Available online at www.pharmaresearchlibrary.com/ijctpr **ISSN: 2321-3760**
Research Article

International Journal of Current Trends in Pharmaceutical Research
IJCTPR, 2013: Vol. 1(4): 247-252
www.pharmaresearchlibrary.com/ijctpr

Formulation and Evaluation of Controlled Release Floating Tablets of Venlafaxine HCl Using Almond Gum

Y. Sravani*[1], S. Md. Shahidullah[1], Ch. Sri Vidya[1], C. Swomya[2]
[1]Department of Pharmaceutics, Dr. Samuel George Institute of Pharmaceutical Sciences, Markapur, Prakasam, A. P. India.
[2]Department of Pharmaceutics, RIPER, Anantapur, A. P. India
Available Online **7 November 2013**

Abstract: The purpose of this research was to prepare a floating drug delivery system of an anti depressant agent, Venlafaxine which is a unique antidepressant, and is referred to as a serotonin-norepinerphrine-dopamine reuptake inhibitor. Eight (F1-F8) various formulations of venlafaxine HCl and Almond gum floating tablets each containing 75 mg of drug were prepared by wet granulation method. Preformulation studies were done by FTIR and DSC and found to be no interaction between the API and excipients. Accurately weighed active ingredient and other excipients were passed through ASTM (American Society for Testing and Materials) mesh no. #80 and mixed thoroughly. The powder blend was granulated using the mixture of PVP and IPA mixture as a granulating fluid. After achieving required cohesiveness the mass was passed through sieve no.#30 to collect wet granules. The granules obtained were dried at 60^{o}c for 2 hrs and kept them in a desiccator for 24 hrs at room temperature. The granules were lubricated with talc (2% w/w) and magnesium stearate (2% w/w) and compressed into tablets using 9 mm round, flat and plain punches on pilot scale tablet compressing machine (MODEL MINI PRESS II MT). Lactose USP was used as a filler in the formulations. The tablets were evaluated for thickness, weight variation, hardness, friability, drug content; in vitro buoyancy test, in vitro drug release. Formulation F5 can be considered as an optimized formulation for gastro retentive floating tablet of venlafaxine HCl. The results of in vitro release studies showed that optimized formulation F5 could sustain drug release (99.70 %) for 12 hours and remain buoyant for more than 12 hours. Natural polymer shows better sustained release properties than synthetic polymer. The developed floating tablets of Venlafaxine HCL may be used in clinic for prolonged drug release for at least 12h in sustained release gastro retentive floating drug delivery system.
Key words: venlafaxine HCl, Almond gum, anti-depressant agent, gastro retentive floating tablet.

Introduction

Oral administration is the most versatile convenient and commonly employed route of drug delivery for systemic action. Floating drug delivery systems were first described by Davis in 1968. Floating drug delivery systems are used to prolong the gastric residence time of dosage form [1]. Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability [2]. The gas generating system consists of hydrophilic matrices prepared with the swellable hydrocolloids like hydroxyl propyl methylcellulose, hydroxyl propyl cellulose, chitosan. 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]. Venlafaxine is a unique antidepressant, and is referred to as a serotonin nor-epinephrine 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].

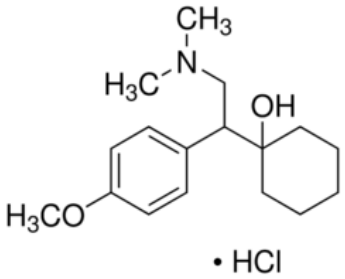

Fig. Chemical structure of Venlafaxine HCl

In this context, it was interested to prepare and evaluate gastro retentive tablets of venlafaxine HCl by using almond gum and gas generating agents thus increasing its absorption, bioavailability, reducing the frequency of dosing and evaluation of physic-chemical parameters of floating tablets.

