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ORIGINAL RESEARCH ARTICLE

Effect Of Gum Rosin And Ethyl Cellulose On In Vitro Release Of Venlafaxine Hydrochloride From Hydrophilic Matrix Tablets

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ABSTRACT

Developing oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. The present work is focused on the effect of gum rosin (GR) and ethyl cellulose (EC) in controlling the release of highly water-soluble drug venlafaxine Hydrochloride from hydrophilic matrices prepared using Hydroxypropyl methylcellulose K100M (HPMC). Tablets were prepared by direct compression method and were evaluated for physicochemical properties, in vitro swelling and release studies. The mechanism of drug release was analyzed using various kinetics models like zero order, first order, Higuchi and Korsmeyer-Peppas equations. Release profiles indicated that, increasing the polymer concentration has drastically retarded the release of venlafaxine hydrochloride. However, even at higher polymer concentration (50% w/w) of HPMC, controlled drug release over a period of 24 hrs could not be obtained. Matrix tablets prepared with combination of hydrophobic polymers namely F6 (50 % w/w HPMC-GR) and F8 (40 % w/w HPMC-EC) gave controlled release of drug over a period of 24 hrs. The mechanism of drug release from all the matrix tablets followed Non-Fickian diffusion as n values lies between 0.4906 to 0.7185 indicating that polymer swelling and relaxation were both involved in the release process. The results of the study revealed that, matrix tablets prepared using HPMC alone could not efficiently control the release of highly water-soluble drug venlafaxine Hcl. The combination of hydrophobic polymers in hydrophilic matrices gave a controlled release over a period of 24hrs.

Key words: Venlafaxine Hydrochloride; Matrix tablets; Direct compression; Controlled release; Non-Fickian diffusion;

INTRODUCTION

Venlafaxine Hcl is an orally active serotonin noradrenalin reuptake inhibitor used in the treatment of major depressive disorders. The successful treatment of depression depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. Venlafaxine Hcl is a highly water soluble drug with the biological half life of 5 hrs and 11 hrs of its active metabolite o-desmethyl venlafaxine (ODV), thus requires two to three time daily dosing to maintain plasma drug concentration[1].

Developing oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce the toxic concentrations, when administered orally [2]. The hydrophilic matrices are one of the most used types of controlled release systems in the world. In comparison with other controlled release devices, they have the advantage of their low cost and simple technology that facilitates their application to an important sector of the population, as well as their safety against the dose dumping [3]. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For

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such drugs it becomes essential to include hydrophobic polymers in the matrix system [4]. In addition, hydrophobic polymers also provide several advantages, ranging from good stability at

varying pH values and moisture levels to well-established safe applications [5].

Hence, the present research endeavor was directed towards the development of controlled release matrix tablets of venlafaxine Hcl by incorporating hydrophobic polymers in hydrophilic matrices. Matrix tablets comprising of HPMC K100M alone and in combination with hydrophobic polymers like ethyl cellulose-45 cps (EC) and gum rosin (GR) were prepared by direct compression. The precompressional powder blend was evaluated and optimized for various parameters like angle of repose, compressibility index and Hausner's ratio so as to make it suitable for direct compression. The prepared matrix tablets were evaluated for their physico-chemical properties such as thickness, hardness, friability, weight variation, drug content and *in-vitro* release; the optimized tablet formulation was subjected to accelerated stability studies as per ICH guidelines.

MATERIALS AND METHODS:

Venlafaxine Hcl was obtained as gift sample from Torrent Pharmaceuticals Ltd, Ahmedabad; Gum rosin was generously supplied as gift samples by Crystal colloids Ltd, Mumbai; HPMC K100M, Ethyl cellulose 45cps were obtained as gift samples from Colorcon Ltd, Goa. All other reagents and solvents used in the study were purchased from S.D Fine Chemicals Ltd, Mumbai and are of analytical grade.

Tablet Preparation:

Matrix tablets of Venlafaxine Hcl were prepared by direct compression method using 8 mm flat-faced punch of 10 station Rimek compression machine. The active ingredient and the excipients were passed through 80 mesh sieve and thoroughly mixed using a mortar and pestle for 10 minutes. PVP K30 was used as binding agent and magnesium stearate, Aerosil were added to the above blend as flow promoters and further mixed for another 10 minutes. In all the formulations the amount of venlafaxine Hcl was kept constant at 84.87 mg equivalent to 75 mg of venlafaxine base. Table I shows different matrix tablets of Venlafaxine Hcl using HPMC alone and in combination with gum rosin and ethyl cellulose (hydrophobic polymers).

