



Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Venlafaxine Hydrochloride Controlled Release Bilayer Tablets: Optimization of Formulation Variable by Using Dyspnea on Exertion

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ARTICLE INFO

Article history:

Received: 08 January, 2020

Revised: 25 February, 2020

Accepted: 03 March, 2020

Published: 30 March, 2020

Keywords:

Bilayer tablet,
Factorial design,
Similarity factor (f_2),
Theoretical drug release,
Venlafaxine HCl.

DOI:

10.25004/IJPSDR.2020.120208

ABSTRACT

The current research work was to develop bilayer tablet of venlafaxine hydrochloride to increase drug efficacy for efficient treatment of depression. The satisfactory result of treatment can be achieved upon the maintenance of drug concentration within an effective level in the body, so a uniform and constant drug supply are desirable. An immediate layer of venlafaxine HCl was formulated using super disintegrants, i.e., croscarmellose sodium (CCS) and sodium starch glycolate (SSG); tablet compact by direct compression. HPMC K100M and ethylcellulose (EC) were utilized as release retarding polymers in sustained release layer by wet granulation technique with the help of PVP K30 in IPA solution (10%) as a granulating agent. Full 3^2 factorial designs were used to find out the optimum quantity of release retardant polymers. Bilayer tablet was evaluated for various parameters, i.e. hardness, friability, weight variation, % drug content, disintegration time (IR layer), and % drug release study. Statically, an analysis was carried out using factor X1 (HPMC K100M) and X2 (EC) for dependent variable % drug release at 8, 12, and 20 hours. A formulation was optimized and a formulation containing 305.36 mg of HPMC K100M and 54.03 mg of ethyl cellulose. Optimized formulation show 47.12 ± 2.1 , 59.89 ± 2.2 , and 89.06 ± 2.3 drug release at 8, 12, and 20 hours, respectively, which is almost similar to theoretical dose calculation with similarity factor f_2 97, 99, and 98%, respectively. Bilayer tablet formulation was observed to be stable and fulfilled all compendia specifications.

INTRODUCTION

Formulation of an advanced drug delivery system of existing drugs can improve performance like safety, efficacy and patient adherence. And need for efficient drug therapy with decreased side effects.^[1]

The multilayered tablets help in the administration of the incompatible drug^[2] and provide release in a controlled manner by forming a boundary or swelling layers. Controlled release systems show different controlled drug release pattern such as extended, constant, multimodal, and pulsatile release profiles.^[3-5]

Bilayered tablets are containing the first layer of a drug as immediate release and the second dose in another layer as extended-release or both as an immediate release.

They are made by compression of two different feed into a single die cavity, another over in first place, in layers. They appear as a sandwich of each layer, seen separately.^[6]

The main principle of sustained drug delivery (SDD) is to increase the efficacy of a drug and to increase safety and patient adherence. Tablet assists in release of two incompatible active pharmaceutical ingredient (API) in two distinct layers at the same time, one by one release of drugs, and the first release layer as immediate release and subsequent layer as a maintenance dose.^[7]

The Bilayer Tablet Press is displacement monitoring, single and double-sided. The various Bilayer tablet techniques are L-OROS, Oros® Push-Pull, DUREDAS™, EN SO TROL, and DUROS Technology.^[8]

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Bi-layer tablet can be employed for various approaches like Polymeric, Floating, Bio-adhesive, and Swelling Delivery System.^[9]

In present investigation, we developed a bilayer tablet for venlafaxine HCl with the aim of maintaining drug concentration in body within an effective level. Venlafaxine is an antidepressive agent and belongs to BCS CLASS-I. It acts by inhibiting norepinephrine and serotonin reuptake and weakly inhibit dopamine reuptake. The drug has a half-life of 5 hours. It is administered 75–375 mg/day, given in 2–3 divided doses and taken with food. It is used for management of major depression (MDD), social phobia, generalized anxiety disorder (GAD), panic disorder with or without agoraphobia, neuropathic pain, and vasomotor symptoms in female after menopause and those suffering with breast cancer.^[10] An initial screening was designed and evaluated for promising immediate release and then drug release controlling layer of bilayer tablets as to optimize drug release after a release of an immediate layer, with an expectation of bioavailability improvement.

