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Formulation and Evaluation of Sustained Release Matrix Tablets of Venlafaxine Hydrochloride

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ABSTRACT

This study examines the sustained release behaviour of venlafaxine hydrochloride from Hydroxyl propyl methyl cellulose & sodium carboxy methyl cellulose. Venlafaxine hydrochloride is an antidepressant agent. The present research endeavor was directed towards the development of a sustained release dosage form of venlafaxine in the form of tablets to be taken once daily. All lubricated formulations were compressed by direct compression. The compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness and *In-vitro* dissolution study. Release studies were carried out using USP type 2 apparatus in 900 ml of Distilled Water as dissolution media. Release kinetics were analyzed using zero-order, Higuchi's square root and Peppa's exponential equations. All formulations showed compliance with pharmacopoeial standards. Among different formulations F7 showed sustained release of drug for 12 hours with 99.73% of drug release respectively. The regression coefficient value of zero order plots was found to be 0.993. The slope of peppas model was found to be 0.981 for F7.Thus the matrix system of HPMC & SCMC was found to be effective in retarding release of venlafaxine hydrochloride.

Keywords: Venlafaxine hydrochloride, HPMC & SCMC,CDR(Cumulative drug release), SR

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INTRODUCTION

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble and insoluble polymers or waxes and osmotic systems have been developed, and intense research has recently focused on the design of SR systems for poorly water soluble drugs.

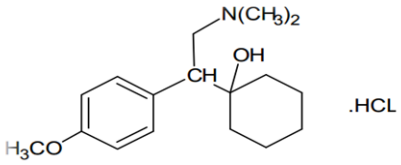

Figure. 1: Chemical structure of Venlafaxine Hydrochloride

Venlafaxine hydrochloride is a antidepressant for oral administration, well absorbed and extensively metabolized in the liver. The aim of this study to formulate and evaluate Venlafaxine hydrochloride sustained release matrix tablets by using different proportion of polymers.

MATERIAL AND METHODS:

Venlafaxine Hydrochloride was a gift sample provided by Lupin Pharmaceuticals Aurangabad. All other chemicals used were of analytical grade and were used as received from different source mentioned in Table 1.

Table.1.Procurement of drug and Excipients

Sr. No.	Materials	Property	Source
1	Venlafaxine Hydrochloride	API	Lupin Pharmaceuticals Aurangabad
2	HPMC(K100M)	Polymer	Ozone International, Mumbai
3	Sodium carboxy methyl cellulose	Polymer	Ozone International, Mumbai
4	Lactose	Diluent	Thomas Baker,Mumbai
5	Magnesium stearate	Lubricant	Meher Chemie , Mumbai
6	Talc	Glidant	Meher Chemie , Mumbai

METHODS:

Preparation of sustain release matrix tablets of Venlafaxine Hydrochloride was done by direct compression method using different drug:polymer ratio. HPMC K-100M & sodium carboxy methyl cellulose is used as sustain release polymers. Table 2 represents the formulation of sustain release matrix tablets.

Table 2: Formulation table

Sr.No.	Ingredients(mg)/Tab	F1	F2	F3	F4	F5	F6	F7
1	Venlafaxine Hcl	84.75	84.75	84.75	84.75	84.75	84.75	84.75
2	HPMC K100M	150	-	85	65	50	100	75
3	SCMC	-	150	65	85	100	50	75
4	Lactose	50.25	50.25	50.25	50.25	50.25	50.25	50.25
5	Talc	5	5	5	5	5	5	5
6	Mag. Sterate	10	10	10	10	10	10	10
7	Total wt.	300	300	300	300	300	300	300

EVALUATION OF TABLETS:

Organoleptic Evaluation:

The Organoleptic evaluation refers to the evaluation of color, odour, shape, taste and special features which include touch and texture. The majority of information on the identity, purity and quality of the material can be drawn from these observations. Different evaluation parameters like solubility, swelling property, pH & viscosity determination of polymers, melting point, bulk density, tapped density, carr's index, hausner's ratio and angle of repose.

Physical characterization of the matrix tablet (post-compressional parameter)

The properties of the compressed matrix tablets, such as hardness, friability, weight variation, and content uniformity is determined using procedure given in Indian pharmacopoeia.

Hardness and Friability:

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction is measured using Monsanto hardness tester for 10 tablets. The friability was determined by testing 20 tablets in Lab line friability tester for 4 min at 25 rpm.

Appearance and thickness:

The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed. The thickness of the tablets is determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

Weight variation:

The weight variation is determined by taking weight of 20tablets using digital electronic balance (Citizen). From each batch twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

Drug content(content uniformity):

The drug content for each batch was determined in triplicate. For each batch 20 tablets are taken, weighed and finely powdered. An accurately weighed quantity of this power was taken and suitably dissolved in water, filtered and analyzed after making appropriate dilutions using U.V. spectrophotometry.(Shimadzu 1800).

