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FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING BILAYERED TABLETS OF VENLAFAXINE HCL

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ABSTRACT

The present study was an attempt to formulate and evaluate the floating bilayered tablets of venlafaxine Hcl. Gastro retentive systems can remain in the gastric region for several hours and hence prolongs the gastric residence time of drugs. The present research work was an attempt to formulate and evaluate gastro retentive floating drug delivery system containing venlafaxine Hcl in the form of tablets using polymers like HPMC K100M, HPMC K15M, HPMC K4M and sodium bicarbonate as gas generating agent. The tablets were prepared by direct compression method. The tablets were evaluated for the pre and post compression parameters such as weight variation, thickness, friability, hardness, drug content, in vitro buoyancy studies, and in Vitro dissolution studies and results were within the limits. The in-vitro dissolution studies were carried out in a USP type-II apparatus in 0.1 N Hcl. Among all the formulations (F1 to F16) prepared, batch F12 was the best formulation which showed buoyancy lag time 6sec and the tablet remained buoyant for 12h.

KEYWORDS: Bilayered Tablets, Venlafaxine Hcl, Direct compression method, Gastric residence time, *In vitro* buoyancy studies.

INTRODUCTION

The oral route is the most promising and convenient route of drug administration. Conventional immediate release system achieves as well as maintaing the drug concentration within the therapeutic effective range, but one has to take such formulations several times a day. Gastro retentive dosage form is a novel drug delivery system which has emerged and

gathered momentum in the research to overcome the above mentioned limitations of conventional sustained release systems. [1] The main approaches that have been examined for gastric retentive dosage forms are, low density systems that cause buoyancy (Floating drug delivery system), high density which retains the dosage form in the stomach, raft forming systems, concomitant administration of drugs or excipients which slow the motility of the gastro intestinal tract, bio adhesion to gastric mucosa, swelling to a large size which prevent the passage of dosage form through the pyloric sphincter. [2] Floating dosage forms with sustained release characteristics are useful in reducing the variability in transit performance. [3, 4] Floating systems are particularly useful for acid soluble drugs that are poorly soluble or unstable in the alkaline intestinal fluids. [5] A bilayered tablet is one made up of two separate layers, with each layer intended for a specific result, layers can be formulated to separate physically or chemically incompatible ingredients or to produce repeat action or to dissolve at different times or to deliver the product to different locations or to give different pharmacological effects. [6] Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize the area of contact between two layers. An additional intermediate layer of inert material may also be included. To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. The compaction of a material involves both the compressibility and consolidation. Venlafaxine Hydrochloride is an orally active serotonin noradrenalin reuptake inhibitor used in the treatment of major depressive disorders. The successful treatment of depression depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of a drug is desired. Venlafaxine Hydrochloride is a highly water soluble drug with the biological half life of 5 hrs and 11 hrs of its active metabolite o-desmethyl venlafaxine (ODV).

MATERIALS AND METHODS

Materials

Venlafaxine hydrochloride purchased from JP Fine chemicals, Pune, India. HPMC K4M, HPMC K15M, Xanthan gum, Sodium bicarbonate, microcrystalline celluose, Potato starch purchased from S.D. Fine Chem. Ltd., Mumbai, India. HPMC K100M, Magnesium sterate purchased from Degussa India Pvt. Ltd., Mumbai. All reagents and ingredients were of analytical grade.

Methods

Direct compression method [7]

Sieving: The active ingredient Venlafaxine HCL was passed through the sieve#22 followed by the other ingredients were passed the same sieve.

Dry mixing: Polymers, MCC, talc, Magnesium stearate were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug. Then the mixed powder is compressed as a sustained release layer.