MATERIALS AND METHODS

Venlafaxine was acquired as a gift sample from Aarti Industries. Ltd., Vapi, Gujarat, India, HPMC K100M. Sodium starch glycolate was acquired as a gift sample from Colorcon, Goa. EC was obtained from Astron Chemicals, Ahmedabad, India. The PVP K30 were obtained from Seva Fine Chemicals, Ahmedabad, India, Dicalcium Phosphate and Tale were obtained from West Coast Laboratories (Mumbai, India), Isopropyl Alcohol was obtained from Thomas Baker, Daman, Mannitol and Magnesium Stearate was obtained from Rankem Ltd. (New Delhi), and Loba Chemie Private Ltd. (Mumbai, India). All chemicals and reagents of analytical grade were used.

METHODS

Dose Calculation Based on Half-life

Total dose calculation in a bilayer tablet, for loading and maintenance dose of venlafaxine in fast release and retarding layer, was done using the following equation.^[11]

Pharmacokinetic evaluation of venlafaxine HCl used for computation of hypothetical drug release profile for 24 hours bilayer tablet was therapeutic concentration (150 mg/m), bioavailability 55%, biological half-life (5 hours), and volume of distribution (7.5 L/kg). The immediate-release part for sustained release venlafaxine HCl was calculated using the following equation and was observed to be 67.5 mg.^[12]

$$D_L = (C_{\max} V_d) / F = 67.5 \text{ mg}$$

Where D_L = Loading dose,

V_d = Volume of distribution,

$C_{\max}$ = maximum plasma concentration,

F = bioavailability fraction.

For 12-hour release profiles, a total dose of HCl required is calculated by equation

$$D_{\text{total}} = \text{Dose} [1 + 0.693 \times (t/t_{1/2})]$$

Where Total = Total dose

Dose = In fast-release layer (67.5 mg)

t = Time (hrs) for which drug retarding layer is desirable (24 hrs)

$t_{1/2}$ = Biological Half-life of API(5)

$$D_{\text{total}} = 67.5 [1 + 0.693 \times (24/5)] = 292.032 \text{ mg}$$

Henceforth, the formulation must drug release 67.5 mg (24.054%) in a first hr as conventional tablets and then 34.52 mg (6.90%) per hour up to 12 hours after that.

Bilayer Tablet of Venlafaxine HCl Formulated

The development of bilayer tablet of venlafaxine HCl was carried in two different stages. The immediate-release layer (IR) of venlafaxine HCl and Sustain layer of venlafaxine HCl was prepared separately. Various preliminary trials were conducted to standardize formula for an individual layer of a bilayer tablet. After the optimization of an individual layer, bilayer tablet was prepared using an optimized formula. Therefore experimental work was divided into three parts.

Immediate-release Layer of Venlafaxine HCl

Various fast release layers were prepared and compact by direct compression. All ingredients were weighed accurately and gone through #80 meshes. Required quantities of drug, polymer, and diluents were mixed thoroughly for 5 minutes, except talc and Magnesium stearate. Talc and magnesium stearate were added as glidant and lubricant, mixed well powder blend for 5 minutes. All formulation of tablets was compressed using Oval shape punch of rotary tablet compression machine (Hardik Engg., Ahmedabad).

Sustained-release (SR) Layer of Venlafaxine HCl

An accurate quantity of drug and other excipients were weighed and mixed uniformly using mortar and pastel. Thirty-two full factorial designs were developed, selecting amounts of HPMC K100M (X_1) and EC (X_2) as two independent factors. The dependent variables selected were drug release at 8 hours (Q8), at 12 hours (Q12), and 20 hours (Q20). The selection of levels was based on a preliminary study carried out. All other processing and formulation variable was kept invariable all through an examination. Table 1 delineates a summary of experimental runs, factor combinations, and the actual value of coded levels to experimental study. A solution PVP K30 prepared in IPA (10%) was added to the tablet powder blend to obtain a damp mass. Extrudes of this mass was obtained by passing it from sieve no # 22; this extrudes mass were dry in hot air oven at 40°C for 30 min. Shifted granules were taken in a polyethylene bag and magnesium stearate and talc were included and mix for 5 min. For the preparation of bilayer tablet, an immediate-release layer was a kept constant and bilayer tablets were formulated



