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Formulation and In Vitro Evaluation of Sustained Release Matrix Tablets of Venlafaxine

Abstract

Sustained release matrix tablets of venlafaxine were formulated using synthetic polymers (ethylcellulose & hydroxypropyl methylcellulose). Six (06) different batches of matrix tablets of venlafaxine (dose 75 mg) were prepared by the wet granulation method. Polymers were used alone or in combination. The physical properties of compressed tablets were evaluated. In vitro release drug studies were performed in phosphate buffer at pH 6.8 over 24 hours. The drug release data fitted well to the First order (R2 = 0.9725 – 0.9900). The n value obtained for most batches ranged from 0.523 to 0.946 indicates that the drug is released through an anomalous or non–Fickian transport. Results revealed that the combination of ethyl cellulose (EC) and hydroxypropyl methylcellulose produced a sustained effect compared to hydroxypropyl methylcellulose alone. Formulation F6 containing single polymer (EC) showed the highest control over initial burst release and extended release of the drug continued up to 16 hours.

Key Words: Sustained Release Matrix Tablets, Venlafaxine, Ethyl Cellulose (EC), hydroxypropyl methylcellulose

Introduction

Oral solid dosage forms are preferred products among all orally administered drugs as i) they consist of unit dosage, ii) they have the greatest capabilities for the maximum dose accuracy, low content variability and cost-effectiveness among all dosage forms, iii) they are light in weight, show good compactness and product identification, as no more processing is required when using a monogrammed punch, iv) they provide ease of swallowing and the low tendency for the drug to hang up over the stomach, particularly when coated, v) they show best physical, chemical and microbiological stability (Lachman *et al.*, 1976).

Oral sustained release drug delivery systems are generally divided into reservoir system, monolithic system and matrix system. Hydrophilic matrix systems get more preference among these systems because of their good compression properties, even when compressed directly and have sufficient swelling characteristics that result in rapid external layer formation, thus modifying drug release (Patil *et al.*, 2010). Among different approaches, the simplest and most commonly used system, as mentioned above, is the hydrophilic matrix system. When a hydrophilic matrix tablet is administered, initially, drug release occurs from swelling, and then a gel layer is formed on the tablet surface. Drug release is retarded by this gel layer. The swelling and sometimes erosion of the polymer matrix contribute to the overall drug release rate. The use of hydrophilic gums can be investigated to evaluate the release of active ingredient for an extended period of time

(Varshosaz *et al.*, 2006).

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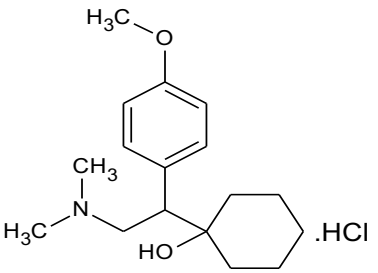

Figure 1: Structural formula of venlafaxine hydrochloride

Venlafaxine is an antidepressant drug molecule introduced by Wyeth in 1993. It is a prototype of selective serotonin nor-epinephrine reuptake inhibitor (SNRI). Venlafaxine is prescribed for treatment of major depressive disorder (MDD), generalized anxiety disorder, and combined indication for anxiety with depression like panic disorder, social phobia and diabetic neuropathy (Aboelwafa *et al*., 2010). Venlafaxine is a commonly prescribed antidepressant drug. In 2007, there were 17.2 million prescriptions of venlafaxine on the US retail market (Top 200 generic drugs by units in 2007 &. (Dahmen *et al*., 1999). Venlafaxine show better efficacy and tolerability than tricyclic antidepressants (TCA) in preventing the migraine attacks. Venlafaxine is effective in the treatment of chronic and acute pain and neurotoxicity in diabetic patients (Durand *et al*., 2011).

The study was designed to evaluate the oral modified release system in vitro that will have capability to maintain plasma level of venlafaxine for prolonged period of time which in turn will reduce the inconvenience and side effects associated with conventional immediate release dosage form of venlafaxine and develop a polymeric oral matrix sustained release tablets for venlafaxine for once daily dosage regimen. To develop a suitable once daily dosage regimen for better compliance and reduce the overall cost of therapy and to evaluate sustained release potential of hydroxy propyl methyl cellulose and ethyl cellulose for highly water-soluble antidepressant drug.

Materials and Methods

Materials

Venlafaxine was obtained as a gift sample from Mass Pharma Pvt. Ltd, Lahore, Pakistan. Ethyl cellulose (EC) and hydroxy propyl methyl cellulose (HPMC) were purchased from Sigma-Aldrich Chemie (Buchs, Germany). Lactose monohydrate was purchased from Merck Chemicals (Karachi, Pakistan). Talc and magnesium stearate were obtained as gift from Novamed Pharmaceuticals, Lahore, Pakistan. Other ingredients like polyvinylpyrrolidone (PVP-K30), isopropyl alcohol (IPA), hydrochloric acid, and disodium hydrogen phosphate anhydrous were purchased from Merck Chemicals (Karachi, Pakistan).

