Investigation of Dissolution Enhancement of Itraconazole by Complexation with β-and Hydroxy Propyl β-Cyclodextrins

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Complex formation of itraconazole (ITR) with β-cyclodextrin (βCD) and hydroxy propyl β-cyclodextrin (HPβCD) in aqueous solution and in solid state and the possibility of improving the solubility and dissolution rate of ITR via complexation with the above cyclodextrins were investigated.The phase solubility studies indicated the formation of a 1:1 M inclusion complex in solution with both βCD and HPβCD.The apparent stability constant (K_c) was 206.2 M^{-1} and 270.7 M^{-1} for βCD and HPβCD complexes, respectively. Differential Scanning Calorimetry (DSC) studies indicated the formation of solid inclusion complexes of ITR-βCD and ITR-HPβCD at 1:4 ratio only. Solid complexes of ITR-βCD and ITR-HPβCD (1:1 and 1:2 M) prepared by kneading and coevaporation methods exhibited higher rates of dissolution and dissolution efficiency values than the corresponding physical mixtures and ITR itself. Higher dissolution rates were observed with kneaded complexes than with those prepared by coevaporation. Increases of 23.4 and 83.4-fold in the dissolution rate were observed respectively with ITR-βCD (1:2 M) and ITR-HPβCD (1:2 M) kneaded complexes.

ITR is an orally active, broad spectrum triazole antifungal agent[1]. It is insoluble in water at all pH's in the range 1 to 12. Because of its poor aqueous solubility, its absolute oral bioavailability[2] is only 55%. Very poor aqueous solubility of the drug may lead to variable dissolution rates and bioavailabilities. The dissolution rate of ITR was earlier improved by solid dispersion techniques[3,4]. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug[5-7]. The objective of the present study has been to investigate the possibility of improving the solubility and dissolution rate of ITR by complexation with βCD and HPβCD. In addition, the physicochemical characteristics of ITR-βCD and ITR-HPβCD solid inclusion complexes were also investigated and the results are reported here.

ITR was a gift sample from M/s Cheminor Drugs Ltd., Pharma Division, Hyderabad, βCD and HPβCD were gift sample from M/s Cerestar Inc. USA Methanol and dichloromethane (M/s Qualigens) were procured from local market.

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 255 nm in 0.1 N HCl was used for the estimation of ITR. The method obeyed Beer's law in the concentration range 0-20 μg/ml. The excipients used in the complexes and SLS used in the dissolution rate study did not interfere in the method.

Solubility studies were performed according to the method reported by Higuchi and Connors[8]. Excess ITR (50 mg) was added to 15 ml of triple distilled water (pH 6.8) containing various concentrations of βCD (0.001-0.006 M) or HPβCD (0.0071-0.0357 M) taken in a series of 25 ml stoppered conical flasks and the mixtures were shaken for 72 h at room temperature (28°) on a rotary flask shaker. After 72 of shaking to achieve equilibrium, 2 ml aliquots were withdrawn at 1 h intervals and filtered immediately using a 0.45 μ nylon disc filter. The filtered samples were diluted suitably and assayed for ITR by measuring at 255 nm against blanks prepared in the same concentration of CD in water so as to cancel any absorb-

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ance that may be exhibited by the CD molecules. Shaking was continued until three consecutive estimations are the same. The solubility experiments were conducted in triplicate.

The solid complexes of ITR and βCD and HPβCD were prepared in 1:1 and 1:2 molar ratios by two methods, kneading and coevaporation. In the kneading method, ITR and βCD or HPβCD were triturated in a mortar with a small volume of a solvent blend of water-methanol-dichloromethane (20:50:30). The thick slurry was kneaded for 45 min and then dried at 55° until dry. The dried mass was pulverized and sieved through 100 mesh. In the coevaporation method, the aqueous solution of βCD or HPβCD was added to the solution of ITR in a solvent blend of methanol and dichloromethane (2:3). The resulting mixture was stirred for 1 h and evaporated at a temperature of 55° until dry. The dried mass was pulverized and sieved through mesh No. 100.

