than in conventional molecular solvents and the catalyst can be recycled from the IL. The synthesized boronate derivatives are important building blocks in organic synthesis and can present biological activity with applicability as anti-tumoral drugs [69]. Still in the field of transition metal catalyzed reactions, RCM is a ruthenium (Ru) catalyzed transformation that conducts to the formation of carbon–carbon double bonds [70]. This reaction belongs to the broad group of olefin metathesis and has gained popularity in the last decade since it enables the synthesis of functionalized heterocycles with applicability in several fields [71]. RCM has been widely explored for the synthesis of pharmaceutical compounds or intermediates such as azepine derivatives [72, 73], gambieric acid along with analogues [74] and acyclonucleoside phosphonates [75], among others. Considering the ability of ILs to stabilize metallic catalyst and the abovementioned advantages of transition metal catalyzed reaction in ILs, Ru mediated RCM soon started to be explored in this reaction media [6, 27, 76, 77]. Even though the initial applications of RCM in ILs revealed a beneficial effect of the tested compounds on the catalytic efficiency, they suffered from reduced stability of the catalyst, a behavior that was previously observed in molecular solvents [78]. The key step on the development of this strategy was the modification of the catalyst through functionalization with an imidazolium group [79, 80]. The obtained catalyst showed to be far more stable than the conventional ones with the additional possibility of being stored for several months. On a distinct perspective there are also reports on the combined use of ILs and VOCs [81] and on the study of RCM in imidazolium ILs under microwave irradiation [82].

RCM in IL media has also been explored during the synthesis of compounds with pharmaceutical interest. (S)-Naproxen can be quantitatively obtained from the asymmetric hydrogenation of 2-arylacrylic acids catalyzed by a Ru catalyst immobilized in bmim [BF$_4$] [36]. The enantioselectivities are similar or higher than those obtained with the homogeneous reaction. The catalyst can be recovered and reused without loss of catalytic activity or selectivity. A similar approach was adopted by Ngo and co-workers who managed to perform the asymmetric hydrogenation of aromatic ketones. In this case, polar bisphosphonic acid-derived Ru catalysts were immobilized in imidazolium ILs [37] for the production of pharmaceutical intermediates free of metal contaminants. The catalytic performance is highly affected by the nature of the IL with n-propyl-2,3-dimethylimidazolium bis (trifluoromethylsulfonyl)amide (dmim [NTf$_2$]) providing the best results in terms of catalyst efficiency, when compared to bmim [BF$_4$] and bmim [PF$_6$]. As before, both IL and immobilized catalyst can be recycled and reused without leaching of Ru into the organic compounds.
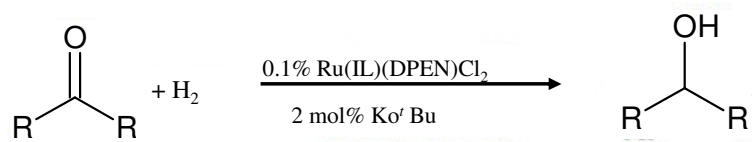
IL = bmim [BF$_4$]; bmim [PF$_6$]; dmim [[NTf$_2$]

DPEN = (R, R)-1,2-diphenylethylenediamine

Scheme 2. Asymmetric hydrogenation of chiral ketones catalyzed by Ru-IL catalysts [37].

3.1.3. Friedel-Crafts Reaction

The Friedel-Crafts acylation reaction represents a synthetic process of great interest to organic chemists of academia and industry being involved in the production of several pharmaceuticals. Since its first description in 1887, this reaction has been increasingly recognized as the method of choice to perform the alkylation of arenes and heteroarenes and form C-C and C-heteroatom bonds [83]. Even though the Friedel-Crafts reaction is traditionally catalyzed by Lewis acids, it is also possible to accelerate the reactions recurring to strong Brønsted-acids including sulfuric acid, hydrofluoric acid or super acids. More environmentally benign options involving alkylation by means of alcohols and styrenes were implemented recently as an alternative to alkyl chlorides. The environmental aspects are worsen by the large amounts of VOCs generally utilized in these reactions [84]. In this context, ILs soon started to be explored in this kind of reaction with interesting results [85]. The first application of an IL in a Friedel-Crafts reaction was accomplished in 1986 and involved the effective utilization of a mixture of 1,3-dialkylimidazolium chloride and aluminum chloride as catalyst [85]. The success of the application is explained by the strong Lewis acidity of acidic chloroaluminate ILs. Since then, it was found that the ILs provide also better alkylate quality than those obtained with conventional catalysts. There is a vast list of applications of IL-catalysts in diverse Friedel-Crafts reactions in a variety of fields, all of them confirming the adequacy of these solvents to the performed reactions [28, 83, 84, 86-88].

Due to the importance of the Friedel-Crafts reaction for the pharmaceutical industry it is not surprising that this reaction was studied in IL media for the production of compounds with pharmaceutical interest. The first report on the synthesis of a pharmaceutical drug was presented by Earle and co-workers [38]. Based on their past experience with Friedel-Crafts reaction of indoles, the researchers managed to synthesize pravadoline, through a combination of Friedel-Crafts reaction and a nucleophilic displacement reaction. In the presence of bmim [PF$_6$], the alkylation of 2-methylindole with 1-(N-morpholino)-2-chloroethane occurs at room temperature with a yield of 95%. The change of the IL to 1-butyl-2,3-dimethylimidazolium hexafluorophosphate (dbmim [PF$_6$]) leads to an increase of yield to 99%.

It must be also highlighted that the production of acidic aqueous wastes is decreased due to the fact that the reaction, performed entirely in IL, does not require a Lewis acid catalyst reducing the acidity of the reaction with consequent reduction of wastes and by-products leading also to increased yields. Moreover, in the adopted scheme the product is easily separated and the solvent is recycled.
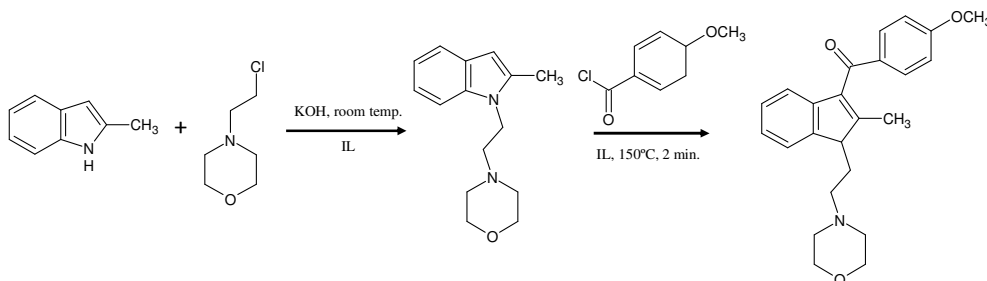
Scheme 3. Synthesis of pravadoline by the Friedel-Crafts reaction in IL media [38].

This reaction was also tested in 1-ethyl-3-methylimidazolium chloride-aluminum chloride (emim [Cl]-AlCl$_3$), a chloroaluminate IL, with results similar to those obtained with a conventional Friedel-Crafts approach and yields between 40 and 89%, with the drawback of producing large amounts of acidic waste.