Table 1: Composition of bilayer tablets

<i>Immediate release layer (100 mg)*</i>									
Venlafaxine HCl									67
Sodium starch glycolate									2
PVP K30									5
Mannitol									23
Magnesium stearate									2
Talc									1
Lake dye									q.s.
<i>Sustained release layer (650 mg)*</i>									
<i>Ingredients</i>	<i>BL-1</i>	<i>BL-2</i>	<i>BL-3</i>	<i>BL-4</i>	<i>BL-5</i>	<i>BL-6</i>	<i>BL-7</i>	<i>BL-8</i>	<i>BL-9</i>
Venlafaxine HCl	225	225	225	225	225	225	225	225	225
HPMC K100M	250	300	350	250	300	350	250	300	350
EC	40	40	40	50	50	50	60	60	60
DCP	120	70	20	110	60	10	100	50	-
Mg stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
PVP K30 in IPA (10%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total wt	750	750	750	750	750	750	750	750	750

*All quantity in milligrams

by changing in sustained release layer. At the first weighted amount of sustained-release, a layer was added to die cavity and slightly compressed to form a uniform layer, then tablets were compressed finally by adding an immediate layer using composition.^[10] The weight of tablet was constant throughout the study. All tablet batches were prepared using an oval punch of a rotary tablet compression machine. Tablets were evaluated for various properties.

Evaluation of Batches of a Bilayer Tablet of Venlafaxine HCl

Weight Variation

Twenty tablets randomly selected and find an average weight of 20 tablets by the individual weighting of tablets using electronic weighing balance (Reptech, Mumbai). Not more than two of individual tablet weights deviation from 20 tablets average weight as per limits are given in IP-2007.^[13]

Hardness

Hardness of the tablet demonstrates its capacity to withstand mechanical shock while handling. Tablet hardness was estimated utilizing Monsanto hardness tester (Dolphin, Mumbai). It is measure in terms of kg/cm². Three tablets were selected randomized from each batch and hardness assessed. Average and standard deviation was computed.^[14]

Thickness

Tablet thickness was measured by vernier caliper (Moore and Wright Precision tool, Digimatic Caliper). Tablet thickness ought to be controlled inside a $\pm 5\%$ variety of

standard value. The mean and standard deviation was also calculated.^[15]

Friability

Friability of a tablet was determined in the laboratory by Roche friability tester (Scintico Instruments, Mumbai). A pre-weighed 20 tablets were put in a friabilator. Friabilator comprises of a plastic chamber that spins at 25 rpm. The tablets were subject to rotation in the friabilator for 100 rotations. At that point tablets were cleaned and reweight; weight reduction is measured. Tablet friability is express in terms of percentage and furthermore, was dictated by following equation:^[16]

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Disintegration Test (IR layer)

The test was utilizing apparatus mentioned in Indian Pharmacopeia 2007 using distilled water is used as disintegration media and temperature maintain $37^\circ\text{C} \pm 2^\circ\text{C}$ and time (seconds) taken for finish tablet crumbling with no acceptable mass remaining is estimated. Each batch was taken three samples and the standard deviation was calculated.^[13]

Drug Content

Tablet crush and accurately weighted powder equivalent to 100 mg of drug and transferred to a volumetric flask containing 100 mL phosphate buffer of pH 6.8. The drug was dissolved by shaking flask and adjusted to volume with buffer. The solution was suitably diluted with phosphate buffer and from resulted solution take 1 mL and dilute it in 10 mL volumetric flask with buffer and absorbance of the

resulted solution was scan at λ_{max} 225 nm in UV-Visible spectrophotometer (1800, Shimadzu, Japan).^[17]

