ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

FORMULATION OF VENLAFAXINE SUSTAINED RELEASE CAPSULE DOSAGE FORM

[1]G. Venkata Ratnam[*], [2]G. Ravi, [1]G. Harish, [1]S. Duraivel, [1]B.Pragati Kumar
[1]Department of Pharmaceutics, Nimra College of Pharmacy
[2]Department of Pharmaceutics, SRMC, Chennai
Corresponding author:venkatgogusetti@gmail.com

ABSTRACT

The aim of the present study is to formulate and evaluate Venlafaxine SR capsules. venlafaxine is a novel anti-depressant used widely for treatment of depression and generalised anxiety disorder, but it is having disadvantage of less biological half life of about 5 hrs due to extensive hepatic first pass metabolism. So in order to maintain the therapeutic concentration of venlafaxine for a prolonged period of time the SR capsules has been formulated. The present research work was directed towards the development of a sustained release dosage form of venlafaxine in the form of capsules to be taken once daily. In the present study polymers such as Ethyl cellulose (10, 20, 50 cps), Hydroxypropylmethylcellulosephthalate, were used as coating polymers which helps in providing sustained release. The dissolution studies of the dosage form was performed and analysed by UV- Spectrophotometer. Different evaluation parameters such as drug- excipient compatibility studies were done by X-ray diffraction, Differential Scanning Calorimetry and *in-vitro* drug release was performed. Different polymers are optimized on the basis of release pattern. The marketed formulation was evaluated for the *in-vitro* release studies and the optimized formulation is compared with the marketed product which is in the form of extended release pellets.

1. INTRODUCTION

Sustained release dosage (J. A. Campbell, 1959) form can be defined as a specific type of programmed release medication which contains in one dosage form equivalent of several single doses of a drug which is released to the body over an extended period of time and there by produces a sustained clinical effect The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. So, sustain release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Venlafaxine (Aukunuru Jithan, 2007) 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 (Thomson, Physicians' desk reference, 2004) and nor epinephrine uptake inhibiton. it lacks the adverse anticholinergic, 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.

2. MATERIALS AND METHODS

Venlafaxine, Hydroxy propyl methyl cellulose, Ethyl cellulose, Eudragit used were of analytical grade.

Drug excipient interaction studies:

DSC studies: DSC thermo grams of pure drug and pellets were carried out to investigate drug possible interaction between drug and utilized polymers. DSC analysis was performed using a DSC200F3 apparatus equipped with a DSC 2 inch cell. Weighed samples (5-10mg) were scanned in Aluminum pans pierced with a perforated lid at 10˚C min^{-1} in 0-450˚C temperature range under static air using nitrogen 60ml/min as purge gas.

XRD studies: X-ray diffraction studies are useful for investigations on the changes of crystal form during processing. The compatibility between the drug and excipients is determined by using X-Ray diffractor. In this 5-10 mg of sample is placed on the pan of an X-ray diffractor and scanned at 2 theta scale. This method of analysis is non destructive and requires a very small sample of the material which can be examined without further processing. The thermogram of pure drug and drug with excipient mixture was compared and checked for their compatibility. The extent of conversion of a crystalline drug to the amorphous form can be determined.

Preparation of Venlafaxine HCl Sustained release capsules: Sugar spheres were procured from the industry and on it drug was coated. Then the drug coated pellets were subjected to barrier coating(Radhika P.R, 2011) with the help of hydroxyl methyl cellulose polymer. Then the barrier coated pellets were subjected to sustained release coating with the help of polymers like ethyl cellulose, then allowed for drying and then 225 mg of pellets were manually filled in capsules.

