International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-2, 2015 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Matrix Tablets of Voriconazole Using Synthetic Polymers

Tejashwini JM*, Ashok Kumar P, Suresh V. Kulkarni

Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, B. H. Road, Tumkur-572 102, India.

Manuscript No: IJPRS/V4/I2/00051, Received On: 08/04/2015, Accepted On: 16/04/2015

ABSTRACT

The intention of this research work was to formulate, develop and evaluate the Sustained Release (SR) Tablets of anti fungal drug voriconazole. The tablets were prepared by wet granulation method. For the Sustained release formulation the dissolution time of the tablet must be optimized in order to have a prolonged release of drug in the dissolution profile. The dissolution time is managed by using polymers HPMC K100, Eudragit RSPO, HPMC K4M, and Carbopol 971P. In the formulations these trails were optimized by changing composition of polymer and its concentration. Micro crystalline cellulose used as diluent, Magnesium stearate as glidant, Talc as lubricant. The different excipients were tested for their compatibility with anti fungal drug voriconazole. The compatibility studies were carried out by FTIR and DSC studies and which shown that there was no chemical and physical interaction occurred. The preformulation parameters such as bulk density, tapped density, compressibility index and hausner's ratio were analysed for prepared granules previous to compression. The thickness, hardness, friability, weight variation and drug content uniformity was evaluated for tablets. The effect of this variable on the drug release profile of voriconazole was also studied. The *in-vitro* drug release were performed in the USP Apparatus-II (Paddle) using 0.1N HCl for l2 hrs and remaining 10 hrs with 6.8phosphate buffer as a dissolution media at 100rpm speed and temperature of 37 ^{0} C ± 0.5 ^{0} C. The sampling was done at periodic time intervals of first two hours with 0.1N HCl and by changing the media with 6.8 phosphate buffer continue the dissolution up to 10 hrs. The cumulative amount of drug release at different time interval was estimated using UV spectroscopical method at 255nm,the F-7 Formulation containing Eudragit RSPO 10% shows release study up to 98.85%,these results indicate that the selected F -7 formulation was stable during the period of accelerated stability studies. All evaluated formulation results was found to be satisfactory.

KEYWORDS

Sustained Release Tablets, Eudragit RSPO, HPMC K4M, Carbopol 971P, FTIR, DSC

INTRODUCTION

Oral drug delivery is the most preferred and convenient choice as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs.

***Address for Correspondence:**
Tejashwini. J. M.
Department of Pharmaceutics, Sree Siddaganga College of Pharmacy, B. H. Road, Tumkur-572 102, India.
E-Mail Id: ashokkumarscp@yahoo.com

Normally conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with resultant undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of

oral Sustained release drug delivery systems. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches.[1]

Sustained release systems consist of any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.[2]

Matrix systems are widely used for the purpose of sustained release. The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.[3]

The need for more potent antifungals with increased activity against resistant pathogens, shorter treatment durations, and fewer adverse effects stimulates the drive for continued development of systemic antifungals. Voriconazole (UK-l109, 496, Pfizer Pharmaceuticals, New York, NY) is the newest azole antifungal agent for the treatment of systemic mycosis. Voriconazole was developed as part of a program designed to enhance the potency and spectrum of activity of fluconazole. Currently both an oral and intravenous formulation are undergoing investigation in Phase III trials. This review discusses various pharmacologic aspects of voriconazole, including the mechanism of action, spectrum of activity, pharmacokinetic profile, clinical efficacy, and adverse effects. A comparison with existing azole antifungals is provided when possible to illustrate the potential role of voriconazole in the clinical setting.[4]

Voriconazole is a triazole antifungal agent. The primary mode of action of Voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. It has half-life about 1.7 hours and its oral bioavailability is 96%. To reduce the dosage frequency and related side effects Voriconazole can be given in the form of sustained release dosage form. This improves bioavailability of the drug, reduces frequency of dosing, thus minimizes side effects and enhances patient compli-ance.[4]

MATERIAL AND METHODS

Raw Materials

Voriconazole was obtained as a gift sample from MSN House hyderabadh. Eudragit RSPO was obtained from strides arcolab Bangalore, and remaining polymers and other expients like Hydroxy propyl methyl cellulose HPMC K100M, HPMC K4M, carbopol 971P, microcrystalline cellulose, PVP K 30, magnesium stearate and talc were obtained from KAPL Bangalore.

Preparation of Matrix Tablets

Tablet formulations were prepared by wet granulation method. Aqueous granulation process was used to prepare Voriconazole SR matrix tablets Proportion of excipients with drug was as given in Table no 1. All ingredients were sifted through sieve no.40. The sifted ingredients were mixed thoroughly in a polybag for 15min. PVP K30 was dissolved in distilled water and used for wet granulation of the final blend. To get the desired wet mass. This wet mass was passed through sieve # 16. The prepared granules were dried at 60 ^{O} C for 1 hour in hot air oven, dried granules were sized by passing it through sieve No.20 and lubricated with magnesium stearate and Talc for 1 minutes. Finally tablets were compressed at 400 mg weight on a 16 station mini rotary tableting machine with 11 mm standard concave punches.