Materials and Methods

Venlafaxine HCL was used as a model drug obtained as gift sample from Dr. Reddy's Laboratories, Hyderabad. Almond gum was purchased from the local market of Anantapur. Sodium bicarbonate, citric acid, Lactose, Talc and Magnesium stearate were procured from Loba Chem, Mumbai. Distilled water was produced in-house. Bruker's IR spectrometer, Dissolution apparatus (8 baskets) of Electrolab TDT-08L, India, UV-Visible spectrophotometer made of UV schimadzu, India and DSC of Mettler Toledo 822E was used in the research work.

Preparation of venlafaxine HCl floating tablets using wet granulation technique:

Venlafaxine HCl floating tablets each containing 75 mg of drug were prepared by wet granulation method. The composition of prepared formulation was shown in table 1. Accurately weighed active ingredient and other excipients were passed through ASTM (American Society For Testing And Materials) mesh no.#80 and mixed thoroughly. The powder blend was granulated using the mixture of PVP and IPA mixture as a granulating fluid. After achieving required cohesiveness the mass was passed through sieve no.#30 to collect wet granules. Obtained granules were dried at 60^{o}c for 2 hrs and kept them in a desiccator for 24 hrs at room temperature. The granules were lubricated with talc (2% w/w) and magnesium stearate (2% w/w) and compressed into tablets using 9 mm round, flat and plain punches on pilot scale tablet compressing machine (MODEL MINI PRESS II MT). Lactose USP was used as a filler in the formulations.

Table.1 Different formulations of venlafaxine HCl tablets

S. No.	Ingredients (mg)	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Venlafaxine HCl	75	75	75	75	75	75	75	75
2	Badam gum	35	70	105	140	175	210	175	175
3	Lactose	181	146	111	76	41	6	61	24
4	PVP (2%)	7	7	7	7	7	7	7	7
5	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
6	Sodium bicarbonate	33.75	33.75	33.75	33.75	33.75	33.75	18.75	45.75
7	Citric acid	11.25	11.25	11.25	11.25	11.25	11.25	6.25	16.25
8	Magnesium stearate (1%)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
9	Talc (1%)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5

Tablet weight = 350 mg; Q.S- represents quantity sufficient

Evaluation of Tablets

Evaluation of powder blend

The powder blend of all formulations was evaluated for Bulk density, Tapped density [13], Compressibility index [14], Hausner ratio [15] and Angle of repose [16]. The results were tabulated in table 2.

Table 2: Results showing pre-compression parameters

S.No	Formulation Code	Angle Of Repose(Degrees)*± SD	Carr's Index*± SD	Hausner's Ratio*± SD
1.	F1	25.17±0.078	6.139±0.745	1.065±0.30
2.	F2	27.74±0.052	8.777±0.792	1.061±0.40
3.	F3	26.21±0.067	6.168±0.704	1.065±0.36
4.	F4	26.78±0.098	7.134±0.607	1.034±0.38
5.	F5	27.29±0.056	9.978±0.345	1.095±0.34
6.	F6	26.78±0.097	11.345±0.345	1.067±0.56
7.	F7	25.09±0.045	10.987±0.456	1.024±0.23
8.	F8	25.45±0.045	6.098±0.342	1.046±0.34

***Values represent mean ± Standard Deviation (SD), n=3**

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. The results were tabulated in table 3.

Table 3: Results of tablet physical properties

s.no	Formulation Code	Weight Variation(%) ****±SD	Hardness(Kg/ Cm^2)*± SD	Friability (%)**±SD	Thickness (mm)*± SD	Drug Content (%)***±SD
1.	F1	354.56±1.56	6.79±0.0173	0.7780±0.017	3.5528±0.71	97.80±0.54
2.	F2	364.87±1.67	6.87±0.0102	0.7472±0.027	3.4512±0.54	98.90±0.56
3.	F3	350.09±2.45	6.43±0.0458	0.7694±0.016	3.9204±0.42	96.98±0.43
4.	F4	356.98±2.34	6.45±0.0340	0.645±0.0130	3.908±0.670	97.98±0.56
5.	F5	360.89±1.76	6.09±0.0130	0.742±0.0740	3.789±0.670	99.99±0.58
6.	F6	354.98±1.98	6.67±0.0173	0.768±0.0340	3.456±0.540	97.67±0.45
7.	F7	357.87±2.04	6.78±0.0230	0.691±0.0560	3.456±0.780	98.67±0.58
8.	F8	359.98±1.34	7.98±0.0670	0.714±0.0760	3.567±0.670	97.09±0.68
All values are mentioned as mean ±SD: Number of trials (n)=3						

