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Original Article

Formulation, Characterization and Optimization of Transdermal Patches of Venlafaxine Hydrochloride Using 3^2 Full Factorial Approach

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ABSTRACT

Introduction: The primary objective of the present investigation was to develop transdermal patches that would extend the half-life of Venlafaxine Hydrochloride and boost its bioavailability. Transdermal patches were made with Ethyl Cellulose (EC) as the lipophilic component and Hydroxypropyl Methylcellulose (HPMC K15M) as the hydrophilic matrix. **Objectives:** The objectives of the present study it to develop effective transdermal patches for Venlafaxine Hydrochloride delivery, optimize their formulation using different polymer ratios and evaluate their quality and drug release properties. **Materials and Methods:** The ideal design matrix was constructed using a 3^2 full factorial approach, which changed the ratio between the hydrophilic and lipophilic matrices. Three different EC and HPMCK15M ratios were used to obtain the best possible formulation. **Results:** The thicknesses of the transdermal patches varied from 0.514±0.004 mm to 0.697±0.004 mm. The produced transdermal patches had an average weight ranging from 194.67±0.578 mg to 241.67±1.528 mg. There were variations in the moisture content of the transdermal patches. All the transdermal patch formulations exhibited uniform drug content and with a minimum variability within the batch. **Conclusion:** The drug content ranged from 94.7±0.6% to 97.33±0.208%. The *in vitro* drug release study depicted that the highest amount of drug was released from P9 (88.21±1.286%) while the lowest was released from P5 (56.47±1.066%) at the end of 24 hr of release study.

Keywords: Transdermal, Venlafaxine Hydrochloride, Sustained release, Optimization, Factorial design.

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INTRODUCTION

Venlafaxine Hydrochloride is an antidepressant and a Serotonin and Norepinephrine Reuptake Inhibitor (SNRI). It also produces desvenlafaxine, an active metabolite that inhibits the reabsorption of serotonin and norepinephrine. Its use is therapeutically approved for adults with Major Depressive Disorder (MDD), panic disorder, social anxiety disorder and Generalized Anxiety Disorder (GAD).[1] Venlafaxine has an approximate 45% absolute bioavailability, which means that 87% of the administered dosage is unchanged removed in the urine.

Controlled release systems are being used more often by researchers to improve the bioavailability of pharmaceuticals. These devices enable the penetration of an active substance from a reservoir to the target surface, where it can be retained for a predefined period of time. Medication delivered via healthy skin with controlled release is one definition of a transdermal drug delivery system. Forty percent of medication delivery candidate products undergoing clinical review in the last few years have been delivered using transdermal delivery systems.[2] Transdermal patches have the potential to reduce the frequency of administration, improve patient compliance and extend the duration of drug release and therapeutic action-all at comparatively modest production costs. Over last two decades, a number of researches have been directed towards the formulation of transdermal patches of hydrophobic and hydrophilic drugs in an attempt to reduce their dose and improve bioavailability.[3-7] However, only a few reports of attempts to control the release of venlafaxine by formulating as transdermal patches were found in literature.[8-11]

Herein we attempted to improve the bioavailability of Venlafaxine Hydrochloride by formulating it as transdermal patch using a blend of Ethyl Cellulose (EC) and Hydroxypropyl methylcellulose

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(HPMCK15M) and utilizing eucalyptus oil to improve skin permeation.

MATERIALS AND METHODS

Materials

Venlafaxine Hydrochloride was purchased from Yarrow Chem Products, Mumbai, Maharashtra. Hydroxypropyl methyl cellulose (HPMC K15M) was procured as a gift sample from Colorcon Asia Pvt. Ltd., (India), Goa and Ethyl Cellulose (EC) from Loba Chemie Pvt. Ltd., Mumbai. Oleic acid, eucalyptus oils were used. Altogether, additional chemicals and solvents were of analytical reagent grade.

