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Formulation Design and *in vitro* Evaluation Studies of Antidepressant Venlafaxine Hydrochloride Oral Drug Delivery Systems

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ABSTRACT: Background: Venlafaxine Hydrochloride a serotonin, nor-epinephrine reuptake inhibitor, oral antidepressant used to treat depression. **Aim:** The present study was aimed at studying controlled release of Venlafaxine Hydrochloride with Guar Gum, Hydroxypropyl methyl cellulose as matrix polymers, Micro crystalline cellulose as binder and Dicalcium phosphate as diluent filler. **Methods:** Tablets were studied for pre, post compression, swelling and *in vitro* dissolution studies. Release kinetic models analyzed drug release. **Results:** Pre-formulation studies revealed that the drug procured was pure. Analytical method was linear and precise. The rheological parameters were within the ideal limits and suitable for compression. Swelling index increased with increase in matrix polymer content. *In vitro* studies showed drug release, sustained for 18 to 24 h. Optimized formulation V5 released 14.32±0.43 % in 2 h. At the end of 12 and 24 h it has released 49.37±0.685 and 98.31±0.435 % of drug respectively and followed Peppa's kinetics with an anomalous (Non-fickian) diffusion mechanism of drug release. The drug release from the swollen gel matrix occurred initially by drug diffusion followed by polymer chain relaxation and erosion. The *in vitro* release kinetics from the majority of formulations followed Peppa's and zero order kinetics. The Peppa's n values indicated drug release via anomalous (non- fickian) diffusion and super case II transport. **Conclusion:** Venlafaxine HCl release from matrix tablets sustained up to 24 h, which could provide better bioavailability and improved patient compliance.

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INTRODUCTION:

To the date, for every disease or disorder state of the patient, proper medication is of prime importance to maintain the patient in good health. To achieve this, the medicine or drug is administered conventionally by one or more of several well defined and popular routes of drug administration including oral, parenteral, rectal, alveolar, ocular and topical. Among these, the oral route lies at the top of the hierarchy. It is a reasonable assumption that drug concentration at the site of action is related to drug plasma level and the intensity of effect is

a function of drug concentration at the target site. The objective of therapeutic regimens is to rapidly raise the plasma concentration to the required level and then to hold it constant for the desired duration of treatment. Sustained- release dosage forms prolong therapeutic activity of drug and reduce the need for repeated dosing [1-5].

In this system, the matrix-forming polymer contains hydrolytically or enzymatically labile bonds and the drug is uniformly dispersed in this matrix. As polymer erodes by hydrolysis or enzymatic cleavage, drugs are released to the surrounding environment. Drug-polymer conjugates: This system involves drug molecules chemically bonded to a polymer backbone. The drug will be released through hydrolytic or enzymatic cleavage of these bonds [6-8].

The kinetics of drug release from membrane-reservoir systems generally follows either a solution diffusion mechanism. In this, the drug transport occurs by first dissolving in the reservoir membrane followed by diffusion across the membrane [10-12].

Here, the drug is dispersed homogeneously throughout an insoluble matrix or swellable hydrophilic substances like stearic acid, beeswax etc. Swellable matrix is popular for sustaining the release of highly water-soluble drugs. The materials are generally hydrophilic gums and may be of natural origin (guar gum, tragacanth), semi synthetic (HPMC, CMC, Xanthan gum) or synthetic (polyacrylamides). The release follows fickian first order diffusion under equilibrium conditions [13-14].

In this technique, tablets are compressed directly from the mixture of drug and excipients without modifying the physical nature of the materials. It is applicable for crystalline substances with good compressible characteristics and flow properties [15].

Slugging may be used to form granules if the tablet ingredients are sensitive to moisture. This involves compaction of components of a tablet formulation by means of a flat punch. These compact masses, called slugs, are then milled and screened to produce granules by using roller compactor machines [16].

The active ingredient, diluent and disintegrants are mixed or blended well using twin shell blenders. Moist materials from wet milling (granules) and are dried. Then lubricant or glidant is added to promote flow of granules. These granules are compressed to tablets [15].

Depression may be described as feeling sad, blue, unhappy, miserable, or down in the dumps. Most of us feel this way at one time or another for short periods [18-20]. The exact cause of depression is not known. It is believed to be caused by chemical changes in the brain. Symptoms of depression can include agitation, restlessness, irritability, change in appetite, fatigue and lack of energy, trouble sleeping or excessive sleeping [18-24].

