Development and Evaluation of a Novel Extended Release Venlafaxine Hydrochloride Matrix Tablets

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ABSTRACT

The aim of the present investigation was to formulate and evaluate hydrophilic matrix tablets of Venlafaxine Hydrochloride to achieve an extended drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. Matrix tablets of Venlafaxine Hydrochloride were prepared using combination of hydrophilic and water insoluble swellable polymers viz. Hydroxypropylmethylcellulose (HPMC) and Calcium Carboxymethylcellulose (Ca CMC). The high water solubility of Venlafaxine Hydrochloride (572 mg/mL), leads to burst release of drug from HPMC matrices. To control this initial burst release, Ca CMC was incorporated in the HPMC matrix system and the drug release behavior of the formulations prepared by HPMC, Ca CMC alone and different drug to polymer ratios of HPMC and Ca CMC were investigated. The formulated tablets were characterized for physical and chemical properties. The combination of HPMC and Ca CMC matrices exhibited extended drug release when compared to the HPMC and Ca CMC matrix alone. The physico-chemical properties of the formulated tablets were found in acceptable limits. Linear and reproducible release profile similar to that of Effexor XL (marketed formulation) was achieved for the optimized formulation (t1/60) independent of pH conditions. Different dissolution models were applied in order to evaluate the release mechanism and release kinetics. The drug release data fit well to the Higuchi expression. The drug release mechanism was found as complex mixture of diffusion, swelling and erosion. The development of matrix tablets using combination of these polymers can be extended to other highly soluble drugs.

Key words: Venlafaxine Hydrochloride; Hydroxypropylmethylcellulose; Calcium Carboxymethylcellulose; Matrix tablets.

INTRODUCTION

A hydrophilic matrix tablet is the simplest and most cost-effective method of fabricating an extended release (ER) solid oral dosage form.1 Extended release matrix tablets are relatively simple systems that are more forgiving of variations in ingredients, production methods, and end-use conditions than coated ER tablets and other systems. This results in more uniform release profiles with a high resistance to dose dumping.2

During the last four decades, hydrophilic swellable polymers have been used to control the release of drug from matrix tablet formulations.3 A typical ER matrix formulation consists of a drug, one or more water-swellable hydrophilic polymers, excipients such as filler or binder, a flow aid (glidant) and a lubricant.2 Drug release from swellable matrix tablets can be affected by glassy-rubber transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation.4

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate.1 While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms.

The presence of water decreases the glassy-rubber temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains can be considered disentangled was demonstrated to correspond to a abrupt change in the rheological properties of the gel.6 A relationship between rheological behavior of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs.7

Swelling controlled release systems are based on the above principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be ob-
served. This behavior is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.

HPMC is identified as the most popular in matrix application because of a number of key features and advantages. An initial burst effect in release of highly water soluble drugs (Venlafaxine Hydrochloride has a solubility of 572 mg/ml) from such matrices is a common occurrence. While Sodium Carboxymethylcellulose alone as rate-controlling polymer is not practical because of accelerating release rates and poor stability, its use in conjunction with Hydroxypropylmethylcellulose may be beneficial.

The purpose of this study was to modulate release of Venlafaxine Hydrochloride (a highly soluble drug) using the synergistic activity of Hydroxypropylmethylcellulose and Calcium Carboxymethylcellulose. Venlafaxine Hydrochloride was the first marketed anti-depressant in the Serotonin-nor epinephrine reuptake inhibitor (SNRI) class. It has been widely used in treatment of remission in depression, treatment resistant depression and extended-release Venlafaxine Hydrochloride for generalized anxiety disorder. It is freely soluble in water and has relatively short elimination half-life (5 h). The bioavailability is very limited (45%) due to the hepatic first pass effect.

