

## DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE FORMULATIONS OF VENLAFAXINE HYDROCHLORIDE

K. Sreenivasa rao, Jadhav Sunita, Patil Prakash\*, B. U. Dattatraya  
RRK'S College of Pharmacy, Bidar, Karnataka, India

Received on: 12/03/2011 Revised on: 23/04/2011 Accepted on: 01/06/2011

### ABSTRACT

In the present study, Venlafaxine was chosen as a model drug which is Anti-Depressant. Because of its short life (5-11hr) and its high water solubility it was chosen as a suitable candidate for sustain matrix tablet formulation. It was formulated in to matrix tablet using hydrophilic polymer such as, HEC Eudragit RS100, and Ethyl cellulose as releases retardants. All the precompressional parameters [angle of repose, Hausner's ratio and Carr's index] were found to be within the standard limits. Tablets were evaluated for hardness, friability, thickness, drug content, in-Vitro release, swelling and stability studies. The effect of polymer concentration binary polymer mixture and wet granulation method on drug release profile was studied. It was observed that the type of polymer and its concentration has influence the drug release from matrix tablet. Matrix tablet content a blend of HEC and ethyl cellulose successfully sustained the release of Venlafaxine for a period of 16hr. Precompressional parameter indicated that granules used for preparing tablets with free flowing. Post-copmressional parameters [hardness, friability, thickness and drug content] were with in the acceptable limit. The concentration of Venlafaxine was kept constant, lactose used as filler. Formulation containing only a single polymer could not control the control the release of venlafaxine as desire

The sustained release from ethyl cellulose and HEC was due to interaction between ethylcellulose chain ionic polymer and HEC chain, non-ionic polymer, which resulted in favorable increase in the water uptake capacity and gel viscosity, leading to better control over the release of Venlafaxine G4 showed the sustained release of Venlafaxine as desired. The study revealed that the ethyl cellulose and HEC G4 can be used for the formulation of sustained release matrix tablet of Venlafaxine.

**KEY WORDS:** Venlafaxine, Matrix tablet, HEC, Ethyl cellulose, Eudragit RS100, Wet granulation.

### \*Address for Correspondence

Prakash Patil, Department of Pharmacology, RRK College of Pharmacy, Bidar, Karnataka State  
India-585402 Email: patil\_pnp@yahoo.co.in

### INTRODUCTION

#### Sustained Release Dosage Forms

To the date, for every disease or disorder state of the patient, proper medication is of prime importance to maintain the patient in good health. To achieve this, the medicine or drug is administered conventionally by one or more of several well defined and popular routes of drug administration including oral, parenteral, rectal, alveolar, ocular and topical. Among these above mentioned popular routes, oral conventional route of drug administration lies at the top of the hierarchy of the conventional routes. It is a reasonable assumption that drug concentration at the site of action is related to drug plasma level and that, in the great majority of cases, the intensity of effect is some function of drug concentration

at the target site. The objective of the most therapeutic regimens is to rapidly raise the plasma concentration to the required level and then to hold it constant for the desired duration of treatment. The extent to which this situation can be achieved depends on many factors, including the minimum effective concentration of the drug, the level at which side effects occur, the dose administered, the rate of drug release from the dosage form, the rate of elimination and the frequency of dosing<sup>1</sup>. Provided that the dose size and frequency of administration are correct, therapeutic 'steady state' levels of the drug can be achieved rapidly and maintained by the repetitive administration of conventional oral dosage forms.

Traditionally patient only takes medication during the day time hours. Plasma levels can therefore fall to sub-therapeutic levels overnight. However, there are a number of major deficiencies of conventional dosage forms, few of which are listed here<sup>1,2</sup>.

Like every failure that sets ahead the path of successes, these above mentioned major deficiencies of drug therapy based on repetitive administration of conventional single oral dosage form, have lead to the development of a more specialized group of oral dosage forms (modified release drug products)<sup>3</sup>. Thus, various modified drug products have been developed to release the active drug from the product at a controlled rate. The term controlled release drug products was previously used to describe various types of oral extended-release dosage forms, including sustained release, sustained action, prolonged action, slow release, long action, and retarded release<sup>4</sup>. Many of these terms for controlled-release dosage forms were introduced by drug companies to reflect a special design for a controlled release drug product or for use as a marketing term. The United States Pharmacopoeia (USP) has adopted the term "extended release" whereas the British Pharmacopoeia (BP) has adopted the term "slow release". The Food and Drug Administration (FDA) of the United States has adopted the term "prolonged release". Both USP and FDA employ the term "delayed release" for enteric coated products<sup>5</sup>.

#### Sustained- release dosage forms

It is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug." It provides prolonged but not uniform release of drug and reduces the need for repeated dosing. Once the maximum level is reached, the amount of drug in the body decrease slowly. So it will take longer to drop below the therapeutic range.

