CHAPTER 8

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Advanced formulation design of venlafaxine hydrochloride coated and triple-layer tablets containing hypromellose

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Abstract
The purpose of this research work was to develop venlafaxine hydrochloride-coated and layered matrix tablets using hypromellose adopting wet granulation technique. The granules and the tablets were characterized. The monolithic tablets were coated with different ratios of ethyl cellulose and hypromellose. The in vitro dissolution study was performed in distilled water. In the layered tablets, the middle layer containing drug was covered with barrier layers containing high viscosity grade hypromellose. Simplex lattice design was used for formulating the layered tablets. The dissolution study of the optimized batches and a reference product was carried out in 0.1 N HCl, phosphate buffer and hydroalcoholic solution. Burst drug release was exhibited by the uncoated tablets, probably due to high aqueous solubility of venlafaxine HCl. The coated tablets showed sustained drug release without burst effect. The drug release was best explained by Weibull model. A unified Weibull equation was evolved to express drug release from the coated tablets. The layered tablets also exhibited sustained release without burst effect due to effective area reduction. The optimized batches showed identical drug release in 0.1 N HCl, phosphate buffer and 10% v/v aqueous alcohol. Layered tablets may well be adopted by the industry due to the possibility of achieving a high production rate.

Keywords: Venlafaxine HCl; hypromellose; coated and layered tablets; Weibull model; radar diagram

Introduction
An active pharmaceutical ingredient is uniformly distributed within a polymer matrix in hydrophilic matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. These dosage forms are designed to deliver the drug at a controlled and predetermined rate, thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time and therefore reducing the frequency of dosing and improving patient compliance. Hydroxypropyl cellulose, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose, Polyox®, Carbopols® and polyvinyl alcohol are representative examples of the hydrophilic polymers that have been extensively examined in the formulation of controlled release systems.

When the drug is freely soluble in water, judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. Hypromellose, formerly known as hydroxypropyl methylcellulose (HPMC) is widely used in the preparation of oral controlled drug delivery systems. Its non-toxic nature and ease of handling makes it an excellent release retardant material. On exposure to aqueous fluids, the polymer hydrates to form a viscous gel layer through which the drug is released by diffusion and/or erosion of the matrix. Ethyl cellulose (EC) is a water insoluble polymer. Ethyl cellulose, low viscosity grade, is used to coat the tablets along with some pore forming agents to control the release of pharmaceutical actives.
The hydrophilic polymers can also be used to formulate layered tablets so as to get required release pattern. The drug delivery system consists of two- or three-layer tablets in which the outer layers are drug-free modulating barriers, while the active ingredient is contained in the central layer or core.10,12,13

Venlafaxine hydrochloride is structurally a novel antidepressant. It imparts its antidepressant effects by inhibiting the neuronal uptake of norepinephrine, serotonin and to a lesser extent, dopamine.14 The short biological half-life (5 ± 2 h) and the fast clearance make the drug, a suitable candidate for the development of once a day formulation. Furthermore, it is required to be taken for a long period by the patients. The use of extended release formulation is associated with less nausea and dizziness at the initiation of therapy.15 Hence to improve the patient compliance as well as to reduce side effects, the drug needs to be formulated in sustained release (SR) dosage form.

The objective of the present study was to formulate venlafaxine hydrochloride SR matrix tablets using hypromellose and to elucidate the release kinetics of venlafaxine hydrochloride from hypromellose matrices. US patents 6,607,751 and 7,090,867 covered the use of cellulose ether (hypromellose) along with microbial polysaccharides for development of modified release tablet of venlafaxine hydrochloride.16,17 US patents 6,274,171 and 6,403,120 employed coating of spheroids with water insoluble excipients like ethyl cellulose.18,19 An effort was made in the present investigation to by pass the patents.

Materials and methods

Venlafaxine hydrochloride (D (v, 0.1)< 2.79 μ, D (v, 0.5)<10.04 μ and D (v, 0.9)<43.98 μ) was received as a gift sample from Cadila Healthcare Ltd., Ankleshwar. Ethyl cellulose 7cPs, hypromellose K100M, hypromellose K4M and hypromellose 6 cPs were used as received from Cadila Healthcare Ltd., Ahmedabad. Microcrystalline cellulose (Avicel PH 101, FMC Biopolymers, USA) and lactose monohydrate (Pharmatose DCL 21, DMV International Inc., The Netherlands) were used as received. Magnesium stearate was purchased from Laser Chemicals, Ahmedabad. Methylene chloride and methanol were purchased from Rankem, New Delhi. Effexor® XR Capsules 150 mg (Wyeth Pharmaceuticals Inc., Expiry date: 04/2011) was used as a reference product.

Preparation and evaluation of venlafaxine hydrochloride film coated matrix tablets

Preparation and evaluation of matrix tablets of venlafaxine hydrochloride

Hypromellose K100M alone or in combination with hypromellose K4M was used as matrix forming material while Avicel PH 101 was used as compression facilitator. The batch size was 500 tablets for batches H1–H8. All the ingredients were passed through mesh #3 prior to wet granulation. Modified release tablets of venlafaxine hydrochloride were prepared by wet granulation method using a blend of isopropyl alcohol and water (90:10) as a binder. The wet mass was dried in a tray dryer at 60 ± 5°C until percentage loss on drying was below 3%. The dried mass was then sieved through mesh #24. The granules were lubricated with 1.5% magnesium stearate. The blend ready for compression was evaluated for angle of repose and Carr's index. The tablets were prepared by compressing the lubricated blend using 16 station rotary tablet press (Karnavati Engineering Ltd., Mehsana, India). The composition of batches (H1–H8) is depicted in Table 1. The thickness and crushing strength were measured on hardness tester (Dr Schleuniger Pharmaton AG, Switzerland). Friability was measured using Roche type friabilitor (Electrolab, Mumbai, India) by rotating the tablets for 4 min at 25 rpm. The tablets were examined for weight variation and in vitro drug dissolution in distilled water.

In vitro dissolution studies

In vitro drug release study (n = 3) was carried out in USP apparatus I (Electrolab TDT 06-T, Mumbai, India) in 900 mL of distilled water at 37 ± 0.5°C. Five mL samples were pulled at predetermined times. The drug solution was replaced with equal volume of distilled water. The samples were diluted with water and analyzed at 226 nm using UV visible spectrophotometer (Shimadzu-1700, Japan). The dissolution study was also performed for reference product (Effexor® XR Capsules 150 mg). The dissolution study of the optimized batches was also performed in 0.1N HCl, phosphate buffer (pH 6.8) and distilled water containing 10% ethanol.

