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Formulation And Evaluation Of Solid Dispersion For Enhancement Of The Solubility Of BCS Class II Drug

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ABSTRACT

The aim of this present work is based on application of various nanotechnology based strategies to achieve the objectives of improved solubility, dissolution rate and oral bioavailability of Itraconazole. The drug with poor water soluble present challenges during dosage form design due to their inadequate solubilization in digestive fluids. So in order to overcome problems associated with poor water soluble drugs there is need to improve their solubility. Itraconazole is an imidazole/triazole type antifungal agent. Itraconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 α-demethylation via the inhibition of the enzyme cytochrome P450 14α-demethylase and belongs to biopharmaceutical classification system class II. Polymers such as PEG 4000 and HPMC were used for solid dispersio Solvent n. For preparation of solid dispersions, various solid dispersion methods (evaporation, Fusion method) were used. The effect of several variables to both solid dispersion preparations was investigated. IR and UV spectral analysis, Differential Scanning Calorimetry were used to characterize solid dispersions. Solid dispersions prepared by various methods were evaluated by methods like Saturation solubility, percent drug content, and by in -vitro dissolution method for percent cumulative drug release. Optimized solid dispersions were further evaluated by XRD, DSC, and SEM.

KEYWORDS

Solid Dispersion, Solubility enhancement, Bioavailability, Fusion method

INTRODUCTION

Drug absorption through gastrointestinal (GI) tract can be restricted by a diversity of parameters with the most remarkable contributors being poor aqueous solubility and/or poor

membrane permeability of the drug molecule. When delivering an active molecule orally, it must primarily dissolve in gastric fluids before it can then cross the membranes of the GI tract to reach blood circulation. Hence, a drug with poor aqueous solubility will generally shows dissolution rate limited absorption, and a drug with poor membrane permeability will normally reveal permeation rate limited absorption. [1]

Itraconazole is used to treat serious fungal or yeast infections.[2] Itraconazole is an imidazole/triazole type antifungal agent. Itraconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 α-demethylation via the inhibition of the enzyme cytochrome P450 14α-demethylase. [3] Solid dispersion is the process that made up of one or more active additives which are distributed in inert carrier in a solid state. [4]

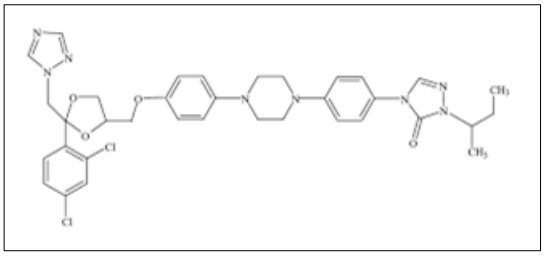

Figure No 1: Structure of Itraconazole

MATERIALS AND METHODS

Materials

Itraconazole was gifted by Vama Pharma Nagpur, India. Polyvinyl pyrrolidone K30 and Polyethylene Glycol 4000, HPMC was purchased from Dr SSK Labs Pvt Ltd, Pune, India.

Methods

Procedure for preparation of the Itraconazole solid dispersion by fusion method

In fusion Method, the drug with PEG-4000 and HPMC were prepared by separately at three different ratios 1:1, 1:2, 1:3. The polymer has been taken in china disc and kept in a mantle for a melting for both drugs. After reaching melting point than add the drug with continuous stirring with a glass rod. After taking it out from the mantle, kept immediate for cooling in an ice bath, after cooling take it out and kept in desiccators separately.

Procedure for preparation of Itraconazole solid dispersion by solvent evaporation method.

In Solvent evaporation method, drug with PEG-4000 and HPMC were prepared by separately at three different ratios 1:1, 1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with 100, 200 and 300mg of PEG- 4000 and HPMC. These drugs were dissolved in methanol and constant stirring. Solution was evaporated under low pressure to get the solid dispersion for both drugs.

Preparation of calibration curve of Itraconazole

Itraconazole drug 10 mg was weighed accurately and then it dissolve in the 10 ml phosphate buffer of pH 6.8 in the 10 ml of volumetric flask and Then from it take 1 ml of stock solution was taken from the 10 ml volumetric flask, to make (100 µg/ml) standard stock solution. 1 ml stock solution was taken in another 10 ml volumetric flask and then final concentration were prepared 2-10 µg/ml with phosphate buffer 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 263 nm. Absorbance values obtained are given in table 1 and calibration curve plotted is shown in figure 2. Regression equation obtained was used to estimate the Itraconazole from in vitro samples.

