EVALUATION OF CROSS-LINKED HYDROXYPROPYL METHYLCELLULOSE GRAFT-METHACRYLIC ACID COPOLYMER AS EXTENDED RELEASE ORAL DRUG CARRIER

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Here, we synthesized a new smart hydrogel matrix system (HPMC-co-MAc) by graft copolymerization of hydroxypropyl methylcellulose (HPMC) with methacrylic acid (MAc). Methylene bisacrylamide (MBAc) was used as crosslinker and benzoyl peroxide (BPO) as thermal based free radical initiator. The structure and morphology of the new polymer were characterized by FT-IR and SEM, respectively. Absorptivity and diffusion coefficients were calculated to assess drug diffusion behaviour. Drug release behaviour was analyzed at pH 3.0, 5.5 and 7.0. The incorporation of venlafaxine hydrochloride increased with an increasing ratio of HPMC and decreased with an increasing ratio of MBAc. In acidic medium, the drug diffusion rate was limited, while rapid release was observed in neutral/basic medium. Drug release followed zero-order kinetics and the mechanism of release was anomalous diffusion. The dissolution profile of the drug was dependent on the pH of the release media and on copolymer composition. HPMC-co-MAc is a suitable material to be applied in therapeutics for once-daily dosing.

Keywords: methacrylic acid, polymer volume fraction, venlafaxine, release profile, absorptivity, cumulative release

INTRODUCTION

Hydrogels are physically or chemically crosslinked polymeric networks that can absorb and hold large amounts of water or biological fluids. They keep structural integrity and the ability to transport substances by diffusion. The amount of water or fluids absorbed by specific hydrogel matrices depends on the hydrophilic nature of polymer chains, degree of crosslinking and polymerization method. A carefully designed hydrogel can combat burst release and ensures site specific drug delivery.[1-3] Stimuli-responsive hydrogels that have an inherent property to sense, process and respond to environmental stimuli are called intelligent or smart polymers. Smart polymers undergo chemical or physical changes in the span of minutes and hours. These changes include modifications in dimension, surface characteristics, size, shape, intermolecular associations and chain mobility.[4,5] The above mentioned distinctive features of bioresponsive polymeric matrices have been utilized in microfluidics, diagnostics, biosensing, biological coating techniques and controlled drug delivery systems. The hydrogel matrices that respond to ionic strength, pH, temperature, antigens, radiation, enzymes, magnetic field and ultrasound have been developed and utilized as controlled drug carriers.[6-9] A better control over therapeutic drug release can be achieved by modulating and controlling the bioresponsive properties of polymers.[10,11] Mass transfer and diffusional properties of hydrogels can be tailored by changing the nature and degree of crosslinking.[12] Drug entrapment and liberation are influenced by diffusion, swelling, polymer volume fraction, porosity and shape geometry of crosslinked hydrogel devices.[13,14] Due to their non-toxicity, biodegradability, low cost and free availability, polysaccharides are preferred over synthetic polymers to synthesize hydrogels. A great deal of research has been focused on modifying the physical and chemical properties of cellulose. Chemically modified cellulose has achieved great importance in industrial applications. Graft copolymerization is a promising technique to impart desired functionality to natural polymers.

Modified polymers with desired properties can be synthesized by grafting certain monomers onto the backbones of polysaccharides by free radical copolymerization in the presence of initiators and multifunctional crosslinkers.[15,16]

HPMC is an inert, biocompatible and widely applied cellulose derivative in drug delivery systems. It is being used in agriculture, coating process, dye and paint removing, textile and cosmetic industry.[17] It is a thoroughly studied polymer used in extended release oral formulations. However, it fails to control the initial sudden liberation of highly water soluble drugs. Rapid dissolution of hydrophilic drugs from the hydrated gel surface of non-crosslinked HPMC matrix is the main cause of burst effect.[18,19]

