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SUSTAINED RELEASE MATRIX FORMULATION OF ANTIDEPRESSANT DRUG: VENLAFAXINE

Vijay R. Mahajan[*1],
Pravin R. Dighe[1], A.S. Dhake[1], V.R. Gudsoorkar[2]

[1]S.M.B.T. College of Pharmacy, Nandi Hills , Dhamangaon Tal . Igatpuri, Dist. Nashik(MH)
[2]M.V.P.' S College of pharmacy, Gangapur Road , Nashik (MH)

ABSTRACT

Development of oral sustained release tablets for highly water-soluble drugs like Venlafaxine hydrochloride with constant release rate has always been a challenge to the pharmaceutical scientists and even the drug is having high first pass metabolism. The present work is focused on the effect of Xanthan gum, Hydroxy Propyl Methyl Cellulose (HPMC) and ethyl cellulose (EC) in controlling the release of highly water-soluble drug venlafaxine Hydrochloride from hydrophilic matrices prepared using Hydroxypropyl methylcellulose K-4 M, K-15 M, and K-100M, Xanthan Gum and Ethyl Cellulose. Tablets were prepared by direct compression method and were evaluated for physicochemical properties and release studies. The mechanism of drug release was analyzed using various kinetics models like zero order, first order, Higuchi and Korsmeyer-Peppas equations. Release profiles indicated that, increasing the polymer concentration has drastically retarded the release of venlafaxine hydrochloride.

Due to shorter half life of venlafaxine, it is a prime requirement to develop a formulation which could extend the release of venlafaxine in the human body and also eliminate daily multiple dosage of venlafaxine.[12]

All the precompressional parameters were found to be within the standard limits. Tablets were evaluated for hardness, friability, thickness, drug content, weight uniformity, content uniformity, in-Vitro release, and stability studies. It was observed that the type of polymer and its concentration has influence the drug release from matrix tablet.

The sustained release from ethyl cellulose and HPMC was due to interaction between ethylcellulose chain ionic polymer and HPMC chain, non- ionic polymer, which resulted in favorable increase in the water uptake capacity and gel viscosity, leading to better

Correspondence to Author

Vijay R. Mahajan

R.H. No. 4 , 'Akshardham', Near Ashoka House, Ashoka Marg, Nashik 422 011

Email: vijaymahajan8@gmail.com

control over the release of Venlafaxine F8 showed the sustained release of Venlafaxine as desired.
The results of the study revealed that, matrix tablets prepared using HPMC alone could not efficiently control the release of highly water-soluble drug venlafaxine Hydrochloride. The combination of hydrophobic polymers in hydrophilic matrices gave a controlled release over a period of 24hrs.
The study also revealed that the ethyl cellulose and HPMC can be used for the formulation of sustained release matrix tablet of Venlafaxine.

Keywords *Venlafaxine Hydrochloride, Matrix tablet, HPMC, Ethyl cellulose, xanthan gum, Direct compression.*

INTRODUCTION

AIM OF THE STUDY:

Venlafaxine Hydrochloride is an orally active serotonin noradrenalin reuptake inhibitor used in the treatment of major depressive disorders. The successful treatment of depression depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. Venlafaxine Hydrochloride is a highly water soluble drug with the biological half life of 5 hrs and 11 hrs of its active metabolite o-desmethyl venlafaxine (ODV), and molecular weight (277.40), thus requires two to three time daily dosing to maintain plasma drug concentration [1]

The hydrophilic matrices are one of the most used types of sustained release systems in the world. In comparison with other sustained release devices, they have the advantage of their low cost and simple technology that facilitates their application to an important sector of the population, as well as their safety against the dose dumping [2]. Developing oral sustained release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical scientists. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce the toxic concentrations, when administered orally [3]. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system [4]. In addition, hydrophobic polymers also provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications [5] Hence, the present research endeavor was directed towards the development of controlled release matrix tablets of venlafaxine Hydrochloride by incorporating hydrophobic polymers in hydrophilic matrices. Matrix tablets comprising of HPMC K-4M, K-15M, K-100M, and in combination with hydrophobic polymers like ethyl cellulose (EC) and xanthan gum were prepared by direct compression. The precompressional powder blend was evaluated and optimized for various parameters like angle of repose, compressibility index and Hausner's ratio so as to make it suitable for direct compression. The prepared matrix tablets were evaluated for their physico-chemical properties such as thickness, hardness, friability, weight variation, drug content, content uniformity and *in-vitro* release; the optimized tablet formulation was subjected to accelerated stability studies as per ICH guidelines.

MATERIALS AND METHOD:

Venlafaxine Hcl was obtained as gift sample from Torrent Pharmaceuticals Ltd, Ahmedabad; xanthan gum was supplied as gift samples by Crystal colloids Ltd, Mumbai; HPMC K4M, K15M, K100M, Ethyl

cellulose were obtained as gift samples from Glenmark Pharma Ltd. All other reagents and solvents used in the study were purchased from Space Laboratories Ltd, Nashik and are of analytical grade.

Tablet Preparation:

Matrix tablets of Venlafaxine Hcl were prepared by direct compression method using 12 mm flat-faced punch of 8 station Rimek compression machine. The active ingredient and the excipients were passed through 60 mesh sieve and thoroughly mixed using a polybag for 10 minutes. PVP K30 was used as binding agent and magnesium stearate, Aerosil were added to the above blend as flow promoters and further mixed for another 10 minutes. In all the formulations the amount of venlafaxine Hcl was kept constant at 84.87 mg equivalent to 75 mg of venlafaxine base. Table I shows different matrix tablets of Venlafaxine Hcl using HPMC alone and in combination with xanthan gum and ethyl cellulose (hydrophobic polymers).

Physicochemical Characterization of Tablets:

Hardness:

For each formulation, tablet hardness was determined using the Monsanto hardness tester. The hardness (kg) of 6 tablets was measured, and the mean hardness was calculated and reported [5].

Friability:

The tablet friability was determined on Roche friabilator (Electrolab). A sample of pre-weighed 10 tablets was placed in Roche friabilator, which was then operated for 100 revolutions. The tablets were then dusted and reweighed.

