Comparative Studies on Solubility and Dissolution Enhancement of Different Itraconazole Salts and Their Complexes

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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 hydrochloride, mesylate and besylate by using addition reaction with hydrochloric acid, methane sulphonic acid and benzene sulphonic acid. Further inclusion complexes of itraconazole were prepared with Captisol (sulfobutyl ether- β -cyclodextrin) by using physical mixing, kneading and co-evaporation techniques. The preparations were characterized 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 exhibited higher percentage drug dissolution from itraconazole complexes than that of the pure drug which can be attributed to the increase in drug solubility provoked by the complexation technique.

Keywords Antifungal, Itraconazole, Hydrochloride Salt, Sulfonates Salt, Sulfobutyl Ether, β Cyclodextrin, Solubility Enhancement

1. 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 characteristics[1]. 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 bioavailability[2]. Kaplan [3] 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 1 mg/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 formation [4-6] or prodrug formation [7]. 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 forms [8].

Pharmaceutical salts [9] 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 properties [10-12]. 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 stability[15].

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 solubility [18]. 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 units [19]. Sulfobutyl ether β -Cyclodextrin (SBE $_7$ - 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 -CDs [23-25]. Some of the investigations also reported that the drug inclusion complex with SBE7- β -CD provided a protective effect against drug-induced cytotoxicity [25]. Based on these advantages, Captisol has been selected to study the effect of improving the physiochemical properties of poorly water-soluble drug itraconazole.

Itraconazole (ITR) is a broad-spectrum triazole antifungal agent with poor aqueous solubility [26]. ITR is weakly basic with pKa of the piperazine ring is 3.7 and highly hydrophobic drug [27]. 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 techniques [8] have been reported for enhancing the solubility and bioavailability of itraconazole, but the salt formation [13,14] and inclusion complexes [18] showed some promising results. Keeping these in the view the present work was planned with an objective to synthesize Itraconazole hydrochloride, mesylate besylate salt forms from Itraconazole. Further these salt forms were studied for improvement of dissolution by preparing inclusion complexes with Sulfobutyl $_7$ Ether β -Cyclodextrin (Captisol®) using physical mixing, kneading and co-evaporation techniques. These preparations were characterized by X-ray diffraction, Fourier Transformed Infrared spectroscopy, Nuclear Magnetic Resonance spectroscopy and also evaluated for solubility, drug content and dissolution studies.

Itraconazole was a gift sample obtained from Pharmatech, Hyderabad, and Sulfobutyl $_7$ Ether β -Cyclodextrin (Captisol®) (average molecular weight 2,163 and degree of substitution 6.5) was obtained from Cydex laboratories. Hydrochloric acid (A.R. grade) 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.

2.1. Preparation of Itraconazole Salts

Itraconazole hydrochloride (ITRH), Itraconazole mesylate (ITRM) and Itraconazole besylate (ITRB) salts were synthesized from itraconazole (ITR) by acid addition reaction using hydrochloric acid, methane sulfonic acid and benzene sulfonic acid (Figure.1, 2 & 3). Itraconazole salts were synthesized from a modified method by using acid addition reaction method [28-30]. In case of ITRH 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 concentrated hydrochloric acid (11.42 mmol) was added and dissolved. The above suspension was heated at 50 °C for 1hr under reflux using rotary evaporator. 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. ITRM and ITRB salts were prepared by following the similar procedure as mentioned above for ITRH salt by taking 1 gm of ITR (1.4 mmol) suspended in about 10 ml of dichloromethane and to this solutions about 400 mg of methane sulfonic acid (4.16 mmol) and 600 mg of benzene sulfonic acid (3.9 mmol) were added and dissolved. The final products were stored in an air tight container and then placed in desiccators.

