Formulation and *IN VITRO* Evaluation of Sustained Release Tablets of Venlafaxine HCl

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Abstract- The sustained release tablets of venlafaxine HCl were prepared by direct compression method using release retarding ability of different grades of HPMC polymers (E4M, E15LV & E50LV) and eudrgit L 100 to extend the release of drug over 24hrs period and thereby improve its bioavailability. The developed tablets were evaluated for pre-compression and post-compression parameters. The results of all formulations were found within the pharmacopeial limits. The optimized formulation (F7) with HPMC E50LV showed the maximum percentage of drug release for 24 hrs was 99.76%. The results indicated that at higher viscosity grades of polymer concentrations drug release was retarded greatly were observed. The drug release was showed by higuchi model followed by zero order release.

Keywords: Venlafaxine HCl, HPMC, sustained release, and direct compression

1. INTRODUCTION

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption [(1)]. Venlafaxine (VEN) is considered a good candidate for incorporation in matrix systems. VEN imparts its antidepressant effects by inhibiting the neuronal uptake of norepinephrine, serotonin, and to a lesser extent, dopamine. The biological half-life was 5 hrs, reported oral bioavailability 45% and the fast clearance make the drug suitable candidate for the development of sustained release formulations [(2)].

2. MATERIALS AND METHODS

2.1. Materials

Venlafaxine hydrochloride is a gift sample provided by Dr. Reddy's Laboratories, Hyderabad. HPMCK4M, HPMCK15M, HPMCK100M, Eudragit RS 100 were procured from Signet Chemical Corporation, Mumbai. Lactose is obtained from Zydus Cadila, Ahmedabad. Magnesium stearate and Talc were obtained from S.D. Fine Chemicals, Mumbai. All the other chemicals and reagents were of analytical grade.

2.2. Methods

Development of matrix tablets by direct compression technology

The appropriately weighed required quantities of polymer (HPMC E4M, HPMC E15LV, HPMC E50LV, and eudragit L100) and lactose were taken in a mortar and mixed precisely; to this specified amount of VEN was introduced and mixed slightly with pestle. The powder is passed through sieve no 30. The entire mixture was put into a plastic bag and blended for 2min. To this magnesium stearate was placed and mixed for 3min; later talc was added and mixed for 5min [(3)]. The mixture equivalent to 75mg was compressed into tablets with 10mm round concave punches at a hardness of 6.5kg/cm^2.

Table 1: Composition of venlafaxine hydrochloride matrix tablets

	Formulation codes											
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Venlafaxine	75	75	75	75	75	75	75	75	75	75	75	75
HPMC E4M	100	150	200	-	-	-	-	-	-	-	-	-
HPMC E15LV	-	-	-	100	150	200	-	-	-	-	-	-
HPMC E50LV	-	-	-	-	-	-	100	150	200	-	-	-
Eudragit L100	-	-	-	-	-	-	-	-	-	100	150	200

Lactose	119	69	19	119	69	19	119	69	19	119	69	19
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Mg. stearate	3	3	3	3	3	3	3	3	3	3	3	3
Total weight (mg) 300 mg												

2.3. Evaluation studies

2.3.1. Pre-compression parameters

The powder blend of all formulations was evaluated for Bulk density, tapped density, compressibility index, hausner ratio and angle of repose [4].

Angle of repose

The angle of repose was determined by using the funnel method. The powder was poured from a funnel that can be raised vertically until a maximum cone height (h) was obtained. The diameter of the heap (D) was measured [5].

Bulk density

Apparent bulk density was determined by pouring the pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight as it is [6].

Tapped density

It was determined by placing a graduated cylinder containing a known mass of drug, excipient blend on mechanical tapping apparatus, which was operated for a fixed number of taps until the powder bed volume has reached a minimum. Using the weight of a blend in a cylinder and with the minimum volume occupied, the tapped density was computed [7].

Compressibility index and Hausner ratio

These were calculated by using the following equation. % Compressibility = $\{(\rho t - \rho b)/ \rho t\} \times 100$ and Hausner ratio = $\rho t / \rho b$.

2.3.2. Evaluation of post-compression tablets

Weight variation

To study the weight variation, 20 tablets from each formulation were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of tablet was determined from the collective weight [8].

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The hardness of tablets was determined by using a Monsanto tablet hardness tester [9].

Friability

It is a measure of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets (10 tablets) were placed in the friabilator which was allowed to revolve for 4 minutes. This device consists of a plastic chamber that is set to revolve around 100 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution [10].

Assay

Ten tablets were taken and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 mL of 6.8 phosphate buffer on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected. The absorbance of supernatant was measured using a UV-Visible Spectrophotometer at λ_{max} of 320 nm [11].

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Ten tablets were taken from each formulation and their thickness was recorded using digital vernier callipers [12].

