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Journal:	<i>RSC Advances</i>
Manuscript ID:	RA-ART-03-2015-003731.R2
Article Type:	Paper
Date Submitted by the Author:	18-Apr-2015
Complete List of Authors:	Mahdavinia, Gholam Reza; University of Maragheh, Chemistry Ettehad, Sanaz; University of Maragheh, Amini, Mojtaba; University of Maragheh, Chemistry Sabzi, Mohammad; North Dakota State University, Mechanical Engineering; University of Maragheh, Chemical Engineering

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis and characterization of hydroxypropyl methylcellulose-g-poly(acrylamide)/laponite RD nanocomposites as novel magnetic- and pH-sensitive carriers for controlled drug release

Gholam Reza Mahdavinia,^{*a} Sanaz Etehadhi,^a Mojtaba Amini,^a and Mohammad Sabzi^b⁵ Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

pH-Responsive magnetic nanocomposite hydrogels based on hydroxypropyl methylcellulose-g-poly(acrylamide)/laponite RD (HPMC-g-PAALap) were developed. The magnetic nanoparticles were synthesized inside HPMC-g-PAALap through an *in situ* method. The structure of nanocomposite hydrogels was characterized by FTIR, XRD, SEM, TEM, and VSM techniques. The TEM micrograph revealed that the magnetite nanoparticles were immobilized onto the laponite RD surface. The FTIR of magnetic nanocomposite showed that carboxylate groups are produced during magnetization in alkaline solution. The swelling capacities of magnetic nanocomposites were obtained higher than that of non-magnetic hydrogel HPMC-g-PAALap, which was assigned to induced carboxylate pendants. Due to the carboxylate groups the magnetic nanocomposites indicated a pH-dependent swelling behaviour. Diclofenac sodium (DS) as a model drug was loaded in nanocomposite hydrogels and the release of drug was investigated on the subject of pH of media and also external alternative magnetic field. At pH 7.4, the content of the released drug was considerably increased as compared with those released at pH 1.2. The magnetic nanocomposite showed magnetic behaviour and the content of released drug was enhanced by increasing the strength of external magnetic field.

Introduction

Hydrogels are hydrophilic polymer networks that can absorb aqueous solutions without any disintegration or dissolutions in media.¹ Hydrogels, especially the ones that are derived from natural polymers, have been used extensively in biomedical applications such as artificial tissue, drug delivery, cell carriers, and wound management.²⁻⁵ Hydrogels based on cellulose and its derivatives have attracted many attentions due to their abundance in nature, biocompatibility, low-cost, and biodegradability.⁶ Over the past two decades, smart hydrogels that respond to external stimuli such as pH, temperature, ionic strength, electric and magnetic fields, have developed extensively because of their potential applications in controlled drug delivery.⁷⁻⁸ Among intelligent hydrogels the magnetic ones are considered as an attractive alternative for controlled drug delivery. Due to the fact that the entrapped drug in magnetic hydrogels can release controllably by applying an external magnetic field, without any contact stimuli.⁹ Magnetite (Fe₃O₄) is the most commonly used magnetic nanoparticles to prepare magnetic hydrogels.¹⁰ For sake of bio-applicability, the magnetite nanoparticles are usually incorporated along with functional polymers/biopolymers such as cellulose, chitosan, and poly(vinyl alcohol).⁹ Generally, the magnetic nanoparticles are combined with hydrogels through two methods including "first-hydrogel" and "first-magnetic nanoparticles".⁹ In the former route, the magnetic Fe₃O₄ is produced by co-precipitation of iron ions inside the hydrogel through an *in situ* method;¹¹ whereas in latter one the hydrogels are synthesized in the presence of the pre-synthesized Fe₃O₄ nanoparticles.¹² It has been reported that when the magnetic hydrogels are produced by "first-hydrogel" approach, the magnetic nanoparticles are unstable and can be quickly leached out. Thus, the "first-magnetic nanoparticles" method is recommended as a suitable method to prepare the magnetic

hydrogels. Furthermore, magnetic cellulose materials have been synthesized by these methods.^{13,14}

Hydroxypropyl methylcellulose, a hydrophilic and water soluble biopolymer, is known as one of the most important derivatives of cellulose, which is used extensively in drug delivery systems.¹⁵ Performance of HPMC-based matrixes were evaluated as drug release systems for various drugs such as theophylline, 5-aminosalicylic acid, and diclofenac diethylamine.¹⁶⁻¹⁸ In our previous work, we have successfully synthesized nanocomposite hydrogels by incorporation of HPMC and laponite RD, and they showed high swelling capacities in salt solutions.¹⁹ Laponite RD nanoparticles are synthetic silicates that interact strongly with cationic ions. The magnetite was immobilized onto laponite RD by co-precipitation of Fe²⁺/Fe³⁺ ions through *in situ* method.²⁰ Leaching of Fe₃O₄ nanoparticles from magnetic laponite RD did not observe due to stabilization of magnetite nanoparticles by laponite RD plates.²¹ In this study, regarding to high swelling capacity of HPMC-g-PAALap in salt solutions and also the immobilized magnetic nanoparticles on laponite RD, we attempted to synthesize magnetic HPMC-g-poly(acrylamide)/laponite RD (mHPMC-g-PAALap) hydrogels through "first hydrogel" method. Moreover, effect of different Fe²⁺/Fe³⁺ ions concentration on structural properties and swelling behaviour of the magnetic nanocomposite hydrogels was investigated. Finally, diclofenac sodium, a non-steroidal and anti-inflammatory drug was loaded into magnetic hydrogels and the release of drug as a function of pH of releasing media and applied external magnetic field was investigated.