Common types of antidepressants include: Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa) and escitalopram (Lexapro). Serotonin norepinephrine reuptake inhibitors (SNRIs), including desvenlafaxine (Pristiq), Venlafaxine (Effexor) and duloxetine (Cymbalta). Other medicines used to treat depression include: Tricyclic antidepressants Bupropion (Wellbutrin), Monoamine oxidase inhibitors [18-24].

Venlafaxine HCl and its active metabolite 0-desmethylvenlafaxine inhibit uptake of norepinephrine and serotonin, to a lesser extent, dopamine. It is the only new drug currently available with both norepinephrine and serotonin blockade in clinical dosages. The adverse effects include dry mouth, dizziness and headache [25-27].

Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 225mg/day, mean±SD steady state plasma clearance of venlafaxine, ODV is 1.3± 0.6 and 0.4±0.2 l/h kg, respectively, and (apparent) steady state volume of distribution is 7.5±3.7 and 5.7±1.8 l/kg, respectively [28-30].

Venlaflaxine HCl is a bicyclic antidepressant and is usually categorized as a serotonin, norepinephrine reuptake inhibitor. It works by blocking the transporter reuptake proteins for key neurotransmitters affecting mood, thereby leaving more active synapse.

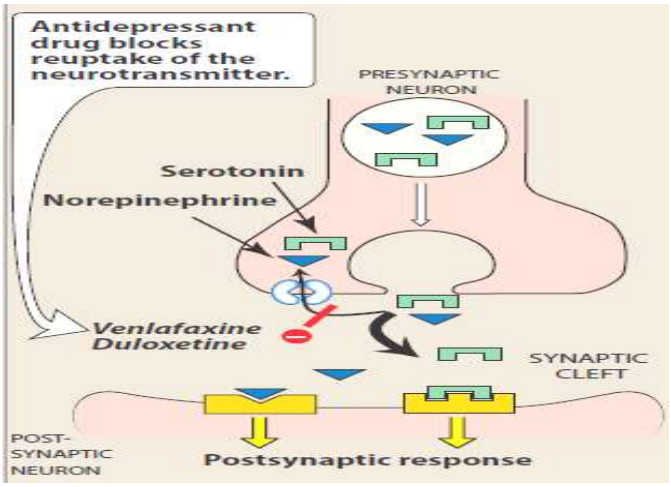

Fig 1. Mechanism of action of serotonin-norepinephrine reuptake inhibitor (SNRI) Venlafaxine hydrochloride.

Venlafaxine at low dosage blocks serotonin reuptake alone, at medium dosages, venlafaxine blocks the reuptake of norepinephrine as well as serotonin, where at dosages above 300 mg/day, it blocks dopamine reuptake in addition to serotonin and norepinephrine (Fig 1) [28-30]. Oral delayed release tablet in adults - at first, a total of the 75 mg per day was taken in smaller doses 2 to 3 times; during the day [28-30].

Mutalik, *et al*. [31] developed sustained release tablets of aceclofenac using HPMC K4M. The tablets were subjected to physicochemical, *in vitro* drug release and stability studies. Dissolution profile comparison with the marketed product, the tablet B7 containing HPMC (45 %) and MCC (30%) exhibited almost similar drug release, as the marketed tablet was stable in accelerated conditions for 6 months. The pharmacokinetic study indicated that B7 tablet produced an extended drug release of drug upto 24 h. Tiwari, *et al*.,[32] prepared and characterized extended release matrix tablets of Zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethylcellulose. Dissolution studies revealed that eudragit preparations were able to sustain the drug release only for 6 h. Combining eudragit and ethylcellulose sustained the drug release for 12 h. *In vitro* drug release data indicated mechanism of drug release by diffusion along with polymeric erosion. Jamzad S, *et al*. [33] prepared multilayered tablets of mefenamic acid and theophylline using ethylcellulose and Eudrajit RS as matrix material. The *in vitro* release profiles showed a release for 10 h with 50 % drug released in 3 h. The release rate followed zero order kinetics and a linear relationship was demonstrated between the *in vitro* drug percentages.