Coating of matrix tablets of venlafaxine hydrochloride

The tablets of selected formulations (Batches H3–H5, 100 gm) were subjected to coating in Gans coater (Gansco Ltd., Mumbai, India) along with placebo tablets (200 gm). Scored placebo tablets of similar geometry

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
<th>H4</th>
<th>H5</th>
<th>H6</th>
<th>H7</th>
<th>H8</th>
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<tbody>
<tr>
<td>Venlafaxine HCl</td>
<td>169.8</td>
<td>169.8</td>
<td>169.8</td>
<td>169.8</td>
<td>169.8</td>
<td>169.8</td>
<td>169.8</td>
<td>169.8</td>
</tr>
<tr>
<td>Hypromellose K100M</td>
<td>90.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>120.0</td>
<td>145.0</td>
<td>K4M</td>
</tr>
<tr>
<td>Hypromellose K4M</td>
<td>-</td>
<td>-</td>
<td>49.8</td>
<td>74.8</td>
<td>99.8</td>
<td>124.8</td>
<td>149.8</td>
<td>99.8</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>65.3</td>
<td>64.8</td>
<td>54.4</td>
<td>54.0</td>
<td>53.7</td>
<td>53.3</td>
<td>52.9</td>
<td>53.3</td>
</tr>
</tbody>
</table>

*a Each batch contains 1.5% magnesium stearate; b 169.8 mg venlafaxine hydrochloride is equivalent to 150 mg venlafaxine.
to the drug containing tablets were used to facilitate the flow of tablets (cascading) in the coating pan. Ethyl cellulose 7 cPs and hypromellose 5 cPs, in different ratios, were added to organic solvents to obtain 10% w/v solution. The coating composition and parameters are shown in Table 2. The process of coating was continued till weight gain was 5%. The coated tablets were evaluated for in vitro drug release in distilled water.

**Drug release kinetics**

In order to investigate the kinetics of drug release from matrix tablets, the data of in vitro drug release were fitted to different models.

Preparation of three-layered venlafaxine hydrochloride tablets

Triple layer tablets were prepared by putting drug free barrier layers on either side of the middle layer. The middle layer contained the venlafaxine hydrochloride, part of hypromellose K100M and Avicel PH 101. The batch size was 2000 tablets. The ingredients were passed through mesh 30# and dry blended. The dry mix was granulated with water and the wet mass was dried in a tray dryer at 60 ± 5°C temperature until percentage loss on drying was below 3%. The blend was then sieved through mesh # 24. These granules formed the core layer. The composition of batches G1–G7 is shown in Table 4. The barrier layer consists of hypromellose K100M, Pharmatose DCL 11 and magnesium stearate. The powder blend of each layer was sequentially filled in the die cavity of rotary press. Finally, the compression force was applied. A 32 station triple-layer tablet compression machine (Karnavati Engineering Ltd., Mehsana, India) was used for compression of tablets. The tablets were evaluated for crushing strength, thickness, friability, weight variation and in vitro drug release. The amount of hypromellose K100M in barrier layer (X₃, 50–70 mg per tablet) and amount of hypromellose K100M in core layer (X₄, 32–52 mg per tablet) were selected as independent variables in the simplex lattice design. The linear interactive full model is shown below:

\[
Y = b_1 X_1 + b_2 X_2 + b_3 X_3 + b_{12} X_1 X_2 + b_{13} X_1 X_3 + b_{23} X_2 X_3
\]

where \(Y\) is the dependent variable; \(b_i\) is the estimated coefficient for the factor \(X_i\). Three-way interactions were suppressed to perform regression analysis. The reduced model was developed by eliminating insignificant terms \((P > 0.05)\) from the full model. The dependent variables were the percentage drug dissolved at 1, 4, 10 and 24 h.

**Water uptake study**

The swelling behavior of tablet of batches H3 and G5 was studied. The tablets were kept in a beaker containing 100 mL distilled water maintained at 37 ± 2°C. At selected time points, the tablets were withdrawn, wiped with tissue paper and weighed. The percentage water uptake by the tablet was calculated using the following formula:

\[
\text{Percentage water uptake} = 100 \times \left( \frac{W_t - W_0}{W_0} \right)
\]

where \(W_t\) is weight of tablet at time \(t\) and \(W_0\) is initial weight of the tablet.

**The radar graphs**

In the dissolution study, higher or lower % drug release, than a target value is permitted up to a certain limit. Shah et al. proposed that the maximum difference can be 10% \((f_2 = 50)\) for establishing similarity in dissolution. The dissolution profile of reference product (EffexorXR 150 mg) was considered as ideal release pattern. The percent drug release of reference product will get a score of five (ideal) on a scale of 0 to 10. The lower and high permissible % of drug release will get a score of zero and 10, respectively. The scores of optimized batches H3 and G5 were calculated at each dissolution time point.

\[
\text{Score} = 5 + \left\{ \left( \% T - \% R \right) / 2 \right\}
\]

where \(\% T\) is percentage drug released from test batch while \(\% R\) is percentage drug released from reference product at the same time.

**The Kopcha model**

The drug release profiles of the optimized formulations (Batches H3 and G5) were fitted to the Kopcha equation.

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**Table 2. Coating composition and parameters.**

<table>
<thead>
<tr>
<th>Coating composition</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl cellulose 7 cPs: Hypromellose 5 cPs</td>
<td>50:50</td>
<td>70:30</td>
<td>90:10</td>
</tr>
<tr>
<td>Methylene chloride: methanol</td>
<td>10:90</td>
<td>10:90</td>
<td>10:90</td>
</tr>
<tr>
<td><strong>Coating Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inlet air temperature (°C)</td>
<td>60 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaust temperature (°C)</td>
<td>45 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peristaltic pump speed (RPM)</td>
<td>5–12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan speed (RPM)</td>
<td>2–10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomization air pressure (kg/cm²)</td>
<td>1.5–2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* RPM (Rotation per minute).
M = At^{1/2} + Bt + C

where M ($\leq 70\%$) is the amount of drug released at time t, A is diffusional term, B is erosional term and C is constant. According to this equation, if diffusion to erosion ratio is equal to one ($A = B$) the release mechanism includes both diffusion and erosion equally. If $A/B > 1$, diffusion prevails, while for $A/B < 1$, erosion predominates. A small value of C indicates the error, large positive value indicates burst release and high negative value is indicative of lag time. Sigma plot was used to solve the Kopcha equation.

**Stability study**

The optimized formulations (Batches H3 and G5) were stored at 40±2°C and 75±5% RH for three months to check the dissolution stability. The tablets were tested for dissolution in distilled water.

