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Design and Optimization of Anti-Depressant Sustained Release Matrix Tablets

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ABSTRACT

The aim of the present work was to design and optimize venlafaxine sustained release matrix tablets. In this the matrix tablets were prepared using various drug to polymer ratio by wet granulation method. 3^2 factorial design was applied to study the effect of concentration of hydroxy propyl methyl cellulose and poly ethylene oxide combination on the percentage cumulative release after 2 hours, 8hours and 17hrs in the core tablet. In vitro release profiles for all the optimized batches were performed which showed a maximum release of 99.84% for 17hours.Surface response graphs were presented to examine the effects of independent variables on the responses studied. The optimized formulation was compared with the available marketed formulation in which the relative dissolution profiles were calculated by similarity and dissimilarity factors. Stability studies were performed for the best optimized batch which was found to be stable after 3 months.

Keywords: Wet granulation method, 3^2 factorial design, Surface response graphs and similarity factor.

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INTRODUCTION

The aim of a drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reaction. New and more sophisticated controlled release or sustained release delivery system are constantly being developed and tested [1].

Sustained release dosage forms are advantageous in having patient compliance, reduction of total dose, reduced 'see- saw' fluctuation and improved efficiency in treatment [2]. Various classes of anti-depressants used now a days have various side-effects such as sedation, hypotension, cardiac arrhythmias, seizure precipitation, enzyme inhibitory action, dose related CNS toxicity, renal diabetes insipidus, loss of libido and failure of orgasm. Hence, there is a need for the development of a controlled release formulation containing new antidepressant drug which will help to overcome above mentioned side-effects.

Venlafaxine hydrochloride, a novel antidepressant was selected as a drug of choice. In this formulation, preparation and characterization of venlafaxine sustained release tablets was performed $.3^2$ factorial design was applied to check the polymer concentration that has pronounced effect on tablet properties and drug release profile of the formulations [3].

MATERIALS AND METHODS

Drug Venlafaxine Hcl was obtained as a gift sample from Aurobindo Pharma Ltd., Hyderabad. Hydroxy propyl methyl cellulose (HPMC), Micro crystalline cellulose (MCC), polyvinyl pyrrolidone, magnesium stearate and stearic acid were purchased from S.D. Fine Chemicals Ltd., Mumbai. Polyethylene oxide (PEO) was obtained from Colorcon India Ltd, Goa. All the chemicals and reagents used were of analytical grade.

Table 1 : Formulation of optimized batches

Ingredients [mg]	F1	F2	F3	F 4	F 5	F6	F7	F8	F9
Venlafaxine Hcl	75	75	75	75	75	75	75	75	75
HPMC K100M*	75	75	75	80	80	80	85	85	85
PEO**	75	80	85	75	80	85	75	80	85
MCC#	66	61	56	61	56	51	56	51	46
Polyvinyl pyrrolidone	8	8	8	8	8	8	8	8	8
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Stearic acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Total weight per tablet is 300 mg
HPMC K100M -Hydroxy propyl methyl cellulose*
PEO-Polyethylene oxide**
MCC-Microcrystalline cellulose#

Preformulation Studies

Preformulation studies are the first step in the rational development of dosage form of a drug substance. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product [4]. A spectrophotometric method based on the measurement of absorbance at 225 nm in Hydrochloric acid (pH 1.2) and Phosphate buffer (pH 6.8), was used in the present study for the estimation of Venlafaxine hydrochloride [5, 6].

Formulation and Evaluation

Initially nine trial batches were formulated by wet granulation method. In these accurately weighed quantities of pre-sieved drug Venlafaxine Hcl, polymers like HPMC and PEO were mixed thoroughly. The binder solution prepared using polyvinyl pyrrolidone is mixed with powder mixture to form a wet mass. The dough mass was passed through 12 mesh sieve to get wet granules. These granules were dried at 65^{o}c and these granules were passed through 18 screen size mesh and then mixed. Stearic acid and magnesium stearate were passed through 40 screen size mesh and added to the above blend .All the prepared matrix tablets were evaluated for the weight variation, hardness, friability and disintegration [7].

In-vitro Drug Release Studies

In-vitro dissolution studies were carried out using USP type II dissolution apparatus with stirring rate of 100 rpm and temperature of 37±0.5 ^{o}c. Initial drug release was carried out in 900 ml of 0.1N Hcl for 2 hrs followed by phosphate buffer pH 6.8 for next 15hrs.The samples were analyzed spectrophotometrically at a wavelength of 225 nm.