Table 1: Absorbance values obtained for Itraconazole

Sr. No	Concentration (µg/ml)	Absorbance (λmax = 263 nm)
1	0	0
2.	2	0.154
3.	4	0.301
4.	6	0.458
5.	8	0.587
6.	10	0.725

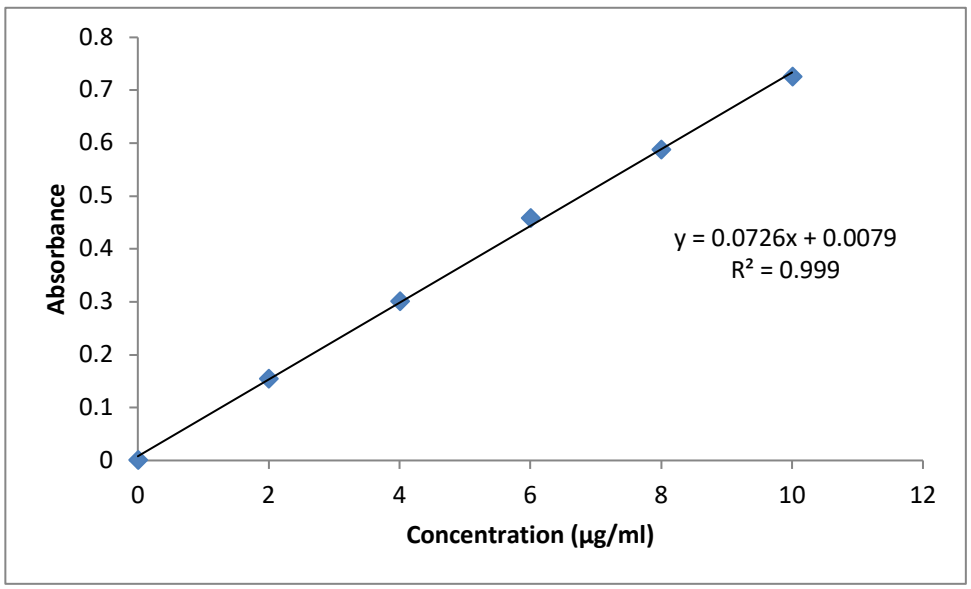

Figure No 2: Standard Graph of Itraconazole

Micromeritic/preformulation studies of Itraconazole solid dispersion

All the formulation of Itraconazole lubricated powder blends was subjected for Micromeritics properties using conventional methods. Bulk density and tapped density was determined by using measuring cylinder method. Hausner's ratios, Carr's index, were determined using the bulk density and tapped density data. An angle of repose was determined by conventional funnel method.

Percentage yield (i.e. recovery) of solid dispersion formed

The % recovery of formulated solid dispersion was resolute after complete removal of moisture. Thus % recovery calculation involves the weight of dried Solid dispersion to sum of the weight of drug and pharmaceuticals required for the formulation.

$$\% \text{ Yield} = \frac{\text{Prepared actual weight of SD}}{\text{Excipients and drug total weight}} \text{X100}$$

Evaluation of Solid dispersion

IR Spectral analysis

To know about the interaction between the drug and carriers used in the formulation, the IR analysis was carried out. The IR spectra of pure Itraconazole and solid dispersions were studied by FTIR. It is scanned over the Frequency range of 4000-400 cm^{-1}.

X-ray powder diffraction (XRDP)

The X-ray powder diffraction pattern for each sample was analyzed using a Diffractometer equipped with a mounting for Bragg-Brentano reflection that was connected to a Monochromator and a DIFFRAC plus channel program. Dimensions were carry out at room temperature using Cu K radiation at 40 mA and 40 kV, with an angular 2 increment of 0.02◦/s and a counting speed of 1.2 s per step. A rotation of 15 rpm was applied to the samples. .

