Venlafaxine is a unique antidepressant, and is referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor\(^1,2\). It works by blocking the transporter “reuptake” proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitter in the synapse. The neurotransmitters affected are serotonin (5-hydroxytryptamine) and norepinephrine (noradrenalin). It is widely prescribed for the treatment of depression, depression with associated symptoms of anxiety, generalized anxiety disorder, and social anxiety disorder. The recommended oral dosages of venlafaxine hydrochloride are typically in the range of 75 to 225 mg per day. Because of its relatively short half-life of 5 h, venlafaxine should be administered in divided dosages throughout the day\(^3\).

Hydrophobic wax matrix systems are being widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance\(^4\). Factorial design is an optimization technique, where all the factors are studied in all possible combinations. This technique is considered most efficient in estimating the influence of individual variables (main effects) and their interaction using minimum experimentation. A Factorial Design for two factors at three levels each \(3^2\) is considered identical to a two factor composite design\(^7\).

**MATERIALS AND METHODS**

Venlafaxine HCl was obtained from Torrent Pharmaceuticals Pvt. Ltd. (Ahemadabad, India), Talc powder by Cosmo Chem. (Pune, India), and lactose, from M/s Loba Chemie Ltd. (Mumbai, India) were procured from commercial sources. All other chemicals used in the study were of analytical grade.

**Drug-excipient compatibility studies:**

Drug-excipient compatibility studies were done by Fourier Transform Infrared Spectroscopy. The drug with other excipients like carnauba wax, bees wax and Eudragit L 100 (on a 1:1 ratio) were subjected to storage at room temperature and elevated temperature in stability chamber at 45\(^o\)/75\(^o\) RH for three month. After three month the samples were taken and IR spectrum of samples were recorded with FTIR spectrometer (460 Plus, Jasco).

**Preparation of wax matrix tablets:**

The preliminary study was done by using various waxes...
such as compritol, precirol, carnauba wax, bees wax and stearic acid. From the preliminary study bees wax and carnauba wax were selected for further study. The bees wax was selected for its retardant effect and carnauba wax to provide mechanical strength to the matrix.

The waxes were molten and then required quantity of drug (venlafaxine HCl) was slowly added to the molten wax. After cooling, the mass was subjected to granulation by passing through the sieve no 16. Granules were mixed with lactose and talc and blend was compressed into flat-faced tablets (200 mg, 8 mm diameter) using a Rimek Mini Press-II MT tablet machine (Karnawati Eng. Ltd., Mehsana, India) to achieve a tablet thickness of 1.5±0.1 mm8-10.

Table 1 lists the composition of different formulations prepared by using varying amounts of bees wax, carnauba wax and lactose along with a fixed quantity of talc.

Factorial Design:
A 3² full FD was constructed where the amounts of Carnauba wax (X₁) and bees wax (X₂) were selected as the factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design11,12. All other formulations and processing variables were kept invariant throughout the study.

Physical evaluation:
Ten tablets from each batch were evaluated for uniformity in tablet weight and thickness. Tablets from each batch were examined for friability using a Roche-type friabilator (Tropical Equipment Pvt. Ltd., Mumbai, India) and hardness using a Monsanto-type hardness tester (Campbell, Mumbai, India)13,14.

In Vitro Release Study15:
Drug release studies (n=3) were conducted for all the formulation combinations using dissolution test apparatus (Veego, DA-6D USP Standard). Distilled water (900 ml) was taken as the release medium at 100 rpm and 37±1º employing USP II paddle method (Apparatus 2). Aliquots of small samples were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 224 nm.

Data Analysis:
The data obtained from dissolution kinetics studies were analyzed using PCP Disso v2.08 software developed by Poona College of Pharmacy, Pune. The computed values of kinetic constant (k) and diffusional release exponent (n) were calculated using logarithmic transformation of the relationship proposed by Korsmeyer, which was

\[ \log(\frac{M_t}{M_\infty}) = \log k + n \log t \] (Eqn. 1),

where \( M_t/M_\infty \) is the fraction of drug released at time t. The values of \( t_{50} \) were calculated by MS-Excel on computers.

Various computations for the current optimization study using RSM were carried out, employing Stat Ease Design Expert Version 7.16. Statistical second-order model including interaction and polynomial terms were generated for all the response variables. The general form of the model is,

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1^2 + \beta_4 X_2^2 + \beta_5 X_1 X_2 + \beta_6 X_1 X_2^2 + \beta_7 X_2 X_1^2 + \beta_8 X_1^2 X_2 + \beta_9 X_2^2 X_1 \] (Eqn. 2),

where \( \beta_0 \) is the intercept, is the arithmetic average of all quantitative outcomes of nine runs, \( \beta_1 \) to \( \beta_8 \) are the coefficients computed from the observed experimental values of Y, and \( X_1 \) and \( X_2 \) are the coded levels of the independent variable(s). The terms \( X_1 X_2 \) and \( X_1^2 \) (i = 1, 2) are the interaction and polynomial terms, respectively. The statistical validity
of the polynomials was established on the basis of Yates’ ANOVA. Subsequently, feasibility as well as grid search was performed to locate the composition of optimum formulations. Also, three-dimensional response surface graphs and contour plots were drawn in MS-Excel using the output files generated by the State Ease Design Expert Version-7 software.

Validation of Optimization Model:
Six optimum formulations were selected by intensive search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of optimum was primarily based on the highest possible values of the response parameters, which are released in 12 h and t_50%.