Experimental

Materials

Hydroxypropyl methylcellulose (HPMC-K100M type; pharmaceutical grade; number average molecular weight 150000) was kindly provided by Aras Bazar Pharmaceutical Co. (Amol, Iran). Laponite RD was obtained from Rockwood Additive Limited (Surface area 370 m²/g, bulk density 1000kg/m³, chemical composition: SiO₂ 59.5%, MgO 27.5%, Li₂O 0.8%, Na₂O 2.8%, loss on ignition 8.2% as provided by manufacturer). Acrylamide (AA) was purchased from Nalco Chemical Co. (Netherlands) and used after recrystallization from acetone. N,N-methylenebisacrylamide (MBA, Fluka) and ceric ammonium nitrate (CAN, Merck) were used as received. Diclofenac sodium was provided by Aldrich Co.; FeSO₄·7H₂O and FeCl₃·6H₂O were purchased from Merck. The other chemicals were analytical grades and used as received.

Synthesis of HPMC-g-PAALap nanocomposite

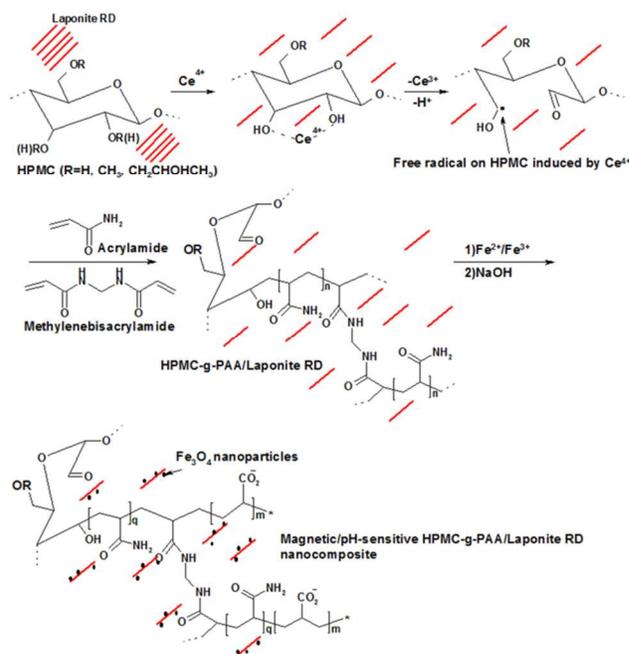
Laponite RD (0.5 g) was dispersed in 50 mL distilled water and allowed to stir for 24 h (speed of stirring was 250 rpm). Then, the dispersed laponite solution was sonicated at frequency of 25 kHz for 20 min. 1 g HPMC was poured in the solution and stirred at ambient temperature for 4 h to allow its complete dissolution. 3 g AA monomer and 0.05 g of MBA (dissolved in 2 mL of distilled water) were then added into solution. Finally, CAN initiator (0.05 g in 2 mL water) was transferred into solution. After 2 h, the synthesized nanocomposite hydrogels were cut into small pieces and immersed in excess distilled water to extract un-reacted components. The purified nanocomposites were dried at ambient temperature until constant weight. The dried samples were milled and sieved to 40-60 mesh sizes and kept away from light and moisture.

Synthesis of magnetic nanocomposite hydrogels

The Fe²⁺/Fe³⁺ ions with constant ratio (nFe²⁺/nFe³⁺ = 0.625/1) were used in all samples based on our previous study.²² The iron salts solutions with desired amounts of FeSO₄·7H₂O and FeCl₃·6H₂O were dissolved in 100 mL distilled water (2.8 g FeSO₄·7H₂O and 4 g FeCl₃·6H₂O; and the other 5.6 g FeSO₄·7H₂O and 8 g FeCl₃·6H₂O). Then, 1 g powdered HPMC-g-PAALap was added to the iron salts solutions and allowed to reach equilibrium swelling for 5 h. The iron ions-loaded nanocomposites were filtered and washed with distilled water three times to remove un-adsorbed iron ions. The Fe²⁺/Fe³⁺-loaded nanocomposites were transferred into NaOH solution (50 mL, 2M) and allowed to form magnetic nanoparticles inside the hydrogel nanocomposites. A simple mechanism for preparation of magnetic nanocomposites was shown in Scheme 1. The corresponding solutions were stirred using mechanical stirrer for 3 h at ambient temperature (24 °C). The synthesized magnetic nanocomposite hydrogels were then removed from alkaline solution and transferred into excess distilled water for neutralization for 4 days with daily refreshing distilled water. The magnetic hydrogel nanocomposites were dried at 40 °C until constant weight. The samples were designated as HPMC-g-PAALap (non-magnetic nanocomposite), mHPMC-g-PAALap1 (magnetic nanocomposite hydrogel obtained from 2.8 g FeSO₄·7H₂O and 4 g FeCl₃·6H₂O), and mHPMC-g-PAALap2 (magnetic nanocomposite hydrogels obtained from 5.6 g FeSO₄·7H₂O and 8 g FeCl₃·6H₂O).