****Values represent mean ± Standard Deviation (SD), n=26**
*****Values represent mean ± Standard Deviation (SD), n=20**
***Values represent mean ± Standard Deviation (SD), n=3**
***Values represent mean ± Standard Deviation (SD), n=3**
***** Values represent mean ± Standard Deviation (SD), n=10**

In vitro Buoyancy studies:

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]. The results were tabulated in table 4.

Table 4: In vitro Buoyancy studies

S.no	Formulation code	Floating lag time(sec)	Floating time(hrs)	Dimensional Stability
1.	F1	35	>12	stable
2.	F2	48	>12	stable
3.	F3	52	>12	stable
4.	F4	64	>12	stable
5.	F5	85	>12	stable
6.	F6	90	>12	stable
7.	F7	120	>12	stable
8.	F8	29	>12	stable

***In vitro* dissolution study:**

The in-vitro dissolution studies were performed by placing the tablets in 900 ml dissolution media of 0.1 HCL kept at a temperature of 37 ± 0.5°c were stirred at a speed of 50 rpm in USP XXXI type II rotating paddle dissolution apparatus (Electrolab TDT-08L, India). The amount of Venlafaxine HCl released after 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11and 12 hours was determined using UV Spectrophotometer. The results were tabulated in table 5 and shown in Fig. 2.

Table 5: *In-vitro* drug release studies

Time (hrs)	F1±STD	F2±STD	F3±STD	F4±STD	F5±STD	F6±STD	F7±STD	F8 ±STD
0.5	25.91±0.101	15.73±0.628	12.19±0.675	11.65±1.138	10.56±0.882	7.86±0.615	6.29±0.593	24.73±0.103
1	31.29±0.095	29.32±0.096	17.1±0.880	17.33±0.597	15.88±0.931	14.43±0.707	12.36±0.685	32.12±0.098
2	45.76±3.781	36.52±1.236	29.53±1.077	26.55±1.297	22.28±1.064	21.49±0.920	18.53±0.876	40.52±1.091
3	61.33±0.750	46.25±1.123	36.65±0.671	32.40±1.341	30.32±1.005	29.06±0.326	25.12±0.295	51.25±1.171
4	74.6±2.066	58.18±0.507	47.98±0.800	36.7±0.407	36.90±0.293	35.62±0.409	33.35±0.391	56.18±0.713
5	88.6±1.2	66.51±1.359	54.72±1.51	47.39±0.598	45.90±0.571	43.09±1.082	40.24±1.076	61.65±1.935
6	98.17±0.822	76.47±1.497	62.85±1.944	55.50±0.538	54.26±0.902	52.51±1.19	49.46±1.05	67.51±0.895
7		88.25±1.16	73.36±0.875	64.78±0.880	61.58±0.840	58.97±0.716	56.67±0.705	76.47±0.290
8		99.31±0.650	83.31±2.270	76.02±0.964	68.62±1.038	63.96±0.355	61.96±0.319	89.25±1.213
9			92.16±0.840	85.29±1.225	76.70±0.282	71.32±0.724	69.79±0.711	98.31±0.682
10			98.73±1.150	93.68±1.388	84.36±0.74	76.96±0.212	75.12±0.209	
11				99.18±1.021	91.57±1.207	81.40±0.796	80.02±0.765	
12					99.70±0.9113	88.52±1.361	92.52±1.421	
All values are mentioned as mean ±SD: Number of trials (n)=3								

