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FORMULATION AND DEVELOPMENT OF VENLAFAXINE EXTENDED RELEASE ORAL MATRIX TABLETS

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ABSTRACT
The main objective of this research is to develop and characterize venlafaxine extended Release Oral Matrix Tablets. Venlafaxine oral tablet is used to treat depression (immediate-release tablet and extended-release tablet). The matrix tablets of venlafaxine hydrochloride are prepared by wet granulation method. in the present formulation, the API venlafaxine is taken 225mg in all the formulations. HPMC K4M, HPMC K15MCR, HPMC K100LV CR, HPMC E50 LV AND Acryl-EZE RSPO polymers were used as rate retarding agents in twelve formulations(F-1 to F-12). the objective of the present study was to develop tablets of various formulations of venlafaxine oral matrix tablets. and the powder blend showed satisfactory flow properties, compressibility. The compressed tablets were undergone for precompression and post compression studies. All the physical characteristics of the fabricated tablets were found to with in the acceptable limits. among the formulations studied, F1,F3,F5,H7 and F9 formulations drug release was very fast and 90% of the drug was released in first 12hrs only. further batches were prepared and F12 containing 1:8 ratio of Eudragit RSPO and HPMC E50LV showed extended release up to 24 hrs and releases 97.54% of drug. The release mechanisms were explored and explained by zero oeder, first order, higuchiand korsmeyer-peppas equations.primary ten formulations were prepared by using two variable amounts of four polymers, HPMC K4M(50 mg,100mg) in the formulations from F-1 to F-2, HPMC K15M CR(50 mg,100mg) in the formulations F3-F4, HPMC K100 LV(50 mg,100mg) in the formulations F5-F6, HPMC E50 LV(50 mg,100mg) in the formulations F7-F8 and Eudragits RSPO in the formulations F9-F10, then two formulations were prepared by using combination of HPMC E50 LV and Eudragit RSPO in the formulations F11-F12. among these 12 formulations F12 was selected as the optimized formulation of extended release tablets for 24 hrs.

KEYWORDS: Acryl-EZE, Anti Depressant, Extended Release Oral Matrix Tablets, Wet Granulation.

INTRODUCTION
Drug delivery systems based on controlled release pattern are increasing in popularity because of their reduced frequency of administration. The main objectives of controlled release drug delivery system is to ensure safety, to improve efficacy of the drugs and to improve patient compliance. this is achieved by better control of plasma drug levels and less frequent dosing, so various methods including; ion-exchanging resin complexes, matrix tablets, osmotic pump as well as microencapsulation process have been utilized to prepare the extended release products.

Venlafaxine belongs to a class of antidepressant drugs called serotonin norepinephrine reuptake inhibitors (SNRIs). SNRIs work by increasing the levels of substances called serotonin and norepinephrine in your brain. Having more serotonin and norepinephrine in your brain can improve your symptoms of depression and anxiety. After oral administration, venlafaxine is completely absorbed from the gastrointestinal tract and undergoes extensive first pass metabolism and having low bioavailability(45%) with biological half life of 5 hrs.

Venlafaxine oral matrix tablets were prepared by wet granulation method by using different grades of HPMC polymers and acrylic acid polymers. HPMC polymers are hydrophilic in nature and acrylic acid polymers are Reliable time-controlled release of active ingredients and Therapeutically customized release profiles. In matrix tablets drug is released either by diffusion, degradation and swelling followed by diffusion. in this study polymethacrylate polymers are pH independent swelling of polymethacrylate RSPO and releases the drug from the matrix. in the present study an attempt have been made to formulate venlafaxine as an extended release oral matrix tablets by using rate retarding polymers and their combination with polymethacrylate polymers.

Table 1: Materials and methods.

Materials and suppliers company name	
Materials	**Supplier**
venlafaxine(API)	Dr.Reddy's, Hyderabad
HPMC K4M	M.B Sugars & pharmaceuticals
Eudragit RSPO	Evonik industries, germany
HPMC K15M	M.B Sugars & pharmaceuticals
HPMC E 50 LV	Cadila pharma, ahmedabad, India.
HPMC K100LV	M.B Sugars & pharmaceuticals
Avicel 102	FMC bio polymer
Magnesium stearate	Loba chemie

PREPARATION OF MATRIX TABLETS
METHODOLOGY
Method

Accurately weigh the drug with polymer(HPMC, Eudragit) and MCC and crospovidone, pass through 40 no. sieve and mix it roperly for 3-5 min in a mortar. prepare the binder solution by dispersing Copovidone in isopropyl alcohol. granulation of the above mixture is done by prepared binder solution until end point is obtained(dough, mass). pass the mass via 16 no sieve and keep in a tray dryer for the dried granules to be obtained. remove the dried granules from oven and pass via sieve 12 to get optimum sized granules. lubrication is done by using aerosol and pvp k30 previously passed through 40 sieves of the granules for 3-4 min. lactose is used as filler. compression is done by using 16 station single retary CADMACH punching machine.

