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Research Article

FORMULATION AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT

Aim and Objective: Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption and onset of accompanying pharmacodynamic effects. The term modified release drug product is used to describe that alter the timing and or the rate of release of the drug substances. The objective of the present study was to formulate and evaluate the sustained release matrix tablet of venlafaxine hydrochloride.

Methods: Venlafaxine hydrochloride is a structurally novel antidepressant for oral administration. It is widely prescribed for the treatment of depression, generalized anxiety disorder, and social anxiety disorder. Venlafaxine hydrochloride is currently available as immediate release tablet and as an extended release capsules under the brand names of Effexor (WYETH AYERST) and Effexor XR (WYETH AYERST). The biological half-life of venlafaxine very short (5 h) and the dose is to be taken 2–3 times a day and the recommended maximum daily dose is 75–450 mg/day.

Results: Venlafaxine hydrochloride is an antidepressant and so it is to be taken for quite a long period. Hence, to reduce the dosing frequency, simple, lower cost sustained release tablets of venlafaxine were preferred for the development

Keywords: Venlafaxine hydrochloride, Hydroxypropyl methylcellulose, Matrix tablets.

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INTRODUCTION

A modified-release dosage form is defined as one for which the drug-release characteristics of time course [1].

EXPERIMENTAL WORK

Preformulation studies

Preformulation testing is the first step in the rational development of dosage form of drugs. It involves the application of biopharmaceutical principles to the physiochemical [2] parameters of a drug with the goal of designing an optimum drug delivery system that is stable, bioavailable and can be mass produced [3].

Analytical evaluation

1. Ultraviolet (UV) spectroscopic analysis.
2. Infrared (IR) spectroscopic analysis.

PREPARATION OF CALIBRATION CURVE OF VENLAFAXINE HYDROCHLORIDE

Procedure

Preparation of primary stock solution

A primary stock solution of venlafaxine hydrochloride was prepared by dissolving 100 mg of pure drug in purified water in 100 ml of volumetric flask and volume made up to 100 ml of with purified water.

Preparation of sample solution

From the primary stock solution, aliquots ranging from 0.05 ml to 0.5 ml were pipetted out and diluted to 10 ml with purified water to get the concentration of 5 µg/ml–30 µg/ml. The absorbance was measured at 274 nm using UV-visible spectrophotometer.

IR spectroscopic analysis

The identification of pure drug and excipients was performed using Fourier-transform (FT-IR) spectroscopy. IR absorption spectra of the pure drug and with different excipients were [4] taken using KBr pressed pellet method [5]. The pellets were prepared by triturating sample and obtained spectra were compared with the reference UV spectroscopic analysis [4]. [6] Pharmaceutical products designed for oral drug delivery are mainly conventional drug delivery systems [7] Sustained drug action pre determined rate by maintaining a relatively constant [8] The effective drug level in the body with concomitant minimization of undesirable side effects [9] The targetted drug action by busing carriers or chemical derivatives to deliver drug to a particular target cell type [10] Targetted release dosage forms may have either immediate or extended release characteristics [11].

FORMULATION DEVELOPMENT

The study involves the formulation of venlafaxine sustained release matrix tablet.

Procedure

1. Weigh and dissolve ethyl cellulose 95% in ethanol to prepare 2%w/w solution.
2. Weigh venlafaxine hydrochloride, hydroxypropyl methylcellulose (HPMC), tale, and magnesium stearate and shift through ASTM#40.
3. Mix the sifted materials for 5 min in a poly bag.
4. Add ethyl cellulose solution to dry mix until getting coherent mass: If required add sufficient ethanol 95%.
5. Air dries the granules and keeps the granules in vacuum oven for overnight.
6. Sift the dried granules through ASTM#20.
7. Weigh talc and sift through ASTM#60.

