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Formulation Development of Venlafaxine Hydrochloride Extended Release Tablet and invitro Characterizations

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Abstract: Venlafaxine is a unique antidepressant that differs structurally from other currently available antidepressants. Short biological half life, low bioavailabilty and frequent administration of drug led rational for development of extended release formulation of Venlafaxine that releases the drug and maintian the plasma drug concentration for more than 12h.Polymers like Hydroxy propyl methyl cellulose (HPMC) K4M and K00M, Novocoat K100M, xanthan gum, Polyox, Carbopol etc. were selected for sustaining the drug release. The tablets were prepared by direct compression method. In vitro drug release study revealed that Novocoat K100M alone was not able to retard the drug release whereas carobopol has high potential to retard the drug release due to its gelling property. The optimized formulation containing combination of HPMC K100M and Polyox WSR303 showed similar drug release profile as marketed formulation VENTAB® XL75. Kinetic modeling of in vitro drug release data was best fitted in Korsmeyer- Peppas equation indicates drug releases by mixed mechanism of diffusion and erosion. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines.
Keywords: Extended release formulation, Venlafaxine Hydrochloride, HPMC, Polyox.

Introduction

Venlafaxine is a bicyclic phenyl ethylamine derivative, unique antidepressant used as first-line therapy in patients with major depression and agitated or retarded symptoms and treatment-resistant depression (1 2). Venlafaxine and its active metabolite, o-desmethylvenlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine [3,4] but have no monoamine oxidase inhibitory activity and a low affinity for brain muscarinic, cholinergic, histaminergic or alpha adrenergic receptors [5,6]. Hence, it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. The successful treatment of depression depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired [7].

Matrix based systems are more widely accepted to develop oral controlled drug delivery as it offers flexibility, cost effective, and regulatory accepted system. A successful hydrophilic system should possess a polymer that will wet, hydrate and hydrate to swell to such extent that forms a gelatinous barrier [8.9]. In this study swell able polymer Hydroxy propyl methyl cellulose (HPMC), Novocoat K100M and polymers forming gel like structure, xanthan gum and carbopol were tried. The steady state half-lives of venlafaxine is 5h, necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug [10].Hence the objectives of our work was to formulated once daily matrix tablet containing 75 mg of Venlafaxine drug to maintain steady blood level, prolong therapeutic action and improved patient compliance.

Materials and method

Materials

Venlafaxine Hydrochloride was obtained as a gift sample from Amoli Organics Pvt. Ltd., Vadodara, India. VENTAB-XL75 was purchased from Intas Pharmaceuticals, Ahmedabad, India. Hydroxy Propyl methyl cellulose Methocel® K4M and K100M were obtained as gift sample from Colorcon Asia Pvt. Ltd. Mumbai, India. Avicel 101 (directly compressible microcrystalline cellulose) obtained from J. Rettenmaier and Sohne Gmbh and Co., Germany was used as a diluent. Talc and magnesium stearate were procured from Bayer India Ltd. India. Polyox(TM) WSR303 was obtained as gift sample from the Dow Chemicals, India. All other excipients and chemicals used were of analytical grade (AR).

Drug –Excipients interaction study

FTIR

An infrared spectrum of pure drug and mixture of drug and polymers was recorded using PERKIN ELMER FTIR spectrophotometer (Spectrum RX1, USA). The scanning range was 500 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.A change in spectrum pattern of drug due to presence of polymers was investigated to identify any chemical interaction.

DSC

The possibility of drug–excipient interaction was further investigated by differential scanning calorimetry. DSC analysis was performed using PERKIN ELMER DSC Pyris-6 (USA) on 2 to 8 mg sample. Samples were heated in an open aluminum pan at a rate of 10°C / min within a 30 to 300°C temperature range under a nitrogen flow of 20 ml/min. An empty sealed pan was used as a reference.

