International Journal of Medicine and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijmpr

Research Article **Open Access**

Formulation and evaluation of film coated pulsatile release tablets of Venlafaxine Hydrochloride

Hyma.P*

Scientific and Applied Research Center, Hyderabad, Telangana

A B S T R A C T

Conventional dosage form of venlafaxine HCl has a poor pharmacokinetic profile and shorter half life (5hrs) that necessitates 2-3 times daily dosing. Thus, this study attempts to design and evaluate a chronomodulated pulsatile drug delivery system of venlafaxine by rupturable coating method. The core containing venlafaxine were prepared by direct compression method and then coated sequentially with an inner swelling layer containing superdisintegrants like sodium starch glycollate, crosscaramellose, crosspovidone and an outer rupturable layer consisted of Eudragit L 100 and S-100 and HPMC E-15. Total 12 formulations with different levels of inner swelling layer and outer polymeric layer were prepared and subjected to various processing and formulative parameters were investigated. In vitro drug release and rupture tests were performed using USP paddle method at 50 rpm in 0.1 N HCl and phosphate buffer of pH 6.8. The results show that as the amount of inner swelling layer increases the lag time decreases and as the Eudragit coating level increases the lag time increases and percent water uptake of time dependent pulsatile release system decreases. The presence of an osmotic agent and effervescent agent helped in shortening of lag time. Results of stability study revealed that the developed pulsatile release formulation was stable over a range of temperature and period tested.

Keywords: Pulsatile Drug Delivery, Lagtime, Venlafaxine HCl

A R T I C L E I N F O

CONTENTS

Article History: Received 28 Aril 2015, **Accepted** 18 May 2015, **Available Online** 15 June 2015

***Corresponding Author**
Hyma.P
Scientific and Applied Research Center, Hyderabad, Telangana
Manuscript ID: IJMPR2567

PAPER-QR CODE

Citation: Hyma.P. Formulation and evaluation of film coated pulsatile release tablets of Venlafaxine Hydrochloride. *Int. J. Med. Pharm, Res*., 2015, 3(3): 1045-1050.

1. Introduction

The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action.[1,2] There are certain conditions for which a release pattern is not suitable. These conditions demand release of drugs after a lag time. In other words, it is required that the drug should not be released at all during the intial phase of dosage form administration. Such a release pattern is known as pulsatile release.[3]

This condition demands release of drug as a "pulse"after a time lag and such a system has to be designed in a way that complete and rapid drug release should follow the lag time.[4]Such systems are know as pulsatile drug delivery systems (PDDS), time controlled systems or Sigmoidal systems. Pulsatile drug delivery system is time and site spefic system, thus providing special and temporal delivery and increasing patient compliance.[5,6] It is defined as the rapid and transient release of certain amount of molecules within a short period immediately after a predetermined off release period. Venlafaxine HCl is an orally active serotonin noradrenalin reuptake inhibitor used in the treatment of major depressive disorders.[7]

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 drug is desired. [8] It is a highly water soluble drug (Class I) with the biological half life of 5 Hrs thus requires two to three time daily dosing to maintain plasma drug concentration.[9,10] So providing its slow release to maintain therapeutic level is the major need of this formulation.

2. Materials and Methods

Materials: Venlafaxine HCl was a gift sample from Dr.Reddy'slaboratories, Sodium starch glycolate, Cross povidone, Eudragit L100 were purchased from Merck specialities Pvt Ltd, Mumbai, Microcrystalline cellulose, PVP K-30, HPMC E-15 were purchased from S.D. Fine Chem. Ltd., Mumbai.

Methods:

Drug-excipient compatibility studies:

Fourier Transform Infra Red Spectroscopy(FTIR): The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The potassium bromide pellets were prepared on KBR press by grounding the solid powder sample with 100 times the quantity of KBR in a mortar.[11] The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 9 t/in2. The infrared spectrum was then taken and the interaction was studied.