***In vitro* Drug Release Study**

In vitro release of all formulations was done in the dissolution apparatus (TDT-06, Electrolab, Mumbai) type II as per IP (2007) dissolution method A. One pre-weighed tablet was placed in dissolution medium. The predetermined time interval was 10 mL aliquots withdrawn, and an equal volume of buffer medium was added. Samples were analyzed by using UV-Visible at λ_{max} 225 nm using 0.1 N HCl and pH 6.8 phosphate buffer as a blank. Absorbance was noted down, and concentration was calculated.^[13]

Accelerated Stability Studies

Optimized formulation was put in stability samples; the study was carried out on Stability Control Chamber (Remi Instruments Ltd.) at 40°C/75% relative humidity for a period of one month. The sample was enveloped by covered aluminum foil, and it was placed in an accelerated stability chamber. Inspecting was at a foreordained time interims of 0, 15, and 30 days. Tablets were assessed for various physicochemical parameters.^[18,19]

RESULT AND DISCUSSION

Pre-compression Parameters

The angle of repose value of BL-1 to BL-9 batches was found between 25.31 ± 2.01 and 29.36 ± 1.14 , respectively. Bulk

density was found between 0.41 ± 0.011 to 0.441 ± 0.010 gm/cm³ respectively. Tapped density was found between 0.494 ± 0.023 to 0.541 ± 0.011 gm/cm³ respectively. Carr index was found between 15.58 and 23.50%, respectively. Hausner's ratio was found between 1.18 to 1.30, respectively. Data were shown in Table 2.

Physical Parameters

A hardness of BL-1 to BL-9 batches tablets was found to range from 7.33 ± 0.58 to 8 kg/cm². This indicated a good mechanical strength of tablets. Friability was calculated that also indicates the tablet's strength. Here, friability values for all tablet batches were found within the prescribed limit of <1%, which passes IP (2007) specification limits. The weight variation BL-1 to BL-9 batches was found between 749.977 ± 0.951 mg to 750.01 ± 1.255 mg, which complied with the test for weight variation. The Thickness was varying from 4.88 ± 0.03 mm to 4.94 ± 0.0388 mm. % drug content was seen between 98.83 ± 0.398 % to 100.7 ± 0.71 % that also falls in normal range. Drug content uniformity was found good for all batches that were more than 98.83%. From results shown in Table 3, all batches show acceptable physical characteristics. The fourier-transform infrared spectroscopy (FTIR) spectra confirmed drug-excipients compatibility with each other as there were no possible interactions observed.

The In-vitro Drug Release Profile of Formulation

In vitro drug release study data was shown in Fig. 1; it was found that batch BL-1, BL-4, and BL-7 showed drug release

Table 2: Evaluation parameters for granules of batches BL-1 to BL-9

Batches	Angle of repose* (°)	Bulk density* (gm/mL)	Tapped density* (gm/mL)	% Carr's index	Hausner's ratio
BL-1	27 ± 1.21	0.423 ± 0.017	0.512 ± 0.019	17.38	1.21
BL-2	25.36 ± 2.29	0.437 ± 0.019	0.541 ± 0.011	19.22	1.24
BL-3	29.36 ± 1.14	0.441 ± 0.010	0.535 ± 0.008	17.57	1.25
BL-4	25.36 ± 1.29	0.429 ± 0.021	0.525 ± 0.017	18.29	1.22
BL-5	25.12 ± 1.01	0.413 ± 0.017	0.497 ± 0.017	16.90	1.20
BL-6	28.54 ± 1.12	0.420 ± 0.021	0.527 ± 0.009	20.30	1.25
BL-7	27.18 ± 1.32	0.427 ± 0.01	0.529 ± 0.013	19.28	1.24
BL-8	25.31 ± 2.01	0.417 ± 0.015	0.494 ± 0.023	15.58	1.18
BL-9	27.48 ± 2.26	0.41 ± 0.011	0.536 ± 0.021	23.50	1.30

*All Values are expressed as mean $\pm$ SD, n = 3.

