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Review Article

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DEVELOPMENT AND ANALYSIS OF VENLAFAXINE HCL EXTENDED-RELEASE MATRIX TABLETS

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ABSTRACT

The aim of this study is to develop a sustained-release tablet formulation of Venlafaxine, an antidepressant, to improve patient compliance and optimize drug therapy outcomes. The sustained-release formulation will provide a extended release of the drug, ensuring prolonged and consistent therapeutic effects, while reducing the frequency of administration. The research will involve formulation development, optimization of sustained-release characteristics, evaluation of in vitro drug release, and assessment of key quality parameters. The study will also include in vitro-in vivo correlation (IVIVC) studies to establish the relationship between in vitro release and in vivo performance. The findings from this research will contribute to the development of an effective and patient-friendly formulation of Venlafaxine, ultimately enhancing patient compliance and treatment outcomes.

KEYWORDS: Venlafaxine, Enhancing Patient Compliance, Controlled Release, Antidepressant.

INTRODUCTION

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, and patient, length of therapy and properties of drug. Most of the oral controlled drug delivery systems (OCDDS) relay on diffusion, dissolution, or combination of both mechanisms, to release the drug in a controlled manner to the gastro intestinal tract (GIT). The physico-chemical properties include crystal nature, solubility, partition coefficient, intrinsic dissolution, etc. dosage form characteristics are controlled and optimized with respect to physico-chemical properties of drug & relevant GI environmental factors. Other factors need to be considered are diseased state, patient compliance & length of therapy. The goal of targeted oral drug delivery systems is to achieve better therapeutic success compared to conventional dosageform of the same drug. This could be achieved by improving pharmacokinetic profile, patient convenience and compliance in therapy.

Oral route of drug delivery has been known for decades as most to a wide extent used route of administration among all routes that have been travel through to learn about it systemic delivery of drugs via various pharmaceutical manufactured products of various dosage forms.

Oral route of administration has been used as either conventional or novel drug delivery system. There are many merits are there for this, not the least of which would include willingness to accept by the patient and facility of administration. Types of extended release system employed for oral route of administration include virtually every at the present time now the theoretical mechanism for such application. This is because the manufacturing of dosage form is more flexibility, since constraint, such as sterility problem and potential damage at the site of administration are minimized. Because of this, it is easy to development of different types of dosage forms by customary those developed for oral route of administration as initial examples.

Regarding orally administered drugs, targeting is not a primary concern, and it is usually done on purpose for active component to permeate to the blood circulation and permeation through the other body tissue (the obvious exception being medication intended for local gastrointestinal tissue treatment). For this justification, most system employed the extended release variety.

Concentration of drug level it will increasing the rate absorption region and also, increase circulating blood levels, which in turn to raise to greater concentration of active content at the site of action *(Banker G.S. and Rhodes C.T., 2009; Chein Y.W., 2009.*

Materials Used

Table 1: List of materials with source.

S. No.	Name of Ingredients	Name of supplier
1	Venlafaxine HCl	Salvavidas Pharmaceutical Pvt. Ltd. Surat, India
2	Carnauba wax	TIPER Meerut
3	Cetyl alcohol	TIPER Meerut
4	Stearic acid	TIPER Meerut
5	Lactose	TIPER Meerut
6	Talc	TIPER Meerut
7	HCl	TIPER Meerut
8	Methanol	TIPER Meerut
9	Acetone	TIPER Meerut
10	NaOH	TIPER Meerut

Preformulation study

Preformulation testing is an investigation of physical and chemical propertiesof a drug substance alone. It is the first step in rational development of dosage form.

Identification of drug

Identification by FTIR Spectroscopy: By pressing Venlafaxine HCl with potassium bromide, Venlafaxine HCl discs were created, and under operational conditions, spectra with a range of 4000 to 400 cm-1 were produced. According to IP, 2007; Skoog D.A., et al., 2004, the absorption maxima in the spectrum obtained with the drug under study match those in the reference spectrum in terms of location and relative intensity.

Melting Point: Melting point of the drug was determined by capillary tube method.

Physicochemical Parameters

Organoleptic properties: The colour, odor and taste of the drug were recorded using descriptiveterminology.

Solubility study

Knowing a drug's aqueous solubility characteristics is crucial since they are required to have a certain level of aqueous solubility in order to produce a therapeutic effect. Various descriptive terms from the Indian Pharmacopoeia, 2007, were used to record the drug's solubility.

Loss on drying: The weight loss, given as a percentage of weight, brought on by water and any volatile material that can be driven off under certain conditions. A shallow glass weighing bottle with a glass stopper was filled with an exactly weighed 1gm sample, and the bottle was then precisely weighed. The bottle was placed in the oven, where the substance was dried for three hours at 105°C. After the bottle was taken out of the oven and weighed again, the loss from drying was computed using the equation below.

$$LOD = \frac{\text{Initial weight of substance} \quad \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

Determination of λ max

On a Shimadzu-1700 UV/Visible spectrophotometer, the reference solution's highest absorption was scanned in the 200–400 nm range. The absorption maximum attained with the chemical under investigation is similar to those in the reference spectrum in terms of location and relative intensity.

Preparation of standard curve of Venlafaxine HCl in 0.1N HCl

To make a stock solution of Venlafaxine HCl, 100 mg of the medication were dissolved in 0.1 N HCl, and the final volume was increased to 100 ml to give the solution a 1000 g/ml concentration. To acquire a concentration of 100 g/ml, 10 ml of the stock solution was pipette-out into a volumetric flask with a capacity of 100 ml. Appropriate aliquots of 1, 2, 3, 4, and 5 ml from the standard stock solution of Venlafaxine HCl were pipetted into a 25 ml volumetric flask, and the final volume was produced with 0.1 N HCl. to achieve 4, 8, 12, 16, and 20 g/ml concentrations. Using an Elico-SL 159 UV-Visible spectrophotometer, absorbance spectra of each solution were obtained at 225.5 nm in comparison to a blank solution of 0.1 N HCl (Patil Prakash et al., 2011).

Preparation of standard curve of Venlafaxine HCl in pH 6.8 phosphate buffer

In order to create a stock solution of Venlafaxine HCl, 100mg of the medication were dissolved in pH 6.8 and the final volume was increased to 100ml, giving the solution a concentration of 1000g/ml. To acquire a concentration of 100g/ml from the stock solution, 10ml was pipette-out into a 100ml volumetric flask. Appropriate aliquots of 1, 2, 3, 4 and 5 ml from the standard stock solution of Venlafaxine HCl were pipette out into a 50 ml volumetric flask, and the final volume was created with pH 6.8. to achieve 4, 8, 12, 16, and 20g/ml concentrations. Using an Elico-SL 159 UV-Visible spectrophotometer, the absorbance spectra of each solution were measured at 226 nm against a pH 6.8 blank (Patil Prakash et al., 2011).

Determination of Percentage purity of Drug

In order to create a stock solution of Venlafaxine HCl, 100 mg of the medication were dissolved in pH 6.8 and

the final volume was increased to 100 ml, giving the solution a concentration of 1000 g/ml. To acquire a concentration of 100 g/ml from the stock solution, 10 ml was pipette-out into a 100 ml volumetric flask. Appropriate aliquots of 1, 2, 3, 4 and 5 ml from the standard stock solution of Venlafaxine HCl were pipette out into a 50 ml volumetric flask, and the final volume was created with pH 6.8. To achieve 4, 8, 12, 16, and 20g/ml conc. Using an Elico-SL 159 UV-Visible spectrophotometer, the absorbance spectra of each solution were measured at 226 nm against a pH 6.8 blank (Patil Prakash et al., 2011).

Fourier transform infrared spectroscopy: *(Bhalekar., et al., 2008; Jadhav Sunita.,et al., 2011; Silverstein R.M., 2003).*

FTIR studies are very helpful in the evaluation of drug polymer interaction studies. If there is any incompatibility between the drug and polymer, these can be predicted by changes in the functional peaks. Infrared spectrum of Venlafaxine HCl was determined on Fourier transform infrared spectrophotometer using potassium bromide dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and various polymers were thoroughly mixed with potassium bromide. The crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 minutes. FTIR instrument were performed under nitrogen atmosphere ata flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} by using Shimadzu (Japan) FTIR spectrophotometer.