This latter approach can also be explored for the production of substituted indoles by Friedel-Crafts acylation of indoles at room temperature [39]. The obtained products are indoles substituted at different positions with diverse functional groups that can be used as pharmacophore blocks for the synthesis of several molecules with pharmaceutical interest. Chloroaluminate ILs integrated also a broader study of Friedel-Crafts acylation for the synthesis of benzophenone derivatives recurring to distinct IL catalyst [40]. Amongst the tested ILs, 1-butyl-3-methylimidazolium chloride-iron chloride (bmim [Cl]-FeCl$_3$), exhibited much higher catalytic activity than that registered for 1-butyl-3-methylimidazolium chloride-aluminum chloride (bmim [Cl]-AlCl$_3$), 1-butyl-3-methylimidazolium chloride-zinc chloride (bmim [Cl]-ZnCl$_2$) and benzene. With this catalyst, reaction yields up to 97% were obtained with shorter reaction times. As before, it was possible to easily isolate the reaction products and the ILs could be recycled and reused with both economic and environmental advantages. As an alternative to the use of imidazolium based ILs, Chen and co-workers explored the potential of pyridinium ILs combined with AlCl$_3$, ZnCl$_2$, FeCl$_3$, SnCl$_2$, SnCl$_4$ and CuCl for the synthesis of an intermediate of coenzyme Q$_{10}$ by Friedel-Crafts alkylation under microwave irradiation [42]. Generally, the catalytic activity of the ILs enhanced with the increase of their Lewis acidity with 1-ethylpyridinium tetrafluoroborate-zinc chloride (etpy [BF$_4$]-ZnCl$_2$) showing the best catalytic activity, with a yield of 89% after 150 seconds of reaction. The method exhibits the same economical and safety advantages described for the abovementioned approaches. In an attempt to provide alternative pathways for this important reaction, Earle and co-workers proposed chloroindate(III) ILs as catalysts for Friedel-Crafts acylations for the production of benzophenone derivatives [41]. The study involved the comparison of the synthesis performance in several chloroindate ILs and 1,2-dichloroethane. It was demonstrated that the best yield was obtained when indium(III) chloride was combined with bmim [NTf$_2$] either as a solution or as a binary IL (bmim [NTf$_2$]-InCl$_3$), with reaction yields between 75 and 96%. No catalytic activity was observed whit bmim [OTf] or bmim [BF$_4$]. The importance and significance of the obtained results is only fully understood considering that the aromatic compounds used for the synthesis are usually non-reactive. This issue is overcome with this approach.

3.1.4. Biocatalysis

Even though nowadays stereoselectivity can be achieved through metal transition catalysis, biocatalysis still remains an important tool for the pharmaceutical industry on the search for stereoisomer drugs instead of racemates [89, 90]. Besides the issue of selectivity, some of the most important features of enzymes, as industrial catalysts, are related with their aptitude to accept a wide range of substrates, even artificial ones, and with their ability to operate in non-aqueous environments [6]. The use of enzymes in synthetic processes does not require the use of protective groups, even in complex molecules, with simplification of the process and reduction of the associated costs. Several industrial processes apply nowadays enzyme-catalyzed reactions for the large-scale production of APIs. As examples, Schering-Plough synthesizes an azole antifungal agent in hundred-kilogram quantities and Bristol-Myers Squibb pharmaceutical research group published a number of plant scale chemo-

enzymatic synthesis performed in organic media. For years, the use of water as solvent in enzymatic reactions limited the field of application of enzymes in biocatalysis and the productivity of some processes, particularly those involving hydrophobic substrates [91]. As a consequence, the applicability of catalysis in non-aqueous solvents was implemented and discussed and as a result, new reaction media were suggested [92]. The possibility of working with hydrophobic substances, the decrease in microbial contamination and reduction of side reactions are the main advantages related with the development of procedures in non-aqueous media. Organic solvents helped to reduce some problems such as the insolubility of hydrophobic compounds and propagation of radicals in aqueous solutions offering benefits related with enzyme stability and selectivity [93, 94]. Due to the well-known drawbacks of VOCs, and reported inactivation phenomena, ILs emerged as an alternative for biocatalysis in the last decade. The applicability of ILs in biocatalysis was explored intensively through the study of an uncountable number of enzymes in huge variety of ILs with structural variability. The results of the majority of these studies are compiled and discussed in several reviews [95-97].

The research in this field indicates that biocatalytic reactions in ILs exhibit higher selectivity and faster rates with enhanced enzyme stability [98], making this association very promising for organic synthesis [90]. The relationship between ILs and enzymes has been discussed by many authors and the main explanations were pointed out. The polarity of ILs seems to be one of the most important factors affecting enzyme stability and selectivity. Indeed, polar solvents increase the solubility of polar substrates conducting to faster and more selective reactions [99]. Other studies reveal that the viscosity of ILs can also have a strong impact on enzyme´s activity [98]. High viscosity may produce a decrease in the rate of diffusion of the species involved in the process with reduction of the interaction of the enzyme with its substrate which can influence negatively the yield of reaction.

The hydrogen bond capacity of ILs has been also considered very important for protein stability and maintenance of its native structure [100]. The classic enzyme thermal unfolding is prevented by the entrapment of enzymes, with small amounts of water, in the hydrogen bond network of ILs [101]. The suppression of side reactions due to the decrease of water in the reaction media has also been associated with the increased yield of enzymatic reactions in ILs [102].

Even though the investigations in the field of biocatalysis in ILs began by the replacement of organic solvents, nowadays there are studies involving biphasic solvents in which water miscible IL are used in aqueous systems. Regarding biphasic systems, the possibility of enzyme reutilization has already been studied with success [102]. There is also the possibility of work in three phase systems in which ILs, organic solvents and water can be associated to modulate the solubility of substrates and enzyme activity [103].

The first study describing an enzymatic reaction in ILs involved the use of a protease, thermolysin, for the synthesis of Z-aspartame, with similar reaction rates but higher enzyme stability than those obtained with traditional organic solvents [104]. After this, many works involving the use of proteases and lipases, among many others, in ILs have been developed, confirming the advantages of these solvents in biocatalysis [6, 105].

In this context, ILs were soon considered interesting alternatives to VOCs on pharmaceutical synthesis and other bioprocess involving pharmaceutical drugs [106]. The kinetic resolution of ibuprofen catalyzed by *Candida rugosa* lipase in IL media is an excellent example of the successful combination of biocatalysis and ILs [43]. Chirality is a key issue

for ibuprofen due to the differences registered between S-(+)-ibuprofen and R-(-)-ibuprofen, with the latter being 100-160 times less active than the first one. For this study, the authors selected seven ILs with structural variability and compared the results with those obtained with isooctane. Bmim [PF_6] improved both the kinetic resolution and the enantioselectivity with high enzyme stability. Studies of the time course conversion and enzyme stability as a function of time in both isooctane and bmim [PF_6] confirmed that this IL is a valid alternative for the kinetic resolution of ibuprofen. Later on, several types of lipases (from *Aspergillus niger AC-54, Candida antarctica, Candida rugosa, Rhizomucor miehei* and *Thermomyces lanuginose*) were studied to perform the resolution of (RS)-ibuprofen in two-phase systems containing bmim [PF_6] and bmim [BF_4] [44]. It was noticed that *C. rugosa* lipase conducted to the best results in terms of conversion degree, enantiomeric excess of remaining acid and *E*-value in a two phase system composed of bmim [PF_6] and isooctane. The influence of the IL was more pronounced on the *E*-value being less significant regarding the conversion degree. A similar tendency was observed with *A. niger* lipase. Acceptable results were also attained with *C. antarctica* lipase in terms of esterification activity and enantioselectivity. This enzyme can also be used for the synthesis of nucleoside drugs esters resorting to an IL as additive [107]. The lipase catalyzed transterification of ribavirin was performed in mixtures of acetone and increasing concentrations of imidazolium ILs (bmim [BF_4], bmim [PF_6] and emim [BF_4]). The best results in terms of transterification extent were obtained with bmim [BF_4] 10%, with an increase of the reaction rate of about 3.5 times when compared with the assay in the absence of IL. These observations were correlated to the increase of solubility of the nucleoside analogue due to the presence of the IL and to enzyme conformational changes. In the presence of bmim [BF_4] the nucleoside synthesis was carried out with excellent regioselectivity, fast reaction rate and high yield.