Evaluation of Pre-compression parameters:

The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index, hausner ratio as per the procedure described in I.P.[12]

Formulation of compressed tablets of Venlafaxine HCl:

1. Preparation of core tablets
2. Coating of tablets

Tablets of Venlafaxine HCl were formulated by incorporating super disintegrants like sodium starch glycolate, cross caramellose sodium and crosspovidone, polyvinyl pyrrolidine-k 30(binder),micro crystalline cellulose (diluent), magnesium stearate and talc etc. The core tablets were further coated with Eudragit-L 100, Eudragit-S100 and HPMC E-15.[13]

Table 1: Formulation Table of Core Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl(mg)	100	100	100	100	100	100	100	100	100
SSG(mg)	6	9	12	-	-	-	-	-	-
CCS(mg)	-	-	-	6	9	12	-	-	-
CP(mg)	-	-	-	-	-	-	6	9	12
PVP-k30(mg)	25	25	25	25	25	25	25	25	25
Mg St(mg)	25	25	25	25	25	25	25	25	25
Talc(mg)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
MCC(mg)	131.5	128.5	125.5	131.5	128.5	125.5	131.5	128.5	125.5
Total wt(mg)	300	300	300	300	300	300	300	300	300

Coating of tablets:

The compressed tablets were subjected to coating with different coating solutions. Eudragit –L 100 , Eudragit-S100 and HPMC E-15 were used as coating polymers and isopropyl alcohol , acetone and water mixture used as solvent. Tri ethyl citrate used as plasticizer, titanium dioxide used as opacifier and talc used as anti tacking agent. [14] Solvent mixture was prepared with IPA, acetone and water mentioned quantity in table. Add the Eudragit powder slowly into 50 % of the diluent mixture and stir until the polymer is completely dissolved (approx. 30–60 minutes). Add talc and triethyl citrate in the remaining diluent mixture and stir for 10 minutes with a magnetic stirrer.[15] Pour the excipient suspension slowly into the Eudragit solution while stirring with a conventional stirrer. Pass the spray suspension through a 0.5 mm sieve. The tablets were coated with aqueous ethanolic solution of Eudragit-L 100 , Eudragit-S 100 and HPMC E-15 using a pan coating system to yield 30 & 50% weight gain.

Table 2: Formulation Table of Coating Tablets.

Ingredient	Composition 1	Composition 2	Composition 3
Eudragit-L 100(gm)	6.25	-	-
Eudragit-S 100(gm)	-	6.25	-
HPMC E-15	-	-	6.25
Tri ethyl citrate(gm)	0.3125	0.3125	0.3125
Titanium di oxide(gm)	0.5	0.5	0.5
Talc(gm)	0.5	0.5	0.5
Iso propyl alcohol(gm)	51.4	51.4	51.4
Acetone(gm)	34.2	34.2	34.2
Water(gm)	4.29	4.29	4.29

Evaluation of the prepared tablets:
Post compression parameters: the tablets were evaluated for the various parameters like hardness, thickness, weight variation, content uniformity and disintegration.

***In -vitro* dissolution studies:**
In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus. The dissolution fluid was 900ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test.[16] Samples of dissolution medium(5ml) were withdrawn for every 2min and assayed for Venlafaxine HCl by measuring absorbance at 225 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8. [17]

Scanning Electron Microscopy:
The optimised coated and uncoated tablets were tested for scanning electron microscopy to know the thickness of the coating layer of the coated tablets when compared with uncoated tablets.[18]

Stability Studies: Stability Studies were carried out at 40^0C temp and 75% RH for 30months. The core tablet and coated tablet of selected formulation were packed in amber-colored bottles tightly plugged with cotton and capped.[19,20] Physical appearance and %drug content was checked at regular time intervals.

3. Results and Discussion

FTIR for drug excipient compatibility:

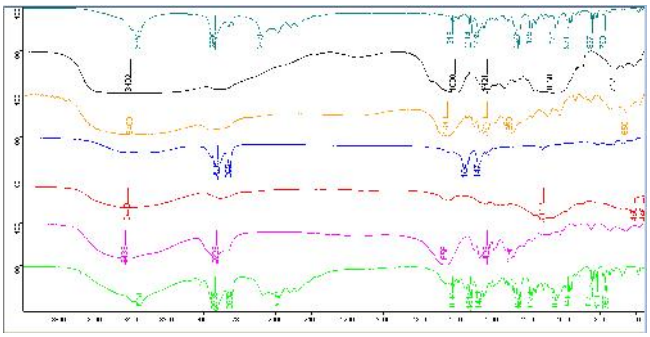

Figure 1 : FTIR Spectrum of Drug and Excipients

The FTIR spectrum of pure venlafaxine HCl has three characteristic peaks at 3352cm-1,2935cm-1,2679cm-1 for O-H stretching vibration, C-H vibration, and O-H phenol functional group respectively. The FTIR spectrum of Venlafaxine HCl optimised formulation has three characteristic peaks at 3351cm-1, 2935cm-1, 2692cm-1.Therefore, pure drug and formulation were almost similar because of the same functional groups. It indicates that there was no interaction between venlafaxine HCl and excipients used in the formulation.

