Dissolution Rate and Formulation Studies on Solid Dispersions of Itraconazole

K.P.R. CHOWDARY* AND SHAIK SRINIVASA RAO
Industrial Pharmacy Division, Department of Pharmaeutical Sciences
Andhra University, Visakhapatnam-530 003

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Solid dispersions of itraconazole (ITR) in polyvinylpyrrolidone (PVP), hydroxy propyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC) and their tablet formulations were investigated with an objective of enhancing the dissolution rate of ITR from tablets. A marked enhancement in the dissolution rate of ITR was observed with all the solid dispersions. HPC gave the highest improvement (7.5 fold) in the dissolution rate of ITR at 10% concentration when compared to ITR itself. XRD indicated the presence of ITR in amorphous form in ITR-HPC solid dispersion and the crystallinity of ITR was much reduced in ITR-HPMC and ITR-PVP solid dispersions. DSC indicated no interaction between ITR and PVP, HPMC and HPC. The solid dispersions could be formulated into tablets. These tablets, apart from fulfilling all official and other specifications, exhibited higher rates of dissolution and dissolution efficiency (DE) values.

Itraconazole (ITR) is an orally active broad spectrum triazole antifungal agent, which provides an effective oral treatment of several deep mycoses including aspergillosis and candidasis[1]. It is insoluble in water at any pH in the range 1 to 12. Because of poor aqueous solubility its absolute oral bioavailability is only 55%[2]. Among various approaches to improve solubility and bioavilability of poorly-soluble drug, solid dispersion technique has often proven to be successfull[3]. No work was reported on the solid dispersions of ITR. In the present study, solid dispersions of ITR in water soluble polymers such as polyvinylpyrrolidone (PVP), hydroxy propyl methyl cellulose (HPMC) and hydroxy propyl cellulose (HPC) were investigated with an objective of enhancing the dissolution rate of ITR. The physicochemical nature of the solid dispersions and the possibility of formulating them into tablets with enhanced dissolution rates was also investigated.

Itraconazole, polyvinyl pyrrolidone (BASF, PVP K-30, Mol. Wt. 40,000), hydroxy propyl methyl cellulose (Pharmacoat 606, 6, cps), hydroxy propyl cellulose-L (Nisso, 6-10 cps), microcrystalline cellulose (FMC, PH 200), croscarmellose sodium (crosslinked carboxymethyl cellulose sodium; Ac-Di-Sol, FMC) were gift samples from M/s Cheminor Drugs Limited, Pharma Division, Hyderabad. Sodium lauryl sulfate (BDH), dichloromethane (Qualigens), methyl alcohol (Qualigens), Talc I.P. and Magnesium streate I.P. were procured from local market.

Solid dispersions of ITR were prepared employing PVP, HPMC and HPC as carriers in the drug and carrier ratios of 19:1, 9:1 and 8:2. The solid dispersions were prepared by dissolving ITR and the polymer (PVP or HPMC or HPC) in a solvent blend of methanol and dichloromethane (4:6) to obtain a clear solution. The solvent was removed by evaporation at 40° under reduced pressure (8 in Hg. Abs). The mass obtained was powdered, mixed and sifted through a mesh No. 100. For physical mixtures ITR and the carriers (PVP, HPMC and HPC) in 9:1 ratio were weighed, mixed well in a mortar and sifted through mesh No. 100.

Tablets each containing 100 mg of itraconazole employing ITR itself and its dispersions in PVP, HPMC and HPC were prepared by direct compression method as per the formulate given in Table 1. The blend of powders was compressed into tablets on a single punch tablet machine (Cadmach) to a hardness of 8-10 kg/sq.cm. In each case 100 tablets were prepared.

The tablets were tested for uniformity of weight as per TP (1996). Disintegration times were determined in a

*For Correspondence

TABLE 1 : FORMULAE OF ITRACONAZOLE TABLETS PREPARED

Ingredient (mg/tablet)	Formulation			
	T_1	T_2	T_3	T_4
Itraconazole (ITR)	100	—	—	—
ITR-PVP (9:1) SD	—	112	—	—
ITR-HPMC (9:1) SD	—	—	112	—
ITR-HPC (9:1) SD	—	—	—	112
Microcrystalline cellulose (Avicel pH 200)	276	264	264	264
Ac-Di-Sol	16	16	16	16
Magnesium stearate	4	4	4	4
Talc	4	4	4	4

SD: Solid Dispersion

Thermonic tablet disintegration test machine (USP) using distilled water as the fluid. Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator.

An UV spectrophotometric method[4] based on the measurement of absorbance at 255 nm in 0.1 N HCl was used for estimation of ITR. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range 0.5-20 μg/ml. The excipients used in the dispersions and sodium lauryl sulfate used in the dissolution rate study did not interfere in the method.