Polymers used - HPMC K100M, HPMC K4M, Carbopol, Eudragit RSPO

Diluent used - MCC

Lubricant used- Magnesium Stearate

Glidant used- Talc

Evaluation of Granules[5,6,7]

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Carr's index (%) = [TBD-LBD] X 100 / TBD

Where, TPD is Tapped bulk density

LBD is Loose bulk density

The physical properties of granules were shown in Table 3.

Evaluation of Tablets [5,6,7]

Post Compression Parameters

A. Thickness and Diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.

C. Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

$$F = \frac{(W \text{ initial}) - (W \text{ final})}{(W \text{ initial})} \times 100$$

D. Weight Variation

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet. All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 4.

E. Uniformity of Drug Content

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of voriconazole, transfer to a 250 ml volumetric flask. Add about 150 ml of 6.8 Phosphate buffer. Shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 6.8 Phosphate buffer Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 6.8 Phosphate buffer Measure the absorbance, of the resulting solution at the maxima at about 255 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

$$Cu/Cs = Au/As * \text{dilution factor}$$

Cu = Concentration of unknown sample,

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample

As = Absorbance of standard sample.[8]

F. In-Vitro Dissolution Study

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37 ± 0.5°C. The Paddles were rotated at a speed of 100 rpm. The prepared tablets of voriconazole tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 6.8) and continue dissolution. 5 ml of solution were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of voriconazole was determined spectrophotometrically at a wavelength of 255nm. At each (hour) time of Withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. On the basis of release studies the formulation which gave desired twice a day release of voriconazole was chosen as the optimized formulation. The dissolution profiles of different formulations are shown in figure 10, 11. Among different formulations F7, F3, F2 were found to be better formulations, they fallowed the sustained release for long period of time in the fallowing order.

F7 > F3> F2.

Drug Release Kinetics

To determine the mechanism of drug release from this formulation, the drug release data of *in-vitro* dissolution study was analyzed with various kinetic equations.

Various kinetic equations. The data were treated according to:

1. Zero order kinetic model – Cumulative % drug released versus time.
2. First order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

Stability Study

The optimized formulation was subjected to stability at 250C± 20C / 60% ± 5% RH, 300C ± 20C / 65% ±5% RH and 400C ± 20C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.

The optimized formulation was subjected to stability at 25^0C± 2^0C / 60% ± 5% RH, 30^0C ± 2^0C / 65% ±5% RH and 40^0C ± 2^0C / 75% ± 5% RH for period of 90 days.

After each month tablet sample was analyzed for physical characteristics and drug release profile.[9]

Table 1: Composition of matrix tablet of voriconazole with different polymer concentrations

Ingredients	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Voriconazole	200	200	200	200	200	200	200	200	200	200
HPMC K 100 M	120 (30%)	100 (25%)	60 (15%)	*	*	*	*	20	40	60 (15%)
Eudragit RSPO	*	*	*	*	120 (30%)	100 (25%)	40 (10%)	40	20	
Carbopol 971P	*	*	*	100 (25%)	*	*	*	*	*	*
HPMC K4M	*	*	*	*	*	*	*	*	*	60 (15%)
PVP K 30	20	20	20	20	20	20	20	20	20	20
MCC	48	68	108	68	48	68	128	108	108	48
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4
Talc	8	8	8	8	8	8	8	8	8	8

RESULTS AND DISCUSSION

Preformulation Studies

Melting Point Determination

Melting point of Voriconazole was found to be in the range 127^0 C, which complied with standards limits range127- 130^0 C, indicating purity of the drug sample.

Solubility

Voriconazole is low soluble in water. It is soluble to the degree of one part in two parts of water and one part in 100 parts of ethanol. It is insoluble in chloroform, acetone, Methylene chloride and ether.

Compatibility Study

Compatibility studies were performed using FTIR spectrophotometer and from DSC analysis

