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Ketoconazole ionic liquids with citric and tartaric acid: Synthesis, characterization and solubility study

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ABSTRACT

Solid forms of drugs have some potential problems such as low solubility, slow dissolution rate, variable bioavailability and polymorphism. One of the strategies to overcome these problems is the preparation of ionic liquid forms of drugs. Recently, active pharmaceutical ingredient (API) was employed to produce an ionic liquid, using a counter-ion. Ketoconazole (KTZ) (synthetic imidazole antifungal drug), which is a practically insoluble drug, citric acid (CA), and tartaric acid (TA) were chosen as counter-ions for preparing the ionic liquid. Different molar ratios (1:1, 1:2.5, 1:5) of KTZ–CA and KTZ–TA were prepared applying solvent evaporation method with methanol as the solvent. The viscosity and the solubility in phosphate buffer (0.1 M) (pH = 6.8 at 37 °C of KTZ–CA and KTZ–CA) were measured. More than three unit differences between pK_a of KTZ and the studied carboxylic acids, characterization by different instrumental analysis methods, and previous studies on imidazole ring and carboxylic acid confirm the formation of ionic hydrogen bond between the imidazole functional group of KTZ and the carboxyl group of CA and TA. The findings of this study indicated that as molar ratio of CA and TA increases, the apparent solubility of the IL improves, while the solubility of the physical mixtures has a minor difference with non-processed KTZ. These results could be utilized in overcoming the disadvantages of KTZ solid form and increasing its solubility.

1. Introduction

Solubility is an important physicochemical property of pharmaceutical compounds [1] and it is considered in different stages of drug discovery and development [2]. Recently, this physicochemical property has been taken into consideration more because of the discovery and development of lead compounds with high molecular weight (lipophilic compounds) in high throughput screening process [3]. Different strategies have been developed to enhance the solubility of poorly water-soluble compounds [4]. Salt formation is a classic and the most preferred approach to improve the solubility of ionizable drugs [5]. A three-unit difference between pK_a of base and acid is required for salt formation of ionizable compounds [6]. Lately, using ionic liquids for solubilization of medicines has been regarded as a more interesting issue in pharmaceutical sciences [7]. Ionic liquids, which are salts in the liquid state, were also considered as a new approach to increase drug's solubility [8]. Mizuuchi et al. utilized imidazolic ionic liquids as potential pharmaceutical solvents to dissolve poorly soluble compounds, i.e. albendazole, danazol, acetaminophen, and caffeine [9]. Choosing a counter-ion to produce an ionic liquid from a given active pharmaceutical ingredient (API) was considered in the literature [10–12]. Over the past two years, preparation of API-based ionic liquids has developed, which is a plan to the liquefaction of drugs [13]. Araujo et al. applied choline with pharmaceutically active anions (the drugs with carboxylate functional groups, i.e. niflumic acid). They reported that these ionic liquid forms improve the aqueous solubility [14]. Different applications of API in drug delivery were reviewed by Rogers et al. [15]. The advantage of ionic liquid-based strategy is making a liquid salt form to overcome the polymorphism of API which is a common problem of the solid state [16].

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Ketoconazole (KTZ) (Table 1) is a synthetic imidazole antifungal drug which is formulated in tablet, topical, and vaginal forms. Currently, anti-diabetic and anti-cancer activities of KTZ were reported in the literature [17,18]. KTZ is categorized in Class II (low solubility and high permeability) of biopharmaceutics classification system (BCS) [19]. An erratic absorption and bioavailability for KTZ are observed due to its high dependence of solubility on pH of dissolution media [20]. It is sparingly soluble in acidic condition of stomach (pH = 1), while it is practically insoluble in intestinal pH (pH = 7) [21]. Different solubilization strategies have been exercised to enhance its solubility and dissolution, i.e. cosolvency [22], solid dispersion [23], nanoparticle formation [24], usage of beta-cyclodextrin [25], ion-exchange fibers [26], cocrystal formation with 4-amino benzoic acid [21], fumaric, succinic, and adipic acids [27], and salt formation with oxalic acid [27]. It is a basic drug with two pK_as: 2.9 (piperazine ring) and 6.5 (imidazole ring) [28]. Its salt formation is due to the proton transfer between imidazole ring and oxalic acid, and it is also involved in hydrogen bond and cocrystal formation with carboxylic acid of different acidic co-formers [27].