Swelling measurements

Degree of swelling (DS) was determined by immersing the dried hydrogel (~0.1 g) in distilled water (100 mL) or buffered



Scheme 1 Mechanism of preparation of magnetic nanocomposite hydrogel.

solutions (50 mL, pH 1.2: 10 mM of HCl/KCl; pH 7.4: 10 mM NaH₂PO₄/Na₂HPO₄) and the hydrogels were allowed to soak in desired solutions for 24 h. The swollen hydrogels removed from solutions and blotted by filter paper to remove surface water, and the amount of absorbed water was calculated using Eq. 1.

$$DS = \frac{W_s - W_d}{W_d} \quad (1)$$

where W_s and W_d are weights of the samples swollen in aqueous solutions and in dry state, respectively. All swelling experiments repeated for three times and the mean of data were shown in figures.

Drug loading and release studies

Diclofenac sodium as a model drug was loaded into HPMC-based hydrogels by immersing a certain amount of them (500 mg) in 100 mL drug solution with initial concentration of 500 mg L⁻¹ (C_0 , mg L⁻¹). The loading of drug into the hydrogels was conducted on a shaker (90 rpm) for 24 h. Afterward, the hydrogels were removed from drug solution and surface adsorbed drug washed with distilled water. After removing the hydrogels, the remained solution of drug was used for estimation Loading Level (LL, %) by adjusting its volume at 100 mL with distilled water. The content of un-loaded drug (C_t , the sum of non-loaded drug and adsorbed part on beads, mg L⁻¹) was determined using UV-Vis spectrophotometer at λ_{max} =276 nm according to calibration curve. The percentage of Loading Level was obtained according to Eq. 2:

$$\text{Loading Level (LL \%)} = \frac{C_0 - C_t}{C_0} \times 100 \quad (2)$$

In vitro release of the diclofenac sodium from hydrogels was evaluated by immersing certain amount of drug loaded magnetic beads into 20 mL buffered solutions with pH=1.2 and 7.4. The releasing studies were carried out on a shaker (90 rpm) and at ambient temperature (24 °C). At specific time intervals, 5 mL of aliquots of the solution was withdrawn and this volume of

aliquots was replaced by 5 mL of fresh buffered solution. The amount of released drug was determined spectrophotometrically at $\lambda_{\text{max}}=276$ nm. The cumulative release (R , %) of drug from the hydrogels was calculated according to Eq. 3:

$$R(\%) = \frac{M_t}{M_\infty} \times 100 \quad (3)$$

where M_t and M_∞ are the mass of drug released at time t and initial loaded drug content, respectively. All releasing data were repeated 3 times and the mean values were shown in graphs (mean \pm S.D., $n=3$).

Also, the magnetically drug release was performed in phosphate buffer pH=7.4 using an external alternating magnetic field (AMF) apparatus (Electromagnet Type E, Newport Instruments, England). Magnetic field frequency was 350 kHz and the strength of magnetic fields (150-450 G) was changed by adjusting the voltage of the equipment. The drug-loaded magnetic nanocomposite (mHPMC-g-PAALap2) was immersed in 20 mL of buffered solution with pH 7.4 and kept between magnetic poles for 180 min. The supernatant was used to determine the content of released drug during 165 min.

Characterization of nanocomposite hydrogels

Morphology of the dried nanocomposites was examined with a scanning electron microscopy (SEM) (VEGAI, XMU, Czech Republic). The samples were sputter coated with gold before examination. The magnetic properties of the nanocomposites were studied with a vibrating sample magnetometer (VSM, Model 7400, Lakeshore Co., USA). The un-crosslinked and wet magnetic nanocomposite was dispersed in ethanol and their transmittance electron microscopy (TEM) micrographs were recorded with a Zeiss EM-900 operating at 80 kV. One-dimensional wide angle X-ray diffraction (XRD) patterns obtained by a Siemens D-500 X-ray diffractometer with wavelength of $\lambda=1.54 \text{ \AA}$ (Cu-K α), at a tube voltage of 35 kV, and tube current of 30 mA. FTIR spectra of the samples were recorded by using a Bruker 113V FTIR spectrometer by preparing their potassium bromide (KBr) pellets.

Results and discussion

FTIR spectroscopy

To confirm the chemical structures of synthesized hydrogels, the FTIR spectroscopy was carried out. Figs. 1a and b show the spectra of neat laponite RD, HPMC, HPMC-g-PAALap, and mHPMC-g-PAALap2. According to the laponite spectrum, the characteristic vibration bands of the clay are appeared at 3649 cm^{-1} (–OH stretch of the lattice hydroxyl lattice), 3450 cm^{-1} (–OH stretching from free H_2O), 1636 cm^{-1} (–OH bending) and 1011 cm^{-1} (Si–O stretching). In the FTIR spectrum of HPMC, the broad absorption band at 3456 cm^{-1} indicates the stretching frequency of the –OH groups. The bands at 2932 and 1065 cm^{-1} represent the stretching vibration of C–H and C–O bonds, respectively. The bending vibration of –OH groups on the HPMC is appeared at 1381 cm^{-1} . In the FTIR of non-magnetic HPMC-g-PAALap (Fig. 2b), the presence of amide groups confirmed by appearing the bands at 3209 and 1659 cm^{-1} which is indicative of stretching and bending N–H bond of amide groups, respectively. Also, the presence of laponite RD is confirmed by a band appeared at 996 cm^{-1} which is related to the Si–O stretching. Compared to the neat laponite RD the Si–O band showed a shifting about 15 cm^{-1} to

