



RESEARCH ARTICLE



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Studies on Solubility and Dissolution Enhancement of Itraconazole by Complexation with Sulfo-Butyl7 Ether β Cyclodextrin

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Abstract

Itraconazole is a potent triazole antifungal drug which has low solubility at physiological pH conditions. Itraconazole is weakly basic ($pK_a = 3.7$) and highly hydrophobic drug. It is categorized as a BCS class II drug. The main objective of the present investigation was to improve the solubility of itraconazole, by preparation of salt forms itraconazole mesylate and itraconazole besylate by using addition reaction with methane sulphonic acid and benzene sulphonic acid. Further inclusion complexes of itraconazole prepared with Captisol (sulfo-butyl ether β -cyclodextrin) by using physical mixing, kneading and co-evaporation techniques. The preparations characterization was performed by using X-ray diffraction, Fourier Transformed Infrared spectroscopy and Nuclear Magnetic Resonance spectroscopy. The solubility of prepared salt was found multifold than the solubility of itraconazole. The dissolution studies of itraconazole complexes exhibited high percentage drug dissolution than that of the pure drug which can be attributed to the increase in drug solubility provoked by the complexation technique. Among all complexes, products prepared by kneading method showed higher percentage drug release.

Keywords: Antifungal; Itraconazole; Sulfonates salt; Sulfo-butyl ether β Cyclodextrin; Solubility enhancement

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INTRODUCTION

Poorly water soluble drugs are posing a problem of satisfactory dissolution within the gastro intestinal tract and there by their oral bioavailability. The recent past has witnessed the modern techniques of drug discovery which lead to an increasing number of drug candidates with unfavorable solubility characteristics¹. Formulation of such compounds for oral delivery has been the most frequent and greatest challenge to scientists in the pharmaceutical industry. Major problem associated with poorly soluble drugs is lack of dissolution there by results in poor and/or variable bioavailability². Kaplan³ has suggested that the solubility of a drug more than 10mg/mL at a pH < 7 is expected to have no dissolution as well as bioavailability related problems but, this could be a problem for drugs whose solubility is below 1mg/mL. Dissolution rate less than 0.1mg/cm²/min were likely to give dissolution rate limited absorption. Solubility of a drug is an intrinsic property and it can only be altered by chemical modification of the molecule by salt formation⁴⁻⁶ or prodrug formation⁷. Dissolution is an extrinsic property which can be modified by various chemical, physical or crystallographic techniques like complexation, particle size reduction, surface or solid state properties. Different techniques have been reported in the literature for improvement of solubility and drug dissolution rates. These techniques are reduction of the particle size by micronisation or nanonisation to increase the surface area, use of surfactants, Cyclodextrin complexation, pro-drug formation, conversion of crystalline to amorphous forms⁸.

Pharmaceutical salts⁹ are important in the process of drug development for converting an acidic or basic drug into a salt by a simple neutralization reaction. Using different chemical species to neutralize the parent drug can produce a diverse series of compounds and this process is traditionally being used for modification of the physicochemical, processing, biopharmaceutical or therapeutic properties of drug substances. Each of the individual salts of a particular drug substance can be considered as a unique chemical entity with their own distinctive physicochemical and biopharmaceutical properties¹⁰⁻¹². It has been estimated that approximately half of all of the active pharmaceutical substances (API) that have been developed were ultimately progressed as pharmaceutically acceptable salts and that salt formation is an integral part of the development process^{13,14}. Sulfonic acid salts particularly alkyl sulfonates such as mesylates and besylates generally results in the formation of high melting point API salts with good solubility and stability¹⁵.

Cyclodextrins (CDs) are useful functional excipients that have enjoyed widespread attention and use. A

number of cyclodextrin-based products have reached the market based on their ability to change undesirable physicochemical properties of drugs^{16,17}. The formation of inclusion complexes provides numerous advantages in pharmaceutical formulation development β -CD were reported to increase bioavailability of poorly soluble drugs by increasing the drug solubility¹⁸. The family of CDs comprises of a series of cyclic oligosaccharides compounds. The three commonly used cyclodextrins are α - cyclodextrins comprised of six glucopyranose units, β - cyclodextrins comprised of seven units and γ -cyclodextrins comprised of eight such units¹⁹. Sulfobutyl ether β -Cyclodextrin (SBE₇- β -CD) [Captisol®]²⁰⁻²² is a chemically modified β -cyclodextrins that is a cyclic hydrophilic oligosaccharide which is negatively charged in aqueous media. The solubility in water for Captisol (70 g/100 ml at 25 °C) is significantly higher than the parent β -cyclodextrin (1.85 g/100 ml at 25 °C). It does not exhibit the nephrotoxicity and cytotoxicity which is generally associated with other β -CDs²³⁻²⁵. Some of the investigations also reported that the drug inclusion complex with SBE₇- β -CD provided a protective effect against drug-induced cytotoxicity²⁵. Based on these advantages, Captisol has been selected to study the effect of improving the physicochemical properties of poorly water-soluble drug itraconazole.

Itraconazole (ITR) is a broad-spectrum triazole antifungal agent with poor aqueous solubility²⁶. ITR is weakly basic with pKa of the piperazine ring is 3.7 and highly hydrophobic drug²⁷. Because of poor aqueous solubility itraconazole on oral administration results in poor bioavailability and inter individual variations in the plasma drug concentrations. ITR has the characteristic of pH dependent solubility having highest solubility at acidic side (4 μ g/ml) compared to basic pH (1 μ g/ml). However, because of highly lipophilic nature (log P= 6.2) it can easily penetrate into intestinal membrane. This indicates the poor aqueous solubility is the main reason for lower plasma concentrations. Various techniques⁸ have been reported for enhancing the solubility and bioavailability of itraconazole, but the salt formation^{13,14} and inclusion complexes¹⁸ showed some promising results. Keeping these in the view the present work has planned with an objective to synthesize Itraconazole mesylate and Itraconazole besylate salt forms from Itraconazole. Further these salt forms have studied for improvement of solubility and dissolution by preparing inclusion complexes with Sulfobutyl Ether β -Cyclodextrin (Captisol®) using physical mixing, kneading and co-evaporation techniques. These preparations are characterized by X-ray diffraction, Fourier Transformed Infrared spectroscopy, Nuclear Magnetic Resonance

spectroscopy and also evaluated for solubility, drug content and dissolution studies.

