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FORMULATION AND EVALUATION OF SOLID DISPERSION FOR DISSOLUTION ENHANCEMENT OF KETOCONAZOLE

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ABSTRACT

Ketoconazole is one of the most commonly used anti-fungal drug. It is a member of imidazole containing compound that is used as a broad spectrum antifungal agent for the treatment or prevention of fungal infections especially against thrush, gastrointestinal infections, and infections of the skin, nails and scalp. Ketoconazole is available as oral tablet, cream and dandruff shampoo formulations. Ketoconazole has a high permeability and its solubility in aqueous media is not sufficient for the whole dose to be dissolved in the fluids under normal conditions. Formulation techniques that accelerate drug dissolution can guarantee a parallel improvement in bioavailability. Different techniques like co-solvent, solid dispersion, chemical modification of drug, liquid solid techniques etc. are available to enhance the solubility of drug. One of the favourable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is the formulation of solid dispersion. Solid dispersions and physical mixtures of ketoconazole were prepared by solvent evaporation method with different polymers viz. crosscarmellose sodium, sodium starch glycolate and Eudragit E100 in different ratio. Drug and excipients compatibilities were studied with FTIR method. The solid dispersion and physical mixtures were further studied for percentage practical yield, in vitro release of drug and solid dispersion with crosscarmellose in ration of 1:7 shows drug release of almost 3 times to the pure drug 20percentage increase with the marketed product. Further the optimised solid dispersion was used to formulate tablet.

KEYWORDS: Biopharmaceutical Classification System, Ketoconazole Solubility, Solid dispersion.

INTRODUCTION

Ketoconazole is the member of imidazole class that is currently used in the treatment of systemic infections. Ketoconazole is classified in the Biopharmaceutics Classification Scheme (BCS) as a class II drug, since it has a high permeability and poor solubility. Ketoconazole is best absorbed at highly acidic levels, so antacids or other causes of decreased stomach acid levels will lower the drugs absorption. Absorption can be increased by taking it with an acidic beverage. It is very lipophilic and tends to accumulate in fatty tissues. Ketoconazole works principally by inhibiting the enzyme cytochrome P450 14-alpha-demethylase (P45014DM).

Ketoconazole is 1-acetyl- 4-[4-[[(2*RS*,4*SR*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine, calculated with reference to the dried substance.

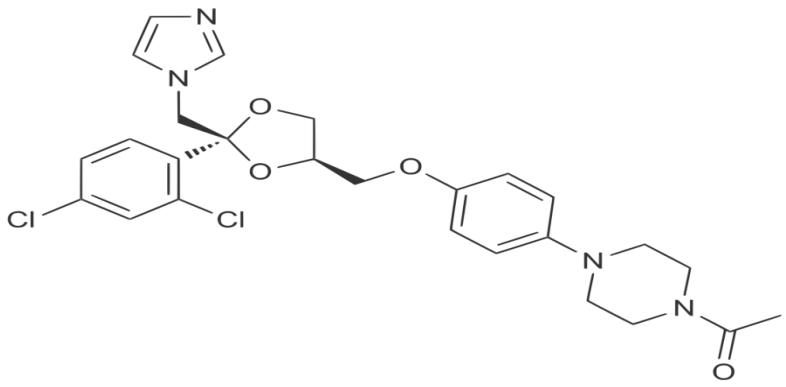


Figure-1-Structure of Ketoconazole

Many solubilization techniques have been described that either changes the nature of solvent environment (co-solvents systems, emulsions, micellization) or the chemical identity of the desired solute (salt formation, prodrugs); however, in comparison drugs into hydrophilic carriers is an alternate option for improving the drug bioavailability. Such dosage forms are referred to as solid dispersions.[1,2,3] A solid dispersion can be defined as "the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent, or melting-solvent method. Aqueous solubility of any therapeutically active pharmaceutical ingredient is a vital property, which plays major role in dissolution, absorption, and bioavailability. To improve the dissolution and bioavailability of poorly

water-soluble drugs, researchers have employed various techniques such as micronization, solubilisation, salt formation, complexation with polymers, changing in physical forms (amorphous), use of prodrugs and drug derivatization, pH alteration and addition of surfactants. Some studies used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs. Among the various approaches, the solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous. . The half-life of ketoconazole is 3.3hrs. The drug shows low pH dependent solubility. It is practically insoluble in water, more soluble in methanol than ethanol. It is well soluble in DMSO. The melting point of Ketoconazole is 146°C.[3,4,5]

MATERIALS

Ketoconazole was kindly provided by Aarti Drug Limited, Maharashtra, Croscarmellose Sodium and Sodium Starch Glycolate (SSG) from Maple Biotech Pvt Ltd, Pune, Maharashtra, Eudragit E-100 from Evonik Degussa India Pvt. Ltd., Mumbai. All other chemicals and reagents used were laboratory reagent grade.

METHOD

PREFORMULATION STUDIES

Preformulation studies focus on those physiochemical properties of the drug that could affect performance and development of an efficacious dosage form. It is necessary to determine purity of active pharmaceutical ingredient (API) before formulation of any dosage form. Preformulation studies are useful in determining the formulation components and physiochemical properties of new drug substance.

Description of drug

The sample of drug was observed for colour, state and solubility.

Drug Identification

By absorption spectrum method

Accurately weighed 10 mg of Ketoconazole and dissolved in sufficient volume of di-chloro methane and 100ml of 0.1N HCl buffer at pH 1.2 then scan was obtained on UV-VIS spectrophotometer. The wavelength at which maximum absorbance obtained was considered as maximum wavelength (λ_{max}). The test spectrum was confirmed with reference spectra. i.e. 269.4nm for the pure drug.[5,6]

By infra-red spectroscopy

Accurately weighed 10 mg of ketoconazole was taken in vial and scanned in FTIR immediate and after 15 days (kept at 50^{o}C) to obtain IR spectrum. [Indian Pharmacopoeia 2007,Vol II].

Drug Excipients Compatibility Study

Before formulating a dosage form it is very necessary to confirm that drug is not interacting with the polymer under certain experimental conditions. Interaction among drug and polymer may affect the efficacy of final dosage form. Drug and excipients were accurately weighed and mixed and the resulting mixtures were scaled in screw glass vials and kept at a 50°C for 15 days.[6,7]

Table 1: Quantity used for Drug – Polymer Identification

S. No.	API and Excipient	Quantity per vial (mg)	No. of Vials	
			Initial	After 15 Days
				50^{0}C
1.	Ketoconazole	10	1	1
2.	Croscarmellose Sodium	10	1	1
3.	Sodium Starch Glycollate	10	1	1
4	Eudragit E-100	10	1	1

Development of standard calibration curve

Accurately weighed 10 mg of drug, dissolved in sufficient volume of Di-chloromethane and then made up volume up to 100 ml with 0.1 N HCl, phosphate buffer with different concentrations (2, 4, 6, 8, 10 and 12 µg/ml) were prepared. The absorbance was obtained at λ_{max} 269.4nm and calibration curve was plotted between concentration and absorbance. All spectral absorbance measurements were made on Shimadzu-1700 UV-visible spectrophotometer.[8,9]

Formulation

Twenty-four different formulation batches of binary systems of ketoconazole i.e. both physical mixture and solid dispersion were prepared with four different polymers croscarmellose sodium, eudragit E100 and sodium starch glycolate in four different ratio (1:1, 1:3, 1:5 and 1:7).

