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Ionic liquid: A green designer solvent for topical delivery of Nano system

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REVIEW

Ionic Liquid: A Green Designer Solvent for Topical Delivery of Nano System

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Abstract

Ionic liquids (ILs) defined as organic salts that produced from combination of organic cation with various types of organic/inorganic anions whose melting point less than 100 °C. Because of their ionic character, most of ionic liquids exhibit useful properties such as no volatility, recyclability, good thermal stability, high conductivity and chemical stability. Ionic liquid cation−anion combinations permits the solvents to be prepared such as N, N-dialkylimidazolium as cation and acetate as anion. Ionic liquid was utilized as solvents or preparation components in various areas of drug delivery systems, also as novel liquid forms of APIs in various stages of design drug delivery systems. Also their incorporation with polymers has enabled the development of drug delivery systems for new therapeutic routes of administration. Recently ionic liquid can be used as solubility and permeability enhancer to deliver drugs with poor aqueous solubility and low lipophilicity by designing topical drug delivery of nano system.

Keywords: Active pharmaceutical ingredients(APIs), Ionic liquid, Topical drug delivery system, Solubility and permeability enhancer

1. Introduction

In the formulation of drug as a dosage form, organic solvents usually utilized for enhancing the solubility of active pharmaceutical ingredients APIs during the *in vitro* study of drugs and during *in vivo* study in an investigating the biological effects of drug on targets and using large quantities of organic solvents constitutes a major health concerns [1]. Recognition of the exact solvents or co-solvents needs to know the purposed route of administration [2]. In such case the choosing of a solvent that act as a vehicle to improve the solubility and enhance permeation result in good bioavailability of drug, it's an attractive replacement to follow up, although its biocompatible. Using of salts that are in liquid state at room temperature currently called ionic liquids (ILs) [3]. Ionic liquids (ILs) considered as organic salts were produced from combination of asymmetric cation with various types of anions whose melting point less than 100 °C, over the last few years, (ILs) have gained significant and growing interest in a variety of research genera such as engineering fluids, food sciences, synthetic chemistry and pharmaceutical sciences due to their useful properties such as no volatility, recyclability, thermal stability and high conductivity, so considered as greener solvent in contrast with traditional organic solvents [4]. Recently, utilizing of these solvents in pharmaceutical applications attributable to their changeable physicochemical properties like polarity, viscosity and catalytic role in the synthesis of pharmaceutical ingredient (PI) and, the most interested, good ability for solubilization of hydrophilic and hydrophobic drugs [5]. So, ionic liquids (ILs) is regarded a novel solvent in pharmaceutical delivery system and formulation of active pharmaceutical ingredient (API) due to unparalleled and tunable physicochemical and biological properties, also utilizing of ILs can improve the pharmacokinetic and pharmacodynamics properties of drugs [6]. Moreover, the incorporation of active ingredients that act

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as cations or anions in synthesis of ILs encourage the transformation of active ingredient from solid into a liquid state (API-ILs). Polymorphism concerns will overcome by this strategy, provides improved solubility and enhanced therapeutic efficacy [7,8]. Confer elasticity in formulation of API-ILs, also it is probable to enhance the permeation of APIs across membranes, this employed for mixing of permeation enhancers with APIs and for utilizing a combination of surfactant with ionic liquid as excipients with novel design [9]. To improve delivery systems of drugs, the formulation of modern systems utilizing polymers with biopolymers was performed by employing ionic liquid as polymerization processes media specially for polymers have opportunity for in situ functionalization [10,11].

1.1. Advantages of ionic liquids

Ionic liquids have several important advantages [12], and according to these advantages ionic liquid considered as a green solvent, which are:

1-Ionic liquids have high polarity.

2-Ionic liquid remain liquid over a wide range of temperature.

3-Ioinc liquids are non-volatile and possess low vapor pressure.

4-Ionic liquid are mostly hydrophilic in nature and rarely hydrophobic.

5-Ionic liquids are thermally stable and resist high temperature up to 300 °C.

6-Ionic liquid have high electrical conductivity.

7-Ionic liquids are incompatible with organic solvents.

1.2. Limitations of ionic liquids

The use ILs have disadvantages such as toxicity due to possibility of release these compounds into water courses or soil. Estimation the risks of ILs, numerous ILs have had their toxicity assessed toward several micro- and macro-organisms over the past few decades. Since the toxic effects of ILs depend on the method of estimating toxicity, it is necessary to briefly summarize and comprehensively discuss the biological effects of ILs according to their structure and toxicity testing levels [13]. However, some ILs are produced from non-renewable energy sources and are poorly biodegradable in the environment, undermined their green character, when designing and synthesizing new chemical products as suggested in the 3rd, 4th and 10th green chemistry principles, not only their efficiency and cost should be considered, but also their toxicity to human health and environment [14]. ILs becomes permanent pollutants and possess hazard to the environment, also high cost of ionic liquid making them impractical for large scale industrial applications like metal electroplating, biocatalyst and electrodeposition. Therefore, the main challenges in the application of conventional ILs has been the cost issues and availability. Myriad issues like availability and toxicity will limit their practical use for larger scale applications of other metals and biomaterials [15].

