CHAPTER - IV

PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION OF ITRACONAZOLE

4.1 INTRODUCTION

Development of solid dosage forms for water insoluble drugs has been a major challenge for pharmaceutical scientists for decades. Numerous efforts have been made to improve water solubility of drug. These includes,

- Reducing particle size to increase surface area (Kubo H. *et al.,* 1996).
- Solubiliation in surfactant systems (Martis L. *et al.,* 1998).
- Formation of water soluble complexes (Cassella R. *et al.*, 1998).
- Use of pro-drug (Trapani G. *et al.,* 1998).
- Manipulation of solid state of drug substance by decreasing crystallinity of drug substance through formation of amorphous solids (Karanth H. *et al.,* 2007).

The term "solid dispersion" is applied to those systems in which drug particles are homogeneously distributed throughout a solid matrix. This system provides the possibility of reducing particle size of drugs to nearly molecular level, to transform the drug from crystalline to partially amorphous. Thus, the development of solid dispersions is a practically viable method to enhance solubility of poorly water-soluble drugs and overcame the limitations associates with previous approaches such as salt formation, solubilization by co solvents, and particle size reduction (Wadke D.A. *et al.,* 1989). Solid dispersions are prepared by using various technique such as kneading technique (trituration method), spray drying technique (Richer C. *et al.,* 2004), hotmelt extrusion (El-Egakey M.A *et al.,* 1971) and supercritical fluid technology (Sunkara G. *et al.,* 2002).

An ideal drug for vaginal delivery system should dissolve in vaginal fluids and disperses throughout the vaginal cavity. Although, optimal action will be observed with solution form of the drug. A colloidal dispersion may also be preferred for local action in vaginal cavity (Garg S. *et al.,* 2003). ITR possess very poor water solubility (~4 µg/ml at acidic pH) that makes it difficult to formulate in bioadhesive vaginal delivery system. One approach, which has been applied for producing BVDDS of ITR, is use of solid dispersion of ITR (SDITR) and hydroxypropyl methylcellulose (HPMC) E15 in which drug particles are homogeneously distributed throughout the hydrophilic polymer (Verreck G. *et al.,* 2003). SDITR can improve wettability of ITR which may help in development of bioadhesive delivery system and dispersing ITR throughout the vaginal cavity. Also, SDITR forms colloidal dispersion in simulated vaginal fluid (SVF) is essential for local action in vaginal cavity.

4.2 MATERIALS

ITR was procured as a gift sample from Intas Pharmaceutical Limited (Ahmedabad, India). HPMC E15 was gifted by Colorcon Asia Pvt. Ltd. (Goa, India). Dichloromethane, methanol, and polyethylene glycol (PEG) 6000 were purchased from S. D. Fine Chemicals (Mumbai, India). Chito Clear® chitosan was received as gift sample from Primax Biopolymers, Irland. β cyclodextrin, PVP K30, d- sorbitol, d-manintol, gurgum, polyvinyl alcohol, were purchased from Himedia (Mumbai, India). All other chemicals used were of analytical grade.

4.3 EXPERIMENTAL

4.3.1 Analytical Method (UV Spectrophotometric Method)

Calibration Curve in Methanol

ITR stock solution was prepared by dissolving 50mg of ITR into 100ml of methanol and further diluting 1 ml of this solution to 10ml. For calibration curve, solution of 5, 10, 15, 20, 25, 30 and 35µg/ml were prepared by diluting 1 to 7ml of standard stock solution to 10ml with methanol. Absorbance was measured at 262nm against methanol as blank. Shimatzu UV-1700 UV visible spectrophotometer with quartz cells of 10-mm path length was used for absorbance measurement.

4.3.2 Preliminary Trials and Optimization Studies

Aim of the preliminary trials was to find out suitable technique and suitable polymers for preparation of SDITR (i.e. homogeneously distribution of ITR throughout the hydrophilic polymer). Various polymers such as PVP K30, d-manintol, PEG 6000, d-sorbitol, chitosan, HPMC E15 premium, and polyvinyl alcohol were explored in various proportions for preparation of SDITR. Different techniques such as simple triturating method (kneading method), conventional solvent evaporation method and spray drying were tried for preparation of solid dispersion.