Differential scanning Calorimetry

Any possible drug polymer interaction can be studied by thermal analysis. The DSC analysis of pure drug, drug with carnauba wax were carried out using Shimadzu to evaluate any possible drug-polymer interaction. The 2mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30ml/min ***(****Atul A. Bodkhe.,et al., 2010).*

Formulation of Venlafaxine HCl extended release matrix tablets

All the ingredients mentioned in Table.3 were pre-weighed and passed the drug through mesh #80. The waxes were molten and then required quantity of drug was slowly added to the molten wax. After cooling, the mass was subjected to granulation by passing through mesh #16. Granules were mixed with lactose and talcand also used for evaluation of flow characteristic *(Bhalekar., et al., 2008).*

Table 3: Composition of Venlafaxine HCl ER matrix tablets.

Ingredients	VF1	VF2	VF3	VF4	VF5	VF6	VF7	VF8	VF9
Venlafaxine HCl	75	75	75	75	75	75	75	75	75
Carnauba wax	53	106	159	-	-	-	-	-	-
Cetyl alcohol	-	-	-	53	106	159	-	-	-
Stearic acid	-	-	-	-	-	-	53	106	159
Lactose	204	151	98	204	151	98	204	151	98
Talc	18	18	18	18	18	18	18	18	18
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

All the quantities are expressed as mg per tablet.

Evaluation of Pre-compression Granules

Angle of Repose

The angle of repose was determined by the funnel method. An accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in sucha way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation *(Lachman L., et al., 1991).*

Table 4: Standard values of angle of repose (°).

S. No.	Flow ability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable*	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

Loose Bulk density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder

Tapped Bulk Density

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The

tapped bulk densities of powder blends were determined using the following formula *(Lachman L., et al., 1991).*

Tapped bulk density = Total weight of powder / Total volume of tapped powder

Hausner's ratio

It is related to interparticulate friction and could be used to predict powderflow properties. Hausner's ratio was determined by following equation, *(Aulton M.E., 2007)*

Hausner's Ratio = Tapped bulk density / Loose bulk density

A Hausner ratio less than 1.25 indicates good flow while greater than 1.5indicates poor flow.

Carr's compressibility Index: *(Aulton M.E., 2007)*

It is a simple index that can be determined on small quantities of powder. The compressibility indices of the powder blends was determined using following formula, Carr's compressibility index (%) = [(TBD-LBD)/ TBD] x100

Table 5: Standard values of Carr"s index.

S. No.	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor*
5	33-38	Very poor*
6	>40	Extremely poor*

* May be improved by glidant

Preparation of ER Matrix Tablets

Hot Melt Granulation Method

All the ingredients motioned in Table.3 were pre-weighed and passed the drug through mesh #80. The waxes were molten and then required quantity of drug was slowly added to the molten wax. After cooling, the mass was subjected to granulation by passing through mesh #16. Granules were mixed with lactose and talc and compressed on a 16- station rotary tablet compression machine using 11mm round, biconcave punches. The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 350mg with different drug polymer ratios like 1:0.7, 1:1.4 and 1:2.1. The various polymers used were carnauba wax, cetyl alcohol and stearic acid. In the formulations prepared, the release retardants included were carnauba wax, cetyl alcohol and stearic acid. Lactose is used as diluent and talc 5 % were used as lubricant and glidant *(Atul A. Bodkhe., et al., 2010).*

Evaluation of Venlafaxine HCl extended releasematrix tablets

Appearance

The tablets were visually observed for capping, chipping and lamination.

Dimension (Thickness and Diameter): *(**Lachman L., et al., 1991)***

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined by using Vernier caliper. Ten tablets from each type of formulation were used and average values werecalculated.

Tablet Hardness: *(**Lachman L., et al., 1991)***

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. 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^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at thispoint was noted in kg/cm^2.

Percent friability

Friability is the measure of tablet strength. 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 pre weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

Weight Variation

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method. Weight variation importance during tablets compression section, each and every time intervals we must check the weight of tablet. If we are not maintaining the weight variation means it will give the deviation of drug content as well as yield of tablets.

Table 6: Specifications of % weight variation allowed in tablets as per I.P.

S. No.	Average Weight of Tablets (mg)	Maximum Percent DeviationAllowed (%)
1	80 or less	10
2	More than 80 but less than 250	7.5
3	More than 250	5

Drug content: *(Patil Prakash., et al., 2011)*

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 100 mg of

Venlafaxine HCl was transferred into a 100 ml standard volumetric flask. Then added 50ml of pH 6.8 phosphate buffer solution. It was gently shaken for 15 minutes. Then made up to the mark with pH 6.8 phosphate buffer solutions. The solution was filtered through a whatman filter paper, diluted suitably and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 226nm using Ph 6.8 phosphate buffer as blank.

***In vitro* Release Studies:** *(Atul A. Bodkhe., et al., 2010)*
The release rate of Venlafaxine HCl from matrix tablets was determined using United States Pharmacopoeia dissolution testing apparatus I (Basket method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed at 50 rpm using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 6.8 from 2-10 hrs at 37 ± 0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably. Absorbance of these solutions was measured at 226 nm using Elico- SL 159 UV-Visible spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were analyzed to study the release kinetics using zero order, first order and matrix, korsmeyer-peppas equations by using PCP disso V3 software.

Stability study: *(Atul A. Bodkhe., et al., 2010)*
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

Preformulation parameters
Identification by FTIR spectroscopy
The FTIR spectrum of Venlafaxine HCl was shown in Fig.1 and the interpretations of FTIR frequencies were showed in Table.7.

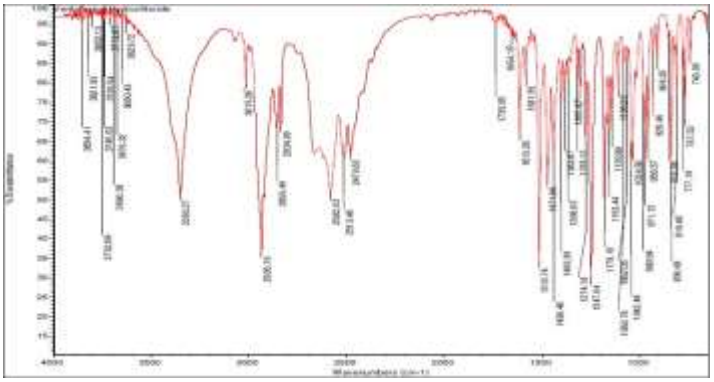

Fig. 1: FTIR spectrum of Venlafaxine HCl.

Interpretation of FTIR Spectrum
Major functional groups present in Venlafaxine HCl shows characteristic peaks in FTIR spectrum. Table 8.1 shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Venlafaxine HCl. Hence, the sample was confirmed as Venlafaxine HCl.

Table 7: Characteristic frequencies in FTIR spectrum of Venlafaxine *HCl.*

Wave No.(cm^{-1})	Inference
3015.28	C-H stretching
2935.16	R-O-CH_3 stretching
1318.13	NH_2 stretching
1153.44	OH stretching
1042.48	CH_2 stretching
836.68	C-H bending
740.09	OH bending

Melting Point
Melting point of Venlafaxine HCl sample was found to be 216^0C. The reported melting point for Venlafaxine HCl was in range of 215 to 217^0C. Hence, experimental values are in good agreement with official values.

Physicochemical parameters of drug
Organoleptic properties
Colour: White or almost white powder
Odour: Odourless
Solubility Study

Table 8: Solubility of Venlafaxine HCl in different solvents.

Name of solvents	Solubility
Distilled water	Freely Soluble
Methanol	Freely Soluble
Acetone	Sparingly Soluble
Phosphate buffer (pH 6.8)	Soluble
0.1N HCl	Soluble

Loss on Drying

Table 9: Percentage loss on drying for Venlafaxine HCl.

S. No.	Percentage LOD	Average % LOD
1	0.107	0.107
2	0.112	
3	0.104	

Analytical methods

Determination of absorption maximum in 0.1 N HCl

The absorption maximum for Venlafaxine HCl in 0.1N HCL was found to be 225.5 nm and absorption maximum was shown in Fig.2.

