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Original Article

PREPARATION AND CHARACTERIZATION OF CROSSLINKED ACRYLIC ACID/HYDROXYPROPYL METHYL CELLULOSE HYDROGELS FOR DRUG DELIVERY

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ABSTRACT

Objective: Hydrogels are high-water content materials prepared from cross-linked polymers that are able to provide sustained, local delivery of a variety of therapeutic agents. Use of the natural polymer, such as HPMC, in hydrogels has been highly pursued thanks to the polymer's hydrophilicity, low toxicity, and biodegradability. The advanced development of these hydrogels has led to new drug delivery systems that release their payloads under varying environmental stimuli.

Method: In the present work, series of pH sensitive acrylic acid/hydroxypropyl methylcellulose (AA/HPMC) hydrogels have been prepared by free radical polymerization in the presence of ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent and benzyl peroxide as initiator. Dynamic and equilibrium swelling studies of prepared hydrogels were investigated in USP phosphate buffer solutions of pH 1.2, 5.5, 6.5 and 7.5 with constant ionic strength.

Results: Swelling coefficient was significantly higher at higher pH as compared to low pH. Increased in swelling of hydrogel was observed due to increase in concentration of AA and HPMC. On the other hand, swelling of hydrogel was decreased by increasing the concentration of EGDMA due to presence of more physical entanglements between hydrogels. Swelling and structural parameters of AA/HPMC hydrogel were investigated by measuring diffusion coefficient, volume fraction of polymer, solvent interaction parameters, molecular weight between crosslinks and crosslinked density. Sol-gel analysis was investigated to calculate the sol fraction and gel fraction of hydrogel. Gel fraction was increased by increasing the concentration of AA and EGDMA and decreased by increasing the concentration of HPMC. Porosity of hydrogels was also calculated. Increased in porosity was observed by increasing the concentration of AA and HPMC due to formation of concentrated solution that prevents the bubble from escaping. Decreased in porosity was observed with increase of crosslinking agent due to physical entanglements between AA/HPMC hydrogels. Isosorbide mononitrate was loaded as model drug and release study was carried out in USP phosphate buffer solutions of pH 1.2, 6.5 and 7.5. The drug release data was fitted into various kinetic models i.e. zero order, first order, Higuchi and Peppas model. Results showed that increased drug release at higher pH and was strongly influenced by swelling behavior of hydrogels. The structure of AA/HPMC hydrogel was characterized by fourier transform infrared spectroscopy (FTIR).

Conclusion: The result confirms that AA/HPMC hydrogels can be effectively used in pH sensitive controlled released vehicle for drug delivery due to rate controlling and swellability nature of hydrophilic HPMC.

Keywords: Acrylic acid, Hydroxypropyl methylcellulose, pH sensitive hydrogels and drug delivery

INTRODUCTION

Stimuli-responsive hydrogels constantly attract the attention of researchers due to their great potential in biomedical applications and tissue engineering [1, 2]. Hydrogels are three-dimensional networks crosslinked via chemical bonds, ionic interactions, hydrogen bonding, hydrophobic interactions or physical bonding which swell significantly in water but do not dissolve. Hydrogels have been used by many investigators in controlled-release drug delivery systems because of their good tissue compatibility and easy manipulation of swelling level and, thereby, solute permeability. The desired kinetics, duration, and rate of solute release from hydrogels are limited to specific conditions, such as hydrogel properties, amount of incorporated drug, drug solubility, and drug-polymer interactions. This review summarizes the compositional and structural effects of polymers on swelling, loading, and release and approaches to characterize solute release behavior in a dynamic state [49]. Ranjha and Doelker [9-11] showed that swelling depends upon monomeric composition and extent of crosslinking. Several types of hydrogel are biodegradable, pH-dependent and temperature sensitive hydrogels [12].

Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems [13, 14]. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion [15, 16]. Then the incorporated drug diffuses out of the system. HPMC is water soluble cellulose derivative. It is hydrophilic, biodegradable and biocompatible polymer. It is worth highlighting that HPMC is non toxic, low cost and used in the formulation of hydrogel for drug delivery [17]. HPMC has been successfully introduced as a rate controlling polymer in solid dispersion of numerous drugs [18-21]. Nochos and Bouropoulos [22] prepared bovine serum albumin (BSA) loaded alginate/HPMC hydrogel beads to study the effect of different alginate/HPMC formulations on release behavior of BSA.

Acrylic acid (AA) is a pH and electrically sensitive material due to its ionic repulsion between anionic charged groups (carboxylic acid). It forms complexes with polybases [23]. Polyacrylic acid (PAA) and its copolymer have been used as a vehicle in drug delivery systems [24]. The hydrogels of PAA having properties of bioadhesive, biocompatible and antibacterial due to their pendent carboxylic groups [25]. PAA is widely used in pharmaceutical processes due to its pH dependent swelling behavior. The pharmaceutical applications of PAA are in the sustained release of drugs in ocular, nasal, buccal, gastro-intestinal, epidermal and transdermal drug delivery system. AA is biocompatible while eliciting little antigenic reaction in vivo [26]. In living cells, AA polymers exhibited high tolerance [27]. Present research focused on developing a novel pH-sensitive acrylic acid/hydroxypropyl methylcellulose (AA/HPMC) hydrogels using ethylene glycol dimethacrylate (EGDMA) as a

crosslinking agent by free radical polymerization. In this respect, various samples with varying polymeric, monomeric compositions and degree of crosslinking were prepared to investigate their effect on the dynamic and equilibrium swelling for site specific drug delivery. Release of the model drug, isosorbide mononitrate from the AA/HPMC hydrogels in USP phosphate buffer of varying pH was studied. Hydrogels were characterized by FTIR to investigate their structure. Network parameters, sol-gel fraction and porosity of hydrogel were also determined.