Table 1: Composition of venlafaxine hydrochloride sustained release matrix tablet

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
		mg/tablets					
1	Venlafaxine hydrochloride	84.86	84.86	84.86	84.86	84.86	84.86
2	Lactose monohydrate	55	55	55	-	-	-
3	Hypromellose (HPMC K15M)	300	-	200	200	150	150
4	Hypromellose (HPMC K100M)	-	300	100	100	100	150
5	Ethyl cellulose 2%w/w	-	-	-	16.66	16.66	16.66
6	Ethanol (95%)	-	-	-	qs	qs	qs
7	Talc	5	5	5	27.62	26.67	27.99
8	Magnesium stearate	450	450	450			

84.86 mg of venlafaxine hydrochloride equivalent to venlafaxine 75 mg, HPMC: Hydroxypropyl methylcellulose

8. Blend the sifted granules and in a poly bag for 30 min.
9. Weigh and sift magnesium stearate through ASTM#40.
10. Lubricate the blend with sifted magnesium stearate for 2 min.
11. Compress the tablets using 12 mm flat punches with break line on upper punch.

EVALUATION OF TABLET

The tablets were evaluated for the following characteristics.

Weight variation

Weigh and dissolve ethyl cellulose 95% in ethanol to prepare 2% W/W solution,Mix the sifted materials for 5mts in a poly bag and the each Venlafaxine hydrochloride weight 84.86mg equal to venlafaine 75mg are shown Table 1.

The test ensures that all the tablets in each batch are of same potency, within reasonable limits. According to the USP weight variation test. The specification of the weight variation limits as per USP is given in the following Table 2.

According to the USP Weight variation test,20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine the weight variation.

Drug content

A total of l0 tablets are triturated using mortar and pestle. A quantity of powder weighed equivalent to 84.86 mg of drug was transferred to 100 ml of standard flask and volume made up to 100 ml with purified water.

Hardness test

A total of 10 tablets from each batch were used and the hardness was expressed in kg/mm^2.

Friability

Friability test was performed to assess the effect of friction and shock which may often cause tablets to chip, cap, or break.

RESULTS

Preformulation studies

UV spectroscopic analysis

Standard calibration curve of venlafaxine hydrochloride

The absorbance was measured at 274 mn against purified water as blank. The values are given in Table 3.

IR spectroscopy study

FT-IR technique was used for the identification of venlafaxine hydrochloride and the blend of finalized formula (F6). The obtained results are given in Table 4.

The IR Spectral studies of blend were carried out to study the interaction between the drug and super disintegrants used. It showed that IR spectrum of pure drug venlafaixne hydrochloride final lubricated blend of table 5 shown some additional peak due to the presents of excipients. Thus on the basis of FT-IR studies, we can conclude that, the drug is compatible with ecipients. The results are shown in Table 5.

Table 2: Specification for weight variation of tablets as per USP

Average weight of tablet	% deviation
130 mg or less	±110
>130 mg but <324 mg	±7.5
324 mg or more	±5

Table 3: Standard curve for venlafaxine hydrochloride

S. No.	Concentration (pg/ml)	Absorbance
1	5	0.186
2	10	0.324
3	15	0.492
4	20	0.676
5	25	0.814
6	30	0.978

Table 4: IR spectra data for venlafaxine hydrochloride

Frequency Hz	Group assigned
3325	0-H stretching vibration
2929.13	C-H stretching
3001.96	C-H aromatic stretching
1273.6	C-N stretching vibration
1366	C-N stretching vibration
1582.77	C=C stretching vibration (aromatic)
1612.11	C=C stretching vibration (aromatic)
1512.64	C=C stretching vibration (aromatic)
1079.79	O-H stretching vibration
830.55	C-H deformation vibration

IR: Infrared

Table 5: IR spectra data for blend

Frequency Hz	Group assigned
2920.18	C-H stretching
1020.18	C-O-C stretching vibration
1250.79	O-H stretching (secondary alcohol)
838.26	C-H deformation
1600	C=C stretching vibration
1500	C=C stretching vibration

IR: Infrared

Flow properties of blend

Six formulations are prepared and the lubricated blend was evaluated for various parameters as follows.

Table 6: Precompression studies of powder blend

Batch code	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner ratio
F1	28°81	0.52	0.66	21.21	1.25
F2	29°68	0.56	0.68	17.64	1.21
F3	27°92	0.52	0.65	20	1.25
F4	26°56	0.58	0.72	19.44	1.24
F5	25°74	0.59	0.72	18.05	1.22
F6	26°10	0.60	0.72	16.66	1.2

