International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 5, 2022

Original Article

ONE FACTOR RESPONSE SURFACE METHODOLOGY (RSM) FOR THE OPTIMIZATION OF ORAL VENLAFAXINE HCL CONTROLLED RELEASE ORGANOGEL

NISHANT OZA[1*], AMI MAKWANA[1], TUSHAR A. GOHIL[2]

[1]C. U. Shah College of Pharmacy and Research, Wadhwan City 363030, Gujarat, India, [2]Smt. C. V. Gajera Pharmacy Mahila College, Amreli 365601, Gujarat, India
Email: ozanishant@gmail.com

Received: 07 May 2022, Revised and Accepted: 25 Jun 2022

ABSTRACT

Objective: The aim of this study was to develop the oral Venlafaxine HCl controlled-release organogel (organogel–CR) by using one-factor response surface methodology (RSM).

Methods: In this study, Drug-excipient compatibility was evaluated by FT-IR. A total of 14 experimental runs were carried out employing the detailed conditions designed by a single factor completely randomized design based on the response surface methodology was used to check the concentration effect of 12-Hydroxy stearic acid (12-HSA) at different cooling rates on drug release at 10 h (Q_{10}) and after 12 h (Q_{12}). Multiple linear regression analysis, analysis of variance (ANOVA) and graphical representation of the influence factor were performed by using design expert 12. The developed organogel was also evaluated for viscosity, strength, transition temperature, diffusivity and Scanning electron microscopy (SEM). Prepared organogel was filled in the capsule and investigated for weight variation, drug content, erosion of organogel and *In vitro* drug release study.

Results: FT-IR results showed that there was no chemical interaction between the drug and excipients. The SEM photograph indicates that the developed organogel was highly viscous with 3D network structure. The experimental confirmation tests showed a correlation between the predicted and experimental responses (R2 = 0.9937 and 0.9709). The results of ANOVA suggested that calculated F values of all dependent variables are greater than tabulated values. The optimal point obtained was located in the valid region and the optimum *in vitro* release of the predicted batch containing 7.9% concentration of 12-HSA with gradual cooling rate. To validate the evolved mathematical models, a checkpoint was selected and its desirability value was found to be 0.866.

Conclusion: Oral controlled release Venlafaxine HCl organogel fix the problem of repeated dosing and patient noncompliance.

Keywords: Venlafaxine HCl, Oral organogel, Controlled release, One-factor response surface methodology

DOI: https://dx.doi.org/10.22159/ijap.2022v14i5.45517. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Venlafaxine HCl, a third generation antidepressant drug, belongs to a group of drugs called selective serotonin and norepinephrine reuptake inhibitors [1, 2]. It affects chemicals in the brain that may be unbalanced in people with depression. It is used to treat the major depressive disorder, anxiety, and panic disorder [3, 4]. The steady state half-life of venlafaxine HCl is 5 h, necessitating the administration 2 or 3 times daily so as to maintain adequate plasma levels of drug [5, 6]. The half-life of venlafaxine HCl is relatively short therefore; patients are directed to adhere to a strict medication routine, avoiding missing a dose. Even a single missed dose can result in withdrawal symptoms. In such cases, the formulation releasing the drug in a sustained manner will aid the patient to adhere to a strict medication routine by avoiding the need to take the dosage form 2 or 3 times daily [7, 8]. An oral organogel is a non-crystalline, non-glossy thermoplastic solid material containing a liquid organic phase entrapped in a 3D cross-linked network. In this gel, liquid can be an organic solvent, mineral oil or vegetable oil. The addition of polar and non-polar solvents leads to the formation of a 3D network which is formed due to the growth of reverse micelles. Organogel consists of both hydrophilic and hydrophobic components that suggest both hydrophilic and hydrophobic drugs can be incorporated [9-11].

Therefore, the aim of the present study is to develop oral organogel–CR of Venlafaxine HCl using 12-HSA at different Cooling rates and to characterize them in terms of viscosity, Strength, and transition temperature diffusivity and SEM. The developed organogel was filled in the capsule and evaluated for weight variation, drug content, Erosion of organogel and *In vitro* drug release study. Therefore, the developed formulation of venlafaxine HCl will deliver the drug slowly into the systemic circulation and provide a desired therapeutic effect for a long period of time.

MATERIALS AND METHODS

Materials

Venlafaxine HCl was received as a generous gift from Tripada Healthcare Pvt. Ltd, Ahmedabad, India. 12-Hydroxy stearic acid (12-HSA) was obtained from Astral Trade Link, Ahmedabad, India. Soybean oil was purchased from Local market. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Drug-excipients compatibility study

Drug-excipient interaction plays a vital role in achieving the stability of the drug in dosage form. To study the physical and chemical interactions between drug and excipients Fourier transform infrared spectroscopy (FT-IR) was used. FT-IR spectra of venlafaxine HCl, mixture (venlafaxine HCl and 12-HSA) and venlafaxine HCl organogel-CR were recorded using KBr mixing method on FT-IR instrument. (FTIR-1700, Shimadzu, Kyoto, Japan) [12, 13].

Preliminary screening and development of oral venlafaxine HCL organogel–CR

In this method, soybean oil was used as a base and 12-HSA was taken as Gelator. Drug solubility was investigated in soybean oil and its release rate was checked in different concentrations of 12-HSA to soybean oil. Organogel trial batches T_1-T_5 were prepared by taking venlafaxine HCl and 12-HSA to soybean oil and their concentration was adjusted as shown in table 1. The mixture was heated at 75 ˚C with gentle stirring to melt the 12-HSA. After the 12-HSA was melted completely, the mixture was poured into the body of a gelatin capsule. Then the capsule was closed with a cap and gradually allowed to cool to solidify the soybean oil [14, 15].