Resorting also to *C. antarctica* lipase, Kurata and co-workers performed the synthesis of caffeic acid phenethyl ester analogues, with antiproliferative effect on tumor cells, in bmim ILs with variable anions [45]. The transesterification reaction of methyl caffeate with various alcohols to produce the abovementioned analogues is favored in the presence of bmim [NTf_2]. Considering the registered changes in activity, it was concluded that the activity of enzyme is anion dependent. The optimized synthetic system resulted on the production of 2-cyclohexylethyl caffeate and 3-cyclohexylpropyl caffeate with conversion yields of 97.6 and 93.8%, respectively. Both compounds exhibit antiproliferative activity higher than caffeic acid and comparable to 5-fluorouracil.

In the field of biocatalysis, it is also important to highlight whole cell catalyzed processes which can present major advantages over the use of isolated enzymes [108]. In biotransformations involving more than one enzyme, the use of whole-cell biocatalysts (recombinant or not) is almost mandatory as it avoids costly and time consuming enzyme purification.
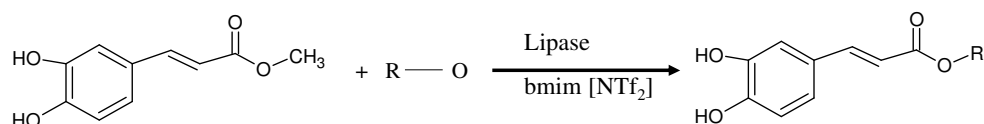
Scheme 4. Synthesis of caffeic acid phenethyl ester in IL media [45].

In addition, the use of cofactors can be avoided and the process can benefit from the intracellular regeneration of cofactor when the membrane of the whole-cell biocatalyst remains stable during the catalytic route. This approach is generally very adequate to asymmetric synthesis due to low water solubility of substrates or products and inhibitory effects of the reactants on the biocatalyst. Considering the issue of membrane integrity, the selection of the solvent in whole cell biocatalysis is of the most importance and can enhance or highlight the mentioned advantages of this catalytic methodology. In this context, it has been demonstrated that ILs can be successfully employed in whole cell biocatalysis in replacement of VOCs [46-49, 108]. Most of the referred applications of whole cell biocatalysis in IL media have pharmaceutical interest. This approach has been mainly applied to the asymmetric synthesis of chiral alcohols [46-50] which are frequently employed as pharmaceutical intermediates [109]. Pfruender and co-workers demonstrated for the first time that a cellular cofactor regeneration system can be active in the presence of water-immiscible imidazolium and ammonium ILs (bmim [PF$_6$], bmim [NTf$_2$] and methyltrioctylammonium– NTf$_2$, moma [NTf$_2$]) [46]. This important demonstration is a result of the study of the *Lactobacillus kefir* catalyzed asymmetric reduction of chloroacetone to (R)-1-(4-chlorophenyl)ethanol in ILs, used as substrate reservoir and extracting agent. The results of the synthetic process were compared with those obtained with commonly used VOCs, like n-octanol and methyl tert-butyl ether (MTBE). In the presence of bmim [NTf$_2$] the chemical yield of the synthesis of the chiral alcohol can be doubled and the purity of the product is excellent. With the other tested ILs the results are very acceptable comparing with MTBE. It was also evidenced that the tested ILs do not affect *L. kefir* membrane integrity and can even enhance it, probably due to changes in morphology. Similar results were obtained in a study of the same process catalyzed by *Escherichia coli and Saccharomyces cerevisiae* [47, 48] confirming that the selected ILs can be applied on the whole cell biocatalyzed production of pharmaceutical chiral alcohols. A set of other commercially available ILs proved to be also good options for the asymmetric reduction of ketones using recombinant *E. coli* as biocatalyst [49, 110]. As before, the tested compounds do not affect negatively the intracellular regeneration of NADH nor cell membrane integrity. More recently, Choi and co-workers confirmed the adequacy of imidazolium ILs, with special focus on bmim [NTf$_2$], for the production of chiral alcohols through the *E. coli* catalyzed synthesis of (S)-3-chloro-1-phenyl-1-propanol, a chiral precursor of anti-depressant drugs [50].

3.1.5. Other Applications

Nucleoside chemistry is one of the most important areas in pharmaceutical research providing compounds with wide application in cancer and viral chemotherapy. The problems associated with the insolubility of nucleoside derivatives have hindered the development of novel strategies and ILs soon started to be explored as reaction media for the solubilization and synthesis of these compounds [51-55, 111]. Uzagare *et al.* performed a deep study of the solubility of 2´-deoxyribonucleosides in several imidazolium ILs [51]. The IL 1-methoxyethyl-3-methyl imidazolium methanesulfonate (moemim [Ms]) proved to be a better option for the solubilization of the nucleosides than any other IL or VOC. The acylation and peracylation of the 2´-deoxyribonucleosides can be performed in this IL with good isolation of the reaction product with yields between 89 and 95%. The same IL was used for the selective benzoylation of nucleosides using benzoyl cyanide [52]. Highly efficient benzoylations in mild reaction conditions (25ºC) are achieved with selective benzoylation of

sugar hydroxyl groups over amine groups and preferential production of O-benzoylated derivatives. The major drawback of this strategy is the formation of the highly toxic HCN, as reaction by-product. As an alternative, the authors studied the process in the presence of 1-methoxyethyl-3-methylimidazolium trifluoroacetate (moemim [TFa]) which exhibits the ability to dissolve both deoxyribo- and ribonucleosides [111]. This IL is a good alternative for the selective benzoylation of nucleosides with high yields, under ambient conditions. These results were of the most importance for the development of three nucleoside based anti-viral drugs namely stavudine, brivudine and trifluridine in three ILs, moemim [Ms], moemim [TFa] and bmim [TFa] [53]. In all cases, the selected ILs showed better solvent properties than the commonly used VOCs like *N,N*-dimethylacetamide. Moreover, the amount of required solvent is reduced due to the high solubility of the synthesized compounds in the ILs. Higher reaction rates are attained with this strategy. The same ILs, with the addition of bmim [Ms], were also applied to the synthesis of antiviral 5-halouracil nucleosides which can be also used as building blocks for the synthesis of other antiviral drugs [54]. As in the abovementioned studies, ILs proved to be good reaction media for this synthesis and in this case could be recovered up to 4 cycles without loss of yield.

Two imidazolium ILs were also selected as reaction media for the synthesis of 2,3-disubstituted-1,3-thiazolinin-4-one derivatives with antiparasitic activity [55]. The synthesis yield is low at room temperature but by increasing the temperature up to 80 or 90ºC the reaction yield increases to 87 and 74% with bmim [PF_6] and bmim [BF_4], respectively. Tests performed with bmim [PF_6] demonstrate that the IL can be recovered and efficiently reused.

This section could not be completed if the works of Zang *et al*. on sonochemical organic synthesis in IL media were not mentioned. Several compounds including 2-aryl-4,5-diphenyl imidazoles [56], pyrazole derivatives [57] and oximes [58] with pharmaceutical interest. For the synthesis of these compounds, the authors combined bmim [OH] [58], emim [OAc] [56] or hmim [SO_4] [57] with ultrasonic irradiation. In all the tested conditions, the reaction time was reduced and the synthesis occurred efficiently with high yields, under mild conditions. Similarly, Heravi managed to synthesize quinolines derivatives, with pharmacological activity, through the combination of hbim [BF_4] and ultrasound, resorting to methanol as co-solvent [59].

