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Research article

Formulation, Development and Evaluation of Sustained Release Mini-tablets in capsule of Venlafaxine Hydrochloride

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Abstract

Venlafaxine hydrochloride is an antidepressant that can help with a lot of different mental illness. This study utilized the direct compression method to formulate Venlafaxine prolonged release mini tablets employing HPMC K100M as the release retarding agent. This method avoid dose dumping, we examined the pre and post compression properties of the enhanced capsule formulation utilizing Venlafaxine hydrochloride mini-tablet. The produced capsule formulation was found to meet the Q point of USP limitations when it came to the in vitro dug release profile after dissolution. The stability test shows of that the improved batchVF8 stayed stable the entire time of study.

Keywords: Venlafaxine HCl, Formulation, Evaluation, Mini-Tablet capsule, HPMC K100M VF8

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, Parenterals, rectal, alveolar, ocular and topical. Among these above mentioned popular routes, oral conventional route of drug administration lies at the top of the hierarchy of the conventional routes. It is a reasonable assumption that drug concentration at the site of action is related to drug plasma level and that, in the great majority of cases, the intensity of effect is some function of drug concentration at the target site1.The objective of the most 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. The extent to which this situation can be achieved depends on many factors, including the minimum effective concentration of the drug, the level at which side effects occur, the dose administered , the rate of drug release from the dosage form , the rate of elimination and the frequency of dosing. Provided that the dose sizeand frequency of administration are correct, therapeutic 'steady state' levels of the drug can be achieved rapidly and maintained by repetitive administration of conventional oral dosage forms. Pre-formulation Studies: The following Pre-formulation studies were performed API Characterization (Venlafaxine HCl): Physical properties: The drug colour, physical appearance, odor of the drug was observed Melting point determination: Melting point of the drug was determined by taking a small quantity of drug in a capillary tube closed at one end which was placed in theil's melting point apparatus. The temperature at which the drug melts was

noted using liquid paraffin as a solvent. Average of triplicate readings was recorded 74.Drug excipients compatibility (FTIR) study: Pure drug and polymers were subjected for FTIR spectroscopic analysis via KBr disk method for compatibility studies and to ascertain whether there was any chemical interaction between the drug and the polymers used. The FT-IR spectra of Venlafaxine HCl pure drug and Drug with polymers are studied for absence of drug polymer interaction via open and closed vial methods with rubber stopper. The physical properties of the physical mixture were compared with those of plain drug.

Pre-formulation studies: Standard graph construction in UV spectrophotometer, Drug characterization, Solubility of drug, Drug excipients compatibility FTIR studies

Pre-compression parameters: Bulk density. Tapped density,. Compressibility index, Hausner's ratio, Angle of repose. To evaluate the formulated tablets for their Pre compression parameters such as: Weight variation Hardness Thickness Friability Swelling Index In vitro Dissolution studies. Comparison of Optimized formulation with marketed product. In-vitro drug release kinetics.

MATERIALS AND METHODS:

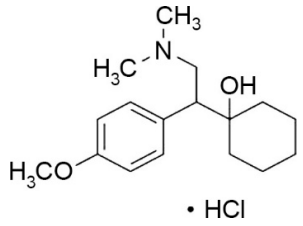
1. Venlafaxine HCl Granules India Ltd, Hyderabad,2. MCC (Avicel PH101) SDFCL, Mumbai 3. Guar Gum SDFCL, Mumbai, 4. HPMC K100M SDFCL, Mumbai,5. Di Calcium Phosphate, DFCL, Hyderabad6. Talc SDFCL, Hyderabad,7. Magnesium Stearate SDFCL, Hyderabad,

Equipments used:

Electronic Balance Wensar,2 UV Spectrophotometer, LABMAN T60-UV,Labman - Labman Scientific, Instruments Pvt. Ltd,3 FTIR Spectrometer PARAGON 1000 Perkin Elmer,4 Tablet Compression Machine Karnavati Rinek,5 Friability Test Apparatus Kshitij Innovations, Harayana,6 Tablet Hardness Tester Pfizer hardness tester,7 Disintegration Test Apparatus Rolex India Ltd, Mumbai,8 Dissolution Test Apparatus,LAB INDIA DS 8000,Lab India Analytical,9 Glassware Borosil,