Methods

Preparation of Sustained Release Matrix Tablets

The wet granulation method was employed for the preparation of sustained-release matrix tablets, and the composition of formulations is given in **Table 1.**

Granulation

All ingredients were screened through USP sieve No. 20 before processing. The ratio of the polymers and the amount of lactose for each batch is shown in Table 1. Concentration of venlafaxine (75mg), PVP K-30 (10mg), talc (2mg), aerosil 10mg and magnesium stearate (2mg) were kept constant in all formulations. Twelve (12) different batches of granules were manufactured by the wet granulation technique. In the preparation of granules, no disintegrating agent was added to the powder mixture in order to avoid the early breakdown of the matrix tablets. A mixture of all ingredients except the lubricant and glidant were mixed in a porcelain mortar using PVP K-30 with ethanol as a granulating solution until a damp mass was formed that easily broke into lumps (not powder) when pressure was applied to it using the thumb. The wet mass was passed through sieve No. 8 to form wet granules. These granules were passed through sieve No. 20 after drying for 1hr at room temperature and then at 50°C in an oven. The dried granules were finally compressed into tablets (Chandrasekhar *et al*., 2011).

Table 1. Formulation Composition of Venlafaxine 75 mg Sustained Release Matrix Tablets

Code	Venlafaxine (mg)	HPMC(mg)	Lactose (mg)	EC (mg)	Aerosil (mg)	PVP (mg)	Talc (mg)	Magnesium Stearate(mg)
F1	75	100	125	-	10	10	2	2
F2	75	150	75	-	10	10	2	2
F3	75	200	25	-	10	10	2	2
F4	75	100	50	75	10	10	2	2
F5	75	75	25	125	10	10	2	2
F6	75	-	-	225	10	10	2	2

Compression

Matrix tablets of venlafaxine, each containing 75mg of active, were developed by compressing dry granules of six different batches using a single punch tablet machine fixed with concave punches and a die set. Talc and magnesium stearate were used as glidant and lubricant, respectively. The lubricant and granules were hands mixed for 5 min in a polythene bag, after which the granules were put in a metallic tray just before compression (M. Ali *et al*., 2010). In each batch, the average weight of the tablet was kept at 324 mg. For each formulation, more than 200 tablets were prepared and then subjected to various evaluation tests in vitro.

Evaluation of Matrix Tablets

Physical Evaluation

Physical parameters like appearance, weight variation, hardness, friability, thickness and content uniformity were evaluated for all batches of tablets according to pharmacopeial standards. These tests are performed as follows.

Weight Variation Analysis

For the weight variation test, the individual weight of twenty tablets was taken by weighing each tablet on an analytical weighing balance (Ohaus corp. the USA), and then twenty tablets were weighed collectively. To get the average weight following formula can be used.

$$\textbf{Average weight of tablet} = \frac{\textbf{Weight of 20 tablets}}{\textbf{20}}$$

Hardness Analysis

Hardness of twenty tablets from each batch was measured by using Monsanto Hardness Tester and then average hardness was calculated by the following formula:

$$\textbf{Average hardness of tablet} = \frac{\textbf{Hardness of 20 tablets}}{\textbf{20}}$$

Friability Analysis

The weight of twenty tablets from each batch was measured accurately on analytical weighing balance and then tested for friability using Roche friabilator. Weighed tablets were placed in the tumbling chamber and rotated at 25 rpm for 4min. After the completion of the rotation, tablets were weighed again. Percentage friability was calculated as:

$$\textbf{Friability}(\%) = \frac{\textbf{Wi} - \textbf{Wf}}{\textbf{Wi}} \times \textbf{100}$$

Where W_i and W_f represent the weight of tablets before and after the test, according to compendium limits, less than 1.0% decrease in weight was acceptable.

Thickness Analysis

To evaluate the thickness of tablets, SS Vernier Caliper was used. From each formulation, twenty tablets were taken for measurement of thickness, and then their average value was taken as their thickness.

Content Uniformity Analysis

For this test twenty tablets from each batch were grinded to a very fine powder with the help of pestle and mortar. A quantity of powder equal to 75mg of drug was measured and assayed as described in USP.

In-vitro Drug Release Studies

Dissolution studies were performed in dissolution medium recommended by USP for sustained release venlafaxine tablets. Phosphate-buffered solution was prepared according to the procedure described in USP and applied for dissolution studies.

Preparation of Simulated Intestinal Fluid at pH 6.8

Purified water was taken in one litter conical flask, and 6.80g of disodium hydrogen phosphate anhydrous (NaH_2PO_4) and 0.896g of sodium

hydroxide were carefully weighed and transferred to the flask. The volume of the flask was made up of distilled water, and the flask was then kept on a magnetic stirrer at 500rpm until the contents were completely dissolved. pH of the buffer solution was checked using a pH-meter and adjusted by using dilute NaOH solution.