lower frequency, showing interaction between clay and polymer functional groups. The FTIR spectrum of mHPMC-g-PAALap2 nanocomposite hydrogel was different from non-magnetic HPMC-g-PAALap hydrogel (Fig. 1b). The presence of produced Fe_3O_4 was evident from the peak appeared at 470 cm^{-1} . Furthermore, new characteristic peaks were appeared at 1550 and 1403 cm^{-1} that are attributed to the asymmetric and symmetric stretching mode of carboxylate anions, respectively. The obtained carboxylate anions in the composition of magnetic nanocomposites are originated from hydrolysis of amide groups to carboxylate in alkaline solution.²³ Also, the bending peak of N–H in amide groups is shifted from 1659 to 1683 cm^{-1} , which indicates the interaction between amide and Fe_3O_4 nanoparticles.²⁴

SEM observation

The surface morphology of HPMC-g-PAALap nanocomposite hydrogel was affected by the presence of magnetic nanoparticles and the SEM micrographs of dry nanocomposites were shown in Fig. 2. In the Fig. 2, one can see the variation in surface microstructure of hydrogels. The non-magnetic nanocomposite showed a much smoother surface (Fig. 2a). Whereas with synthesizing the magnetite nanoparticles inside the HPMC-g-PAALap hydrogels, a more irregular and rough structure on the surface of the magnetic nanocomposites can be seen. Moreover, this phenomenon can be originated from the conversion of amide pendants to carboxylate groups, which was confirmed by FTIR results.²³

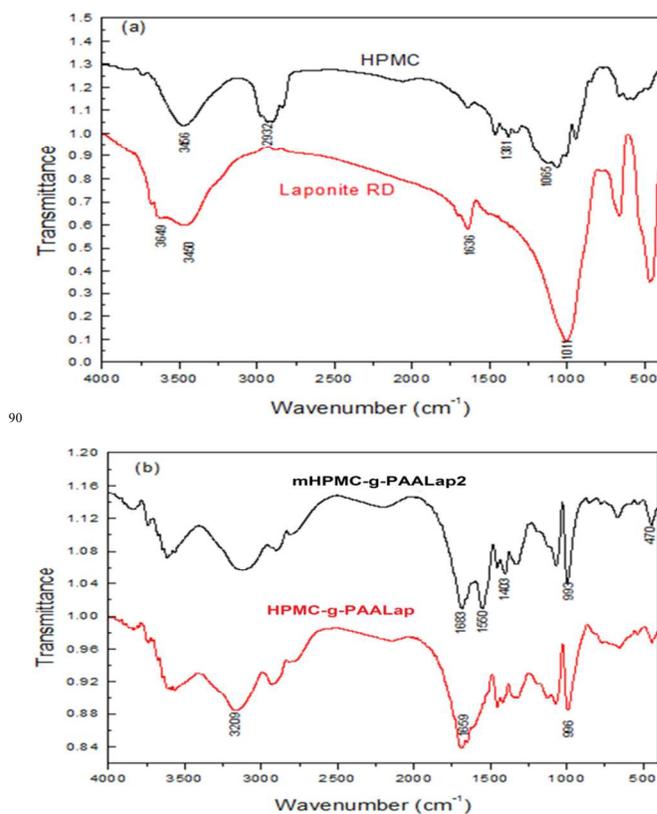


Fig. 1 FTIR of laponite RD and HPMC (a); FTIR of HPMC-g-PAALap and mHPMC-g-PAALap2 nanocomposite hydrogels (b).

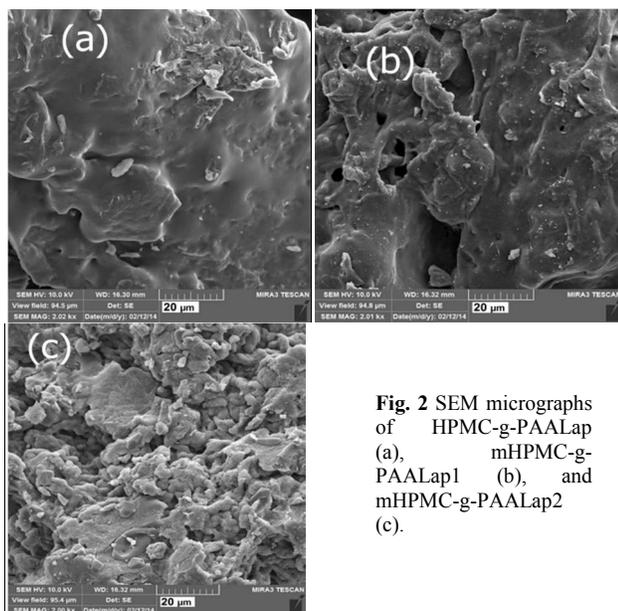


Fig. 2 SEM micrographs of HPMC-g-PAALap (a), mHPMC-g-PAALap1 (b), and mHPMC-g-PAALap2 (c).

