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DESIGN AND OPTIMIZATION OF VENLAFAXINE HYDROCHLORIDE CONTROLLED RELEASE TABLETS USING HPMC $K_{15}M$

Vidyadhara S *, Sasidhar RLC, Ramya Krishna N and Sai Deepika K
Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chowdavaram, Chandramoulipuram, Guntur – 522 019. Andhra Pradesh, India.

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ABSTRACT
Venlafaxine hydrochloride was formulated as oral controlled release matrix tablets using hydrophilic polymer such as hydroxypropyl methyl cellulose (HPMC K_{15} M) along with electrolytes. In this work a new attempt was made for *in situ* interactions between drug and electrolytes were devised to control the release of highly water soluble drugs from oral hydrophilic monolithic systems. Electrolytes such as Calcium carbonate, magnesium trisilicate, sodium bicarbonate were used at different concentrations in various formulations, while drug and polymer concentrations were maintained constantly at 1:1 ratios in all the formulations. These electrolytes were used to monitor matrix swelling and gel properties. These findings indicated that the swelling and gel formation in the presence of ionizable species within the hydrophilic matrices provide an attractive alternative for controlled drug delivery from a simple monolithic system. FTIR studies were carried out for some selected formulations, which indicated that there were no interactions between drug and excipients used.

Key words: *Venlafaxine Hydrochloride; HPMC $K_{15}M$; Electrolytes; Controlled release; Matrix tablets.*

INTRODUCTION

Recently numerous hydrophilic polymers have been investigated and are currently used in design of complex controlled release systems.[1-3] The polymers that are most widely used in the design of controlled release of drug include nonionic hydroxypropyl methylcellulose (HPMC) and polyethylene oxides (PEO's). The major challenge in the development of new controlled release devices is to achieve optimal drug concentration at the site of action. To achieve optimal drug concentration at the site of action, liberation of the drug from the device must be controlled accurately as possible.[4] The dissolution in a monolithic matrix for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. The limitation of hydrophilic polymer may be circumvented through modification of physical and chemical infrastructure of the polymeric gel system by using electrolytes.

In the present investigation, studies were under taken for design and development of oral controlled release drug delivery system of venlafaxine HCl tablets by matrix diffusion technique. Venlafaxine a phenyl ethyl amine derivative, is an anti-depressant (Serotonin-norepinephrine reuptake inhibitor) used in the treatment of depression.[5] It also weakly inhibits dopamine reuptake. It is freely soluble in water and methanol. Venlafaxine is readily absorbed from the gastrointestinal tract. After oral doses it undergoes extensive first pass metabolism in the liver mainly to the active metabolite O-desmethyl venlafaxine. The mean elimination half life of venlafaxine and O-desmethyl venlafaxine is about 5 and 10 hrs respectively. Based on these physicochemical and biopharmaceutical properties, Venlafaxine HCl was selected as a drug candidate for developing controlled release matrix tablet formulations.[6] In the present work, a reliable process has been established for inducing insitu reactions between pharmaceutically acceptable electrolytes and drug which influences the intragel swelling dynamics and relative physical integrity of the swollen matrix structure. Furthermore, that may produce heterogenous domains within the swollen gel boundary. In the past, alkaline compounds (or) buffers have been included in solid oral formulations for several acidic drugs that undergo dissolution rate limited absorption.[7] The same principle of addition of buffers, osmotically active agents, surfactants (or) combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques.[8] However more specific strategy has been employed to apply the same principle to design a simple directly compressible, monolithic controlled release system. In general the application of buffers and ionizable compounds in dosage form design has essentially been limited to the minimization of localized GIT adverse effects and the solubility dependency of poorly soluble compounds.[9,10] The aim of this work was to provide and expand on a means to design , formulate and develop a novel oral monolithic, controlled release tablet dosage form of a drug that may be tailored to provide quasi study state drug release over an

***Correspondence :** svidyadhara@gmail.com

extended period of time.[11] The rationale behind the mechanism and dynamics of electrolytes induced matrix stiffening and structural changes to the gel is the basis of controlled drug release which also been elucidated.