Dissolution Studies

Dissolution studies are mandatory requirements in development and evaluation of sustained release formulations. Dissolution studies were conducted using USP apparatus II at 50rpm and 37 ± 0.5°C. In each vessel, 900ml of dissolution medium (Phosphate buffered solution at pH 6.8) was added. Six tablets from each formulation were subjected to dissolution studies. Each tablet was placed in the bottom of dissolution media carefully at the same time and then system was started. The samples were taken at predetermined time intervals of 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24h. Each sample of 5ml was withdrawn dissolution medium and was replaced with equal amount of fresh buffered solution. Sample was suitably diluted, and an absorbance reading was taken at 226nm wavelength using UV spectrophotometer.

Standard Solution of Venlafaxine

Standard solution was prepared, by taking 75mg of venlafaxine in 900ml of phosphate buffer solution of pH 6.8. Absorbance of resulting standard solutions was determined by using UV-visible spectrophotometer Schimadzu) at 226nm wavelength. To determine cumulative percent drug release at various time intervals, absorbance of sample solutions was compared with absorbance of standard solution. Formula employed is:

$$\textit{Percent Drug Release} = \frac{\textit{Absorbance of sample solution}}{\textit{Absorbance of standard solution}} \times 100$$

Fourier Transform Infrared Spectrophotometry

Fourier transform infrared (FTIR) spectrum using attenuated total reflectance (ATR) technology for drug, a drug with EC, a drug with HPMC and drug with both polymers were taken using Bruker FTIR (Tensor 27 series, Germany) and opus data collection software was used to evaluate the interaction between drug and polymers. Small number of powdered samples were directly placed onto the pike miracle ATR cell in such a way that the sample covers the ZnSe crystal surface, and the arm of assembly is rotated so that a compact sample mass is formed onto the cell and scanned over a range of 4000 cm-1 to 400 cm-1. Before taking a spectrum of any sample, a blank background scan is performed with an empty cell plate. And then above procedure is repeated after placing the sample to be analyzed onto the pike miracle ATR cell.

Release Kinetics Analysis

Various mathematical kinetic models were applied to describe kinetics of drug release from developed matrix
tablets. The best suited model was selected on the basis of best fit experimental results. Dissolution data was determined, and data subjected to different distinct models i.e., zero-order, first-order and Higuchi to determine venlafaxine release kinetics. Furthermore, drug release behavior from venlafaxine matrix tablets was further characterized by Korsmeyer–Peppas model [28]. Models are given by Equations 1(zero-order), 2(first order), 3(Higuchi) and 4(Korsmeyer–Peppas), respectively:

$$Q_t = k_0 t \quad (1)$$

$$\log Q_t = \log Q_0 k_1 t \quad (2)$$

$$Q_t = k_H t^{1/2} \quad (3)$$

$$\frac{Mt}{M\infty} = k_{KP} t^n \quad (4)$$

where Q_t is the amount of drug released at time t; Q_0 is initial amount of drug in the formulation, k_0, k_1, k_H, and k_{KP} are release rate constants for zero-order, first-order, Higuchi and Korsmeyer–Peppas models, respectively. In Equation 4, M_t and M_∞ are the amount of drug released at time t and ∞, while n is, the diffusion coefficient.

Results

Weight Variation Analysis

All formulations were subjected to weight variation analysis, and results are compared with USP acceptance criteria. Data obtained from this test are shown in **Table 2**.

Table 2. Results of Weight Variation Analysis of Venlafaxine tablets

Weight Variation Analysis				
Formulations	Average weight (mg)	Maximum weight (mg)	Minimum weight (mg)	USP Acceptance Criteria (Standard±5%)
F1	326.4±1.24	347.06	306.48	299..00 to 348.00
F2	316.25±1.59	328.19	312.7	299..00 to 348.00
F3	334.7±2.2	334.03	301.73	299..00 to 348.00
F4	330.55±1.72	341.12	3017.92	299..00 to 348.00
F5	323.42±1.13	344.17	324.5	299..00 to 348.00
F6	311.23±1.65	337.24	307.4	299..00 to 348.00

Hardness Analysis

To measure hardness of all sustained release formulations Monsanto hardness tester was used. Hardness of twelve batches of sustained release tablets of venlafaxine is shown in **Table 3.**

Table 3. Hardness of different Formulations of Sustained-Release Venlafaxine

Hardness Analysis			
Formulations	Mean force (kg)	Maximum force (kg)	Minimum force (kg)
F1	9.98±.43	12.2	10.2
F2	11.92±0.8	13.4	10.6
F3	12.68±0.56	13.8	10.7
F4	9.95±1.2	11.3	9.8
F5	10.13±0.51	12.6	10.2
F6	10.86±0.34	12.1	9.8

