Original Research Paper

Physicochemical evaluation and in vitro release studies on itraconazolum sulfate salt

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To counter the poor aqueous solubility of itraconazole (ITC), its sulfate salt (ITCSUL) was synthesized and characterized by 1H NMR, MS, FTIR, DSC, XRPD, DLS and SEM. Antifungal properties of ITCSUL were confirmed against different fungal pathogens by broth micro-dilution 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.

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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 posaconazole [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 utilisable 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, β-cyclodextrin (β-CD) and hydroxypropyl-β-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 fumigatus, Microsporum canis, Microsporum gypseum 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. gypseum 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 itraconazolum 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. 1H 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 (CDCl3) 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
0–1000 m/z. Data interpretation was performed using X’Calibur software [17].

2.2.2.4. Differential scanning calorimetry (DSC). DSC analysis was performed using Mettler Toledo 821° DSC (Mettler Toledo, Switzerland) operating with STAR® software version Solaris 2.5.1 (Mettler Toledo, Switzerland). Temperature axis and cell constant were calibrated using indium. Samples were heated at 10 °C/min over the temperature range of 25–400 °C under dry nitrogen flow (80 ml/min) in pin-holed aluminum pans.

2.2.2.5. X-ray powder diffraction (XRPD). The XRPD patterns of ITC and ITCSUL were determined using X-ray diffractometer (PAAnalytical’s X’Pert Pro, Almelo, Netherlands) with CuKα radiation, voltage 40 kV, current 60 mA, scan range 3–50° 2θ and scan rate 4°/min.

2.2.2.6. Scanning electron microscopy (SEM). SEM was performed using a Jeol Scanning microscope (Jeol Inc., Japan) with a 15 kV accelerating voltage. The surfaces of samples for SEM were previously made electrically conductive in a sputtering apparatus (Jeol Fine Coat, ion sputter, JFC-1100, Japan) by evaporation of gold. Magnifications of ×1000 and ×5000 were used.

2.2.2.7. Hot stage microscopy (HSM). HSM was carried out using Zeiss Axioplan-2 microscope (Microptic, Netherlands) fitted with Linkam 44 hot stage THMS600 (Linkam Scientific Instruments, UK). Images were captured using attached Nikon, Eclipse 80i camera. The samples were mounted in air/silicone oil and heated from 25 to 375 °C.

2.2.2.8. Dynamic light scattering (DLS). The mean particle size and size distribution of ITC and ITCSUL powders were determined by dynamic light scattering in Mastersizer 2000S (Malvern Instruments Ltd., Worcester, UK). Dry samples of ITC and ITCSUL (3 g) were analyzed using single narrow analysis mode for a size range of 0.1–2000 μm.

2.2.3. Flow properties

The parameters governing flow properties of ITCSUL were calculated using US Pharmacopoeia (2007) methods. The bulk volume of the undisturbed powder when filled in a 50 ml graduated cylinder was measured and bulk density (BD) was calculated. Then the cylinder was tapped for around 500 times and final volume indicated tapped volume of the powder which provided tapped density (TD). Hausner’s ratio and compressibility index were calculated using Equations (1) and (2).

\[
\text{Hausners ratio} = \frac{\text{TD}}{\text{BD}}
\]

(1)

\[
\text{Compressibility index} = \frac{100(\text{TD} - \text{BD})}{\text{TD}}
\]

(2)

2.2.4. UV spectrophotometric method development

Various standards (2–25 μg/ml) were prepared from a 100 μg/ml stock solution of ITC and ITCSUL in simulated gastric fluid (SGF) without pepsin. These standards were subsequently used to prepare calibration curves of the drug and the salt at λmax 254 nm. The method was validated with respect to linearity, accuracy, and precision.

2.2.5. Solubility study

Solubility study was performed by method described by Yu et al., 1999 [18]. Briefly, an excess amount of each sample was added in 5 ml of solvent taken in a 25 ml conical flask and shaken horizontally in shaker bath at 37 ± 1 °C for 72 h. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analyzed spectrophotometrically.

