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Synthesis of Chemically Cross-Linked Hydroxypropyl Methyl Cellulose Hydrogels and their Application in Controlled Release of 5-Amino Salicylic Acid

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The objective of this study was to achieve the colon-specific delivery of an anti-ulcerative colitis drug using hydroxypropyl methyl cellulose (HPMC) hydrogels. HPMC hydrogels containing poly ethylene glycol (PEG) as cross-links have been prepared by reacting HPMC sodium salt with polyethylene glycol dichloride.

The effect of cross-linking agent on swelling behavior of HPMC-PEG hydrogels, were investigated. Swelling parameters such as equilibrium degree of swelling, swelling ratio and network parameter such as molecular mass between cross-links (M_c) were determined. The cross-linking concentrations were 0.5%, 1%, 1.5%, and 2% (based on weight of HPMC). The equilibrium swelling ratio (Q) of cross-linked HPMC hydrogels increases from 13.2 to 27.1 as the cross-linker percentage increases from 0.5% to 2%. 5-Aminosalicylic acid (5-ASA) was used as a model of an anti-inflammatory drug. Cross-linked HPMC hydrogels were found to be a promising drug delivery system for the drugs to be delivered to the colon.

Keywords cross-linked hydroxypropyl methyl cellulose; hydrogel; 5-amino salicylic acid; colon-specific drug delivery

INTRODUCTION

The site-specific drug delivery to the colon has a number of important implications in the field of pharmacotherapy. Applications of colon-specific drug delivery include the local treatment of large intestine disorders, and the oral administration of protein and peptide drugs. Several diseases such as inflammatory bowel syndrome (IBS), can be treated more effectively by local delivery of anti-inflammatory agents to the large intestine on the other hand the large intestine may be optimal for peptide delivery because of high residence time and low digestive enzymatic activity (Chourasia & Jain, 2003).

Several approaches utilized in achieving colon targeting include use of pH-sensitive polymer coating (Davaran et al., 2001), time-dependent formulations (Wiwattanapatapee et al., 2003), bacterial degradable coating (Gelan, 1996; Kinget et al., 1998; Schacht et al., 1996; Van den Mooter et al., 1994), biodegradable polymer matrix and hydrogels (Akala et al., 2003; Chen et al., 2005; Yang et al., 2002).

In recent years, the use of hydrophilic polymers, in particular cellulose derivatives, has attracted considerable attention for the development of controlled release technology in the formulation of pharmaceutical products, due to their ability to form gels in aqueous medium (Vueba et al., 2003).

Hydroxypropyl methyl cellulose (HPMC) is used to control drug release from several pharmaceutical systems because of its nontoxic nature, easy compression, swelling properties and accommodation to high levels of drug. To date, delayed onset of drug delivery has successfully been achieved through the application of HPMC (Pina & Veiga, 2000). To evaluate the feasibility of using a particular hydrogel as a drug delivery device, it is important to know the structure and properties of the associated polymer network that forms during swelling. In the polymeric network hydrophilic groups or domains are present which are hydrated in an aqueous environment thereby creating the hydrogel structure. In the cross-linked polymeric networks, the amount and type of cross-links influence many of the network properties (Baumgartner et al., 2003).

Recently hydrogels based on polyethylene glycol (PEG) have attracted considerable attention in controlled release technology because of their excellent physicochemical properties and good biocompatibility. Synthetic and natural polyols such

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as poly (vinyl alcohol) (PVA), and cellulose ethers such as hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), etc. … offer some advantages over PEG based hydrogels (Hirt, 2001). For example, the availability of pendent hydroxyl groups along the polymer backbone adds versatility in terms of the various modifications that could be made to the polymer. Furthermore, cellulose derivatives possess greater bioadhesive properties than PEG (Peppas & Mongia, 1997).

Synthesis of a novel HPMC hydrogels with PEG 200 cross-links is reported for the first time in present article. The HPMC-PEG hydrogels would combine the advantages of both components. The polymer volume fraction of hydrogel in the swollen state, $V_{2,s}$, the average molecular weight of the polymer chains between cross-linked points (M_c), and the volume swelling ratio of hydrogel have been discussed.