Table 7: Post compression studies of Venlafaxine hydrochloride matrix tablet

Batch code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Weight variation (mg)
F1	5.41±0.01	2.83±0.41	0.52	100.2	450±1.08
F2	5.41±0.02	3.00±0.45	0.50	101.3	450±1.03
F3	5.40±0.02	3.17±0.26	0.45	99.87	450±1.29
F4	5.20±0.02	3.33±0.26	0.32	100.3	411±1.03
F5	5.10±0.04	3.25±0.27	0.34	99.8	361±084
F6	5.21±0.02	3.42±0.20	0.28	100.4	411±0.78

Angle of repose

The present study was undertaken to formulate Venlafaxine hydrochloride matrix tablet with three polymers namely Lactose mono hydrorate , hypromellose , ethyl cellulose and in combination of three super disintegrants and by dry granulation technique. Before compression of the granules physical characters such as bulk density, tapped density, angle of repose, compressibility index and hausner ratio was determined and tabulated in Table 6.

Bulk density

The bulk density of various granules is measured using graduated cylinder. The bulk density was found in the range of 0.52–0.60 g/cm. The results are given in Table 6.

Tapped density

The tapped density of lubricated blends was determined using measuring cylinder. The tapped density was found in the range of 0.65–0.72 g/cm. The results are given in Table 6.

Compressibility index and Hausner ratio

The compressibility index and Hausner ratio of various lubricated blends were calculated using bulk density and tapped density data.

- The compressibility index was found in the ratio of 16.66–21.21%.
- The present study was undertaken to formulate Venlafaine hydrochloride matrix tablet dispersible tablet with three polymers namely sodium starch glycolate, cros carmellose sodium and in combination of three super disintegrants and by dry granulation technique. Before compression of the granules physical characters such as bulk density, tapped density, angle of repose, compressibility index and hausner ratio was determined and tabulated in Table 6.

The angle of repose of all batches was found between 20° and 30° Wh1C1'l indicates that the blends are having good flow property. The results of compressibility index (l6.66–21.21%) and Hausner ratio (1.2–1.25) indicate that the blends are having fair to good flow property.

EVALUATION OF VENLAFAXINE HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS

Weight variation

The compressed tablets were evaluated for physical properties and the results are tabulated for Hardness test, Thickness test, Friability test, % of weight variation test and Estimation of drug content values showed in Table 7.

Table 8: *In vitro* drug release profile for batch F1 to F6

Time (h)	Cumulative % drug release				
F1	F2	F3	F4	F5	F6
77.84	86.1	79.4	49.44	60.72	13.62
79.4	92.2	82.3	50.26	66.36	26.28
83.2	94.8	90.8	51.0	69.36	38.16
87.6	95.3	96.9	53.16	70.44	49.72
89.8	96.8	102.2	55.96	72.0	55.8
92.16	97.8		61.08	74.52	60.05
94.82	98.2		63.72	77.16	62.52
97.6	99.82		64.8	79.44	65.16
98.8	101.6		67.44	82.08	68.16
100.9			69.72	84.36	71.52
			74.16	87.0	75.72
			78.36	89.52	79.08

Table 9: Release profile of innovator product (EffexorTm-XR)

Time (h)	Average % venlafaxine hydrochloride released
2	<30
4	30–55
8	55–80
12	65–90
24	<90

The prepared tablets were evaluated for weight variation. All the tablets are the acceptable range of weight variation as per USP specification, i.e., less than 15%. The results are given in Table 7.

Thickness

The thickness of the tablets was determined by Vernier caliper and found in the range of 5.40–5.44 mm. The results are given in Table 7.

Hardness

Hardness of tablets was calculated by Monsanto Hardness tester and found in the range of 2.5–2.7 kg/cm^2. The results are given in Table 7.

Friability

Tablets were evaluated using Roche friabilator and friability of tablets was observed in acceptable range of 0.28–0.52% (<1%), which shows that the tablets are mechanical stable and could handle the rigors of transportation and handling. The results are given in Table 7.

Estimation of drug content

The tablets were evaluated for drug content by assay method. The drug content was found in the range of 99.8–l00.4%. The results are given

Table 10: Kinetic release data for optimized formulation

Zero-order plot		Higuchi plot		Korsmeyer and Peppas plot	
Time (h)	**Cumulative % drug release**	**Square root of time**	**Cumulative % drug release**	**Log time**	**Log cumulative % drug release**
1	13.62	1.00	13.62	0.00	0.82
2	26.28	1.41	26.28	0.30	13
3	38.16	1.73	38.16	0.47	1.41
4	49.52	2.00	49.52	0.60	1.58
5	55.8	2.23	55.8	0.69	1.69
6	60.05	2.44	60.05	0.77	1.74
7	62.52	2.64	62.52	0.84	1.77
8	65.16	2.82	65.16	0.90	1.79
9	68.16	3.00	68.16	0.95	1.81
10	71.52	3.16	71.52	1.00	1.83
11	75.72	3.31	75.72	1.04	1.87
12	79.08	3.46	79.08	1.07	1.89

in Table 7.