2.2.6. Antifungal susceptibility test

Broth microdilution method has been suggested for the determination of minimum inhibitory concentration (MIC) of antifungal agents [19]. Filter sterilized stock solutions of ITC and ITCSUL were prepared in dimethyl sulfoxide. The wells of sterilized microplates were filled with sterile media 280 μl and 10 μl of inocula were added in each well and mixed thoroughly. Various strengths of filter sterilized solutions (10 μl) of ITC and ITCSUL were poured in the wells to make their final concentration of drug in 0.03125–16 μg/ml range. Microplates were incubated at 25 °C for 5 days. The MIC was defined as “the lowest concentration that produced prominent inhibition of visual growth”.

2.2.7. Preparation of cyclodextrin physical mixtures

The physical mixtures were prepared by screening together repetitively (until homogenous) 500 mg of ITC (or 569.5 mg of ITCSUL) with 804.3, 1608.5 and 2412.8 mg of HP-β-CD and 1092.3, 2184.7 and 3277 mg of HP-β-CD for preparing 1:1, 1:2 and 1:3 M ratios respectively. The 1:1, 1:2 and 1:3 physical mixtures of ITC with β-CD will be referred to as ITC-β1, ITC-β2 and ITC-β3 whereas those with HP-β-CD will be referred to as ITC-HP-β1, ITC-HP-β2 and ITC-HP-β3 respectively. Correspondingly the 1:1, 1:2 and 1:3 physical mixtures of ITCSUL with β-CD will be denoted as ITCSUL-β1, ITCSUL-β2 and ITCSUL-β3 whereas those with HP-β-CD will be designated ITCSUL-HP-β1, ITCSUL-HP-β2 and ITCSUL-HP-β3 respectively.

2.2.8. Dissolution testing

The USP paddle method was employed for the in vitro dissolution studies using 900 ml of enzymeless simulated gastric fluid (SGF) having pH 1.2 ± 0.02, maintained at 37 ± 1 °C and stirred at 100 rpm. The amount of ITC taken for the study was 100 mg whereas that for ITCSUL and the cyclodextrin mixtures of ITC and ITCSUL taken were 100 mg drug equivalent. At predetermined intervals, 5 ml of the samples were taken with replacements, filtered through a 0.45 μm membrane filters and spectrophotometrically analyzed at 254 nm. The study was carried out in triplicate.

The percent drug released (in 180 min) from ITC and ITCSUL were compared by means of two-way ANOVA followed by Tukey’s test using statistical software (GraphPad Prism 5). P < 0.001 was denoted for statistical significance.

In addition, the pharmacokinetic parameters like percentage drug dissolution in 10 min (DP10) and half-life of release (T50%) were used to evaluate improvement of dissolution rate of ITCSUL and ITCSUL CD physical mixtures as compared to ITC as well as marketed ITC capsules.

Also, dissolution efficiency (DE%) at 180 min was utilized to assess the enhancement in extent of dissolution. This is termed as the area under the dissolution curve up to a certain
time \( t \), expressed as a percentage of the curve at maximum dissolution (\( Y_{100} \)), over the same time period [20]. This is explained in the Equation (3).

\[
\text{DE\%} = \frac{\int_0^t Y \cdot dt}{Y_{100} \cdot t} \cdot 100
\]

(3)

where, \( Y \) = %age of dissolved drug, \( t \) = given time interval.

The dissolution profiles of ITCSUL as well as physical mixtures with CDs were compared against dissolution profile of commercial ITC capsule using the FDA approved model independent approach of similarity factor [21], which is expressed as the Equation (4).

\[
f_2 = 50 \cdot \log \left\{ 1 + \left( \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{-0.5} \right\} \cdot 100
\]

(4)

where, \( n \) = number of time points, \( R_i \) = dissolution value of the reference (prechange) batch at time \( t \), \( T_i \) = dissolution value of the test (postchange) batch at time \( t \).

3. Results and discussion

The salt was prepared with a reaction yield of 90%. The results of various spectral and thermal characterization techniques have been enlisted below. The proposed minimum energy ball and stick model structure of the drug salt has been shown in Fig. 1.

3.1. \(^1\)H NMR spectrum

The two peaks representing eight piperazine ring protons originally encountered from \( \delta \) 3.15—3.17 ppm and \( \delta \) 3.22—3.24 ppm in ITC spectra were shifted to \( \delta \) 3.22—3.25 ppm and \( \delta \) 3.35—3.38 ppm in case of ITCSUL. The downfield shift in \(^1\)H NMR observed for ITCSUL salt in comparison to ITC can be attributed to the deshielding effect caused due to salt formation at piperazine nitrogen atoms.

