RESEARCH ARTICLE

Formulation and Evaluation of Venlafaxine Hydrochloride Osmotic Tablets

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ABSTRACT

Sustained-release tablets of venlafaxine HCl were designed using a controlled porosity osmotic formulation. This study aimed to develop and test an osmotic pump tablet with controlled porosity containing venlafaxine hydrochloride. Because of its excellent water solubility and near-to-one bioavailability, the antidepressant venlafaxine hydrochloride (VH) is placed in Biopharmaceutical Classification System (BCS) class 1. Its short elimination half-life of 5 hours means that patients rarely take it as directed because they have to take two doses each day to make up for it. As a result, there is a high clinical and economic potential for a VH controlled administration dose form that can increase patient compliance. We looked on the dynamics between pharmacological excipients using FTIR. The core of the tablet was made using wet granulation, and the tablets were then covered. After 24 hours of in vitro testing, the drug's release profile was consistent with expectations. It was discovered that the rate of drug release increased with increasing pore former concentration, however, the percentage weight gain of the tablet coating inversely associated with the amount of pore former used. Drug release was investigated in relation to pore past weight development and weight percentage. SEM confirmed optimised (F7) batch's micro porous structure.

Keywords: Venlafaxine hydrochloride, micro-porous, controlled porosity osmotic pump tablet, antidepressant.

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INTRODUCTION

The pharmaceutical business spends the vast majority of its research and development money on the creation of novel medication delivery mechanisms. This is because developing a new chemical entity takes a lot more effort and resources than adding an NDDS.[1] Drugs can be released gradually over time using some typical drug delivery systems. Many factors, such as the medication's physicochemical qualities, the inclusion of excipients, physiological factors like the presence or absence of meals, and the pH of the gastrointestinal tract (GI), can influence the rate and amount of drug absorption from conventional formulations.[2] However, factors such as pH, GI motility, and the presence of food in the GI tract may influence oral controlled release dose forms. One of the most promising drug delivery technologies is osmotically controlled drug delivery systems (OCDDS), which utilize osmotic pressure as a driving mechanism for the regulated distribution of active drugs.[3] Due to the semi-permeable nature of the rate-controlling membrane and the design of the deliver orifice employed in osmotic systems, there is a high degree of in vitro/in vivo correlation in drug release.[4]

In osmosis, water diffuses over a semi-permeable membrane when there is a disparity in osmotic pressure between the two sides.[5] Modern osmotic tablets include a delivery hole created

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by integrating a leachable substance into the coating. Once the tablet's water-soluble component is dissolved in water, an osmotic pumping system is set into motion. By diffusing into the centre, water creates an osmotic gradient that regulates the medication release rate via the microporous membrane.[6] Since it is highly water soluble and absorbs almost completely into the body, the antidepressant venlafaxine hydrochloride (VH) is classified as a class 1 drug in the BCS. Patients typically don't take their medication as prescribed because of its short elimination half-life of 5 hours and the need for twice-daily administration. To improve patient compliance, there is a high demand for a dosage form that can deliver VH in a regulated fashion.[7] This study aimed to create a Venlafaxine hydrochloride formulation with a sustained release profile by employing an osmotic controlled porosity drug delivery system.

MATERIALS AND METHODS

The medication venlafaxine hydrochloride was gifted by Mumbai-based Cipla Pharmaceutical Corporation. Additional chemicals from Pallav Chemical in Mumbai were NaCl, KCl, dextrose, lactose, sucrose, MCC, PVP k30, PEG, mannitol, magnesium stearate, talc, NaOH, HCl, and coating agent (Cellulose acetate). All additional compounds were of the analytical variety.[8,9]

Compatibility Study (Drug-excipients)

To ascertain the likelihood of any drug-excipient interactions, a compatibility study was conducted with prospective formulation excipients and venlafaxine hydrochloride. Excipients used in the study include sodium chloride and microcrystalline cellulose. For 10 days, a 1:1 mixture of the drug and excipients was kept at 40°C. The materials were examined for chemical interaction by IR after 10 days.[10,11]

Experimental Design

In the current study, the pore-former (weight/weight) and the weight growth (weight/weight) were chosen as components in a 32 complete factorial design. The two components' levels were chosen based on the preliminary research before the experimental design was used.[12-15] The study's other formulation and processing factors always remained unchanged. -1, 0 and +1 are coded values. Coded levels translated into real units:

Independent variable: %Pore former (X1), %Weight gain (X2).