MATERIALS AND METHODS

Chemicals:

Itraconazole was a gift sample obtained from Pharmatech, Hyderabad, and Sulfolbutyl₇ Ether β -Cyclodextrin (Captisol®) (average molecular weight 2,163 and degree of substitution 6.5) was obtained from Cydex laboratories. Benzene sulfonic acid (A.R. grade) and Methane sulfonic acid (A.R. grade) were purchased from Merck. All other chemicals used in this study were of analytical grade.

Preparation of Itraconazole Salts:

Itraconazole mesylate (ITRM) and Itraconazole besylate (ITRB) salts were synthesized from itraconazole (ITR) by acid addition reaction using methane sulfonic acid and benzene sulfonic acid (Fig.1 & Fig.2). In case of ITRM preparation, accurately weighed about 1 gm of ITR (1.4 mmol) and was dissolved in about 10 ml of dichloromethane in a rotary evaporator flask. To this solution about 400 mg of methane sulfonic acid (4.16 mmol) was added and dissolved. The mixture was refluxed at 50°C for one hour. After one hour 700 mpa vacuum was applied while reaction. The reaction was continued for one hour to form a precipitate of salt. The mixture was allowed to stand overnight at room temperature. The precipitated product was collected, dried at 60°C for 1 hour and shifted through #100 mesh sieve. ITRB salt was prepared by following the similar procedure as mention above for ITRM salt by taking 1 gm of ITR (1.4 mmol) and 600 mg of benzene sulfonic acid (3.9 mmol). The final products were stored in an air tight container and then placed in desiccators.

Solubility Studies:

Solubility studies for pure ITR, ITRM and ITRB were carried in purified water and simulated gastric fluid (pH 1.2 - 0.1 N Hydrochloric Acid). In each case excess amount of sample was added to 10 ml of solvent and agitated at 37°C in a rotary test tube shaker for 24 hrs. After equilibration, the samples were filtered using 0.45 μ m Millipore filters, suitable diluted and analyzed for the content itraconazole by measuring the absorbance at 258 nm using Shimadzu UV-Visible spectrophotometer²⁸.

Phase Solubility Studies:

A phase solubility study²⁹⁻³³ was carried out to investigate the effect Captisol on the solubility of Itraconazole, Itraconazole mesylate and Itraconazole besylate using the method reported by Higuchi and Connors. Captisol was added and dissolved in simulated gastric fluid (pH 1.2-0.1N HCL) to obtain concentrations of 5, 10, 20, 40 and 80 mM. To each of these solutions excess amounts of Itraconazole, Itraconazole mesylate and Itraconazole besylate were added separately and were shaken using test tube

shaker at 25°C for 72 hr. After equilibrium, the solutions were filtered using 0.45 μ filters and diluted suitably to determine the concentration of Itraconazole, Itraconazole mesylate and Itraconazole besylate at 258 nm using UV-Visible spectrophotometer System. A graph was plotted between Itraconazole, Itraconazole mesylate and Itraconazole besylate concentrations (in mM) against the concentration of Captisol (in mM). The stability constant for the complex was determined from the graph using the following equation.

$$K_s = \frac{\text{slope}}{S_0(1 - \text{slope})}$$

Where slope was obtained from the graph and S_0 was the equilibrium solubility of itraconazole, Itraconazole mesylate and Itraconazole besylate in 0.1 N HCl.

Preparation of Inclusion Complexes:

The inclusion complexes of ITR, ITRM and ITRB with Captisol (1:2 and 1:3) were prepared by using physical mixing, kneading and co-evaporation technique³⁴. Physical mixture was prepared by simple mixing in a mortar with pestle for 10 min. The powders of ITR, ITRM, ITRB and Captisol of required molar ratios are simply mixed in mortar with pestle and then sieved through 100 #. Kneaded (KN) product was obtained by triturating equimolar quantities of ITR, ITRM, ITRB and Captisol of required molar ratios in a mortar with a small volume of solvent blend of water: methanol: dichloromethane at a volume ratio of 2:5:3. During this kneading process few drops of solvent were introduced to maintain a suitable consistency. The resulting mass was dried in an oven at 55 °C until they get dry and the solid was finally grounded and then sifted through #100 sieve. In co evaporation technique, aqueous solution of Captisol was added to the solution of ITR, ITRM and ITRB in a solvent blend of methanol: dichloromethane at a volume ratio of 2:3. The resultant mixture was stirred for 1 hr and evaporated at a temperature of 55 °C until dry. The dried mass was pulverized and sifted through #100 sieve.

Fourier Infra Red Spectroscopy (FTIR):

Fourier transform infrared spectroscopy (FTIR) spectra of ITR, ITRM, ITRB, Captisol, ITR-Captisol complexes, ITRM-Captisol complexes and ITRB-Captisol complexes were recorded using a Fourier Transform Infrared spectrophotometer (Perkin Elmer, Spectrum Two). The samples were scanned from 400–4000 cm^{-1} with a resolution of 4 cm^{-1} by using KBr pellet technique.

X-ray diffraction analysis:

Powder X-ray diffraction (XRD) patterns of ITR, ITRM, ITRB, Captisol, ITR-Captisol complexes, ITRM-Captisol complexes and ITRB-Captisol complexes were recorded on a PAN Analytical X'Pert powder X-ray diffractometer (X-Perto PRO) using Ni-filtered, Cu $K\alpha$ radiation, a voltage of 40 kV and 60 mA current. The

scanning rate was 4°/min over the diffraction angle range (2θ) of 3–50°.

NMR Spectroscopy:

The $^1\text{H-NMR}$ spectra of pure ITR, ITRM and ITRB were taken in DMSO on a Bruker Ultra shield 400 MHz nuclear magnetic resonance (NMR). Chemical shift values are interpreted for confirmation.

