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Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF VENLAFAXINE HYDROCHLORIDE

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ABSTRACT

The objective of the present investigation have developed a gastroretentive floating tablets for sustained release of venlafaxine hydrochloride by direct compression method. Various grades of low density polymers (HPMC K4M, HPMC K15M and Xanthan gum) were used for formulation of the tablets. The tablets were evaluated for thickness, weight variation, hardness, friability, drug content; *in vitro* buoyancy test, *in vitro* drug release and Fourier transform infrared (FT-IR) spectroscopy. Formulation F3 can be considered as an optimized formulation for gastroretentive floating tablet of venlafaxine HCl. The results of *in vitro* release studies showed that optimized formulation F3 could sustain drug release (98.05%) for 12 hours and remain buoyant for more than 12 hours. This formulation best fit model as matrix and it shows non-fickian type of drug release.

Keywords: Floating tablet, Venlafaxine hydrochloride, Gastroretentive, Hydroxypropylmethyl, Cellulose, Buoyancy, Xanthan gum.

INTRODUCTION

Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability[1]. The floating dosage form has been used most commonly. This technology is suitable for drugs with an a bsorption window in the stomach or in the upper part of the small in testine, drugs acting locally in the stomach[2]. The controlled gastric retention time of solid dosage forms may be achieved by the mechanism of Floatation[3], Mucoadhesion[4] sedimentation[5] Expansion[6] or by the simultaneous administration of pharmacological agents that delay gastric emptying[7]. The principle of buoyant preparation offers a simple and practical approach to achieved increased gastric residence time for the dosage form and sustained drug release. Venlafaxine is a unique antidepressant, and is referred to as a serotonin-norepinerphrine-dopamine reuptake inhibitor[8]. Venlafaxine and its active metabolite, O-desmethyl venlafaxine (ODV) inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine[9]. Hence it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants[10] .The biological half life of venlafaxine is 5 hours reading to more dosing frequency[11]. Hence, it is necessary to develop a sustained release formulation of venlafaxine HCL. Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose can be achieved with floating drug delivery system[12].

In this context, it was interested to prepare and evaluate gastroretentive tablets of venlafaxine HCl based on gel forming polymers using various grades of hydroxy propylmethyl cellulose (HPMC) and Xanthan gum which will retain the dosage form in the stomach and provide the sustained drug release.

MATERIALS AND METHODS

Venlafaxine HCL was used as a model drug obtained as gift sample from Lupin Pharmaceuticals, Pune. HPMC K4M, HPMC K15M and HPMC K 100M were obtained from Yarrow chem Products, Mumbai.

Preparations of Venlafaxine HCl floating tablets

Tablets were made by direct compression. Venlafaxine HCL was mixed with the required quantities of polymers HPMC K4M, HPMC K15M, Xanthan gum, sodium bicarbonate and citric acid by geometric mixing. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. Finally the mixture was compressed on a rotary tablet machine (Cemac, Ahmadabad) using 8-mm standard flat-face punches to get 250 mg weights of tablets. Composition of all formulation is given in Table 1.

Table 1: Formulation composition of floating tablets of venlafaxine

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
HPMC K4M	37.5	75	112.5	-	-	-	-	-	-
HPMC K15M	-	-	-	37.5	75	112.5	-	-	-
Xanthan gum	-	-	-	-	-	-	37.5	75	112.5
Sodium bi carbonate	70	70	70	70	70	70	70	70	70
Citric acid	10	10	10	10	10	10	10	10	10
MCC	90	52.5	15	90	52.5	15	90	52.5	15
Mg.Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of Tablets

Evaluation of powder blend

The powder blend of all formulations was evaluated for Bulk density[13], Tapped density[13], Compressibility index[14], Hausner ratio[15] and Angle of repose[16].

Evaluation of tablet properties

The prepared tablets were tested for Weight variation, Hardness (Monsanto hardness tester), Thickness (Vernier caliper), Friability (Roche friabilator) and drug content.

Floating property

The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called total floating time[17].

In vitro Drug Release Study

The release rate of Venlafaxine HCl floating tablets was determined using USP Type 2 Apparatus. The dissolution test was performed in triplicate, 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 were measured at 224 nm using U.V-Visible Spectrophotometer.

Mechanism 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.

FT-IR spectroscopy Study:

The infrared spectrum of Venlafaxine HCl pure drug and the physical mixture of optimized formulation were recorded in-between 400 to 4000 cm^{-1} on FT-IR. The IR spectra for the test samples were obtained using KBr disc method using an FT-IR spectrometer.