Figure 1. Synthesis of Itraconazole Hydrochloride from Itraconazole

2. Materials and Methods

Figure 2. Synthesis of Itraconazole Mesylate from Itraconazole

Figure 3. Synthesis of Itraconazole Besylate from Itraconazole

2.2. Solubility Studies

Solubility studies for pure ITR, ITRH, 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 µm Millipore filters, suitable diluted and analyzed for the itraconazole content by measuring the absorbance at 258 nm using Shimadzu

UV-Visible spectrophotometer [31].

2.3. Phase Solubility Studies

Phase solubility study [32-36] was carried out to investigate the effect of Captisol on the solubility of ITR, ITRH, ITRM and ITRB 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 ITR, ITRH, ITRM and ITRB were added separately and shaken using orbit shaker at 25°C for 72 hr. After equilibrium, the solutions were filtered using 0.45µ filters and diluted suitably to determine the itraconazole content at 258 nm using UV-Visible spectrophotometer. The graphs were plotted between solubility of ITR (concentration in mM) from pure ITR, ITRH, ITRM and ITRB against the concentration of Captisol (in mM). The stability constant for the complex was determined from the graph using the following equation.

$$K_s = \frac{\text{slope}}{s_0(1 - \text{slope})}$$

The slope was obtained from the graph and S_0 was the equilibrium solubility of ITR, ITRH, ITRM and ITRB in 0.1 N HCl.

2.4. Preparation of Inclusion Complexes

The inclusion complexes of ITR, ITRH, ITRM and ITRB with Captisol (1:2 and 1:3 ratios) were prepared by using physical mixing, kneading and co-evaporation technique [37]. Physical mixture was prepared by simple mixing in a mortar with pestle for 10 min. The powders of ITR, ITRH, 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, ITRH, 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, ITRH, 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.

2.5. Fourier Infra Red Spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) spectra of ITR, ITRH, ITRM, ITRB, Captisol, ITR-Captisol complexes, ITRH-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.

2.6. X-ray Diffraction Analysis

Powder X-ray diffraction (XRD) patterns of ITR, ITRH,

ITRM, ITRB, Captisol, ITR-Captisol complexes, ITRH-Captisol, 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 α radiation, a voltage of 40 kV and 60 mA current. The scanning rate was 4°/min over the diffraction angle range (2 θ) of 3–50°.

2.7. NMR Spectroscopy

The ^1H -NMR spectra of pure ITR, ITRH, 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.

2.8. Drug Content Estimation

Accurately weighed 50 mg of the sample and transferred into 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 itraconazole content 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.

2.9. In vitro Dissolution Studies

In vitro dissolution studies [38] 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.

3. Results and Discussion

3.1. Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectrum of Itraconazole showed (Figure 4a) 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 (Figure 4b) has got chemical shift values at 2.3(1), 3.6(2) for phenyl and S=O respectively and Itraconazole mesylate (Figure 4c) 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.

3.2. Solubility Studies

The solubility of ITR was found to be 1.388µg/mL in purified water and 7.59µg/mL in 0.1N HCl. The solubility of ITR salts ITRH, ITRM and ITRB in purified water was found to be 23.86µg/mL, 165.86µg/mL and 191.64µg/mL respectively. The solubility of ITR salts ITRH, ITRM and ITRB in simulated gastric fluid was found to be 93.60µg/mL, 402.6µg/mL and 508.7µg/mL respectively. These results clearly indicated that prepared salts have considerable influence on improvement of ITR solubility.

3.3. Phase Solubility Studies

The effect of Captisol on the aqueous solubility of ITR,

ITRH, ITRM and ITRB was evaluated using the phase solubility method. The results (Table 1.) showed an increase in the solubility of ITR, ITRH, ITRM and ITRB with increase in Captisol concentration which indicates the effect of complexation. According to Higuchi and Connors, phase solubility study indicated (Figure 5) that the curves can be classified as the AP type (the solubilizer was proportionally more effective at higher concentrations). The positive curvature indicated that the existence of soluble complexes is with an order greater than one. Therefore, the theoretical molar ratio (1:2 and 1:3) were chosen to prepare the solid complexes through different methods. The slope value were lower than one i.e., for ITR, ITRH, ITRM and ITRB was 0.7801, 0.035, 0.0386 and 0.0106 respectively.