Drug Content Estimation:

Accurately weighed 50 mg of the sample and transferred in to a 50 ml volumetric flask. Then 25 ml of 50% methanol: 0.1N HCl mixture was added and shaken for 15 minutes to completely dissolve the drug. The volume is made up to 50 ml with 50% methanol: 0.1N HCl mixture. The resulted solution was filtered through 0.45 μm filter and suitable diluted and analyzed for the content itraconazole by measuring the absorbance at 258 nm using Shimadzu UV-Visible spectrophotometer. The drug content of all the

inclusion complexes was estimated by following the same method.

In-vitro dissolution studies:

In vitro dissolution studies³⁵ were carried out in 900 ml of simulated gastric fluid of pH 1.2 using USP Type-II (Paddle) dissolution test apparatus (M/s. Electro Lab India). Sample equivalent to 100 mg of ITR, a speed of 75 rpm and a temperature of 37 ± 0.5 °C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted whenever necessary and assayed for ITR by measuring absorbance at 258 nm. The dissolution studies were carried for the pure ITR and the prepared ITR salts inclusion complexes. Commercial ITR capsules Sporonax[®] was also evaluated for dissolution for comparison. All the dissolution experiments were conducted in triplicate and the mean values are reported.

RESULTS

Preparation of Itraconazole Salt Forms:

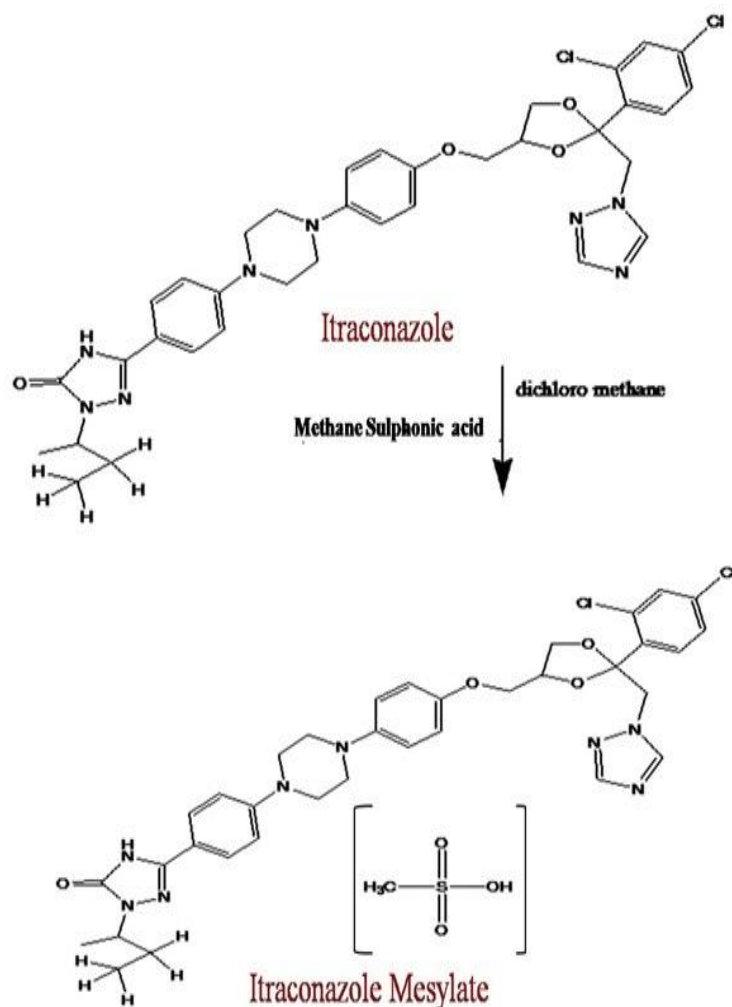


Fig.1. Synthesis of Itraconazole Mesylate from Itraconazole

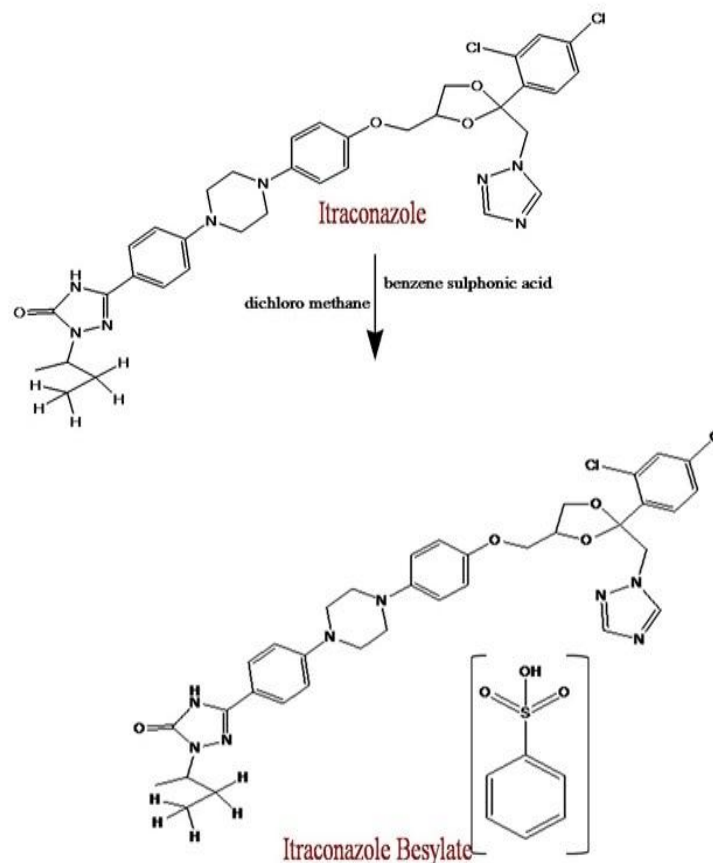


Fig.2. Synthesis of Itraconazole Besylate from Itraconazole.