MATERIALS AND METHODS:

Venlafaxine Hydrochloride was procured from Granules India Ltd, Microcrystaline cellulose (Avicel pH101) by SD Fine Chemicals, Guar Gum by SD Fine Chemicals, HPMC K4M by SD Fine Chemicals, Dicalcium phosphate by SD Fine Chemicals, Talc and Magnesium Stearate by SD Fine Chemicals.

UV Analytical Method development studies:

***Determination of λ_{max} of Venlafaxine HCl*:**

Drug standard stock solution (1000 µg/ml) was prepared by dissolving accurately weighed 100 mg of Venlafaxine HCl in pH 6.8 Phosphate buffer in volumetric flask to 100 ml (1000 µg/ml). From this 1 ml was diluted to 100 ml to get 10µg/ml solution, which is scanned between 200 to 400 nm [34].

***Calibration curve of Venlafaxine HCl*:**

From Venlafaxine HCl standard stock solution (1000 µg/ml), 10 ml solution was diluted to 100 ml using pH 6.8 Phosphate buffer (100 µg/ml). From this 0.5, 1.0, 1.5, 2.0, 2.5 ml of solutions were taken into different volumetric flasks and made up to 10ml with pH 6.8 Phosphate buffer to get 5, 10, 15, 20, and 25 µg/ml respectively. The absorbance of these solutions was measured at λ_{max} 225 nm [35].

Pre-formulation Studies:

The drug colour, physical appearance, odour of the drug was observed [36].

***Melting point*:**

Melting point of the drug was determined in Theil's melting point apparatus. The temperature at which the drug melts was noted [36-37].

***Drug excipient compatibility (FTIR) study*:**

Venlafaxine HCl pure drug and Drug with polymers are studied for absence of drug polymer interaction via KBr disk method [38-39].

Pre compression parameters:

***Bulk density*:**

Bulk density, is the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. 10 gm powder blend was sieved and introduced into a 20 ml cylinder, without compacting. The powder was carefully leveled and the unsettled apparent volume, Vo, was noted. The bulk density was calculated by formula;

Bulk density = M / V_o ….(1)

Where, M is weight of sample, V_o is apparent volume of powder [41].

***Tapped density*:**

After bulk density the cylinder containing sample was tapped in a tapped density apparatus providing 100 drops per minute and this was repeated until the difference between succeeding measurements is less than 2 % and then tapped volume, V measured. The tapped density was calculated by;

Tapped density = M / V ….(2)

Where, Tap is Tapped density, M is Weight of sample, V is Tapped volume of powder [42].

Compressibility Index:

Carr's Index is a measure of powder compressibility. It is determined from the bulk and tapped densities. Compressibility index is calculated by [43];

Carr's Index = [(tap - b) / tap] × 100 …(3)

Where, b is Bulk density, Tap is Tapped density.

Angle of repose:

It is defined as the maximum possible angle between the surface of the powder pile and horizontal plane. The fixed funnel method was employed; A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the formula;

$\tan \theta = h / r$ ….(4)

Where tan θ is angle of repose, h is height of the cone and r is radius of the cone base [44].

Formulation development of tablets:

The tablets (V1 to V11) were prepared by direct compression as per the below process, to prolong the release of Venlafaxine HCl (Table 1). Total weight of the tablet was 250 mg. Venlafaxine HCl and all other ingredients were passed through sieve no # 60. All the ingredients were mixed thoroughly in their increasing order of weight by triturating up to 15 min. The powder mixture was lubricated with talc and magnesium stearate. Tablets were compressed on a tablet compression machine using 10 mm flat punches with compression pressure 5 kg /cm^2 [45].

Post compression evaluation of tablets:

***Weight variation test*:**

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percent Weight deviation = (Individual weight – Average weight / Average weight) × 100 [46].

***Hardness*:**

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. The hardness of three tablets was determined using Pfizer hardness tester (kg/cm^2) [47].

***Thickness*:**

Thickness for tablets was measured by vernier calliper and presented in mm [46].

***Friability*:**

Pre-weighed tablets were placed in the Roche friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were dedusted and weighed, loss in weight of tablet is the measure of friability and is expressed in percentage as [47];

Friability (V) = $[(W_1-W_2) / W] \times 100$ ….(5)

Where, W_1 is Initial weight of three tablets, W_2 is the weight of the three tablets after testing.