**Results and discussion**

The aim of present study was to develop venlafaxine hydrochloride sustained release tablets using hypromellose as a matrix forming polymer. The composition of eight formulations is shown in Table 1. The values of angle of repose and Carr’s index of the lubricated blends were in the range of 24–28°C and 16–19%, respectively. The flow can be graded as fair to excellent. The standard concave tablets showed acceptable crushing strength (> 6 kp) and friability (< 1%). The problems of weight variation and content variation were not observed.

The reference product, Effexor®XR capsules contained coated pellets. The dissolution of the reference product was performed in distilled water and was targeted for the formulated venlafaxine hydrochloride matrix tablets. The reason for choosing distilled water as a dissolution medium is that the food and drug administration (FDA) endorses the use of it as a dissolution medium for the generic version of venlafaxine hydrochloride. The reference product exhibited sustained drug release. The result shown in Figure 1 reveals that the drug release was less than 25% in first 2 h from Effexor® XR capsule. The slower initial drug release indicates that the pellets of reference product might be coated with water insoluble coating agent.

The higher aqueous solubility of venlafaxine HCl (572 mg/mL) and higher surface area of pellets are important considerations. The impact of high aqueous solubility and surface area can be nullified by coating. Figure 1 shows the in vitro drug release profile of the batches H1–H8. None of the batch showed drug release profile comparable to Effexor® XR capsules up to 4 h. The drug release from few batches was comparable to the reference product after 4 h. Although hypromellose K100M (27–30%) and hypromellose K4M (12–30%) were used in matrix, the required drug release pattern could not be achieved (Figure 1). It has been reported that in case of a highly soluble, high dose drug, matrix tablet formation with hydrophilic polymers like hypromellose may lead to an initial burst release because of presence of the drug on the surface and the periphery of the matrix tablet. The problem of fast drug release in earlier phase of dissolution testing can be resolved either by coating the matrix tablet or by formulating layered tablets.

A coat of low viscosity grade ethyl cellulose (EC) can retard the initial burst release of highly soluble drug. Hypromellose (6 cPs) was used in different ratios as a pore former in the coat to regulate the drug release through semipermeable film of ethyl cellulose. Batches H3–H5 were coated with coating composition A, B and C (Table 2) to coat the tablets up to 5% weight gain. The drug release profiles of coated tablets are shown in Figure 2. As the proportion of EC increases in coating composition, the drug release was retarded. The initial burst was inhibited by the insoluble but permeable coat of EC (7 cPs). The coating complements the hydrophilic matrix, preventing rapid drug dissolution and release from the surface of the matrix and thus retarding drug release at
the initial stage of dissolution. Thus barrier properties of EC must be responsible for slower drug release. Swelling and relaxation of the hypromellose K100M matrix may cause rupturing of ethyl cellulose film during the dissolution testing. Axial relaxation of the matrix tablet caused the film to open along the circumference of the tablets. The drug release was predominantly controlled through gelled hypromellose K100M after rupturing of the coat. Figure 3a represents the condition of tablets after 1, 4 and 20 h from batch H3.

The drug release from tablets coated with composition 'A' showed faster drug release compared to reference product while the tablets coated with composition 'C' showed lag time of 4 to 5 h. The drug release was incomplete (< 60%) from the formulations coated with composition 'C'. The higher percentage of EC (90%) in the coat may be responsible for slow and incomplete drug release. The tablets of batches H3-H5, coated with composition 'B', showed identical release profile to the reference product as, values were 84, 72 and 69, respectively. Thus coating composition 'B' was chosen. The batch H3 was ranked as optimized batch as it showed highest dissolution similarity ($f_2 = 84$).

The goodness of fit test was used to determine the mechanism of drug release. A FORTRAN software, developed in house, was used to fit to zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull model. The drug release data of batches H3-H5 and reference product were subjected to data treatment. The least value of sum of square and Fischer's ratio were used to select the most appropriate kinetic model (Table 3).

The formulator is always interested in modeling performance of his products. True optimum formulation can be identified if the data is explained mathematically. The current approach of FDA, quality by design, is also to appreciate the systemic and sound formulation development. The Weibull model showed superior fit amongst all the tested models. The dissolution data of batches H3-H5 were used for derivation of unified Weibull model. The Weibull equation is given below:

$$M = 1 - e^{-(t/T_d)^\beta}$$

where $M$ is the cumulative amount of drug released at time $t$, $\beta$ is slope parameter (slope) and $\alpha$ is the scale parameter (intercept). The term $T_d$ (time necessary to dissolve 63.2% of drug) using the relationship $\alpha = \frac{T_d}{3.322}$. The linear equation of slope ($r=0.99$) was evolved using the data of slope of batches H3-H5 using the method reported by Kirilmaz. The linear equation of slope ($r=0.99$) was evolved using the data of slope of batches H3-H5 using the method reported by Kirilmaz:

$$M = 1 - e^{\left(\frac{t}{T_d}\right)^\beta}$$

where $X$ is percentage of hypromellose K4M. The computed values of $T_d$ were 6.8, 7.1 and 7.4 for batches H3, H4 and H5, respectively. The evolved model was validated by comparing the calculated and predicted release profiles. The calculated percent drug release and experimental percent drug release of the optimized batch H3 can be considered as comparable since $f_2$ was equal to 76. It is possible to predict the drug release pattern from any batch within the factor space using Table 3. Results of model fitting of selected batches and reference product (Effexor® XR capsules).

<table>
<thead>
<tr>
<th>Function</th>
<th>Batch</th>
<th>F ratio</th>
<th>R-square</th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero-order</td>
<td>H3</td>
<td>6.86</td>
<td>0.992</td>
<td>10.66</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td>H4</td>
<td>5.89</td>
<td>0.993</td>
<td>10.29</td>
<td>0.934</td>
</tr>
<tr>
<td></td>
<td>H5</td>
<td>5.92</td>
<td>0.993</td>
<td>10.07</td>
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<td></td>
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<tr>
<td>First-order</td>
<td>H3</td>
<td>8.95</td>
<td>0.994</td>
<td>-0.168</td>
<td>4.64</td>
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<tr>
<td></td>
<td>H4</td>
<td>10.58</td>
<td>0.993</td>
<td>-0.156</td>
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<tr>
<td></td>
<td>H5</td>
<td>10.62</td>
<td>0.993</td>
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<tr>
<td>Hixson-Crowell</td>
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<td>3.43</td>
<td>0.997</td>
<td>0.221</td>
<td>-0.026</td>
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<tr>
<td></td>
<td>H4</td>
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<td>0.996</td>
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<tr>
<td></td>
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<td>5.38</td>
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<td></td>
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<td>0.991</td>
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<td>Korsmeyer-Peppas</td>
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<tr>
<td></td>
<td>H4</td>
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<td>0.911</td>
<td>25.09</td>
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<tr>
<td></td>
<td>H5</td>
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<td>0.900</td>
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<tr>
<td>Weibull</td>
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<td>0.998</td>
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<td></td>
<td>H4</td>
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<td></td>
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<td>2.84</td>
<td>0.998</td>
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</tr>
<tr>
<td></td>
<td>Effexor®</td>
<td>9.40</td>
<td>0.995</td>
<td>1.40</td>
<td>-1.06</td>
</tr>
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</table>

\[ X = \frac{T_d}{0.0105x + 0.9407} \]

$T_d$ is time necessary to dissolve 63.2% of drug.
the unified Weibull equation (Equation 7). This investigation demonstrates that the release of venlafaxine hydrochloride can be modified by changing the amount of polymer.