Venlafaxine is a third generation antidepressant and is considered first line therapy in depression and painful polyneuropathies due to diabetes.[20,21] It is a potent reuptake inhibitor of serotonin (5-HT) and noradrenaline, but shows poor affinity for dopaminergic, histaminic, cholinergic and α-adrenergic receptors.[22] Its absorption after oral administration is very high and more than 90% of the administered dose is absorbed within two hours after administration.[23,24] The mean half-life of venlafaxine is 4 hours. Therefore, it is frequently administered two to three times a day. Depression is a chronic disorder and requires long term care and treatment.[25] Conventional immediate release formulations of antidepressants usually release higher amounts of drug and are associated with nausea, dizziness, poor adherence and even cessation of therapy. Sustained release formulations are superior over immediate release formulations in terms of reduced complications, lower peak plasma concentration, longer duration to reach peak plasma concentration and improved tolerance.[26] The development of oral dosage forms for sustained release of highly water soluble drugs over an extended period of time has always been a big challenge for pharmaceutical scientists.[27] High water solubility, short half-life and adverse outcomes associated with immediate release venlafaxine formulations make it a highly desirable candidate to be developed in extended release dosage form.[28]

In our afore work, we formulated a crosslinked graft copolymer matrix of HPMC (HPMC-g-AAc) using acrylic acid as monomer, tetraethylene glycol dimethacrylate as crosslinker and ammonium persulphate and sodium metabisulphite were applied as a redox pair to initiate free radical graft copolymerization in aqueous media. HPMC-g-AAc proved suitable as a pH-responsive matrix and extended the release of drug to 24 h.

The present work was carried out to synthesize HPMC hydrogels using MAc as monomer, MBAc as crosslinker and BPO as free radical initiator. The new graft copolymer HPMC-co-MAc sustains the release of venlafaxine and significantly retards initial dose dumping due to high water solubility. The rate and extent of drug release were influenced by the degree of crosslinking and swelling index. The dissolution profile strongly supports the extended release potential of HPMC-co-MA hydrogels for once-daily dosing via oral route.

EXPERIMENTAL

Materials

Methacrylic acid, methylene bisacrylamide and benzoyl peroxide were purchased from E. Merck, Germany. Hydroxypropyl methylcellulose and venlafaxine hydrochloride were cordially gifted by Mass Pharma Pvt. Ltd. Lahore, Pakistan. Ethanol, sodium hydroxide, hydrochloric acid, sodium chloride and potassium dihydrogen phosphate were purchased from Sigma Aldrich, UK. Distilled water was prepared in our laboratory.

Crosslinking and grafting

The synthesis of hydrogels was carried out in glass ampoules by thermal based free radical copolymerization.[29] A homogenous aqueous solution of HPMC (2% w/v) was prepared in a conical flask. Specific quantities of MAc and MBAc were added to a measured amount of HPMC solution, as presented in Table 1. The mixture was homogenized with continuous stirring for 30 minutes at 400 rpm. BPO was added as 1% (w/w) of monomer (MAc). The total weight of the reaction mixture was made 100 g by adding distilled water. Then, the mixture was bubbled with nitrogen gas for 30 minutes and transferred to glass ampoules. The ampoules were capped and placed in water bath (Memmert, Germany). The temperature scheme for the copolymerization reaction was 50 ºC for 3 h, 55 ºC for 4 h, 60 ºC for 5 h and 65 ºC for 6 h. A soft and elastic hydrogel was formed and allowed to cool at room temperature. The hydrogel was removed in the form of flexible rolls. The rolls were cut into 7 mm and 3 mm size hydrogel discs. The 7 mm hydrogel discs were washed in absolute ethanol for one week. Complete extraction of unreacted moieties was ensured by measuring the pH (780 pH-Meter, Metrohm, Germany) of ethanol before and after 24 h extraction. Constant pH of ethanol before and after extraction ensures complete removal of unreacted chemical

traces. The washed gels were dried in an oven at 50 ºC to constant weight. The dried gels were used to analyze absorptivity, diffusion coefficient, drug incorporation, dissolution profile and mechanism of release. The other type of discs was used to determine gel fraction.