4.3.3 Preparation of SDITR

SDITR were prepared by spray drying technique, using specific amount of ITR and diffrerent proportion of HPMC E15 premium. ITR and HPMC E15 were dissolved in a mixture of dichloromethane and methanol 80:20 (v/v) to obtain homogeneous non aqueous dispersion. Spray drying of these solutions was conducted using a laboratory-scale spray dryer (Labultima-Lu 227, Mumbai, and India.) under the following conditions: inlet air temperature 70°C; outlet air temperature 50°C; aspirator level 1600; pump speed 5.0 ml/min.

4.3.4 Evaluation of Solid Dispersions

4.3.4.1 Drug Solubility

The solubility of ITR was determined in the simulated vaginal fluid (SVF) for solid dispersions prepared with PEG 6000, d-sorbitol, PVP K30, d-manintol, chitosan, HPMC E15 premium, and polyvinyl alcohol. Solid dispersions equivalent to 10mg ITR was transferred in test tube and add 10ml of SVF. The tube was sonicate for 10 minute followed by shaking at room temperature for 24h. After shaking, tube containing solution was centrifuged at 2000RPM for 10 min. Then, upper portion was filtered through 0.45µm membrane filter. Pipette out 1ml of this filtrate, transfer into 10ml volumetric flask and diluted with SVF upto mark. ITR concentration was then determined by UV spectrophotometer using SVF as blank.

4.3.4.2 Differential Scanning Calorimetry (DSC)

Thermal characteristics of physical mixtures of ITR and HPMC E15 Premium and the solid dispersions were determined by differential scanning calorimetry (DSC 60, Shimadzu, Japan). Samples equivalent to 2mg of ITR were placed in aluminum pans and DSC analysis were carried out at a nitrogen flow of 30 ml/min and heating rate of 15°C/min from 38°C to 200°C.

4.3.4.3 Powder X- ray Diffraction (XRD)

The powder X-ray diffraction patterns were determined for ITR, HPMC E15 premium alone, their physical mixture and solid dispersions. X-ray diffractograms were obtained using the X-ray diffractometer (Rigaku American Corporation, England) with voltage 1 kV, current 300 mA and 2θ over a 5 - 80 range.

4.3.4.4 Content Uniformity

Solid dispersions equivalent to 10mg of ITR was dispersed in 10ml of water and were sonicated for 10min to destroy any agglomerates. Subsequently, diluted with methanol and analyzed by using UV spectrophometer at 262nm. Content uniformity of solid dispersions was analyzed in triplicate.

4.3.5 Stability Study

To assess the chemical and physical stability of solid dispersions, prepared SDITR was stored at accelerated stability conditions (40±2°C and 75±5% RH) and intermediate stability condition (30±2°C and 65±5% RH) for the period of six months.

A visual inspection for change in color and ITR content estimation was carried out periodically at the end of 1, 2, 3 and 6 months of the stability study. The physical stability was assessed by the DSC method as describe above.

4.4 RESULTS AND DISCUSSION

4.4.1 Calibration Curve of ITR

An overlay spectrum of ITR in methanol is shown in **Fig.** 4.2 Experimental set (5, 10, 15, 20, 25, 30 and 35µg/ml) was analyzed in triplicate by using UV spectrophotometer. **Table** 4.1 represents absorbance response of three experimental set. The calibration curve for ITR was constructed by plotting mean absorbance values vs. concentration; this was found to be linear over an analytical range of 5-35 µg/ml. **Fig.** 4.1 shows the calibration curve of ITR. A linear regression by the least squares method was then applied. The calculated value for the determination of coefficient (R^2) was found 0.9998 indicating strong linear relationship between the variables.

Table. 4.1 Absorbance response of ITR in different experimental set.