In our recently published paper [21], we intended to synthesize the cocrystal or salts of KTZ with citric acid (CA) and tartaric acid (TA). Surprisingly, an ionic liquid was achieved instead of the expected cocrystal or salts. Therefore, ionic liquids of KTZ with TA and CA in different molar ratios were synthesized, using solvent evaporation method. They were characterized with Fourier transform infrared spectrophotometer (FT-IR) in order to find the intermolecular interactions between KTZ and carboxylic acids. The solubility of synthesized ionic liquids in different molar ratios was investigated in phosphate buffer solution (pH 6.8) at 37 °C, and the results were compared with the solubility of KTZ and physical mixtures of KTZ powder with CA and TA.

2. Methods and materials

2.1. Materials

KTZ from Arasto Pharmaceutical Chemicals Inc. (Tehran, Iran), methanol (99%) from Scharlau Chemie (Barcelona, Spain), hydrate CA, TA, sodium hydroxide, sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid from Merck (Darmstadt, Germany) were purchased. All the materials were analytical grade and used without further purification. Distilled water was used for the preparation and dilution of the solutions.

2.2. Synthesis and characterization of KTZ–CA and KTZ–TA

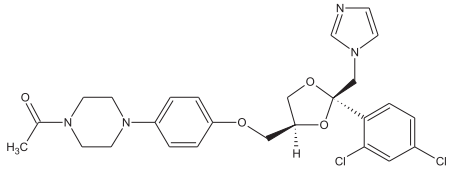
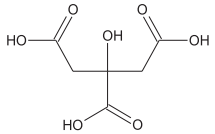
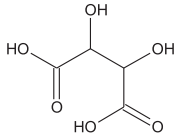
Solvent evaporation method was selected to prepare binary mixtures of KTZ with CA and TA (KTZ–CA and KTZ–TA). Different molar ratios of 1:1, 1:2.5, and 1:5 of KTZ–CA and KTZ–TA were added to 20 mL of absolute methanol (common solvent for KTZ, CA, and TA) separately and were dissolved by sonication for 30 min, and then the obtained clear solutions were left at 40 °C for 96 h for solvent evaporation.

The thermal properties of KTZ, CA, and TA (crystalline solid) were investigated, using differential scanning calorimetry (DSC) (PerkinElmer, USA) from (30–200 °C), and KTZ–CA and KTZ–TA (liquid form) were assessed from (−50 to 200 °C). The samples were studied by FT-IR (Bruker, USA) to evaluate the potential interactions between the studied compounds. For solid samples, a homogenous mixture was prepared in KBr; afterwards, the powder was gently pressed under vacuum conditions with a compression force flat face punch (for 30 s) to produce the KBr pellet. NaCl aperture plate and sandwiching it under another aperture plate were used to get FT-IR spectrum of liquid samples. In addition, ionic liquid formation (ionization carboxylic acids) was checked by ^{1}HNMR-400 MHz (Bruker, USA). Viscosity measurements were performed by means of a cone and plate viscometer (HAAK, Germany) at room temperature. Various shear rate moduluses or n (0.1, 0.2, 0.4, 0.8, 1, 2, and 4) were applied to test samples, and stress coefficients or s were read throughout the instrument panel. Shear rate is directly proportional to shearing stress and its slope is the viscosity of fluid. Table 2 list a summary of chemicals and synthesized ionic liquids in this study.

2.3. Solubility measurement of KTZ–CA and KTZ–TA in different molar ratios at pH 6.8

Solubility of KTZ, different molar ratios (1:1, 1:2.5, 1:5) of KTZ–CA and KTZ–TA, and their physical mixture were measured in phosphate solution at pH 6.8 (0.1 M) and 37 °C for simulation of intestinal fluid, since KTZ exhibits limited solubility under basic conditions. To determine the apparent solubility, 100 mg equivalent of KTZ was determined from each molar ratio of synthesized compounds. For the physical mixture, 100 mg of KTZ and equivalent

Table 1
Structure of KTZ, CA, TA and corresponding pK_a.

Compounds	Structure	pK_a
Ketoconazole (KTZ)		2.9 (piperazine ring), 6.5 (imidazole ring)
Citric acid (CA)		3.13, 4.76, 6.40
Tartaric acid (TA)		2.98, 4.34