Micrometric Properties of Core Tablets:

Table 3: Micrometric Properties of Core Tablets

Formula	Micromeretic properties of powder blend				
	Angle of Repose (θ) ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	27.53±0.38	0.378±0.019	0.424±0.021	10.81±0.17	1.12±0.025
F2	28.57±0.23	0.388±0.025	0.437±0.018	11.11±0.12	1.12±0.037
F3	26.31±0.23	0.368±0.032	0.424±0.025	13.15±0.26	1.15±0.032
F4	27.83±0.58	0.388±0.022	0.437±0.032	11.11±0.21	1.12±0.020
F5	26.42±0.28	0.378±0.017	0.437±0.029	13.51±0.17	1.15±0.018
F6	28.98±0.23	0.378±0.013	0.424±0.024	10.81±0.26	1.12±0.029
F7	29.41±0.23	0.368±0.011	0.424±0.019	13.15±0.12	1.15±0.031
F8	28.35±0.45	0.378±0.032	0.378±0.032	10.81±0.19	1.12±0.039
F9	26.32±0.24	0.370±0.035	0.427±0.028	13.17±0.27	1.15±0.035

Evaluation Parameters of Compressed Tablets

Table 4: Evaluation Parameters of Compressed Tablets

Formulation code	Weight variation (n=10)mg	Uniformity of thickness Mean(n=10)mm	Hardness Mean (n=10) (kg/cm^2)	Mean Friability (n=10)%	Mean Content Uniformity of Drug(%)n=3	Disintegration time (mins)
F1	301.1	3.85	4.50	0.87	96.35	8..55
F2	299.8	3.91	3.91	0.82	98.04	4..39
F3	300	4.23	4.67	0.92	98.79	9..55
F4	304.1	3.72	4.13	0.88	97.41	3..33
F5	298.6	3.80	3.82	0.75	98.63	5..12
F6	302.3	3.74	3.79	0.72	97.77	3..12
F7	306.8	3.71	3.87	0.80	96.84	4..26
F8	299.1	3.96	4.06	0.74	95.36	3..37
F9	307.2	3.82	3.95	0.86	95.81	3..18