Table1: Preliminary screening of oral venlafaxine organogel–CR

Batch	Drug (mg)	12-HAS (%)	Soybean oil (mg)	Total weight of organogel (mg)
T_1	75	2	513	600
T2	75	4	501	600
T3	75	6	489	600
T4	75	8	477	600
T5	75	10	465	600

Evaluation of venlafaxine organogel–CR

Viscosity of the formulated organogel was determined using Brookfield digital viscometer at 37±1 ˚C. Gel Strength was measured using Nikansui gel strength tester. Gel-sol transition temperature was determined by a simple tube inversion method. The surface morphology of the gel was observed using a Scanning electron microscope (SEM). The sample was placed in the sample holder and the photomicrographs were taken using tungsten filament as an electron source and GSE detector at 467x magnification [16].

Diffusivity of drug in organogel: The diffusion coefficient of venlafaxine HCl in organogel was determined by forming organogel in the plastic syringe (2.5 ml) with the tip removed. The syringe was vertically fixed and immersed in phosphate-buffered saline (pH 6.8) containing venlafaxine HCl at 37±0.5C. The solution was gentl y stirred at 50 rpm. After 24 h, the syringe was removed from the solution. The remaining organogel was recovered from the syringe by pushing the plunger. Oil matrix was sliced every 1.5 mm and discs of organogel were obtained. The venlafaxine HCl concentration in each disc was determined using a given formula.

$$\frac{C_i}{C_0} = 1\text{-erf}\left\{\frac{x}{2\sqrt{Di.\,t}}\right\}$$

C_i = concentration of venlafaxine HCl in the disc, C_0 = concentration of venlafaxine HCl at the surface of the organogel phosphate buffer solution border, X= Distance from the organogel phosphate buffer solution border to the center of the disc, t = time, Di = Diffusion coefficient [17-19].

Evaluation of capsule

Weight variation: From each batch, 10 capsules were selected randomly and weighed individually for weight variation [20].

Drug content: Drug content was determined by dissolving one capsule in chloroform and then extracting the drug with pH 1.2 HCl. These solutions were further diluted with pH 1.2 HCl and absorbance was measured under a UV-visible spectrophotometer at 227 nm [21].

Erosion of organogel: Organogel formed in the gelatin capsule was weighed and incubated at 37C in 10 ml test solution. For the disintegration test, the organogel was kept in pH 1.2, Phosphate buffer containing pH 6.8 and Phosphate buffer (pH 6.8) simulated intestinal fluid containing 375 U/ml of lipase. The solution was continuously stirred at 50 rpm during the incubation period. At specific time intervals, the organogel was removed from the test solution and dried in a vacuum for 12 h. The weights of organogel before and after incubation were measured and fitted to the following equation to calculate the erosion rate constant (k).

$$(W_d + W_i)^{1/3} = 1 - kt$$

Where W_d and W_i are the dried weight of an organogel after and before incubation, respectively. k is the erosion constant and t is incubation time [22].

In vitro drug release study: The release of Venlafaxine from the Organogel was evaluated by the dissolution test (Paddle method). Dissolution test was performed for the first 2 h in pH 1.2 HCl as simulated gastric fluid and then in the Phosphate buffer (pH 6.8) containing 375 U/ml of lipase as simulated intestinal fluid. The rotation rate of the paddle was kept at 50 rpm and 900 ml of volume of test solution was taken. At fixed intervals, aliquots were withdrawn and replaced with fresh dissolution medium. Samples from the dissolution medium were analysed by UV spectrophotometer (Shimadzu 1700) at 227 nm. The concentration of drug released at different time intervals was determined by measuring absorbance [23, 24].

(CRD) for oral venlafaxine organogel–CR

To study the effect of one quantitative factor i.e. concentration of gelator (12-HSA) and one categorical factor i.e. type of cooling on responses drug release, one factor response surface methodology was developed. This single-factor experiment can be described as a completely randomized design (CRD). The completely randomized design means there is no structure among the experimental units. The runs which differ only in the percentage of 12-HSA and these were done in random order. Each measured response can be written as the overall mean plus the treatment effect plus a random error.

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij} \text{ Where, i = 1,., a } j = 1,.,n_i$$

Generally, treatment effect is defined so that they sum to 0, a constraint on our definition of our parameters, $\sum \tau = 0$. This is not the only constraint one could choose, one treatment level could be a reference such as the zero level for 12-HSA and then everything else would be a deviation from that. The experimental error terms are assumed to be normally distributed, with zero mean and if the experiment has constant variance, then there is a single variance parameter σ^2. In this design, one numerical factor was used at 5 levels for the quadratic model. The Concentration of gelator (12-HSA) was taken as a Numeric factor and rate of cooling was taken as categorical factor. ANOVA and Graph were generated by using Design Expert 12 software. The checkpoint formulation was identified, prepared and evaluated for all parameters, to validate the chosen experimental design and the resultant data of response properties were quantitatively compared with that of their predicted values [25, 26].

Stability study

The Accelerated Stability Study was carried out according to the ICH Guidelines. The optimized batch of Venlafaxine HCl organogel–CR was kept for 6 mo under the storage condition 40C± 0.5 at 75±1% RH. After storage, the organogels were evaluated for *in vitro* drug release and the data were calculated and compared with the dissolution profile. The dissolution profile of products was compared using a f_2 which was calculated from following formula,

$$f_2 = 50 \log\left[\{1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\}^{-0.5} x100\right]$$

Where log is logarithm to the base 10, n is the number of time points, $\sum$ is the summation over all time points, R_t is the mean dissolution value of the reference profile at time t and T_t is the mean dissolution value of the test profile at the same time point. The USFDA draft guidance document contains more information on the similarity factor (f_2). The value of the similarity factor (f_2) between 50 and 100 suggests that the two dissolution profiles were similar [27].

