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Research Article

PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION OF ITRACONAZOLE

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ABSTRACT
The aim of the present study was to improve the dissolution rate and oral bioavailability of a poorly water soluble drug, itraconozole (ITR) by its adsorption on a porous calcium silicate (FLR). The drug was adsorbed on FLR by adsorption method. solid dispersion of various composition were prepared using Porous Calcium Silicate (FLR), Silicic Acid, Colloidal Silica and Silica Gel (Neutral) (2:1, 1:1, 1:2, 1:3, Physical mixture). Crystallinity of the drug in the solid dispersion was evaluated by differential scanning calorimetry and powder X-ray diffraction analysis. Itraconazole was released at a much higher rate from solid dispersion and physical mixture as compared to that as of itraconazole faster dissolution was exhibited by solid dispersion containing 1:2 ratios of drug and polymer compared to physical mixture and itraconazole. The increase in dissolution rate of the drug may be due to decrease in crystalinity.
Keywords: Porous calcium silicate, solid dispersion, dissolution rate, itraconazole

INTRODUCTION

Solubility is the major problem for various drugs in pharmaceutical industry. Many drugs show poor aqueous solubility, which result in poor bioavailability of the drug. Solubility enhancement processes are widely used in pharmaceutical industry to improve the dissolution and bioavailability of poorly water soluble drug. The efficacy of drug response is mainly dependent on dissolution and bioavailability. Solid dispersion technique can be used to increase the dissolution and absorption of several in soluble drug. Number of insoluble drugs has been shown to improve their dissolution character when converted to solid dispersion. In 1972, Monkhouse and Web suggested a new approach of increasing the dissolution rate of insoluble drug by using adsorbent. It is based on concept of increasing the surface available for contact with dissolution media and this is accomplished by equilibration of drug in an organic solvent (acetone) on an insoluble excipient with an extensive surface e.g. fumed silicone dioxide. The drug is deposited in "Minuscular form" on surface of an adsorbent, this new term implies that the drug has undergone, molecular micronization when it is dispersed on the extensive surface of microparticulate adsorbent. The use of adsorbent can facilitate the dissolution process of insoluble drug. The drug studied include indomethacin, aspirin, griseiofulvin, reserpin, probucol[1,2]. Itraconazole (ITR) is a broad spectrum antifungal agent and belongs to trizole group indicated in the treatment of local and systemic fungal infections[3]. Itraconazole is weakly basic (pKa = 3.7) and highly hydrophobic. Classified as Biopharmaceutical Classification System II drug, ITR has poor aqueous solubility and poor dissolution in gastrointestinal tract. Because of poor aqueous solubility, ITR on oral administration results in poor bioavailability and inter individual variations in the plasma drug concentrations. And ITR has the characteristic of pH dependent solubility having highest solubility at acidic side (4 µg/ml) compared to basic pH (1 ng/ml). However, because of highly liphophilic nature (log P = 6.2) ITR can easily penetrate into intestinal membrane. It is insoluble in water at all pH in the range 1 to12. Because of its poor aqueous solubility, its absolute oral bioavailability was reported as 55 %[4-5]. Solid dispersions proven to be efficient strategy in enhancing the oral bioavailability of liphophilic drugs. Solid dispersions have been defined as "the dispersion of one or more active ingredients in an inert excipient or matrix" where the active ingredients could exist in finely crystalline, solubilized or amorphous states. Different polymers have been utilized in the preparation of solid dispersions as inert matrices, however met with some challenges such as stability, process etc. These challenges created the way to prepare the solid dispersions with alternative materials such as lipids. These lipid formulations range from simple solutions of drugs in dietary triglycerides to the use of complex mixtures of triglycerides, partial glycerides, surfactants, co surfactants and co solvents to solubilize the drugs[6-8]. The dissolution rate of ITR was earlier improved by solid dispersion technique. Florite RE (FLR) is a Porous Calcium Silicate (FLR) that has the structure of assembled petal like flakes presenting a lot of pores in its surface. The pore shows a particular size distribution with two peaks at 1o to 0.15 micro m, which are attributed to inter particles and intra particle pores, respectably FLR is capable of absorbing a very large amount of oil (4-6 ml/g) through its numerous pores and thus it has been used to prepare solid formulations of oily drugs such as vitamin E[9]. In the present investigation, an attempt was made to improve the dissolution rate of itraconazole through the preparation of solid dispersion of itraconzole and Porous Calcium Silicate (FLR), Silicic Acid, Colloidal Silica and Silica Gel (Neutral) by adsorption method.