Preparation of Venlafaxine matrix tablet

Extended release matrix tablets, each containing 75 mg Venlafaxine were prepared by direct compression method. The composition of various formulations was shown in table 1.Polymer composition was selected on the basis of trial taken for the formulated preparation. All the ingredients weighed accurately, passed through 40 mesh and mixed in geometric order. Mixing was continued for 10 min to achieve uniform mixing. Then the mixture was mixed with gliandant and lubricant talc and magnesium stearate in a blender for 5 min. Different polymers were used alone or in combination to formulated extended release matrix table.The lubricated blend was than compressed into a tablet using 12mm standard concave punches on single punch tableting machine (Cadmach machinery Co. Pvt. Ahmedabad, India). Each tablet contains 75 mg of Venlafaxine base and total tablet weight was varied from 290 mg to 340 mg depending upon polymer concentration. All the tablet formulations were stored in air tight container till further use.

Physical characteristics

Evaluation of powder blends

The powder blends were evaluated for flow property (angle of repose), loose bulk density, tapped bulk density, compressibility index and drug content [11]. Angle of repose was determined by fixed funnel method. Loose and tapped density was determined by cylinder method and for Carr's Index (CI) value following equation used: Carr's Index = tapped bulk density-loose bulk densityx100/tapped bulk density. Hausner's ratio was also calculated to define the flow property. A Hausner's value between 1.12 to 1.25 indication of good flow property [12].

Evaluation of tablets

The prepared tablets were evaluated for their physical parameters like hardness, thickness, weight variation, friability and drug content. For hardness testing Monsanto hardness tester and for frability Roche friabilator (Campbell Electronics, Mumbai, India) was used to determine the value. Vernier caliper was used to measure the thickness of the tablets. Weight variation was performed as per official method [13].

Drug Content Estimation

Three tablets containing Venlafaxine Hydrochloride were crushed to a fine powder. Weigh accurately a quantity of powder equivalent to 75 mg of Venlafaxine Hydrochloride, transfer to a 100ml volumetric flask and about 100ml of purified water, mix and sonicated for 2h.Water was added slowly until the clear solution was obtained. The final volume was made up to 100 ml with purified water. This was filtered through What man filter paper No. 41 and suiatbly diluted.Drug conten was determined by using double beam UV-spectrophotometer 1600 (Shimadzu) at 226 nm. The drug content was calculated using the standard plot concentration vs absorbance.

In vitro drug release

In vitro drug release was carried out using USP type II dissolution apparatus containing 900 ml of distilled water. The apparatus was operated at 50 rpm at a temperature of 37 ± 0.5°C. 10 ml of aliquot was withdrawn at 5, 10 15 and 24 h intervals and absorbance was recorded using UV

Spectrophotometer at 226 nm. The marketed formulation VENTAB XL -75 mg was also evaluated for the various physicochemical parameters such as appearance, weight variation, drug content and in vitro drug release.

Kinetic analysis of release data

The obtained dissolution data was fitted to Zero order, First order, Higuchi,Hixon -Crowell and Korsmeyer- Peppas equations to understand the rate and mechanism of drug release from the prepared formulations. The correlation coefficients values were calculated and used to find the fitness of the data.

Zero order equation $Q_t = Q_o + K_o t$ [14], describe the systems where the drug release rate is independent of concentration of the dissolved substance, where, Q_o = initial amount of drug, Q_t = cumulative amount of drug release at time t, K_o= zero order release constant, t = time in h

First order release equation $\text{Log } Q_t = \text{Log } Q_o + Kt/2.303$ [15], the drug release rate depends on its concentration, where, Q_o = initial amount of drug, Q_t = cumulative amount of drug release at time t, K = first order release constant, t = time in h

Hixon-crowell equation $M_o^{1/3} - M_t^{1/3} = K$ [16], describes the drug release by dissolution and with the changes in surface area and diameter of the particles or tablets. M_o = Initial amount of drug, M_t = Cumulative amount of drug release at time t, K = Hixson-crowell release constant, t = time in h.

Higuchi release equation $Q = K_H t^{½}$ or $M_t/M_o = K t^{½}$ [17] , the Higuchi equation suggests that the drug releases by diffusion mechanism. Q = cumulative amount of drug release at time t, K_H = Higuchi constant ,t = time in h

Korsmeyer-Peppas: $F = (M_t / M_\infty) = K_m t^n$ [17], which described drug release from a polymeric system, Where F=Fraction of drug released at time t, M_t=Amount of drug released at time t, M_∞=Total amount of drug in dosage form, K_m= Kinetic constant, n= Diffusion or release exponent, t = time in h.