Table 3: Physical parameter of bilayer tablets of batches

Batches	Hardness* (kg/cm ²)	Friability (%)	Weight uniformity* (mg)	Thickness* (mm)	Drug content* (%)
BL-1	7.33 ± 0.58	0.179	749.44 ± 1.147	4.88 ± 0.068	99.13 ± 0.211
BL-2	7.33 ± 0.58	0.290	749.777 ± 1.468	4.843 ± 0.075	99.43 ± 0.216
BL-3	8 ± 0.00	0.231	750.477 ± 1.180	4.90 ± 0.1	98.83 ± 0.398
BL-4	7.67 ± 0.58	0.345	749.443 ± 1.279	4.89 ± 0.090	100.7 ± 0.71
BL-5	7.67 ± 0.58	0.119	750.01 ± 1.255	4.913 ± 0.065	99.86 ± 0.734
BL-6	7 ± 0.00	0.200	750.31 ± 1.09	4.893 ± 0.015	100.25 ± 0.705
BL-7	7.67 ± 0.58	0.166	749.977 ± 0.951	4.893 ± 0.015	100.25 ± 0.705
BL-8	7.33 ± 0.58	0.151	749.576 ± 1.094	$.903 \pm 0.021$	99.89 ± 0.842
BL-9	7.33 ± 0.58	0.162	749.243 ± 1.085	4.94 ± 0.0388	99.89 ± 0.802

*All Values are expressed as mean $\pm$ SD, n = 3.



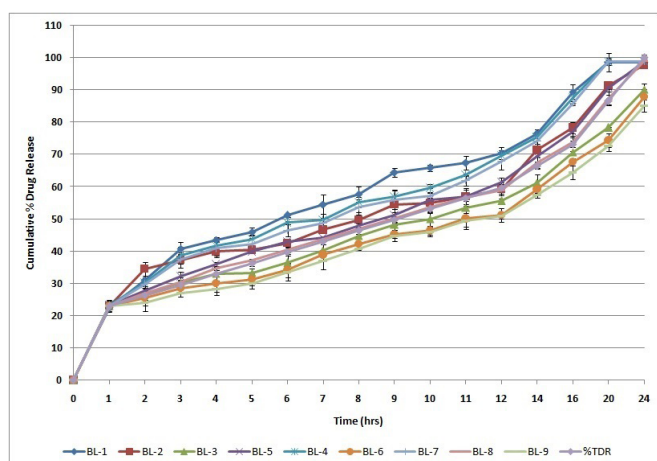


Figure 1: In-vitro drug release study of Bilayer Tablet of BL-1 to BL-9 with %TDR

Fig. 1: In-vitro drug release study of bilayer tablet of BL-1 to BL-9 with %TDR

up to 20 hours, and its give 98.71 ± 0.6 , 98.91 ± 1.3 , and 98.95 ± 0.8 % drug release respectively. The batch BL-2, BL-5, and BL-8 were able to release drug up to 24 hrs and give 97.78 ± 1.1 , 98.78 ± 1.8 , and 99.11 ± 0.5 % drug release, respectively. Batch BL-3, BL-6, and BL-9 have resulted in a show that drug release retarding up to 24 hours, but it gives only 90.21 ± 1.7 , 87.88 ± 2.3 , and 85.17 ± 1.9 % drug releases respectively. So batch BL-8 (300 mg HPMC K100M, 60 mg EC) showed maximum % drug release than other batches.^[10]

Optimization of Bilayer Tablet Using 3² Factorial Design

For all nine batches of bilayer tablets prepared independent variable, i.e., amount of HPMC K100M (X₁) and amount of

EC (X₂), depended variable like % drug release at 8 hours (Q₈), at 20 hours (Q₁₂), and 20 hours (Q₂₀) was evaluate and tabulated in Table 4.^[20]

A two-independent variable, a three-level full factorial design was constructed RSM performs 9 runs. All observed 9 formulations were fit to a non-linear mathematic model; utilizing design expert 10.0.1 was shown in Table 5. It was seen that the best fit model was quadratic model along with the regression equation created for every response tabulated in Table 5. Model p-value was less than 0.05; model to best fit quadratic model. Multiple regression analysis (R²) suggests a proportion of measure of variety around mean as explained by the model. A negative value in the regression equation indicates response value decreases as the amount of factors increases.