Drug release from hydrophilic matrices is known to be a complex interaction involving swelling, diffusion and erosion mechanisms. This work was an attempt to determine the relative contribution of the different drug release mechanisms exhibited by venlafaxine hydrochloride matrix tablets produced with non-ionic cellulose ether Hydroxypropylmethylcellulose (HPMC) and anionic cellulose ether Calcium Carboxymethylcellulose (Ca CMC). Granules of Venlafaxine Hydrochloride were prepared by using HPMC, Ca CMC alone and different drug to polymer ratios of mixture of HPMC and Ca CMC. The tablets were evaluated physically and chemically. An in-vitro release study (studies) was carried out to evaluate their performance as rate-controlling polymers. Earlier work has demonstrated that with certain water soluble drugs, a blend of appropriate grades of HPMC and Na CMC may minimize the release of drug during the initial phase of the release profile. This tends to “flatten” the shape of the release profile i.e., produce a more “zero order” release.  

MATERIALS AND METHODS

Materials
Venlafaxine Hydrochloride was obtained from Dr. Reddy’s Laboratories Ltd., Hydroxypropylmethylcellulose (HPMC K100M) was purchased from Dow chemical, USA, and Calcium Carboxymethylcellulose, E.C.G-505 (Ca CMC USP/NF, EP, JP) was a gift sample from Signet chemicals, Mumbai. Dicalcium Phosphate Dihydrate (DCP) was purchased from Penwest, IA, Povidone K-30 (PVPK- 30) was purchased from ISP (India) Pvt. Ltd, Aerosil 200 was purchased from Degussa India Pvt. Ltd., Mumbai and Magnesium stearate was purchased from Mallinckrodt Specialty Chemicals., Louis, MO, USA. All other solvent and chemicals used are of analytical reagent grade.

Methods
Drug-excipients interaction studies
The possibility of drug-excipient interaction was investigated using a Perkin-Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller with an intercooler-2 cooling system (Perkin-Elmer Instruments, Waltham, MA, USA). About 3-5 mg of sample was placed in perforated aluminum-sealed 50-µl pans, and the heat runs for each sample was set from 40°C to 300°C at 5°C/min, under an inert environment using nitrogen. The apparatus was calibrated using indium/cyclohexane. The differential scanning calorimetry (DSC) thermograms of pure drug and physical mixtures of drug-excipients were recorded.

Preparation of matrix tablets
Matrix tablets were prepared by wet granulation technique using low shear granulator (Planetary Mixer, Kenwood, UK). All the ingredients were weighed accurately and passed through # 40. Drug was mixed with polymers HPMC K100M and Ca CMC (E.C.G 505) and granulated with Povidone (PVP-K30) which was dissolved in isopropyl alcohol. Granules were dried in Rapid dryer (Retsch TG 200, Germany) at 50°C. Granules were passed through #24. Dicalcium Phosphate and Aerosil 200 were passed through #40 and mixed with the dried granules. Lubrication of the granules was carried out with Magnesium Stearate. Compression was done on a Kambert Eight station tablet compression machine, with 11.8 mm biconvex, round shaped punches producing matrix tablets with a weight 650 mg, 6.45 mm in height with a hardness of 14-16 Kp. Formulation details are shown in Table 1 and the ratio of drug to polymers in different formulations is presented in Table 2.

Table 1: Unit compositions of Venlafaxine hydrochloride matrix tablets

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Formula Composition (in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Venlafaxine Hydrochloride*</td>
<td>172.17</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>344.34</td>
</tr>
<tr>
<td>Ca CMC (E.C.G-505)</td>
<td>344.34</td>
</tr>
<tr>
<td>DCP</td>
<td>64.74</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>62.50</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>q.s.</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1.25</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>5.00</td>
</tr>
<tr>
<td>Total Tablet Weight</td>
<td>650</td>
</tr>
</tbody>
</table>

*172.17 mg of Venlafaxine Hydrochloride Equivalent to 150.00 mg of Venlafaxine (compensated based on moisture content and drug purity)