Physicochemical Characterization Of Tablets:

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester and the average was calculated. Tablet

hardness was determined using the Monsanto hardness tester. The hardness (kg) of 6 tablets was measured, and the mean hardness was calculated and reported[6]. The tablet friability was determined on Roche friabilator (Electrolab). A sample of pre-weighed 10 tablets was placed in Roche friabilator, which was then operated for 100 revolutions. The tablets were then dusted and reweighed. Percent friability (F) was calculated as follows.

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test[7]. The crown-to-crown thicknesses of 10 tablets from each batch were determined using vernier calipers. To study weight variation, 20 tablets were weighed individually using an electronic balance (AX-200, Shimadzu Corporation, Japan) and the test was performed according to the official method. Further to investigate the integrity of drug in the matrix formulations, tablets were subjected to FT-IR and DSC studies.

Swelling studies:

The swelling of the polymers upon hydration by the test medium was determined by a method similar to the equilibrium weight gain method. The matrix tablets were weighed and placed in tared metallic baskets. These baskets were then immersed in 900 ml of phosphate buffer of pH 7.2 and rotated at 75 rpm at 37±0.5 °C (USP XXIV basket method). At specified time intervals, the baskets containing the matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percent degree of swelling was calculated as follows.

$$\text{Percent degree of swelling} = [(Ws - Wd)/Wd] \times 100$$

Where Ws is the weight of the swollen matrix at time t and Wd is the weight of the dry matrix [8]. The swelling study was done in triplicate for all samples tested.

In Vitro Drug Release Studies:

The tablets were subjected to in vitro drug release studies for a period of 24 hrs using 8 station USP

dissolution apparatus (Electro Lab, TDT-O8L, and Mumbai). Dissolution studies were carried out using acid buffer of pH 1.2 as a dissolution medium for first 2 hrs, and phosphate buffer of pH 7.2 medium up to 24 hrs at 37± 0.5 °C and 75 rpm. Five milliliter sample was withdrawn at regular time intervals and replaced with freshly prepared buffer medium. The sample withdrawn were filtered through Whatman filter paper and after suitable dilution, analyzed spectrophotometrically at 224 nm using Shimadzu-1700 UV-Visible spectrophotometer.

Mechanism Of Drug Release:

To investigate the mechanism of drug release from the matrix tablets, various kinetics models like zero order, first order, Higuchi's equations were applied to the *in-vitro* release data obtained from different formulations. However, these models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe the drug release behavior from polymeric systems.

Log (Mt/Mf) = Log k + n Log t

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release (Kuksal A et al).

Stability studies:

The optimized formulation was strip packed (Al–Al strip, 0.04 mm) and subjected to accelerated stability studies as per ICH guidelines i.e. room temperature, 30 °C / 60% RH and 40 °C / 75% RH. Sampling was done at predetermined time intervals of 0, 15, 30, 60, 90 and 180 days. Tablets were evaluated for the different physico-chemical parameters viz. appearance, weight variation, thickness, hardness, friability, drug content and in vitro release [9,10].

RESULTS AND DISCUSSION:

The use of hydrophilic polymer alone for controlling the drug release of highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer (Jain NK et al). Hence, the present study is aimed to investigate the effect of hydrophobic polymers like gum rosin and ethyl cellulose on hydrophilic matrices for controlling the release of highly water soluble drug venlafaxine Hcl.

Precompressional Evaluation of Powder Blend:

The method employed for matrix tablet preparation was direct compression for which the drug or powder blend of drug and polymer should possess good flow properties. Pure venlafaxine Hcl exhibited angle of repose (52.16 ± 0.28°) indicating extremely poor flow property. It was further supported by high Carr's index value (23.54 ± 0.25%) and Hausner's ratio (1.42 ± 0.02). Hence lubricant and glidant were added to improve the flow properties of drug. The flow property of precompressional mixture was enhanced by increasing the polymer level. With the addition of flow promoters, acceptable ranges in the micromeritic properties of the powder blend was obtained in all the formulations studied. The results of micromeritic evaluation of the powder blend are presented in (**Table 1.)**

Table No. 1 Composition of Venlafaxine Hcl matrix tablets formulated with HPMC alone and in combination with hydrophobic polymers.

