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European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 9–15

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Once daily sustained release tablets of venlafaxine, a novel antidepressant

Sapna N. Makhija[1], Pradeep R. Vavia*

Pharmaceutical Division, Department of Chemical Technology (Autonomous), University of Mumbai, Mumbai, India

Received 9 January 2002; accepted in revised form 24 April 2002

Abstract

Venlafaxine is a unique antidepressant that differs structurally from other currently available antidepressants. Sustained release tablets of venlafaxine to be taken once daily were formulated with venlafaxine hydrochloride equivalent to 75 mg of venlafaxine base. Matrix system based on swellable as well as non-swellable polymers was selected for sustaining the drug release. Different polymers viz. hydroxypropylmethylcellulose (HPMC), cellulose acetate, Eudragit RSPO, ethylcellulose etc. were studied. Combinations of non-swellable polymers with HPMC were also tried in order to get the desired sustained release profile over a period of 16 h. The effect of drug to polymer ratio on in vitro release was studied.

The marketed formulation was evaluated for different parameters such as appearance, weight variation, drug content and in vitro drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. These were evaluated for appearance, weight variation, thickness, hardness, friability, drug content and in vitro drug release at selected time intervals. In vivo studies were carried out for the optimized formulation in 12 healthy human volunteers and the pharmacokinetic parameters were compared with the marketed one. © 2002 Published by Elsevier Science B.V.

Keywords: Venlafaxine; Matrix system; Hydroxypropylmethylcellulose; Cellulose acetate; Eudragit RSPO; Ethylcellulose; In vivo studies

1. Introduction

Venlafaxine is a unique antidepressant that differs structurally from other currently available antidepressants [1]. Venlafaxine and its active metabolite, *o*-desmethylvenlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine [2,3] but have no monoamine oxidase inhibitory activity and a low affinity for brain muscarinic, cholinergic, histaminergic or alpha-adrenergic receptors [4,5]. Hence, it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. The steady state half lives of venlafaxine and ODV are 5 and 11 h, respectively, necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug [6].

The present research endeavour was directed towards the development of a sustained release dosage form of venlafaxine in the form of tablets to be taken once daily. Different polymers viz. hydroxypropylmethylcellulose (HPMC), ethylcellulose, cellulose acetate, Eudragit RSPO etc. were tried. Different grades of HPMC studied include Methocel K15M and K100M. Combinations of non-swellable polymers with HPMC K100M were also tried to get the desired release profile with a reduced HPMC requirement. Different grades of ethylcellulose (7, 45 and 100 cps) were studied in combination with HPMC K100M. The tablets were evaluated for different physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and in vitro release. The marketed formulation was evaluated for different physico-chemical parameters and the in vitro release of venlafaxine from the developed formulations was compared with the marketed one. The marketed product is available as capsules containing venlafaxine hydrochloride equivalent to venlafaxine 75 mg in the form of extended release pellets [7].

The optimized formulation was subjected to accelerated stability studies as per ICH guidelines [8]. Pharmacokinetic studies [9–12] were carried out for the optimized formulation and compared with the internationally marketed formulation.

2. Materials and methods

2.1. Materials

Venlafaxine hydrochloride was obtained from M/s Alem-

* Corresponding author. Pharmaceutical Division, Department of Chemical Technology (Autonomous), University of Mumbai, Nathalal Parikh Marg, Matunga, Mumbai-400019, India. Tel.: +91-22-414-56-16; fax: +91-22-414-56-14.

E-mail addresses: prv@pharma.udct.ernet.in (P.R. Vavia).

[1] Tel.: +1-617-266-0547.

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PII: S0939-6411(02)00049-8

bic Ltd, Baroda, India. Methocel K15M and K100M were obtained as gift samples from M/s Colorcon Asia Pvt Ltd, India. Cellulose acetate (CA) was procured from M/s Eastman Chem. Co., USA. Eudragit RSPO (E-RS) was obtained as a gift sample from M/s Rohm Pharma, Germany. Ethylcellulose (EC) 7, 45 and 100 cps was obtained from M/s Signet Chem. Corporation, India. Vivapur 101 (directly compressible microcrystalline cellulose) obtained from M/s J. Rettenmaier and Sohne Gmbh and Co., Germany was used as a diluent. Aerosil 200, talc and magnesium stearate were gifted by M/s Bayer India Ltd, India.

