Formulation development of sustained release swellable matrix tablet of venlafaxine HCl using a combination of hydrophilic and hydrophobic polymers

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Abstract

The objective of this work was to develop a sustained-release swellable matrix tablet of highly water-soluble Venlafaxine HCl. Venlafaxine is a unique antidepressant that differs structurally from other currently available antidepressants. The anti-depressive drug Venlafaxine HCl was selected as a model drug due to its low bioavailability &short biological half-life of 5 ± 2hrs. The tablets were prepared using the wet granulation method. Eudragit RSPO, HPMC K4M, and Glyceryl monostearate were used as the rate-controlling polymers. After the preparation of the matrix tablet, it was evaluated for physical characteristics such as hardness, friability, thickness, weight variation, drug content, and dissolution study. The in-vitro release profile of the optimized batch showed the sustaining ability of the drug for 12 hrs. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines and it displayed the stability for a given period.

KeyWords: Sustained release formulation, Venlafaxine HCl, HPMC K4, Eudragit RSPO, Glyceryl monostearate, matrix tablet.

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Introduction

A novel antidepressant Venlafaxine HCl is a bicyclic phenylethylamine derivative. It is a unique antidepressant used for first-line therapy in patients with major depression and agitated/retarded symptoms and treatment-resistant depression.[1] Venlafaxine HCl and its active metabolite, o-desmethyl venlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin, and to a lesser extent dopamine [2,3] but have no monoamine oxidase inhibitory activity and a low affinity for brain muscarinic, cholinergic, histaminergic, or alpha-adrenergic receptors. [4, 5]The recommended daily dose of Venlafaxine hydrochloride is 75 to 450 mg/day.[6] The steady-state half-lives of Venlafaxine and ODV are 5±2 and 11±2 hours, respectively, necessitating the administration 2 or 3 times daily so as to maintain adequate plasma levels of the drug.[6, 7] The half-life of Venlafaxine is relatively short, and, therefore, patients are directed to adhere to a strict medication routine & avoiding missing a dose. Even a single missed dose can result in withdrawal symptoms.[6, 8] The successful treatment of depression depends on the maintenance of an effective drug concentration level in the body for which a constant and uniform supply of the drug is desired. [11] In such cases, the formulation releasing the drug in a sustained manner will aid the patient to adhere to a strict medication routine by avoiding the need to take the dosage form 2 or 3 times daily.

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The use of sustain released formulation is associated with fewer adverse effects of nausea and

dizziness. [6, 9]The major objective of this study was to prepare matrix tablets of Venlafaxine HCl by using the wet granulation method, to characterize the physical and physico- chemical properties of the prepared tablets, and to study the in-vitro release pattern of these prepared tablets by using the Dissolution apparatus.

2. Materials and method

2.1 Materials

Venlafaxine HCl was obtained as a gift sample from Cipla Pharmaceutical Pvt. Ltd., Kurkumbh, Maharashtra, India. Hydroxy Propyl methyl cellulose Methocel® K4M was obtained as a gift sample from Colorcon Asia Pvt. Ltd. Mumbai, India. Eudragit RSPO was obtained as a gift sample from Evonik Degussa India Pvt. Ltd. Dicalcium phosphate was purchased from Research-lab Mumbai, India. Lactose and glycerol monostearate were purchased from Research-lab fine chem. Industries Mumbai, India. Magnesium stearate was purchased from Pure Chem. Laboratories Pune and talc were obtained from Analab fine chemicals, Mumbai, India. All other excipients and chemicals used were of analytical grade (AR).

2.2. Methods

2.2.1 Preparation of Venlafaxine matrix tablet

The sustained-release matrix tablets of Venlafaxine HCl were prepared using natural and synthetic polymers such as HPMC K4, Eudragit RSPO, and Glyceryl monostearate [11]. To improve therapeutic efficacy, systemic absorption, and patient compliance a sustained release matrix tablets of Venlafaxine HCl (VHl) has been developed. The best combination of polymers and their ratios were selected, and tablets were punched using the direct compression method [12].