DSC Studies

Differential scanning calorimetry (DSC) Thermal analysis was conceded out using TA SDT 2960 DSC differential scanning calorimeter. 3 – 5 mg amount of sample was sealed in an aluminum pan while an empty aluminum pan was exploited as a reference. And then the sample heated in the range of 30 to 450 ° C with an underlying heating rate of 10°C/min. Dry nitrogen at flow rate of 40 ml/min was used to cleanse DSC cell.

SEM Studies

By using the Model-JEM-100S, Jeol, Tokyo Japan SEM, observed pure drug Itraconazole

and their solid dispersion surface characteristics.

Drug Content

The entire prepared solid dispersions formulations equivalent to 100 mg of Itraconazole were weighed accurately and dissolved in 100 ml of phosphate buffer pH 6.8 in a separate volumetric flask. The solution was filtered, diluted suitably with same solvent and drug content is analyzed at 263 nm respectively by UV-spectrophotometer.

Dissolution studies of Itraconazole

IN-VITRO dissolution studies of all formulations were carried out using 900 ml of 0.1 N hydrochloric acid containing 0.5 % of Sodium lauryl Sulphate at 37 ± 0.5°C as the dissolution medium in a Type II apparatus (LABINDIA, DISSO 2000) at a stirring speed of 100 rpm. The sodium Lauryl sulphate adds to dissolution medium to maintain sink condition. Accurately weighed pure Itraconazole solid dispersions containing 100 mg of were used sprinkled directly to surface of the dissolution medium. Five milliliter sample solution of dissolution medium were withdrawn at the time interval 10, 20, 30, 40, 50 and 60min and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 0.5°C) in order to maintain constant volume of dissolution medium. The withdrawn samples were filtered and analyzed for drug content at 263 nm and cumulative percentage of drug dissolved was calculated. The amount of drug removed in each sample was compensated in the calculations. All experiments were performed in triplicate.

Curve fitting analysis (Kinetics of drug Release)

Formulation were done by studying the release information with zero order, first order kinetics, Higuchi and Korsemeyer equation. The release mechanism was understood by fitting the data to Korsmeyer Peppas model.

RESULT AND DISCUSSION

Micromeritic/preformulation studies of Itraconazole solid dispersion

The results of Micromeritics properties of solid dispersion of Itraconazole formulations were as below

Table No 2: Micromeritic studies of Itraconazole solid dispersion

Parameters	Bulk Density (g/cm3) ±S.E.M.	Tapped Density(g/cm3) ±S.E.M.	% Compressibility index	Hausers ratio	Angle of repose
Formulation code					
IHF1	0.313± 0.004	0.357 ± 0.005	12.5	1.14	31°47'
IHF2	0.294 ± 0.009	0.334 ± 0.007	11.76	1.13	30°46'
IHF3	0.334 ± 0.006	0.385 ± 0.004	13.33	1.15	28°18'
IPF1	0.315± 0.005	0.350 ± 0.004	13.5	1.13	31°37'
IPF2	0.283 ± 0.007	0.345 ± 0.006	12.73	1.15	30°56'
IPF3	0.337 ± 0.005	0.392 ± 0.003	12.37	1.14	27°18'
IHS1	0.323± 0.006	0.347 ± 0.004	12.5	1.14	31°47'
IHS2	0.287 ± 0.008	0.354 ± 0.006	11.67	1.15	32°46'
IHS3	0.333 ± 0.007	0.387 ± 0.005	12.39	1.13	29°18'
IPS1	0.313± 0.004	0.347 ± 0.005	12.5	1.14	31°47'
IPS2	0.274 ± 0.006	0.354 ± 0.007	11.78	1.13	31°46'
IPS3	0.338 ± 0.007	0.385 ± 0.006	13.37	1.15	28°18'

Itraconazole was found to be identical with standards given in analytical profile of drug substances.

Percentage yield

The results of percentage yield of solid dispersion of Itraconazole formulations were as below

Table No 3: Percentage yield of solid dispersion of Itraconazole

Sr. No.	Formulationcode	% yield
1	IHF1	85.16
2	IHF2	81.85

3	IHF3	93.79
4	IPF1	95.36
5	IPF2	91.89
6	IPF3	94.29
7	IHS1	89.67
8	IHS2	91.23
9	IHS3	90.89
10	IPS1	89.98
11	IPS2	95.45
12	IPS3	91.93

The % yield was found good with formulated SD. The Batch IPS2 has showed maximum yield of 95.45.