The apparent stability constant (KS) of ITR: Captisol, ITRH:Captisol, ITRM:Captisol and ITRB: Captisol complex were obtained as 51.322 M⁻¹, 254.73 M⁻¹, 213 M⁻¹ and 375 M⁻¹ from the initial linear plot of the phase-solubility diagrams.

Figure 4. NMR Peaks of (a) Itraconazole (Pure API) (b) Itraconazole Besylate salt (c) Itraconazole Mesylate salt

Table 1. Phase solubility studies

S. No	Concentration of Captisol (mM)	Concentration of ITR (mM)	Concentration of ITRH (mM)	Concentration of ITRM (mM)	Concentration of ITRB (mM)
1	0	6.912×10^{-5}	0.00019	0.193	0.19
2	5	0.00312	0.359	0.386	0.616
3	10	0.00493	0.550	0.503	1.160
4	20	0.00884	1.587	0.734	2.537
5	40	0.0222	2.589	1.658	4.253
6	80	0.0552	34.087	3.080	7.810
Stability Constant (k _s)		51.322 M ⁻¹	254.73 M ⁻¹	51.322 M ⁻¹	375 M ⁻¹

Figure 5. Phase Solubility Graph of ITR and ITR salts with SBE7 β cd

Figure 6. IR spectra of (a) ITR (Pure Drug) (b) ITRH (c) ITRM (d) ITRB (e) Captisol (SBE7 β -CD) (f) ITRH-C-KN (g) ITRM-C-KN (h) ITRB-C-KN

3.4. Infra Red Spectroscopy (IR)

Infra red spectra of pure drug (Figure 6) indicated the presence of characteristic peaks of carboxylate group (O-C-O) in the range of 1550-1660 cm^{-1} , C-N stretch from 1073 cm^{-1} , chlorine group at 700-850 cm^{-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 studies revealed that Itraconazole HCL showed two typical bands at 3369 and 3283 cm^{-1} due to N-H primary stretching vibration and a band at 3170 cm^{-1} due to N-H secondary stretching and characteristics bands at 1623 and 1560 cm^{-1} assigned to

C=N stretching. 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.

3.5. X-ray Powder Diffraction (XRD)

The XRD pattern of ITR and ITR complexes samples are shown in Figure 7. The pure drug spectra has shown intense and sharp at 16, 20 and 28 $^{\circ}$ 2 θ 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.

Figure 7. XRD Pattern of (a) ITR (b) ITRM (c) ITRB (d) ITRH (e) ITRH-C-PM (f) ITRH-C-EV (g) ITRH-C-KN (h) ITRM-C-PM (i) ITRM-C-EV (j) ITRM-C-KN (k) ITRB-C-EV (l) ITRB-C-KN

3.6. 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 $75.66 \pm 0.34\%$ w/w to $99.45 \pm 0.18\%$ w/w. The low standard deviation values indicated the uniformity of drug content of the prepared complexes.

Table 2. Different itraconazole complexes and their drug content

Complexes	Method	Terminology	Drug content (% w/w)	
			1:2	1:3
ITR + C	KN	ITR-C-KN	97.23 ± 0.12	87.23 ± 0.17
	EV	ITR-C-EV	93.83 ± 0.14	81.36 ± 0.23
	PM	ITR-C-PM	85.89 ± 0.21	75.66 ± 0.34
ITRH + C	KN	ITRH-C-KN	98.45 ± 0.58	93.86 ± 0.52
	EV	ITRH-C-EV	94.88 ± 0.21	91.39 ± 0.24
	PM	ITRH-C-PM	89.04 ± 0.41	90.11 ± 0.45
ITRM + C	KN	ITRM-C-KN	98.64 ± 0.19	95.64 ± 0.14
	EV	ITRM-C-EV	94.55 ± 0.15	94.55 ± 0.16
	PM	ITRM-C-PM	90.99 ± 0.12	77.94 ± 0.33
ITRB + C	KN	ITRB-C-KN	99.45 ± 0.18	93.86 ± 0.25
	EV	ITRB-C-EV	94.88 ± 0.20	91.39 ± 0.26
	PM	ITRB-C-PM	89.04 ± 0.29	80.11 ± 0.21

3.7. 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 Figure 8a, 8b & 8c respectively.