2.2.1.a By using the hydrophilic and hydrophobic polymer

Sustained release matrix tablets, each containing 75 mg Venlafaxine were prepared by wet granulation method using hydrophilic and hydrophobic polymers. The composition of various formulations was shown in Table 1. Accurately weighed ingredients were passed through #60 mesh and geometrically mixed. Mixing was continued for 30 min to achieve uniform mixing and prepared a dump mass by slowly addition of water to the dry powder mixture. Then dump mass was passed through the 16 mesh to prepare granules. Prepared granules were mixed with glidant and lubricant talc and magnesium stearate in a blender for 10 min. The lubricated blend was then compressed into a tablet using 12mm standard concave punches on the Rotary tablet punching machine (12 stations Cip machinery lab press). Each tablet contains 75 mg of Venlafaxine, and the total tablet weight was 200mg. All tablet formulations were stored in an airtight container till further evaluation.

Table 1: Formulation composition of various batches with Eudragit and HPMC polymer

Ingredients	FI	FII	FIII	FIV	FV	FVI	FVII
Venlafaxine HCl	75	75	75	75	75	75	75
HPMC K4M	22	22	22	20	10	50	50
Eudragit RSPO	25	25	35	60	60	30	40
Lactose	70	-	-	-	-	-	-
DCP	-	70	60	35	45	37	27
Mg stearate	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5
PVP	2	2	2	2	2	-	-
Total weight (mg)	200	200	200	200	200	200	200

2.2.1.b By using the Glyceryl monostearate matrix forming agent

The sustained release tablet of venlafaxine HCl was prepared by using glyceryl monostearate. Weighed quantity of glyceryl monostearate melt in porcelain dish at 55°C and drug was added with continuous stirring. This mixture was then allowed to cool. It was further passed through sieve #16 to get the uniform powder and the remaining ingredients filler and lubricant were added to the powder blend with proper mixing and finally, tablets were compressed.

Table 2: Formulation composition of various batches with glycerol monostearate

Ingredient	GM 01	GM 02	GM 03	GM 04
Venlafaxine HCl	75	75	75	75
Glyceryl monostearate	40	30	45	50
Di-calcium phosphate	80	90	75	70
Magnesium stearate	2	2	2	2
Talc powder	3	3	3	3
Total weight (mg)	200	200	200	200

2.2.2 Physical characteristics

2.2.2. a Evaluation of powder blend

The powder blends were evaluated for flow property angle of repose, bulk density, tapped density, compressibility index, and drug content. [13] The angle of repose was determined by the fixed funnel method. Bulk and tapped density were determined by the cylinder method. Carr's Index (CI) value was calculated using the following equation:

Carr's Index = Tapped density-bulk densityx100/tapped density. ----eq. no.1

Hausner's ratio was also calculated to define the flow property.

Hausner's ratio = Tapped density/Bulk density ----eq. no.2

Evaluation of tablets

The prepared tablets were evaluated for their physical parameters like hardness, thickness, weight variation, friability, drug content, and Disintegration & Dissolution Study. Hardness was determined by a Monsanto hardness tester. Vernier caliper was used to measure the thickness & diameter of the tablets. The weight variation test was determined by weighing 20 tablets. The Friability study was conducted by using a Roche friability tester (Dolphin) on 10 tablets. [14]

2.2.2. b Dug Content Estimation

Tablets containing Venlafaxine HCl were crushed to a fine powder. Weighed accurate quantity of powder equivalent to 75 mg of Venlafaxine HCl was transferred to a 100mL volumetric flask containing 6.8 phosphate buffer. The solution was then mixed properly and sonicated for 30 minutes. Buffer was added slowly until a clear solution was obtained. The final volume was made up to 100 with the same buffer. This solution was further filtered through Whatman filter paper No. 41 and subsequently diluted for analysis purposes. Drug content was determined by using a double beam UV-spectrophotometer V-630(Jasco) at 225 nm. The drug content was calculated using the standard plot concentration vs absorbance.