It is always desirable in industry to develop few test formulations that show identical in vitro drug dissolution to that of the reference formulation. In the event of failure of bioequivalence with one formulation, the second formulation may be used for bioequivalence study without further delay and the advantage of early filing of abbreviated new drug application (ANDA) can be obtained by a company. The selection of biobatch may also be done after considering other factors such as cost, ease of validation and patent related issues. Hence another formulation was also developed using layered technology.

Multilayer tablets have been developed by scientists for obtaining control of drug release from hydrophilic polymeric systems. The surface area exposed to the dissolution medium is reduced in layered tablet and hence the burst drug release is arrested. Based on preliminary trials on the formulation of triple layer tablet, the amount of hypromellose K100M (X1) and of Pharmatose DCL 11 (X2) in barrier layers and the amount of hypromellose K100M (X3) in core layer were selected as independent variables in the Simplex lattice design (Table 4).

The purpose of addition of lactose in the barrier layer was to facilitate the drug release through the channels formed due to dissolution of lactose. The formulated batches showed acceptable crushing strength (> 6 kp) and friability (< 1%). The problems of weight variation and content variation were not observed. The release profile of the seven batches is shown in Figure 4.

The drug release at different time (Y1, Y4, Y10 and Y24) was selected as dependent variable. The low and high values of independent variable were transformed as 0 and 1, respectively. The three-way interaction (X1X2X3) was ignored while performing multiple regression analysis. The reduced models containing significant terms are shown below:

\[
Y_1 = 11.15X_1 + 15.26X_2 + 13.02X_3 \tag{8}
\]
\[
Y_4 = 39.13X_1 + 54.31X_2 + 49.59X_3 - 39.05X_1X_3 \tag{9}
\]
\[
Y_{10} = 76.65X_1 + 88.56X_2 + 81.76X_3 \tag{10}
\]
\[
Y_{24} = 99.71X_1 + 98.73X_2 + 99.33X_3 \tag{11}
\]

The check-point batch G8 (X1 = 0.6, X2 = 0.2 and X3 = 0.2) was prepared to validate models (Equations 8–11). The experimental values of Y1, Y4, Y10 and Y24 were determined as 12.5, 45.7, 83.4 and 98, respectively. The computed values were 12.3, 45.8, 80.1 and 99.4. Good agreement between observed and predicted values shows predictive capability of equations.

The selection of optimized batch was done by allowing 5% difference in dissolution between the reference (Effexor® XR capsules) and test products at each pull out time. The batch G5 met this criteria (f2 = 82). It has been previously shown in this paper that coated composition H3 also met the criteria of 5% maximum difference at each dissolution point. The results of analysis of variance (ANOVA) showed insignificant difference between

![Figure 4. Comparative dissolution profiles of venlafaxine hydrochloride three-layered tablets in distilled water (→G1, →G2, →G3, →G4, →G5, →G6, →G7 and →Reference).](image)

| Table 4. Compositions of three-layer tablets of venlafaxine hydrochloride. |
|-----------------|---|---|---|---|---|---|---|
| **Ingredients (mg)** | G1 | G2 | G3 | G4 | G5 | G6 | G7 |
| **Core layer** | | | | | | | |
| Venlafaxine HCl | 169.8 | 169.8 | 169.8 | 169.8 | 169.8 | 169.8 | 169.8 |
| Hypromellose K100M | 32.0 (0) | 32.0 (0) | 32.0 (1) | 32.0 (0) | 42.0 (0.5) | 42.0 (0.5) | 38.7 (0.33) |
| Avicel PH 101 | 53.0 | 53.0 | 53.0 | 53.0 | 53.0 | 53.0 | 53.0 |
| **Barrier layer** | | | | | | | |
| Hypromellose K100M | 90.0 (1) | 60.0 (0) | 60.0 (0) | 75.0 (0.5) | 75.0 (0.5) | 60.0 (0) | 70.0 (0.33) |
| Pharmatose DCL11 | 50.0 (0) | 70.0 (1) | 50.0 (0) | 60.0 (0.5) | 50.0 (0) | 60.0 (0.5) | 56.7 (0.33) |
| Magnesium stearate | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |

*Parenthesis shows the transformed values of independent variables; **169.8 mg venlafaxine hydrochloride is equivalent to 150 mg venlafaxine.*
The dissolution data of the reference product and the test formulations (Batches H3 and G5) in 0.1N HCl and phosphate buffer (pH 6.8) are depicted in Figure 5. The optimized batches showed similar dissolution in acidic and basic dissolution media. The solubility, swelling and gelling tendencies of major ingredients in tablets may have remained same in the acidic and basic medium.

The FDA has recently suggested the testing of modified release dosage forms in dissolution media containing ethanol. The FDA mentions that the potentially fatal interaction of a modified release system might be observed on consumption of alcohol which results in impairment of the formulation and dose dumping. Ten percent ethanol, typical of those found in alcoholic beverages, was included in dissolution media (distilled water). The dissolution study of batches H3 and G5 was performed using same dissolution conditions with and without ethanol. Batches H3 and G5 showed similarity factor (f2), 78 and 83, respectively, with and without ethanol. The matrix of hypromellose did not collapse in either water or hydroalcoholic medium. Ethyl cellulose used in present study contain more than 46.5% ethoxy group and hence, it is freely soluble in ethanol but insoluble in water and so insoluble in 10% ethanolic solution. Thus we can conclude that both the developed formulations are robust and are safe even if alcohol is consumed.

The radar diagrams of batches H3 and G5 are shown in Figure 6. The dissolution pull times are shown on the periphery of radar diagrams. The outer surface of radar graphs shows highest score (10) while the centre shows lowest score (zero). Ideally, all the data points should fall on score line of five, i.e. in the middle of radar diagram. The radar diagrams of batches H3 and G5 shows that, most of the data points fall on or near the ideal line. The sums of absolute value of difference between reference and test at all time points were 13.1 and 13.2, respectively, for batches H3 and G5. The low values of computed difference quantitatively show the difference.