MATERIALS AND METHODS

Materials

For the preparation of AA/HPMC crosslinked hydrogels, acrylic acid (AA) (Sigma Aldrich, Germany) was used as monomer. Hydroxypropyl methylcellulose (HPMC) (Methocel E5, China) and ethylene glycol dimethacrylate (EGDMA) (Sigma Aldrich, Germany) were used as polymer and crosslinking agent respectively. Benzyl peroxide and distilled water were used as initiator and solvent respectively. Isosorbide mononitrate, a drug, is used for loading into hydrgels. All chemicals were of analytical grade.

Synthesis of AA/HPMC crosslinked hydrogels.

In the present work a series of crosslinked hydrogels of different concentration of AA/HPMC were synthesized. HPMC solution was prepared by adding weighed amount of HPMC in 1/3 of distilled water while stirring and heat at 90 °C then add remaining water to form clear solution. Benzyl peroxide used as initiator at a concentration of 1 % wt of AA, was dissolved in AA. Both solutions were mixed and homogenized. A varying amount of EGDMA as a crosslinker was added to above solution. Final weight of solution was made 100 gm with water and stirred continuously to homogenize. These solutions were poured in to glass tubes (pyrex). The air above the solution in the tubes was removed by nitrogen bubbling for 15-20 minutes. The capped tubes were placed in the water bath for polymerization and temperature was gradually increased from 45 °C to 65 °C to avoid auto acceleration and bubble formation. The temperature program was 45 °C for 1 hour, 50 °C for 2 hours, 55 °C for 3 hours, 60 °C for 4 hours and 65 °C for 24 hours. After cooling to room temperature, cylinders were removed from tubes and were cut into 6 mm lengths. The cylinders of AA/HPMC were washed with 60/40 % v/v ethanol water for 1-2 weeks, for complete removal of unreacted monomers. During this period the solvent was changed daily. These gels disc were thoroughly washed until the pH of the washing media was same as that of ethanol water mixture before washing. Then discs were dried, first at room temperature and then in oven at 45 °C to constant weight and stored in the desiccators for further use. Table 1 shows the different formulations of AA/HPMC. The presumptive structure of prepared gel is shown in Fig. 1.

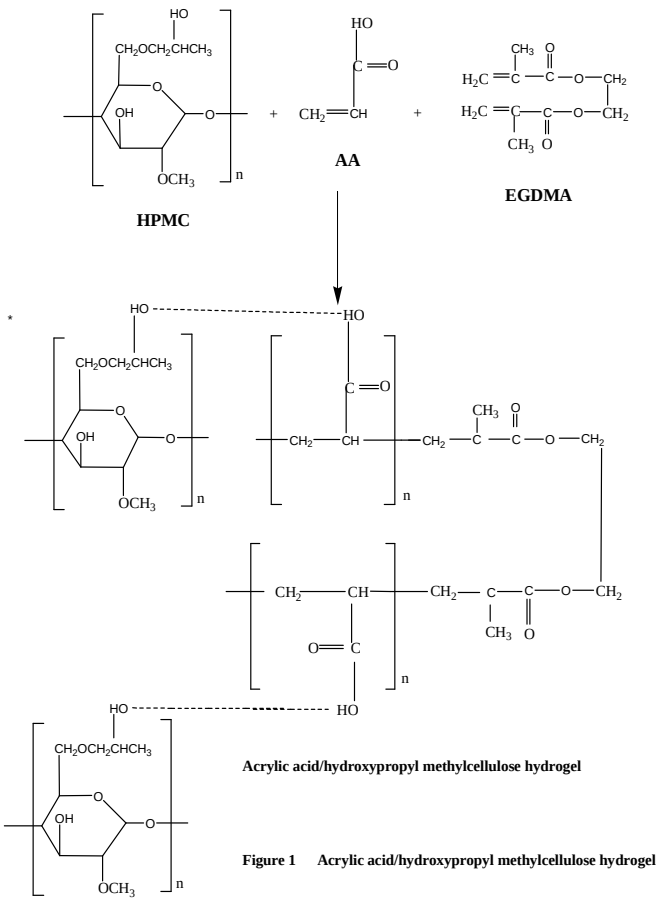

Figure 1 Acrylic acid/hydroxypropyl methylcellulose hydrogel

Table1: Different Formulations Of Aa/Hpmc Hydrogel

Sample code	AA/100 gm solution	HPMC/100 gm solution	AA/HPMC (wt %)	EGDMA	EGDMA/100 gm of AA	EGDMA mol %
A_1	16.25	3.75	81.25/18.8	0.07	0.40	0.18
A_2	21.25	3.75	85/15	0.05	0.40	0.23
A_3	26.25	3.75	87.5/12.5	0.10	0.40	0.29
B_1	18.25	1.25	93.11/6.89	0.07	0.40	0.20
B_2	18.25	2.5	87.11/12.89	0.07	0.40	0.20
B_3	18.25	3.75	82.02/17.98	0.07	0.40	0.20
C_1	21.25	3.75	85/15	0.06	0.20	0.13
C_2	21.25	3.75	85/15	0.04	0.30	0.18
C_3	21.25	3.75	85/15	0.11	0.50	0.29

Preparations of buffer solutions.

