Research Article

ONCE DAILY VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE TABLETS: COMPARISON BETWEEN MATRIX TABLET AND PELLETS

Sritharan Seetharaman[1] and Narayanan Nallaperumal[2]
[1]Vinayaka Missions University, Salem, Tamilnadu, India.
[2]Joint Director of Medical Education (Pharmacy), Directorate of Medical Education, Chennai, India.
***Corresponding author's E-mail:** sri_tha_ran@yahoo.com

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ABSTRACT

This study aims to evaluate the in vivo and in vitro performance of simple, cost effective and conventional single layer matrix tablet compared to pellets based on pelletization technology. Venlafaxine and its active metabolite ortho desmethyl venlafaxine is an anti-depressant. Extended release tablets of Venlafaxine hydrochloride to be taken once daily were formulated with Venlafaxine hydrochloride equivalent to 150 mg of base. Matrix system based on swellable polymer Hydroxypropyl methylcellulose was selected for extending the drug release. The optimized formulation was subjected to stability studies at accelerated condition. Test and marketed formulations were evaluated for appearance, weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. *In vivo* studies were carried out for the optimized formulation in 12 healthy human volunteers and pharmacokinetic parameters were compared with the marketed one.

Keywords: Venlafaxine Hydrochloride, Pelletization technology, Matrix system.

INTRODUCTION

Venlafaxine and its active metabolite ortho desmethyl venlafaxine are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine hydrochloride is (R/S)-1-[2- dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride or (±)-1-[α- [(dimethylamino) methyl] - p-methoxybenzyl] cyclohexanol hydrochloride.[1]

Its molecular formula is $C_{17}H_{27}NO_2HCl$. Venlafaxine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water. Venlafaxine hydrochloride extended release capsules – 150 mg, 75 mg and 37.5 mg is available in US market with trade name Effexor XR that is a registered trade name of Wyeth Pharmaceuticals Inc. and it is based on pelletization technology.[1]

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent.[1]

US Patent no. 6274171[2] describes its invention as follows "Extended release drug formulations are conventionally produced as compressed tablets by hydro-gel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropyl methylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4966768[3]. U.S. Pat. No. 4389393[4] discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropyl methylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4138475[5] discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is

composed of ethyl cellulose, optionally, with hydroxypropyl methylcellulose and/or a plasticizer.

Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4535186[6]. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients."

The present research endeavor was directed towards the development of an extended release dosage form of Venlafaxine hydrochloride in the form of simple, cost effective, single layer matrix tablet, which would be bioequivalent to Effexor XR (US market). High viscous Hydroxypropyl methylcellulose (HPMC) was used to control the release of drug. The tablets were evaluated for different physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and in vitro release.

MATERIALS AND METHODS

Materials

Venlafaxine Hydrochloride was obtained from Orchid Chemicals and Pharmaceuticals Limited, Chennai, India. Methocel K 100 and Plasdone S 630 were obtained from Dow chemical and ISP respectively. Aerosil 200, Talc and Magnesium stearate were obtained from Degussa, Luzenac and Mallinckrodt respectively. Hydroxypropyl Cellulose (Klucel EXF) was obtained from Aqualon.

Drug-excipient interaction studies

The possibility of drug-excipient interaction was investigated by HPLC analysis. Drug excipient compatibility study was performed with excipients mentioned above. Study was conducted by preparing homogeneous mixture of excipient with drug, filled in glass vials were exposed to 40±2°C / 75±5% RH and 60°C for 4 weeks. Samples were analyzed for related substances.

Formulation

Tablets were prepared by wet granulation using Isopropyl alcohol. Formulation details are shown in Table 1. All the intra granular ingredients were weighed accurately and passed through #30 mesh sieve and added into Rapid Mixer Granulator. Sufficient quantity of IPA was added and granulated. Granulated wet mass dried and milled using multi mill fit with 1 mm screen. Milled granules mixed with extra granular excipients that were already passed through # 60 mesh using octagonal blender for 5 minutes. Compression was done on a cadmach 16 station compression machine using 17*7 mm caplet shaped punch.

Coating dispersion was prepared by dissolving HPC in IPA. Talc was dispersed into solution under stirring. 5% w/w dispersion was prepared and 5% w/w build up was given onto compressed tablets using perforated coating pan.

Table 1: Composition of formulations

Ingredients	Formulation I		Formulation II	
Intra granular	**mg/tablet**	**%**	**mg/tablet**	**%**
Venlafaxine HCl	169.72*	26	169.72*	26
HPMC K 100M	250	38	300	46
Avicel pH 101	98.78	15	48.78	8
Plasdone S630	115	18	115	18
Isopropyl alcohol	q.s	q.s	q.s	q.s
Extra granular				
Aerosil 200	5.5	1	5.5	1
Talc	5.5	1	5.5	1
Magnesium stearate	5.5	1	5.5	1
Weight of core tablet	650	100	650	100
Coating				
Klucel EXF	29.25	5% w/w coat	29.25	5% w/w coat
Talc	3.25		3.25	
Isopropyl alcohol	q.s		q.s	

* Equivalent to 150 mg of Venlafaxine

Evaluation

The tablets were evaluated for different physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and in vitro release. *In vitro* release was studied using USP I dissolution test apparatus in different pH buffers for a period of 24 h. HPLC method was used as the method of analysis.