Absorptivity

The absorptivity of hydrogels was measured by performing swelling experiments on dry and preweighed hydrogel discs. The swelling properties were evaluated in buffer solutions of pH 3.0, 5.5 and 7.0 at 25 °C. The matrix disc was immersed in 100 mL of relevant absorption media at room temperature. Each time, the swollen gel disc was removed from absorption media at predetermined time intervals. The excess of surface solvent was gently blotted with filter paper (Whatman, Filter Paper 1), weighed on an analytical balance (Shimadzu AUX 220, Germany) and again placed carefully in the same solution. A digital vernier caliper (AZ-1-108-1501, China) was used to measure dimensions. The swelling experiments were continued until equilibrium swelling was achieved. The equilibrium mass swelling ratio (Q_m) of hydrogel slabs were calculated by the following equation:[30]

$$Q_m = \frac{M_{eq}}{M_d}$$

where M_{eq} and M_d indicate mass at equilibrium swelling and initial mass of dry gel disc, respectively.

Polymer volume fraction

The polymer volume fraction (v2, s) is the fraction of polymer in the fully swollen state. Equilibrium volume swelling (V_{eq}) data were used to determine the polymer volume fraction in the fully swollen state at pH 3.0, 5.5 and 7.0. For this purpose, the following equation was used:[31]

$$v2,s = \frac{1}{V_{eq}}$$

Table 1
Hydrogel composition per 100 g of reaction mixture

Formulation	HPMC (%g/g)	MAc (%g/g)	MBAc (%g/g)	MAc/HPMC Ratio
X1	0.4	35.0	0.2	98.87/1.13
X2	0.6	35.0	0.2	98.31/1.69
X3	0.8	35.0	0.2	97.77/2.23
X4	1.0	35.0	0.2	97.22/2.78
Y1	1.0	35.0	0.1	97.22/2.78
Y2	1.0	35.0	0.3	97.22/2.78
Y3	1.0	35.0	0.5	97.22/2.78
Y4	1.0	35.0	0.7	97.33/2.78

Diffusion coefficient

Diffusivity in polymeric matrices is a complex phenomenon. The major factors that affect the diffusivity are polymeric network structure, nature of solvent and hydrodynamic interactions. Diffusivity of hydrogel discs can be defined as the rate of material (solid, fluid or gas) diffusing across unit area of hydrogel surface against a concentration gradient in unit time. The diffusion coefficient was measured by using the swelling data at pH 7.0 by the equation given below:[32]

$$D_c = \pi\left(\frac{l\theta}{4.Q_{eq}}\right)^2$$

where D_c denotes the diffusion coefficient of hydrogels, Q_{eq} is the equilibrium weight swelling ratio of gel matrices, Θ is the slope of the linear part of swelling curves for the initial 12 h dynamic swelling experiments and l is the initial sample thickness of the dry hydrogel slab before swelling.

Percent gel fraction

Thin copolymer discs were placed in deionized water for two weeks. The extracted hydrogels were removed from deionized water and dried to equivalent weight in an oven at 55 °C. Percent gel-fraction was measured by the following equation:[33]

$$\text{Gel fraction} = \frac{M_d}{M_e} \times 100$$

where M_d is the weight of the dry gel piece and M_e is the weight of the dry gel piece after extraction in deionized water.

Incorporation of drug in hydrogel matrix

Hydrogels are materials that absorb a drug from a solution based on diffusion. Washed, dried hydrogel discs of uniform weight (0.50 g) were soaked in 5.0%w/v venlafaxine solution in distilled water. The soaked hydrogels were removed from the drug solution after 24 hour absorption in the drug solution. The excess of surface water was blotted gently with

blotting paper and weighed using an analytical balance. The following relation was used to calculate the amount of venlafaxine entrapped in hydrogel:[34]

$$M_0 = M_s - M_d \times 5\%$$

where M_0 denotes the quantity of venlafaxine loaded, M_s is the mass of swollen gel and M_d is the representative weight of the dry gel before drug loading. The loaded discs were stored at 55 °C for further study.