Code	Venlafaxine Hcl (mg)	HPMC (mg)	Gum rosin (mg)	Ethyl cellulose (mg)	MCC (mg)
F1	84.87	150	---	---	232.63
F2	84.87	200	---	---	182.63
F3	84.87	250	---	---	132.63
F4	84.87	75	75	---	232.63
F5	84.87	100	100	---	182.63
F6	84.87	125	125	---	132.63
F7	84.87	75	---	75	232.63
F8	84.87	100	---	100	182.63
F9	84.87	125	---	125	132.63

All tablets contain 5% w/w polyvinyl pyrollidone K30, 1% w/w Magnesium stearate and 0.5 % w/w Aerosil.

Post Compressional Evaluation Of Tablets:

In order to avoid the effect of tablet hardness and thickness on in vitro *drug* release, these two parameters have been maintained at specific values i.e. hardness at about 6-7 kg/cm^2 and thickness at about 5-6 mm. The tablets of different batches of HPMC alone and in combination with Gum rosin and ethyl cellulose were found uniform with respect to hardness (6.3 to 6.8 kg/cm^2) and thickness (5.13 to 5.79 mm). The friability (0.36 to 0.58%) and weight variation (0.87 to 1.37%) of different batch of tablets were found within prescribed limits. Drug content (99.04 to 100.27%) was found uniform within the batches of different tablets. Hence tablets containing drug, polymer, diluent and lubricant could be prepared satisfactorily by direct compression method. The results of physico-chemical evaluation of tablets are given in(**Table 2**).

Table No. 2 Precompressional and post compressional evaluation of various matrix formulations of venlafaxine Hcl.

Code	Precompressional evaluation of powder blend[#]			Post compressional evaluation of matrix tablets				
	Angle of repose (θ)	Compressibility (%)	Hausner's ratio	Hardness[+] (kg/cm^2)	Friability[†] (%)	Thickness[†] (mm)	Weight variation* (%)	Drugcontent[**] (%)
F1	29.24±0.10	18.421±0.21	1.21±0.12	6.7±0.30	0.55±0.03	5.14±0.06	1.37±0.48	99.17±0.21
F2	25.17±0.05	17.814±0.20	1.22±0.17	6.6±0.28	0.48±0.06	5.39±0.02	0.97±0.65	99.04±0.16
F3	21.30±0.07	16.475±0.14	1.19±0.13	6.3±0.35	0.38±0.01	5.13±0.01	1.19±0.16	99.64±0.38
F4	24.22±0.01	16.467±0.12	1.19±0.07	6.5±0.33	0.58±0.01	5.23±0.03	0.87±0.34	100.6±0.33
F5	27.77±0.07	17.551±0.04	1.21±0.11	6.8±0.55	0.52±0.02	5.42±0.01	1.10±0.19	99.36±0.65
F6	26.56±0.23	15.288±0.11	1.18±0.23	6.5±0.64	0.44±0.01	5.79±0.04	1.07±0.37	98.70±0.42
F7	24.08±0.14	19.230±0.27	1.23±0.02	6.6±0.40	0.46±0.04	5.34±0.03	1.15±0.75	99.17±0.49
F8	26.56±0.02	17.274±0.12	1.20±0.17	6.4±0.46	0.42±0.02	5.7±0.05	1.26±0.35	100.27±0.6
F9	27.96±0.10	17.289±0.03	1.20±0.21	6.8±0.24	0.36±0.03	5.22±0.04	0.84±0.29	99.65±0.52
Pure drug	52.16 ±0.28	23.54 ± 0.25	1.42 ±0.02	---	---	---	---	---

All values are expressed as mean ± SD. [#]n=3, [+]n=6, [†]n=10, *n=20, **n=3.

