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# Designing and evaluation of extended release tablet of Venlafaxine hydrochloride using hydrophobic matrix

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## 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 37.5 mg of venlafaxine base. Matrix system based on non swellable polymers was selected for sustaining the drug release. Different polymers and waxes viz. hydroxypropylmethylcellulose (HPMC), stearic acid, cetyl alcohol, ethyl cellulose etc. were studied. Combinations of non-swellable waxes with HPMC were also tried in order to get the desired sustained release profile over a period of 24 h. The effect of drug to wax 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 40$^{o}$C/70% RH. These were evaluated for appearance, weight variation, thickness, hardness, friability, drug content and in vitro drug release at selected time intervals.

**Keywords:** Venlafaxine, Matrix system, Cetyl alcohol, Stearic acid, Ethyl cellulose.

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## 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 endeavor was directed towards the development of a sustained release dosage form of venlafaxine in the form of tablets to be taken once daily. The main objective

of this work was to develop the SR tablet of Venlafaxine HCl with the wax as retarding matrix and to match the release profile with the innovators product i.e Effexor™-XR (venlafaxine HCl) (Wyeth Lederle)[7] which is given in table (1),

| Time (Hours) | Average % venlafaxine hydrochloride released |
|---|---|
| 2 | <30 |
| 4 | 30-55 |
| 8 | 55-80 |
| 12 | 65-90 |
| 24 | >90 |

**Table (I) Release profile for Effexor™-XR capsule (venlafaxine HCl) (Wyeth Lederle)**
**Different polymers viz. cetyl alcohol, stearic acid, hydroxypropylmethylcellulose (HPMC), ethyl cellulose, etc. were tried. Different grades of HPMC studied include K4M and K100M.**

Ethyl cellulose of (100 cps) were studied in combination with both the waxes. 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 37.5 mg in the form of extended release pellets [8]. The optimized formulation was subjected to stability studies.

## Materials and methods

### 2.1. Materials

Drug, waxes, polymers, solvents and reagents were sponsored by the VAMA pharmaceuticals, Wadi, Nagpur, Maharashtra, India.

### 2.2. Drug–excipient interaction studies

The possibility of drug–excipient interaction was investigated by differential scanning calorimetry. The DSC thermo grams of pure drug, individual excipient and drug–excipient mixtures were recorded. The samples were separately sealed in aluminium cells and set in Mettler Tolleredo thermal analyzer. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of $10^0$C/min over a temperature range of 30–300 $^0$C. Alumina was employed as the reference standard.

### 2.3. Formulation

Tablets were made by hot melt granulation. All ingredients were weighed accurately and drug was passed through 80 mesh sieve. The wax was heated up to the $70^0$C and the drug was added to melted wax at $50^0$C. The mixture was stirred continuously to get the solid soft mass which was passed through the 16 mesh sieve. Granules were mixed with weighed quantities of aerosil and magnesium stearate previously passed through 100 mesh sieve. Compression was done on a Prism ten punches single station tablet press using round (7mm convex) punches. Initially pharmagrade sugar and PVPK 30 were tried with cetyl alcohol with the drug. A combination of HPMC with cetyl alcohol was also tried. Cetyl alcohol and only PVPK 30 was also tried. Finally the ethyl cellulose 100 cps was tried to get the desired

release profile. The formulation was also developed by using a stearic acid and ethyl cellulose.

### 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 Distilled water 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 227 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

The optimized formulation was packed in high density polyethylene bottle (F8–F12) and subjected to stability studies at $40^0$C/75% RH. Sampling was done at predetermined time intervals of 0, 15, 30, 45 and 60 days. Tablets were evaluated for the different physico-chemical parameters viz. appearance, weight variation, thickness, hardness, friability, drug content and in vitro release. In vitro release was determined by UV spectrophotometry at 227 nm.

## Results and Discussion

The DSC thermogram for the drug gave a sharp melting endotherm at 215.38C. The individual excipient 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 thermo grams of the drug (VEN), individual excipient and drug–excipient mixtures are depicted in Fig. i.