FTIR spectroscopy

Analysis of FTIR result ensuring that absence of interface among polymer with drug Itraconazole. Thus, carriers such as PVP K30 and PEG 400 used in formulation were compatible with drug. As shown in figure 3.

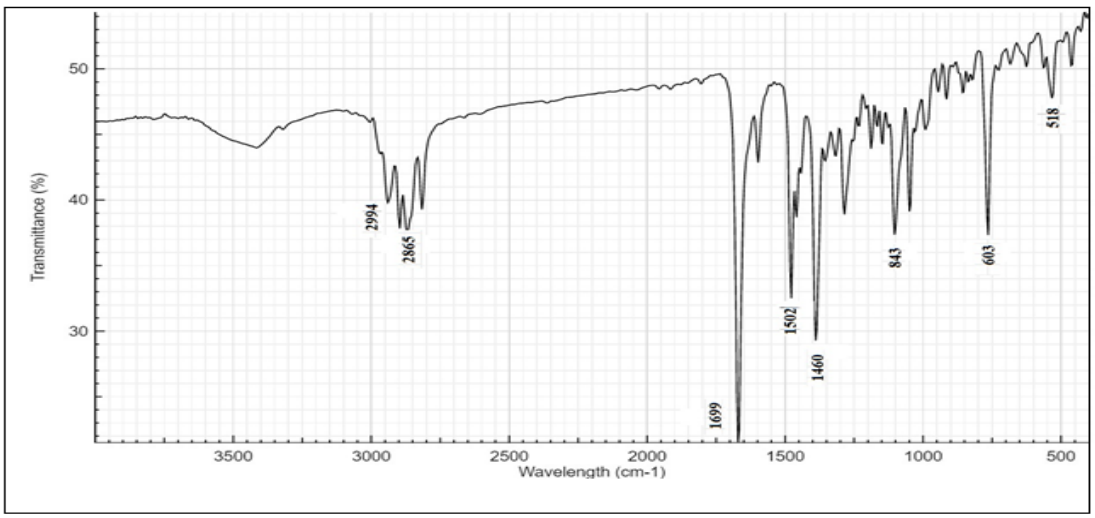

Figure No 3: FTIR spectrum of Itraconazole

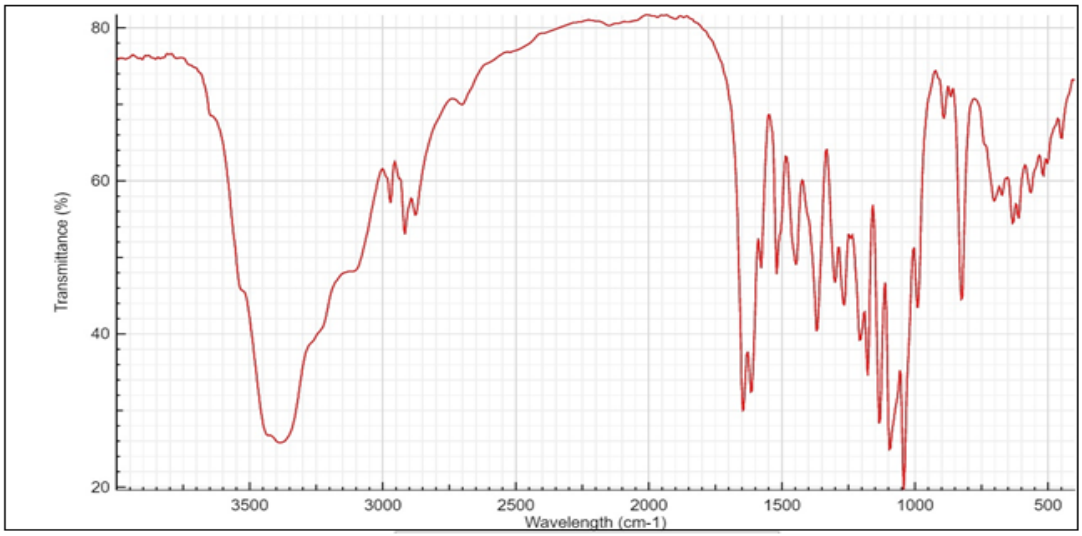

Figure No 4: FTIR Spectra of Drug Excipients Compatibility

X-ray diffraction analysis

Pure Itraconazole showed the characteristic peaks in the 2θ range of 15-30^0, which indicates that, the unprocessed Itraconazole was a crystalline material. As shown in figure 5.