1.3. Properties of ionic liquid

Properties of ionic liquid include melting point, density, thermal stability, volatility, viscosity, and solubility of materials rely on alternatives on organic component and by the counter ion. Ions variation can be performed to adjust their chemical and physical properties, fine tuning of properties is probable by changing the length and branching of the alkyl groups incorporated into the cation. Abundant of ionic liquids have even been advanced for specific synthetic problems. For this reason, ionic liquids have been termed "designer solvents" [16].

1.3.1. Melting point

Ionic liquids should be liquid at room temperature when used as a substitute to organic solvents, hence the melting point of ionic liquid must be that of water in order to work with them at room temperature. The melting point magnitude is present related to the composition and structure of ionic liquids. Hence, careful selection of cation and anion in preparation of ionic liquid determines its melting point [17].

1.3.2. Density

Density of ionic liquid determined by anion and cation that were utilized in preparation of ionic liquid. The density ionic liquids are between 1.0 and 1.35 gcm^{-3}, which observed practically. Organic anion bulkiness found in ionic liquid determines its density. As bulkiness increase, density tends to decrease [18].

1.3.3. Thermal stability

Solvents that were used in the synthesis must be thermally stable at any temperature of the working. Ionic liquids have good stability compared to organic solvents, and found to be stable at or above 400 °C. Anion in ionic liquid responsible greatly for thermal stability of liquids when compared to cations. Thermal stability of ionic liquids may decrease with anion hydrophilicity [19].

1.3.4. Viscosity

The viscosity of ionic liquid should be intermediate when compared with viscosity of organic solvents, that mean neither low viscous nor high viscous that make ionic liquid difficult to handle or hard to mix with the substances that were used at starting of synthesis [20].

1.3.5. Volatility

The main problem that present in organic solvent is volatility, that make them reduplicate the process which can be prevented by using of ionic liquids, because most of these liquids are non-volatile, the process repeatability is low [21].

1.4. Purity ionic liquids

The presence of impurities in the ionic liquids cause changes in the physical and chemical properties of these liquids, so the ionic liquids purification is necessary. The most pollutants of ionic liquids are halides or organic and water based substrates, that usually produced from unreacted materials (ionic liquid precursors that remain unchanged to the end). Ionic liquids have ability to absorb moisture, so hydrophobic ionic liquids are moisture-absorbing. Generally, drying of ionic liquids were performed by heating under vacuum, but it is difficult to remove water completely because of hydrogen bonding). Reducing the density and modulating the chemical properties of ionic liquids in presence of water [22,23].

1.5. Preparations of conventional ionic liquid

The pyridinium and methylimidazolium ions considered as good starting step to develop of ILs. The common ILs precursor structure based on alkyl imidazolium and pyridinium ions. Preparation of conventional ILs by use of N-alkylimidazole has been made by the reaction of 1-methylimidazole with butyl chloride in the presence of acetonitrile as catalyst usually was applied towards the end of the last century [24].

1.6. Preparation of protic ionic liquid

Researchers reported alternative procedure to manufacture ILs through acidic reactions by using protonator such as strong acids. Due to high proton activity of strong acid, they become as alternative method to metathesis reaction, such as sulfuric acid that utilized for reactions including N-alkylimidazoles [25].

1.7. Cation and anions of ionic liquids

The cation of ionic liquid composited of an organic structure with positive charge. The most utilized cations in ionic liquids are nitrogen or phosphorous containing organic ions. The presence of cation in ionic liquid usually influence the physical and chemical properties of them. Anion of ionic liquid consists of negatively charged weakly basic compound, which may be an organic or inorganic. The common anions of ionic liquids are nitrate, acetate, borate or sulphate ions [26]. Some examples of cation and anion present in ionic liquids are given in (Table 1).