To finish this section, two applications with immense potential to be implemented in pharmaceutical synthesis must be highlighted due to their importance on the safety and therapeutics perspective. Firstly, the oxidation of ketones, largely applied to the synthesis of antibiotics and steroids, was already performed in IL media resorting to imidazolium ILs as an alternative to the commonly used dichloromethane, chloroform and acetonitrile [112]. The most promising ILs were bmim [BF_4] and 1-methylimidazolium acetate (mim [OAc]) providing yields of lactone and ester synthesis between 65 and 95%.
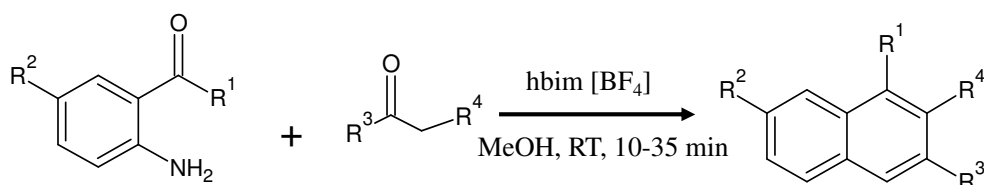
Scheme 5. Condensation of ketones to produce quinolone derivatives in the presence of hbim [BF_4] [59].

Again, ILs could be recycled 3 times without loss of yield. Finally, we highlight the major importance of the work of Hwang and co-workers regarding the formation of amyloid from α-synuclein in IL media. There are a number of amyloid related diseases that largely depend on the development of novel therapeutic strategies based on amyloid formation. However, amyloid formation is usually a very slow process which hinders more effective developments on this field. In this work, a set of imidazolium ILs and one pyridinium IL were tested and in all cases the ILs acted as stimulators of amyloid formation with decrease of the lag time of the process. Amongst the tested compounds, emim [NTf$_2$] is a stronger promoter when compared with other ILs.

3.2. ILs as Drug Vehicles

Solubility is one of the most important properties during drug development. It limits the concentration that a dosage form can incorporate and the rate at which the molecule dissolves from the solid form. It is then a key property for gastro-intestinal absorption of orally administered drugs. In fact, poor aqueous solubility of drugs is one of the major causes for low systemic exposure and, consequently, lack of *in vivo* activity [2, 113]. From the total amount of new chemical entities developed in the pharmaceutical industry, 40% fail to reach higher development levels due to solubility problems [114, 115]. The importance of solubility during drug development is illustrated by the *Biopharmaceutics Classification System (BCS)* which is basically a guide for the prediction of the intestinal drug absorption, provided by the U.S. FDA [116]. In this classification system, prediction relies in only two major parameters: solubility and intestinal permeability. In this context, it is not surprising that the search for novel strategies to increase the solubility of new drug candidates is one of the biggest concerns of both industry and academic researchers. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, among others. The selection of the strategy to be adopted is highly dependent on drug´s property, site of absorption, and characteristic of the dosage form [117].

ILs are well-known for their solvation properties that make them able to dissolve a wide range of organic and inorganic compounds [118]. This property has been associated with the fact that ILs form a highly solvating and little coordinating media. Additionally, the short range repulsive interactions between anions and cations enhance the solvent power of ILs [119]. In the pharmaceutical field, it has been demonstrated that ILs are capable of dissolving several drugs that are insoluble or poorly soluble in water and in the solvents commonly used in these applications [8, 13, 51, 111, 120-126]. Additionally, their inherent tunability associated with the possibility of designing a specific IL for a specific application are major attractions of these compounds in this field. Generally, there is an increase of the solvency of ILs with the increase of the alkyl side chain of the cation [127].

The studies with nucleoside derivatives of Kumar and co-workers illustrate the importance of solubility studies in a stage prior to synthesis [52, 53, 111]. As described in section 1.3.1.5, imidazolium ILs present better solvent properties for both deoxyribo- and ribonucleosides than the commonly used VOCs. These findings opened new perspectives regarding the synthesis of nucleoside derivatives in IL media.

The pioneering researches of Professor´s A.T. Florence group boosted the pharmaceutical utilization of ILs as solvents or drug reservoirs [121-123]. This application is mainly related with the ability of ILs to dissolve poorly water-soluble molecules drugs like albendazole and danazol [122], dexamethasone [121, 123], penicillin V, progesterone and dehydro-epiandrosterone [123]. For instance, the solubility of albendazole increased more than 20,000 times in hmim [PF$_6$] and more than 10,000 in bmim [PF$_6$]. The issue of IL´s water miscibility was also explored during this evaluation considering the preferential utilization of aqueous systems during drug´s formulation. The water miscibility of poorly water-miscible ILs, like bmim [PF$_6$], can be enhanced through the addition of a more water miscible IL with higher effects for more hydrophilic ILs. The variation of danazol solubility is far more significant with very good results in the water miscible IL bmim [BF$_4$]. Hexafluorophosphate ILs of the imidazolium group were tested as solvents and reservoirs of progesterone, dehydroepiandrosterone, dexamethasone, sucrose and penicillin V [123]. It should be highlighted that the solubility decreases with the increase of the alkyl chain length from bmim to omim. All the ILs are adequate for the entrapment and release of solubilized drugs. Distinctly, the same ILs were utilized to evaluate the release rate of solubilized hydrophilic and hydrophobic drugs by means of the passage of an electric current through the immiscible ILs [121]. The application of electric current to the ILs increases the release of both solubilized drugs with the highest variation being registered for omim [PF$_6$]. Similarly, Smith *et al*. studied the solubility of ibuprofen and paracetamol in bmim [PF$_6$] and hmim [PF$_6$] at different temperatures. Even though both ILs are good solvents of both drugs, the solubilities are higher in hmim [PF$_6$] than in bmim [PF$_6$]. ILs with trifluoromethanesulfonate and NTf$_2$ anions were selected to dissolve isoniazide [124], N-acetyl-L-cysteine, coumarin and 4-hydroxycoumarin [125]. Trifluoromethanesulfonate ILs are better solvents for isoniazide [124], N-acetyl-L-cysteine and 4-hydroxycoumarin than NTf$_2$ ones [125]. The inverse was observed for coumarin [125]. The solubility of isoniazide was also studied in ammonium ILs, together with other antibiotic drug pyrazinecarboxamide [128]. Amongst the tested compounds, didecyldimethylammonium nitrate is the best solvent for both drugs with isoniazid exhibiting higher solubility than pyrazinecarboxamide in all the tested ILs.

ILs can also be design to provide tunable and adequate hydrophilic-lipophilic balance to enhance water solubility of poorly soluble APIs [126]. This was evidenced recently on a study with amphotericin B and itraconazole, two complex, amphiphilic drugs with reduced water solubility. The selection of the anions and cations took in consideration not only the desired hydrophilic-lipophilic balance but also safety issues keeping in mind that they must be approved for consumption. Thus, acetate ILs based on short-chain fatty amines were synthesized (by choosing complementary functionality in one or both ions) and their effectiveness as solvents was evaluated. The adopted strategy proved to be a good option not only for the solubilization of drugs in the ILs but also to solubilize and maintain the drug in aqueous media.