All other solvents and reagents were purchased from Ranbaxy chemicals, India and were of analytical grade.

2.2. Drug–excipient interaction studies

The possibility of drug–excipient interaction was investigated by differential scanning calorimetry. The DSC thermograms of pure drug, individual excipients and drug–excipient mixtures were recorded. The samples were separately sealed in aluminium cells and set in Mettler TA 4000 thermal analyzer. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30–300°C. Alumina was employed as the reference standard.

2.3. Formulation

Tablets were made by direct compression. All ingredients were weighed accurately and passed through 40 mesh sieve. Drug was mixed with excipients in geometric proportion for 10 min. Weighed quantities of aerosil, talc and magnesium stearate were passed through 40 mesh sieve and then blended with the above mass for 2 min. Compression was done on a Cadmach single station tablet press using round (9 and 11 mm FFBE and 12 mm s/c) and capsule shaped (17.5×8.5 mm^2) punches. Initially Methocel K15M was tried in the ratio 1:2 with respect to the drug. Different ratios of Methocel K100M were tried. Combinations of non-swellable polymers with HPMC K100M were also tried to get the desired release profile with a reduced HPMC requirement.

2.4. Evaluation

The tablets were evaluated for different physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and in vitro release. Methanol was used as extraction solvent for determining the drug content. In vitro release was studied using USP XXIII Type 1 Dissolution Test Apparatus in phosphate buffer pH 7.2 for a period of 24 h. Effect of type and amount of polymer on the release of venlafaxine was studied. UV spectrophotometry was used as the method of analysis. Detection wavelength was 224 nm. The marketed product was evaluated for the different physico-chemical parameters such as appearance, weight variation, drug content and in vitro drug release.

2.5. Stability studies

Formulations were selected for stability on the basis of the in vitro drug release profile and the values of coefficient of regression for Higuchi kinetics, Higuchi rate constant and t_{90}. 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/60% 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. A simple, sensitive and stability indicating high-performance liquid chromatography (HPLC) method was developed and validated for content analysis during accelerated stability studies [13]. The method reported in literature was modified in order to give resolution between the drug and its degraded product. The HPLC system consisted of a Jasco PU-980 HPLC pump equipped with a Jasco UV-975 detector. Data integration was done using a Borwin software package V1.21. The column used was C 8 Spherisorb (25 cm × 4.6 mm, 5 μ). The mobile phase consisted of acetonitrile: sodium dihydrogen orthophosphate (0.04 M) pH 6.8 (75:25 v/v) at a flow rate of 1.5 ml/min. Analysis was done at a wavelength of 224 nm. In vitro release was determined by UV spectrophotometry at 224 nm.

2.6. In vivo studies

A total of 12 volunteers participated in the study. Six volunteers were given the optimized formulation and six the marketed formulation with water. The volunteers were fasted overnight at least 10 h prior to dosing with water ad libitum. Before administration, 5 ml blood was withdrawn from forearm vein using sterile disposable syringe and needle. During the hours of food restriction, no beverages like tea, coffee, milk etc. were permitted other than water specifically allowed for drug administration. Blood (5 ml) was withdrawn at 1, 2, 3, 4, 5, 6, 7, 10, 13 and 24 h. Blood samples were collected from the forearm vein using sterile disposable syringes and needles into sterile glass centrifuge tubes containing heparin. The samples were centrifuged immediately at 4000 rpm and the plasma was stored in light protected containers at −20°C till the time of analysis. The drug was extracted from plasma by a suitable extraction method. To 1 ml of plasma, 1.5 ml of saturated sodium borate solution was added in a stoppered test tube. This was vortexed for 1 min. The drug was extracted into 4 ml of isopropylether by vortexing for 10 min. This was centrifuged at 3000 rpm for 10 min. The organic phase was collected separately. Isopropylether (3 ml) was again added to the aqueous fraction and vortexed for 10 min. This was again centrifuged at 3000 rpm for 10 min. The aqueous phase was discarded and both the organic portions (7 ml) were taken in a fresh stoppered test tube and 0.3 ml of 0.01 N

