INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF VENLAFAXINE HCl

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Article Received on: 09/10/12 Revised on: 01/11/12 Approved for publication: 02/12/12

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ABSTRACT

The purpose of the present investigation is to formulate gastroretentive floating tablets of Venlafaxine hydrochloride thus increasing its gastric residence time as well as bioavailability and therapeutic efficacy. Venlafaxine HCl having a short biological half-life of 4h is eliminated quickly from the body leading to low therapeutic efficacy. Therefore a sustained release medication was advantageous so as to achieve the prolonged therapeutic effect and to reduce peak and valley effect in plasma concentration. This can be circumvented by formulating modified gastro retentive sustained release dosage forms which resides in the stomach for sufficient time to release the drug in vicinity of the absorption zone. Nine formulations of Venlafaxine HCl tablets were formulated by hot melt extrusion technique (HME) using three polymers like HPMC K15M, Xanthan gum and Guar gum in a various concentrations. Bees wax was used as a melting aid and sodium bicarbonate was used as a gas generating agent. The prepared tablets were evaluated for pre and post compression parameters, buoyancy time, floating lag time and *in vitro* dissolution study. *In vitro* dissolution study was carried out in pH 1.2 buffer. It had been found that increase in polymer concentration diminishes drug release profile. The *in vitro* cumulative % drug release of nine formulations ranged from 88.58 – 99.19 with more than 12h buoyancy. The in vitro drug release of optimised formulation followed Higuchi kinetics and the drug release mechanism was found to be non- fickian type.

KEYWORDS: Venlafaxine hydrochloride, hot melt extrusion, Gastroretentive drug release.

INTRODUCTION

Oral controlled drug delivery systems helps to achieve stable therapeutic plasma drug concentrations in contrary to the conventional formulations. These dosage forms show better patient compliance and predictable drug release profiles. However these were not designed to counter the problems associated with physiological conditions of the body such as gastric emptying which significantly affects the bioavailability and in turn the therapeutic efficacy of the dosage form[1]. Thus gastroretentive dosage forms such as hydrodynamically balanced systems, altered density systems, mucoadhesives were formulated which concentrates the dosage form in GIT, release the drug in absorption zone and prolong the gastric residence time by counteracting gastric emptying process. This channels the complete controlled release of the drug in absorption zone before elimination of the dosage form from the body thus improving the bioavailability of the drug[2-5]. Venlafaxine HCl is a serotonin and nor adrenaline reuptake inhibitor (SNRI).It doesn't interact with adrenergic, cholinergic, histaminic receptors thus having no sedative action, fast onset of action, safer in overdose, no usual side effects. It has a half life of 4 hours thus necessitating multiple administration of the dosage form[6-8]. The present objective of the study is to formulate gastroretentive floating tablets of Venlafaxine HCL by hot melt extrusion technique thus increasing its absorption, bioavailability, reducing the frequency of dosing and evaluation of physico-chemical parameters of floating tablets.

MATERIALS AND METHODS

Venlafaxine hydrochloride was obtained from Lupin pharmaceuticals, Xanthan and guar gum were obtained from Himedia laboratories; HPMC K15M was obtained from spectrum pharma; beeswax was obtained from ambrosia natural products; MCC, Magnesium stearate and Talc were obtained from S.D. Fine chemicals; sodium bicarbonate was obtained from Nice laboratories. The remaining reagents used were of analytical grade.

Preparation of Venlafaxine Hydrochloride Floating Tablets[9-11]

Tablets were prepared by Hot Melt Extrusion (HME) method. It is the process of embedding drug in a polymeric carrier. Specifically, HME dosage forms are complex mixtures of API, functional excipients, and processing aids, which are blended uniformly. The calculated amount of bees wax was melted in a china dish. To this, geometrical mixture blend of polymers, diluents was added followed by the active pharmaceutical ingredient. Mix it well before solidification and later the mass was removed from hot plate by scrapping until it attains room temperature and the coherent mass passed through sieve no 36 to form granules. The formed granules were then made to pass through sieve no 100 to remove any fines. The formed granules are then mixed with calculated amount of glidant and lubricants for the processing operations and the granules then are tabletted using rotary tablet punching machine (cadmach) to obtain 300 mg tablets. Composition of all formulations was given in (Table 1).