Optimization by 3^2 Factorial Design

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The factors were selected based on preliminary study. The concentration of HPMC (X1) and the concentration of PEO (X2) were selected as independent variables. The percentage drug release at 2, 8 and 17 hours respectively are selected as dependent variables. Finally the best selected optimized formulation was evaluated [8]. To determine the drug release mechanism and to compare the release profile differences among the sustained release matrix tablets, the amount of drug released versus time was used. The release data were analyzed with the following mathematical models like Zero order, First order, Higuchi and Peppas models [9]. The best optimized formulation was compared with the available marketed product Venlor XR. Evaluation tests and dissolution studies parameters are studied for the marketed product and checked for their similarity and dissimilarity factors [10, 11]. Stability studies were performed for 3months to the best optimized formulation [12].

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Similarity Factor

$$f2 = 50 \log \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100$$

Dissimilarity Factor

$$f1 = \{ [\sum_{t=1}^{n} | R_t - T_t | / [\sum_{t=1}^{n} R_t] \} .100$$

RESULT AND DISCUSSION

Table 2 : Physical properties of pre compression blend

Formulation code	Angle of Repose (°)	Tapped Density (gm/ml)	Bulk Density (gm/ml)	Hausner's Ratio	Carr's Index (%)
F1	28.64	0.473	0.404	1.18	15.22
F2	23.72	0.512	0.452	1.16	14.06
F3	24.24	0.504	0.429	1.17	14.88
F4	23.22	0.704	0.593	1.19	17.04
F5	24.45	0.688	0.622	1.18	17.98
F6	27.67	0.720	0.629	1.14	15.18
F7	24.42	0.515	0.437	1.18	15.15
F8	29.16	0.666	0.616	1.12	18.60
F9	28.13	0.694	0.625	1.20	16.73

The Angle of repose was determined by fixed funnel method. Table 2 shows the angle of repose and was in the range of 23.22 to 29.16 which revealed that the granules of all the batches (F1to F9) had good flow characteristics and flow rates. The Carr's index was in the range of 14.06 to 15.28 shows that the granules of batches (F1, F2, F3, F6&F7) had good flow properties while the batches (F4, F5, F8& F9) showed fair flow properties. The Hausner's ratio was in the range of 1.12to1.20 shows that formulations (F1, F2, F3, F5, F6, F7, and F8) had good flow properties. Formulations (F4&F9) had Hausner ratio in the range of 1.19 to 1.20 shows fair flow property.

Table 3 : Evaluation parameters of Optimized batches

Formulation Code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)
F1	300±0.116	5.4±0.12	5.21±0.17	0.53±0.12
F2	301±0.127	5.4±0.13	5.39±0.18	0.36±0.17
F3	302±0.111	5.6±0.27	5.18±0.12	0.39±0.12
F4	300±0.116	5.7±0.20	5.24±0.12	0.47±0.14
F5	299±0.121	5.4±0.42	5.23±0.11	0.38±0.25
F6	300±0.116	5.7±0.74	5.12±0.14	0.39±0.16
F7	302±0.120	5.8±0.32	5.36±0.12	0.41±0.18
F8	300±0.187	5.5±0.27	5.25±0.16	0.56±0.13
F9	301±0.121	5.5±0.45	5.13±0.12	0.42±0.16

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Figure 1 : Invitro release profile of optimized batches F1-F9