The ability of this hydrogel for controlled release of 5-amino salicylic acid (5-ASA), a drug used in the treatment of inflammatory bowel diseases was also studied.

MATERIALS AND METHODS

Materials

5-Amino salicylic acid (5-ASA) was obtained from Aldrich. Hydroxypropyl methyl cellulose (HPMC 2208, Methocel K4M colocon, England), poly ethylene glycol (PEG), thionyl chloride, sodium, dimethyl sulfoxaide (DMSO) were obtained from Merck.

IR spectra were run on a Shimadzu model 4300. The amount of released 5-ASA was determined using a UV/Vis spectrophotometer (Shimadzu model 160). In order to study the microstructure of hydrogel surface scanning Electron Microscope (SEM, LEO model 440i) was used.

Preparation of HPMC Hydrogels

Sodium (2.3 g) was dissolved in 50 mL absolute ethanol. The excess of ethanol was evaporated in vacuum. The remaining sodium ethoxide was solubilized into 50 mL of anhydrous DMSO under nitrogen, and 3 g of HPMC was added. The mixture was stirred vigorously to produce a gelatinous product. The residual alcohol was removed with gentle N_2 current. The resulting poly alcoholate was dissolved in 50 mL benzene .Polyethylene glycol dichloride was prepared by reaction of PEG_{200} (0.02 mol) with thionyl chloride (0. 2 mol) in 300 mL toluene in the presence of pyridine (0.02 mol) at reflux conditions and was added as cross-linker. The mixture was stirred for 10 hr at room temperature. The polymer was precipitated into methanol. The resulting pale yellow colored gel was collected and dried in vacuum.

IR: (KBr) cm^{-1} 3450, 1631, 1450, 1126, 1079.

Swelling Measurements

Dynamic swelling measurements were made by gravimetric measurements. The hydrogel samples were placed in a beaker and were suspended in 500 mL of distilled water. The hydrogel sample was removed from the distilled water at different intervals quickly blotted free of surface water using filter paper and weighed on an analytical balance and then returned to the distilled water. The dynamic swelling experiments were performed in distilled water and the increase in mass was followed as a function of time.

The swelling ratio (Q) of the hydrogels was calculated from the following relation (Davaran et al., 1998).

$$(Q) = W_S / W_d \tag{1}$$

Network Studies

The average molar mass between cross-links M_c was determined by using equilibrium swelling studies.

The M_c was calculated by

$$\frac{1}{\overline{M}_C} = \frac{2}{\overline{M}_n} - \frac{(\vartheta - V_1)\left[Ln(1-V_{2,5}) + V_{2,5} + X_1 V_{2,5}^2\right]}{\left(V_{2,5}^{1/3} - \frac{V_{2,5}}{2}\right)} \tag{2}$$

$$\overline{M}_C = -V_1 . d_\rho \frac{V_{2,s}^{1/2} - V_{2,s/2}}{L_n(1-V_{2,s}) + V_{2,5} + XV_{2,s}^2} \tag{3}$$

Where M_c is the number average molar mass of the chain between cross-links, V_1 is the molar volume of water (18.1 cm^3/mole), $V_{2,s}$ is volume fraction of polymer in the swollen gel at equilibrium. X is the Flory-Huggin's interaction parameter between solvent and polymer and dp is the density of cross-linked HPMC. $\nu_{2,s}$ Was determined according to the literature (Peppas & Barr, 1986) cross-linked HPMC hydrogels were prepared at different polymer concentrations. A hydrogel sample was first weighed in air, W_a, then in non solvent (heptane), W_h, and knowing the density of heptane, ρ_h, the volume of swollen gel, V_s, was calculated from

$$V_s = \frac{W_a - W_h}{\rho_h} \tag{4}$$

The volume of polymer, V_p, in a swollen hydrogel sample was determined from

$$V_p = \frac{W_a . (C/100)}{\rho_\rho} \tag{5}$$

Where c is the weight percent of polymer in hydrogel sample, and ρ_ρ is the density of the dry polymer.