Drug and Excipient Profile:

Venlafaxine Hydrochloride



Molecular formula: $C_{17}H_{27}NO_2$ HCl, Molecular weight: 313.9 d, Melting point: 2160C, Category: Oral antidepressant

METHODOLOGY:

Analytical Method development studies: Analytical Method used in the determination of Venlafaxine HCl: The analytical method was developed for the analysis of the drug using UV Spectrophotometer. Preparation of Phosphate Buffer pH 6.8: Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml of buffer. Determination of λ max of Venlafaxine HCl: Drug standard stock solution (1000µg/ml) was prepared by dissolving accurately weighed 100 mg of Venlafaxine HCl in the little quantity of pH 6.8 Phosphate buffer in 100 ml volumetric flask. The volume was then made up to 100 ml to obtain the solution of 1000 µg/ml. Scanning of Venlafaxine HCl in H 6.8 Phosphate buffer solution by UV-spectrophotometer: from the standard stock solution, 1 ml was diluted to 100 ml with pH 6.8 Phosphate buffer. The resulting solution containing 10µg/ml was scanned between 200 to 400 nm72.Calibration curve of Venlafaxine HCl: From the 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 0.5ml, 1.0ml, 1.5ml, 2.0ml, 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 the concentrations of 5 µg, 10 µg, 15 µg, 20 µg, and 25 µg respectively. The absorbance of these solutions was measured at λ max 225 nm using UV-Spectrophotometer taking pH 6.8 Phosphate buffer as blank. Then a graph was plotted by taking Concentration on X-axis and Absorbance on Y-axis.

Pre-formulation Studies:

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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 (AvicelPH101)(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
HPMCK100M (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 level codes	-1	-1	-1	0	0	0	1	1	1	-0.5	+0.5
	-1	0	1	-1	0	1	-1	0	1	-0.5	+0.5

Guar Gum-(-1,0, 1): (25,50,75mg):(10,20,30%); HPMC K4M-(-1, 0, 1): (25,50, 75mg):(10,20, 30%);

Formulation design with factors and levels of Venlafaxine HCl tablets

F. Code	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**VC10**	**V5**	**VC11**
X1	-1	-1	-1	0	0	0	1	1	1	-0.5	0	+0.5
X2	-1	0	1	-1	0	1	-1	0	1	-0.5	0	+0.5
mg	25,25	25,50	25,75	50,25	50,50	50,75	75,25	75,50	75,75	37.5,37.5	50,50	62.5,62.5
%	10,10	10,20	10,30	20,10	20,20	20,30	30,20	30,20	30,30	15,15	20,20	25,25

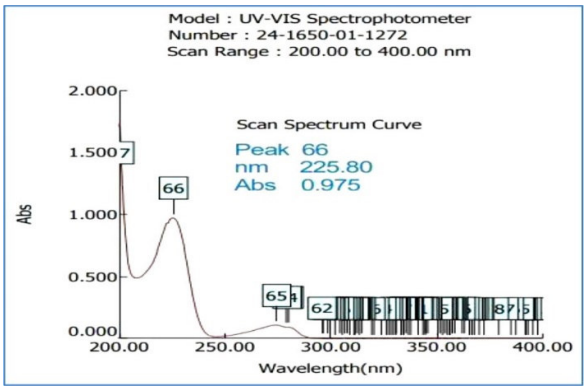
X1-GuarGum; X2-HPMCK100M.

Results and Discussion:

Characterization of Venlafaxine Hydrochloride: The physical characterization indicated white crystalline powder appearance with characteristic odor for pure Venlafaxine HCl. The melting point of Venlafaxine HCl was found to be 216°C which is correlated to the reported values range 215°C – 217°C.