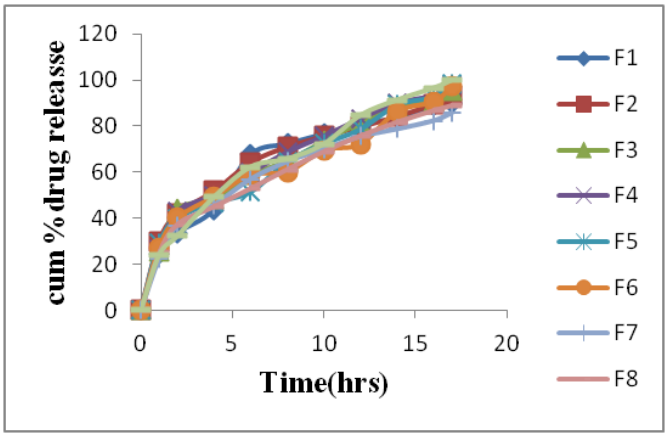

Table 4 : In-vitro dissolution study for optimized batches

Percentage Drug release									
Tme (hrs)	F1	F 2	F 3	F 4	F 5	F6	F7	F8	F9
1	24.41±0.126	29.84±0.132	25.63±0.132	26.7±0.163	29.01±0.162	27.10±0.124	22.35±0.125	24.77±0.124	23.98±0.126
2	33.63±0.112	42.01±0.154	43.78±0.123	42.77±0.145	39.86±0.154	40.07±0.121	36.89±0.132	37.23±0.142	32.16±0.124
4	43.7±0.132	51.78±0.153	48.34±0.146	50.06±0.134	46.72±0.125	49.24±0.122	45.64±0.121	44.91±0.130	49.07±0.116
6	67.63±0.108	64.27±0.141	58.76±0.146	59.74±0.164	51.34±0.163	58.76±0.131	56.96±0.135	52.85±0.128	62.16±0.103
8	72.32±0.123	71.08±0.121	64.83±0.174	68.65±0.127	64.56±0.123	60.12±0.162	64.53±0.142	61.13±0.163	65.67±0.132
10	76.61±0.121	75.68±0.132	73.46±0.145	75.64±0.182	72.31±0.141	69.5±0.112	70.01±0.137	68.9±0.126	72.1±0.146
12	80.76±0.132	79.85±0.167	81.65±0.165	83.21±0.145	78.62±0.132	72.14±0.141	75.45±0.115	75.81±1.125	84.6±0.116
14	83.67±0.103	84.3±0.123	88.24±0.184	90.04±0.142	89.21±0.124	86.34±0.121	78.67±0.132	81.72±0.132	91.21±0.141
16	88.96±0.123	89.67±0.123	90.67±0.164	93.26±0.162	92.64±0.122	90.54±0.321	82.31±1.142	86.77±0.152	96.45±0.102
17	90.01±0.132	93.36±0.165	95.32±0.164	97.89±0.153	98.47±0.134	97.36±01 44	85.67±0.131	88.91±0.131	99.84±0.114

Table 3 shows that Weight variation of optimized batches was found to be in the range of 299 ± 0.121 to 302 ± 0.120. All the batch tablets are within the specified limits. The Hardness was in the range of 5.4 ± 0.12 to 5.8 ± 0.32 which is within the specified limits. The thickness was found in the range of 5.12 ± 0.14 to 5.39 ± 0.18 and is within the limits.

The friability was found in the range of 0.36 ± 0.17 to 0.56 ± 0.13 which is within the limits. The disintegration time was found to be in the range of 11.12 ±0.26 to 13.53 ± 0.27 for all the batches (F1&F9).

From table 4 the optimized batch formulations showed a % drug release range from 24.41 to 99.84.Formulation F9 showed 99.84 % of drug release. All the batches showed release for a period of 17hrs. From all of the optimized batches F9 showed maximum percentage of drug release with maximum sustained release action. So formulation F9 was selected as optimized formulation. The optimized formulation F9 followed Zero order with Higuchi kinetics with quasi-Fickian diffusion.

Table 5 : Comparative evaluation for marketed and best optimized batch

Parameters	Marketed product	Formulation (f9)
Wt variation (mg)	286±0.15	301±0.12
Hardness (kg/cm²)	5.2±0.12	5.5±0.45
Thickness (mm)	5.1±0.17	5.13±0.12
Friability	0.53±0.18	0.42±0.16
D.T (min.sec)	12.56±0.12	12.16±0.17
Assay %	99.89	98.67

From table 5 the evaluation parameters like weight variation, Hardness, Thickness, Friability, Disintegration time, and assay values are reported for the marketed product. The percentage drug release was found to be 100.95 for the marketed product when compared to the optimized formulation F9 which has 99.84 percent drug release.

Figure 2, 3 & 4 shows the response surface plots for the optimized formulation F9 at 2, 8 and 17hrs.This ensures that the concentration of HPMC and PEO polymers affected the response variables.

Figure 5 shows the comparative percentage drug release for the optimized formulation and the marketed product XR. Table 6 indicates the similarity and dissimilarity values for the optimized formulation F9 and the marketed product. Similarity (f2) value was found in the range from 50.05 to 51.56 which indicates that the optimized product and the marketed product release are similar. Dissimilarity (f1) value was found in the range from 3.68 to 9.10 which shows that there was a minor difference between the optimized and marketed product.

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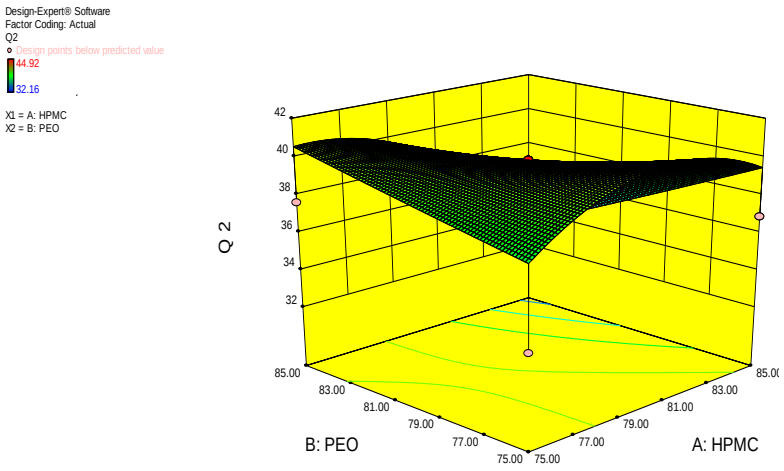