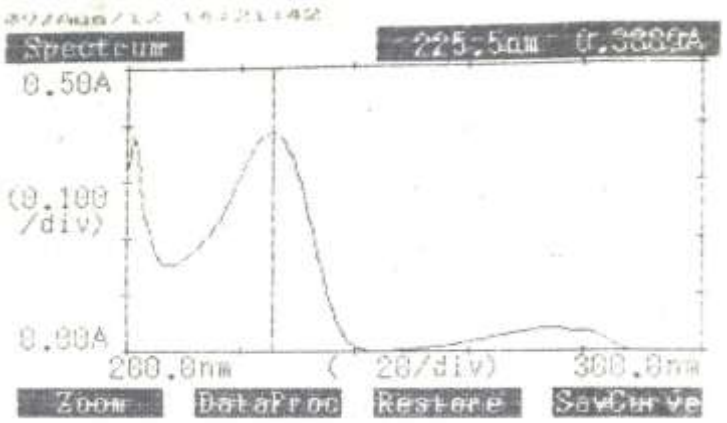

Fig. 2: λ_{max} observed for Venlafaxine HCl in 0.1N HCl.

Determination of absorption maximum in pH 6.8 phosphate buffer

The absorption maximum for Venlafaxine HCl in pH6.8 phosphate buffer was found to be 226nm and absorption maximum was shown in Fig.3.

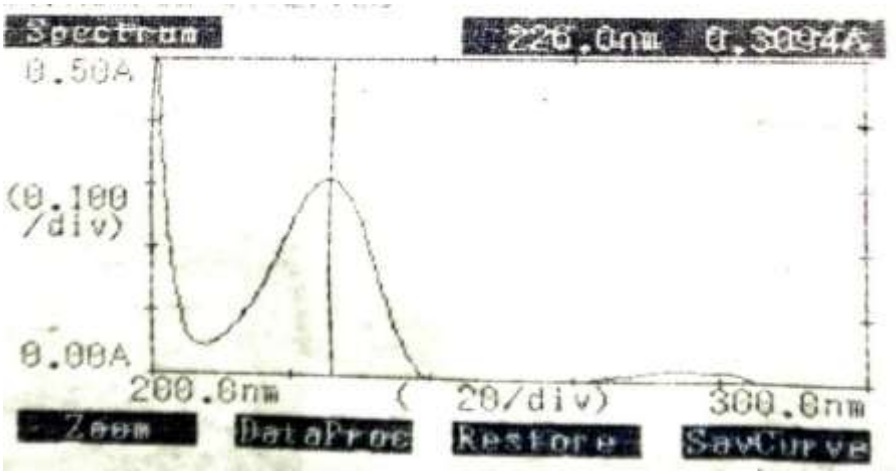

Fig. 3: λ_{max} observed for Venlafaxine HCl in pH 6.8 phosphate buffer.

Preparation of standard graph of Venlafaxine HCl in 0.1NHCl

Absorbance was obtained in various concentrations of Venlafaxine HCl in 0.1N HCl were given in Table.9 & shown in Fig.3. The graph of absorbance vs. concentration for Venlafaxine HCl was found to belinear in the concentration range of 4-20µg/ml. The calibration curve parameters shown in Table. 1 . So the drug obeys Beer- Lambert‟s law in the range of 4-20µg/ml.

Table 10: Conc. & abs. of Venlafaxine HCl in 0.1N HCl.

S. No	Conc. (µg/ml)	Abs.
1	0	0.000
2	4	0.137
3	8	0.265
4	12	0.390
5	16	0.512
6	20	0.633

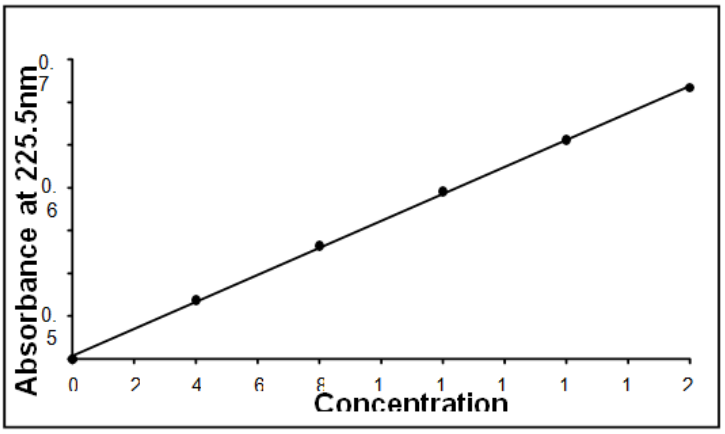

Fig. 4: Calibration curve of Venlafaxine HCl in 0.1N HCl.

Table 11: Calibration parameter values in 0.1 N HCl.

S. No	Parameters	Values
1	Correlation coefficient (r)	0.9997
2	Slope (m)	0.0315
3	Intercept (c)	0.0074

Preparation of standard graph of Venlafaxine HCl in pH 6.8phosphate buffer

Absorbance obtained for various concentrations of Venlafaxine HCl in pH 6.8 phosphate buffer were given in Table 8.6 and shown in Fig.5. The graph of abs vs conc. for Venlafaxine HCl was found to be linear in the concentration range of 420µg/ml. The calibration curve parameters shown in Table. 1 2 . So the drug obeys Beer Lambert‟s law in the range of 4–20µg/ml.

Table 12: Concentration and absorbance of Venlafaxine HCl inpH 6.8 phosphate buffer.

S. No	Conc. (µg/ml)	Abs.
1	0	0.000
2	4	0.111
3	8	0.213
4	12	0.312
5	16	0.415
6	20	0.522

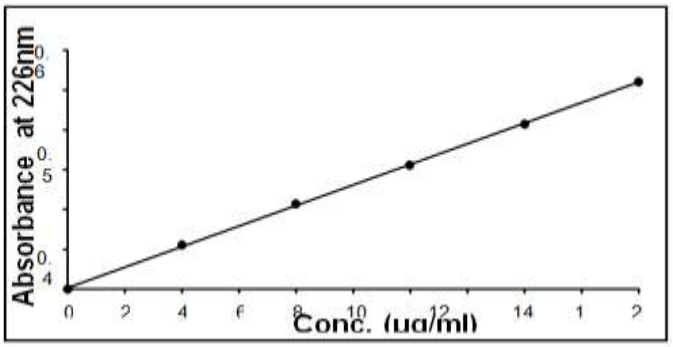

Fig. 5: Calibration curve of Venlafaxine HCl in pH 6.8.

Table 13: Calibration parameter values in pH 6.8 phosphate buffer.

S. No	Parameters	Values
1	Correlation coefficient (r)	0.9998
2	Slope (m)	0.0258
3	Intercept (c)	0.0035

Percentage purity of drug

The percentage purity of drug was calculated by using calibration graphmethod and represented in Table.14.

Table 14: Percentage purity of Venlafaxine HCl in pure drug.

S. No.	Purity (%)	Avg. purity (%)
1	99.98	100.09
2	100.12	
3	100.17	

The reported percentage purity for Venlafaxine HCl was 99 to 102%.

FTIR

FTIR spectrums of Venlafaxine HCl with different polymersused in formulation are shown in Fig.6,7,8 & Table.15.

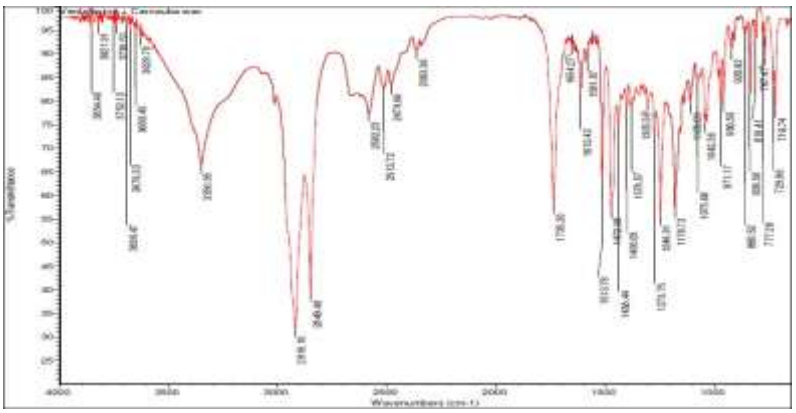

Fig. 6: FTIR spectrum of Venlafaxine HCl with carnauba wax.