Table 2: Different ratios of drug to polymers in different matrix formulations

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Venlafaxine Hydrochloride</th>
<th>HPMC</th>
<th>Ca CMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>F2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>F3</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>F4</td>
<td>1</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>F5</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F6</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Physicochemical Evaluation
The tablets were evaluated for different physico-chemical parameters such as appearance, weight variation, thickness, hardness, friability, Drug content and in-vitro release. Methanol was used as an extraction solvent for determining the drug content. In-vitro release was studied using USP type I (Model No. Lab India disso 2000) at 100 rpm in water 900 ml, 37±0.5°C for 24 hours. In order to mimic the human digestive tract physiological conditions, a pH change or sequential method was adopted. The studies were carried out in pH 1.2 (2 hours) followed by pH 6.8 phosphate buffer for 24 hours. Effect of type and concentration of polymer on drug release of Venlafaxine Hydrochloride was studied. The marketed product Effexor XL capsule was also evaluated for in-vitro studies and compared with the test product. The sample analysis was carried out by UV Spectrophotometric method. The absorbance values were observed at 224 nm. The solvent used for the dilution is Distilled water.
Drug release kinetics

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration.\(^{19}\) The first order Eq.(2) describes the release from system where release rate is concentration dependent.\(^{20}\) Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.\(^{21}\) Eq.(3). The Hixson-Crowell cube root law Eq.(4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.\(^{22}\)

\[
\text{Log } C = \text{Log } C_o - kt / 2.303 \quad —— (2)
\]

Where, \(C_o\) is the initial concentration of drug and \(K\) is first order constant.

\[
Q = k t^{1/2} \quad —— (3)
\]

Where, \(K\) is the constant reflecting the design variables of the system.

\[
Q_o^{1/3} - Q t^{1/3} = K_{HC} t \quad —— (4)
\]

Where, \(Q\) is the amount of drug released in time \(t\), \(Q_o\) is the initial amount of the drug in tablet and \(K_{HC}\) is the rate constant for Hixson- Crowell rate equation.

The following plots were made: cumulative % drug release versus time (zero order kinetic model); log cumulative of % drug remaining versus time (first order kinetic model); cumulative % drug release versus square root of time (Higuchi model); log cumulative % drug release versus log time ( Korsmeyer model ) and cube root of drug % remaining in matrix vs. time ( Hixson-Crowell cube root law ).

The Korsmeyer derived a simple relationship which described drug release from a polymeric system Eq (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer- Peppas model.\(^{23}\)

\[
M / M_o = k \tau^n \quad —— (5)
\]

Where \(M / M_o\) is the fraction of drug released at time \(\tau\), \(k\) is the rate constant and \(n\) is the release exponent.

Swelling study

The swelling index of tablets was determined in purified water at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated using the following equation:

\[
\text{Swelling index} = \left( W_t - W_i \right) / W_i \quad —— (6)
\]

in which \(W_i\) is the initial weight of tablet, and \(W_t\) is the weight of the tablet at time \(t\).

Texture analysis

The swelling behavior of the formulations was investigated through textural analysis of swollen tablets. Tablets were placed in the dissolution vessels under conditions identical to those described above for dissolution testing. The hydrated tablets were removed at predetermined intervals, patted lightly with tissue paper, and subjected to textural profiling to determine gel layer thickness, movement of the erosion and swelling fronts and total work of probe penetration into the entire matrix. All measurements were carried out in triplicate for each time point and tablets were discarded. Textural analysis was performed using a TA.XT2i texture analyzer equipped with a 5 kg load cell and Texture Expert software (Texture Technologies Corp, Scarsdale, NY/ Stable Micro Systems, Godalming, UK). The force–displacement–time profiles associated with the penetration of a 2 mm round-tipped steel probe into the swollen matrices were monitored at a data acquisition rate of 200 points per second as previously described.\(^{24}\) Probe approached the sample at pre-test speed of 1.0 mm/s. Once a trigger force of 0.005N was detected (at contact of the probe with tablet) the probe was advanced into the sample at a test speed of 0.5 mm/s until the maximum force of 20N was reached. Swollen thickness was determined by measuring the total probe displacement value recorded and by the observation of textural profiles. Total work of penetration, which is a measure of gel strength and resistance to probe penetration, was also determined from the textural profiles.