#### MATERIALS AND METHODS

##### Procurement of Drug and Excipients

The drug, excipients, chemicals/ reagents and equipments used for various experiments are enlisted as follows:-

Materials Venlafaxine (cipra Ltd), Hydroethylcellulose, Ethylcellulose 10cps, Eudrajit RS100 (Signet Chemicals) Dicalcium phosphate (Emcure Pharm Ltd), Magnesium Stearate (S.D.Fine Chemicals)

##### Profile of drug

##### Venlafaxine HCl

Venlafaxine Hydrochloride (VFX) is an orally active serotonin noradrenaline reuptake inhibitor used for the treatment of major depressive disorders.<sup>6,7,8</sup>

#### Structure



**Molecular formula:** C<sub>17</sub>H<sub>27</sub>NO<sub>2</sub> HCl

**Molecular weight:** 313.87

**CAS:** [99300-78-4]

**Chemical name:** (R/S)-1-[2-(dimethylamino)-1(4 methoxyphenyl) ethyl] cyclohexanol

hydrochloride or (±)-1-[α- [(dimethyl-amino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride.

**Solubility:** 572 mg/ml

**Melting point:** 215-217 °C

**Partition coefficient:** (octanol/water) 0.43

**Proprietary names:** Dobupal; Eflexor; Effexor; Trevilor; Trewilor, Vandral

#### Pharmacokinetics

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

#### Pharmacodynamics

The mechanism of the antidepressant action of Venlafaxine HCl in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS.

Preclinical studies have shown that Venlafaxine HCl and its active metabolite, o-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine uptake and weak inhibitors of dopamine reuptake. Venlafaxine HCl and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine HCl and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

**Characterization of Venlafaxine Hydrochloride****Melting Point**

The melting point was determined by open capillary method.

The reported melting point is about 215<sup>0</sup>C – 217<sup>0</sup>C.

**Spectroscopic Studies****IR spectrum interpretation**

The infra red spectrum<sup>9</sup> of pure Venlafaxine hydrochloride sample was recorded and the spectrum analysis was done.

**UV Spectroscopy (Determination of  $\lambda_{max}$ )**

Stock solution (100 $\mu$ g/ml) of Venlafaxine HCl was prepared in distilled water. This solution was appropriately diluted with distilled water to obtain a concentration of 40  $\mu$ g/ml. The solution was kept in a fused silica cuvette 10 mm. The UV spectrum was recorded in the range of 200-400 nm on Shimadzu 1601 double beam UV-visible spectrophotometer at 1 cm, slit width. The same procedure was carried out in the solvents such as 0.1N HCl and pH 6.8 phosphate buffer. The spectrum and wavelength of maximum absorption<sup>9</sup> were recorded.

**Preparation of Standard Curve**

10 mg of Venlafaxine HCl was weighed accurately and transferred to a 100 ml volumetric flask. This was dissolved in 0.1N HCl and volume made upto 100 ml. This solution was treated as the stock solution and contains 100  $\mu$ g/ml of Venlafaxine hydrochloride solution. From this stock solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 ml were withdrawn and diluted the each sample with 0.1N HCl to obtain concentrations of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50  $\mu$ g/ml. Absorbance of these solutions were measured at 226.5 nm against blank solution i.e., 0.1N HCl. Same procedure was followed for the preparation of standard curve in distilled water and pH 6.8 phosphate buffer. The coefficient of correlation and equation for the line are determined.

**Preparation of Matrices by Wet Granulation**

Different tablet formulations were prepared by wet granulation technique. All the powders were passed through ASTM (American Society of Testing and Materials) 80 mesh. Required quantities of drug, polymer, diluent and dry binders such as ethylcellulose and eudragit were mixed thoroughly. Sufficient quantity of ethanol(95%) was sprinkled over the powder mixture to obtain enough cohesiveness. The cohesive mass was then sieved through 16/22 mesh. The granules were dried at 40<sup>0</sup>C for 12 hours and thereafter kept in desiccator for 12 hours. Once dry, the granules retained on 22 mesh were mixed with granules that passed through 22 mesh. Talc and magnesium stearate were finally added as glidant and lubricant and mixed well with granules for 5 minutes.

**Formulation code**

Tablets containing HEC in wet granulation and dicalcium phosphate - G

**Characterization of Granules****Infrared spectroscopy**

Fourier transform- infrared (FT-IR) spectra of drug, hydrophilic polymers, binders and granules were obtained on Shimadzu 8400 S FTIR spectrophotometer. The spectra were scanned over the wave number range from 3900 – 400 cm<sup>-1</sup>.