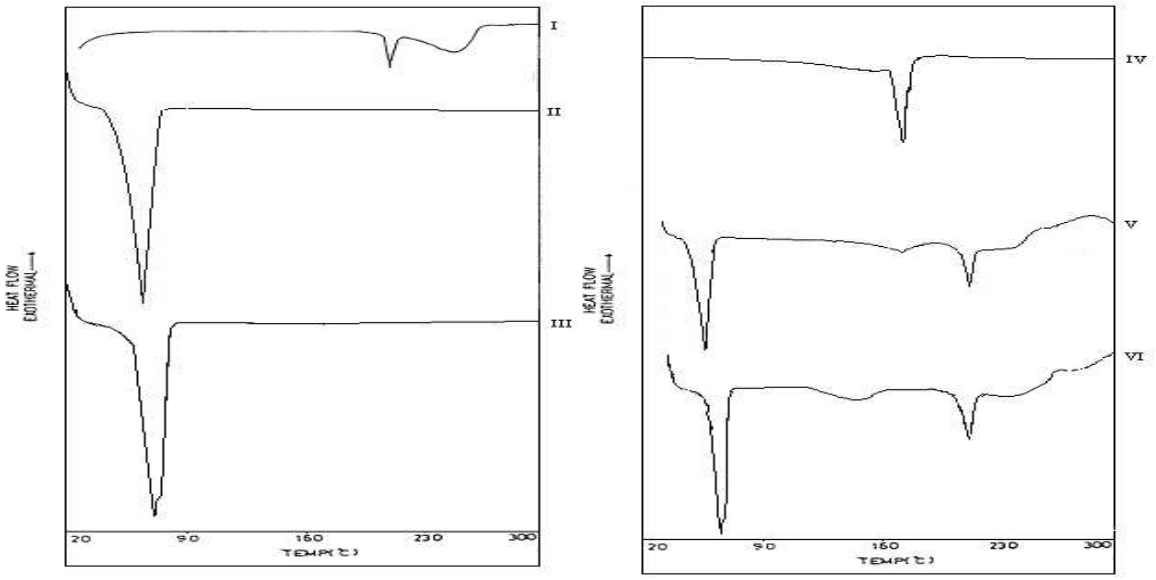


**Fig. (I). Differential scanning thermo grams; I.VEN HCl, II. Cetyl alcohol, III. Stearic acid, IV. Ethyl cellulose, V. Tablet with Cetyl alcohol. VI. Tablet with Stearic acid**

Initially pharmagrade sugar, Lactose and PVPK 30 were tried with cetyl alcohol with the drug (F1 to F4). Combinations of HPMC with cetyl alcohol was also tried (F5, F6). Finally

the ethyl cellulose 100 cps was tried to get the desired release profile (F7, F8). The formulation was also developed by using a stearic acid and ethyl cellulose after cetyl alcohol.

**Table. (II). Composition of the different formulations**

| Ingradientts mg/tab | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venlafaxine HCl | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 | 43 |
| Cetyl Alcohol | 42.5 | 85 | 42.5 | 85 | 85 | 85 | 80 | -- | -- | -- | -- | -- |
| Stearic acid | -- | -- | -- | -- | -- | -- | -- | 80 | 80 | 80 | 80 | 80 |
| Pharma Grade Sugar | 44.5 | 2.0 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Lactose | -- | -- | 44.5 | 2.0 | -- | -- | -- | -- | -- | -- | -- | -- |
| PVPK 30 | 2 | 2 | 2 | 2 | -- | -- | -- | -- | -- | -- | 9 | 7 |
| HPMCK4M | -- | -- | -- | -- | 4 | -- | -- | -- | -- | -- | -- | -- |
| HPMC K100M | -- | -- | -- | -- | -- | 4 | -- | -- | -- | -- | -- | -- |
| Ethyl Cellulose | -- | -- | -- | -- | -- | -- | 3 | 10 | 10 | 2 | -- | 2 |
| Aerosil | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 1.5 | 1.5 | 2 | 2 | 2 |
| Magnessium Stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0.5 | 0.5 | 1 | 1 | 1 |
| Total (mg) | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 128 | 135 | 135 |

In-vitro release profile of formulation batch $F_1$ showed the initial burst effect. It might be due to high erosion rate of matrix (Fig ii).

