Title:

Full Title: Preparation and Characterization of the Sustain Release Tablet of Venlafaxine Hcl from Polymeric Matrix

Short Title: Preparation and Characterization of the Sustain Release Tablet of Venlafaxine Hcl from Polymeric Matrix

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Abstract-

This study examines the sustained release behaviour of venlafaxine hydrochloride from Eudragit RSPO, HPMC K4, Dicalcium phosphate, Glyceryl monosterate, Lactose, PVP, Magnesium stearate, Talc. Venlafaxine hydrochloride is an antidepressant agent. The present research endeavor was directed towards the development of a sustained release dosage form of venlafaxine in the form of tablets to be taken once daily. All lubricated formulations were compressed by direct compression. The compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness and In-vitro dissolution study. Release studies were carried out using USP type-II apparatus in 900 ml of Distilled Water as dissolution media. Release kinetics were analyzed using zero-order, Higuchi's square root and Peppa's exponential equations. All formulations showed compliance with pharmacopoeial standards. Among different formulations F7 showed sustained release of drug for 12 hours with 99.73% of drug release respectively. The regression coefficient value of zero order plots was found to be 0.993. The slope of peppas model was found to be 0.981 for F7.Thus the matrix system of HPMC & SCMC was found to be effective in retarding release of venlafaxine hydrochloride.

KEYWORDS- Venlafaxine hydrochloride, CDR (Cumulative drug release), SR

INTRODUCTION

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients by using various pharmaceutical dosage forms, such as tablets, capsules, pills, liquids, and ointments etc. as drug carriers. So the oral route is the most often used for administration of drugs. Tablets are the popular oral dosage form available in the market and are preferred by patients and physicians mostly. This type of drug delivery systems is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This would result in significant fluctuation of drug level.1-4so to improve this fluctuation of drug level in the systemic circulation & to improve the patient compliance recently several technical advancement has been made. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity. (1-4) the term "sustained release" is known to have existed in the medical &

pharmaceutical literature for many decades. It is widely used to retard the release of a drug in systemic circulation & its plasma profile which gives sustained action.(1-4)In the sustained release method therapeutically effective concentration of drug in the systemic circulation can be achieved over an extended period of time.6 **Sustained release**= these are drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug.[1-5]

Pre-Formulation Studies:

The Physicochemical properties of the drug play a very important role in performance of the Drug and the development of dosage form. Hence, in order to develop a safe, stable and effective Dosage form the performulaion study of Venlafaxine hydrochloride was carried effectively.

Determination of Melting Point-

The Melting point of Venlafaxine Hydrochloride was determined by capillary method.[6]

Solubility-

The solubility of Venlafaxine Hydrochloride was tested in different solvents like Distilled water, Ethanol, Dichloromethane, Methanol at ambient temperature, dissolving a specific amount of medication (10mg) in 10ml of each solvent. The solubility was detected visually and also using UV-visible spectroscopy.[7]

UV Spectrophotometric Analysis-[8-9]

Determination of λ max of Venlafaxine Hydrochloride in pH Phosphate Buffer 6.8

A. Preparation of standard solution and scanning of drug spectra:-

Stock solution: 10 mg of Venlafaxine HCl was accurately weighed and add into 100 mL volumetric flask and dissolved in phosphate buffer pH 6.8. The volume was made up to 100 mL to get a concentration of (0.1 mg/ml) stock solution-1 (SS-I). Scanning of Drug: From stock solution-1 (SS-I), 1 mL was withdrawn and the volume was made up to 10 mL with phosphate buffer pH 6.8 to get a concentration of 10µg/ml. UV scan range was taken between the wavelengths 200-400 nm. It gives a peak at 224 nm and the same was selected as λmax for Venlafaxine HCl.

B. Calibration curve in phosphate buffer pH 6.8:

From the stock solution-I (SS-I) 0.5, 1, 1.5, 2 and 2.5 ml were withdrawn and volume ere made up to 10 mL with phosphate buffer pH 6.8 to give a concentration of 5,10,15,20, 25 µg/ml. Absorbance of these solutions were measured against a blank of phosphate buffer pH 6.8 at 224 nm for Venlafaxine HCl and absorbance values were summarized in the table 13. Calibration curve was plotted.

Drug-Excipients Compatibility Study by FTIR Spectroscopy [9-11]

For the purpose of identifying any potential chemical interaction between the drug and the excipients, a method called infrared spectra was used. A physical mixture (1:1) of the drug and its excipients was prepared and mixed. The mixture was scanned using Bruker FTIR Spectrophotometer from 3500-500 cm^{1}. IR spectrum observed the physical combination was compared to that of the pure drug and excipients.

Differential Scanning Calorimetry-[12]

The DSC studies was carried out for pure drug Venlafaxine hydrochloride. The thermogram revealed occurrence of sharp endothermic peak at 219.5^{0}C, confirming crystalline nature of the drug.