X-ray diffraction (XRD)

XRD patterns were used to evaluate dispersion of laponite RD nanoclay as well as crystalline structure of the magnetic nanoparticles. Fig. 3a indicates the X-ray diffractograms of neat laponite RD and HPMC-g-PAALap nanocomposite. The XRD profile of pristine laponite RD showed a broad peak from

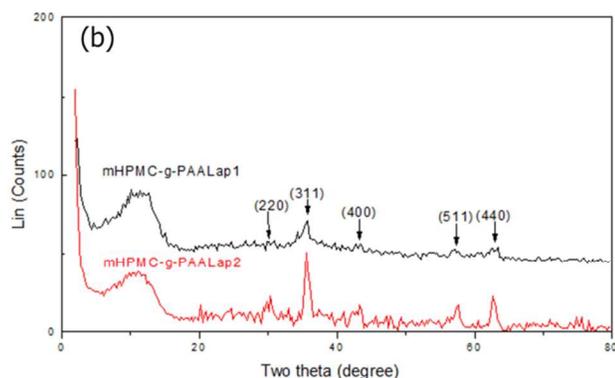
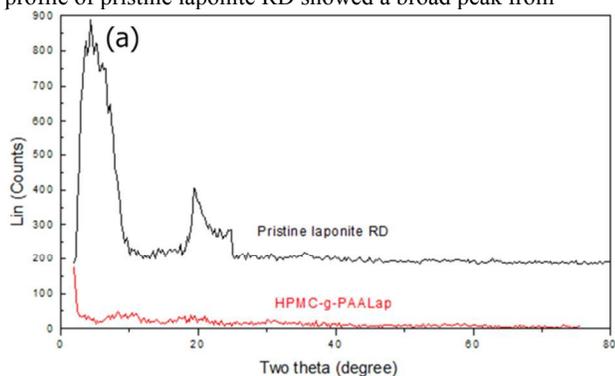


Fig. 3 XRD patterns of laponite RD and HPMC-g-PAALap (a); XRD patterns of mHPMC-g-PAALap1 and mHPMC-g-PAALap2 (b).

$2\theta=2.5^\circ$ to 9.5° with a diffraction peak at about $2\theta=6.1^\circ$ which is assigned to the clay platelets with d-spacing of 14.2 Å. By

introducing laponite RD in HPMC-based hydrogel the diffraction peak at $2\theta=6.1^\circ$ is almost disappeared, which indicates that clay nanoplatelets are well exfoliated in hydrogel matrix. The presence of Fe_3O_4 nanoparticles in mHPMC-g-PAALap1 and mHPMC-g-PAALap2 nanocomposites are confirmed by the peaks appeared at $2\theta=30.3^\circ$, 35.5° , 43.3° , 57.2° , and 62.8° which are attributed to the indices (220), (311), (400), (511), and (440) of magnetic Fe_3O_4 nanoparticles, respectively (Fig. 3b). These data are suggesting a spinal crystalline structure for the magnetite Fe_3O_4 particles formed on the surface of laponite.²⁵

TEM result

The laponite RD powder has long-ranged stacked layers, whereas with its dispersion in water media, it delaminates to laponite RD platelets.²⁶ In spite the XRD pattern of mHPMC-g-PAALap2 that exhibited clearly the presence of magnetic Fe_3O_4 nanoparticles, but no free magnetite nanoparticles inside the nanocomposite are detectable in its corresponding TEM micrograph (Fig. 4a). The absence of free magnetic nanoparticles can be arisen from the result of cation exchangeability of laponite RD that helps the nanoparticles to form preferably on the surface of laponite RD nanoplatelets. In fact, the cation exchange can occur between Na^+ in clay and Fe^{3+} and/or Fe^{2+} ions, and accordingly the synthesized Fe_3O_4 nanoparticles can be located on the surface of clay.²⁷ Tzitzios et al. have also immobilized magnetic nanoparticles on the laponite RD layers and reported similar observation.²¹

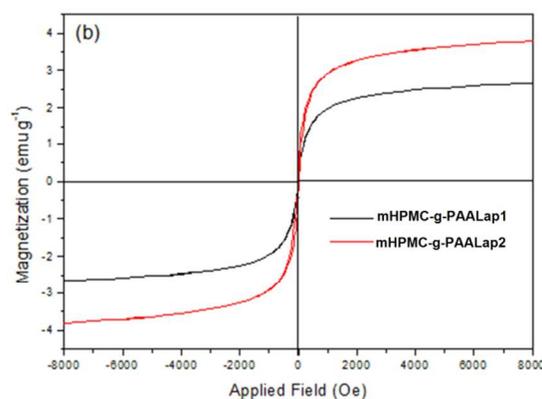
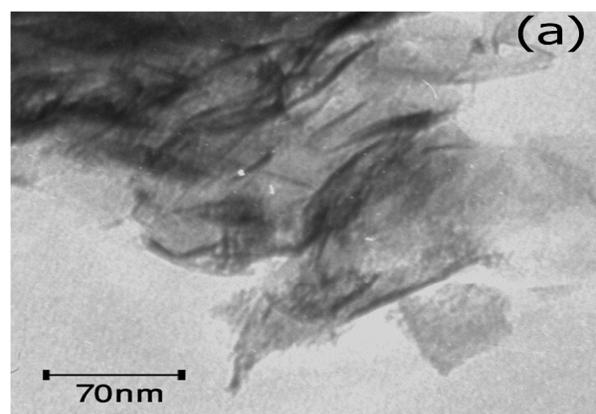


Fig. 4 TEM image of mHPMC-g-PAALap2 (a), magnetic hysteresis loops of magnetic nanocomposite hydrogels (b).