RESULTS AND DISCUSSION

Drug excipients compatibility study

To study the physical and chemical interactions between drugs and excipients Fourier transform infrared spectroscopy (FT-IR) was used. FT-IR spectra of venlafaxine HCl, the mixture of venlafaxine HCl with 12-HSA and Venlafaxine HCl organogel-CR were recorded using KBr mixing method on FT-IR instrument. The drug exhibited peaks due to alcohol group, amide group, and C-H, C=O, C-O, C-N and C=C stretching. It was observed that there were no changes in drug main peaks in the IR spectra of venlafaxine HCl, mixture and Venlafaxine HCl organogel-CR as shown in fig. 1 [28].

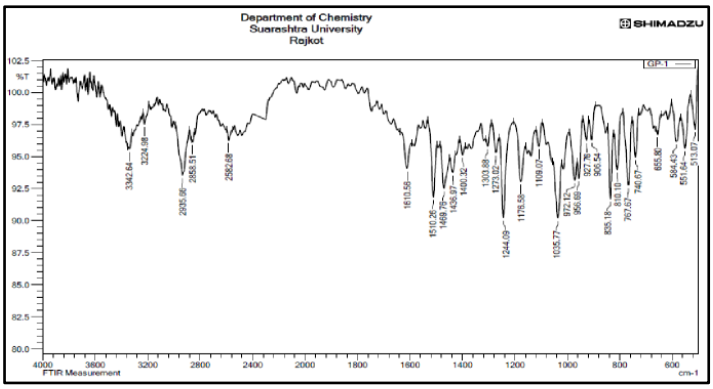

Fig. 1A: FT-IR spectra of venlafaxine HCl

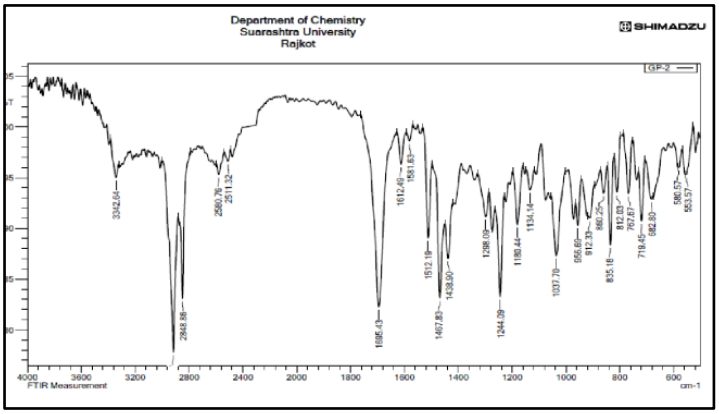

Fig. 1B: FT-IR spectra of physical mixture of 12-HSA and venlafaxine HCl

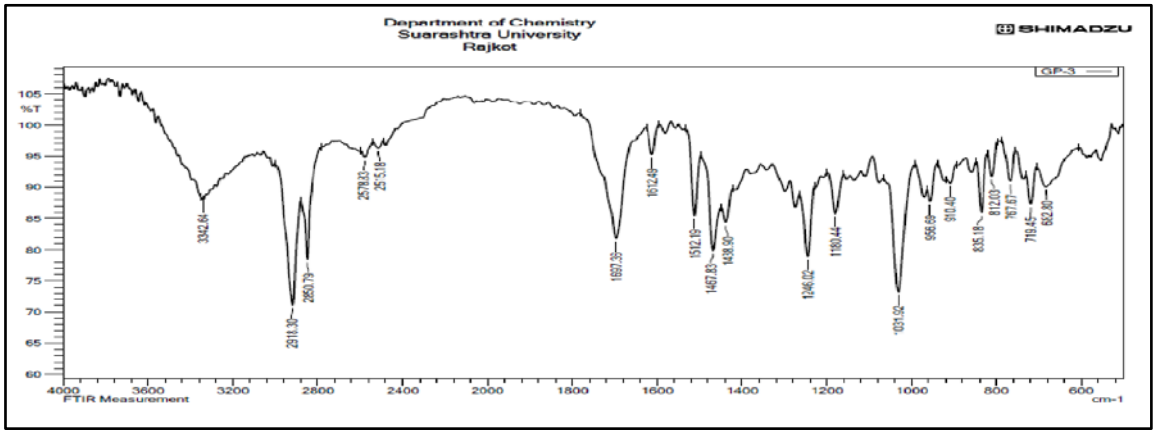

Fig. 1C: FTIR spectra of Venlafaxine HCl organogel-CR

Preliminary screening and evaluation of oral venlafaxine organogel-CR and capsule

From the results of weight variation, it was found that all the capsules were having a deviation of less than±1.16%, which means all capsules have uniform weights. The gel strength and transition temperature of prepared organogel were increased with an increase in the concentration of 12-HSA as shown in table 2. The viscosity of the organogel increases with an increase in the concentration of 12-HSA. No significant difference was observed among the diffusion coefficients of different organogel. Therefore, it was concluded that the difference in the concentration range of 2-10% of 12-HSA did not affect the diffusivity of venlafaxine HCl in the organogel.

Batch T_1 to T_5 did not show significant erosion in simulated gastric fluid. The erosion rate of organogel in pH 1.2 showed that organogel was very stable in simulated gastric fluid and passed into the intestine without disintegration. Then the erosion rate in pH 6.8 showed that an organogel containing 2% of 12-HSA gradually eroded up to 72.22 % of the initial weight. As the concentration of 12-HSA increased, the organogel hardly eroded in the simulated intestinal fluid. The result showed that organogel eroded most easily in the presence of lipase at pH 6.8. The erosion of organogel having 2% of 12-HSA in the simulated intestinal fluid with lipase, the weight of gel significantly decreased after 4 h, wherein the erosion of organogel having 2% of 12-HSA in the simulated intestinal fluid without lipase, the weight of gel did not significantly decrease even after 8 h. So it was concluded that the organogel eroded most easily in presence of lipase [29].