Phosphate buffer solutions of pH 1.2, 5.5, 6.5 and 7.5 were prepared by using potassium dihydrogen phosphate (KH_2PO_4). The concentration of buffering agent was 0.2 M. The pH of these solutions was adjusted by adding HCl or NaOH solution of 0.2 M. Ionic strength was kept constant to 0.11 by adding calculated amount of NaCl. Swelling characterization. To study the swelling behavior of cross-linked polymers, dynamic and equilibrium swelling ratios were calculated as under;

Dynamic and equilibrium swelling studies. The dynamic and equilibrium swelling ratio were studied in 100ml phosphate buffer solution of pH 1.2, 5.5, 6.5 and 7.5.

Dried hydrogels were left to swell in a solution of desired pH (1.2-7.5), at a temperature of 37°C. For dynamic swelling, swollen gels removed from the solution, blotted with filter paper, weighed, at regular intervals for 8 h and placed in the same flask. The swelling ratio of each hdrogel was calculated from the following relation [28].

$$q = \frac{W_h}{W_d} \quad (1)$$

where W_h is the weight of swollen gel at time t, and W_d is the initial weight of dry gel.

Equilibrium swelling studies. The Swelling of the samples were continued until they attain a constant weight. For equilibrium swelling the swollen gels were weighed regularly to a constant weight which takes 2-3 weeks.

$$q_{(Eq)} = \frac{W_h}{W_d} \quad (2)$$

Diffusion coefficient. Release of drug from the hydrogels generally occurs by a diffusion mechanism. Water diffusion coefficient of hydrogel was calculated by the following equation:

$$D = \pi \left(\frac{h.\theta}{4.q_{eq}} \right)^2 \quad (3)$$

where D is the diffusion coefficient of the water, q_{eq} is the swelling of the gel at equilibrium, θ is the slop of linear part of the swelling curves and h is the initial sample thickness before swelling [29].

Fig. 2: Different samples of AA/HPMC hydrogel

Characterization of network structure of AA/HPMC hydrogels

Solvent interaction parameters (χ). Solvent interaction parameters are calculated by Flory-Huggins theory. Equation used to calculate (χ) values is given below:

$$\chi = \frac{\ln(1 - V_{2,s}) + V_{2,s}}{V_{2,s}^2} \quad (4)$$

$V_{2,s}$ (ml/mol) is the volume fraction of the swollen gel in equilibrium state and **(χ) is** the Flory-Huggins polymer solvent interaction parameters[29].

2.6.2 Molecular weight between crosslinks (Mc). Flory-Rehner theory is used to calculate the values of Mc between two adjacent crosslinks that represents the degree of crosslinking of hydrogel networks. Mc value was determined by equilibrium swelling data. Mc is calculated by the following equation [30];

$$Mc = \frac{dpVs \left(V_{2,s}^{1/3} - V2,\ s/2 \right)}{\ln\left(1 - V2,\ s\right) + V2,\ s + \chi V_{2,s}^2} \quad (5)$$

Volume fraction of polymer (V_{2s}). It is the measure of amount of fluid that a hydrogel can incorporate into its structure in swollen state. It is calculated by the following equation [31];

$$V_{2s} = \left[1 + \frac{d_p}{d_s} \left(\frac{M_a}{M_b} - 1 \right) \right]^{-1} \quad (6)$$

where d_p and d_s are the densities (gm/ml) of the polymer and solvent respectively. M_a and M_b are the masses (gm) of swollen and dry gels respectively. V_{2s} (ml/mol) is the volume fraction of the swollen hydrogel in the equilibrium state and χ is the Flory-Huggins polymer interaction parameters.

Crosslinked density (Q). Crosslinked hydrogels are characterized by crosslinked density. The value of q is calculated by the following relation [12];

$$Q = \frac{M_c}{M_r} \quad (7)$$

where M_r is the molar mass of repeating unit and is calculated as;

$$M_r = \frac{m_{HPMC} M_{HPMC} + m_{AA} M_{AA} + m_{EGDMA} M_{EGDMA}}{m_{HPMC} + m_{AA} + m_{EGDMA}} \quad (8)$$

where m_{HPMC}, m_{AA} and m_{EGDMA} are the masses of HPMC, AA and EGDMA respectively. While M_{HPMC}, M_{AA} and M_{EGDMA} are the molar masses of HPMC, AA and EGDMA respectively.

Sol-gel fraction.

Hydrogel samples were cut into pieces with a length of 3-4 mm, dried in a vaccum oven at 45°C to a constant weight (W_o), and subjected to Soxhlet extraction for 4 h with deionized water as solvent. Uncrosslinked polymer was removed with this extraction from the gel structure. Extracted gels were dried again in a vaccum oven at room temperature to constant weight (W_1). The gel fraction was calculated according the following equation [32];

$$\text{Sol fraction (\%)} = \left[\frac{W_o - W_1}{W_o} \right] \times 100 \quad (9)$$

Gel fraction (%) = 100- Sol fraction (10)

Porosity measurement.