Tablet weight uniformity limits as per Indian Pharmacopoeia

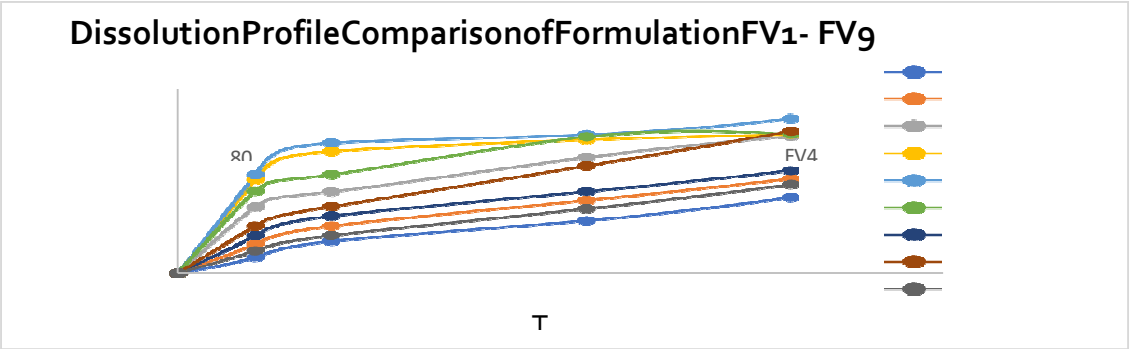
Average tablet weight (mg) (I.P)	**Maximum percentage limits**
Less than80	10
80–250	7.5
Morethan250	5



Standard graph data of Venlafaxine HCl pure drug candidate

In-Vitro drug release studies: The cumulative percentage drug release from mini-tablets in capsules was studied in USPII dissolution apparatus with following conditions (Phosphate buffer pH 6.8; 900Ml, 50RPM; 37°±5°C; 60 Minutes) and the outcome of the release profile was depicted in Table . The optimized formulation was found to be VF8 suffice the Q point criteria as per USP. According to the USP monograph of Venlafaxine extended release formulation, the Q point criteria was given as NMT 40% at 3 Hours, 35-60% at 6 hours, 60-85% at 16 hours & NLT 75% at the end of 24 hours . Formulation was designed targeting the criteria of Q point by altering the ratios of hydroxypropylmethyl cellulose and sodium starch glycolate**.**

Dissolution (Hours)	VF1	VF2	VF3	VF4	VF5	VF6	VF7	VF8	VF9
24HoursDissolutionin6.8pHPhosphate Buffer									
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	10.27	19.03	43.15	60.98	64.19	53.45	24.46	30.81	14.58
6	20.88	30.81	53.14	79.49	84.98	64.31	37.29	43.46	24.58
16	34.33	47.53	75.54	87.14	90.35	88.87	53.27	70.05	42.04
24	49.44	61.66	89.36	90.35	100.71	90.47	66.90	92.51	57.77



Release Kinetics: The estimations of Ko, R^2&N values were shown in Table for optimized formulation (VF8) Up on interpretation of data, revealed that optimized formulation follows First order release kinetics and Korsmeyer-Peppas Diffusion model based on R^2value and Non-Fickian Transport mechanism as value of optimized formulation (VF8) is 0.5367. According to Korsemeyer-peppas model; n value between 0.5-1.0 suggests Non-FickianTransport Mechanism.

Table9: Kinetic Data for Optimized Formulation (VF8)

Kinetic Models	Ko	R^2	N
Zero Order	13.513	0.9366	3.5835
First Order	2.0252	0.9626	-0.0481
Korsmeyer-Peppas	1.2288	0.9995	0.5367
Higuchi	-1.5171	0.9983	19.169

Stability studies: The findings on the improved formulation's short-term accelerated stability (VF8) showed that the drug content and in-vitro dissolution, as shown in table, remained within acceptable ranges.

