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A Comprehensive Review on Ionic Liquids for Solubilization of Nutraceuticals

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ABSTRACT

Ionic liquids (ILs) containing bioactive molecules have emerged as potential alternatives for solubility enhancement and ultimately enhances therapeutic efficiency. ILs are considered advantageous over conventional solvents in terms of availability, storage condition, and synthesis. The application of ILs, especially in pharmaceutical and nutraceutical delivery, has shown great promise. In the presented article, the present aspects of ILs on their toxicity profiles and properties are elaborated. Further, a foreseeable prospect for the use of ILs in nutraceutical and pharmaceutical applications is presented.

INTRODUCTION:

Nowadays, several new drug molecules are being developed their properties have been studied. Most of the drug molecule comply with various properties but fails to comply with the solubility, bioavailability & toxicity. The most important challenge for the pharmaceutical industry is to increase the solubility, bioavailability, and reduced toxicity of predicting drug molecules. This challenge has the force to develop the new formulation method, new solvents to increase the bioavailability. The volatile organic solvents which are used for various purpose have a very harmful effect on the environment. Too many wastes are being produced from the industry by using volatile organic solvents for synthesis and other manufacturing processes. It is very important to use environment-friendly and less toxic solvents which will increase synthesis conditions and also allow the green chemistry principles and also the waste should be minimized[1–4].

Liquid salt was the term used in the past century which was used to describe the salts which melt below 100ºC. Liquid salt become more popular due to its low melting point and was a similar term to ionic liquids [5]. Various drugs that are already marketed bear problems like poor solubility, speedy metabolism & excretion, less permeability from the body [6]. The poorly water-soluble drug is not absorbed properly when given orally & it has to be dissolved in gastrointestinal (GI) fluid. For this reason, other routes for drug delivery have to be used. Ionic liquids are seen to improve the absorption of the poorly water-soluble drug. Again one common method that can be used to enhance the absorption is pre-disposed the drug in lipid [7]. Ionic liquids find very much importance in topical drug delivery systems they can solubilize springily soluble drugs, enhance drug loading capacity and enhance interpenetration of topical drug delivery systems. The traditional emulsions are prepared by using hydrophilic & hydrophobic ILs which are very useful in delivering the drug. Successful incorporation of ILs in emulsion has been studied [8,9]. Transcutaneous immunization is a novel method alternative to vaccination to deliver the drug. The transcutaneous method has very advantages like it is a needle-free injection, avoids first-pass metabolism, improved patient compliance. This method can be very useful for poorly water-soluble drugs & protein by using ILs as solvents [10].

Ionic liquids (ILs) has become topic of interest for researchers and industry as well [11,12] as it has a wide range of application including green chemistry, electrochemistry, bio-technology, nano-technology, material separation due to their unparalleled physical and chemical properties[13,14]. Thermal stability, nonflammability, wide liquid phase range, low vapor pressure are amongst the major properties of ILs [12]. ILs are considered as "designer solvents" due to their flexibility in use [11,15,16].

Paul Walden was the pioneer to report the first IL ethyl ammonium nitrate back in 1914 and the melting point was found to be 12ºC [13,15,17,18]. ILs can be defined as compounds that are composed of ions and have a melting point of less than 100ºC [11,15]. Their low melting point is due to the asymmetry of at least one of the ions and weak intermolecular attraction. They are composed of organic cations and organic or inorganic anions. The organic cations are derivatives of pyridinium, cholinium, imidazolium, ammonium, phosphonium, pyrrolidinium, and morpholinium [16]. ILs are considered as a "green compound" that is used as an option to toxic, flammable, hazardous compounds &can bring down the use of volatile organic compounds (VOCs) [16,19]. ILs can be specifically designed according to the needs as the cation & anion have versatility in arrangement [19].

Classification of ILs is done in a different category according to different characterization as follow.

1. According to evolution:

ILs are broadly classified into 3 generations according to the properties.

a. First-generation ILs

These were composed of dialkyl imidazolium & alkyl pyridinium cation and metal halide anions. They were used as solvents. These ILs are water & air sensitive.

b. Second generation ILs

These ILs are stable to air & water. They were designed to perform specific tasks such as extraction, nanotechnology, biotechnology, etc.

c. Third generation ILs

They are used as an active pharmaceutical ingredient (API) by seeing their biocompatibility and toxicity [9,11,20,21].

2. According to use:

a. Room temperature ILs (RTILs)

They are liquid below 100ºC & are used as solvents [22,23].

b. Task-specific ILs (TSILs)

These are generally considered as second-generation ILs & are prepared for specific use [24,25].

c. Supported IL membranes (SILMs)

They are used as filters for the separation of gases generally CO_2 [26,27].

d. Polyionic liquids (PILs)

Polyionic liquids are the polymerization product of ionic liquid monomer repeating units [15,28,29].