Materials & Method:

Material:

Venlafaxine Hydrochloride was received as a gift sample from Cipla Pvt. Ltd. Eudragit RSPO, HPMC K4, Dicalcium phosphate, Glyceryl monosterate, Lactose, PVP, Magnesium stearate and Talc were obtained from Research lab. All the material used for formulation of Venlafaxine Hydrochloride tablets.

Method

FORMULATION OF MATRIX TABLETS OF VENLAFAXINE HCL:[13]

The preparation method of matrix tablet by wet granulation technique.

Experimental Design

Based on initial exploratory studies, the two most significant independent formulation factors influencing the cumulative release in the initial hour and the drug release rate over a 8-hour period are HPMC K4 and Eudragit RSPO.A central composite design (CCD) with α=1 was utilized, studied at three levels each, using Design-Expert software (version 13, Stat-Ease Inc., USA). This

trial design aimed to optimize these factors concerning the response variables. To identify any non-linearity in the factor-response relationship, the face centered central composite design (CCF) was selected. Consequently, nine experimental runs of the CCD matrix were conducted

INGREDIENT	FI	FII	FIII	FIV	FV	FVI	FVII	FVIII	FIX
Venlafaxine HCl	75	75	75	75	75	75	75	75	75
HPMC K4	22	40	22	22	10	20	10	30	40
Eudragit RSPO	25	60	25	35	25	60	60	50	50
Lactose	70	-	-	-	-	-	-	-	-
DCP	-	-	70	60	30	35	45	37	27
Mg. stearate	3	3	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5	5	5
PVP	2	2	2	2	2	2	2	-	-
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight(mg/Tablet	200	200	200	200	200	200	200	200	200

Table No: 1 Composition of various formulations

COMPOSITION OF MATRIX TABLETS OF VENLAFAXINE HCL:

The matrix tablet of Venlafaxine HCl was prepared by using combination of hydrophilic and hydrophobic polymers. In this composition polymers like HPMC K4 and Eudragit RSPO were used. Di calcium phosphate was used as filler. Common lubricants were used e.g. magnesium stearate and talcum powder. Compositions of all formulations are shown below in table

Preparation of Granules:

• Venlafaxine HCl, HPMC K4, Eudragit RSPO were accurately weighed and sieved through mesh # 60.

• Mixed the material in planetary mixer for 10 min and add slowly water to get a damp mass for granules preparation. These prepared damp masssieved through mesh # 16.

• Dried the granules at 600C for 30-40 min again passed through mesh #20.

• Then accurately weighed the magnesium stearate and talc passed through mesh # 40.

• The prepared granules and sieved lubricants were mixed together in polyethylene bag for 10 minutes.

• And these granules were evaluated for pre-compression parameters

Compression of tablet:

• Lubricated granules were compressed by using punch size 8 mm with 12 station rotary punching tablet machine (Cip machineries lab press).

• And finally prepared tablets were evaluated for the post compression parameters

EVALUATION OF PRE-COMPRESSION PARAMETERS OF GRANULES: [14-15]

a. Angle of Repose (Θ):

This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed. (129)

$$\tan^{-1}\theta = \frac{h}{r} \text{ ----------Eq. no. 7}$$

Where, Θ = angle of repose,

h = height of the heap, & r = radius of the heap

Table No: 2 The relationship between angle of repose and powder flow is shown in table

SR. NO.	ANGLE OF REPOSE	POWDER FLOW
1	< 25	Excellent
2	25.30	Good
3	30-40	Passable
4	> 40	Very poor

Bulk density:

An accurately 2g quantity of powder from each formula was weighed. Then filled into a 10 mL measuring cylinder & measure the volume of the powder. Calculate the bulk density by using the following formula.

$$Bulk\ density = \frac{m}{v}$$ ----------Eq. no. 8

Where, m = mass of powder,

V = volume of powder

C = Tapped density:

An accurately weighed 2g quantity of powder from each formula was filled into a 10 mL measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2-seconds intervals. The tapping was continued until no further change in the volume was noted. The tapped density was calculated by using following formula.

$$Tapped\ density = \frac{m}{v - v0}$$ ---------- Eq. no. 9

Where, m = mass of powder,

V = before tapping volume of powder

V0 = after tapping volume of powder.

Compressibility Index (%):

The flow ability of powder can be evaluated by comparing the bulk density (D0) and tapped density (Df) of powder and the rate at which it packed down.

