



Mini Review

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Applicability of Ionic Liquids in Topical Drug Delivery Systems: A Mini Review



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Abstract

The Pharmaceutical Industry has several challenges to overcome, such as poor drug solubility, skin permeation, problems related with the stability of the prepared delivery systems, as well as the type of administration to be used. When choosing the most suitable route of administration, non-invasive routes of administration are preferably chosen, with the oral administration being one of the most used. However, the delivery of drugs through the skin can be an alternative route of administration that avoids the gastrointestinal tract, and overcomes complications associated with the parenteral route since it is a non-invasive technique and is widely accepted among patients. Nonetheless, when formulating these delivery systems other problems need to be addressed, such as the low solubility of many drugs and the reduced stability of some of the developed systems. Thus, finding functional excipients that help to overcome these problems is fundamental.

In this context, the valuable properties of ionic liquids will be reviewed herein, particularly with respect to their application in the pharmaceutical field and in topical delivery. Furthermore, some studies, that show the value of ionic liquids as drug solubility/loading, permeation enhancers in topical drug delivery systems, will be summarized.

Keywords: Drug Delivery Systems; Ionic Liquids; Topical Drug Delivery; Solubility; Permeation; Toxicity; Functional Ingredients

Abbreviations: %: Percentage; [Bmim][Br]: 1-Butyl-3-methylimidazolium bromide; [Bmim][C12SO3]: 1-Butyl-3-methylimidazolium dodecane sulfate; [Bmim][PF6]: 1-Butyl-3-methylimidazolium hexafluorophosphate; [C1mim][(CH3O2)PO2]: dimethylimidazolium dimethylphosphate; [C2mim][Br]: 1-Ethyl-3-methylimidazolium bromide; [C4mim][Br]: 1-Ethyl-3-butylimidazolium bromide; [C6mim][Br]: 1-Ethyl-3-hexylimidazolium bromide; [CDHP]: Choline dihydrogen phosphate; [Cho][Glu]: (2-Hydroxyethyl) trimethylammonium glutamate; [Cho][Phe]: (2-Hydroxyethyl) trimethylammonium-L-phenylalaninate; [Emim][EtSO4]: 1-Ethyl-3-methylimidazolium ethyl sulfate; [Hmim][Cl]: 1-Hexyl-3-methylimidazolium chloride; [HOEIM][Cl]: 1-Hydroxyethyl-3-methylimidazolium chloride; [HPyr][Cl]: Hexylpyridinium chloride; DMBA: Dimethylbenz(a)anthracene; ETO: Etodolac; IL/o: Ionic liquid-in-oil; IL/w: Ionic liquid-in-water; ILs: Ionic Liquids; IPM: Isopropyl myristate; m2: Square metre; ME: Microemulsion; nm: Nanometers; O/W: Oil-in-water; RTILs: Room Temperature Ionic Liquids; SEPINEO™ P600: Acrylamide/sodium acryloyldimethyltaurate copolymer/isoheptadecane / polysorbate 80; Span 20: Sorbitan laurate; TPA: 12-O-tetradecanoylphorbol-13-acetate; Tween 80: Polyoxyethylenesorbitan monooleate; W/O: Water-in-oil

Introduction

Nowadays, several possibilities for drug administration are already known and widely used. The choice of the most suitable route of administration to use depends on factors such as the drug to be used, its pharmacokinetic profile, as well as the desired target site [1,2]. Furthermore, the choice of route of administration to be used also depends on other factors such as its invasiveness [2]. Thus, non-invasive routes of administration are preferably chosen [2]. And the oral administration is one of the most used [3]. However, despite the advantages inherent in oral and even parenteral use, the pharmaceutical industry has been encouraged to explore alternative administration routes that also allow efficient and effective drug delivery [4].

The delivery of drugs through the skin is widely accepted among patients [5]. Can be an alternative route of administration that avoids the gastrointestinal tract, and overcomes complications associated with the parenteral route since it is a non-invasive technique [2]. Another drawback that the pharmaceutical Industry faces when developing drug delivery systems relates to the low solubility of many drugs as well to the reduced stability of those systems. Thus, finding functional excipients that help to overcome these problems is fundamental. Recently, some studies have shown the relevance of using ionic liquids (ILs) to improve drug solubility/loading, permeation of topical drug delivery systems [6-12].