IN VITRO DISSOLUTION STUDY

In vitro drug release study of venlafaxine hydrochloride sustained matrix tablet was carried out in purified water at temperature 37±0.5'c with basket rotation at 100rpm for 12hrs.

In order to find out the order of release and mechanisms, which was predominantly influence the drug release from the tablets, the in vitro dissolution data was subjected to graphical treatment is percentage cumulative drug release VS time.

In vitro dissolution profile of first three batches (F1, F2, F3) shown burst release. Among the net three batches (F4, F5, F6) F6 shown good control in initial time points(upto 4th hr) and matching with release profile of EFFEOR XR are shown in Table 8.

Release profile of innovator product was mentioned in Time in the ranges of 2,4,8,12,24 vs average of venlafaxine hydrochloride are shown in Table 9.

Here the data was plotted as a graph according to Zero order plot, Higuchi plot, korsmeyer & peppas plot , cumulative percentage of drug release along Y-axis and square root of time (hrs) along-axis are shown Table 10.

STUDY OF DRUG RELEASE KINETICS

The data were plotted as graph according to zero-order kinetics, cumulative percentage of drug release along Y-axis and time (h) along X-axis.

The data were plotted as a graph according to Higuchi's plot, cumulative percentage of drug release along Y-axis and square root of time (h) along X-axis. The plot was found to be linear and the linear regression coefficient value is R2=0.963l so it is obvious that the drug release obeys gel diffusion mechanism.

The data were plotted as a graph according to Peppers plot log cumulative percentage of drug release along Y-axis and log time (hrs) along X-axis.

DISCUSSION

The main goal of this work to develop sustained release matrix tablets of venlafaxine hydrochloride and to find out the effect of polymers on the various parameters of tablets such as dissolution and drug release.

Venlafaxine hydrochloride is an antidepressant having short biological half-life (5 h). Hence, to reduce the dosing frequency and the side effects, sustained release matrix tablet was formulated.

Three formulations were prepared by direct compression using different grades of hydroxypropyl methylcellulose polymers such as Kl5M and KIOOM. Further, three formulations were taken with ethyl cellulose (2 %w/W) dispersion in ethanol (95%) by wet granulation process.

SUMMARY

Venlafaxine hydrochloride is a structurally novel antidepressant for oral administration. The drawback of venlafaxine hydrochloride is short half-life. To give dose for long-term therapy with multidose regimen, patient compliance is the difficult to achieve. Hence, to reduce the dosing frequency, simple, lower cost sustained release tablets of venlafaxine hydrochloride were preferred for the development.

Analytical method was developed for venlafaxine hydrochloride using UV spectrometer at Kmax of 274 mn. It obeys the Lambert's law between 5 and 30 µg/ml. FT-IR study of pure drug, excipients, and blend of final formula was studied and the result confirms that the drug is compatible with other excipients. Three formulations of venlafaxine hydrochloride tablet were prepared by direct compression process, with different ratio of HPMC Kl5M and KIOOM. The dissolution of compressed tablets showed initial burst release.

Hence, three batches were formulated using ethyl cellulose (2%w/w) dispersions in ethanol (95%) and using HPMC KISM and KIOOM by wet granulation process. The formulated tablets are shown good control initial time points. Among the batches taken, batch F6 shown a controlled release characteristics. All the formulations were evaluated for physical parameters such as weight variation, thickness, hardness, and friability.

The results indicate that all the formulations were within the acceptable limit.

CONCLUSION

The venlafaxine hydrochloride sustained release matrix tablets shown controlled release profile as per the release profile of the innovator is EffexorTm_XR. The sustained release of this matrix tablet reduces the dosing frequency and reduces the side effects, by which in a long-term therapy, it may be useful as a product with patient compliance for the treatment of major depression disorder.

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