Formulation and Evaluation of Venlafaxine HCl Sustained Release Pellets
D.R. Brahmareddy*, A.V.S Madhulatha and R. Priyanka

ABSTRACT
Background: Venlafaxine Hydrochloride is a unique antidepressant that differs structurally from other currently available antidepressants. Short biological half life, low bioavailability and frequent administration of drug led for rational development of 300mg sustained release osmotic tablets of Venlafaxine Hydrochloride that releases the drug and maintain the plasma drug concentration for more than 8hrs. Controlled release (CR) / Sustained release (SR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate.

Methods: The main objective of the work is to develop a pharmaceutically equivalent. Antidepressant Venlafaxine Hydrochloride controlled release formulation were developed and compared to marketed formulation. Innovator and Prototype evaluation were performed to assess the release of branded product. Preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms. Preformulation testing is too done generate information useful to the formulation in developing stable and bioavailable dosage forms.

Results: Based on in vitro release studies, formulation 7(lot-2) was found to be optimum, for venlafaxine hydrochloride 150 mg sustained release pellets.

INTRODUCTION
Venlafaxine [1-4] is a unique novel antidepressant that differs structurally from other currently available antidepressants. Venlafaxine and its active metabolite O-desmethyl venlafaxine is having the action of selective serotonin and nor epinephrine uptake inhibition. It lacks the adverse anti cholinergic, sedative and cardiovascular effects of tricyclic antidepressants. The half lives of venlafaxine and its active metabolite are about 5 and 11 hours respectively. It is one of the majorly prescribed drug in US market about 17 billion prescriptions. Venlafaxine is more hydrophilic in nature and is having the disadvantage of extensive hepatic first pass metabolism. So to overcome and to maintain sustained level of venlafaxine in plasma levels the sustained formulation is selected in the form of capsules that are to be taken once daily. The present research work was directed to develop SR capsule of venlafaxine HCL and to match the release profile with the innovators products i.e Effexor TM -XR. (Venlafaxine HCl). The formulated capsules were evaluated for in-vitro release. The optimized formulation was evaluated for in-vitro release and compared with the marketed one. The marketed product is available as capsules containing venlafaxine hydrochloride equivalent to 75mg in the form of extended release pellets. The optimized formulation was subjected to stability studies.

MATERIALS AND METHODS
Venlafaxine, Sugar, Sodium CMC, Maize starch, Potato starch, Pregelatinised starch, Colloidal anhydrous silica, Xanthan gum, Titanium dioxide, Magnesium stearate, Talc and Eudragit NE 30D used were analytical grade.

Preparation of buffers and reagents
Sodium hydroxide solution, 0.2 M
8.0 g of sodium hydroxide was dissolved in distilled water and diluted to1000 ml with distilled water.

Potassium dihydrogen phosphate solution, 0.2 M
27.218 g of potassium dihydrogen phosphate was dissolved in distilled water and diluted to 1000 ml.

Hydrochloric acid solution, 0.1N
8.5 ml of concentrated hydrochloric acid was diluted with distilled water and volume was made up to 1000 ml with distilled water. pH (1.2) was adjusted with dilute hydrochloric acid.

Phosphate buffer solution, pH 6.8
250 ml of 0.2 M potassium dihydrogen phosphate was placed in a 1000 ml volumetric flask, 112 ml of 0.2 M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 6.8 with dilute sodium hydroxide.

Interference of additives
Each additive weighing 10 mg was placed separately in a series of 50 ml volumetric flasks containing 10g/ml drug solutions in phosphate buffer solution pH, 6.8. The flasks were kept aside for 45 minutes with occasional shaking. The solutions were filtered and the absorbencies of these solutions were measured at 226 nm against blank reference. The absorbance of these solutions was compared with the absorbance of drug solutions without any additive.
FORMULATION DEVELOPMENT

Drug coating

A coating solution containing appropriate concentration of drug, binder, and other excipients was prepared. Then, the solution was sprayed on to the non-pareil seeds by using Wurster bottom spray (FBP), by maintaining all appropriate parameters like spray rate, bed temperature, inlet temperature, and exhaust RPM. Dried form of coated pellets were obtained.

Seal coating

Here, all the ingredients, which were used for drug coating, were used, except drug. The coating solution was sprayed on to the drug-coated pellets obtained from drug coating technique. Using same mechanism and by maintaining the appropriate parameters.