Dependent variable: %Cumulative drug release Q6 (Y1), Q18 (Y2) and Q24 (Y3).

Preparation of Coating Solution

The coating mixture made up of PEG400, cellulose acetate, and sorbitol (a pore-forming agent) (plasticizer). A precisely measured amount of cellulose acetate (4% weight/weight) was mixed to acetone (70% w/w). The mixture was agitated until a clear solution formed. A little amount of deionized water was used to dissolve the precisely weighed amount of sorbitol (25% w/w of the total weight of the polymer), which was then combined with IPA (30% w/w). The IPA (30% w/w) solution was supplemented with the measured amount of PEG400 (10% w/w of the total weight of the polymer). The cellulose acetate solution was then gradually filled with the solution. For 30 minutes, the mixture was continually mixed.[14]

Preparation of Factorial Design Formulation

The non-aqueous (IPA) granulation technique was used to create the tablets. In accordance with the recipe listed in Table 1, the ingredients were precisely measured. The PVP K30 alcoholic solution was added after the components had been kneaded in the mortar and pestle for 15 to 20 minutes to generate wet mass. Sieve no. 22 was used to filter the mass. The final grains were left to air dry for 12 hours. Then, lubricants were added to the dried granules. According to the process, the prepared granules underwent evaluations for factors including bulk density, tapped density, Carr index, Angle of repose, and Hauser's ratio. The 12-station rotating tablet machine compressed the core tablets to an average weight of 300 mg using 11 mm concave punches with a hardness of 6–7 kg/cm^2. After that, a coating mixture was applied to the tablets.[15]

Table 1: Factorial design formulations

Ingredients (milligram)	*Formulations*								
Core tablets	F01	F02	F03	F04	F05	F06	F07	F08	F09
Venlafaxine HCL	75 (All)								
NaCl	10	10	10	10	10	10	10	10	10
Mannitol	50	50	50	50	50	50	50	50	50
Lactose	75	75	75	75	75	75	75	75	75
MCC	75	75	75	75	75	75	75	75	75
Mag. stearate	03	03	03	03	03	03	03	03	03
Talc	02	02	02	02	02	02	02	02	02
PVPK30	10	10	10	10	10	10	10	10	10
Total Weight	300	300	300	300	300	300	300	300	300
Coating									
% Pore former (w/w)	20	20	20	25	25	25	30	30	30
% Weight gain(w/w)	3	5	7	3	5	7	3	5	7

Evaluation of Core Tablet

Some of the tablets in the batch were chosen randomLy to be examined for various qualities, including weight variation, hardness, thickness, friability, and assay. Diameter and thickness standards were maintained with the help of vernier calipers. The tablet's mean diameter and thickness were calculated, along with other size characteristics. The tablet's durability was tested using a Monsanto hardness tester. Twenty tablets of each formulation were weighed using an electronic scale to analyze weight variation, and the test was carried out per the recommended procedure. For each formulation, the core tablet's content homogeneity was assessed. Weighing the tablets, we next ground them into a powder. In a volumetric flask, a sample precisely weighing 100 mg of venlafaxine hydrochloride was taken. 100 cc of deionized water was used to dissolve the content. This solution was diluted appropriately after being filtered with Whatman filter paper. Absorbance at 225.20 nm was used to calculate the concentration of the medication in the solution.[16]

Drug release (*In-vitro*)