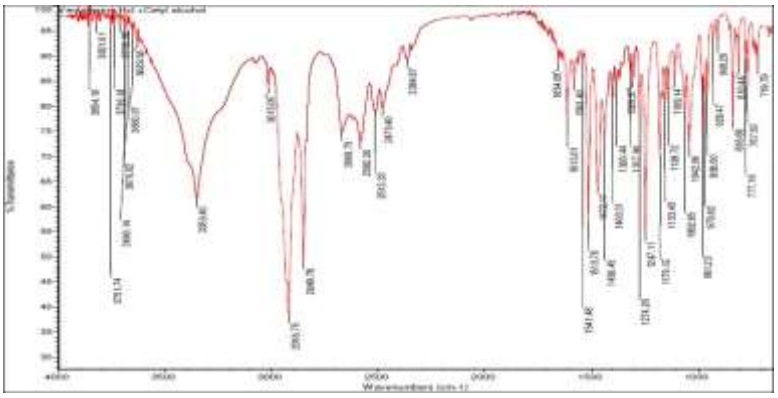

Fig. 7: FTIR spectrum of Venlafaxine HCl with cetyl alcohol.

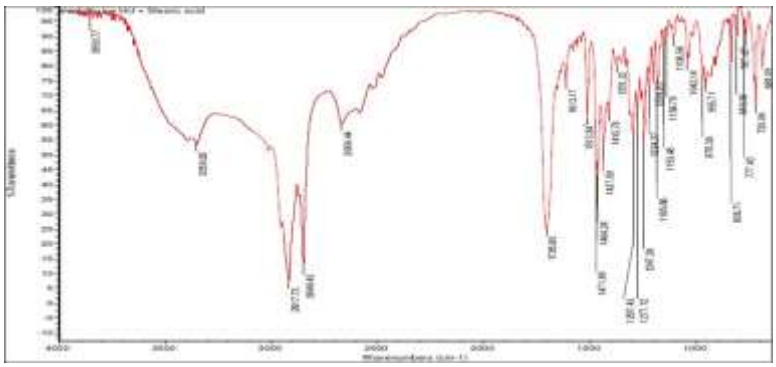

Fig. 8: FTIR spectrum of Venlafaxine HCl with Stearic acid.

Table 15: FTIR peaks observed for Venlafaxine HCl with different polymers used in formulations.

Functionalgroups	Peaks observed (wave no. (cm^{-1}))			
	Venlafaxine HCl	Venlafaxine HCl + Carnauba wax	Venlafaxine HCl + Cetyl alcohol	Venlafaxine HCl + Stearic acid
C-H stretching	3015.28	3015.19	3015.05	3015.16
R-O-CH_3 stretching	2935.16	2919.10	2918.75	2917.73
NH_2 stretching	1318.13	1305.56	1317.90	1376.12
OH stretching	1153.44	1178.73	1153.45	1153.48
CH_2 stretching	1042.48	1042.36	1042.06	1042.14
C-H bending	836.68	836.50	836.68	836.71
OH bending	740.09	767.47	767.53	767.45

Differential scanning Calorimetry

The compatibility and interactions between drug and best formulation polymer were checked using differential scanning Calorimetry and the results were shown in Fig.9 & 10.

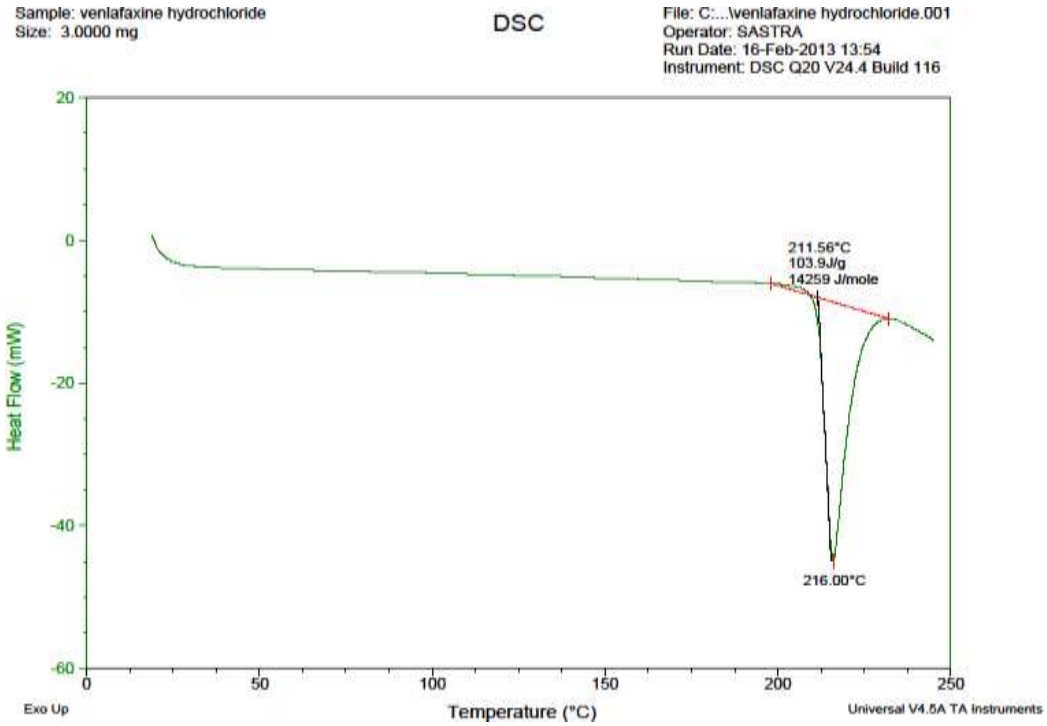

Fig. 9: DSC thermal analysis of Venlafaxine HCl.

According to Fig.9 and 10 & Table 16, DSC thermogram showed that there was no major difference in onset temperature and peak temperature when compared with pure drug thermogram. Therefore it could indicate that there was no incompatibility between drug and best formulation polymer.

Table 16: DSC thermogram parameters of Venlafaxine HCl withCarnauba wax.

S. No.	DSC thermogram	Onset temperature(°C)	Peak temperature(°C)
1	Venlafaxine HCl	211.56	216.00
2	Venlafaxine HCl +carnauba wax	205.90	211.08

Evaluation of granules

The granules of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows: -

Angle of repose

Angle of repose ranged from 21.31°± 0.05 to 23.27°± 0.43. The results were found to be below 25° and hence the blend was found to have excellent flow ability. (Table.16).

Loose bulk density and tapped bulk density

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.454 ± 0.00 to 0.476± 0.00 g/ml; and 0.526 ± to 0.555 ± 0.00 g/ml respectively.

Table 17: Flow characteristics of powder blends.

FormulationCode	Angle of repose (°)*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausnerratio*	Carr's index (%)*
VF1	22.43±0.02	0.476±0.00	0.555±0.00	1.16±0.01	14.28±0.62
VF2	21.72±0.01	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
VF3	23.12±0.03	0.476±0.00	0.555±0.00	1.16±0.01	14.28±0.62
VF4	22.23±0.06	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
VF5	21.31±0.05	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
VF6	22.82±0.12	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
VF7	23.27±0.43	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
VF8	22.74±0.39	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
VF9	23.24±0.51	0.454±0.00	0.526±0.00	1.15±0.01	13.68±0.44

*All the values were expressed as mean± SD, n=3

Evaluation of extended release matrix tablets

Table 18: Physico-chemical parameters of Venlafaxine HCl matrix tablets.

F. Code	Dimension		Hardness (kg/cm^2)*	Friability (%)*	Weight variation (mg)*	Drug content (%w/w)*
	Diameter (mm)*	Thickness (mm)*				
VF1	11.16±0.01	4.51±0.01	6.70±0.05	0.114±0.03	350.70±0.75	99.43±0.20
VF2	11.19±0.01	4.45±0.02	6.15±0.01	0.185±0.01	353.15±1.12	99.39±0.27
VF3	11.15±0.02	4.53±0.01	7.10±0.02	0.085±0.05	350.81±1.23	99.75±0.11
VF4	11.17±0.02	4.49±0.01	6.50±0.03	0.142±0.07	351.71±1.24	99.31±0.18
VF5	11.16±0.01	4.52±0.01	6.85±0.04	0.100±0.03	350.30±1.68	100.01±0.20
VF6	11.19±0.02	4.44±0.01	6.05±0.05	0.200±0.02	352.86±0.17	99.24±0.41
VF7	11.18±0.02	4.47±0.02	6.30±0.02	0.171±0.01	352.13±1.50	100.03±0.21
VF8	11.17±0.01	4.50±0.01	6.65±0.01	0.128±0.09	351.21±0.10	100.38±0.26
VF9	11.18±0.01	4.48±0.02	6.45±0.03	0.157±0.05	352.10±0.65	99.49±0.24

*All the values were expressed as mean ± SD, n=3.

