A REVIEW ARTICLE ON SUSTAINED RELEASE TABLET OF VENLAFAXINE HYDROCHLORIDE AN ANTIDEPRESSANT DRUG

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ABSTRACT

The main objective and aim of the presenting review article is to provide information about drug Venlafaxine Hydrochloride as an Antidepressant drug. And how we can manufacture sustained release tablet of it. Oral route is most conventional for route of administration to obtain rapid and complete systemic drug abortion and onset of action. That’s why we preferred oral route. This review article involve the venlafaxine hydrochloride drug profile, need of development of sustained release tablet, excipient used in sustained release tablet and different technique used to manufacturing, and evaluation parameter.

Keywords: Venlafaxine Hydrochloride, Sustained Release Tablet, Manufacturing Technique for Sustained Release Tablet, Evaluation Parameter of Sustained Release Tablet.

INTRODUCTION

Depression is a major depressive disorder. Globally it is estimated that 5% of adult suffer from depression. People aged 12-25 have highest rate of depression. Venlafaxine hydrochloride belongs from class SNRI (Selective serotonin and norepinephrine reuptake inhibitor). It is used for other depressive disorder too like anxiety.

Venlafaxine Hydrochloride-

The antidepressant venlafaxine HCl belongs to the SNRI class. Wyeth’s initial introduction came in 1993. Within 3 days of oral multiple dosage therapy, venlafaxine and o-desmethyl venlafaxine steady-state plasma concentrations are reached. Over the 75 to 450 mg/day dosing range, these concentrations showed linear kinetics. Venlafaxine is a member of the SNRI class. SNRIs are a group of drugs that effectively alleviate chronic pain.
SNRI reduce depression by altering the neurotransmitters that allow brain cells to communicate. In BCS class 1, venlafaxine HCl is classified, being both very soluble and permeable.

1. **DRUG PROFILE**

1. **Drug name:** venlafaxine hydrochloride
2. **Molecular weight:** 313 g/mole
3. **Molecular formula:** C₁₇H₂₇NO₂.HCl
4. **Molecular structure:**

   ![Molecular structure of venlafaxine HCl](image)

5. **Chemical name:** 1-[2-(dimethylamino)-1-(4 methophenyl) ethyl] cyclohexane.

6. **Physicochemical properties:**
   - **Appearance:** white crystalline powder
   - **Solubility:** Slightly soluble in ethanol and methanol, and freely soluble in water.
   - **Melting point:** 215-217°C

7. **Pharmacokinetics profile:**
   - **BCS class:** class I
   - **Half Life:** 4.5 70 5.5 hrs.
   - **Bioavailability:** 42±15 %
   - **Protein binding:** 27±2 parent compound.
   - 30 ±12 %active metabolites.
   - **Therapeutic use:** The neurotransmitter that brain cells utilise to communicate is affected by venlafaxine HCl. It is an effective dual inhibitor of norepinephrine (NE) and serotonin (5-HT) reuptake that is orally active.
8. **Mechanism of Action:**

The mechanism of action of the antidepressant venlafaxine hydrochloride is thought to entail inhibition of the serotonin (5-HT) and norepinephrine uptake pumps with uptake. At larger doses, NE inhibition is particularly relevant. SNRIs treat depression by ultimately causing alterations in the brain's chemistry and communication between circuits known to control mood. Serotonin levels are raised with SNRI drugs, additionally norepinephrine in the brain.

![Diagram of SNRI mechanism](image)

**Fig.1. Mechanism of SNRI class**

9. **Pharmacokinetics:**

- **Absorption**: Venlafaxine hydrochloride orally administrated it rapidly get absorbed from GIT
- **Distribution**: 30±12 active metabolites and 272 parent compounds bind to proteins.
- **Metabolism**: The liver processes venlafaxine HCL extensively and absorbs it efficiently.
- **Excretion**: Thus, the primary route of excretion for venlafaxine and its metabolites is renal elimination.

2. **ADVANTAGE OF SUSTAINED RELEASE TABLET**

- Allow for the maintenance of a body's drug level. Constant
- Reduce the possibility of drug burst relearning
- Increase patient compliance, especially for long-term conditions.
- Zero order delivery is feasible, and the release rate depends on the type of polymer.
- Less medication is administered frequently.
- More practical.
It is possible to better control drug absorption and maximise availability with a little dose.

- Increase treatment effectiveness.
- Delivers API to target site directly.

3. **NEED OF DEVELOPMENT OF SUSTAINED RELEASE TABLET**

- Use fewer dosage tabs with sustained release.