Friability Analysis

A Friability test was performed for all 12 formulations. USP states that acceptance criteria for friability test are less than 1% reduction in weight and all formulated tablets of venlafaxine were in acceptance limits, as shown in **Table 4.**

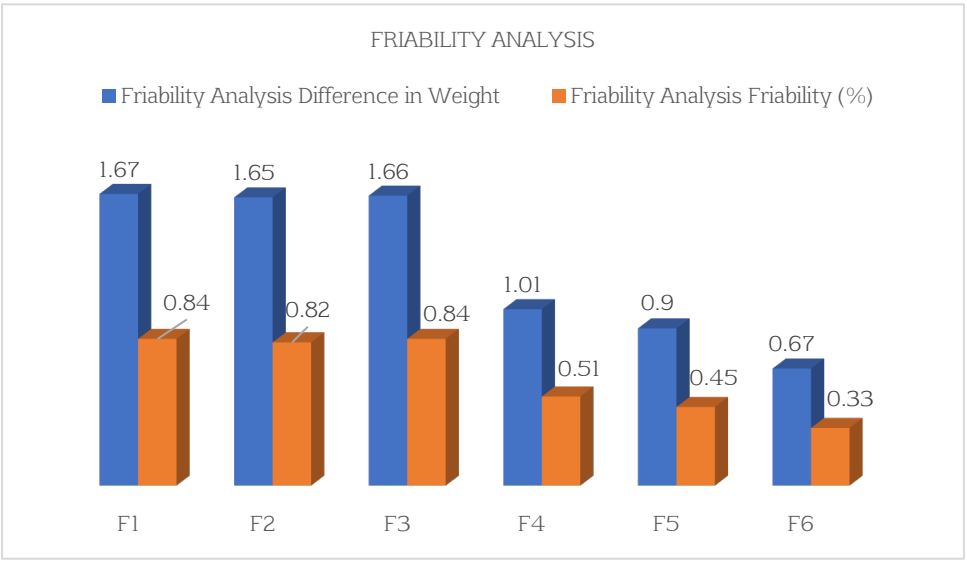

Figure 2 A: Friability Analysis

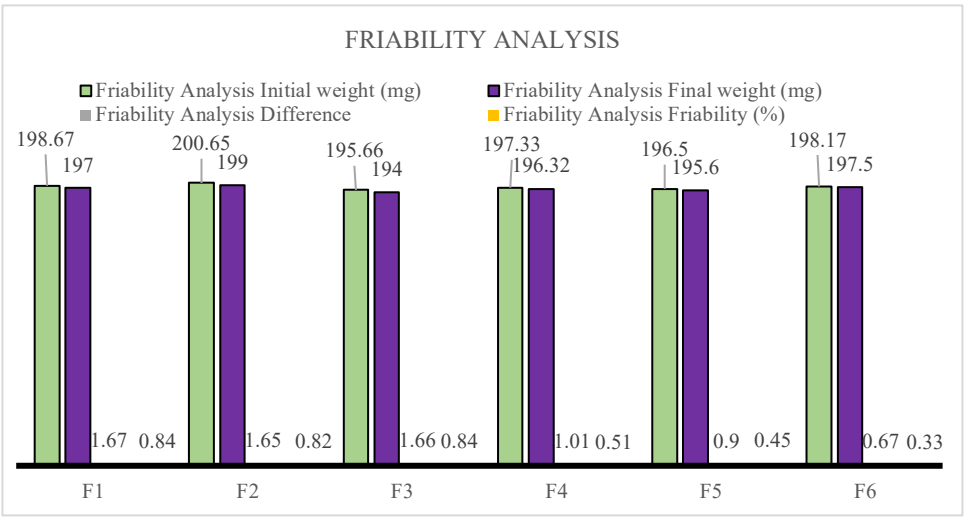

Figure 2 B: Friability analysis

Table 4. Friability Results for Matrix Tablets of Venlafaxine Developed by using different Proportions of EC and HPMC

	Friability Analysis			
Formulations	Initial weight (mg)	Final weight (mg)	Difference	Friability (%)
F1	198.67	197	1.67	0.84
F2	200.65	199	1.65	0.82
F3	195.66	194	1.66	0.84
F4	197.33	196.32	1.01	0.51
F5	196.5	195.6	0.9	0.45
F6	198.17	197.5	0.67	0.33

Thickness Analysis

Vernier calliper was employed for thickness evaluation of matrix tablets. Minimum and maximum thickness values were also determined. The thickness of different formulations of venlafaxine is given in **Table 5**.