***In vitro* dissolution studies**

Table.19: Dissolution profile of formulation VF1.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	16.02±0.93	12.02	8.01	0.50
2	28.63±0.47	21.48	15.17	0.94
3	39.77±0.72	29.83	21.51	1.38
4	50.34±0.94	37.76	27.40	1.82
5	60.21±0.98	45.16	32.98	2.26
6	72.29±0.95	54.22	38.52	2.80
7	80.41±0.73	60.31	43.93	3.18
8	84.41±0.74	63.31	48.74	3.38
9	86.26±0.73	64.70	52.80	3.49
10	88.27±1.00	66.21	56.25	3.63

*****All values were expressed as mean ±SD, n=3.

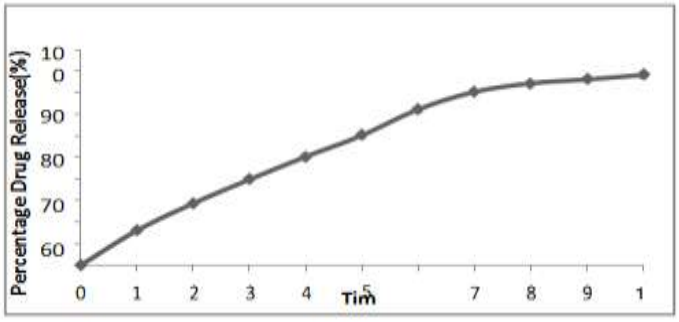

Fig. 11: *In vitro* drug release profile of formulation VF1.

Table 20: Dissolution profile of formulation VF2.

Time (hours)	Percentage drugreleased*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	14.78±0.71	11.09	7.39	0.50
2	27.69±0.47	20.77	14.32	0.97
3	35.73±0.92	26.80	20.12	1.31
4	43.35±0.47	32.52	24.97	1.70
5	51.94±0.92	38.96	29.51	2.16
6	62.27±0.71	46.71	34.11	2.71
7	76.99±0.71	57.75	39.19	3.44
8	84.99±0.46	63.75	44.41	3.82
9	87.31±0.93	65.49	49.05	3.94
10	90.89±0.70	68.16	53.05	4.16

*****All values were expressed as mean ±SD, n=3.

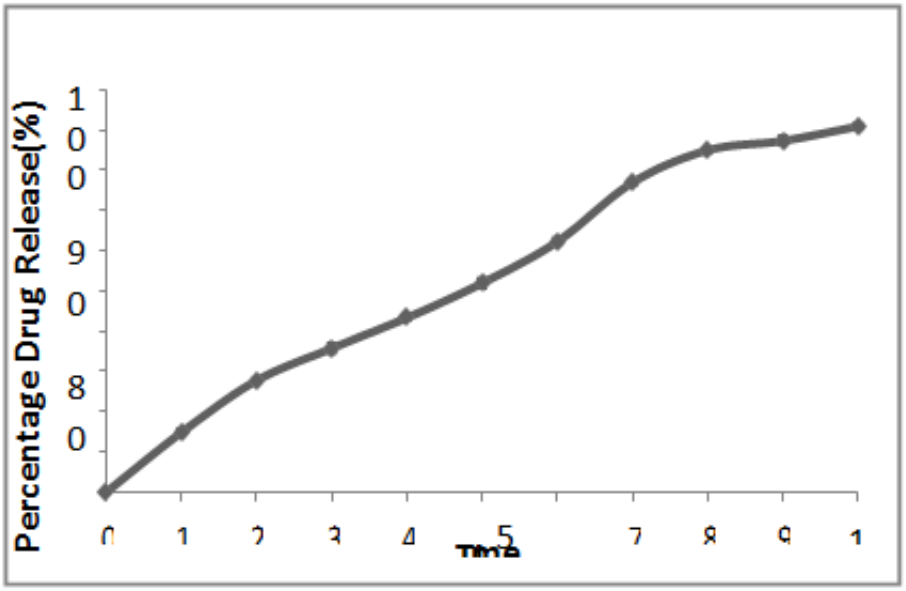

Fig. 12: *In vitro* drug release profile of formulation VF2.

Table 21: Dissolution profile of formulation VF3.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	12.31±0.93	9.23	6.15	0.50
2	23.04±0.46	17.29	11.92	0.97
3	30.13±0.93	22.60	16.81	1.33
4	41.43±0.46	31.07	21.55	1.92
5	47.68±0.93	35.77	26.15	2.26
6	56.76±0.45	42.57	30.50	2.78
7	63.10±0.94	47.33	34.70	3.15
8	72.72±0.45	54.54	38.85	3.73
9	81.47±0.94	61.10	43.10	4.24
10	93.04±0.45	69.78	47.52	4.89

*****All values were expressed as mean ±SD, n=3

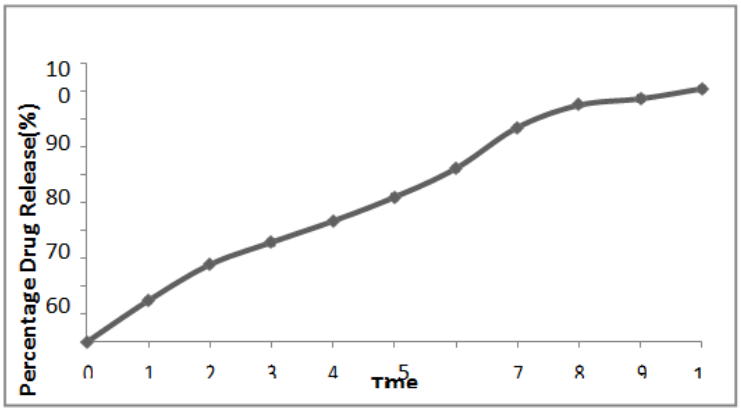

Fig. 13: *In vitro* drug release profile of formulation VF3.

Table 22: Dissolution profile of formulation VF4.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	17.87±0.93	13.41	8.94	0.50
2	31.42±0.92	23.57	16.79	0.93
3	49.69±0.46	37.27	24.72	1.51
4	57.85±0.46	43.39	31.98	1.79
5	71.62±0.93	53.72	38.53	2.31
6	74.79±0.46	56.10	44.31	2.45
7	78.45±0.93	58.84	48.93	2.63
8	81.66±0.46	61.25	52.82	2.83
9	82.56±0.93	61.93	56.07	2.89
10	83.47±0.45	62.61	58.77	2.96

*****All values were expressed as mean ±SD, n=3.

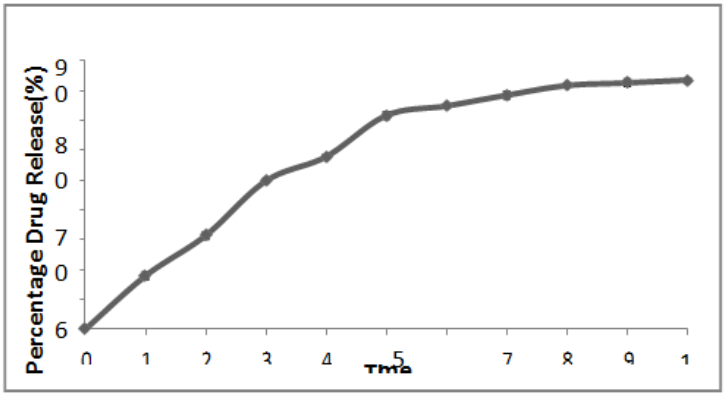

Fig. 14: *In vitro* drug release profile of formulation VF4.