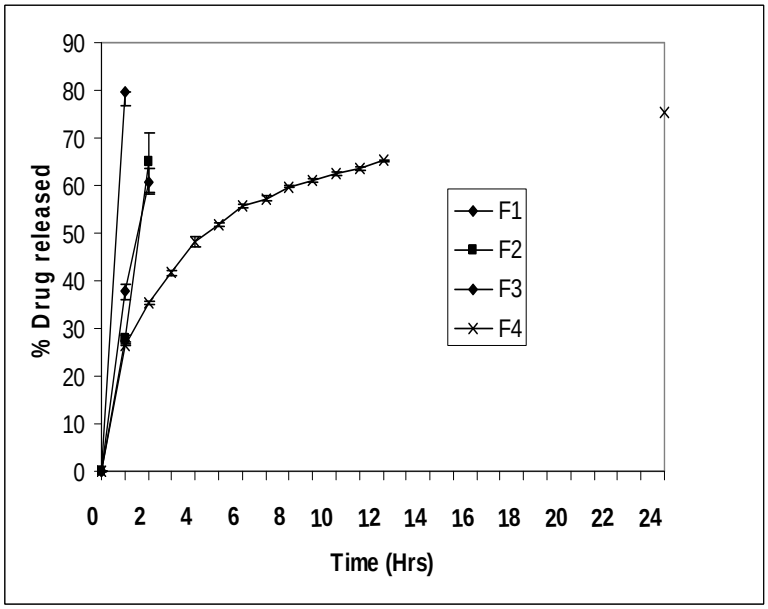


**Fig (II). In-vitro drug release from Venlafaxine HCl ($F_1$) to ($F_4$) matrix tablets using cetyl alcohol**

The release of the drug from the F5 shows the 94% drug release in two hrs. Suggesting that use of higher viscosity HPMC[9]. The release from F6 was 72% in first two hrs but it was also not helping to set the release profile.