Figure 2 : Surface Response plot of response Y1 at 2hrs

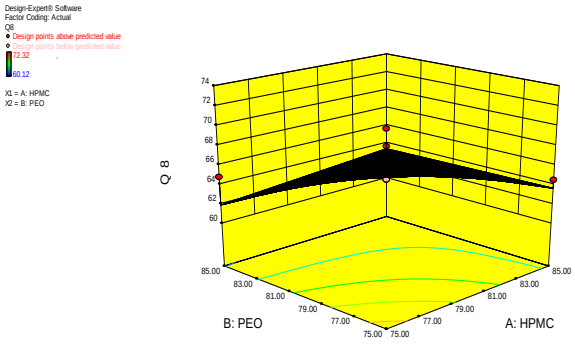

Figure 3 : Surface Response plot of response Y2 at 8hrs

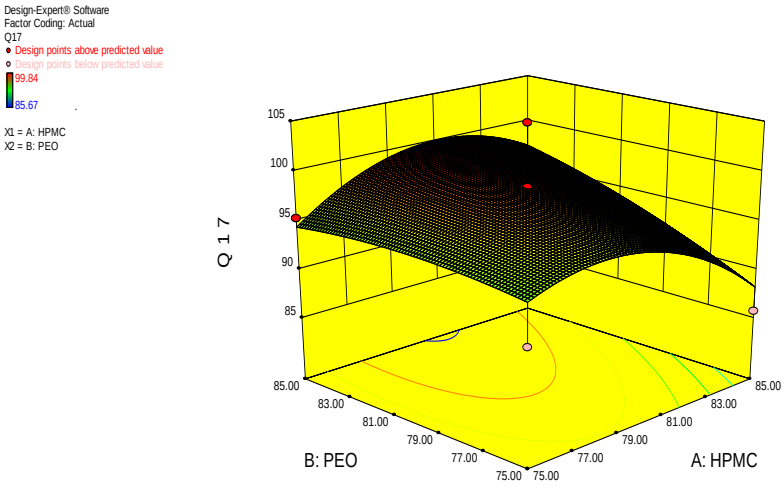

Figure 4 : Surface Response plot of response Y2 at 17rs

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Table 6: Similarity and Dissimilarity factors

Time	Similarity factor f2	Dissimilarity factor f1
1	50.91	3.68
2	51.05	8.57
4	51.29	6.94
6	51.35	5.78
8	51.43	8.25
10	51.51	7.85
12	51.46	4.66
14	51.49	9.10
16	51.53	8.82
17	51.56	6.71

Figure 5 : Comparative release profiles with marketed product

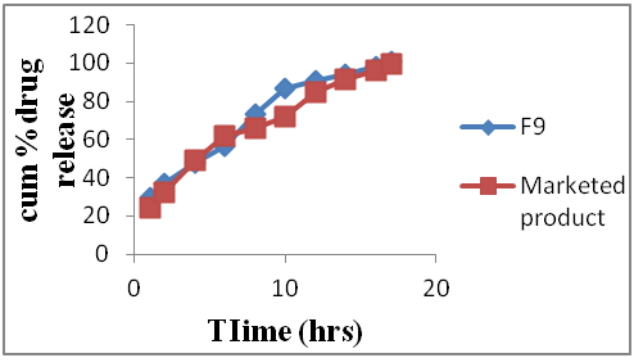

Table 7 : Stability studies

S.No	Parameters	25^{0}C/60%RH			40^{0}C/75%RH		
		0Day	1Month	3Months	0Day	1Month	3Months
1	Weight variation	301±0.16	301±0.23	302±0.12	301±0.17	302 ±0.21	303 ±0.14
2	Thickness	5.13±0.12	5.11±0.19	5.14±0.23	5.13±0.17	5.21 ±0.14	5.28 ±0.15
3	Hardness	5.5±0.45	5.6 ±0.38	5.3 ±0.12	5.4 ±0.24	5.6 ±0.12	5.7 ±0.27
4	Friability	0.42 ±0.16	0.41±0.23	0.36 ±0.15	0.41±0.16	0.39 ±0.12	0.43 ±0.21
5	Disintegration	12.16±0.17	12.09±021	14.06±0.14	12.21±0.23	14.97±0.121	14.06±0.23
6	Assay	98.67	98.21	97.45	98.96	97.10	97.43
7	%Drug release	99.84	98.76	98.21	99.21	98.89	98.93

Stability studies for optimized formulation F9 at 25 ^{o}c/60% RH and 40 ^{o}c/60%RH

Stability studies data (table no 7) showed that there was no significant variation in drug release.

Therefore it was concluded that the best optimized formulation F9 was stable over the chosen temperature and humidity for 3 months.

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CONCLUSION

From the above results it was concluded that F9 optimized formulation might be suitable for large scale preparation of sustained release matrix tablets.

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