Table 23: Dissolution profile of formulation VF5.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	15.09±0.46	11.32	7.55	0.50
2	29.24±0.71	21.94	14.86	0.98
3	38.53±0.93	28.90	21.20	1.35
4	50.03±0.70	37.52	26.97	1.84
5	57.57±0.93	43.18	32.34	2.19
6	60.98±0.71	45.74	36.83	2.38
7	72.13±0.45	54.10	41.07	3.01
8	77.32±1.16	57.99	45.28	3.32
9	82.38±0.71	61.79	49.12	3.63
10	86.07±1.88	64.56	52.63	3.89

*****All values were expressed as mean ±SD, n=3.

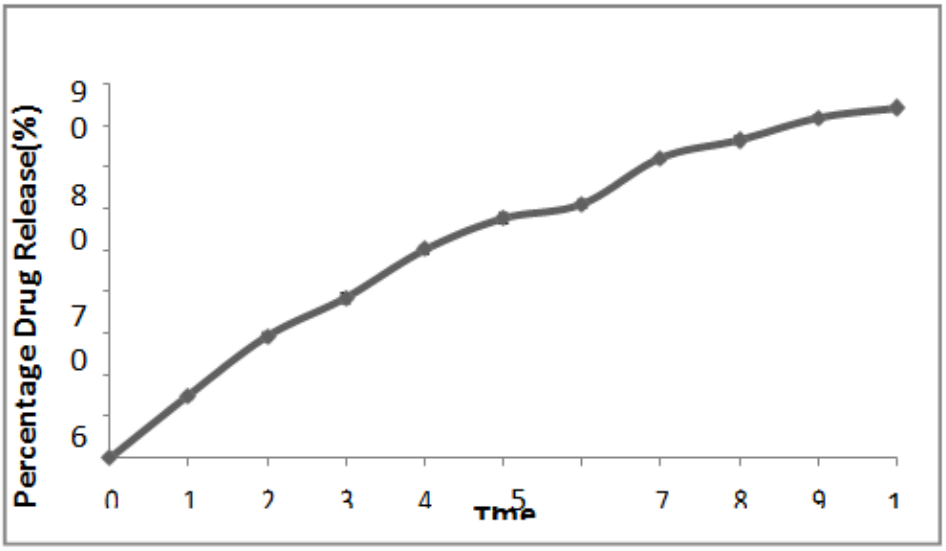

Fig. 15: *In vitro* drug release profile of formulation VF5.

Table 24: Dissolution profile of formulation VF6.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	13.39±0.71	12.02	8.01	0.50
2	26.30±0.92	21.48	15.17	0.94
3	35.25±0.46	29.83	21.51	1.38
4	44.73±0.93	37.76	27.40	1.82
5	51.93±0.46	45.16	32.98	2.26
6	59.17±0.93	54.22	38.52	2.80
7	70.16±0.47	60.31	43.93	3.18
8	75.65±0.94	63.31	48.74	3.38
9	82.24±0.69	64.70	52.80	3.49
10	87.33±0.97	66.21	56.25	3.63

*****All values were expressed as mean ±SD, n=3.

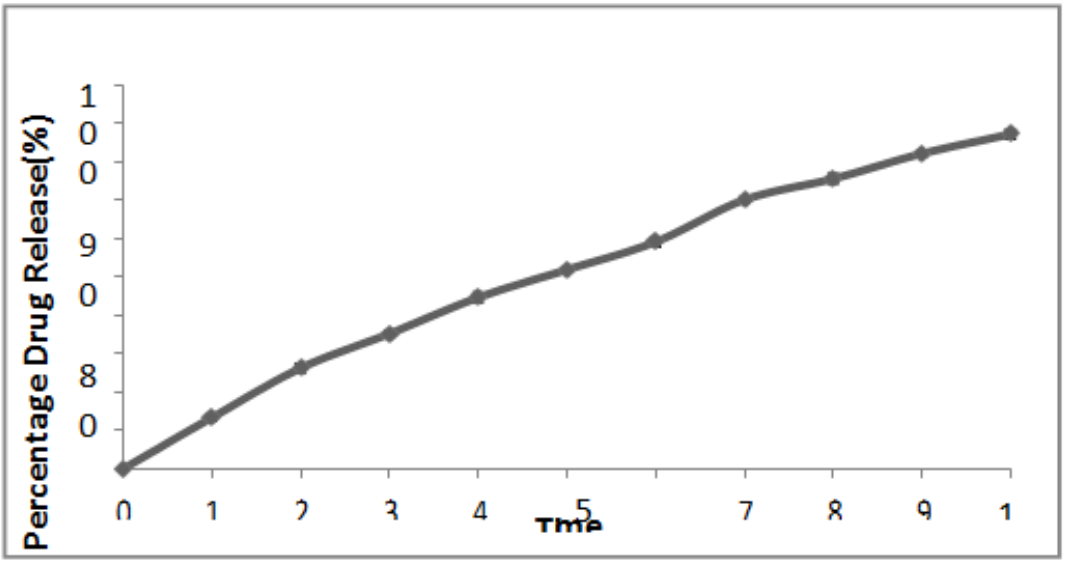

Fig. 16: *In vitro* drug release profile of formulation VF6.

Table 25: Dissolution profile of formulation VF7.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	18.95±0.71	10.04	6.70	0.50
2	29.42±0.71	19.72	13.27	0.99
3	37.16±0.94	26.44	19.11	1.37
4	46.18±0.45	33.55	24.33	1.82
5	54.31±0.94	38.95	29.13	2.20
6	63.12±0.69	44.38	33.53	2.60
7	71.81±0.72	52.63	37.98	3.21
8	75.45±0.69	56.74	42.35	3.52
9	80.50±0.70	61.69	46.42	3.92
10	85.88±0.93	65.50	50.25	4.25

***All values were expressed as mean ±SD, n=3.

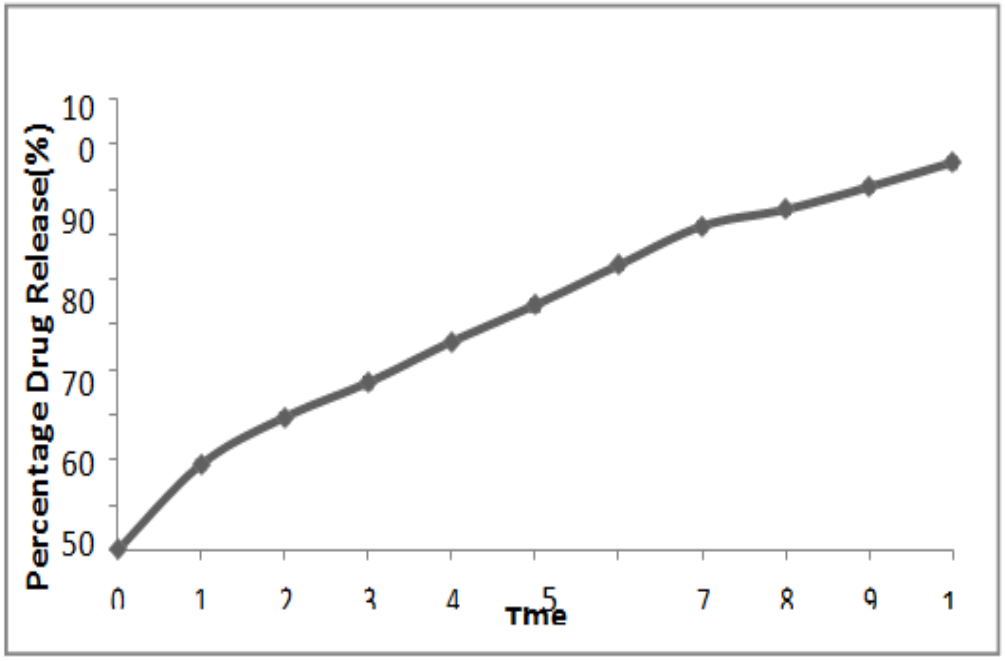

Fig. 17: *In vitro* drug release profile of formulation VF7.

Table 26: Dissolution profile of formulation VF8.

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	15.71±0.71	14.22	9.48	0.50
2	25.84±0.93	22.07	16.83	0.86
3	33.56±0.72	27.87	22.32	1.20
4	41.32±1.18	34.63	27.16	1.65
5	50.52±0.94	40.74	31.78	2.08
6	62.55±0.73	47.34	36.27	2.55
7	77.58±0.49	53.86	40.72	3.03
8	80.17±0.73	56.59	44.84	3.25
9	84.78±0.74	60.38	48.52	3.58
10	86.47±1.44	64.41	51.99	3.95

***All values were expressed as mean ±SD, n=3.

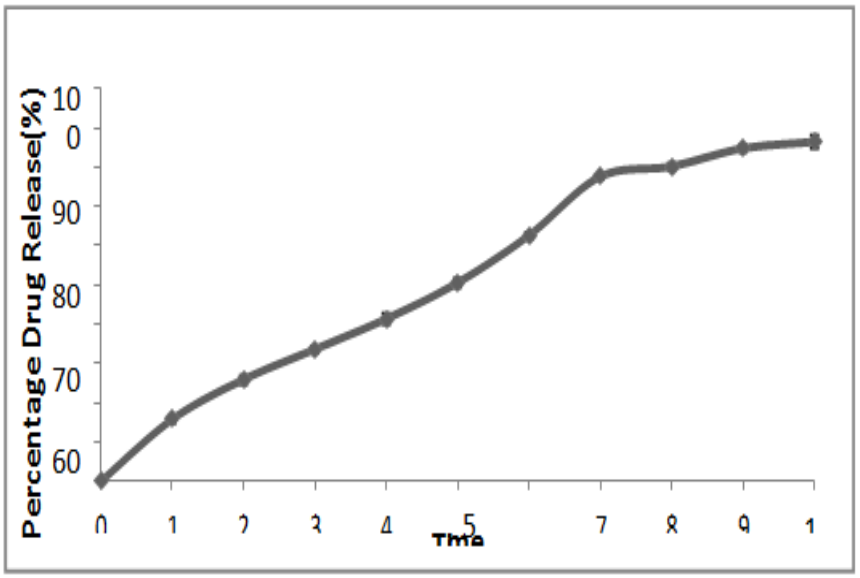

Fig. 18: *In vitro* drug release profile of formulation VF8.