***In vitro* dissolution study and kinetic modeling of drug release:**

Release rate of all the formulations were studied up to 12 hours using USP apparatus 2(Paddle method) at 50 rpm. The Dissolution media is Distilled Water for 12 hrs.(900 ml)maintained at 37°C ±0.5°C temperature. Dissolution parameters are mentioned in Table 3.

Table 3: Dissolution parameter:

Dissolution apparatus	USP Type 2, Paddle
Dissolution media	Distilled Water
Volume of the media	900 ml.
Sampling volume	5 ml.
Rotation speed	50 rpm.
Temperature	37 ± 0.5 ^{o}C

Kinetic modeling of drug release:

To find out the mechanism of drug release from hydrophilic matrix, all seven formulation of the prepared matrix tablets of Venlafaxine Hydrochloride are subjected to *in-vitro* release studies. The result obtained in *in-vitro* release studies were plotted indifferent kinetic model of release data treatment as follows

1. Cumulative percent drug released vs. time (zero order rate kinetics)

2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)

3.Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)

4. Log of cumulative % release Vs. log time (Peppas Exponential Equation).

RESULTS AND DISCUSSION:

All the formulation batches of Venlafaxine Hydrochloride sustain release matrix tablets evaluates and the resulta are mentioned below according to methods carried out.

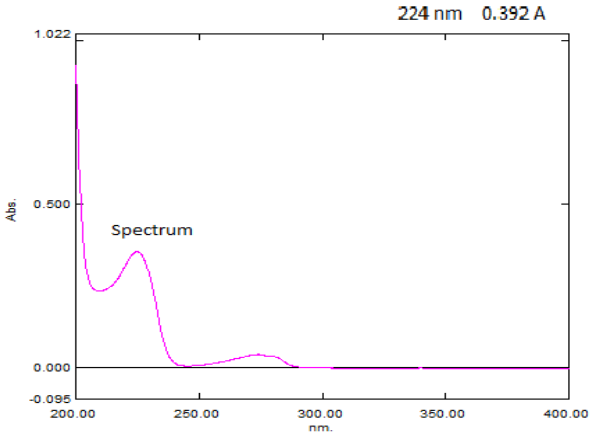

Figure. 2: UV Spectra of Venlafaxine Hydrochloride

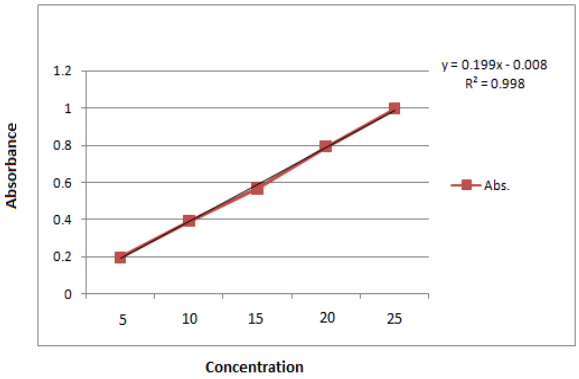

Figure. 3: Calibration curve of Venlafaxine Hydrochloride in Distilled Water.

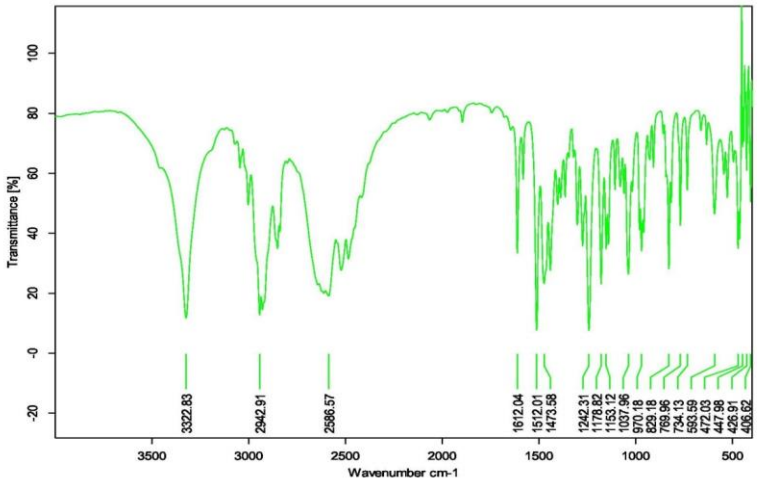

Figure. 4: FTIR spectra of Venlafaxine Hydrochloride.