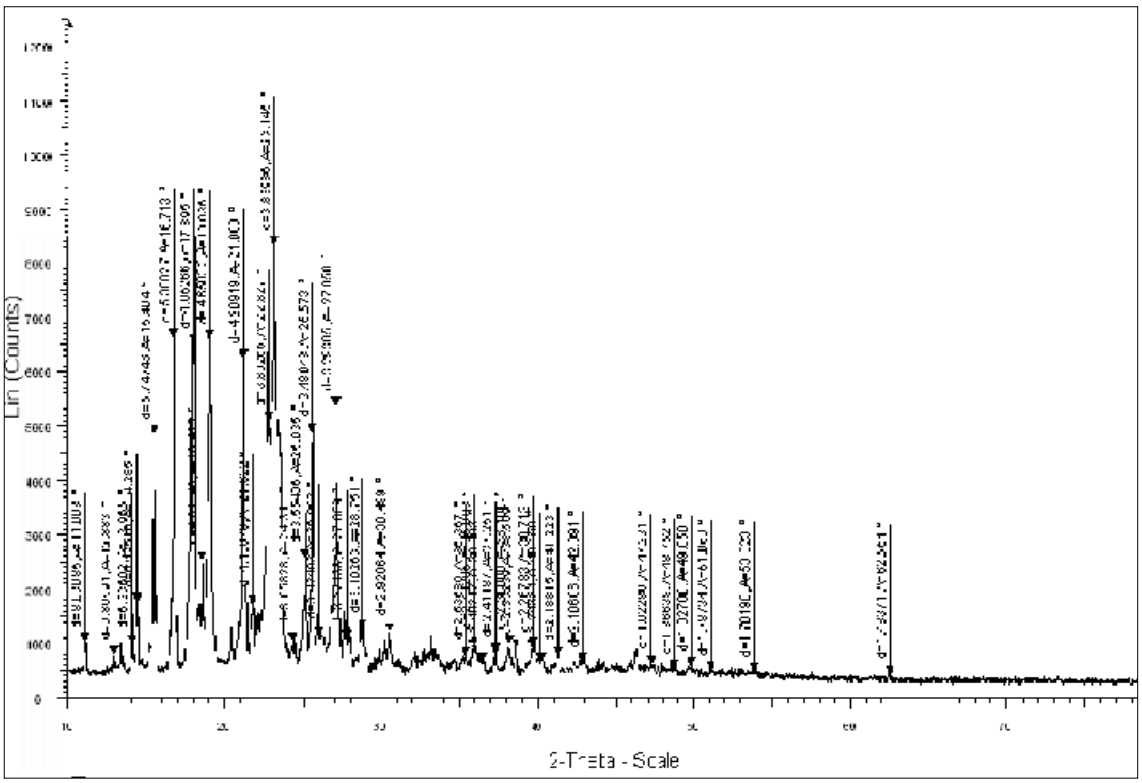

Figure No 5 : XRD of Itraconazole SD

DSC Thermogram

The unprocessed Itraconazole showed a characteristic endothermic melting peak at 188^0 indicating that the drug Itraconazole highly crystalline in nature.