The pure drug showed the dissolution of 16.89% in 90 minutes indicating the poor solubility and thereby dissolution. The dissolution of simple physical mixture complexes ITR and Captisol complexes of 1:2 and 1:3 weight ratios was found to be 18.86 % and 21.31 % w/w respectively, kneading complexes was found to be 32.84 % and 49.87 % w/w and co-evaporates was found to be 26.61 % and 42.34 % w/w respectively. The data indicated that the only drug complexes with captisol could not able to increase the dissolution to the required level.

Figure 8a. Percentage drug release of complexes prepared by Physical mixtures method

Figure.8b. Percentage drug release of complexes prepared by Kneading mixtures method

Figure.8c. Percentage drug release of complexes prepared by Co-Evaporation method

Figure.8d. Percentage drug release of complexes comparison with Sporanox®

Further the dissolution of itraconazole salt complexes with captisol at a weight ratio of 1:2 and 1:3 in physical mixing was found to be 50.12 % and 44.19 % w/w, 51.58 % and 38.90 % w/w and 57.36 % and 48.83 % w/w respectively for ITRH, ITRM and ITRB. The kneading mixtures showed the dissolution of 98.72 % and 89.72 % w/w, 93.81 % and 79.65 % w/w and 98.14 % and 90.73 % w/w respectively for ITRH, ITRM and ITRB. The co-evaporation mixtures showed the dissolution of 73.96 % and 70.68 % w/w,

71.96 % and 88.43 % w/w and 67.92 % and 85.64 % w/w respectively for ITRH, ITRM and ITRB. The data clearly indicated that the itraconazole hydrochloride, mesylate and besylate salt complexes with Captisol can significantly increase the dissolution of ITR. For comparison the dissolution of commercial Sporanox capsules dissolution also performed which showed 95.38 % ITR release in 90 minutes (Shown in Figure 8d).

Table 3. Dissolution parameters of Itraconazole

Sample	Dissolution Efficiency (DE ₉₀ %)	Difference Factor (f_1)	Similarity Factor (f_2)
ITR	13.84	78	17
Sporanox	69.48	-	-
ITR-C-PM (1:2)	14.87	85	16
ITR-C-PM (1:3)	17.19	74	18
ITRH-C-PM (1:2)	40.38	38	31
ITRH-C-PM (1:3)	37.69	41	29
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
ITRH-C-KN (1:2)	74.80	09	62
ITRH-C-KN (1:3)	72.86	17	48
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
ITRH-C-EV (1:2)	58.88	18	48
ITRH-C-EV (1:3)	58.75	20	46
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

The dissolution efficiency (DE₉₀) [39] at 90 minutes was calculated and the values are shown in Table 3. Pure itraconazole showed DE₉₀ 13.84% and commercial Sporanox capsules showed 69.48%. The salt complexes showed maximum DE₉₀ 74.80%, 67.42% and 73.97% for kneading mixtures of ITRH, ITRM and ITRB respectively.

The difference factor (f_1) and similarity factor (f_2) [40] values Shown in Table 3. The results indicated that the salt complexes with captisol prepared by kneading method at weight ratio of 1:2 showed f_1 values of 9 in all cases of ITRH, ITRM and ITRB and the f_2 values was 62, 65 and 64 respectively. These values indicate the equivalence in dissolution of the prepared complexes with commercial Sporanox capsules.