Drug Delivery through the Skin

Delivery through the skin can be divided into two classes: dermal/topical delivery and transdermal delivery. Absorption of drugs through the skin occurs in both delivery systems although the local where the drug is intended to produce effect is different. In the transdermal delivery it is intended that the drug, applied to the skin, reaches the blood circulation to produce a systemic therapeutic effect [2,3,13]. On the other hand, in the topical delivery the target site is within the skin itself, with minimal or without systemic absorptions. This system is generally used for the treatment of local diseases such as dermatological treatments, e.g. psoriasis, acne, fungal infections [14,15] and/or contact dermatitis [16]. Moreover, the topical drug delivery system can still be applied to healthy skin through cosmetic formulations [15]. There are several types of formulations capable of topically delivering drugs and the most commonly used are solutions, emulsions, suspensions, semisolids, sprays and solids [15].

Topical Drug Delivery Systems

The topical drug delivery, comparatively with other routes, mainly with the oral route, avoids the first pass metabolism and other inconveniences such as pH, presence of enzymes and gastric emptying time associated to the gastrointestinal tract [3,15,17]. Furthermore, topical administration has more advantages such as: large area of application in comparison with buccal or nasal cavity, improved patient compliance and acceptance, ease and convenience of application, suitability for self-medication, painless and non-invasive administration, allowing the use of drugs with narrow therapeutic window and short biological half-life, ease of dose termination in the event of any adverse reactions and allows direct access to target site and consequently a more specific drug delivery, providing an alternative in circumstances where oral dosing is not possible [3,17,18].

However, there are known disadvantages associated with the use of topical delivery systems for drugs, some of which are related to the drug, such as poor drug solubility/loading to be used and others with the characteristics and properties of the skin, that may lead to skin irritation, due to the drug and excipients, difficulty in the absorption of drugs with a high particle size, poor permeability of some drugs, possible denaturation of drugs by the enzymes in the epidermis and possible occurrence of allergic reactions [17]. Thus, considering some of these disadvantages, for the development of formulations for topical application it is fundamental to know and understand the characteristics and properties of the skin and of the drugs to incorporate in the developed topical systems.

The Skin barrier

The skin is the largest and one of the most important organs of the human body, covering about 1.7 m² and representing

approximately 10% of the total body mass of an adult [19]. This structure has several functions but its primary function is to provide an effective barrier between the human body and the external environment by protecting it against external factors that can induce damages, such as chemicals, ultraviolet radiation, allergens and microorganisms and the loss of water and nutrients [19,13]. Human skin is composed of the appendages, eccrine and apocrine sweat glands and hair follicles, and by three different main layers: the epidermis, the dermis and the hypodermis [13]. The stratum corneum, often referred as non-viable epidermis, is the outermost layer and primary barrier of the skin due to its unique structure consisting of layers of flattened corneocytes surrounded by lipid bilayers composed mainly of ceramides [20]. Most of the compounds applied topically penetrate the skin through the intercellular route, by passing the lipid bilayers of the stratum corneum, although, in some circumstances, they also penetrate across the transcellular route [20]. Therefore, since certain layers of the skin may limit the bioavailability of some drugs, a careful selection of the drugs is essential as well as of the excipients used and a clear understanding of their properties to develop formulations for topical drug delivery.

Ionic Liquids

Skin has a hydrophilic and a hydrophobic domain and consequently the drug used needs to have the ability to permeate both domains [19]. However, poor drug solubility of many drugs in water and in most pharmaceutical grade solvents, used in the developed topical formulations, represents an obstacle. Hence, several efforts have been made to find ingredients that may assist in this challenge, and ionic liquids have been used for this purpose [6-12]. ILs are salts, with an organic cation and an inorganic or organic [21-23], that are liquid at temperatures below 100 °C or even at room temperature [21,24,25]. These latter are known as Room Temperature Ionic Liquids (RTILs).