MATEIALS AND METHODS

Materials

Itraconazole was gift sample from M/s Intas Pharma ltd, Ahmadabad, India. Porous calcium silicate is purchased by Loba Chem, Mumbai, India. silicic acid , colloidal silica and silica gel (neutral) and all solvent were procured from local market.

Preparation of Itraconazole loaded solid dispersions

In the present work, solvent evaporation method was used to prepare solid dispersion of itraconazole. Drug (50 mg) and adsorbents (25-150 mg) were accurately weighed. In a 50 ml. beaker, the drug was dissolved in sufficient quantity of chloroform. Then adsorbent was taken in mortar and drug solution in chloroform was poured slowly with continuously trituration stirring to obtain the uniform mixture or slurry of drug with the adsorbent. The solvent was allowed to evaporate and dried sample was kept in dessicator over anhydrous calcium chloride. After complete removal of solvent, the solid mass was pulverized and passed through 100 mesh sieves and kept in air tight containers. The various composition of solid dispersion are given in Table 1.

Table 1: Formulae of Solid Dispersion of Itraconazole with Different Adsorbents

S. No.	Name of adsorbent	Product name assigned	Drug (mg)	Adsorbent (mg)	Ratio of drug to adsorbent	Nature of product
1	Porous Calcium Silicate (FLR)	FI_1	50	25	2:1	Solid Dispersion
		FI_2	50	50	1:1	Solid Dispersion
		FI_3	50	100	1:2	Solid Dispersion
		FI_4	50	150	1:3	Solid Dispersion
		FI_{pm}	50	100	1:2	Physical Mixture
2	Silicic Acid	SI_1	50	25	2:1	Solid Dispersion
		SI_2	50	50	1:1	Solid Dispersion
		SI_3	50	100	1:2	Solid Dispersion
		SI_4	50	150	1:3	Solid Dispersion
		SI_{pm}	50	100	1:2	Physical Mixture
3	Colloidal Silica	CI_1	50	25	2:1	Solid Dispersion
		CI_2	50	50	1:1	Solid Dispersion
		CI_3	50	100	1:2	Solid Dispersion
		CI_4	50	150	1:3	Solid Dispersion
		CI_{pm}	50	100	1:2	Physical Mixture
4	Silica Gel (Neutral)	GI_1	50	25	2:1	Solid Dispersion
		GI_2	50	50	1:1	Solid Dispersion
		GI_3	50	100	1:2	Solid Dispersion
		GI_4	50	150	1:3	Solid Dispersion
		GI_{pm}	50	100	1:2	Physical Mixture

Evaluation of prepared solid dispersion of itraconazol

Determination of Drug Content in Solid Dispersions

Dispersion system equivalent to 10 mg of itraconazole was taken in 10 ml volumetric flask and dissolved in 0.1 N HCl. The volume was made up to the mark with 0.1 N HCl and filtered. One ml of filtrate was further diluted to 10 ml with 0.1 N HCl and absorbance was recorded at 259.6 nm using GBC Cintra 10 spectrophotometer.

Particle Size Determination

Particle size of itraconazole and its different solid dispersions was determined by optical microscopy. A little amount of product was suspended in the distilled water previously equilibrated with itraconazole. One drop of this suspension was placed on a glass slide and covered with a cover slip and sealed by soft paraffin. The size of about 100 particles was measured with calibrated ocular micrometer fitted in the eye piece of optical microscope.

Infrared Spectroscopy

Infrared spectra's were obtained for plain itraconazole, and solid dispersion formulation (FI3) for evaluating the chemical compatibility of ITR with the excipients used in the formulation development. Spectra's were taken after preparing the pellet with 2-3 mg of sample with potassium bromide using FTIR spectrometer (Jasco) and the sample was scanned from 4000-400 cm^{-1}.

