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Solubility enhancement of glibenclamide in choline–tryptophan ionic liquid: Preparation, characterization and mechanism of solubilization

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ABSTRACT

A new ionic liquid solvent was prepared from choline as a cation and tryptophan as the anion. The produced ionic liquid was characterized by NMR, UV and HPLC. The obtained solvent was shown to form in a ratio of 1:1 (choline: tryptophan). The produced solvent was shown to increase the solubility of the low water solubility drug glibenclamide. The mechanism of the observed solubility enhancing effect of the drug was investigated and it did not seem to be simply due to increase in the pH of the medium. The most likely mechanism of increase in the solubility of glibenclamide (Glib) is the formation of complex hydrogen bonds and π–π interaction of the aromatic rings.

1. Introduction

Ionic liquids (ILs) are salts composed of negative and positive ions and present as liquids at room temperature. Although any cation and anion might serve as components of ionic liquids most of the reported studies involved a bulky cation such as alkylpyridinium, tetraalkylammonium or tetraalkyl–phosphonium [1]. The most reported anions for ILs were based on sulfonates, hexafluorophosphates, and tetrafluoroborates [2]. In the last few years ILs were gaining increasing interests because of their peculiar properties and large potential uses. These include their use as solvents in much industrial process such as chemical synthesis, extraction, and chromatography and in chemical batteries [3]. Ionic liquids can exist with various ranges of properties such as viscosity (from low to highly viscous), polarity (low to high polarity), electrical conductivity (generally all have high conductivity), acidity and basicity (low to high) [4].

Although some recent studies have shown the favorable effects of ILs in the pharmaceutical fields, such as solubilizing agents, stabilizing agents and drug delivery modulators [5], their use in medical applications is still limited. The major reason behind that is believed to be concerns regarding their toxicity and biodegradability [6]. However, the toxicity issue might be overcome by choosing the cations and anions of the IL to be known as safe chemical (this is known as Generally Regarded Safe) [7].

A striking increase in the solubility of some drugs (compared to water) has been observed with the use of some ILs. In some cases 60 thousand times increase in solubility has been reported [8]. Drugs whose solubility was significantly improved by the use of ILs included acyclovir, albendazole and danzole [9].

Dissolution of a drug is a key step to its therapeutic effect; hence low water solubility of drugs affects their bioavailability and consequently their therapeutic efficacy [10]. Therefore, ILs might resolve the problem of many low water soluble drugs by working as excellent solvents [8].

In this paper we report on the preparation and characterization of an IL composed of choline as the cation component and the amino acid tryptophan as the anion component. Those ions were chosen so that if successful their use in human would be acceptable as their main components were generally regarded as safe [11]. Glib which is an antidiabetic drug and is known to be of low water solubility, was employed as a model drug in this study to test the solubilizing power of the prepared IL. Glib is a weak acidic drug ($pk_a = 5.5$) that is classified as a class II drug (low solubility, high permeability drugs), and has a molecular weight of 490 with a melting point of 173–175 °C [12–17].

Several approaches have been previously reported in attempts to improve the solubility of Glib, including in situ controlled crystallization [12], co-solvent solubilization [13], inclusion complexes with cyclodextrins [18] and raising of pH [19]. To the best of our knowledge there have been no reports on solubilizing Glib with the aid of ionic liquids.

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2. Experimental

2.1. Chemicals

HPLC Grade acetonitrile was obtained from Merck (Germany), choline hydroxide solution (45% w/w) from Acros (New Jersey/USA) and tryptophan (99% purity) were obtained from Fluka (Switzerland). Glib was obtained from Sharon bio-medicine (Mumbai/India).

2.2. Preparation and characterization of choline–tryptophan IL

A solution of choline hydroxide (45% w/w) was added to an equivalent molar amount of amino acid (with slight excess of amino acid) in accordance to the equation in Fig. 1, the byproduct, water was evaporated at 40–50 °C using vacuum rotary evaporator. To the residue, 90 ml of acetonitrile and 10 ml of methanol were added to precipitate any excess un-reacted amino acid, and it was stirred vigorously. The mixture was then filtered to remove excess un-reacted amino acid. Filtrate was evaporated using rotary evaporator to remove solvents. Then liquid product was dried under vacuum for 2 days at 80 °C.

2.3. Equipment

All UV measurements were made using a spectroscan 80D UV–Vis spectrophotometer, Biotech Engineering Management (UK). Conductivity measurements were carried out using WTW 315I (Germany) while pH measurements were carried out using Hanna/pH 211, (Germany) pH meter. Chromatographic analysis of Glib was carried out using Spectra System P4000 HPLC pump equipped with a Knauer PDA detector. The employed mobile phase consisted of 50% acetonitrile and 50% 25 mM phosphate buffer that was adjusted to pH 4.5 and the detection wavelength was set at 380 nm. The employed column was Ace C18 (100 mm × 4.6 mm × 3 μm). Nuclear magnetic resonance ^{1}H-NMR spectra was recorded on a Bruker AVANCE III-500 MHz spectrometer with TMS as internal standard.