Table 2: Formulation batches with formulation code

S.NO.	METHOD	RATIO Drug: Polymer	Formulation code		
			CCS	SSG	EE 100
1.	Physical	1:1	PM 1	PM 5	PM 9

2.	mixture	1:3	PM 2	PM 6	PM 10
3.		1:5	PM 3	PM 7	PM 11
4.		1:7	PM 4	PM 8	PM 12
5.	Solid dispersion	1:1	SD 1	SD 5	SD 9
6.		1:3	SD 2	SD 6	SD 10
7.		1:5	SD 3	SD 7	SD 11
8.		1:7	SD 4	SD 8	SD 12

Formulation of physical mixture

Physical mixtures of ketoconazole were prepared by mixing ketoconazole with the hydrophilic carriers for 5 min in a mortar until a homogenous mixture was obtained. The resulting mixture was then sieved. The powders were stored in screw cap bottles in desiccators for further analysis.[9,10]

Formulation of solid dispersion

Solvent Evaporation method: Drug and polymer was taken in different ratio (1:1, 1:3, 1:5 and 1:7) to form solid dispersions by solvent evaporation method using di-chloro methane as solvent. The required amount of ketoconazole was dissolved in sufficient volume of di-chloro methane with continuous stirring in a beaker with glass rod by taking small quantities of ketoconazole. After that the required amount of carrier/polymer was dispersed properly into it by glass rod. This mixture was then placed on hot plate at 45^{o} C with continuous stirring until no trace amount of solvent was remaining. The dried mass was scraped out with spatula, pulverized and passed through 44 mesh sieve, packed and stored in screw-cap bottles in dessicator for further analysis.[10,11]

Evaluation of Solid Dispersion

The formulations of solid dispersion were evaluated by the following parameters.

Percentage Practical Yield

The percentage practical yield of physical mixture and solid dispersion was then calculated by using the following formula and results are shown respectively[6],

$$\text{Percentage Yield} = \frac{\text{weight of solid dispersion obtained}}{\text{tolal weight of drug and polymer}} \times 100$$

Dissolution study of Solid dispersion

Accurately weighed preparations equivalent to 20 mg of Ketoconazole was filled into a capsule (size 0) and placed in the basket (Dissolution apparatus I) in vessel containing 500 ml

of dissolution media (1.2pH HCL buffer) maintained at 37 ± 0.5°C at 100 rpm. Prefect sink conditions maintained during the drug release studies. Five milliliter aliquots were withdrawn through a 5µm membrane filter at the interval of 5, 10, 15 30, 35 and 60 min and replaced with fresh buffer dissolution media. The collected samples were analyzed spectrophotometically at λ_{max} 269.4 nm using double beam UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution of pure ketoconazole and commercial product were performed similarly and compared with solid dispersion. The release profile data were analyzed for cumulative percent dissolved at different time intervals.[12]

OPTIMIZATION OF THE FORMULATION

ANOVA: ANOVA was applied to determine significant difference between the formulations. The p values (table12) showed that there was a significant difference between formulations of the drug with different polymers. The solid dispersion of Ketoconazole with Croscarmellose sodium (1:7) showed highest dug release i.e. 90.09%. This optimized formulation was used for the preparation of the tablet.[12,13]

Formulation and Evaluation of Tablet of Optimized Solid Dispersion Formulation

Formulation of Powder blend

The powder blend was prepared by using solid dispersion, lactose 15% as diluent, talc 3% as glidant and magnesium stearate 2.0% as lubricant and mixed them properly. The quantities of all the ingredients are shown in the table 3.

Table 3: Composition of optimized solid dispersion tablet.

S. No.	Ingredients	Role	Quantity per 1 tablet (mg)
1.	Ketoconazole: Croscarmellose Sodium	Solid dispersion	20:140
2.	Direct compressible Lactose	Diluent	30.0
3.	Talc	Glidant	6.0
4.	Magnesium stearate	Lubricant	4.0

Evaluation of powder blend

The evaluation of the powder blend was done by following parameters.[13,14]

a. Bulk density

The bulk density of the formulated granules was evaluated using a bulk density apparatus. It is expressed in gm/ml and is calculated by formula, given in table 13.

Bulk Density (ρ_b) = $\frac{Mass\ of\ the\ powder\ (M)}{Volume\ of\ the\ bulk\ powder\ (V_b)}$

b. Tapped density

The tapped volume was measured by tapping the powder to constant volume on tap density apparatus. It is expressed in gm/ml and is calculated by formula, given in table 13.

Tapped Density (ρ_t) = = $\frac{Mass\ of\ the\ powder\ (M)}{Tapped\ Volume\ of\ the\ powder\ (V_t)}$

c. Compressibility Index and Hausner Ratio

The Compressibility index (I) and Hausner's ratio (HR) measure of the property of a powder to be compressed and the flowability of granule. Carr's index and Hausner's ratio were calculated using following formula and is given in table 13.

Carr's Index (I) = $\frac{\rho t-\rho b}{\rho t}\times 100$

Hausner's ratio (HR) = $\frac{\rho t}{\rho b}$

Where, ρ_t – Tapped density of the powder, ρ_b – Bulk density of the powder

Table 4: Carr's index & Hausner ratio of powder blend.

Compressibility index (%)	Flow Property	Hausner ratio
5-15	Excellent	1.00-1.11
12-16	Good	1.12-1.18
18-21	Fair to Passable	1.19-1.25
23-35	Poor	1.35-1.45
33-38	Very poor	1.46-1.59
>40	Extremely poor	>1.60

d. Angle of repose

Angle of repose was determined by Neumann's method and calculated by using the formula for unlubricated as well as lubricated granules. It is calculated by formula given below and shown in table 13.

$\tan\theta = \frac{h}{r}$

$\theta = \tan^{-1}\frac{h}{r}$

Where, h = height of pile, r = radius of the pile base.[14,15]

Table 5: Angle of repose as an indication of powder flow properties

Flow Property	Angle of Repose (Degrees)
Excellent	<25
Good	20-30

Passable-may hang up	30-40
Very poor	>40

Compression of Powder Blend into Tablet

Based on the dissolution profile, powder blend containing solid dispersion of Ketoconazole with cross Croscarmellose sodium (1:7) was selected as optimized formulation for the preparation of tablets. Tablets were formulated by wet granulation method using motorized single punch tablet compression machine.[15]

TABLET EVALUATION

The following evaluation parameters were used to evaluate the tablets.

Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablets.

Tablet thickness

Thickness of tablets was measured using Vernier Calipers. It was determined by checking ten tablets from final formulation (table 14). It is expressed in mm.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester (table 14). It should not be more than 5 kg/cm^2.

Friability

It is performed as per IP specification and shown in table 14. Maximum loss of weight (from a single test or from the mean of the three tests) not more than 1.0 per cent is acceptable for the tablets**.**

Uniformity of Weight

Weigh individually 20 units selected at random or, for single dose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage as shown in table 14.

Disintegration test

The in vitro disintegration time was determined using Disintegration Test Apparatus. To test for disintegration, one tablet was placed in each of the six tubes of apparatus and one disc was added to each tube. The basket rack assembly was positioned in pH 1.2 0.1N HCL buffer at 37±0.2^{o} C. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in minutes and is shown in table 14.

In-vitro dissolution test

In vitro dissolution studies for all the fabricated tablets were carried out using USP apparatus II (paddle method) in 900 ml of 0.1N HCl buffer (pH 1.2) as dissolution media, maintained at 37±0.5^{o}C at 50 rpm. Five milliliters aliquots were withdrawn at 5, 10, 15, 30, 45, 60 min and replaced by 5 ml of fresh dissolution media (37^{o}±0.5^{o}C). The collected samples were analyzed after suitable dilution (if required) at λ_{max} 269.4nm using UV-VIS spectrophotometer against HCL buffer (pH 1.2) as the blank. The release profile data were analyzed for cumulative percent dissolved at different time intervals as shown in table [10].