RESULTS AND DISCUSSION

Gastroretentive tablets of venlafaxine HCl were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 24 hours. The tablets were made using different gel forming polymers such as HPMC K4M, HPMC K15M and Xanthan gum to optimize the drug content, *In vitro* buoyancy and *In vitro* drug dissolution studies. The selection of viscosity grade of a polymer is an important consideration in the formulation of [18].

Different grade of viscosity of HPMC K4M, HPMC K15M and Xanthan gum polymers is known to be beneficial in improving floating property and release characteristics[19]. Sodium bicarbonate and citric acid was used as a gas generating agent. Methyl carboxy cellulose (MCC), Magnesium stearate and Talc were employed for their Disintegration, lubricant and glidant property respectively. The powder blend of nine formulations (F1&F2) was evaluated for angle of repose, bulk density, tapped density, carr's index, and hausner ratio showed the pre-compressed blend has good flow property (Table 2).

Results of physical characterization are shown in Table 3.

The hardness of tablets ranged from 3.75 ± 0.18 to 4.55 ± 0.54kg/cm^2. The thickness of the tablets was in between 3.186 ± 0.36 to 249.33 ± 4.45 mg indicating consistency in each batch. The friability was found to be 0.18 to 0.27%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content was found to be 97.23% to 99.54% with low deviation indicating batch to batch consistency. (Table 3)

In vitro buoyancy studies in pH 1.2, revealed good buoyancy for all the formulations (Table 4).

Table 2: Flow properties of powder blend

Formulation	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hauser Ratio
F1	28.13	0.486	0.614	18.12	0.154
F2	25.45	0.468	0.623	19.43	0.142
F3	28.67	0.431	0.591	22.10	0.065
F4	30.89	0.463	0.591	24.67	0.110
F5	24.34	0.521	0.632	17.32	0.146
F6	23.13	0.541	0.642	18.45	0.098
F7	31.23	0.437	0.623	28.78	0.012
F8	25.41	0.483	0.587	26.53	0.088
F9	24.58	0.510	0.610	21.32	0.112

Table 3: Physical evaluation parameters and drug content

Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Weight Variation (mg)	Friability (%)	Drug Content (%)
F1	4.5±0.24	3.384±0.4	248.60 ±5.12	0.1	97.23
F2	3.75±0.18	3.276±0.6	249.33±4.45	0.27	99.12
F3	4.45±0.37	3.186±0.3	245.80±4.63	0.19	98.32
F4	3.80±0.26	3.186±0.4	246.09±2.43	0.22	99.54
F5	4.55±0.54	3.234±0.6	248.05±4.51	0.18	99.43.
F6	4.40±0.35	3.45±0.06	245.37±3.89	0.21	98.67
F7	4.50±0.50	3.50±0.07	247.50±4.39	0.1	98.12
F8	4.20±0.25	3.28±0.02	248.25±2.68	0.19	99.48
F9	4.45±0.25	3.50±0.04	248.25±3.47	0.24	98.25

Table 4: Buoyancy of Venlafaxine HCl tablets

Formulation code	Lag time (sec)	Total floating time (h)
F1	26	>12
F2	20	>12
F3	30	>12
F4	36	>12
F5	28	>12
F6	39	>12
F7	37	>12
F8	34	>12
F9	38	>12

Citric acid and sodium bicarbonate combination was used as the effervescent base. Upon contact with the acidic medium, the fluid permeated into the tablet, causing neutralization reaction to occur, which generates carbon dioxide (CO_2). The swelling polymer traps the CO_2 so generated and thus provides continued buoyancy. Preliminary studies were done to estimate the ideal amount of the effervescent base needed to obtain short floating lag time together with prolonged buoyancy. This revealed that citric acid and sodium

bicarbonate in the amount 10 mg and 70 mg were optimum for the desired formulation to provide good buoyancy with floating lag time less than a minute. All the tablets floated in the buffer solution for more than 12 h. The gas generating base decreases the lag time by accelerating the hydration of the swelling polymer, thus allowing a higher floating duration because of constant generation and subsequent trapping of CO_2. Citric acid was used to accelerate the CO_2 generation; also it permits the generation of CO_2 even if the gastric pH is abnormally high[20].

In vitro dissolution studies of all the formulation of gastroretentive tablets of venlafaxine HCl were carried out in 0.1N HCl. The study was performed for 12 hours and cumulative drug release calculated at every 1hour. (Table 5 and fig.1, 2, and 3).