hydrochloric acid was added. This was vortexed for 15 min. Centrifugation at 3000 rpm for 10 min gave clear separation of the two layers. The organic phase was discarded and 1 ml of hexane was added to the aqueous phase. This was vortexed for 5 min and then centrifuged at 3000 rpm for 15 min. The hexane layer was discarded and the residual aqueous phase was analyzed using HPLC with UV detection [14]. The HPLC system consisted of a Jasco PU-980 HPLC pump equipped with a Jasco UV-975 detector. Data integration was done using a Borwin software package V1.21. The column used was C 8 Supelcosil (25 cm × 4.6 mm, 5 μ). The mobile phase consisted of acetonitrile: ammonium dihydrogen orthophosphate (0.1 M) pH 4.4 (16.5:83.5 v/v) at a flow rate of 1.0 ml/min. Analysis was done at a wavelength of 229 nm. A non-compartmental model was adopted for calculating the pharmacokinetic parameters. The parameters employed to evaluate were C_{max}, t_{max} and AUC values. C_{max} and t_{max} were read directly from the observed plasma concentration against time profile. AUC and other parameters such as K_{el} and $t_{1/2}$ were computed from observed plasma concentration against time profile. The data obtained was statistically analyzed by analysis of variance (ANOVA) at 5% probability levels. The extent of absorption from the test formulation relative to the marketed one was calculated as the relative bioavailability by using the formula given below:

Relative bioavailability

$$= (AUC_{(0-t)} \text{ of test}/AUC_{(0-t)} \text{ of marketed}) \times 100$$

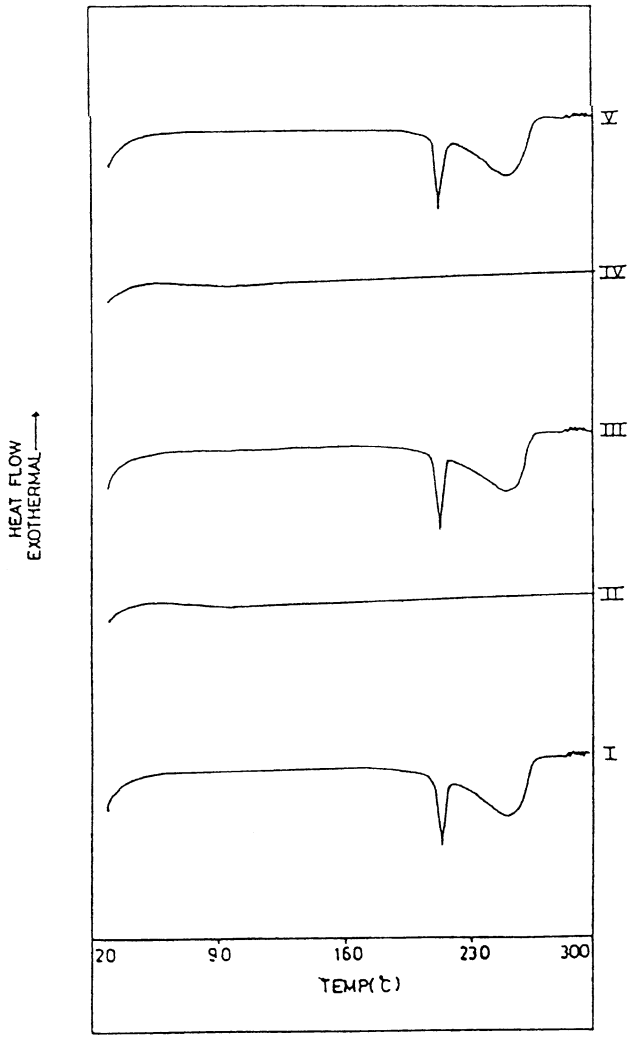

Fig. 1. Differential scanning calorimetric thermograms: I, VEN; II, HPMC K100M; III, VEN + HPMC K100M; IV, CA; V, VEN + CA.