Figure 7 shows the average value of water uptake of the optimum batches (H3 and G5). The study showed that water uptake by layered tablet (batch G5) was little more as compared to the coated tablets (batch H3). The water insolvency of EC may be responsible for slower water uptake by the coated tablets. The water taken up by the tablet is responsible for gelling of hypromellose. Figures 3a and 3b show pictorial presentation of the tablets of batches H3 and G5. The tablets of batches H3 and
G5 showed J2 values of 82 and 84, respectively, when stored at accelerated conditions for three months.

Conclusion

High aqueous solubility of venlafaxine hydrochloride resulted in burst drug release when uncoated monolithic tablets were developed using hypromellose. The matrix tablets coated with ethyl cellulose and hypromellose showed drug release comparable to Effexor® XR capsules. The coating functions as a barrier to ingress of dissolution medium and diffusion of drug solution through the coat. The ratio of EC (water insoluble) to hypromellose (water soluble) will dictate the properties of coat and drug release. The drug release was explained by Weibull model. The use of unified Weibull model is demonstrated to investigate the influence of minor changes in the formulation. The drug regulatory authority may consider this as a positive point since the impact of minor change in formulation can be predicted. Three-layered tablets were also developed using hypromellose and Pharmatose DCL 21 in barrier layer to modulate the drug release. The main reason for prevention of burst drug release could be reduction in surface area of tablet exposed to the dissolution medium. The optimized formulations showed pH independent release and the dissolution pattern was unaltered in presence of 10% ethanolic solution. The production rate of triple layer tablets will be higher than that of coated pellets (reference product) and hence the developed formulations appear to be an attractive option to industry to consider for bioequivalence study. A drug release profile similar to that of the reference product (Effexor® XR Capsule) was achieved by adopting systemic formulation approach. The use of radar diagram is demonstrated.

Acknowledgements

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Formulation design of venlafaxine HCl tablets

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Research Article

Fabrication of Triple-Layer Matrix Tablets of Venlafaxine Hydrochloride Using Xanthan Gum

Mukesh C. Gohel1,2 and Shital H. Bariya1

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Abstract. The objective of present investigation was to develop venlafaxine hydrochloride-layered tablets for obtaining sustained drug release. The tablets containing venlafaxine hydrochloride (150 mg) were prepared by wet granulation technique using xanthan gum in the middle layer and barrier layers. The granules and tablets were characterized. The in vitro drug dissolution study was conducted in distilled water. The tablets containing two lower strengths were also developed using the same percentage composition of the middle layer. Kinetics of drug release was studied. The optimized batches were tested for water uptake study. Radar diagrams are provided to compare the performance of formulated tablets with the reference products, Effexor XR capsules. The granules ready for compression exhibited good flow and compressibility when xanthan gum was used in the intragranular and extragranular fractions. Monolayer tablets failed to give the release pattern similar to that of the reference product. The drug release was best explained by Weibull model. A unified Weibull equation was evolved to express drug release from the formulated tablets. Lactose facilitated drug release from barrier layers. Substantial water uptake and gelling of xanthan gum appears to be responsible for sustained drug release. The present study underlines the importance of formulation factors in achieving same drug release pattern from three strengths of venlafaxine hydrochloride tablets.

KEY WORDS: layered tablet; radar diagram; venlafaxine hydrochloride; weibull model; xanthan gum.

INTRODUCTION

An active pharmaceutical ingredient is uniformly distributed within a polymer matrix in hydrophilic matrix system (1). The drug release is extended over a much greater time from a matrix system as compared to immediate release dosage forms. In the recent years, preparation of matrix tablets has been demonstrated with the publication of numerous patents and research papers and their utilization in new products. The widespread and successful use of such polymeric systems could be attributed to their ease of manufacturing, relatively low cost, high biocompatibility, favorable in vivo performance, and versatility in controlling the release of drugs with a wide range of physicochemical properties (2,3).

Xanthan gum is a hydrophilic polymer, secreted from Xanthomonas campestris (a Gram-negative, yellow-pigmented bacterium) (4). It is used for the fabrication of matrices with uniform drug release characteristics (5–11). Xanthan gum is the only bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate microorganisms. Xanthan gum contains glucose 37%, mannose 43.4%, glucuronic acid 19.5%, acetate 4.5%, and pyruvate 4.4%. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse. This property makes xanthan gum a useful ingredient for controlled release and sustained release (SR) applications. Its compatibility with a wide variety of ingredients makes it particularly effective in these applications. Xanthan gum has been evaluated as a hydrophilic matrix for different model drugs including theophylline (12), cephalixin (13), prednisolone (14), indomethacin (15), and diclofenac sodium (16).

Venlafaxine imparts its antidepressant effects by inhibiting the neuronal uptake of norepinephrine, serotonin, and to a lesser extent, dopamine (17). The short biological half-life (5 ± 2 h) and the fast clearance make the drug suitable candidate for the development of once-a-day formulation. Furthermore, it is an antidepressant, and so it is required to be taken for quite a long period. The recommended dose of venlafaxine hydrochloride is 75 to 450 mg/day. The use of extended release formulation is associated with less nausea and dizziness at the initiation of therapy (18). Effexor® XR capsules containing coated pellets were used as reference product. The major advantages of multiplier approach over the coating method are higher productivity, shorter processing time, and minimum variation between and within batches.

US patents 7090867 and 6607751 and patent application 2003091634 covered the use of cellulose ether along with microbial polysaccharide for the development of modified...
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release tablet of venlafaxine hydrochloride. US patents 6274171 and 6403120 employed coating of spheroids (pellets) with water insoluble excipients like ethyl cellulose. An effort was made in the present investigation to develop functional dosage forms of venlafaxine hydrochloride using a hybrid technique of direct compression and wet granulation. The objective of the present study was to obtain drug-release profile similar to that of the reference product using a simpler method.

MATERIALS AND METHODS

Venlafaxine hydrochloride \( (D_v, 0.1) 279 \mu, D_v (0.5) 10.04 \mu, \) and \( D_v (0.9) 43.98 \mu \) was received as a gift sample from Cadila Healthcare Ltd., Ankleeshwar. Xanthan gum was obtained from Alok International, Mumbai. Microcrystalline cellulose (Avicel PH 101, Avicel PH 102) and lactose monohydrate (Pharmatose DCL 21) were received from Colocol Asia Pvt. Ltd., Goa. Magnesium stearate was purchased from Lasser Chemicals, Ahmedabad. Effexor® XR Capsules (Wyeth Pharmaceuticals Inc.) containing 150, 75, and 37.5 mg of venlafaxine HCl with expiry dates 04/2011, 01/2011, and 04/2011, respectively, were used as reference products.