Magnetic properties evaluating

The hysteresis loops of magnetic nanocomposites were also studied using VSM technique between ± 9 kOe at 298 K (Fig. 4b). The saturation magnetizations of mHPMC-g-PAALap1 and mHPMC-g-PAALap2 were obtained 2.6 and 3.8 emu g^{-1} , respectively. The saturation magnetization of mHPMC-g-PAALap2 was obtained 1.46 fold of mHPMC-g-PAALap1 and this result was in agreement with the content of iron ions used to prepare magnetic nanocomposites. The obtained saturation magnetization was sufficient to separate the nanocomposites from aqueous solutions by applying a permanent magnet.

Swelling studies

The swelling behaviour of hydrogels depends on the nature of hydrophilic polymers as well as the composition of swelling media. So, the swelling behaviour of nanocomposites in terms of the magnetic nanoparticles concentration (in distilled water) and pH of swelling media were investigated in this study. It was observed that the magnetization of iron ions-loaded HPMC-g-PAALap nanocomposite in alkaline solution has significant effect on swelling capacity of magnetic nanocomposites. The swelling capacities of both mHPMC-g-PAALap1 (129 g g^{-1}) and mHPMC-g-PAALap2 (85 g g^{-1}) magnetic nanocomposites were enhanced considerably compared with that of HPMC-g-PAALap nanocomposite (10 g g^{-1}). Increasing water absorbency of magnetic hydrogels can be attributed to the produced anionic carboxylate groups and subsequently created electrostatic repulsive forces between the charged sites (COO^-) which led to increased swelling.²³ Lower swelling capacity of mHPMC-g-PAALap2 compared to mHPMC-g-PAALap1 can be assigned to high content of magnetic Fe_3O_4 nanoparticles. The interactions between magnetite and functional groups on hydrogel can lead to increased physical crosslink points, resulting a decreased in water absorbency.²⁸

To investigate the sensitivity of the nanocomposite hydrogel to pH, firstly the equilibrium swelling of the nanocomposites was studied at various pH values ranged from 2.0 to 10.0 (Fig. 5a). No additional ions (through buffer solution) were added to medium for setting pH, because absorbency of a superabsorbent is strongly affected by ionic strength.²³ Therefore, stock NaOH (pH 13.0) and HCl (pH 1.00) solutions were diluted with distilled water to reach desired basic and acidic pH values, respectively. According to the Fig. 5a, HPMC-g-PAALap hydrogel showed pH-independent swelling behaviour due to lack of any pH-sensitive function groups. Contrary to HPMC-g-PAALap, both magnetic nanocomposites showed pH-dependent swelling behaviour, originating from their induced carboxylate groups (the pK_a of carboxylate pendants on hydrogels is about 4.7). Thus, the decreased water absorbency at pH values of 2 and 4 can be attributed to the protonation of carboxylate groups and consequently, disappearing the electrostatic repulsions between anionic pendants. The high swelling capacity of corresponding nanocomposites at $\text{pH} \geq 6$ is because of conversion of non-ionic carboxylic acid pendants to anionic carboxylate.²⁸ The pH-dependent swelling reversibility of the hydrogels was examined in buffered solutions (Fig. 5b). The figure demonstrates the mHPMC-g-PAALap1 and mHPMC-g-PAALap2 reversibility to absorb water upon changing the pH in acidic and basic region.

Drug release studies

For practical applications, one of the most important factors in the drug delivery systems is loading level (LL) of drug into

