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MODULATION OF DRUG RELEASE KINETICS OF A HIGHLY WATER SOLUBLE DRUG FROM HYDROPHILIC MATRICES

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ABSTRACT

Venlafaxine is a novel antidepressant having relatively short elimination half-life necessitating its administration, two or three times daily so as to maintain adequate plasma levels of drug. However, the high aqueous solubility and limited bioavailability poses a challenge in controlling the drug release from matrix. The aim of this work was to investigate the influence of sodium carboxymethylcellulose (blanose) on the initial burst release from a hydroxypropylmethylcellulose (methocel) matrix formulation containing venlafaxine hydrochloride. At the same total concentration, sodium carboxymethylcellulose alone as the rate-controlling polymer was not achieved because of accelerating release rates and poor stability, its use in conjunction with hydroxypropylmethylcellulose may be beneficial. The mixture of the two cellulose ethers, ionic (blanose) and non-ionic (methocel), used as polymeric carriers in hydrophilic matrices tends to "flatten" the shape of the release profile i.e., produce a more "zero order" release and there was no chemical interaction between drug and polymer as confirmed by FTIR studies. The predominant release mechanism varied with matrix composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in the mixture of the two cellulose ethers formulation. A reduction in the initial burst effect, a commonly observed phenomenon with highly soluble drugs and hydrophilic matrices, was achieved.

Keywords: Hydroxypropylmethylcellulose, Sodium carboxymethylcellulose, Venlafaxine hydrochloride, extended release, Synergistic interaction.

1. INTRODUCTION

A hydrophilic matrix tablet is the simplest and most cost-effective method of fabricating an extended release (ER) solid oral dosage form[1]. Extended release matrix tablets are relatively simple systems that are more forgiving of variations in ingredients, production methods, and end-use conditions than coated ER tablets and other systems. This results in more uniform release profiles with a high resistance to drug dumping.

During the last four decades, hydrophilic swellable polymers have been used to control the release of drug

from matrix tablet formulations[2]. A typical ER matrix formulation consists of a drug, one or more water-swellable hydrophilic polymers, excipients such as fillers or binder, a flow aid (glidant) and a lubricant. Drug release from swellable matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation[3].

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e., water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result ofa combination of these two mechanisms.

The presence of water decreases the glassy-rubbery temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in the rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains can be considered disentangled was demonstrated to correspond to an abrupt change in the rheological properties of the gel[4]. Boniferoni *et al*. (1995) showed a relationship between rheological behavior of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs[5].

Swelling controlled release systems are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport[6]. Therefore, transport can be reduced to three driving forces. Thepenetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-

order release[7].

A hydrophilic matrix, controlled-release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer. Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion.

Hypromellose (HPMC) is identified as the most popular in matrix application because of a number of key features and advantages[2]. An initial burst effect in release of highly water soluble drugs (venlafaxine hydrochloride has a solubility of 572 mg/mL) from such matrices is a common occurrence[10]. While sodium carboxymethylcellulose (NaCMC) alone as rate-controlling polymer is not practical because of accelerating release rates and poor stability, its use in conjunction with hydroxypropylmethylcellulose may be beneficial[9].

The purpose of this study was to modulate release of venlafaxine hydrochloride (a highly soluble drug) using the synergistic activity of hydroxypropylmethylcellulose and sodium carboxymethylcellulose. Venlafaxine was the first marketed anti-depressant in the serotonin-nor epinephrine reuptake inhibitor (SNRI) class. It has been widely used in treatment of remission in depression, treatment resistant depression, and extended- release venlafaxine for generalized anxiety disorder. It is freely soluble in water (572mg/mL) and has relatively short elimination half-life (5 h). The bioavailability is very limited (40%) due to the hepatic first pass effect[8].