Table 2: Formulation development.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
venlafaxine(mg)	225	225	225	225	225	225	225	225	225	225	225	225
Microcrystalline cellulose(diluent)(mg)	200	150	200	150	200	150	200	150	200	150	130	70
Crospovidone(disintegrant)(mg)	90	90	90	90	90	90	90	90	90	90	90	90
HPMC K4M(mg)	50	100	--	--	--	--	--	--	--	--	--	--
HPMC K15M CR(mg)	--	--	50	100	--	--	--	--	--	--	--	--
HPMC K100 LV(mg)	--	--	--	--	50	100	--	--	--	--	--	---
HPMC E50LV(mg)	--	--	--	--	--	--	50	100			100	160
Eudragit RSPO(mg)	--	--	--	--	--	--	--	--	50	100	20	20
PVP k30(4%)	24	24	24	24	24	24	24	24	24	24	24	24
Colloidal silicondioxide(2%)	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate(mg)	1	1	1	1	1	1	1	1	1	1	1	1
Total tablet weight(mg)	600	600	600	600	600	600	600	600	600	600	600	600

Evaluation of venlafaxine granules

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Bulk density(B.D): It is defined as ratio of total mass of the powderto the bulk volume of powder.
It is expressed in g/cc and is given by,
$B.D=m/v_o$

Where,
M= Mass of powder, V_o = Bulk volume of powder

Tapped density is defined as ratio of total mass of the powder to the tapped volume of powder.It is expressed in g/cc and is given by:
$T.D=M/V_t$

Where,
M= Mass of powder,V_t = Tapped volume of powder

Compressibility Index(C.I): the flow ability of powder can be evaluated by comparing the bulk density(BD) and tapped density(TD) of powder and the rate at which it packed down.compressibility index was calculated using the following formula;
C.I=100×(1-1/H.R).

Hausner's ratio(H.R): It is measurement of frictional resistance of the drug. the ideal rang should be 1.2-1.5, it was determined by the ratio of tapped density and bulk density.
Hausner's ratio = (Tapped density)/(Bulk density)

Flow properties (Angle of repose (Ɵ))

It is the maximum angle possible between surface of pile of powder and the horizontal plane, can be used to measure frictional forces in a powder.
$Ɵ= \tan^{-1}(h/r)$

Where,
Ɵ= angle of repose
H is height of the powder in cms

R is the radius of heap of powder

B) Evaluation of matrix tablets

This includes;

Uniformity of weight (weight variation): 20 tablets were weighed individually and collectively. average weight was calculated from the total weight of all tablets. the individual weights were compared with the average weight. the percent deviation was calculated using the following formula:

$$\%\text{deviation} = \frac{\text{individual weight-average weight}}{\text{Average weight}} \times 100$$

The percentage difference in the weight variation should be with in the permissible limits of 10% as per the limits mentioned as per Indian pharmacopoeia.

Hardness test: Hardness(diametral crushing strength) is a force required to break a tablet across the diameter. the hardness of a tablet is an indication of its strength. the hardness was tested using Monsanto hardness tester.

Friability testing of tablets: To evaluate the degree of friability of the tablets from each batch, ten tablets were randomly selected, dusted and weighed. The tablets were placed in a Roche friabilator & subjected to its tumbling action at 25 revolutions per minute for 4 minutes. Then after, the tablet were once again dusted and reweighed to determine the % loss of weight.

$$\text{Friability} = \frac{\text{weight of the tablet before test- weight of the tablet after test}}{\text{Weight of the tablet before test}} \times 100$$

Thickness: thickness of the tablets was calculated by the use of vernier calipers.

Disintegration studies of tablets: Six tablets from each batch were utilized for disintegration studies in distilled water at 37°c using an educational sciences – disintegration apparatus. The disintegration time was taken to be the time where no granule of any tablet was left on the mesh of the apparatus.

In-vitro drug release studies: In-vitro drug release studies were undertaken using USP-II apparatus (paddle method). The dissolution medium was 900 ml of pH 6.8 buffers as the dissolution medium. the medium was allowed to equilibrate to temp of 37.0 ± 0.5°C. the tablet was placed in the vessel and the vessel was covered the apparatus was operated for 24 hrs in pH 6.8 buffer at 50 rpm. at definite time intervals of 5ml of the aliquot of sample was withdrawn and filtered(0.45µm). the volume replaced with equivalent amount of the fresh dissolution medium. the samples were analyzed spectrophotometrically at 226 nm using UV-spectrophotometer.

Content uniformity: For determination of drug content three tablets from each formulation were weighed individually and powdered. the quantity of powder was equivalent to 10mg. the equivalent weight venlafaxine was transferred into 100ml volumetric flask diluted to 100ml with sufficient amount of buffer(pH 1.2). then aliquot of the filtrate was diluted suitably and analysed spectrophotometrically at 226nm against blank.

RESULTS AND DISCUSSION

Standared calibration curve of venlafaxine in phosphate buffer pH 6.8

Wavelength of maximum absorption:226 nm.