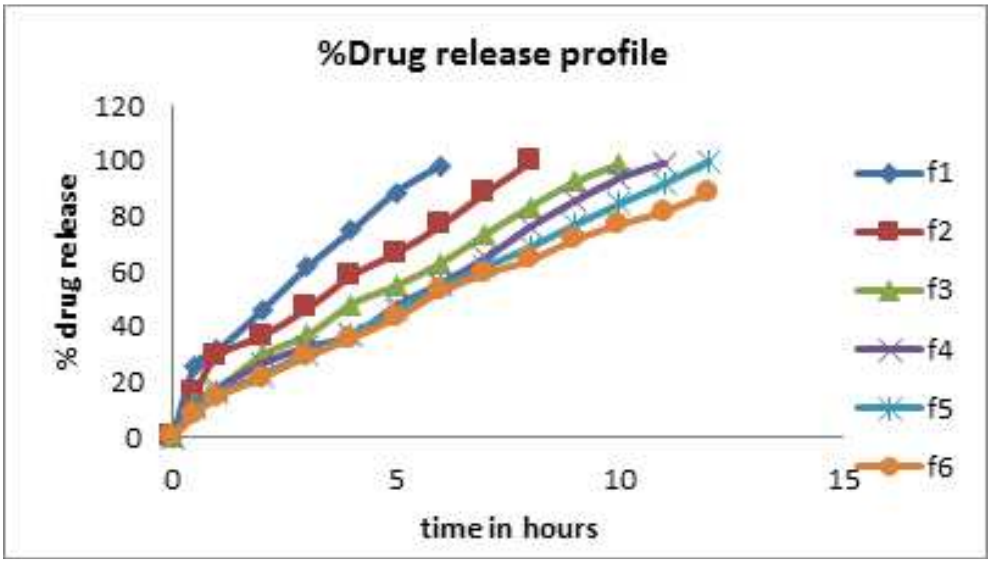

Fig. 2 Cumulative percent drug release profile of formulations prepared using badam Gum

Study of drug release kinetics:

The venlafaxine HCl release data were plotted in various kinetic models, including zero order (cumulative percent amount of drug release versus time), first order (log percent amount remained to be release versus time), Higuchi's square root time kinetics (cumulative percentage of drug release versus square root of time), Korsmeyer-Peppas exponential kinetics (log cumulative percentage of drug released versus log time) and Hixon Crowell' s cube root kinetics (cube root of percent drug released versus time) to describe the rate and mechanism of drug release.

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.

Results and Discussion

The present work is aimed at formulating and evaluation of venlafaxine Hcl controlled release floating tablet dosage forms with longer plasma half lives and longer intracellular half lives, avoid rapid absorption of drug through floating prolonging exposure and the period of pharmacologic activity. For this purpose natural polymers such as almond gum and gas generating agents are used as the key excipients. The tablets containing native polymer were shown that the drug was released for a shorter period up to 10 hrs. F1, F2, F3 were showed 100 % drug release by 6 to 8 hrs respectively. By increasing the native polymer concentration drug release was continued for longer period up to > 12 hr from F4, F5 and F6. F5 showed 99.70% drug release in 12 hrs. But in F6 formulation increasing in concentration of polymer decreasing the drug release rate and not reached 100% release in 12 hr, when compared with the F5 formulation. Up to F1 to F6 formulations gas generating agents sodium bicarbonate and citric acid constantly 45mg added in 3:1 ratio which aid in floating the drug up to 12 hrs .But in remaining formulations F7, F8 gas generating agents were added in different ratios 25mg and 65mg to native polymer concentrations of 50%. In F7, F8 formulations ,drug release rate shown 92.52±1.421 and 98.31±0.682 + respectively in 12hrs and 9hrs.By comparing the F7, F8 formulations containing 50% native polymer with F5 formulation containing the same polymer concentration shows that good controlling drug release rate in F5 formulation. It shows that increasing (65%) or decreasing (25%) the concentrations of gas generating agents did not show controlled release rate upto 12 hrs. F5 formulation shows the best optimized formulation for controlling drug release rate. Time period of controlling drug release had good agreement with concentration of the polymer. F5 formulation showed the drug release for a period of >12hrs. Upon fitting the dissolution data in different kinetic models, the obtained r^2 values were well fitted in the zero order models. The release exponent n values of peppas were found $>0.45 \leq 0.89$ indicating non-fickian anomalous transport in case of all formulations prepared by using badam gum.