2.2.2. c In vitro drug release

In vitro drug release was carried out using a USP type II dissolution apparatus containing 900mL of 0.1 N HCl for 2 hours and then 6.8 pH phosphate buffer as a dissolution medium. The speed of the basket was 50 rpm at a temperature of 37 ± 0.5°C. Five ml of aliquot was withdrawn at specific time intervals and absorbance was recorded using a UV spectrophotometer at 225 wavelengths. [16, 17]

2.2.2.d Accelerated stability study of tablets:

The stability study was done on drug products under different storage conditions. To check the quality of drug products under influence of a variety of environmental factors such as humidity, temperature, and light. A stability study was done according to ICH guidelines. ICH specifies the length of study and storage conditions.

Study	Temperature	Humidity	Time
Long-term testing	25ºC ± 2ºC	60% RH ± 5%	12 months
Accelerated testing	40ºC ± 2ºC	75% RH ± 5%	6 months

The selected formulation was packed in polythene by hand sealed bag and stored at 25ºC ± 2ºC / 60% RH ± 5% and 40ºC ± 2ºC / 75% RH ± 5% for 3 months and evaluated for their physical appearance, drug content, and drug excipients compatibility study on monthly basis. (18, 19)

3. Results & Discussion

3.1 Evaluation Of Pre-Compression Parameter Of Granules:

Table 4: Physical Properties of all granules

Formulation	Angle of repose (Θ) ± SD	Bulk density ± SD	Tapped density ± SD	Carr's Index ± SD	Hausner's Ratio ± SD
FI	29º ± 2	1.66 ± 0.025	1.91 ± 0.020	13.70 ± 0.02	1.166 ± 0.003
FII	24.33º ± 2.08	1.67 ± 0.036	1.95 ± 0.03	14.34 ±0.026	1.167 ± 0.0032
FIII	20º ± 2.64	1.65 ± 0.032	1.92 ± 0.02	14.50 ± 0.01	1.149 ± 0.002
FIV	17.66º ± 1.53	1.64 ± 0.02	1.89 ± 0.03	13.23 ± 0.04	1.152 ± 0.0031
FV	26º± 1.73	1.66 ± 0.036	1.90 ± 0.04	14.73 ±0.035	1.172 ± 0.004
FVI	27º ± 3	1.68 ± 0.005	1.91 ± 0.025	12.00 ±0.025	1.136 ± 0.0025
FVII	22.33º ± 2.08	1.61 ± 0.020	1.88 ± 0.035	14.36 ± 0.02	1.156 ± 0.0033

3.1.1. Angle of repose:

The values obtained for the angle of repose for all (FI-FVII) formulations are tabulated in table no.4. The values were found to be in the range from 18º-29º. This indicates good flow property of the granules for all formulations.

3.1.2. Compressibility index:

The value obtained for the compressibility index for all (FI-FVII) formulations are tabulated in table no. 4. Compressibility index value ranges between 12.01% -14.73% indicating that the granules have the good flow property for compression of all formulations.

3.1.3. Hausner's ratio:

The values obtained for Hausner's ratio for all (FI-FVII) formulations are in table no. 4. Hausner's ratio values range between 1.136-1.172 indicating that the granules have the desired flow property for compression of all formulations. All the pre-compression parameters of all formulations were found to be satisfactory; the granules show good flow properties for compression.

3.2. Evaluations of the tablets for physicochemical characteristics.

Table 5: Physical properties of all Formulation

Formulations	Diameter (mm) ± SD	Thickness (mm) ± SD	Weight-variation (mg) ± SD	Hard-ness(kg/cm2) ± SD	Friability (%) ± SD	Drug content (%) ± SD
FI	8.44 ± 0.028	2.75 ± 0.031	200.2 ± 2.38	7.36 ± 0.018	0.53 ± 0.019	98.13 ± 0.024
FII	8.54 ± 0.015	2.86 ± 0.016	200.0 ± 1.92	5.54 ± 0.024	0.65 ± 0.020	98.90 ± 0.028
FIII	8.46 ± 0.022	2.85 ± 0.029	199.4 ± 2.40	4.36 ± 0.027	0.58 ± 0.019	97.31 ± 0.019
FIV	8.45 ± 0.032	2.78 ± 0.015	198.6 ± 2.30	6.62 ± 0.031	0.57 ± 0.015	97.89 ± 0.019
FV	8.432 ± 0.019	2.91 ± 0.016	199.2 ± 3.11	5.83 ± 0.031	0.62 ± 0.0152	98.68 ± 0.018
FVI	8.458 ± 0.038	2.85 ± 0.019	199.8 ± 1.48	6.76 ± 0.033	0.71 ± 0.0158	97.50 ± 0.019
FVII	8.468 ± 0.043	2.81 ± 0.015	201.2 ± 2.38	6.91 ± 0.023	0.54 ± 0.019	98.35 ± 0.023

3.2.1. Shape of the tablet

Microscope examination of tablets from each formulation batch showed a circular shape with no cracks.