Table 4. Dissolution kinetics of Itraconazole

Sample	Zero order	First order	Peppas	Higuchi	First order rate constant (k_1)	n- value
ITR	0.7398	0.7633	0.9731	0.9452	0.0017	0.3393
Sporonax	0.9492	0.99622	0.9899	0.9721	0.0293	0.6897
ITR-C-PM (1:2)	0.9693	0.9680	0.9767	0.9163	0.0021	0.6514
ITR-C-PM (1:3)	0.8105	0.8309	0.9391	0.9626	0.0023	0.5553
ITRH-C-PM (1:2)	0.8340	0.8890	0.9830	0.9760	0.0060	0.485
ITRH-C-PM (1:3)	0.7490	0.8000	0.9460	0.9410	0.0040	0.4550
ITRM-C-PM (1:2)	0.7185	0.7873	0.9267	0.9317	0.0069	0.4255
ITRM-C-PM (1:3)	0.7487	0.8078	0.9857	0.9547	0.0046	0.3487
ITRB-C-PM (1:2)	0.8215	0.9070	0.9925	0.9827	0.0069	0.4017
ITRB-C-PM (1:3)	0.8233	0.8958	0.9870	0.9760	0.0046	0.3565
ITR-C-KN (1:2)	0.7296	0.7720	0.9477	0.9306	0.0023	0.3649
ITR-C-KN (1:3)	0.7688	0.8469	0.9857	0.9620	0.0069	0.3712
ITRH-C-KN (1:2)	0.8930	0.9180	0.9950	0.9970	2.3210	0.393
ITRH-C-KN (1:3)	0.7660	0.9650	0.9520	0.9540	1.9340	0.3970
ITRM-C-KN (1:2)	0.9311	0.9691	0.9646	0.9762	0.0161	0.5779
ITRM-C-KN (1:3)	0.8361	0.9654	0.9543	0.9847	0.0161	0.4974
ITRB-C-KN (1:2)	0.9021	0.9583	0.9922	0.9892	0.0418	0.5546
ITRB-C-KN (1:3)	0.8592	0.9891	0.9767	0.9890	0.0253	0.5064
ITR-C-EV (1:2)	0.9160	0.9373	0.9875	0.9848	0.0023	0.6526
ITR-C-EV (1:3)	0.8420	0.8908	0.9694	0.9804	0.0046	0.5416
ITRH-C-EV (1:2)	0.810	0.937	0.973	0.974	1.658	0.4430
ITRH-C-EV (1:3)	0.743	0.873	0.946	0.943	1.547	0.4090
ITRM-C-EV (1:2)	0.9229	0.9866	0.9928	0.9866	0.0138	0.6005
ITRM-C-EV (1:3)	0.8660	0.9896	0.9845	0.9855	0.0230	0.4808
ITRB-C-EV (1:2)	0.8968	0.9693	0.9826	0.9857	0.0115	0.5515
ITRB-C-EV (1:3)	0.9195	0.9953	0.9945	0.9905	0.0207	0.5490

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 study clearly indicated the usefulness of itraconazole hydrochloride, mesylate and besylate salt complexes with sulpho butyl₇ ether β CD in improving the solubility and dissolution rate of itraconazole. Among all the complexes the ITRH and ITRB complexes with captisol at a weight ratio of 1:2 prepared by kneading method showed higher dissolution rate.

4. Conclusions

The present study showed that itraconazole a poorly soluble drug exhibits very poor *in vitro* dissolution. The simple drug complexes with captisol also could not able to extend the dissolution rate. The salt form of ITR such as

itraconazole hydrochloride, besylate and mesylate salt forms could significantly improve the solubility and dissolution rate of itraconazole. Further the complexation of these salts with captisol has improved the dissolution rate of ITR. Among all the complexes the ITRH and ITRB complexes with captisol at a weight ratio of 1:2 prepared by kneading method showed higher dissolution rate and comparable with commercial Sporano[®] capsules.

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