Table 2: Evaluation of preliminary screening batch of oral venlafaxine organogel–CR

Batch	Weight of capsule (mg)	Viscosity (cps)	Gel strength (g/cm²)	Diffusivity coefficient (cm²/sec.)	Erosion rate constant (h^{-1})		
					pH 1.2	pH 6.8	pH 6.8 with lipase
T_1	700±0.33 %	2490±15	800±16	$2.32\times10^{-6}\pm0.02$	0.027±0.002	0.030±0.001	0.065±0.002
T_2	700±0.45 %	2585±10	900±11	$1.81\times10^{-6}\pm0.03$	0.014±0.003	0.023±0.002	0.051±0.003
T_3	700±0.47 %	2670 25	1300±16	$2.22\times10^{-6}\pm0.01$	0.013±0.002	0.012±0.001	0.044±0.001
T_4	700±0.74 %	2780±15	1800±24	$2.00\times10^{-6}\pm0.04$	0.015±0.001	0.007±0.003	0.030±0.001
T_5	700±1.16 %	2830±12	2100±10	$2.23\times10^{-6}\pm0.02$	0.015±0.003	0.007±0.001	0.010±0.002

(n=6)

In vitro drug release rate was decreased with an increase in the concentration of 12-HSA. The amount of drug released from organogel containing 2%, 4%, 6%, 8% and 10% of 12-HSA during 8 h, reached 99.87%, 90.05%, 86.63%, 80.18% and 76.13% respectively. The amount of Venlafaxine HCl released from an organogel containing 8% and 10% of 12-HSA during 12 h, reached 97.24% and 90.01%, respectively. The result was showing that an organogel formed by 12-HSA has the potential for controlled release.

Evaluation of factorial design batches

The formulation layout for the completely randomized design batches are shown in table 3. Evaluations of factorial batches are shown in table 4. The gel strength and transition temperature of prepared factorial batches were increased with an increase in concentration. Viscosity of all the batches of organogel–CR was found in the range of 2624±52 cps to 2864±82 cps. No significant difference was observed among the diffusion coefficients of different organogel. So, it was concluded that the difference in the concentration range of 6-10% of 12-HSA did not affect the diffusivity of venlafaxine HCl in the organogel. All factorial batches of capsules having a deviation were less than±7.5% that means that all capsules have uniform weights. Drug content of the all prepared batches were found in the range of 91.20±0.84% to 96.26±0.96%.

The increased concentration of 12-HSA in the organogel decreased erosion rate in phosphate buffer pH 6.8 with lipase. Thus, it was concluded that the variation in the release rate of the drug in organogels is due to decreased erosion rate. There was no significant erosion in simulated gastric fluid, which suggests that the organogel was very stable in simulated gastric fluid and passed into the intestine without disintegration. All Batches of the organogel were found to follow zero order kinetic models. The dissolution data of all formulations were fitted in the Korsmeyer-Peppas equation and showed good linearity. All batches showed non-fickian diffusion with diffusion exponent value between $0.45<n<0.89$. SEM photographs of organogel were shown in fig. 2, which clearly showed the gel forming the highly viscous with 3D structure [30].

Table 3: One-factor design layout, experimental runs and their combinations

S. No.	Batch No.	12-HSA (X_1)	Cooling rate (X_1)	Q_{10} (Y_1)	Q_{12} (Y_1)
1	F_1	-1	Level 1	91.92±1.0	100±1.4
2	F_2	-1	Level 1	92.26±1.4	100±1.0
3	F_3	-0.5	Level 1	88.92±1.2	99.71±1.2
4	F_4	0.5	Level 1	82.40±0.8	94.49±1.5
5	F_5	1	Level 1	77.76±1.0	89.82±1.0
6	F_6	1	Level 1	77.52±1.3	88.78±1.3
7	F_7	0	Level 1	87.97±1.1	96.51±0.8
8	F_8	-1	Level 2	97.64±1.5	100±1.1
9	F_9	-1	Level 2	97.54±1.1	100±1.1
10	F_{10}	-0.5	Level 2	89.86±1.2	97.92±1.2
11	F_{11}	0.5	Level 2	87.46±1.0	98.51±1.0
12	F_{12}	1	Level 2	80.02±1.0	94.09±0.8
13	F_{13}	1	Level 2	80.15±1.5	94.01±1.3
14	F_{14}	0	Level 2	88.22±0.8	97.70±1.4

Coded levels translated in actual units

Numeric factor		Categoric factor	
Coded level	Actual value of % of 12-HAS	Coded level	Actual value of Cooling rate
-1	6	Level 1	Gradual cooling
-0.5	7	Level 2	Rapid cooling
0	8		
0.5	9		
1	10		

(n=6)