2. Applications of ionic liquids in drug delivery

2.1. Ionic liquid as solvents of active pharmaceutical ingredients (APIs)

Active pharmaceutical ingredients (APIs) that are poorly soluble in aqueous media usually solubilized in organic liquids such as ethanol or dimethyl sulfoxide) during pharmaceutical preparation [27]. ILs was investigated as promising solvents, co-solvents, in addition to their use as surfactant can improve the solubility of active ingredients, utilizing of ionic liquid as substitutional liquids were firstly performed by Jaitely et al., 2008 [28], using ionic liquid based on imidazolium for solubilizing dexamethasone and progesterone. Then various studies determined the improvement of solubility by different orders of extent for analgesic, antifungal and chemotherapeutic drugs by utilizing ionic liquid and comparing to their water solubility [29]. Careful selection of ionic liquid cations and anions has confirmed to instruct the solubilization mechanism of active ingredient with poor aqueous solubility and ionic liquid solvation mechanism. Hydrophilic–lipophilic balance between the components of ionic liquid encourages the formation of systems and solubilizing agents to enhance the water solubility of active ingredients of various

Table 1. Examples of cations and anions used in ionic liquid.

Cations	Anions
N, N-dialkylimidazolium	Acetate
Alkylphosphonium	Hexafluorphosphate
Alkylammonium	Tetrafluroborate
Pyrazolium	Methylsulfate
Thiazolium	Hexafluroantimonate
Triazolium	Chloride, bromide and iodide
N-alkylpyridium	Nitrate

pharmacological classes [30]. Moira M et al., 2020 prepare Ionic-Liquid-in-Water nanoemulsions toward systemic delivery of amphotericin B, amphotericin B (AmB) is an agent that poses a challenge for intravenous drug delivery due to its hydrophobicity and severe side effects that are attributed to the self-aggregation of AmB in aqueous solution, ionic-liquid-in-water nano emulsion drug delivery system that harnesses the unique properties of ionic liquids. The complex drug AmB serves as a model pharmaceutical agent to demonstrate the robustness of ionic-liquid-in-water nanoemulsions. High concentrations of AmB were solubilized in a new hydrophobic dicholinium-based ionic liquid. The absorption spectrum of AmB in an ionic liquid mixture and prepared nanoemulsion indicates AmB solubilization in the monomeric form. The hydrophobic ionic liquid exhibits high *in vivo* biocompatibility [31]. J C Riedl et al., 2022 develop a design of concentrated colloidal dispersions of iron oxide nanoparticles in ionic liquids, explain that the system under study consists of iron oxide nanoparticles (NPs) dispersed in ethylmethylimidazolium, the thermal stability of these nanoparticle dispersions is then analyzed on the short and long term up to 200 °C, ionic liquid-based colloidal dispersions of iron oxide NPs in an ionic liquid stable over years at room temperature can be obtained [32].

2.2. Liquid forms of APIs

Bioavailability and therapeutic efficacy of poorly-water soluble APIs represents problem, as result, the APIs may defeat in last stages of preparation or constitute side effects associated with their precipitation [33]. Furthermore, APIs in solid form may exhibit various bioavailability profiles correlated with incident of various polymorphs, which would comprise an issue when polymorph is inadequate, that mean highest toxicity is administrated [34]. So, active ingredients formation in liquid forms can be useful design to prevent such problems. Ionic liquid is inert and display a set of unique features, from which is possible to highlight, if properly designed, their high thermal and chemical stability and a strong solvation ability for a wide variety of compounds, also low volatility and tunable properties which can be adjusted by properly selecting the nature of hydrogen bonding pairs to display a wide liquid range, water −compatibility, non-flammability and biocompatibility or biodegradability [35]. The proper selection of cation−anion combinations in ILs enables the use of drugs as ion components, allowing for the conversion of solid active pharmaceutical ingredients into liquid forms (API-ILs). Thus, this strategy solves the problem of polymorphism and provides improved bioavailability, and ideally boosts therapeutic properties [36]. Moreover, in comparison with powder forms of APIs, the liquids exceed energy barrier concerned with the enthalpy of fusion, exhibiting good solubility in water and consequently good therapeutic activity [37]. Ionic liquid gives an indication that improvement the physical stability and enhancement drug solubility and permeability regarded as a promising application. Appropriate selection of the ILs constituents permits active pharmaceutical ingredient use as cations or anions, resulting in liquid state drugs (API-ILs). The first development of API-ILs was performed by stoimenovski et al., 2011 [38,39], with design of ranitidinium docusate ([Ran][Doc]), which enhanced API absorption and present as liquid at room temperature [40]. This invention opened the way for obtaining new forms of APIs with dual pharmacological activity [41,42]. These ionic liquids also can be produced by employing of the strategy of prodrug to one ion of API-IL, that mean including a compound with inert biological activity and undergoes conversion into active compound of API-IL either by enzyme or by introducing the free acid/base of the conjugate base/acid within the formulation of the salt [43].