Concentration and absorbance of venlafaxine in phosphate buffer pH 6.8:

Table no: 3: Standard curve of venlafaxine.

s.no	concentration(µg/ml)	Absorbance at 226 nm
1	0	0
2	2	0.16
3	4	0.34
4	6	0.51
5	8	0.67
6	10	0.86

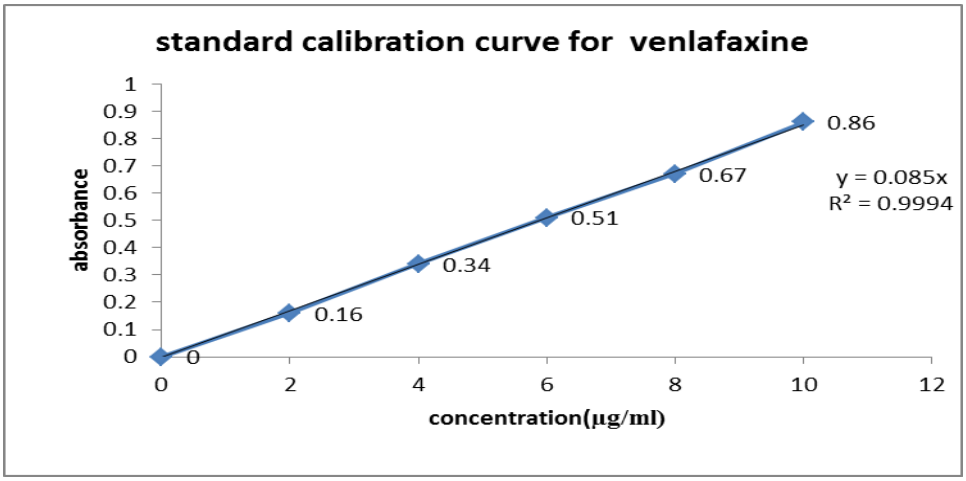

Fig no. 1: Standared calibration curve for venlafaxine.

Table no: 4: Physical observation of compatibility study.

Drug & excipients (ratio 1:1)	Observation			Results
	Room temp	40˚c/75% RH after 30 days	2-8˚c after 30 days	
venlafaxine(API)	White to off white powder	White to off white powder	White to off white powder	compatible
HPMC K4M + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible
Eudragit RSPO + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible
HPMC K15M + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible
HPMC E 50 LV + Carbamazepine	White to off white powder	White to off white powder	White to off white powder	compatible
HPMC K100LV + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible
Micro crystalline cellulose + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible
Crospovidone + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible
Magnesium stearate + venlafaxine	White to off white powder	White to off white powder	White to off white powder	compatible

From the above Drug–Excipient compatibility studies data, it is clear that venlafaxine is compatible with all the excipients tested above. Since there was no interaction (or) physical change observed between the drug and all other excipients, the selected excipients were found to be compatible with the drug.

Table 5: Summary of Excipients Selection.

S NO	EXCIPIENTS	CATEGORY
1.	Microcrystalline cellulose(avicell)	Diluent
2.	Crospovidone(ludipress)	Disintegrant
3.	HPMC K4M(methocell)	Rate retarding polymer
4.	HPMC K15M CR	Rate retarding polymer
5.	HPMC K100 LV	Rate retarding polymer
6.	HPMC E50LV	Rate retarding polymer
7.	Eudragit RSPO	Rate retarding polymer
8.	Colloidal silicondioxide(mg)	Glidant
9.	Magnesium stearate	Lubricant

Evaluation of powder blend

Bulk density, tapped density, % compressibility, hausner's ratio and angle of repose.

Table 6.

F.No	Bulk Density(g/ml)	Tapped Density(g/ml)	Compressibility Index(%)	Hausner's Ratio	Angle of Repose(˚)
F1	0.503±0.05	0.59±0.01	15.68±0.01	1.24±0.01	25.07±
F2	0.513±0.03	0.599±0.03	15.42±0.05	1.20±0.03	23.74±0.02
F3	0.519±0.01	0.56±0.06	15.47±0.01	1.22±0.01	25.16±0.01
F4	0.506±0.05	0.598±0.01	14.88±0.03	1.21±0.02	26.32±0.05
F5	0.508±0.02	0.578±0.06	15.53±0.01	1.16±0.05	27.02±0.01
F6	0.515±0.05	0.588±0.5	15.63±0.05	1.15±0.02	29.73±0.03
F7	0.512±0.03	0.571±0.03	15.67±0.04	1.18±0.01	25.82±0.02
F8	0.515±0.02	0.578±0.02	15.22±0.05	1.22±0.03	28.01±0.01
F9	0.508±0.08	0.579±0.04	14.92±0.02	1.16±0.04	24.02±0.05
F10	0.511±0.02	0.587±0.01	15.42±0.01	1.10±0.01	22.3±0.02
F11	0.513±0.06	0.579±0.02	15.65±0.02	1.37±0.03	29.01±0.01
F12	0.511±0.07	0.601±0.03	14.60±0.05	1.27±0.01	28.5±0.06

Physical parameters of tablets of each formulation:

Table 7.