Total work of penetration = \( W = \zeta F dD \quad —— (7) \)

Where \(W\) is work done by the probe, \(F\) the force applied, and \(dD\) the total probe displacement.

Stability Studies

Optimized formulation (F5) was exposed to open exposure study at 40±2°C and 75±5% RH for a period upto 1 month. The samples were evaluated for physicochemical parameters viz. drug content and in-vitro release study.

RESULTS AND DISCUSSION

Drug excipients interaction studies

The DSC thermogram for the drug exhibited a sharp melting endotherm at 213.43°C. The physical mixture for the optimized formulation F5 did not show any characteristic peak. Extra peaks were observed in the above said physical mixture just before the drug, due to loss of water from Dicalcium Phosphate Dihydrate. There was no significant shift in endotherm of Venlafaxine Hydrochloride in the drug excipients mixture (physical mixture) indicating compatibility of the drug with all the excipients used in the optimized formulation. The comparative DSC thermograms of the drug (Venlafaxine Hydrochloride) alone, physical mixture of drug with other inactive ingredients and physical mixture of drug with other inactive ingredients and Dicalcium Phosphate Dihydrate alone are shown in Figure 1a, 1b, 1c and 1d.
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Analysis of Venlafaxine hydrochloride matrices

The contents of all the formulations were found to be uniform, since the amount of the active ingredient (Venlafaxine Hydrochloride) in each of the 10 units tested was within the range of 97.1%–100.5% and the relative standard deviations were less than 2.0%, indicating uniform mixing of all the inactive ingredients with active pharmaceutical ingredient (API). The mean values for hardness were over 14.0-16.0 kp and all formulations exhibited a friability of less than 0.5% during the friability determination. The physico-chemical evaluation results and assay for different batches of Venlafaxine Hydrochloride matrix tablets are summarized in Table 3.

Table 3: Physical parameters and assay for Venlafaxine hydrochloride matrix tablets

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Hardness (kp)</td>
<td>12 ± 0.34</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>6.45 ± 0.2</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Assay (%)</td>
<td>97.1 ± 0.83</td>
</tr>
</tbody>
</table>

Table 4. Release kinetics of different matrix formulations of Venlafaxine hydrochloride versus marketed formulation

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order R²</th>
<th>First order Kₚ</th>
<th>Higuchi R²</th>
<th>Hixon-crowell R²</th>
<th>Kₜw</th>
<th>Korsmeyer-Peppas n value</th>
<th>Kᵢp</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.852</td>
<td>2.604</td>
<td>0.956</td>
<td>0.037</td>
<td>0.858</td>
<td>21.03</td>
<td>0.799</td>
</tr>
<tr>
<td>F2</td>
<td>0.761</td>
<td>2.395</td>
<td>0.976</td>
<td>0.067</td>
<td>0.541</td>
<td>24.19</td>
<td>0.705</td>
</tr>
<tr>
<td>F3</td>
<td>0.833</td>
<td>2.437</td>
<td>0.951</td>
<td>0.033</td>
<td>0.801</td>
<td>20.8</td>
<td>0.774</td>
</tr>
<tr>
<td>F4</td>
<td>0.933</td>
<td>3.211</td>
<td>0.996</td>
<td>0.046</td>
<td>0.99</td>
<td>20.1</td>
<td>0.865</td>
</tr>
<tr>
<td>F5</td>
<td>0.896</td>
<td>3.46</td>
<td>0.966</td>
<td>0.063</td>
<td>0.975</td>
<td>21.23</td>
<td>0.81</td>
</tr>
<tr>
<td>F6</td>
<td>0.925</td>
<td>2.731</td>
<td>0.991</td>
<td>0.028</td>
<td>0.984</td>
<td>17.89</td>
<td>0.856</td>
</tr>
<tr>
<td>Marketed formulation</td>
<td>0.835</td>
<td>3.735</td>
<td>0.996</td>
<td>0.063</td>
<td>0.954</td>
<td>21.44</td>
<td>0.725</td>
</tr>
</tbody>
</table>

In-vitro drug release

The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium. The hydrated gel layer thickness determines the diffusional path length of the drug.

