International Journal of Chemistry and Pharmaceutical Sciences

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Research Article **Open Access**

Formulation and evaluation of pulsatile release tablets of Venlafaxine Hydrochloride

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A B S T R A C T

Conventional tablet 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, and an outer rupturable layer consisted of Eudragit L 100 and ethyl cellulose and HPMC E-15. 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 prolongs the lag time and percent water uptake of time dependent pulsatile release system decreases.

Keywords: pulsatile drug delivery, eudragit, venlafaxine HCl, HPMC

A R T I C L E I N F O

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Article History: Received 18 June 2015, **Accepted** 10 August 2015, **Available Online** 27 September 2015

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Manuscript ID: IJCPS2669

PAPER-QR CODE

Citation: S. Masood Ahmed, et al. Formulation and evaluation of pulsatile release tablets of Venlafaxine Hydrochloride. *Int. J. Chem, Pharm, Sci.*, 2015, 3(9): 1946-1950.

1. Introduction

Venlafaxine is a representative of new class of antidepressants. It acts by inhibiting selectively the uptake of serotonin and nor adrenaline but shows no affinity for neurotransmitter receptors [1]. Hence it lacks the adverse

anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. However, the main limitation to therapeutic effectiveness of venlafaxine is its poor bioavailability (40-45%) and short biological half life (5hr) necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug. This necessitates the development of pulsatile delivery system which permits direct access of the active constituent to the systemic circulation thereby by-passing first-pass metabolism.

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 known 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.

2. Materials and Methods

Materials: Venlafaxine HCl was a gift sample from Dr. Reddy's laboratories, 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]

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:

Tablets of Venlafaxine HCl were formulated by incorporating super disintegrants like sodium starch glycolate, crosscaramellose 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, Ethyl cellulose and HPMC E-15. [13]

Coating of tablets:

The compressed tablets were subjected to coating with different coating solutions. Eudragit –L 100, Ethyl cellulose 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]. The tablets were coated with aqueous ethanolic solution of Eudragit-L 100, Ethyl cellulose and HPMC E-15 using a pan coating system to yield 30 & 50% weight gain.

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 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]

3. Results and Discussion

FTIR for drug excipient compatibility:

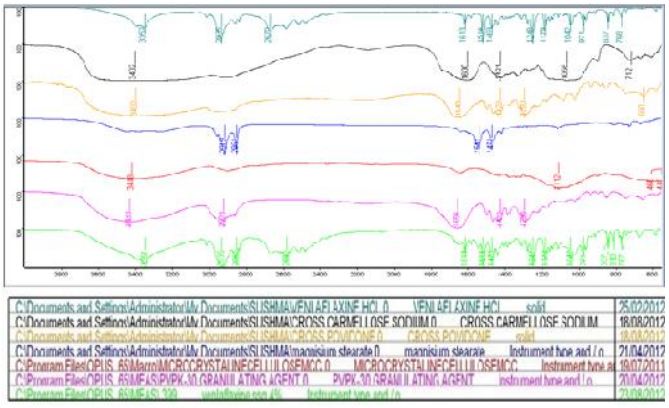

Figure 1: FT-IR spectrum of Drug and Excipients

The FT-IR 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.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.

Cumulative percentage Drug release

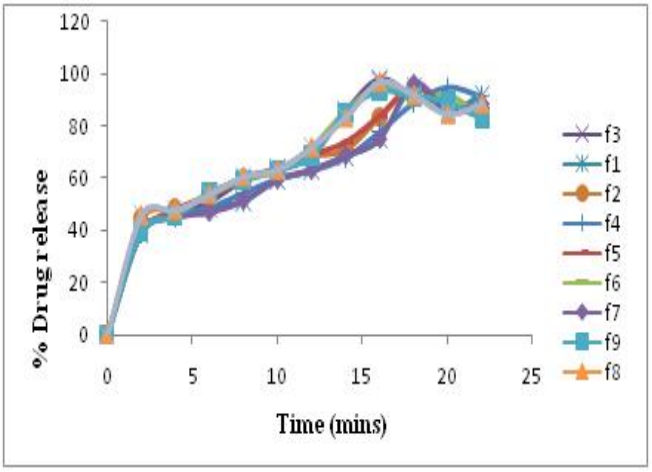

Figure 2: Cumulative percentage Drug release of Core formulations

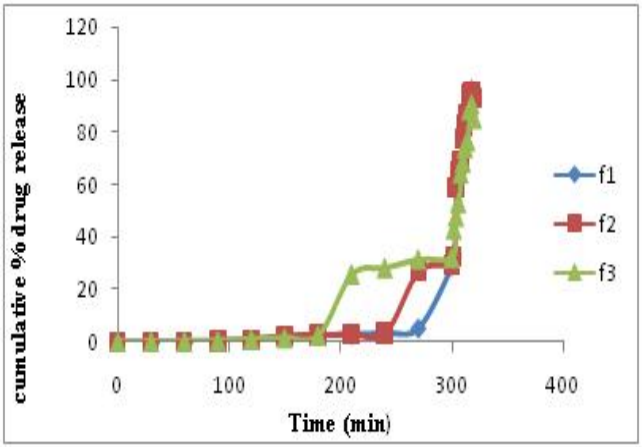

Figure 3: Cumulative % drug release of Coated Formulations

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. 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