***Drug content determination*:**

Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Venlafaxine HCl were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml pH 6.8 Phosphate buffer and was made up to 100 ml. The solution was suitably diluted and the absorbance was determined by using the UV-Visible Spectrophotometer at 225 nm [47].

***In vitro drug release studies*:**

Apparatus was USP-II, (Paddle); Dissolution Medium is pH 6.8 Phosphate buffer; rpm was 50; Sampling intervals (h) at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h; Temperature was 37 $\pm$ 0.5 °C. A 900 ml of pH 6.8 Phosphate buffer was placed in vessel and the USP apparatus –II (Paddle) was assembled. The medium was allowed to equilibrate to temp of 37 $\pm$ 0.5 °C. Tablet was placed in the vessel and was operated at 50 rpm. Samples were withdrawn at definite time intervals viz., 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h respectively maintaining sink conditions up to 24 h. Samples were diluted suitably with pH 6.8 Phosphate buffer and absorbance measured at 225 nm by using UV-Visible Spectrophotometer. Absorbance was used for quantification of drug release [48-50].

***In vitro drug release kinetics studies*:**

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer peppas release model [51,52].

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line. $M_t / M_\infty = K t^n$. Where, M_t / M_∞ is the fraction of drug released at time 't', k represents a constant, 'n' is the diffusional exponent, which characterizes the type of release mechanism during

Table 1. Formulation table of Venlafaxine HCl (VFH) tablets.

Ingredients (mg)		V1	V2	V3	V4	V5	V6	V7	V8	V9	VC10	VC11
Ven. HCl		75	75	75	75	75	75	75	75	75	75	75
MCC		12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Guar Gum		25	25	25	50	50	50	75	75	75	37.5	62.5
HPMC K4M		25	50	75	25	50	75	25	50	75	37.5	62.5
Talc (2 %)		5	5	5	5	5	5	5	5	5	5	5
Mg. Stearate (1 %)		2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
DCP		105	80	55	80	55	30	55	30	5	80	30
TW (mg)		250	250	250	250	250	250	250	250	250	250	250
Design codes	Guar gum: X1	-1	-1	-1	0	0	0	1	1	1	-0.5	+0.5
	HPMC K4M: X2	-1	0	1	-1	0	1	-1	0	1	-0.5	+0.5
	Quantity: mg	25,25	25,50	25,75	50,25	50,50	50,75	75,25	75,50	75,75	37.5,37.5	62.5,62.5
	Percentage: %	10,10	10,20	10,30	20,10	20,20	20,30	30,20	30,20	30,30	15,15	25,25
X1- Guar Gum; X2- HPMC K4M.												

MCC - Avicel PH101, 5 %; Guar Gum - 10, 20, and 30 %; HPMC K4M - 10, 20, and 30 %; DCP - Di Calcium Phosphate, TW - Tablet weight; Ven – Venlafaxine.

the dissolution process. In this model, a plot of log (M_t/ M∞) versus log (time) is linear [53,54].

RESULTS AND DISCUSSION:

Characterization of Venlafaxine HCl: The physical characterization showed white crystalline powder value range 215ºC – 217ºC indicated the Venlafaxine HCl sample was pure.

UV analytical studies of Venlafaxine HCl:

The absorbance maxima of Venlafaxine HCl was found to be 225 nm, which is nearly same as literature value. The standard graph was found to be linear and obeys beer's law in the range of 0 – 25 µg/ml with good correlation coefficient r^2 0.9999. The method developed was found to be linear and accurate (Fig 2).

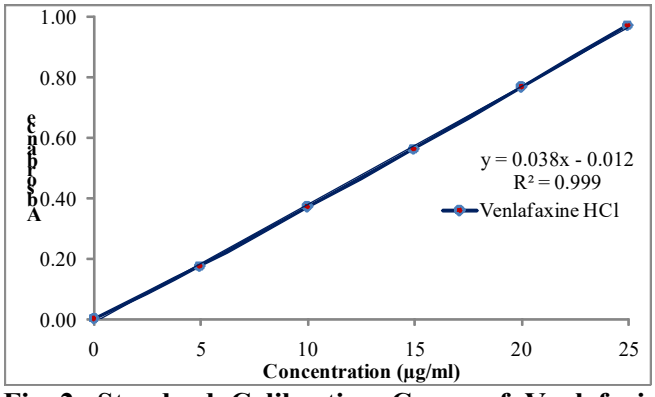

Fig 2. Standard Calibration Curve of Venlafaxine HCl.