Cumulative percentage Drug release

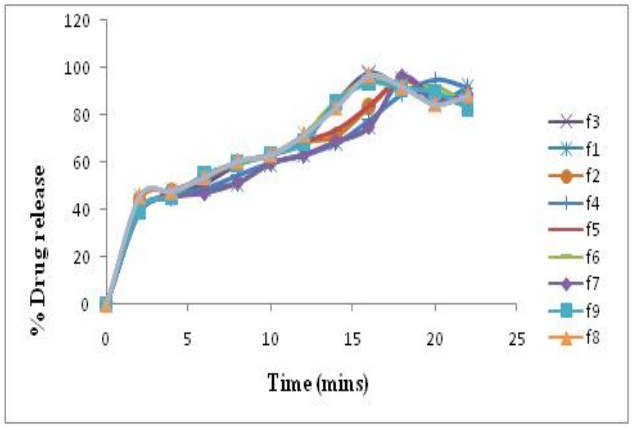

Figure 2: Cumulative percentage Drug release of Core formulations

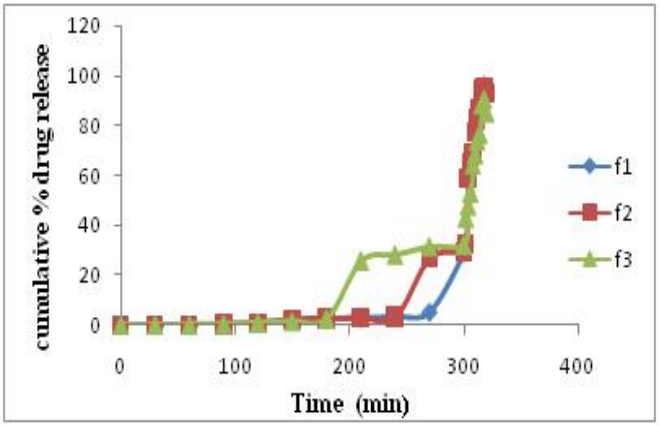

Figure 3: Cumulative % drug release of Coated Formulations

In-vitro dissolution results showed that the fast and complete drug release after lag time was observed in formulations C-F1,C-F2,C-F3. And expected lag time was observed (4 $^1/_2$hr) in formulation C-F1.Hence,C-F1 is considered as the optimized formulation. The results of the in-vitro dissolution studies and graphical plots shown that as the as the amount of inner swelling layer increases the lag time decreases and as the Erudragit coating level increases the lag time increases and %water uptake of pulsed release tablets decreases.[21,22] The results of the in-vitro drug release studies and graphical plots shown that, significant difference in drug release behaviour was observed for release study in different pH solutions.

Scanning electron micrograph

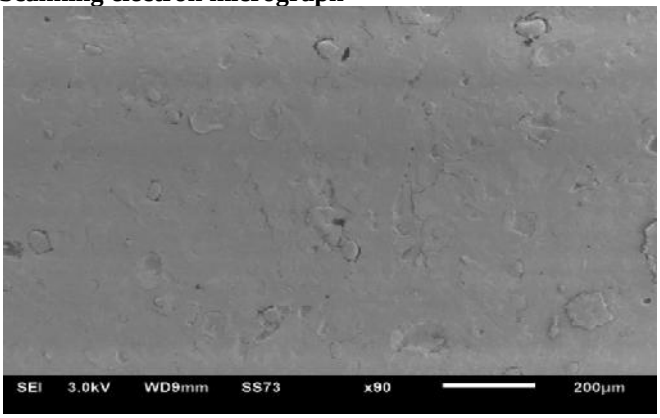

Figure 4: Scanning electron micrograph of the tablet (a) core tablet

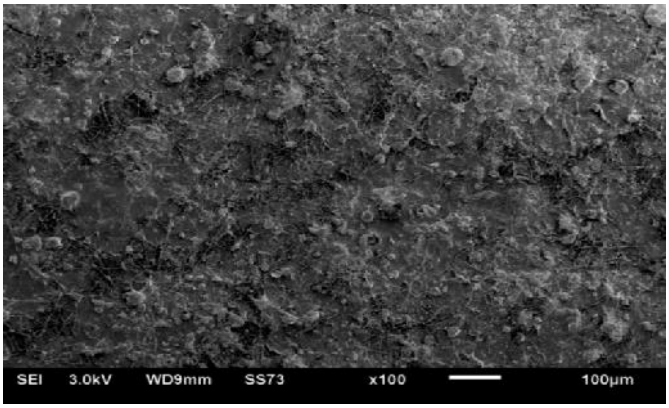

Figure 5: Scanning electron micrograph of the tablet (b) coated tablet

The photographic results from SEM of optimized formulation shows two parts of the system which clearly visible namely core tablet(a)with swelling layer and coated tablet (b)with polymer layer. The SEM also revealed that the tablet had a fairly smooth and tight surface.[23]

Stability Data:

Table 5: Stability Data

Time in months	% Drug Content in Core Tablets	% Drug Content in Coated Tablets
0	98.79	99.86
1	97.35	99.39
2	94.73	98.41
3	92.80	97.62

Stability studies were conducted for optimised formulation 40^0c/75 RH for a period of 3 months. The results indicated that the selected formulations showed no change in physical appearance and they are stable over a range of temperature and period tested. Drug content was affected to a lesser extent in case of the core tablet. While in case of coated formulations no change was observed.

4. Conclusion

From the results obtained in the present study, it can be concluded that The present study was done to develop a novel pulsatile drug delivery system of venlafaxine HCl by polymeric coating of fast dissolving core tablets. In all formulations the lag time is directly proportional to an outer Eudragit coating level and inversely proportional to an inner swelling layer concentration. An inner swelling layer sodium starch glycolate 4% and an outer Eudragit coating level(L-100) are the promising concentrations for the development ChrDDS of venlafaxine HCl which was expected to release the after a lag time of five hours. Optimised formulation was found stable for the period and conditions examined. The lag time criterion of 5 hrs was satisfied by formulation C-F1.The dosage form can be taken at bed time and will release the contents in the early morning hours when depressant attacks are more potent. Thus, highly water soluble drug was formulated as time dependent controlled release delivery system; where the drug is release is delayed till completion of lag time chronotherapeutic effect as compared to conventional marketed formulation of venlaflaxine HCl.