MATERIALS AND METHODS

Materials

Venlafaxine HCl (gift sample from M/S Dr. Reddy labs, Hyderabad). Hydroxy Propyl methyl cellulose $K_{15}M$ (gift sample from Dow Chemicals Asia pvt., Ltd., Mumbai). Microcrystalline Cellulose (commercially procured from Colorcon Chemicals Asia pvt., Ltd., Mumbai). Sodium Bicarbonate (commercially procured from Qualigens Fine Chemicals, Mumbai). Calcium Carbonate (commercially procured from Thermo Fischer Scientific India Ltd., Mumbai). Magnesium Trisilicate (commercially procured from Loba Chemie Pvt., Ltd., Mumbai). All chemicals used in this investigation were of analytical grade.

Preparation of matrix tablets

Venlafaxine HCl controlled release matrix tablets were prepared by direct compression process. The controlled release matrix tablet formulations consisted of drug, polymer, diluent and electrolytes. The ratio of drug and polymer were maintained constant while the electrolyte concentration was varied. The weight of all the tablet formulations was maintained uniformly by using MCC as diluent. The compositions of various tablet formulations were given in table 1. The materials were individually weighed, passed through sieve no: 60 and blended for 15 minutes by using double cone blender. The powder mixture was then lubricated with 1% talc and magnesium stearate and blended for 5 minutes. Then the powder blends were directly compressed into matrix tablets using Clit 10 station mini press. To minimize the processing variables all batches of tablets were compressed, under identical condition. The powder blends were evaluated for flow properties such as angle of repose and compressibility index.

Table 1: *Composition of various controlled release matrix tablets of Venlafaxine HCl*

Ingredients mg/ Tablet	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
Venlafaxine HCl	75	75	75	75	75	75	75	75	75	75	75
HPMC K15M	75	112.5	75	75	75	75	75	75	75	75	75
Sodium Bicarbonate	--	--	20	30	40	--	--	--	--	--	--
Calcium Carbonate	--	--	--	--	--	20	30	40	--	--	--
Magnesium Trisilicate	--	--	--	--	--	--	--	--	20	30	40
MCC	149	111	129	119	109	129	119	109	129	119	109
Talc	1.5	1.5	2	2	2	2	2	2	2	2	2
Total Tablet wt. (mg)	300	300	300	300	300	300	300	300	300	300	300

Evaluation of physical properties

The physical parameters such as weight uniformity, friability, hardness and drug content were evaluated for the prepared matrix tablets as per the standards of official compendium[12].

Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1 N HCl at 37±0.5°C. After 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hrs, tablet from each dissolution basket was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.[13] The swelling index for various selected formulations of matrix tablets were shown in Table 2.

Table 2: *Swelling Index of Controlled Release Matrix Tablets of Venlafaxine HCl*

S.No	Formulation	Swelling Index (%)		
		1 hr	6hr	10hr
1	F-5	66.6	92.0	153.3
2	F-8	73.3	96.3	142.6
3	F-11	116.6	100.0	137.6

$$\text{Swelling index} = \frac{\text{(Wet weight of tablet - Dry weight of tablet)}}{\text{Dry weight of tablet}}$$

Drug release studies

Dissolution studies on all the formulation were performed in a calibrated 8 station dissolution apparatus equipped with paddles employing 900 ml of distilled water as a medium.[14]

The paddles were operated to rotate at 75 rpm and the temperature was maintained at 37±1^{0}C throughout the studies. Samples were withdrawn at regular intervals up to 12 hrs and each time samples were replaced with equal volume of fresh medium to maintain the volume of dissolution medium constant throughout the experiment. Drug content of the samples were determined by ELICO double beam UV spectrophotometer at 225nm, after suitable dilution. To analyze the mechanism of drug release from the obtained data, various calculations were analyzed based on the equation like first order constant, Higuchi constant and the koresmeyer peppas constant respectively.