Preparation and Evaluation of Venlafaxine Hydrochloride Tablets

Modified release tablets of venlafaxine hydrochloride were prepared by hybrid wet granulation technique. Xanthan gum was used as a matrix forming material while Avicel PH 101 was used as a granulation facilitator and compression aid. The drug, intragranular fraction of xanthan gum (25% of total xanthan gum), and Avicel PH 101 were blended and granulated with water using rapid mixer granulator (Saral Engineering Company, Mumbai, India). The wet mass was dried in a tray dryer at 60°C temperature until loss on drying was below 3%. The partially dried blend was sieved through mesh #24. The granules were blended using conta blender (Saral Engineering Company, Mumbai, India) for 10 min with the extragranular fraction of xanthan gum (batch A1 to A3) and Avicel PH 102 (batch A3). The formulation of monolayer tablets of venlafaxine hydrochloride (A1, A2, and A3) is shown in Table I. The blends were lubricated with magnesium stearate. The granules ready for compression were evaluated for angle of repose, Carr’s index, and Hausner ratio. The batch size was 1,000 tablets for batches A1 to A3. The tablets were prepared by compressing the lubricated blend using 16 station rotary tablet press. Triple layer tablets were prepared by putting drug-free barrier layers on either side of the middle layer. The granules of middle layer were prepared as described above. Table I depicts the composition of batches A4 to A9. The core was made only of intragranular composition and the drug free barrier layer consisted of xanthan gum, Avicel PH 102 or pharmatose DCL 11, and magnesium stearate (extragranular composition, Table I). Each layer was sequentially filled in die cavity. Finally, the compression force was applied. The “Rimek” triple layer tablet compression machine (Karnavati Engineering Ltd., Mehsana, India) was used for compression of layered tablets. The batch size was 2,000 tablets for batches A4 to A9. The monolayer and triple layer tablets were examined for uniformity of weight, thickness, crushing strength, friability, and in vitro drug dissolution. The thickness and crushing strength were measured on hardness tester (Dr. Schleuniger Pharmatron AG, Switzerland). Friability was measured using Roche type friabilator (Electrolab, Mumbai) by rotating the tablets for 4 min for 100 rotation.

Modified release tablets of venlafaxine hydrochloride with lower strengths were also formulated. From industrial point of view, it is always preferable to go for scale-up-scale-down for different strengths. The composition of granules for middle layer and barrier layers were kept same as that of batch A8, but the weight of barrier layer was changed to obtain release profile similar to that of reference product. Table II shows composition of tablets of lower strengths. The optimized formulation in each category was compared using similarity factor \( (f_2 \text{ value}) \) (19). The amount of drug released from the three strengths were compared using surface area of the tablets. The tablet was assumed to be cylinder in shape; hence, the surface area was calculated using the following equation:

\[
\text{Surface area} = 2\pi rh + 2\pi r^2
\]

Where \( r \) is radius of the tablet in centimeters and \( h \) is thickness of the tablet in centimeters. Round punches with 10 mm diameter were used for preparing batches A1 to A8. The batches B1 to B4 and C1, C2 were prepared using punches with 7.8 mm diameter. The thickness of the venlafaxine

<table>
<thead>
<tr>
<th>Table I. Composition of Venlafaxine Hydrochloride Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredients (mg)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Intragranular composition*</td>
</tr>
<tr>
<td>Venlafaxine hydrochloride(^{b})</td>
</tr>
<tr>
<td>Xanthan gum</td>
</tr>
<tr>
<td>Avicel PH 101</td>
</tr>
<tr>
<td>Extragranular composition*</td>
</tr>
<tr>
<td>Xanthan gum</td>
</tr>
<tr>
<td>Avicel PH 102</td>
</tr>
<tr>
<td>Pharmatose DCL 11</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
</tbody>
</table>

* For batches A4 to A9, intragranular composition and extragranular composition represent core and barrier layer, respectively

\(^{b}\) 169.8 mg venlafaxine hydrochloride is equivalent to 150 mg of venlafaxine base
Table II. Composition of Venlafaxine Hydrochloride Tablets

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>C1</th>
<th>C2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intragranular composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine hydrochloride</td>
<td>84.9</td>
<td>84.9</td>
<td>84.9</td>
<td>84.9</td>
<td>42.5</td>
<td>42.5</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>21.3</td>
<td>21.3</td>
<td>21.3</td>
<td>21.3</td>
<td>10.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Avicel PH 101</td>
<td>26.5</td>
<td>26.5</td>
<td>26.5</td>
<td>26.5</td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td><strong>Extragranular composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>75.0</td>
<td>60.0</td>
<td>50.0</td>
<td>37.5</td>
<td>45.0</td>
<td>37.5</td>
</tr>
<tr>
<td>Pharmatose DCL 11</td>
<td>60.0</td>
<td>48.0</td>
<td>40.0</td>
<td>30.0</td>
<td>36.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>7.5</td>
<td>6.0</td>
<td>5.0</td>
<td>3.8</td>
<td>4.5</td>
<td>3.8</td>
</tr>
</tbody>
</table>

hydrochloride tablets were 0.60, 0.45, and 0.39 cm, respectively, for batches A8, B3, and C1. Hence, the surface area of batches A8, B3, and C1 was 3.45, 2.11, and 1.91 cm², respectively. The drug release in milligrams per square centimeter was calculated and converted in percent value (Table III).

**In Vitro Dissolution Studies**

*In vitro* drug-release study \( (n=3) \) was carried out in USP apparatus I (Electrolab TDT 06-T, Mumbai, India) in 900 mL of distilled water at 37°C±0.5°C. Five-milliliter samples were pulled at predetermined times. The drug solution was replaced with equal volume of distilled water. The samples were diluted with water and analyzed at 226 nm using UV visible spectrophotometer (Shimadzu-1700, Japan). The dissolution study was also performed for reference products (Effexor® XR Capsules 150, 75, and 37.5 mg). The optimized batch was also investigated for drug dissolution in distilled water containing 10% ethanol.

**Water-Uptake Study**

The swelling behavior of batches A8, B3, and C1 was studied (25). The tablets \( (n=3) \) were kept in beaker containing 100 mL distilled water at 37°C±2°C. At selected time points, the tablets were withdrawn, wiped with tissue paper, and weighed. The percent water uptake by the tablet was calculated using the following formula:

\[
\text{Percentage water uptake} = 100 \times \frac{W_t - W_0}{W_0} \tag{2}
\]

Where \( W_t \) was weight of tablet at time \( t \) and \( W_0 \) was initial weight of the tablet.