3. Results and discussion

The DSC thermogram for the drug gave a sharp melting endotherm at 215.3°C. The individual excipients did not show any characteristic peaks. There was no shift in the endotherm of venlafaxine in the drug–excipient mixtures indicating compatibility of the drug with all the excipients. The comparative DSC thermograms of the drug (VEN), individual excipients and drug–excipient mixtures are depicted in Fig. 1.

Methocel K15M was tried in the concentration 1:2 with respect to the drug. Drug release was fast, indicating that a higher viscosity grade of Methocel would be required to retard drug release. HPMC of higher viscosity grade swells to a greater extent as it has a greater intrinsic water uptake property than that of a lower viscosity grade [15]. Hence, Methocel K100M was selected for further studies to retard drug release.

Different ratios of Methocel K100M studied were 1:2, 1:3, 1:4 and 1:5 with respect to the drug. Drug release was fast with HPMC K100M 1:2 with 90% drug released in 8 h. The overall drug release is affected by the rate of water uptake and the diffusion rate of the drug through the swollen gel. High polymer content results in a greater amount of gel being formed. This gel increases the diffusional path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result, a reduction in drug release rate is obtained. Methocel K100M in the ratio 1:4 with respect to the drug (F1) provided the desired sustained release profile for a period of 16 h. The release followed Higuchi kinetics with $r = 0.9977$.

Table 1
Composition of the different formulations

Ingredients (mg/tablet)	F1	F2	F3	F4	F5
VEN	84.87	84.87	84.87	84.87	84.87
Methocel K100M	340	187	127	187	187
E-RS	–	187	–	–	–
CA	–	–	382	–	–
EC 7 cps	–	–	–	230	–
EC 100 cps	–	–	–	–	230
Vivapur 101	–	–	–	40.0	40.0
Aerosil 200	10.0	12.0	10.0	10.0	10.0
Purified talc	9.0	12.0	12.0	12.0	12.0
Magnesium stearate	6.0	10.0	9.0	9.0	9.0

Table 2
Release kinetics parameters for different formulations

Formulations order		F1	F2	F3	F4	F5	Marktd. Pdt. I	Marktd. Pdt. II
Zero	t_{50}	5.7649	5.7544	5.8975	5.5718	5.2975	7.0279	7.0826
	t_{90}	13.6359	13.7515	13.0741	12.6584	12.0551	13.5572	13.7071
	m	5.0819	5.0018	5.5737	5.6445	5.9193	6.1262	6.0382
	r	0.9536	0.9493	0.9577	0.9404	0.9482	0.9809	0.9881
First	t_{50}	4.4508	4.4603	4.4247	4.3903	4.0929	4.7411	4.9533
	t_{90}	14.2553	15.8374	13.5880	16.2423	14.2551	10.0715	11.8759
	m	−0.0713	−0.0614	−0.0763	−0.0589	−0.0688	−0.1311	−0.1009
	r	0.9435	0.9949	0.9866	0.9901	0.9965	0.7942	0.8865
Higuchi	t_{50}	4.5070	4.5015	4.6215	4.4374	4.1709	5.7522	5.8122
	t_{90}	14.6134	14.7511	13.7998	14.0094	13.0502	14.9850	15.2716
	m	23.5324	23.2687	25.5587	24.4439	25.4741	27.1614	26.7196
	r	0.9977	0.9979	0.9924	0.9919	0.9939	0.9727	0.9680

E-RS being a hydrophobic polymer should lower the water penetration and provide effective release retardation when used in combination with a hydrophilic polymer such as Methocel in matrix. Drug release was fast with Methocel K100M and E-RS in the ratio 1:2.2:0.4 with respect to the drug. Hence E-RS content was increased in further batches. Methocel K100M and E-RS in ratios 1:2.2:0.8, 1:2.2:1.2 and 1:2.2:2.2 were tried with respect to the drug. The formulation with ratio 1:2.2:2.2 (F2) provided the desired 16 h sustained release profile following Higuchi kinetics with $r = 0.9979$. Thus E-RS lowered the amount of Methocel K100M required when used in matrix combination.