Similarity factor (f_2) analysis

In-vitro drug release profile of Venlafaxine HCl extended release tablets was compared with drug release profile of marketed formulation VENTAB® XL75 tablets under similar experimental conditions. The data obtained from in vitro drug release was used to determine the similarity factor between marketed and optimized product. Similarity factor was calculated using the formula, $f_2 = 50 \log \{[1+ (1/N) \Sigma (Ri - Ti)^2]^{-0.5} X100\}$, where N is number of time points, Ri and Ti are dissolution of reference and test products at time i respectively. F2 values greater than 50 considered as product similarity between two products and have similar drug release behavior.

Stability study

The optimized formulation (F10) was packed in high density polyethylene bottle and subjected to stability studies at 40 °C± 2 °C/75±5% RH. Sample was withdrawn at predetermined time intervals of 0, 30, 60 and 90 days. Tablet was evaluated for the different physicochemical parameters viz. appearance, weight variation, thickness, hardness, friability, drug content and in vitro release.

Table 1: Formulation composition of various batches

Ingredients	FI	FII	FIII	FIV	FV	FVI	FVII	FVIII	FIX	FX
Venlafaxine HCl	86	86	86	86	86	86	86	86	86	86
Novocoat100M DC	100	100	87	87		110	-		-	-
HPMC100M	-	-		-	129	125	110	70	125	160
HPMCK4M	-	-	17	42	-	-	-	55	-	-
Xanthan gum	-	-	-	-	-	70		-	-	-
Polyox WSR 303	-	29	-	-	-	-		25	25	55
Cabopol 71G	-	-	60	-	-	-	70	-	-	-
Cabopol 934 NF	-	-	-	25	-	-	-	-	-	-
Lactose	-	-	17	17	-	-	-	-	-	-
Starch 1500	-	-	-	-	55	-	-	-	-	-
Avicel PH102	84	55	54	63	-	64	54	34	34	33
Mg stearate	10	10	10	10	10	10	10	10	10	3
Talc	10	10	10	10	10	10	10	10	10	3
Total (mg)	290	290	340	340	290	340	340	290	290	340

Figure 1.DSC thermogram of pure drug (A) and physical mixture of drug and polymers(B)

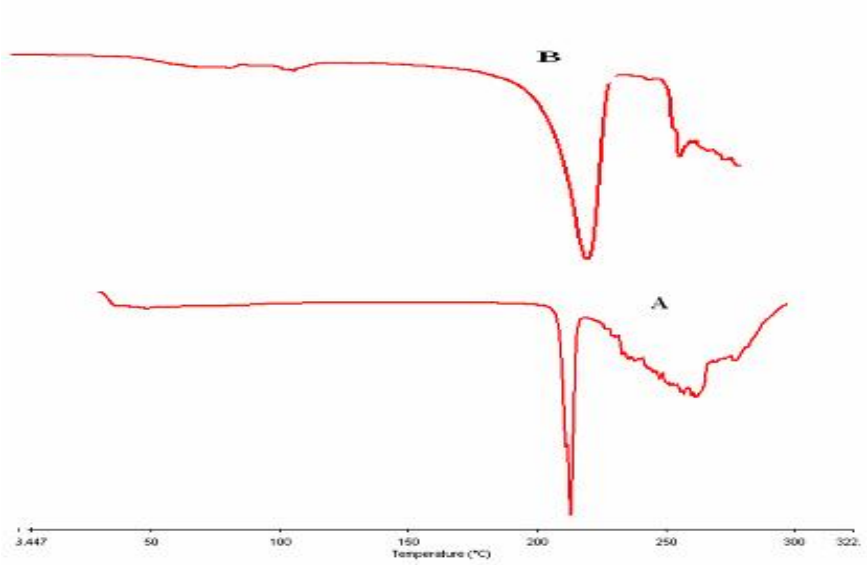
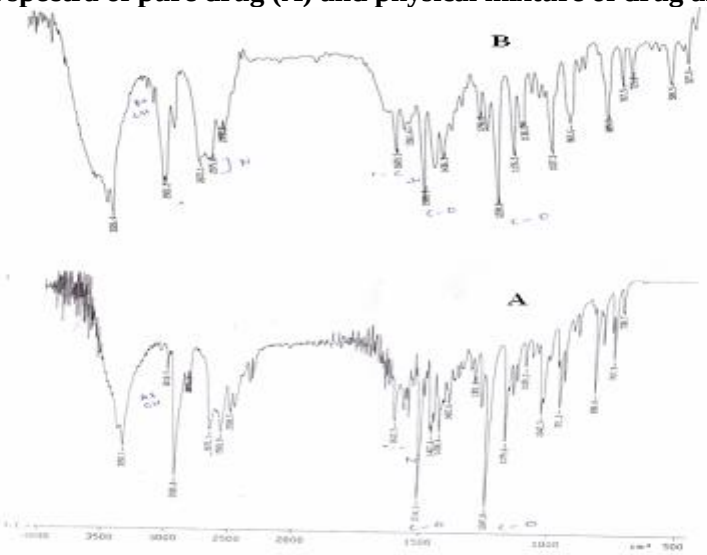