Percent friability (F)

was calculated as follows. $\mathbf{F = (1\text{-}W_0 / W) \times 100}$

Where,

$\mathbf{W_0}$ is the weight of the tablets before the test.

W is the weight of the tablet after the test [6].

Thickness and weight variation:

The crown-to-crown thicknesses of 10 tablets from each batch were determined using vernier calipers. To study weight variation, 20 tablets were weighed individually using an electronic balance (AX-200, Shimadzu Corporation, Japan) and the test was performed according to the official method. Further to investigate the integrity of drug in the matrix formulations, tablets were subjected to FT-IR and DSC studies.

In Vitro Drug Release Studies:

The tablets were subjected to in vitro drug release studies for a period of 14 hrs using 8 station USP dissolution apparatus. Dissolution studies were carried out using phosphate buffer of pH 6.8 medium up to 14 hrs at 37± 0.5 °C and 75 rpm. Five milliliter sample was withdrawn at regular time intervals and replaced with freshly prepared buffer medium. The sample withdrawn were filtered through Whatman filter paper and after suitable dilution, analyzed spectrophotometrically at 224.80 nm using UV-Visible spectrophotometer.

Mechanism Of Drug Release:

To investigate the mechanism of drug release from the matrix tablets, various kinetics models like zero order, first order, Higuchi's equations were applied to the *in-vitro* release data obtained from different formulations. However, these models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems.

Log (Mt/Mf) = Log k + n Log t

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release (Kuksal A et al).

Stability studies:

The optimized formulation was strip packed (Al–Al strip, 0.04 mm) and subjected to accelerated stability studies as per ICH guidelines i.e. room temperature, 30 °C / 65% RH and 40 °C / 75% RH. Sampling was done at predetermined time intervals of 0, 15, 30, 60, 90 and 180 days. Tablets were evaluated for the different physico-chemical parameters viz. appearance, weight variation,

thickness, hardness, friability, drug content and in vitro release [8,9].

Table No. 1 Composition of Venlafaxine Hcl matrix tablets formulated with HPMC K-4 M, K-15 M, K-100M and in combination with xanthan gum and ethyl cellulose (hydrophobic polymers).

Code	Venlafaxine Hcl	HPMC K-4 M (mg)	HPMC K-15 M (mg)	HPMC K-100 M (mg)	Xanthan gum (mg)	Ethyl cellulose (mg)	MCC (Avicel) PH 102 (mg)	PVP K-30 (mg)	Aerosil (mg)	Mg stearate (mg)
VLF1	84.87	200	---	---	---	---	232.63	23	54	36
VLF2	84.87	---	200	---	---	---	232.63	23	54	36
VLF3	84.87	---	---	200	---	---	232.63	23	54	36
VLF4	84.87	100	100	---	---	---	232.63	23	54	36
VLF5	84.87	---	100	100	---	---	232.63	23	54	36
VLF6	84.87	100	---	100	---	---	232.63	23	54	36
VLF7	84.87	---	---	---	200	---	232.63	23	54	36
VLF8	84.87	---	---	100	---	100	232.63	23	54	36
VLF9	84.87	---	---	---	---	200	232.63	23	54	36
VLF10	84.87	---	---	100	100	---	232.63	23	54	36
VLF11	84.87	---	---	---	100	100	232.63	23	54	36

Precompressional Evaluation of Powder Blend: The method employed for matrix tablet preparation was direct compression for which the drug or powder blend of drug and polymer should possess good flow properties. Pure venlafaxine Hcl exhibited angle of repose (51.12 ± 0.28°) indicating extremely poor flow property. It was further supported by high Carr's index value (22.14 ± 0.25%) and Hausner's ratio (1.41 ± 0.02). Hence lubricant and glidant were added to improve the flow properties of drug. The flow property of precompressional mixture was enhanced by increasing the polymer level. With the addition of flow promoters, acceptable ranges in the micromeritic properties of the powder blend was obtained in all the formulations studied. The results of micromeritic evaluation of the powder blend are presented in **Table 2.**

Post Compressional Evaluation Of Tablets: In order to avoid the effect of tablet hardness and thickness on in vitro *drug* release, these two parameters have been maintained at specific values i.e. hardness at about 4-6 kg/cm^2 and thickness at about 4-5 mm. The tablets of different batches of HPMC alone and in combination with xanthan gum and ethyl cellulose were found uniform with respect to hardness (4.8 to 5.5 kg/cm^2) and thickness (4.13 to 4.79 mm).

The friability (0.49 to 0.68%) and weight variation (0.87 to 1.37%) of different batch of tablets were found within prescribed limits. Drug content (99.04 to 100.27%) was found uniform within the batches of different tablets. Hence tablets containing drug, polymer, diluent and lubricant could be prepared satisfactorily by direct compression method. The results of physico-chemical evaluation of tablets are given in **Table 2**.

Table No. 2 Precompressional and post compressional evaluation of various matrix formulations of venlafaxine **Hcl.**