Determination of Drug Content

Solid dispersions of Ketoconazole were placed in 20 ml volumetric flask. Di-chloro methane (10 ml) was added, mixed thoroughly using a rotating shaker for 1hour. The volume was made up to the mark with Di chloro methane. The solution was suitably diluted with Di chloro methane and spectrophotometically assayed for drug content at λ_{max} 269.4nm.[16].

DRUG RELEASE KINETICS

Model Independent Parameters

Dissolution efficiency

The dissolution efficiency (DE) of a pharmaceutical different dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It is calculated by following equation.

$$DE=\frac{SA}{R}\times 100$$

Where SA is shaded area and R is rectangle area ($y_{100} \times t$)

y is the drug percent dissolved at time t.

DISSOLUTION PROFILE COMPARISON

Determination of Similar Factor (f2) and difference factor (f1)

A model independent approach estimate the dissimilarity factor (f1) and similarity factor (f2) to compare the dissolution profile of optimized formulation (SD4) with commercial product. The dissolution study of optimized Ketoconazole solid dispersion tablet was performed and compared with commercial conventional release tablet by calculating the similarity factor and difference factor. The following equations were used for calculating f1 and f_2.

$$f1 = \frac{\sum_{t=1}^{n}(Rt-Tt)}{\sum_{t=1}^{n} Rt} \times 100$$

$$f2 = 50 \log \{[1+\frac{1}{n}\sum_{t=1}^{n}(Rt-Tt)^2]^{-0.5} x100\}$$

Where n = no of time points, R_t = dissolution value of the reference batch at time t, T_t = dissolution value of the test batch at same time point. Number of time points, n = 6 where both products ≥ 85%. Number of points in R_t and T_t must be the same and must be the similar to n**.** The standard values of similarity factor and dissimilarity factor are ≥ 50 and ≤ 15 respectively.

Model Dependent Kinetics

Data obtained from in vitro release studies was fitted to various kinetics equations to find out the mechanism of release of drug from the formulation compared to the commercial preparation. The kinetics models used were Zero order, First order, Weibull model, Higuchi and Korsmeyer Peppas model. In order to obtained meaningful information for release models, the drug release profiles were fitted to various kinetic models. Table 19 summarized the correlation coefficient for different release kinetic models of optimized formulation and Commercial product. Models with higher correlation coefficient were judged to be more appropriate model for dissolution data. The in vitro release data obtained from Formulation SD4was fitted to kinetic models shown in Table 19. In case of zero order $(Q_t = Q_0 + K_0 t)$ the graph was plotted in cumulative percent of drug released versus time and in first order release kinetics (Log C= log C_0- Kt/2.303) the graph was plotted in log cumulative percent of drug remaining versus time. For Higuchi model kinetics ($Q= K_H \times t^{1/2}$) the graph was plotted in cumulative percent of drug released versus square root of time, and for higuchi model [$m= 1- \exp(\frac{-(t-Ti)b}{a})$] the graph was plotted in log cumulative percent of drug released versus log time (Figure 13-14). The release of formulation SD4 was indicated

by highest r^2 values in Korsmeyer Peppas model and equivalent to that of Commercial product which also showed highest value of r^2 in Korsmeyer Peppas model.

RESULT AND DISCUSSION

Description of drug.: Properties of drug related to colour,odour are given in table 6.

Table 6: Description of Ketoconazole.

S. No.	Properties	Inference
1.	Colour	White Coloured
2.	Solubility	Practically insoluble in water, soluble in Di -chloromethane and acetone.
3.	Odour	Odourless

Drug Identification (λ_{max})

By Absorption spectrum method: The accurately weighed quantity of drug was dissolved in sufficient volume of acetone and scan was obtained on UV-VIS spectrophotometer. The wavelength at which maximum Abs.orbance obtained was considered as maximum wavelength (λ_{max}) i.e 269.4 nm for the drug.[15]

By infra-red spectrum method:

Drug and polymers identified by infra-red spectrum which are compared with its standard IR. The IR spectrum given below shown that the peaks obtained in the test spectrum is similar to that given in standard.

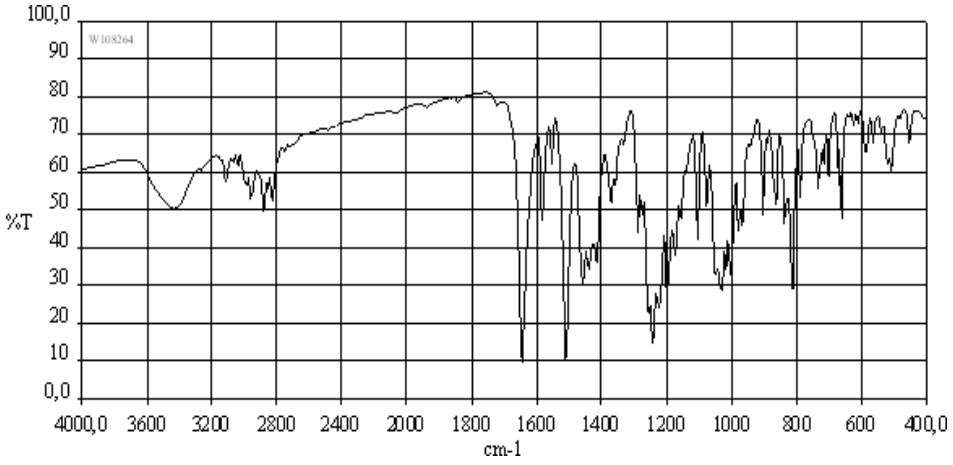


Figure 2: Reference FT IR spectrum of ketoconazole

The IR spectrum of ketoconazole revealed the presence of peak at 3085.89 cm^{-1} due to N-H stretching while peaks at 2927.74 and 2740.66 cm^{-1} is due to aliphatic C-H stretching. Strong absorption peaks observed at 1743.53 and 1689.53 cm^{-1} were assigned to drug carbonyl

stretching vibration (C=O). A peak at 1612 cm^{-1} indicates the aromatic ring and a peak at 1238 cm^{-1} is due to C-O Ar group. Peaks obtained in spectrum of pure drug (immediate & after 15 days) were similar to that given in standard

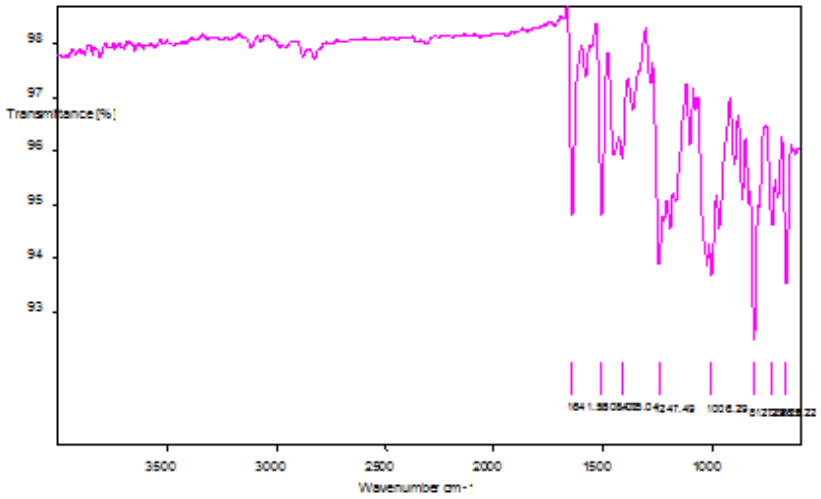


Figure 3: FT IR spectrum of ketoconazole (Fresh sample)