Table 27: Dissolution profile of formulation VF9.

Time (hours)	% drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	14.93±0.71	11.20	7.47	0.50
2	23.98±0.46	17.99	13.47	0.88
3	30.15±0.93	22.61	18.00	1.21
4	39.75±0.70	29.81	22.24	1.76
5	47.69±0.47	35.77	26.54	2.22
6	59.86±0.96	44.90	31.08	2.89
7	71.17±0.71	53.38	36.00	3.46
8	77.43±0.46	58.08	40.79	3.79
9	82.34±0.71	61.76	45.13	4.07
10	88.50±0.46	66.38	49.16	4.45

*****All values were expressed as mean ±SD, n=3.

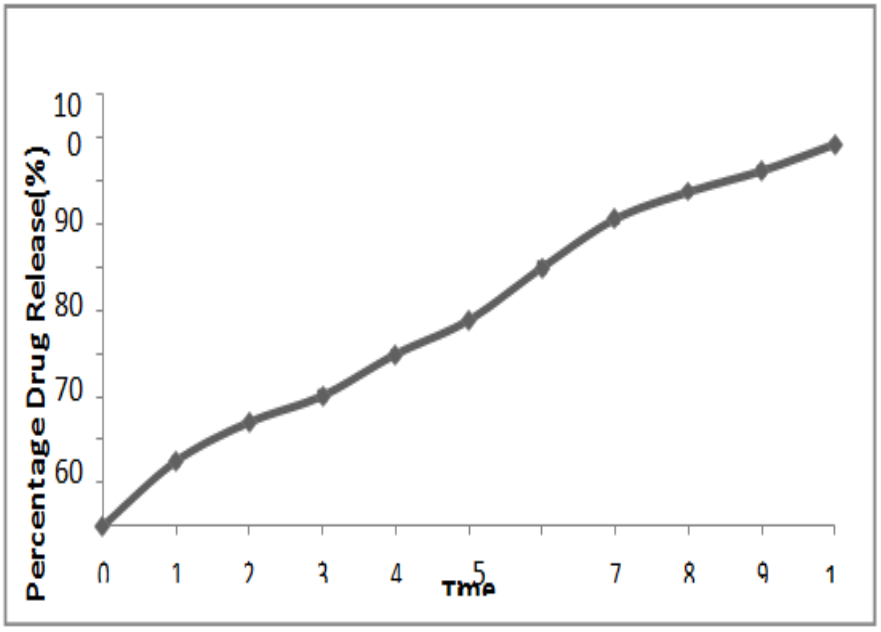

Fig. 19: *In vitro* drug release profile of formulation VF9.

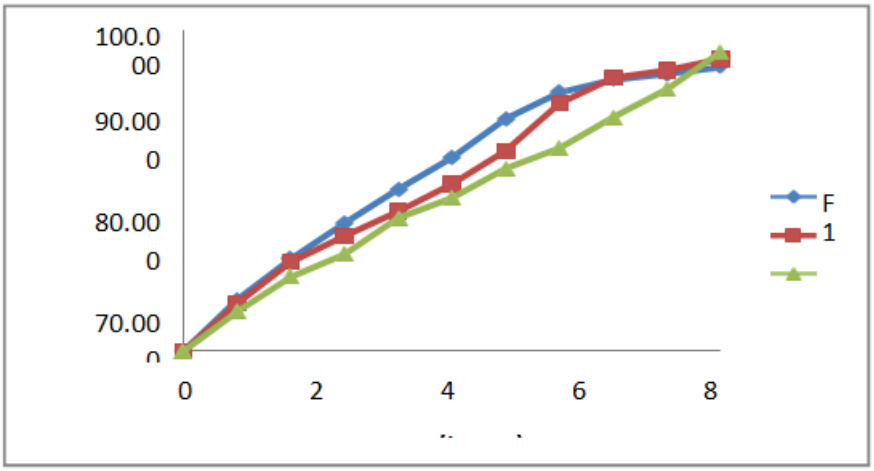

Fig. 20: *In vitro* drug release profile of formulations containing carnaubawax polymer.

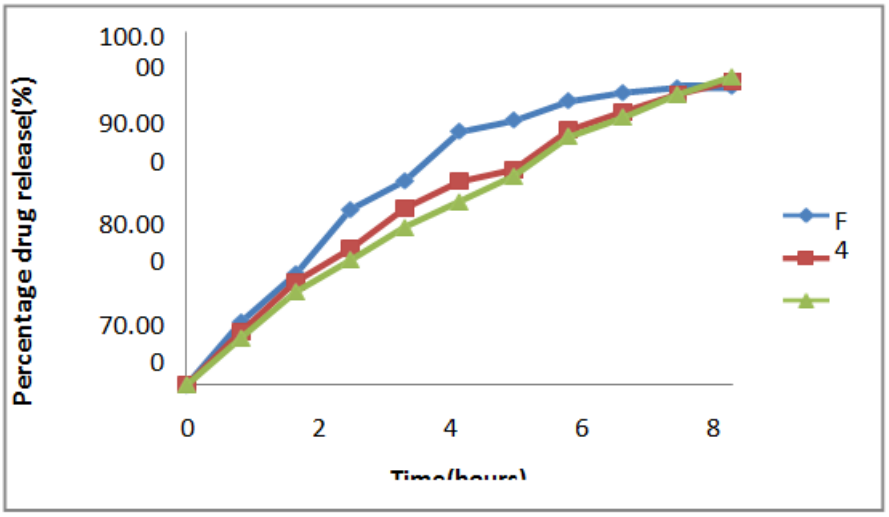

Fig. 21: *In vitro* drug release profile of formulations containing cetylalcohol polymer.

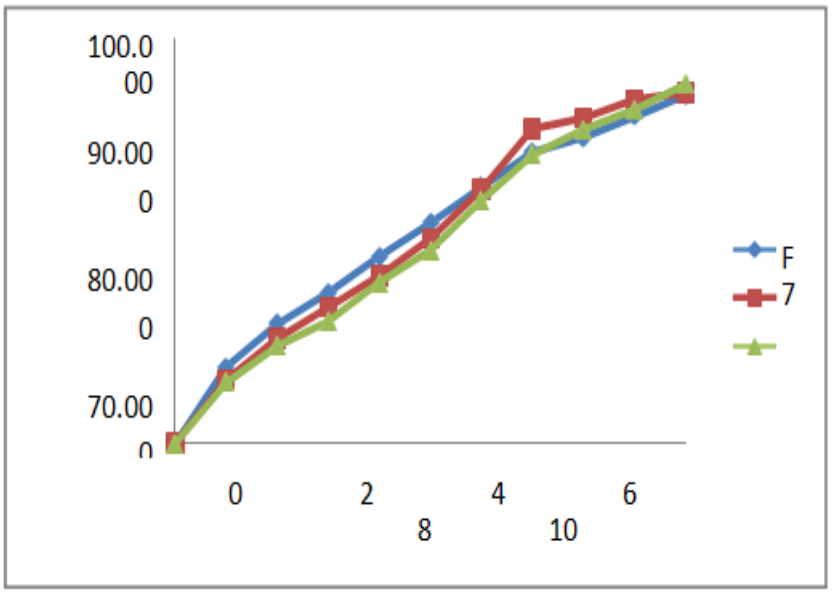

Fig. 22: *In vitro* Drug Release profile of formulations containing stearicacid polymer.