One more method was used to calculate drug incorporation: the loaded hydrogel discs were crushed with the help of a pestle and mortar. The crushed hydrogel powder was transferred to a conical flask containing methanol and stirred for 2 h at 400 rpm. Then, the contents were transferred to test tubes and centrifuged at 5000 rpm for 30 min. The supernatant was collected, diluted and mixed suitably with distilled water. The drug contents were measured spectrophotometrically using the standard calibration curve. The standard calibration curve was constructed by measuring the absorbance of the drug solution in the concentration range of 1-30 µg/mL at 226 nm.

Cumulative release and mechanism of drug diffusion

Venlafaxine release experiments were carried out at 37±0.5 °C for 24 h in 900 mL dissolution media at 50 rpm. The dissolution experiments were performed at pH 3.0, 5.5 and 7.0 in a dissolution apparatus (PT-DT7 Pharma Test, Germany). A sample of 2 mL of release medium was collected at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, and 24 h of dissolution. The aliquot was diluted suitably with the same buffer solution and the absorbance was measured by a spectrophotometer at 226 nm (UV-1600 Shimadzu, Germany). The cumulative release of venlafaxine from each hydrogel matrix formulation was calculated by the following formula:

$$\text{Cumulative Release} = \frac{A_t}{A_\infty} \times 100$$

where A_t indicates absorption at time t and A_∞ indicates the absorption of the total amount of drug extracted from hydrogel discs.

To determine the order and mechanism of venlafaxine release from HPMC-co-MA matrices, the drug release data were fitted to various mathematical models. The equation describing zero-order kinetics is given below:[35]

$$F_t = K_0 t$$

where K_0 is the zero-order release constant and F_t is the fraction of venlafaxine release in time t.

The mathematical relation of first-order kinetics is given as:[36]

$$\ln F_t = \ln F_0 + K_1 t$$

where K_1 denotes the first-order release constant, F_t – the amount of drug release in time t and F_0 indicates the initial amount of drug in the copolymer slab.

Higuchi equation is given below:[37]

$$F_t = K_2 t^{1/2}$$

where K_2 represents the Higuchi constant and F_t is the fraction of drug released in time t.

Peppas power law relationship is described as follows:[38]

$$M_t/M_\infty = K_3 t^n$$

where M_t/M_∞ represents the fractional release of venlafaxine, M_∞ is the amount of venlafaxine released at equilibrium, M_t is the release of venlafaxine at time t, K_3 is a constant associated with attributes of drug and polymer matrix and n is the release exponent that is based on the mechanism of diffusion and the shape of the matrix device. When the value of n approaches 0.5, the mechanism of release is Fickian, when 0.5>n<1, the mechanism of release is non-Fickian, while n=1 indicates case II transport.

FT-IR analysis

IR spectra of HPMC and HPMC-co-MA hydrogels were recorded on an ATR-FT-IR Perkin Elmer instrument, Germany. The hydrogel disc was crushed to powder in a pestle and mortar before recording the spectra. The spectra were recorded in the range of 4000 to 500 cm^{-1} with a resolution of 2 cm^{-1}.

Scanning electron microscopy (SEM)

JEOL JSM-6460 LV (USA) instrument was used to study the surface properties of the prepared hydrogels. SEM photographs of HPMC-co-MAc matrices were taken at accelerated voltage.