Methods

Drug-polymer compatibility study

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of physical mixture of drug and excipient (Figure 1) were recorded in between 400-4000 wave number (cm^{-1}). Deletion of the peaks of the pure drug in the mixture spectra is usually taken as an indication of incompatibility of the drug and excipients.[12]

Differential Scanning Colorimetry (DSC)

Differential Scanning Calorimetry (DSC) of the drug and polymer was also studied to check for compatibility among the components.

The DSC thermogram of venlafaxine presented as sharp endothermic peak at 285°C suggesting decomposition of the drug. In the thermogram of the physical mixture, the endotherm of the melting of HPMC K15M was present while the endotherm of drug decomposition was lost, suggesting a slight shift in drug decomposition in presence of the excipients (Figure 2).

Formulation of Transdermal Patches

Solvent casting was used to create transdermal patches containing Venlafaxine Hydrochloride on a 38.46 cm^2 Petri dish. The polymers were carefully weighed, dissolved in 10 mL of water-ethanol (1:1) solution and agitated with a magnetic stirrer for 30 min to produce a transparent solution. After that, they were left aside (Table 1). Venlafaxine Hydrochloride was weighed exactly, then dissolved in the previously specified solution and mixed until a clear solution was obtained. As a permeation enhancer, 10% w/w of eucalyptus oil and 30% w/w of oleic acid were added to the polymer, respectively, as a plasticizer. Following a drying time of 24 hr at room temperature and lubrication with glycerin, the uniform solution was moved to a Petri plate. There was an upside-down funnel placed over the petridish.[1]

Optimization of Patch Formulation

The optimization was done using a 3^2 full factorial approach with 13 runs using the concentration of HPMCK15M and EC as the 2 independent factors affecting the release (response) of the drug at 24 hr from the patches.[13]

The data was analyzed using Design Expert 7.0.0 trial version and the quadratic model was generated for predicting the release of drug from the formulations.

Evaluation of Transdermal Patches

Physical Appearance and Weight Uniformity

We assessed the homogeneity, transparency, clarity, color and smoothness of the created patches. By weighing each formulated patch separately and comparing its weight to the average weight of the produced patches, the patches were subjected to mass variation. Using an analytical balance that had been calibrated, patch weight was found.

Thickness

Each patch's thickness was measured with a Vernier caliper at 6 different points and the average was calculated.

Surface pH

The surface pH of the transdermal patches was measured with a calibrated pH meter. In a test tube, a transdermal patch measuring 1 cm^2 and 1 mL of distilled water were incubated for two hr at room temperature (25±2°C). The pH of the surface was measured using the wet patch after the water in the test tube was decanted. The pH electrode was placed in the swollen section of the patch three times in order to get the average pH.

Folding Endurance

To evaluate folding endurance, one patch was folded repeatedly from the same position until it broke or cracked. The number of times the film could be folded from the same position without cracking or breaking served as a measure of folding endurance.

Tensile Strength

The produced patches' tensile strength was assessed using lab-made pulley apparatus. The initial patch length was measured using a scale. The transdermal patch was secured to a weighing pan by a rope that crossed a pulley on one side and a weighing balance hook on the other. The pan was gradually filled with weight until the patch broke or cracked. The tensile strength was calculated using the overall weight of the pan. The following calculation was used to calculate the force required to induce the transdermal patch to break or crack-

$$Tensile\ Strength = F/[a \times b\left(1 + \frac{L}{l}\right)]$$

Where, L is the patch's length (in centimeters), I is its elongation (in centimeters) before to breaking or cracking and is the patch's breadth, b is its thickness (in centimeters) and F is the force required to shatter the patch.

Drug Content Test

Three 4 cm^2 pieces were taken from each patch by slicing off zones from different areas. These parts were dissolved in 10 mL of ethanol and shaken on a vortex shaker for an hour in order to completely dissolve the patches. 0.1 mL of the final solutions were removed and diluted to 10 mL in a second volumetric flask after they had passed through the Whatman paper filter. The absorbance of this solution was measured at 225 nm using a UV-visible spectrophotometer, enabling the computation of the drug content.

