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COMMUNICATION

Investigation of Dissolution Enhancement of Itraconazole by Solid Dispersion in Superdisintegrants

K. P. R. Chowdary* and Sk. Srinivasa Rao

Industrial Pharmacy Division, Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530 003, India

ABSTRACT

Solid dispersions of itraconazole (ITR) in lactose, microcrystalline cellulose (MCC), and three superdisintegrants (Primogel, Kollidon CL, and Ac-Di-Sol) and their formulation into tablets were investigated with an objective of enhancing the dissolution rate of ITR from tablet formulations. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) were used to characterize the dispersions. A marked enhancement in the dissolution rate of ITR was observed with all the excipients. The order for the excipients to enhance the dissolution rate was Ac-Di-Sol > Kollidon CL > Primogel > MCC > lactose. Solid dispersions in superdisintegrants gave much higher rates of dissolution than the dispersions in other excipients. Ac-Di-Sol gave the most improvement (28-fold) in the dissolution rate of ITR at a 1:1 drug: excipient ratio. Solid dispersions in superdisintegrants 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. XRD indicated the presence of ITR in amorphous form in the dispersions. DSC indicated a weak interaction between ITR and the excipients. Micronization and conversion of the drug into the amorphous form and the fast disintegrating and dispersing action of the superdisintegrants contribute to the enhancement of the dissolution rate of ITR from its solid dispersions in superdisintegrants and their corresponding tablet formulations.

* To whom correspondence and reprint requests should be addressed.

INTRODUCTION

Itraconazole (ITR) is an orally active, broad spectrum triazole antifungal agent. It provides an effective oral treatment of several deep mycoses, including aspergillosis and candidiasis (1). It is a powder that is white to slightly yellowish, and it is insoluble in water at pH in the range 1 to 12. Because of its poor aqueous solubility, its absolute oral bioavailability is only 55% (2).

Among the various approaches, solid dispersion techniques have often proved to be very successful to improve the dissolution and bioavailability of poorly soluble drugs (3). A number of water-soluble materials, such as citric acid, polyethylene glycols, polyvinyl pyrrolidone, and more, and water-insoluble materials, such as silica gel, starch, microcrystalline cellulose (MCC), and so on, are reported (4,5) as carriers for solid dispersions to improve the dissolution rates.

In the present study, solid dispersions of ITR in lactose, MCC, and three superdisintegrants (Primogel, Kollidon CL, and Ac-Di-Sol) and their formulation into compressed tablets were investigated with an objective of enhancing the dissolution rate of ITR from tablet formulations. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) were used to characterize the dispersions.

EXPERIMENTAL

Materials

Itraconazole (a gift sample from M/s Cheminor Drugs, Ltd., Hyderabad, India), lactose IP, microcrystalline cellulose (FMC, PH-105), sodium starch glycolate (Primogel), crospovidone (Kollidon CL, BASF), croscarmellose sodium (Ac-Di-Sol, FMC), talc IP, magnesium stearate IP, sodium lauryl sulfate (SLS; BDH), and dichloromethane (Qualigens) were used.

Preparation of Solid Dispersions of Itraconazole

ITR-excipient dispersions in the ratios 9:1, 1:1, and 1:9 were prepared employing lactose, MCC, Primogel, Kollidon CL, and Ac-Di-Sol as excipients. ITR was dissolved in dichloromethane to a clear solution. The ITR solution was then poured onto the excipient, put in a mortar, and mixed thoroughly. The wet solid mixture was dried at 60°C for 4 hr. The dried mass was mixed well and sifted through 100 mesh.

Preparation of Physical Mixtures

ITR and excipient (lactose, MCC, Primogel, Kollidon CL or Ac-Di-Sol) were passed through 100 mesh and then accurately weighed in a 1:1 ratio. They were mixed well in a mortar and sifted through 100 mesh.

Estimation of Itraconazole

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 was validated for linearity, accuracy, precision, and interference. The method obeyed Beer's law in the concentration range 0–20 μg/ml. The excipients used in the dispersions and SLS used in the dissolution rate study did not interfere in the method.

Preparation of Itraconazole Tablets

Two series of tablets, each containing 100 mg of ITR, were prepared by a conventional wet granulation method employing starch paste as the binder. In one series, ITR itself and potato starch (15%), Primogel (4%), Kollidon CL (4%), and Ac-Di-Sol (4%) were used as disintegrants. In another series, solid dispersions of ITR in superdisintegrants (1:1) were used. Tablet granulations were compressed into tablets to a hardness of 6–8 kg/cm^2 on a Cadmach single-punch tablet machine.

Tablets were tested for uniformity of weight as per the Indian Pharmacopeia (1996). Disintegration times were determined in a Thermonic tablet disintegration test machine (USP standard) 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.

Dissolution Rate Study

The dissolution rate of ITR from the solid dispersions and the tablets 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. 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°C ± 1°C 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.

X-ray Diffraction Study

X-ray powder diffraction patterns of ITR and its solid dispersions were obtained using a Philips X-ray powder diffractometer (model PW 1710) employing CuK_α radiation. The diffractograms were run at 2.4°/min in terms of the 2θ angle.

