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.

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 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]. 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 targeted drug action by using caryers 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.
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 5 mts in a poly bag and the each Venlafaxine hydrochloride weight 84.86 mg equal to venlafaxine 75 mg 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 10 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/mm².

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 nm 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 venlafaxine 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 excipients. The results are shown in Table 5.

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

| S. No. | Ingredients                                      | F1    | F2    | F3    | F4    | F5    | F6    |
|--------|--------------------------------------------------|-------|-------|-------|-------|-------|-------|
| 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   | 100   |
| 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

| S. No. | Concentration (pg/ml) | Absorbance |
|--------|-----------------------|------------|
| 1      | 5                     | 0.186      |
| 2      | 10                    | 0.324      |
| 3      | 15                    | 0.492      |
| 4      | 20                    | 0.674      |
| 5      | 25                    | 0.814      |
| 6      | 30                    | 0.978      |

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          |

| S. No. | Frequency Hz | Group assigned |
|--------|--------------|----------------|
| 3325   | H-O 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) |
| 888.26       | C-H deformation |
| 1600         | C=C stretching vibration |
| 1500         | C=C stretching vibration |

IR: Infrared

Table 1: Composition of venlafaxine hydrochloride sustained release matrix tablet

| S. No. | Ingredients                                      | F1 | F2 | F3 | F4 | F5 | F6 |
|--------|--------------------------------------------------|----|----|----|----|----|----|
| 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 | 100 |
| 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 | | | |

Table 3: Standard curve for venlafaxine hydrochloride

Table 4: IR spectra data for venlafaxine hydrochloride

| Frequency Hz | Group assigned |
|--------------|----------------|
| 3325         | O-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) |
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| 888.26       | C-H deformation |
| 1600         | C=C stretching vibration |
| 1500         | C=C stretching vibration |

IR: Infrared
Table 6: Precompression studies of powder blend

| Batch code | Angle of repose ° | Bulk density (g/cm³) | Tapped density (g/cm³) | Compressibility index (%) | Hausner ratio |
|------------|-------------------|----------------------|------------------------|---------------------------|---------------|
| F1         | 28±1              | 0.52                 | 0.66                   | 21.21                     | 1.25          |
| F2         | 29±6              | 0.56                 | 0.68                   | 17.64                     | 1.21          |
| F3         | 27±9              | 0.52                 | 0.65                   | 20                        | 1.25          |
| F4         | 26±5              | 0.58                 | 0.72                   | 19.44                     | 1.24          |
| F5         | 25±7              | 0.59                 | 0.72                   | 18.05                     | 1.22          |
| F6         | 26±10             | 0.60                 | 0.72                   | 16.66                     | 1.20          |

Table 7: Post compression studies of Venlafaxine hydrochloride matrix tablet

| Batch code | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | Drug content (%) | Weight variation (mg) |
|------------|----------------|-------------------|----------------|------------------|-----------------------|
| F1         | 5.4±0.01       | 2.8±0.41          | 0.52           | 100.2            | 450±1.08              |
| F2         | 5.4±0.02       | 3.00±0.45         | 0.50           | 101.3            | 450±1.03              |
| F3         | 5.4±0.02       | 3.17±0.26         | 0.45           | 99.87            | 450±1.29              |
| F4         | 5.2±0.02       | 3.33±0.26         | 0.32           | 100.3            | 411±1.03              |
| F5         | 5.1±0.04       | 3.25±0.27         | 0.34           | 99.87            | 361±0.04              |
| F6         | 5.2±0.02       | 3.42±0.20         | 0.28           | 100.4            | 411±0.78              |

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

| Time (h) | 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  | 47.92  |
| 89.9     | 96.8   | 102.2  | 55.96  | 72.0   | 58.9   |
| 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   |        |        |        |        |
| 78.36    | 89.52  |        |        |        |        |

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 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/cm². 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 99.8–100.4%. The results are given 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=0.9631 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 K15M and K100M. 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 K15M and K100M. 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 K15M and K100M 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 EFFEOR 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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