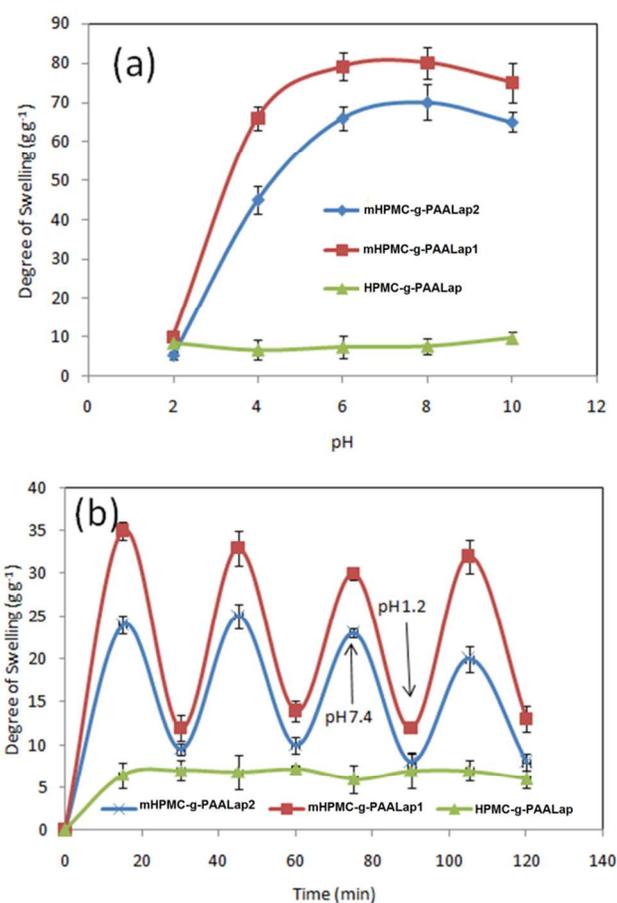
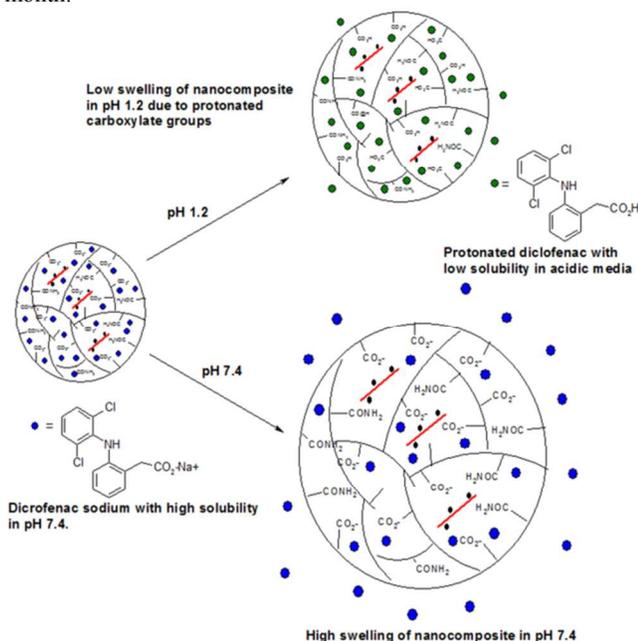


Fig. 5 Effect of pH on swelling behaviour of hydrogels (a), and pH-dependent swelling reversibility of the hydrogels in pHs 1.2 and 7.4 (b). (mean \pm 4, n = 3)

carriers, as the high loading level makes the carriers more affordable.⁹ It was found that the LL of magnetic nanocomposites is higher compared with that of non-magnetic hydrogel. The LL of HPMC-g-PAALap, mHPMC-g-PAALap1, and mHPMC-g-PAALap2 were obtained 9, 68, and 47 %, respectively. The high LL is mainly due to the high swelling capacity of magnetic hydrogels.

In vitro drug release of nanocomposites was investigated. Since the magnetic hydrogels showed pH-dependent swelling behaviour, firstly the effect of pH value on the release of DS from hydrogels has been studied. The drug release profiles at pH values of 1.2 and 7.4 versus time were illustrated in Fig. 6a. At pH = 1.2, all hydrogels showed low cumulative release of drug. Due to pH-sensitivity of magnetic hydrogels and their low swelling capacity in acidic media, their low content of drug release in acidic pH is expectable. During 100 min, low release content (less than 5 %) was observed for three hydrogels. In fact, the low release of DS at pH = 1.2 can be attributed to the poor solubility of DS drug in acidic pHs.²⁹ The low solubility of DS at pH = 1.2 is originated from the presence of weak carboxylic acid on the drug with pK_a of about 4. Then, the hydrogels were transferred from pH = 1.2 to phosphate buffer solution with pH = 7.4 and the DS drug was began to release into media. As the pH of PBS media is higher than the pK_a of DS, the protonated form of drug is converted to its sodium salt with high solubility in media. From the initial slope of release profiles, it can be concluded that the release profiles of drug from hydrogels are

consistent with the swelling behaviour of hydrogels. The more swelling capacity, the high drug release is observed. The effect of pH on drug release behaviour of nanocomposite was shown in Scheme 2. During 350 min, the content of released drug from nanocomposites was lower compared to the conventional hydrogels. This can be attributed to the presence of laponite RD that comprises a large surface area and can makes strong interactions with drugs.²⁰ The release of pyrene from Poly(ethylene glycol)/laponite hybrids has been investigated and the corresponding hybrids had a sustained release of drug till one month.³⁰



Scheme 2 Drug release behaviour of nanocomposite by varying the pH of releasing media.

To analyze the release kinetics, data of the release processes at pH = 7.4 were modeled according to the power law model (Eq. 4). This model is expressed as follows:³¹

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

where, M_t/M_∞ is the fraction of DS drug released at time of t ; k indicates the Ritger-Peppas constant. In the Ritger-Peppas model, n is the release exponent and indicative of transport mechanism. The transport mechanism of release from matrix can be Fickian type diffusion (diffusion kinetic) and non-Fickian (diffusion kinetic and polymer relaxation kinetic) when n is ≤ 0.45 and $0.45 < n < 0.89$, respectively.³² The release constants were obtained from fitting of experimental data with corresponding models and tabulated in Table 1. According to regression coefficients (R^2), the kinetic data showed well-fitting with the Ritger-Peppas model. In addition, the n values indicated that the transport mechanism of drug from hydrogels was Fickian and involved diffusion kinetic.