Table10:Stability studies of Venlafaxine Optimized Formulation (VF8)

Stability Conditions	**40°C±2°C/75%RH ±5%RH(V**	
Formulation	**OptimizedTrial(VF8)**	
	Initial	**After3 months**
DissolutionTime(Hours)	**%CumulativeDrugRelease**	
0	0.00	0.00
3	30.81	31.12
6	43.46	43.54
16	70.05	68.82
24	92.51	93.33
AverageDrugContent %	100.08	99.86

SUMMARY

Standard Graph of Venlafaxine Hydrochloride Sodium: Standard graph of Venlafaxine Hydrochloride was constructed using concentration 5, 10,15, 20, 25 (µg/ml) in 6.8 pH phosphate buffer. It is evident from the figure 6 & 7 that the graph is linear with regression coefficient value of R2 = 0.9997 and slope = 0.0389 at λ max of 225nm. IR spectrum of Venlafaxine Hydrochloride shows a broad peak at IR spectrum of Venlafaxine Hydrochloride shows a broad peak at 3393.81 cm-1 may be due to O-H stretching, 3063.86cm-1 Aromatic C-H stretching, 2995.03 cm-1 may be due to aliphatic C-H stretching, 1613.27 cm-1 may be due to C-C Stretching, 1060.70 cm-1 may be due to C-N Stretching, 1041.10 cm-1 may be due to C-O stretching, 811.13 cm-1 may be due to C-Cl stretching. From IR overlay Spectra interpretation of drug was done with individual excipients and formulation mixture and observed that there is no appreciable change in the positions of the characteristic bands. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the excipients used.

Results obtained were found within the pharmacopoeial limits and showed good flow properties for all the formulations.

Results obtained in Table; were found within the acceptable limits for friability and weight variation. Thickness was found in the range of 2.22-2.80 mm; Hardness was found in the range of 51-68 N and Drug content was found in the range of 96.29-101.65 %. The cumulative percentage drug release from mini-tablets in capsules was studied in USP-II dissolution apparatus with following conditions (Phosphate buffer pH 6.8; 900Ml, 50RPM; 37°±5°C; 60 Minutes) and the outcome of the release profile was depicted in Table. The optimized formulation was found to be VF8 suffice the Q point criteria as per USP.

Formulation was designed targeting the criteria of Q point by altering the ratios of Hydroxy propyl methyl cellulose and sodium starch glycolate. The estimations of Ko, R2 & N values were shown in Table for optimized formulation (VF8) Upon interpretation of data, revealed that optimized formulation follows First order release kinetics and Korsmeyer-Peppas Diffusion model based on R2 value and Non-Fickian Transport mechanism as n value of optimized formulation (VF8) is 0.5367. According to Korsmeyer-Peppas model; n value between 0.5-1.0 suggests Non-Fickian Transport

Mechanism: The findings on the improved formulation's short-term accelerated stability (VF8) showed that the drug content and in-vitro dissolution, as shown in table, remained within acceptable

CONCLUSION

The most commonly used method of modulating the drug release is to include it in a matrix system. Diffusion controlled polymeric matrix devices have been widely used as drug delivery systems owing to their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Venlafaxine and its active metabolite o-desmethyl Venlafaxine (ODV) inhibit the neuronal uptake of nor epinephrine, serotonin and to a lesser extent dopamine but have no monoamine oxidase inhibitory activity. It lacks the adverse anti-cholinergic, sedative and cardiovascular effects of tricyclic antidepressants. Venlafaxine HCl and its active metabolite o-desmethyl Venlafaxine have a short half life of 5 h and 11h respectively and the usual oral dosage regimen is 75 to 375 mg taken two to four times daily. To reduce the frequency of administration and to Improve the patient compliance; a once daily sustained release formulation of Venlafaxine is desirable. The drug is very soluble in water and hence judicious selection of release retarding Excipients is necessary to achieve a constant in vivo input rate of drug. Hence in the present work an attempt has been made to develop once daily sustained release matrix tablets of Venlafaxine HCl using Guar gum, hydroxy propyl methyl cellulose and other polymers for controlled drug release.

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