3.2. Mass spectrum

ITCSUL salt exhibits a molecular \((M^+ + 1)\) ion peak at 705.53 m/z corresponding to molecular weight of ITC confirming the integrity of the parent molecule after salt formation (Fig. 2).

3.3. FTIR spectrum

FTIR spectrum for ITCSUL showed the characteristic sulfate asymmetric \( \text{SO}_3 \) stretch band at 1121 cm\(^{-1}\), the peak which was not present in spectra of ITC base, affirming the incorporation of sulfate ions in ITC molecule (Fig. 3). The broad band at 3406 cm\(^{-1}\) may be associated to O—H stretch due to presence of traces of water molecules in ITCSUL.

Fig. 1 – Synthetic scheme of itraconazolium sulfate (equimolar amounts of ITC and sulfuric acid were taken).

Fig. 2 – Mass spectrum of ITCSUL.

Fig. 3 – FTIR spectra of: ITC (A) and ITCSUL (B).
3.4. **DSC thermogram**

DSC thermograms of ITC and ITCSUL are presented in Fig. 4. Characteristic sharp melting endotherm of ITC was observed at 170 °C, in agreement with the melting point of ITC. The decomposition exotherm initiated at 350 °C. On the other hand, DSC thermogram of ITCSUL depicted initial broad endotherm below 100 °C possibly due to presence of trace solvent. At 185 °C, glass transition was observed followed by a broad endotherm initiating from 238 to 312 °C and finally decomposition exotherm starting at 340 °C.

3.5. **X-ray diffractogram**

The X-ray diffractograms are shown in Fig. 5. The XRPD patterns for ITC exhibited sharp characteristic peaks which can be used as a fingerprint whereas ITCSUL showed a halo pattern indicating the amorphous nature of the salt.

3.6. **Scanning electron micrographs**

The scanning electron micrographs are presented in Fig. 6. The SEM images of ITC illustrated its acicular needles. On the other hand ITCSUL exhibited irregularly shaped particles distinctly smaller in size.

3.7. **Hot stage micrographs**

The results of hot stage microscopy are shown in Fig. 7. When viewed in polarized light, ITC produced sharp birefringence pattern depicting the crystalline nature of the sample. The ITC crystals started melting at a temperature of 172 °C and the melting was completed at 176 °C and decomposition was observed above 350 °C. However, ITCSUL showed no birefringence when viewed under polarized light further the loss of crystalline nature after salt formation. No sharp melting was observed and the decomposition was observed above 340 °C.

3.8. **Dynamic light scattering**

The DLS technique showed prominent reduction in particle size of the drug after salt formation (Fig. 8).

3.9. **Powder flow and compressibility parameters**

The powder flow and compressibility parameters are explained in Table 1. The mean values of bulk density and tapped density were increased for ITCSUL in comparison to ITC. Therefore, the ITCSUL salt sample exhibited heavier particles than ITC. Carr’s index and Hausner ratio have been widely used to estimate the flow properties of powders. A Hausner’s ratio value of less than 1.20 indicates good flow whereas above 1.5 indicates poor flow. Similarly Carr’s index value less than 15% indicates good flow and the value greater than 25% indicates poor flow. The Hausner’s ratio of ITC was 1.191 which increased to 1.745 for ITCSUL. Also, the value of compressibility index of ITCSUL was found to be more than twice the value of ITC. This reflects the poorer flow properties of the salt in comparison to ITC. However, flow characteristics of the salt were improved after ITCSUL-CD mixtures as demonstrated by their reduced Hausner’s ratio values of 1.63–1.24 and compressibility index values of 14.00–19.33.
3.10. Solubility study

The solubility study revealed remarkable increase in solubility of salt as compared to ITC (Fig. 9). The aqueous solubility of ITC which is reported to be 1 ng/ml [22] was enhanced to 23,000 times after ITCSUL salt formation. Also in comparison to free base, about 275 and 7 fold increase of solubility in ethanol and propylene glycol respectively were observed for ITCSUL.