Regression analysis ANOVA data for a dependent variable Y₁, Y₂, and Y₃ were for percentage drug release at 8, 12, and 20 hours, as all models of p-values were less than 0.05, all depended variable (Y₁, Y₂, and Y₃) best fitted quadratic model. Comparably, R² values for responses Y₁, Y₂, and Y₃ are 0.9984, 0.9976, and 0.9969, respectively.

% drug release at 8 hours

$$Q_8 = 47.88 - 6.49X_1 - 1.83X_2 + 0.017X_1X_2 + 0.86X_1^2 + 0.47X_2^2 \quad \text{..... (2)}$$

The amount of drug released at 8 hours from BL-1- BL-9 batches of bilayer tablets varied from 40.74 to 57.74 %. A p-value (p < 0.05) concluded that the impact of X₁ and X₂ was a prominent drug retarding effect at 8 hours. In the regression equation, a negative indication of X₁ and X₂ indicates that response value decreases as amounts of factors are raised.

Table 4: Composition of factorial batches with responses

Sr. No.	Batch	Coded factor level		% drug release at 8 hrs (Q ₈)	% drug release at 12 hrs (Q ₁₂)	% drug release at 20 hrs (Q ₂₀)
		X ₁	X ₂			
1	BL-1	-1	-1	57.74 ± 2.3	70.38 ± 1.9	98.59 ± 2.8
2	BL-2	0	-1	49.80 ± 2.3	59.3 ± 1.9	91.49 ± 1.3
3	BL-3	+1	-1	44.75 ± 0.1	55.61 ± 0.7	78.33 ± 0.2
4	BL-4	-1	0	55.26 ± 1.6	69.69 ± 1.6	98.77 ± 1.1
5	BL-5	0	0	47.9 ± 0.2	61.44 ± 1.3	90.70 ± 2.1
6	BL-6	+1	0	42.21 ± 0.21	51.25 ± 2.1	74.38 ± 2.1
7	BL-7	-1	+1	53.66 ± 2.3	67.89 ± 2.7	98.85 ± 0.6
8	BL-8	0	+1	46.89 ± 1.6	59.03 ± 1.3	87.29 ± 2.1
9	BL-9	+1	+1	40.74 ± 0.3	50.95 ± 0.9	72.67 ± 1.7

Table 5: Summary of statistical analysis of measured responses

Dependent variables	Q ₈ = % release at 8hrs		Q ₁₂ = % release at 12hrs		Q ₂₀ = % release at 20 hrs	
	P value	Coefficients	P value	Coefficients	P value	Coefficients
Intercept	0.0002	47.88	0.0021	61.21	0.0031	90.72
X ₁	<0.0001	-6.49	0.0003	-8.36	0.0004	-11.64
X ₂	0.0013	-1.83	0.0169	-2.07	0.0695	-1.89
X ₁ X ₂	0.9324	0.017	0.3771	-0.54	0.1294	-1.73
X ₁ ²	0.0488	0.86	0.4592	-0.63	0.0386	-4.16
X ₂ ²	0.1764	0.47	0.5005	0.57	0.8144	0.30

% drug release at 12 hours

$$Q_{12} = 61.21 - 8.36X_1 - 2.07X_2 - 0.54X_1X_2 - 0.63X_1^2 + 0.57X_2^2 \quad \dots\dots\dots(3)$$

The amount of drug released at 12 hours from BL-1-BL-9 batches of bilayer tablets varied from 50.95% to 70.38%. A p-value ($p < 0.05$) concluded that the impact of X_1 and X_2 was a prominent drug retarding effect at 12 hours. In the regression equation, a negative indication of X_1 and X_2 indicates that response value decreases as amounts of factors are raised.

