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Physicochemical evaluation and *in vitro* release studies on itraconazolium sulfate salt

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ABSTRACT

To counter the poor aqueous solubility of itraconazole (ITC), its sulfate salt (ITCSUL) was synthesized and characterized by ^{1}H NMR, MS, FTIR, DSC, XRPD, DLS and SEM. Antifungal properties of ITCSUL were confirmed against different fungal pathogens by broth microdilution method. Enhanced solubility of the salt in various pharmaceutical solvents was observed. Approximately 5.5 fold increase in percentage drug release from ITCSUL than that of ITC in 3 h was observed. Further, the physical mixtures of ITCSUL with two cyclodextrins; β-cyclodextrin (β-CD) and HP-β-cyclodextrin (HP-β-CD) were prepared in 3 M ratios. The *in vitro* release studies of CD mixtures of ITC and ITCSUL exhibited markedly enhanced dissolution in comparison to ITC and ITCSUL respectively. The promising *in vitro* performance of ITCSUL and ITCSUL CD mixtures along with advantage of expedient preparation suggest their potential applications in designing a better oral drug delivery system.

1. Introduction

Among the routes of administration, oral drug delivery remains the preferred route since antiquity due to its simplicity and patient compliance. However, some drugs with poor aqueous solubility especially those of BCS Class II cause biopharmaceutical and pharmacokinetic hurdles in developing successful oral drug delivery of these drugs [1]. It has been reported that approximately 45% of the top 200 oral drug products from the US, Britain, Spain and Japan are poorly water soluble [2]. This emphasizes the requirement of new water soluble active pharmaceutical ingredients and better formulation strategies for existing drug molecules.

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Itraconazole (ITC) is a broad spectrum antifungal agent used in the treatment of infections caused by a variety of pathogenic fungi. It possesses better safety profile than other triazole counterparts like fluconazole, ravuconazole and posconazole [3,4]. Therefore, ITC is indicated for the treatment of fungal infections like blastomycosis, histoplasmosis, including chronic cavitary pulmonary disease and disseminated non-meningeal histoplasmosis, aspergillosis (pulmonary and extrapulmonary) in both immunocompromised and nonimmunocompromised patients [5–7]. Moreover, itraconazole is known to be less nephrotoxic than Amphotericin B, therefore it could also be indicated in patients who are intolerant to or refractory to Amphotericin B therapy [8].

However, ITC being a BCS Class II drug possesses a poor aqueous solubility which results in its inadequate and variable absorption which in turn results in erratic bioavailability [9,10]. Owing to its safety profile and broad spectrum antifungal efficacy, there is a strong need to counteract the drawback of poor solubility of ITC to render this valuable molecule more utilizable especially through oral route.

The attempts in recent years to enhance the solubility and the dissolution profile of ITC include solid dispersion method [11], micro- and nanoparticulate systems [12] and emulsified systems [13]. However, these techniques mostly require dedicated plant facility and in addition are also less favored due to higher cost factors associated with their raw materials and equipment. In addition, the manufacture of commercial ITC capsules involves use of toxic solvents and several tedious unit operations [14].

Salt formation, alternatively, is a convenient and inexpensive technique which can be used to tune the physicochemical properties like aqueous solubility and hence bioavailability of an ionizable drug due to polar character imparted by the counter anions. A recent report describes dihydrochloride salt of itraconazole, which provided better solubility and dissolution performance than the free base drug itself [15]. However, this salt is not expected to work accordingly in *in vivo* conditions due to chloride common ion effect as explained by Miyazaki et al. [16]. This prompted us to investigate the prospect of sulfate salt of ITC. The salt was prepared by a convenient addition reaction of itraconazole and sulfuric acid. The characterization was performed using different spectral and thermal techniques. The salt was tested for any loss in antifungal efficacy against four fungal pathogens. Also, the dissolution performance of the salt by preparing its physical mixtures with two cyclodextrins namely, beta-cyclodextrin (β-CD) and hydroxypropyl-beta-cyclodextrin (HP-β-CD) was studied.

2. Materials and methods

2.1. Materials

2.1.1. Chemicals and reagents

ITC was provided as a gift sample by Nosch Labs Pvt Ltd, Hyderabad, India. Commercial ITC capsules (Candistat®, 100 mg/capsule, Merck India Ltd.) were procured from local market.

2.1.2. Organisms and culture media

Aspergillus fumigates, *Microsporum canis*, *Microsporum gypsum* and *Trichophyton rubrum* were procured form Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh.

2.1.3. Composition of media for A. fumigates (Czapek media)

Czapek concentrate was prepared by dissolving sodium nitrite (30 g), potassium chloride (5.0 g), magnesium sulfate heptahydrate (5.0 g) and ferrous sulfate heptahydrate (0.1 g) in up to 100 ml of distilled water. The prepared Czapek concentrate (10 ml) was dissolved in distilled water along with dipotassium hydrogen phosphate (1.0 g), yeast extract (5.0 g), sucrose (30.0 g) and agar (15.0 g) to provide Czapek media. The final volume of the media was adjusted to 1000 ml by adding appropriate quantity of distilled water.

2.1.4. Composition of media for M. canis, M. gypsum and T. rubrum (Sabouraud media)

Special peptone (10.0 g), dextrose (20.0 g) and agar (15.0 g) were dissolved in water added to make the volume to 1000 ml.

2.2. Methods

2.2.1. Synthesis of itraconazolium sulfate salt

The sulfate salt of ITC was synthesized by acid addition method already illustrated in our previous report [17]. Briefly, a solution of ITC (5 g, 7.09 mmol) in chloroform (20 ml) was refluxed with methanolic solution 50% (v/v) of sulfuric acid (7.09 mmol) for 15 min. Then the reaction mixture was washed with water using separating funnel and dried over anhydrous sodium sulfate followed by evaporation of chloroform under reduced pressure. The resulting pale white residue was dissolved in methanol and reprecipitated by addition of cold water. The precipitates were filtered and dried under vacuum.

2.2.2. Characterization of ITCSUL

The following analytical techniques were used for the characterization of the prepared salt:

2.2.2.1. *^{1}H NMR spectroscopy*. NMR spectra were recorded on 400 MHz Bruker FT-NMR spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Deuterated chloroform ($CDCl_3$) was used as a solvent [17].

2.2.2.2. *Fourier transform infrared spectroscopy (FTIR)*. FTIR absorption spectra were recorded using FTIR spectrometer (Perkin Elmer Co., Waltham, USA). KBr disks of the samples were prepared and scanning was performed over a range of 500–4000 cm^{-1} with a resolution of 4 cm^{-1}.

2.2.2.3. *Mass spectrometry (MS)*. Mass spectrograph was obtained by LCQ mass spectrometer (Finnigan MAT, UK) in Atmospheric Pressure Chemical Ionization (APCI) mode with an inner temperature of 200 °C. Samples were dissolved in methanol, filtered (0.45 μm), and analyzed in the range of