FTIR Studies

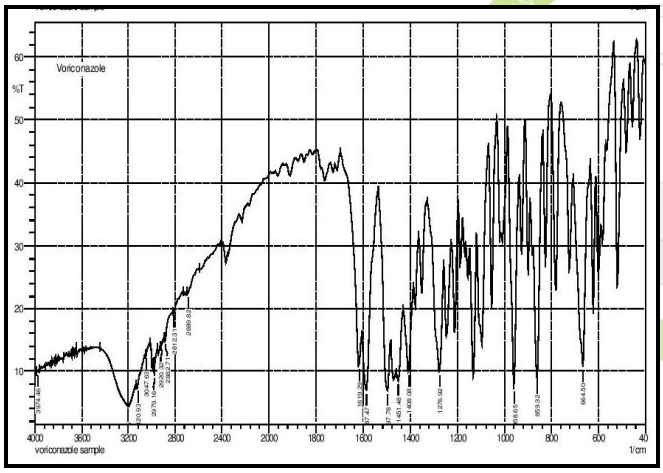

Figure 1: FTIR of pure Voriconazole

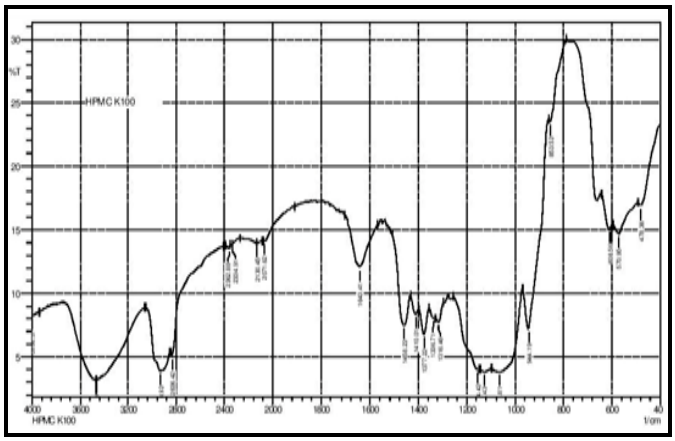

Figure 2: FTIR of HPMC K100

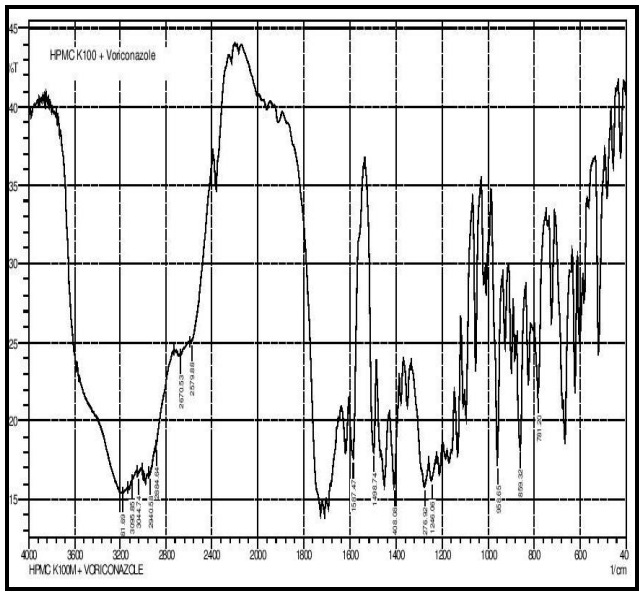

Figure 3: FTIR of HPMC K100M + Drug

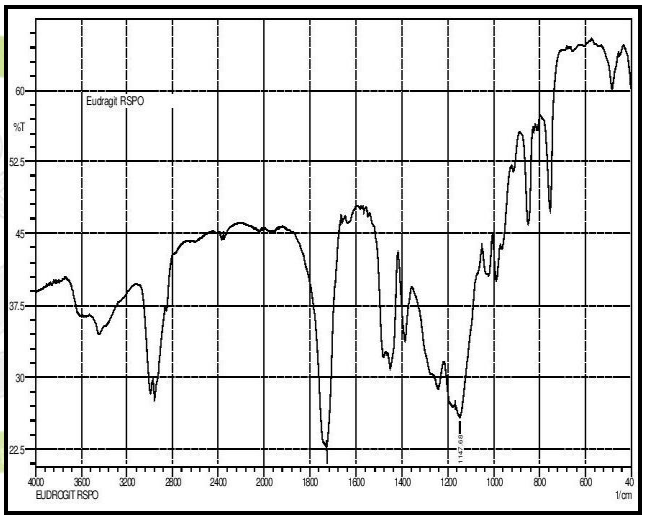

Figure 4: FTIR of Eudragit RSPO

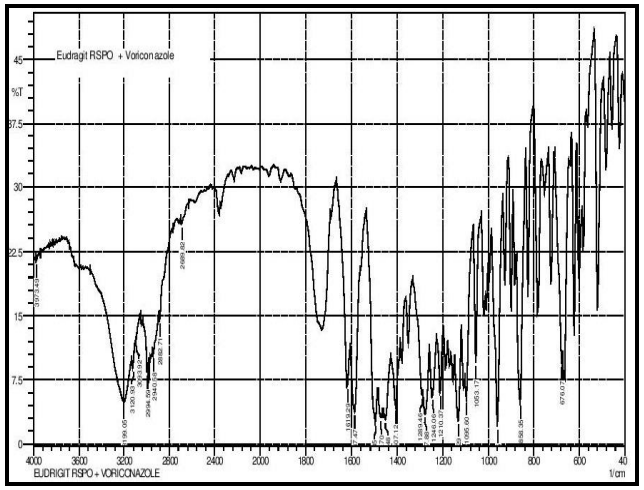

Figure 5: FTIR of Eudragit RSPO + Drug

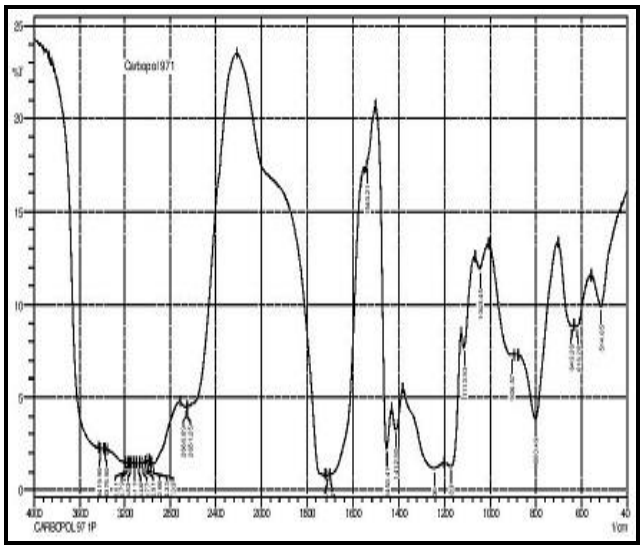

Figure 6: FTIR of Carbopol 971P

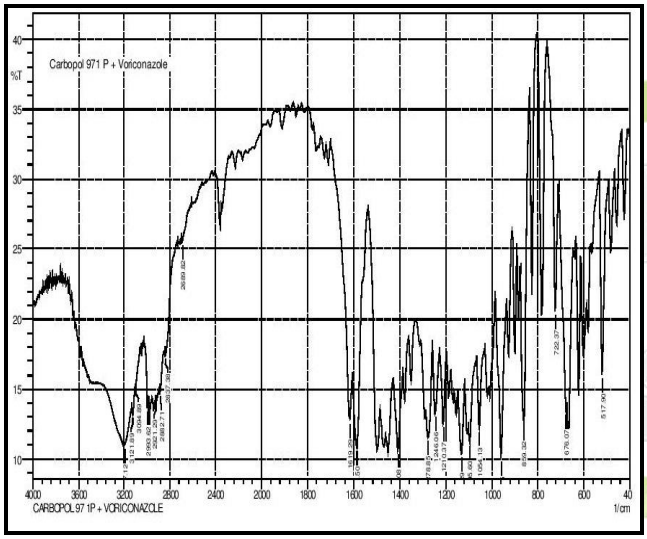

Figure 7: FTIR of carbopol 971P + Drug

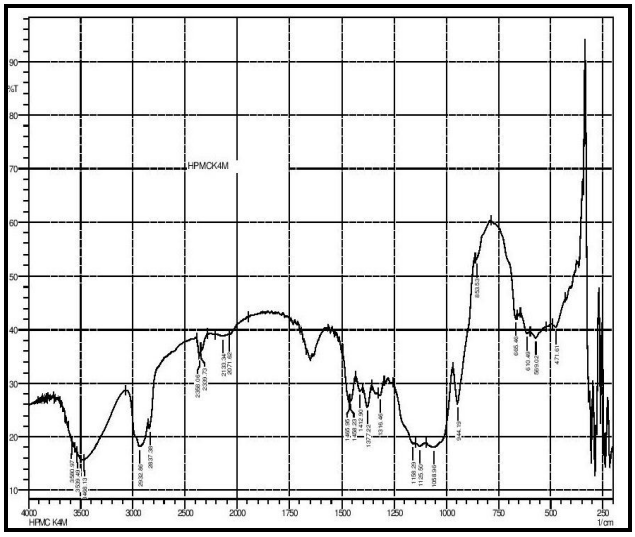

Figure 8: FTIR of HPMC K4M

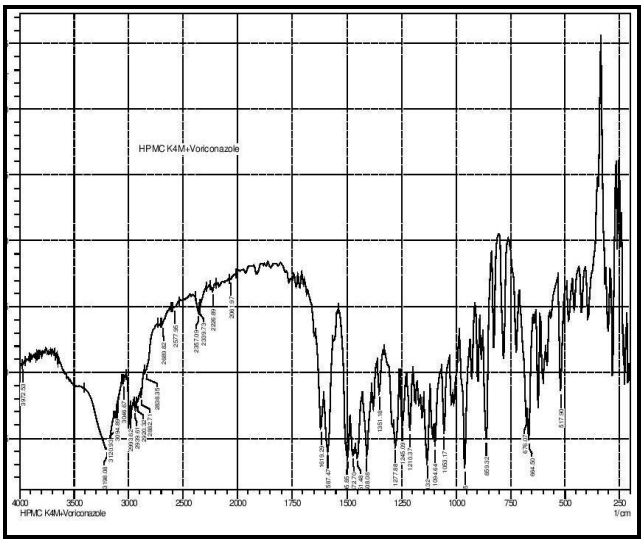

Figure 9: HPMC K4M + Drug

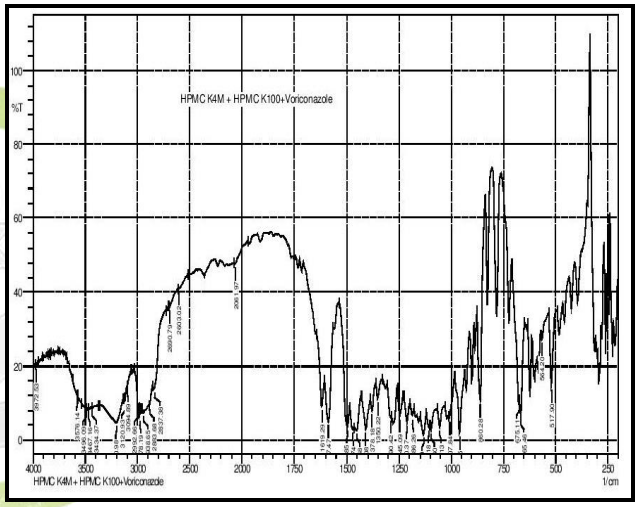

Figure 10: HPMC K4M +HPMC K100 M + Drug

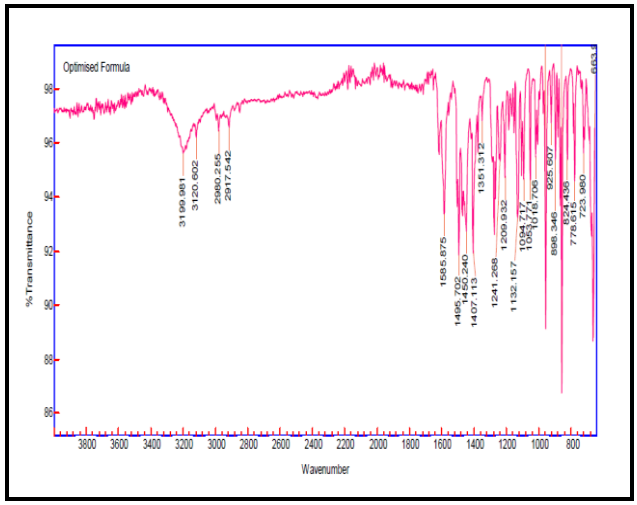

Figure 11: Optimised formula containing Drug + Eudragit RSPO Polymer

Table 2: Functional group analysis of drug, polymer and optimised formula by FTIR studies