Concentration (µg/ml)	Absorbance measured at 262nm			Avg.	SD	%RSD
	Set- 1	Set- 2	Set- 3			
5	0.249	0.247	0.252	0.249	0.003	1.029
10	0.461	0.470	0.467	0.466	0.004	0.908
15	0.702	0.707	0.713	0.707	0.006	0.815
20	0.911	0.929	0.923	0.921	0.009	1.008
25	1.141	1.162	1.149	1.151	0.011	0.913
30	1.368	1.395	1.403	1.389	0.018	1.330
35	1.581	1.615	1.609	1.602	0.018	1.110

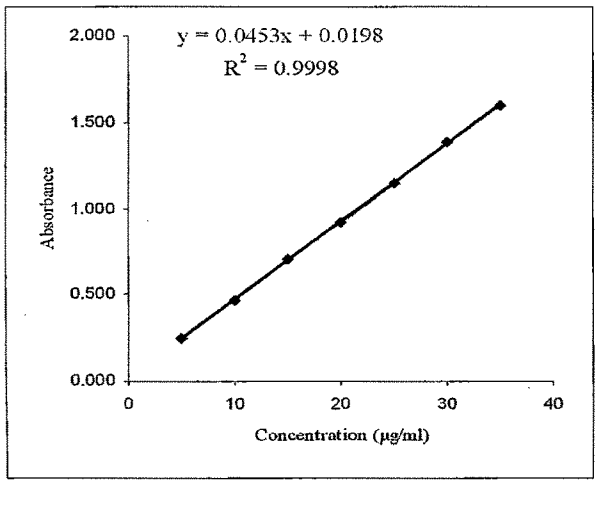

Fig. 4.1 Calibration curve of ITR in methanol

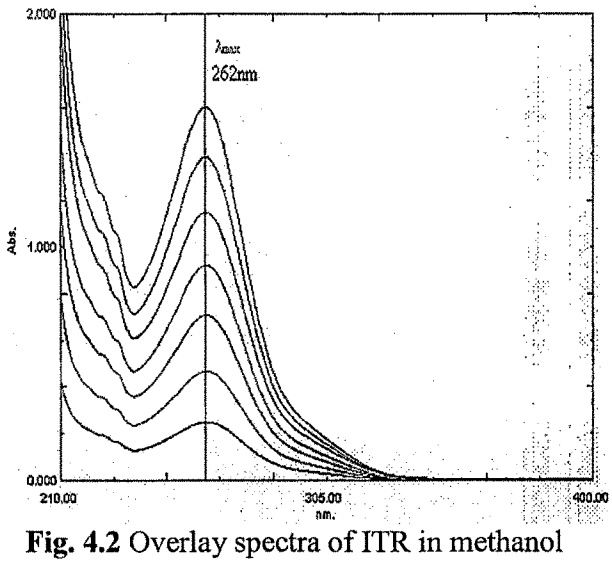

Fig. 4.2 Overlay spectra of ITR in methanol

4.4.2 Solubility

In preliminary trials, solid dispersions of ITR were prepared with various polymers by using simple triturating method and conventional solvent evaporation method. The results of solubility studies (given in **Table** 4.2) showed that SDITR prepared with d-manintol, PEG 6000, PVP K30, d-sorbitol and polyvinyl alcohol did not enhance the solubility of ITR. The extent of increase in solubility of ITR with HPMC E15 premium was observed greater than other polymers. Hence, HPMC E15 premium was selected from preliminary trials for preparation of SDITR. **Fig.** 4.3 showed UV spectrum of SDITR. The maximum absorbance of SDITR was found at 265nm. In order to optimize drug-polymer ratio, various proportion of ITR: HPMC E15 premium (1:1, 1:1.5, 1:2, and 1:3) was tried. SDITR prepared by spray drying technique showed greater extent of solubility as compared to conventional solvent evaporation method. ITR: HPMC E15 premium ratio 1:2 showed more solubility than 1:1.5 w/w, but consideration of formulation point 1.5w/w ratio was selected for further study. The size of a potential dosage form with 100 mg dose was considered in this assessment by choosing the lowest polymer/drug ratios that gave adequate physiochemical properties.