Stability studies

The optimized formulation was subjected to accelerated stability study at accelerated condition i.e. 40±2°C / 75±5% RH. The optimized formulation was packed in PVC/PVdC based blister pack. Description, Water Content, Assay, Related Substance and dissolution were studied during stability. In case of dissolution, method recommended by US-FDA was followed by using USP I apparatus; Water – 900 ml; 100 RPM[7].

In vivo studies

Fed study was conducted in 12 healthy, adult, male human subjects. A randomized, two treatment, two sequence, two period, two way cross over bioequivalence study was done in which test formulation was compared with Effexor XR capsules 150 mg (Wyeth, USA). Only fed study was performed as per recommendation by US-FDA as fasted study causes nausea and vomiting[8]. In case of fed study subjects were housed in clinical facility to

ensure overnight fasting of 10 hours before administration of high fat, high calorie breakfast and dosing was done 30 min after the breakfast. Subjects remained in the facility till 24 hours post dose and again reported for 36 and 48 hours ambulatory blood samples in each period. Subjects were dosed in sitting position using 240mL of water and remained seated for first 4 hours. No fluid was allowed 1 hour before & after dosing and a standard meal was provided at 4, 9 and 13 hours after dosing during each period. The washout period between two periods was 7 days. Upon completion of the study, the physical examination and clinical laboratory measurements were repeated. Sampling was done at pre-determined time intervals of 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 36, 48 hours. The pharmacokinetic and statistical analysis was performed using WinNonlin® version 5.0 (Pharsight Corporation, USA).

Pharmacokinetic analysis was performed by means of a model independent method. The maximum Venlafaxine concentration (C_{max}) and the corresponding peak times (T_{max}) were determined by the inspection of the individual drug plasma concentration–time profiles. The elimination rate constant (λ_z) was obtained from the least-square fitted terminal log-linear portion of the plasma concentration – time profile. The elimination half-life ($T_{1/2}$) was calculated as 0.693/ λ_z. The area under the curve to the last measurable concentration (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity as ($AUC_{0-t} + C_t/ \lambda_z$, where C_t is the last measurable concentration. For the purpose of statistical bioequivalence analysis AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were considered as primary variables[9].

Study protocols were approved by an Independent Ethics Committee - The Ethical Jury, Chennai. The studies were conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization's Good Clinical Practices guidelines, and the guidelines of Indian Council of Medical Research for Biomedical Research on Human Subjects and Good Clinical Practices for Clinical Research in India. Healthy, willing, volunteers of age between 18 and 50 years were selected on the basis of laboratory evaluations during screening, medical history, clinical examination, X-ray, ECG recordings, urine screen for drugs of abuse and alcohol breath test. Informed consent was obtained from the subjects after explaining the nature and purpose of the study.

RESULTS AND DISCUSSION

Drug Excipient compatibility data shown in Table 2 suggests that both the temperature and moisture doesn't affect the stability of mixture indicating compatibility of drug with Excipients studied.

For the formulation development, Methocel K 100 was selected as controlled release polymer to get swellable controlled release dosage form[10-13]. Two different formulations were made as specified in Table 1. 38% and 46% of polymer was used respectively in formulation I and II. Dissolution study was performed using US-FDA recommended dissolution method USP I; Water; 900 ml; 100 RPM. Similarity factor F_2 was calculated to select the formulation that is similar to innovator. Table 3 depicts the dissolution results and F_2 values. Fig. 1 illustrates the dissolution profile.

Table 2: Drug Excipient Compatibility Study

Ingredients (Ratio)	Initial	Total Impurities	
		40^0C/75%RH – 4th week	60^0C – 4th week
Drug*	0.06	0.06	0.06
Drug + Methocel K 100 (1:20)	0.07	0.07	0.07
Drug + Plasdone S 630 (1:20)	0.06	0.06	0.07
Drug + Avicel pH 101 (1:20)	0.07	0.07	0.06
Drug + Aerosil 200 (1:5)	0.07	0.06	0.07
Drug + Talc (1:5)	0.06	0.06	0.06
Drug + Magnesium Stearate (1:5)	0.06	0.07	0.06

* Drug – Venlafaxine Hydrochloride

Table 3: Dissolution release profile

Time	Marketed Formulation	Formulation I	Formulation II
0	0.00	0.00	0.00
1	5.00	7.20	6.20
2	17.70	24.90	22.30
4	42.63	47.40	43.50
6	58.97	63.50	59.10
8	69.13	75.70	71.70
12	80.43	90.20	87.70
16	87.77	94.90	95.00
20	92.97	96.20	97.10
24	96.70	96.90	98.00
F_2 value		**55**	**63**