3. According to the cation group present in ILs:

ILs can be divided into four categories

a. A dialkyl imidazolium cation

b. An N-alkyl pyridinium cation

c. An alkylammonium cation

d. A phosphonium cation [2,30].

4) According to synthesis and structure:

ILs are divided into four classes as follows:

a. Aprotic ionic liquids (APILs)

These are the ILs which contains organic molecular ion as cations. ILs of this form were obtained when Hurley and Weir mixed N-substituted alkyl and aryl pyridinium halides with different metal chlorides and nitrates [31].

b. Protic ionic liquids

These are produced by the simple transfer of a proton from Brønsted acid to Brønsted base. [30,32,33]. Protic ILs have a low melting point, high conductivity, and fluidity as compared to APILs. These are more cheaper and convenient to synthesize [2].

c. Inorganic ionic liquids

These are the ILs that are obtained in both aprotic and protic ILs form.

d. Solvate ionic liquids:

This class has to be uncontrived and needs to be distinguished as it contains multivalent cation salt. Molten salt hydrates were the first member of this class [31].

ILs offers a wide range characteristics application in healthcare especially in drug delivery (in drug dissolution, as permeation enhancers, as API), biosensing (in glucose sensing) [18]. Considering the drug delivery system many challenges have to face because of poor solubility of drug molecule which may lead to poor absorption and bioavailability [1]. To increase the solubility of drug various organic solvents are which has certain limitations to use due to their toxic effect and sometimes produces a large quantity of the waste product that has to be used. By considering these limitations of polar organic solvents it is highly desirable to use green solvents i.e. ILs [1,18]. Various strategies have been used to overcome the various problems drugs as a solid dispersion, crystal engineering, prodrugs, salt formation [1].

It is seen that the solubility of the drug also depends on the type of ILs used. If we look at the chemistry of ILs they are the molten salts and are present in a liquid state below 100ºC and contain bulky, asymmetric cations and anions which give more applications [21]. As the ILs are known as designer solvents the properties of ILs can be changed by changing the combination of cations and anions. By this changing of combinations the toxicity can also be reduced to a certain level using the biocompatible organic cations and inorganic anions [1].

Although there are many applications of ILs there is some difficulty as well regarding packaging, portability, leakage, and considering some specific properties like low diffusion coefficient and high viscosity, difficulties in product purification and recycling & high cost. To overcome the problem of fluidity particularly the use of nanoconfined ILs is desirable. ILs are confined into nanoporous matrices of definite shape and size according to the geometrical limitations [34–36].

ILs are issued as a very bright solvent for many uses but they should be biocompatible when used with biomolecules. ILs have come forward as a catalytic media also. By combining the biocatalyst and ionic liquids some different results are seen from the reactions like redox, esterification, hydrolysis in the presence of various enzymes [16,37]. The toxicity study of the ILs has been studied and seen that the toxicity can be reduced by changing the combination of cations and anions [4]. The ionic liquid which is most miscible can act as an enzyme deactivating agent at less water content. Environment-friendly solvents are being developed which mainly focus on ammonium-based ionic liquids e.g., the cholinium (N, N, N-tri-methyl hydroxyethyl ammonium, $[N_{1\ 1\ 1\ (2OH)}]^{+}$) family. This salt tends to be a biocompatible and less toxic solvent. For the first time when water and hydrophilic ionic liquids were mixed, it increases the enzymatic activity of lipase up to 50%[37]. For inorganic/organic compounds and natural polymers, the solvation power of ILs is high. ILs can act as solvent and reaction media as well [38].

If we consider a biomolecule i.e., a protein which is an essential molecule for living beings, it will be interesting to see the biocompatibility of ILs with protein. As protein has various biological properties, the production has to be boost rapidly & while production three-dimensional structure of the protein must be maintained as it is required for its functional activity. Protein-based drugs have shown very strong efficacy in curing disease. Various techniques have been used for the stabilization of protein like genetic modification, chemical modification, the addition of stabilizing agents, immobilization but those techniques do not avoid protein denaturation. The stability of protein can be maintained by lyophilization. Using various methods still, long-term stability is not obtained. ILs have come out as an alternative to organic solvents in various chemical reactions. ILs are good solvents for enzymatic reactions too. As ILs are liquid at room temperature it helps to stabilize the proteins for longer periods but still the thermal stability of protein depending upon the right choice of ILs used. Some properties of ILs like polarity, hydrogen bonding, hydrophobicity can alter the stability and activity of proteins[39,40]. Cyclic dipeptides (CDs) can act as an important biomolecule to evaluate protein folding properties. for the solid-like core of globular proteins, CDs have shown reasonable advantages. CDs have the backbone of six-membered diketopiperazine ring gives more advantages in thermodynamics of protein model compound & also in protein stability [41].