Drug release from hydrophilic matrices is known to be a complex interaction involving swelling, diffusion and erosion mechanisms[10-13]. This work was an attempt to determine the relative contribution of the different drug release mechanisms exhibited by venlafaxine hydrochloride matrix tablets produced with non-ionic cellulose gum hydroxypropylmethylcellulose (HPMC) and anionic cellulose gum sodium carboxymethylcellulose (NaCMC). Granules of venlafaxine hydrochloride were prepared by using HPMC, NaCMC alone and different drug to polymer ratios of mixture of HNCMC (HPMC and NaCMC in 1:1 ratio). To increase the flowability and compressibility of the granules, and to prevent its adhesion to the die and punch, Aerosol and Magnesium stearate (Mg. St.) were added to the granules in a 1:4 ratio before punching. The tablets were analyzed to determine their hardness, friability and % composition. An in-vitro release study was carried out to evaluate their performance as rate- controlling agents. With certain water soluble drugs, a blend of appropriate grades of HPMC and NaCMC may minimize the release of drug during the initial phase of the release profile. This tends to "flatten" the shape of the release profile i.e., produce a more "zero order" release[14, 15].

2. MATERIALS AND METHODS

2.1. Material

Venlafaxine hydrochloride was a gift

from Dr.Reddy's Laboratories Ltd., Srikakulam,Hydroxypropylmethylcellulose (HPMC) was purchased from Dow chemical, USA, and sodium carboxymethylcellulose (NaCMC) was obtained from Hercules, USA. Di calcium phosphate (DCP), polyvinylpyrolidinek-30 (PVPK- 30), Isopropyl alcohol, Aerosil and Magnesium stearate (Mg. st) were of analytical reagent grade and used without further purification.

2.2. Matrices preparation

Matrices were prepared by the wet granulation method using povidone (PVPK-30) as the binding agent, Isopropyl alcohol as the wetting agent and dibasic calcium phosphate (DCP) as the diluent. Granules were prepared, to increase the flowability and compressibility of the granules, and to prevent its adhesion to the die and punch, Aerosil and Magnesium stearate (Mg. st) were added to the granules in a ratio of 1:4 before punching. Then 500 ± 5 mg of the prepared granules was compressed using a manesty (Cadmach, India) single punch tablet machine, with 11.0 mm biconvex, round shaped punches producing matrix tablets 4.41 mm in height with a mean crushing strength of 9.8 kg/cm2 (Pfizer, Mumbai). Under the same conditions all the formulations of venlafaxine hydrochloride tablets containing HPMC, NaCMC and HNCMC (HPMC: NaCMC ratio was 1: 1) were prepared and the formulation details are shown in Table 1.

2.3. Analysis of tablets

The hardness and friability of the tablets were measured in a hardness tester (Pfizer, Mumbai) and friabilator (Electrolab, Mumbai), respectively. The uniformity of drug content of all batches (10 units tablets) was analyzed in a spectrophotometer (model UVPC 1601, Shimadzu, Japan), in a 1 cm quartz cell, at 225 nm.

2.4. In vitro analysis

The dissolution test was carried out using apparatus 1 USP (Model No. TDT-08L, Electrolab, Mumbai) purified water up to 24 h. The temperature was maintained at 37 ± 0.5°C and the rotation speed was 100 rpm. At suitable intervals, samples were withdrawn, filtered, diluted when necessary with purified water and analyzed spectrophotometrically (model UVPC1601, Shimadzu, Japan) at 225 nm. The mean cumulative percentage of drug was calculated and plotted against time. During the drug release studies, all the formulations were checked at intervals for their physical integrity.

2.5. Drug release kinetics

The Korsmeyer and Peppas equation was used to analyze the data obtained from the *in vitro* release studies to evaluate the kinetic models and release mechanism of VFHCL from the matrices.

The Korsmeyer and Peppas equation[19] is: $Mt/M\infty = k\ t^n$. Where $Mt/M\infty$ is the fraction of drug released at time t, k is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is an exponent used to characterize the transport mechanism (Table 2). For example, $n = 0.45$ for Case I or Fickian diffusion, $0.45 < n < 0.89$ for anomalous behaviour or non- Fickian transport, $n = 0.89$ for Case II transport, and $n > 0.89$ for Super Case II

transport[17]. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient.

Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion[11].