X-Ray Diffraction Study

The crystanillity of plain drug (ITR), FLR and solid dispersion (FI_3) was analyzed by using (X-ray generator and Goniometry Rigaku Japan). XRD technique was carried out using X-ray diffractometer and Cu kα radiation (α-0.15418) Parallel beam optics was used with 1 mm entrance slit. The diffraction pattern was measured with voltage 30 Kv and current 100 mA in area of $10 < 2\theta < 90$ in continuous scan mode of 3θ/minute (scan speed). $\lambda = 1.54\ A^0$ was used and steps 0.02 were used for diffraction.

Differential Scanning Calorimetry (DSC)

DSC studies were conducted using a TA instrument, Model Q200 equipped with RCS- 90(-90°C to 450°C) cooling unit. DSC was performed with 2 mg sample in Tzero pan-Aluminium, encapsulated with Tzero lid-Aluminium by T zero press. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min. Samples are heated at a temperature range of 0 to 300°C with ramping at 10°C.

Dissolution Rate

The dissolution rate of plain drug and solid dispersions was determined using Tablet Dissolution Rate Test Apparatus Type-I, (Veego) 900 (nine hundred) ml of 0.1N HCl with 0.5 % sodium lauryl sulphate (SLS) was used as dissolution medium maintained at 37 ± 0.5^0C and 100 rpm. SLS (0.5 %) was added to the dissolution media to maintain sink condition. Absorbance's of each sample was recorded at 259.60 nm using GBC Cintra 10 spectrophotometer. The data for the dissolution rate of plain drug (ITR), different solid dispersions and physical mixtures of drug with adsorbents are given in graphically represented in Figure 10-15.

Table 2: Particle Size Distribution

S. No.	Formulation	Avg. size (
1	FI1	17.84
2	FI2	16.52
3	FI3	16.13
4	FI4	18.06

Table 3: Infra red bands in IR spectra (in cm^{-1}) of Itraconazole and its solid dispersionFI_3

Functional group	ITR	FI_3
C=C ring stretching (Aromatic)	1551,1584	1552, 1584
C-H stretching (Aromatic)	3064	3065
C-H stretching (Alkyl)	2970	2968
C-H banding (Alkyl)	1384, 1455	1380, 1455
C=O stretching (Ketone)	1698	1696
C-N stretching (Triazole)	1229	1228
N=N=N stretching (Triazole)	1513	1513
N-H stretching (Amino)	3464	3465

Table 4: Data of XRD of ITR, FLR and solid dispersion FI_3

S. No.	Sample	Angle (and spacing d	1	2	3	4	5	6	7	8	9	10
1	ITR		15	16	17	18	19	20	21	22	23	24
		d	351	462	540	554	580	630	585	293	255	285
2	FLR		15	16	17	18	19	20	21	22	23	24
		d	-	-	-	-	-	-	-	-	-	-
3	FI_3		15	16	17	18	19	20	21	22	23	24
		d	-	-	-	112	111	143	-	-	-	-

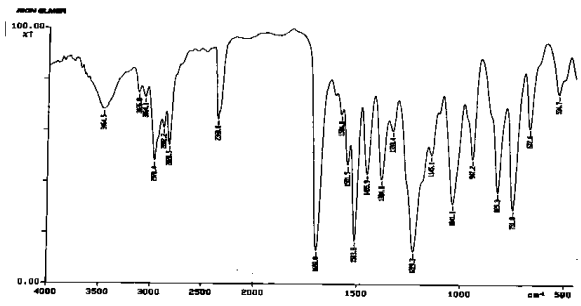

Figure 1: IR spectrum of Itraconazole

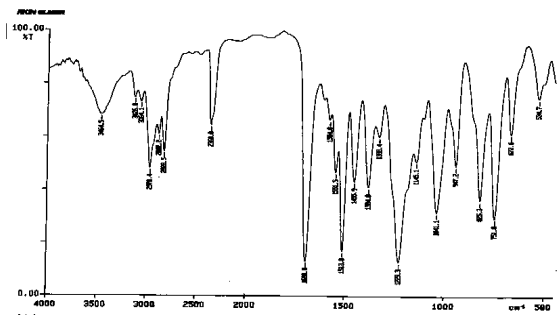

Figure 2: IR spectrum of solid dispersion (FI_3)