The following are the equations used:

$\ln Q = k.t$ ……1

$Q = k.t$ ……2

$Mt/M\infty = ktn$…….. 3

Where Q in the equation 1 is cumulative percent drug remained, while Q in the equation 2 is cumulative amount of drug released, Mt/M^{∞} is the fraction of drug released, t is the release time and k is the constant incorporating the structural and geometrical characteristics of the release device. If the value of n= 0.45 indicates Case I (Fickian) diffusion or square root of time kinetics, $0.45 < n < 0.89$ indicates anomalous (Non-Fickian drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, n= 0.89 indicates case II transport and n>0.89 indicates super case II transport. Linear regression analysis was performed for all these

equations and regression coefficients (r) are determined.

The dissolution profiles of all the prepared matrix tablet formulations for venlafaxine hydrochloride were compared with the marketed extended release tablet formulation of venlafaxine hydrochloride by using a model independent approach of similarity factor *f2,* with all time points included in the *in vitro* dissolution studies [15-16]. The equation for calculating similarity factor is

$$f_2 = 50 + \log \{[1+ (1/n) \text{“}_{t=1} * n (R_t-T_t)^2]^{-0.5} \times 100\}$$

Where 'n' is the number of dissolution time and R_t and T_t are the reference (theoretical) and test dissolution values at time't'. Dissolution profile was considered satisfactory if f_2 value lies more than 50. Two dissolution profiles are considered similar when the *f*2 value is 50 to 100.

RESULTS AND DISCUSSION

The present study was under taken for design and evaluation of the controlled release matrix tablets of venlafaxine hydrochloride with HPMC $K_{15}M$, by employing various pharmaceutically acceptable electrolytes as drug release retardants. All batches of tablets were produced under similar conditions to avoid processing variables. The compositions of various matrix tablets were given in Table 1. These tablets were preliminarily evaluated for various physical parameters such as weight uniformity, hardness, friability and for drug content. All batches of tablets with different electrolyte composition were within the weight range of 299-301 mg. Hardness of the matrix tablet formulations were constant for all batches and were maintained at 5-6 kg/cm^2. Friability loss of formulations was negligible and was less than 0.2% for all the batches. Drug content was uniform in all the batches of matrix tablet formulations and was within the range. All the matrix tablets were prepared under identical conditions and were found to be stable. The results of physical parameters evaluated for various matrix tablets are given in Table 3.

Table 3: *Physical parameters of Venlafaxine HCl Controlled release Matrix Tablets*

S. No	Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (mg/tablet)
1	F-1	302±2.0	6.5±0.3	0.12	74.3±0.5
2	F-2	301±3.0	6.0±0.3	0.12	74.2±0.5
3	F-3	296±3.0	6.5±0.3	0.18	75.4±0.5
4	F-4	302±3.0	6.0±0.3	0.16	74.6±0.5
5	F-5	300±3.0	6.5±0.3	0.18	74.8±0.3
6	F-6	301±2.0	6.5±0.3	0.14	75.2±0.5
7	F-7	302±2.0	6.5±0.3	0.15	75.5±0.2
8	F-8	303±3.0	6.5±0.3	0.13	75.4±0.3
9	F-9	302±3.0	6.0±0.3	0.16	74.3±0.2
10	F-10	300±3.0	6.5±0.3	0.18	75.4±0.2
11	F-11	296±3.0	6.0±0.3	0.19	74.7±0.5

From the *in vitro* dissolution studies, it was observed that formulations F5, F8 & F11 showed greater inhibition of release rate of venlafaxine from the tablet matrix. The dissolution profiles of various matrix tablets were shown in figures 1-4 and their corresponding kinetic data was shown in table 4.