Using USP Apparatus 2, the release rate of venlafaxine HCl from CPOP (n = 3) was calculated (Paddle). 900 cc of water was used for the dissolution test, which was run for 24 hours at 100 rpm. The medium's temperature was held constant at 37 ± 0.5ºC. 5 mL aliquots were taken out every 2, 4, 6, 8, 10, 12, 14, 16, 18, and 24 hours. Fresh dissolving media was used to replace the samples that were removed (Table 2). The samples were filtered using Whatman filter paper before being subjected to a 225.20 nm spectrophotometric analysis.[17]

Drug Release Kinetics

Fitting the dissolving profiles of each formulation to the following kinetic models was accomplished using PCP Disso software: zero-order kinetics, first-order kinetics, Higuchi, Hixson-Crowell, Korsmeyer, and Peppas. The model with the highest R^2 value was determined to be the best.[18]

Design Expert's Analysis (Software)

The two components were assessed at each of three levels in a 32 complete factorial design. Software called Stat Ease Design Expert 13 was used to statistically treat and interpret the data.

Surface Morphology Study

The SEM was used on the surfaces of the improved formulation (F7) before and after dissolution to analyse the surface morphology of the coated membrane.

Stability Study

The chosen optimized formulation (F8) was packaged in aluminum foil and submitted to stability studies in accordance with ICH requirements, 40 ± 2°C, and 75 ± 5% RH. This formulation provided the desired zero-order release over a prolonged length of time (Thermo lab). Samples were taken out at 1, 2, and 3-month intervals. The samples' appearance, assay, and *in-vitro* release profile were all assessed.[19]

RESULT AND DISCUSSION

The maximum absorbance (max) was discovered at 225 nm when the venlafaxine HCl medication in pH 1.2 (0.1N HCl) was scanned using a UV (200–400 nm) using pH 1.2 as a blank. Using 0.1 N HCL as the solvent, a calibration study of venlafaxine HCL was carried out. A value of 0.999 for the regression coefficient was discovered.

Differential Scanning Calorimetry (DSC) Study

The thermal behavior of venlafaxine hydrochloride was evaluated using a SHIMADZU DSC-60 DSC. With a high temperature of 214.7°C, the melting endotherm was the only distinguishing characteristic of the DLTZ DSC thermogram (Figure 1).

Drug-excipients Compatibility Study

Compatibility experiments with prospective formulation excipients were conducted to ascertain the likelihood of a pharmacological excipient interfering with or being incompatible with VH. The IR study reveals that the drug's peaks have not changed. The investigation found no drug-excipient interactions or incompatibilities.

Evaluation of Granules and Core Tablet

The produced granules were assessed for factors including bulk density, tapped density, carr index, angle of repose, and Hausner's ratio. The angle of repose, bulk density, and tapped density were discovered to be 27.25 ± 0.68°, 0.5010 ± 0.0062, and 0.5454 ± 0.0035 gm/cm^{3,} respectively. It was discovered that Hausner's Ratio and Carr's index were 1.08 ± 0.0025 and 8.14 ± 0.0052%, respectively.

All of the core formulation pills had a bright white, smooth surface, a rounded, curved face, and an excellent feel. The tablet is a white, 11 mm concave tablet in appearance. The following values were discovered to be accurate: 0.503 ± 0.015% for friability, 6.833 ± 0.288 Kg/cm^2 for hardness, and 100.51 ± 1.091% for drug content. Every reading is recorded in three copies, n SD.[20,21]

Dissolution Studies

Osmotic tablets were put in pure water through a 24 hours *in-vitro* drug release test. Hence, it was demonstrated that a rise in pore concentration resulted in an equivalent increase in drug release from the system; nevertheless, drug release was

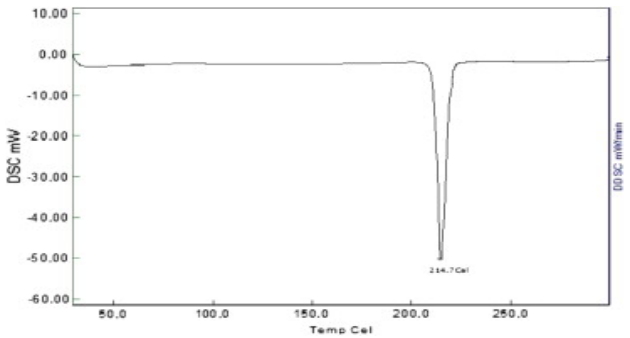

Figure 1: DSC of venlafaxine.