Compressibility index is calculated by

$$\textit{Compressibility index}\ (\%) = \frac{(Df - D0)}{Df} \times 100 \text{----------} \quad \textbf{Eq. no. 10}$$

Where, D0 = Bulk density,

D f = Tapped density

The Relationship between % compressibility and Type of flow is shown in table

a. **Hausner's Ratio:**

It is the ratio of tapped density to bulk density. [130, 131]

$$\textit{Hausner's Ratio} = \frac{Df}{D0} \text{----------Eq. no. 11}$$

Where, D_0 = Bulk density

D_f = Tapped density

Table No:3 Relationship between ratio and Type of flow

SR. NO.	RATIO	FLOW
1	Less than 1.25	Good flow
2	Greater than 1.5	Poor flow
3	Between 1.25 to 1.5	Added glident to improve flow

Physico-chemical Evaluation of Tablets

All prepared matrix tablets were evaluated for the following parameters such as shape of tablet, hardness, friability, drug content and drug release properties.

a. Shape of Tablets:

Tablets were examined under the microscope for the shape of the tablet.

b. Tablet Dimensions:

Thickness and diameter were measured using a calibrated Vernier caliper. 3 tablets of each formulation were picked randomly and thickness was measured individually. [129]

c. Weight variation:

The causes for weight variation can be divided into granulation and mechanical problems. If the granule size is large, the dies will not be uniformly filled. Similarly mechanical problems can be traced of lower punches of non-uniform length. The average weight is determined by weighing 20 tablets. Not more than two tablets deviate from the average weight by a percentage greater than that given and no tablet deviates by more than double that percentage. Weight variation tolerances for uncoated tablets are shown in table no.10.

SR. NO.	AVERAGE WEIGHT OF TABLETS (MG)	MAXIMUM DIFFERENCE ALLOWED
1	130 or less	10
2	130-324	7.5
3	More than 324	5

Table No: 4 Average weight of tablets

a. Hardness:

Hardness was measured using in Monsanto Hardness tester that measures the pressure with coiled spring. [129]

b. Friability:

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). 6 tablets were initially weighed (W_0 initial) and transferred into friabilator.

The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again ($W_f$final). The % friability was then calculated by- [129]

$$\%F = 100 \times \left(1 - \frac{w0}{wf}\right) \quad \text{— Eq. no. 12}$$

% friability of tablets less than 1% was considered acceptable

Determination of dissolution profile:

Freshly prepared dissolution media was placed in vessels of dissolution test apparatus USP type II model (figure no.12).According to USP standard the tablet was placed first 2hrs in 0.1N HCl and further in phosphate buffer pH 6.8. These conditions of biopharmaceutical test were considered to mimic the body environment according to pharmacopeias. Dissolution study was conducted on six matrix tablets of Venlafaxine HCl using USP type II apparatus. The temperature was maintained at 37.5±1ºC and rotating speed of baskets was 50 rpm. At the specific time interval 5 mL sample solution was withdrawn from each vessel and filtered through whatmann filter paper. Same amount of dissolution medium was added in the vessels to maintain the sink condition. Further dilute the sample up to 10 mL with phosphate buffer pH 6.8. (136)then measure the absorbance of standard and Sample solution in 1 cm cell on a suitable UV spectrophotometer at 225 nm, using dissolution medium as blank. Record the absorbance and calculate the percentage of Venlafaxine HCl dissolved in dissolution media by using following formula.

$$\text{Drug release} = \frac{Absorbance\ of\ tablets}{Absorbance\ of\ standard} \times 100$$

RELEASE KINETICS:

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were modeled in following types:

1) Cumulative percentage drug released Vs Time (In-vitro drug release kinetics)
2) Cumulative percentage drug released Vs Square root of time Higuchi‟s model)
3) Log cumulative percentage drug released Vs Time (First order release kinetics)
4) Log cumulative percentage drug released Vs Log time (Peppas model)(56, 57)

Results and Discussion:

Pre-formulation Evaluation

Solubility:

Table No: 5 Solubility Study of Venlafaxine hydrochloride

Sr. No.	Solvent	Solubility data
1.	Water	Freely Soluble
2.	Dimethyl sulfoxide	Soluble

Melting Point:

Sr.No	Standard M.P. (°C)	Observed M.P. (°C)	Mean M.P. (°C)
1	215-217 (°C)	214 (°C)	216(°C)
2		218 (°C)	
3		216(°C)	

Table No: 6 Melting Point of Venlafaxine hydrochloride

UV Visible Spectroscopy

Determination of λ max

The UV visible spectrum of Venlafaxine hydrochloride in Phosphate buffer pH 7.4 shows λ_{max} 234 nm as shown in figure