FTIR Compatibility Studies:

The spectra of Venlafaxine HCl exhibited characteristic peaks at 3013.01, 2936.37, 1317.69, 1153.60, 1041.10, 836.77 and 740.56 cm^{-1} due to C- H stretching, R-O-CH_3 stretching, NH_2 stretching, OH stretching, CH_2 stretching, C-H bending and O-H bending respectively. The replication of drug peaks showed drug polymer compatibility and drug stability in the formulations (Fig 3, 4).

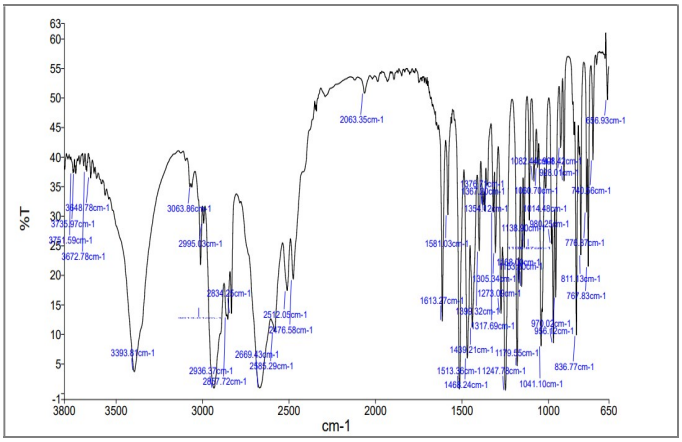

Fig 3. FTIR spectrum of Pure Venlafaxine HCl pure drug.

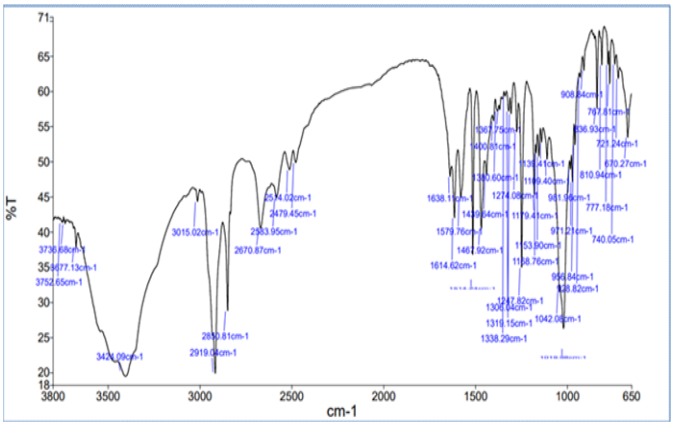

Fig 4. FTIR spectrum of Venlafaxine HCl Optimized formulation V5.

In this investigation an attempt was made to develop controlled release matrix tablets containing Venlafaxine HCl 75 mg. The matrix tablets were prepared by direct compression using different matrix carriers Guar gum and HPMC K4M, Micro Crystalline Cellulose as binder and Dicalcium Phosphate as diluent filler.

Bulk density and True densities were found to be < 1 for all the formulation powders which indicate better compactability. Carr's Compressibility index was found to be less than 17 % and hausner ration less than 1.20 for all formulations indicated ease of compaction. The angle of repose (θ°) studies obtained in the range of 25.19 to 22.98 indicated that, the powder beds of all the formulations are freely flowable and easily compressible. The powder beds of all formulations exhibited good rheological properties within the limits (Table 2).

Table 2. Pre Compression flow properties of Venlafaxine HCl Blends.