3.11. Antifungal susceptibility study

Four common fungal strains causing infections in humans were used to determine susceptibility against ITCSUL. The MIC for ITC and ITCSUL exhibited no difference (MIC observed were 0.5, 0.25, 0.25 and 0.25, respectively for A. fumigates, T. rubrum, M. canis and M. gypsum), and hence no loss of antifungal efficacy of the drug against all four fungal strains studied. In addition to this, the broth microdilution study also

![Fig. 6](image1.png) SEM images of: ITC at 1000× magnification (A) and 5000× magnification (B); and ITCSUL at 1000× magnification (C) and 5000× magnification (D).

![Fig. 7](image2.png) The HSM images of: ITC depicting acicular crystal habit prior to melting (A), melting initiating at 172 °C (B), followed by decomposition above 350 °C (C). Hot stage micrographs of: ITCSUL revealing amorphous particles (D), and no sharp melting but decomposition above 340 °C (E).
elucidated the order of antifungal activity of ITCSUL which was found to have similar hierarchy of antifungal activity as ITC.

3.12. Dissolution study

The dissolution profiles of ITC, ITCSUL and respective CD mixtures in simulated gastric fluid are represented in Fig. 10. It was observed that only about 8.4% of drug was released from free base form in 3 h, whereas from ITCSUL salt form approximately 26.4% drug was released in the same time. Thus, more than 3 fold enhancements of dissolution from ITCSUL in comparison to ITC was achieved. It was found that physical mixtures of ITC with different ratios of and β-CD and HP-β-CD resulted in enhancement of drug release with a maximum of about 2 fold using ITC HP-β-CD (17.54%) in 1:3 M ratio.

The CD physical mixtures of ITCSUL exhibited noticeable enhancements. In case of ITCSUL with β-CD physical mixtures, 1:1, 1:2 and 1:3 M ratios provided around 44.7, 51.8 and 59.5% drug released in 3 h respectively. Whereas, the ITCSUL HP-β-CD in 1:1, 1:2 and 1:3 ratios exhibited approximately 53.6, 60.0 and 65.5% drug release in 3 h respectively.

Table 2 depicts the dissolution rate parameters for ITC, ITCSUL and their CD physical mixtures. Superior percent releases in 10 min were reported for both types of CD mixtures of ITCSUL as compared to ITC and its CD mixtures. From the commercial capsule, 16.25% drug was released in 10 min whereas, higher DP10 values using ITCSUL with β-CD physical mixtures (10.1–21.6% approximately) and ITCSUL with HP-β-CD physical mixtures (19.7–37.8% approximately) were achieved.

$T_{50\%}$ is considered as the factor, describing the dissolution rate of drug and it was observed that ITCSUL-β-3 and all molar ratios of ITCSUL with HP-β-CD physical mixtures showed lesser $T_{50\%}$ values of all CD physical mixtures of ITCSUL were markedly lesser than Candistat® suggesting instant release of drug from these physical mixtures, and slow release from Candistat®.

The DE% in 180 min was enhanced clearly for both ITCSUL and ITCSUL CD physical mixtures in comparison to ITC and ITC CD mixtures. The DE% value of ITC was only 5.11%, which was improved after physical mixtures were prepared with β-CD and HP-β-CD, and the maximum DE% was nearly 15% for ITC-β-CD-3. The three molar ratios, 1:1, 1:2 and 1:3 of ITCSUL with β-CD physical mixtures exhibited DE% of 38.00, 44.55 and 53.07 respectively. While, the values of DE% for ITCSUL with HP-β-CD physical mixtures in 1:1, 1:2 and 1:3 M ratios were 48.06, 54.51 and 60.25% respectively. Thus, the DE% values of ITCSUL with HP-β-CD physical mixtures were found to be manifold than that of plain ITCSUL (17.31%). Also, it was found that DE% of ITCSUL-HP-β-3 was higher than that of Candistat® (58.70%)

Two factor ANOVA was performed to assess the influence of two factors explicitly salt formation and increasing cyclodextrin content in physical mixtures on dissolution profile. The results of two factor ANOVA showed significant ($p < 0.001$) enhancement of percent drug dissolved in 3 h for the two factors studied.