Functional coating

After drug and seal coating this step plays most important role in sustaining the drug release. This is also called as polymer coating, where a coating solution containing appropriate concentration of polymer was prepared and sprayed on to the drug-coated pellets obtained from drug coating technique. Using same mechanism and by maintaining the appropriate parameters.

The development of present study was mainly based on the process of binding of drug to non-pareil seeds and binding of polymer on to drug coated non-pareil seeds. During this process, a variety of possible binders were used in order to bind the drug onto the NPS. The main aim was to compile and match the parameters of marketed products. The dose of venlafaxine is 150 mg and all attempts were made to get required analytical and physical parameters for the final product.

Prototype Formulation

After studying the patents on venlafaxine HCl sustained release pellets, a list of binders, which can be used, was prepared which included various binders like maize starch, potato starch, and pregelatinised starch. Feasibility trial was performed in order to bind the drug on to the non-pareil seeds using these binders.

Evaluation of sustained release pellets [5-8]

The pellets were evaluated for in process quality control tests. The following tests were performed for sustained release pellets.

Angle of repose

The angle of repose of venlafaxine HCl pellets was determined by the funnel method (Repos gram). The accurately weighed quantity of pellets was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the pellets. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

\[ \tan \theta = \frac{h}{r} \]

Where \( h \) and \( r \) are height and radius of the pellets cone, respectively. Flow properties for different values of angle of repose were given below.

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined. Venlafaxine hydrochloride was passed through a #18 sieve to break the clumps, if any. Accurately weighed 50 g of the drug was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14 ± 2 mm. The tapped volume \( V_t \) was measured to the nearest graduated unit. The tapping was repeated additional 750 times. Again the tapped volume was measured to the nearest graduated unit. The LBD and TBD were calculated in g/ml using following formulae.

\[ \text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}} \]
\[ \text{TBD} = \frac{\text{weight of the powder/tapped volume of the packing}}{\text{tapped volume}} \]

Content of active ingredients (assay)

The amount of active ingredient(s) present in drug coated pellets was determined. 421 mg of pellets were accurately weighed and placed in 100ml flask. The volume was made to 100ml using phosphate buffer, pH 6.8. The flask was placed in sonicated for 10 mints. 1 ml of the solution from the stock solution was pipette out into a 100ml volumetric flask. Volume was made up to 100ml with phosphate buffer, pH 6.8. Out of this, 1 ml was pipette out into a test tube and 9 ml of phosphate buffer pH 6.8 was added. Absorbance was measured at 226nm using UV. Percentage of drug present in the sample was calculated.

Friability test

Friability is the loss of weight of pellets in the container due to removal of fine particles from the surface. This in-process quality control test was performed to ensure the ability of pellets to withstand the shocks during process, handling, and transportation. Roche friabilator was used to measure the friability of tablets. It was rotated at 25rpm. 5 g pellets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the pellets were exposed to rolling, resulting from free falling of pellets within chamber of the friabilator. After 100 rotations the pellets were taken out from the friabilator and intact pellets were again weighed collectively after removing fines using sieve #44 sieve. Permitted percentage friability limit is 0.8%. The percentage friability was determined using the formula.

\[ \text{Percent friability} = \frac{(W1 - W2)}{W1} \times 100 \]

Where

\( W1 \) = weight of the pellets before test
\( W2 \) = weight of the pellets after test

Particle size distribution

This practice was done for the pellets obtained after functional coating whether to check average size of the pellets. 100 gms of the pellets are shifted in to a sieve...
shaker where a series of sieves was placed (16#, 22#, 25#, 30#). The machine was run for 5 mints, all the meshes are taken out and retained granules were collected by respective mesh and the percentage retention of pellets by that mesh was calculated. Average particle size was determined. A graph was plotted taking average size on x-axis and percent weight under size on y-axis.

**Effect of medium**

*In vitro* drug release of the samples was carried out using USP type II dissolution apparatus (paddle type). The dissolution medium used was phosphate buffer pH6.8 was placed into the dissolution flask maintain the temperature of 37°C ±0.5°C and rpm 100. Accurately weighed pellets were placed in each flask of dissolution apparatus. The apparatus was allowed to run for 24 hrs. The samples measuring 10 ml were withdrawn then filtered through a 10 micrometer filter. The fresh dissolution medium was replaced every time with the same quantity of the sample. Filtered samples were suitably diluted with phosphate buffer and analyzed at 226 nm. The cumulative percentage drug release was calculated.