Due to high solubility in water ILs have the disadvantage that they can be toxic for the environment and biological product. These could act as a pollutant for wastewater. The increase in the alkyl chain of cations of ILs results in higher toxicities for the biological system. The toxicity of ILs can be decreased as the negatively charged atoms increases on the cation [42]. To evaluate the potential impact of ILs on the environment the complete life cycle of ILs should be considered i.e., from starting materials to their discharge in the environment. Various studies have been carried out to study the ILs ecotoxicity, biodegradability & bioaccumulation. Some standardized assays are conducted by the Organization of Economic Co-operation and Development (OECD) and the International Organization for Standardization (ISO) for assessment of biodegradability. The toxicity of ILs can be measured in biological models of the distinct level of complexity like bacteria, fungi, fish, plant, algae, and mammalian cell lines. To identify the (eco)toxicological effect of ILs on the environment along with the biological organism in silico models are also been developed [43].

Perfluorinated compounds (PFCs) have some different physicochemical properties & their utilization in the industry has increased rapidly due to their vast application like a lubricant, polymer, surfactants, insecticides, etc. PFCs have several applications like uranium enrichment, in separation method, as dielectric solvents. In biomedical PFCs find use in an *in-vivo* gas carrier in liquid ventilation. PFCs have expanded their use in ILs and have given rise to the Fluorinated Ionic Liquids (FILs). In FILs the fluorine chains are of varying length. The formation of small fluorinated groups in FILs can be controlled by fluorinated alkyl chains present in FILs which can help to adjust the fluorinated solutes. FILs have specific applications in reducing environmental toxicity and in biomedicals [44]. Like PFCs another class of compounds i.e. Perfluoroalkanoate Anions helps to reduce the toxicity when combined with choline-based ILs and this combination is very useful in the aqueous biphasic system (ABS). ABS comprises two aqueous phases which are formed by combining two different polymers, or a combination of salt & polymer, or combining two different salts. But now the ABS is formed by using ILs i.e., the combination of ILs & polymer, ILs & salts, and ILs + polymer + salts. The cholinium cations are combined with carboxylate anions like lactate, formate, benzoate to ABS which are nontoxic and biodegradable, specially designed system to which is used in separation and purification of biological product [45].

As the ILs have a wide range of applications so it's necessary to know the different properties of it. These properties may affect the stability, activity of the enzymes. Some physical and chemical properties are:

1) Density

It is the physical property of ionic liquids and is very necessary to know the density because generally, every application requires density knowledge. Density is generally reported at 20°

or 25° C [46]. The density of ILs is more than organic solvents which range from 0.9 to 1.7 g.cm^3.It is seen that ILs containing larger organic cations have lower density. Temperature, pressure, molecular mass, interactions between molecules are some factors that can affect the density of ILs [13].

2) Viscosity

ILs are more viscous than molecular solvents which can affect the diffusion of solutes. The viscosity of ILs at room temperature varies from <10 to >1000 cP. Viscosity is very necessary to analyze the efficacy of fluid as a solvent. The high viscosity of ILs sometimes become a disadvantage for some industrial process like pumping, stirring, mixing & mass transfer operations [44,46].

3) Melting point

Due to low melting point & low vapor pressure ILs are very good alternatives for organic solvents. Most of the ILs undergo variable rates of supercooling due to which it makes difficult to measure melting point. For RTILs the variation in melting point can occur because of H-bonding capability, charge distribution & symmetry. Factors affecting the melting point of ILs are molecular shape, rotational freedom, electrostatic interaction & symmetry [13,46].

4) Thermal stability

Thermal stability is reported by using thermal gravimetric analysis (TGA). Generally, the ILs which are used as solvents are stable at a high-temperature limit so while using it in the reactions it does not create any problem. The onset temperature at TGA is reported as the thermal stability of ILs & it is an easy to measure and reproducible method. Sometimes the decomposition occurs before the onset temperature therefore Isothermal gravimetric analysis is used to determine the thermal stability. It is seen that the ILs having higher onset temperature are more stable than ILs having lower onset temperature when evaluated under the same conditions [46].