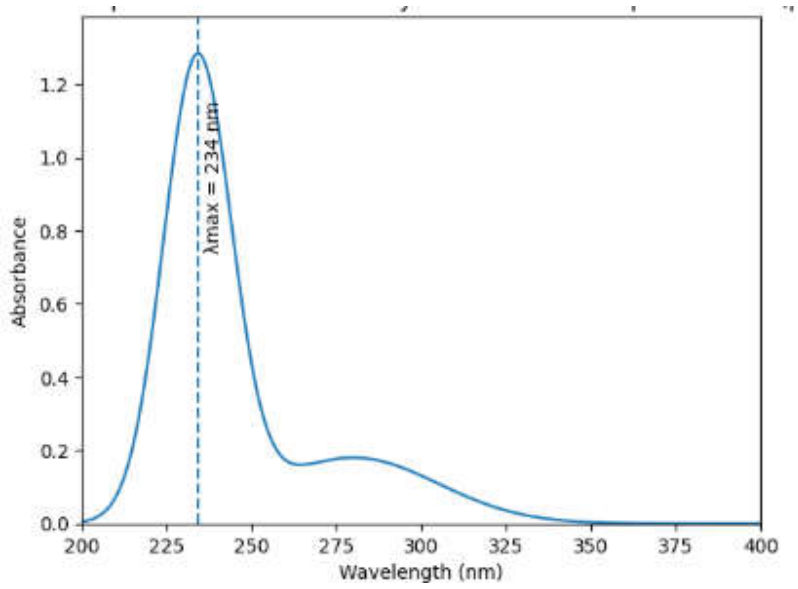


Fig No: 1 **UV visible spectrum of Venlafaxine hydrochloride**

Calibration Curve of Venlafaxine Hydrochloride in Phosphate Buffer 7.4-

The following table 7.4 shows the calibration curve data of different dilutions of Venlafaxine Hydrochloride in Phosphate buffer pH 7.4 at wavelength 234 nm. The calibration curve was plotted as shown in figure 7.1 in concentration range of 2-10 µg/ml. After regression of data as shown in table 7.4 value of R^2 was found to be 0.9997 which indicated linearity.

Table No: 7 Calibration Curve data of Venlafaxine Hydrochloride in Phosphate buffer pH 7.4 at wavelength of 234 nm.

Sr. No.	Concentration (µg/ml)	Absorbance
1.	2	0.07
2.	4	0.135
3.	6	0.209
4.	7	0.273
5.	10	0.341