Nuclear magnetic resonance spectroscopy (NMR):

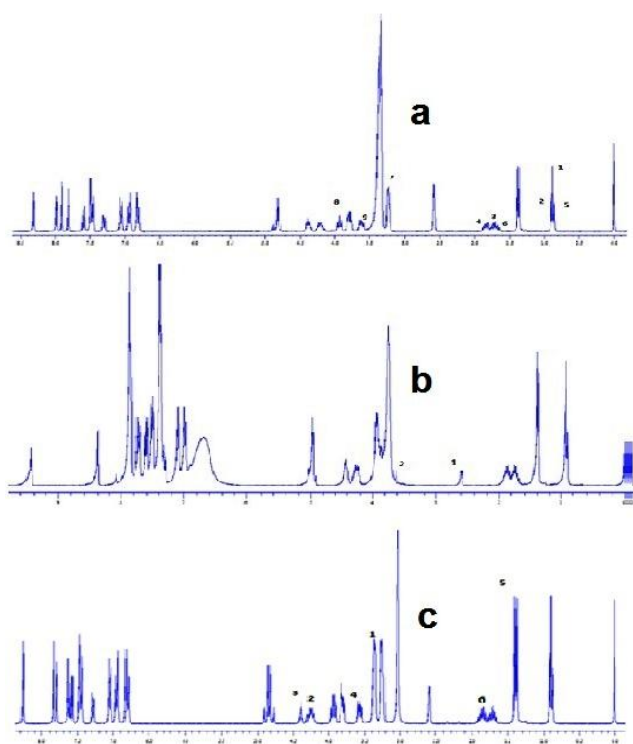


Fig.3. NMR Peaks of (a) Itraconazole (Pure API) (b) Itraconazole Besylate salt (c) Itraconazole Mesylate salt

Phase Solubility Studies:

S. No	Concentration of Captisol (mM)	Concentration of ITR (mM)	Concentration of ITR Mesylate(mM)	Concentration of ITR Besylate(mM)
1	0	6.912×10^{-5}	0.193	0.19
2	5	0.00312	0.386	0.616
3	10	0.00493	0.503	1.160
4	20	0.00884	0.734	2.537
5	40	0.0222	1.658	4.253
6	80	0.0552	3.080	7.810
Stability (k_s)	Constant	51.322 M⁻¹	213 M⁻¹	375 M⁻¹

mM – Milli molar
Table 1. Phase Solubility Data

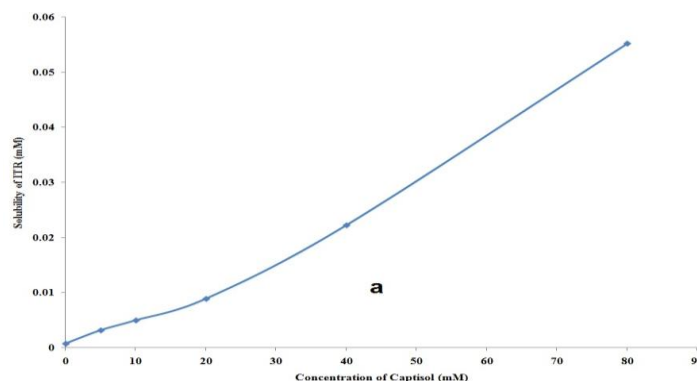


Fig.4a. Phase Solubility Graph of Itraconazole with SBE7Bcd

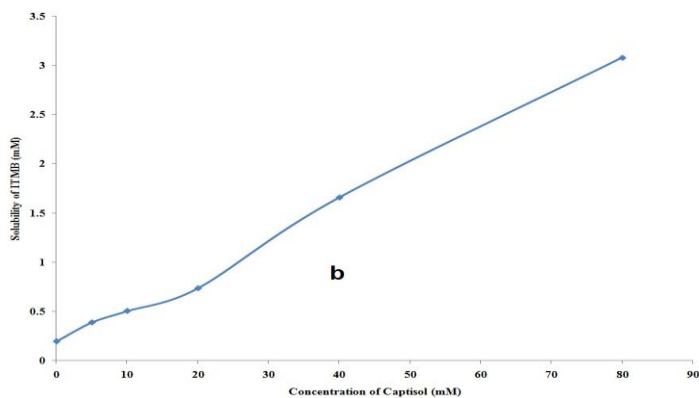


Fig.4b. Phase Solubility Graph of Itraconazole Mesylate with SBE7 β -CD

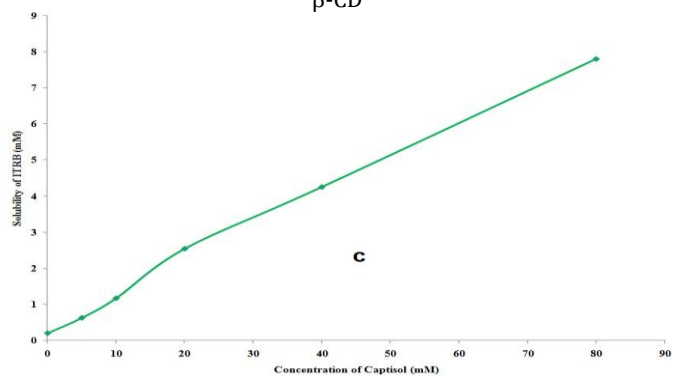


Fig.4c. Phase Solubility Graph of Itraconazole Besylate with SBE7 β -CD

Infra red spectroscopy (IR):

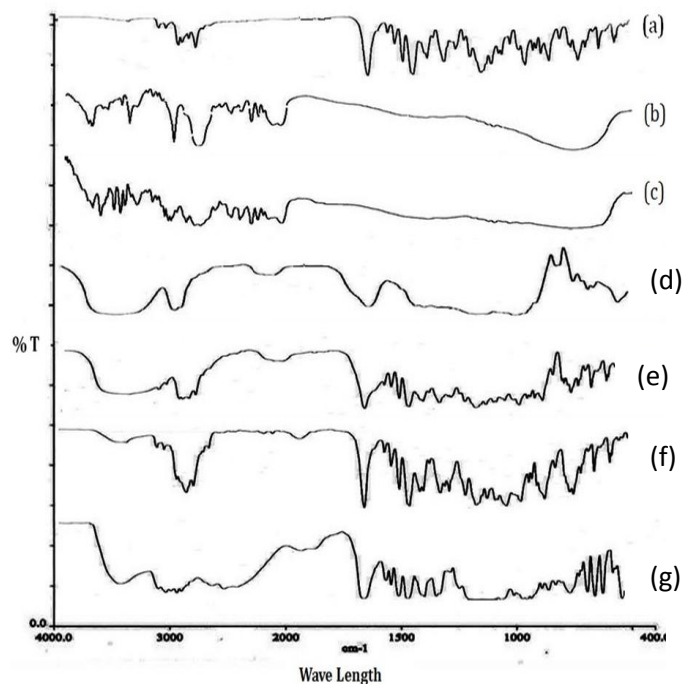


Fig.5. IR spectra of (a) ITR (Pure Drug) (b) ITRM (c) ITRB (d) Captisol (SBE7 β -CD) (e) ITR-C-KN (f) ITRM-C-KN (g) ITRB-C-KN