Table 1 Parameters k and n according to Ritger-Peppas model for release of DS from nanocomposite hydrogels in pH 7.4.

	k	n	R^2	Transport mechanism
HPMC-g-PAALap	0.078	0.22	0.97	Fickian
mHPMC-g-PAALap1	0.083	0.3	0.99	Fickian
mHPMC-g-PAALap2	0.079	0.27	0.99	Fickian

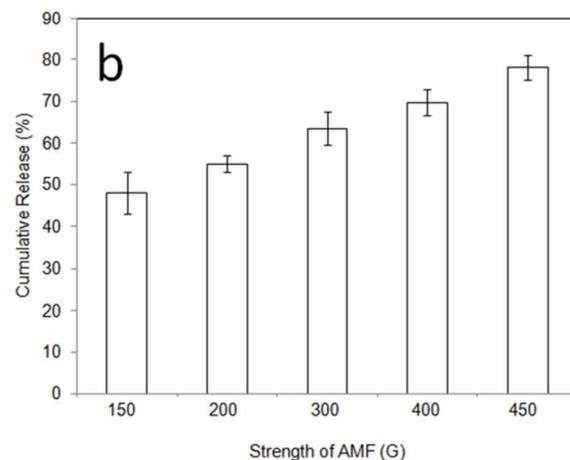
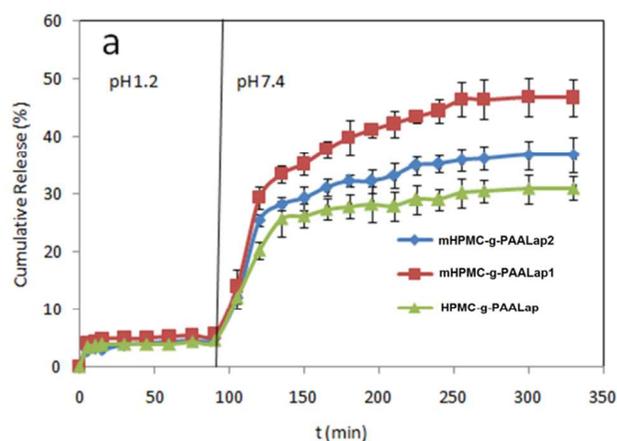


Fig. 6 (a) Influence of pH of releasing media on cumulative release of drug from nanocomposites, (b) effect of strength of external alternative magnetic field (AMF) on content of released drug from mHPMC-g-PAALap2 [pH 7.4, $t=180$ min] (mean \pm s, $n=3$).

So that the synthesized magnetic nanocomposite hydrogels showed magnetic properties, mHPMC-g-PAALap2 hydrogel was selected to investigate its drug release behaviour under alternating magnetic fields (AMF) with strength ranging from 150 to 450 G. The pH of releasing media was adjusted at 7.4 by phosphate buffer. The cumulative release of DS was shown in Fig. 6b. As can be seen from the results, the drug release was affected by the strength of applied magnetic field. These results clearly reveal that the amount of released drug enhanced by increasing the strength of magnetic field. An appropriate reason for the increased drug release upon applying the AMF may be assigned to the alignment of magnetic nanoparticles with the applied AMF. Due to the constant motion of magnetic nanoparticles, the fluctuating of applied AMF can act as stimulus to agitate the magnetic nanoparticles. This agitation results in a motion of magnetic nanoparticles and leads to relax of polymer backbones, which causing an enhancement in the content of released drug.^{33,34} The increase of the strength of AMF from 150 to 450 G led to an increase in drug release again. The relaxation phenomenon of polymer chains may be led to mechanical deformation and subsequent tensile stresses, resulting in an enhancement in the amount of released DS.³⁴ During 180 min and in the absence of AMF, the content of released drug from mHPMC-g-PAALap2 was about 39% (Fig. 6a). Fig. 6b shows that by action magnetic fields the content of released drug was

higher than that of 39%, and cumulative releases were obtained between 45 and 77%.

Conclusion

In this study, pH-responsive magnetic hydroxypropyl methylcellulose-g-poly(acrylamide)/laponite RD hydrogels were successfully synthesized, and the Fe₃O₄ nanoparticles were prepared inside HPMC-g-PAALap nanocomposites by co-precipitation of iron ions through *in situ* method. In spite that the FTIR and XRD results confirmed the presence of magnetic nanoparticles, free magnetic nanoparticles were not observable by in TEM image. In fact, the Fe₃O₄ nanoparticles were immobilized on the laponite RD clay. During magnetization of Fe²⁺/Fe³⁺-loaded HPMC-g-PAALap nanocomposites the amide groups were hydrolyzed to produce anionic carboxylate groups. Due to the electrostatic repulsion between anionic carboxylate, the swelling of magnetic hydrogels were obtained higher than that of non-magnetic nanocomposite hydrogel. The magnetic nanocomposite hydrogels demonstrated excellent pH-sensitivity and can be considered as a good carrier for drug controlled release. The controlled release of diclofenac sodium was examined at pH = 7.4, and the content of released drug was considerably increased as compared with those released at pH = 1.2. The release of drug from magnetic nanocomposite was affected by applying external alternative magnetic field.

^a Department of Chemistry, Faculty of Science, University of Maragheh, 55181-83111, Maragheh, Iran.; E-mail: grmnia@maragheh.ac.ir; Fax:+984137276060; Tel:+984137273068.

^b Department of Chemical Engineering, Faculty of Engineering, University of Maragheh, 55181-83111, Maragheh, Iran.

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