Table 4: Evaluation of factorial design batches

Batch	Gel strength (gm/ cm²)	Gel transition temperature (°C)	Viscosity (cps)	Diffusivity coefficient (cm²/sec.)	Drug content (%)	Erosion rate constant (h^{-1})		
						pH 1.2	pH 6.8	pH 6.8 with lipase
F_1	1200±45	42±2	2624±52	$1.93\pm0.11\times10^{-6}$	94.93±1.23	0.008±0.001	0.008±0.003	0.031±0.001
F_2	1250±15	41±4	2638±43	$1.92\pm0.11\times10^{-6}$	95.20±0.45	0.010±0.002	0.082±0.001	0.033±0.002
F_3	1500±54	45±1	2720±94	$1.94\pm0.11\times10^{-6}$	92.80±2.43	0.010±0.001	0.007±0.001	0.025±0.001
F_4	1950±60	52±1	2826±63	$1.96\pm0.11\times10^{-6}$	93.06±1.67	0.008±0.001	0.005±0.001	0.013±0.001
F_5	2100±50	55±3	2851±64	$1.97\pm0.11\times10^{-6}$	94.66±3.33	0.007±0.002	0.004±0.002	0.006±0.002
F_6	2150±34	56±2	2858±85	$1.98\pm0.11\times10^{-6}$	95.46±0.56	0.008±0.001	0.004±0.001	0.008±0.001
F_7	1750±75	49±1	2797±72	$1.95\pm0.11\times10^{-6}$	92.53±1.89	0.008±0.001	0.006±0.001	0.021±0.001
F_8	1250±46	43±3	2656±44	$1.91\pm0.11\times10^{-6}$	91.73±2.56	0.009±0.002	0.006±0.001	0.030±0.001
F_9	1250±45	42±4	2650±55	$1.89\pm0.11\times10^{-6}$	95.20±1.52	0.009±0.001	0.009±0.001	0.031±0.001
F_{10}	1550±35	46±2	2705±62	$1.92\pm0.11\times10^{-6}$	92.80±0.63	0.008±0.001	0.007±0.001	0.024±0.002
F_{11}	1900±81	51±3	2829±76	$1.94\pm0.11\times10^{-6}$	91.20±0.84	0.009±0.001	0.005±0.001	0.014±0.001
F_{12}	2050±78	56±2	2860±54	$1.95\pm0.11\times10^{-6}$	94.93±1.23	0.010±0.001	0.005±0.001	0.008±0.002
F_{13}	2100±53	55±1	2864±82	$1.97\pm0.11\times10^{-6}$	95.73±1.65	0.010±0.002	0.005±0.001	0.007±0.001
F_{14}	1700±45	48±2	2790±79	$1.93\pm0.11\times10^{-6}$	96.26±0.96	0.011±0.001	0.006±0.002	0.019±0.001

(n=6)

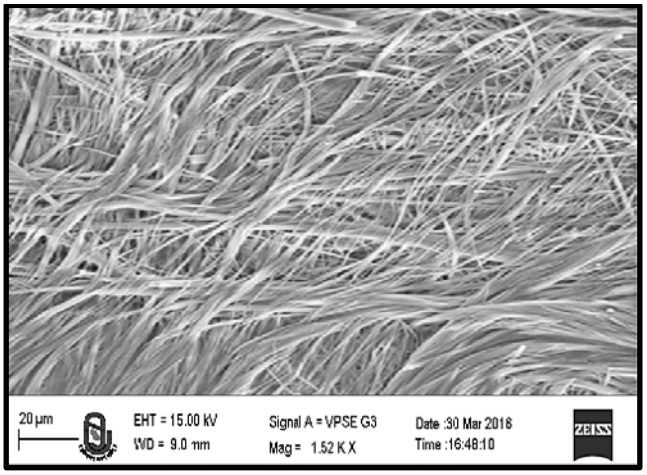

Fig. 2: SEM of venlafaxine organogel

Completely randomized design (CRD) for oral Venlafaxine organogel–CR

From the all potential physical variables for a dosage form, some precise variables have more important effects on *in vitro* release of dosage form than others, called dependent variables. From these designated variables, further optimization of dosage form would be possible. Hence, in this study *in vitro* drug release studies after 10 h (Q_{10}) and after 12 h (Q_{12}) were selected as dependent variables. The mathematical relationship between the factors and responses generated using multiple linear regression analysis could be adequately characterized by the following polynomial equations are given below,

Q_{10} =+84.49-7.88*A+2.22*B-0.73*A*B-2.68*A^2

Rate of cooling gradual cooling

Q_{10} =+72.93+7.16*A-0.67*A^2

Rate of cooling rapid cooling

Q_{10} =+83.18+6.43*A-0.67*A^2

Q_{12} =+98.02-4.06*A+1.05*B+1.28*A*B-2.11A^2

Rate of cooling gradual cooling

Q_{12} =+84.60+5.76*A-0.53A^2

Rate of cooling rapid cooling

Q_{12} =+76.46+7.09*A-0.53A^2

Polynomial equation was used to draw the conclusion after considering the magnitude of the coefficient and the mathematical sign it carries (positive or negative). The positive or negative value of all coefficients showed the effect of the lone factor (main effect) or interaction effect of factors to gather on response variable might be either increased or decreased. In the polynomial equation for Y_1, the negative value of coefficient b_1 described the opposite effect of Factor 1 on response drug release. It indicated that increased concentration of 12-HSA decreased drug release. Positive value of coefficient b_2 described a synergistic effect for Factor 2 so as the increased rate of cooling increased drug release [31].

ANOVA study of Q_{10}

The result of the ANOVA study of Q_{10} was shown in table 5. In this study, the F-value was found to be 352.31, which implies that the model was significant. P-Values of "Prob>F" less than 0.05 indicate model terms were significant. In this case, A, B, AB, A^2 were significant model terms. Values greater than 0.05 indicate the model terms were not significant. If there were many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The "Lack of Fit F-value" of 30.22 implies the Lack of Fit is significant. There is only a 0.31% chance that a "Lack of Fit F-value" this large could occur due to noise. The "Pred. R-Squared" of 0.9869 is in reasonable agreement with the "Adj. R-Squared" of 0.9908 as shown in table 6. "Adeq. Precision" measures the signal-to-noise ratio. A ratio greater than 4 is desirable. Ratio of 49.76 indicates an adequate signal. The plot of the predicted value of Q_{10} versus the actual value of % of Q_{10} (fig. 3A) shows a straight line. Therefore, it concluded that the equation has good predictive ability. Interaction and nonlinearity was not observed.