They have numerous prized characteristics such as low vapour pressures [21,26], possibility of recycling [27], negligible volatility [28], non flammability [10,26,27], high ionic conductivity [29], high thermal and chemical stability [29] and also their ability to dissolve inorganic, organic and polymeric materials, which becomes extremely relevant when using these salts as ingredients in delivery systems [21]. Another extremely important property of ILs is their high suitability for alterations, since this allows their properties to be tailored accordingly to a specific application, by intentionally modifying their anions and/or cations, [26,27,29,30]. In terms of their categorisation, ILs have been generally classified in three generations (Figure 1), according to the structure and chemical properties of the ILs [9,31]. The first generation of ILs are composed by the dialkylimidazolium and alkylpyridinium cations with metal halide anions and although they have valuable properties they are air- and water-sensitive.

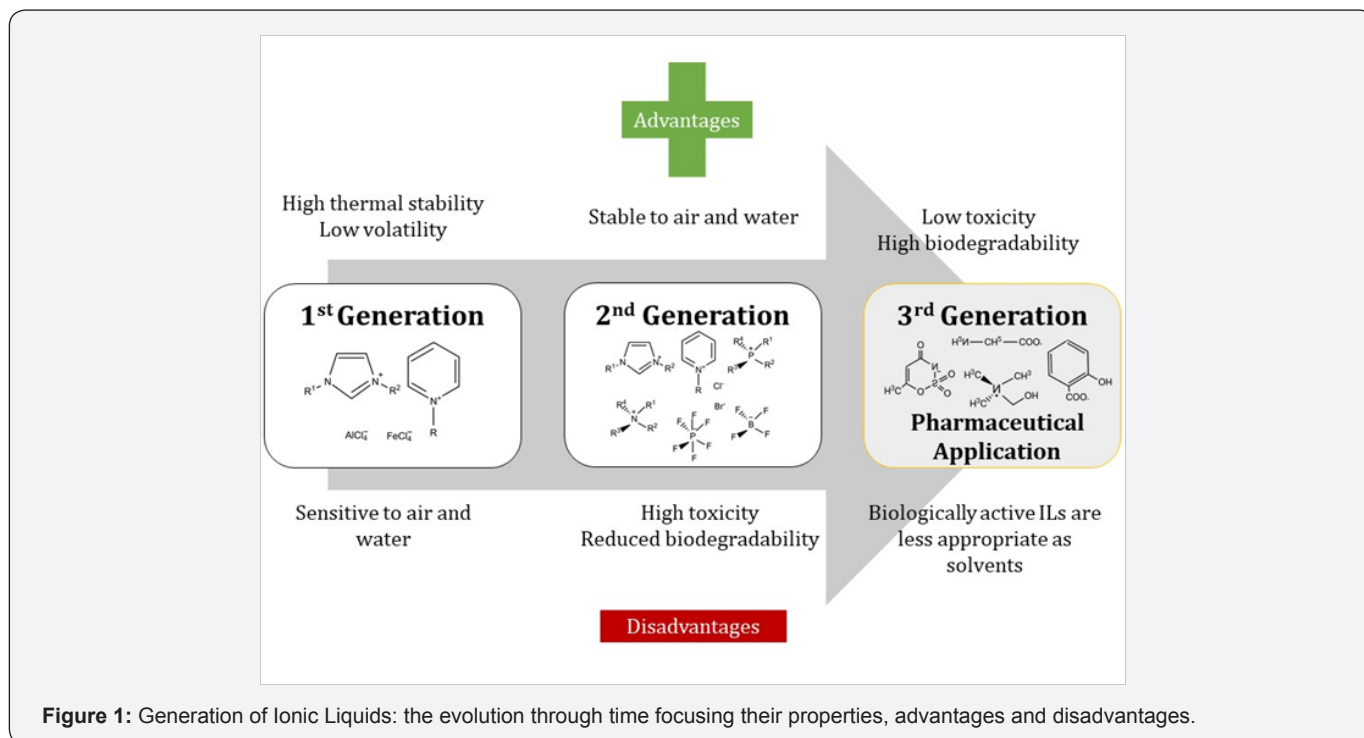


Figure 1: Generation of Ionic Liquids: the evolution through time focusing their properties, advantages and disadvantages.

