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Original Research Article

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

Putta Rajesh Kumar*[1], Meena N[2], Poojitha P[3], Sowjanya P[4], Shivaleela U[5], Sharma JVC[6]

[1,2,3,4,5] Department of Pharmaceutics, [6] Department of Pharmacognosy

Joginpally BR Pharmacy College, Hyderabad-500075, Telangana, India

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Abstract:

Background: Venlafaxine Hydrochloride a serotonin, nor epinephrine reuptake inhibitor, oral antidepressant used to treat major depressive disorder, social anxiety disorder and also panic disorder.

Objective: The present study was aimed at studying controlled release of Venlafaxine Hydrochloride with Guargum, Hydroxy propyl methyl cellulose as matrix polymers, Micro crystalline cellulose as binder and Dicalcium phosphate as diluent diluent. Talc, magnesium sterate as glidant and lubricants.

Methods: Venlafaxine Hydrochloride tablets were studied for pre compression, post compression, swelling and *in vitro* dissolution studies. Tablet drug release was analyzed by release kinetic models.

Results: Preformulation 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±0.430% 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 anomalous (Non fickian) diffusion mechanism of drug release.

Discussion: Drug content of all tablets was consistent. The drug release from swollen gel matrix occurred initially by drug diffusion followed by polymer chain relaxation and erosion. The *in vitro* release kinetics from 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 form tablets sustained up to 24 h which could provide better bioavailability of the drug candidate and improved patient compliance for antidepressant therapy.

Keywords: Venlafaxine HCl, controlled release matrix tablets, guar gum, Hydroxy propyl methyl cellulose, *In vitro* studies, Release kinetics.

Introduction

Sustained release dosage forms: 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, 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 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].

Chemically controlled systems: Biodegradable systems, in these systems the matrix-forming polymer contains hydrolytically or enzymatically labile bonds and drug is uniformly dispersed in this matrix. As polymer erodes by hydrolysis or enzymatic cleavage, drug is 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].

Membrane reservoir system: 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 reservoir membrane followed by diffusion across membrane [10-12].

Matrix systems: 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].

Formulation approaches for controlled release tablets: [15-17]

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

Dry granulation technique: 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.

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

Depression: 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 brain. Symptoms of depression can include agitation, restlessness, irritability and change in appetite, fatigue and lack of energy, trouble sleeping or excessive sleeping [18-24].

Medications for Depression: Common types of antidepressants include: Selective serotonin re-uptake 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: Venlafaxine HCl and its active metabolite 0-desmethylvenlafaxine inhibit uptake of nor epinephrine and serotonin, to a lesser extent, dopamine. It is the, only new drug currently available with both nor epinephrine and serotonin blockade in clinical

dosages. The adverse effects include dry mouth, dizziness and headache [25-27].

Pharmacokinetics: Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 225mg/day, mean±SD steady state plasma clearance of venlafaxine and 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].

Mechanism of action: Venlaflaxine HCl is a bicyclic antidepressant and is usually categorized as a serotonin, nor epinephrine reuptake inhibitor. It works by blocking the transporter reuptake proteins for key neurotransmitters affecting mood, thereby leaving more active synapse. Venlafaxine at low dosage blocks serotonin reuptake alone, at medium dosages, venlafaxine blocks the reuptake of nor epinephrine as well as serotonin, where at dosages above 300 mg/day, it blocks dopamine reuptake in addition to serotonin and nor epinephrine[28-30] (Figure 1).

Dosing of Venlafaxine for Depression: Oral delayed release tablet in adults - at first, a total of the 75 mg per day was taken in smaller doses 2-3 times; during the day [28-30].

Mutalik et al.,[31] developed sustained release tablets of aceclofenac using HPM C K4M. The tablets 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 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 hrs. Combining eudragit and ethylcellulose sustained the drug release for 12 hrs. *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 hrs with 50% drug released in 3 hrs. The release rate followed zero order kinetics and a linear relationship was also 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, HPMCK4M 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 diluted to 100 ml to get 10µg/ml 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 so as 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:

Characterization of Venlafaxine HCl: 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 introduced into 20 ml cylinder, leveled and the unsettled apparent volume, Vo, was noted. The bulk density was calculated by formula; Bulk density = M / V_o. 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 tapped density apparatus provides 100 drops per minute and this was repeated until difference between succeeding measurements is > 2 % and then tapped volume, V measured. The tapped density was calculated by; Tapped density= M / V. 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; Carr's Index = [(tap - b) / tap] × 100. Where, b is Bulk density, Tap is Tapped density [43].

Angle of repose: It is the maximum possible angle between surface of 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 pored 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 θ = h / r. 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 sterate. Tablets were compressed on 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: Preweighed 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; % Friability = [(W_1-W_2) / W] × 100. Where, W_1 is Initial weight of three tablets, W_2 is weight of the three tablets after testing [47].