Differential Scanning Calorimetry

DSC was performed on ITR and its solid dispersions using a Sieko (Japan) DSC model 220C. Samples were sealed in aluminum pans, and the DSC thermograms were recorded at a heating rate of 10°C/min from 50°C to 300°C.

RESULTS AND DISCUSSION

All the solid dispersions prepared were fine and free flowing powders. Low coefficient of variation (<2%) in the percentage ITR content of the dispersions indicated uniformity of drug content in each batch prepared. The physical state of the drug in the dispersions was evaluated by XRD and DSC. The X-ray diffractograms of ITR, lactose, and MCC exhibited characteristic diffraction patterns because of their crystalline nature. The diffractograms of Primogel, Kollidon CL, and Ac-Di-Sol did not show sharp peaks, whereas in the case of ITR dispersions

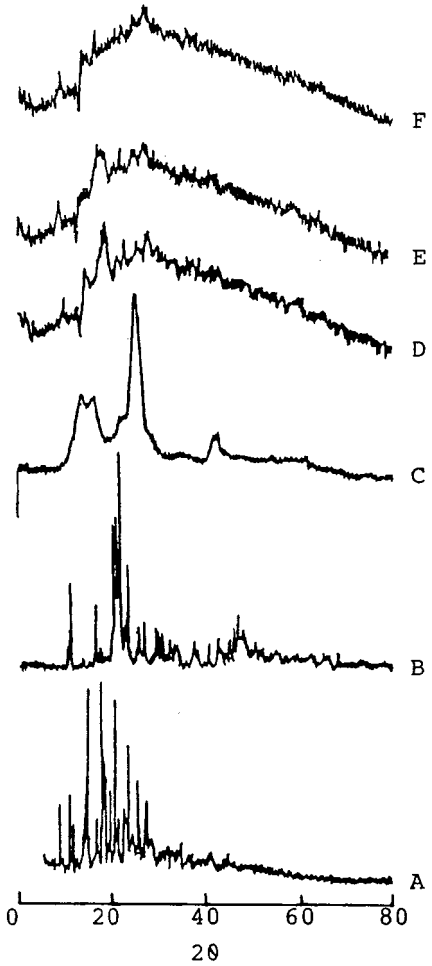

Figure 1. X-ray diffractograms of (A) itraconazole and its solid dispersions (1:1) in (B) lactose, (C) MCC, (D) Primogel, (E) Kollidon CL, and (F) Ac-Di-Sol.

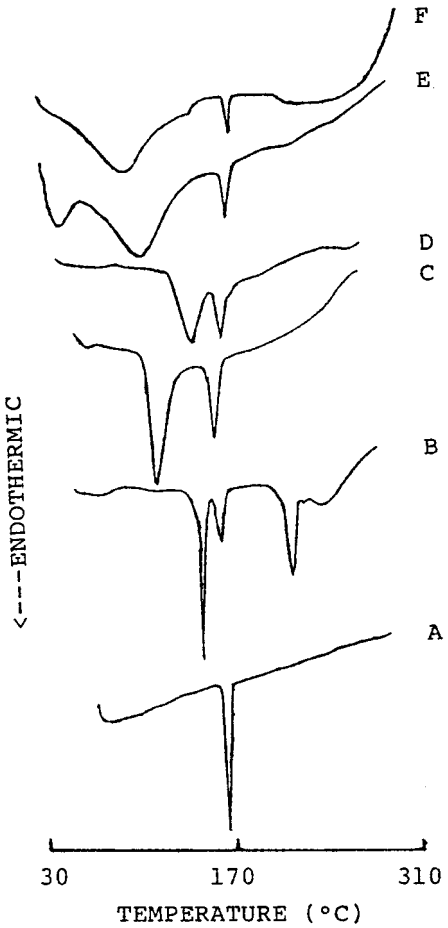

Figure 2. DSC thermograms of (A) itraconazole and its solid dispersions (1:1) in (B) lactose, (C) MCC, (D) Primogel, (E) Kollidon CL, and (F) Ac-Di-Sol.

Table 1

Dissolution of Itraconazole from Physical Mixtures and Solid Dispersions

Excipient, Drug:Excipient Ratio, Form	Percentage ITR Dissolved			DE_{60} (%)	$K \times 10^2$ ($mg^{1/3} \cdot min^{-1}$)
	15 min	30 min	60 min		
ITR	12.2	21.9	35.6	20.0	0.29 (4.4)[a]
Lactose, 1:1, PM	13.8	25.1	37.8	21.5	1.41 (1.2)
Lactose, 1:1, SD	18.9	46.1	81.9	44.0	2.87 (2.4)
MCC, 1:1, PM	14.1	26.3	39.2	22.4	1.50 (2.0)
MCC, 1:1, SD	30.7	68.9	88.5	56.6	4.98 (1.0)
Primogel, 1:1, PM	15.0	28.7	46.7	27.1	1.64 (4.8)
Primogel, 1:1, SD	46.1	76.7	87.2	63.1	5.98 (3.7)
Killidon CL, 1:1, PM	17.6	30.2	46.4	27.8	1.74 (3.3)
Kollidon CL, 1:1, SD	57.1	87.3	89.1	69.4	7.69 (2.2)
Ac-Di-Sol, 1:1, PM	23.6	36.3	50.3	32.5	2.17 (3.0)
Ac-Di-Sol, 1:1, SD	63.2	88.8	89.2	71.5	8.02 (2.5)