**Evaluation of granules****Angle of Repose**

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were 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 granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.<sup>10</sup>

$$\tan \theta = h/r$$

$$\text{Hence, } \theta = \tan^{-1} h/r$$

Where,  $\theta$  = angle of repose

h = height of the cone

r = radius of the cone base

**Bulk Density**

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas:

$$\text{LBD} = \text{Weight of the powder} / \text{Volume of the packing}$$

$$\text{TBD} = \text{Weight of the powder} / \text{Tapped volume of the packing.}$$

**Compressibility Index**

The compressibility of the granules was determined by Carr's Compressibility<sup>11</sup> Index.

$$\text{Carr's compressibility index (\%)} = [(TBD-LBD) \times 100] / TBD$$

**Preparation of tablets**

The granules prepared by wet granulation of drug, filler and hydrophilic polymers were compressed into flat faced tablets using by using KBr press. The diameter of the die was 12mm and the batch size prepared for each formulation was of 20 tablets.

**Evaluation of Tablets****Thickness and Diameter**

Thickness and diameter of tablets was determined using Vernier caliper. Five tablets from each batch were used, and average values were calculated<sup>12</sup>.

**Weight variation Test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

**Drug content**

Five tablets were weighed individually and triturated. Powder equivalent to the average weight of the tablet was weighed and drug was extracted in water for 6 hours. The solution was filtered through 0.45 $\mu$  membrane. The absorbance was measured at 226.5 nm after suitable dilution.

**Hardness**

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester

(Cadmach). The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm<sup>2</sup>. Then constant force was applied by rotating the knob until the tablet fractured<sup>13</sup>. The value at this point was noted in kg/cm<sup>2</sup>. Generally, a minimum of 4 kg/cm<sup>2</sup> hardness is considered acceptable for uncoated tablets.

**Friability**

For each formulation, the friability of 6 tablets was determined using the Roche friabilator (Lab Hosp.). This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows,

$$\% F = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

**In Vitro Release Studies**

*In vitro* drug release study for the prepared matrix tablets were conducted for period of 8 hours using a six station USP XXVI type II (paddle) apparatus at 37<sup>0</sup>C  $\pm$  0.5<sup>0</sup>C and 50 rpm speed. The dissolution studies were carried out in triplicate for 8 hours in phosphate buffer of pH 6.8 under sink condition. At first half an hour and then every 1- hour interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 226.5 nm for Venlafaxine HCl by a UV-spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard.

**Polymer swelling or water uptake studies**

The rate of test medium uptake by the polymer was determined by equilibrium weight gain method. The study was carried out in the USP/NF dissolution apparatus I. The polymer matrices were accurately weighed, placed in dissolution baskets, immersed in 0.05M phosphate buffer (pH 6.8) and maintained at 37 $\pm$ 0.5<sup>0</sup>C in the dissolution vessels. At regular intervals, the pre weighed basket-matrix system was withdrawn from the dissolution vessel, lightly blotted with a tissue paper to remove excess test liquid and re-weighed. The percent water uptake, i.e degree of swelling due to absorbed test liquid, was estimated at each time point using the following equation

$$\% \text{ water uptake or polymer swelling} = \frac{(W_s - W_i) \times 100}{W_p}$$

Where  $W_s$  is the weight of the swollen matrix at time  $t$ ,  $W_i$  is the initial weight of the matrix, and  $W_p$  is the weight of the polymer in the matrix.

**Matrix erosion studies**

The standard USP/NF dissolution apparatus I was used for this purpose.

The dry matrices were weighed, placed in dissolution baskets, and subjected to dissolution in 500ml of 0.05M phosphate buffer (pH 6.8) maintained at 37 $\pm$ 0.5<sup>0</sup>C with the baskets rotating at 100 rpm. At regular intervals, basket-matrix assemblies were removed from the dissolution vessels and dried to a constant weight in a hot air oven at 50<sup>0</sup>C. The percentage matrix erosion at time  $t$ , was estimated from the following equation:

$$\text{Matrix erosion (\%)} = \frac{(W_i - W_t)}{W_i} \times 100$$

Where  $W$  is the initial weight of the matrix,  $W_t$  is the weight of the matrix

Subjected to erosion for time  $t$ .

## RESULTS

### Characterization of Venlafaxine Hydrochloride

The characterization of drug was carried out by conducting various physicochemical tests including melting point determination, spectral analysis such as UV spectrum and IR Spectrum for pure Venlafaxine HCl.

The melting point was found to be in the range of 215°C – 217°C which is in good agreement with the reported values.

### UV Spectroscopy

UV absorption spectrum showed  $\lambda_{\text{max}}$  to be 226.5 nm. The graph of absorbance vs. concentration for pure Venlafaxine HCl was found to be linear in the concentration range of 5 – 50  $\mu\text{g/ml}$  at 226.5 nm. Hence the drug obeys Lambert – beer's law in this range.

The IR spectra of the samples showed lack of significant interaction between the drug and polymer as all characteristic bands of Venlafaxine HCl were in IR spectra of the formulations.

### Evaluation of granules

All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeial limit for percentage deviation for the tablets of more than 250mg is  $\pm 5\%$ . The average percentage deviation of all the tablet formulations was found to be within the above limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements. Good uniformity in drug content was found among different batches of tablets, and percentage of drug content was more than 95%. The formulation showed a comparatively high hardness value of  $4.9 \pm 0.26 \text{ kg/cm}^2$ .