Table 5. Thickness Analysis of Matrix Tablets of Venlafaxine

Formulations	Average thickness (mm)	Maximum thickness (mm)	Minimum thickness (mm)
F1	4.56±0.056	4.7	4.5
F2	4.59±0.062	4.7	4.6
F3	4.6±0.35	4.7	4.5
F4	4.51±0.73	4.6	4.4
F5	4.61±0.53	4.7	4.7
F6	4.5±0.046	4.6	4.5

Content Uniformity Analysis

From each batch twenty tablets were selected for content uniformity test and assayed using UV-spectrophotometer

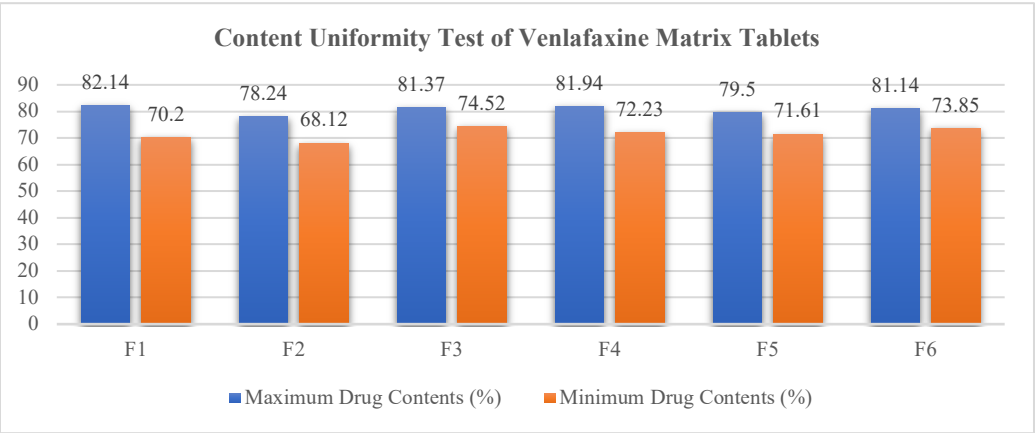

Figure 3: Content Uniformity

Table 6. Results of Content Uniformity Test of Venlafaxine Matrix Tablets

Formulations	Mean Drug contents (%)	Maximum drug contents (%)	Minimum drug contents (%)	USP acceptable criteria (Mean±15%)
F1	73.21±1.20	82.1.45	70.2	63.58 to 83.89
F2	76.33±1.29	78.24	68.12	66.52 to 86.14
F3	76.78±1.34	81.37	74.52	66.96 to 86.66
F4	76.41±0.96	81.94	72.23	66.65 to 86.17
F5	72.63±0.81	79.5.22	71.61	62.09 to 89.17
F6	75.05±1.31	81.14	73.85	65.59 to 85.51

In vitro Drug Release Studies

Release profile of all formulations was determined and shown in the following **Figure 4.**

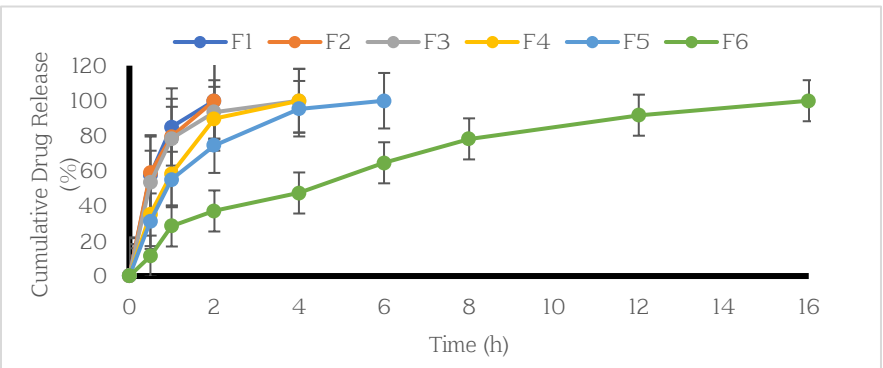

Figure 4: Cumulative percentage release of venlafaxine from 6 trials of matrix tablets. The release was studied in phosphate buffer pH over the period of 16 hours using USP type II apparatus.

Effect of Increasing Concentration of EC

Table 7 consists of three different formulations of sustained release tablets prepared with different polymer ratios and Figure 4.1 depicts their release profiles graphically. Effect of increasing concentration of polymers on the release pattern of drug was observed by considering such batches with increasing concentration of EC from lowest to highest level (F4, F5 &F6).

Table 7. Increasing concentration of EC in different formulations of venlafaxine

Formulations	EC (mg)
F4	75
F5	125
F6	225

Table 8. Increasing concentration of HPMC in different formulations of venlafaxine

Formulations	HPMC (mg)
F1	125
F2	75
F3	25

Release Kinetics for Sustained Release Matrix Tablets

For evaluation of release kinetics of sustained release matrix tablets of venlafaxine, DD Solver dissolution data modelling add-in program for MS-excel was used. Release data up to 24 hours of all formulations was subjected to different models, and results obtained after application of these models are given in **Table 9**.