FC	Bulk density (g/cc) (X±SD)	Tapped Density (g/cc) (X±SD)	Carr's Index (%) (X±SD)	HR	Angle of Repose (°) (X±SD)
V1	0.50±0.003	0.60±0.09	16.17	1.193	24.7±0.41
V2	0.51±0.004	0.60±0.13	15.22	1.180	24.0±0.12
V3	0.49±0.005	0.58±0.15	14.96	1.176	23.0±0.13
V4	0.41±0.003	0.48±0.17	14.95	1.176	25.2±0.51
V5	0.42±0.008	0.50±0.08	17.28	1.209	24.3±0.36
V6	0.40±0.010	0.47±0.16	13.78	1.160	23.8±0.27
V7	0.46±0.110	0.55±0.12	15.59	1.185	24.71±0.13
V8	0.52±0.140	0.61±0.13	14.73	1.173	24.90±0.43
V9	0.41±0.120	0.47±0.12	13.81	1.160	22.98±0.32
V10	0.41±0.090	0.45±0.10	10.36	1.116	23.85±0.25
V11	0.42±0.130	0.49±0.08	14.71	1.172	24.81±0.53

FC – Formulation code, WU – Wight uniformity, each data is presented as Mean ± Standard deviation, n=3. HR - Hausner Ratio.

Venlafaxine HCl tablet ingredient powders were mixed in increasing order of weights and passed through a sieve # 60. The powder blends of formulations later mixed with lubricant (talc) and glidant (magnesium stearate). Then subsequently blended powder beds of all formulations V1 to V11 were compressed into tablets using 10 mm diameter, flat faced punches at a pressure 5 kg /cm^2.

The weight and thicknesses of the tablets were found to be fairly uniform and consistent. Tablets with binder MCC at 5 % w/w showed adequate hardness (4.37 to 4.88 Kg/ cm^2). The hardness was adequate to withstand stress. The drug content of all formulations 98.82 to 95.98 % was uniform and consistent. The friability all of the tablet formulations was found to be minimum i.e. < 1 %, indicates all tablets withstand against chipping or cracking. Swelling index showed that, increase in polymer content increased swelling index (Table 3).

Table 3. Post Compression flow properties of Venlafaxine HCl Tablets.

FC	WU (mg) (X±SD)	Thickness (mm) (X±SD)	Hardness (Kg/cm^2) (X±SD)	Friability (%) (X±SD)
V1	248.77±0.681	2.22±0.020	4.53±0.101	0.70±0.020
V2	247.36±0.819	2.28±0.015	4.37±0.127	0.65±0.031
V3	249.55±0.475	2.35±0.025	4.81±0.055	0.64±0.022
V4	248.85±0.252	2.30±0.021	4.88±0.061	0.69±0.015
V5	249.36±0.310	2.30±0.020	4.71±0.119	0.81±0.010
V6	247.64±0.959	2.31±0.044	4.65±0.102	0.76±0.014
V7	248.42±0.935	2.27±0.010	4.78±0.042	0.79±0.025
V8	249.22±0.424	2.37±0.015	4.65±0.080	0.81±0.016
V9	246.84±0.299	2.30±0.021	4.69±0.071	0.75±0.012
V10	248.36±0.594	2.25±0.030	4.45±0.114	0.76±0.008
V11	247.50±0.834	2.31±0.021	4.52±0.075	0.79±0.020

FC – Formulation code, WU – Wight uniformity, each data is presented as Mean ± Standard deviation, n=3.

In vitro Dissolution Studies:

The V1 formulation with guar gum 10 % and HPMCK4M 10 % matrix released 12.95, 73.44, and 95.66 % drug by the end of 2, 12, and 24 h respectively. The release was as per peppa's order with r^2 0.9929. The Peppa's 'n' value was found to be 0.8903 indicate drug release kinetics followed anomalous (non-fickian) diffusion. The V2 formulation with guar gum 10 % and HPMCK4M 20% matrix released 9.96, 59.085, and 95.26 % drug by the end of 2, 12, and 24 h respectively. The release showed zero order with r^2 0.9949. The Peppa's 'n' value was found to be 0.9617 indicate drug release kinetics followed Super Case II transport. The V3 formulation with guar gum 10 % and HPMCK4M 30% matrix released 7.63, 53.55, and 96.52 % drug by the end of 2, 12, and 24 h respectively. The release showed zero order with r^2 0.9802. The Peppa's 'n' value was found to be 1.0766 indicate drug release kinetics followed Super Case II transport. The *In vitro* release studies of V1, V2 and V3 formulations sustained drug release by increasing amount of HPMCK4M which is ideal for controlled release formulations.