HPMC K4M was tried in the concentration of 1:1.5 with respect to the drug. Drug release was fast, indicating that a higher viscosity grade of HPMC K100M would be required to retard drug release. HPMC of higher viscosity grade swells to a greater extent as it has a greater intrinsic water uptake property than that of a lower viscosity grade.25 Hence, HPMC K100M was selected for further studies to retard drug release.

A single polymer gives a faster release compare to polymer combination in optimized proportion. The high release rate of Ca CMC matrix is due to quick gel erosion rate of the polymer. The tablets containing only HPMC showed faster release profile at initial time points and later on it was almost constant after 12 hours to 24 hours. Tablets with Ca CMC alone, showed a relative faster drug release, 90% of the total content is delivered within 12 hours. Formulations containing combination of HPMC and Ca CMC gave a slow and precise release for 24 hours. As the concentration of polymers combination increased the release rate was found to decreased but after a certain level i.e. Drug: HPMC: Ca CMC (1:1:1), when concentration of Ca CMC increased to 1.5 percent and rest drug and HPMC kept constant i.e. 1:1, initially the release was not changed much but later on the drug was not released completely even after 24 hours.

The in-vitro drug release profiles of Venlafaxine Hydrochloride from tablets containing HPMC, Ca CMC and in combination in different proportions are shown in Figure 2. From the in-vitro release results it was evident that as the
amount of polymer in the matrix increased, there was a greater degree of polymer hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway and drug release rate. Optimized formulation (F5) gave a consistent and reproducible release profile which is comparable with that of marketed formulation (Effexor XL) in water; similarity factor ($f_2$) was 66. The dissolution profile of the optimized formulation versus marketed formulation is shown in Figure 3.

**Swelling studies**

The swelling index was calculated with respect to time shown in Table 5. As time increases, the swelling index was increased, this may be due to weight gain by tablets was increased proportionally with rate of hydration up to 6 hours later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium shown in Figure 5. The direct relationship was observed between swelling index and gel concentration. It has been observed that the cumulative percent drug release decreases with increasing concentration of gel and swelling index. This slower release is because of the formation of a thick gel structure that delays the drug release from the matrix tablets, where hydration of individual particles results in extensive swelling. This results in continuous visco elastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium.

**Table 5: Swelling index of different matrix formulations of Venlafaxine hydrochloride**

<table>
<thead>
<tr>
<th>Time (in hrs)</th>
<th>F1</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83.87</td>
<td>48.00</td>
<td>73.30</td>
<td>69.9</td>
<td>72.89</td>
</tr>
<tr>
<td>2</td>
<td>134.40</td>
<td>92.54</td>
<td>123.40</td>
<td>104.4</td>
<td>118.54</td>
</tr>
<tr>
<td>3</td>
<td>147.15</td>
<td>104.65</td>
<td>140.03</td>
<td>125.6</td>
<td>137.65</td>
</tr>
<tr>
<td>4</td>
<td>163.28</td>
<td>115.58</td>
<td>155.06</td>
<td>139.2</td>
<td>148.35</td>
</tr>
<tr>
<td>5</td>
<td>191.70</td>
<td>129.65</td>
<td>180.36</td>
<td>165.64</td>
<td>177.53</td>
</tr>
<tr>
<td>6</td>
<td>194.00</td>
<td>135.69</td>
<td>187.20</td>
<td>172.5</td>
<td>180.23</td>
</tr>
<tr>
<td>7</td>
<td>195.39</td>
<td>135.70</td>
<td>193.86</td>
<td>166.41</td>
<td>190.32</td>
</tr>
<tr>
<td>8</td>
<td>196.01</td>
<td>142.56</td>
<td>194.06</td>
<td>166.87</td>
<td>191.54</td>
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<tr>
<td>9</td>
<td>196.27</td>
<td>148.06</td>
<td>195.87</td>
<td>164.8</td>
<td>193.10</td>
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<td>10</td>
<td>196.31</td>
<td>147.90</td>
<td>196.28</td>
<td>166.37</td>
<td>192.36</td>
</tr>
</tbody>
</table>

Figure 2: Comparative drug release profiles of batches F1 to F6 and marketed formulation in water.