Code	Angle of repose (θ)	Compressibility (%)	Hausner's ratio	Hardness (Kg/cm^2)#	Friability† (%)	Thickness† (mm)	Weight variation* (%)	Drug content** (%)
VLF1	29.21±0.10	18.21±0.21	1.21±0.12	5.7±0.30	0.55±0.03	4.14±0.06	1.37±0.48	99.17±0.21
VLF2	24.17±0.05	17.14±0.20	1.22±0.17	5.6±0.28	0.48±0.06	4.39±0.02	0.97±0.65	99.04±0.16
VLF3	23.30±0.07	16.75±0.14	1.19±0.13	5.3±0.35	0.38±0.01	4.13±0.01	1.19±0.16	99.64±0.38
VLF4	22.22±0.01	16.67±0.12	1.19±0.07	5.5±0.33	0.58±0.01	4.23±0.03	0.87±0.34	100.6±0.33
VLF5	25.77±0.07	17.51±0.04	1.21±0.11	5.8±0.55	0.52±0.02	4.42±0.01	1.10±0.19	99.36±0.65
VLF6	28.56±0.23	15.88±0.11	1.18±0.23	5.5±0.64	0.44±0.01	4.79±0.04	1.07±0.37	98.70±0.42
VLF7	26.08±0.14	19.30±0.27	1.23±0.02	5.6±0.40	0.46±0.04	4.34±0.03	1.15±0.75	99.17±0.49
VLF8	29.56±0.02	17.74±0.12	1.20±0.17	5.4±0.46	0.42±0.02	4.7±0.05	1.26±0.35	100.27±0.6
VLF9	24.96±0.10	17.89±0.03	1.20±0.21	5.8±0.24	0.36±0.03	4.22±0.04	0.84±0.29	99.65±0.52
VLF10	24.12±0.05	17.34±0.20	1.21±0.17	5.5±0.28	0.44±0.06	4.38±0.02	0.92±0.65	99.01±0.16
VLF11	23.12±0.07	16.24±0.14	1.18±0.13	5.8±0.35	0.32±0.01	4.11±0.01	1.16±0.16	99.26±0.38
Pure drug	51.12 ±0.28	22.14 ± 0.25	1.41 ±0.02	---	---	---	---	---

All values are expressed as mean ± SD. # n=3, † n=10, *n=20, **n=3.

Compatibility studies:

The comparison of FT-IR spectrum of pure drug with FT-IR spectra of optimized formulations VLF6 and VLF8 showed no appreciable change in the positions of characteristic absorption bands. All the major bands present in the spectrum of the pure drug are clearly observed in the IR spectra of formulations with negligible change in their positions.

(This study clearly suggests that the drug remains in its normal form even in its formulations without undergoing any type of interaction with the polymer or other excipients present in the formulations. The differential scanning colorimetry (DSC) thermogram of pure drug venlafaxine Hcl showed an endothermic peak indicating the melting point 210-215 °C which is in total agreement with literature value of the drug[11]. The DSC thermograms of the optimized formulations VLF6 and VLF8 also exhibited the same type of endothermic peaks showing the melting point of formulation VLF6 m.p at 210 °C and F8 m.p at 210.61 °C. Though there is little variation in the appearance of the thermograms of formulations, it is clear that the melting point of pure drug and the formulations is almost same with negligible difference in the melting range. From this observation we can draw a conclusion that the drug is not showing any type of interaction with the polymers or other excipients of the formulations.

Dissolution:

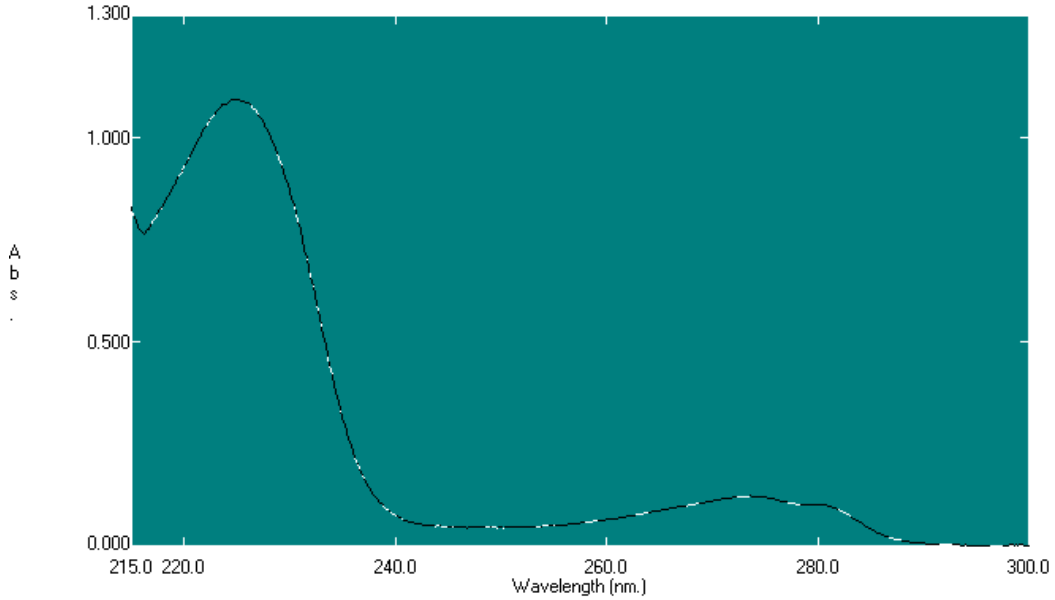
The study was carried out using USP apparatus II (paddle)

Medium : Phosphate buffer (pH 7.2), 900 ml.
Speed : 75 rpm
Temperature : $37^0C \pm 0.5^0C$

One tablet was placed in the dissolution medium and apparatus was run. At intervals of 1, 2, 3, 4, 5, 6, 8, and 10 hours 5 ml aliquots were withdrawn and replacement was made each time with 5 ml of fresh dissolution medium. Each 5 ml sample was filtered through Whatman filter paper no. 41. The absorbance was measured at 224.80 nm.

Cumulative percent drug released was found at each time point. Values of t_{50} (time for 50 % dissolution), t_{70} (time for 70 % dissolution) were determined graphically. Dissolution data was given zero order, first order, and Higuchi's square root kinetic treatment.

Fig.1. UV spectrum of Venlafaxine.