Table 2: Drug release *(In-vitro)* of F01 to F09 formulation

S N	*Time*	*F01 %R*	*F02 %R*	*F03 %R*	*F04 %R*	*F05 %R*	*F06 %R*	*F07 %R*	*F08 %R*	*F09 %R*
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	2	2.25 ± 0.06	2.25 ± 0.06	4.12 ± 0.33	11.45 ± 0.38	4.99 ± 0.08	8.30 ± 0.28	11.77 ± 0.8	8.09 ± 0.15	3.51 ± 0.1
3	4	9.58 ± 2.68	8.10 ± 0.16	9.90 ± 0.55	18.32 ± 0.11	16.96 ± 1.63	17.86 ± 0.31	34.09 ± 0.2	25.76 ± 0.4	9.27 ± 0.0
4	6	21.58 ± 0.95	15.05 ± 0.32	10.25 ± 0.12	36.37 ± 0.16	33.28 ± 0.13	30.41 ± 0.52	41.71 ± 0.1	30.27 ± 0.1	25.19 ± 0.9
5	8	29.46 ± 0.38	16.45 ± 0.38	11.56 ± 0.45	42.70 ± 1.18	36.17 ± 0.12	37.05 ± 0.32	58.95 ± 1.	39.27 ± 0.2	26.45 ± 0.2
6	10	30.94 ± 0.27	18.25 ± 0.35	11.85 ± 0.08	51.96 ± 0.97	43.45 ± 0.60	38.73 ± 0.15	68.95 ± 0.1	53.91 ± 0.3	31.12 ± 0.1
7	12	37.19 ± 0.62	21.84 ± 1.73	12.73 ± 0.17	59.18 ± 0.16	57.79 ± 0.10	40.55 ± 0.26	79.16 ± 0.4	62.70 ± 0.2	39.64 ± 0.6
8	14	39.45 ± 0.18	26.13 ± 0.76	14.50 ± 0.62	60.86 ± 0.10	59.09 ± 0.14	45.63 ± 1.22	80.56 ± 1.8	68.92 ± 0.1	46.43 ± 1.5
9	16	46.44 ± 0.21	29.67 ± 0.60	15.18 ± 0.18	61.91 ± 0.23	59.51 ± 0.33	47.48 ± 0.59	82.89 ± 0.1	74.10 ± 0.3	53.73 ± 1.2
10	20	49.08 ± 0.51	34.92 ± 0.68	16.63 ± 0.12	63.18 ± 0.16	60.23 ± 0.11	49.23 ± 0.34	87.35 ± 0.3	77.45 ± 0.1	51.96 ± 0.2
11	24	52.08 ± 0.12	38.33 ± 0.55	17.75 ± 0.02	64.46 ± 0.38	61.93 ± 0.65	55.25 ± 0.85	89.41 ± 0.1	89.63 ± 0.3	58.78 ± 0.3

* All reading taken in triplicate, n ± SD

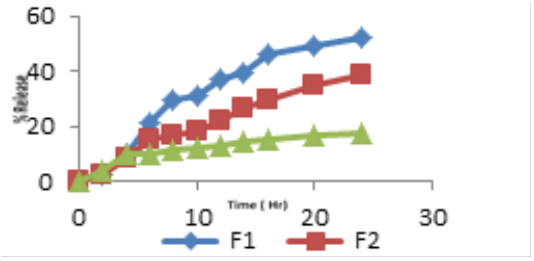

Figure 2: Dissolution profile of formulation F1 to F3

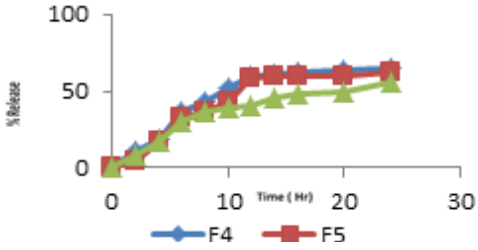

Figure 3: Dissolution profile of formulation F4 to F6

once again suppressed following an increase in external coat thickness (or %weight gain). Pore-forming sorbitol significantly impacts the release profile (Figure 2 to 4). Decreased pore former concentration prevents full drug release. Formulation F7 passes the USP dissolution test.1 with no rejections.[22,23]