Finally $\nu_{2,5}$ was calculated from Eq (6).

$$\nu_{2,s} = \frac{V_p}{V_S} \tag{6}$$

Drug Loading on Hydrogel

5-ASA was dissolved in distilled water to produce 10mM solution. Dried gel disks were soaked in drug solution at room temperature for 3 days. Then, the swollen hydrogels were dried for 1 week in desiccator.

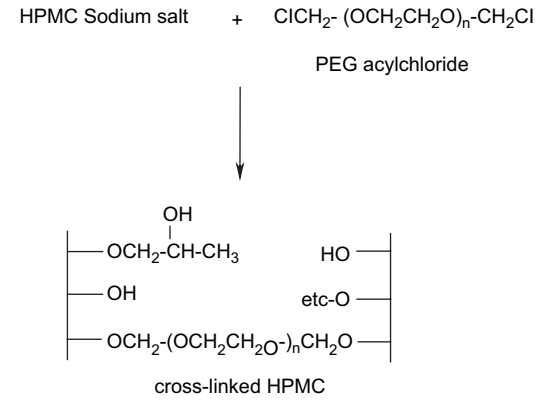

FIGURE 1. Typical reactions illustrating the preparation of PEG-HMPC hydrogels.

Drug Content Measurements

To determine maximum drug content within the dried hydrogel, 50 mg of hydrogel was dissolved in 100 mL of HCl (0.1 N) under continuous stirring and stored at 4°C to aid complete dissolution. The amount of the drug was quantified using a spectrophotometric method at 302 nm in the presence of a blank prepared from hydrogel containing all materials except the drug. Drug loading was determined as the percentage of the amount obtained to the applied amount.

Drug Release from Hydrogels

Hundred milligrams of drug-loaded hydrogel disks were immersed in 50 mL of PBS (phosphate buffer saline) solution (pH 7.4) at room temperature.

For estimation of drug released 5 mL of release medium was withdrawn periodically, and the amount of drug released into the medium was quantified by measuring the absorbance of the drug at 328 nm.

RESULTS AND DISCUSSION

Hydrogel Preparation

This study only concerns the cross-linked networks whose properties were varied enough to provide different swelling behavior. We have considered HPMC hydrogels, which differ by the presence of hydrophilic PEG cross-links. The topology of the networks was modified by varying the amount of cross-linking agent. Figure 1. shows the typical reaction illustrating the preparation of PEG cross-linked HPMC.

The reaction of poly ethylene glycol dichloride with sodium salt of HPMC forming cross-linked HPMC is based on the well known Williamson etherification reaction.

A series of cross-linked HPMC was prepared by varying the amount of cross-linked agent to understand the effect of variations in cross-linking yield, swelling behavior and drug release properties of the hydrogels. The yields of cross-linking reaction are listed in Table 1. For a given amount of HPMC, the yields increased as the cross-linking was reduced.

In order to study the microstructure of hydrogel matrix, SEM micrographs of hydrogels were recorded which are shown in Figure 2. The SEM image of the cross-section of pure hydrogels appears smooth and non-porous and does not have grain boundaries. The morphology of the hydrogels was independent of the cross-linking agent content.

The SEM studies were also performed to determine the structure of drug-loaded hydrogels and directly observed the particles entrapped inside the hydrogel matrix (Figure 3). The SEM image of HPMC-PEGIV (Figure 3D) shows about 3–4 μm size aggregates of drug and holes embedded in a smooth matrix. The SEM image of HPMC-PEGI in Figure 3A shows that it had a different structure than the other drug-loaded hydrogels. The cluster type aggregates were not formed in this case.

Dynamic and Equilibrium Swelling Studies

Swelling ratio (Q) of the hydrogels can be calculated by Eq. 1.

The equilibrium swelling ratio of cross-linked HPMC hydrogels increases from 13.2 to 27.1 as the cross-linker percentage increases from 0.5% to 2%. A further increase in

TABLE 1
Preparation and Properties of Cross-Linked HPMC

Sample	Cl-PEG-Cl (%)*	Yield (%)
HPMC-PEGI	0.5	84
HPMC-PEGII	1	82
HPMC-PEGIII	1.5	75
HPMC-PEGIV	2	73

*Based on weight of HMPC.