The V4 formulation with guar gum 20 % and HPMCK4M 10 % matrix released 18.60, 56.41, and 97.84 % drug by the end of 2, 12, and 24 h respectively. The release was linear and as per zero order with r^2 0.9936. The Peppa's 'n' value was 0.7184 indicate drug release kinetics followed anomalous (non fickian) diffusion. The V5 formulation with guar gum 20 % and

HPMCK4M 20 % matrix released 14.32, 49.37, and 98.31 % drug by the end of 2, 12, and 24 h respectively. The release showed peppa's release with r^2 0.9977. The Peppa's 'n' value was found to be 0.7690 indicate drug release kinetics followed anomalous (non-fickian) diffusion. The V6 formulation with guar gum 20 % and HPMCK4M 30 % matrix released 6.98, 44.38, and 98.94 % drug by the end of 2, 12, and 24 h respectively. The release showed zero order with r^2 0.9943. The Peppa's 'n' value was found to be 1.0105 indicate drug release kinetics followed Super Case II transport. The *In vitro* release studies of V4, V5 and V6 formulations sustained drug release with increasing amount of HPMCK4M (10,20 and 30 %) ideal for controlled release.

The V7 formulation with guar gum 30 % and HPMCK4M 10 % matrix released 10.63, 42.52, and 97.43 % drug by the end of 2, 12, and 24 h respectively. The release was linear and as per zero order with r^2 0.9907. The Peppa's 'n' value was 0.8580 indicate drug release kinetics followed anomalous (non-fickian) diffusion. The V8 formulation with guar gum 30 % and HPMCK4M 20 % matrix released 6.55, 37.01 and 95.31 % drug by the end of 2, 12, and 24 h respectively. The release showed peppa's release with r^2 0.9905. The Peppa's 'n' value was found to be 0.9799 indicate drug release kinetics followed Super Case II transport. The V9 formulation with guar gum 30 % and HPMCK4M 30 % matrix released 5.22, 31.53, and 93.18 % drug by the end of 2, 12, and 24 h respectively. The release showed peppa's release with r^2 0.9880. The Peppa's 'n' value was found to be 1.0889 indicate drug release kinetics followed Super Case II transport. The *in vitro* release studies of V7, V8, and V9 formulations sustained drug release with increasing amount of HPMCK4M (10, 20, and 30 %) ideal for controlled release (Fig 5).

The Optimized V5 formulation released 12.03, 53.31, and 97.43 % drug by the end of 2, 12, and 24 h respectively. The release showed peppa's order with r^2 0.9956. The Peppa's 'n' value was 0.8579 indicate drug release kinetics followed anomalous (non-fickian) diffusion.

The marketed formulation released 12.93, 73.68, and 99.24 % drug by the end of 2, 12, and 20 h respectively. The release showed peppa's release with r^2 0.9924. The Peppa's 'n' value was found to be 0.8823 indicate drug release kinetics followed anomalous (non-fickian) diffusion. The *in vitro* drug release studies showed that optimized formulation comparatively sustained the drug release than marketed formulation which is ideal for controlled release dosage form to achieve extended drug release profile (Fig 6).

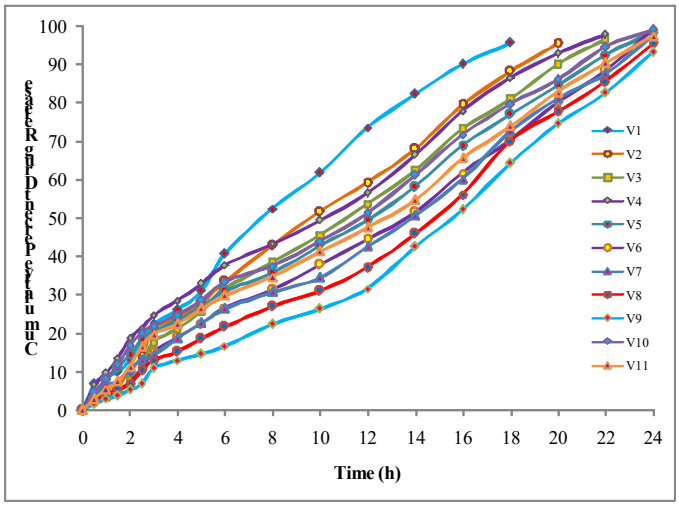

Fig 5. *In vitro* release data of Venlafaxine HCl from V1 to V11 Tablet formulations.