Preparation of floating bilayer tablet: The bilayer tablet was prepared by direct compression method. Development of floating bilayer tablets of Venlafaxine hydrochloride was carried out in three stages. Two layers (floating layer and sustained release layer) were formulated separately using different concentrations of polymers in different ratios. After optimization of individual layers by in-vitro studies and statistical methods bilayer tablet was prepared using optimized formulae. Bilayer tablet was prepared on the tablet compression machine. First the floating layer was precompressed on compression machine manually and the sustained release layer were loaded on top of precompressed layer and punched with 9mm punch on compression machine.

Development of Floating Bilayered Tablets

FTIR Studies: FTIR spectra of drug and drug–excipients blends were recorded on an IR spectrophotometer (Shimadzu Corporation, Japan.) in the range of 4000–5000 cm^{-1} using potassium bromide.

Bulk density [8]

It is the ratio of total mass of the powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard a sieve # 20) into a measuring cylinder and the initial volume was noted.

It is expressed in g/cc and is given by

$B.D = m/V_O$

Where, m=mass of the powder, V_O= bulk volume of the powder

Tapped density

It is the ratio of the total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for

750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$T.D = m/V_i$

Where, m= mass of the powder, Vi = tapped Volume of the powder

Hausner's Ratio

It is a measurement of frictional resistance of the drug. The Ideal range should be 1.2 –1.5, it was determined by the ratio of tapped density and bulk density.

H.R = T.D / B.D

Weight variation test [9]

20 tablets were weighed individually and collectively. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Hardness test

Hardness (diametral crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using a Monsanto hardness tester. The average of the five determinations was determined and reported.

Friability test

Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from the free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula:

$F= (W_1 – W_2)/W_1 \times 100$

Where,

W_1 = weight of the tablets before test, W_2 = weight of the tablets after test

Content Uniformity Test

For determination of drug content three tablets from each formulation were weighed Individually and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight venlafaxine hydrochloride was transferred into 100 ml volumetric flask diluted to 100ml with sufficient amount of 0.1N HCL. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 226nm against blank.

Swelling Characteristics [10]

Swelling property of the tablet was determined by placing it in the dissolution test apparatus, in 900 ml of 0.1 N HCL at 37 ± 2 0C. The weight and volume reached by the matrix tablets over time was determined by withdrawing the tablets periodically from dissolution medium. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess test liquid. The volume of the tablets was obtained by measuring the thickness and diameter, considering a right circular cylinder form. The determined weight and volume were used to calculate the tablet density over the dissolution study. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation.

WU % = Wt. of swollen tablet – Initial wt. of tablet / Initial wt. of tablet × 100

Floating lag time and the total floating time

Floating behaviour studies were performed on both the floating layer and bilayer floating tablet, carried out in a USP Dissolution Testing Apparatus II (Paddle type) at paddle speed 50 rpm in 900ml 0.1 N HCl at 37 ± 0.2 °C for 24 hrs to mimic in vivo conditions. For determining the optimized floating lag time and total floating time of the delivery system, various formulations prepared.The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken at a floating lag time, the duration of system floatation and also the relative matrix integrity was observed visually.

***In- vitro* dissolution studies [11]**

The release rate of Venlafaxine Hcl floating tablets was determined using USP Type 2 Apparatus. The dissolution test was performed using 900ml of 0.1N Hcl, at 37± 0.5˚C at 50 rpm for 12 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were

filtered through a 0.45µm membrane filter and diluted if necessary. Absorbance of these solutions was measured at 226 nm using U.V-Visible Spectrophotometer.

Stability studies [12]

The optimized matrix tablets were subjected to stability studies(as per ICH guide lines) at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH The products were evaluated for their physical characteristics, drug content, and In-vitro drug release profiles over a period of 3 months.

RESULTS AND DISCUSSION

FTIR Studies

From the FTIR data it was evident that the drug and excipients doses not have any interactions**.** Hence, they were compatible. Bulk density, Tapped density, Hausner's ratio results were shown in Table no. 1

Table.1. Evaluation Parameters of Floating bilayered tablets.