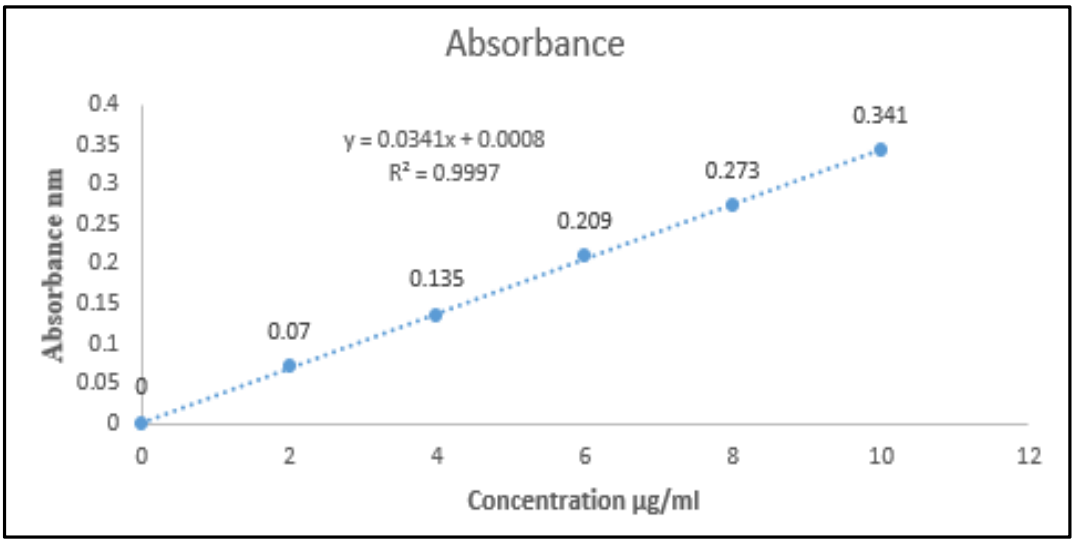


Fig No: 2 Calibration Curve of Venlafaxine Hydrochloride in Phosphate Buffer 7.4

FTIR Spectroscopy of Venlafaxine Hydrochloride-

The FTIR spectrum of Venlafaxine Hydrochloride is as shown in figure

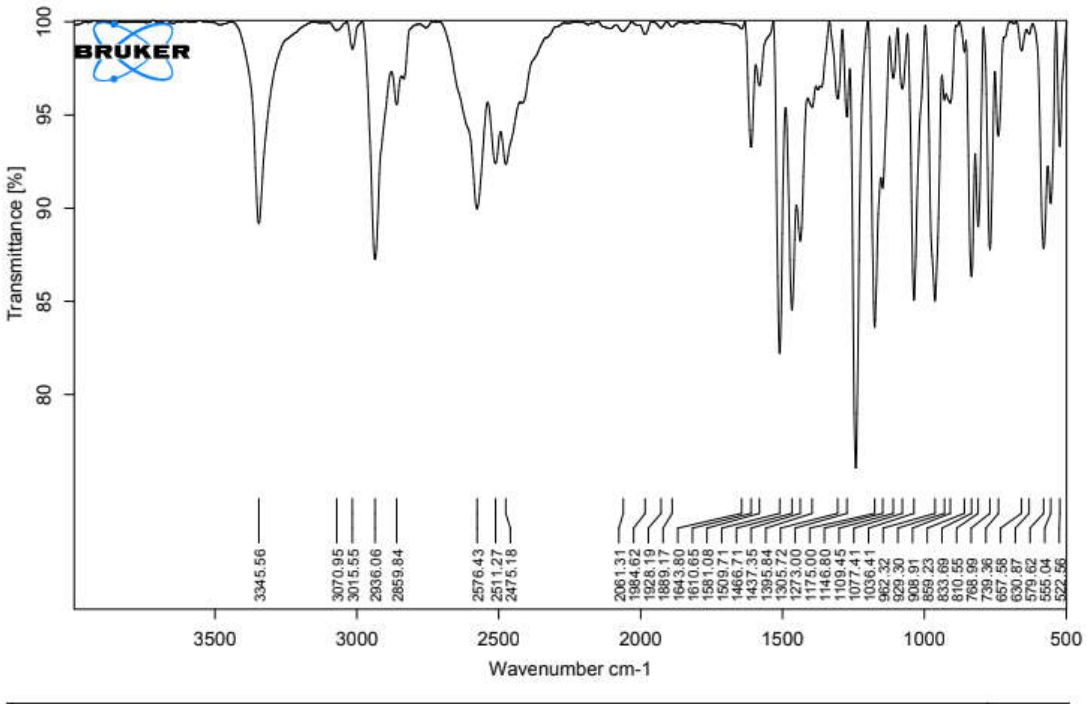
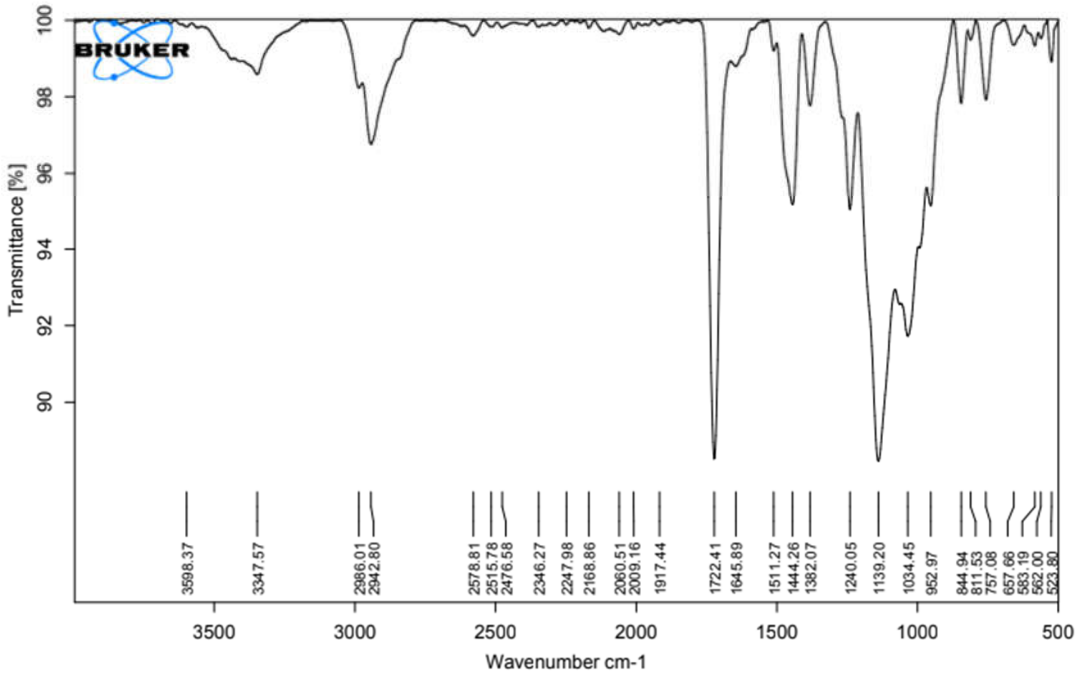


Fig No: 3 FTIR spectra of Venlafaxine hydrochloride

Compatibility Studies:

The FTIR spectra of physical mixture of Venlafaxine Hydrochloride and polymer Eudragit RSPO, HPMC K4 have retained characteristics peaks of pure drug and hence confirmed no significant interaction between drug and polymer mixture. **Figure 4** shows that FTIR spectra of drug and physical mixture.



F. **Differential Scanning Calorimetry-**

The DSC studies was carried out for pure drug Venlafaxine hydrochloride. The thermogram revealed occurrence of sharp endothermic peak at 219.5^{0}C, confirming crystalline nature of the drug.