Also on the perspective of the use of ILs as solvents of pharmaceuticals, there are already informations on the influence on drug´s properties that determine their pharmaceutical profile and *in vivo* behavior [129]. These informations were gathered during the study of imidazolium ILs as solvents of nimesulide, a widely used NSAID with reduced water solubility. The binding of nimesulide to human serum albumin (HSA) as well as its interaction with micelles of hexadecylphosphocholine to calculate partition coefficients, were studied in the presence and in the absence of emim [Ms] and emim [TfMs] 1%. As in aqueous

media, in the presence of the selected ILs, nimesulide binds strongly to HSA by means of spontaneous interactions. The studied drug-IL systems exhibit properties that favor the interaction with biological membranes, evidenced by the high Kp values. Thus, there are good perspectives for the effective absorption and distribution *in vivo*.

ILs can also be incorporated in IL-in-oil microemulsions to be used as carriers of poorly soluble drugs [7-10]. Microemulsions are self-assembled structures widely recognized as vehicles for encapsulation, stabilization, and delivery of pharmaceutical drugs [130]. They are thermodynamically stable colloidal dispersions formed by water and oil and stabilized by an interfacial film or surfactant. The initial report on this topic was elaborated by Professor´s Goto group and involved a four component system composed of dimethylimidazolium dimethylphosphate (dmim $[(CH_3O)_2PO_2]$), isopropyl myristate, polyoxyethylene sorbitan (Tween-80) and sorbitan laurate (span-20) for the delivery of acyclovir [8, 9]. The IL was selected as the most adequate compound on solubility studies that were performed with seven imidazolium ILs. The increase of IL content on the micelle conducts to an increase of micelle volume and the incorporation of acyclovir results on a slight decrease of the mean diameter. The efficiency of the proposed delivery system was studied *in vitro* recurring to a porcine skin model using Franz-type diffusion cells. Skin permeability and the transdermal permeation of acyclovir increases when IL based microemulsions are used. The insertion of IL 4%wt in the microemulsion leads to a reduction of less than 20% in cell viability (human epidermal model LabCyte^{TM} EPI-MODEL 12). With these pioneering studies, the authors confirmed the adequacy of these microemulsions to perform transdermal drug delivery. In continuation, the authors studied a set of imidazolium ILs as dispersed phase [7]. It was noticed that hydrophilic ILs with coordinating anions can be solubilized on the core of Tween-80/ span-20/ isopropyl myristate micelles and form stable microemulsion droplets more effectively. It is important to highlight that the solubility of the ILs in the microemulsion follow the same tendency as in water. The potentialities of the delivery system were further explored with methotrexate and dantrolene, two poorly water soluble drugs. The solubility of both drugs is enhanced in microemulsions with dmim $[(CH_3O)_2PO_2]$ with further increase by higher IL concentration. Similarly, Dobler and co-workers prepared oil-in-water and water-in-oil microemulsions containing hmim [Cl] and bmim [PF_6] and evaluated the influence of the ILs on the properties of the micellar systems [131]. The ILs can be successfully incorporated in the micelles and due to their antimicrobial activity can have the effect of a preservative. As related above, skin permeation is enhanced in the presence of ILs.

Other microemulsion systems were explored as vehicles of insoluble drugs such as curcumin [132], dopamine and acetylcholine [133]. The hydrophilic IL bmim [BF_4] increases about 7 times the association of curcumin with CTAB and induces a decrease of association in the case of cationic surfactants like sodium dodecylsulfate (SDS), acting like a modulator of drug´s solubilization in micellar systems. On a distinct perspective, the micellization and surface behavior of 1-tetradecyl-3-methylimidazolium bromide (tmim [Br]) was studied in the presence of dopamine and acetylcholine aiming the evaluation of the applicability of the micellar system in drug delivery [133]. The selected IL exhibits better surface activity and better drug carrier performance than the structurally similar cationic surfactant, tetradecyltrimethylammonium bromide. Imidazolium ILs are also good solvents for the release of APIs from styrene-divinylbenzene polymeric vehicles as demonstrated by Ramos-Rodriguez and co-workers [127]. The studies conducting to this conclusion were based on atomistic and mesoscopic simulations that evaluated solubility parameters and the diffusion

of albendazole from the polymeric vehicle to an aqueous medium modified with bmim [BF$_4$], bmim [PF$_6$] or hmim [Br]. The diffusion of albendazole was related with the solvent power of the studied ILs, with bmim [PF$_6$] inducing higher release from the vehicle than bmim [BF$_4$] or hmim [Br] due to the higher polarity of [PF$_6$]. The evolution of the research on this field has been only foreclosed by one of the most delicate issues that concerns with ILs: toxicity. Further developments on the use of ILs as carriers or solvents of drugs are largely dependent on the preparation of safer ILs with reliable toxicity data that could be readily accepted as GRAS and used as excipients in pharmaceutical formulations.

3.3. ILs as Active Pharmaceutical Ingredients

Despite the technological advances of the last decades, nowadays there is still a significant rate of failure during drug development in the pharmaceutical industry. A study conducted between 1990 and 2002 revealed that only 40% of the drugs that pass phase I and II clinical trials will reach the market [134]. Failure was associated with lack of efficacy (50%), safety concerns (30%) or both (20%). The issue of efficacy is quite intriguing considering that this is the major concern of phase II clinical trials. Drug´s efficacy is tightly associated with bioavailability that in turns is dependent on fundamental properties such as solubility, dissolution rate and lipophilicity. Besides economical and judgmental reformulations, the strongest possibilities to overcome this failure rates are to profile drug-like properties as early as possible and work on lower-risk compounds.

Typically, the pharmaceutical industry is based on solid and crystalline forms of APIs with claimed advantages in terms of purity, solubility and thermal stability [135, 136]. It is also commonly accepted that solid forms of APIs facilitate isolation, manufacturing and product handling with reduction of the costs of the overall production process. This tendency is further encouraged by a vast amount of guidelines, most of them provided by FDA, concerning the manufacturing and quality control of solid pharmaceuticals with a notorious lack of guiding principles for liquid dosage forms. However, solid forms of APIs often suffer from low solubility and polymorphic conversion which can influence negatively the bioavailability of the drug and ultimately its therapeutic effect [136].

Polymorphism is the ability of a compound to exist as two or more crystalline phases that exhibit distinct arrangements and/or conformations of the molecule in the crystal lattice [135, 137, 138]. Thus, polymorphs display different physical, thermodynamic, spectroscopic, interfacial and mechanical properties. Moreover, the different lattice energies of polymorphs can originate different solubilities and dissolution rates, affecting the bioavailability of pharmaceutical drugs. Polymorphism is one of the major concerns of the pharmaceutical industry during drug development due its impact during formulation and on pharmacological effect, as the conversion can occur throughout drug manufacturing or storage [138]. During drug development, if polymorphs are detected the most active and stable is selected. As examples, acetaminophen (paracetamol) can be presented in two forms with distinct compression properties [137] and the antiviral drug ritonavir has an inactive polymorph that exhibits the ability to inactive the active polymorph [139]. Ranitidine hydrochloride has been subject of deep discussion and legal litigation due to an attempt to approve a more active polymorph than the patented and commercialized by GSK. However and despite all the concerns on this topic, problems with commercialized drugs can still occur.

Particle size is another problem related to solid forms of pharmaceuticals, so that there are rigid guidelines concerning this aspect. It is known that particle size influences several parameters that determine drugs´ bioavailability and stability [140].

In this context one cannot also forget the problems of solubility of the majority of the novel drug candidates that hinder their future commercialization [113]. It is then important to control critically polymorphism, solubility and particle size during the development of solid APIs to avoid failures in posterior phases.