For porosity measurement, the solvent replacement method was used. Dried hydrogels were immersed in absolute ethanol over night and weighed after blotting excess ethanol on the surface. The porosity was calculated from the following equation [33];

$$\text{Porosity} = \frac{(M_2 - M_1)}{\rho V} \times 100 \quad (11)$$

where M_1 and M_2 are the masses of the hydrogel before and after immersion in ethanol, respectively, ρ is the density of absolute ethanol and V is the volume of the hydrogel.

Drug loading.

Samples which showed maximum swelling were used for drug loading and release studies. The drug loading into the disks of hydrogel was achieved by soaking them for 1 week in solution of the drug. A 1% w/v drug solution in distilled water was used for drug loading. After achieving the equilibrium value, swelled hydrogels were removed from the drug solution, blotted with laboratory tissue paper, first dried at room temperature and then they were placed in an oven at 40-45°C for 1 week for removing the absorbed solvent. Stability of drug is not affectd at that temperature and drug remains stable. Because DSC and other tests are performed at higher temperature such as at about 95°C [48]. Determination of drug loading**.** Three methods were used for detrmining percent drug loading in hydrogels. The first method used to calculate the amount of drug loaded in hydrogel was determined by the following equation:

Amount of drug = W_D-W_d

Drug loading (%) = $[(W_D-W_d)/W_d] \times 100$ (12)

W_d and W_D are the weight of dried hydrogels before and after immersion in drug solution respectively. In another method, amount of drug entrapped in hydrogels was calculated by repeatedly extracting the weighted quantity of loaded gels by using deionized water. Each time 25ml fresh 50% deionized water solution was used until there was no drug in the solution. Drug concentration was determined spectrophotometrically at λ_{max} 215 nm. Amount of drug present in all portions was considered as total amount of drug loaded into hydrogel.

The drug loaded content into the hydrogels was also determined from volume of the drug solution absorbed by the disks at equilibrium. Volume of drug solution absorbed by the disks can be calculated by knowing the density and weight of drug solution. Amount of drug absorbed by the disks was also calculated and values were given in Table 2.

Table 2: **Amount of isosorbide mononitrate loaded in different formulations of AA/HPMC hydrogels**

Sample code	Amount of isosorbide mononitrate loaded (g/g of dry gel)		
	By swelling	By extraction	By weight
A_1	0.0332	0.0345	0.0367
A_2	0.0347	0.0357	0.0372
A_3	0.0359	0.0368	0.0385
B_1	0.0296	0.0315	0.0336
B_2	0.0397	0.0435	0.0465
B_3	0.0403	0.0455	0.0472

Table 3: Dynamic and equilibrium swelling coefficient of AA/HPMC hydrogels

Sample code	Dynamic swelling coefficient				Equilibrium swelling coefficient			
	pH 1.2	pH 5.5	pH 6.5	pH 7.5	pH 1.2	pH 5.5	pH 6.5	pH 7.5
A_1	1.89	2.30	3.86	4.45	3.82	05.63	23.26	s
A_2	2.07	2.80	4.40	5.43	4.23	08.22	28.47	s
A_3	2.11	3.54	5.21	6.62	4.33	12.61	45.27	s
B_1	1.85	3.01	4.80	5.97	3.83	9.33	40.20	s
B_2	2.17	3.06	5.01	6.02	4.80	9.89	40.82	s
B_3	2.22	3.55	5.52	6.97	4.91	14.50	56.30	s
C_1	1.93	2.70	4.37	5.70	4.10	8.60	37.74	s
C_2	1.91	2.60	4.16	5.20	4.08	7.90	32.64	s
C_3	1.89	2.50	3.71	4.90	3.90	6.70	26.83	s

"s" stands for samples broken

Table 4: Amount of isosorbide mononitrate (%) released from AA/HPMC hydrogels

Sample code	(%) Amount of isosorbide mononitrate released		
	pH 1.2	pH 6.5	pH 7.5
A_1	29.04	54.17	70.00
A_2	30.35	58.03	75.59
A_3	31.85	61.85	82.31
B_1	38.95	61.25	80.63
B_2	35.15	64.05	86.95
B_3	32.10	68.50	91.65

Drug release studies.

Drug release was measured with a dissolution apparatus (Pharmatest; type PT-DT 7, Germany) associated with UV-Vis. Spectrophotometer (IRMECO, UV-Vis. U2020). The weighted polymer disk was immersed in 500 ml dissolution medium which was at stirred at a rate of 100 rpm for maintaining a uniform drug concentration in the medium. The dissolution media was maintained at 37°C. With each sampling, the solution was changed with fresh medium, maintaining the total volume constant. The determination of drug released was carried out at λ_{max} 215 nm with readings taken up to 12 h. Drug released was conducted in 0.2 M USP phosphate buffer solution at pH of 1.2, 6.5 and 7.5. Analysis of drug release kinetics. For drug release kinetics different models such as zero order, first order, Higuchi and Korsmeyer-Peppas are used. Equations used for these models are as follows;

Zero- order kinetics: $F = K_o t$ (13)

Where F_t represents the fraction of drug release in time t and K_o is the zero order release constant.