3. RESULTS AND DISCUSSION:

3.1. Analysis of venlafaxine hydrochloride matrices

Tablets with a weight of 500 mg, a diameter of 11.02 mm and a height of 4.41 mm were obtained and subjected to quality control tests such as hardness, friability and drug content. The contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the 5 units tested was within the range of 97.1%–100.5% and the relative standard deviations were less than 2.0%, indicating uniform mixing of polymer, DCP and drug. The mean values for hardness were over 9.8 kg/cm^2 and all formulations exhibited a friability of less than 0.5% during the friability determination.

3.2. In vitro drug release

The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium. The hydrated gel layer thickness determines the diffusional path length of the drug. Methocel K15M was tried in the concentration of 1:1.5 with respect to the drug. Drug release was fast, indicating that a higher viscosity grade of Methocel would be required to retard drug release. HPMC of higher viscosity grade swells to a greater extent as it has a greater intrinsic water uptake property than that of a lower viscosity grade[18]. Hence, Methocel K100M was selected for further studies to retard drug release.

In- vitro drug release profiles of venlafaxine hydrochloride from tablets containing HPMC, NaCMC and HNCMC in different polymer proportions are shown in Fig. 1. The dissolution medium used was purified water up to 24 h. It was found that as the amount of polymer in the matrix increased, there was a greater degree of polymer hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway and drug release rate. The value of n exponent is 1.017, typical of a dissolution behavior characterized by a sigmoid, s-shaped, curve. The high release rate of NaCMC matrix is due to quick gel erosion rate and a high erosion degree given characteristic of the polymer to the overall system.

The tablets containing NaCMC, in fact, show a relative slow initial drug release during the first hour but then the release rate increases quickly; 90% of the total content is delivered within 12h. For the matrices containing HPMC the release of the drug is predominantly attributable to the contribution of fickian diffusion (n value is 0.7789) with a minimal contribution of polymer relaxation and matrix erosion. In the case of HNCMC (NaCMC –HPMC in the ratio of 1:1) systems, the n value (0.9072) indicates a zero order release kinetic. The drug release rate is nearly constant and the release process is slower compared to that of the matrices containing the single polymer concentration. This could be due to the interactions between NaCMC chains, ionic polymer, and HPMC chains, non-ionic polymer. The

HNCMC formulations exhibited a well controlled effect by the use of the synergistic interaction between two cellulose gums to produce a strong and elastic gel around the core of the matrices in the presence of a ternary component by controlling the drug release from the matrices containing HNCMC formulation.

3.3. Determination of the release kinetics

To evaluate the drug release kinetics, formulations showing a significant slow release were chosen. In general, the mechanism of drug releasefrom polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front" defined at an exact speed; simultaneously, the thickness of the area increases with time in the opposite direction. The mechanism of drugrelease can be described by a second phenomenon that involves the disentanglement and erosion of the polymer[19, 20] and for Methocel tablets, the release process involves the penetration of water into the dry matrix, followed by hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

By using the Korsmeyer and Peppas model[16] Equation, the *n* values were obtained between 0.78 and 1.02 (Table 3) for all formulations. These values are characteristic of anomalous kinetics (non Fickian) and super case–II transport, suggesting that more than one mechanism may be involved in the release kinetics. In the case of HPMC and NaCMC formulations show anomalous and super case II transport kinetics respectively, but in the case of HNCMC both the anomalous (HNCMC, HNCMC2) and case II (HNCMC3) transport was found. For all the venlafaxine hydrochloride matrix formulations, the contribution of polymer relaxation occurs throughout the entire dissolution period. This was also apparent from the *n* values obtained (Table3), which approach anomalous and super case–II transport. In the HNCMC formulations, the ratio of 1:1.5 reflects zero order release of VFHCL.

3.4. FTIR studies:

IR spectroscopy was obtained by a FTIR spectrophotometer (H400-84100, Shimadzu, Japan) using KBR pellets and scanning range was 4400 to 400 cm^{-1} at a scan period of 1 min. From the FTIR spectra of pure drug and blend of HNCMC3 extended release matrix tablet it is clear that the characteristic peaks at 3350 (O-H stretching), 2937 (C-H stretching), 1513 (C=C stretching), 1467 (C-H bending), 1244 (C-N vibrations) cm^{-1} are present in both the pure drug and its formulation containing extended release polymer matrices, without any change in their positions, indicating no chemical interaction between drug and excipients, as confirmed by the FTIR studies. Physical observation during dissolution testing showed that the tablets were intact even after 24 hours, probably because of the matrix integrity.