RESULTS AND DISCUSSION
FTIR spectrum shows no evidence of interaction between drug and studied excipients. All the major drug peaks (functional group) at 3669 cm\(^{-1}\) [CH stretch]; 1438 cm\(^{-1}\) [N-(CH\(_3\))\(_2\)] and 2995 cm\(^{-1}\) [OH] were seen in subsequent spectra of drug and excipients kept together. The literature documented that significant reduction in the dose frequency can be achieved via SR drug delivery system of venlafaxine HCl\(^{17,18}\). Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interaction on response variable\(^{19}\).

The nine formulations were designed, using various higher and lower levels of carnauba wax and bees wax (Table 1). All the preparations of each formulation passed weight variation test; the weight variation in all the nine formulations was found to be 198.5 mg to 202.8 mg, which was within pharmacopoeial limits. The hardness was found to be between 6 to 7 kg/cm\(^2\). Friability of all the formulations was found to be less than 0.5%. In the current study, Table 3 shows that with the increasing amount of carnauba wax and bees wax, the release after 12 h is decreased and time taken for 50% drug release increases linearly.

Table 3 lists various dissolution kinetic parameters computed for all nine batches. In the current study, in all the nine cases studied, the n varied between 0.2437 and 0.6068. Further, the magnitudes of kinetic constant (k) ranges between 10.47 and 49.02; consequently, the value of t_50% varies in between 1 h 17 min to 12 h 42 min according to wax content.

The mathematical relationship constructed for the studied response variables are expressed as Eqns. 2 and 3. All the polynomial equations were found to be highly statistical significant (P< 0.001) as determined by ANOVA. Release 12 h= 71.46–6.89X 1+0.13X 2–11.88 X 1X 2–0.65 X 1\(^2\)+2.34 X 2\(^2\)–0.17 X 1 X 2\(^2\)–0.65 X 1\(^2\)–0.36 X 1 X 2\(^2\)–0.91 X 2\(^2\)–0.25 X 1\(^2\)–0.54 X 1 X 2\(^2\)–0.34 X 2\(^2\)–0.65 X 1\(^2\)–0.36 X 1 X 2\(^2\) (Eqn. 3) and T50%= 5.26+1.71 X 1+0.16 X 2\(^2\)+3.66 X 1 X 2\(^2\)+0.36 X 1\(^2\) X 2\(^2\)+0.11 X 1\(^2\) X 2\(^2\)+0.23 X 1 X 2\(^2\)+0.094 X 1\(^2\) X 2\(^2\) (Eqn. 4)

Application of two-way ANOVA based factorial analysis indicates that a high amount of carnauba wax and bees wax has a significant influence on release after 12 h and time required for 50% of drug release (P<0.001). (fig. 1), shows that release after 12 h varies in a nearly linear descending pattern with decrease in the amount of waxes. (fig. 2) also exhibits a near linear trend of t_50%, but in ascending order. As there is no confounding of the contour lines in figs. 1 and 2, both the waxes seem to contribute independently towards drug release.

For all the six optimum formulations, the value of n ranged between 0.685 and 0.839, visibly indicating a peppas release behavior approaching. Evidently, the values of dissolution parameters had a propensity to range optimally between relatively controlled limits rather than those of the original formulations designed as per 3\(^2\) factorial designs. The release profile of optimum formulations shows superiority in the drug release as depicted in the figs. 3a and b.
TABLE 4: COMPARISON OF OBSERVED AND PREDICTED RESPONSE PARAMETERS

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Formulation composition Carnauba/Bees wax</th>
<th>Response property</th>
<th>Experimental value</th>
<th>Predicted value</th>
<th>Percentage error</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>18.75/41.71</td>
<td>Release 12 h</td>
<td>77.16</td>
<td>76.29</td>
<td>1.127</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T_{50}%</td>
<td>4.40</td>
<td>4.31</td>
<td>0.681</td>
</tr>
<tr>
<td>A2</td>
<td>21.56/44.53</td>
<td>Release 12 h</td>
<td>73.47</td>
<td>73.64</td>
<td>-0.231</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T_{50}%</td>
<td>5.003</td>
<td>4.99</td>
<td>0.259</td>
</tr>
<tr>
<td>A3</td>
<td>31.87/34.68</td>
<td>Release 12 h</td>
<td>75.88</td>
<td>75.20</td>
<td>0.896</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T_{50}%</td>
<td>4021</td>
<td>4.26</td>
<td>-1.187</td>
</tr>
<tr>
<td>A4</td>
<td>34.68/37.03</td>
<td>Release 12 h</td>
<td>72.18</td>
<td>72.78</td>
<td>-0.831</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T_{50}%</td>
<td>4076</td>
<td>4.83</td>
<td>-1.470</td>
</tr>
<tr>
<td>A5</td>
<td>47.81/27.65</td>
<td>Release 12 h</td>
<td>74.29</td>
<td>74.31</td>
<td>-0.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T_{50}%</td>
<td>4.19</td>
<td>4.13</td>
<td>1.431</td>
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<td>A6</td>
<td>52.50/29.53</td>
<td>Release 12 h</td>
<td>70.42</td>
<td>71.64</td>
<td>-1.732</td>
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<td></td>
<td></td>
<td>T_{50}%</td>
<td>4.80</td>
<td>4.87</td>
<td>-1.458</td>
</tr>
</tbody>
</table>

Mean (±SD) of percent error -0.2117±1.110

The results are average of three determinations. n- Diffusional release exponent, k-Kinetic constant
Table 4 shows the values of observed and predicted responses using factorial design along with the percentage predicted errors for these six optimum formulations. The predicted error for the response variables ranged between -1.73 and 1.43%, with the mean±standard deviation of the percentage error being -0.2117±1.110%. Also, the linear plots between the predicted and observed responses demonstrated high of r² (ranging between 0.9701 and 0.9977), indicating excellent goodness of fit. Thus, the low magnitudes of error, as well as the significant values of r², designate a high prognostic ability of Response Surface Methodology (RSM).

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REFERENCES