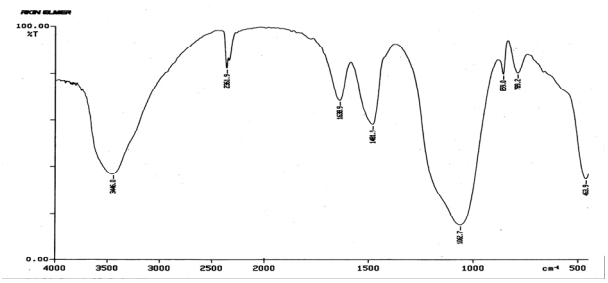

Figure 3: IR spectrum of porous calcium silicate (FLR)

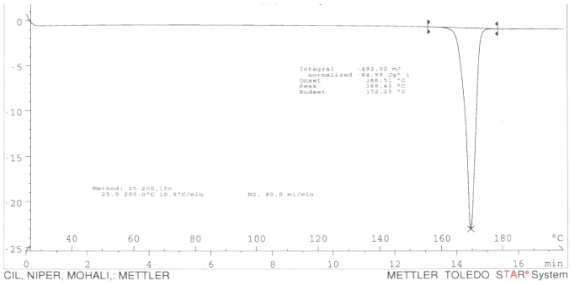

Figure 4: DSC thermogram of plain drug (Itraconazole)

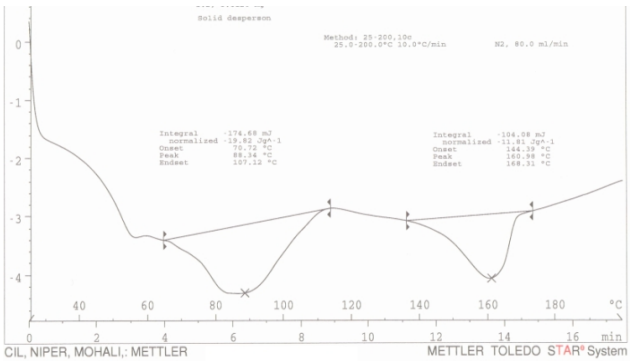

Figure 5: DSC thermogram of solid dispersion (FI_3)

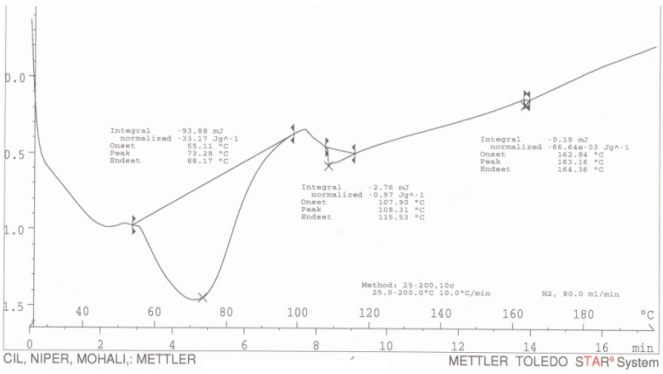

Figure 6: DSC thermogram of porous calcium silicate (FLR)

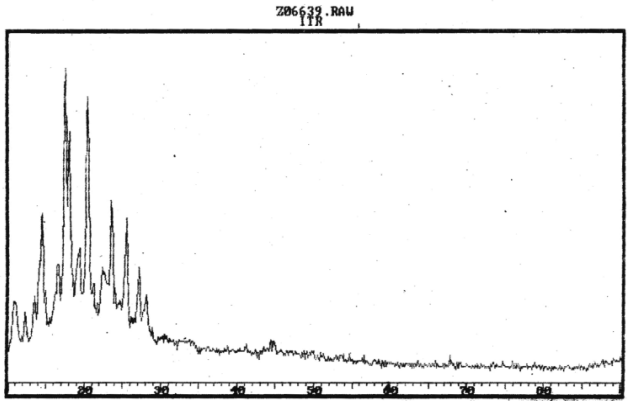

Figure 7: XRD graph of plain drug (Itraconazole)