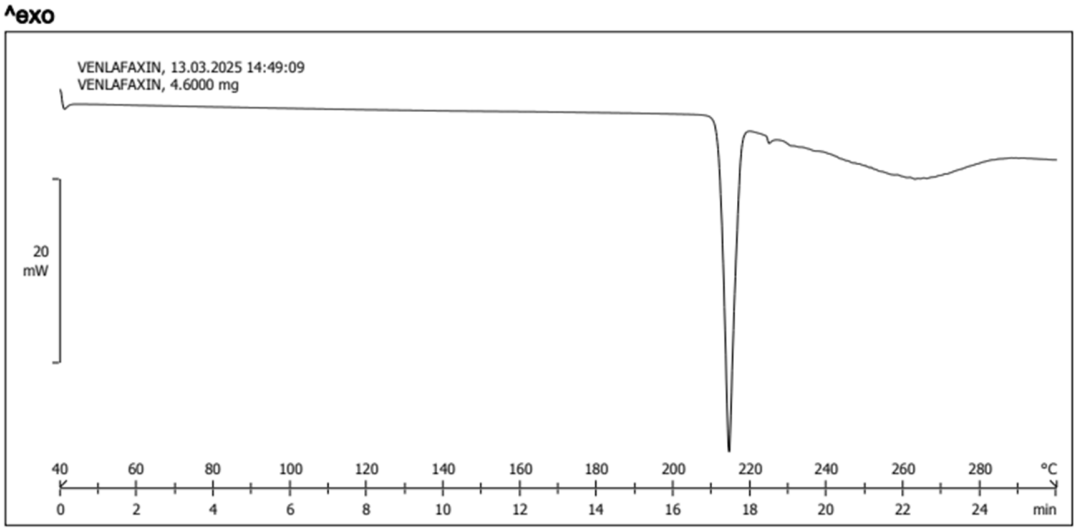


Fig No: 5 DSC Thermogram of Venlafaxine Hydrochloride

Evaluation of Venlafaxine Hydrochloride Tablets

7.3.1 Flow properties:

Flow properties describe how a powder or granular material behaves under movement or flow conditions. These properties are essential across various industries, including pharmaceuticals, and material science, where powder flow ability significantly affects manufacturing efficiency and product quality. Below is an overview of key flow properties.

Table No: 8 Evaluation of flow properties of Optimize F7 Batch of Venlafaxine Hydrochloride Tablets

Parameter	F7 Batch of Venlafaxine Hydrochloride Tablets
Bulk Density (gm/ml)	0.40 ±0.0 153
Tapped Density (gm/ml)	0.41 ±0.0 2
Angle of Repose (gm/ml)	24.19 ±0.6 9
Carr's Index (gm/ml)	7.60 ± 0.81
Hausner's Ratio (gm/ml)	1.03 ± 0.051

Hardness (*N*):

The average hardness values for all formulations were measured using a Monsanto hardness tester. The results are detailed in Table no. 7.12. The hardness values range from 3.26±0.025 to 4.02±0.0643 kg/cm2.

Friability:

All formulations exhibited a friability percentage below 1%, confirming the tablets' mechanical strength.

Thickness (mm):

Thickness of all formulations was measured by using vernier Calipers. The Thickness value ranges from 2.25±0.010 to 2.82±0.0306

Weight variation test:

The weight variations for all formulas are presented in Table No. 7.12. As the percentage of weight variations was within 7.5% of the average weight, all formulated optimized batch of Venlafaxine Hydrochloride (F7) passed the weight variation test. The tablets demonstrated consistent weights and acceptable standard deviation values.

Table No:9 Evaluation of Tablets of F7 Batch of Venlafaxine Hydrochloride Tablets

Parameter	Evaluation of Tablets of F7 Batch of Venlafaxine Hydrochloride Tablets
Thickness (mm) ±SD	2.25± 0.010
Hardness (Kg/cm2) ±SD	3.5± 0.37
Friability (%) ±SD	0.49± 0.026
Weight variation (mg) ±SD	200± 1.5

Post-Compression Evaluation Result

In-Vitro* Drug Release*:

Release rate of all the formulations were studied up to 08 hours using USP apparatus 2(Paddle method) at 50 rpm. The Dissolution media is Distilled Water for 12 hrs.(900 ml)maintained at 37°C ±0.5°C temperature. Dissolution parameters are mentioned as Dissolution apparatus USP

Type 2, Paddle, Dissolution media Distilled Water, Volume of the media 900 ml. sampling volume 5 ml. Rotation speed 50 rpm. Temperature 37 ± 0.5 0C

Table No: 10 *In-Vitro* Release of Venlafaxine Hydrochloride Tablets

Sr. No.	Time	F1%	% F2	% F3	%F4	%F5	%F6	%F7	%F8	%F9
1	60	15.72	14.42	18.97	16.35	17.67	12.25	14.35	16.37	15.18
2	120	19.93	18.19	18.19	21.93	20.16	17.75	19.41	23.41	19.88
3	180	24.61	23.51	23.14	24.07	25.7	21.1	24.46	26.8	24.28
4	240	28.65	26.68	30.65	29.55	28.45	26.21	29.34	33.46	30.7
5	300	32.5	37.46	39.5	36.54	33.67	29.18	37.61	42.54	35.71
6	360	33.77	43.31	43.31	45.21	45.7	39.98	51.73	48.42	44.35
7	420	39.38	55.7	59.74	54.38	60.08	50.61	64.02	60.19	56.65
8	480	41.99	63.52	63.11	61.35	71.69	59.57	78.96	65.08	64.72