3.3.1. Control and Modulation of Physico-Chemical and Biological Properties of Pharmaceutically Active ILs

The most common strategy of the pharmaceutical industry to overcome inadequate physico-chemical properties is salt formation [13, 135, 136]. Recent estimations indicate that around 50% of all drugs utilized in the pharmaceutical industry are salts with improved properties regarding the corresponding neutral molecules. As for neutral drugs, FDA has got lists of approved conterions which include organic and inorganic ones. Even though this strategy hinders some of the abovementioned problems, the possible combinations are relatively small and the industry recurs systematically to the same ions.

In this context, an IL approach, in the design of novel APIs, appears to be appropriate as it enables uncountable possible cation-anion combinations while providing distinctive properties unreachable in solid salts namely enhanced solubility and absence of polymorphic forms [12, 14, 141]. In this pharmaceutically active ILs (IL-APIs), the cation and the anion can both present biological activity or the counterion can have the ability to reduce the adverse effects of the active ingredient or change its solubility, for example. The possibility of combining more than two ions in the same compound cannot be forgotten as it can provide an additional biological activity or property. In these cases, the total charge of the cations is balanced by the total charge of the anions [142, 143]. Even though not predictable, synergistic or additive effects must also be considered as they may provide novel treatment possibilities and distinct drug delivery options. Furthermore, the assertive combination of appropriate anions and cations empowers the chemical manipulation of the compounds with specific objectives related with the manufacturing process, the stability of the formulations, their bioavailability and eventual adverse effects. In this perspective, it is important to highlight that small modification of an API can result on dramatic changes of its properties and eventually on its classification in the BCS. Thus, the IL approach can be profitable not only from the technological perspective but also on the pharmacological point of view since the possibility of modulate the abovementioned properties can facilitate the interaction of the compounds with biological membranes with consequent increase in their bioavailability and higher probabilities to actuate *in vivo*.

3.3.2. Synthesis and Profiling of Active Pharmaceutical Ingredients with IL Properties

The synthesis of APIs with IL properties is based on the evident similarity between IL-forming cations and APIs and on the assumption that the majority of bioactive ions present properties to form low melting salts, namely adequate size, diffuse charge and asymmetry. The initial developments on this field demanded a deep knowledge not only of the biological action of the ions but also of their ability to form ILs. Even though a critical ion selection is not a guarantee for IL formation, the most determining aspect during IL-APIs´ synthesis is

definitely ion selection. Independently from the objective, the ions must be GRAS compounds with properties to be incorporated in pharmaceutical formulations either as APIs or excipients.

At this point, it is notorious that the research in this field is still mainly focused on the synthesis of novel compounds through the association of ions of distinct pharmacological groups or with diverse excipient properties. This is related with the relatively easy implementation of synthetic procedures based on metathesis reactions after the selection of ions with pharmaceutical interest. Moreover, the intensive investment on novel APIs with IL properties is still motivated by the enthusiasm related with the possibility of associating ions with the objective of modulate the pharmacological activity and physico-chemical properties while obtaining dual activity compounds.

The research group of Professor Rogers developed pioneer work regarding the synthesis and characterization of APIs with IL properties with a significant amount of papers and patents on this topic [12, 13, 141-147]. The first experiences on this field were reported on an interesting article exploring the so called *third evolution of ILs* [14]. Table 2 summarizes the most significant IL-APIs synthesized in the last years as well as their main properties and pharmacological activity.

Ranitidine docusate, lidocaine docusate and didecyldimethylammonium ibuprofenate can be synthesized through simple metathesis reactions to overcome issues of polymorphism, solubility and bioactivity [14]. The compounds exhibit dual activity since they incorporate well-known and widely used pharmaceutical ions and counterions with emollient (docusate) or antibacterial properties (didecyldimethylammonium). The association of docusate to lidocaine results on a hydrophobic API with increased thermal stability and enhanced bioactivity from topical application, possibly due to a slower release profile and higher skin permeability associated to the presence of the emollient. The three IL-APIs present low surface tension and low contact angles due to weak cation-anion interactions [161].

The IL-API approach enables the synthesis of compounds based on specifically selected ions. For instance benzalkonium and didecyldimethylammonium can form a dual active IL by combination with ibuprofen with applicability for the treatment of inflammation caused by bacterial infections [12]. Benzalkonium can also be used to form ILs with anions with similar activity, such as sulfacetamide. The result is an IL-API with enhanced antibiotic activity that can potentially reduce bacterial resistance. Similarly acetylsalicylic acid and salicylic acid can be combined with antimicrobial (cetylpyridinium, benzethonium, benzalkonium and hexetidinium), analgesic (tramadolium), local anesthetic (lidocainium and procainium) and antiarrhythmic (procainiumamade) cations to obtain dual activity IL-APIs with advantages in terms of solubility and functionality [145]. These combinations result in low melting or liquid salts at room temperature. However, acetylsalicylate IL-APIs suffer from low stability and their therapeutic application can only be guarantee if moisture is rigorously controlled. From the selected combinations, salicylate IL-APIs incorporating antibacterial actions, such as benzalkonium salicylate and cetylpyridinium salicylate exhibit promising physical and chemical properties that foresee their utilization in antimicrobial applications. This was further confirmed through the study of protein binding affinity, partition coefficients and surfactant properties of benzalkonium salicylate, cetylpyridinium salicylate and emim salicylate [148].

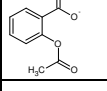**Table 2. Pharmacological activity and main features of IL-APIs**
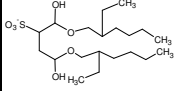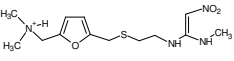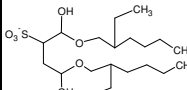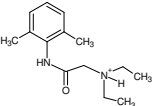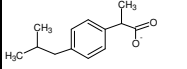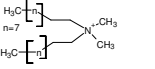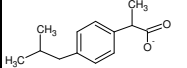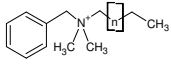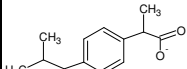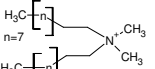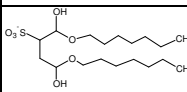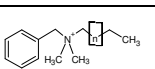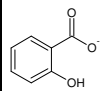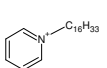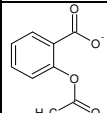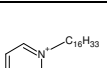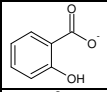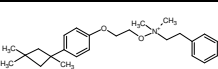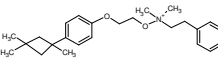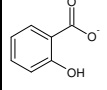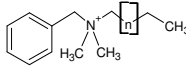
IL-API	Anion	Cation	Pharmacological activity	Main features	Ref.
Ranitidine docusate			Histamine H_2 receptor antagonist Emollient	- Absence of polymorphs - Low surface tension - Low contact angles	[14]
Lidocainium docusate			Local anesthetic Emollient	- Higher skin permeation	
Didecyldimethyl-ammonium ibuprofenate			Antibacterial Anti-inflammatory	- Anion with primary biological activity	
Benzalkonium ibuprofenate			Antibacterial Anti-inflammatory	- Appropriate to combat inflammation associated to bacterial infections	[12]
Didecyldimethyl-ammonium ibuprofenate			Antibacterial Anti-inflammatory	- Appropriate to combat inflammation associated to bacterial infections	
Benzalkonium sulfacetamide			Antibacterial Anti-acne	- Reduction of bacterial resistance	
Cetylpyridinium salicylate			Antibacterial Anti-inflammatory	- Improved solubility - Strong bind to HSA - High partition coefficient - Slightly toxic (aquatic toxicity)	[145, 148, 149]
Cetylpyridinium acetylsalicylate			Antibacterial Anti-inflammatory	- Water sensitive - Low stability	[145]
Benzethonium salicylate			Antibacterial Anti-inflammatory	- Improved solubility	[145, 149]
Benzethonium acetylsalicylate			Antibacterial Anti-inflammatory	- Water sensitive - Low stability	[145]
Benzalkonium salicylate			Antibacterial Anti-inflammatory	- Improved solubility - Strong bind to HSA - High partition coefficient - Slightly toxic (aquatic toxicity)	[145, 148, 149]