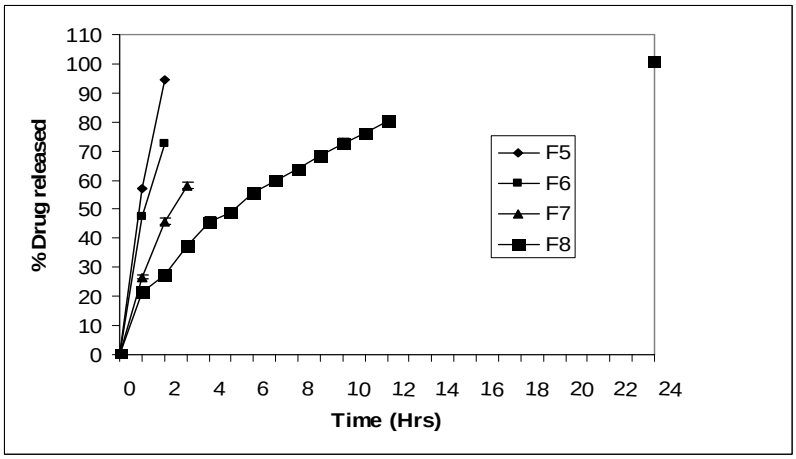


**Fig (III). In-vitro drug release from Venlafaxine HCl ($F_5$) to ($F_8$) matrix tablets using cetyl alcohol**

Thus, the ethyl cellulose (3mg) was tried in F7 and it was found that 58% of drug was released in three hrs. This forced to increase the amount of ethyl cellulose in F10, which was a optimized batch which was found to follow the release profile of the innovator. (Fig.3). After developing formulation with the cetyl alcohol, the stearic acid was tried. Fig.4 shows the release patterns of venlafaxine HCl from matrix tablets made with stearic acid, drug wax ratio 1:2. It has been observed that the venlafaxine HCl matrix tablets formulation batch F12 was found to be most promising and matches the release profile of the innovator product. The formulation batch $F_8$ and $F_{12}$ shows about 100% drug release at the end of 24 hrs. The formulation batch $F_8$ and $F_{12}$ showed the zero-order release means drug release is constant with time. In case of cetyl alcohol tablet without ethyl cellulose ($F_1$ to $F_6$ ) the release was found to be burst and all the drug releases in the few hrs., the in-vitro drug release rate after 4-5 hr become slow due to high swelling rate of guar gum but here addition of pectin maintained the release rate by acting a eroding material.

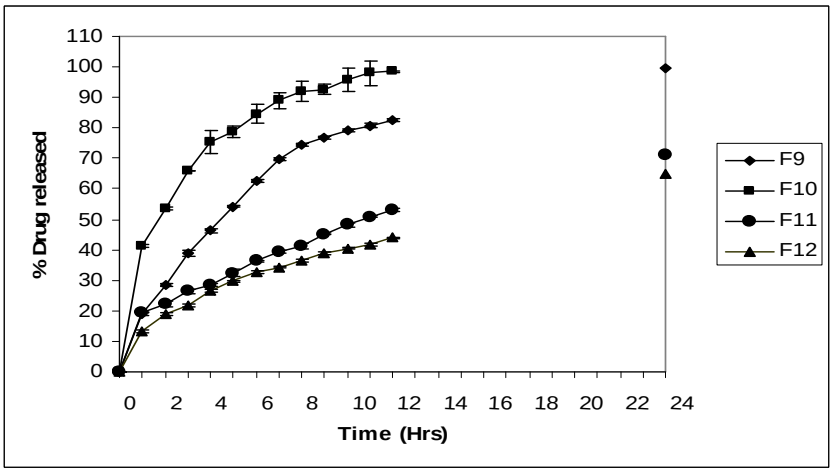


**Fig (IV). In-vitro drug release from Venlafaxine HCl ($F_9$) to ($F_{12}$) matrix tablet stearic acid**

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, 3, 4. The marketed product is available as capsules containing venlafaxine hydrochloride equivalent to venlafaxine 37.5 mg in the form of extended release pellets. From the in vitro release studies of marketed formulation only 16 % drug released in first hour. Drug release was found to follow zero order kinetics with r 0.5673 for marketed

formulation. The formulation was found to provide sustained release for a period of 24 h with 81% drug being released in 12 h.

| Formulations order | Constants | F8 | F12 | Venlor XR (Cipla) |
|---|---|---|---|---|
| Zero | R | 0.9292 | 0.5584 | 0.5673 |
| | k | 7.7350 | 6.4131 | 6.4289 |
| Korsmeyer-Peppas | R | 0.9908 | 0.9809 | 0.9749 |
| | k | 20.0360 | 21.0254 | 20.0360 |
| Hixon Crowel | R | 0.7689 | 0.9792 | 0.9836 |
| | k | -0.0481 | -0.0402 | -0.0424 |

**Table (III) Release kinetics for optimized formulations**

The drug release profiles from the marketed formulations are shown in Fig. 5. The release kinetics parameters are shown in Table 2. In case of formulation F8 and F12 where ethyl cellulose is 10mg/tab and 2 mg/tab respectively, drug release follows zero order kinetics with r value 0.9292 and 0.5584 respectively, 80-82 % drug released in 12 h. Our aim was to achieve 98–100% release in 24 h. Hence these formulas were chosen for stability. There was no change in the different physico-chemical parameters of the tablets at $40^0$C and 70% RH conditions of temperature and humidity.