F.no	Weight varation (mg)	Thickness(mm)	Hardness(kp)	Friability(%)	Assay(%)
F1	598.67	6.1	7.1	0.06	97.49
F2	599.33	6.5	6.83	0.04	98.24
F3	601.33	5.8	6.93	0.03	98.32
F4	601.67	5.9	7.5	0.09	99.42
F5	602.00	6.7	7.03	0.02	98.87
F6	598.00	6.8	7.33	0.04	100.05
F7	599.67	6.8	7.10	0.03	98.99
F8	599.00	6.9	6.80	0.08	97.64
F9	601.33	5.8	6.90	0.06	99.45
F10	599.21	6.5	7.5	0.05	99.56
F11	598.00	6.9	6.85	0.02	97.56
F12	597.02	6.8	7.6	0.06	100.35

- Each value represents the mean ± standard deviation(n=3)

Dissolution data table

Table 8: In-vitro drug release study.

Time in hours	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	0
2	18.38	18.96	20.42	20	24.13	22.28	18.68	16.89	17.91	17.5	15.2	10.7
4	39.13	36.25	39.38	38.33	46.45	40.85	36.02	32.12	35.41	34.38	24.58	18.62
6	54.75	51.04	55.41	50	61.57	56.47	49.92	49.82	51.67	47.91	33.12	27.27
8	72.45	68.33	74.58	67.29	74.07	68.31	69.56	64.25	69.16	65.2	41.05	34.83
10	84.46	75.41	88.13	77.91	88.49	74.38	85.23	73.92	82.5	72.5	51.02	42.54
12	93.29	84.16	93.75	86.67	96.25	86.61	93.39	83.53	95	81.04	58.1	49.98
14		90.83		97.08		97.62		90.68		87.29	66.3	56.5
16		97.29						96.23		91.25	77.1	63.54
18										96.66	84.93	72.23
20											97.49	81.04
24												97.54

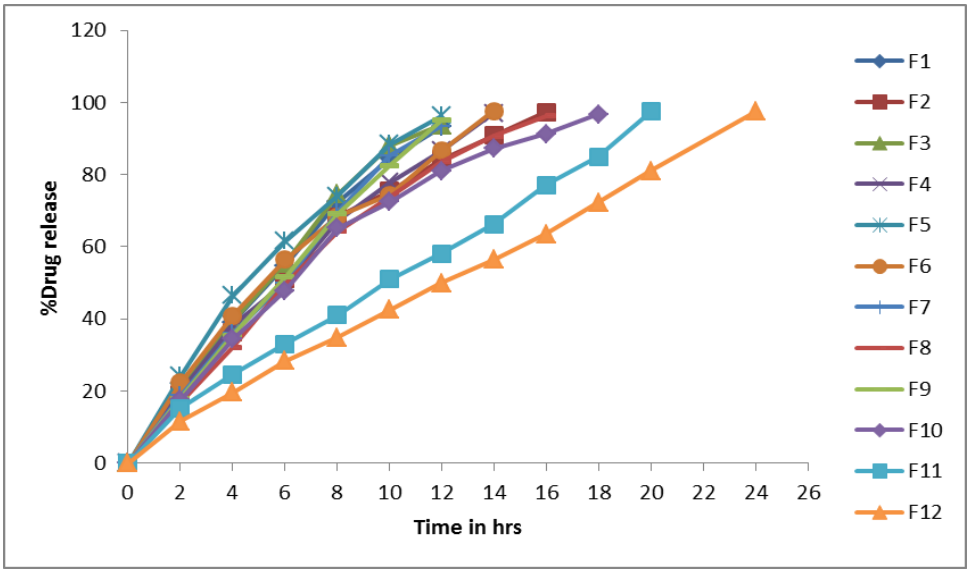

Figure 1: Cumulative % drug released formulations F1-F12.

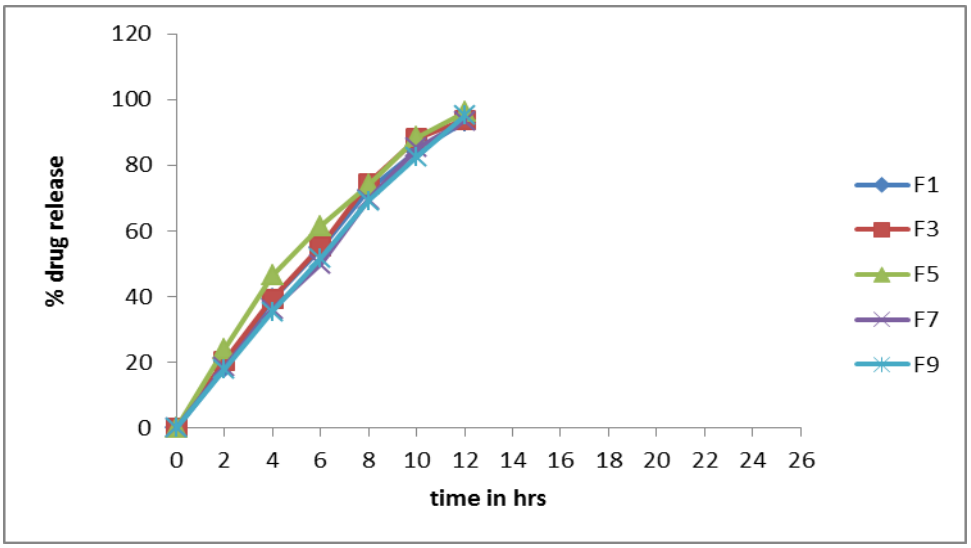

Figure 2: Cumulative % drug released formulations F1, F3, F5, F7 & F9 (8.3% polymer).