3.2.2. Tablet dimensions

Tablets' mean thicknesses were almost uniform for all the formulations and were found to be in the

range of 2.75mm - 2.91mm. The diameters of all the tablets range from 8.43-8.47mm.

3.2.3. Weight variation test

All the tablets passed the weight variation test the values were found to be 198.6-201.2mg and the standard limit is 130-324mg maximum difference allowed is 7.5 mg. as the % weight variation was within the Indian Pharmacopeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

3.2.4. Hardness test

The measured hardness of tablets of each batch was within the range 4.36kg/cm2 - 7.36kg/cm2. Tablet hardness was increased as increasing the compression force. This ensures good handling characteristics of all formulations.

3.2.5. Friability test

The % Friability was NMT 1% in all the formulation ensuring that the tablets were mechanically stable.

3.2.6 Drug content

The percentage of dug content was found to be between 97.31% - 98.90% of Venlafaxine HCl, which was within acceptable limits.

3.2.7 In-vitro drug release studies using phosphate buffer pH6.8:

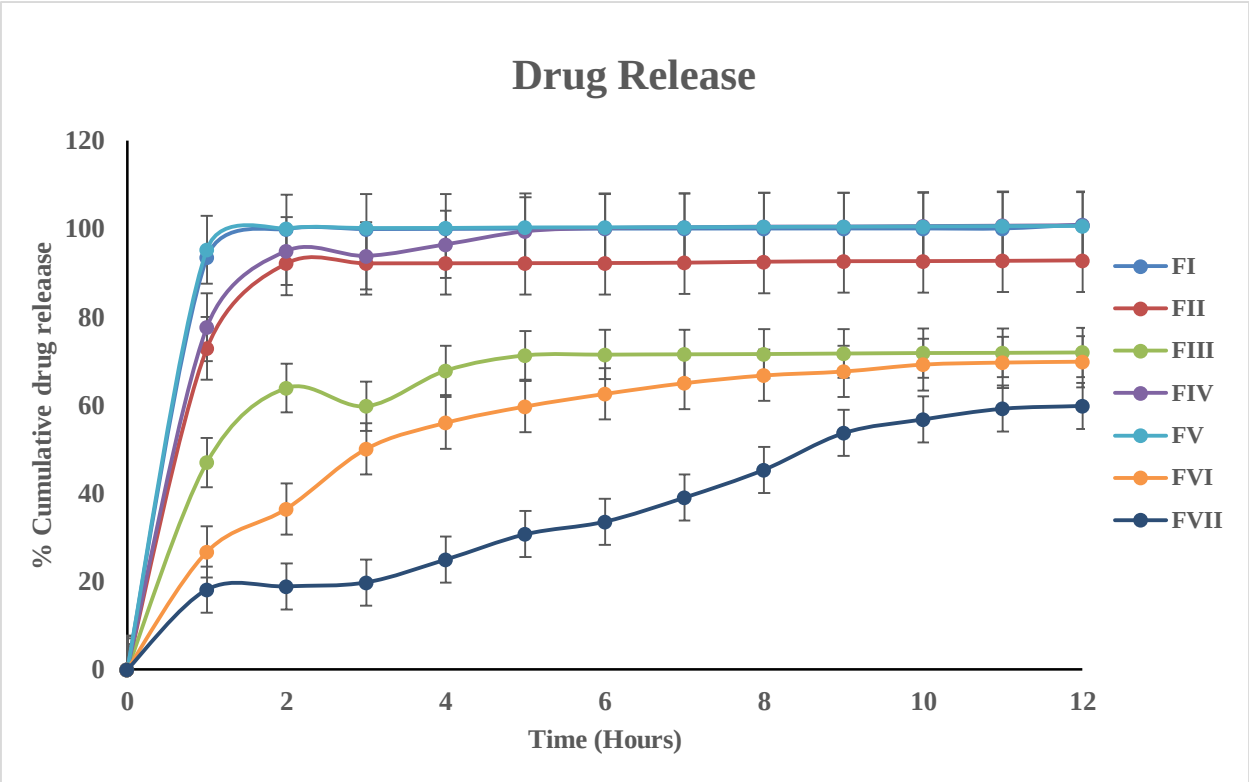

Figure 3: Dissolution profile plots of FI to FVII

The in-vitro drug release of the Venlafaxine HCl matrix tablet is carried out in the USP type-II apparatus by using phosphate buffer pH 6.8. The dissolution profile values of all formulations are shown in table no.6. The graph of % cumulative drug release v/s time (hrs) is shown in figures no.3, 4. In the formulation containing lactose was dissolved in 2 hrs showing a drug release of about 99.98%. In the next formulation, lactose was replaced with dicalcium phosphate. In the second formulation, the tablet completely dissolved in 5hrs with a cumulative release of about 92.18% (FII). The quantity of polymer Eudragit RSPO was increased in the next formulation FIII. It displayed the cumulative release of about (FIII) 71.31% in 5 hrs. But the % CR was slightly decreased so in the next formulation (FIV) higher quantity of hydrophobic polymer Eudragit RSPO was taken and the quantity of hydrophilic polymer such as HPMC K4 was decreased. In the formulation (FIV) % CR