Compatibility studies:

The comparison of IR spectrum of pure drug with IR spectra of optimized formulations F6 and F8 showed no appreciable change in the positions of characteristic absorption bands. All the major bands present in the spectrum of the pure drug are clearly observed in the IR spectra of formulations with negligible change in their positions (**Fig.1**). This study clearly suggests that the drug remains in its normal form even in its formulations without undergoing any type of interaction with the polymer or other excipients present in the formulations. The differential scanning colorimetry (DSC) thermogram of pure drug venlafaxine Hcl showed an endothermic peak indicating the melting point 210-215 °C which is in total agreement with literature value of the drug[11]. The DSC thermograms of the optimized formulations F6 and F8 also exhibited the same type of endothermic peaks showing the melting point of formulation F6 m.p at 210 °C and F8 m.p at 210.61 °C. Though there is little variation in the appearance of the thermograms of formulations, it is clear that the melting point of pure drug and the formulations is almost same with negligible difference in the melting range (**Fig. 2**). From this observation we can draw a conclusion that the drug is not showing any type of interaction with the polymers or other excipients of the formulations.

Fig. 1: IR spectra of venlafaxine Hcl pure drug (A), optimized HPMC-GR matrix tablets (B) and HPMC-EC matrix tablets (C)

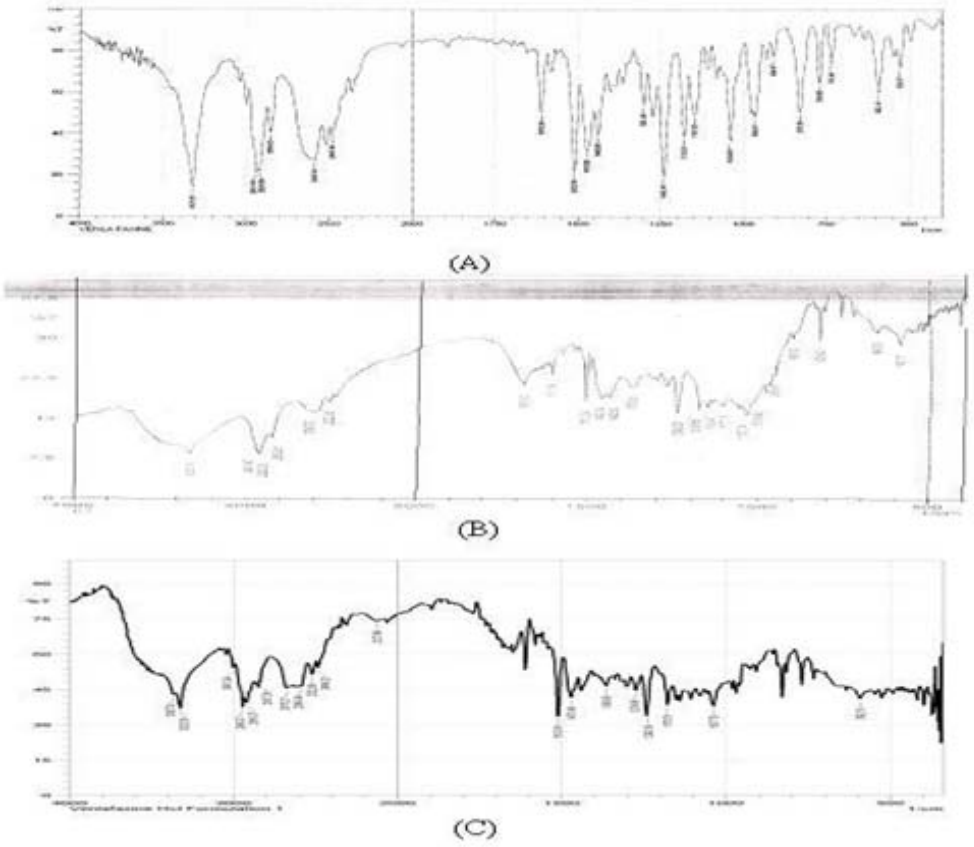
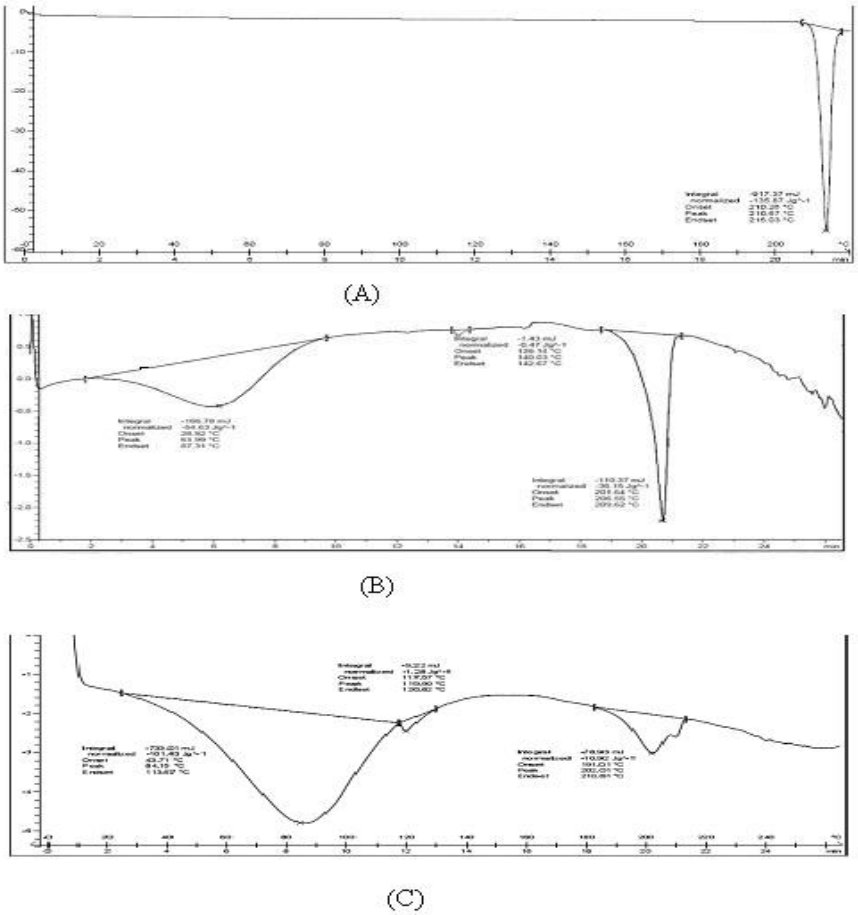