2.3. Ionic liquid as permeation enhancers and microemulsion components

The improvement of permeation of APIs across the biological membranes can be obtained by combining permeation enhancers with APIs through APLs-IL design approach, this approach firstly developed by Megwa et al., 2000 [44], that combine anion of salicylate with cation of quaternary ammonium to enhance the permeability of the active ingredients across skin. Following this work, different studies accomplished to enhance salicylates permeability across biological membranes, recorded as novel salicylate-ILs and ionic liquid with of poly (ethylene glycol) derivatives [45]. The careful selection of biocompatible cations, like amino acids, has been also considered for this purpose [46]. The prolinium ethylester ibuprofenate (API-IL) showed permeation improvement of active ingredient approximately ten times through the skin of pig compared to its solubilized form in ethanol solution, without significant toxicity to fibroblast cells [47]. Furthermore, ionic liquid preparations were developed to present tunable lipophilic-hydrophilic character, that mean increasing the aqueous solubility and improving the permeability of active ingredient across the biological membranes, such ionic liquid designated as surface-

active ionic liquids (SAILs) have been regarded as modern drug carriers and the achievement of these liquids compared with traditional surfactants, with first exhibiting superior ability [48,49]. The membrane perturbation is depending on alkyl chain hydrophobicity that present in anion and cation of ionic liquid. After these elucidations, ILs were investigated concerning their ability for fluidizing the cell membranes; ionic liquid with hydrophobic characteristics like imidazolium based-IL cause destabilization of membranes and create channels across the biological membranes for transporting of API, while ionic liquid with hydrophilic characteristics lead to an opposite behavior [50]. So careful selection of the ionic liquid composition and therapeutic target result in enhancement transdermal delivery of different active pharmaceutical ingredients without disclosing the membrane impartiality with the IL hydrophobic/hydrophilic balance [51,52] Outright the probability of forming micelles using SAILs has been inspected to develop intravenous, topical and transdermal delivery [53,54]. In previous delivery route, microemulsion can be produced by ionic liquid. Microemulsions are colloidal dispersion of oil and water that stabilized by surfactant molecules [55]. Ionic liquids could be the promising substituent for oil, aqueous phase, and surfactant, enhancing the permeability of APIs across biological membranes [56]. *C. Wang* et al.2018 prepare ionic liquid-microemulsions for the transdermal delivery of dencichine. Two imidazaolium based ionic liquid were used in the study which are 1-hydroxyethyl-3-methylimidazolium chloride ([HOEIM]Cl) and 1-butyl-3-methylimidazolium dodecanesulfate ([BMIM]C12SO3) were combined with aqueous and surfactant phases respectively for enhancement of permeation across the skin. The nano-system was optimized depending on a pseudo-ternary phase diagram. The optimized formula consists of 50% water phase/[HOEIM]Cl mix (1:1), 20% Tween 80/[BMIM]C12SO3 mix (1:1) as surfactant, 10% propylene glycol as co-surfactant and 20% IPM as oil phase. Microemulsion characterizations are droplets sizes (47.7 ± 1.5 nm), pH (6.71 ± 0.04), zeta potential (−14.83 ± 3.64 mV) and viscosity (31 ± 4 mPa). In-vitro assay of skin permeation indicates better enhancement of ILs preparation on the topical delivery of dencichine, which was approximately 10-fold that of the drug aqueous solution. Moreover, in-vivo pharmacodynamics evaluation suggested better hemostatic activity of dencichine by the topical application of the vehicle [57]. So, the present study suggested that the ionic liquid microemulsion regarded as a promising nano-scale vehicle for the topical application of drug to obtain a desirable pharmacological activity effects.

3. Conclusion

Ionic liquids considered as competitive alternatives for using of organic solvents and surfactants to enhance active ingredient solubility for delivery of drugs. Enhanced solubility that obtained by utilizing of ionic liquid s are various demand of extent higher in comparison to those that produced in an aqueous medium, viable to special types of APIs. In spite of these favorable results, comprehensive studies concerning drug stability in ionic liquid medium, while processing their storage for long term, and the *in vivo* test of bioavailability for these preparations are still required. Moreover, other classes of ionic liquid must be inspected, especially considering ionic liquid with biocompatible properties, also the exceedingly inspected imidazolium-based. The set cation−anion blend of ionic liquid also permitted new drugs in liquid form to achieved with enhanced physical, chemical and biological properties such as preventing the polymorphism concerns and enhancing the solubility through overcome the enthalpy energetic barrier of melting, so enhancing bioavailability. Ionic liquid was developed to produce either single activity or double therapeutic response and enable an administration by various routes. Utilizing of ionic liquid as enhancer for permeability and as microemulsions components that act as oil, surfactant or water phase has increased topical and transdermal delivery of various classes of drugs, allowing good permeation across biological membranes. Studies deficiency on improvement of therapeutic action and unknown information about the pharmacokinetic and pharmacodynamics parameters of ionic liquid and IL-APIs after administration still prevents their envisaged commercial application.

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Conflict of interest

The authors declare no conflict of interest.

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