Sl. no	Functional group	Reference region	Observed region
	PURE DRUG		
1	C-O-H Bonds	1440-1220 cm^{-1} (bending appear as broad and week peak)	1408 cm^{-1}
2	C-O Bonds	1260-1000 cm^{-1} (stretching vibrations)	1277.88 cm^{-1}
3	CH3	1375cm^{-1} (Bending absorption)	1276 cm^{-1}
4	-C=H	1350-1000cm^{-1} Stretching	1276.92 cm^{-1}
5	Aromatic ring	900-690 cm^{-1} Stretching	859.32 cm^{-1}
6	C=N	1690-1640 cm^{-1} (Stretching)	1619.29 cm^{-1}
7	C-N	1350-1000 cm^{-1} (Stretching)	1290 cm^{-1}
8	C=C-C	1700-1680 cm^{-1} (conjugation)	-
9	C=C	1600-1475 cm^{-1} (Stretching)	1587.47 cm^{-1}
10.	**Eudragit RSPO** polymer C=O	1100-1150 (Stretching vibration)	1147.68
11.	Optimized formula C=N	1690-1640 cm^{-1} (Stretching)	1619 cm^{-1}
12.	-C=H	1350-1000cm^{-1} Stretching	1659 cm^{-1}
13.	C-N	1350-1000 cm^{-1} (Stretching)	1289 cm^{-1}
14.	C-O-H Bonds	1440-1220 cm^{-1} (bending appear as broad and week peak)	1448 cm^{-1}
15.	C-O-H Bonds	1440-1220 cm^{-1} (bending appear as broad and week peak)	1246 cm^{-1}
16.	C-O-H Bonds	1440-1220 cm^{-1} (bending appear as broad and week peak)	1289 cm^{-1}
17.	C=N	1350-1000 cm^{-1} (Stretching)	1053 cm^{-1}
18.	Aromatic ring	900-690 cm^{-1} Stretching	858.35 cm^{-1}

Differential Scanning Calorimetry

Thermogram of voriconazole is shown in figure 12.which indicates of pure drug is 133 ^{0}C and melting peak of optimised formulation (F-7) is 134.14^0 C, was observed in the Figure 13, change in temperature is due to various concentrations of drug and other excipient and also in optimised formulation. This shows that there is no interaction between dug and optimised formulation F -7. DSC studies revealed that there was no much shift in the melting point of a drug when mixed with other excipients is compared to the pure drug this indicates that there is no interaction between drug and excipients.