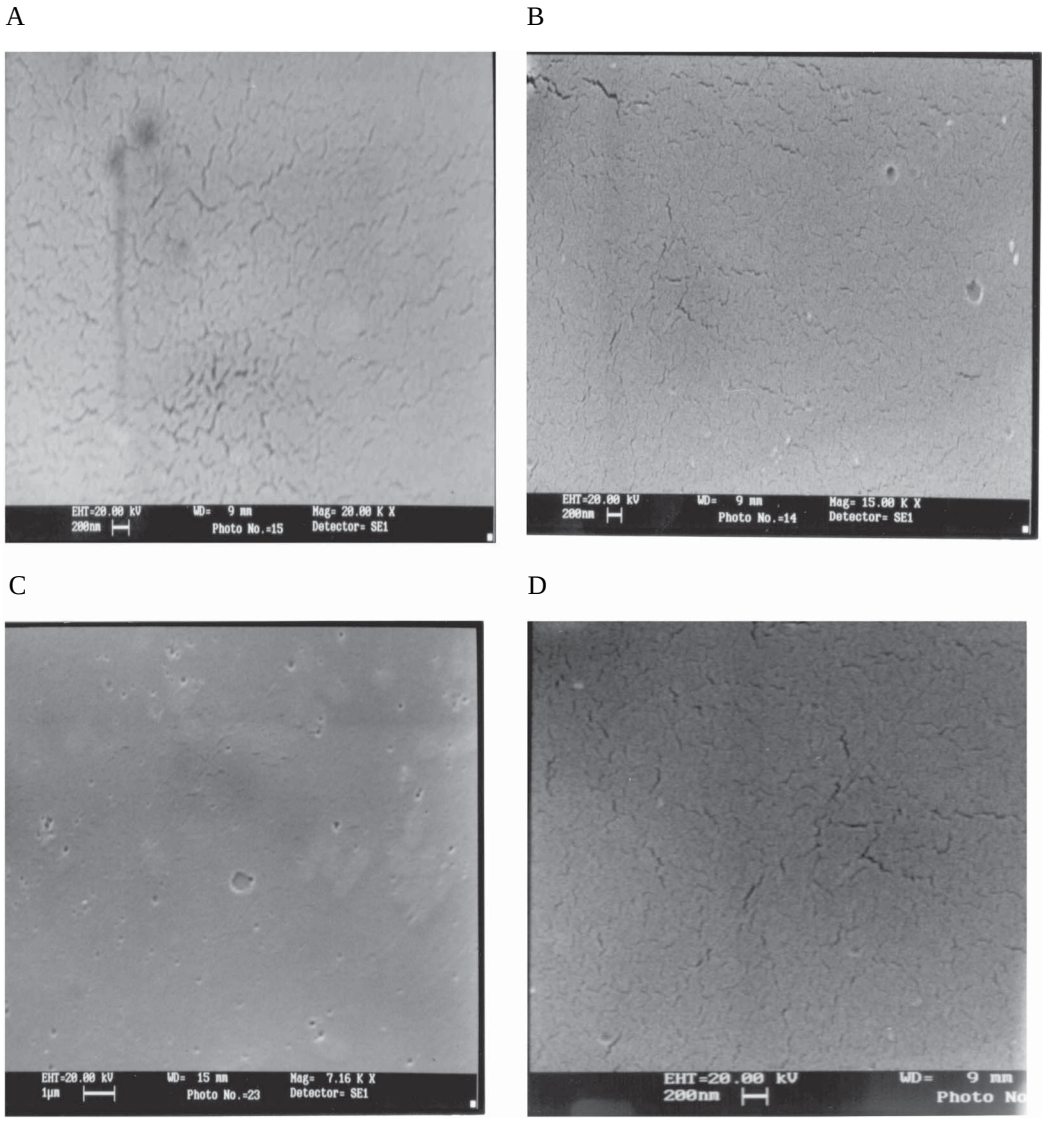

FIGURE 2. SEM images of cross-linked HPMC hydrogels, (a): HPMC-PEGI, (b): HPMC-PEGII, (c) HPMC-PEGIII, (d) HPMC-PEGIV.

cross-linker concentration resulted in more HPMC dissolving causing a lower yield of useful gel.