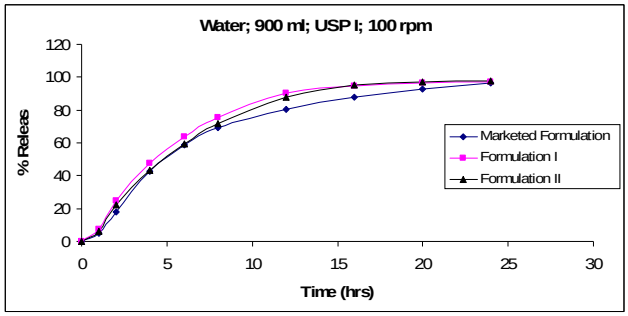

Figure 1: *In vitro* dissolution release profiles of Venlafaxine hydrochloride

F_2 value suggests that formulation II is similar to that of the innovator. Formulation II was subjected for multi-media dissolution data generation in 0.1N HCl, pH 4.5, pH 6.8 and similar dissolution as that of water was found as drug exhibits pH independent solubility.

There was no change in the different physico-chemical parameters of the tablets at the accelerated stability conditions. Thus, the formulation was stable at accelerated conditions of temperature and humidity,

Table 4 shows the stability data of formulation II in PVC/PVdC pack.

Table 4: Stability result of formulation II at 40±2°C/75±5% RH

Test	Specification	Initial	1M	2M	3M
Description	*	**	**	**	**
Water content (%)	NMT 7.0	4.61	4.38	4.52	4.66
Assay (%)	90 - 110	101.0	101.2	100.0	101.2
Related Substance (%)					
Highest unknown	NMT 0.2	0.05	0.06	0.07	0.07
Total impurities	NMT 1.5	0.14	0.13	0.14	0.13
Dissolution					
Time (hr)	% Drug Release				
1	NMT 15	6	7	7	7
8	60 - 80	72	71	73	71
24	NLT 85	97	95	96	97

* White to off white colored round shallow convex tablets; **Complies.

In vivo studies were carried out for test formulation II and marketed formulation. The plasma levels of Venlafaxine were determined. The mean concentration-time profiles for the marketed and developed formulation II of Venlafaxine hydrochloride are shown in Fig. 2 and Table 5 shows the plasma concentration – time profile and pharmacokinetic parameters with statistical results respectively.

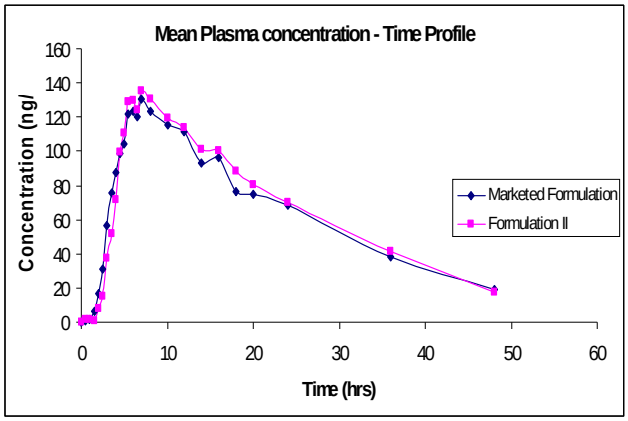

Figure 2: Plasma concentration – time profile of Venlafaxine hydrochloride 150 mg – Fed Condition

Table 5: Statistical analysis of pharmacokinetic data – Fed study

Product / Statistics	C_{max} [ng/mL]	$AUC_{(0-t)}$ [ng.h/mL]	$AUC_{(0-inf)}$ [ng.h/mL]	T_{max} (h)
Formulation II				
Arithmetic Mean	167.147	2988.133	3260.331	6.364
Geometric LSMean	160.31	2665.42	2850.48	6.0*
% CV	34.2	49.0	53.6	
Marketed Formulation				
Arithmetic Mean	167.279	2921.468	3147.759	5.955
Geometric LSMean	165.3	2693.97	2838.29	5.5*
% CV	24.4	38.6	54.4	
T/R [%]	**96.98**	**98.94**	**100.43**	
90% Confidence Interval [T/R]				
Lower limit [%]	**80.23**	**83.82**	**84.06**	
Upper limit [%]	**117.22**	**116.79**	**119.99**	
Power	0.6251	0 .7299	0.6751	
ISCV [%]	24.60	20.36	23.69	

T/R ratio of 12 volunteers shows that formulation II is bioequivalent to marketed formulation. The fact that the test formulation is bioequivalent to marketed formulation indicates that test formulation is also capable of releasing the drug for longer period of time comparable to that of marketed formulation. Proposed test product is having added advantage as it is very simple, conventional, process friendly and cost effective formulation compare to the marketed formulation where process involves extrusion spheronization followed by controlled release coating using fluidized bed processor.

CONCLUSION

Single layer hydrophilic polymer based once daily extended release tablet of Venlafaxine hydrochloride was successfully formulated using Methocel K 100 M. The optimized formulation was found to be stable at the accelerated stability conditions. The pharmacokinetic studies show that desired bio-profile can be achieved with the simple matrix formulation compared to complex pelletization based formulation.

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