First- order kinetics: $\ln (1-F) = -K_1 t$ (14)

Where F represents the fraction of drug release in time t and K_1 is the first order release rate constant.

Higuchi model: $F = K_2 t^{1/2}$ (15)

Where F represents the fraction of drug release in time t and K_2 is the Higuchi constant.

Korsmeyer-Pappas model: $M_t/M\infty = K_3 t^n$ (16)

Where $M_t/M\infty$ is the fraction of drug release at time t. K_3 is the release rate constant and n is the release exponent. n value is used to characterize different drug release from hydrogels.. When n = 0.5 order of release was Fickan, n= 1 responds to case- 11 transport, while 0.5 <n<1 the diffusion mechanism is non fickian [34, 35, 36, 37].

To study release kinetics, drug release studies were plotted as log cumulative percectage drug release versus time.

FTIR spectroscopic studies

Hydrogel samples were crushed with pestle in an agate mortar. The crushed material was mixed with potassium bromide (Merck IR spectroscopy grade) in 1:100 proportions and dried at 40°C. The mixture was compressed to 12mm semitransparent disk by applying a pressure of 60 kN (Pressure guage, Shimadzu) for 2 min. The FTIR spectrum over the wavelength range 4000-400 cm^{-1} was recorded using FTIR spectrometer (FTIR 8400S, Shimadzu).

RESULTS AND DISCUSSION

Effect of pH on swelling and on drug release from AA/HPMC hydrogels

AA/HPMC hydrogels showed pH sensitive behavior and the results of that behavior were given in table 3. From these results it was cleared that there is significant difference in degree of swelling at various pH. Dried hydrogels were immersed in 0.2M USP phosphate buffer solution of pH 1.2, 5.5, 6.5 and 7.5. The swelling ratio of hydrogels in acidic medium is always less than that in alkaline medium. AA has carboxylic group. On increasing the pH of medium above pKa value of AA (4.26), its hydrophilicity increases after ionization which results in swelling due to ionization of carboxyl groups. The ionization in turn stretches the coiled molecules to an extent which depends on the percent ionization of the carboxyl groups [10]. The presence of HPMC in the hydrogels also increases the swelling as the pH of medium increases. This behavior can be explained due to high hydrophilicity and swellability nature of HPMC. It has been reported that HPMC is the dominant hydrophilic polymer that swell to significant extent upon contact to water [38]. Isosorbide mononitrate is selected as model drug due to its water solubility. For drug loading six samples were selected (A_1, A_2, A_3, B_1, B_2, B_3) which show substantial swelling. To investigate the effect of pH on drug release behavior, dissolution profiles were obtained in solutions of pH 1.2, 6.5 and 7.5. Table 4 shows percentage drug release for different AA/HPMC hydrogel at various pH. In all samples drug released increased, as the pH of the medium was increased. The results of drug release can be correlated with the results of swelling which showed that water uptake by the polymer increased with increasing pH of the medium.

Effect of monomer concentration on swelling and on drug release from AA/HPMC hydrogels

AA/HPMC hydrogels of different monomeric composition (16.25/3.75, 21.25/3.75, 26.25/3.75) using EGDMA as crosslinking agent (0.4% of AA) were prepared to investigate the effect of monomeric composition on swelling and on drug release. Figure 3 shows the effect of AA concentration on the dynamic swelling behavior as a function of pH of swelling medium keeping HPMC concentration and degree of crosslinking constant.

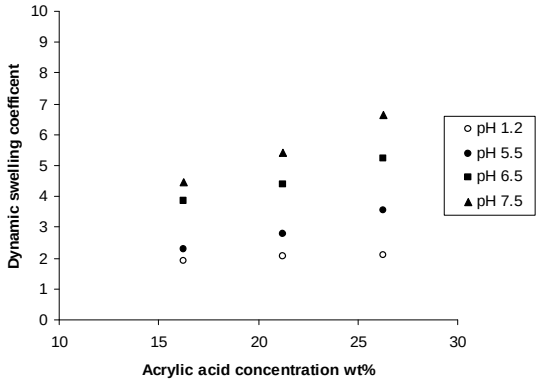

Fig. 3: Dynamic swelling behavior after 8 hours of AA/HPMC hydrogel with different acrylic acid concentrations (16.25%, 21.25%, and 26.25%) keeping concentration of HPMC and EGDMA constant in solutions of various pH at 37°C.

It was observed that swelling of gel increased with increase of AA concentration. Table 3 shows that dynamic and equilibrium swelling coefficients do not increase substantially at low pH but at higher pH there is significant increase in swelling coefficient with increase in AA concentration. It is due to availability of more carboxyl groups for ionization. As a result electrostatic repulsion increases that causes chain relaxation of originally coiled molecules. Drug released studies were carried out at pH 1.2, 6.5 and 7.5 for 12 hrs to investigate the effect of AA concentration. Figure 4 shows that as AA content in hydrogel increased, drug released increased. Table 8 shows that drug released increased from 29.04 to 54.17% and to 70% at pH 1.2, 6.5 and 7.5 respectively. Huang et al [26] prepared guar gum poly (acrylic acid) hydrogels and observed the similar swelling and drug release behavior. They reported that the swelling and ketoprofen release increased with increase in PAA content in the gel structure.