On the other hand, the second generation of ILs are known to have the advantage to be stable to air and water and are normally formed by the dialkylimidazolium, alkylpyridinium, ammonium and phosphonium cations and the tetrafluoroborate and hexafluorophosphate anions. Finally, the third generation is constituted by biodegradable and natural ions or by ions with known biological activities and choline-based ILs with amino acids are amongst the most usual ILs in this last generation [9,31]. Hence, this last generation of ILs are very exciting materials to work with due to their possible applications in pharmaceuticals, ecology and/or biology fields and choline-based ILs with amino acids are the most usual ILs in this last generation [9,31]. ILs have also been classified into four main categories, according to the cation that constitutes them, either dialkylimidazolium, N-alkylpyridinium, phosphonium or a alkylammonium cation [11,27].

The most studied IL are the imidazolium-based, since they are stable, within reductive and oxidative conditions and they have a lower viscosity and an easier synthesis [11,27]. However, they have been described as being toxic, with their toxicity dependent on the size of the alkyl chain which limits their applicability, particularly in the pharmaceutical field [11,32,33]. Nonetheless, these ILs have been proven useful as solvents, catalysts or even as solubility promoters [11,21]. The pyridinium-based ILs, have also been used as solvents [11,27,34] and catalysts [35] in several organic reactions and even in the synthesis of pharmaceutical compounds [36].

On the other hand, although phosphonium-based ILs have also been used as catalysts and solvents in several reactions [37,38] they have higher thermal stability than imidazolium- and

ammonium-based salts, and thus are more suitable for reactions at temperatures above 100 °C [39]. Regarding the more recent quaternary ammonium-based ILs, they have been described as the less toxic class of ILs [22,40] and consequently have been described in the literature as “green” alternatives to the solvents normally used in the pharmaceutical industry [40]. It becomes clear that ILs have been broadly used as solvents, catalysts and reaction media in several reactions [26] and their possible applicability in the health area is very appealing. None the less, the toxicity of this class of compounds needs to be carefully considered.

ILs in Topical Drug Delivery Systems

As mentioned previously, ILs may be tailored to be incorporated in different types of mediums such as water, oils or hydro alcoholic solutions, depending upon the ion present, which allows them to be included in different drug delivery systems, such as topical systems. One of the earliest works, that studied the incorporation of ionic liquids in this topical delivery systems, was done by Dobler and co-workers [21]. In this study, oil-in-water (O/W) and water-in-oil (W/O) emulsions were prepared with two different ILs, [Hmim][Cl] and [Bmim][PF₆], to replace the water and oily phases, respectively and both ILs were successfully incorporated into the stable emulsions. These emulsions showed antimicrobial activity in a range above 5 % of IL, and a higher skin penetration, especially the formulation containing [Bmim][PF₆], the lipophilic IL. After this work, the same group investigated the influence of the ILs, [HPyr][Cl], [CDHP] and [Emim][EtSO₄], in drug skin penetration and their antimicrobial properties in an emulsion-gel of 4-hydroxybenzoic

acid propyl ester, caffeine and testosterone [11]. In terms of skin penetration of the hydrophilic drug, caffeine, after 24 h, this parameter was two-fold higher when compared with the formulation in the absence of [HPyr][Cl]. While the testosterone, the lipophilic drug, did not observe any modifications in the skin penetration. Furthermore, the addition of imidazolium- and pyridinium-based ILs reduced strongly the viscosity of the emulsion-gel with SEPINEO™ P600, without modifying the rheology of the hydroethylcellulose gel. It was also showed that over storage time (3 months), all formulations were stable. Thus, results indicate that the studied ILs may be useful to enhance skin penetration in topical formulations.

Furthermore, ILs have also been studied in a minor scale, through the preparation of ionic liquid-in-oil (IL/o) microemulsions (ME) as drug carriers of poorly aqueous soluble drugs, such as acyclovir, methotrexate and 1-[(5-(p-nitrophenyl) furfurylidene) amino] hydantoin sodium (dantrolene sodium) [29,30]. In these studies, Moniruzzaman and co-workers incorporated nanometer-sized ILs droplets in isopropyl myristate (IPM) with a blend of Tween80 and Span20, with the ILs as a dispersed phase. This study demonstrated a higher solubilisation of studied drugs in the ILs ME. These studies also showed that the percentage of ILs used in the ME strongly affects the toxicity of the system, and although with 4% of IL, 80% of cell viability is maintained, pure IL leads to a significant decrease in cell viability.