Formulation code		F-1	F-2	F-3	F-4	F-5	F-6
Zero order	$k0$	3.649	3.310	3.051	4.797	4.154	3.852
	R^2	0.9769	0.9906	0.9968	0.7911	0.8670	0.9435
1st order	K_1	0.058	0.049	0.044	0.114	0.080	0.066
	R^2	0.9857	0.9840	0.9840	0.9660	0.9729	0.9858
Higuchi	K_H	14.307	12.866	11.747	19.557	16.742	15.277
	R^2	0.9174	0.8980	0.8727	0.9169	0.9360	0.9358
Korsmeyer-peppas	K_{kp}	6.378	4.756	3.565	15.680	11.797	8.496
	n	0.805	0.874	0.946	0.585	0.634	0.723
	R^2	0.9944	0.9970	0.9979	0.9274	0.9595	0.9859

Table 9. Kinetic Parameters of Various Models Applied

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectrum of venlafaxine, EC and tablets mixture (Figure 10) are revealed here.

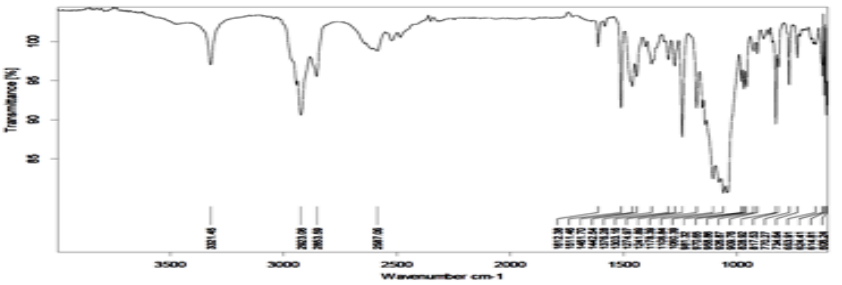

Figure 10: FTIR spectrum of EC and venlafaxine tablet matrix

Discussion

Controlled release matrix tablets of venlafaxine were prepared by wet granulation method by applying mainly HPMC and ethyl cellulose. Prepared matrix tablets were subjected to various evaluation tests. FTIR was used to evaluate compatibility. Ethylcellulose showed promising capability for the development of sustained-release formulations of highly water-soluble venlafaxine as compared to that of HPMC.

The uniformity of drug in dosage forms is usually determined by weight variation analysis (USP, 2004). Uniform loading of the drug is assured by weight variation analysis. In the production of tablets, powders having good compressibility and flowability are used. Irregular flow of powders produces changes in die filling and subsequently change tablet weight and potency (Prescott *et al.*, 1994). Weight variation analysis was performed for all batches of tablets formulated with various concentrations of polymers, shown that all tablets had uniform weight. It indicates the excellent flow properties of granules. Weight variation test gives scattering weights of individual tablets about average weight. United State Pharmacopoeia states that for uncoated tablets, the allowed percentage deviation for a tablet of weight greater than 250 mg is 5 %, and more than two of individual tablets should not deviate from average weight by more than allowed percentage deviation, and none should deviate by double permitted deviation. Table 2 shows that none of the batches of tablets failed the weight uniformity test. The average weight of tablet measured and falls in range as described in official weight variation tests. Weight variation indirectly helps to assure content or potency uniformity (S. Jain *et al.*, 2008).

An important physical property of the tablet is its mechanical strength which is manifested in terms of hardness. The pressure exerted on a tablet during its formation results in the form of the hardness of a tablet, and it depends upon the composition, shape, thickness and size of tablets. The shock of handling, packing and shipping can withstand only that tablet having proper hardness to ensure their strength. Thus, adequate hardness of the tablet is necessary requirement for its acceptance. Measurement of tablet hardness is particularly important for pharmaceutical products with possible bioavailability trouble (Atul *et al.*, 2010). Two other important factors affected by hardness are tablet disintegration and more significantly, the drug dissolution rate (Lieberman *et al.*, 1980). Under normal conditions, pressure variation by tablet press results in a hardness difference. In this study, all parameters of the compression machine were set equally, so it can be said that the nature and number of polymers employed in tablet production affected the hardness of tablets. Measured hardness values of 6 different formulation batches of sustained release matrix tablets of venlafaxine are shown in Table 3. It was observed that the hardness of tablets depends upon polymer concentration. Thus, value of hardness increases with increasing concentration of either polymer because of the good compressive behavior of polymers (Mughal *et al.*, 2011).

Friability is an assessment of the mechanical strength of a tablet and tablets ability to remain intact during transport stress. Good friability keeps the tablet in appearance acceptable to the patient. Friability depends on particle size distribution, moisture content and temperature (NAKABAYASHI *et al.*, 1980). Moisture may disturb inter-particulate bonds and enhance porosity to change tablet strength, thus changes friability. For user acceptance, sufficient resistance to friability is required. Friability tests are significant merely when they are correlated to the effect of packing equipment on tablets. For tablets with capping or breaking faults, friability cannot be evaluated. The maximum allowed weight loss for a batch of tablets subjected to a friability test is 1% (Commission, 2011). The ability of the tablet to resist pressure and damage linked with handling, packing and transportation is measured by the friability test. Nature and quantity of binder may affect this parameter of the tablet because binders give cohesive nature to particles in tablets. Percentage friability of matrix tablets of venlafaxine is shown in Table 4. which shows that percent friability of all the formulations is within acceptable limits. Results showed that there is no relation between the concentration of polymers and friability of tablets, so other factor involved may be compression force. The granules are packed together tightly by applying high compressional force, and weight loss during friability decreased (AHMED *et al.*, 2001).