Fig. 2: DSC thermogram of venlafaxine Hcl pure drug (A), optimized HPMC-GR (B) and HPMC-EC matrix tablets (C)



Swelling studies:

Investigation of polymer swelling and erosion is a valuable exercise to better understand the mechanism of release and the relative importance of participating parameters. Matrix tablets of HPMC were found intact throughout the period of swelling (08 to 18 hrs) in phosphate buffer of pH 7.2 and also the percent of swelling index was proportionate to the polymer level. On comparing the swelling indices of different matrix formulations, it was observed that, tablets containing combination of hydrophilic-hydrophobic polymer blends swelled less than that of formulations containing hydrophilic polymer alone (respective graphs not shown). This could be due to presence of non-swellable hydrophobic polymers, which minimized the swelling of the matrix tablets.

In vitro release studies:

In vitro dissolution studies are valuable tools to judge quality and stability of sustained release dosage forms and are often used to predict in vivo performance. The effect of polymer level on release was studied by varying the levels of HPMC in the matrix tablets. The release pattern of matrix tablet containing 30, 40 and 50% w/w HPMC is depicted in (**Fig. 3**). The release rate from F1, F2 and F3 was found to be 99.40, 99.71 and 98.55% at the end of 11^{th}, 14^{th} and 16^{th} hrs respectively. As the proportion of HPMC was increased, there was a progressive decline in the release rate because of formation of thick gel structure that delayed the drug release from the matrices, where hydration of HPMC resulted in extensive swelling and increase in the diffusion path length. Swelling studies of HPMC matrices also showed proportionate increase in the swelling with increase in polymer level. The observation was in accordance with previous reports (Gohel MC et al). However, the results of the in vitro drug release studies indicated that, matrix tablets prepared using HPMC alone could not efficiently control the release of drug even with increased levels of polymers (up to 50%w/w) and thus indicated the need for hydrophobic polymers in the HPMC matrices for controlling the drug release over a period of 24 hrs.