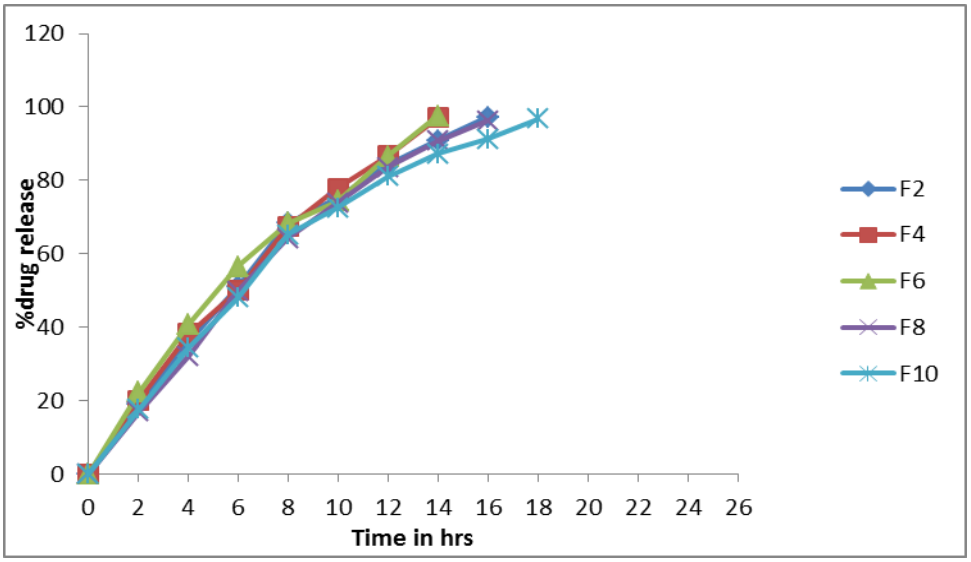

Figure 3: Cumulative % drug released formulations F1, F3, F5, F7 & F9(16.6% polymer).

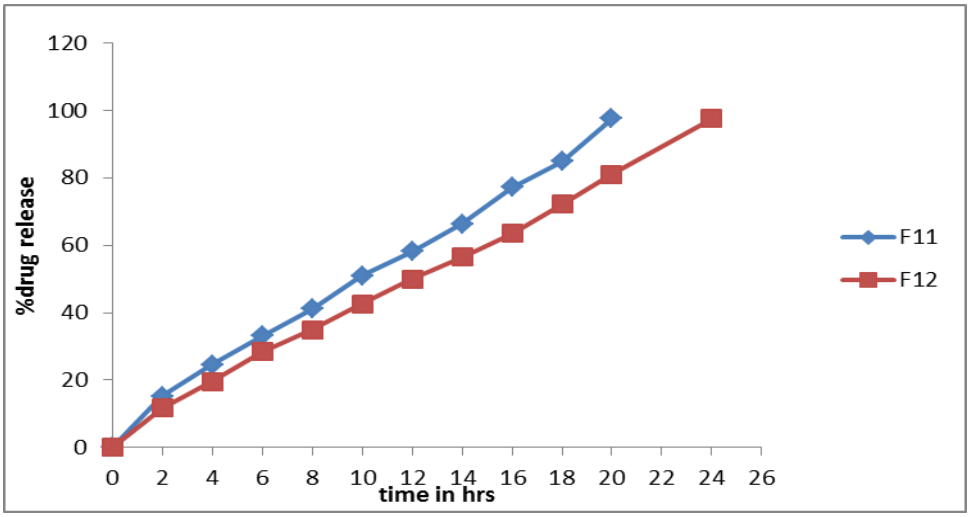

Figure 4: Cumulative % drug released formulations F11 & F12(1:4 and 1:8 ratios of polymers).

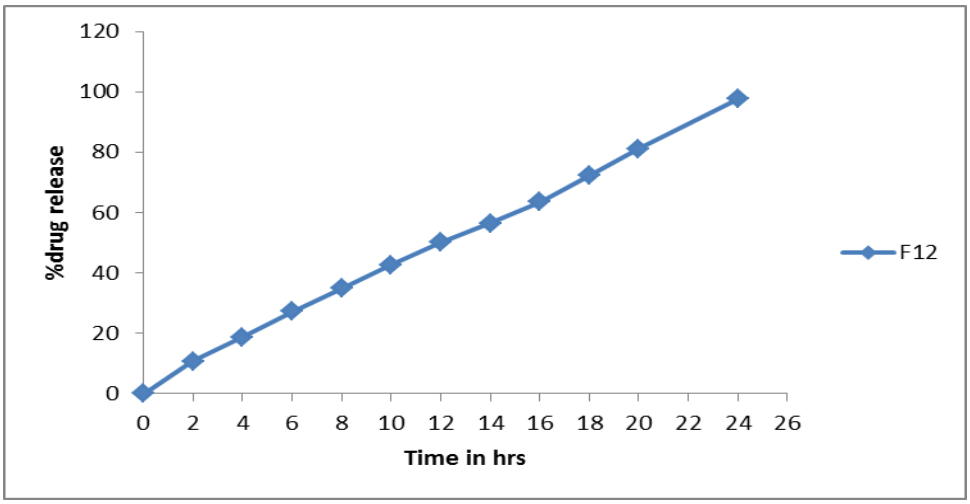

Figure 5: Cumulative % drug released formulations F12(1:8 ratios of polymers).