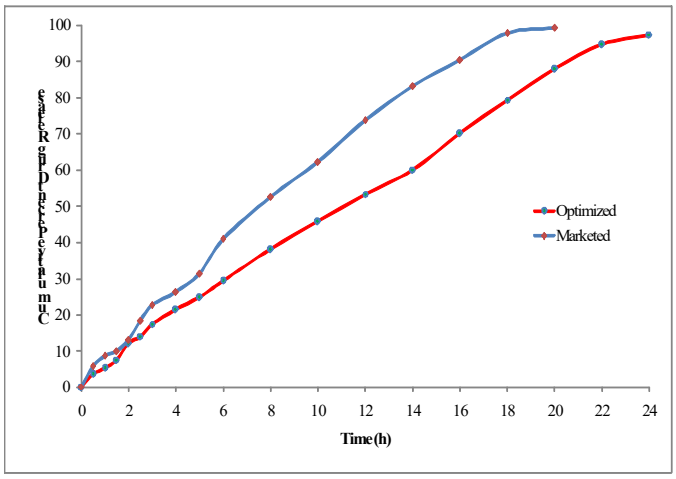

Fig 6. *In vitro* drug release of Optimized and marketed Venlafaxine HCl formulations.

The *in vitro* release kinetics studies revealed all formulations showed high regression coefficients and the drug release for majority of formulations exhibited Peppa's and zero order kinetics. The peppa's diffusion exponent (n); revealed mechanism of drug release due to anomalous (non fickian) diffusion and super case II transport for all tablets.

CONCLUSION:

The absorbance maxima for Venlafaxine HCl obtained during this study corroborates with the literature value. Melting point of Venlafaxine HCl obtained was within the range of literature value. The FTIR spectral studies indicated drug polymer compatibility. The rheological properties indicated free flow of all formulations. The weight of the tablets was found to be fairly uniform for 250 mg tablet. The thickness of the tablets was found to be consistent. The hardness of tablets indicated good

mechanical strength. The drug content was uniform and reproducible. The friability of all formulations was found to be minimum. Increase in polymer content, increased swelling index of the tablets for 24 h. Formulations V1, V2 and V3 released 12.95, 9.96, 7.63 % in the first 2 h of dissolution. At the end of 12 and 24 h they released 73.44, 59.08, 53.55 % and 95.66, 95.26, 96.52 % of drug into the dissolution media respectively. Formulations V4, V5 and V6 released 18.60, 14.32, 6.98 % in the first 2 h of dissolution. At the end of 12 and 24 h they released 56.41, 49.37, 44.38% and 97.84, 98.31, 98.94 % of drug into the dissolution media respectively. Formulations V7, V8 and V9 released 10.63, 6.55, 5.22 % in the first 2 h of dissolution. At the end of 12 and 24 h they released 42.52, 37.01, 31.53 % and 97.43, 95.31, 93.18 % of drug into the dissolution media respectively. Formulations V10, and V11 released 16.65, 11.31 % in the first 2 h of dissolution. At the end of 12 and 24 h they released 51.27, 47.44 % and 99.08, 97.43 % of drug into the dissolution media respectively.

Optimized formulation V5 and marketed formulation released 12.03, 12.93% in the first 2 h of dissolution. At the end of 12 and 24 h they released 53.31, 73.68 % and 97.43, 99.27 % of drug into the dissolution media respectively. The release kinetics analysis studies revealed drug release was controlled up to 24 h and the majority of formulations followed anomalous (non-fickian) diffusion and Super Case II transport. The Venlafaxine HCl release from all the developed formulations followed the pattern as V9 > V2 > V8 > V1 > V3 > V7 > V4 > V5 > V6. The drug release from the swollen polymer gel matrix occurred via initially drug diffusion followed by polymer chain relaxation and erosion. Drug release profile of optimized V5 formulation when compared with marketed preparation exhibited controlled release of drug for 24 h. Increase in polymer content, improvement in the drug release period and 'n' value nearing 1 for matrix tablets indicated the release of Venlafaxine HCl has been controlled and prolonged. The controlled release tablets of Venlafaxine HCl containing matrix carriers guar gum and HPMC could be formulated to sustain drug release for 24 h.

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