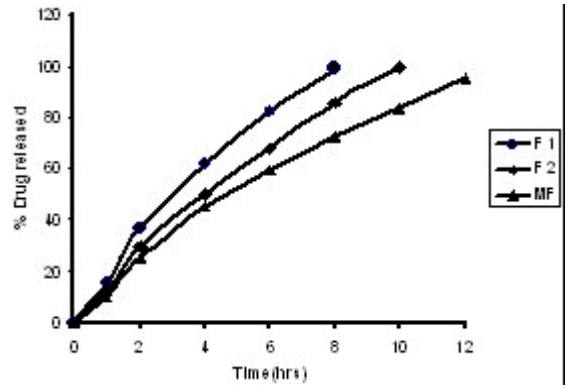

Fig. 1: *Drug release profile for controlled release matrix tablets of Venlafaxine hydrochloride*

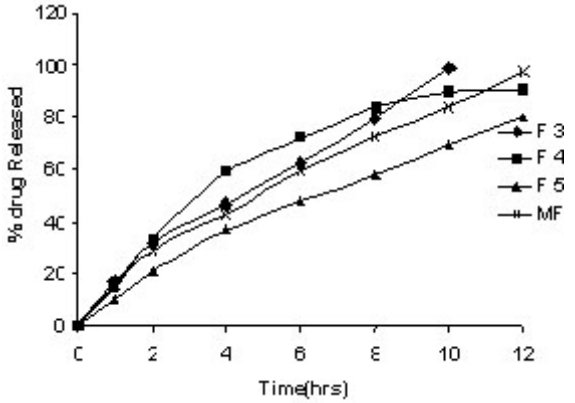

Fig. 2: *Drug release profiles of various controlled release formulations of Venlafaxine hydrochloride with Sodium Bicarbonate*

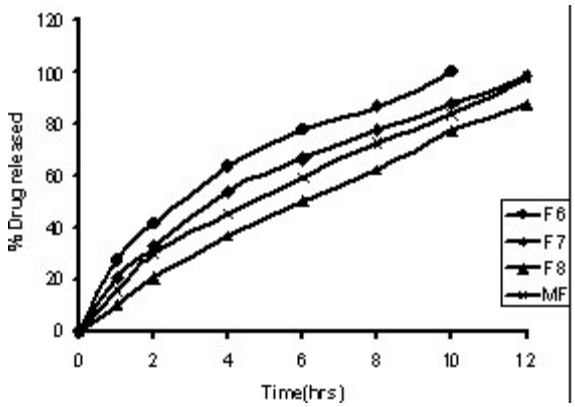

Fig. 3: *Drug release profiles of various controlled release formulations of Venlafaxine hydrochloride with Calcium carbonate*

By the addition of electrolytes into the matrix tablet formulations, it was possible to reduce the release rate of drug over an extended period of time. The inclusion of electrolyte within the matrix tablet for controlling the release rate of venlafaxine hydrochloride might lead to the formation of free base of venlafaxine and fundamental structural changes in gel boundary, thus

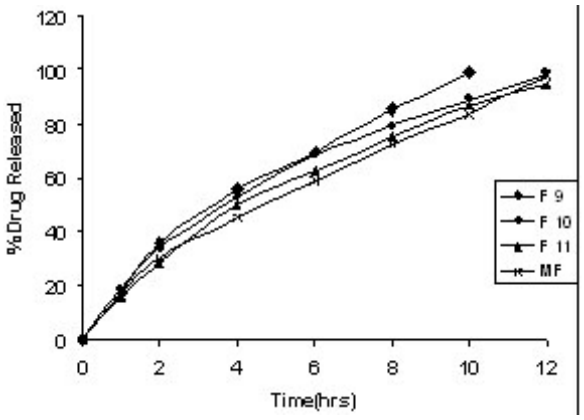

Fig. 4: *Drug release profiles of various controlled release formulations of Venlafaxine hydrochloride with Magnesium Trisilicate*

Table 4: *In Vitro Pharmacokinetic parameters of controlled release matrix tablets of Venlafaxine HCl*