values were 95.01% (FIV) 109.63% in 9 hrs. In this formulation, the time is more but the %CR is also high so again decreases the quantity of polymer such as HPMC K4 was decreased (FV). It showed a cumulative drug release of about 108.68% (FV) in 4 hrs. In this formulation quantity of Eudragit RSPO was kept constant. The quantity of hydrophobic polymer such as Eudragit RSPO was decreased and the quantity of hydrophilic polymer HPMC K4 was increased in the next formulation (FVI). In the formulation (FVI) the values of % CR was (F6) 69.22% in 10 hrs. In this formulation quantity of Eudragit RSPO was slightly decreased so the total %CR was 100% in 10 hrs. Hence, for getting sustained release the quantity of HPMC K4 was increased in the next formulation (FVII). In this formulation total %CR was 93.48% in 12 hrs. Thus, it was selected as the final optimized formulation.

From the results, it was observed that increasing the amount of polymer in the formulations, resulted in an increased rate and decreased amount of drug release from the tablet. In the combination of HPMC K4 and Eudragit RSPO polymer-based tablets, the release of the drug was found to be faster. The maximum drug release was found to be 93.48% over a period of 12 hours in the combination of a hydrophilic polymer and hydrophobic polymer such as hydroxy propyl methyl cellulose and Eudragit RSPO respectively (FVII). This indicates that the minimum quantity of hydroxy propyl methyl cellulose and maximum quantity of Eudragit RSPO are required to prepare the sustain release matrix tablets of Venlafaxine HCl.

The formulation FVII was compared with the prolonged-release marketed product by conducting a comparative in vitro dissolution study. The marketed product (Venlor XR 37.5) Manufactured by Cipla Ltd. KumrekRangposhikkim, India showed 60.21 % drug release at 12 hrs while formulation FVII showed a drug release of 85.18 % for 12 hrs. In vitro dissolution profile of the marketed product in comparison to the formulation was shown in figure no. 4.