The SR tablet gradually dissolves. They accomplish this by releasing tiny amounts into the patient’s system over time.

- By constantly delivering the medicine, it produces long-lasting therapeutic effects.
- Continue the effort.

**CHARACTERISTICS OF SUSTAINED RELEASE TABLET**

- Even thickness.
- Consistent homogeneity of weight.
- Low friability, reduced drug blood level swings, and improved disease bioavailability with a low dose.
- Rapid absorption and excretion.

4. **LIMITATIONS OF FOR SUSTAINED RELEASE TABLET**

- Chances of dose dumping.
- Dose retrieval is difficult.
- High cost of formulation.
- Need for additional patient education.
- Reduced potential for accurate dose adjustment.
5. INGREDIENTS USED IN SUSTAINED RELEASE TABLET

Table no.1: List of ingredient

<table>
<thead>
<tr>
<th>Ingredient Used</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropyl methylcellulose K4M</td>
<td>Polymer</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose K 15</td>
<td>Polymer</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose K 100</td>
<td>Polymer</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>Synthetic polymer, Absorb water.</td>
</tr>
<tr>
<td>Xanthum gum</td>
<td>Polymer, Stabilizing agent</td>
</tr>
<tr>
<td>Microcrystalline cellulose (MCC)</td>
<td>Anti-cacking Bulking agent</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Diuretic</td>
</tr>
<tr>
<td>Dicalcium phosphate (DCP)</td>
<td>Buffering, Stabilizer</td>
</tr>
<tr>
<td>Talc</td>
<td>Glidant</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
</tr>
<tr>
<td>Eudragit</td>
<td>Polymer, Taste masking, Prevent drug release in saliva. Permeable polymer</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>Binder Flavouring Fixative Filler</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose (SCMC)</td>
<td>Flocculating agent, Thickening agent, Water retaining</td>
</tr>
</tbody>
</table>

6. DIFFERENT TECHNIQUES THAT ARE USED TO MANUFACTURED IN SR TABLET:

Table no.2: techniques used in tablet

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry granulation</td>
<td>Dry granulation uses mechanical compression(slugs) or compaction(roller compaction) to facilitate the agglomeration of dry powder particles.</td>
</tr>
<tr>
<td>Wet granulation</td>
<td>Wet granulation uses granulation liquid(binder/solvent) to facilitate the agglomeration by formation of wet mass by adhesion.</td>
</tr>
<tr>
<td>Direct compression</td>
<td>Direct compression process consists of three steps: raw material, blending, tableting, and coating.</td>
</tr>
</tbody>
</table>
7. EVALUATION PARAMETERS FOR SUSTAINED RELEASE TABLET AS PER IP

Here we classify the tests/parameters by pre-compression parameters and post-compression parameter.

A. Pre-compression tests:

We have to prepare the mixture of API and excipients to form homogeneous powder, so these tests are performed for the powder before compression.

1. Angle of repose

The purpose of measuring the angle of repose is to ascertain both the flow characteristics of powder and the level of interparticle friction. In this experiment, we measured the height of the pile and the radius of the pile generated using the fixed-height funnel method.

Formula for calculation:
\[ \tan \theta = \frac{h}{r} \]

Table no.3

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Flow ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-30</td>
<td>Excellent flow</td>
</tr>
<tr>
<td>31-35</td>
<td>Good flow</td>
</tr>
<tr>
<td>36-40</td>
<td>Fair</td>
</tr>
<tr>
<td>41-45</td>
<td>Passable</td>
</tr>
<tr>
<td>46-55</td>
<td>Poor flow/cohesive</td>
</tr>
<tr>
<td>56-66</td>
<td>Very poor flow</td>
</tr>
<tr>
<td>&gt;66</td>
<td>Approximately no flow</td>
</tr>
</tbody>
</table>

2. Car’s index and Hausner’s ratio:

For the purpose of determining the compressibility factor, these two experiments are conducted. We must determine the bulk density and tapped density for these two ratios.

Formula for calculation:

Car’s index = \( V_0 - V^f \) / \( V_0 \)  
Hausner’s ratio: \( V_0 / V^f \)

Table no.4

<table>
<thead>
<tr>
<th>Limits</th>
<th>Car’s index</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>0-10</td>
<td>1.1-1.11</td>
</tr>
<tr>
<td>Good</td>
<td>10-15</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>Fair</td>
<td>16-20</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>Passable</td>
<td>21-25</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>Poor</td>
<td>26-31</td>
<td>1.35-1.45</td>
</tr>
</tbody>
</table>
B. Post-compression tests

1. Physical appearance:
   i. Colour
   ii. Odour
   iii. Taste
   iv. Texture
   v. Breaking line
   vi. Shape

2. Weight variation:

   The calibration of an electronic balance was used to perform the test weight fluctuation. Take 20 tablets at random from each batch, then weigh each tablet individually. Next, take. Determine the average weight. Comparing a person's weight to the average.