Table 5: Drug Release profile of Tablets

Sampling time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	42.21±1.4	32.46±2.5	23.12±1.5	30.94±3.2	25.75±1.7	21.19±2.3	23.28±2.4	17.16±2.1	12.65±2.1
2	54.42±2.2	37.7±1.4	31.84±1.9	38.98±3.1	31.08±1.5	31.44±2.1	32.27±1.4	21.24±2.6	14.38±2.3
3	65.36±2.1	45.24±1.4	42.16±1.9	52.6±2.9	37.05±1.6	41.02±2.4	42.73±2.8	23.68±2.4	19.27±21
4	71.52±2.2	54.96±1.2	49.52±2.3	55.68±2.7	41.46±1.8	51.11±2.6	48.40±1.2	20.68±2.1	23.61±2.2
5	77.82±1.4	58.57±1.4	54.65±1.6	63.01±3.1	46.65±1.8	56.65±2.3	52.38±2.6	31.17±2.3	27.86±2.3
6	84.23±2.2	64.3±1.7	63.52±1.6	72.85±2.8	51.67±1.7	63.91±2.4	58.09±2.2	35.75±2.1	30.23±2.1
7	93.5±1.8	79.89±1.2	70.21±2.2	75.93±3.2	54.70±1.4	73.84±2.1	64.45±2.1	45.99±2.3	32.36±2.3
8	98.23±2.5	85.24±1.4	77.65±2.2	88.41±3.1	59.12±1.5	79.56±2.5	69.26±2.4	53.96±2.2	37.24±2.2
9		88.86±1.9	85.23±1.4	93.72±3.4	68.59±1.6	80.81±2.3	71.32±2.5	59.40±2.3	42.92±2.3
10		91.06±1.4	90.88±2.1	99.96±2.8	79.52±1.8	81.27±2.4	73.93±1.5	61.76±1.9	47.33±2.4
11		99.12±1.8	95.03±1.4		88.48±1.7	85.39±2.3	76.54±2.2	66.25±2.1	53.01±2.1
12			98.05±1.5		94.93±1.6	90.91±2.1	81.47±2.4	70.98±2.3	58.53±2.3

Data represents mean ± SD (n=3)