RESULTS AND DISCUSSION

Influence of hydrogel composition on equilibrium swelling

Equilibrium swelling ratios of the new polymer matrices at pH 3.0, 5.5 and 7.0 have been presented in Figures 1 and 2. Equilibrium mass swelling ratios increased gradually with the increase of HPMC in the feed composition. This increase in swelling ratio was associated with the hydrophilic nature of HPMC. Due to the hydrophilic nature of HPMC, the HPMC-co-MAc matrix system has high capacity to absorb and retain water.[39] The equilibrium swelling ratio gradually decreased with the increasing ratio of MBAc. The increase in the concentration of crosslinker in the feed composition results in tight junction point formation in the crosslinked matrices. The tightly crosslinked polymers have high crosslinked density due to which chain mobility, porosity and hence, swellability of hydrogel is restricted.[40] Swelling of hydrogel was highest at pH 7.0 and lowest at pH 3.0. High swelling ratio at high pH is due to high ionization of grafted carboxylic groups at basic pH. The repulsive forces among ionized groups are

responsible for the expansion of the crosslinked network structure. Water enters the expanded network rapidly. Once water enters the network channel, the osmotic pressure created inside the gel further expands the network channel, thereby enhancing the swelling capacity of the hydrogels at high pH. However, at low pH, water swelling ratio is negligible due to the presence of protonated carboxylic groups. The presence of protonated pendant carboxylic groups keeps the hydrogel structure intact and water uptake is restricted.[41]

Polymer volume fraction

As shown in Table 2, it is clear that polymer volume fraction decreased with the increase in HPMC feed ratio and increased with a high MBAc ratio in the synthesis solution. Each experiment was performed three times. The mean of these values is presented. Polymer volume fraction was highest at pH 3.0, because at this pH polymer swelling is negligible, hence polymer ratio is high. Low values of polymer volume fraction at pH 5.5 and 7.0 are an indication of high swelling and expansion ability of hydrogels at high pH.

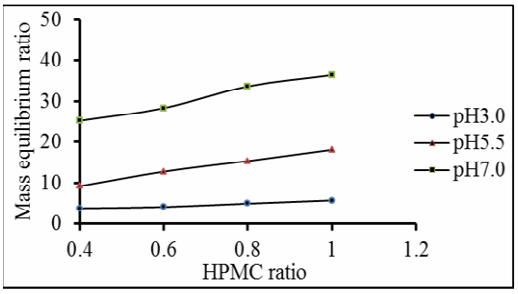

Figure 1: Mass equilibrium swelling ratio – effect of HPMC ratio

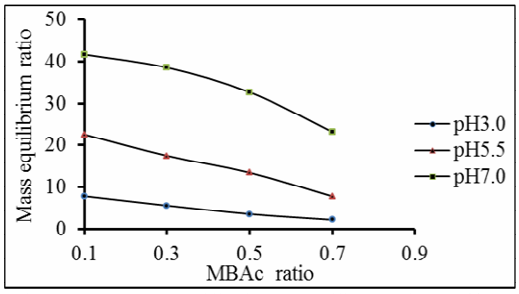

Figure 2: Mass equilibrium swelling ratio – effect of MBAc ratio

Table 2
Diffusion coefficient, gel fraction, drug loading and polymer volume fraction

Formulation	Diffusion coefficient (10^{-3} cm^2/s)	Gel fraction (%age)	Venlafaxine incorporation (mg/0.5 g disc)	Polymer volume fraction pH 3.0	pH 5.5	pH 7.0
X1	3.37	88.67	98.34	0.260	0.156	0.037
X2	3.54	90.27	107.73	0.233	0.120	0.032
X3	3.89	91.56	115.19	0.188	0.111	0.027
X4	5.21	92.37	123.34	0.163	0.104	0.026
Y1	6.57	86.51	157.89	0.121	0.062	0.023
Y2	4.78	89.37	119.6	0.173	0.076	0.025
Y3	3.29	93.51	91.88	0.272	0.081	0.037
Y4	2.87	95.69	73.73	0.421	0.171	0.044

Diffusion coefficient

Diffusion coefficient represents a kinetic parameter and is based on the segmental mobility of the polymer network chains. The high contents of water absorption of the new matrices are due to molecular diffusion and mass flow. Diffusion coefficient increased with the increase of HPMC ratio and decreased with the increase of crosslinking ratio, as shown in Table 2. The effect of HPMC and MBAc can be explained based on equilibrium swelling studies.[42] There was an increase in the diffusion coefficient with the increase of equilibrium swelling ratio and vice versa. The high values of the diffusion coefficient at pH 7.0 could also be associated with rapid swelling at high pH and low polymer volume fraction that result in the high expansion of the crosslinked mesh.