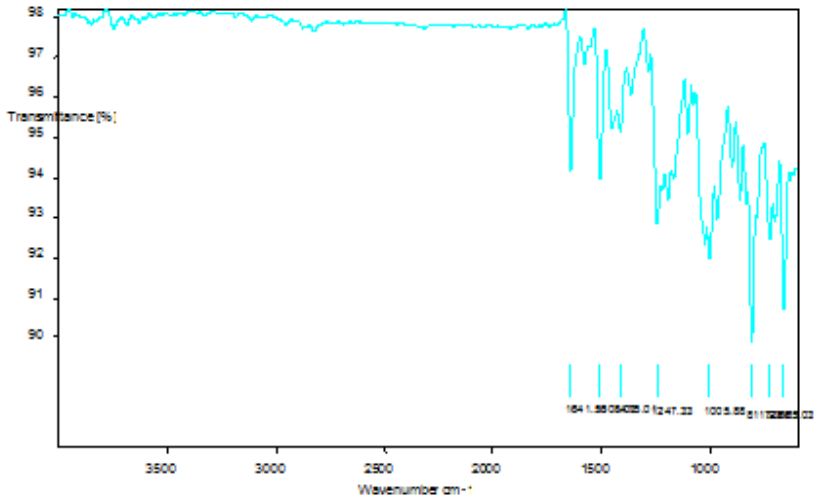


Figure 4: FT IR spectrum of ketoconazole (After 15 days)

Peaks obtained in spectrum of pure drug (immediate & after 15 days) were similar to that given in standard.

Drug excipients compatibility study by FTIR

Drug and excipients were accurately weighed and mixed and the resulting mixtures were scaled in screw glass vials and kept at a 50°C for 15 days (Table1).

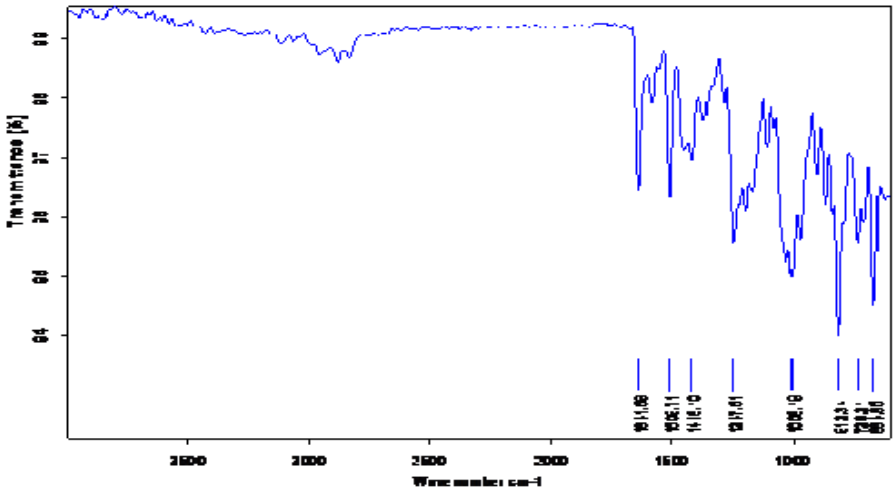


Figure 5: FT IR spectrum of ketoconazole+ Eudragit E 100 (Fresh sample)

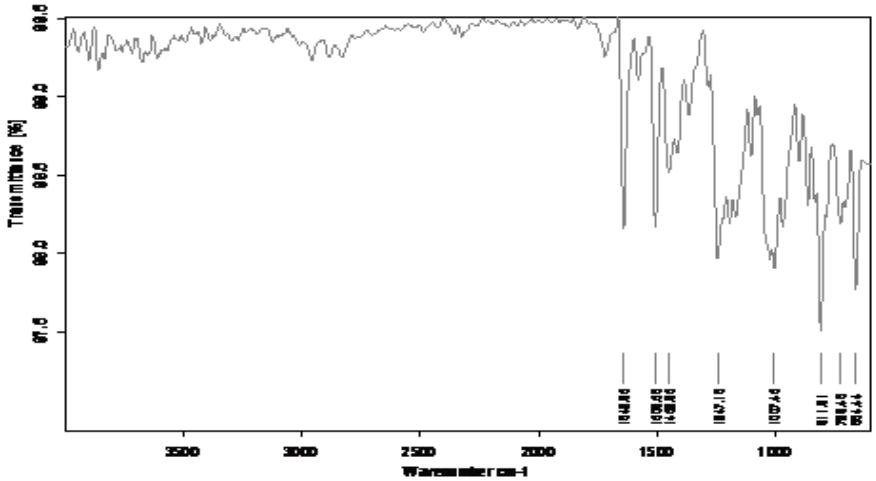


Figure 6: FT IR spectrum of ketoconazole+ Eudragit E 100(After 15 days)

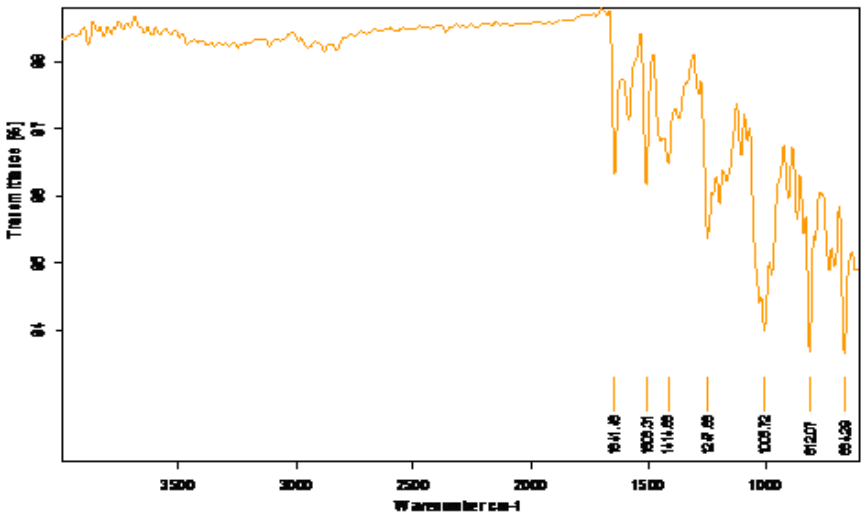


Figure 7: FT IR spectrum of ketoconazole+ Sodium starch glycolate (Fresh sample)

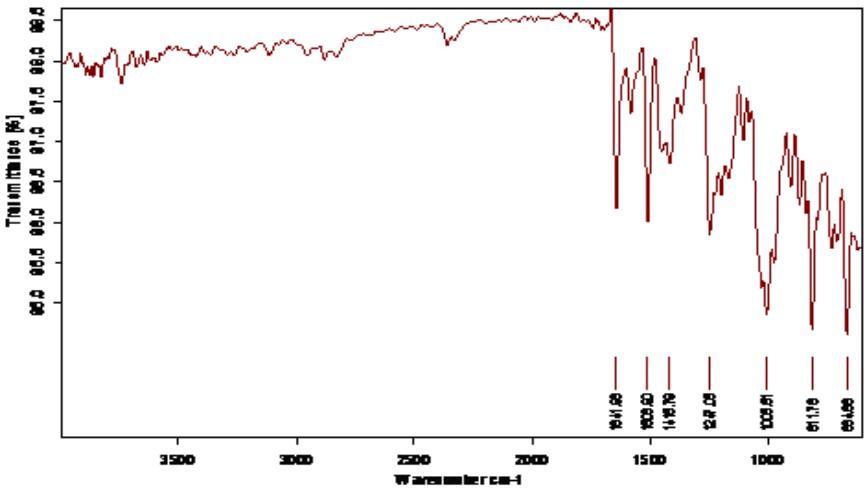


Figure 8: FT IR spectrum of ketoconazole+ Sodium starch glycolate(After 15 days)