**The Radar Graphs**

In the dissolution study, higher or lower % drug release than a target is permitted up to a certain limit. Shah *et al.* proposed that the maximum difference can be 10% \( (\pm 50) \) for establishing similarity (26). The reference products dissolution data were used as ideal release pattern. The ideal % drug release will get a score of 5 on a scale of 0 (ideal -10%) to 10 (ideal +10%). The lower and high permissible % of drug release will get a score of 0 and 10, respectively. The score of optimized batches \( (A8, B3, \text{ and } C1) \) were calculated at each dissolution time point.

\[
\text{Score} = 5 + \left(\frac{\left(\% R_i - \% R_t\right)}{2}\right) \tag{3}
\]

Table III. Comparison of Drug Release Profile Per Unit Surface Area of All Strengths

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>A8</th>
<th>B3</th>
<th>C1</th>
<th>A8</th>
<th>B3</th>
<th>C1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.7</td>
<td>5.2</td>
<td>2.6</td>
<td>13.1</td>
<td>14.5</td>
<td>13.5</td>
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<tr>
<td>2</td>
<td>9.9</td>
<td>7.6</td>
<td>4.8</td>
<td>22.8</td>
<td>21.3</td>
<td>24.2</td>
</tr>
<tr>
<td>4</td>
<td>19.1</td>
<td>15.4</td>
<td>8.9</td>
<td>44.0</td>
<td>43.3</td>
<td>45.4</td>
</tr>
<tr>
<td>6</td>
<td>26.0</td>
<td>21.4</td>
<td>12.0</td>
<td>59.8</td>
<td>62.2</td>
<td>61.2</td>
</tr>
<tr>
<td>8</td>
<td>32.5</td>
<td>25.6</td>
<td>14.5</td>
<td>74.9</td>
<td>72.8</td>
<td>74.0</td>
</tr>
<tr>
<td>10</td>
<td>37.3</td>
<td>28.8</td>
<td>16.2</td>
<td>85.8</td>
<td>81.0</td>
<td>82.5</td>
</tr>
<tr>
<td>16</td>
<td>40.0</td>
<td>32.0</td>
<td>17.5</td>
<td>92.1</td>
<td>90.0</td>
<td>89.0</td>
</tr>
<tr>
<td>24</td>
<td>42.9</td>
<td>36.0</td>
<td>19.1</td>
<td>98.7</td>
<td>101.1</td>
<td>93.7</td>
</tr>
</tbody>
</table>
Fabrication of Venlafaxine Hydrochloride-Layered Tablets

Where %T is percentage of drug released from test batch while %R is percentage of drug released from reference product at the same time.

RESULTS AND DISCUSSION

Xanthan gum has ability to take up water when it comes in contact with aqueous environment. The processing of xanthan gum becomes difficult due to its sticky nature on wetting, especially when it is used in higher amount. The concept of adding a part of xanthan gum intragranularly and a part extragranularly was adopted to achieve ease in processibility and flexibility in achieving the desired drug-release profile. Use of xanthan gum both intragranular and extragranularly permits addition of higher amount of xanthan gum compared with the classical wet granulation technique. The concept can be adopted only for those excipients that show good flow and compression behavior like xanthan gum. The drug release pattern can be tailored by adjusting the proportion of intragranular and extragranular fraction. The process can be considered as a hybrid process between wet granulation and direct compression.

The reference product, Effexor® XR capsules contained coated pellets. The dissolution of the reference product was performed in distilled water and was targeted for the formulated venlafaxine hydrochloride matrix tablets. The reason for choosing distilled water as a dissolution medium is that the Food and Drug Administration (FDA) endorses the use of it as a dissolution medium for the generic version of venlafaxine hydrochloride. The reference product exhibited sustained drug release. The result shown in Fig. 1 reveals that the drug release was less than 25% in first 2 h. The pellets of reference product might be coated with water insoluble coating agent.

The granules of batches (A1 to A9) showed good flow and compressibility as the value of angle of repose, Carr’s index, and Hausner ratio were in the range of 22° to 26°, 15% to 18%, and 1.17 to 1.22, respectively. The developed tablets fulfilled the requirements of crushing strength (>6 kp) and friability (<1%). The problems of weight variation and content variation were not observed. Moreover, high speed tablet press can be used for manufacturing of tablets. It is well known that preparation of pellets and subsequent coating requires expertise and time.

The batches A1, A2, and A3 were compressed as monolayer matrix tablets while batches A4 to A9 were compressed as three-layer matrix tablets. In the batches A1 and A2, xanthan gum to venlafaxine hydrochloride ratio was 1:1 and 1.5:1, respectively. The data for in vitro dissolution show that with increase in the amount of xanthan gum, the drug release was decreased (Fig. 1). Neither batch A1 nor batch A2 showed release profile similar to that of the reference product. The two most important challenges in the development of matrix tablets are slow drug release in the earlier phase and complete drug release in the terminal phase with a fairly uniform drug release in between. The batch A1 showed faster drug release until 4 h and comparable drug release with the reference product thereafter while batch A2 showed comparable drug release up to 2 h and slow drug release thereafter. The high aqueous solubility of venlafaxine hydrochloride and high gel viscosity appears to be responsible for the behavior of batches A1 and A2. Thus, it can be concluded that by varying the amount of xanthan gum in uncoated monolayer tablets, the required release profile could not be achieved. Our objective was to avoid the use of time consuming two stage procedures, i.e., compression and subsequent solvent coating or pelletization and coating for the development of sustained release venlafaxine HCl formulation.

The multilayered matrix system overcomes inherent disadvantages of nonlinearity associated with diffusion controlled matrix devices by providing adequate drug-release rate with time (27). Few researchers developed multilayer tablets for modulating release of active pharmaceutical ingredient (API) from hydrophilic polymeric system (17,28–31). The use of xanthan gum has not been explored in layered tablets. Geomatrix® technology was used to reduce the active surface area to engineer the API release at the initial time points. Directly compressible microcrystalline cellulose (Avicel PH 102) was added to the xanthan gum to augment compressibility and increase weight of barrier layer. It is very important to remember that the middle layer and barrier layers should maintain their integrity in the layered tablets during manufacturing, storage, and drug-release study. The excipients were selected considering the stated objectives. The middle layer was formulated using 25% of the total xanthan gum present in the formulation to prevent quick drug release. The gelled particles of xanthan gum provide the required hindrance to drug release. Figure 2 represents the comparative release profile of monolayer matrix tablet (A3) and triple-layer matrix tablet (A4) of same composition. The release rate is reduced in batch A4 compared to batch A3. The probable reason could be availability of limited surface area in batch A4. However, the drug release from batch A4 was slower than the release shown by the reference.