Table.1.Formulation Table of Venlafaxine sustained release pellets

S. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Venlafaxine	94.5	94.5	94.5	94.5	94.5	94.5
2	Sugar Spheres	78.5	78.5	78.5	78.5	78.5	78.5
3	Pvp k-30	15	15	15	15	15	15
5	HPMC6 CPS	15	10	15	10	15	10
6	HPMC3 CPS	12	12	12	12	12	12
8	Ethyl cellulose 10 cps	10	15	….	….	….	….
9	Ethyl cellulose 20 cps	---	---	10	15	….	….
10	Ethyl cellulose 50 cps	---	---	---	---	10	15

Evaluation of Physical Parameters:

Percentage Yield: All the controlled release venlafaxine (Shams ME, 2006) pellets prepared by fluid bed coating were evaluated for percentage yield of pellets. The actual percentage yield of pellets was calculated by using the following formula. The % yield of various batches of pellets were given in table

$$\text{percentage yield of pellets} = \frac{\text{Practical yield of pellets}}{\text{Theoritical yield of pellets}}$$

Drug Content: One gram of pellets (Hardman Limbard Gilman, 2001) was taken from each batch and was crushed into fine powder. The powdered material was transferred and mixed with water. About 10ml of the solution was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using Millipore filter. Then the filtrate was subsequently diluted and the absorbance was measured. This test was repeated six times for each batch of pellets. The drug content of various batches of pellets was given in the table

***In-vitro* Dissolution studies:** The capsules were evaluated for *in-vitro* release studies. In-vitro release study was done by using USP II apparatus using 900ml of distilled water (Hiren P. Patel, 2010) as medium for a period of 24hours. Effect of type of amount of polymer on the release of venlafaxine was studied on the basis of release pattern. UV spectrophotometer (Michael & Aulton, 2011) was used as the method of analysis at a wavelength of 227nm. The marketed product was taken evaluated for drug content and *in-vitro* drug release and the optimized formulation was compared with the marketed one.

Stability studies: The optimized formulation (Ladani Aniket, 2011) was packed in suitable container and subjected to stability studies at 40°C and 75% RH. Sampling was done at different intervals of time. The capsules were evaluated for drug content and *in-vitro* drug release. *In-vitro* drug release was determined (Atul A.Bodkhe, 2010) (K. Sreenivasa rao, 2011) (Adhimoolam Senthil, 2011) with the help of UV spectrophotometer at 227nm.

3. RESULTS AND DISCUSSION

DSC analysis: By DSC curves, the thermal behavior of Pure Drug Venlafaxine HCl shows peak endotherm at 214.4°C corresponding to loss of water of crystallization and melting of pure drug. Thermal behavior of Venlafaxine HCl with excipients shows peak endotherm at 204°C. The reduction of height and sharpness of endotherm is due to loading of excipients. The endothermic change and broadening of peak from 265°C to 263°C is due to loading of excipient complex. The results were shown in figures 1, 2. It confirms there was no interaction was observed between drug and excipients. It concludes that, excipients were not affecting the characteristic of drug due to pelletization process and indicates the amorphous nature of Drug excipients complex.

XRD analysis: By the spectra obtained by XRD, the pure Venlafaxine shows sharp peaks which indicate crystalline nature of pure drug. The spectra obtained by Venlafaxine HCl with excipients shows increase and slight shift in height of peaks, which indicates the crystalline nature of peaks. The results were shown in figures 3, 4. A slight change was observed in the spectra; the peaks of less height indicate the amorphous nature of compound. By the obtained result it can be concluded that there was no interaction between drug and excipient complex