4. CONCLUSION

In-vitro release studies demonstrated that the release of venlafaxine hydrochloride from all the systems considered is sustained. The mixture of the two cellulose ethers, ionic (NaCMC) and non-ionic (HPMC), used as polymeric carriers in hydrophilic matrices, enables to obtain "zero-order" release kinetics and there was no chemical interaction between drug and polymer as confirmed by FTIR studies. At the same total concentration, NaCMC alone as the rate-controlling polymer was

not achieved because of accelerating release rates and poor stability, its use in conjunction with HPMC may be beneficial. The predominant release mechanism varied with matrix composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in HNCMC.

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Table 1: Composition (mg per tablet) of VFHCL (170mg) tablets (500mg)

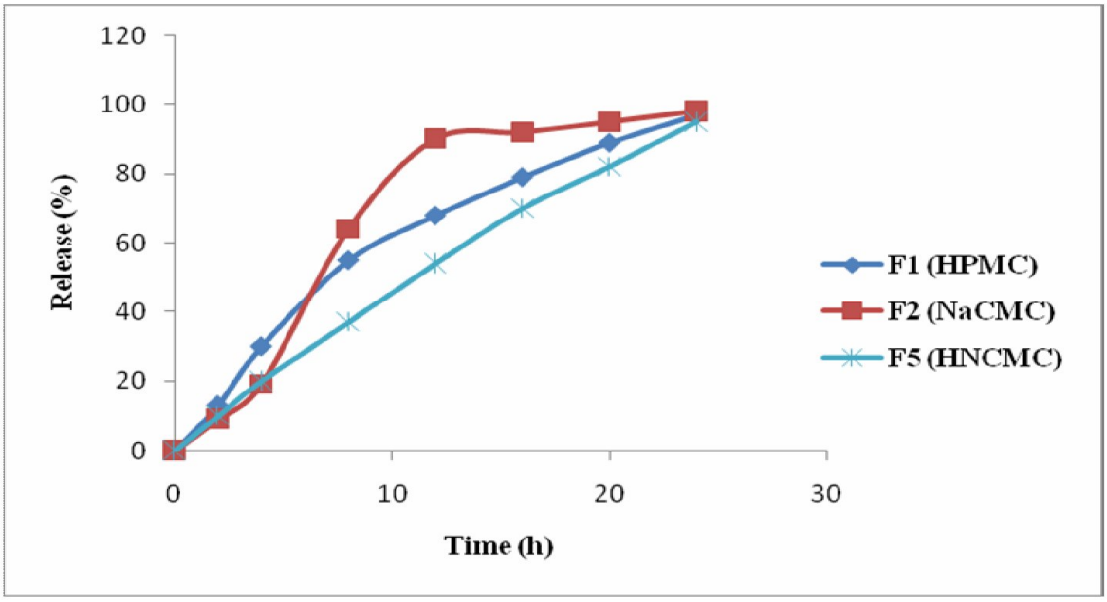
Formulation (drug: polymer)	HPMC (mg)	NaCMC (mg)	DCP (mg)	PVP K-30 (mg)	Aerosil (mg)	Mg. st (mg)	Hardness (mean±SD, Kg/cm^2)	Friability (mean±SD, %)	Assay (mean±SD, %)
F1 HPMC **(1:1.5)**	255.00	-	53.75	15.00	1.25	500.00	9.5 ± 0.34	0.10 ± 0.03	97 ± 0.83
F2 NaCMC **(1:1.5)**	-	255.00	53.75	15.00	1.25	500.00	9.6 ± 0.25	0.30 ± 0.02	98 ± 0.38
F3 HNCMC1 **(1:0.5)**	42.50	42.50	223.75	15.00	1.25	500.00	9.7 ± 0.34	0.20 ± 0.03	98 ± 0.71
F4 HNCMC2 **(1:1.0)**	85.00	85.00	138.75	15.00	1.25	500.00	9.8 ± 0.20	0.10 ± 0.02	99 ± 0.78
F5 HNCMC3 **(1:1.5)**	127.50	127.00	53.75	15.00	1.25	500.00	9.6 ± 0.16	0.20 ± 0.04	99 ± 0.69