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 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, 24 h; Temperature was 37°C± 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°C ± 0.5°C. Tablet was placed in the vessel and was operated at 50 rpm. Samples was 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, 24 h respectively maintaining sink conditions up to 24 hrs. Samples diluted suitably with pH 6.8 Phosphate buffer and measured at 225 nm by using UV. Absorbance was used for quantification of drug release [48-50].

***In vitro* drug release kinetics to dissolution data:** To analyze the mechanism of the drug release rate kinetics of dosage form, the obtained data fitted into zero-order, first order, Higuchi, and Korsmeyer peppa's model [51-52].

Korsmeyer Peppa's model: The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer Peppa's equation. The exponent 'n' indicates mechanism of drug release calculated through the slope of the straight Line. $M_t/ M_\infty = K t^n$. Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, 'n' is the diffusional exponent, which characterizes type of release mechanism during 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 appearance with characteristic odour for pure Venlafaxine HCl. The melting point of Venlafaxine HCl was found to be 216ºC which is correlated to reported value range 215ºC – 217ºC indicated the Venlafaxine HCl sample was pure.

UV analytical studies of Venlafaxine HCl: The absorbance maximum 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 (Figure 2).

FTIR Compatibility Studies: The spectra of Venlafaxine HCl exhibited characteristic peaks at 3013.01 cm^{-1}, 2936.37 cm^{-1}, 1317.69 cm^{-1}, 1153.60 cm^{-1}, 1041.10 cm^{-1}, 836.77 cm^{-1} and 740.56 cm^{-1} due to C- H stretching, R-O-CH3 stretching, NH2 stretching, OH stretching, CH2 stretching, C-H bending and O-H bending respectively. The replication of drug peaks showed drug polymer compatibility and drug stability in the formulations (Figure 3, 4).

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 HPMCK4M, Micro Crystalline Cellulose as binder and Dicalcium Phosphate as diluent.

Bulk density and True densities were found to be less than 1 for all the formulation powders which indicate better compactability. Carr's 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) was in the range of 25.19 to 22.98 indicated that, powder beds of all the formulations are freely flowable and easily compressible. The powder blends of all formulations exhibited good rheological properties within the limits (Table 2).

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 of all tablets 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).

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 (Figure 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 0.9977. The Peppa's 'n' value was 0.7690 indicate drug release 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 (Figure 6).

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.

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

Ingredients (mg)		V1	V2	V3	V4	V5	V6	V7	V8	V9	VC10	VC11
Venlafaxine HCl		75	75	75	75	75	75	75	75	75	75	75
MCC (Avicel PH101) (5%)		12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Guar Gum (10, 20, 30%)		25	25	25	50	50	50	75	75	75	37.5	62.5
HPMC K4M (10, 20, 30%)		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
Di Calcium Phosphate		105	80	55	80	55	30	55	30	5	80	30
Tablet weight (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.												

Table 2: Pre Compression flow properties of Venlafaxine HCl Blends

F. Code	Bulk density (g/cc±SD)	Tapped Density (g/cc±SD)	Carr's Index (%)	Hausner Ratio	Angle of Repose ($Ø^0$±SD)
V1	0.505±0.003	0.602±0.09	16.17	1.193	24.69±0.411
V2	0.509±0.004	0.600±0.13	15.22	1.180	24.04±0.122
V3	0.491±0.005	0.577±0.15	14.96	1.176	23.01±0.128
V4	0.408±0.003	0.479±0.17	14.95	1.176	25.19±0.510
V5	0.418±0.008	0.505±0.08	17.28	1.209	24.33±0.361
V6	0.405±0.010	0.469±0.16	13.78	1.160	23.82±0.272
V7	0.462±0.110	0.547±0.12	15.59	1.185	24.71±0.126
V8	0.517±0.140	0.607±0.13	14.73	1.173	24.90±0.428
V9	0.410±0.120	0.475±0.12	13.81	1.160	22.98±0.323
V10	0.407±0.090	0.454±0.10	10.36	1.116	23.85±0.247
V11	0.416±0.130	0.487±0.08	14.71	1.172	24.81±0.532

Table 3: Post Compression flow properties of Venlafaxine HCl Tablets

F. Code	Weight Uniformity (mg±SD)	Thickness (mm±SD)	Hardness (Kg/cm²±SD)	Friability (%±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