Drug: Polymer Interaction Study:

The drug-excipient interaction study was carried out using Fourier transform infrared spectroscopy (FT-IR) by KBr pellet method. To study the compatibility of various formulation excipients with Venlafaxine HCl, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and punched into small discs after mixing with anhydrous KBr. These discs were placed in the sample chamber for analysis.

Evaluation Parameters[12-15]

Pre Compression Parameters

Angle of repose (θ):

It is the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height of pile, r = radius of the base of the pile.

Bulk density (D_b):

It is the ratio of mass of the powder taken to its bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

Where, D_b = Bulk density (gm/cc), M =Mass of powder (g), V_o = Bulk volume of powder (cc)

Tapped density (D_t):

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

Where, D_t = Tapped density (gm/cc), M = Mass of powder (g), V_t = Tapped volume of powder (cc)

Compressibility Index:

An indirect method of measuring powder flow from bulk densities was developed by carr. The percentage compressibility of powder was a direct measurement of the potential powder arch or the bridge strength and stability. Carr's index of each formulation was calculated according to equation given below :

$$\% \text{ compressibility} = \frac{D_f - D_o}{D_f} \times 100$$

Where, D_t = Tapped density, D_o = Bulk density

Post Compression Parameters:

Thickness:

Control of physical dimension of the tablet such as thickness is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier callipers. It is measured in mm.

Hardness:

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.Three tablets were randomly picked and hardness of the tablets was determined.

Friability:

Tablet strength was tested by using Roche Friabilator. 20 tablets were weighed and placed in the friabilator and operated for 100 revolutions (25 rpm for 4min), taken out and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was then calculated by,

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{intial})} \times 100$$

Weight variation:

Ten tablets were selected randomly from each batch were weighed individually and together in a single pan balance. The average weight was noted. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} \times 100$$

Where, PD = Percentage deviation, W_{avg} = Average weight of tablet, $W_{initial}$ = individual weight of tablet

Uniformity of drug content:

The drug content was performed to check the dose uniformity in the formulation. Randomly ten tablets were weighed and powered. A quantity equivalent to 100mg of Venlafaxine HCl was added in to a 100ml volumetric flask and dissolved in 0.1N HCl, shaken for 10 minutes and made up to the volume with 0.1N HCl. After suitable dilutions the drug content was determined by UV spectrophotometer (Elico Ltd. SL 159) at 224nm against blank.

Swelling Index:

Measurement of swelling rate of the floating matrix tablet was carried to gain insight the observed phenomenon of drug release with the rates of polymer hydration. Swelling index of the dosage form is conducted by using USP dissolution apparatus-II(LABINDIA DS 8000) in 900 ml of 0.1N HCl which is maintained at 37±0.5°C, rotated at 50 rpm. At selected regular intervals, the tablet was withdrawn and the excess water was blotted with tissue paper and the swelling index was calculated using following formula.

$$\% \text{ Swelling Index} = \{(W_t) - (Wo)/ (Wo)\} \times 100$$

Where, Wt = weight of the swollen tablet, Wo = initial weight of the tablet.

Buoyancy studies:

The *in-vitro* floating behavior (buoyancy) of the tablets was determined by floating lag time. The tablets were placed in 100 ml beaker containing 0.1 N HCl (pH 1.2). The floating lag time (time taken by the tablet to reach the surface) and total floating time (floating duration of the tablet) were determined.

In vitro Drug Release Study:

The release rate of Venlafaxine HCl floating tablets was determined using USP Type II Apparatus (paddle type). 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 were measured at 224 nm using U.V-Visible Spectrophotometer.

Mechanism of Drug Release[16-17]:

To analyse the drug release mechanism and rate of kinetics, the information obtained from dissolution studies were fitted in to zero order, first order, Higuchi, Hixson-Crowell and Korsemeyer peppa's release model.