Thickness evaluation is an important quality control test during production. The physical dimensions of tablets are very significant because of many reasons. Smooth and elegant packaging of tablets is possible with uniform thickness. If the thickness is not uniform, then the required number of thicker tablets becomes difficult to pack in container. Similarly, it becomes difficult to fit tablet in tablet's

pocket in case of unit dosage packaging. Tablet thickness can be set depending on the tablet weight. Majority of tablets vary from 2 mm to 5 mm depending on the diameter of the tablet. Twenty tablets were measured for their thickness and their mean value was taken as their thickness. All 6 batches were found to have average thickness ranges between 4.5±0.046 mm to 4.65±0.38 mm that is similar to results of past work by (Shah *et al.*, 2009).

UV-VIS spectroscopy was employed for the assay of all formulations of venlafaxine matrix tablets. According to the United States Pharmacopoeia (2002), sustained release matrix tablets of venlafaxine should have not less than 85.0% and not more than 115.0% of the labelled quantity of venlafaxine. Table 6 showed that the content of venlafaxine in the batches fell within acceptable official criteria as specified in USP.

Dissolution is the rate of mass transfer from a solid thing into dissolution medium or solvent under uniform conditions of liquid/solid interface, solvent composition and temperature. The main step of drug dissolution is the reaction of solid drug with components of dissolution media. This reaction occurs at the solid–liquid interface, and consequently, three factors are involved in dissolution kinetics, specifically flow rate of dissolution media toward the solid-liquid border, rate of reaction at interface and diffusion of dispersed or dissolved drug particles from the interface into bulk solution (Singhvi *et al.*, 2011). Figure 4 illustrate the graphical release profile of venlafaxine from sustained-release matrix tablets.

Release profiles of matrix tablets with varying amount of EC are represented in Table 7, from lowest to highest levels. F4, F5 and F6 contain 75, 125 and 225 grams of EC, respectively. Retardation effect on the release of drug was increased from low to high concentrations of EC polymer. Formulation F1containing 75mg of EC releases 100 5 venlafaxines within 6 hours. F2 formulation with 125mg EC releases 100% drug within 8 hours. However, when EC concentration was 225mg, the highest of all formulations, the sustained release effect was significant. 100% drug release occurred within 20 hours. The sustained release effect was delayed up to 16 hours. Burst effect, as well as sustained release behavior, was highly dependent on the EC ratio. EC is a hydrophobic polymer and has the capability to hinder water molecules for rapid penetration in matrix tablet. The initial burst of venlafaxine is due to the presence of the drug on the surface of the matrix. Afterwards, drug release is gradually sustained. Being highly water-soluble, it is very difficult to control the burst effect as well as to develop a sustained release formulation of venlafaxine. Conventional rapid release venlafaxine tablets are associated with severe gastric effects, non-compliance by patients, cessation of therapy and even suicidal attempts by patients. Therefore, all these results show that with an increase in the amount of EC, drug burst as well as sustained effect is decreased. This phenomenon may be attributed to the hydrophobic character of EC in the matrix tablet. Water penetration to hydrophobic matrix is decreased; thereby hydration and dissolution are reduced. Drug dissolves slowly and drug diffusion from matrix is slow and gradual. Sustained release of venlafaxine from F6 is up to 16 hours. F6 formulations can be easily applied for once-daily dosing (Shaikh et al., 2011). Therefore, the effective diffusion coefficient of the drug decreased and hence the release rate of the drug was retarded (Ford *et al.*, 1985) and (Varshosaz *et al.*, 2006). Formulations F1, F2 and F3 contain a very high concentration of HPMC, as shown in Table 8. Drug release was very rapid from these matrix tablets because of the high ratio of hydrophilic polymers. Burst effect was there as well as all drug released within 2 hours. Increasing HPMC concentration did not show a significant retard effect over the release of venlafaxine. This phenomenon may be explained by the hydrophilic nature of venlafaxine and HPMC. However, HPMC is famous for sustain drug release effect. However, HPMC sustains effect is practical either for hydrophobic or less soluble drugs. When drugs are the highly water-soluble, gelling or swelling effect of HPMC proves insufficient to control the burst of highly water-soluble drugs as well as ineffective for long tern sustain release. In our formulations, it looks like rater HPMC being hydrophilic promotes or aids in the rapid dissolution of venlafaxine. Figure 4 shows though used in a higher ratio, HPMC showed insignificant effects to slow release of venlafaxine and complete drug dissolution occurred within 2 hours (Al-Saidan *et al.*, 2005).