ANOVA study of Q_{12}

The results of ANOVA study of Q_{12} was shown in table 5. The Model F-value of 75.97 implies the model is significant. P-Values of "Prob.>F" less than 0.05 indicate model terms were significant. In this case A, B, AB, A^2 were significant model terms. Values greater than 0.05 indicate the model terms were not significant. If there were many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The "Lack of Fit F-value" of 8.99 implies the Lack of Fit is significant. There is only a 2.69% chance that a "Lack of Fit F-value" this large could occur due to noise. The "Pred. R-Squared" of 0.9390 is in reasonable agreement with the "Adj. R-Squared" of 0.9579. as shown in table 6. "Adeq. Precision" measures the signal-to-noise ratio. A ratio greater than 4 is desirable. Ratio of 22.484 indicates an adequate signal. The plot of the predicated value of Q_{12} versus the actual value of % of Q_{12} (Figure. 3B) shows a straight line. Therefore, it concluded that the equation has the good predictive ability. Interaction and nonlinearity was not observed. This model can be used to navigate the design space [32].

Table 5: Result of ANOVA study for the dependent variable

Q_{10}					
Source	**SS**	**d_f**	**MS**	**F value**	**p-value Prob>F**
Model	650.04	4	162.51	352.31	<0.0001
A-12 HAS	558.38	1	558.38	1210.52	<0.0001
B-Rate of cooling	69.18	1	69.18	149.97	<0.0001
AB	4.74	1	4.74	10.27	0.0107
A^2	17.75	1	17.15	38.47	0.0002
Residual	4.15	9	0.46	-	-

Q_{10}					
Source	**SS**	**d_f**	**MS**	**F value**	**p-value Prob>F**
Lack of fit	4.04	5	0.81	30.22	0.0031
Pure error	0.11	4	0.027	-	-
Cor total	654.19	13	-	-	-
Q_{12}					
Source	SS	d_f	MS	F value	p-value Prob>F
Model	189.21	4	47.30	75.97	<0.0001
A-12 HAS	148.11	1	148.11	234.73	<0.0001
B-Rate of cooling	15.41	1	15.41	24.43	0.0008
AB	14.75	1	14.75	23.37	0.0009
A^2	10.94	1	10.94	17.34	0.0023
Residual	5.68	9	0.63	-	-
Lack of fit	5.21	5	1.04	8.99	0.0269
Pure error	0.46	4	0.12	-	-
Cor total	194.89	13	-	-	-

DF is degree of freedom, SS is sum of squares, MS is mean square and F is Fischer's ratio.

Table 6: Statistical parameters obtained from ANOVA study

Response	Std. Dev	Mean	C. V%	R-Squared	Adj. R-squared	Pred. R-Squared	Adeq. Precision
1	0.68	87.76	0.77	0.9937	0.9908	0.9869	49.766
2	0.79	96.67	0.82	0.9709	0.9579	0.9390	22.484

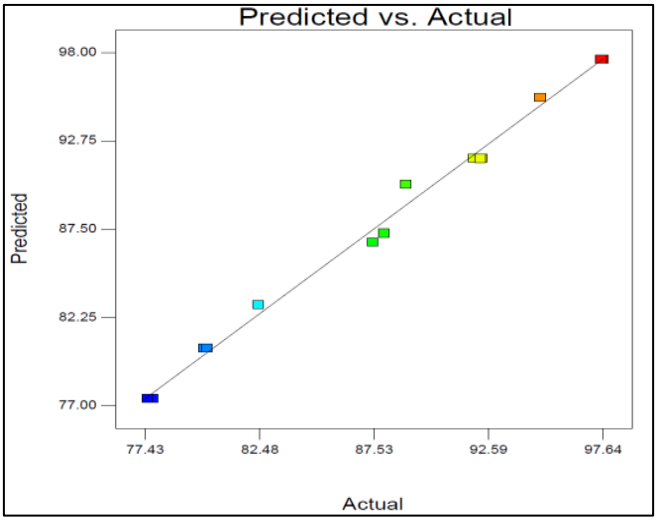

Fig. 3A: Predicted Vs actual value of Q_{10}

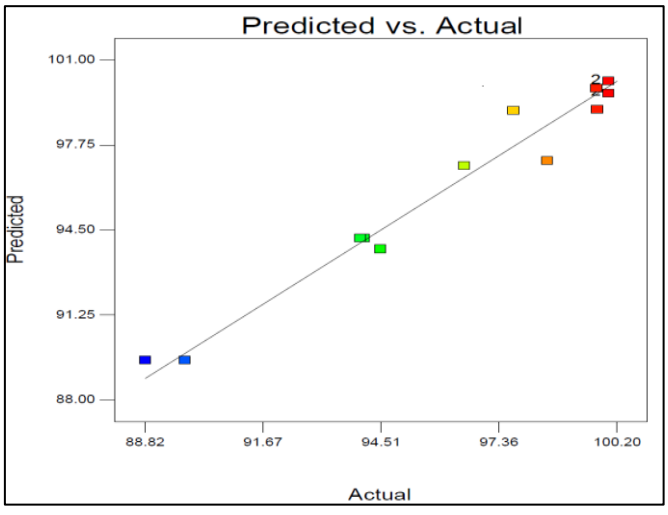

Fig. 3B: Predicted Vs actual value of Q_{12}

Selection of optimized formulation

The main objective of formulation development was to investigate the optimum level of variables which affect a process and the finished product has the best possible characteristics. The batch containing 7.9% concentration of 12-HSA with gradual rate of cooling was found to be an optimized batch by using an experimental design. The optimized batch showed 97.2% release within 12 h. As per fig 4 and table 7, the desirability value for the determination of the optimized batch was found to be 0.866, which was nearby 1 [33].