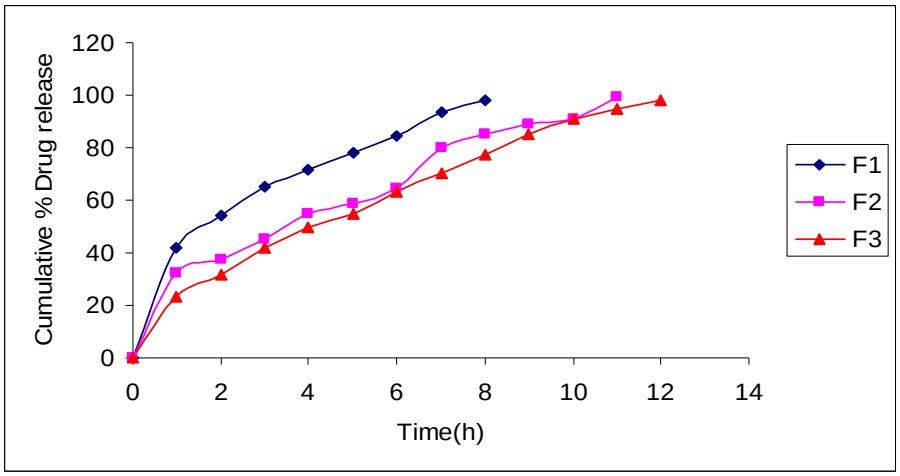

Fig. 1: Cumulative % drug release of HPMC K4M Vs Time

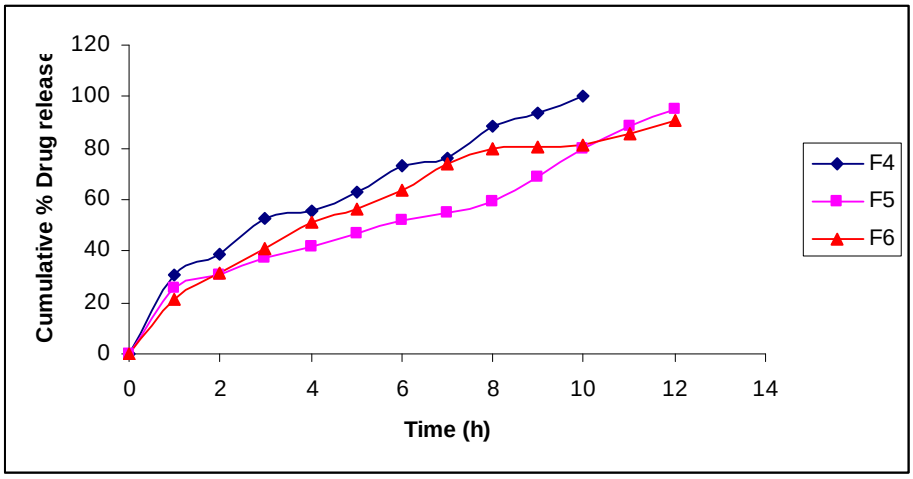

Fig. 2: Cumulative % drug release of HPMC K15M Vs Time

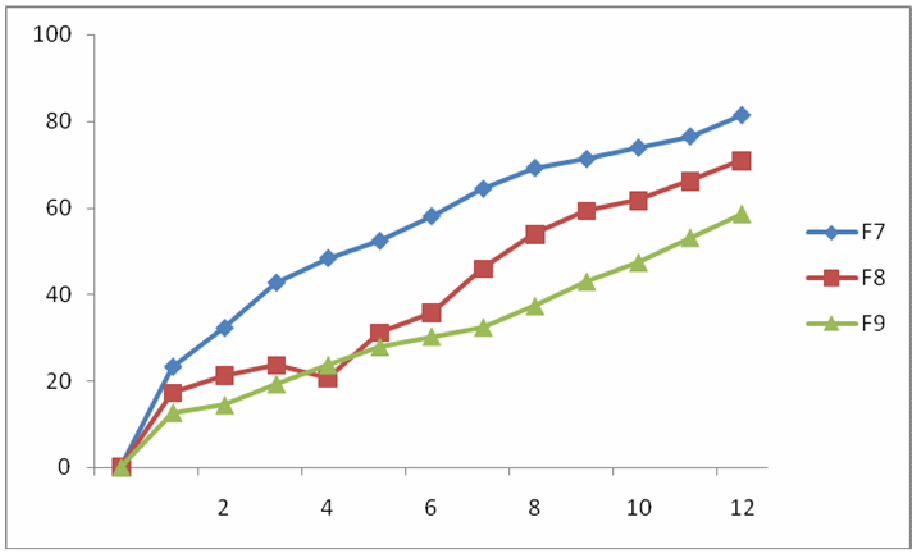

Fig. 3: Cumulative % drug release of Xanthan gum Vs Time

Among the formulations F1, F2and F3 prepared with HPMC K4M, formulation F3 was found to be 98.05 ± 1.5 in 12hours, formulations F1&F2 unable to sustain the drug release for desired period of time, and this may be due to different polymer concentration in all the three formulations. All these three formulations floated for 12hours. Formulation F1and F2 failed to show desired drug release profile. Formulation F3showed the desired drug release profile and floated with a lag time of 30 sec, for this reason it was considered as best formulation among all the three formulations (Fig. 1). On the other hand formulations F4, F5and F5 prepared with HPMC K15M showed drug release from formulations F5andF6 was 94.93 ± 1.6 and 90.91±2.1 in 12 hours respectively. Formulation F4 was unable to sustain the drug release within the desired period of time. Moreover formulations F5 and F6 failed to meet the desired drug release profile (Fig 2).Further formulations F7, F8 and F9 prepared with xanthan gum showed drug release of 81.47 ± 2.4, 70.98 ± 2.3 and 58.53 ± 2.3 respectively. This result reflects that xanthan gum has more drug release retarding property than that of HPMC. During dissolution of tablet containing xanthan gum instantly form viscous gel layer that slow down in sweep of dissolution fluid towards the core of tablet. The strong viscous gel layer and very slow rate of erosion make xanthan gum more release retarding as compared to HPMC

The n values of Korsmeyer-Peppas model of the best formulations are in between 0.55-0.85. Therefore the most probable mechanism that the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion.

Table 6: Release kinetics of optimized formulations

S. No.	Formulation	Zero order	First order	Higuchi	Korsmeyer & Peppas	Peppas(n)
1	F3	0.9668	0.9850	0.9887	0.9943	0.585

FT-IR spectra of the Venlafaxine HCl and drug with HPMC K4M revealed that there is no shifting of the peaks indicating the compatibility of the HPMC K4M polymer with the drug (figure 4a, 4b).