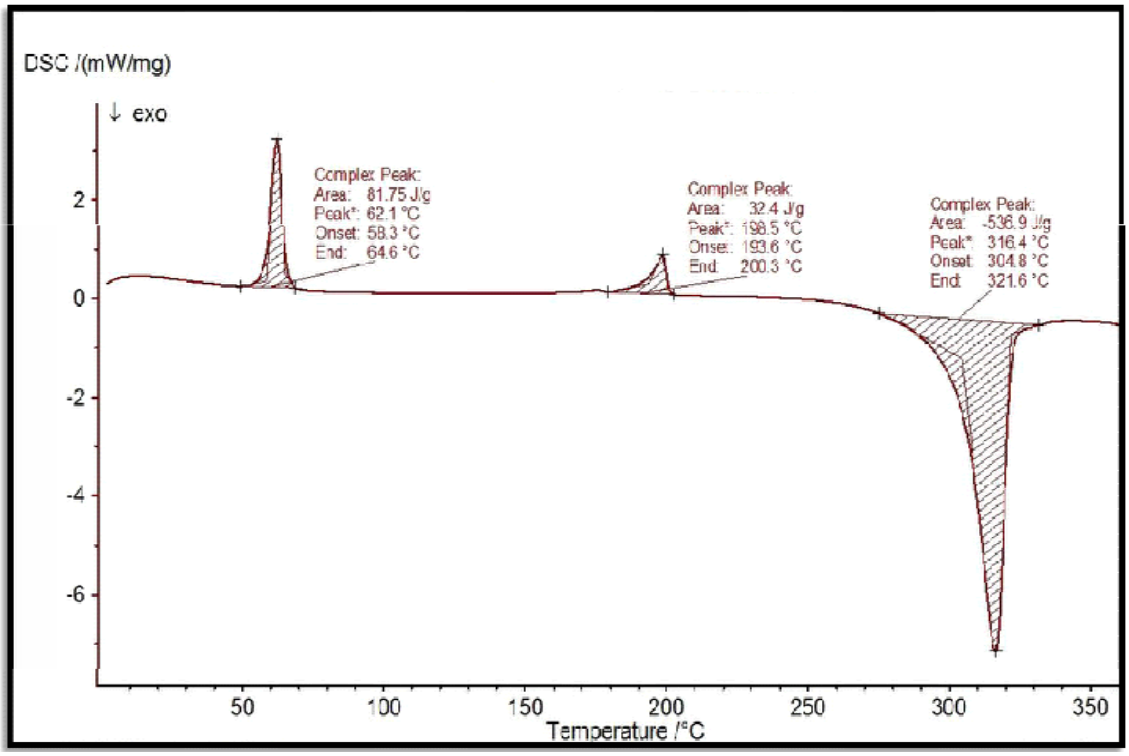

Figure No 6: DSC of Itraconazole SD

SEM Studies

The result of for Itraconazole SEM of SD formulation with PVPK30 .The study clearly reveals the difference between SEM of Itraconazole and its SD formulation. Also observed definite morphological changes in crystal of drug. As shown in figure 6.

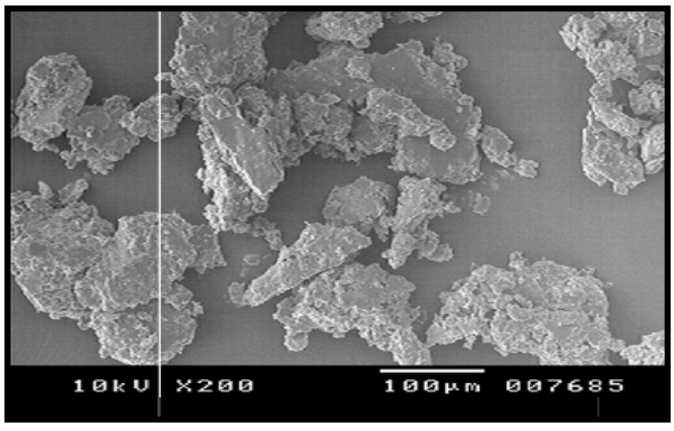

Figure No. 7: SEM of Itraconazole SD

Dissolution studies of Itraconazole

Solid dispersions were tested for In-Vitro dissolution study by utilizing USP type-2 Dissolutions Testing Apparatus (6 vessel assembly, Paddle-type II) at 100 rpm. 900ml of 0.1N HCL solution was used as dissolving media. Results are interpreted in the table 4 and drug release showed in figure 8.

Table No. 4: In-Vitro Drug Release of Itraconazole Solid Dispersion by Solvent Evaporation method by using PEG-4000

Time in (min)	% Drug Release			
	Itraconazole	IPS1 (1:1)	IPS2 (1:2)	IPS3 (1:3)
0	0	0	0	0
10	10.20±1.8	23.7± 1.02	28.4± 1.12	27.9± 1.11
20	18.20±1.6	38.8± 1.10	45.3± 1.01	46.7± 1.02
30	21.9±1.0	57.7± 1.1	61.4± 1.14	59.8± 1.6
40	27.20±1.3	72.4± 1.25	75.5± 1.10	72.4± 1.13
50	29.10±1.5	85.6± 1.16	87.9± 1.3	81.5± 1.05
60	35.6±1.0	94.6± 1.06	97.7± 1.05	95.2± 1.09