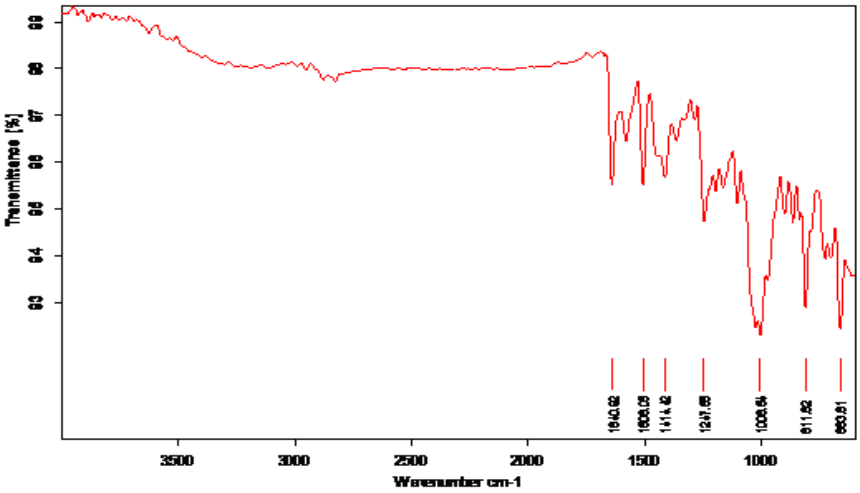


Figure 9: FT IR spectrum of ketoconazole+ Croscarmellose sodium (Fresh sample)

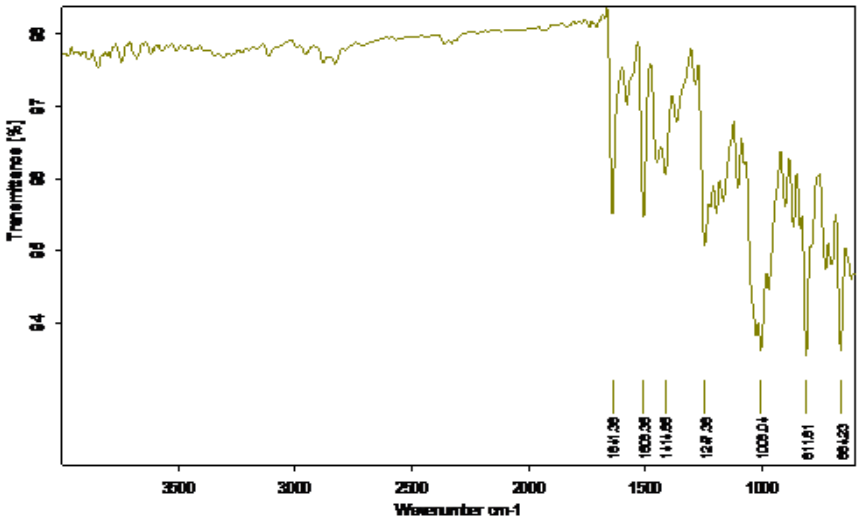


Figure 10: FT IR spectrum of ketoconazole+ Croscarmellose sodium (After 15 days)

Analytical method

Preparation of phosphate buffer solutions: The different buffer solutions were prepared and calibration curve were obtained respectively.

Preparation of standard calibration curve: Obtained Absorbance are shown in the tables and standard calibration curves of ketoconazole in different solvents of varying pH are shown in figures:11.

Table 7: Standard calibration curve in 0.1N HCl at λ_{max} 269.4 nm

Concentration	Absorbance
20	0.090
40	0.194
60	0.215
80	0.287
100	0.329

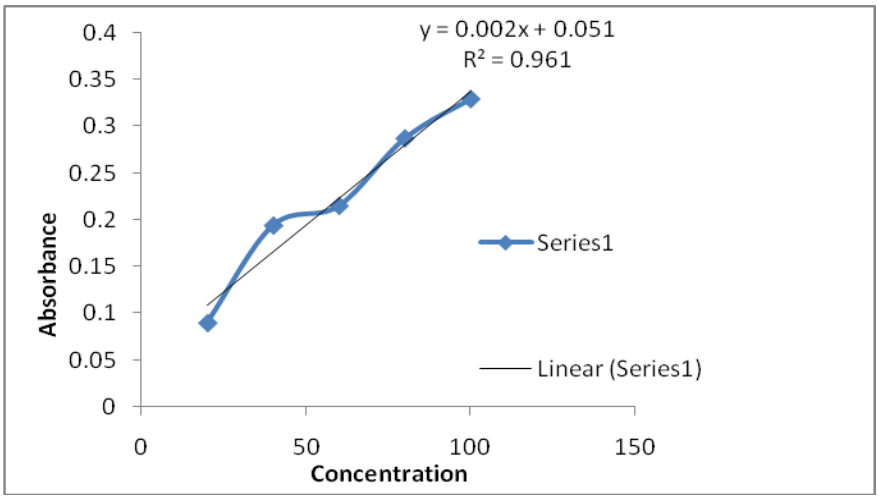


Figure 11: Standard calibration curve in 0.1N HCL at $\lambda_{max\ 269.4\ nm}$

Formulation

Twelve different formulation batches of binary systems of ketoconazole i.e. both physical mixture and solid dispersion were prepared with 3 different polymers croscarmellose sodium, eudragit E100 and sodium starch glycolate in 4 different ratio (1:1, 1:3, 1:5 and 1:7) as shown in Table (2).

Evaluation Tests

The formulations of physical mixture and solid dispersion were evaluated by the following parameters.

Percentage practical yield: Percentage practical yield of different formulation was determined by weighing the solid dispersion after drying. The percentage practical yield of different formulations was in range of 80 - 98% as shown in Table 8 and 9. The maximum percentage practical yield was found in SD6.

Table 8: Percentage practical yield of physical mixture

S. No.	Formulation No.	% Practical Yield	S. No.	Formulation No.	% Practical Yield
1.	PM 1	95.25	**7.**	PM 9	94.67
2.	PM 2	94.25	**8.**	PM 10	94.88
3.	PM 3	95.25	**9.**	PM 11	95.00
4.	PM 4	94.25	**10.**	PM 12	94.45
5.	PM 5	95.00	**11.**	PM 13	95.43
6.	PM 6	94.50	**12.**	PM 14	96.33

Table 9: Percentage practical yield of solid dispersion

S. No.	Formulation No.	% Practical Yield	S. No.	Formulation No.	% Practical Yield
1.	SD 1	90.00	**7.**	SD 9	93.00
2.	SD 2	93.75	**8.**	SD10	91.25
3.	SD 3	92.83	**9.**	SD11	87.50
4.	SD 4	93.00	**10.**	SD12	89.67
5.	SD 5	91.50	**11.**	SD13	83.50
6.	SD 6	94.25	**12.**	SD14	85.50

(PM-Physical mixture, SD-Solid dispersion).

(PM1-4= Physical mixture of Croscarmellose sodium, PM5-8=Physical mixture of sodium starch glycolate,PM9-12=Eudragid E-100).

(SD1-4= Solid dispersion of Croscarmellose sodium, SD5-8= Solid dispersion of sodium starch glycolate,SD9-12=Eudragid E-100).

Drug release/in vitro release studies of the formulations.