Gel fraction

Gel fraction presents the strength of hydrogel matrices and is an indicator to assess the extent of reactants consumed in the free radical copolymerization reaction. Gel fraction increased upon the increase of HPMC and MBAc ratio in the reaction mixture (Table 2). This trend can be explained by the fact that the increase in polymeric and monomeric ratios provides more free sites for completion of the free radical polymerization reaction.[43]

Drug entrapment

The effect of polymeric and crosslinking ratio on the average value of venlafaxine loading in the hydrogel is shown in Table 2. With the increase of HPMC ratio, the amount of drug loaded increased. The hydrophilic nature of HPMC allows high absorption of the drug solution in the hydrogel matrices. The amount of drug loading decreased with the increase of MBAc ratio. The increase of MBAc ratio produces firmly crosslinked hydrogels due to which the space available for water diffusion and drug entrapment is decreased. The highest drug loading was observed in the formulation with the lowest MBAc ratio.[44]

Cumulative release and mechanism of drug diffusion

Average values (n=3) of cumulative drug release have been presented in Figures 3 and 4. The cumulative release from HPMC-co-MAc matrices corresponds with the swelling ratio, diffusion coefficient and pH of the dissolution media. After 24 h dissolution, the highest cumulative release of venlafaxine (100%) was found for formulations X4 (highest HPMC ratio) and Y1 (lowest crosslinking ratio) at pH 7.0. At pH 3.0, less than 25% fraction of loaded drug was released after 24 h. The cumulative release increased with the increase of HPMC ratio and decreased with the increase of crosslinking ratio. The copolymer samples that showed the highest swelling ratio, diffusion coefficient and venlafaxine loading also presented the highest cumulative drug release.[45] HPMC-co-MAc hydrogels showed sustained release of venlafaxine hydrochloride up to 24 h. The data obtained by applying mathematical models to the dissolution data have been presented in Table 3. The data indicate that the release pattern of the prepared formulations is best explained by zero-order release kinetics, followed by Higuchi's model. The mechanism of venlafaxine release was in most cases through anomalous diffusion. Only two formulations (X1 and Y4) followed Fickian diffusion at pH 3.0 and 5.0.

FT-IR analysis

Figure 5 exhibits the FT-IR spectra of (a) HPMC and (b) newly formed HPMC-co-MAc copolymer. The FT-IR spectra of HPMC show a peak at 2927 cm^{-1}, which corresponds to –CH stretching of methyl and propyl groups. The peaks at 1691 cm^{-1} and 1610 cm^{-1} are assigned to –CO stretching of six membered cyclic rings. The intense peaks at 1057 cm^{-1} and 946 cm^{-1} denote stretching of the pyranose ring and stretching of C-O-C. The peak at 1720 cm^{-1} in the spectra of HPMC-co-MAc corresponds to the stretching vibration of –C=O in –COOH functional group. It indicates grafting of MAc on the backbone of HPMC. The peak at 1460 cm^{-1} corresponds to the asymmetric stretch of –C=O. The peak at 1163 cm^{-1} is due to stretching of the ether linkage. The absorption band of the –OH stretch of the carboxylate group appears in the range of 3500-2500 cm^{-1}. The FT-IR spectra of the newly developed polymer matrix confirm the chemical grafting of MAc on HPMC.