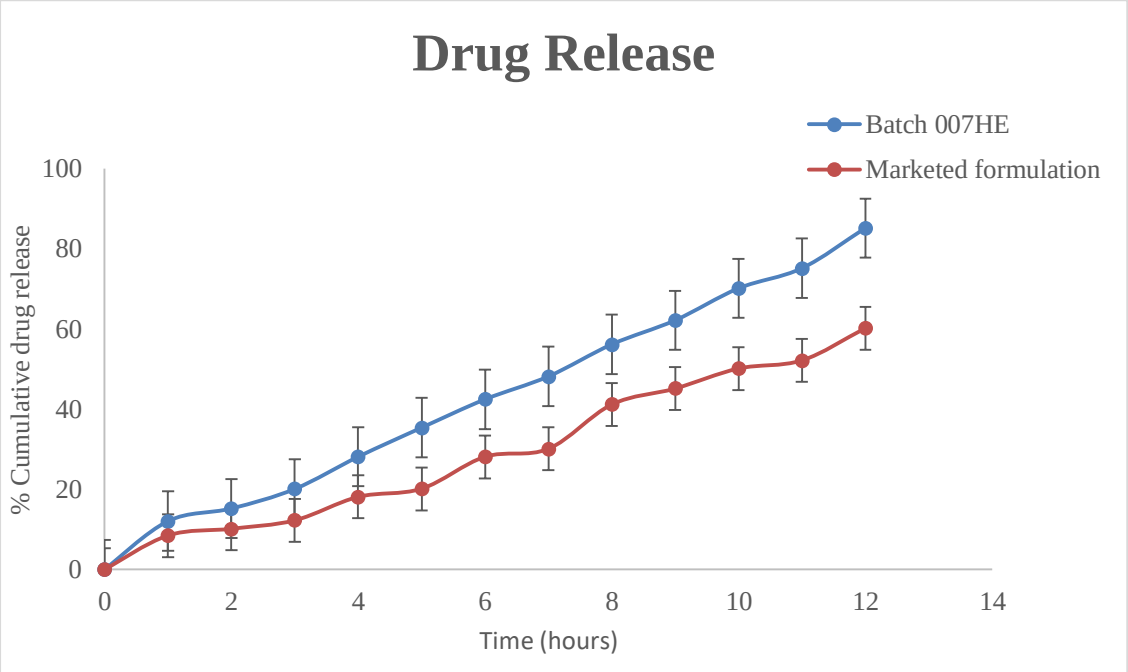

Figure 4: Comparison of Drug release profile with marketed formulation

Formulated FVII had better-sustained drug release in comparison to the marketed product. Thus, it could be concluded that when HPMC K4 and Eudragit RSPO were taken at the concentration of 50:40 and formulated by the wet granulation method showed better and sustained release.

3.3 Stability study: - Stored at 25ºC / 60% RH:

Table 7: Evaluation parameter for stability study at 25ºC / 60% RH.

Para-meter	Diameter(mm)	Thick-ness (mm)	Weight-variation (mg)	Hard-ness(kg/cm2)	Friability (%)	Drug content (%)
Initial batch	8.46 ± 0.021	3.05 ± 0.029	200.2 ± 1.49	6.2 ± .05	0.60 ± 0.056	99.58 ± 1.58
1 month	8.47 ± 0.020	3.09 ± 0.035	201.3 ± 1.53	6.6 ± 0.7	0.63 ± 0.076	98.07 ± 1.64
2 month	8.45 ± 0.018	3.10 ± 0.032	199.8 ± 1.56	5.9 ± 0.2	0.59 ± 0.072	98.88 ± 1.66

Stored at 40ºC at 75% RH:

Table 8: Evaluation parameter for stability study at 40ºC/75% RH.

Para-meter	Diameter(mm)	Thick-ness (mm)	Weight variation (mg)	Hard-ness(kg/cm2)	Friability (%)	Drug content (%)
Initial Batch	8.45 ± 0.013	3.15 ± 0.029	199.8 ± 1.98	6.1 ± 0.4	0.59 ± 0.060	98.98 ± 1.09
1 month	8.48 ± 0.015	3.19 ± 0.036	202.6 ± 2.51	5.96± 0.8	0.57 ± 0.070	98.48 ± 0.62
2 month	8.49 ± 0.018	3.13 ± 0.034	200.5 ± 1.88	6.4 ± 0.18	0.71 ± 0.055	97.99 ± 0.89

4. Conclusion

Venlafaxine HCl sustained release matrix tablet was successfully formulated with HPMC K4M and Eudragit RSPO as matrix former polymer. An optimum concentration of HPMC K4M and Eudragit RSPO in combination was able to provide the desired release with the innovator profile requirement. Dissolution matrix-controlled release was found to be a mechanism for drug release from optimized formulation. The developed formulation is expected to reduce the frequency of administration thereby reducing the chance of adverse effects associated with frequent administration of Venlafaxine HCl tablets.