Formulation	Zero Order Constant		First Order Constant		Higuchi Constants		Peppas Constant	
	K	R^2	K (mg.h)	R^2	K (h^{-1})	R^2	n value	R^2
Marketed	14.35	0.89	0.21	0.96	35.42	0.98	0.60	0.986
F-1	15.24	0.97	0.31	0.99	33.02	0.99	0.50	0.978
F-2	14.38	0.89	0.18	0.93	30.68	0.98	0.55	0.996
F-3	14.70	0.89	0.22	0.95	29.21	0.99	0.60	0.998
F-4	15.23	0.91	0.19	0.98	26.76	0.99	0.62	0.997
F-5	13.33	0.92	0.16	0.99	25.68	0.99	0.62	0.997
F-6	11.83	0.84	0.11	0.97	32.73	0.98	0.70	0.995
F-7	12.70	0.89	0.24	0.86	30.13	0.98	0.62	0.989
F-8	11.38	0.93	0.18	0.97	29.22	0.99	0.62	0.992
F-9	15.53	0.93	0.15	0.95	33.73	0.99	0.70	0.992
F-10	9.58	0.85	0.230	0.84	30.75	0.99	0.58	0.997
F-11	8.78	0.85	0.202	0.99	28.29	0.99	0.58	0.994

including the textural variations in the swollen matrix. Further it may be due to higher pKa values of electrolytes, which can display higher buffer threshold for maintaining suitable pH inside the matrix. Electrolytes such as sodium bicarbonate with pH values greater than 7.0 might exert a better and desired control on drug release from matrix tablet. As the dissolution medium enters the periphery of the tablet, there is a rapid electrolyte water interaction with significant chemical reaction through electrolyte solubilization and subsequent events that may lead to both initial suppression and later enhancement of polymer swelling. During this infiltration process, the electrolyte present in the gel boundary could have been converted to bicarbonate form (for example sodium bicarbonate) due to which the hydrochloride form of venlafaxine hydrochloride leads to the formation of free base of venlafaxine. The passive and actively formed electrolytes within the gel matrix would compete for water leading to dehydration of polymer molecules, thus leading to dehydration of polymer molecules, thus leading to suppression of initial swelling which was seen up to 2 to 3 hours within formulations containing high concentration of electrolytes. After 3 hour the water attracted by electrolytes into the polymer matrix could result in solubilising the drug molecules which would diffuse by penetration of water leading to enhancement of swelling. The swelling index characteristics of various matrix tablets were given in Table 3. From these alterations and mechanisms of intragel changes, it appears possible to inhibit drug dissolution rate. This inhibition in dissolution rate appears to be time-dependent phenomenon. Since, as more water enters the gel matrix layer–by-layer, the electrolytes and their by products are diluted and any drug base may be revert to its hydrochloride form, which is subsequently released [17]. The dissolution profiles of venlafaxine hydrochloride matrix tablet formulations were compared with marketed controlled release formulation of venlafaxine hydrochloride extended release tablets. The similarity factors were calculated for these matrix tablet formulations. The similarity factor f_2 values were in the range of 19–89. The formulations F7, F10 and F11 showed the similarity factor values above 50 indicated that the release profiles for these formulations were similar to that of marketed formulation. The FTIR spectra of venlafaxine hydrochloride exhibited principle peaks at wave numbers 3350 cm^{-1} [CH stretch], 1438 cm^{-1} [N-$(CH_3)_2$] and 2935 cm^{-1} [OH] shown in figures 5-8. The FTIR spectra of matrix tablet formulations F5, F8 & F11 exhibited all the principle peaks present in the venlafaxine hydrochloride pure drug. The results revealed that there were no major interaction between the drug and the excipients.