Release kinetic studies

Table 9: Represention of zero order kinetics.

Time (hrs)	2	4	6	8	10	12	14	16	18	20	24
F12(%CDR)	10.7	18.62	27.27	34.83	42.54	49.98	56.5	63.54	72.23	81.04	97.54

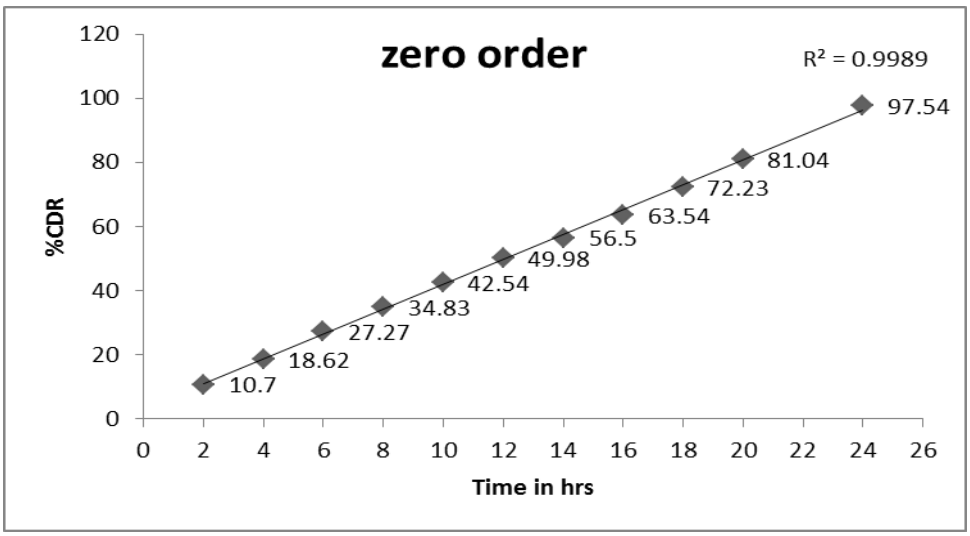

Figure 6: Zero order kinetic studies of F12.

Table 10: Represention of first order kinetics.

Time (hrs)	2	4	6	8	10	12	14	16	18	20	24
First order (log% remaining)	1.95	1.91	1.86	1.814	1.75	1.69	1.63	1.56	1.44	1.27	0.39

Figure 7: First order kinetic studies of F12.

Table 11: Representation of Higuchi model.

SQRT	1.4	2	2.4	2.8	3.2	3.5	3.7	4	4.2	4.47	4.89
Higuchi model (%CDR)	10.7	18.62	27.27	34.83	42.54	49.98	56.5	63.54	72.23	81.04	97.54

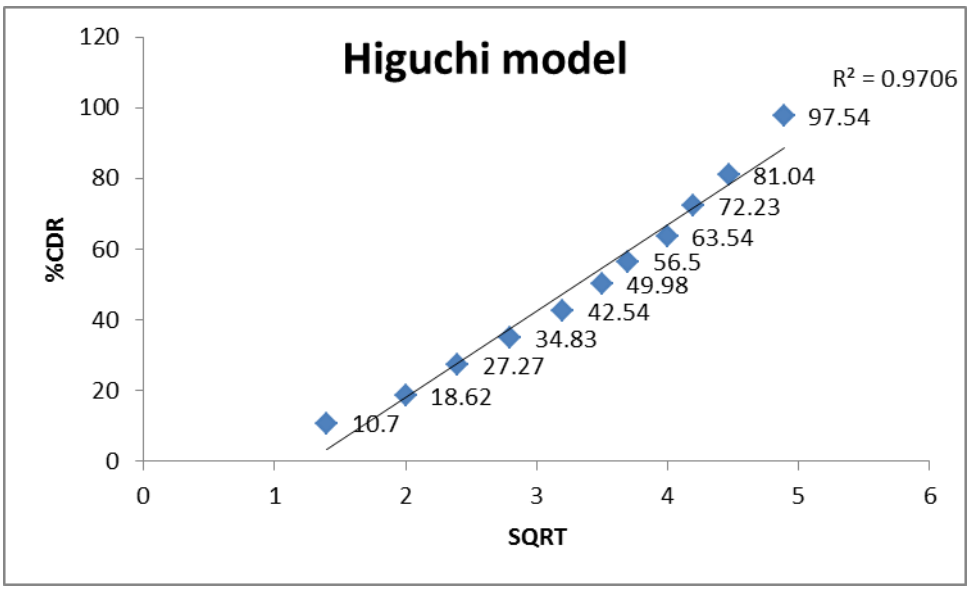

Figure 8: Higuchi equation of F12.