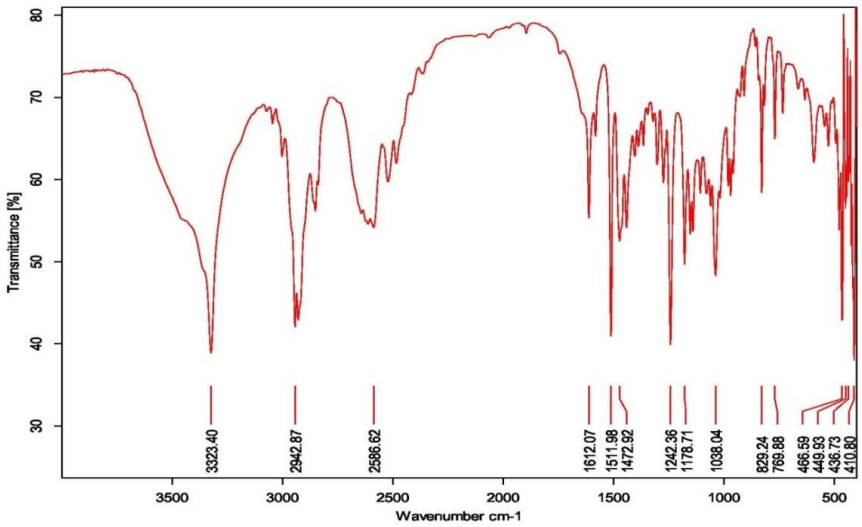

Figure 5: FTIR spectra of hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose and Venlafaxine Hydrochloride.

Interpretation of FTIR spectra of Venlafaxine Hydrochloride :

Interpretation of FTIR spectra has been done based on chemical structure of Venlafaxine Hydrochloride (Figure. 1) and in spectra the walength found at 3322.83= 0-H (stretch), 2586,2942= C-H (stretch), 769 = C-H (bend), 1612= C-C (stretch), 1153 = C-N (stretch) (Figure. 4 & 5).

Table 4: Physical characteristics of prepared tablet blend (pre-compressional):

Sr.no.	Parameter	F1	F2	F3	F4	F5	F6	F7
1	Angle of Repose(Ɵ)	27.68	28.53	29.86	29.13	27.57	28.54	28.23
2	Bulk Density(g/ml)	0.46	0.44	0.47	0.45	0.58	0.52	0.48
3	Tapped Density(g/ml)	0.54	0.51	0.56	0.53	0.67	0.68	0.58
4	Carr's Index (%)	14.81	13.72	16.O7	15.09	14.72	22.37	14.96
5	Hausner Ratio	1.17	1.15	1.19	1.177	1.17	1.16	1.2

Table 5: Evaluation of prepared tablets

Sr.no	Parameters	F1	F2	F3	F4	F5	F6	F7
1	Uniformity of weight (mg)	300±3	302±4	299±1	300±3	298±2	301±1	302±2
2	Thickness (mm)	2±0.1	2.1±0.2	2±0.12	2±0.1	2±0.12	2.1±0.1	1.9±0.1
3	Friability (%)	0.39	0.24	0.35	0.39	0.40	0.250	0.45
4	Tablet hardness (kg/cm^2)	5.2±0.2	4.8±0.1	5±0.3	4.8±.04	5.1±0.2	4.9±0.1	5±0.25
5	Assay (%)	101.12 ±0.24	99 ±0.65	99.76 ±0.76	99 ±0.5	100 ±0.25	98.24 ±0.24	101 ±0.55

Table 6: In-vitro drug release study (Cumulative % Drug Release)

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
1	16.72	15.35	19.97	18.67	13.25	15.422	17.37
2	20.93	20.41	27.46	21.16	18.75	19.19	24.41
3	25.61	25.46	24.145	26.70	22.10	24.508	27.8
4	29.65	30.34	31.65	29.45	27.21	27.68	34.46
5	33.50	38.61	40.504	34.67	30.18	38.46	43.54
6	34.77	52.73	51.13	46.7	40.98	44.31	49.42
7	40.38	65.02	60.74	61.08	51.61	56.7	61.192
8	42.99	79.96	64.11	72.69	60.57	63.52	66.08
9	45.82	92.24	68.367	83.07	71.321	75.363	79.23
10	49.97	97.67	78.93	85.91	78.217	81.196	86.17
11	57.40	94.35	89.55	92.233	85.149	94.001	95.1
12	60.99	89.29	90.68	97.503	91.24	98.41	99.7

Table 7: Drug release kinetics of formulation (R-Value)