PM = physical mixture; SD = solid dispersion.
[a] Figures in parentheses are coefficient of variation (%) values.

in lactose, MCC, Primogel, Kollidon CL, and Ac-Di-Sol, the sharp diffraction peaks of ITR disappeared (Fig. 1). The lack of sharp peaks in the diffractograms of solid dispersions indicates that the drug is in the amorphous form in these dispersions.

The DSC thermograms of ITR and its dispersions are shown in Fig. 2. The DSC thermograms of ITR exhibited an endothermic peak at 168°C, corresponding to its melting point. Solid dispersions of ITR in various excipients also showed a melting peak of ITR, but at slightly lower temperatures, in the range 159°C–165°C, indicating a weak interaction between the ITR and the excipients.

The dissolution of ITR itself and from all the solid dispersions obeyed the Hixson-Crowell cube root dissolution rate model ($r = 0.98–0.99$). The corresponding dissolution rates and dissolution efficiency DE_{60} values calculated per the method of Khan (6) are given in Table 1. Solid dispersions of ITR exhibited higher rates of dissolution and DE_{60} values than the corresponding physical mixtures and ITR itself (Table 1). The order for the excipients to enhance the dissolution rate was Ac-Di-Sol > Kollidon CL > Primogel > MCC > lactose. A 10-, 17-, 21-, 26-, and 28-fold increase in the dissolution rate of ITR was observed with lactose, MCC, Primogel, Kollidon CL, and Ac-Di-Sol, respectively, at a 1:1 drug:excipient ratio. In each case, the dissolution rate increased

Table 2

Dissolution of Itraconzole from Tablets Formulated with Its Dispersions in Superdisintegrants

Formulation	Excipient (%)	Percentage ITR Dissolved			DE_{60} (%)	$K \times 10^3$ (min^{-1})
		15 min	30 min	60 min		
T1	Potato starch (15%)	2.3	3.2	6.4	3.3	1.2 (1.6)[a]
T2	Primogel (4%)	17.3	28.1	50.2	27.3	11.0 (3.6)
T3	Kollidon CL (4%)	18.4	33.0	62.0	32.8	13.3 (3.0)
T4	Ac-Di-Sol (4%)	29.3	57.0	76.8	48.6	28.4 (4.5)
T5	ITR-Primogel (1:1), SD	39.9	65.2	88.7	56.9	35.1 (2.8)
T6	ITR-Kollidon CL (1:1), SD	49.2	72.3	93.1	63.0	43.1 (1.2)
T7	ITR-Ac-Di-Sol (1:1), SD	56.5	76.9	92.5	66.9	48.9 (3.6)

SD = solid dispersion.
[a] Figures in parentheses are coefficient of variation (%) values.

as the proportion of excipient increased. Superdisintegrants, Primogel, Kollidon CL, and Ac-Di-Sol gave higher improvement in the dissolution rate of ITR.

Monkhouse and Lach (5) attributed this kind of increase in the dissolution rate to the micronization of drug particles on the large surface of the excipient when the solvent is evaporated during the preparation of the dispersions. In addition to the micronization, conversion of ITR to an amorphous form during the preparation might have also contributed to the increased dissolution rates observed with the solid dispersions. Since the amorphous form is the highest energy form of a pure compound, it produces faster dissolution rates. The higher dissolution rates observed with the dispersions in superdisintegrants when compared to other excipients may be due to their easy and rapid dispersibility in the aqueous dissolution fluids.

All the tablets prepared were found to contain ITR within the 100% ± 5% of the label claim. Hardness of the tablets was in the range of 7–9 kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was <1% in all the batches prepared. All the tablet formulations rapidly disintegrated within 2–3 min except the one made with potato starch as the disintegrant.

Dissolution of ITR from the tablets followed first-order kinetics (r = 0.98–0.99). The corresponding first-order dissolution rates K_1 and DE_{60} values are given in Table 2. Tablets formulated employing dispersions of ITR in superdisintegrants gave much higher dissolution rates and efficiency values than the tablets formulated employing ITR itself and Primogel, Kollidon CL, and Ac-Di-Sol as disintegrants in their effective concentration ranges.

CONCLUSIONS

The results of the study indicated that the dissolution rate of ITR can be significantly enhanced by its solid dispersion in lactose, MCC, Primogel, Kollidon CL, and Ac-Di-Sol. Superdisintegrants (Primogel, Kollidon CL, and Ac-Di-Sol) gave much higher rates of dissolution than other excipients (lactose and MCC). Ac-Di-Sol gave the highest improvement (28-fold) in the dissolution rate of ITR at a 1:1 drug:excipient ratio. Solid dispersions in superdisintegrants 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.

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