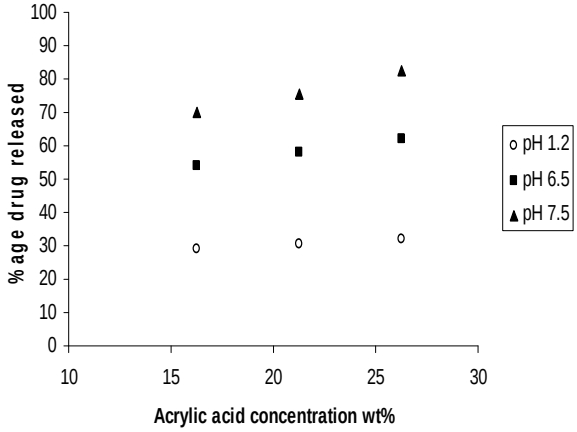

Fig. 4: Effect of acrylic acid concentration on isosorbide mononitrate release after 12 hours from AA/HPMC hydrogel with 0.4% EGDMA as cross linking agent in solutions of pH 1.2, 6.5 and 7.5 at 37 °C

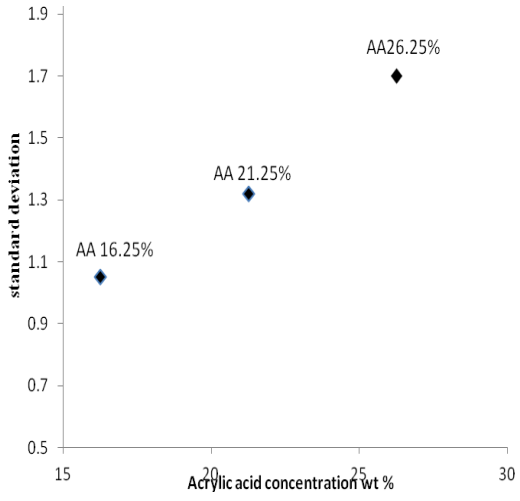

Fig. 3(a): Effect of standard deviation on dynamic swelling behavior after 8 hours of AA/HPMC hydrogel with different acrylic acid concentrations (16.25%, 21.25%, and 26.25%) keeping concentration of HPMC and EGDMA constant in solutions of various pH at 37°C.

Effect of polymer (HPMC) concentration on swelling and on drug release from AA/HPMC hydrogels.

Three formulations of AA/HPMC hydrogels with varying concentration of HPMC 1.25/18.25, 2.5/18.25 and 3.75/18.25 keeping AA and EGDMA (0.4% of AA) concentration constant were synthesized and subjected to swelling studies in buffer solutions of pH 1.2, 5.5, 6.5 and 7.5. In table 3 results showed that both dynamic and equilibrium swelling ratios decreased at pH 1.2 and substantially increased at pH 5.5, 6.5 and 7.5. Figure 5 shows the effect of HPMC concentration on dynamic swelling of these hydrogels.

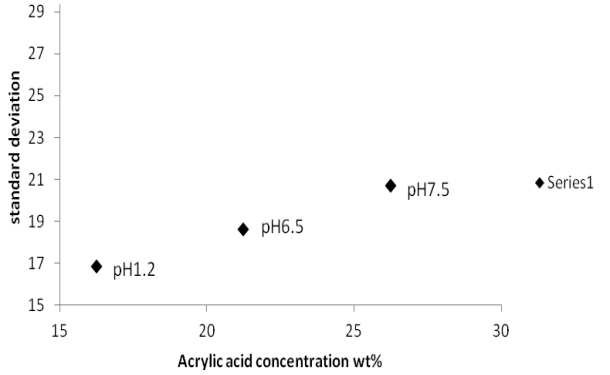

Fig. (4a): Study of standard deviation on isosorbide mononitrate release after 12 hours from AA/HPMC hydrogel with vary concentration of acrylic acid and 0.4% EGDMA as cross linking agent in solutions of pH 1.2, 6.5 and 7.5 at 37 °C

It was observed that by increasing the HPMC concentration swelling will be increased. It is due to the hydrophilicity and swellability nature of HPMC [38]. This behavior is due to the increase ratio and hydroxypropyl contents of HPMC. Because hydroxypropyl groups show more affinity to water molecules and lead to higher water solubility of the polymer. Effect of HPMC concentration on drug released was carried out at pH 1.2, 6.5 and 7.5 for 12 hrs. At pH 1.2 (acidic) drug released rate was extremely low as we increased the concentration of HPMC but at high pH 6.5 and 7.5 it was increased by increasing the concentration of HPMC [37]. Figure 6 showed the effect of HPMC concentration on drug release at different pH. It was observed that by increasing the contents of HPMC drug release rate was increased at high pH. This can be attributed to the high swellability nature of HPMC. In