Figure2. FTIR spectra of pure drug (A) and physical mixture of drug and polymers (B)



Result s and discussion

Drug excipients interaction

DSC thermogram showed a sharp endothermic peak at 215-217 °C which is corresponding to melting of the drug fig 1. Preformulation study indicated that slight broadening of endothermic peak taken place due to melting effect of hydrophilic polymers. FTIR spectrum of Venlafaxine HCl showed a characteristic stretching band of O-H at 3500 cm^{-1} , aromatic C=H starching at 1609cm^{1} , C-O stretching at 1500 cm^{-1} and C-N stretching at 1176 cm^{-1} wave number fig 2. These characteristic stretching bands were retained after preformulation study revealed no chemical interaction.

Physical characteristics

For direct compression, powder formulation should have good flow ability and compressibility hence they were evaluated for their physical properties (table2). It was found that all the powder blends have good flow property as they showing angle of repose value less than 30 degrees, represents good flow property. Carr's index value was found to be less than 21 that also

indicate that powder blends have excellent flow ability [11].

Formulated matrix tablets evaluated for physical parameters such hardness, weight variation and friability, results shown in table 3. Friability was found to be less than 1%, acceptable as per prescribed limits. According to USP specification, tablets weighing more than 324 mg, ±5% and tablet weighing between 130-324 mg, ±7.5% deviation from the mean weight are acceptable[12]. Results shown in table 4 indicated that all the formulations were showing low weight variation and showing high degree of drug content uniformity with drug content more than 98%.

In vitro drug release

FI and FII formulation were prepared using Novacoat K100M and Polyox WSR303.These tablets were found to be friable, maximum hardness acheived was 3 kg/cm^2 and showed 60% and 50% drug release in first 5h. This initial burst release may be attributed to low polymer concentration that cuases formation of weak gel barrier upon hydration which tend to eroded much more quickly and at the same time higher solubility of Venlafexine drug led to rapid dissolution of drug from the matrix tablet.

FIII-FIV, HPMC K4M and various grades of Carbopol were added to control the initial burst release and subsequently prolong release. These polymers have fast swelling and gelling property. It controlled the initial burst release with 24% drug release in first 5h but the maximum release achievable was only 66% even after 24 h of dissolution, showing high release retardant potential of this combination. To achieve the desire drug release profile as marketed formulation, HPMC K100M along with Starch 1500 as diluent was tried for matrix tablet (FV). The release profile of FV formulation was found to be satisfactory but compressibility of the blend was very poor and tablet failed in friability test Fig 3.

Table2. Physical characteristics of powder formulation ([a]n=3, ±SD)

Formulations	Angle of repose[a] (θ)	LBD	TBD	Carr's Index	Hausner's ratio
FI	23.45±0.5	0.212	0.234	8.55	1.10
FII	24.54±0.43	0.231	0.245	5.71	1.06
FIII	25.50±0.35	0.256	0.301	14.95	1.17
FIV	26.33±0.45	0.264	0.312	15.38	1.18
FV	25.45±0.56	0.231	0.292	20.98	1.26
FVI	26.34±0.45	0.227	0.275	17.45	1.21
FVII	25.06±0.32	0.245	0.286	14.33	1.16
FVIII	25.35±0.55	0.265	0.306	13.39	1.11
FIX	24.38±0.54	0.243	0.298	18.45	1.18
FX	25.6±0.55	0.285	0.331	13.89	1.17

[a]loose Bulk Density, [b]TBD-Tapped Bulk Density

Table3. Physical parameters of matrix tablets (n=10, ±SD)