Table 12: Representation of Korsmeyer peppas theory.

Log T	0.301	0.602	0.778	0.903	1	1.079	1.146	1.204	1.255	1.301	1.38
Korsmeyer peppas model (Log %CDR)	1.029	1.269	1.435	1.541	1.628	1.698	1.752	1.803	1.858	1.908	1.989

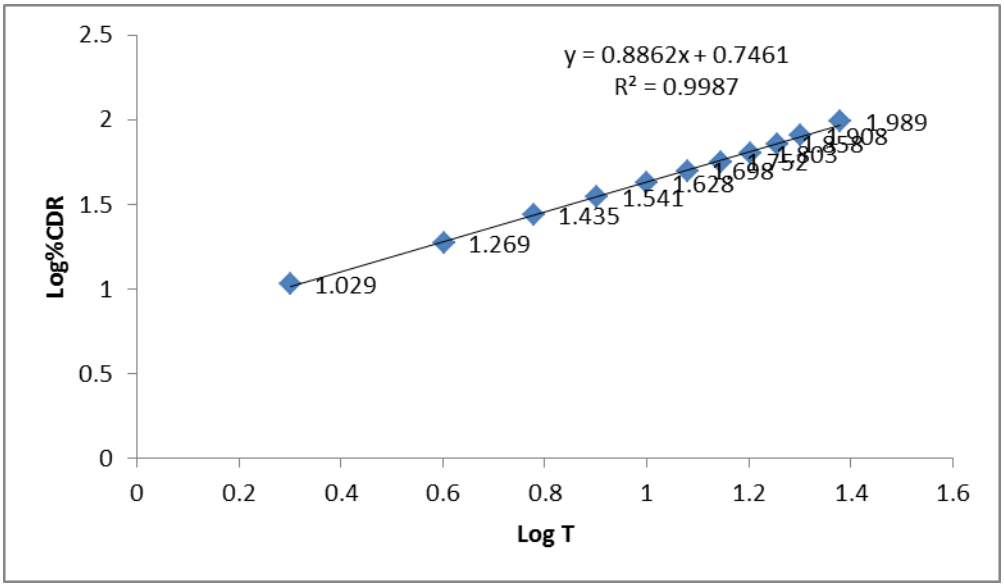

Figure 9: Korsmeyer peppas theory for F12.

Table 13: Representation of Hixson-crowell plot.

Time (hrs)	2	4	6	8	10	12	14	16	18	20	24
Cubeth root of % drug remaining)	4.46	4.33	4.17	4.02	3.85	3.68	3.51	3.31	3.02	2.66	1.34

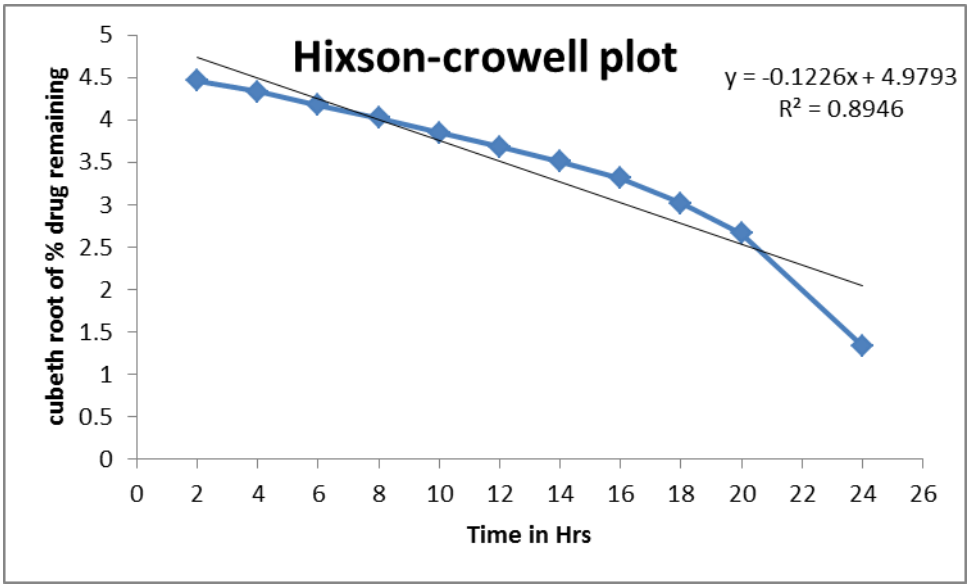

Figure 10: Hixson-crowell plot.

The kinetic investigation of the release profile gave us useful insight into the mechanism of drug release from the tablets. the release did not show any burst effect or lag time, which is indicative of a homogeneous drug distribution in the polymer matrix. the dissolution data was subjected to regression analysis and were fitted to kinetic models, viz, zero order, first order, peppas and higuchi. it was found that most of the formulations followed korsmeyer peppas release.