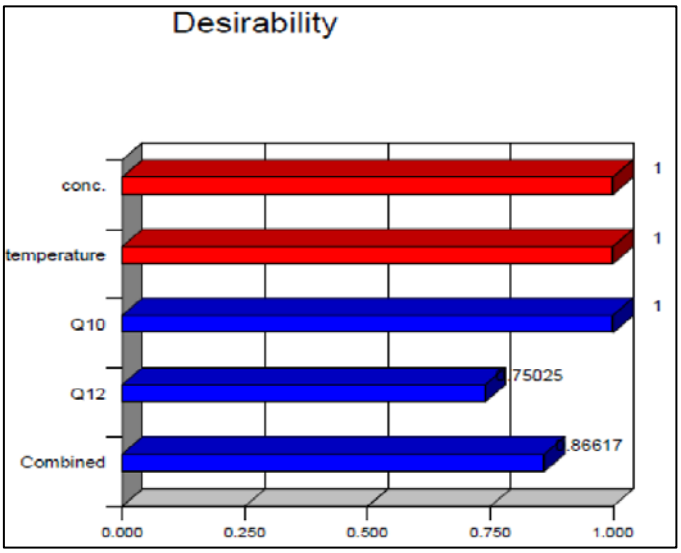

Fig. 4: Desirability of value of response

Table 7: Solutions obtained based on desirability

Solution No.	12-HAS	Rate of cooling	Q_{10}	Q_{12}	Desirability	
1	7.9	Gradual cooling	87.58	97.20	0.866	Selected

Validation of optimized formulation

A checkpoint batch was designed according to the desirability function. To assess the validity of the prediction, a checkpoint batch as per shown in table 8 was prepared and evaluated under the same conditions as outlined for the other batches. The Evaluation was shown in table 8 and response data was compared with that of the required data. The result was found within acceptable limits that assure adequate composition of controlled release organogel. The drug release profile was built-in to zero order, first order, Higuchi kinetics, Korsmeyer-peppas and Hixson Crowell. It was found that the drug release is best built-in to the zero order. The obtained response variable of the checkpoint batch is compared with the target response parameter as shown in table 9. The bias for predicted versus actual response was acceptable [34].

Table 8: Composition and evaluation of optimized batch

Composition	
Cooling rate	**Gradual cooling**
Ingredients	Quantity
Venlafaxine HCl	75 mg
12-Hydroxy stearic acid	7.9 %
Soybean oil	477.5
Evaluation	
Evaluation parameter	Result
Gel strength	1750±12 gm/cm^2
Gel transition temperature	50±0.5 ˚C
Viscosity	2796±50 cps
Diffusivity coefficient	2.19±0.1×10^{-6} cm^2/sec.
Erosion rate constant	0.041±0.002 h.$^{-1}$

(n=6)

Table 9: Comparison of predicted and obtained responses

Parameter	Predicted	Observed	% Bias
Q_{10}	87.58	85.02±1.2	2.56
Q_{12}	97.20	96.50±1.8	0.52

(n=6)