Table 1: Formulation composition of floating tablets of venlafaxine

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	75	75	75	75	75	75	75	75	75
Guar gum	45	75	90	_	_	_	_	_	_
Xanthan gum	_	_	_	45	75	90	_	_	_
HPMC K15M	_	_	_	_	_	_	45	75	90
Bees wax	45	45	45	45	45	45	45	45	45
MCC	75	55	30	75	55	30	75	55	30
Sodium bicarbonate	45	45	45	45	45	45	45	45	45
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10

Total weight: 300mg

Table 2: Flow properties of powder blends

Formulation	Angle of repose	Bulk Density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)
F1	28 .1	0.372	0.452	17.699
F2	29. 3	0.381	0.472	19.279
F3	30. 1	0.386	0.469	17.697
F4	30 .2	0.368	0.457	19.474
F5	32. 7	0.372	0.465	20
F6	33. 3	0.389	0.472	17.584
F7	28 .1	0.372	0.459	18.954
F8	28 .5	0.361	0.451	19.955
F9	29. 2	0.364	0.458	20.524

Table 3: Physical evaluation parameters and drug content

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average weight variation(mg)	Drug content
F1	3.36	5.32	0.64	301.2	98.25
F2	3.48	5.60	0.57	300.7	97.45
F3	3.32	5.42	0.52	301.5	98.26
F4	3.46	5.44	0.53	300.2	98.35
F5	3.37	5.83	0.44	299.8	97.79
F6	3.35	5.91	0.45	301.3	99.35
F7	3.49	5.40	0.51	299.2	98.35
F8	3.46	5.55	0.53	298.7	98.45
F9	3.36	5.64	0.51	301.4	97.95

Table 4: Buoyancy of venlafaxine HCL Tablets

Formulation code	Floating lag time (sec)	Floating duration (hrs)
F1	29	>12
F2	33	>12
F3	38	>12
F4	29	>12
F5	36	>12
F6	34	>12
F7	26	>12
F8	24	>12
F9	32	>12

Table 5: Degree of swelling

Time (hrs)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	38.8	41.3	43.2	34.7	38.3	41.5	15.8	18.8	24.2
2	70.2	72.36	75.88	69.2	73.5	72.15	33.2	37.9	35.9
4	107.7	109.7	115.45	106.7	108.7	112.5	57.4	68.2	70.5
6	134.7	141.1	148.5	128.7	135.8	141.4	87.9	99.7	115.9
8	159.1	162.2	166.4	158.8	163.7	164.6	109.7	110.5	125.6
10	168.6	172.4	178.8	164.3	168.5	172.4	119.5	124.1	136.8
12	176.3	178.5	184.3	171.4	174.3	181.4	128.3	132.9	138.1

Table 6: *In vitro* dissolution studies: Cumulative percent drug release of formulations

Time (hrs)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	22.76	20.76	18.92	21.84	27.53	26.92	26.46154	28.92308	26.15385
2	32.12	31.19	28.87	32.89	41.9	34.30	41.07009	39.85299	35.22222
3	42.15	40.74	37.95	43.84	50.84	42.95	49.91282	48.3812	41.72479
4	53.61	51.74	48.93	51.62	57.12	49.03	57.57265	55.57094	50.57009
5	59.13	57.41	55.66	59.29	63.74	55.76	64.96581	62.95299	58.54017
6	65.61	62.49	60.58	68.23	65.6	62.53	71.16752	68.22051	63.93761
7	74.89	71.91	70.30	71.83	70.60	68.26	78.01709	75.05385	67.97863
8	80.84	77.07	75.14	77.60	75.76	72.78	83.3641	79.30769	72.8094
9	85.28	81.49	79.55	83.72	79.24	78.41	88.58462	85.8906	79.04957
10	89.12	85.01	83.36	88.17	83.05	82.83	93.98547	88.81538	83.78376
11	92.53	87.62	85.66	91.72	89.81	87.43	99.10598	95.29231	89.00342
12	94.25	90.55	88.58	94.21	93.98	91.59		99.18718	93.17265

Table 7: Release kinetics of optimized formulation

S.No	Formulation	Zero order	First order	Higuchi	Korsemeyer-peppa's		Hixon Crowell
					R^2	*n* value	
1	F8	0.929	0.821	0.999	0.998	0.499	0.957