λ max = 224.80 ηm

Fig.2. Dissolution of marketed formulation of Venlafaxine XR (Veniz XR)

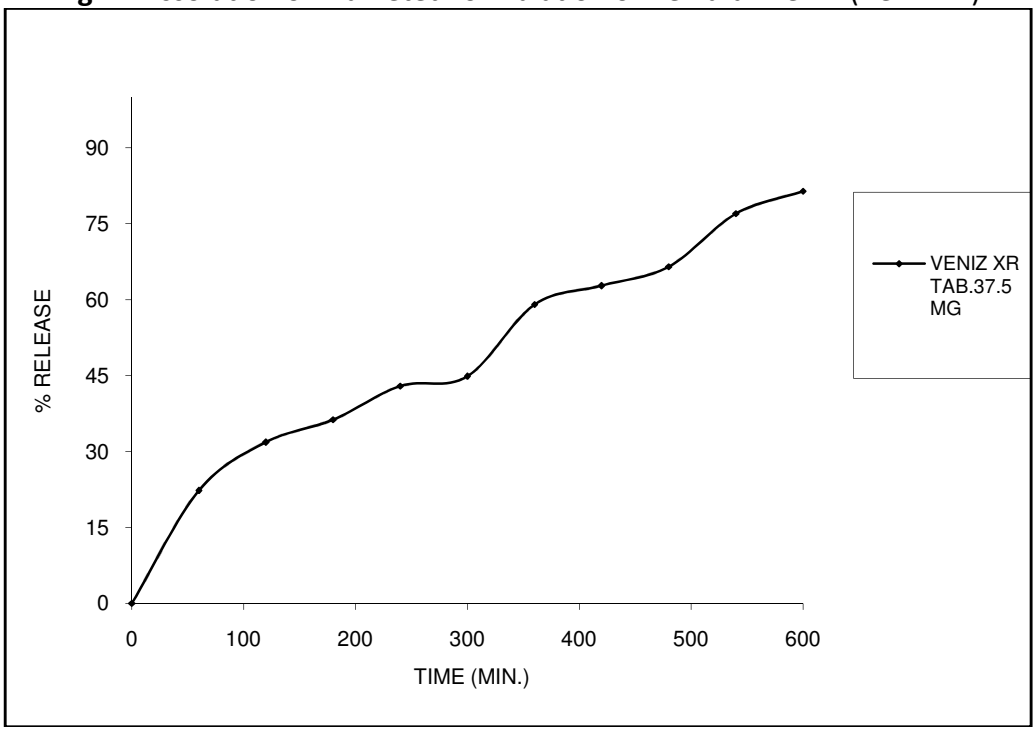


Fig.3. Dissolution of marketed formulation of Venlafaxine SR (Venaxine SR)

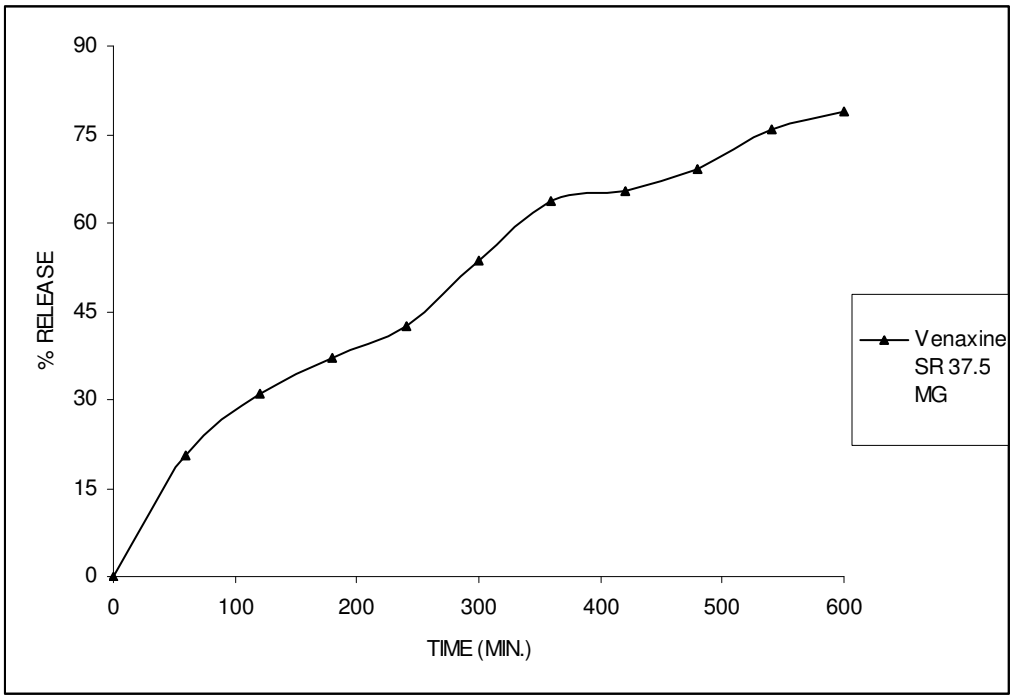


Fig.4 Effect of drug- carrier ratio on dissolution of matrix tablet of Venlafaxine with HPMC K-4 M and HPMC K-15 M.

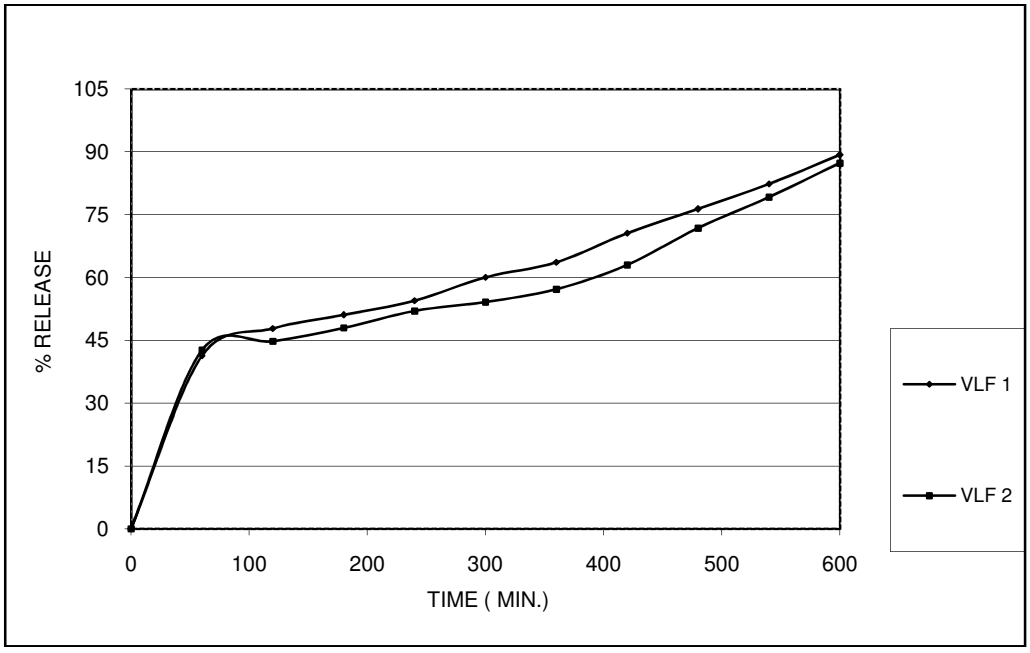


Fig.5. Effect of drug- carrier ratio on dissolution of matrix tablet of Venlafaxine with HPMC K-100 M.