Conclusion

Floating tablet of venlafaxine HCl was formulated as an approach to increase gastric residence time and there by improve its bioavailability. Formulation F5 showed better controlled drug release in comparison to the other formulations, the extent of drug release was found to be 98.70% at the desired time 12 hrs. The drug release pattern of formulation F5 was best fitted to higuchi model and zero 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 F5 was carried out by using FT-I spectroscopy in this analysis drug excipients interactions was not observed. Hence it was concluded that formulation F5 can be taken as an ideal or optimized formulation of gastro retentive tablets for 12 hours as it fulfils all the requirements for controlled release tablet.

References

1. Davis, S.S. Formulation Strategies for absorption Windows. DDT. 2005, 10, 4.
2. Padmavathy J, Saravanan D, Rajesh D. Formulation and evaluation of ofloxacin floating tablets using HPMC. Int J Pharm Pharm Sci; 2011, vol 3, issue1:170-173.
3. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a Novel controlled release system for gastric retention. Pharm. Res; 1997, vol14:815-819.
4. Ponchel G, Irache J. M. Specific and nonspecific bioadhesive particulate system for oral delivery to the gastrointestinal tract. Adv. Drug Del. Rev; 1998, 34:191-219.
5. Davis SS, Stockwell AF, Taylor MJ. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm. Res;1986,3, 208-213
6. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastro retentive dosage forms. J. Controlled Release; 2003, 90: 143—162.
7. Groning R., Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev. Ind. Pharm.; 1984, 10: 527- 539.
8. Keith S. Advances in Psychotropic Formulations. Prog Neuro Psycopharmacol Biol Psych. 30, 2006, 996-1008.

9. Ric AM, Moyer A, Haskins JT, Andree TH, Husbands GE. Biochemical, Neurophysiological and behavioral Effects of Wy- 45,233 and other identified Metabolites of the Antidepressant Venlafaxine. Drug Dev Res; 1991, 23: 191-199.
10. Simona JS, Aguair Lm. Extended Release Venlafaxine in relapse prevention for patients with major Depressive disorders. J Psychiatr Res; 2004, 38: 249-257.
11. Troy S.M, Parker VD, Fruncillo RJ, Chiang ST. The Pharmacokinetics of Venlafaxine when given in a twice – daily regimen, J Clin Pharmacol; 1995 35:404-409.
12. Shinde Anilkumar. J. Gastro retentive drug delivery system- An overview, Pharmainfo.net; 2008:6(1).
13. Shah D, Shah Y, Rampradhan M. Development and Evaluation of Controlled Release Diltiazem Hydrochloride Micro particles Using Cross-linked Poly Vinyl Alcohol. Drug Dev Ind Pharm.; 1997, 23: 567-564.
14. Aulton ME and Wells TI. Pharmaceutics: The science of Dosage Form Design, 2nd edition, Churchill Livngstone, London; 1998, 247-248.
15. Lachman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd edition. Lea and Febiger, Philadelphia; 1987, 317-318.
16. Cooper J, Gunn C. Powder flow and compaction: Tutorial pharmacy, 6th edition CBS Publishers and Distributors, New Delhi; 1986, 211-213.
17. Ponchel R, Irache JM. Specific and Non-Specific Bioadhesive Particulate System for Oral Delivery to the Gastrointestinal Tract. Adv Drug Del Rev. ;1998, 34: 191- 219.