To assess the influence of hydrophobic polymers in controlling the drug release, six matrix formulations containing combination of HPMC-GR (F4-F6) and HPMC-EC (F7-F9) with equal proportions were prepared in different polymeric levels like 30, 40 and 50% w/w. The release profile of venlafaxine Hcl from HPMC-GR matrix formulations F4, F5, and F6 were found to be 99.31, 99.40 and 99.28% at the end of 18^{th}, 20^{th} and 24^{th} hr respectively. It was also observed from the swelling study that the percentage of swelling index was proportionate with the polymer level. Similarly, the matrices prepared using combinations of HPMC with EC were subjected for dissolution studies. The release pattern of matrix tablets containing HPMC-EC (F7-F9) is depicted in Fig. 4. The release rate from matrix formulations F7, F8, and F9 was found to be 99.36, 99.58 and 92.37% at the end of 19^{th}, 24^{th} and 24^{th} hrs respectively. The release profiles from HPMC-GR formulations showed higher drug release compared to those prepared with HPMC-EC combination. This could be due more hydrophobic nature of EC than gum rosin. In all the above formulations, delay in drug release was observed due to the presence of hydrophobic polymers like gum rosin and ethyl cellulose, which restricted the penetration of dissolution medium in side the matrix and also the formation of gel layer around the matrix. The observation is further supported by penetration theory, which states that, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse with more hydrophobic particles present, and the theory predicts that fewer clusters of soluble drug substance are formed. Furthermore, the presence of finite drug clusters is more statistically plausible. The resulting pore network becomes less extensive and more tortuous resulting in slower drug release [12,13,14]. The same effect was also reported for the delayed release of hydrophilic drugs like Propranolol hydrochloride [15], Tramadol Hcl (Tiwari SB et al), Diltiazem Hcl (Enayatifard et al) Zidovudine[16] due to the presence of hydrophobic polymers in the hydrophilic matrices. In conclusion, the matrix tablets prepared with polymeric combination of HPMC-GR and HPMC-EC showed better controlled release than those prepared using HPMC alone.

Fig. 3: Effect of polymer level on *in vitro* release of venlafaxine Hcl from HPMC matrix tablets

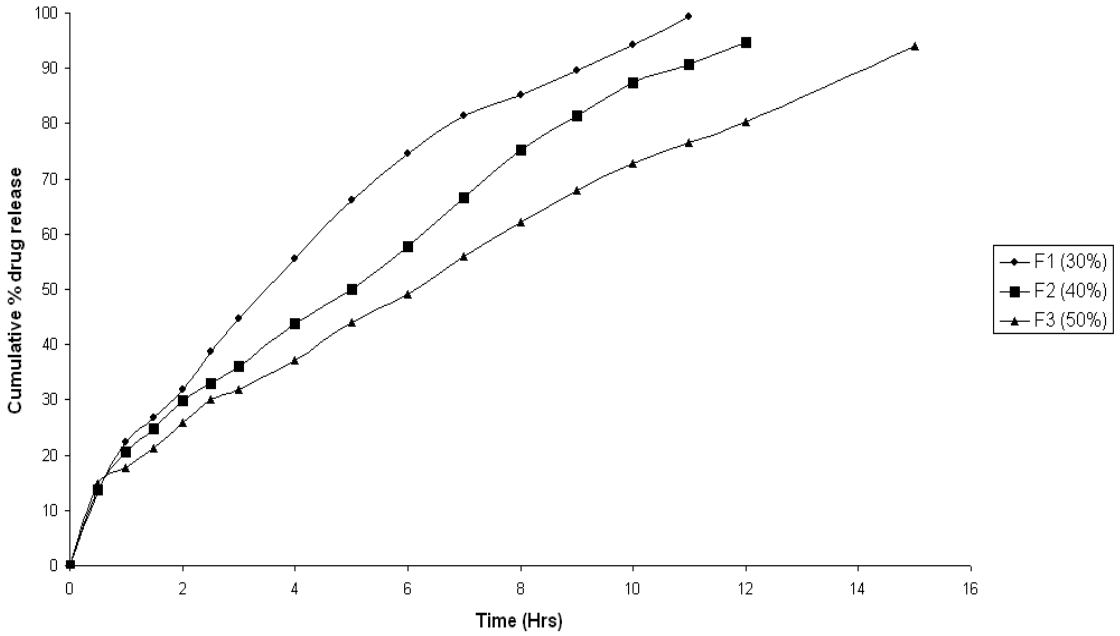
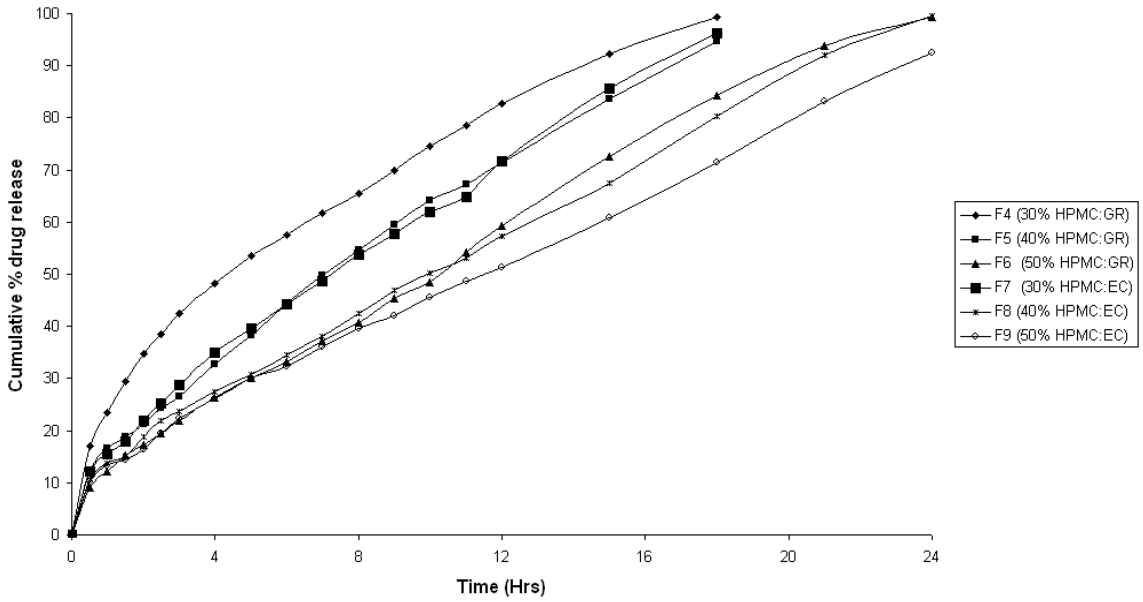