Dissolution studies

The dissolution rate was studied by using USP type II apparatus at 50 rpm, 0.1N HCl (pH 1.2) and 6.8pH phosphate buffer, 900 ml was used as dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5°c. An aliquot of dissolution medium was withdrawn at a specific time intervals, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24hrs and it was filtered. The absorbance of the filtered solution was checked by UV spectroscopy at 224 nm wavelength and % of drug release was determined from the standard calibration curve [13].

2.3.3. Kinetic modelling

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, higuchi, and korsmeyer-peppas release model [14].

3. RESULTS AND DISCUSSION

Physical properties of all prepared powder blends are within the limits as per USP. It means the flow ability of powder blends is excellent. The granules had shown good flow properties with angle of repose values ranging from 25.61 to 29.85. Carr's index values indicate that all the formulations had good flow properties. The results of the parameters of many of the blends were in the limits and comply with the standards.

Table 2: Precompression parameters of powder blend **(**Mean±SD; n=3)

Formulation codes	Angle of repose (°)	Bulk density (gm/cc$^{3)}$	Tapped density (gm/cc^{3})	Carr's index (%)
F1	28.31 ±1.16	0.296 ± 0.16	0.329 ± 0.14	17.213 ± 0.09
F2	27.34 ±1.21	0.289 ± 0.12	0.357 ± 0.19	19.126 ± 0.19
F3	26.08 ±1.07	0.264 ± 0.09	0.305 ± 0.05	14.691 ± 0.21
F4	29.16 ±1.46	0.289 ± 0.15	0.331 ± 0.18	21.136 ± 0.34
F5	27.11 ±1.14	0.305 ± 0.08	0.375 ± 0.13	18.512 ± 0.15
F6	28.56 ±1.86	0.297 ± 0.14	0.368 ± 0.16	20.341 ± 0.19
F7	29.85 ±1.26	0.309 ± 0.18	0.329 ± 0.09	16.528 ± 0.29
F8	25.69 ±1.35	0.282 ± 0.11	0.335 ± 0.21	22.491 ± 0.36
F9	28.37 ±1.22	0.275 ± 0.19	0.317 ± 0.11	19.152 ± 0.27
F10	25.61 ±1.19	0.291 ± 0.17	0.351 ± 0.07	20.135 ± 0.31
F11	29.32 ±1.35	0.278 ± 0.06	0.348 ± 0.18	19.586 ± 0.22
F12	23.46 ±1.41	0.283 ± 0.10	0.369 ± 0.10	18.128 ± 0.16

3.1. Evaluation of physical parameters

Sustained release tablets of venlafaxine were evaluated for weight variation, hardness, thickness, friability and assay. The total weight of each formulation was maintained; the weight variation of the tablets were within the permissible limits of 10%, as specified for tablet weighing more than 300 mg. Hardness of the tablet was found to be 5.8 to7.0 kg/cm^2 and was maintained in order to minimize the effect of hardness on the drug release. The tablet thickness was also used to assess the quality of tablets. The thickness of tablets ranged from 4.04 to 4.81 mm. Friability of the formulations was found to be in range of 0.56 to 0.70%. Assay studies of all formulations were ranged from 95-99% which is within acceptable range according to pharmacopeia limits.

Table 3: Evaluation parameters of sustained release tablets (Mean±SD; n=3)

Formulation codes	Weight variation (mg)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Drug content (%)
F1	312 ± 4.2	0.43	6.1 ± 0.15	4.15 ± 0.01	98.12 ± 3.4
F2	297 ± 3.9	0.59	6.8 ± 0.17	4.28 ± 0.02	97.46 ± 2.9
F3	305 ± 5.1	0.61	6.2 ± 0.16	4.64 ± 0.01	98.25 ± 3.8
F4	318 ± 2.6	0.42	5.9 ± 0.19	4.20 ± 0.01	96.91 ± 3.5
F5	326 ± 3.4	0.51	6.6 ± 0.14	4.04 ± 0.02	95.27 ± 4.3
F6	310 ± 4.7	0.47	6.9 ± 0.24	4.59 ± 0.02	96.39 ± 5.1
F7	331 ± 3.9	0.54	6.5 ± 0.22	4.35 ± 0.01	97.18 ± 3.1
F8	324 ± 4.5	0.49	6.1 ± 0.15	4.29 ± 0.02	98.69 ± 4.6
F9	315 ± 6.2	0.62	7.0 ± 0.17	4.57 ± 0.02	99.35 ± 5.7
F10	334 ± 5.8	0.68	5.8 ± 0.12	4.48 ±0.01	98.49 ± 3.4
F11	302 ± 4.9	0.57	6.0 ± 0.13	4.81 ±0.02	99.12 ± 5.8
F12	319 ± 3.7	0.36	6.4 ± 0.10	4.73 ±0.01	98.86 ± 4.9

3.2. *In vitro* drug release studies

The results indicated that F1, F2 and F3 formulations are prepared by HPMC E4M; they showed release 84.37 to 93.58%. The F4, F5 and F6 were made by HPMC E15LV; they found release was 92.26 to 97.89% unable to control the release of drug over 24hrs time period. Whereas formulations contain HPMC E50LV; F7, F8 and F9 releases 90.18 to 99.76%. Formulations F10, F11 and F12 were developed by eudragit L100; they were showed release 87.04 to 94.14%. Based on the release studies, the formulation F7 is selected as the optimized formulation, the release was found to be 99.76% in 24hrs and results are shown in Fig 1.