X-ray powder diffraction (XRD):

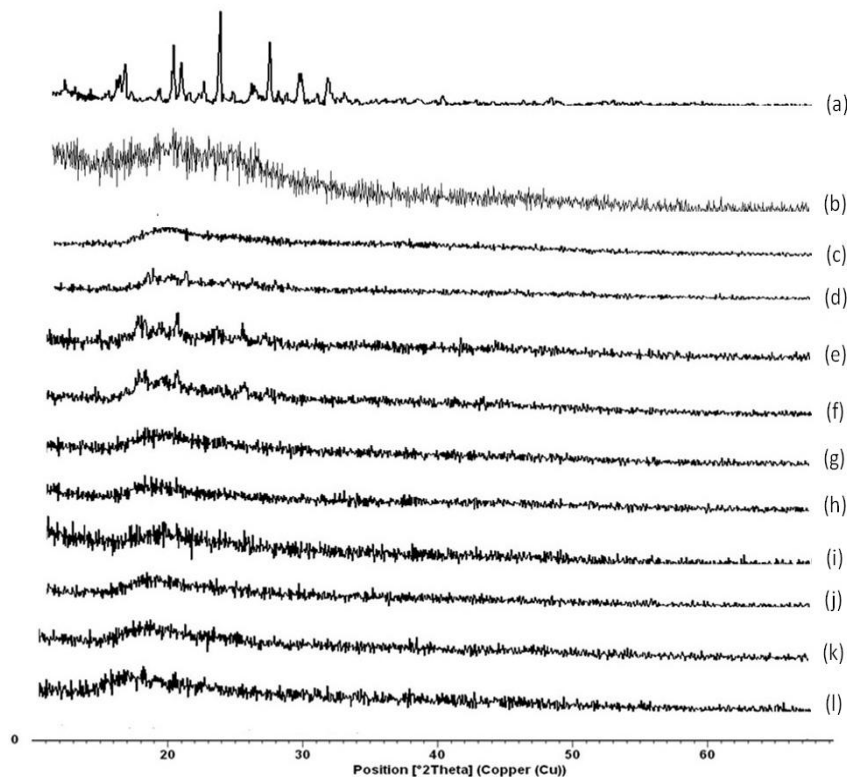


Fig.6. XRD Pattern of (a) ITR (Pure Drug) (b) ITRM (c) ITRB (d) Captisol (SBE7 β -CD) (e) ITR-C-PM (f) ITR-C-EV (g) ITR-C-KN (h) ITRM-C-PM (i) ITRM-C-EV (j) ITRM-C-KN (k) ITRB-C-PM (l) ITRB-C-EV (m) ITRB-C-KN

Drug content estimation:

Complexes	Method	Terminology	Drug content (% w/w)	
			1:2	1:3
Itraconazole + Captisol	Kneading	ITR-C-KN	97.23±0.12	87.23±0.17
	Co-Evaporation	ITR-C-EV	93.83±0.14	81.36±0.23
	Physical Mixture	ITR-C-PM	85.89±0.21	75.66±0.34
Itraconazole mesylate + Captisol	Kneading	ITRM-C-KN	98.64±0.19	95.64±0.14
	Co-Evaporation	ITRM-C-EV	94.55±0.15	94.55±0.16
	Physical Mixture	ITRM-C-PM	90.99±0.12	77.94±0.33
Itraconazole besylate + Captisol	Kneading	ITRB-C-KN	99.45±0.18	93.86±0.25
	Co-Evaporation	ITRB-C-EV	94.88±0.20	91.39±0.26
	Physical Mixture	ITRB-C-PM	89.04±0.29	80.11±0.21

Table 2. Different itraconazole complexes and their drug content

In vitro dissolution study of Complexes:

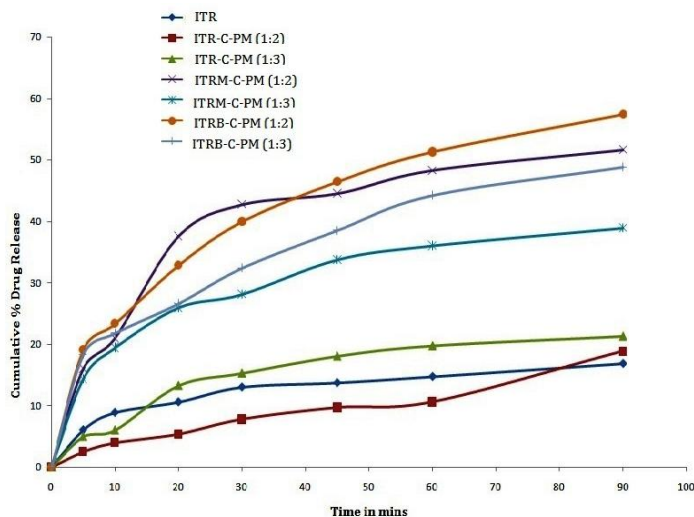


Fig.7a. Percentage drug release of complexes prepared by Physical mixtures method