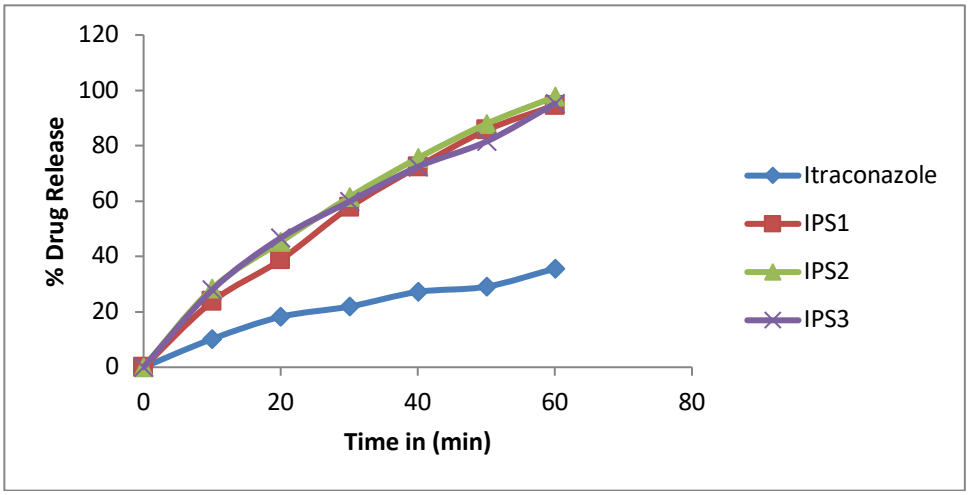

Figure No 8: In Vitro Drug Release of Itraconazole Solid Dispersion by Solvent Evaporation method by using PEG-4000

The invitro dispersion studies of pure drug and all solid dispersion formulation with different ratios 1:1, 1:2, 1:3 by using two different carriers such as PEG 4000 and HPMC. The prepared solid dispersions of Itraconazole equivalent to 100 mg of pure drug and dissolution studies were carried out in dissolution USP Type II apparatus (LABINDIA, DISSO 2000) containing 900 ml of 0.1 N hydrochloric acid containing 0.5 % of Sodium lauryl Sulphate at 37 ± 0.5°C. The samples were taken at different interval of time. 0 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60min. also absorbance were recorded at 263 nm. From this invitro studies the solid dispersion containing drug and PEG4000 (1:2) released maximum 97.7% W/V (Solvent

evaporation method). From this invitro studies it conclude that the solid dispersion containing Itraconazole and PEG4000 (1:2) (Solvent evaporation method) showed high release. The studies proved that one of the fast releasing dosage form for poorly water soluble Itraconazole by using solid dispersion technology.

Kinetics Release studies of Itraconazole

By fitting the experimental data to models such as zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas best fitted model is evaluated for solid dispersion.

Table No 5: Release kinetics of Itraconazole solid dispersion by solvent evaporation method by using PEG- 4000

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2
IPS1 (1:1)	0.988	0.938	0.997	0.996
IPS2 (1:2)	0.991	0.877	0.980	0.999
IPS3 (1:3)	0.989	0.886	0.973	0.997

Table 5 represents the values of the best-fit parameters of the Krosmeyer-Peppas model. Which provided the best adjustment curves for the kinetics of drug release for created solid dispersion tablets.

CONCLUSION

From the findings of various physical and chemical tests, it can be concluded that Solid dispersions method significantly improved the dissolution profile of Itraconazole. IR and UV spectral analysis of solid dispersions indicated that there was no probable interaction between drug and carriers. Dissolution rate of solid dispersions increased with increased concentration of polymer like PVP K30 and PEG 4000. From this invitro studies the solid dispersion containing drug and PEG 4000 (1:2) released maximum 98.3% W/V (Solvent evaporation method). Solid dispersions prepared by solvent evaporation method showed more solubility enhancement with enhanced dissolution as compared to solid dispersions prepared by solvent evaporation method. SEM studies showed well separated, dense spherical particles with a smooth surface of Itraconazole.

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