Table 2: Exponent n of Power law and drug release mechanism from polymeric controlled drug delivery system of different geometry

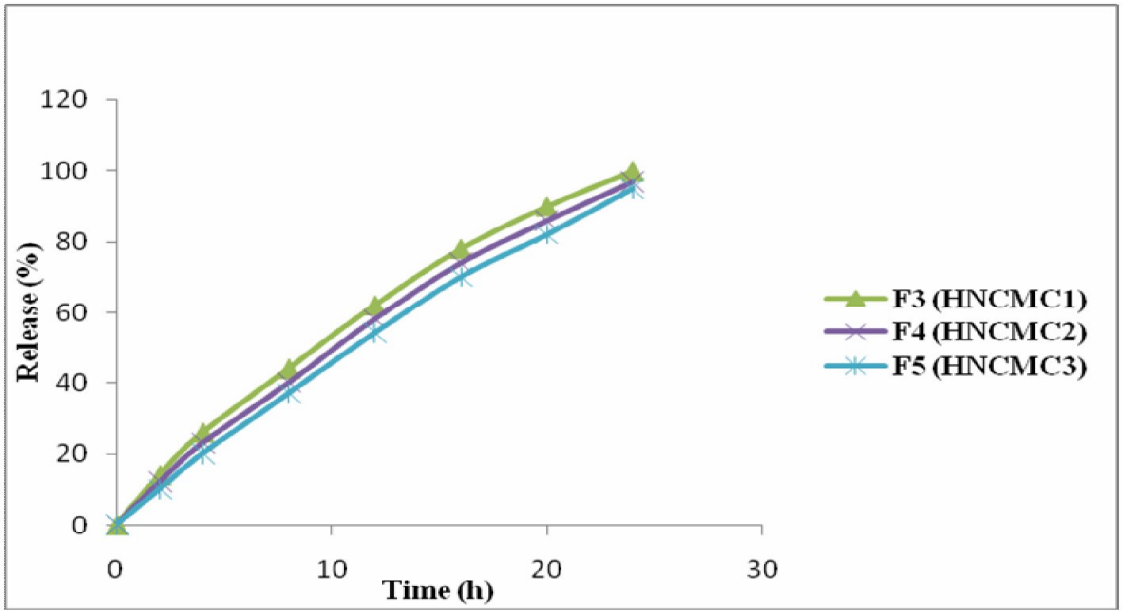
Exponent,			Drug Release Mechanism
Thin Film	**Cylinder**	**Sphere**	
0.	0.4	0.4	Fickian Diffusion
0.5<n<1.0	0.45<n<0.89	0.43<n<0.85	Anomalous diffusion
1.	0.8	0.8	Case II transport
n> 1.0	-	-	Super case II transport

Table 3: Values of n (exponent for release kinetics)

Formulation	n values	R	Transport
F1 HPMC **(1:1.5)**	0.778	0.96	Anomalous
F2 NaCMC **(1:1.5)**	1.017	0.96	Super case II
F3 HNCMC1 **(1:0.5)**	0.795	0.99	Anomalous
F4 HNCMC2 **(1:1.0)**	0.844	0.99	Anomalous
F5 HNCMC3 **(1:1.5)**	0.907	0.99	zero order



(a)



(b)

Figure 1: *In- vitro* release profile of VFHCL from tablets with (a) HPMC, NaCMC and Mixture of HPMC and NaCMC; (b) different drug: polymer ratios of mixture of HPMC and NaCMC. (In HNCMC. 1, 2 and 3 are the ratios of 1:0.5, 1:1 and 1:1.5 drug: polymer concentration in the tablets. Each point represents mean ± SE, n = 3.)

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