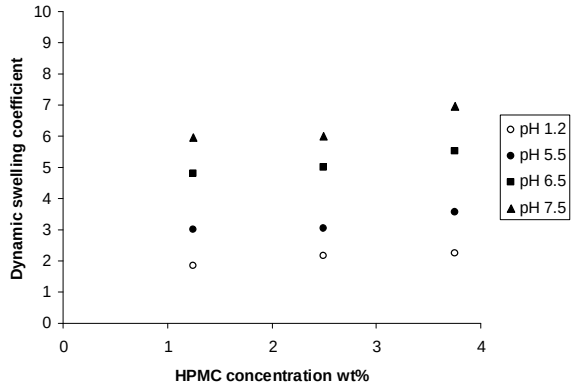

Fig.5: Dynamic swelling behavior after 8 hours of AA/HPMC hydrogel with different HPMC concentrations (1.25%, 2.5%, and 3.75%) keeping concentration of AA and EGDMA constant in solutions of various pH at 37°C.

terms of polymeric network, it is dominated by the physical entaglements between AA, drug and HPMC chains rather than electrostatic interactions [22]. Drug released from hydrophilic hydroxypropyl methylcellulose through polymer chain relaxation with volume expansion, and then the incorporated drug diffuses out of the system [15, 16].

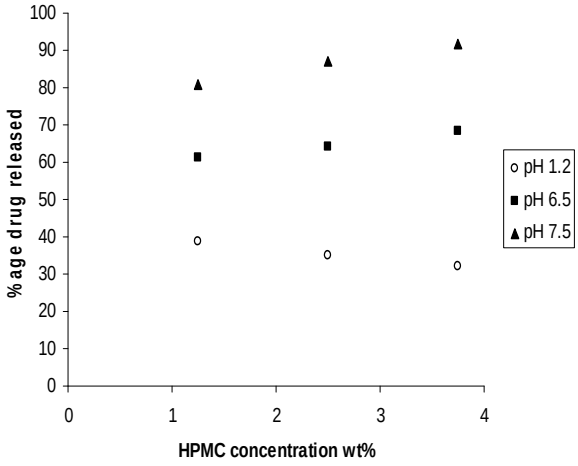

Fig. 6: Effect of hydroxypropyl methylcellulose concentration on isosorbide mononitrate release after 12 hours from AA/HPMC hydrogel with 0.4% EGDMA as cross linking agent in solutions of pH 1.2, 6.5 and 7.5 at 37°C

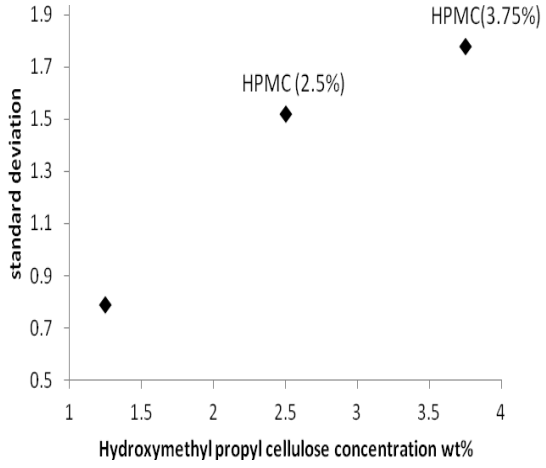

Fig. 5(a):Study of standard deviation on dynamic swelling behavior after 8 hours of AA/HPMC hydrogel with different HPMC concentrations (1.25%, 2.5%, and 3.75%) keeping concentration of AA and EGDMA constant in solutions of various pH at 37°C.

Effect of crosslinker (EGDMA) concentration on swelling of AA/HPMC hydrogels.

A series of AA/HPMC hydrogels of different crosslinking agent concentration (0.2%, 0.3% and 0.5% of AA) were prepared keeping AA and HPMC contents constant to investigate the effect of EGDMA on swelling behavior of hydrogels as shown in table 4. It was observed in figure 7 that swelling of gel decreased with increase of

EGDMA concentration due to presence of more physical entanglements between hydrogels. This provides elastic restrains forces to retarding the expanding of the network [40].

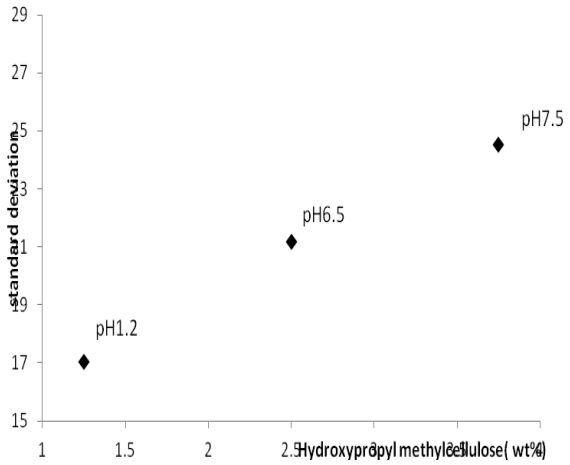

Fig. 6(a): Study of standard deviation on hydroxypropyl methylcellulose concentration on isosorbide mononitrate release after 12 hours from AA/HPMC hydrogel with 0.4% EGDMA as cross linking agent in solutions of pH 1.2, 6.5 and 7.5 at 37°C