The release rate of API can be increased by incorporation of soluble pore forming material in the barrier layers (Batch A5), by reducing the percent of polymer in core layer (Batch A6), or by reducing the percent of polymer in the barrier layers (Batch A7). Figure 3 shows that incorporation of water soluble excipients such as lactose monohydrate (Pharmatose DCL 11) facilitated the API release rate after 2 h as desired. Batch A6 showed higher drug release than the required release due to quick tablet erosion. Batch A7 showed drug-release profile very close to the reference product. Batches A8 and A9 were prepared to fine-tune the
drug release (Fig. 3). The batches A7, A8, and A9 showed similarity factor $f_2$ values of 62, 74, and 70, respectively.

The FDA has recently enforced the testing of modified release dosage forms in dissolution media containing ethanol. The FDA mentioned that the potentially fatal interaction of a modified release system might be observed on consumption with alcohol which resulted in impairment of the formulation and dose dumping (32). Hence, effect of ethanol on release of venlafaxine hydrochloride was studied. Ten percent concentration of ethanol typical of those found in alcoholic beverages was included in dissolution medium (distilled water). The dissolution study of batch A8 was performed using same dissolution conditions with and without ethanol. Batch A8 showed similarity factor ($f_2$) 92 with and without ethanol. The matrix of xanthan gum will not collapse in presence of alcohol since it is insoluble in alcohol (33). Thus, we can conclude that the developed formulation is robust and is safe to take with alcohol. Batch A8 was selected for development of tablets with other strengths, i.e., 75 and 37.5 mg.

The Effexor® XR capsules are available in three strengths, 150, 75, and 37.5 mg. Respective strengths were used as reference for development of venlafaxine hydrochloride tablets. Four batches of venlafaxine hydrochloride with 75-mg drug content and two batches of venlafaxine hydrochloride with 37.5-mg drug content were prepared and evaluated (Table II). The comparative release profiles are shown in Figs. 4 and 5. The batch B1 showed slower drug release as the thickness of barrier layer was higher compared to that of batch A8. The batches B1, B2, B3, B4, C1, and C2 showed $f_2$ values of 60, 70, 83, 89, and 79, respectively. Hence, the tablets of batches B3 and C1 were selected and evaluated for swelling behavior.

It is well known that the drug-release profile from the SR tablet changes with the surface area of tablet. To correlate the drug-release rate from tablets of different strength, the surface area of optimized batches was calculated followed by normalization of drug release in milligrams per unit area. For batches A8, B3, and C1, the complete release corresponded to 43.43, 35.61, and 19.63 mg/cm$^2$. The drug release was expressed in terms of percentage considering the three computed values. The results shown in Table III reveals that the percentage of drug release from the three optimized batches, using calculated normalized amount of drug release (mg/cm$^2$), was almost identical. The percentage composition of core layer of the three batches was identical. However, the barrier layer composition was different. Formulation development time can be shortened in industry simply by focusing on barrier layer composition.

The goodness-of-fit test was used to determine the mechanism of drug release. The in vitro dissolution data of batches A7, A8, and A9 were fitted to different mathematical models using software developed in FORTRAN language.
Fabrication of Venlafaxine Hydrochloride-Layered Tablets

Fig. 6. Water uptake of optimized batches of venlafaxine hydrochloride tablets of all strengths

Weibull model showed best fit. The dissolution data of Effexor XR capsule was also subjected to model fitting. The Fisher's ratio \( F \) was 20 for the Weibull model. The next objective was to develop unified equation to correlates drug release from different batches within the area of interest with time. Weibull equation is given below (34):

\[
M = 1 - e^{-\frac{t}{\alpha}}
\]

Where \( M \) is the cumulative amount of drug released at time \( t \), \( \beta \) is slope parameter (slope), and \( \alpha \) is the scale parameter (intercept). The term \( \alpha \) was replaced by term \( T_d \) (time necessary to dissolve 63.2% of drug) using the relationship \( \alpha = T_d^\beta \). The unified Weibull model was:

\[
M = 1 - e^{-\left(\frac{t}{T_d}\right)^\beta}
\]

(5)

As \( \beta \) is equal to equation of slope, the Eq. 5 can be written as shown below:

\[
M = 1 - e^{-\left(\frac{t}{T_d}\right)^\beta}
\]

(6)

The linear equation of slope \( r=0.99 \) was evolved by the method reported by Kirilmaz using the dissolution data of batches A7 to A9. The values of \( T_d \) for batches A7, A8, and A9 were 6.54, 6.41, and 6.13, respectively. The evolved model was validated by comparing calculated and predicted release profiles. The calculated percent drug release and experimental percent drug release of the optimized batch A8 can be considered as comparable since \( r \) is equal to 88. Thus, by using the unified weibull equation (Eq. 6), we can modulate the drug-release pattern. This investigation demonstrates that the release of venlafaxine hydrochloride can be modified by changing the amount of xanthan gum and using the triple-layer concept. The optimized batches B3 of venlafaxine hydrochloride 75 mg and C1 of venlafaxine hydrochloride 37.5 mg also followed the Weibull model and the calculated \( F \) values were 9 and 6, respectively.

Figure 6 shows the average value of water uptake of the optimum batches (A8, B3, and C1). The study showed that all three batches showed almost identical and substantial water uptake. The water taken up by the tablet is responsible for gelling of xanthan gum.

The radar diagrams of batches A8, B3, and C1 are shown in Fig. 7. The dissolution pull times are shown on the periphery of radar diagrams. The outer surface of radar graphs shows highest score (10) while the centre shows lowest score (0). Ideally, all the data points should fall on score line of 5, i.e., in the middle of radar diagram. The radar diagrams of batches A8, B3, and C1 show that the formulated batches and reference products show almost similar dissolution at all the time points. The sums of absolute value of difference between reference and test at all time points were 8.7, 8.9, and 5.9, respectively, for batches A8, B3, and C1. The low values of computed difference quantitatively show the difference.

**CONCLUSION**

The drug-release rate was found to be dependent on the percentage of xanthan gum, pore-forming agent-like pharma-tose DCL 11, and surface area of the formulation exposed to the dissolution medium. The optimized formulation showed media-independent drug release in distilled water and in 10% aqueous ethyl alcohol solution. The drug release was explained by Weibull model. The use of unified Weibull model is demonstrated to investigate the influence of minor changes in the formulation. A drug-release profile similar to that of the reference product (Effexor® XR Capsule) was achieved by adopting systemic formulation approach. The use of radar diagram is demonstrated.