Fig. 4: Effect of hydrophobic polymers on *in vitro* release of venlafaxine Hcl from HPMC matrix tablets



Mechanism of drug release:

To investigate the mechanism of drug release from the matrix tablets, various kinetics models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the *in-vitro* release data obtained from different formulations. As observed from the (**Table: 3**), the values of correlation-coefficient (r^2) for all the formulations were high enough to evaluate the drug dissolution behavior. The value of release exponent (n) was found to be a function of polymer used and the physicochemical property of a drug molecule itself. When the data was plotted in Korsmayer-Peppas equation, linear plots were obtained for all the formulations with high correlation coefficient (r^2) values ranging from 0.9870 to 0.9984. Further, when the drug release data was put into Higuchi equation, good correlation coefficient (r^2) values ranging from 0.9536 to 0.9991 were obtained, indicating that the drug release was diffusion controlled. The drug release from all matrix tablets followed anomalous (non-fickian) release mechanism as n values Korsmayer-Peppas equation lies between

0.4906 to 0.7185, indicating that polymer swelling and relaxation were both involved in the release process. For all the formulations, the best fit with highest correlation coefficient was observed for Korsmayer-Peppas equation compared to Higuchi equation, Zero-order and first order equations.

The stability studies were carried out for the selected formulations (F6 and F8) as per ICH guidelines for a period of six months indicated the absence of any physical changes (hardness and friability) during the study period. The drug content was found above 98% at the end of six months and the release of drug was also not affected. Thus the optimized formulations remained stable at the accelerated conditions of temperature and humidity.

Table No. 3 *In-vitro* release kinetics data based on best curve-fitting method for different matrix tablets of venlafaxine Hcl. (n=3)

Code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	n	r^2	n	r^2	n	r^2	n	r^2
F1	10.480	0.9834	-0.1565	0.8760	34.866	0.9747	0.7110	0.9957
F2	7.4652	0.9801	-0.0942	0.9451	29.024	0.9795	0.6450	0.9922
F3	5.8710	0.9780	-0.0660	0.9223	24.603	0.9823	0.6310	0.9955
F4	4.9607	0.9235	-0.0875	0.8298	23.410	0.9991	0.4906	0.9984
F5	5.0000	0.9799	-0.0572	0.9140	22.679	0.9794	0.6408	0.9898
F6	4.0641	0.9901	-0.0647	0.7983	21.068	0.9573	0.6814	0.9870
F7	5.0021	0.9810	-0.0609	0.8720	22.655	0.9784	0.6452	0.9960
F8	3.8942	0.9901	-0.0656	0.7288	20.252	0.9632	0.6410	0.9881
F9	3.5115	0.9885	-0.0371	0.9055	18.280	0.9637	0.6280	0.9879