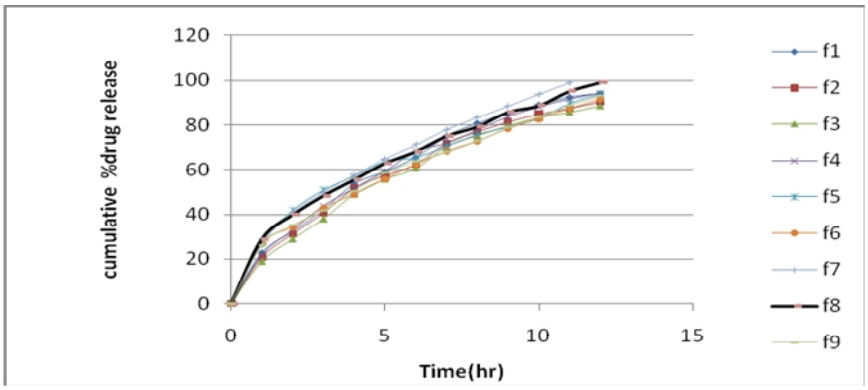

Figure 1: Cumulative drug release of formulations F1-F9

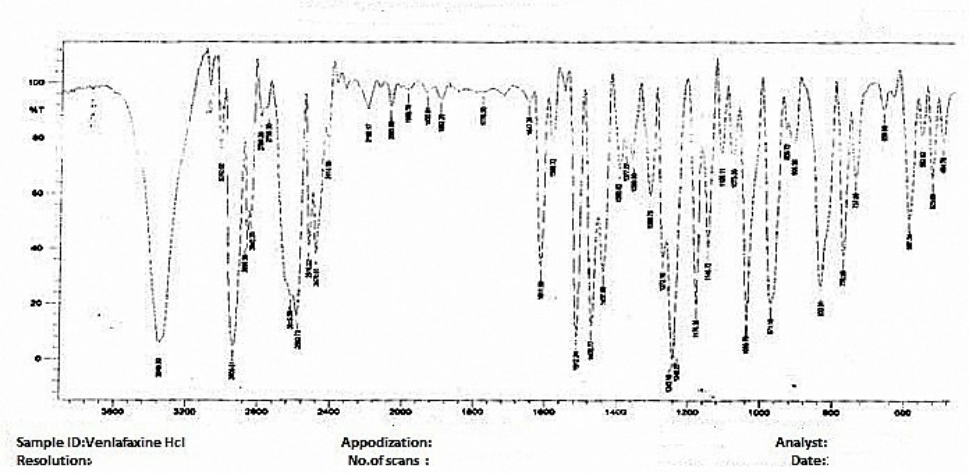

Figure: 2a

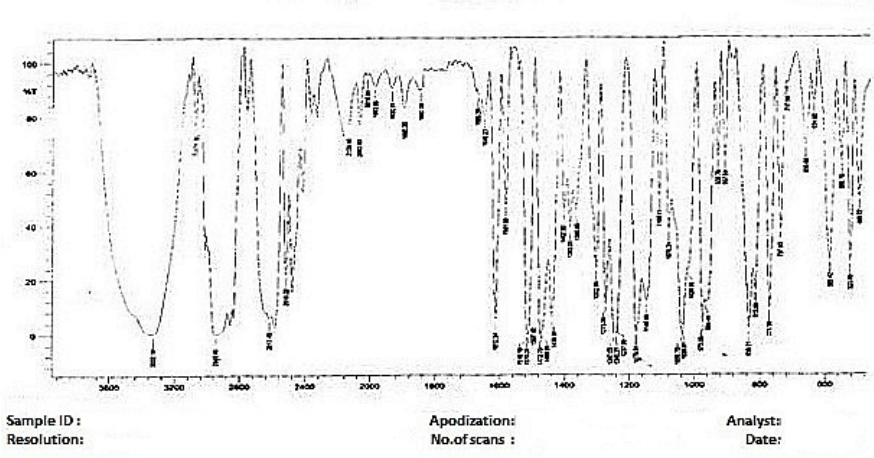

Figure: 2b

Figure 2a & 2b: FTIR spectra of pure drug and physical mixture of optimised formulation (F8)

RESULTS AND DISCUSSION:

The powder blends of nine formulations (F1-F9) were evaluated for various physical properties such as tapped density, bulk density, angle of repose and compressibility index. The results indicated good packing and flowing properties of the blend and were tabulated in (Table 2) .the angle of repose values ranged from good (F1, F2, F7, F8, F9) to passable (F3, F4, F5, F6) while the Carr's index values ranged from good to fair as per the IP specifications indicating good flow and packing properties of the powder blend.