DSC was performed with a DSC model 220 C (Sieko, Tokyo, Japan). The samples were sealed in a aluminum pans and the DSC thermograms were recorded at a heating rate of 5°/min from 40° to 300°.

Dissolution rate of ITR in pure form and from physical mixtures and inclusion complexes was studied using a USP 23 three-station dissolution rate test apparatus (model DR-3, M/s Campbell Electronics) with a paddle stirrer. The dissolution fluid was 900 ml of 0.1 N hydrochloric acid containing 0.5% SLS. SLS (0.5%) was added to the dissolution fluid to maintain sink condition. Pure drug or physical mixture or inclusion complex equivalent to 100 mg of ITR, a speed of 75 rpm and a temperature of 37±1° were used in each test. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45 μ) at different time intervals, suitably diluted and assayed for ITR by measuring absorbance at 255 nm. The dissolution experiments were conducted in triplicate.

The phase solubility diagrams for the complex formation between ITR and βCD and HPβCD are shown in fig. 1. The aqueous solubility of ITR was increased linearly (r=0.998) as a function of the concentration with βCD. The phase solubility diagram of ITR-βCD (fig. 1A) can be classified as type A_L according to Higuchi and Connors[8]. Because the straight line had a slope less than unity, the increase in solubility was due to the formation of a 1:1 M complex. With HPβCD the phase solubility diagram (fig. 1B) was of the A_p type. The positive curvature indicated the existence of soluble complexes with

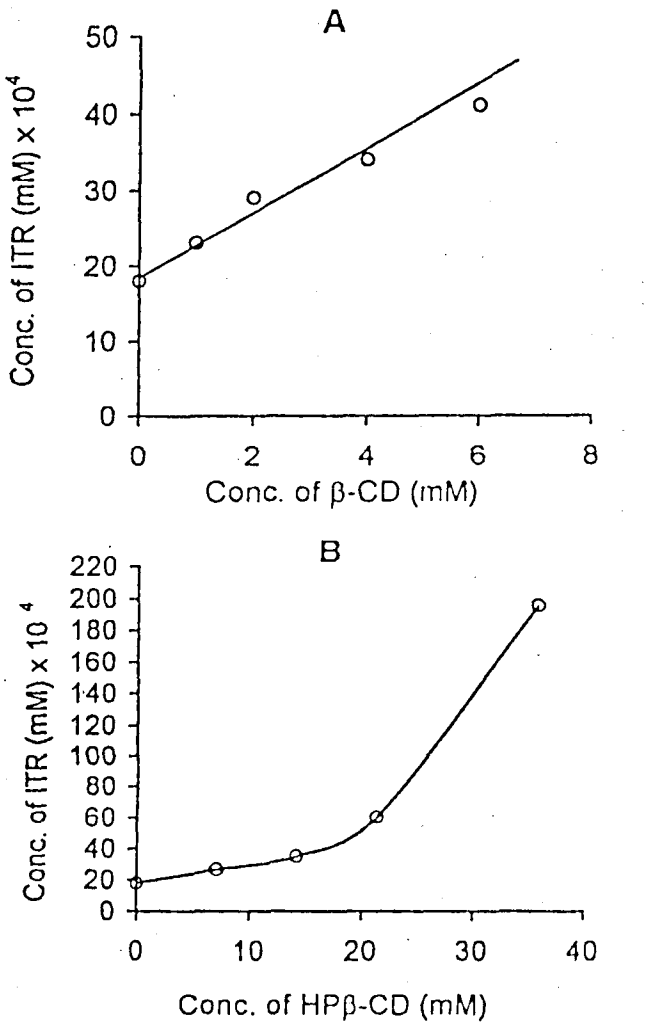

Fig. 1: Phase solubility Patterns

Phase solubility of ITR-βCD (A) and ITR-HPβCD (B) at 28°

an order greater than one in HPβCD. The apparent stability constant (K_c) obtained from tne slope of the linear portion of phase solubility diagram was found to be 206.2 M^{-1} and 270.7 M^{-1} respectively with βCD and HPβCD. These values of stability constant (K_c) indicated that the ITR-CD complexes formed are adequately stable. Solid inclusion complexes of ITR-βCD and ITR-HPβCD were prepared by kneading and coevaporated methods.