<table>
<thead>
<tr>
<th>Table 1 – List of powder flow and compaction parameters (mean ± SD, n = 3).</th>
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<td><strong>Entries</strong></td>
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<tr>
<td>ITC</td>
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<tr>
<td>ITCSUL</td>
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<td>ITC-β-1</td>
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<td>ITC-β-2</td>
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<td>ITC-β-3</td>
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<td>ITC-HP-β-1</td>
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The similarity factor $f_2$ values of CD mixtures of ITCSUL were found to be better than ITC, ITC CD mixtures and ITCSUL inferring considerable sameness of dissolution profile of ITCSUL-$\beta$-3, ITCSUL-HP-$\beta$-1 and ITCSUL-HP-$\beta$-2 to that of commercial capsules.

According to modified Noyes Whitney equation, the rate of dissolution of a drug is directly proportional to available surface area for dissolution and solubility of the compound in dissolution medium. In our studies we observed substantial decrease in particle size of ITC after salt formation was described by DLS, optical microscopy and SEM images. Also, solubility studies indicated better solubility of ITCSUL than ITC free base in SGF. Thus, both parameters influencing the dissolution rate were improved due to salt formation.

In addition, changing a crystalline form to amorphous state is one of the most popular approaches to improve solubility and dissolution of poorly soluble drugs. The loss of crystalline nature of ITC after salt formation was illustrated by XRPD patterns, SEM images as well as thermal analytical techniques.

Also, the inclusion phenomenon of cyclodextrins on ITC-SUL in presence of an aqueous medium as explained by Tao et al. can be another major reason for this amplification in dissolution rate [15]. This effect was more prominent in case of physical mixtures of ITCSUL and HP-$\beta$-CD than in ITCSUL and $\beta$-CD which may be explained on the basis of better aqueous solubility of HP-$\beta$-CD as compared to $\beta$-CD.

4. Conclusion

Based on the present results, it could be concluded that preparation of ITCSUL requires a facile single step and economical process. The physicochemical properties were modified after salt formation without impeding the antifungal action of the drug against tested pathogenic fungal strains. The better solubility of ITCSUL than ITC in various pharmaceutical solvents, and the enhanced dissolution profiles of the salt as well as its CD physical mixtures in comparison to ITC (and its CD mixtures) emphasize the extensive investigation of the salt as a candidate for clinical use. As the itraconazole is a BCS Class II drug, its bioavailability is dissolution rate limited. Therefore, ITCSUL salt may provide excellent tools for designing variety of oral conventional as well as novel drug delivery systems.

4.1. Itraconazolium sulfate (ITCSUL)

Yield 90%; pale white solid; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.88–0.92 (t, 3H, CH$_3$, $J = 7.40$ Hz), 1.38–1.40 (d, 3H, CH$_3$, $J = 6.72$ Hz), 1.60–1.92 (m, 2H, CH$_2$), 3.22–3.25 (d, 4H,
piperazine CH₂, J = 9.96), 3.35–3.38 (d, 4H, piperazine CH₂, J = 10), 3.47–3.51 (m, 1H, CH), 3.78–3.83 (m, 2H, dioxolane CH₂), 3.90–3.94 (m, 1H, dioxolane CH), 4.25–4.39 (m, 2H, N—CH₂), 4.74–4.86 (m, 2H, O—CH₂), 6.79–6.81 (d, 2H, 2× Ar—H, J = 10.88 Hz), 6.93–6.95 (d, 2H, 2× Ar—H, J = 9.08 Hz), 7.03–7.05 (d, 2H, 2× Ar—H, J = 9.04 Hz), 7.41–7.43 (d, 2H, 2× Ar—H, J = 6.96 Hz), 7.47–7.48 (d, 1H, Ar—H, J = 6.76 Hz), 7.56–7.58 (d, 1H, Ar—H, J = 8.44 Hz), 7.61 (s, 1H, triazolone CH), 7.89 (s, 1H, triazole CH), 8.20 (s, 1H, triazole CH). MS (APCI): 705.53 (M+1). Anal. Calcd. for C₃₅H₄₂Cl₂N₂O₂S: C, 52.50; H, 5.02; N, 13.94; O, 15.93; S, 3.99. Found: C, 52.61; H, 4.93; N, 14.14; O, 16.10; S, 4.25.

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