Drug Release Kinetics

In the current investigation, PCP Disso Version 2.08 software was used to examine the dissolve in order to study the kinetics of the drug release mechanism. The findings demonstrated that the majority of factorial design formulations followed zero-order dissolving mode. Table 3 displays the R^2 value for each dissolving model.

Response Surface Plot

Three-dimensional plots, displaying the solutions as curvature surfaces as a function of the independent variables, were constructed using the quadratic model derived from the regression analysis. Scatter plots of the response vs the independent variables are shown on the response surface. Figure 5-7 displays response surface plots generated in Design

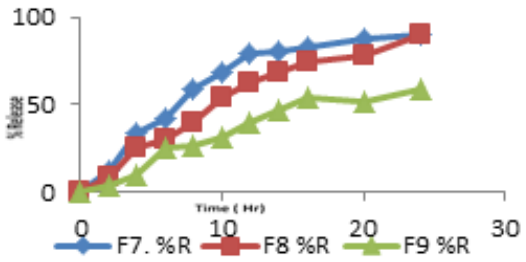

Figure 4: Dissolution profile of formulation F7 to F9

Expert 13 to illustrate the impact of independent variables on outcomes (Q6, Q12, and Q24).

Optimization (Model Validation)

For the model validation, the two formulations OF1 and OF2 were created. The basic tablet characteristics were examined and confirmed to be within tolerances. In Table 4, along with the outcomes of the experiment, are the values of the reactions anticipated by the developed model. The results demonstrated a strong correlation between the experimental values and those predicted by the model, demonstrating its applicability.[24]

Surface Morphology Study

Microphotographs showing the results of scanning electron microscopy (which was used to evaluate the surface of coated tablets before and after dissolution studies) are shown in (Figure 8). Before being exposed to water, the coated tablets' surfaces were smooth, and the coats seemed to be pore-free. The figure depicts the membrane structure before breakdown. The membrane's post-dissolution microporous structure was discovered, as shown in the SEM image of the membrane. This substantial porosity is a result of sorbitol, a water-soluble adjuvant, leaching during medication release during breakdown.[25]

Stability Study

According to ICH requirements, the improved formulation F7 underwent a three-month accelerated stability assessment at 40 ± 2°C and 75 ± 5% RH. Medication release profile and visual appearance such as size, color change, and thickness

Table 3: Kinetic study

Formulation code	R^2					*n*	*K*
	Zero order	*1st order*	*Matrix*	*Peppas*	*Hix. crow.*		
F01	0.9285	0.9659	0.9493	0.9304	0.9555	1.1871	1.7730
F02	0.9835	0.9934	0.9474	0.9714	0.9912	1.0666	1.5596
F03	0.7975	0.9814	0.7592	0.9463	0.7853	0.5136	3.7193
F04	0.9568	0.9123	0.9603	0.8339	0.8909	0.7430	7.9153
F05	0.8767	0.9249	0.9482	0.9420	0.9122	0.9849	3.9642
F06	0.9782	0.8577	0.9328	0.9590	0.9113	0.7256	6.5435
F07	0.9579	0.9527	0.9497	0.8554	0.9361	0.7992	9.2147
F08	0.9927	0.9620	0.9580	0.9766	0.9828	0.9260	5.6186
F09	0.9580	0.9776	0.9402	0.9675	0.9737	1.1332	2.1497