This could be due to the presence of more ethylcellulose which is generally responsible for more hardness of the tablet. In the present study the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability. Formulations were found to be harder as compared to HEC formulations and corresponding values for friability for formulations were low as compared to HEC formulations. The friability values ranged from  $0.54\% \pm 0.08$  to  $0.83\% \pm 0.09$ .

## DISCUSSION

The current investigation deals with the optimization of Sustained release matrix tablets of Venlafaxine Hcl using hydrophilic Polymers. Polymers used were HEC, Ethyl cellulose and Eudragit RS100. The hydrophilic matrices for Venlafaxine Hcl (water soluble drug) containing a blend of one or more gel forming polymers. The compositions of the formulations are shown in Table NO 2. The concentration of Venlafaxine Hcl was kept constant at 75mg. Lactose was used as filler.

### Characterization of Venlafaxine Hcl

#### Melting point

The melting point was found to be in the range of 215°C – 217°C which was in good agreement with the reported values.

### Spectroscopic Studies

#### UV Spectroscopy (Determination of $\lambda_{\text{max}}$ )

The  $\lambda_{\text{max}}$  of Venlafaxine Hcl was found to be at 226.5 nm in distilled water and phosphate buffer of pH 6.8 is shown in Figure no 1. Standard graph of Venlafaxine Hcl in distilled water and phosphate buffer of pH 6.8 is shown in Figure no 2. Good linearity was observed with the plot. Its 'r' value in distilled water was 0.99983 and in phosphate buffer of pH 6.8 the value was 0.9993 are shown in Table No 6 which were very nearer to '1' and hence obeyed "Beer – Lambert" law.

#### Determination of infrared absorption spectrum

The FT-IR spectra of Venlafaxine Hcl is shown in figure no 3 and spectral assignments for Venlafaxine Hcl is shown in Table no 7 the IR spectrum indicated characteristic peaks belonging to functional group such as principle peaks at wave no 3320, 1622 and 1250.

#### Determination of Interaction between drug and used polymers

The FT-IR spectra of all combinations containing drug and one or more polymers also shows the characteristic peaks same as that of the pure drug.

The FT-IR spectrum of all the combinations containing drug and one or more polymer shows same or slightly shift in peak values when compared with the characteristic peak values of the pure drug.

Thus, from the above it is concluded that there is no interaction between the Venlafaxine Hcl and used polymers.

#### Evaluation of Granules

The granules were prepared by wet granulation method using 10 % (w/w) starch paste as binder. Pre-compressional parameters i.e. angle of repose (21.60 to 24.30), percent compressibility (15), and Hausner's ratios

(1.08 to 1.20) are shown in Table No 11. These results indicate that granules are good flowing in character.

The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower Hausner's ratios, lower compressibility index values. Compressibility index values up to 15% result in good to excellent flow properties. And thus the granules were suitable for compression.

### Evaluation of Tablets

The results of Postcompressional parameters. All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeia limit for percentage deviation for the tablets of more than 300mg is  $\pm 5\%$ . The average percentage deviation of all the tablet formulations was found to be within the above limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements. Good uniformity in drug content was found among different batches of tablets, and percentage of drug content was more than 95%. The all formulations shows required hardness this could be due to presence of starch paste which is generally responsible for more hardness of the tablet.

In the present study the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable properties and complied with the in-house specifications for weight variation Postcompressional parameters i.e. hardness, friability, thickness, weight variation, and drug content were within acceptable official IP limits.

### Dissolution Study

In-vitro drug release study for the prepared matrix tablets were conducted for period of 15-16 hours using a USP XXVI type II (paddle) apparatus at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  and 50 rpm speed. The dissolution studies were carried out in triplicate in phosphate buffer of pH 6.8 under sink condition. At first half an hour and then every 1-hour interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 226.5 nm for Venlafaxine Hcl by a UV- spectrophotometer.

The drug release data for HEC containing formulation. and The formulation with HEC 20 %, releases drug in 9 hrs, The formulation with HEC 30 %, releases drug in 10 hrs, And the formulation with HEC 40 %, releases drug in 11 hrs. The quick release from HEC containing system is due to high solubility of HEC at pH 6.8.

This polymer characteristic gives to the matrix a quick gel erosion rate and a high erosion degree of the overall system. Means matrices with only HEC as release rate

retardant were not able to control the release rate for very soluble drug Venlafaxine Hcl for 16 hrs.

The drug release data for Natural polymer Ethylcellulose. And The formulation with Ethylcellulose 20 %, releases drug 98.70% in 9 hrs, The formulation with Ethylcellulose 30 %, releases drug 98.43 % in 10 hrs, And the formulation with Ethylcellulose 40 %, releases drug 97.24 % in 11 hrs.