Percent Moisture Content

After being individually weighed, the transdermal films were stored at room temperature for 24 hr in desiccators filled with fused calcium chloride. Using the provided methodology, the films were reweighed after a day to ascertain the percentage moisture content.

$$\%\ moisture\ content = \frac{Initial\ patch\ weight}{Final\ patch\ weight} \times 100$$

In vitro Permeation Study

Researchers used a Franz diffusion cell with a 30 mL receptor compartment capacity to conduct *in vitro* penetration investigations of the transdermal patches. Following the placement of the prepared 4 cm^2 patch between the donor and receptor compartments of the diffusion cell, the dialysis membrane was installed between them. Protonate buffer saline pH 7.4 was added to the receptor compartment of the diffusion cell. The entire assembly was secured to a magnetic stirrer and magnetic beads were used to continually agitate the solution in the receptor compartment at a speed of 50 revolutions per minute while maintaining a temperature of 37±0.5°C. The 1 mL aliquots were taken out at various intervals (0, 2, 4, 6, 8, 12 and 24 hr) and the drug content was measured using UV at 225 nm with the proper dilution. At each sample withdrawal, the receptor phase was replaced with an identical volume of phosphate buffer (37°C) and the cumulative amount of drug penetrated per square centimeter of patches was plotted versus time.[14-16]

RESULTS AND DISCUSSION

Visual inspection was performed on each created patch to assess its physical appearance. The patches' outward appearance produced positive outcomes. It was discovered that every prepared patch had the following qualities: it was opaque, smooth, flexible and non-stick. Table 2 presents various properties of the formulated patches.

The Franz diffusion cell was utilized to ascertain the quantity of medication that seeped through or was discharged from the transdermal patches. P9 released the most drugs (88.21±1.286%) during the 24 hr release testing, while P5 released the least amount (56.47±1.066%). This was the result of an *in vitro* drug release investigation (Figure 3).

OPTIMIZATION OF FORMULATION

As the two independent parameters influencing the drug's release (response) at 24 hr from the patches, the concentration of HPMCK15M and EC were fitted to optimization using a 3^2 complete factorial approach with 13 trials.

In order to forecast the drug release from the formulations, a quadratic model was created after the data was assessed using the trial version of Design Expert 7.0.0. The software came up with three ideal answers.

The software examined the potential mathematical models for formulation optimization in terms of residual sum of squares and

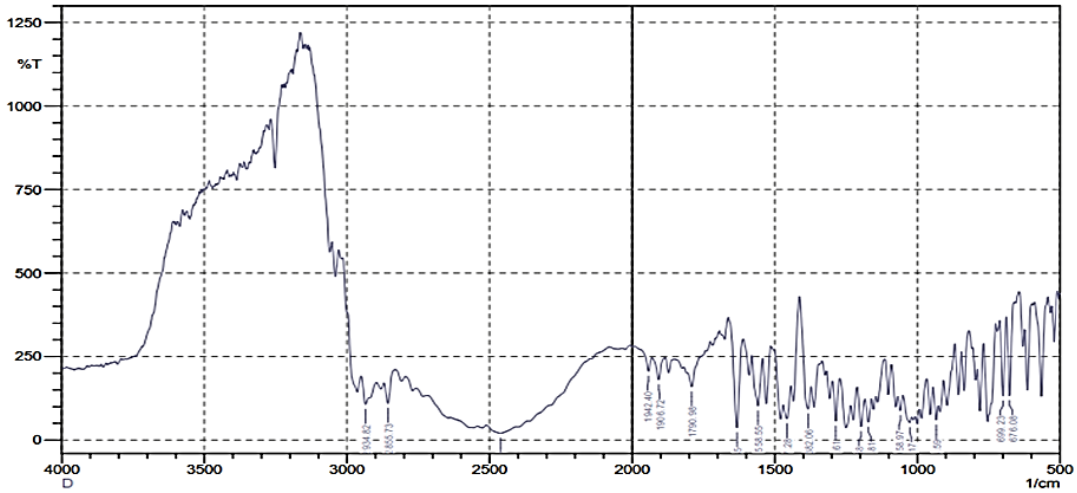

Figure 1: FTIR spectra of physical mixture (venlafaxine+HPMCK15M+ethylcellulose).