Formulation	Average Weight(mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
FI	286.8±0.2	3.55±0.04	3-4	0.98±0.12	98.55
FII	286.8±0.3	3.66±0.05	3-4	0.68±0.15	99.55
FIII	341.5±0.18	3.74±0.07	6 -8	0.58±0.14	98.75
FIV	342.1±0.23	3.36±0.03	6-7	0.71±0.15	99.45
FV	286.2±0.24	3.67±0.06	4-5	1.1±0.13	98.67
FVI	340.0±0.26	3.73±0.04	6-8	0.26±0.14	99.12
FVII	341.3±0.19	3.71±0.05	5- 7	0.58±0.11	99.45
FVIII	290.3±0.14	3.70±0.04	6-7	0.57±0.12	98.99
FIX	287.6±0.19	3.69±0.06	4-5	0.57±0.14	99.55
FX	341.6±0.21	3.70±0.07	7-8	0.65±0.14	99.45

Figure3. In vitro drug release profile of FI-V batches

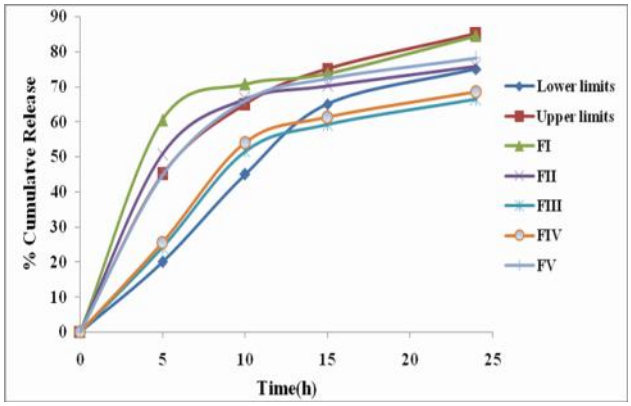


Figure 4. In vitro drug release profile of FVI-FX batches

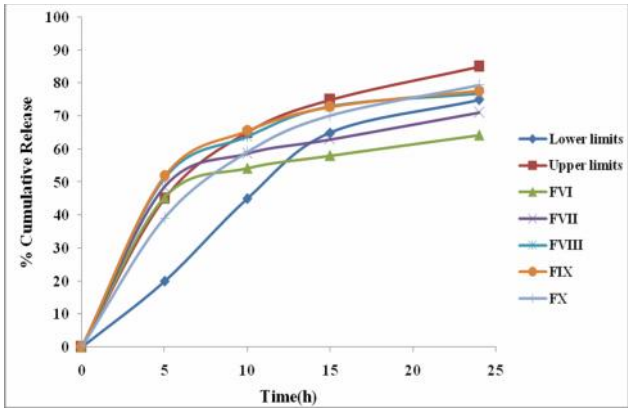


Figure 5. *Invitro* drug release profile of optimized and marketed formulation

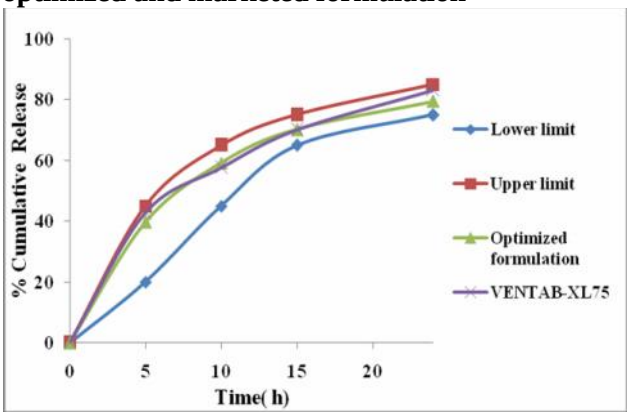
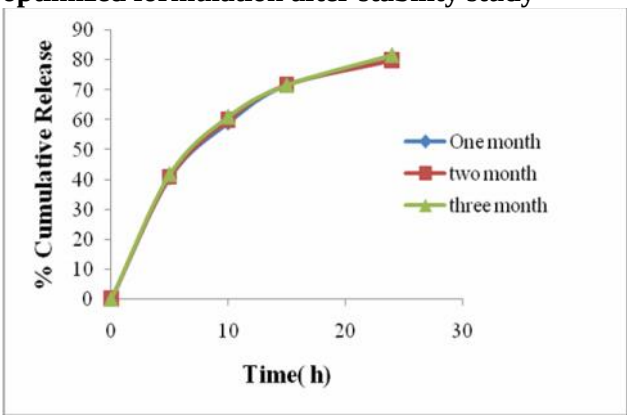