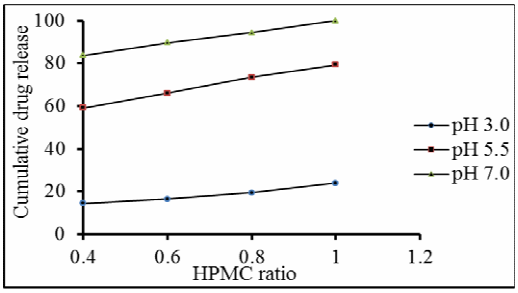

Figure 3: Cumulative drug release – effect of HPMC ratio

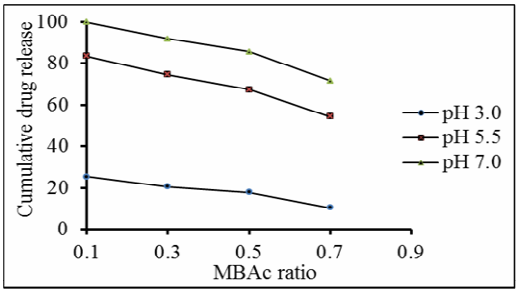

Figure 4: Cumulative drug release – effect of MBAc ratio

Table 3
Kinetic parameters of venlafaxine diffusion

Formulation	Medium pH	Higuchi		First order		Zero order		Peppas	
		r	$K_2t^{1/2}$	R	K_1t	r	K_0t	r	n
X1	3.0	0.9357	1.6819	0.6256	1.8217	0.9910	0.8135	0.9935	0.45
	5.5	0.9195	5.7559	0.6698	1.9023	0.9854	6.7085	0.9971	0.43
	7.0	0.9758	7.9745	0.6483	2.1237	0.9764	9.2156	0.9975	0.65
X2	3.0	0.9167	7.5181	0.5823	1.7972	0.9845	1.1187	0.9811	0.81
	5.5	0.9308	3.6345	0.6895	1.8185	0.9644	7.8913	0.9943	0.59
	7.5	0.9857	4.3547	0.6738	2.9452	0.9872	7.5782	0.9939	0.65
X3	3.0	0.9555	0.9185	0.6737	1.9378	0.9853	0.8913	0.9864	0.79
	5.5	0.9362	2.6731	0.6475	2.3564	0.9787	3.7842	0.9926	0.81
	7.5	0.8345	5.1679	0.6197	1.9143	0.9538	9.2206	0.9914	0.83
X4	3.0	0.9335	1.3122	0.6591	1.4775	0.9784	0.8591	0.9856	0.65
	5.5	0.9157	1.6494	0.6324	1.8139	0.9776	4.6494	0.9903	0.57
	7.0	0.8993	7.5274	0.6843	2.2751	0.9955	7.9568	0.9829	0.75
Y1	3.0	0.9763	0.8921	0.7123	2.5174	0.9917	0.9345	0.9956	0.71
	5.5	0.9677	3.5164	0.6626	1.8416	0.9889	3.8659	0.9927	0.73
	7.0	0.9483	6.3957	0.7937	2.1393	0.9943	9.3137	0.9955	0.66
Y2	3.0	0.9134	1.7123	0.5967	3.3207	0.9779	1.1162	0.9867	0.77
	5.5	0.9461	4.8553	0.6743	2.8967	0.9673	4.2147	0.9957	0.73
	7.0	0.9148	8.5587	0.6471	3.1628	0.9862	8.6945	0.9973	0.53
Y3	3.0	0.9261	1.4521	0.6184	3.6149	0.9847	0.7833	0.9978	0.69
	5.5	0.9164	3.6745	0.6591	1.7561	0.9847	3.9563	0.9944	0.65
	7.0	0.9315	5.8423	0.6966	2.5674	0.9943	6.8539	0.9841	0.59
Y4	3.0	0.8837	0.8756	0.6419	2.3751	0.9657	0.9149	0.9911	0.41
	5.5	0.9341	4.6191	0.5937	1.7138	0.9831	5.2134	0.9928	0.44
	7.0	0.9237	6.8765	0.6751	2.6547	0.9845	6.2674	0.9933	0.69