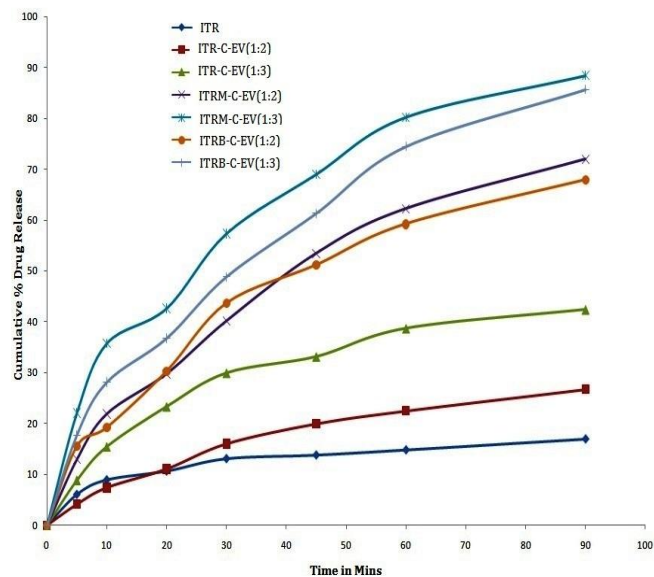


Fig.7c. Percentage drug release of complexes prepared by Co-Evaporation method

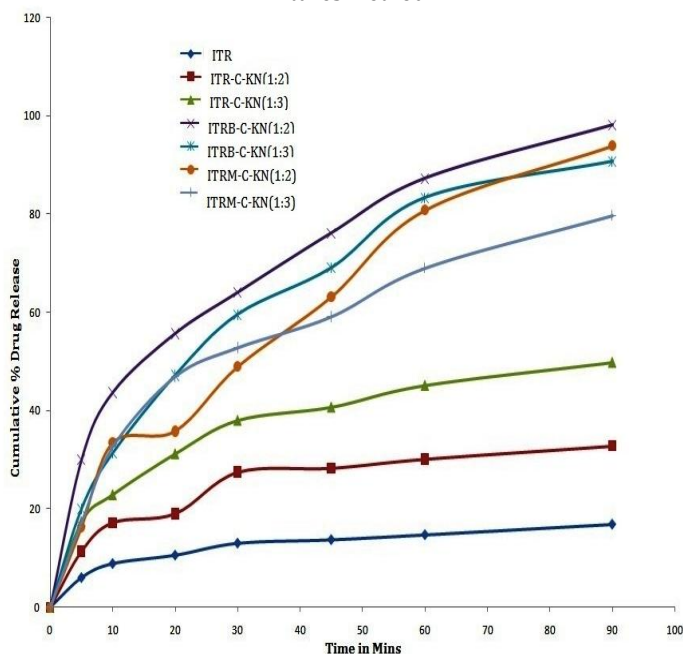


Fig.7b. Percentage drug release of complexes prepared by Kneading mixtures method]

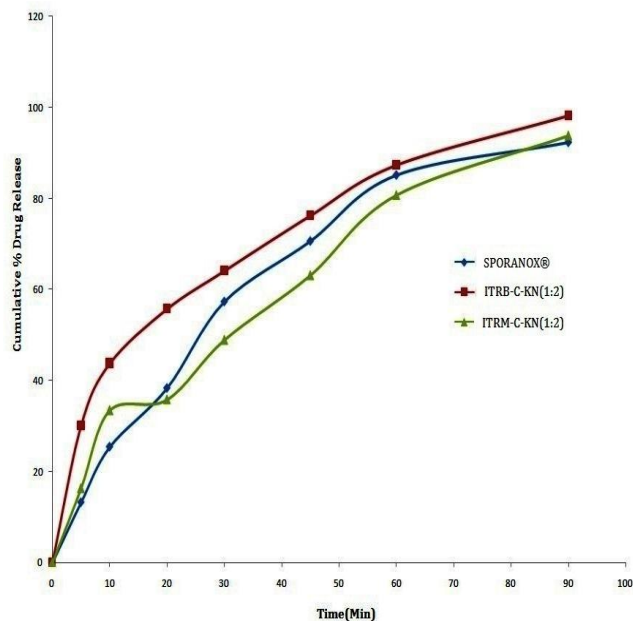
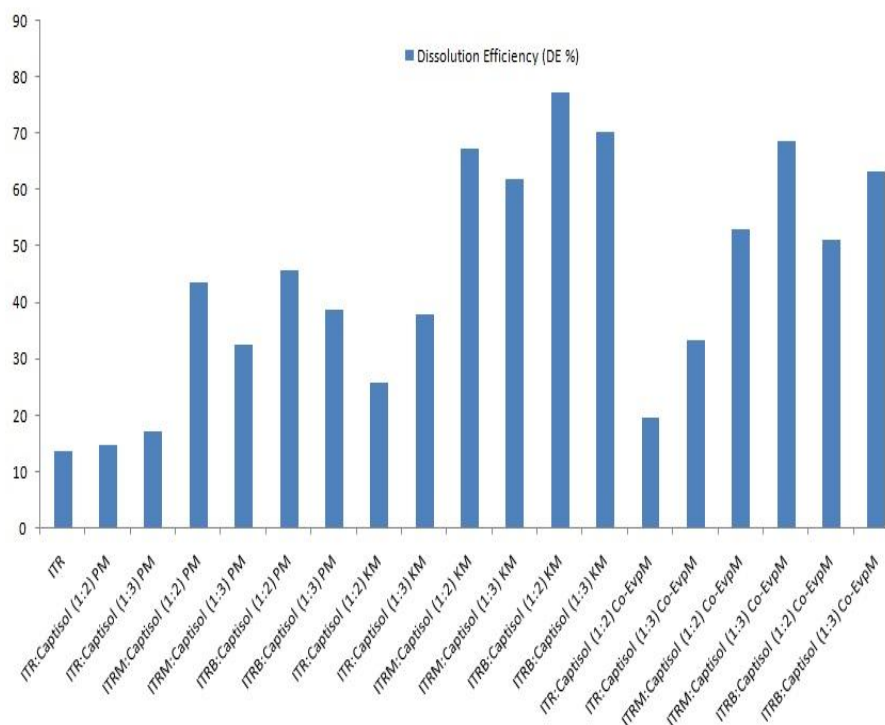