   Weight variation given as a percentage of variance.

<table>
<thead>
<tr>
<th>Average weight of tablet</th>
<th>Percentage of deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80mg or less than 80mg</td>
<td>10.0±2 %</td>
</tr>
<tr>
<td>More than 80mg but less than 250mg</td>
<td>7.5±2%</td>
</tr>
<tr>
<td>250mg or more than 250mg</td>
<td>5.0±2%</td>
</tr>
</tbody>
</table>

3. Hardness:

   The "crushing strength" of a tablet is its hardness. The force needed to break the tablet depends on its hardness. Compression that is directed diagonally ten pills were tested using the Monsanto, Pfizer, Erweka, and Schleuniger hardness testers.

<table>
<thead>
<tr>
<th>Tablet type</th>
<th>Hardness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>4kg-10kg</td>
</tr>
<tr>
<td>Hypodermic and chewable tablet</td>
<td>3kg</td>
</tr>
<tr>
<td>Sustained release tablet</td>
<td>4kg-7.5kg</td>
</tr>
</tbody>
</table>

4. Friability:

   The stage of being floppy, the likelihood or propensity for a tablet's solid components to fragment when rubbed. The friabilator device is used to conduct this test. 20 tablets were randomly tested in a lab friability testing for 4 minutes and 25 revolutions.
Formula for calculation:

\[ \% \text{ of friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \]

Limit of friability is not more than 1.0 \%.

5. **Dissolution study:**

The USP type II (Paddle apparatus) device is used to measure the rate of sustained release tablet dissolution. We must prepare a dissolution medium of phosphate buffer 6.8 pH and 0.1 N HCl for this test. Set the rotation speed in 900 ml to 50 rpm and the temperature to 370°C. After a predetermined amount of time, the dissolution media must be filtered and removed. And a UV-visible spectrophotometer at its maximum wavelength was used to check the filtered solution. Calculate the cumulative percent of medication release as well.

**Drug release kinetics:**

Mathematical models for drug release study

i. **Zero Order Model**

It is ideal way to improve therapeutic effect and avoid side effect of drug. Here drug release rate independent on concentration.

**Equation:**

\[ Q_t = Q_0 + K_0 t \]

- \( Q_0 \) = initial amount of drug.
- \( Q_t \) = cumulative amount of drug release at time (t)
- \( K_0 \) = zero order release constant
- \( t \) = time in hours

Graphical representation = % CDR v/s Time.

ii. **First Order Model**

First order is occurred when a constant proportion of the drug is eliminated per unit time.

\[ Q_t = Q_0 e^{-kt} \]

- \( Q_0 \) = initial amount of drug.
- \( Q_t \) = cumulative amount of drug release at time (t)
- \( k \) = first order release constant
- \( t \) = time in hours

Graphical representation = % CDR v/s Time
iii. Higuchi Model

The Higuchi model was originally conceived to describe the release of a drug.

\[ Q = k_{H} t^{1/2} \]

- \( Q \) = cumulative amount of drug release at time (t)
- \( k_{H} \) = higuchi constant
- \( t \) = time in hours

Graphical representation: amount of drug release v/s square root of time in hrs.

iv. Korsmeyer – Peppas model

This model of drug release is simply known as “power law” describing drug release.

\[ F = \frac{M_{t}}{M} = K_{m} t^{n} \]

- \( F \) = fraction of drug released at time \( t \)
- \( M_{t} \) = amount of drug release at \( t \)
- \( M \) = total amount of drug in dosage form
- \( K_{m} \) = kinetic constant
- \( n \) = diffusion or release exponent
- \( t \) = time in hrs.

Graphical representation: log % of drug release v/s log time in hrs

8. Marketed formulation of Venlafaxine Hydrochloride:

1) Venish SR 37.5/75/150
2) Venzee XR 37.5
3) Venlavin SR 37.5
4) Effexor XR
5) Velfex 37.5
6) Venzee XR 150
7) Velax SR 75
8) Verivan ER 37.5
9) Vendas XR 75
10) Psyfax 37.5 ER
11) Ventab XL 37.5
12) Venlift OD 150
13) Ventab XL 150
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