References

Ladani Aniket, Dr. Patel Mandev, Patel Vipul, Fabrication Of Multi-Layer Matrix Tablets Of Venlafaxine Hydrochloride Using Hypromellose And Xanthan Gum, International Journal Of Drug Development & Research, July-September 2011, Vol. 3,Issue 3,Issn 0975-9344,Pg.No:291-299.

Muth E.A., Moyer J.A., J.T. Haskins, Andree T.H. and Husbands G.E.M., Biochemical, neurophysiological and behavioural effects of Wy-45,233, its enantiomers and other identified metabolites of the antidepressant venlafaxine, Drug Dev. Res., 1991, 23, 191–199.

Cusack B., Nelson A. and Richelson E., Binding of antidepressants to human brain receptors: focus on newer generation compounds, Psychopharmacol. 1994, 114,559–565.

Muth E.A., Haskins J.T., Moyer J.A., Husbands G.E., Nielson S.T. and Sigg E.B., Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ether cyclohexanol derivative, Biochem. Pharmacol. 1986, 35, 4493–4497.

Madgulkar A.R., Bhalekar M.R., Kolhe V.J. and Kenjale Y.D., Formulation and optimization of sustained release tablets of venlafaxine resonates using response surface methodology, Indian J. Pharm. Sci., 2009, 71, 387-394.

Saltiel E, Ellrodt,Gray A, Monk, John P, Langley, Mark S. A Review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. Drugs 1988; 36: 387-428.

Olver JS, Burrows GD, Norman TR. The treatment of depression with different formulations of Venlafaxine: a comparative analysis. Human psychopharmacology 2004; 19: 9-16.

Rowe RC, Sheskey PJ, Weller PJ. Xanthan Gum. Handbook of Pharmaceutical Excipients, 4th Edition. London Pharmaceutical. 2003; 691-693.

Bariya SH, Gohel MC. Fabrication of triple layer Matrix Tablets of Venlafaxine Hydrochloride using Xanthan Gum. AAPS Pharm Sci Tech, Jun 2009; 10 (2): 624-630.

Darphade SM, Shejul AA, Tathe PR and Biyani KR, Formulation and characterization of sustained release matrix Tablet of Metoprolol Succinate by using combination of natural and synthetic polymer, International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 4 (3) Jul–Sep 2013, pg.no:901-906.

Dheeraj Baviskar1, Rajesh Sharma and Dinesh Jain, Modulation of drug release by utilizing pH-independent matrix system comprising water soluble drug verapamil hydrochloride, Pak. J. Pharm. Sci., Vol.26, No.1, January 2013, pp.137-144.

Hadjiioannou T.P., Christian G.D., Koupparis M.A. and Macheras P.E. Quantitative Calculations in Pharmaceutical Practice and Research, VCH Publishers Inc., New York,1993 pp.345-348

Indian Pharmacopiea , Government of India, Ministery of Health and Family welfare, 4th edition, New Delhi. The controller of publication; 1996.

Bourne D.W.A., Pharmacokinetics. In: Banker GS, Rhodes CT,

Modern Pharmaceutics, 4th ed., Marcel Dekker Inc., New York, 2002, 67-92.

Lavanya K, Sunitha P, Anil Kumar A, Venkata Ramana K, New Simple UV Spectrophotometric Method For Determination of Venlafaxine Hydrochloride in Bulk And Pharmaceutical Dosage Forms, Research Article, International Journal of Pharmaceutical Quality Assurance; Vol4,Issue1, January-March 2013, 1-3.

United State Pharmacopoeia -34 National Formulary – 29 2011, volume - I, page no: 281-282.

A. H. Beckett and J. B. Stenlake, Practical Pharmaceutical Chemistry, 4th edition, Part- II, pg. no: 379-405.

Lachman Leon, Lieberman H.A. and Kanig J.L, The theory and Practice of industrial pharmacy 3rd edition, Varghese publishing house Bombay, 296-302.

International Conference on Harmonization (ICH), Harmonized Tripartite guidelines for stability testing of new drugs substances and products Q1A (R2) 2003 feb6.