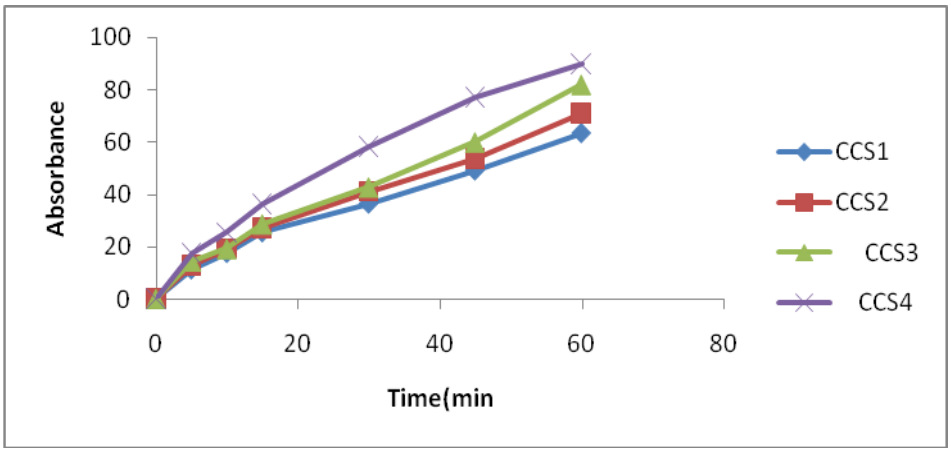
Dissolution Studies of Solid Dispersion Formulations.

Ketoconazole solid dispersions showed a dissolution pattern better than the pure Ketoconazole. Ketoconazole solid dispersion with Croscarmellose sodium showed a marked increase in the cumulative % drug release up to 90.09%. Similarly solid dispersion of Ketoconazole with sodium starch glycolate was up to 82.10 and solid dispersion of ketoconazole with eudragit E 100 was up to 60.00% .Thus on the basic of above observation SD4 formulation was selected for the final formulation for tablet formation.

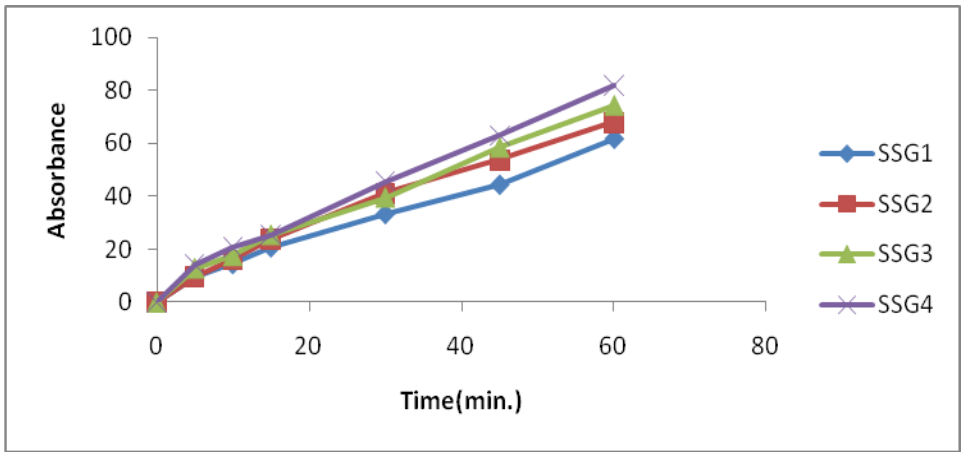
Table 10: Dissolution Studies of tablet of Optimized solid dispersion Formulation, Pure Drug and Commercial Conventional Release Tablet

S. No.	Batch	Cumulative % Release at Different Time Intervals (min)					
		5	10	15	30	45	60
1.	Pure drug	3.56	9.79	14.50	20.79	25.56	30.90
2.	Commercial conventional tablet	23.94	30.59	39.76	51.46	60.43	76.90
3.	SD1	11.32	17.59	25.45	36.45	49.07	63.30
4.	SD2	12.87	19.15	27.02	41.13	53.77	71.14
5.	SD3	14.43	19.16	25.58	42.70	60.01	82.06
6.	SD4	17.53	25.39	36.39	58.31	77.26	90.09
7.	SD5	9.77	14.48	20.77	33.30	44.34	61.65
8.	SD6	9.77	16.03	23.88	41.08	53.72	67.98
9.	SD7	12.87	17.60	25.46	39.56	38.40	74.24
10.	SD8	14.43	20.71	28.59	39.81	63.13	82.10
11.	SD9	0.46	3.57	8.24	14.49	25.44	39.54
12.	SD10	2.01	5.13	11.36	20.74	31.71	39.85
13.	SD11	2.01	8.23	16.03	25.43	34.88	52.15
14.	SD12	3.56	9.79	19.16	28.57	42.7	60.0

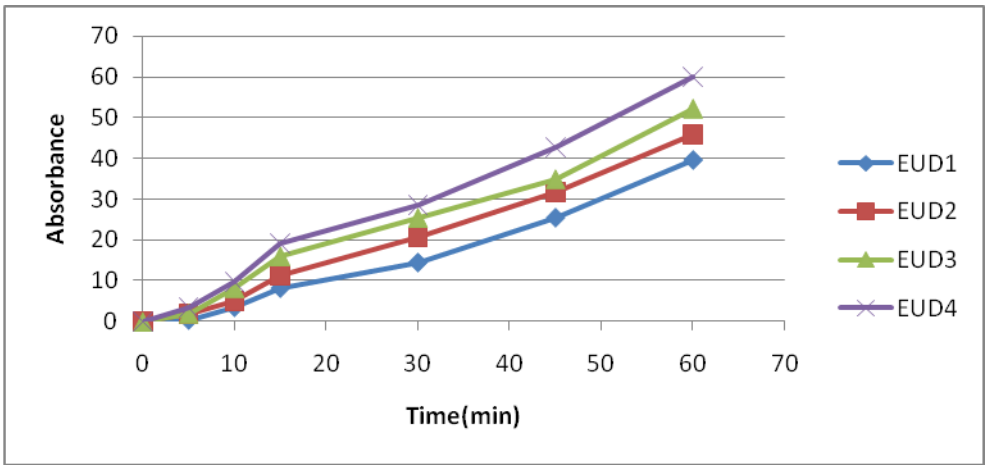
In-vitro dissolution profile of SD of drug with Croscarmellose sodium.



In vitro dissolution study of SD of sodium starch glycolate.



In-vitro dissolution profile of SD of drug with Eudragit E 100.



CCS: Croscarmellose sodium, SSG: Sodium starch glycolate, EED:Eudragid E-100

Figure 12: In-vitro dissolution profile of solid dispersion (SD) of drug with different polymers.

DRUG CONTENT STUDY

The drug content of the formulations were determined and reported in table11.

Table 11: Drug content.

S. No.	Formulation No.	Drug Content	S. No.	Formulation No.	Drug Content
1.	PM 1	95.15	13.	SD 1	99.15
2.	PM 2	96.63	14.	SD 2	98.63
3.	PM 3	96.78	15.	SD 3	99.25
4.	PM 4	95.84	16.	SD 4	99.34
5.	PM 5	93.69	17.	SD 5	97.02
6.	PM 6	95.82	18.	SD 6	96.33
7.	PM 7	94.33	19.	SD 7	96.67
8.	PM 8	93.63	20.	SD 8	97.09
9.	PM 9	93.25	21.	SD 9	96.82
10.	PM10	94.21	22.	SD10	95.93
11.	PM11	95.63	23.	SD11	95.75
12.	PM12	94.02	24.	SD12	95.69

OPTIMIZATION OF THE FORMULATION

ANOVA: The solid dispersion of ketoconazole with Croscarmellose sodium (1:7) showed highest dug release i.e. 90.09%. This optimized formulation was used for the preparation of the tablet. ANOVA showed significant difference between the formulations. The p values showed that there was a significant difference between formulations of the drug with different polymers. The p vales and F values are given in the Table 12 as follows.

Table 12: p and F values of solid dispersion and mixture

S. No.	Formulation	p value	F value	Degree of freedom
1.	CCS	0.0564	2.396	27
2.	CCS (SD+PM)	0.0589	4.374	55
3.	SSG	0.0796	2.495	27
4.	SSG (SD+PM)	0.0654	6.484	55
5.	Eud E 100	0.0646	3.340	27
6.	Eud E 100 (SD+PM)	0.0534	7.413	55

Formulation and Evaluation of Tablet of Optimized Solid Dispersion Formulation

Formulation of Powder blend

The powder blend was prepared by using solid dispersion, lactose 20% as diluent, talc 3% as glidant and magnesium stearate 2.0% as lubricant and mixed them properly.