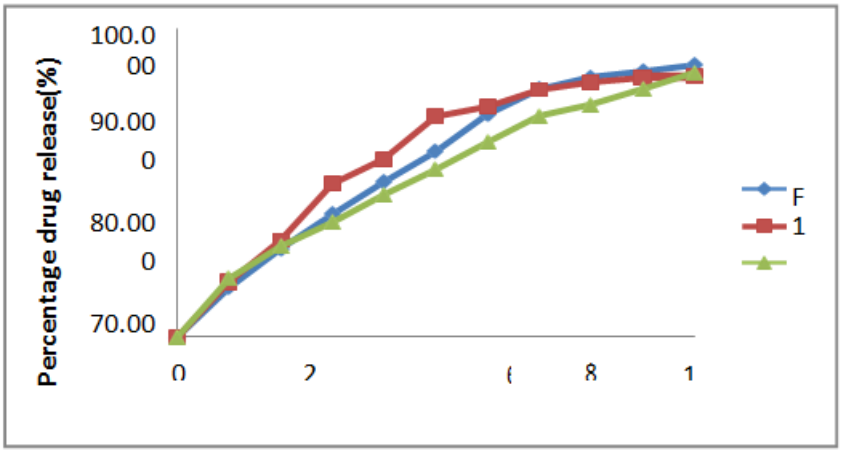

Fig. 23: *In vitro* drug release profile for different polymers at 15%concentration.

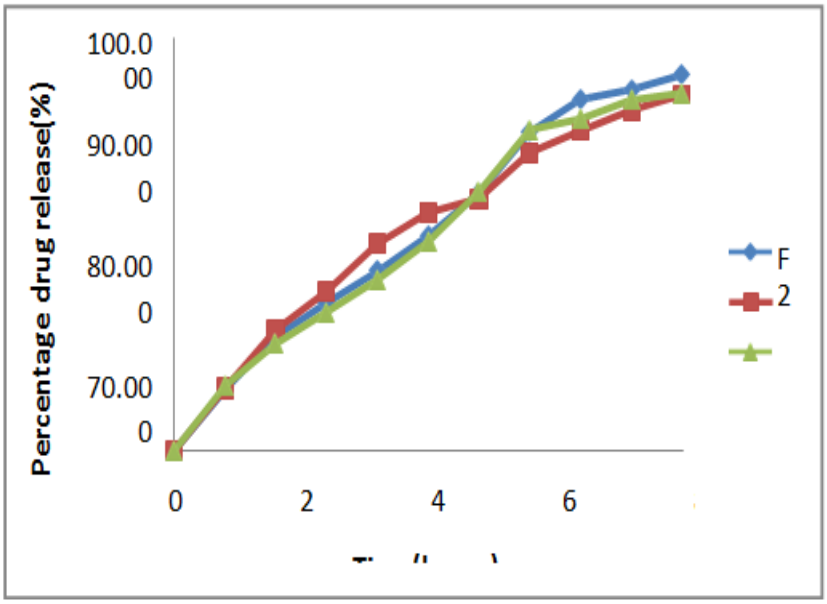

Fig. 24: *In vitro* drug release profile for different polymers at 30%concentration.

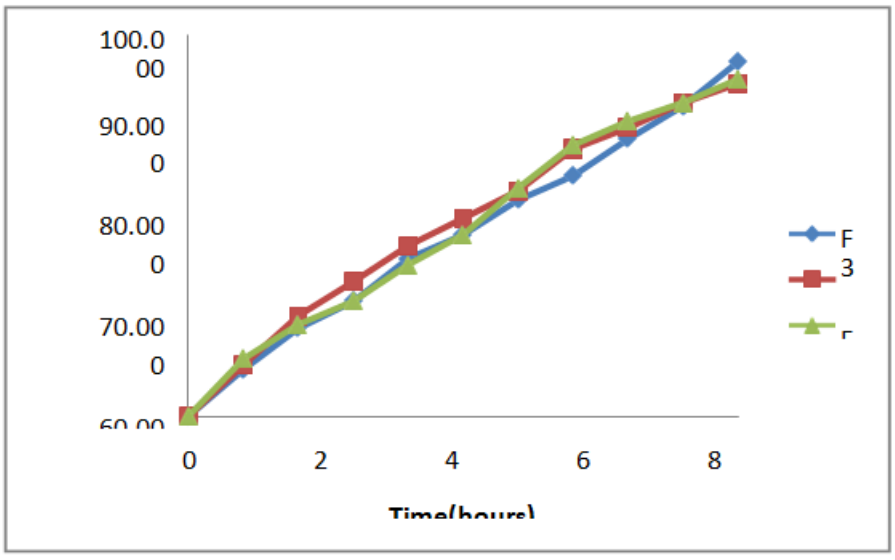

Fig. 25: *In vitro* drug release profile for different polymers at 45%concentration.

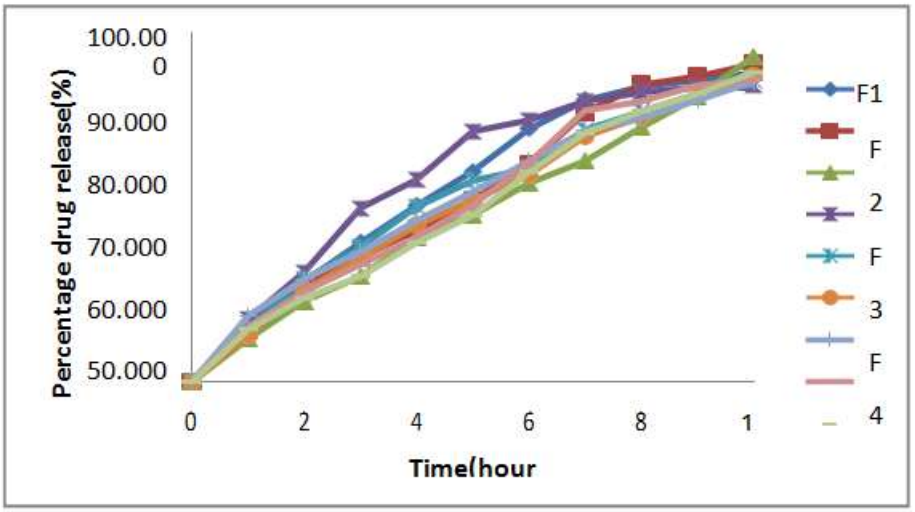

Fig. 26: *In vitro* drug release profile of VF1 to VF9.

Stability study

Table 28: Stability studies of best formulation VF3 (40°C ± 2°C at 75% ±5%).

Characteristic	Initial	1st Month	2nd Month	3rd Month
Appearance*	Pale yellow	No change	No change	No change
Hardness (kg/cm^2)*	7.10±0.02	7.05±0.01	7.00±0.03	6.95±0.01
Friability (%)*	0.085±0.05	0.083±0.03	0.081±0.01	0.080±0.02
Drug content (%)*	99.75±0.11	99.61±0.23	99.43±0.10	99.12±0.14
In vitro* drug release atthe end of 12 hours	93.04±0.45	92.86±0.31	92.60±0.27	92.37±0.16

*All the values were expressed as mean ± SD; n=3

CONCLUSION

In the present study, an attempt was made to formulate the oral extended release matrix tablets of Venlafaxine HCl to provide a dosage form for prolonged period of time, in order to improve efficacy, reduce the frequency of total dose and better patient compliance. Infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction. The extended release matrix tablets were prepared by Hot melt granulation method using different polymers like carnauba wax, cetyl alcohol and stearic acid as release retardant polymers. The granules were evaluated for angle of repose, bulk density, compressibility index and hausner‟s ratio. All the tests revealed that granules showed excellent flow properties. The resulting monolithic tablets were evaluated for thickness, diameter, weight variation test, hardness, friability and drug content. All the tablet formulations showed acceptable pharmaco-technical properties and complied with pharmacopoeial standards. *In vitro* release studies revealed that the release rate was decreased with increase in polymer proportion. In the present studies, matrix formulation VF3 containing Carnauba wax were probably showing maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation VF3 as best formulation among all nine formulations. Based on release exponent (n) values, it was concluded that mechanism of drug release was found to be diffusion coupled with erosion (anomalous transport mechanism). From the stability studies, there was no significance difference in hardness, friability, drug content and *in vitro* release profile for the best formulation.

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