Results of the dynamic swelling behavior of cross-linked HPMC hydrogels are presented in Figure 4.

The effect of pH on swelling properties of the hydrogels was also studied. Figure 5 shows the influence of pH on swelling behavior of HPMC-PEGIV at 37°C. As shown in the Figure 5 the pH of the media influenced swelling ratio. The mass swelling ratio of hydrogel as a function of pH ranged from 4 at pH 1 to 27 at pH 7.

The hydrogel was less stable at pH 1 and showed a smaller maximum swelling index. This behavior can be attributed to the partial breaking of the ether bongs between HPMC and PEG cross-links at acidic medium which results in the degradation of the hydrogel network.

Network Studies

The average molar mass between cross-links (M_c) values of the cross-linked HPMC hydrogels was calculated by Eq. 4. The effect of cross-linking agent ratio on M_c has been shown in Figure 6, which indicates decrease in M_c values with increase in cross-links amount.

Drug Release Studies

The drug loading efficiency was very high (> 98%) in all samples showing negligible drug loss during the loading procedure. The release kinetics of a loaded hydrogel is closely related to its water sorption kinetics, and it has been already established that a highly swelling hydrogel should release a greater amount of solute entrapped with in the gel. The release

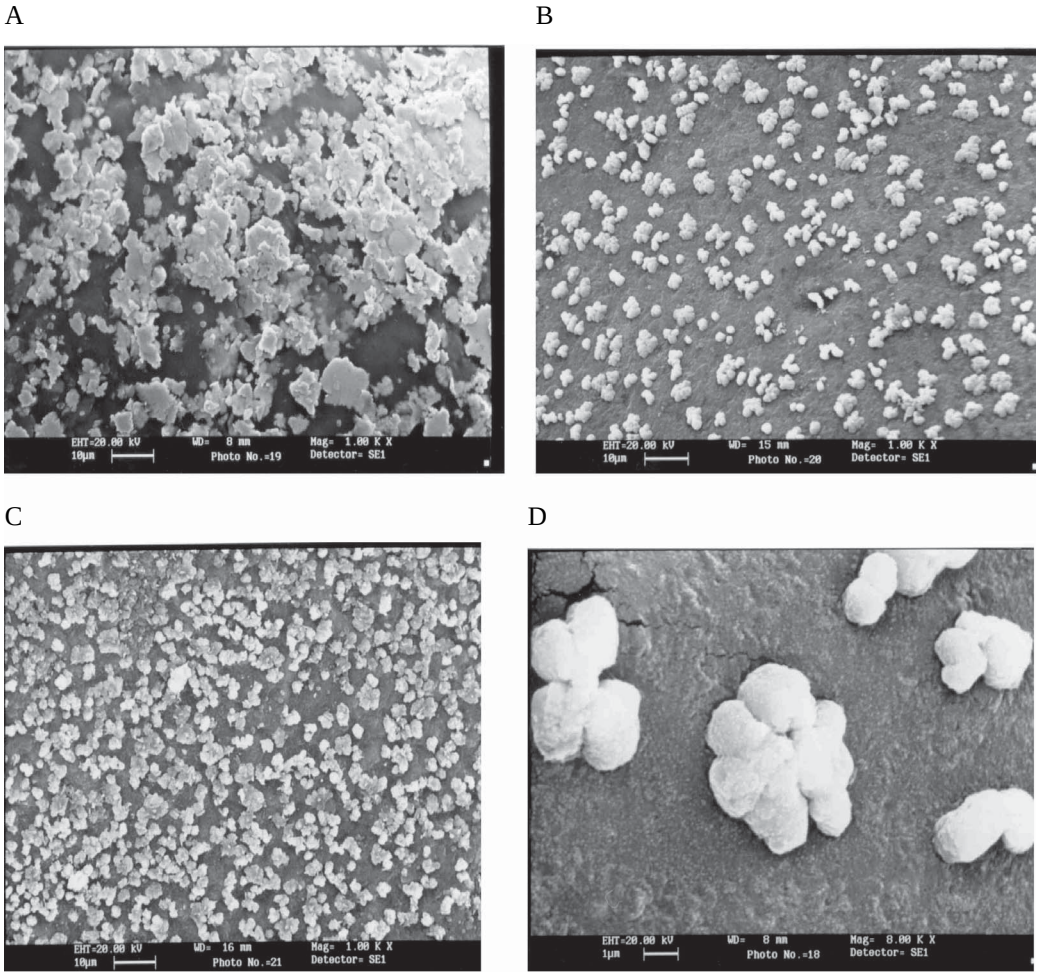

FIGURE 3. SEM image of HPMC-PEG hydrogels containing 5-ASA; (a) HPMC-PEGI, (b) HPMC-PEGII, (c) HPMC-PEGIII, (d) HPMC-PEGIV.

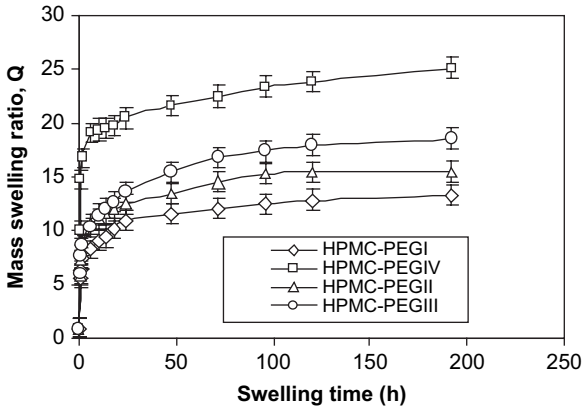

FIGURE 4. The mass swelling index, Q, as a function of swelling time.

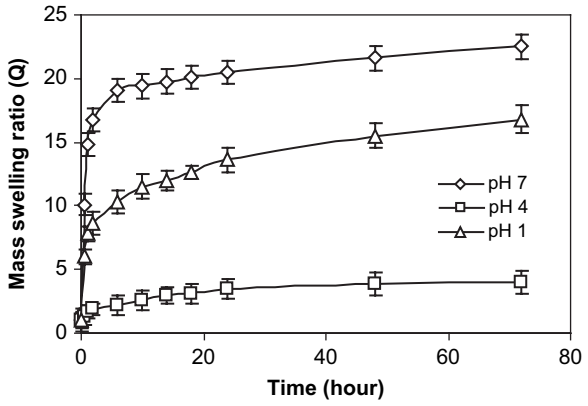

FIGURE 5. Effect of pH on mass swelling ratio, Q, of HPMC-PEGIV at 37°C.

of solute from hydrogel involves the absorption of water into the matrix and simultaneous release of solute via diffusion, as governed by Flick's law.

To study the effect of pH on the release pattern of 5-ASA, release experiments were carried out in buffered solutions (pH 7.4 and pH 1) at 37°C. These experiments were performed

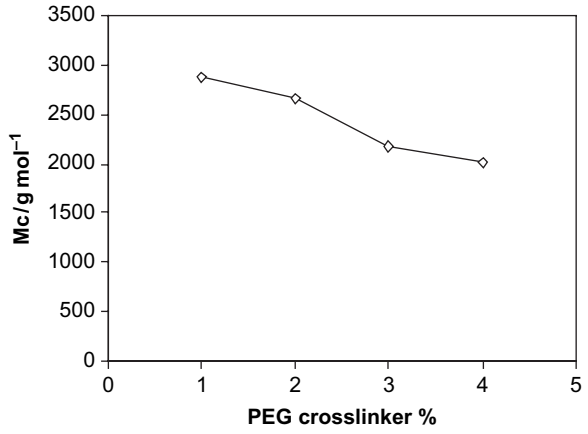

FIGURE 6. Plot between M_c and cross-linker concentration in HPMC-PEG hydrogels.

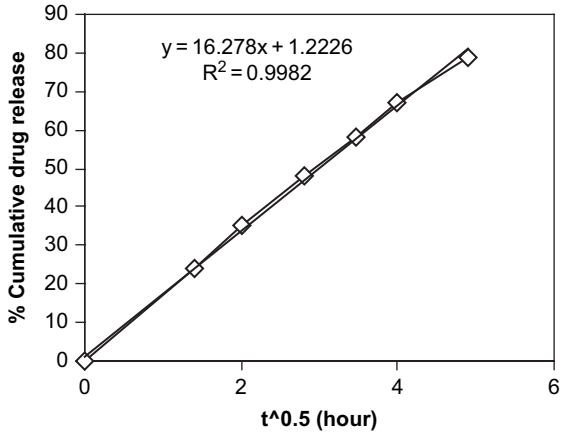

FIGURE 8. Fickian interpretation of 5-ASA release from HPMC-PEGIV.