The dissolution late of ITR from the solid dispersions and tablets was studied using USP XXI 3-station dissolution rate test apparatus (Model DR-3, M/s Campbell Electronics) with a paddle stirrer. Nine hundred milliliters of 0.1 N hydrochloric acid containing 0.5% sodium lauryl sulfate (SLS) was used as dissolution fluid. SLS (0.5%) was added to the dissolution fluid to maintain sink condition. Solid dispersion equivalent to 100 mg of ITR or one tablet containing 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 itraconazole by measuring absorbance at 255 nm. The dissolution experiments were conducted in triplicate.

X-ray powder diffraction patterns of TTR and its solid dispersions were obtained using Philips X-ray Powder Diffractometer (Model PW 1710) employing Cu-kα-radiation. The diffractograms were run at 2.4°/min in terms of 20 angle.

DSC was performed on ITR and its solid dispersions using a Sieko, Japan DSC 220C Model. Samples were sealed in aluminium pans and the DSC thermograms were recorded at a heating rate of 10°/min from 30-300°.

All the solid dispersions prepared were found to be fine and free flowing powders. Low coefficient of variation < 2%) in the percent ITR content of the preparations indicated uniformity of drug content in each batch prepared. The physical state of the drug in the dispersions was evaluated by XRD and DSC. X-ray diffractograms Fig. 1 of ITR exhibited characteristic diffraction patterns because of its crystalline nature. The diffractogram of PVP, HPMC and HPC did not show sharp peaks. In the case of ITR-HPC (9:1) solid dispersion the sharp diffration peaks of ITR have disappered Fig. 1 indicating conversion of crystalline ITR to amorphous form in this solid dispersion. Whereas in the case of ITR-HPMC (9:1) and ITR-PVP (9:1) dispersions, the number of diffraction peaks and their heights were much reduced when compared to ITR itself indicating reduced crystallinity of ITR but not complete conversion to amorphous form in these solid dispersions.

The DSC thermograms of ITR and its dispersions are shown in Fig. 2. The DSC thermogram of ITR exhibited an endothermic peak at 168° corresponding to its melting point. Solid dispersions of ITR in PVP, HPMC and HPC also showed the melting peak of ITR at 167°

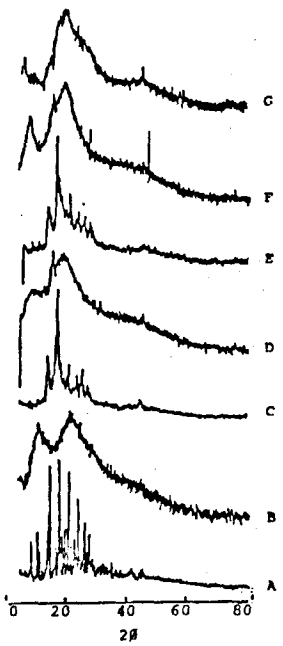

Fig. 1 : X-ray diffractograms of itraconazole (A), PVP (B), HPMC (D), HPC (F) and solid dispersion of ITR (9:1) in PVP (C), HPMC (E) and HPC (G)

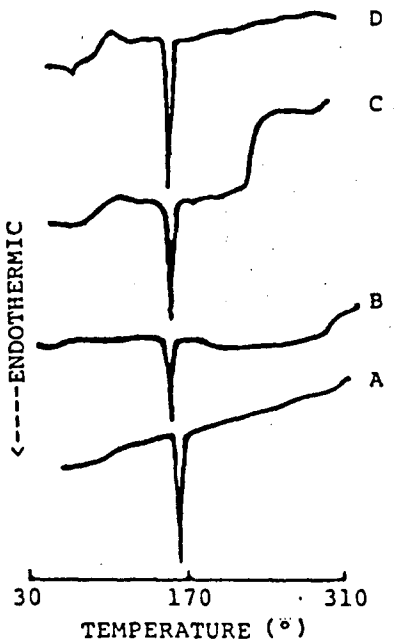

Fig. 2 : DSC thermograms of itraconazole (A) and solid dispersion of ITR (9:1) in PVP (B), HPMC (C) and HPC (D)

indicating no interaction between ITR and the carriers in the solid dispersions.

ITR dissolution was faster from all the solid dispersions when compared to ITR itself and the corresponding physical mixtures (Table 2). The dissolution of ITR itself and from various solid dispersions obeyed Hixson-Crowell's cube root dissolution rate law. Plots of ($W_o^{1/3}$-$W^{1/3}$) Vs. time were found to be linear ($r > 0.98$) where 'W_o' is initial mass and 'W' is the mass remained at time 't'. The corresponding dissolution rates and dissolution efficiency (DE_{60}) values calculated as per Khan[5] are given in Table 2. The dissolution rate of ITR was increased as the concentration of the carrier in the dispersion was increased from 5 to 10%. At 20% concentration, a reduced dissolution was observed with all the three carriers due to aggregation and granular nature of the product formed. Hence, a 10% carrier concentration was considered optimum for enhancing the dissolution rate of ITR. Among the three carriers, HPC gave highest improvement (7.5 fold) in the dissolution rate of ITR at 10% concentration. The higher dissolution rate observed with this dispersion is due to the presence of ITR in amorphous form in this dispersion. Since the amorphous form is the highest energy form of a pure compound, it produced faster dissolution rate. Micronisation, reduced crystallinity in the case of other solid dispersions and improved wettability of drug particles due to hydrophillic carriers are also responsible for improved and higher dissolution rates and DE values observed with the solid dispersions.