Figure 3: *In-vitro* release profiles of extended release matrix formulation of optimized batch vs. marketed formulation in water.

The optimized formulation exhibit pH independent release profile in different physiological pH media. The $f_2$ was found to be 64 in comparison with the marketed formulation (Effexor XL). The result of pH change method is shown in Figure 4.

Figure 4 : *In-vitro* release profiles of extended release matrix formulation of optimized batch vs. marketed formulation in pH 1.2 followed by pH 6.8 phosphate buffer.

**Determination of the release kinetics**

Based on various mathematical models, the magnitude of the release exponent ‘n’ indicates the release mechanism. The values of drug release kinetics using different mathematical models are depicted in Table 4. Formulations containing HPMC and Ca CMC alone had n value 0.534 and 0.392 respectively is beyond the limits of korsmeyer model (power law). In case of polymers combination (HPMC and Ca CMC) systems, the n value range from 0.517-0.961 which appears to indicate a coupling of diffusion and erosion mechanism- so-called anomalous diffusion. The correlation ($R^2$) was used as an indicator of best fitting for each of the model. The optimized batch F5 fits best in Higuchi model where the $R^2$ value is 0.975 and $K_H$ (Higuchi dissolution constant) is 21.23. In case of polymers combination the drug release rate is nearly constant and the release process was slower compared to that of the matrices containing a single polymer. This could be due to the interactions between anionic chains of Ca CMC and nonionic chains of HPMC with the drug. The formulations contains combination of HPMC and Ca CMC exhibited a well controlled effect by the use of the synergistic interaction between two cellulose ethers to produce a strong and elastic gel around the core of the matrices in the presence of a ternary component by controlling the drug release from the matrices.
Textural analysis (TA)
The total work of penetration calculated as the area under the force–displacement curve indicates matrix stiffness or rigidity. It depicts the change in work of penetration versus time as the exposure to swelling medium is extended and hydration is increased. In formulation F5 sharp decrease in work of penetration from 0 hour (dry tablet) to 4 hours is observed which reflects the initial high rate of hydration of tablets. Between 4 to 24 hours decrease in work of penetration is observed which is attributed to the soluble nature of drug in providing for greater water penetration and subsequently weakening of the gel structure is shown in Figure 6. The inward movement of the fully hydrated region as well as increase in total thickness of swollen tablet for each time point is apparent in all texture analysis profiles. Determination of total tablet thickness and swelling front movement using force-displacement profiles provided more evidence that the rate and extent of gel formation is significantly influenced by the nature of excipient used.

Stability studies
No significant changes in physicochemical parameters and in-vitro drug release were observed after 1 month of open exposure study at 40±2°C and 75±5% RH. The drug content of the optimized batch was 99.5%. The in-vitro release profile at initial and after 1 month stress study is depicted in Figure 7.

CONCLUSIONS
Matrix based once daily extended release tablets of Venlafaxine were successfully formulated using combination of Ca CMC and HPMC (K100 M). In-vitro release studies in water, pH 1.2 and pH 6.8 phosphate buffers (sequential method) demonstrated that the release of Venlafaxine Hydrochloride is comparable to that of the marketed formulation. The results indicated that the release kinetics of drug is independent of pH of the media. The release was found to follow Higuchi kinetics for the optimized formulation. The optimized formulation was also found stable upon exposure to accelerated temperature and humidity conditions.

REFERENCES


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