Evaluation of Tablets

Pre-compression parameters

Table 13: Physical parameters of powder blend evaluation

S. No.	Parameters	Results
1.	Bulk density	0.641 gm/ml
2.	Tapped density	0.743 gm/ml
3.	Carr's index	15.08%
4.	Hausner ratio	1.15
5.	Angle of repose	$21^{o}.60$"

Post-compression parameters

Evaluation of the tablets prepared from optimized solid dispersion showed that all the parameters were within limits and are shown in table 14.

Table 14: Evaluation of prepared tablet.

S. No.	Parameter	Result
1.	Thickness	3.28 mm
2.	Hardness	4.1 kg/cm^2
3.	Friability	0.95 %
4.	Weight variation	144-154 mg
5.	Disintegration time	6.30 min.

Table 15: Dissolution profiles of pure drug, optimized formulation of solid dispersion and commercial conventional release tablet

S. No.	Batches	Cumulative % Release at Different Time Intervals in min					
		5	10	15	30	45	60
1.	Ketoconazole (API)	3.56	9.79	14.50	20.79	25.56	30.90
2.	Commercial conventional tablet	23.94	30.59	39.76	51.46	60.43	76.90
	Ketoconazole	36.12	45.07	52.13	62.39	74.90	90.09

3.	Solid dispersion tablet with CCS(1:7)						

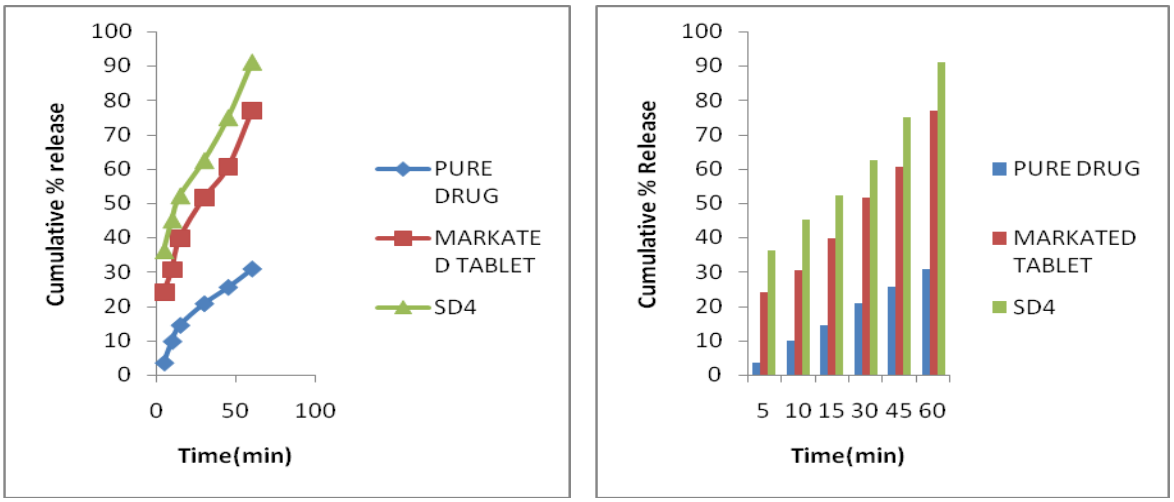


Figure 13: Cumulative % release of drug from pure drug, commercial Conventional release tablet and solid dispersion of drug with Croscarmellose sodium.

DRUG RELEASE KINETICS

Model Independent Parameters

Dissolution efficiency

Tablet prepared by solid dispersion of drug with Croscarmellose sodium (optimized formulation, (SD4) showed greater percentage dissolution efficiency {%DE} from conventional commercial tablet within 60 min as shown in table.

Table 16: Dissolution efficiency of optimized solid dispersion tablet and conventional commercial tablet.

S. No.	Formulation	% DE
1.	Optimized solid dispersion tablet	90.09
2.	Conventional commercial tablet	76.90

Dissolution profile comparison

Determination of Similar Factor (f_2) and Difference factor (f_1)

The similarity and difference factor obtained for Ketoconazole was found to be within the standards i.e. 52 and 6.51 respectively as shown in Table 17. There was no significant variation in the in vitro drug release profile of commercial product and optimized solid dispersion tablet. The calculated similarity factor (f2 value) was 52. It was more than standard value indicating similarity between both the dissolution profiles. Calculation of

difference factor (f_1) and similarity factor (f_2) for optimized formulation and commercial conventional release tablet is given below in table17.

Table 17: Calculation of Difference factor (f_1) and Similarity factor (f_2)

Time	R_t	T_t	$\{R_t - T_t\}$	$(R_t - T_t)^2$	Similarity factor (f_2)	Difference factor (f_1)
5	23.9	17.53	6.37	40.576	52	6.51
10	30.6	25.39	5.21	27.144		
15	39.8	36.39	3.41	11.628		
30	51.5	58.31	-6.81	46.376		
45	60.4	77.26	-16.86	284.25		
60	76.9	90.09	-13.19	173.97		
Sum				583.96		

R_t = Cumulative percentage dissolved of reference product (commercial) at time t

T_t = Cumulative percentage dissolved of test product (Solid dispersion) at time t

6.8.3 Model Dependent Kinetics

Data obtained from dissolution studies was fitted to various kinetics equations to find out the mechanism of release of drug from the formulation compared to the commercial preparation. The kinetics models used were Zero order, First order, Higuchi model and Korsmeyer Peppas model. The following table 19 shows release kinetics of optimized formulation solid dispersion tablet & Commercial conventional release table18.

Table 18: Release kinetics of optimized formulation solid dispersion tablet & Commercial conventional release tablet

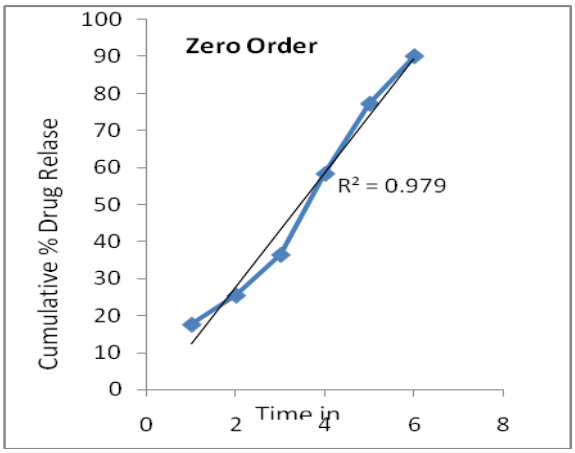
Time (min)	Square Root of Time	log time	%CDR		log % CDR		log % CDR remaining	
	SD4	Commer-cial	SD4	Commer-cial	SD4	Commer-cial	SD4	Commer-cial
5	0.288	-1.0793	17.53	23.94	1.243	1.379	1.916	1.881
10	0.4074	-0.7798	25.39	30.59	1.404	1.485	1.872	1.841
15	0.5	-0.602	36.39	39.76	1.560	1.599	1.803	1.779
30	0.707	-0.301	58.31	51.46	1.765	1.711	1.620	1.686
45	0.866	-0.1249	77.26	60.43	1.887	1.781	1.356	1.597
60	1	0	90.09	76.90	1.954	1.885	0.996	1.363

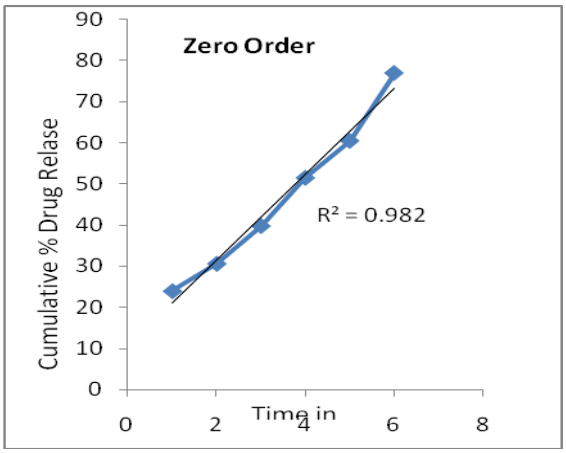
Table18, summarized the correlation coefficients for different release kinetic models of Ketoconazole optimized tablet and commercial conventional release tablet. The release of formulation SD4 was indicated by highest r^2 values 0.996 in Korsmeyer Peppas model, and equivalent to that of commercial product which also showed highest value of r^2 0.989 in

Korsmeyer Peppas model. This model was judged to be more appropriate model for dissolution data.