All the tablets prepared were found to contain ITR within 100±5% of the labeled claim. Hardness of the tablets was in the range of 8-10 kg/sq.cm. and was satisfactory. The percentage weight loss in the friability test was less than 1% in all the batches prepared. All the tablet formulations disintegrated rapidly within 2 min fulfilling the official disintegration time specification for uncoated tablets. Dissolution of ITR from the tablets followed first order kinetics ($r > 0.98$). The corresponding first order dissolution rates (K_1) and / DE_{60} values calculated as per Khan[5] are given in Table 2. Tablets compressed from solid dispersions (T_2, T_3, T_4) gave higher rates of dissolution and dissolution efficiency values when compared to the tablets made with ITR itself (T_1) and the two commercial brands of itraconazole capsules (C_1 and C_2).

Thus the dissolution rate of ITR can be significantly enhanced by its solid dispersion in PVP, HPMC and HPC. These dispersions could be formulated into

TABLE 2 : DISSOLUTION RATE OF ITRACONAZOLE FROM SOLID DISPERSIONS AND TABLETS

Formulation	Per cent ITR dissolved at 3 times (min) x $\bar{x}$ ± s.d			DE_{60}(%)	K x 10^2 $\bar{x}$±s.d.	K_1 x 10^3 ($mg^{1/3}min^{-1}$)	(min^{-1})
	15	30	60				
Itraconazole (ITR)	12.2±1.8	21.9±1.0	35.6±1.0		19.9±0.3	0.90 (1.9)*	-
ITR-PVP (19:1) SD	8.9±1.2	28.2±2.4	65.9±1.8		30.6±1.5	1.70 (5.8)	-
ITR-PVP (9:1) PM	12.8±0.3	21.5±0.3	37.5±0.3		20.7±0.3	1.19 (1.4)	-
ITR-PVP (9:1) SD	9.6±0.5	30.8±0.7	74.0±1.5		33.3±0.7	1.78 (2.9)	-
ITR-PVP (8:2) SD	8.8±0.5	28.7±0.3	71.4±1.6		31.5±0.4	1.64 (1.4)	-
ITR-HPMC (19:1) SD	7.9±1.3	20.4±1.8	51.8±2.4		22.7±1.5	1.15 (8.6)	-
ITR-HPMC (9:1) PM	13.3±0.2	22.3±0.4	39.4±0.7		21.4±0.2	1.23 (2.8)	-
ITR-HPMC (9:1) SD	26.0±2.3	52.7±1.3	84.5±1.4		48.8±0.4	3.42 (3.4)	-
ITR-HPMC (8:2) SD	28.2±1.6	50.8±2.3	77.4±1.5		46.5±1.0	3.25 (6.1)	-
ITR-HPC (19:1) SD	7.4±0.7	17.3±0.7	43.4±2.1		19.2±0.7	0.96 (5.2)	-
ITR-HPC (9:1) PM	14.1±0.4	24.2±0.5	41.3±0.8		23.0±0.2	1.37 (2.6)	-
ITR-HPC (9:1) SD	30.9±1.3	82.1±1.6	92.3±1.0		62.6±0.8	6.75 (3.9)	-
ITR-HPC (8:2) SD	21.1±1.5	49.4±2.7	79.8±1.3		44.5±1.0	3.13 (7.0)	-
T_1	44.0±1.8	52.9±1.5	62.1±1.6		46.7±1.5	-	25.1 (3.1)
T_2	65.8±1.1	91.1±0.5	99.4±0.2		76.2±0.5	-	80.6 (2.4)
T_3	65.0±1.1	95.2±0.7	99.6±0.5		77.1±0.2	-	101.8 (4.5)
T_4	68.7±1.1	95.4±0.5	99.6±0.8		77.9±0.8	-	102.9 (3.9)
C_1	12.7±0.6	26.5±3.6	56.7±11.2		26.1±4.1	-	10.0 (2.6)
C_2	44.9±1.4	77.6±2.3	97.8±2.7		66.1±1.9	-	49.9 (4.8)

SD: Solid Dispersion; PM: Physical Mixture; T_1, T_2, T_3, T_4 are tablets formulated employing ITR itself and its solid dispersions (9:1) in PVP, HPMC and HPC respectively; C_1 and C_2 are two commercial brands of itraconazole capsules; *Figures in parentheses are coefficient of variation (%) values; K = Hixson - Crowell's cube root dissolution rate constant; K_1 = First order dissolution rate constant.

tablets by direct compression method. The resulting tablets, apart from fulfilling all official and other specifications, exhibited higher dissolution rates of itraconazole.

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