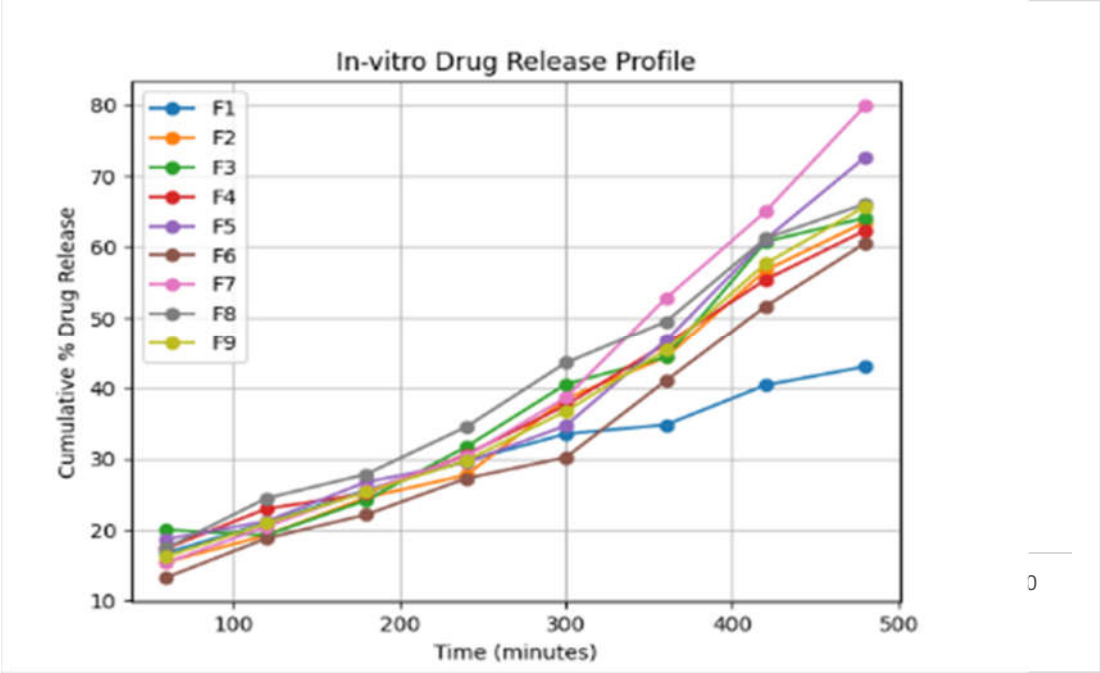


Fig No: 6 In vitro Drug release profile

Kinetic modeling of drug release:

To find out the mechanism of drug release from hydrophilic matrix, all Nine formulation of the prepared matrix tablets of Venlafaxine Hydrochloride are subjected to in-vitro release studies. The result obtained in in-vitro release studies were plotted indifferent kinetic model of release data treatment as follows

1. Cumulative percent drug released vs. time (zero order rate kinetics)

2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)

3. Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)

4. Log of cumulative % release vs. log time (Peppas Exponential Equation).

1. Cumulative percent drug released vs. time (zero order rate kinetics)

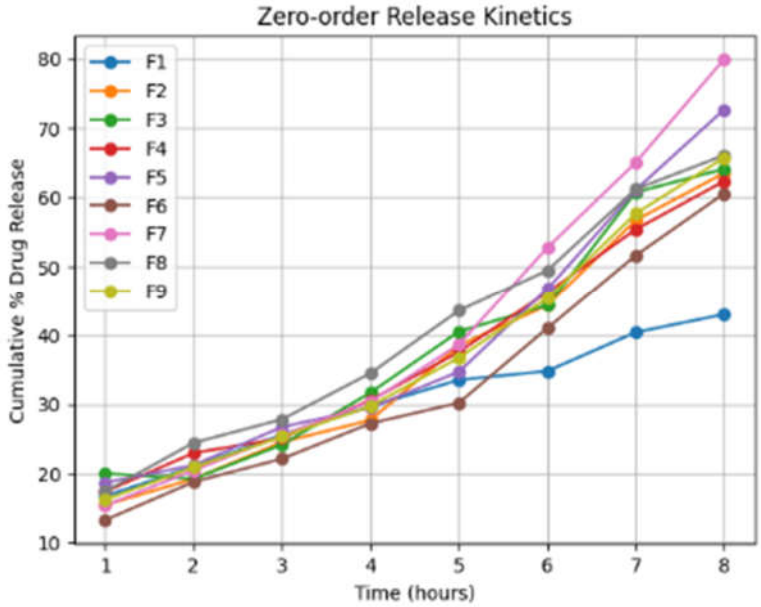


Fig No: 7 Cumulative percent drug released vs. time (zero order rate kinetics)

Log cumulative percent drug retained vs. time (First Order rate Kinetics)