Table 1: Formulation of Venlafaxine Hydrochloride Loaded Transdermal Patches.

Formulation code	Venlafaxine Hydrochloride (mg)	HPMCK15M (mg)	EC (mg)	Oleic acid (%w/w)	Eucalyptus oil (%w/w)
P1	180	100	50	30	10
P2	180	125	75	30	10
P3	180	150	75	30	10
P4	180	125	75	30	10
P5	180	100	100	30	10
P6	180	125	75	30	10
P7	180	100	75	30	10
P8	180	125	75	30	10
P9	180	150	50	30	10
P10	180	125	75	30	10
P11	180	125	100	30	10
P12	180	125	50	30	10
P13	180	150	100	30	10

lack of fit. For estimating the release, the research recommended using quadratic and linear models. But the cubic model was aliased and hence disregarded despite being discovered to be remarkably significant (Table 3).

The quadratic model was processed by ANOVA to obtain the mathematical model for predicting the maximum release of venlafaxine from the patches (Eq. 1).

$$\% \text{ Drug Release} = 164.32638 - 0.62897*HPMCK15M - 1.97851*EC - 0.000824*HPMCK15M*EC + 0.00410786*HPMCK15M2 + 0.012068*EC2 \quad \text{Eq. 1}$$

The statistical parameters for the Eq. 1 are presented in Table 4.

A model's significance is suggested by its F-value of 7.08. Noise-induced "Model F-Value" of this magnitude has a mere 1.15% probability of occurring. Significant model terms are indicated by "Prob>F" values less than 0.0500. An important lack of fit is suggested by the "Lack of Fit F-value" of 852.15. A significant "Lack of Fit F-value" like this is 0.01% likely to be the result of noise (Figure 4). The overall mean is a stronger predictor of your reaction than the present model, according to a negative "Pred R-Squared". The ratio of signal to noise is measured by "Adeq Precision". One prefers a ratio higher than 4. An acceptable signal is indicated by our ratio of 8.977 (Table 5). To move around the design space, utilize this model.

The processing of the results was done to maximize the release of the drug form the patches and three numerical solutions were obtained by the software.

Solutions for Maximizing Release

The study explores formulations of venlafaxine transdermal patches utilizing different ratios of HPMCK15M and EC.

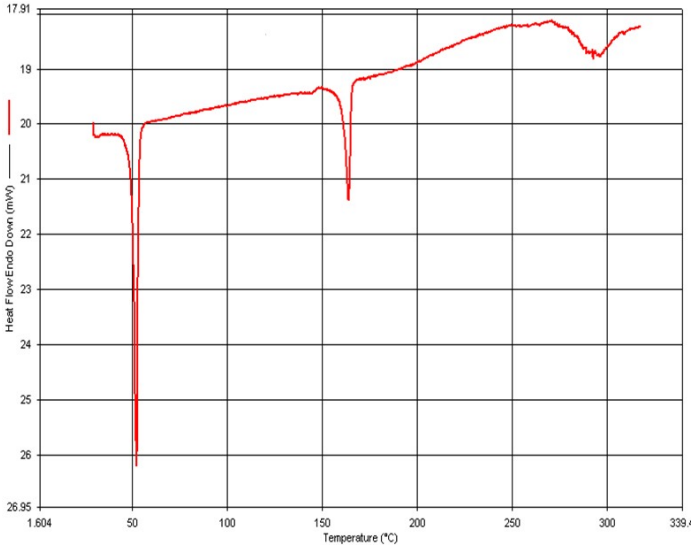

Figure 2: DSC thermogram of Physical mixture.

Formulation 1, comprising 150 units of HPMCK15M and 50 units of EC, demonstrated the highest release rate (87.47%) and desirability (0.98), while Formulation 3, with 150 units of HPMCK15M and 93.9 units of EC, exhibited the lowest release rate (71.43%) and desirability (0.47).