When this hydrophilic ethylcellulose matrix tablet come in contact with dissolution medium they take up water and swell forming a viscous gel layer barrier. The initial swelling of the guar gum may aid the dissolution of freely soluble drug and then dissolved drug diffuse out of the swollen gel barrier into the dissolution medium. Thus, the release rate is depends on the strength of the gel barrier. It has observed that cumulative percent drug release decreases with increasing concentration of the Ethylcellulose from 20 % to 40%. But the only single polymer is not able to retard the drug release for 16 hrs the Ethylcellulose releases the drug quickly because of low viscosity of gel barrier layer.

From the above single polymer dissolution study it is clear that single polymer were not able to control the drug release for 16hrs so there is need to use combination of two or more polymer

The drug release data for combination of HEC, G4, formulation retards the drug releases for 13 hrs this formulation were able to release 96.70% drug and our dose of the drug is 100 mg that means about 96 mg of drug is released. Where as G4 and G5 retards the drug releases for 14 hrs and the percent of drug release is 96.42 % & 94.30 % respectively.

This could be due to swelling as well as erosion of the polymer occurs simultaneously both of them contributing to the overall drug release rate. From the dissolution profile of this combination it is clear that increasing the HEC content of SR tablets prolonged the dissolution time this could be due to CMC decrease water uptake and erosion of the tablet in dissolution medium which describes the slower release with increasing CMC concentration. The release about 90% formulation may be of HEC than the G4 formulation and also due to lactose which is soluble in water means lactose acts as channeling agent which creates pores to the matrix system, these polymer characteristic gives to more drug release. The HEC tablets achieved the highest degree of hydration; indicate that the ionic interactions between the cellulose ethers increased the water uptake capacity to a greater extent.

The control release above 16hrs was seen with formulation containing combination of HEC the slower release from this combination was due to interaction

between HEC chains. The capacity of to form hydrogen bonds with the hydroxyl group of HEC led to a synergistic effect on gel viscosity that explain the better control of these polymers on the release of Venlafaxine Hcl.

The dissolution data containing combination of HEC and Ethylcellulose/Eudragit RS100. The formulations of combination of Ethylcellulose and HEC contains 2, 4 4 & 8 % of Ethylcellulose/EudragitRS100 in G4, G5 and respectively at the same time amount of HEC concentration is goes on decreasing.

The effect of change of amount of polymers is clearly seen in the dissolution pattern of Venlafaxine Hcl release from matrices

The percent of Venlafaxine Hcl released from this combined formulation in 17hrs is as follows

G4 (4% Etylcellulose) -- 73.32 %

G5 (8 % Eudragit) -- 68

From the above data it is clear that as concentration of Ethylcellulose/Eudragit is increased the percent of Venlafaxine Hcl released is decreased. This is due to formation of thicker layer which is resistant to the drug release.

The actual reason behind this slower release is nature of / Ethylcellulose/Eudragit on exposure to dissolution fluids gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core of the matrix tablet, in all the formulations of Ethylcellulose/Eudragit this viscous gel layer is form but the strength of this formed gel layer around the matrix tablet is different that depends on several factors such as particle size, force of compression, presence of other excipients, viscosity of polymer, solubility of the drug.

All the four type of combined formulation i.e. G4, and G5 were found swollen and retained their physical integrity till the end of the 16hrs dissolution study except that the edges of the swollen formulations were rounded off due to slight erosion of swollen gum.

The dissolution data containing combination of HEC and Ethylcellulose/Eudragit.

The percent of Venlafaxine Hcl released from this combined formulation in 17hrs is as follows

G3 (2%EC) -- 85.60 %

G4 (4 % EC) -- 78.54 %

G5 (4 % ERS) -- 73.32 %

G6 (8% ERS)

In G3 formulation EC content is only 2 % when this EC matrix tablet came in contact with dissolution medium it take up medium into the system which is responsible for dissolution of active constituent and then drug diffuse out of the system formulation but due to less guar gum less

viscous gel layer is formed this gel layer becomes more viscous when guar gum content is more.

Because of above reasons the difference in drug release pattern is seen in G3, G4, G5 and G6 formulations of Venlafaxine Hcl matrix tablet.

Based on the dissolution pattern of all the formulations the better formulation was G4.

Dosage form which can release 80 – 100% of drug in about 11- 16 hours is considered to be a better formulation because the transit time in GIT is around 11-16hours in the absence of any special gastro retentive methods. The matrix tablets cannot reside in small intestine beyond 16 hours. Therefore, we presume that dosage form which release most of the drug incorporated in 16 hrs is a better formulation. After the complete drug is released it will be absorbed based on the Physico-chemical and biological factors.