Formulation Code	Zero Order	First Order	Higuchi Model	Peppas Model	Best Fit Model
F1	0.9310	0.9759	0.9838	0.9852	Peppas model
F2	0.9760	0.7842	0.8593	0.9331	Zero Order
F3	0.9816	0.9336	0.9489	0.9561	Zero Order
F4	0.9874	0.8907	0.9220	0.9540	Zero Order
F5	0.9927	0.9183	0.9120	0.9723	Zero Order
F6	0.9943	0.8330	0.9173	0.9721	Zero Order
F7	0.9932	0.7760	0.9412	0.9815	Zero Order

***In vitro* Dissolution Study and Kinetic modeling of drug release**

The percent cumulative release pattern of all formulations was given in the table.6. A plot of cumulative percentage versus time for sustain release matrix tablets revealed that the release pattern was slow. The initial drug release of all formulations were found to be in the range of 13.25-19.97 for the first hour depending on polymer concentration indicate no burst release but the release was fond to be more controlled in later stages in the tablets with higher proportion of polymer. The release mechanism of first formulations F1 is Diffusion type of release mechanism. Formulation no.F2 was having Dissolution type of release mechanism & formulation F3-F7 having both Diffusion- Dissolution type of release mechanism. The formulations F1 having HPMC as polymer with concentration 50% and indicate 60.99% of drug release within 12 hours. Hence release pattern of formulations no.F1 were not within the desirable limit. However formulationF2 having SCMC as polymer with concentration 50% and indicate 97.67% of drug release within 10 hours. Hence, release pattern of formulations no.F2 was found to be within the desirable limit. Formulations no.F3, F4, F5, F6, F7 having both HPMC and SCMC as polymers with concentration 50.00%. In that F5 contain 16.66% HPMC and 33.33% SCMC as polymer and indicate 91.24% of

drug release within 12 hours. Formulations no, F6 contain 33.33% HPMC and 16.66% SCMC as polymer and shows 98.41% of drug release within 12 hours. Formulation F7 having 25% HPMC and 25% SCMC as polymer and indicate 99.73% of drug release within 12 hours. From release pattern study, it was found that release rate increase with decreases in polymers proportion and those formulations having both Diffusion- Dissolution type of release mechanism shows release pattern of drug within the desirable limit. The tablets formulations were found to be swelling to different extents forming a gel like structures during the release period depending upon the Polymers proportion.

In order to investigate the release mechanism, the data were fitted to different models representing zero-order, first-order, Higuchi's square root of time $_{VS}$ Log cumulative percent drug release. From the table no.7, it is concluded that the fabricated tablets followed peppas release for formulation no.F1. Zero order release pattern for formulation no.F2, F3, F4, F5, F6 and F7.

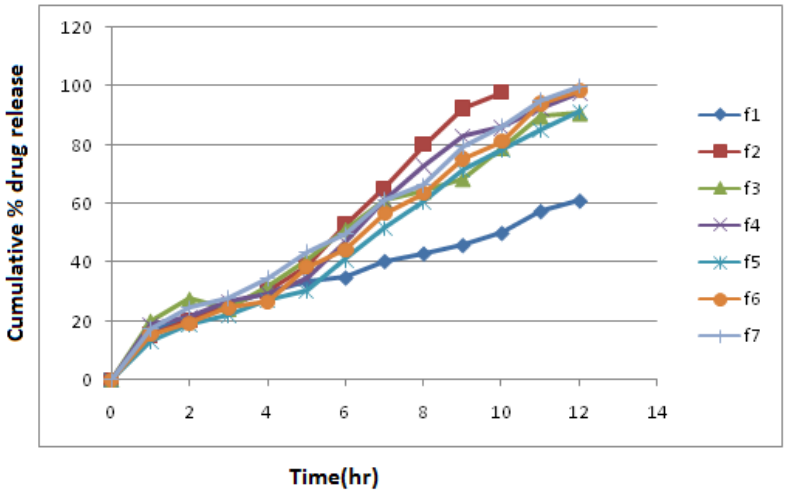

Figure 6: Zero order release profile of all formulation.

CONCLUSION:

The result of the present study demonstrated that the hydroxy propyl methyl cellulose and sodium carboxy methyl cellulose can be used as a drug release retardant and drug release was dependent on polymers proportion. The drug release was extended over a period of 12 hours and the mechanism of drug release was observed to be following zero order release. This is mainly due to formation of a thick gel structure that delays drug release from tablet matrix. Thus, the polymer could serve as a new effective drug release retardant exhibited sustained activity of Venlafaxine Hydrochloride, with better patient compliance. Observation of all formulations for physical characterization had shown that, all of them comply with the specification of official

pharmacopoeias and standard references. The *in-vitro* release data was plotted for various kinetic models and indicating zero order for formulations no F7 with regression coefficient R^2 value 0.9932.Thus Sustained release matrix tablets of Venlafaxine Hydrochloride of good quality were prepared by direct compression method and formulation no. F7 considered to be optimized or ideal.

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