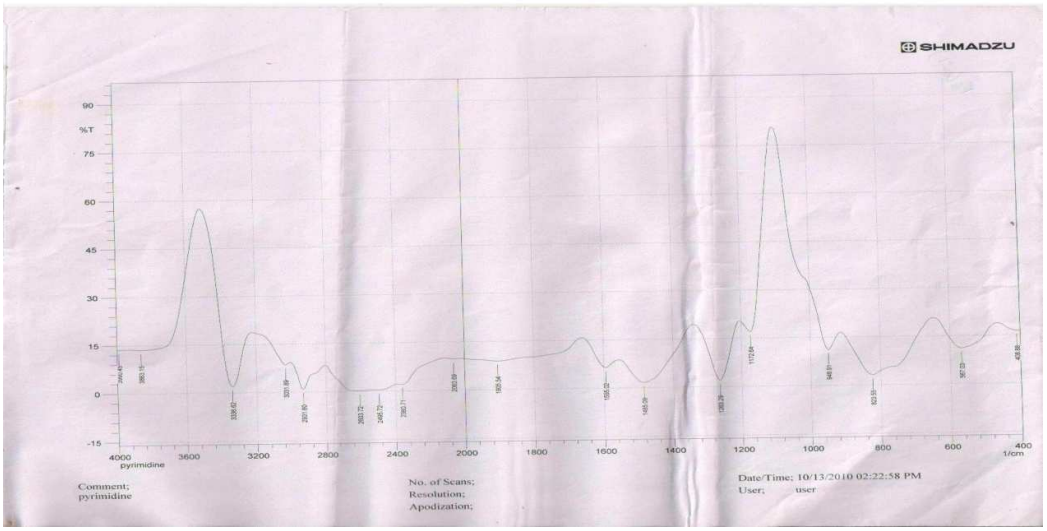

Fig. 4.a: The FTIR spectra of pure drug

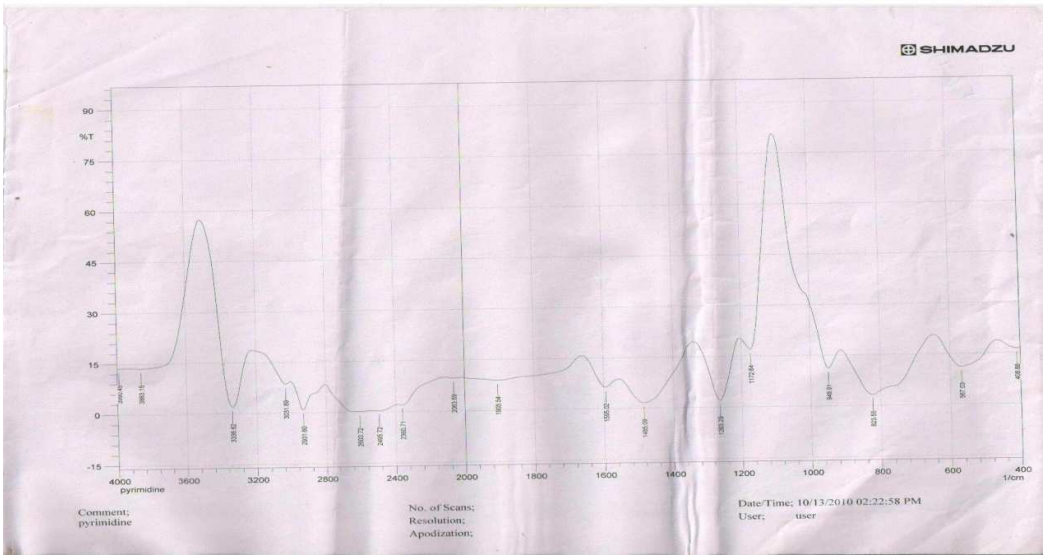

Fig. 4.b: The FTIR spectra of Physical mixture of optimized formulation

CONCLUSION

Floating tablet of venlafaxine HCl was formulated as an approach to increase gastric residence time and there by improve its bioavailability. Formulation F3 showed better controlled drug release in comparison to the other formulations, the extent of drug release was found to be 98.05% at the desired time 12 hrs.The drug release pattern of formulation F3 was best fitted to Korsmeyer-Peppas model and first order kinetics.Further the results reflect that release of drug from the tablets by non-fickian diffusion or anomalous diffusion. Drug- excipients interaction of formulations F3 was carried out by using FT-I spectroscopy in this analysis drug-excipients interactions was not observed. Hence it was concluded that formulation F3 can be taken as an ideal or optimized formulation of gastroretentive tablets for 12 hours as it fulfils all the requirements for extended release tablet.

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