### Swelling study

The swelling behavior of various polymer blends was analyzed to compare their water uptake capacity. A hydrophilic matrix system is a dynamic system composed of polymer wetting, hydration, and dissolution. At the same time other soluble excipients or drug will also wet, dissolved and diffuse while insoluble ingredients will be held in place until the polymer erodes or dissolve since the diffusional release of a soluble drug such as Venlafaxine Hcl may primarily be controlled by gel thickness (diffusion layer), increasing polymer level tends to decrease drug release, The most common explanation of the effect of increase in polymer level on drug release is that, it results in the increase in the thickness of gel layer, which retards drug diffusion out of the tablet.

The result of swelling study indicate that swelling index value for formulation high is G4 and the value of swelling index for G4 is higher. In general, because the drug core of polymer tablets in glassy, the drug contained in them cannot diffuse unless swelling takes place. On swelling drug molecules dissolve in water and are released by diffusion. The process of swelling, erosion and drug release can occur simultaneously and are interconnected. A polymer ability to retard the drug release rate is related to its viscosity.

HEC polymer have besides hydrophilic hydroxypropyl substituent's also hydrophobic methoxyl groups and have exhibited a lower hydrophilicity As noted during swelling of hydroxyethyl cellulose derivative (HEC) the macromolecular chains absorb water, leading to an expansion of the network formed and formation of a quasi equilibrium structure. This network structure usually is held together by physical chain entanglements, hydrogen bonds, tie junctions or tie points produced by various types of forces. Upon further absorption of water, these

gels may start disentangling, indicating a competitive phenomenon of swelling and dissolution.

Matrices that contained lower concentration of HEC tends to release the drug in shorter time periods, while release slowed as concentration of this gelling polymer increased, confirming the dominant role played by the swellable hydrophilic polymer in the release of Venlafaxine Hcl from these tablets<sup>13</sup>. As the concentration of HEC is increased, release rate of drug is decreased due to gel layer, which control the release of the drug.

The Viscosity increasing polymers such as were also deemed to be essential for maintaining integrity and their role was complementary to the predominant gel-forming polymers are helped to retain the integrity of matrix.

### Release Kinetics

The dissolution data were examined for models of first order, zero order, Higuchi, Korsmeyer Peppas and Hixon crowell model. The derived correlation coefficient ( $r^2$ ) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism limiting drug release. For all formulations containing HEC, Ethyl cellulose/Eudragit and their combination the n values ranged from 0.5 – 0.54 except for G4, G5. These values are closely approximate with  $n=0.5$  indicating Fickian diffusion. This was also further confirmed with good correlation coefficient found in all formulations with Higuchi's kinetics. The small deviation from n values from its actual value may be because of association of diffusion and erosion of polymer simultaneously. The formulations G4, G5 follow anomalous behaviour. The slope values n, indicated an anomalous behaviour. Hence diffusion coupled with erosion may be the mechanism for drug release

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Table 1 Pharmacokinetic parameters of Venlafaxine HCl

Oral absorption	> 92%
Plasma half life (ODV)	5h (11 h)
Volume of distribution (ODV)	7.51.kg-1 (5.71.kg-1)
Plasma protein binding (ODV)	27% (30%)
Plasma clearance (ODV)	1.2-1.7 l/h/kg (0.4 l/h/kg)

(ODV) – O- desmethylvenlafaxine

**Table 2 Formulation design of Venlafaxine hydrochloride tablets by wet granulation method using HEC**

Ingredients(per tablet)	G1	G2	G3	G4	G5	G6
Venlafaxine HCl	84.87	84.87	84.87	84.87	84.87	84.87
Hydroxyethyl cellulose HHX	84.87	169.74	169.74	169.74	169.74	169.74
Ethylcellulose(2%w/w)	-	-	8	-	-	-
Ethylcellulose (4%w/w)	-	-	-	16	-	-
EudrajitRS100(4%w/w)	-	-	-	-	16	-
Eudrajit RS100(8%w/w)	-	-	-	-	-	32
Ethanol	qs	qs	qs	qs	qs	qs
Dicalcium phosphate	222.6	137.39	129.39	121.39	121.39	105.39
Magnesium stearate(%w/w)	4	4	4	4	4	4
Talc(%w/w)	4	4	4	4	4	4

(All ingredients are taken in mg per tablet)  
The quantity of Venlafaxine HCl taken is equivalent to 75mg of Venlafaxine

**Table 3 Relationship between angle of repose ( $\theta$ ) and flowability**

Angle of Repose ( $\theta$ )	Flowability
< 20	Excellent
20 – 30	Good
30 – 34	Passable
> 40	Very poor

**Table 4 Relationship between % compressibility and flowability:**

% Compressibility	Flowability
5 - 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 - 35	Poor
33 – 38	very Poor
> 40	Extremely Poor

**Table 5 Specifications for tablets as per Pharmacopoeia of India**

Average weight of Tablet	% Deviation
80 mg or less	10
More than 80mg but less than 250 mg	7.5
250 mg or more	5

Table 6 Wavelength of maximum absorption ( $\lambda_{\max}$ ) in different solvents

Sr.No	Solvent	$\lambda_{\max}$
1	Water	226.5 nm
2	0.1 N HCL	226.5 nm
3	pH 6.8 Phosphate Buffer	226.5 nm