Combination of Methocel K100M and CA tried initially was 1:1:1with respect to the drug. Here 90% drug was released in 8 h. Hence Methocel K100M concentration was increased from 1 to 1.5. Of the two combinations tried viz. Methocel K100M and CA 1.5:3 and 1.5:4.5, the desired sustained release in 16 h was achieved with HPMC:CA in 1.5:4.5 ratio (F3) with Higuchi rate constant 25.55/square root time and r value 0.9924.

Combinations of different grades of EC (7, 45 and 100 cps) with HPMC K100M in different ratios were tried. Two ratios of Methocel K100M and EC 7 cps were tried viz. 1:2.2:1.2 and 1:2.2:2.7 with respect to the drug. With 1:2.2:1.2, drug release was fast with 90% drug released in 10 h. In order to retard drug release, amount of EC was increased to 2.7 (F4). This was found to give the desired sustained release profile for a period of 16 h. Drug release was found to follow Higuchi kinetics with $r = 0.9919$. Higher viscosity grades of EC were tried with an aim to reduce the amount of EC 7 cps required to provide the desired sustained release profile. EC 45 and 100 cps were studied in different concentrations. Methocel K100M

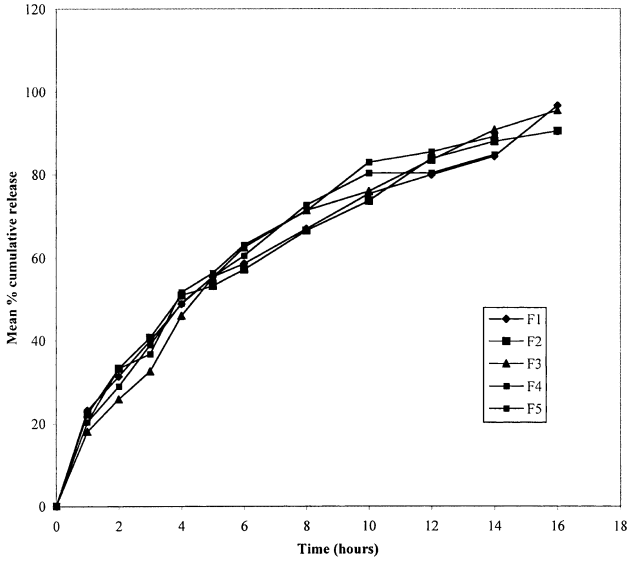

Fig. 2. In vitro release profiles for venlafaxine from the different formulations.

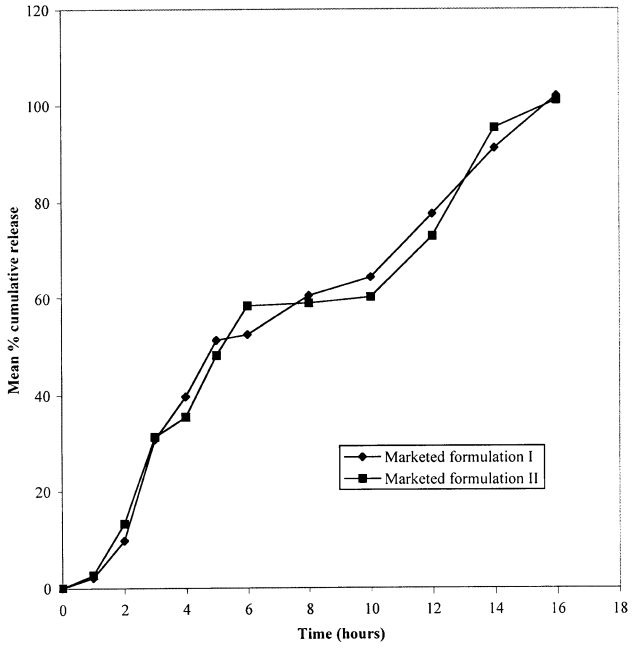

Fig. 3. In vitro release profiles for venafaxine from the marketed formulations.