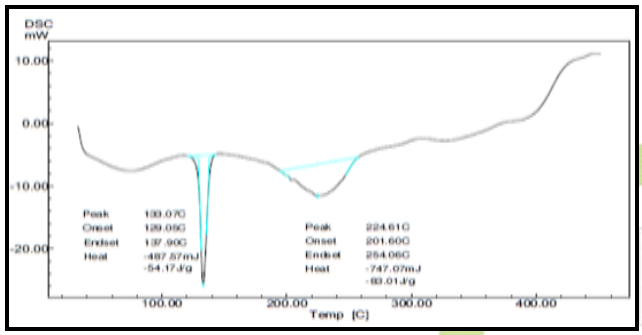

Figure 12: DSC Thermogram of voriconazole

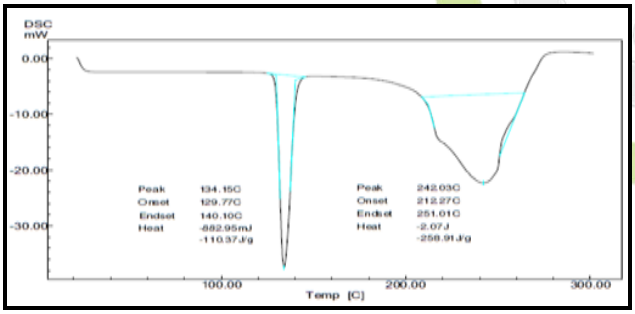

Figure 13: DSC Thermogram of optimised formulation F7

The drug and other excipients and also in optimized formulation was evaluated by FTIR and DSC. FTIR spectrum of pure drug was compared with that of formulations F-7. All peaks corresponding to the different functional groups of pure drug were present in the formulations which indicate there was no interaction between the drug and excipients as shown in figures 1 to 10. DSC Studies review that, the peaks obtained from pure and optimised formulations of voriconazole shows the peak range (127-130 ^{o} C) of its melting point (133 ^{o} C), (Figure: 12 and 13).

Evaluation of Pre-Compression Parameters

Precompressional parameters of Voriconazole blends were evaluated for bulk density, tapped density, angle of repose, compressibility index and hausner's ratio shows (Table 3). The Bulk densities were found to be in the range of 0.553 to 0.592 gm/cc, Tapped densities were in the range of 0.615 to 0.685 gm/cc, Compressibility index and Hausner's ratio were in the range of 11.25 to 13.57 %and 1.17 to 1.29 and Angle of repose were found to be between 24.22 to 29.74 (Table 3)

Evaluation of Post Compression Parameters

The punches used to compress the tablets were 11mm, standard cancave shaped. The shape and size of the tablets were found to be within the limit. Thicknesses of the tablets were found to be in the range of 4.25 to 4.5 mm. The results are given in the Table No.4. The hardness of the tablets was found to be in the range of 6.8 to 7.2 Kg/cm^2. It was within the range of monograph specification. The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The drug content of the tablets was found to be in the region of 98.76 to 99.65%. It was within the range of monograph of specification. Weight variation is pass the limit and it found to be within the range of monograph of specification. (Table 4)

Drug Release Studies

In vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing basket at 100rpm using 900ml 0.1N HCl for 2 hours an continue the dissolution with 6.8 phosphate buffer as a dissolution medium up to remaining hours. The results were evaluated for 12 hours, as per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7 ,F-8 F-9 and F-10 however 95.35%, 89.37%, 93.32%, 74.29%, 42.71%, 58.49%, 98.85%, 54.54%,98.5%, 54.1% and 78.15% release over a period of 12 hours. Formulation F-1, F-9 failed to sustain release beyond 11 hours, among all the formulation, F-2,

F-3, F-4, F-5, F-6, F-7, F-8, F-10 shows 89.37%, 93.32%, 74.29%, 42.71%, 58.49%, 98.85%, 54.54%, and 50.23% and release at the end of 12 hours. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration. The dissolution studies were carried out for 12 hours. As per the result of dissolution study formulation F-3 showed reasonable release 93.32%, respectively. F-7 showed good drug release profile 98.85% they showed excellent matrix integrity during the period of study, when compare to other formulations. Based on all these results, formulation F-7 is selected as the optimized formulation with 98.90%, drug release. (Figure 14).

Kinetics Studies

Correlation coefficients of different mathematical models for formulations F- 1 to F-10

The release data fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetics data of all formulations F1-F10 could be best expressed by zero order equations as the plots shows highest linearity (0.956 to 0.999) than first order (0.768 to 0.997) The n values obtained from korsmeyer peppas plots range from (0.801 to 0.995) indicates that mechanism of release formuations F1 to F10 was anomalous (non Fickian) diffusion. (Table 6).

Table 4: Evaluation of Pre-Compression parameters

Parameters	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F 10
Angle of repose	24.22	27.22	25.15	28.39	29.74	25.20	24.44	24.69	25.16	25.62
Loose bulk density (LBD) (g/ml)	0.553	0.580	0.592	0.575	0.549	0.571	0.575	0.541	0.581	0.583
Tapped bulk density (TBD) (g/ml)	0.632	0.655	0.685	0.648	0.621	0.648	0.658	0.615	0.656	0.659
Compressibility index (%)	12.5	11.71	13.57	11.26	11.59	11.26	12.61	12.03	11.43	11.53
Hausner's ratio	1.142	1.129	1.157	1.223	1.17	1.219	1.144	1.136	1.10	1.16

Table 5: Evaluation of Post Compression parameters

Parameters	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Thickness (mm)	4.31	4.33	4.31	4.27	428	4.25	4.26	4.28	4.26	4.32
Hardness (kg/cm^2)	7.0	6.8	6.92	6.73	6.6	7.0	6.8	7.0	7.0	6.9
Friability (%)	0.429	0.334	0.398	0.403	0.454	0.382	0.436	0.459	0.389	0.396
Drug content (%)	98.76	99.19	99.52	99.45	99.89	99.25	99.65	99.19	99.32	99.56
Weight variation	Pass	pass	pass	Pass	pass	pass	pass	pass	Pass	pass