Figure 6. *Invitro* drug release profile of optimized formulation after stability study



FVI, inclusion of natural gum like xanthan gum as release retardant polymer gave good tablets but the release was very slow and only 64% drug release was found at the end of 24h of dissolution. Formation of a firm gel barrier by the xanthan gum might be responsible for this prolonged release.

FVII, a combination of HPMC K100M and Carbopol 71G was tried. Owing to rapid hydration and swelling of HPMC K100M and gelling property of Carbopol drug release was retarded till the end of 24h but release was not as per set limit.

Further trials were taken with Methocel® and Polyox®. FIII and FIX showing good release profile but best release profile followed to marketed formulation was found with formulation FX. FX showed 39.07%, 59.12%, 70.16% and 79.42% drug release at the end of 5h, 10h, 15h and 24h.Thus a combination of Methocel® K100M and Polyox® WSR 303 was optimized to give the desired release profile similar to the marketed formulation (FX)). The prepared tablets have good physical charactertics and compressibility. Similarity factor (F2 value) between Marketed formulation and optimized formulation FX was found to be 61.48. The optimized formulation was subjected for stability study as per ICH guideline after packing suitably. Stability testing revealed no changes in physiochemical properties and release profile of the optimized formulation Fig.6.

Kinetic analysis of release data

To understand the rate and mechanism of drug release from optimized tablet formulation, dissolution data was fitted into different release kinetic models. The model that best fitted the release data was selected based on the correlation coefficient value (r^2) obtained from various kinetic models. *Invitro* drug release profile from all these formulations could be best expressed by Korsmeyer-Peppas equation as plot showed highest linearity with r^2 value 0.976-0.998 (table 4). In Korsmeyer-Peppas equation, linear plot was obtained for optimized formulation with high correlation coefficient (r^2) value 0.998. It was concluded that the optimized formulation followed mixed mechanism of diffusion and erosion so called anomalous diffusion mechanism for drug release.

Table4. *In vitro* drug release kinetics parameters

Formulation	Zero order		First order		Higuchi		Hixon-Crowell		Korsmeyer-Peppas		
	r^2	K	r^2	k	r^2	k	r^2	k	N	r^2	K
FI	0.821	25.80	0.937	1.861	0.956	9.11	0.900	-2.83	6.84	0.979	-0.311
FII	0.830	22.75	0.911	1.87	0.962	7.38	0.844	-2.57	8.53	0.976	-0.276
FIII	0.923	19.49	0.960	1.959	0.927	1.084	0.948	-1.26	13.58	0.988	0.570
FIV	0.919	11.26	0.959	1.956	0.978	-0.666	0.946	-1.28	12.43	0.987	0.656
FV	0.868	20.00	0.943	1.901	0.977	4.86	0.923	-2.33	7.88	0.988	0.433
FVI	0.82	19.59	0.890	1.89	0.959	6.73	0.868	-2.68	14.37	0.963	-1.39
FVII	0.838	20.69	0.917	1.890	0.973	6.11	0.914	-2.84	11.35	0.980	-0.911
FVIII	0.842	22.28	0.926	1.88	0.968	6.89	0.899	-2.62	8.06	0.995	0.02
FIX	0.916	15.87	0.983	1.943	0.993	1.85	0.897	-2.65	7.91	0.990	-0.046
FX	0.914	15.45	0.982	1.91	0.993	2.077	0.963	-2.10	8.676	0.998	0.80

Conclusions:

Venlafaxine HCl extended release matrix tablet was successfully formulated with HPMC K100M and Polyox WSR ®303 as matrix former polymer. An optimum concentration of HPMC and Polyox in combination was able to provide the desired release with innovator profile requirement. Diffusion coupled with erosion Release was found to be mechanism for drug release from optimized formulation. Developed formulation is expected to reduce the frequency of administration thereby reduces the chance of adverse effect associated with frequent administration Venlafaxine HCl tablets.

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