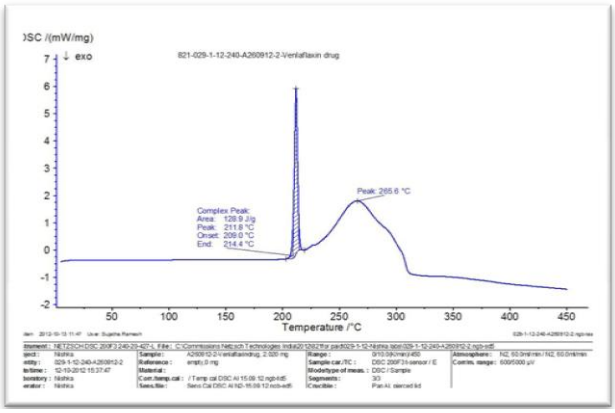

Figure.1. DSC curve of Venlafaxine

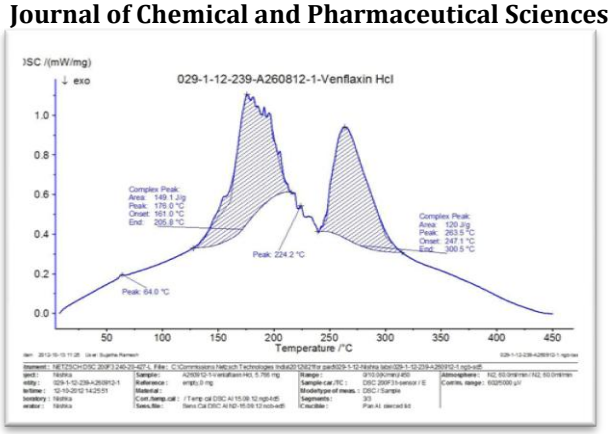

Figure.2. DSC curve of venlafaxine capsule dosage form

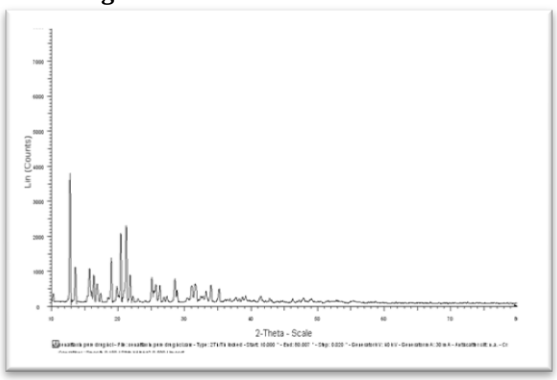

Figure.3. XRD thermo gram of Venlafaxine hydrochloride

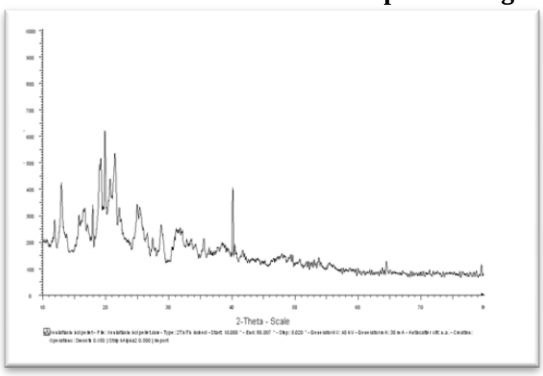

Figure.4. XRD thermo gram of Venlafaxine hydrochloride capsule dosage form

Table.2.Physical parameters of Venlafaxine hydrochloride capsules

S. NO	FORMULATIONS	% YIELD	DRUG CONTENT
1.	F1	91.50.3	97.5±0.5
2.	F2	92.3±0.5	96.5±0.4
3.	F3	92.2±0.3	98.8±0.5
4.	F4	94.3±0.2	98.7±0.3
5.	F5	94.6±0.4	100.2±0.2
6.	F6	96.2±0.3	100.8±0.4

Table.3. *In-Vitro* dissolution parameters of Venlafaxine capsules

S. NO	FORMULATIONS	FIRST ORDER CONSTANT	HIGUCHI CONSTANT
1.	F1	0.987	0.962
2.	F2	0.990	0.971
3.	F3	0.989	0.968
4.	F4	0.994	0.973
5.	F5	0.983	0.969
6.	F6	0.997	0.974

Venlafaxine hydrochloride pellets were prepared by using solution layering technique. Non pariel sugar beads were used to coat the venlafaxine HCL. The drug layer was further coated with HPMC as sub coating and finally the pellets were coated with ethyl cellulose. All batches of pellet formulations are formulated and manufactured under identical conditions. All the pellet formulations were evaluated for physical parameters such as % yield and drug content. The percent yields of various coated pellets were in the range of 91 to 96 %. All the physical parameters evaluated for various batch of pellets were given in table. The percent of drug content in various pellet formulations were found to be in the range of 97 to 100%. Dissolution studies were performed on all of the controlled release pellets by using USP-II paddle apparatus.

The drug release from the capsule formulation was very poor in the formulation 1 and as the concentration of the ethyl cellulose increased the release rate decreased. It was observed that increase in the concentration of polymers ethyl cellulose resulted in delay in the drug release. It was observed that increase in the HPMC concentration showed initial delay in drug release up to 2 hours and further rate of release was

increased. All the capsule formulations were found to be linear with first order release and the R^2 values were in the range of 0.980 to 0.997, it was shown in figure 6. Thus the rate of drug release from all the pellet formulations was concentration dependent. The Higuchi's plots for all the pellet formulations were found to be linear with R^2 values in the range of 0.962 to 0.974, it was shown in figure 7.