Formulation	Bulk density	Tapped density	Hausner's ratio
F1	0.43±0.02	0.55±0.02	1.21±0.23
F2	0.42±0.05	0.54±0.06	1.19±0.54
F3	0.41±0.03	0.52±0.08	1.24±0.67
F4	0.40±0.06	0.54±0.04	1.23±0.21
F5	0.41±0.08	0.52±0.07	1.19±0.35
F6	0.41±0.04	0.52±0.08	1.29±0.78
F7	0.38±0.09	0.54±0.01	1.31±0.83
F8	0.44±0.07	0.50±0.04	1.24±0.94

Tablet thickness, hardness, weight variation, friability and drug content of formulated Tablets of batches from F1 to F9are presented in Table 2.

Table.2. Evaluation Parameters of Floating bilayered tablets.

S. No	Weight variation (mg)	Thickness (mm)	Friability (%)	Hardness kg/cm^2	Content uniformity
F1	392.7±5.35	3.6±0.02	0.707±0.18	6.24±0.23	101.10±0.05
F2	393.7±5.19	3.8±0.04	0.830±0.08	6.4±0.28	98.19±0.17
F3	393.2±3.69	3.8±0.06	0.739±0.11	6±0.44	99.28±0.21
F4	393.8±3.74	3.78±0.08	0.709±0.11	6.36±0.32	97.16±0.17
F5	392.5±4.99	3.79±0.10	0.827±0.12	6.26±0.38	101.18±0.14
F6	392±5.86	3.8±0.02	0.792±0.10	6.62±0.23	97.68±0.23
F7	392.05±5.78	3.6±0.08	0.724±0.17	6.28±0.48	99.41±0.10
F8	391.1±5.19	3.7±0.06	0.689±0.14	5.96±0.54	98.19±0.17

Table 3: Percentage Cumulative drug release of formulations F-1 to F-8.

Time (hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0.30	28.56±1.2	52.79±1.6	40.24±1.1	36.19±1.6	37.99±1.5	21.77±1.9	33.09±0.9	22.76±1.1
1	30.29±0.3	55.92±0.7	43.69±0.2	39.22±1.0	40.15±1.6	26.66±1.2	36.26±0.9	25.85±1.1
2	56.22±1.2	61.25±1.9	48.92±1.7	45.99±1.1	51.59±1.3	39.16±0.9	41.85±1.0	36.82±1.6
4	67.27±0.7	67.44±1.0	54.35±0.9	52.49±0.5	55.74±1.2	52.95±0.8	47.65±1.2	60.25±0.1
5	74.32±1.6	80.72±0.9	69.99±1.4	66.72±0.7	69.92±0.1	66.13±1.1	53.18±1.6	77.15±1.5
6	81.65±1.1	84.55±0.9	82.91±1.9	77.76±1.5	79.13±1.5	70.95±1.4	68.21±1.7	82.92±0.9
12	83.35±0.6	86.91±0.2	88.92±0.9	89.02±1.0	84.92±1.1	79.63±0.5	82.32±0.9	90.65±1.1

In Vitro Buoyancy Studies

In-vitro buoyancy studies were carried out for all formulations. Based on the In-vitro buoyancy study results F8 formulation was optimized. The Results were shown in Table 4.

Table 4: Floating properties of formulations F-1 to F-8.

S. No	Formulation Code	Lag Time (min)	Floating Time (hr)	Swelling index %
1	F-1	<1	>10	92.05
2	F-2	<1	>11	94.06
3	F-3	<1	>11	94.22
4	F-4	<1	>12	97.87
5	F-5	<1	>11	95.55
6	F-6	<1	>10	92.05
7	F-7	<1	>10	93.45
8	F-8	<1	>12	98.25