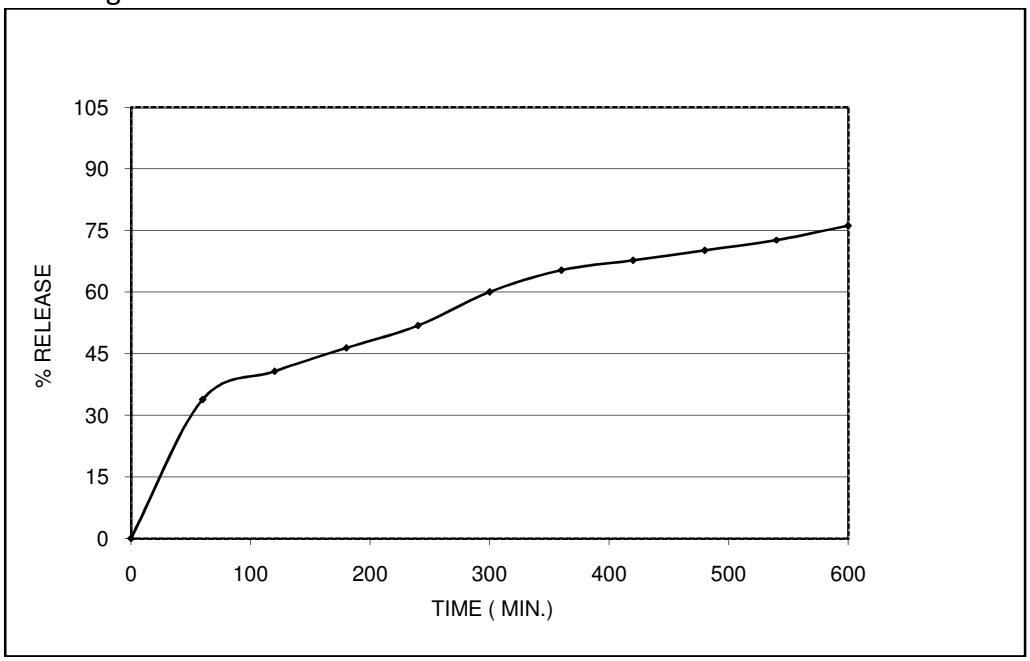


Fig.6. Effect of drug- carrier ratio on dissolution of matrix tablet of Venlafaxine with HPMC K-100 M and Ethyl cellulose.

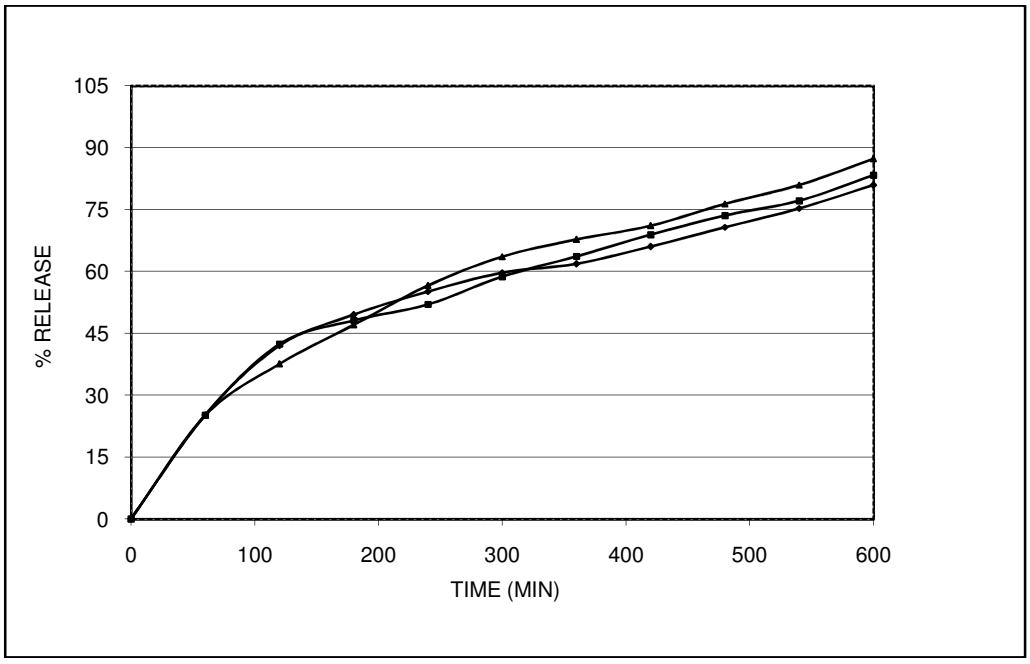


Fig.7 Effect of drug- carrier ratio on dissolution of matrix tablet of Venlafaxine with HPMC K-100 M and Xanthan Gum.