The dissolution profiles of venlafaxine hydrochloride formulations were compared with marketed controlled release formulation of venlafaxine extended release pellets which were formulated as capsule; it was shown in Figure 8. Stability studies were conducted on selected formulation F6. The stability studies indicated that there was no visible and physical changes observed in the pellet formulations after storage. It was also observed that there was no significant change in the drug release before and after the stability study. It was shown in Figure 9. The controlled release characteristics remained unaltered. Thus the selected extended release capsule formulation was found to be quite stable.

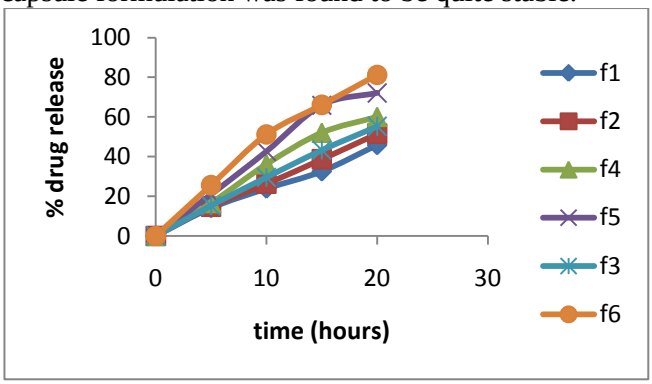

Fig 5 Drug release profiles for venlafaxine sustained release capsules

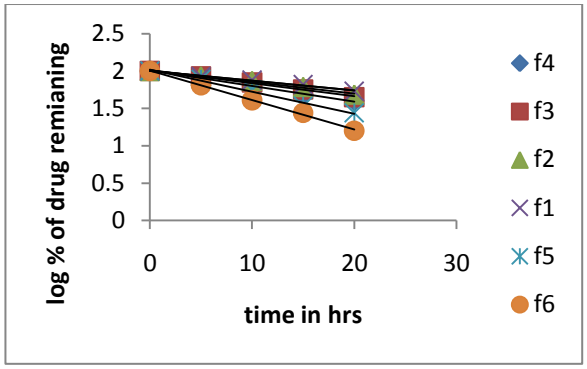

Fig 6 first order plots for formulations F1-F6

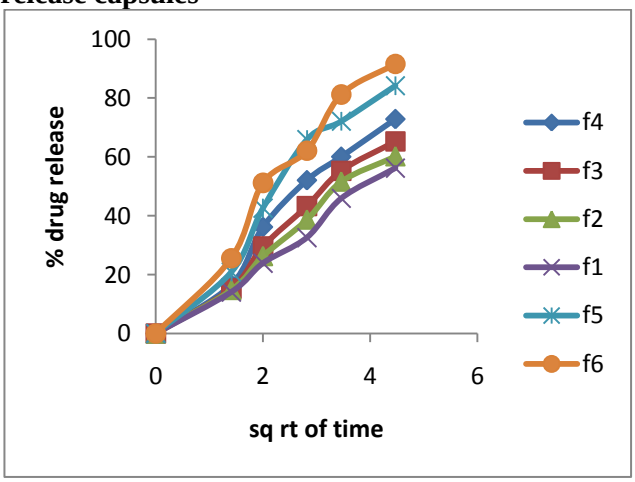

Fig 7 Higuchi plots for formulations F1-F6

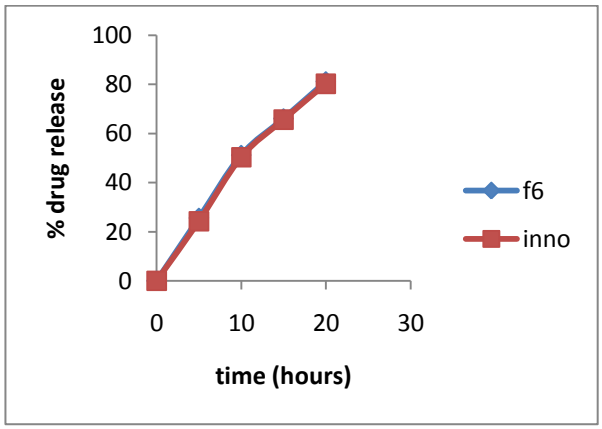

Fig 8 comparison of optimized formula and innovator product

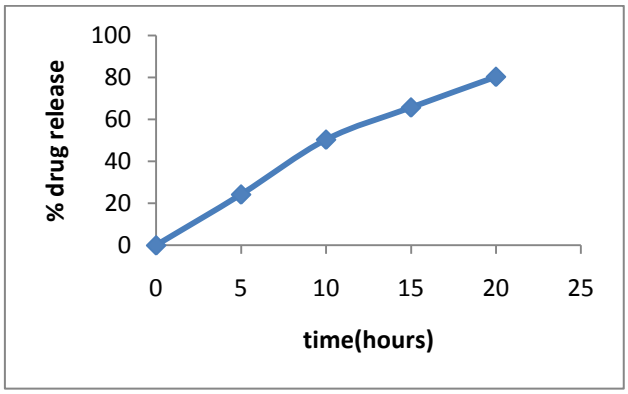

Fig 9 drug release profiles of venlafaxine capsules after stability studies

4. CONCLUSION

Venlafaxine pellets prepared by solution/suspension layering technique using the mixture of polymers such as EC 10 cps and HPMC was found to be relatively more efficient. These capsules can be used as such for oral controlled delivery of venlafaxine up to 20 hrs.

REFERENCES

Adhimoolam Senthil, Thakkar Hardik Kumar Rajesh Bhai, Dave Mehulkumar Vinod Bhai, Lad Tejas Bharat Bhai, Bhagya Lakshmi Battu, Formulation and evaluation of mucoadhesive microspheres of venlafaxine, International journal of research journal of pharmacy, 2(4), 2011, 194-199.