Fig: 1 Floating time at 82 sec

Fig: 2 Floating lag time at 12h

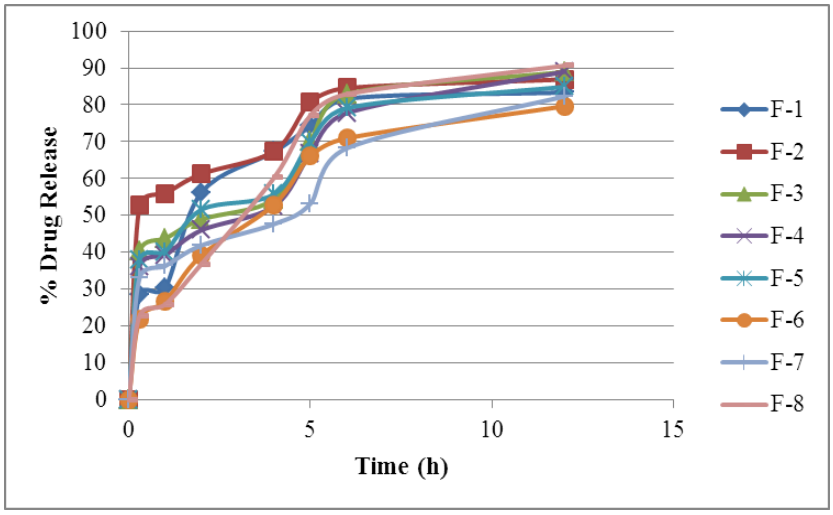

Fig: 3 Percentage Cumulative drug release graphs of formulations F-1 to F-8.

In the present study, the high viscosity grade HPMC K100M as specified by USP was used as hydrophobic matrix forming agent. It forms a strong gel in aqueous media which may be useful to control the drug release of both, water soluble as well as water insoluble drugs from formulations. The half life of venlafaxine hydrochloride is 5 hrs. So the drug release up to 10 hrs will be able to show the pharmacological action up to 12 hrs. In an attempt to prolong the drug release of drug up to 10 hrs, the release retarding agent Xanthan gum, HPMC K4M, K15M, K100M were used. HPMC K100M is a high viscosity grade polymer and results in an increased hydration rate. Consequently distance required for drug to travel from tablet to dissolution medium increases. Furthermore, crosslinking in the interpolymer chain increases with increasing viscosity of polymer grade. Formulation F-8containing HPMC K100M in different concentration shows the sustained release the drug for up to12 hrs. So, among all the formulations F-8 is considered as optimized formulation.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F8 after 3 Months, parameters like % drug release and assay values at various conditions(at 40^0C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in Table 5.

Table 5: Results of stability studies for optimized formulation F-8.

S. No	Parameters	Initial	1 month	2 month	3 month	Limts as per speciffication
1	40 ^{0}C/75% RH % Release	99.28	99.22	99.11	99.02	Not less than 85 %
2	40 ^{0}C/75% RH Assay Value	99.31	99.28	99.22	99.17	Not less than 90% Not more than 110 %

CONCLUSION

In the present study an attempt has been made to formulate floating bilayer matrix tablets of venlafaxine HCL, which can be expected to ensure patient compliance by reduction of dosing frequency, sustained release of drug, more uniform plasma levels and less dose related side effects. The floating bilayer matrix tablets were prepared by direct compression method. Floating layer precompressed on compression machine manually and on the precompressed layer sustained release layer was loaded and punched on compression machine automatically. Total 8 batches were prepared and powder blends before compressions were subjected for evaluation of flow properties. All the parameters were within the limit showing good flow properties. Data from preformulation compatibility studies suggested that there is no interaction between the excipients and the drug and the same was confirmed from IR spectroscopy.Weight variation test showed that the weights of all the formulations were within pharmacopoeial limits. Drug content in all the developed formulations was found to be uniform with sufficient hardness confirming a good mechanical strength to them. In vitro dissolution studies had shown a satisfactory drug release from all the formulations. Based on *In-vitro* drug release, F8 shows up to 12hrs and it was selected as optimized formulation.

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