Fig.7d. Percentage drug release of complexes comparison with Sporanox®

Sample	Dissolution Efficiency (DE ₉₀ %)	Difference Factor f_1	Similarity Factor f_2
ITR	13.84	78	17
Sporonax	69.48	-	-
ITR-C-PM (1:2)	14.87	85	16
ITR-C-PM (1:3)	17.19	74	18
ITRM-C-PM (1:2)	43.61	33	33
ITRM-C-PM (1:3)	32.48	49	25
ITRB-C-PM (1:2)	45.83	32	35
ITRB-C-PM (1:3)	38.85	42	29
ITR-C-KN (1:2)	25.75	56	23
ITR-C-KN (1:3)	38.04	38	31
ITRM-C-KN (1:2)	67.42	9	64
ITRM-C-KN (1:3)	61.86	17	51
ITRB-C-KN (1:2)	73.97	9	65
ITRB-C-KN (1:3)	70.16	10	60
ITR-C-EV (1:2)	19.55	72	19
ITR-C-EV (1:3)	33.32	50	26
ITRM-C-EV (1:2)	52.97	23	42
ITRM-C-EV (1:3)	68.68	9	62
ITRB-C-EV (1:2)	51.19	26	40
ITRB-C-EV (1:3)	63.22	11	59

Table 3. Dissolution parameters of Itraconazole

Fig.8. Dissolution Efficiency (DE₉₀ %) of Itraconazole and Itraconazole salts complexes with PM, KM and EV methods

Sample	Zero order	First order	Peppas	Erosion	Higuchi	First order rate constant (k_1)	n- value
ITR	0.7398	0.7633	0.9731	0.7559	0.9452	0.0017	0.3393
Sporonax	0.9492	0.99622	0.9899	0.9900	0.9721	0.0293	0.6897
ITR-C-PM (1:2)	0.9693	0.9680	0.9767	0.9689	0.9163	0.0021	0.6514
ITR-C-PM (1:3)	0.8105	0.8309	0.9391	0.8243	0.9626	0.0023	0.5553
ITRM-C-PM (1:2)	0.7185	0.7873	0.9267	0.7648	0.9317	0.0069	0.4255
ITRM-C-PM (1:3)	0.7487	0.8078	0.9857	0.7886	0.9547	0.0046	0.3487
ITRB-C-PM (1:2)	0.8215	0.9070	0.9925	0.8810	0.9827	0.0069	0.4017
ITRB-C-PM (1:3)	0.8233	0.8958	0.9870	0.8738	0.9760	0.0046	0.3565
ITR-C-KN (1:2)	0.7296	0.7720	0.9477	0.7582	0.9306	0.0023	0.3649
ITR-C-KN (1:3)	0.7688	0.8469	0.9857	0.8220	0.9620	0.0069	0.3712
ITRM-C-KN (1:2)	0.9311	0.9691	0.9646	0.9875	0.9762	0.0161	0.5779
ITRM-C-KN (1:3)	0.8361	0.9654	0.9543	0.9326	0.9847	0.0161	0.4974
ITRB-C-KN (1:2)	0.9021	0.9583	0.9922	0.9826	0.9892	0.0418	0.5546
ITRB-C-KN (1:3)	0.8592	0.9891	0.9767	0.9699	0.9890	0.0253	0.5064
ITR-C-EV (1:2)	0.9160	0.9373	0.9875	0.9307	0.9848	0.0023	0.6526
ITR-C-EV (1:3)	0.8420	0.8908	0.9694	0.8753	0.9804	0.0046	0.5416
ITRM-C-EV (1:2)	0.9229	0.9866	0.9928	0.9713	0.9866	0.0138	0.6005
ITRM-C-EV (1:3)	0.8660	0.9896	0.9845	0.9651	0.9855	0.0230	0.4808
ITRB-C-EV (1:2)	0.8968	0.9693	0.9826	0.9494	0.9857	0.0115	0.5515
ITRB-C-EV (1:3)	0.9195	0.9953	0.9945	0.9854	0.9905	0.0207	0.5490

Table 4. Dissolution kinetics of Itraconazole

DISCUSSION

Preparation of Itraconazole Salt Forms:

Itraconazole is converted into the salt forms of Itraconazole Mesylate and Itraconazole Besylate by acid reaction method. The prepared mixtures were pale white free flowing powders. The samples were subjected for confirmation by studying NMR studies.

Nuclear magnetic resonance spectroscopy (NMR):

NMR spectrum of Itraconazole (as showed in Fig.3a) the chemical shift values at 0.8(1), 0.9(2), 1.7(3), 1.9(4), 0.8(5), 1.6(6), 3.2(7) and 3.9(8) for methyl, ethyl, N-H, N-H, R-CH₂, C=C, C-Cl and O-C₆ H₅ respectively. Itraconazole besylate (shown in Fig.3b) has got chemical shift values at 2.3(1), 3.6(2) for phenyl and S=O respectively and Itraconazole mesylate (shown in Fig.3c) has shown at 3.3(1), 4.2(2), 4.3(3), 3.6(4), 1.4(5) and 2.3(6) for -OH, -OH, -OH, S=O, CH₃-C=O and phenyl groups respectively. These values indicated the salt conversion of itraconazole into itraconazole mesylate and itraconazole besylate.

Solubility Studies:

The solubility of ITR was found to be 1.388 μ g/mL in purified water and 7.59 μ g/mL in 0.1N HCl. The solubility of ITRM was found to be 165.86 μ g/mL and 402.6 μ g/mL in purified water and 0.1 N HCl respectively. The solubility of ITRB in purified water was 191.64 μ g/mL and in 0.1N HCl was 508.7 μ g/mL. These results clearly indicated that prepared salts have considerable influence on improvement of ITR solubility.

Phase Solubility Studies:

The effect of Captisol on the aqueous solubility of ITR, ITRM and ITRB were evaluated using the phase solubility method. The results (Table 1.) showed an increase in the solubility of ITR, ITRM and ITRM with increase in Captisol concentration which indicates the effect of complexation. According to Higuchi and Connors, phase solubility study indicated that the curves can be classified as the AP type (the solubilizer was proportionally more effective at higher concentrations, shows in phase-solubility diagrams (in Fig.4a, 4b & 4c). The slope value were lower than one i.e., for itraconazole, itraconazole mesylate and itraconazole besylate was 0.7801, 0.0386 and 0.0106 respectively. Hence, the theoretical molar ratio (1:2 and 1:3) was chosen to prepare the solid complexes through different methods.