5) Effect of cation and anion

Cations and anions are responsible for the stable and unstable formation of ILs & to determine stability along with different compounds. It is seen that anions are strongly polarizable and more hydrated than cations so, the anions are more effective than cations. The kosmotropic and chaotropic properties of the ions determine the interaction in the ILs [39].

6) Hydrophilicity & Hydrophobicity

The hydrophobicity can be determined by using the partition coefficient. In the case of enzymes, it is seen that the enzymes are shown more stability in hydrophobic ILs than in hydrophilic ILs because hydrophobic ILs are not capable of withdrawing water from the enzyme. As the hydrophobicity of ILs enhances the stability and function of the enzyme [39].

7) Hydrogen bond capacity

Cations and anions form a network in ILs due to the presence of hydrogen bonds. The hydrogen bonding capacity determines the nucleophilicity of ILs. The basicity of the ILs increases as the hydrogen bonding capacity increases. Enzyme activity and stability can be affected by hydrogen bond basicity and nucleophilicity. For C_n mim based ILs hydrogen bonding is not the main factor for interaction. In imidazolium-based ionic liquids, the interaction between cation and anion occurs due to which a network is formed and polar & non-polar regions are formed when a molecule is inserted in this network which forms an interaction between IL and molecule [32,39].

Synthesis of ILs

The ethyl ammonium nitrate was the first IL discovered in 1914 at room temperature which was synthesized by the addition of concentrated nitric acid with ethylamine [47].

The ionic liquids can be divided into two major groups.

1. Simple salts

It's made up of a cation and anion.

For example, ethyl ammonium nitrate is a simple salt.

2. Binary ionic liquid

The salt where equilibrium is concerned.

For example, aluminum chloride and 1,3- dialkyl imidazolium chlorides containing a variety of different ionic species. Their properties and melting point are depending upon the mole fractions of aluminum chloride and 1,3- dialkyl imidazolium chloride [48].

ILs can be synthesized into two steps [47,48]

1. By the formation of the desired cation

The desired cation can either be synthesized by an acid protonation of the amine or by amine quaternization reactions with an acid and heating the mixture with a haloalkane.

2. Anion exchange

To form ionic liquids based on Lewis's acid an anion exchange reaction can be performed by treatment of halide salts with Lewis's acid.

$AlCl_3$ is the most extensively studied and used Lewis's acid-based ionic liquids. Such salts involve simple mixing of the halide salt and Lewis's acid and form the ionic species more than one, depending on the ratio of quaternary halide salt.

Characterization of ILs

1. X-ray

X-ray diffraction technique is used to detect the geometry of a molecule. This technique relies on the elastic scattering of X- rays from the structures having long-range order. Then the X-rays are diffracted by the crystal since the wavelength of the X-rays is close to the interatomic space in the crystal [49].

2. Differential Scanning Calorimetry (DSC)

The DSC technique assesses whether the process is exothermic or endothermic. Differential scanning calorimetry detects the differences in melting point between mole fractions of the sample to determine the eutectic point [50].

3. Fourier Transform Infrared Spectroscopy (FTIR)

Molecules change the synthesis of ILs. With the FTIR spectroscopy, the functional group is analyzed. Structural changes, hydrogen bonding interactions are observed on the FTIR spectrum [51].

4. Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectroscopy accesses the electronic structure of molecules as well as their functional groups. The peaks in the NMR spectrum give information on hydrogen bonds. The number of peaks indicates the chemical environment of molecules [52].

5. Solubility

To study solubility an excess amount of drug added to each IL. It is stirred and allowed to reach an equilibrium condition at room temperature, then it is centrifuged after 24 hrs. When the saturation is reached, the solution is filtered using a suitable filter membrane to separate the undissolved solids from the liquid. The supernatant liquid containing the dissolved drug is taken in a small amount and dilute to get a value of absorbance. The concentration of the drug in the ionic liquid is determined by spectrophotometrically [53].

Application of ILs in nutraceuticals delivery

ILs are used for enhancing the therapeutic action of bioactive. ILs exhibit high potency for APIs to function as an alternative solvent, also incorporate bioactive into their formulation. The method contributes to enhanced solubility, stability as well as bioavailability of promising nutraceuticals. Its ability to increase solubility for various bioactive and to improve the pharmacokinetic indicate the importance of ILs used as alternatives to traditional solvents as well as other techniques in many drug delivery applications.

CONCLUSION:

ILs can be used as common solvents for the solubilization of potential nutraceuticals. ILs are also believed to play a key role in the nutraceutical's delivery. ILs also have a lot of uncertainty related to their toxicity and chemical inertness. However, for the broad application to be accepted, it is important to address a few more substantive research and the lack of characterization of any aspects of the effects of additives.

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