The thermal behaviour of ITR-CD inclusion complexes was studied using DSC to confirm the formation of the solid complexes. DSC thermograms of ITR and ITR-CD solid complexes are shown in fig. 2 The DSC thermograms of ITR exhibited an endothermic peak at 170° corresponding to its melting point. βCD and HPβCD showed broad endothermic peaks at 115° and 73° respectively. With

TABLE 1: DISSOLUTION OF ITR AND ITS INCLUSION COMPLEXES WITH βCD AND HPβCD

Product	Mean percent ITR dissolved in time (min)						DE_{60}	$K_1 x10^2$
	5	10	15	30	45	60	(%)	(min^{-1})
ITR	—	—	12.2	21.9	27.6	35.6	20.0	0.67
			(4.5)	(4.4)	(2.8)	(2.5)	(3.8)	(3.70)
ITR-βCD (1:1 M) PM	—	—	14.0	26.7	34.8	42.9	24.2	0.89
			(3.5)	(2.2)	(1.7)	(1.1)	(1.2)	(2.25)
ITR-βCD (1:1 M) CC	7.8	13.3	25.7	59.1	67.9	72.5	46.8	2.40
	(3.8)	(4.5)	(3.1)	(2.0)	(1.9)	(1.8)	(1.7)	(3.75)
ITR-βCD (1:1 M) KC	16.7	30.6	54.3	73.9	79.8	84.2	61.9	3.20
	(3.0)	(4.5)	(2.9)	(2.0)	(1.6)	(2.0)	(2.2)	(4.60)
ITR-βCD (1:2 M) PM	—	—	19.2	32.5	38.3	46.5	28.3	1.07
			(3.1)	(1.8)	(1.5)	(1.2)	(0.7)	(0.93)
ITR-βCD (1:2 M) CC	12.8	19.2	37.0	66.6	76.0	85.3	55.1	3.54
	(4.6)	(3.1)	(2.4)	(1.3)	(1.3)	(1.1)	(1.6)	(3.60)
ITR-βCD (1:2 M) KC	46.1	76.7	91.0	99.8	99.9	99.9	87.8	15.67
	(2.1)	(1.5)	(0.4)	(0.5)	(0.3)	(0.3)	(0.4)	(0.89)
ITR-HPβCD (1:1 M) PM	—	—	18.0	34.8	40.1	50.0	29.4	1.14
			(4.4)	(1.7)	(1.4)	(1.2)	(1.0)	(1.75)
ITR-HPβCD (1:1 M) CC	18.7	37.2	67.1	86.7	95.1	99.7	73.8	7.06
	(4.2)	(1.6)	(1.6)	(0.9)	(1.7)	(3.0)	(1.2)	(2.97)
ITR-HPβCD (1:1 M) KC	24.1	50.1	71.6	94.9	99.1	99.1	79.7	10.76
	(4.1)	(2.3)	(1.8)	(0.8)	(0.3)	(0.3)	(0.6)	(2.30)
ITR-HPβCD (1:2 M) PM	—	—	28.7	40.1	52.8	63.2	38.3	1.40
			(1.9)	(1.4)	(1.3)	(1.2)	(1.3)	(0.71)
ITR-HPβCD (1:2 M) CC	46.4	67.3	94.1	100.0	100.0	100.0	87.7	17.98
	(1.5)	(1.0)	(0.6)	(0.3)	(0.3)	(0.3)	(0.1)	(3.10)
ITR-HPβCD (1:2 M) KC	93.9	97.8	100.2	100.0	100.0	100.0	95.3	55.88
	(0.5)	(0.5)	(0.4)	(0.4)	(0.4)	(0.4)	(0.1)	(2.64)