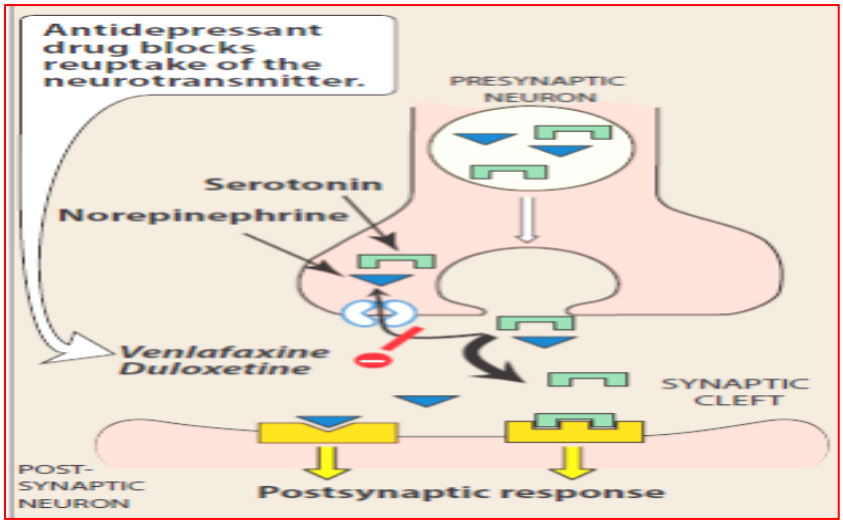

Fig. 1: Mechanism of action of serotonin-norepinephrine reuptake inhibitor (SNRI) Venlafaxine hydrochloride