Another IL/o ME with 5-fluorouracil (5-FU) was developed using IPM, Tween 80/Span 20 and [Bmim][Br] as IL [41]. In this study, the solubility of 5-FU was also enhanced with results showing a solubility 2.6 times higher in the presence of the IL than in aqueous solution. On the other hand, small and mono disperse droplets were formed and ex vivo permeation studies in animal models also showed an increase of this parameter for 5-FU when compared to aqueous solution and W/O ME. Additionally, in vivo studies using dimethylbenz(a)anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mice skin carcinogenesis model proved that erythema and irritation was not observed as side effects, that results were supported by the histopathological analysis.

Another study prepared an ionic liquid-in-water (IL/w) ME with Etodolac (ETO) containing [Bmim][PF₆], Tween 80 and ethanol [42]. Ex vivo permeation studies using rat skin and it showed that the IL/w ME had a higher ETO permeation comparing with the oily solution of ETO and to the O/W ME. Also, IL containing system was more effective in controlling in vivo inflammation than the oily solution or O/W ME or the sold formulation of ETO. More recently, some studies have been done comparing imidazole-based and choline-based ILs, both classes used at non-toxic concentrations, to show their ability as functional ingredients in topical delivery systems [11,33]. In these study, three imidazole-based ILs, [C2mim][Br], [C4mim]

[Br] and [C6mim][Br] and two choline-based ILs, [Cho][Phe] and [Cho][Glu] were studied and since incorporation in topical formulations was sought, their cytotoxicity was characterized in human keratinocytes (HaCat cells). Furthermore, caffeine and salicylic acid were used as model actives and their solubility and permeation through pig ear skin, in the presence and absence of the studied ILs, was evaluated. Results showed that at non-toxic concentrations, cell viability was maintained, the choline-based ILs were more suited as functional ingredients, since they allowed a higher enhancement in drug solubility, particularly for caffeine. Furthermore, results also showed that [Cho][Phe] and [Cho][Glu], do not impact drug permeation which may be relevant to ensure low incidence of adverse effects in topical formulations where low drug permeation is pursued. On the other hand, the imidazole-based ILs proved to be more toxic, with their toxicity enhancing with the size of the alkyl chain, and when used at non-toxic concentrations, their utility as solubility promoters was less evident. Furthermore, the authors also evaluated the incorporation of caffeine into O/W emulsions and gels using the two choline-based ILs at non-cytotoxic concentrations, and all formulations were stable after stress stability studies, showing that these ILs did not influence the rheology of O/W emulsions and gels. Hence, Choline and amino acids based ILs that have been described as less toxic and more environmentally-friendly [22], show the promising ability to be used as functional ingredients in topical delivery systems.

More recently, two imidazolium-based ILs, [HOEIM][Cl] and [Bmim][C₁₂SO₃], were also incorporated into ME with Dencichine [43]. Results of the in vitro skin permeation proposed a 10-fold improvement for the formulation with ILs, because the nano carrier with ILs disrupted the regular skin barrier properties and reorganised the corneocytes that modify the stratum corneum surface properties. Furthermore, the in vivo pharmacodynamic analysis demonstrated an important haemostatic activity of Dencichine by topical application, as well as, a reduced cell toxicity and skin irritation. These results show once again, that ILs may have multiple utilities when incorporated in topical Delivery systems [44-63].

Conclusion

This mini-review shows the valuable properties of Ionic Liquids and their potential applicability in the Pharmaceutical and Medical fields, particularly as functional ingredients in topical drug delivery systems. The structure and functional flexibility of ILs may be useful for their incorporation in different mediums, allowing them to be included indifferent topical drug delivery systems, and improving their performance. Currently, there are some studies that already show this ability of ionic liquids to work as performance enhancers of topical delivery systems. Nonetheless, the characteristics of the ILs used are truly relevant for their efficacy, particularly when considering their toxicity, which may be a limitative characteristic. In fact,

for these salts truly act as functional ingredients, they need to be functional at non-toxic concentrations where cell viability is maintained. In this context, recent studies have already shown that some ILs may be more suited as functional ingredients, in terms of their toxicity. Furthermore, the interaction between ILs and other excipients or functional ingredients needs also to be considered.

Nonetheless, ILs have the remarkable ability to be tailored accordingly to a desired goal, and consequently, much is still to be done in this area to encounter new ILs that may be truly useful in enhancing the performance of a topical delivery system.

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