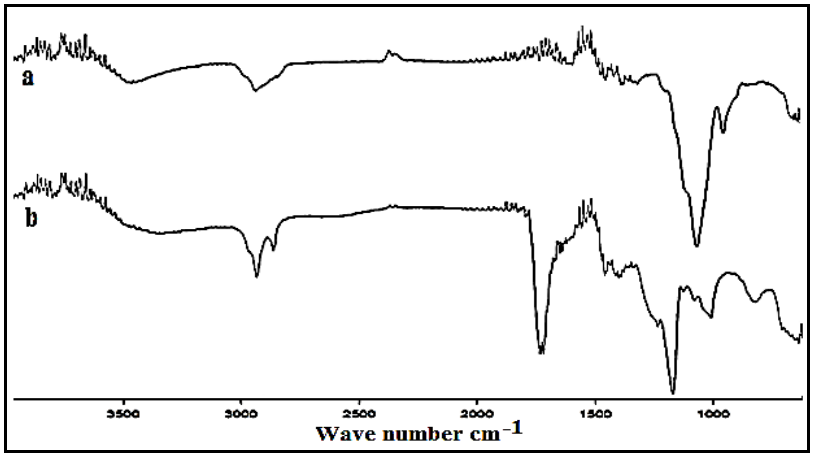

Figure 5: FTIR spectra of (a) HPMC, (b) HPMC-co-MAc hydrogels

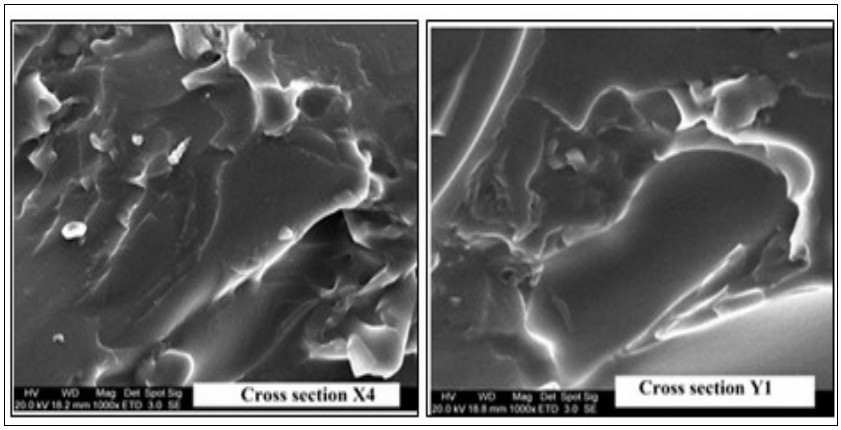

Figure 6: SEM micrographs of HPMC-co-MAc hydrogels

SEM analysis

The SEM micrographs show a three dimensional, pitted and porous network structure. The SEM images at different magnifications are presented in Figure 6. Swelling and drug loading is achieved due to diffusion of water and drug molecules into the porous mesh of the crosslinked hydrogel matrices. The presence of the crosslinked network mesh helps to control the diffusion of water and hence of the dissolved drug from the hydrogel matrix.

CONCLUSION

In this study, we have synthesized HPMC-co-MAc hydrogels by free radical copolymerization. FT-IR and SEM analyses confirmed the development of a new copolymer with porous morphology. The effects of polymeric and crosslinking ratio on the swelling profile, diffusion coefficient, drug incorporation and release behaviour have been explored. It was found that we can load desired amounts of venlafaxine hydrochloride by soaking hydrogels in aqueous drug solution. HPMC-co-MAc was a suitable matrix in retarding the burst effect up to 24 h dissolution at pH 3.0, 5.5 and 7.0. At pH 3.0, only a limited amount of drug release (<25%) occurred after 24 h dissolution. However, 100% drug release was found in the release medium of pH 7.0 over the same time period of dissolution. The findings of the study suggest that HPMC-co-MAc copolymer matrix is a potential extended release oral carrier to combat burst release and could be applied in therapeutics for sustained once-daily dosing.

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