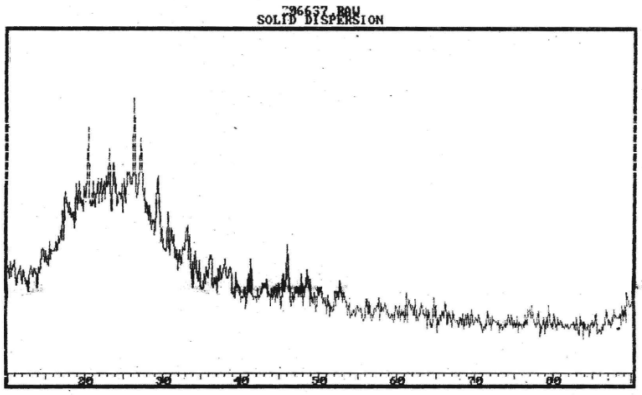

Figure 8: XRD graph of solid dispersion (FI_3)

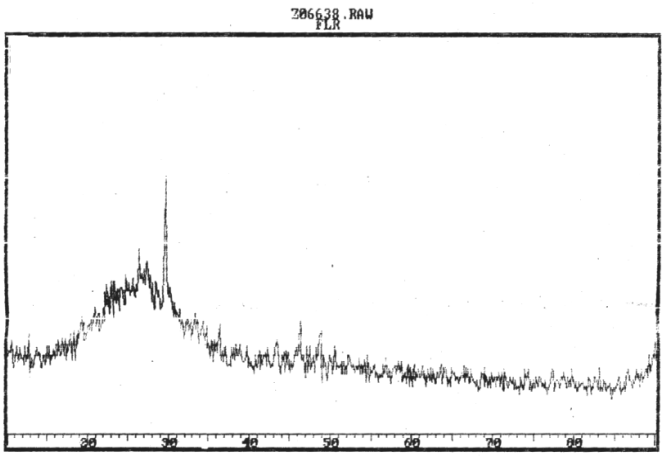

Figure 9: XRD graph of porous calcium silicate (FLR)

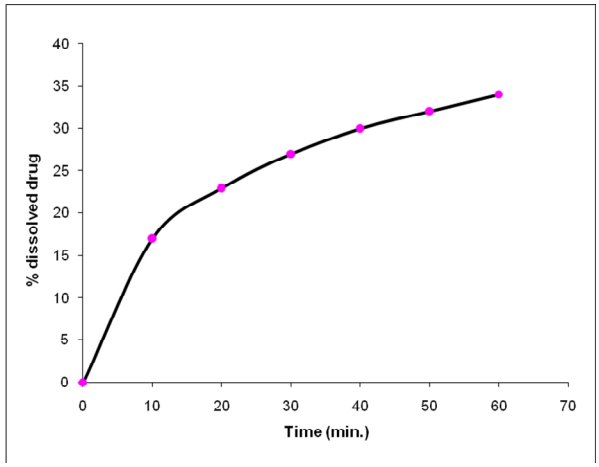

Figure 10: Dissolution rate of Itraconazole-(Plain Drug) in 0.1 N HCl containing 0.5 % SLS

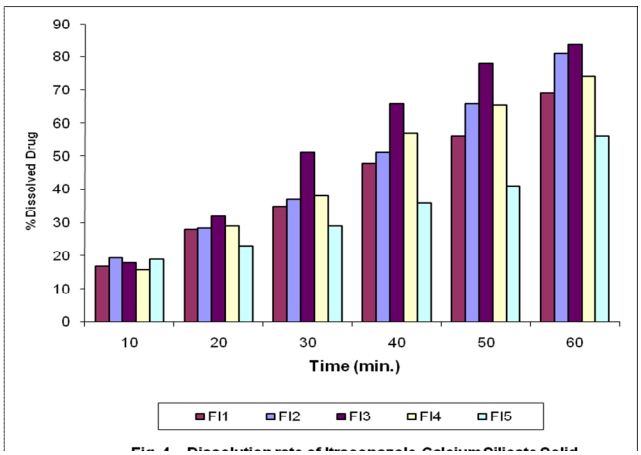

Figure 11: Dissolution Rates of Itraconazole-Calcium Silicate Solid Dispersions in 0.1N HCl containing 0.5 % SLS