CONCLUSION

This formulation requires less number of excipients, offering ease of optimization of formula and is cost-effective; it involves less number of processing steps so it is easy to formulate an organogel. Excipients used i.e. soybean oil and 12-hydroxy stearic acids, are willingly biodegradable so it is relatively safe and non-hazardous. Oral controlled release organogel solves the problem of repeated dosing and patient noncompliance. The formulation (organogel containing soybean oil) shows erosion in the presence of pancreatic lipase present in intestinal fluid. The optimized batch was considered to be the best among all other batches since it exhibited a good dissolution profile. The optimized batch shows 85.02% drug release at 10 h and 96.5 % drug release at 12 h.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Andrews JM, Ninan PT, Nemeroff CB. Venlafaxine: a novel antidepressant that has a dual mechanism of action. Depression. 1996;4(2):48-56. doi: 10.1002/(SICI)1522-7162(1996)4:2<48:AID-DEPR2>3.0.CO;2-B, PMID 9160640.
2. Olver JS, Burrows GD, Norman TR. Third-generation antidepressants: do they offer advantages over the SSRIs? CNS Drugs. 2001;15(12):941-54. doi: 10.2165/00023210-200115120-00004, PMID 11735614.
3. Holliday SM, Benfield P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. Drugs. 1995;49(2):280-94. doi: 10.2165/00003495-199549020-00010, PMID 7729333.
4. Haskins JT, Moyer JA, Muth EA, Sigg E. Inhibition of noradrenergic neuronal activity by the novel bicyclic compounds, Wy-45030 and Wy-45881. Soc Neurosci 1984;10:262.
5. Troy SM, Parker VD, Fruncillo RJ, Chiang ST. The pharmacokinetics of venlafaxine when given in a twice-daily regimen. J Clin Pharmacol. 1995;35(4):404-9. doi: 10.1002/j.1552-4604.1995.tb04081.x, PMID 7650231.
6. Jyoti P. Development and optimization of extended-release venlafaxine HCl matrix tablet. Asian J Pharm Tech Innov. 2013;3(2):76-80.
7. Jain S, Datta M. Montmorillonite-alginate microspheres as a delivery vehicle for the extended oral release of venlafaxine hydrochloride. J Drug Deliv Sci Technol. 2016;33:149-56. doi: 10.1016/j.jddst.2016.04.002.
8. Dilip M, Kumbhar VD, Havaldar KKM, Remeth JD, Vishwajeet SG, Rahul B. Londhe. Formulation and evaluation of sustained release tablets of venlafaxine hydrochloride for the treatment of depressive disorders. Asian J Pharm Res. 2017;7(1):8-14.
9. Jose J, Gopalan K. Organogels: A versatile drug delivery tool in pharmaceuticals. Res J Pharm Technol. 2018;11(3):1242-6. doi: 10.5958/0974-360X.2018.00231.7.
10. Purohit B, Gupta N, Jain S. Formulation and evaluation of diclofenac sodium organogel. Res J Pharm Technol. 2013;6(4):375-8.
11. Nithya R, Kumari B. Development and characterization of reverse micelle based pluronic lecithin organogel containing imatinib mesylate. Res J Pharm Technol. 2021;14(3):1209-14. doi: 10.5958/0974-360X.2021.00215.8.
12. Abdelmonem R, Eltahan M, El-Nabarawi M. Development and evaluation of taste masked oro-disintegrating tablets of itopride hcl using different co-processed excipients: pharmacokinetics study on rabbits. Int J App Pharm. 2022;14(3):69-79. doi: 10.22159/ijap.2022v14i3.44398.
13. Carlson E, Chandler W, Galdo I, kudla T, Ta C. Automated integrated forced degradation and drug-excipient compatibility studies. JALA: Journal of the Association for Laboratory Automation. 2005;10(6):374-80. doi: 10.1016/j.jala.2005.09.005.
14. Garg T, Bilandi A, Kapoor B. Oraganogel advanced and novel drug delivery system. Int Res J Pharm. 2011;2(12):15-21.
15. Fayez SM, Gad S. Formulation and evaluation of etodolac lecithin organogel transdermal delivery systems. Int J Pharm Pharm Sci. 2005;7:325-34.
16. Jayaprakash R, Hameed J, Anupriya A. An overview of transdermal delivery system. Asian J Pharm Clin Res. 2017;10(10):36-40. doi: 10.22159/ajpcr.2017.v10i10.19909.
17. Sharma G, Devi N, Thakur K, Jain A, Katare OP. Lanolin-based organogel of salicylic acid: evidences of better dermatokinetic profile in imiquimod-induced keratolytic therapy in BALB/c mice model. Drug Deliv Transl Res. 2018;8(2):398-413. doi: 10.1007/s13346-017-0364-9, PMID 28224375.
18. Vigato AA, Querobino SM, de Faria NC, de Freitas ACP, Leonardi GR, de Paula E. Synthesis and characterization of nanostructured lipid-poloxamer organogels for enhanced skin local anesthesia. Eur J Pharm Sci. 2019;128:270-8. doi: 10.1016/j.ejps.2018.12.009, PMID 30553060.
19. Vintiloiu A, Leroux JC. Organogels and their use in drug delivery-a review. J Control Release. 2008;125(3):179-92. doi: 10.1016/j.jconrel.2007.09.014, PMID 18082283.
20. Patil IS, Patil OA, Mandake GCR, Nitalikar MM. Development and evaluation of telmisartan pulsatile drug delivery by using response surface methodology. Asian Journal of Pharmaceutical Research 2018;8(4):205-14. doi: 10.5958/2231-5691.2018.00035.7.
21. Mahesh PG, Jeganath S. Formulation and evaluation of venlafaxine hydrochloride sustained release matrix tablet. Asian J Pharm Clin Res. 2018;11(16):170-4.
22. Upadhyay KK, Tiwari C, Khopade AJ, Bohidar HB, Jain SK. Sorbitan ester organogels for transdermal delivery of sumatriptan. Drug Dev Ind Pharm. 2007;33(6):617-25. doi: 10.1080/03639040701199266, PMID 17613026.
23. Aimetti AA, Machen AJ, Anseth KS. Poly(ethylene glycol) hydrogels formed by thiol-ene photopolymerization for enzyme-responsive protein delivery. Biomaterials. 2009;30(30):6048-54. doi: 10.1016/j.biomaterials.2009.07.043. PMID 19674784.
24. Swain S, Behera A, Dinda SC, Patra CN, Jammula S, Beg S. Formulation design, optimization and pharmacodynamic evaluation of sustained release mucoadhesive microcapsules of venlafaxine HCl. Indian J Pharm Sci. 2014;76(4):354-63. PMID 25284934.
25. Duangjit S, Kraisit P. Optimization of orodispersible and conventional tablets using simplex lattice design: the relationship among excipients and banana extract. Carbohydr Polym. 2018;193:89-98. doi: 10.1016/j.carbpol.2018.03.087, PMID 29773401.
26. Kraisit P, Sarisuta N. Development of triamcinolone acetonide-loaded nanostructured lipid carriers (NLCs) for buccal drug delivery using the box-Behnken design. Molecules. 2018;23(4):E982. doi: 10.3390/molecules23040982, PMID 29690622.
27. Adan J, Singh R. Formulation and evaluation of Aloe vera topical gels. Int J Phys Sci. 2010;2:551-5.
28. Pathan IB, Shingare PR, Kurumkar P. Formulation design and optimization of novel mouth dissolving tablets for venlafaxine hydrochloride using the sublimation technique. J Pharm Res. 2013;6(6):593-98. doi: 10.1016/j.jopr.2013.04.054.
29. Sharma D, Kaur D, Verma S, Singh D, Singh M, Singh G. Fast dissolving oral films technology: a recent trend for an innovative oral drug delivery system. Int J Drug Deliv. 2015;7(2):60-75.
30. Kraisit P. Impact of hydroxypropyl methylcellulose (HPMC) type and concentration on the swelling and release properties of propranolol hydrochloride matrix tablets usning a simplex centroid design. Int J Appl Pharm. 2019;11:143-51. doi: 10.22159/ijap.2019v11i2.31127.
31. Duangjit S, Kraisit P. Optimization of orodispersible and conventional tablets using simplex lattice design: the relationship among excipients and banana extract. Carbohydr Polym. 2018;193:89-98. doi: 10.1016/j.carbpol.2018.03.087, PMID 29773401.

32. Sankalpa KB, Mathew SM. Response surface optimization of extraction parameters of green tea. Int J Agric Environ Biotechnol. 2017;10(2):209. doi: 10.5958/2230-732X.2017.00024.9.
33. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771-83. doi: 10.1208/s12248-014-9598-3, PMID 24854893.
34. Collins LM, Dziak JJ, Li R. Design of experiments with multiple independent variables: a resource management perspective on complete and reduced factorial designs. Psychol Methods. 2009;14(3):202-24. doi: 10.1037/a0015826, PMID 19719358.