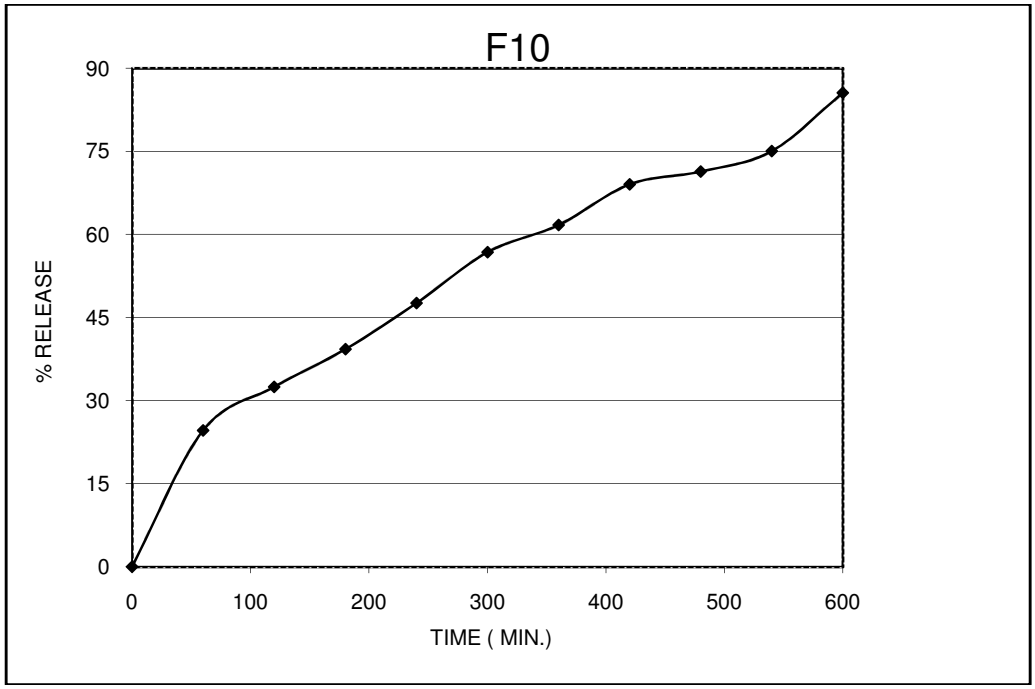


Fig.8. Mean (± S.D.) First order kinetic treatment for marketed formulation of Venlafaxine.

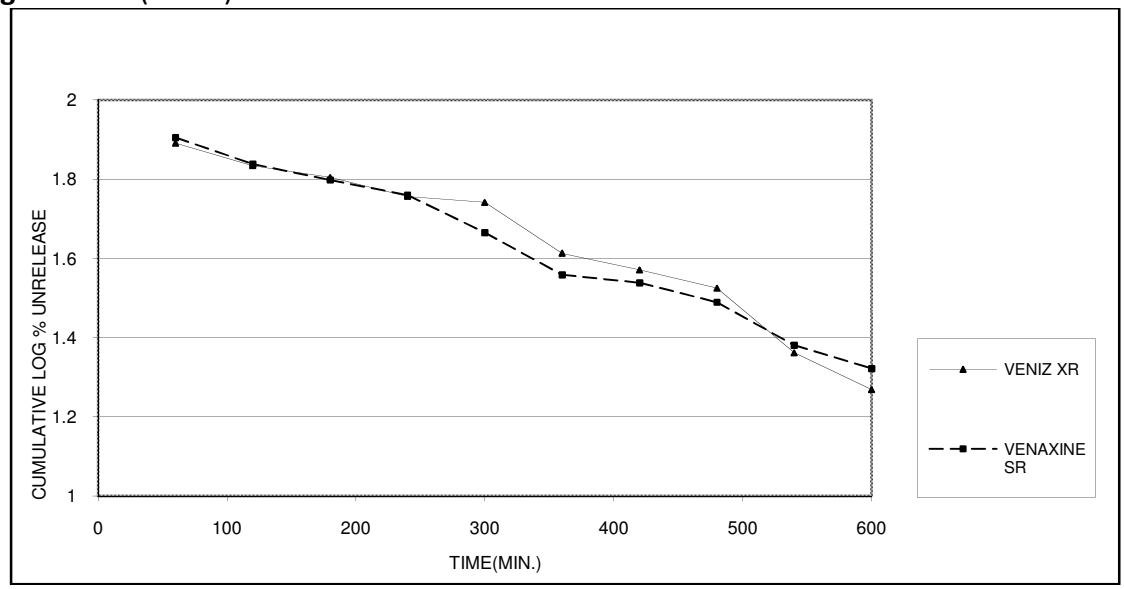


Fig.9. Mean (± S.D.) First order kinetic treatment for matrix tablets of Venlafaxine with HPMC K-100 M and Ethyl cellulose.

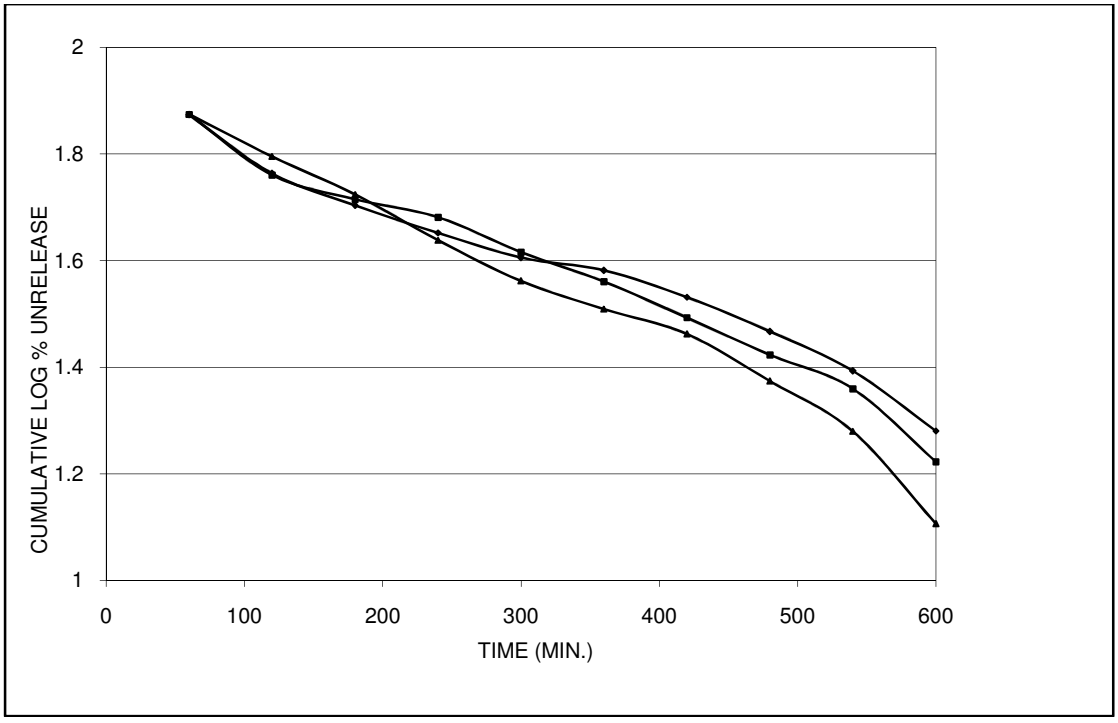


Fig.10. Mean (± S.D.) Higuchi kinetic treatment for marketed formulations of Venlafaxine [VENIZ XR and VENAXINE SR]