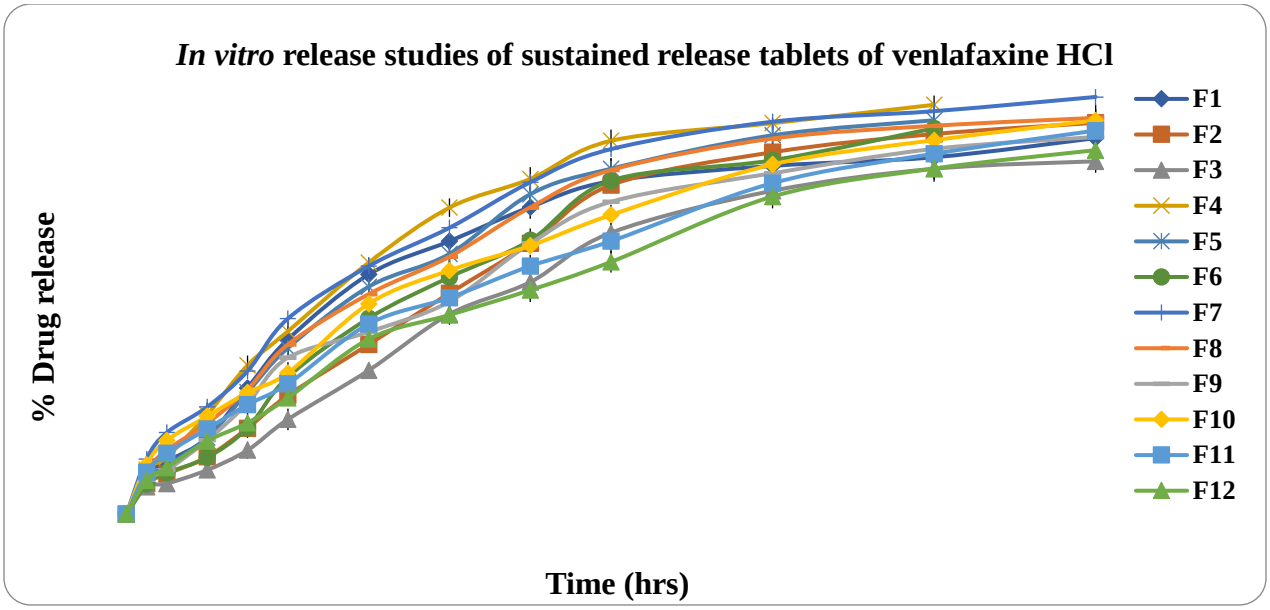

Fig 1: *In vitro* release studies of sustained release tablets of venlafaxine HCl

3.2. Kinetic modelling of the data

The mechanism of release for the optimized formulations was determined by finding the R^2 value for each kinetic model viz. zero-order, first-order, higuchi, and korsmeyer-peppas corresponding to the release data of formulations. For most of the formulations the R^2 value of higuchi and zero-order model is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows higuchi and zero-order model mechanism.

4: Regression coefficient (R^2) values of different kinetic models

Formulation codes	Zero order	First order	Higuchi	Peppas
	R2	R2	R2	R2
F1	0.927	0.214	0.973	0.670
F2	0.917	0.259	0.976	0.700
F3	0.879	0.109	0.936	0.682
F4	0.922	0.272	0.973	0.743
F5	0.913	0.296	0.979	0.759
F6	0.926	0.108	0.972	0.791
F7	0.935	0.339	0.979	0.742
F8	0.910	0.033	0.963	0.758
F9	0.928	0.011	0.956	0.776
F10	0.913	0.304	0.963	0.679
F11	0.918	0.210	0.969	0.702
F12	0.905	0.176	0.968	0.726

4.CONCLUSION

The preparation of sustained release tablets of venlafaxine HCl using release retarding ability of different grades of HPMC polymers (E4M, E15LV & E50LV) and eudrgit L 100 to extend the release of drug over 24hrs period and thereby improve its bioavailability. The optimized formulation (F7) showed better control on the drug release and release was 99.76% and all physical parameters are within the limits. Based on the results indicated that at higher viscosity grades of polymer concentrations drug release was retarded greatly were observed. The drug release was showed by higuchi model followed by zero order release.

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