Table 3
Pharmacokinetic parameters for formulation F1 and marketed formulation

Formulation F1	Subject	C_{max}	t_{max}	K_{el}	$t_{1/2}$	AUC_{0-24}	$AUC_{0-\alpha}$
	I	46.667	4	0.0746	9.293	496.618	605.293
	II	51.753	4	0.0736	9.417	566.515	694.120
	III	49.246	4	0.0968	7.158	558.199	632.781
	IV	50.250	4	0.0788	8.797	539.258	651.579
	V	51.594	4	0.0847	8.179	553.864	651.046
	VI	48.260	4	0.0739	9.377	542.016	663.387
	Mean ± SD (% RSD)	49.628 ± 1.9775 (3.985)	4 ± 0 (0)	0.0804 ± 0.00908 (11.292)	8.704 ± 0.8924 (10.254)	542.745 ± 24.7704 (4.564)	649.701 ± 29.7457 (4.578)
Marketed formulation	I	32.805	5	0.1386	4.998	398.160	425.205
	II	34.411	5	0.1599	4.332	392.417	409.828
	III	34.614	5	0.1746	3.969	375.384	388.209
	IV	32.341	5	0.1725	4.019	370.373	383.293
	V	34.143	5	0.1494	4.639	382.930	403.305
	VI	37.306	5	0.1783	3.887	380.398	392.196
	Mean ± SD (% RSD)	34.270 ± 1.7458 (5.094)	5 ± 0 (0)	0.1622 ± 0.01578 (9.728)	4.307 ± 0.4386 (10.183)	383.277 ± 10.414 (2.717)	400.339 ± 15.628 (3.904)

and EC 45 cps were tried in the ratios 1:2.2:0.8 and 1:2.2:1.2 with respect to the drug. Drug release was found to follow Higuchi kinetics with 90% drug released in 10 and 11 h, respectively. Methocel K100M and EC 100 cps combination was tried in different ratios viz. 1:2.2:0.8, 1:2.2:1.2 and 1:2.2:2.7 with respect to the drug. The desired sustained release profile for a period of 16 h was obtained with ratio 1:2.2:2.7 (F5). Drug release was found to follow Higuchi kinetics with $r = 0.9939$. From all the batches it was seen that the viscosity of EC did not significantly affect the release profile. Thus, addition of a small amount of EC lowered the amount of Methocel K100M required when used in combination. The composition of the different formulations is shown in Table 1. The release kinetics parameters are shown in Table 2. The drug release profiles for the different formulations are shown in Fig. 2.

The marketed product is available as capsules containing venlafaxine hydrochloride equivalent to venlafaxine 75 mg in the form of extended release pellets. Inactive ingredients include cellulose, hydroxypropylmethylcellulose, ethylcellulose, gelatin, iron oxide and titanium dioxide. From the in vitro release studies, a lag time was seen with both the marketed formulations with only 2% drug being released in an hour. Drug release was found to follow zero order kinetics with $r = 0.9809$ and 0.9881 for marketed formulations I and II, respectively. The formulations were found to provide sustained release for a period of 16 h with 90% drug being released in 14 h. The drug release profiles from the marketed formulations are shown in Fig. 3. The release kinetics parameters are shown in Table 2.

In case of formulation F1 where Methocel K100M is 1:4 with respect to the drug, drug release follows Higuchi kinetics with r value 0.9977, 90% drug released in 14 h. Our aim was to achieve 95–100% release in 16 h. Hence this formula was chosen for stability. There was no change in the different physico-chemical parameters of the tablets at all the conditions. Thus, the formulation was stable at accelerated conditions of temperature and humidity.