The apparent stability constant (KS) of ITR: Captisol, ITR Mesylate: Captisol and ITR Besylate: Captisol complex were obtained as 51.322 M⁻¹, 213 M⁻¹ and 375 M⁻¹ from the initial linear plot of the phase-solubility diagrams.

Infra red spectroscopy (IR):

Infra red spectra of pure drug (shown in Fig.5) indicated the presence of characteristic peaks of carboxylate group (O-C-O) in the range of 1550-1660cm⁻¹, C-N stretch from 1073cm⁻¹, chlorine group at 700-850cm⁻¹, benzene moiety from 3100-300 cm⁻¹. The salt forms itraconazole mesylate and itraconazole

besylate have got a characteristic peak of S=O group in the range of 1345- 1365. FTIR results suggested that there is no significant chemical interaction between the drug and the Captisol complexed products, which confirms the stability of drug in the powdered form.

X-ray powder diffraction (XRD):

The solid-state form, like as crystalline, polymorphs, solvates or amorphous solids of a drug substance, can have a significant impact on drug's solubility, dissolution rate, stability in a pharmaceutical formulation and bioavailability. A crystal has an ordered arrangement of molecules and atoms, maintained in contact through non-covalent interactions. On the other hand, amorphous solids are characterized by a random state. Although the amorphous solids are often susceptible to changes during storage, the amorphous form of a drug is generally more soluble, due to free energies involved in the dissolution process. This characteristic of solubility is a useful property, particularly if the drug has low aqueous solubility.

The XRD pattern of ITR and ITR complexes samples are shown in Fig.6. The pure drug spectra has shown intense and sharp at 16, 20 and 28 °2θ indicating its crystalline nature. The XRD patterns of salts and the complexed products have been found to have no peaks indicating their amorphous nature and inclusion complex formation with Captisol.

Drug content estimation:

The percentage drug content of different itraconazole complexes are shown in Table 2. The drug content was found to be in the range of 75.66±0.34% w/w to 99.45±0.18% w/w. The low standard deviation values indicated the uniformity of drug content of the prepared complexes.

In vitro dissolution study of Complexes:

The dissolution profiles of itraconazole from pure drug and different complexes prepared by physical mixture, kneading technique, co-evaporation techniques are shown in Fig. 7a, 7b & 7c respectively. Itraconazole pure drug has dissolved only 16.89 % in 90 minutes indicating the poor solubility and thereby dissolution. The dissolution of 1:2 and 1:3 weight ratio ITR:captisol physical mixture complexes in 90 minutes is 18.86 % and 21.31 % w/w respectively, kneading method complexes showed 32.84 % and 49.87 % w/w drug release and the co-evaporation complexes showed dissolution of 26.61 % and 42.34 % w/w respectively. The data indicated that the pure drug complexes with captisol could not able to increase the dissolution to the required level. The dissolution of 1:2 and 1:3 weight ratio ITRM : captisol physical mixture complexes in 90 minutes is 51.58 % and 38.90 % w/w respectively, kneading method complexes showed 93.81 % and 79.65 % w/w drug release and the co-evaporation complexes showed dissolution of 71.96 % and 88.43 %

w/w respectively. The dissolution of 1:2 and 1:3 weight ratio ITRB : captisol physical mixture complexes in 90 minutes is 57.36 % and 48.83 % w/w respectively, kneading method complexes showed 98.14 % and 90.73 % w/w drug release and the co-evaporation complexes showed dissolution of 67.92 % and 85.64 % w/w respectively. The data clearly indicated that the itraconazole mesylate and besylate salts complexes with Captisol could significantly increase the dissolution to the required level. For comparison the dissolution of commercial Sporanox capsules dissolution also performed which showed 92.3 % ITR release in 90 minutes (Shown in Fig.7 (d)).

The dissolution efficiency (DE₉₀)³⁶ at 90 minutes was calculated and the values are shown in Table III and Fig. 8. Pure itraconazole showed DE₉₀ 13.84%, ITRM:captisol (1:2 weight ratio) complexes prepared by kneading showed 67.42% and ITRB:captisol (1:2 weight ratio) complexes prepared by kneading showed 73.97%. DE₉₀ of Sporonax capsules in 69.48% and the data indicates that the itraconazole mesylate and besylate salt complexes with captisol prepared by kneading technique are efficient in improving the dissolution of ITR and are comparable with commercial Sporonax capsules. The similarity factor and difference factor as showed in Table 3 also indicated that ITRM-C-KN (1:2) and ITRB-C-KN (1:2) are comparable with commercial Sporonax capsules.

The kinetics of ITR release from complexes was studied by subjecting the dissolution data to zero order, first order kinetics (as shown in Table 4). The results indicated that the drug release follows first order kinetics. The mechanism of drug release was found to be by diffusion. The correlation values peppas equation indicated the dissolution follows fick's law of diffusion. The difference factor (f_1) and similarity factor (f_2)³⁷ values of ITRB: Captisol (1:2 molar ratio) prepared by kneading method showed 9 and 65 (Shown in Table III). In the similar manner difference factor (f_1) and similarity factor (f_2) values of ITRM: Captisol (1:2 molar ratio) prepared by kneading method showed 9 and 64. These values have indicated the equivalence of dissolution profile for ITRB:Captisol (1:2 molar ratio) and ITRM:Captisol (1:2 molar ratio) prepared by kneading method to that of commercial capsules Sporanox®.The study clearly indicated the usefulness of itraconazole mesylate and besylate salt complexes with sulpho butyl₇ ether β CD in improving the solubility and dissolution rate of itraconazole.

CONCLUSION

Based on present study and results it is concluded that formation of besylate and mesylate salt forms could significantly improve the solubility and dissolution rate of itraconazole. These results also suggested that an itraconazole besylate salt complex of sulfo derivative cyclodextrin (Captisol) prepared by kneading

technique has greater solubility and dissolution rate when compared with pure drug itraconazole and comparable with commercial Sporanox® capsules.

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