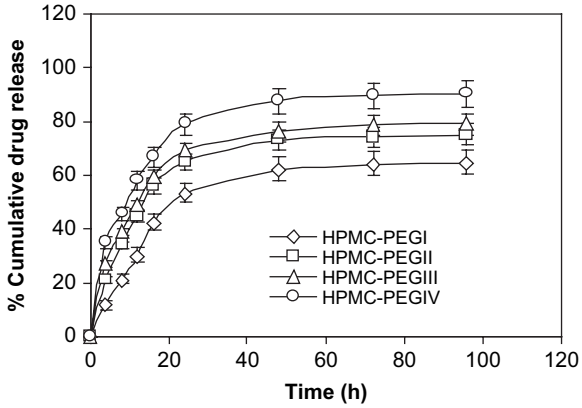

FIGURE 7. Release of 5-ASA from HPMC-PEG hydrogels at 37°C, pH 7.4 (Average ± SD, n = 3).

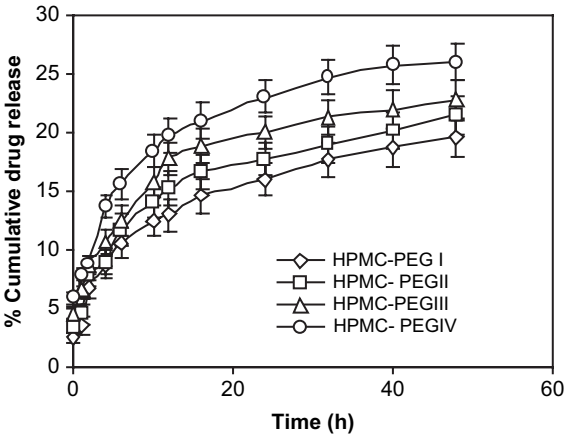

FIGURE 9. Release of 5-ASA from HPMC- PEG hydrogels at 37°C, pH 1 (Average ± SD, n = 3).

in triplicate and the average values are presented graphically (Figures 7 and 9).

Figure 7 presents release profiles of HPMC-PEG I, HPMC-PEG II, HPMC-PEG III, and HPMC-PEG IV at pH 7.4. All samples showed continuous drug release for 24 hr. The extent of drug release after 24 hr were between 55% and 80%.

The release percent is affected by PEG content. Since the swelling is greater for more PEG containing hydrogel, the release of the drug is faster in HPMC-PEG IV.

Figure 8 shows a typical release profile of 5-ASA from HPMC-PEG. It can be seen that the release was Fickian since a straight line was obtained up to 80% of the total release in the plot of cumulative release % versus $t^{1/2}$.

Figure 9 presents release profiles of cross-linked HPMC hydrogels at pH 1.

As shown in the Figure 9 all hydrogels released 5-ASA only in small amount (<15%) after 6 hr. The release of 5-ASA from HPMC-PEG I, HPMC-PEG II, HPMC-PEG III, and HPMC-PEG IV having no significant difference at pH 1.

As shown in Figure 9 the release of the drug from the hydrogels increased continuously with time, and the amount of drug release increased as the environment pH increased. The pH of the media influenced the swelling of the hydrogel and the drug release from the hydrogels is directly related to percentage swelling. Another factor to be considered is the effect of pH on the drug solubility. As the pH increases, the solubility of 5-ASA increases which might increase the drug release.

CONCLUSION

It has been shown that the swelling and drug release properties of cross-linked HPMC hydrogels depends on the cross-linking concentration and pH. As conclusion, it could be said that a drug delivery system prepared by combination of a hydrophobic polymer and a polysaccharide has the capability to be applied as a colonic delivery system. Achieving this potential needs further researches in this area.

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