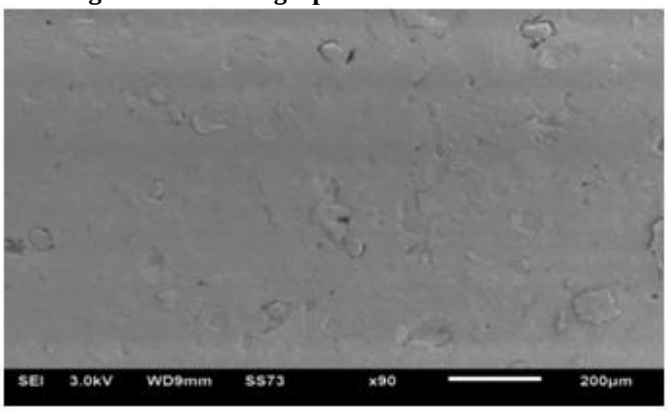

Figure 4: Scanning electron micrograph of the tablet (a) core tablet

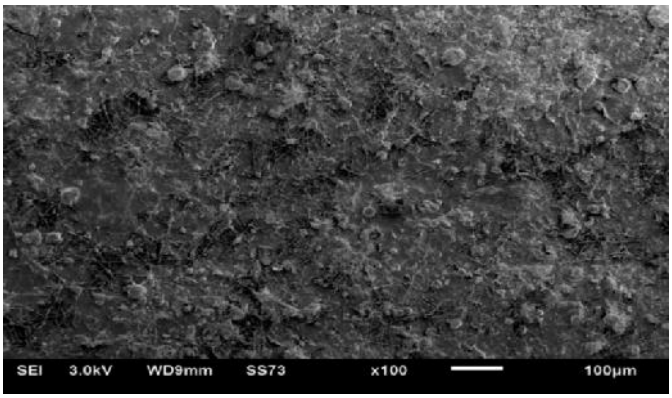

Figure 5: Scanning electron micrograph of the tablet (b) coated tablet

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]

4. Conclusion

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 Chr DDS 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.

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)	3	6	9	-	-	-	-	-	-
Acdisol (mg)	-	-	-	3	6	9	-	-	-
Pearlitol (mg)	-	-	-	-	-	-	3	6	9
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

Table 2: Formulation Table of Coating Tablets

Ingredient	Composition 1	Composition 2	Composition 3
Eudragit-L 100(gm)	6.45	-	-
Ethyl cellulose	-	6.45	-
HPMC E-15	-	-	6.45
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

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	26.43±0.37	0.318±0.009	0.404±0.011	12.81±0.10	1.02±0.005
F2	25.67±0.21	0.328±0.015	0.427±0.014	10.11±0.11	1.12±0.007
F3	22.21±0.25	0.348±0.022	0.414±0.012	11.15±0.22	1.13±0.012
F4	25.63±0.52	0.338±0.012	0.407±0.022	13.11±0.20	1.12±0.010
F5	21.32±0.25	0.368±0.007	0.447±0.020	12.51±0.13	1.13±0.008
F6	25.68±0.21	0.358±0.003	0.434±0.021	11.81±0.21	1.12±0.009
F7	26.31±0.21	0.318±0.001	0.404±0.015	14.15±0.11	1.13±0.001
F8	24.25±0.46	0.368±0.022	0.328±0.030	12.81±0.14	1.11±0.007
F9	27.52±0.27	0.330±0.025	0.417±0.022	12.17±0.20	1.14±0.034

Table 4: Evaluation Parameters of Compressed Tablets

Formulation code	Weight variation mg	Uniformity of thickness Mean mm	Hardness Mean (kg/cm^2)	Mean Friability %	Mean Content Uniformity of Drug (%)	Disintegration time (mins)
F1	300.1	3.15	4.21	0.97	97.35	7.55
F2	297.8	3.45	3.45	0.82	99.04	6.39
F3	302	4.21	4.32	0.92	95.56	8.55
F4	303.1	3.67	4.34	0.88	96.74	5.33
F5	296.6	3.76	3.72	0.75	97.43	5.12
F6	300.3	3.21	3.34	0.72	96.65	3.17
F7	302.8	3.34	3.63	0.80	99.83	4.12
F8	298.1	3.78	4.12	0.74	97.73	3.67
F9	303.2	3.80	3.56	0.86	98.14	3.78

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