% drug release at 20 hours

$$Q_{20} = 90.72 - 11.64X_1 - 1.89X_2 - 0.173X_1X_2 - 4.16X_1^2 + 0.30X_2^2 \quad \dots\dots\dots(4)$$

The amount of drug released at 20 hours from BL-1-BL-9 batches of bilayer tablet varied from 72.67% to 97.59%. A p-value ($p < 0.05$) concluded that the impact of X_1 and X_2 was a prominent drug retarding effect at 20 hours. In the regression equation, a negative indication of X_1 and X_2 indicates that response value decreases as amounts of factors are raised.

All variables show less than $p < 0.05$, all factors demonstrated a remarkable change in responses.

Contour plots and 3D response plots were constructed using Design Expert 10.0.1; (Figs. 2, 3, and 4) indicates an effect of interaction between factors on dependent variables. Response surface plot was used for further enlightening of dependent and independent variables

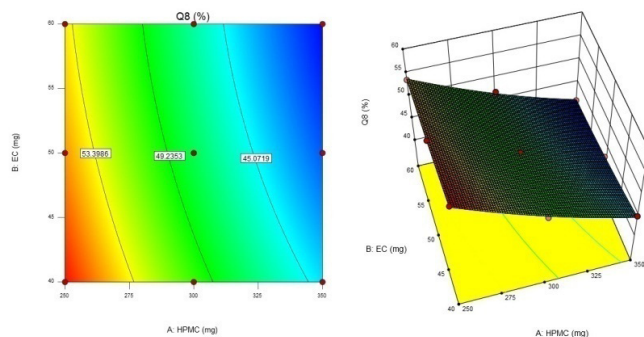


Figure 2: Response surface and contour plot showing the effects of X_1 and X_2 on the % drug release at 8 hrs (Q8).

Fig. 2: Response surface and contour plot showing the effects of X_1 and X_2 on the % drug release at 8 hrs (Q8).

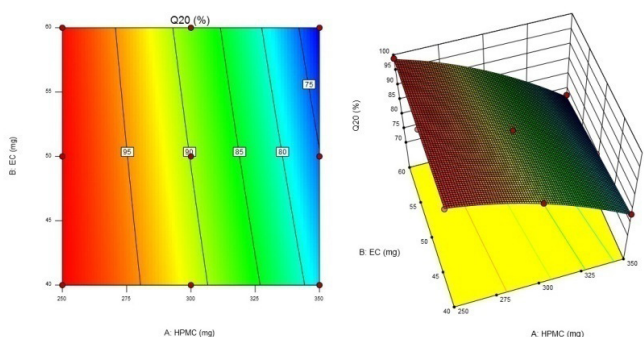


Figure 4: Response surface and contour plot showing the effects of X_1 and X_2 on the % drug release at 20hrs (Q20).

Fig. 4: Response surface and contour plot showing the effects of X_1 and X_2 on the % drug release at 20hrs (Q20).

relationship. Fig. 2 depicts an interaction impact among HPMC and EC on % drug release as a response. With the rise HPMC amount and EC amount, a linear decrease in % drug release was seen. 3D surface plot data was shown in Figs. 3 and 4, characterizing a more drug retarding with an increase in amount of HPMC and EC.

Validation of Optimized Batch

Design-expert software use for optimization of formulation and contour plots of all respondents use and criteria of the level selected; base on overlay plot final factor concentration for X_1 and X_2 were 305.36 mg and 54.03 mg. Further, this value base solved equation 2, 3, and 4, which gives theoretical % cumulative drug release of 46.39%, 59.79 and 86.58% at 8, at 12, and at 20 hours, respectively. A checkpoint formulation was prepared to utilize the above amount of factors. Estimated values of *in vitro* drug release at 8, at 1, and at 20 hours were found to be 47.12 ± 2.1 , 59.89 ± 2.2 , and 89.06 ± 2.3 , respectively, which show close agreement to theoretical values.