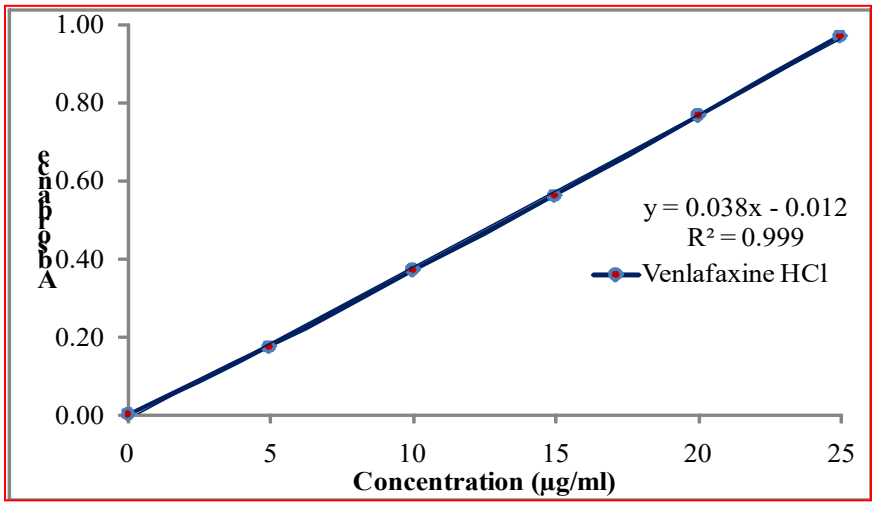

Fig. 2: Standard Calibration Curve of Venlafaxine HCl

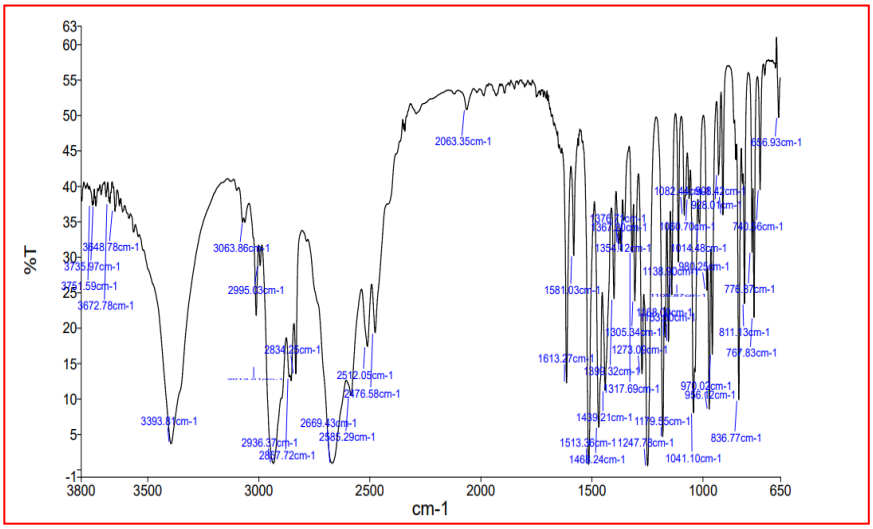

Fig. 3: FTIR spectrum of Pure Venlafaxine HCl pure drug

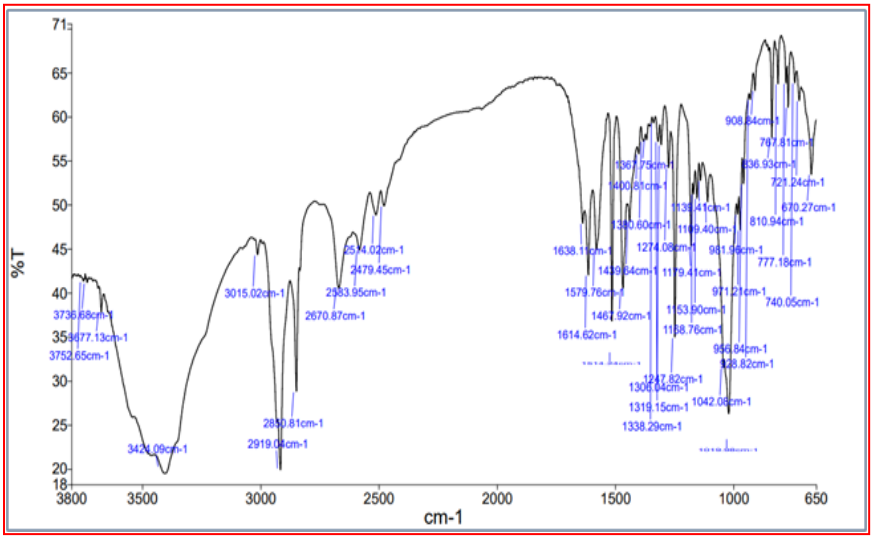

Fig. 4: FTIR spectrum of Venlafaxine HCl Optimized formulation V5

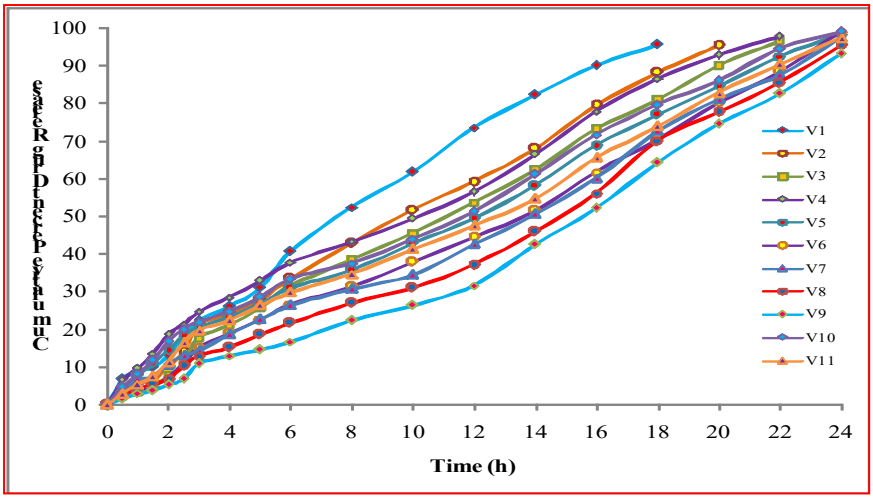

Fig 5: *In vitro* release data of Venlafaxine HCl from V1 to V11 Tablet formulations

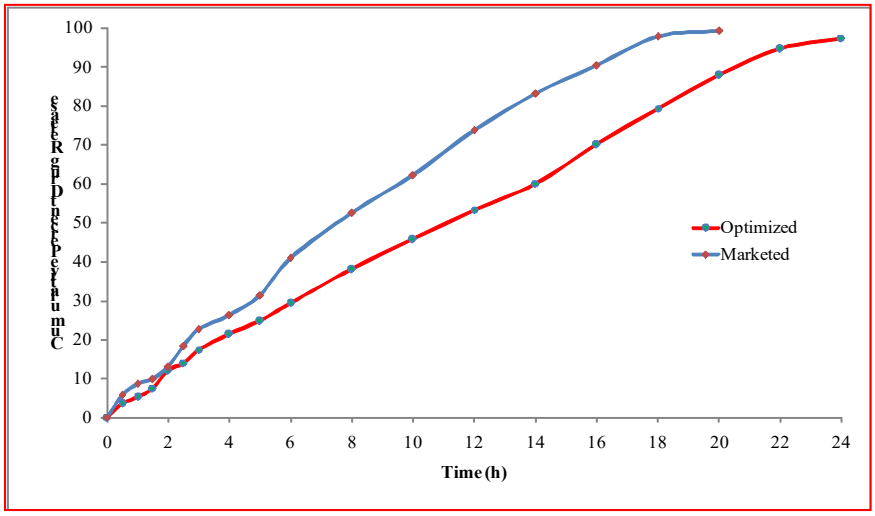

Fig 6: *In vitro* drug release of Optimized and marketed Venlafaxine HCl formulations

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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