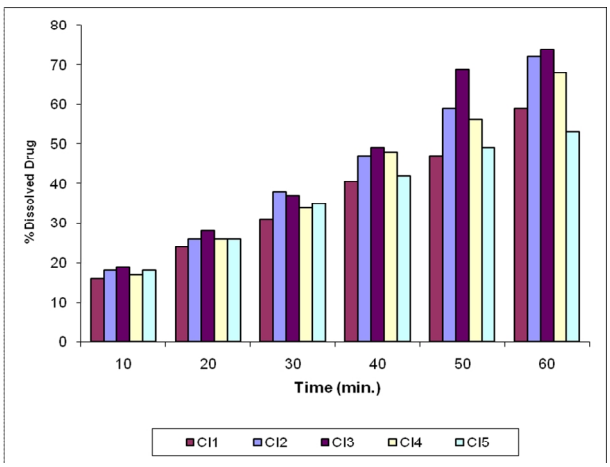

Figure 12: Dissolution Rates of Itraconazole-Collodial Silica Solid Dispersions in 0.1 N HCl Containing 0.5 % SLS

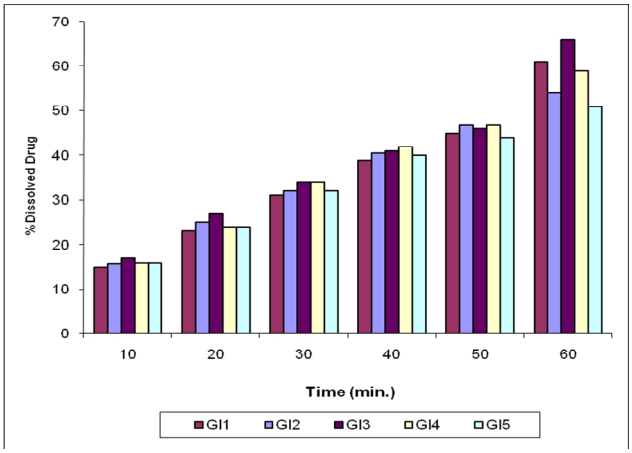

Figure 13: Dissolution Rates of Itraconazole-Silica Gel Solid Dispersions in 0.1N HCl Containing 0.5 % SLS

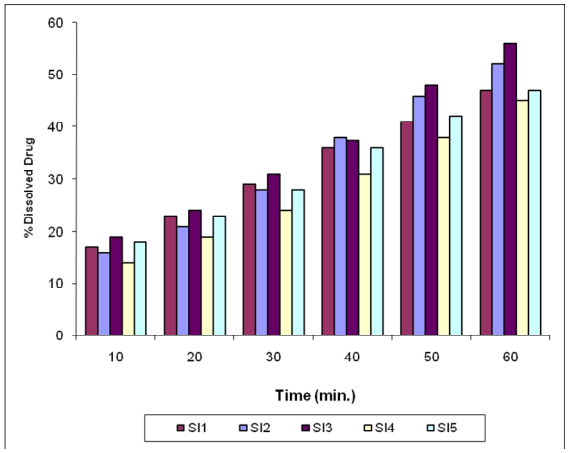

Figure 14: Dissolution Rates of Itraconazole-Silicilic Acid Solid Dispersions in 0.1N HCl Containing 0.5 % SLS

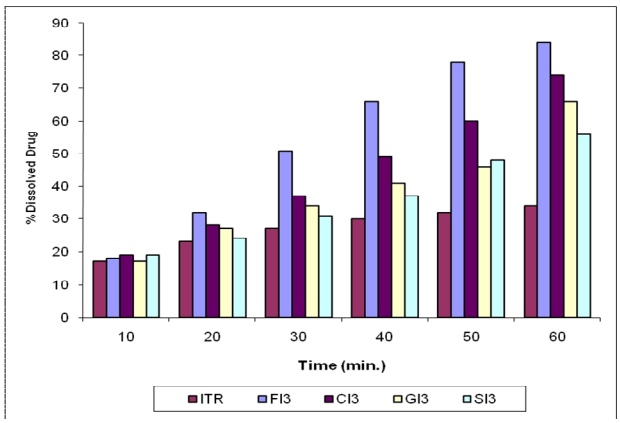

Figure 15: Comparison of Dissolution Rate of Selected Solid Dispersion with Plain Drug in 0.1N HCl Containing 0.5 % SLS