Table 4.2 Solubility of SDITR in SVF

Preparation Method	**Polymers**	**Solubility (µg/ml)**
Conventional solvent evaporation	d-sorbitol	-
	PEG 6000	12.33 ± 3.80
	PVP K30	-
	Chitosan	15.70 ± 2.10
	d-manintol	-
	polyvinyl alcohol	-
	HPMC E15 premium (1:2)	38.45 ± 2.83
Spray drying	HPMC E15 premium (1:1)	32.33 ± 3.05
Spray drying	**HPMC E15 premium (1:1.5)**	**87 ± 3.61**
Spray drying	HPMC E15 premium (1:2)	94.33 ± 2.08
Spray drying	HPMC E15 premium (1:2.5)	98.33 ± 2.52
ITR powder	-	-

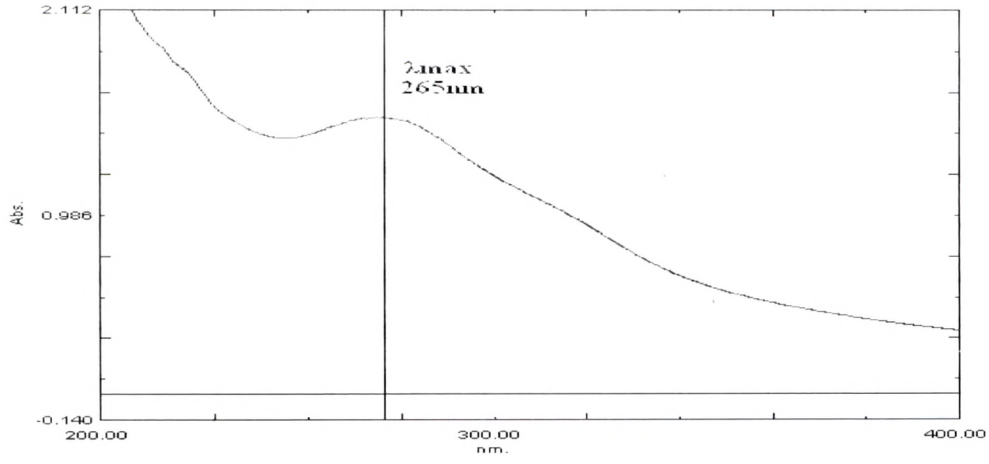

Fig. 4.3 UV spectrum of SDITR in SVF

4.4.3 Differential Scanning Calorimetry

DSC studies were carried out for thermal characterization of solid dispersion. DSC thermogram obtained for pure ITR, HPMC E15, their physical mixture and SDITR are shown in **Fig.** 4.4. Pure ITR shows sharp endotherms at 166°C that corresponds to melting point of ITR. DSC thermogram of SDITR shows complete absence of ITR peak which indicates formation of an amorphous solid dispersion of ITR and HPMC E15 within investigated range of drug polymer ratios.

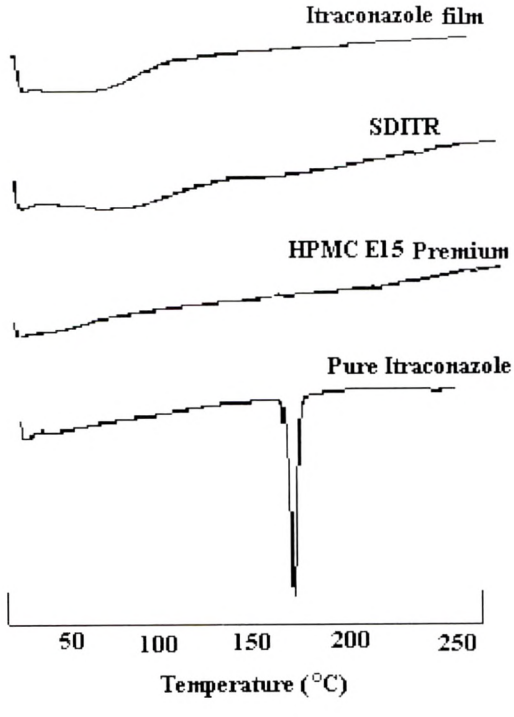

Fig. 4.4 Overlay DSC thermograms of ITR, HPMC, physical mixture and solid dispersion.