Release data of venlafaxine release was evaluated by zero-order, first-order, Higuchi and Korsmeyer peppas models as demonstrated in Table 9. All formulations of EC such as F4, F5 &F6 followed zero order drug release because of more linearity of regression line. Second best fit model is 1st order release pattern because values of regression coefficient (R^2) ranging from 0.9725 to 0.9900 for 3 formulations and graphs between percent cumulative

drug release and square root of time were almost linear. Therefore, mechanism of drug release from sustained release matrix tablets was diffusion controlled. Higuchi describes drug release as a diffusion process based on the Fick's law. This model can be employed to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems and matrix tablets with water soluble drugs (Suvakanta et al., 2010). Korsmeyer-Peppas equation was also applied on release data to determine release behaviour of drug from sustained release matrix tablets. Korsmeyer-Peppas model explains drug release from matrices, where "n" is release exponent and its value predicts mechanism of drug release from matrices. $0.45 \leq n$ corresponds to Fickian diffusion and non-Fickian when $0.45 \leq n \leq 0.89$. While 0.89 value of "n" exponent reveals typical zero-order (Case II transport) release and $n \geq 0.89$ indicates super case II transport (Siepmann *et al.*, 2001). Values of n in this study, calculated as per algorithm proposed by (Peppas *et al.*, 1989), ranged between 0.523 and 0.946. Some formulations show a non-Fickian release pattern, some approach to zero-order, while formulations having high levels of both polymers in combination reached super case II transport. Non-Fickian release pattern involves both phenomena in combination like drug diffusion and polymer relaxation, generally known as anomalous transport pattern (Kumar *et al.*, 2011). Matrix solubility is a direct function of the value of kinetic constant (K_{kp}), and Table 9 shows that the values of K_{kp} reduce with an increase in the concentration of either gum (Peppas *et al.*, 1989). Values of K_1 are much lower than values of K_0, which represented that release of drug was controlled primarily by Fickian diffusion and polymer relaxation (case II transport) mechanism was also contributed. It was seen that with the increasing concentration of polymer, swelling and erosion of tablets was affected. Rate of drug release from matrix tablets tended to decrease with increase in concentration of either EC (Chandrasekhar *et al.*, 2011). Retarding effect of both polymers on drug release is due to increase in viscosity of gel layer of polymer around the matrix tablet, or it is due to slow erosion of the surface of the matrix tablet. Both polymers (EC and HPMC) have the capability of gel formation in aqueous media; however, in this case of a highly water-soluble drug, gelling of HPMC showed poor control and venlafaxine was rapidly released from the matrix within two hours. However, the matrix of EC showed good potential for reducing burst and sustained the release of venlafaxine sufficient to develop once daily dosing. In the case of EC diffusion coefficient of venlafaxine was decreased. Slow Erosion of EC polymer at the surface of matrix was the dominant feature to sustain the release of venlafaxine (Shaikh *et al.*, 2011).

Compatibility of venlafaxine with polymers was studied by FTIR Spectra of venlafaxine & EC matrix tablets (Figure 10). Distinctive peaks of venlafaxine at 1731 $cm^{-1}$and 3272 cm^{-1} were indicative of carbonyl and amine stretching, respectively (Ingole et al., 2013). The major peaks of venlafaxine (1731 $cm^{-1}$and 3272 cm^{-1}) were also present in spectrum of drug-polymers mixture which showed that major peaks of drug were not affected in the presence of EC, which is an indicative of drug stability and compatibility of drug-polymer matrix. Therefore, it was concluded that no potential interaction exists between drug and polymers.

Conclusions

Sustained release matrix tablets of venlafaxine were developed by using EC and HPMC alone and in combination. All the batches of tablets passed the uniformity of weight test and drug content test. All the batches of tablets passed hardness test and thickness test. All the batches of tablets passed the friability test. Tablets containing only EC as release modifier showed sustained drug release up to 16 hours. Tablets having HPMC exhibited poor sustained drug release and burst release effect for initial 30 minutes. The study has shown that HPMC and EC used in combination showed better control over burst release and showed moderate extended-release properties. The release profiles fit into zero order and first order better than the rest, thus the drug may have been released through these models of drug kinetics. The release exponent 'n' determined was between 0.45 and 0.89 thus, the drug is released through anomalous or non-Fickian diffusion except two formulations that showed super case II transport. Drug-polymer interaction was excluded through analysis of FTIR studies. Ethylcellulose, when used single polymeric retardant material (F6), showed the highest potential not only to control the initial burst effect (reduced in F6 to <11% at first 30 minutes of the dissolution) but also extended the release of venlafaxine up to 16 hours. F6 has the strongest potential to be developed as once a day oral delivery of venlafaxine.

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