Table 7 IR interpretation of Venlafaxine, HEC, and granules containing ethanol alone as a granulating agent

Peaks $\text{cm}^{-1}$	Groups	Stretching/Deformation
3320	O-H	Stretching
3051	Aromatic C-H	Stretching
2821	Aliphatic C-H	Stretching

Table 8 IR interpretation of Venlafaxine, HEC, and granules containing 1%w/v and EC 2% w/v as a granulating agent

Peaks $\text{cm}^{-1}$	Groups	Stretching/Deformation
3320	O-H	Stretching
2821	Aliphatic C-H	Stretching
1208	C-O	Stretching
1039	Asymmetric C-O-C	Stretching

Table 9 IR interpretation of Venlafaxine, HEC, and granules containing 2%w/v and ERS 4% w/v as a granulating agent

Peaks $\text{cm}^{-1}$	Groups	Stretching/Deformation
3320	O-H	Stretching
2821	Aliphatic C-H	Stretching
1727	C=O	Stretching
1039	Asymmetric C-O-C	Stretching

Table 10 Dissolution data of formulation containing Hydroxyethyl cellulose

Time (hr)	G1	G2	G3	G4	G5	G6	Marketed
0.5	38.47	19.97	17.61	13.25	19.58	15.08	3.42
1	50.14	32.15	24.15	20.51	30.25	22.67	5.51
2	69.56	49.91	35.68	29.63	38.45	33.19	16.54
3	80.88	57.33	41.55	38.54	45.25	40.58	30.66
4	89.45	66.54	49.84	44.52	51.86	48.94	40.22
5	99.11	76.85	54.21	52.87	58.88	56.72	51.24
6		84.12	62.89	60.11	66.84	62.53	53.67
7		88.19	71.94	68.58	74.59	70.05	57.45
8		94.34	79.71	73.87	82.54	76.81	62.79
9		96.44	83.11	77.27	88.41	79.97	65.86
10		97.45	87.90	82.26	92.83	83.98	68.91
11		98.33	92.77	87.84	97.45	89.44	74.23
12			96.36	91.48	99.61	93.56	80.99
13			101.10	93.53		97.12	83.44
14				96.98		99.74	87.88
15				98.67			93.85
16				101.01			100.01

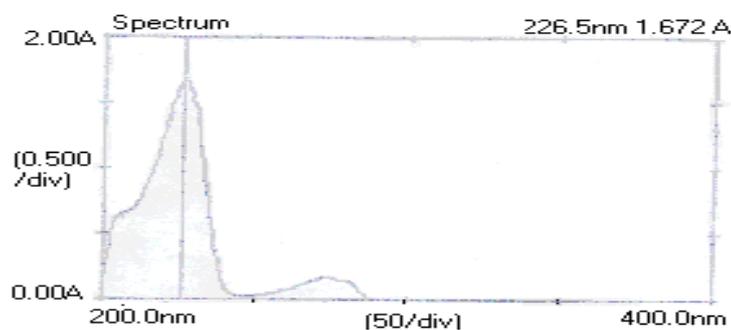


Fig 1 UV Spectrum of Venlafaxine HCl.

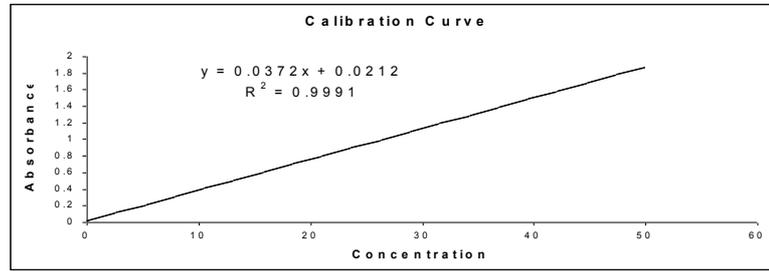


Fig 2 Standard Curve of Venlafaxine HC

B. IR spectrum interpretation:

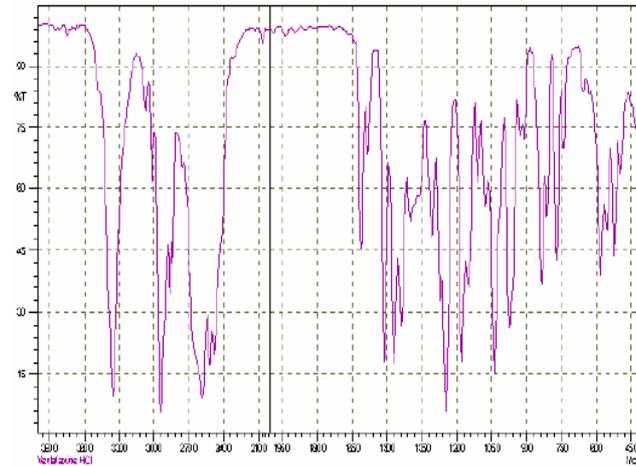


Fig 3 IR spectrum indicated characteristics peaks belonging to measure functional groups such as principal peaks at wave number 3320, 1622, 1250 cm<sup>-1</sup>