Table 6: Correlation coefficients of different mathematical models for formulations F- 1 to F-10

Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas	
				R^2	n values
F1	0.993	0.911	0.974	0.991	0.950
F2	0.980	0.878	0.937	0.919	0.819
F3	0.956	0.767	0.778	0.989	0.622
F4	0.969	0.878	0.901	0.981	0.937
F5	0.975	0.962	.0.931	0.950	0.970
F6	0.992	0.965	0.951	0.988	0.999
F7	0.982	0.768	0.976	0.983	0.970
F8	0.992	0.969	0.950	0.977	0.801
F9	0.986	0.867	0.976	0.991	0.950
F10	0.999	0.997	0.990	0.995	0.994

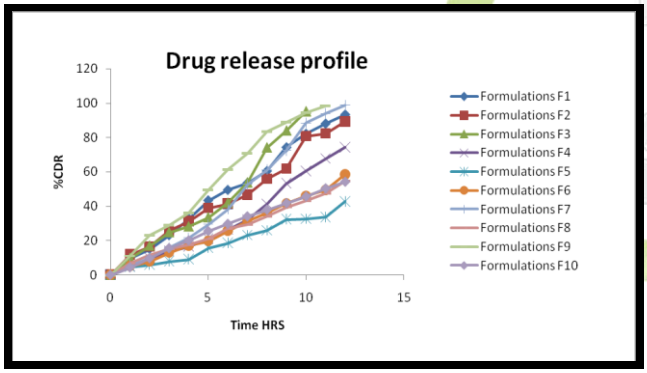

Figure 14: Drug release profile F1-F10

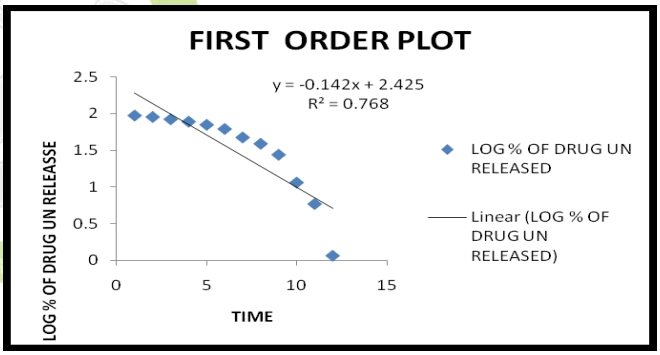

Figure 16: First order equation for optimised F7 Formulation

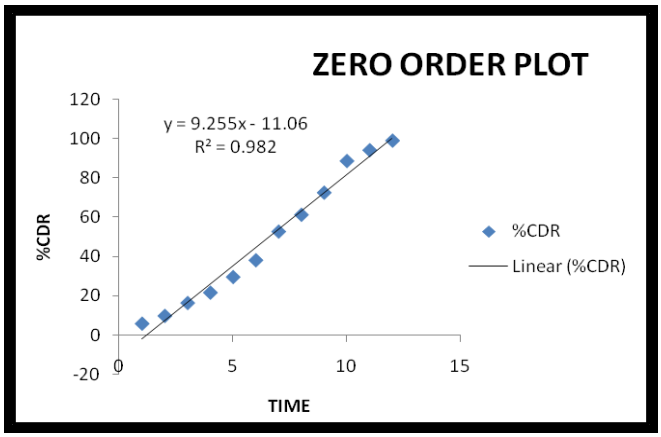

Figure 15: Zero order equation for optimised F7 formulation

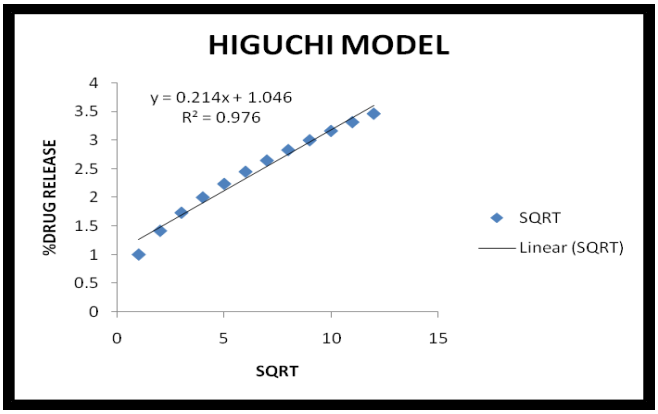

Figure 17: Higuchi Equation for optimised F-7 formulation

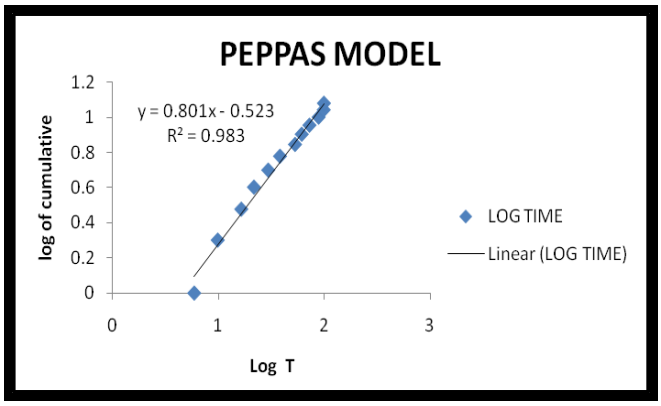

Figure 18: Korsmeyer's Peppas Equation for optimised F-7 Formulation

The Stability Studies

The stability studies for optimized formulation F7 was carried out based accelerated stability conditions & study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that revealed that the optimized formulation was stable under accelerated condition.