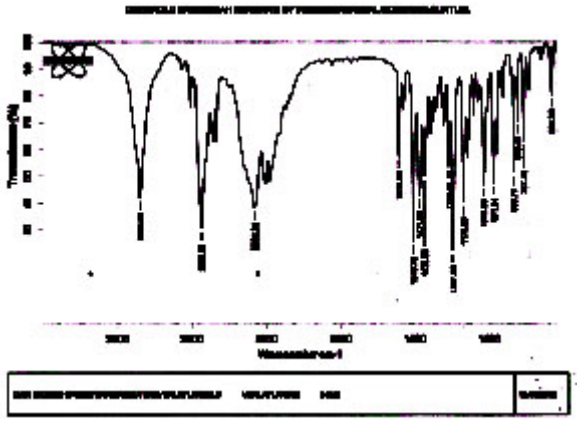

Fig. 5: *FT IR spectra of Venlafaxine HCl Pure Drug*

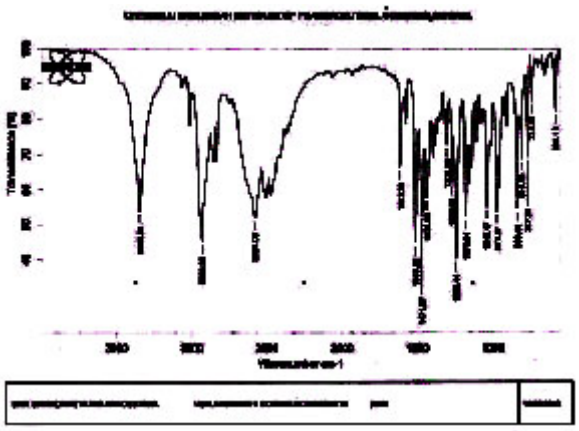

Fig. 6: *FT IR spectra of Venlafaxine HCl (F 5)*

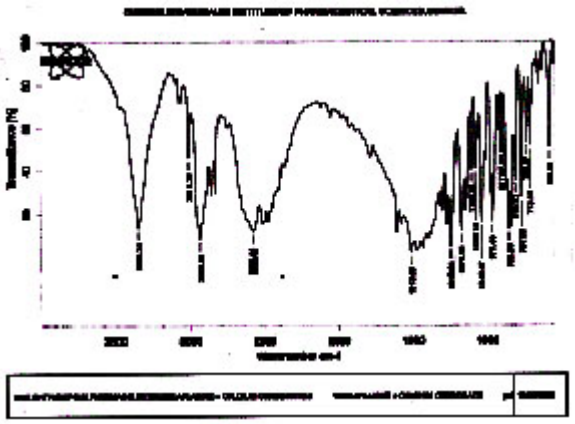

Fig. 7: *FT IR spectra of Venlafaxine HCl (F 8)*

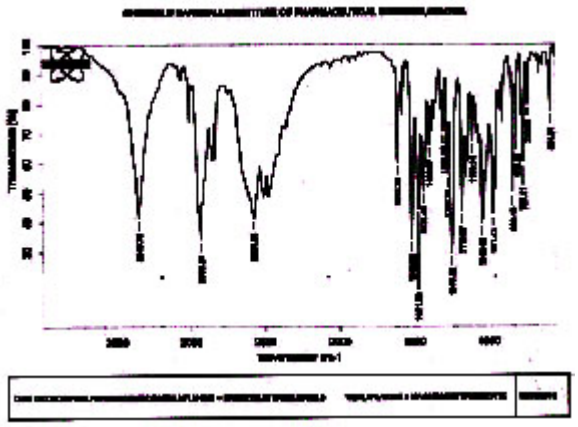

Fig. 8: *FT IR spectra of Venlafaxine HCl (F 11)*

CONCLUSION

This work has provided a novel and a simple approach to formulate an oral controlled release drug delivery system designed for delivery of venlafaxine HCl over an extended time period. An important feature of this system is the potential for generating constant drug release. The formulations F5, F8 & F11 were found to extend the drug release over an extended period of time. Hence these formulations were found to be suitable for once a day matrix tablet administration for treating the depression patients. Their physical parameters were within Indian pharmacopoeial specified limits.

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