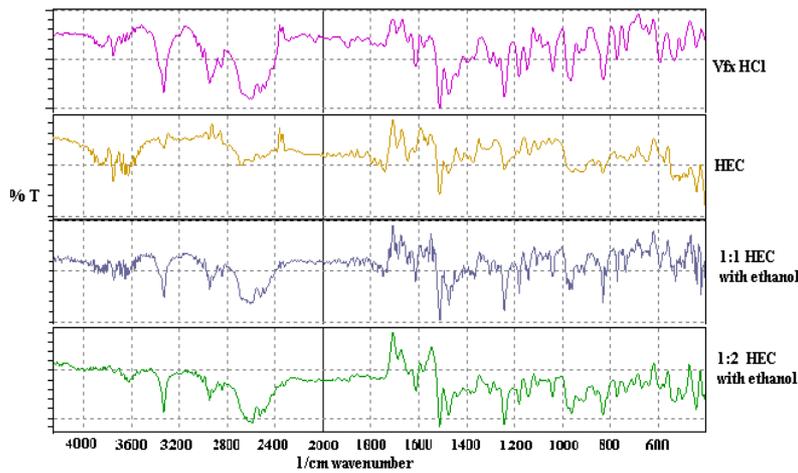


Fig 4 IR spectrum of Venlafaxine, HEC, and granules containing ethanol alone as a granulating agent

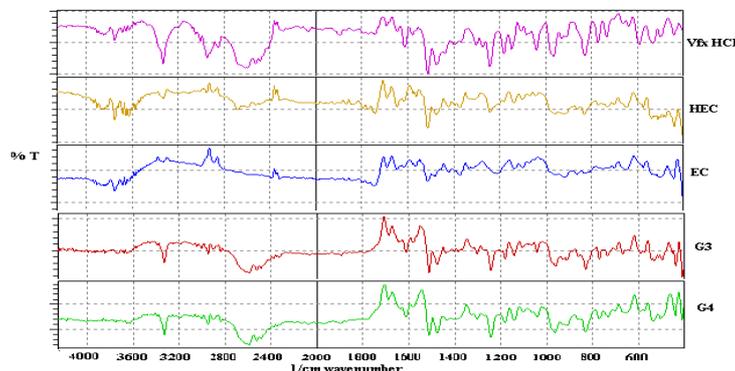


Fig 5 IR spectrum of Venlafaxine, HEC, and granules containing EC 1%w/v and EC 2% w/v as a granulating agent.

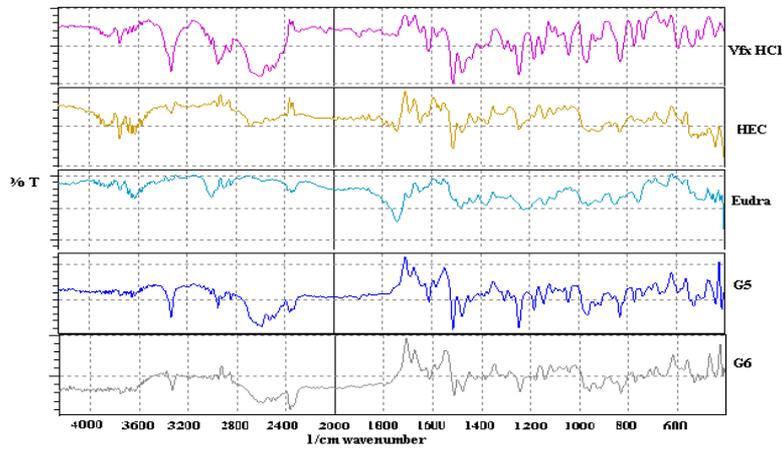


Fig 6 IR spectrum of Venlafaxine, HEC, and granules containing ERS 2%w/v and ERS 4% w/v as a granulating agent.

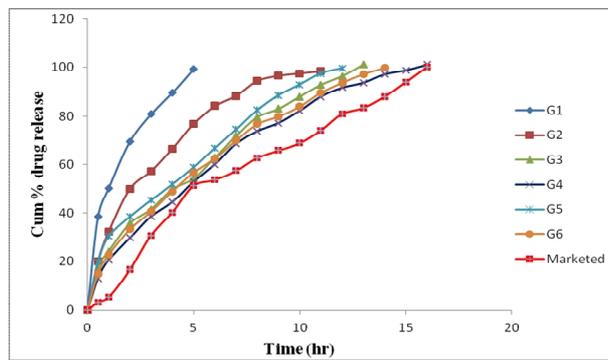


Fig 7 Dissolution profile of formulation containing Hydroxyethyl cellulose

Source of support: Nil, Conflict of interest: None Declared