Dissolution characteristics of Physical Mixture (PM), Coevaporated Complex (CC) and Kneaded Complex (KC) of ITR, ITR-βCD and ITR-HPβCD. K_1 is first-order dissolution rate constant. Figures in parentheses are coefficient of variation values.

both βCD and HPβCD, thermograms of 1:1 and 1:2 M ITR-CD systems showed the persistence of the endothermic peak of ITR at 170°, indicating that a true inclusion complex had not formed at 1:1 and 1:2 molar ratio in the solid state. The DSC thermograms of ITR-CD (1:4) systems did not show the melting endotherm of ITR. The disappearance of the endothermic peak with these systems indicated the formation of solid inclusion complex of ITR-CD at a 1:4 molar ratio with both βCD and HPβCD.

The dissolution characteristics of ITR and ITR-CD systems are given in Table 1. The dissolution of ITR followed first order kinetics (r=96-0.99). Solid complexes of ITR-βCD and ITR-HPβCD (1:1 and 1:2 M) prepared by both the methods exhibited higher rates of dissolution and dissolution efficiency[9] values than the corresponding physical mixtures and ITR itself. Solid complexes

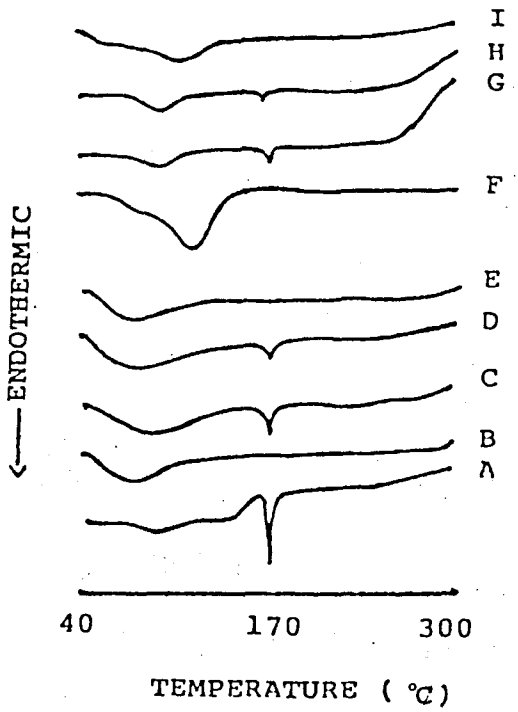

Fig. 2: DSC thermograms of ITR and its inclusion complexes.

DSC thermograms of itraconazole (A), β-cyclodextrin (F), hydroxy propyl β-cyclodextrin (B) and inclusion complexes of ITR-HPβCD, 1:1 M (C), ITR-HPβCD, 1:2 M (D), ITR-HPβCD, 1:4 M (E), ITR-βCD, 1:1 M (G), ITR-βCD, 1:2 M (H), ITR-βCD, 1:4 M (I) prepared by kneading method.

prepared by the kneading method exhibited higher dissolution rates and efficiency values than those prepared by the coevaporated method in each case. Increases of 4.8 and 23.4-fold in the dissolution rate with βCD and 16.1 and 83.4-fold with the HPβCD were observed, respectively, with 1:1 and 1:2 M solid inclusion complexes prepared by the kneading method when compared to ITR itself. The higher dissolution rates observed with kneaded complexes may be due to the better interaction of drug and CD during the kneading process. HPβCD gave markedly higher enhancement in the solubility and dissolution rate of ITR than βCD.

Thus, the results of the study indicated the formation of ITR-βCD and ITR-HPβCD inclusion complexes at a 1:1 molar ratio in solution with a stability constant of 206.2 M^{-1} and 270.7 M^{-1}, respectively. Whereas, solid inclusion complexes of ITR-βCD and ITR-HPβCD were formed at a 1:4 M ratio. Solid complexes of ITR-βCD and ITR-HPβCD (1:! and 1:2 M) prepared by kneading and coevaporation methods exhibited higher rates of dissolution and dissolution efficiency values than the corresponding physical mixtures and ITR itself.

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