2.4. Conductimetric, pH, UV measurements, NMR spectra, and titration curve of the IL

Solutions containing increasing concentrations of IL (in water) were prepared in the range (9.76×10^{-2} — 50% w/w). Conductivity and pH of each solution were measured along with UV scans in the range 200–400 nm. Samples of IL (100 mg) in 50 ml of distilled water were titrated with 0.1 M HCl that was previously standardized against sodium carbonate. The acid was added in increments of 0.5 ml until no obvious change in pH was observed for five successive additions. Proton NMR spectra were obtained for IL alone (50 mg in 1.0 ml deutorated DMSO), Glib alone (20 mg in 1.0 ml deutorated DMSO), mixture of Glib 20 mg and IL 50 mg (in 1.0 ml deutorated DMSO), and for solutions containing increasing concentrations (0.03–50% w/w) of IL in deutorated D_2O.

2.5. UV spectroscopic titration of IL with glib

Aliquot (900 μl) of 0.25 M solution of IL in water, was placed in a micro-volume UV quartz cell (both blank and sample cells). Increments of 10 μl of 0.018 M Glib solution (in 0.25 M solution of IL in distilled water) were added gradually to both of sample and reference cells. After each addition, the mixture was properly mixed (using a micro pipette) and scans recorded, after 3 min, in the range 200–500 nm.

2.6. Measurement of solubility of glib in IL

The solubility of Glib was measured in solutions containing increasing concentration of IL in water (0.1–50 g %) as well as in phosphate buffers (50 mM) having different pH values in the range 6–12. Excess amount of Glib was added to 1 ml of the relevant phosphate buffer, or IL solutions until no further material could be dissolved. Samples were placed on a shaker water bath (37 °C) for 48 h, centrifuged for 10 min, and 100 μl of the supernatant were transferred to a new sample vial and 900 μl of mobile phase were added in order to bring about ten times dilution of the sample. The diluted sample was injected onto HPLC where the method described by British pharmacopeia (2007) for determination of Glib was adopted. The method employed a mobile phase consisting of 50% of phosphate buffer and 50% acetonitrile at flow rate 1 ml/min and pH 4.5, with UV detection at 380 nm. A calibration curve was constructed using Glib solutions of increasing concentrations in the range (0.0625–0.500 mg/ml) and a linear equation with a correlation coefficient of 0.998 could be obtained. A typical linear equation, that was employed to determine the concentration of Glib in solubility samples, could be given by: $A = 1119.6\,X + 8.39$ where A is the peak area and X is the concentration in mg/ml).

3. Results and discussion

A yellowish viscous ionic liquid substance was obtained. The formation of IL between choline and tryptophan was evidenced through different techniques such as NMR, pH measurements UV and conductimetric measurements. NMR spectra of the obtained IL showed disappearance of the acidic proton of tryptophan at about 11.1 ppm (Fig. 2) as also reported previously [20] which indicate the formation of IL through ionic attraction between negative and positive charges of tryptophan and choline respectively. The obtained NMR spectrum for the IL (Fig. 2) showed a distinct singlet at 3.1 ppm that belongs to the 9 methyl protons of choline and five separate signals in the aromatic region 6.8–7.6 ppm (two triplets, one singlet and two doublets) which essentially belong to the five aromatic protons of tryptophan. Since the ratio of the peak integration for the methyl singlet to any individual signal in the aromatic proton region was 9:1; it could be concluded that the stoichiometry of the formed ionic liquid was 1:1.

A HPLC method was developed in order to enable measurement of the IL in aqueous phase and consequent determination of partition coefficient. Calibration curve was constructed by plotting peak area against concentration in the range 0.08–20 g %. However, the resulting calibration plot showed two linear phases with the initial phase (at low concentration range; 0.08–1.5 g %) having a slope almost zero. At higher concentration range (2.5–20 g %) the relationship was linear and could be expressed by the equation: $A = 164\,X + 4.0$, where A is the peak area of the IL and X is its concentration (g %).

The intersection point between the two phases correspond to ~1.7 g %, which suggests that the ionic liquid exits as an ion pair at concentrations higher than 1.7 g % but dissociates to individual ions at concentrations less than that. However, the linear part (in the range 2.5–20 g %) was employed to calculate the concentration of the IL in

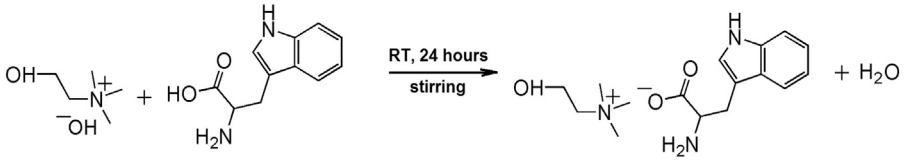

Fig. 1. Reaction equation for choline–tryptophan ionic liquid.