CONCLUSION:

In light of the aforementioned discussion, it can be concluded that, the matrices comprising of HPMC alone could not efficiently control the release of highly water soluble drug Venlafaxine Hcl; however the drug release can be efficiently retarded over a period of 24 hrs when hydrophobic polymers such as gum rosin and ethyl cellulose were incorporated in the hydrophilic matrices prepared using HPMC.

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REFERENCES:

1. Madgulkar AR, Bhalekar MR, Kolhe VJ, Kenjale YD. Formulation and optimization of sustained release tablets of venlafaxine resonates using response surface methodology. Indian J Pharm Sci 2009; 71 (4): 387-394.
2. Krishnaiah YSR, Karthikeyan RS, Satyanarayana V. A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. International Journal of Pharmaceutics 241 (2002) 353–366.
3. Miranda A, Millán M, Caraballo I. Study of the critical points in lobenzarit disodium hydrophilic matrices for controlled drug delivery**.** Chem. Pharm. Bull. **54**(5) 598—602 (2006).
4. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and in vitro, in vivo evaluation of extended- release matrix tablet of zidovudine: influence of combination of hydrophilic and hydrophobic matrix formers. AAPS PharmSciTech 2006; 7 (1) E1-E9.
5. Tiwari SB, Krishna Murthy M, Pai R, Mehta PR and Chowdary PB. Controlled Release Formulation of Tramadol Hydrochloride Using Hydro-philic and Hydrophobic Matrix System. AAPS PharmSciTech 2003; 4 (3) Article 31
6. Gupta AK. Introduction to pharmaceutics.2nd ed. Vol. 1. New Delhi: CBS Publications; 1993: 270.
7. Lieberman HA, Lachman L and Schwartz JB. Pharmaceutical dosage forms: Tablets,

Vol 2; New York, Marcel Dekker Publishers; 1990: 201- 43.

8. Nerurkar J, Jun HW, Prince JC, Park MO. Controlled release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rate. Eur J Pharm Biopharm 2005; 61: 56-68.
9. Grimm W.. Extension of the international conference on harmonization tripartite guideline for stability testing of new drug substances and products to countries of climatic zones III and IV, Drug Dev. Ind. Pharm. 24 (4) (1998) 313–325.
10. Makhija SN and Vavia PR. Once daily sustained release tablets of venlafaxine, a novel antidepressant. Eur J Pharm Biopharm 2002; 54: 9–15
11. Clarke's Analysis of Drugs and Poisons/monographs/venlafaxine. 3rd ed. Pharmaceutical Press 2005.
12. Holman LE, Leuenberger H. The relationship between solid fraction and mechanical properties of compacts – the Percolation Theory model Approach. Int J Pharm 1988; 46: 35-44.
13. Leuenberger H, Rohera BD, Haas C. Percolation Theory – a novel approach to solid dosage form design. Int J Pharm 1987; 38: 109-115.
14. Enayatifard R, Saeedi M, Akbari J and Tabatabaee YH. Effect of Hydroxypropyl Methylcellulose and Ethyl Cellulose Content on Release Profile and Kinetics of Diltiazem HCl from Matrices. Trop J Pharm Res 2009; 8 (5): 4 25.
15. Khandai M, Chakraborty S, Sharma A, Panda A, Khanam N and Panda k. Development Of Propranolol Hydrochloride Matrix Tablets: An Investigation On Effects Of Combination Of Hydrophilic And Hydrophobic Matrix Formers Using Multiple Comparison Analysis. International Journal of Pharmaceutical Sciences Review and Research 2010; 1 (2): 1-7.
16. Kar RK**,** Somohapatra S and Barik BB. Design and characterization of controlled release matrix tablets of Zidovudine. Asian Journal of Pharmaceutical and Clinical Research 2009; 2 (2): 54-61.