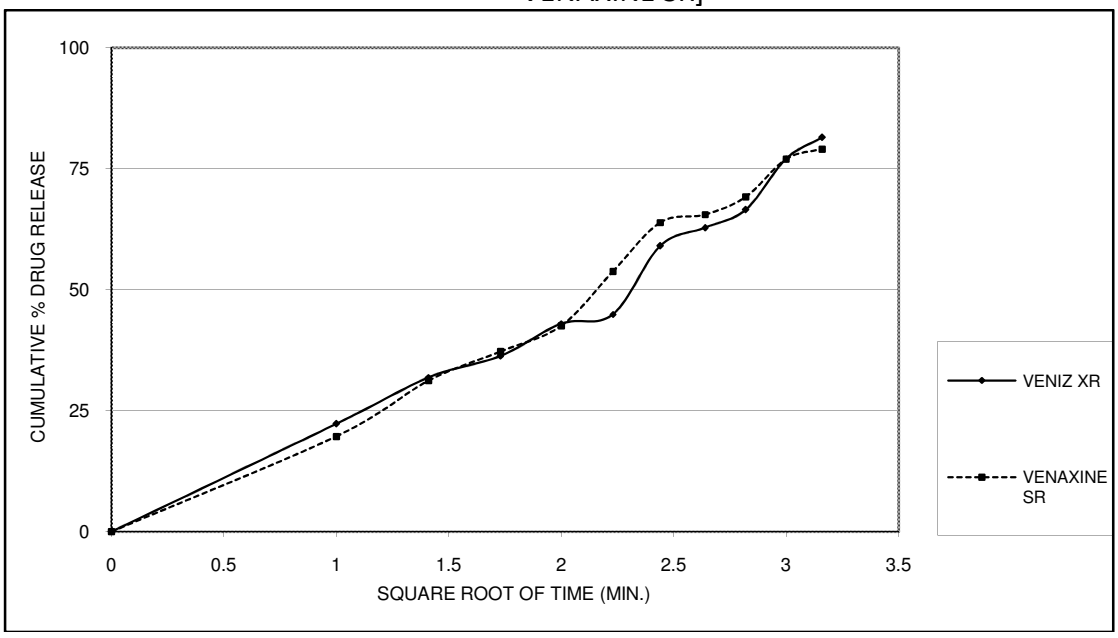


Fig11. Mean (± S.D.) Higuchi kinetic treatment for matrix tablets of Venlafaxine with HPMC K-100 M and Ethyl cellulose.

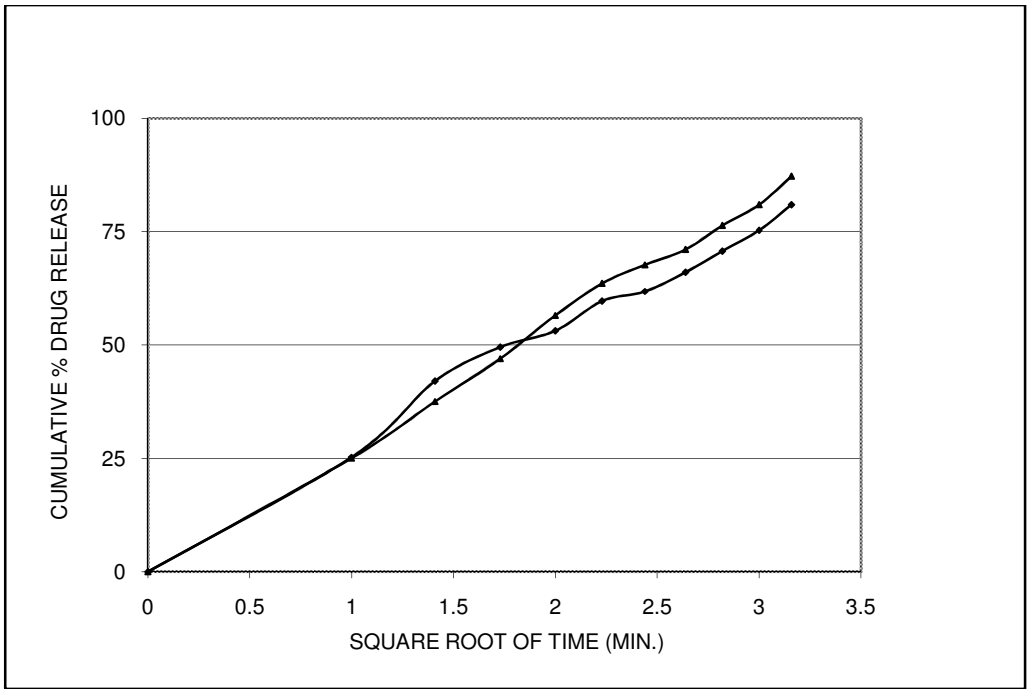


Table 3. Comparison of in-vitro profiles of Veniz XR and Venaxine SR marketed formulations using Similarity factor, Difference factor, and Mean Dissolution Time (MDT).