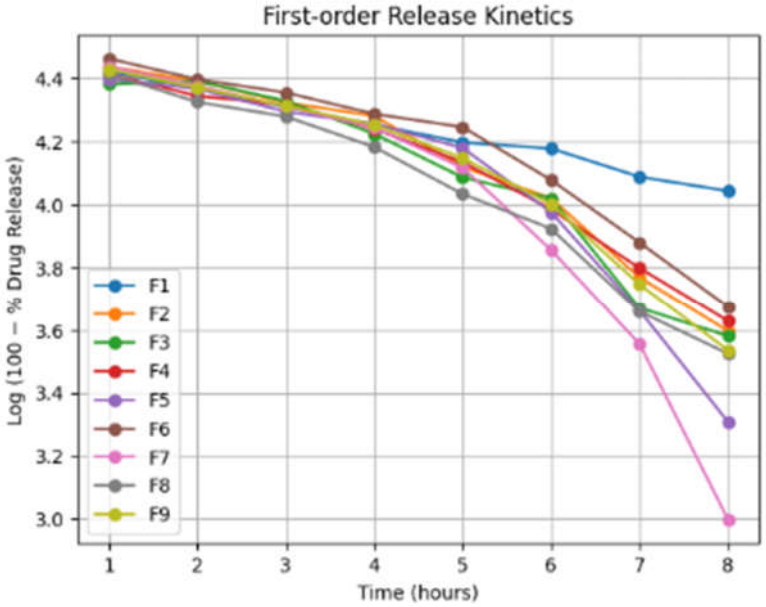


Fig No: 8 Log cumulative percent drug retained vs. time (First Order rate Kinetics)

Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)

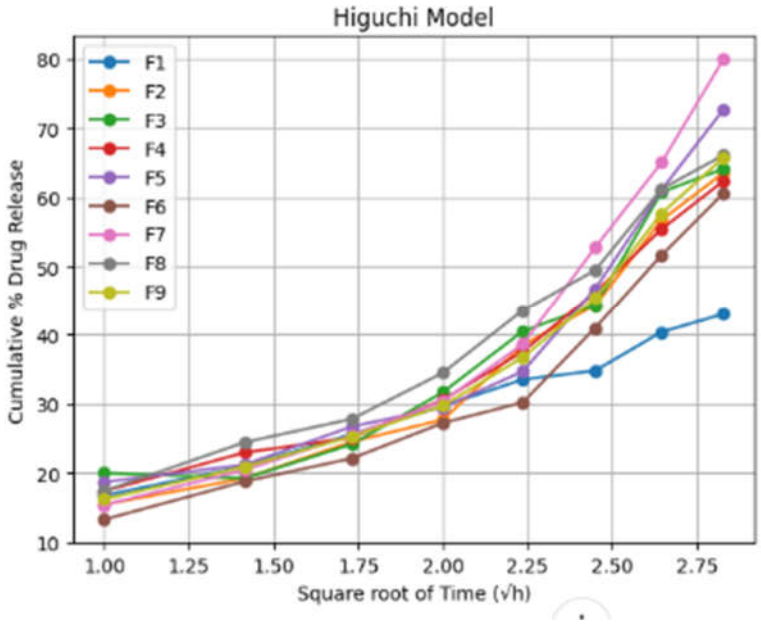


Fig No: 9Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)

Log of cumulative % release vs. log time (Peppas Exponential Equation).

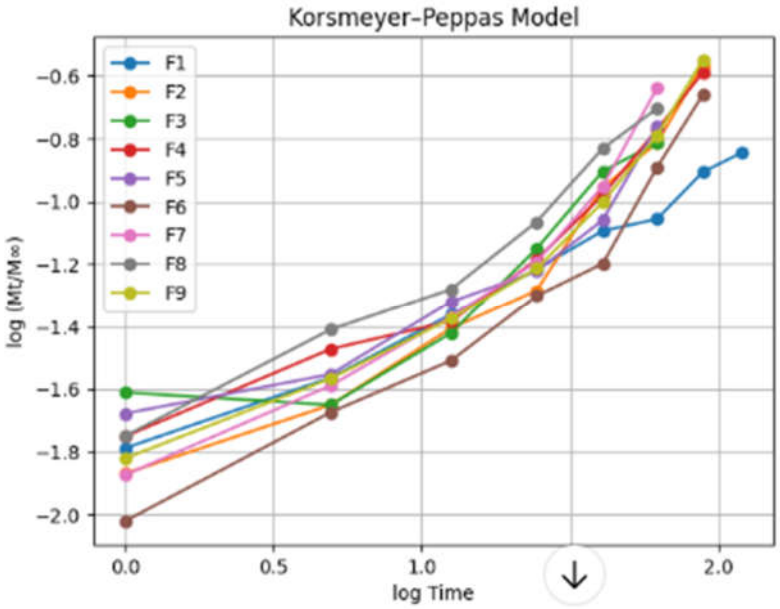


Fig No: 10 Log of cumulative % release vs. log time (Peppas Exponential Equation).

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