The model selected model comprised of highest level of HPMC and lowest level of EC. The contour plot and the 3D-surface plot of the effet of factors on release is presented in Figure 4.

DISCUSSION

Venlafaxine Hydrochloride transdermal patches were made with Ethyl Cellulose (EC) acting as the lipophilic component and Hydroxypropyl Methyl cellulose (HPMC K15M) acting as the hydrophilic matrix. Eucalyptus oil (10% polymer weight) was

utilized as a permeation enhancer to help the medicine penetrate into the dermis and oleic acid (30% polymeric weight) was used as the plasticizer to achieve the elasticity of the patches. The most common and straightforward technique for creating transdermal patches is the solvent casting method. Solvent evaporation from the patch can be regulated with the use of an inverted funnel.

The optimization design matrix was generated using a 3^2 full factorial approach varying the ratio of the hydrophilic and the lipophilic matrix. EC and HPMCK15M were used in 3 different ratios to obtain the most optimized formulation

The patches' surface pH values ranged from 5.28±0.006 to 5.62±0.015, indicating that they are suitable for human use and may not cause skin irritation when applied.

The transdermal patches had a thickness that varied between 0.514±0.004 mm and 0.697±0.004 mm. This variation in thickness may be explained by the types and concentrations of polymers; for example, a rise in the hydrophilic polymer HPMCK15M concentration resulted in an increase in the transdermal patch's thickness.

Weight variations were observed for the formulated transdermal patches, which ranged from 194.67±0.578 mg to 241.67±1.528 mg. The weight variation data indicated that an increase in the concentration of HPMC led to an increase in the weight of the patches. This could be attributed to the fact that HPMC has a higher affinity for water and can absorb more moisture, which results in an increased patch weight; additionally, because the HPMCK15M polymer is more hygroscopic than EC, this could lead to water retention in the patches, which would increase their weight.

Between 7.23±0.158% and 10.33±0.158% was the different moisture contents of the transdermal patches that were devised.

Table 2: Physical Characterization of Prepared Transdermal Patches.

Formulation code	Thickness (mm)	Average weight (mg)	Surface pH	Moisture content (%)	Tensile Strength
P1	0.514±0.004	194.67±0.578	5.28±0.006	7.23 ± 0.158	9.59±0.006
P2	0.564±0.004	225.67±2.309	5.36±0.006	7.87 ± 0.058	9.40± 0.016
P3	0.633±0.003	241.33±1.528	5.57±0.026	10.33 ± 0.158	10.52±0.015
P4	0.563±0.004	223.33±2.082	5.61±0.012	7.87 ± 0.058	9.93±0.021
P5	0.537±0.003	197.33±2.082	5.39±0.025	7.13 ± 0.058	9.61±0.013
P6	0.565±0.003	224.21±3.000	5.57±0.025	7.77 ± 0.058	9.83±0.113
P7	0.526±0.004	197.67±1.548	5.58±0.040	7.2 ± 0.100	9.62±0.011
P8	0.562±0.004	230.33±1.528	5.58±0.031	7.73 ± 0.058	9.83±0.021
P9	0.592±0.003	241.67±4.163	5.59±0.020	10.13 ± 0.058	10.33±0.025
P10	0.565±0.003	223.67±2.517	5.61±0.015	8.07 ± 0.058	9.77±0.029
P11	0.609±0.002	219.33±2.082	5.58±0.021	8.07 ± 0.058	9.80±0.025
P12	0.541±0.003	224.67±0.577	5.59±0.021	7.87 ± 0.058	9.81±0.035
P13	0.697±0.004	241.67±1.528	5.62±0.015	9.9 ± 0.1	10.41±0.035

All the values are expressed as Mean±SD.