Table19: Model dependent parameters of tablet of optimized formulation and commercial conventional release tablet

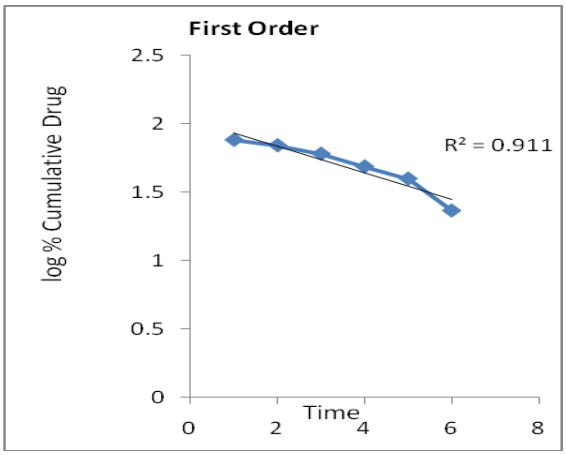
S. No.	Formulations	Evaluation parameter	Zero order	First order	higuchi model	Peppas model
1.	Tablet of optimized formulation	Value of r^2	0.979	0.895	0.994	0.996
2.	Commercial formulation	Value of r^2	0.982	0.911	0.984	0.989





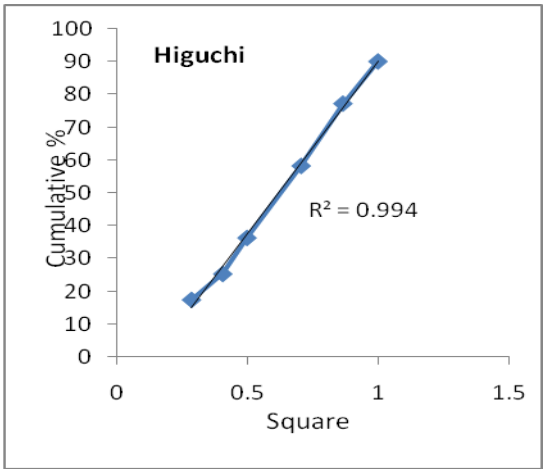
Release kinetics of SD4	Release kinetics of commercial conventional release tablet

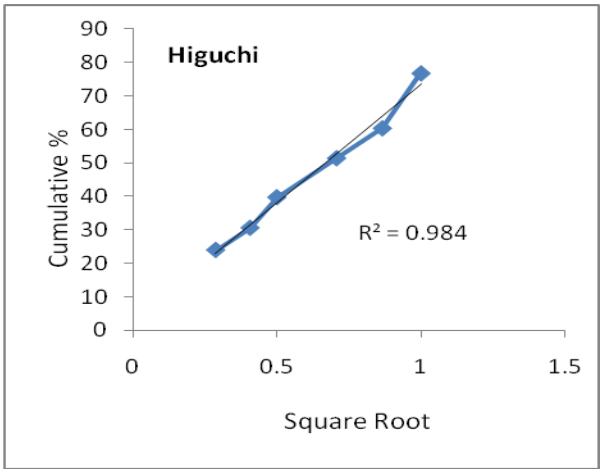
Figure 14: Comparison with Zero order release kinetics of Solid dispersion of crosscarmilose sodium and conventional release tablet.



Release kinetics of SD4	Release kinetics of commercial conventional release tablet

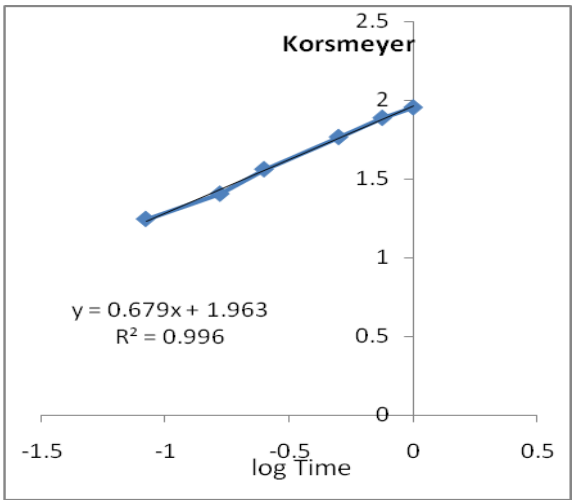
Figure 15: Comparison with First order release kinetics of Solid dispersion of crosscarmilose sodium and conventional release tablet.

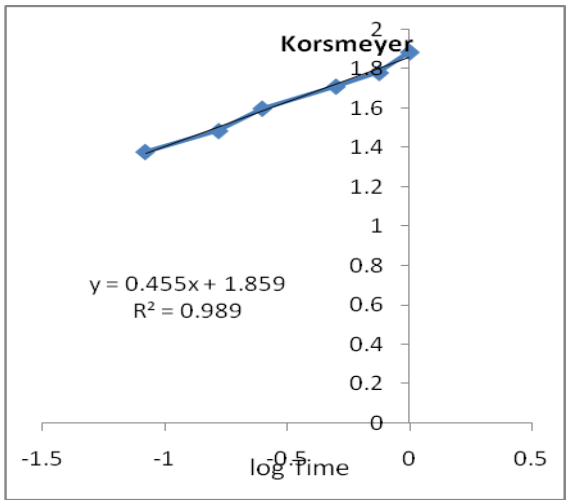




Release kinetics of SD4	Release kinetics of commercial conventional release tablet

Figure 16: Comparison with Higuchi model kinetics of Solid dispersion of crosscarmilose sodium and conventional release table.





Release kinetics of SD4	Release kinetics of commercial conventional release tablet

Figure 17: Comparison with Korsmeyer Peppas model of Solid dispersion of Croscarmellose sodium and conventional release tablet.

The conventional marketed tablet and the formulated tablet follows Korsmeyer Peppas model of kinetics, thus the formulated tablet dosage form meets with the marketed tablet.

CONCLUSION

This research showed that when Ketoconazole was dispersed in suitable water-soluble carriers such as Croscarmellose sodium, sodium starch glycolate; its dissolution was enhanced compared with pure drugs. In compare to this, all water soluble carrier Croscarmellose sodium gave the best result from both the physical mixture and solid

dispersion in 1:7(drug: polymer) ratio. By in-vitro study, it was clearly proved that preparation of solid dispersion of Ketoconazole with Croscarmellose improved the dissolution rate of Ketoconazole. The FTIR spectroscopic studies showed the absence of any specific chemical interaction between Ketoconazole and Croscarmellose in solid state. Finally, it can be concluded that Ketoconazole solid dispersions with Croscarmellose sodium provide a promising way to enhance solubility and dissolution rate of Ketoconazole.

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