Table 2. (Continued)

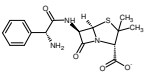| IL-API	Anion	Cation	Pharmacological activity	Main features	Ref.
Benzalkonium acetylsalicylate			Antibacterial Anti-inflammatory	- Water sensitive - Low stability	[145]
Hexetidinium salicylate			Antibacterial Anti-inflammatory	- Improved solubility	
Lidocainium salicylate			Local anesthetic Anti-inflammatory	- Improved solubility	
Procainium salicylate			Local anesthetic Anti-inflammatory	- Improved solubility	
Procainamidium salicylate			Antiarrhythmic Anti-inflammatory	- Improved solubility	
Tramadolium salicylate			Analgesic Anti-inflammatory	- Improved solubility	
Tramadolium acetylsalicylate			Analgesic Anti-inflammatory	- Water sensitive - Low stability	
Emim salicylate			Low antibacterial activity Anti-inflammatory	- Improved solubility - Strong bind to HSA - Higher partition coefficient - Practically harmless (aquatic toxicity)	[145, 148, 149]
Emim ampicillin			Antibacterial	- Improved solubility -Higher thermal stability Higher partition coefficient	[150-152]
C2OHmim ampicillin			Antibacterial	-Improved solubility -Higher thermal stability Higher partition coefficient	
Choline ampicillin			Antibacterial	- Low toxicity - Improved solubility -Higher thermal stability - Higher partition coefficient	
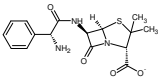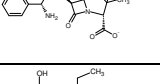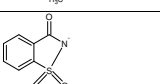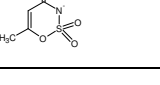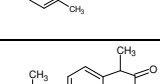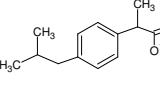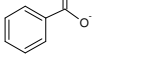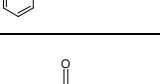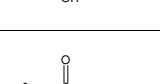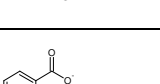
IL-API	Anion	Cation	Pharmacological activity	Main features	Ref.
TEA ampicillin			Antibacterial	- Improved solubility -Higher thermal stability - Higher partition coefficient	[150-152]
Cetylpyridinium ampicillin			Antibacterial	-Higher thermal stability - Higher partition coefficient	
T3htdph ampicillin			Antibacterial	-Higher thermal stability - Higher partition coefficient	
Tetracycline docusate			Antibacterial Emollient	- Lower solubility - Higher partition coefficient	[153]
Benzethonium saccharinate			Antibacterial		[154]
Propantheline acesulfamate			Muscarinic acethylcoline receptor antagonist	- Crystalline solids with low melting points - Absence of polymorphs	[154, 155]
Propantheline p-toluenesulfonate			Muscarinic acethylcoline receptor antagonist		
Lidocainium ibuprofenate			Local anesthetic Anti-inflammatory	- API-SILPs - Fast release - Controlled solubility	[146]
Tetrabutylphos-phonium ibuprofenate			Antibacterial Anti-inflammatory		
Tuaminoheptane benzoate			Nasal decongestant Preservative	- Solid or liquid and water soluble or insoluble depending on the ration	
Amantadine benzoate			Antiviral/antipar-kinson Preservative	-Higher solubility (but still poor water soluble)	
Tuaminoheptane salicylate			Nasal decongestant Anti-inflammatory Keratolytic	- Water soluble or insoluble depending on the ratio	[156]
Amantadine salicylate			Antiviral/antipar-kinson Anti-inflammatory Keratolytic	- Water insoluble	
2-Pyrrolidino-ethanol salicylate			Anti-inflammatory Keratolytic	- Water soluble or insoluble depending on the ratio	

Table 2. (Continued)

IL-API	Anion	Cation	Pharmacological activity	Main features	Ref.
Tuaminoheptane gentisate			Nasal decongestant Analgesic	- Solid - Water soluble	
Amantadine gentisate			Antiviral/antiparkinson Analgesic	- Water insoluble	
2-Pyrrolidino-ethanol gentisate			Analgesic	- Higher solubility than gentisic acid	
Tuaminoheptane salicylate			Nasal decongestant Anti-inflammatory Keratolytic	- Rapid membrane permeation	[157]
Bromohexinium ibuprofenate			Mucolytic Anti-inflammatory		
Lidocainum etodolac			Local anesthetic Anti-inflmmatory	- Higher skin permeability - Safe and well tolerated (results of clinical trials)	[158-160]
Benzethonium docusate			Antibacterial Emollient	- Water insoluble - Moderately toxic (aquatic toxicity)	
Benzethonium bistriflimide			Antibacterial	- Water insoluble - Moderately toxic (aquatic toxicity)	
Trihexyltetradecyl-phosphonium bistriflimide			Antibacterial	- Water insoluble	[149]
Trihexyltetradecyl-phosphonium docusate			Antibacterial Emollient	- Water insoluble	
Trihexyltetradecyl-phosphonium salicylate			Antibacterial Anti-inflammatory	- Water insoluble	

The three compounds bind strongly and spontaneously to human serum albumin and exhibit the ability to form micelles. Moreover, the determined partition coefficients are up to 6 times higher than for sodium salicylate. These features indicate that these IL-APIs can exert direct effect on cell membranes and present adequate properties to be incorporated in antimicrobial pharmaceutical formulations, mainly topical ones.

Also in the field of antimicrobials, the thermal stability, solubility and melting point of ampicillin can be dramatically changed by association with organic cations such as emim, 1-hydroxy-ethyl-3-methylimidazolium (C_2OHmim), choline, tetraethylammonium (TEA),

cetylpyridinium and trihexyltetradecylphosphonium [150-152]. IL-APIs can be obtained through the neutralization of moderately basic ammonia solutions of ampicillin with the mentioned cations. The obtained compounds present more adequate partition properties which result in enhanced membrane affinity and permeation [151]. Choline ampicillin is the most interesting compound resulting from this association as it presents adequate solubility and low toxicity. In terms of bacterial resistance reversion, the compound with highest potential is cetylpyridinium ampicillin [152]. Another interesting approach, explored since the first experiences with IL-APIs through the use of docusate [14], is to couple a bioactive ion with a well-known excipient as counterion. A good example is the synthesis of tetracycline docusate to modulate important biopharmaceutical properties of tetracycline [153]. Even though the solubility of the drug decreases to half on the IL format, both octanol-water and liposome-water partition coefficients show a favorable trend concerning *in vivo* activity. This approach is also very well illustrated by the synthesis of stable IL-APIs based on benzethonium and propantheline combined with artificial sweeteners such as acesulfamate, saccharinate and *p*-toluenesulfonate, via metathesis reaction [144, 154, 155]. The obtained compounds overcome issues of polymorphism, typical for instance of propantheline bromide and modify the thermal properties and solubility of the compounds. The utilization of sweeteners can be also interesting to camouflage the unpleasant taste of specific APIs being good options to integrate oral formulations.