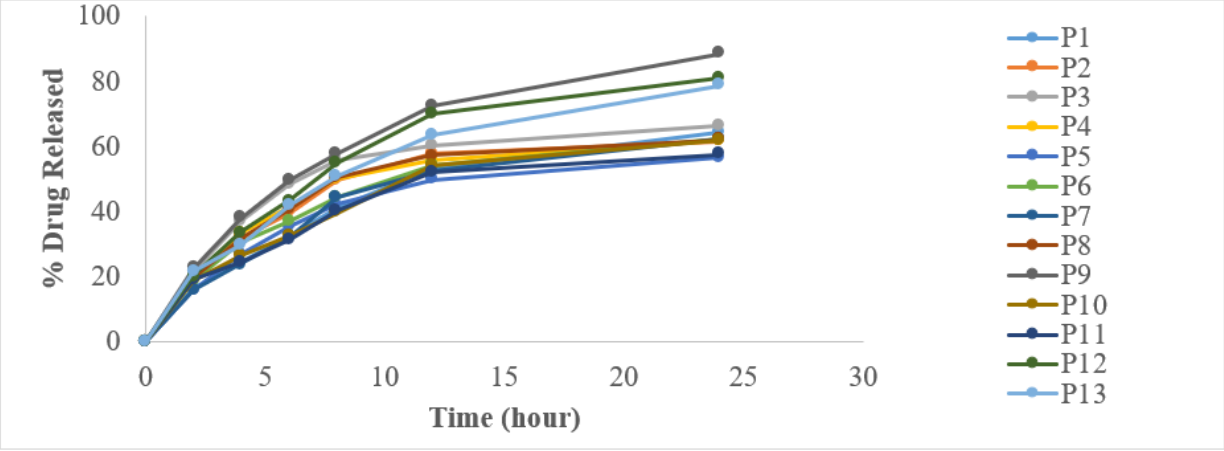

Figure 3: *In vitro* Release of Venlafaxine Hydrochloride from Transdermal Patches.

Table 3: Data utilized for optimizing the formulation.

Formulation	HPMC K15M (mg)	EC (mg)	Drug content (%)
P1	100	50	94.73 ± 0.404
P2	125	75	95.7 ± 0.173
P3	150	75	97.27 ± 0.153
P4	125	75	95.87 ± 0.058
P5	100	100	94.7 ± 0.6
P6	125	75	95.57 ± 0.265
P7	100	75	94.7 ± 0.600
P8	125	75	95.7 ± 0.265
P9	150	50	97.17 ± 0.115
P10	125	75	95.6 ± 0.173
P11	125	100	95.8 ± 0.100
P12	125	50	95.53 ± 0.231
P13	150	100	97.33 ± 0.208

Table 4: Model Summary Statistics.

Source	Std. Deviation Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	Press	
Linear	6.65087	0.612759	0.53531	0.194647	919.9437	Suggested
2FI	7.00222	0.613687	0.484916	-0.73356	1980.227	
Quadratic	5.189624	0.834958	0.717071	-0.67792	1916.67	Suggested
Cubic	0.270894	0.999679	0.999229	0.992259	8.84268	Aliased

Table 5: ANOVA for Response Surface Quadratic Model.

Std. Dev.	5.189624	R-Squared	0.834958
Mean	66.32538	Adj R-Squared	0.717071
C.V.%	7.824491	Pred R-Squared	-0.67792
PRESS	1916.67	Adeq Precision	8.977267

Once more, higher HPMCK15M concentration formulations led to higher moisture content formulations. Water can be absorbed and retained by HPMCK15M in transdermal patches since it is a hydrophilic material.

Because increased folding endurance keeps patches from breaking or getting damaged easily and makes them appear high-quality, folding endurance is crucial for patches. Over 70 folding were demonstrated by all of the transdermal patches that were produced. The standard patch requirements are met by all transdermal patches, as can be seen from this. Transdermal patches' folding durability was not significantly impacted by varying polymer Concentrations (HPMCK15M and EC), while folding endurance rose with increasing HPMC content. The flexible patch formulation was achieved by using Oleic acid as a plasticizer. The transdermal patches that were created showed tensile strength values that fell within the permitted range for transdermal patches, ranging from 9.59±0.006 kg/cm^2 to 10.41±0.035 kg/cm^2.