Formulation Code	T_{50} (Hrs.)	T_{70} (Hrs.)	Similarity factors (f_2)	Difference factor (f_1)	Mean Dissolution Time(MDT)
(Veniz XR).	5.4	8.3	--	--	3.28
(VenaxineSR)	4.6	8.2	--	--	3.06
VLF1	2.7	6.9	44.02	26.98	3.00
VLF2	3.6	7.8	48.51	18.16	3.16
VLF3	4.3	8.1	50.06	15.37	2.82
VLF4	3.8	8.0	51.34	18.91	2.14
VLF5	3.6	7.6	54.04	16.86	2.43
VLF6	3.1	6.5	46.68	23.57	2.35
VLF7	3.2	7.8	52.19	16.83	2.60
VLF8	3.5	7.3	52.23	18.2	2.99
VLF9	3.3	6.7	48.26	20.63	3.02
VLF10	4.2	6.5	62.43	9.87	3.35
VLF11	4.1	7.0	44.35	15.05	3.38
VLF12	4.1	7.2	57.68	13.37	3.48

♦ **Evaluation of matrix tablets of Venlafaxine**

1) Thin layer chromatography (TLC)

All the formulations resolved into clear separate spots of Venlafaxine having Rf values nearly identical with that of pure Venlafaxine. There was no significant interaction between the drug and carriers used for preparing matrix tablets. Data of Rf values is indicated in Table 3.

2) Drug content estimation

Table 2, shows the percentage drug content of various formulations of Venlafaxine.The values indicate uniform distribution of drug.

3) FTIR spectral analysis

FTIR spectra of pure Venlafaxine and mixture with HPMC K -15 M, K- 100 M, Ethyl cellulose and Xanthan Gum were done.

The FTIR spectra show that there was no significant interaction between drug and carrier. Peaks of both drug as well as carrier are indicated and interpreted.

4) UV spectrum

UV spectrum analysis of drug and formulations shows that λ max of drug and formulations were near about same. This indicates that there was no interaction between drug and carrier. The UV spectra are shown in Fig. 1.

Kinetic treatment of dissolution data

Dissolution of formulations was given zero order, first order, and Higuchi's square root kinetic treatment.

In vitro dissolution Comparison of prepared matrix tablet formulations by Similarity factors (f_2)

The f_2 values for each of the products tested in this study are given in table 3.It was found that release profiles of tablet formulations VLF3, VLF4, VLF5, VLF7, VLF8, VLF10, and VLF12 showed in vitro dissolution performance similar to the reference marketed tablet. Although the f_2 values for formulations VLF1, VLF2, VLF6, VLF9, VLF11 were near the lower limit of the similarity range.

In vitro dissolution Comparison of prepared matrix tablet formulations by Difference factors (f_1)

The f_1 values for each of the products tested in this study are given in table 3.It was found that release profiles of tablet formulations VLF10, VLF11, and VLF12 showed in vitro dissolution performance similar to the reference marketed tablet. Although the f_1 values for rest of the formulations were near the lower limit of the similarity range.

In vitro dissolution Comparison of prepared matrix tablet formulations by Difference Mean Dissolution time (MDT)

The mean dissolution time values for each of the formulation tested in this study are given in table 3. It was found that, MDT value for prepared matrix tablet formulations of VLF1, VLF2, VLF3, VLF8, VLF9, VLF10, VLF11, VLF12 are nearly same as compared with the marketed formulation Veniz XR and Venaxine SR.

RESULTS AND DISCUSSION

The use of hydrophilic polymer alone for controlling the drug release of highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer (Jain NK et al). Hence, the present study is aimed to investigate the effect of hydrophobic polymers like xanthan gum and ethyl cellulose on hydrophilic matrices for controlling the release of highly water soluble drug venlafaxine Hcl.

CONCLUSION

Hydrogel based once daily-sustained release matrix tablets of venlafaxine were successfully formulated using Methocel K100M. Addition of an optimum concentration of ethyl cellulose / Xanthan Gum to HPMC based formulations was found to provide the desired release with a reduced HPMC requirement. Release was found to follow Higuchi kinetics in all the developed formulations.

REFERENCES

1. Madgulkar AR, Bhalekar MR, Kolhe VJ, Kenjale YD. Formulation and optimization of sustained release tablets of venlafaxine resonates using response surface methodology. Indian J Pharm Sci 2009; 71 (4): 387-394.
2. Miranda A, Millán M, Caraballo I. Study of the critical points in lobenzarit disodium hydrophilic matrices for controlled drug delivery**.** Chem. Pharm. Bull. **54**(5) 598—602 (2006).
3. Krishnaiah YSR, Karthikeyan RS, Satyanarayana V. A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. International Journal of Pharmaceutics 241 (2002) 353–366.
4. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and in vitro, in vivo evaluation of sustained- release matrix tablet of zidovudine: influence of combination of hydrophilic and

hydrophobic matrix formers. AAPS PharmSciTech 2006; 7 (1) E1-E9.
5. Gupta AK. Introduction to pharmaceutics 2 nd ed. Vol. 1. New Delhi: CBS Publications; 1993: 270.
6. Lieberman HA, Lachman L and Schwartz JB. Pharmaceutical dosage forms: Tablets,Vol 2; New York, Marcel Dekker Publishers; 1990: 201- 43.
7. Nerurkar J, Jun HW, Prince JC, Park MO. Controlled release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rate. Eur J Pharm Biopharm 2005; 61: 56-68.
8. Grimm W.. Extension of the international conference on harmonization tripartite guideline for stability testing of new drug substances and products to countries of climatic zones III and IV, Drug Dev. Ind. Pharm. 24 (4) (1998) 313–325.
9. Makhija SN and Vavia PR. Once daily sustained release tablets of venlafaxine, a novel antidepressant. Eur J Pharm Biopharm 2002; 54: 9–15
10. Thomson, Physician's Desk Reference, Thomson PDR, Motwale, NJ, 58th edition ,2004, 3413-3425
11. Sweetman SC , Martindale, The complete Drug Reference pharmaceutical Press, Royal Pharmaceutical Society of Great Britain,UK , 33 rd edition; 2001 : 312-313
12. Hasmukh A. Patel ,Sunil Shah ,Dinesh O. Shah ,P.A. Joshi , Sustained release of venlafaxine from venlafaxine–montmorillonite–polyvinylpyrrolidone composites , Science, Volume, January 2011, Pages 126–130.

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