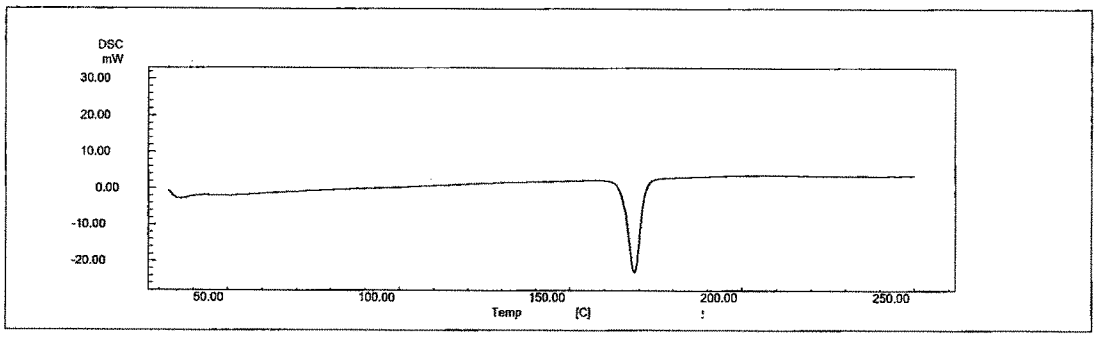

Fig. 4.5 ITR thermogram

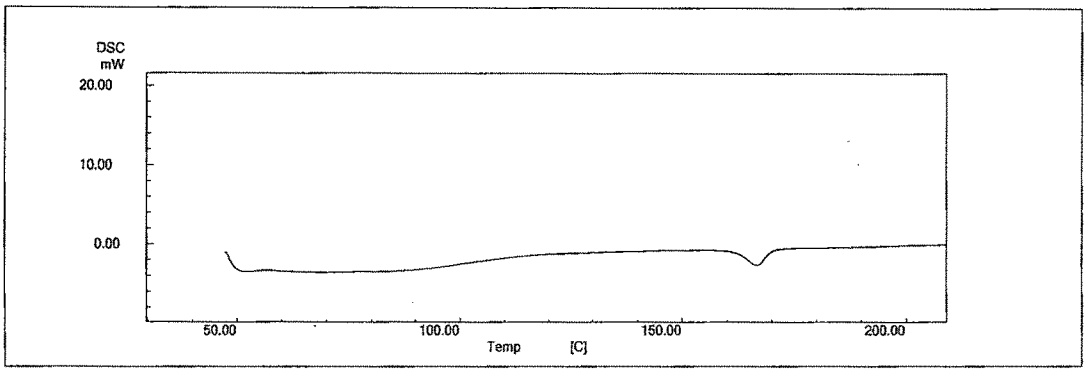

Fig. 4.6 Thermogram of physical mixture

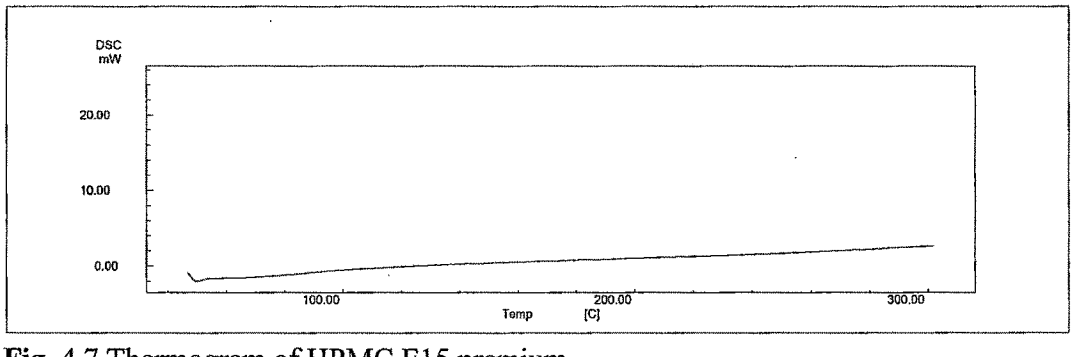

Fig. 4.7 Thermogram of HPMC E15 premium

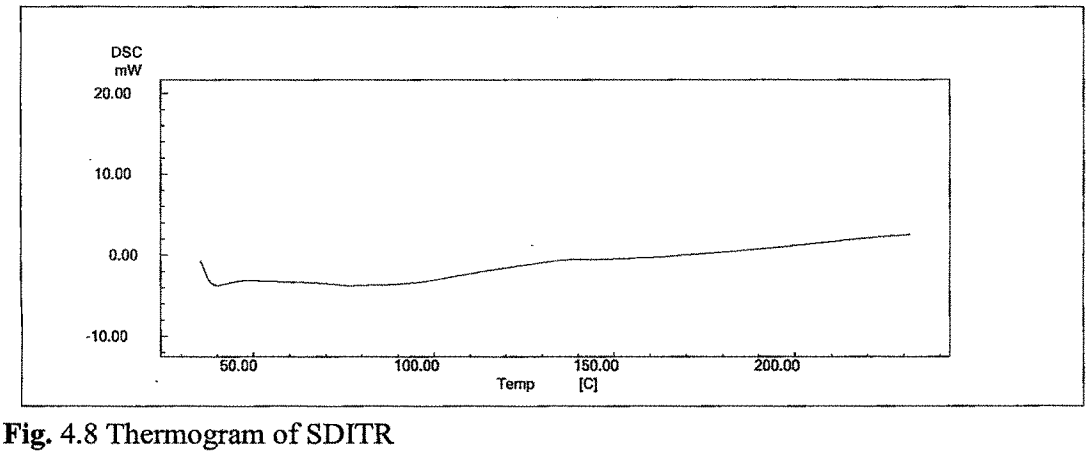

Fig. 4.8 Thermogram of SDITR

4.4.4 Powder X- ray Diffraction

Fig. 4.9 shows the representative XRD patterns of pure powder ITR, HPMC E15 and solid dispersions. Absence of crystalline peak for HPMC E15 indicates amorphous behavior. The characteristic crystalline peak was observed for pure ITR. However, SDITR did not show the crystalline peak which indicates transition of ITR from crystalline to an amorphous state, results in enhance solubility of drug in SVF.