RESULT AND DISCUSSION

Solvent evaporation method was used to prepare solid dispersion of itraconazole. Drug (50 mg) and adsorbents (25-150 mg) were accurately weighed. In a 50 ml. beaker, the drug was dissolved in sufficient quantity of chloroform. Then adsorbent was taken in mortar and drug solution in chloroform was poured slowly with continuously trituration stirring to obtain the uniform mixture or slurry of drug with the adsorbent. The solvent was allowed to evaporate and dried sample was kept in dessicator over anhydrous calcium chloride. Among solid dispersions, ITR-Calcium silicate FI3 released maximum drug 84 % in 60 minutes while CI3, GI3, SI3 were next in decreasing order of drug release 74 %, 66 % and 56 % respectively (Figures 15). Porous Calcium silicate adsorbent is better than other adsorbent because FI1 (61 %), FI2 (81 %), FI3 (84 %), FI4 (74 %) showed better release than other products (Figures 11-15). In case of dissolution rate study, the products of FI group showed the best results. When FI group was analyzed for particle size distribution the product FI3 had the smaller average surface diameter (16.13 µm) than ITR (26.20 µm), FI1 (17.84 µm), FI2 (16.52 µm) and FI4 (18.06 µm) (Table 2). The particle size analysis showed that FI3 had the smallest particle size. Therefore, product FI3 was further characterized by IR, DSC and XRD studies. The IR spectra of FLR, solid dispersion (FI3) shows all peaks similar to those observed in IR spectra of Itraconazole. This indicated that there is no interaction between itraconazole (drug) and FLR (Adsorbent) as shown in Table 3 and Figures 1-3. Thermal analysis of drug (Itraconazole) porous calcium silicate (FLR), and solid dispersion (FI3) was performed using DSC. The crystallinity of drug was evaluated by DSC and powder XRD. DSC thermogram of ITR exhibited an endothermic peak at 168^0C corresponding to its melting point. Solid dispersion (FI3) also showed the endothermic peak at 161ºC which is near to the melting point of ITR indicating no interaction between ITR and calcium silicate in solid dispersion. The DSC thermogram of ITR showed sharp peak at 168^0C with enthalpy -1 and has crystalline nature which showed less dissolution rate than its solid dispersion. The DSC thermogram of solid dispersion (FI3) had no sharp peak and the sharp peak of ITR had changed into broad peak at 161ºC, which may be due to change of crystalline form of ITR into amorphous form which exhibited faster dissolution rate also as shown in Figures 4-6. X-ray diffraction showed some important peaks in the range of 15^0–24^0. In case of plain drug, intensity of sharp peaks revealed the crystalline nature of drug. But in X-ray diffraction of solid dispersion FI3, these peaks were not found as shown in Table 4 and Figures 7-8. This may be attributed to change of crystalline ITR into its amorphous form in solid dispersion or decrease in the crystallinity. This is supported by the findings reported by Nakai[10]. Nakai reported that crystallinity of benzoic acid was deceased when it formed a hydrogen bond with sylanol group of silica when it was adsorbed on surface of silica. Both amorphization and decreased crystallinity of TAS 301 might be due to both hydrogen bond with C=O group of TAS 301 and sylanol group of FLR. Similarly in our study the

hydrogen bending had occurred between C=O group of ITR and sylanol group of FLR. This was further supported by the fact that FI3 product showed the maximum dissolution rate.

CONCLUSION

In the recent years the utilization of porous calcium silicate such as FLR in the enhancement of oral bioavailability of poorly soluble drugs has become prominent. In the present work the solid dispersion with porous calcium silicate such as FLR for poorly water soluble drug like itraconazole is prepared by solvent evaporation method. The *in vitro* dissolution tests studies, DSC and XRD proved the efficacy of the formulation in the aqueous solubility enhancement compared to plain drug. The enhancement of dissolution rate can be attributed to the factors such as reduced particle size, amorphous form of drug, increased solubility of drug. Hence it is concluded that the oral bioavailability of poorly soluble drugs can be increased by preparation of solid dispersions by solvent evaporation method using porous calcium silicate.

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