The tablets manufactured by melt granulation technique were then evaluated for post compression parameters such as hardness, thickness, friability, weight variation, uniformity of drug content in conformity with the standard procedures and the results obtained were within the limits and are tabulated in (Table 3)

Hardness of the tablets ranged from 5-6kg/cm^2 indicating good integrity of the tablets and the friability of all formulations were in the permissible range of less than 1%.all formulations were within permissible limits of weight variation (7.5%P.D for tablets ranging from 130-324 mg

according to U.S.P). Drug content uniformity in all formulations was calculated and the presence of active ingredient ranged from 97-99%.

In -vitro buoyancy studies were performed in 1.2 pH 0.1N HCl and all formulations exhibited floating time more than 12 hours and floating lag time ranging from 24sec-39 sec and are tabulated in (Table 4) . The base involved in the formulation up on exposing to gastric juice undergoes neutralization reaction leading to formation of co_2 gas, which gets entrapped within the swelling polymer thus providing buoyancy to the systems. The released co_2 also assist in the hydration of the polymer thus decreasing the lag time. The bees wax incorporated in the formulation also aid as floating enhancer giving the required buoyancy to the system. The formulations are evaluated for degree of swelling and results were tabulated in (Table 5) and it was found that natural polymers exhibited greater degree of swelling compared to synthetic polymers.

In vitro dissolution studies were performed in 0.1N HCL (1.2 pH) and results are tabulated in (Table 6) and graphs were depicted in (Figure 1). Formulations F1,F2,F3 F4,F5,F6 showed drug release of 94.25,90.55,88.58,94.21,93.98 and 91.59% respectively at the end of 12 hours. This was accountable to higher degree of swelling of natural polymers and increase in the diffusion path length of formulations for drug release.

Formulation F7 was unable to sustain the drug release for 12 hrs and shown 99.10% of drug release at the end of 11 hrs. However, formulation F8 and F9 showed drug release of 99.18 and 93.17 % respectively at the end of 12 hours. F8 showed the desired drug release profile for 12 hours with better lag time of 24 sec. Thus it was selected as an optimised formulation. An increase in polymer concentration causes increase in viscosity of the gel as well as the gel layer with longer diffusion path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate.

The *in-vitro* drug release data of the floating tablets were evaluated kinetically by zero order kinetics, first order kinetics, Higuchi model, Hixson-Crowell and korsmeyer Peppa's models. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, Hixon-crowell and Peppa's models for optimized formulation F8 was found to be0.929,0.821,0.999,0.957 and 0.998 respectively and they were tabulated in (Table7). The optimized formulation F8 followed Higuchi's kinetics, since the regression coefficient is 0.999 also plots were found to be linear, which indicates that the drug release depended on the square root of the time and predominantly controlled by diffusion process. The mechanism of drug release was predicted using Korsmeyer–Peppa's equation. The n value of optimized formulation F8 is 0.49 respectively and is between "0.45 to 0.85". This indicates that the drug release depends on swelling, diffusion, and erosion. All formulations follow the non-Fickian/anomalous type of diffusion.

FT-IR spectra of the Venlafaxine HCl and drug with HPMC K15M revealed that there is no shifting of the peaks indicating the compatibility of the polymer with the drug (figure 2a&2b)

CONCLUSION:

This study discusses the preparation of gastroretentive tablets of Venlafaxine Hcl. The effervescent-based floating drug delivery was a promising approach to achieve *in-vitro* buoyancy. The addition of gel-forming polymer HPMC K15M, natural polymers and gas-generating agent sodium bicarbonate was essential to achieve *in-vitro* buoyancy. Formulation F8 showed desired drug release profile over 12 hrs following Higuchi release kinetics and all formulations followed non-fickian diffusion.

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Source of support: Nil, Conflict of interest: None Declared