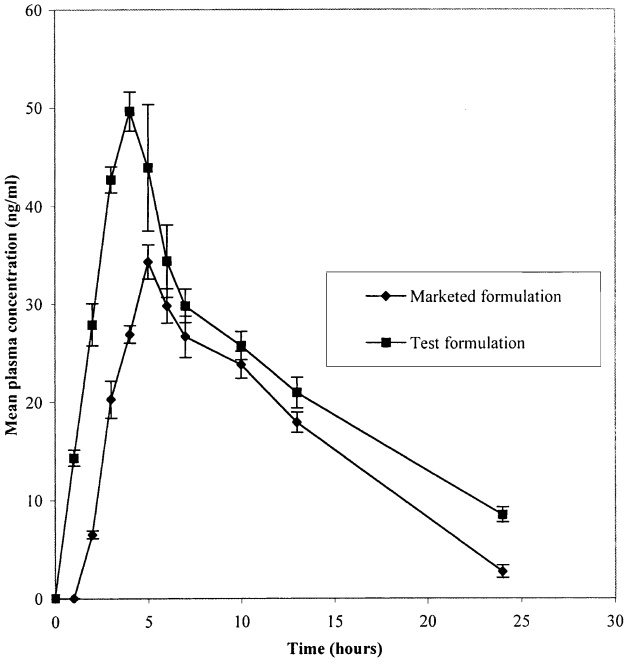

Fig. 4. Mean plasma levels for venlafaxine from the test and marketed formulations.

Table 4
Results of ANOVA test for comparison of pharmacokinetic parameters for F1 and marketed formulations[a]

Parameters	F ratio between the products	F ratio between the subjects
C_{max}	191.37 (S)	0.88 (NS)
K_{el}	154.73 (S)	1.55 (NS)
$t_{1/2}$	144.33 (S)	1.46 (NS)
AUC_{0-24}	162.09 (S)	0.53 (NS)
$AUC_{0-\alpha}$	271.16 (S)	0.64 (NS)

[a] NS, non-significant; S, significant.

In vivo studies were carried out for formulation F1 and marketed formulations and the plasma levels of venlafaxine were determined. Non-compartmental analysis was applied to the plasma level data and the pharmacokinetic parameters were calculated by model independent method. The computed pharmacokinetic parameters for F1 and marketed formulation II are summarized in Table 3. The plot of VEN plasma concentration versus time for F1 and marketed formulations is illustrated in Fig. 4. Results of ANOVA treatment are summarized in Table 4.

After administration of the optimized formulation F1, the drug was observed to achieve plasma levels rapidly. After 1 h, plasma concentrations of 13–15 ng/ml were observed. However, in case of the marketed formulation, a lag time of 1 h was seen with plasma concentrations of just 5–6 ng/ml achieved in 2 h. The mean peak plasma concentrations for F1 and marketed formulations were 49.628 and 34.270 ng/ml and these were achieved at 4 and 5 h, respectively. The blood levels were seen upto a period of 24 h for both the formulations with 8.461 and 2.683 ng/ml for F1 and marketed formulation, respectively. The developed formulation showed higher area under the plasma concentration–time curve and hence better bioavailability.

A significant difference between the products was found for all the pharmacokinetic parameters. However, between the subjects the difference was not significant indicating that there was less subject-to-subject variation. The relative bioavailability was found to be 141.61%.

4. Conclusions

Hydrogel based once daily sustained release tablets of venlafaxine were successfully formulated using Methocel K100M. Addition of an optimum concentration of ethyl cellulose/Eudragit 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. The optimized formulation was found to be stable at all the stability conditions. The pharmacokinetic studies show that the lag time observed with the marketed formulation was not seen with the developed formulation. The developed formulation had better bioavailability compared to the marketed formulation.

Acknowledgements

The authors would like to thank M/s Alembic Ltd, Baroda, India for gift sample of venlafaxine hydrochloride and University Grants Commission, Government of India for the financial assistance.

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