Table 7: Hardness of optimised formulations after stability studies

No. of days	F-7		
	Hardness (Kg/cm^2)		
	25^{0}C / 60% RH	30^{0}C / 65% RH	40^{0}C / 75% RH
0	7.0	7.0	7.2
15	6.9	6.9	7.0
30	6.9	6.9	7.
45	6.8	6.8	6.9
60	6.8	6.85	6.9
75	6.7	6.80	6.83
90	6.7	6.78	6.8

Table 8: Friability of optimised formulations after stability studies

No. of days	F-7		
	Friability (%)		
	25^{0}C / 60% RH	30^{0}C / 65% RH	40^{0}C / 75% RH
0	0.459	0.415	0.43
15	0.436	0.352	0.41
30	0.412	0.341	0.386
45	0.396	0.330	0.352
60	0.383	0.321	0.30
75	0.256	0.265	0.286
90	0.180	0.186	0.183

Table 9: %Drug release of optimised formulations after stability studies

No. of days	F-7		
	% Drug release		
	25^{0}C / 60% RH	30^{0}C / 65% RH	40^{0}C / 75% RH
0	98.85	98.85	98.85
15	98.79	98.80	98.77
30	98.72	98.76	98.63
45	98.66	98.72	98.58
60	98.60	98.70	98.50
75	98.55	98.67	98.47
90	98.00	98.50	98.44

CONCLUSION

In this study matrix tablet of voriconazole was prepared by wet granulation technique, using Eudragit RSPO polymers as retardant. Low permeable nature of Eudragit RSPO played a major role in retarding the rug release. The drug and other excipients and also in optimized formulation was evaluated by FTIR and DSC. It showed there is no much interaction between drug and polymers also with optimised formula F-7. The formulations F-7 showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release etc, were evaluated for all the formulations. Based on these results formulation F-7 was found to be the most promising formulation. The optimized formulation F-7 follows zero order, its regression coefficient values were ranges from (0.956 to 0.999).The optimised formulation follows anomalous (non Fickian) diffusion (Table No.6), this confirms that the drug release through the matrix was diffusion. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 90 days which revealed the stability of the formulations. The results suggest that the developed sustained-release tablets of voriconazole could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of voriconazole in the treatment of systemic fungal infections.

ACKNOWLEDGEMENT

The authors are thankful to the Management, Sree Siddaganga College of Pharmacy, Tumkur for providing necessary facilities to carry out this work.

REFERENCES

1. Ratnaparkhi, M.P,Gupta Jyoti, P. (2013). Sustained Release Oral Drug Delivery System-An Overview. *Terminology*, *3*, 4.
2. Sarika, P., Ashutosh, B., Deepak, S. (2013). Sustained release matrix technology and recent advance in matrix drug delivery system: a review. *International Journal of Drug Research and Technology*, *3*(1), 12-20.
3. Kumar, V., Prajapati, S. K., Soni, G. C., Singh, M., & Kumar, N. (2012). Sustained release matrix type drug delivery system: a review. *World Journal of Pharmacy and Pharmaceutical Sciences*, *1*(3), 934-960.
4. Janelle, A. S., Susan, M. A. R. (2000).The Annual Pharmacotherapy, (Vol.1), 1032-43.
5. Patel, N. A., Makwana, S. T., Patel, Z. P., Solanki, S. M., (2012). Formulation & evaluation of once daily sustained release matrix tablet of pramipexole dihydrochloride. *International Journal for Pharmaceutical Scholars*, *1*(2), 370-6.
6. Deepak, P., Abhishek, J., Jatav Rakesh, K., & Hariharanand, S. (2011). Formulation and Evaluation of Pioglitazone Hydrochloride Matrix Tablet Containing Aloe Barbadensis Miller Mucilage Natural Antidiabetic Agent. *International Journal of Drug Discovery and Herbal Research*, *1*(3), 157-163.
7. Venkataramudu, T. S., Firoz, C. Y., Vikram, A., Divya Sree, K., & Murali Krishna, T. (2012). Design and characterisation sustained release matrix tablets of repaglinide using natural polymers. *International Journal of Pharmaceutics*, *2*(2), 73-83.
8. Barot, N., Darshan, M., Praful, D. B. (2014). Formulation development and evaluation of sustained release matrix tablets of repaglinide. *International Journal of Pharmaceutical Research and Bio-Science*, *3*(2), 370-96.
9. Kurian, J. K., Kumar, P. A., & Kulkarni, S. V. Influence of natural, synthetic polymers and fillers on sustained release matrix tablets of sildenafil citrate. *Der Pharmacia Lettre*, *6* (2), 106-17.