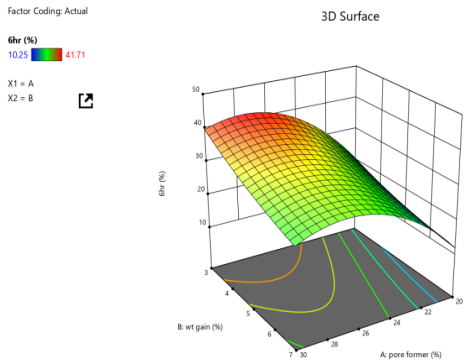

Figure 5: Response surface plot of Q6

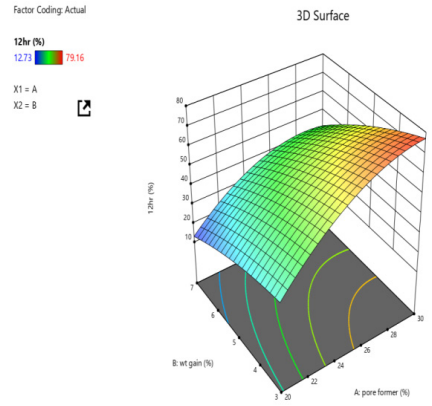

Figure 6: Response surface plot of Q12

Table 4: Comparison of predicted and experimental values of OF1 and OF2

Responses	*OF1*		*OF2*	
	Predicted	*Experimental*	*Predicted*	*Experimental*
Q6	38.85	39.50	31.5	30.54
Q12	71.82	72.25	62.30	64.52
Q24	83..38	84.53	83.94	82.36

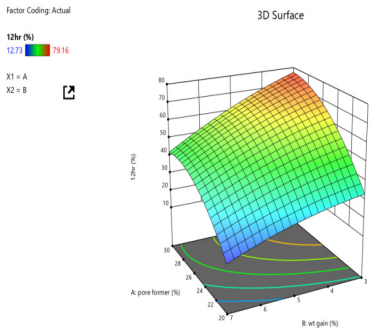

Figure 7: Response surface plot of Q24

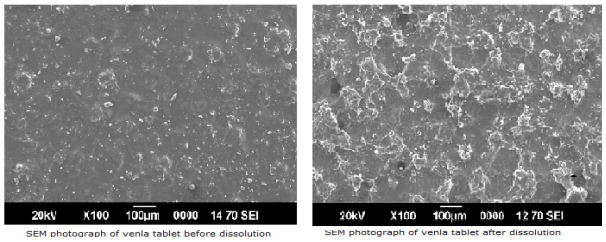

Figure 8: SEM photograph of venlafaxine tablet before and after dissolution study

Table 5: Stability study data of venlafaxine HCL tablet.

Tests	*Limits*	*Initial*	*1 Month*	*2 Months*	*3 Months*
Appearance	No change	No any change			
Assay	Venlafexine HCl USP (NLT 90% to NMT 110% of labeled amount of venlafexine HCl)	100.51	100.44	100.50	100.48
Cumulative release (%)	2 hr =10 to 30%	11.77	10.80	11.65	11.75
	4 hr =33 to 53%	34.09	34.10	34.95	34.89
	8 hr = 58 to 78%	58.95	58.61	58.55	59.02
	12 hr =68 to 88%	79.16	79.56	79.02	79.35
	20 hr = NLT 80%	87.35	87.92	87.36	87.65

were observed over 3 months. The findings of the expedited stability studies showed that the parameters had not changed significantly based on the information in Table 5. The medication content maintained more than 100% for 3 months.[26] As a result, formulation F7 is regarded as stable.

CONCLUSION

Venlafaxine hydrochloride sustained-release tablets were created using controlled porosity osmotic technology. With the aid of a 32 factorial design and careful observation of the chosen formulation factors, the intended release of venlafaxine from the Controlled Porosity Osmotic Pump (CPOP) was accomplished. The study's variables for pore former, *i.e.,* sorbitol and weight growth i.e., coat weight of cellulose acetate, had a discernible impact on the formulation's Q6, Q12, and Q24 responses. It has been demonstrated that as pore concentration increased, drug release from the system was also observed to rise. However, drug release decreased as weight gain increased. *In-vitro* release investigations established that release was significantly reliant on the concentration of pore former and weight gain of the tablet coating but independent of dissolution media and agitation intensity.

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