Atul A. Bodkhe, Prashant Zurao, Chandewar A.V, Jaiswal S.B, Designing and evaluation of extended release tablet of venlafaxine using hydrophobic matrix, Scholars Research Library, 2(1), 2010, 329- 335.

Aukunuru Jithan, oral drug delivery technology, Pharma book syndicate, 2007, Oral formulation 165- 166.

Campbell J. A., Eino Nelson, and Chapman DG, Sustained Release Medication. *CANAD m.a.j*. July 1(81), 1959, 15-16.

Hardman Limbard Gilman; Good Man & Gilman's The Pharmacological Basis of Therapeutics 10th Edition; Mc Graw Hill, 2001, Drugs & The Treatment of Psychiatric Disorders, 457- 474.

Hiren P. Patel, Dr. J.K.Patel. Ravi R. Patel. Dr.Manish P.Patel, Pellets: A general overview. International Journal of Pharma World Research,1(2), 2010, 1-15

K. Sreenivasa rao, Jadhav Sunitha, Patil Prakash, B,U.Dattatraya, Development and evaluation of sustained release formulations of Venlafaxine hydrochloride, International journal of research in ayurveda & pharmacy, 2(3), 2011, 948-960.

Ladani Aniket , Dr.Patel Mandev, Patel Vipul, Fabrication of Multi-Layer Matrix Tablets of Venlafaxine Using Hypromellose and Xanthum gum, International Journal of Drug Develpoment & Research,3(3), 2011, 291-299.

Michael & Aulton, Aultons Pharmaceutics, The Design & Manufacture of Medicines, Churchil Living Stone, 3rd edition, 2011, Stability testing, 661- 664.

Radhika PR, Dedeepya Karanam, Sivakumar T, Fabrication of sustained release matrix tablets of venlafaxine hydrochloride using eudragits. *International journal of research in ayurveda & pharmacy*, 2(4), 2011, 1386-1389.

Shams ME, Arneth B, Hiemke C, Dragicevic A, Müller MJ, Kaiser R, Lackner K, Härtter S"CYP2D6. Polymorphism and clinical effect of the antidepressant Venlafaxine, J Clin Pharm Ther, 31 (5), 2006, 493–502.

Thomson, Physicians' desk reference, Thomsdon PDR, Motvale, NJ, 58th edition, 2004, 3413-3424.