The 'n' value for F12 was found to be 0.886, which indicates that the release approximates non-fickian diffusion mechanism.

Hixson-crowell plot of the formulation were shown in Fig no: 10. the regression coefficient of formulation F12 was found to be 0.894. these results indicated that the release rate was limited by the drug particles dissolution rate and erosion of the polymer matrix.

Stability studies: There was no significant change in physical and chemical properties of the tablets of formulation F12 after 3 months. parameters quantified at various time intervals were shown.

Table 13: Results of stability studies of optimized formulations F12.

S.No	parameters	Initial	1 month	2 month	3 month	Limits as per specification
1	40°C/75%RH %Release	97.54	97.42	97.08	96.4	Not less than 85%

DISCUSSION

In the present study an attempt has been to formulate and evaluate ER matrix tablets of venlafaxine HCL by wet granulation technique, employing swellable polymers like HPMC(K4M,K15M,E50LV,K100LV) and Eudragit, were taken along with pharmaceutically acceptable easily available inert excipients and twelve formulations were prepared. the formulation was subjected to both pre and post formulation studies. The drug sample showed similar results as reported.

1) **Solubility:** Solubility of drug is important factor affecting its release from drug delivery system. hence solubility analysis of drug sample of venlafaxine HCL was done. the solubility of the venlafaxine was determined and found to be freely soluble in methanol, sparingly soluble in methylene chloride and soluble in water.
2) **UV spectroscopic analytical method:** Standard curve of venlafaxine HCL in ater as shownin Table no:3. wavelength of maximum absorption was found to be 226nm. the venlafaxine HCL obeyed the Beer's-Lambert law in concentration range of 2-12µg/ml at this wavelength. this is well correlated with the reported value(226nm).
3) **Drug interaction study:** Physical observation of drug and excipients had done to check compatibity between drug and excipients. this study provides no interaction between drug and polymer.

The granules prepared by wet granulation method were evaluated for various flow properties. the granules of all batches showed good flow properties evident from the results shown in table-6. the angle of repose values were ranged from 25 to 29. the results were found to be below 30; hence they have good flow ability. the carr's index ranged from 15.8 to 14.43 and hausner's ratio value ranged from 1.10 to 1.22 hence they have good flow and free flow ability.

Physical characterization of ER tablets of venlafaxine HCL:

Tablet thickness, hardness, weight variation, riability and drug content of formulated tablets of btaches from F! to F12 are presented.

1) **Uniformity of weight:** All the prepared tablets of venlafaxine HCL were evaluated for weight variation. the weight of all the tablets was found to be uniform with low values of standard deviation and with in the prescribed IP limits of ±7.5%.
2) **Hardness and friability:** The hardness of the tablet formulations was found to be in the range of 7.6 to 6.8kg/cm^2. the friability values were found to be in the range of 0.02 to 0.08%.
3) Uniformity of drug content:
4) The low values of standard deviation indicates uniform drug content with in the tablets. the percent drug content of all the tablets was found to be in the range of 97.49 to 100.35 percent(which was with in the acceptable limits of ±5%)
5) **In-vitro dissolution study:** In-vitro dissolution studies were performed in pH 6.8 buffers on the above promising formulation, namely, formulation 12. in the dissolution studies the ratio (1:8) of Eudragits and HPMC E50 LV were showing better drug release up to 24hrs.

Effect of polymers(HPMC and Eudragit RSPO) on in-vitro release venlafaxine HCL:

In present study, the high viscosity grade HPMC and Eudragit RSPO as specified by USP was used as hydrophilic and hydrophobic matrix forming agent. it forms a strong gel in aqueous media which may be useful to control the drug release of both, water soluble as well as water insoluble drugs from formulations.

The half life of venlafaxine HCL is 5hrs. so the drug release up to 24hrs will be able to show the pharmacological action up to 24 hrs. in attempt to prolong the drug release of drug up to 24hrs, the release retarding agents are combination of Eutragit RSPO and HPMC E50LV were used.

Formulations containing HPMC K4M, HPMC K15 M, HPMC K100Lv, HPMC E50 LV and Eudragits could not efficiently retard the drug release up to 24 hrs. The HPMC E 50 LV shows better extended relase than comared to remaining HPMC polymers. Along with that Eudragits showed better extended release up to 18 hrs. based up on that extended release properties of polymers they are selected for the development of ratios. from the above results formulation containing Eudragit RSPO and HPMC E50 LV 1:8 ratio formulation F12 shows the extended release the drug for up to 24 hrs. so, among all the formulations F12 is considered as optimized formulation.

6) **Stability studies:** There was no significant change in physical and chemical properties of the tablets of formulation F12 after 3 months, parameters like %drug release and at various conditions(at 40°C/75%RH) as per ICH guidelines quantified at various time intervals were shown in table and dissolution profile.

CONCLUSION

The results were significant effect on the release of drug from the tablets. formulation F12 was selected as

optimised formulation. the kinetic treatment of the drug release data of the prepared formulations followed Korsmeyer peppas theory drug release profile. combination of Eudragit RSPO and HPMC E50LV are good polymer systems for the formulation of extended release matrix tablets.

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