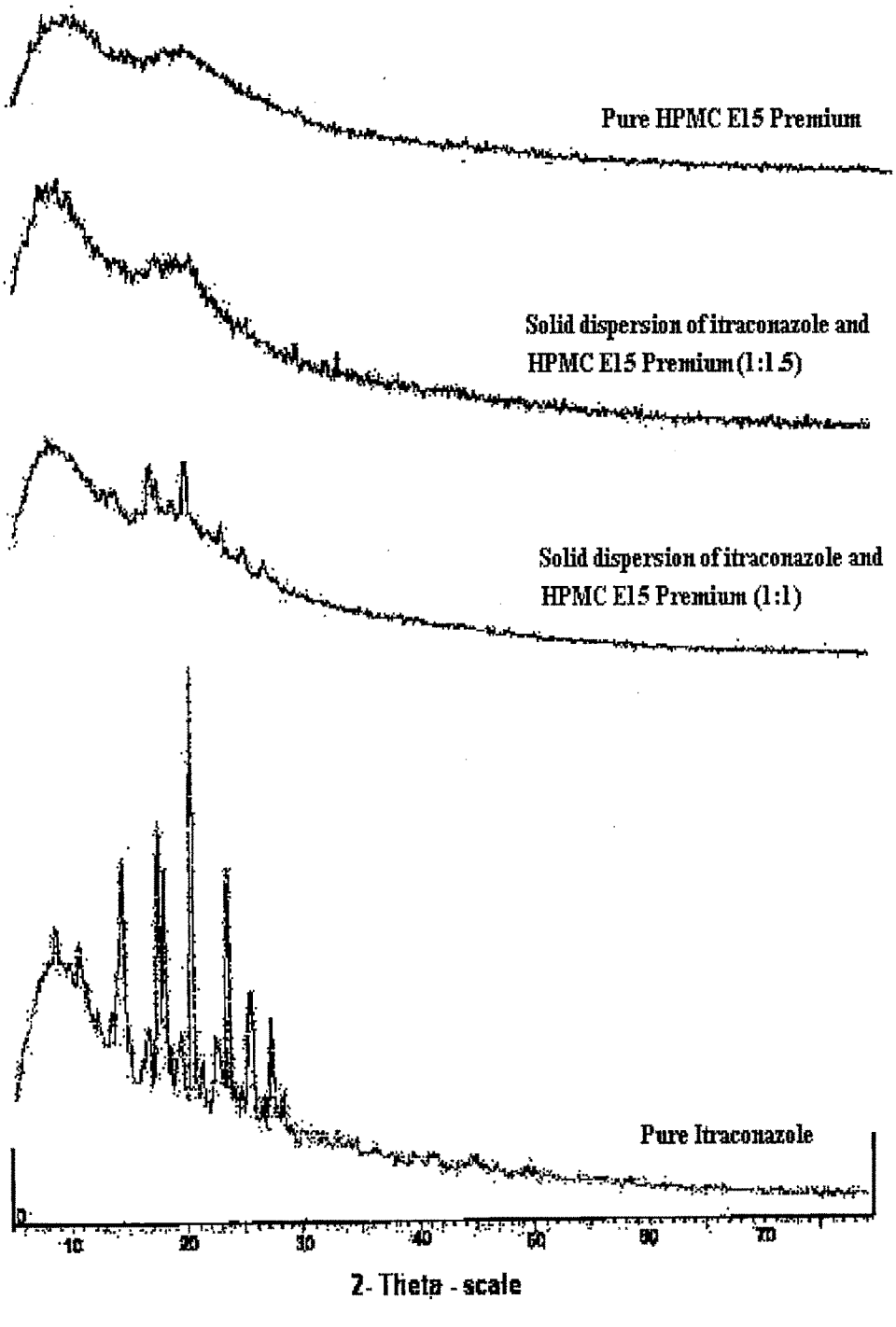

Fig. 4.9 Overlay of X- ray diffraction pattern for pure ITR, HPMC and SDITR

X -ray diffraction patterns of the physical mixtures were similar to those obtained for the pure ITR. Taken together with DSC data, these results indicate a formation of amorphous ITR in solid dispersions with HPMC E15 premium at drug: polymer ratio of 1:1.5.

4.4.5 Drug Content in Solid Dispersions

The assay of solid dispersions prepared using spray dried method was found in range of 97.20 to 103.45%. Therefore, the spray drying method appears applicable for preparation of SDITR with high content uniformity.

Table. 4.3 Content uniformity of ITR in solid dispersions prepared by spray drying method

Drug :Polymer ratio (ITR:HPMC E15)	**Solid dispersions equivalent to 10mg of ITR(mg)**	**ITR content in solid dispersions (%)**	**Mean ± SD (n=3)**
Pure drug	10	99.96	99.23 ± 1.00
	10	100.26	
	10	98.27	
1:1	20	97.62	99.01 ± 1.56
	20	98.70	
	20	100.70	
1:1.5	25	102.47	102.1 ± 1.47
	25	103.35	
	25	100.48	
1:.2	30	99.6	100.04 ± 1.81
	30	98.49	
	30	102.03	
1:2.5	35	98.5	97.47 ± 1.0
	35	96.51	
	35	97.39	

4.4.6 Stability Studies

Overall results from the stability studies indicated that there is no significant change observed in color, and assay of ITR in solid dispersions stored at intermediate and accelerated conditions. Also, no recrystallization of the ITR was observed in this time period suggesting their physical stability under different storage condition. These observations indicate that

SDITR prepared with HPMC E15 by spray drying method is stable up to 6 months under the storage conditions tested.

4.5 CONCLUSION

Solid dispersions of ITR prepared successfully with HPMC E15 by spray drying method. ITR was presented as an amorphous state in the solid dispersions at the drug to polymer ratio of 1:1.5 (w/w) according to results of XRD and DSC analysis. It shows greater extent of increase in drug solubility over the pure drug. The solid dispersion technique used in our study involve simple preparation step and produced solid dispersions with high content uniformity.

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