All post-compression evaluation parameters were performed and results (as shown in Table 6) are found to be within limits. In Fig. 5, there was a correlation of *in vitro* drug release of check-point batch with percentage

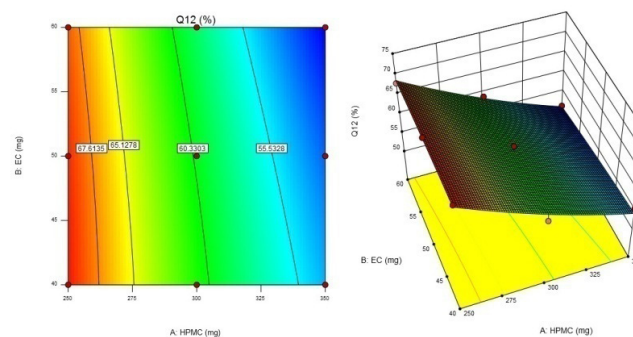


Figure 3: Response surface and contour plot showing the effects of X_1 and X_2 on the % drug release at 12hrs (Q12).

Fig. 3: Response surface and contour plot showing the effects of X_1 and X_2 on the % drug release at 12 hrs (Q12).

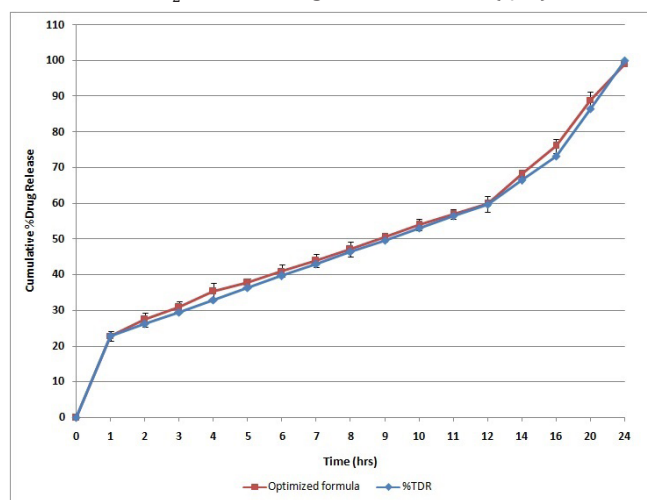


Fig. 5: *In-vitro* drug release profile of optimized batch and Theoretical % drug Release profile



Table 6: Evaluation of bilayer tablets of optimize batch

Evaluation parameter	Observation
Thickness (mm)	4.913 ± 0.065
Hardness (kg/cm ²)	7.67 ± 0.58
Weight variation	750.05 ± 0.9002
Friability (%)	0.119
Drug content (%)	99.69 ± 0.786

theoretical drug release. It revealed that the cumulative percentage drug release of bilayer tablets is similar to the percentage theoretical drug release with similarity factor (f₂) is 87%.

Accelerated Stability Studies

The stability study of optimized batch was performing as per ICH guidelines and revealed that no significant changes in physical parameters (i.e., color, odor, and hardness) when put in stability chamber at temperature and humidity conditions of 40°C/ 5% RH. The result shows that no significant change in drug content was seen over a time of one month.

CONCLUSION

The bilayer tablet of venlafaxine hydrochloride to increase drug efficacy for efficient treatment of depression was developed. The satisfactory result of treatment can be achieved upon the maintenance of drug concentration within an effective level in the body, so a uniform and constant drug supply are desirable. The fast release layers were prepared and compact by direct compression using super disintegrant (SSG and CCS). Pre and post-compression assessment parameters had seen to be acceptable for the optimized sustained and immediate-release layer of venlafaxine hydrochloride. An optimized batch of sustained-release (305.36 mg HPMC K100M, 54.03 mg EC) was considered best showing the desired drug release for instant and retarding layer, respectively. Hence the designed bilayered tablet possesses all the formulation qualities, and we achieved % drug release as per body requirement and comparable to theoretical drug profile, but if it is feasible or not for the production on the large scale must be explored.

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HOW TO CITE THIS ARTICLE: Dalvadi HP, Patel PJ, Vashi N, Paul A. Venlafaxine hydrochloride controlled release bilayer tablets: Optimization of formulation variable by using DoE. *Int. J. Pharm. Sci. Drug Res.* 2020;12(2):141-147. **DOI:** 10.25004/IJPSDR.2020.120208