5. References

1. Sharagil L, Pony S. “Applied Bio-pharmaceutics and Pharmacokinetics”. 5th ed. Singapur ; pp. 481-2.
2. RobertW, ThomaP.“Drug therapy for hyper cholestemia and Dyslipidemia. In: Goodmen and Gilmans. The pharmacological basis of therapeutics. 10th ed. McGraw- hill. *Medical publishing division*. **2003**: 971-972.
3. Filippatos TD, Derdemezis CS, Elisaf MS. Department of Internal Medicine, School of Medicine, University of Loannina Greece. Available from: *articles Diet forhyperlipidemia.mht.* Scott MG. Atherogenic dyslipidemia associated with metabolic syndrome and Insulin resistance. vol 8. Suppl 1.
4. Bi-Botti CY. “Chronopharmaceutics: Gimmick or clinically relevant approach to drugdelivery”- *A Review. J Control Rel*., 98(3).337-353.
5. Jain NK. “Controlled and novel drug delivery”.1st Ed. New Delhi: CBS Publishers.
6. Bussemer T, Otto I, Bodmeier R. “Pulsatile drug delivery system Crit” *Rev Ther Drug Carrier Syst*., **2001,** 18(5): 433-58.
7. Gothaskar AV, Joshi AM,and Joshi NH. “ Pulsatile drug delivery system”-*A review. Drug Del Tech*., **2004**, 4(5).
8. Anil K. Anal. “Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds”.*Recent Patents on Drug Delivery & Formulation*.1.73-78.
9. Bjorn Lemmer. The clinical relevance of chronopharmacology in therapeutics. Pharmacological Research. **1996**, 33(2): 107-115.
10. Sarasija S, Stutie P. Chronotherapeutics: Emerging role of Biorhythms in optimizing drug therapy.” *Indian J Phrm Sci.,* 67(2)2005.135-140.
11. Peep Veski. Chronopharmaceutical Drug Delivery. Institute of pharmacy. University of Tartu, Estonia.
12. Libo Yang, James SC, Joseph AF. Colon specific drug delivery: new approaches and *in-vitro/in-vivo* evaluation r*eview. Int. j. pharm*., 253.1-15.
13. Shivakumar HG, Pramod KTM, Kashappa GD. Pulsatile drug Delivery systems. *Indian J Pharm Educ*., 37(3).125-128.
14. Sangita V.Timing is everything. http://www.pharmaquality.com/Feature.7ahtm.
15. Zhang Y, Zhang Z, Fang Wu. A novel pulsed release system based on swelling Osmotic pumping mechanism.” *J. Control. Release.88.47*-55.
16. Qureshi J. Chronomodulated drug delivery system of salbutamol Sulphate for the treatment of nocturnal asthma. *Indian. J. Pharm. Sci*., **2008**, 70(3): 351-356.
17. Lin S, Lin K, Li M. et al., Influence of excipients, Drugs & osmotic agents in the inner core on the time-controlled disintregation of compression coated ethyl cellulose tablets. *Journal of pharmaceutical sciences.* **2002**, 91(9): 2040-2046.

18. Arora S, Ali J, Ahuja A, Baboota S, Qureshi J. Pulsatile drug delivery systems: An approach for controlled drug delivery. *Indian. J. Pharm Sci.*, **2006**, 68(3): 295-300.
19. Gothoskar A, Joshi A, Joshi N. "Pulsatile drug delivery systems:" A *Review Drug delivery technology*. 4, 3-9.
20. Survase S, Kumar N. Pulasatile drug delivery: Current scenario Current Research & Information on Pharmaceutical Science. **2007**, 8: 1-8.
21. Phillip J, Percel, Vishnupad, Krishna S, Venkatesh, Gopi M, Lee, Der Yang. Timed pulsatile drug delivery system U.S. patent no. **2006**, 14(5): 24-32.
22. Puttipipatkhachorn S. Development of pulsatile release tablets with swelling and rupturable layers. *J. Controlled Release.* **2004**, 95: 149-159.