With the least amount of variation within the batch, every transdermal patch formulation showed consistent medication content. From 94.7±0.6% to 97.33±0.208%, the drug content was found. For transdermal application, this medication content range is considered appropriate. The data demonstrated a clear correlation between the concentration of HPMCK15M and the increase in drug loading in the patch. This may be explained by the hydrophilic nature of HPMCK15M, which exhibited an affinity for venlafaxine with good water solubility. In turn, this increased venlafaxine loading was caused by HPMCK15M's retention of water.

More hydrophilic polymer, HPMCK15M and less lipophilic polymer, EC, were used in the formulation of the patches that showed faster drug release. The study additionally showed that an increase in hydrophilic polymer led to an increase in the formulation's burst impact and medication release.

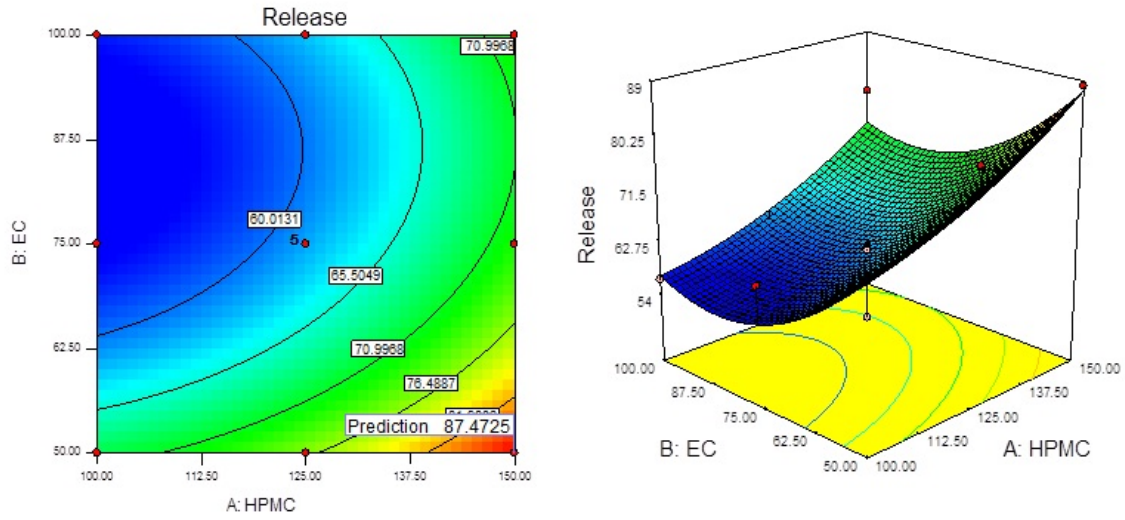

Figure 4: Surface Response Graph for the Selected Model.

CONCLUSION

The results obtained from the study could be seconded by optimizing the formulation using various design approaches in order to obtain a highly optimized formula that might be able to sustain the release of venlafaxine for even higher time duration so that the formulation once applied could be able to manage major depression for several days.

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ABBREVIATIONS

HPMC: Hydroxy propyl methyl cellulose; **EC:** Ethyl cellulose; **FTIR:** Fourier Transform Infrared Spectroscopy; **DSC:** Differential scanning Calorimetry; **SNRI:** Serotonin and norepinephrine reuptake inhibitor; **MDD:** Major depressive disorder; **GAD:** Generalized anxiety disorder; **UV:** Ultraviolet; **ANOVA:** Analysis of Variance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

The study aimed to develop transdermal patches of venlafaxine to extend its half-life and enhance bioavailability. Various formulations were created using Ethyl Cellulose (EC) and Hydroxypropyl Methyl Cellulose (HPMC K15M) matrices through a 3^2 full factorial approach. These patches underwent characterization for thickness, weight, moisture content, pH, folding endurance, tensile strength, drug content and *in vitro* permeation. Optimization using Design Expert software led to a quadratic model predicting drug release, with the optimized formulation containing higher HPMC and lower EC concentrations. Results indicated consistent drug content and acceptable physical properties. The study concludes that further optimization may yield sustained-release formulations suitable for managing major depression over extended periods.

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