Distinctly, the advantages of the liquid properties of an IL can be combined with the benefits of solid state by means of the immobilization of IL-APIs on mesoporous silica [146]. The study of the sorption, stability and release profile of tetrabutylphosphonium ibuprofenate and lidocainium ibuprofenate confirm that this strategy can be a tool for drug delivery with the ability to control the release of the adsorbed compound by manipulating the IL properties. There are evidences of total and fast leaching of the IL-API in physiological conditions (phosphate buffer saline, pH 7.4, 37ºC) and enhanced thermal stability of the IL-API compared with its liquid form.

The prodrug approach is also a possibility when dealing with pharmaceutically active ILs [147]. Prodrugs are pharmacologically inactive derivatives of a related drug molecule that demand a spontaneous or enzymatic transformation *in vivo* to release the active drug. They can be idealized to overcome pharmaceutical, pharmacokinetic, or pharmacodynamic problems such as chemical instability, reduced solubility, unacceptable taste or odor, insufficient oral absorption, inadequate blood-brain barrier permeability and toxicity, among others [162]. The combination of an IL strategy with the prodrug approach can be an important tool for the development of APIs with improved properties and higher possibilities to actuate efficiently *in vivo*. This was explored through the functionalization of acetaminophen (paracetamol) through esterification with chloroacetyl chloride to obtain a neutral acetoxy derivative [147]. This was subjected to further alkylation with typical IL precursors to form chloride salts or to anion exchange with silver docusate to obtain prodrug docusate ILs. This new prodrugs present low water solubility and are readily hydrolyzed in physiological conditions suggesting good bioactivity.

This section could not be closed without a mention to the importance of protic ILs (PILs) in the pharmaceutical field, namely as APIs. PILs are a subclass of ILs formed by the reaction of a Brønsted acid with a Brønsted base [100]. The main difference between PILs and other ILs is the proton transfer from the acid to the base that originates proton-donor and -acceptor sites, which can be used to build up a hydrogen-bonded network. The simplicity of the

synthetic route for the production of PILs makes these compounds very promising for pharmaceutical applications [145, 156, 157, 163]. It is then possible to obtain PIL-APIs from acids and bases commonly used in the pharmaceutical industry. As examples, salicylic, benzoic and gentisic acids can form PIL-APIs through the combination with pharmaceutical bases such as tuaminoheptane, amantadine and 2-pyrrolidinoethanol, ethylamine and diethylamine, among others [156, 164]. The variable properties of the obtained compounds can be explored to modulate their membrane permeation. Studies with model membranes suggest that PIL-APIs with low ionicity can readily cross the lipid bilayer, probably as hydrogen bond complexes [157, 164]. Considering that PIL-APIs exist mainly as ion-pairs their behavior is similar to that of neutral species and thus can cross membranes more easily than ionic species. It is also possible that, proton transfer, at the point of dissolution into the membrane, plays a key role in the transport.

Even though it is controversial, in this group of compounds one can also include oligomeric ILs that result from the combination of non-stoichiometric ratios of the selected acids and bases [165]. This results in the formation of hydrogen-bonded moieties containing both ions and some neutral non-ionized compound. Thus, the composition of these liquids can range from fully ionized to partially ionized or non-ionized species generating intensive debate regarding the classification of these compounds. These are proton transfer IL systems in which the proton is shared by two or more cationic or anionic moieties leading to a controlled reduction of melting point with expansion of the liquid range. Oligomerization can be also applied to the formation of pharmaceutically active compounds as demonstrated by Bica and Rogers through the synthesis of oligomeric tetrabutylphosphonium salicylates and lidocainium salicylate [13, 163].

Recently, MEDRx Co. Ltd. (a Japanese pharmaceuticals company) and IL Pharma Inc. (a subsidiary of MEDRx Co., Ltd.) developed an etodolac-lidocaine patch (MRX-7EAT) for the treatment of pain and inflammation using ILTS® (Ionic Liquid Transdermal System) [158-160]. The patch presents higher skin permeability than the conventional etodolac patch with a consequent increase of the systemic exposure to etodolac. The results of non-clinical and clinical studies confirmed the safety and tolerability of the product [159, 160].

Considering the future pharmaceutical utilization of IL-APIs the toxicity and biodegradability of these compounds must be carefully evaluated and discussed as usually performed with conventional pharmaceutical drugs. Even though this compounds are synthesized from GRAS materials, the evaluation of toxicity must include the study of their effects on humans as well as their environmental impact since the principal pathway for their release is the aquatic environment due to their low volatility. Up to now there is very few information concerning the issues of toxicity and biodegradability and the available data refers to *in vitro* assays based on human carboxylesterase and *Vibrio fischeri* [149]. The effect of the abovementioned salicylates [148] on aquatic bacteria *Vibrio fischeri* ranges from practically harmless to slightly toxic. Due to its antimicrobial activity compounds incorporating the cetylpyridinium cation tend to be more toxic for both humans and the aquatic environment than those incorporating benzethonium and benzalkonium. These salicylates are only slightly more toxic than their original starting materials. This marginally enlarged risk is totally compensated by the benefits that accrue from the dual activity of the compounds. Interestingly, the anion bistriflimide can modulate the toxicity of the IL-APIs. For instance, the toxicity of benzethonium and phosphonium cations is decrease when combined with bistriflimide to form an IL-API. Not surprisingly, the toxicity of IL-APIs

resulting from the association of benzethonium or trihexyltetradecylphosphonium with the docusate anion is related almost exclusively to the toxicity of the cations, due to the innocuous nature of this anion.

4. FINAL REMARKS AND FUTURE TRENDS

The pharmaceutical utilization of ILs either as solvents, carriers or APIs has increased in the last years with successful examples both at the industrial and academic level.

The peculiar properties of ILs are of pivotal importance for their application as substitutes of conventional VOCs during the synthesis of pharmaceutical drugs and in other phases of pharmaceutical processing. With adequate compound selection the use of ILs as pharmaceutical solvents can result on a significant reduction of the human and environmental impact of pharmaceutical synthesis while providing higher yield synthetic routes as described for biocatalytic synthesis. The appearance of greener ILs with more attractive properties in terms of toxicity and biodegradability further foments their incorporation in pharmaceutical formulations as part of drug delivery systems with improved properties in terms of drug release profile and pharmacologic activity. This seems to be one of the most promising application of ILs in a near future being a full acceptance of this approach mainly dependent on the abovementioned toxicity concerns and on evidences of adequate pharmaceutical profiles of the involved drugs.

Despite the high resistance of the pharmaceutical industry to this concept, the synthesis of APIs with IL properties is undoubtfully the most exciting and captivating application in this field. The possibility of obtaining dual activity compounds or drugs with improved properties either concerning their efficiency or their undesirable effects opens countless possibilities for drugs with reduced bioavailability and for the treatment of diseases with particular and complex demands in terms of pharmacological intervention. The recent advances with IL-API prodrugs further enhances these possibilities. Studies with pharmaceutically active silica supported ILs offer also promising perspectives in the field of nanotechnology, mainly through the association of IL-APIs with nanoparticles for drug delivery.

The implementation of the IL strategy for the synthesis of novel drugs in the pharmaceutical industry demands only a deep change in mentalities of the involved institutions and the creation of specific tools to perform drug´s purification and manipulation on the liquid state. Legal and approval issues are largely facilitated by the well-known safe nature of the anions and cations used to synthesize novel IL-APIs. In conclusion, the conditions for the insertion of more products based on the IL-API concept in the pharmaceutical market are created and it is expect that once the abovementioned advantages are clearly evidenced by influential authorities the concept will disseminate rapidly.

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