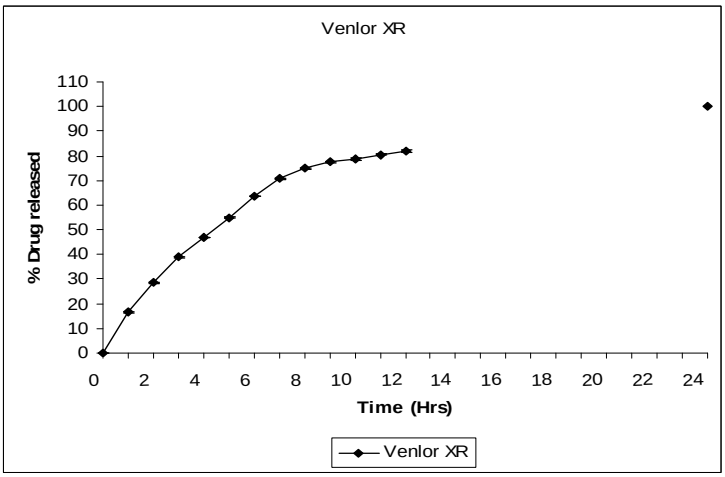


**Fig.(IV) In-vitro drug release from Marketed formulation (Venlor XR, Cipla Ltd.)**

## Conclusion

Tablet of venlafaxine HCl were successfully formulated using hydrophobic matrix. Addition of an optimum concentration of ethyl cellulose to formulations was found to provide the desired release with innovator profile requirement. Release was found to follow zero, krossmayer-peppas and hixon-crowel models. All the formulation batches tested for physical parameters like weight variation, hardness, friability and drug content, all were found to be within the I. P. limits. The optimized formulations were found to be stable at all the stability conditions. During stability studies, no significant variation (1 to 4%) in drug release was observed, indicating that formulation batch $F_8$ and $F_{12}$ were stable over the chosen condition for 2 months. The optimized formulation batch $F_8$ and $F_{12}$ showed better drug release profile

with VENLOR XR (Venlafaxine HCl, pellets in Capsule, Cipla). This was concluded from the similarity factor ($f_2$), which was found to be 60.79 and 93.73 respectively. Combination of cetyl alcohol and ethyl cellulose is an interesting polymer mixture for the preparation of SR matrix tablet because of no water swell ability, non toxicity and low cost of cetyl alcohol and good binding capacity.

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**References**

[1] S.M. Holliday, P. Benfield, *Drugs* 49 (2) (**1995**) 280–294.
[2] J.T. Haskins, J.A. Moyer, E.A. Muth, E.B. Sigg, Inhibition of noradrenergic neuronal activity by the novel bicyclic compounds, Wy- 45,030 and Wy-45,881, *Soc. Neurosci. Abstr*. 10 **(1984**) 262.
[3] E.A. Muth, J.A. Moyer, J.T. Haskins, T.H. Andree, G.E.M. Husbands, *Drug Dev. Res*. 23 (**1991**) 191–199.
[4] B. Cusack, A. Nelson, E. Richelson, *Psychopharmacology* 114 (**1994**) 559–565.
[5] E.A. Muth, J.T. Haskins, J.A. Moyer, G.E. Husbands, S.T. Nielsen, E.B. Sigg, *Biochem. Pharmacol.* 35 (**1986**) 4493–4497.
[6] S.M. Troy, V.D. Parker, R.J. Fruncillo, S.T. Chiang, *J. Clin. Pharmacol*. 35 (**1995**) 404–409.
[7] Patent: Deborah M. Sherman, Plattsburgh; John C. Clarck, Peru, Both of NY (US); John U. Lamer, St. Albans, VT (US); Steven A. White, Champlain, NY (US), Wyeth Madison NJ (US), US 6,419,958 B2 **(2002**).
[8] Physicians' Desk Reference, 54th ed., Medical Economics Company Inc., New Jersey, **2000,** pp. 3233–3242..
[9] L.S.C. Wan, P.W.S. Heng, L.F. Wong, *Drug Dev. Ind. Pharm*. 19 (10) (**1993**) 1201–1210.