**Release kinetics**

Data obtained from the *in vitro* release studies fitted to various kinetic equations such as zero order, first order.

**Zero order release kinetics**

It defines a linear relationship between the fractions of drug released versus time.

\[ Q = k_0 t \]

Where

\( Q \) is the fraction of drug released at time \( t \) and \( k_0 \) is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

**First Order Release Kinetics**

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics. The equation used to describe first order kinetics is \( \ln (1-Q) = k_1 t \)

Where, \( Q \) is the fraction of drug released at time, (t) and \( k_1 \) is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

**Stability studies** [9-13]

The pellets were filled in “0” size blue/blue capsules. The filled capsules were packed in aluminum foil and placed in walk in stability chamber at 40±2°C and 75±5% RH for 1 month. After 1 month the capsules were taken out and all evaluation tests were performed.

**RESULTS AND DISCUSSION**

Suitable analytical method based on UV-Visible spectrophotometer was developed for venlafaxine hydrochloride. \( \lambda_{max} \) was 226 nm in phosphate buffer solution, pH 6.8 (Fig.1).

**Fig.1:** UV spectrum of venlafaxine Hcl in phosphate buffer solution, pH 6.8

Drug coating of venlafaxine HCl on to the nonpareil seeds was achieved by using Pregelatinised starch as a binder. The concentration of Pregelatinised starch was 5 %. The seal coating was done by using Pregelatinised starch and the concentration of Pregelatinised starch was 11.9 %. Eudragit NE 30D in a concentration of 8.6 % w/v was optimized as coating polymer for 150 mg sustained release pellets of venlafaxine HCl. Titanium dioxide in a concentration of 4.26% w/w was optimized for coating composition. Venlafaxine 150 mg pellets were coated with two different coating compositions. Based on *in vitro* release studies, formulation 7(lot-2) was found to be optimum (Fig.2), for venlafaxine hydrochloride 150 mg sustained release pellets.

**Fig.2:** Comparison of *In vitro* release profile of marketed drug (150 mg), venlafaxine sustained release pellets and formulation no.7 (lot-2).

Venlafaxine release from the developed formulations in this was inversely proportional to the amount of polymer in the coating formula. Drug release from the developed formulations follows first- order. The manufacturing procedure was standardized and found to be reproducible. At accelerated stability conditions developed formulations were found to be stable for one month. *In vitro* release profiles of optimized formulations of venlafaxine HCl 150 mg sustained release pellets were found to be similar to that of US Marketed drug. The \( f_1 \) and \( f_2 \) values were found to satisfactory (Table.1). The *peppas* graph is drawn and slope value is calculated and m value obtained is 0.7535(Table.2).
Table 1. Comparison of data of similarity and dissimilarity factor between formulation.7 (Lot-2) and Marketed Drug

<table>
<thead>
<tr>
<th>Sampling time (hr)</th>
<th>Cumulative percentage drug Release</th>
<th>Marketed 150 mg drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formulation no. 7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>17.2</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>27.6</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>51.1</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>18</td>
<td>79.5</td>
<td>89.7</td>
</tr>
<tr>
<td>24</td>
<td>86.4</td>
<td>98.9</td>
</tr>
<tr>
<td>F1</td>
<td>15.8</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>48.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Comparison of orders of in vitro Release of Venlafaxine HCl

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi model</th>
<th>Peppas model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch 7 (Lot-2)</td>
<td>0.9207</td>
<td>0.9875</td>
<td>0.9559</td>
<td>0.9889</td>
</tr>
</tbody>
</table>

This Value Indicates That It Follows Non Fickian Law of Diffusion and it Goes Erosin Mechanism. The conclusions arrived in this thesis indicated that the sustained release pellets of venlafaxine hydrochloride, 150 mg, developed in this investigation was found to be equivalent to innovator’s US market product, based on in vitro release studies. Thus the objectives envisaged in this thesis were arrived. Further studies are needed to investigate this formulation for its performance in vivo and its equivalence with the marketed product, Effexor. Thus, objectives of the present thesis are achieved.

REFERENCE