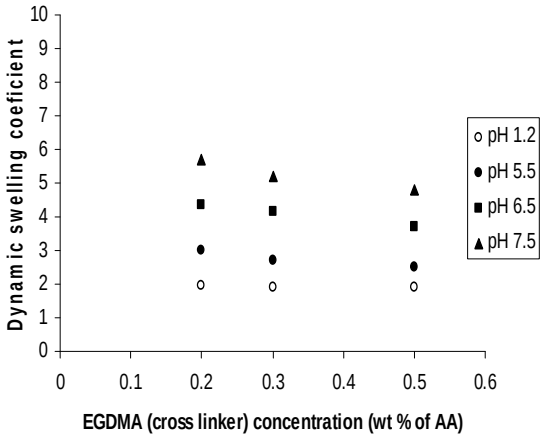

Fig. 7: Dynamic swelling behavior after 8 hours of AA/HPMC hydrogel with different EGDMA concentrations (0.2%, 0.3% and 0.5%) keeping concentration of AA and HPMC constant in solutions of various pH at 37°C.

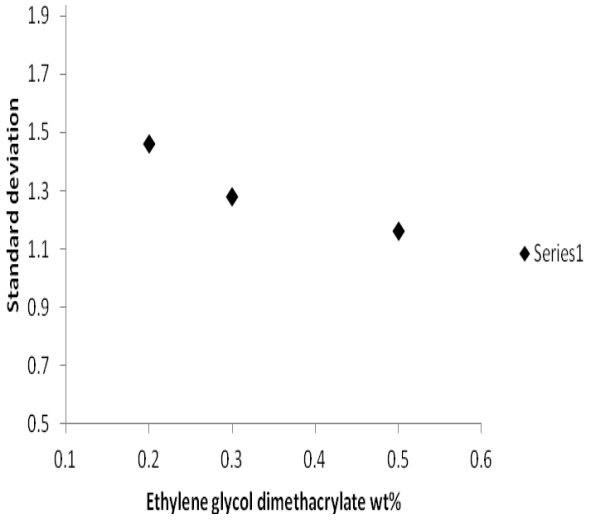

Fig. 7:study of standard deviation on dynamic swelling behavior after 8 hours of AA/HPMC hydrogel with different EGDMA concentrations (0.2%, 0.3% and 0.5%) keeping concentration of AA and HPMC constant in solutions of various pH at 37°C.

Diffusion coefficient of polymers (D)

Diffusion coefficient is indirectly measure of solute diffusion into hydrogel. Fick's law of diffusion was applied during membrane permeation method or sorption and desorption phenomenon. Table 5 showed that diffusion coefficient decreased with the increasing of AA and HPMC concentration because swelling of polymer increase as the concentration of AA and HPMC increase but increased by increasing the concentration of EGDMA due to decrease of swelling of polymer [41].

Molecular weight between crosslinks (Mc), volume fraction of polymer ($V_{2,s}$) and solvent interaction parameters (χ).

Results shown in table 5 that increased in values of molecular weight between crosslinks (Mc) were observed by increasing the concentration of AA and HPMC. Higher swelling of hydrogel was reported due to impart of carboxylic groups into polymer chain and hydrophilic nature of HPMC respectively. Crosslinked density (q) is also related to the values of Mc of AA and HPMC. Solvent interaction parameters (χ) were studied to check the effect of solvent interaction between polymer and solvent. It was reported that greater values (χ) weaker the values of interaction between polymer and solvent. Due to hydrophilic nature of HPMC, higher the concentration of HPMC gave lower values of (χ) [41].

Table 5: Flory-Huggins network parameters of AA/HPMC hydrogels

Sample code	$V_{2,s}$	χ	M_c	M_r	q(Mc/Mr)	D× 10^{-6} (cm^2/sec)
A_1	0.0565	0.5197	964.99	102.31	09.43	0.1904
A_2	0.0346	0.5118	2275.00	096.35	23.61	0.0953
A_3	0.0293	0.5099	3027.85	92.37	32.78	0.0415
B_1	0.0327	0.5111	2512.89	82.69	30.38	0.0564
B_2	0.0283	0.5096	3213.56	91.65	35.06	0.0529
B_3	0.0221	0.5075	4897.39	99.60	49.16	0.0352
C_1	0.0286	0.5097	3149.02	93.77	33.57	0.0659
C_2	0.0302	0.5103	2873.03	93.86	30.61	0.0805
C_3	0.0391	0.5134	1833.40	96.44	19.00	0.1071

$V_{2,s}$: volume fraction of polymer at equilibrium swelling in USP phosphate buffer solution, **χ:** solvent interaction parameter, **M_c**: average number molecular weight between crosslinks, **M_r:** molar mass of the repeating unit, **q**: number of links between two crosslinks, **D**: diffusion coefficient at pH 6.5

Sol-Gel fraction.

Figures 8 to 10 show the effects of acrylic acid, hydroxypropyl methylcellulose and crosslinking agent (EGDMA) concentration on the gel fraction of different formulations of AA/HPMC hydrogels. It was observed that by increasing the concentration of AA (A_1 to A_3) and EGDMA (C_1 to C_3) gel fraction increases while sol fraction decreases and by increasing the concentration of HPMC (B_1 toB_3) gel fraction decreases while sol fraction increases [42]. Hossam M et al [43] synthesized novel gels of CMC and AA and showed that gel fraction increases by increasing AA. As the concentration of crosslinking agent increases, there will be more crosslinking so gel fraction will increase. Sol-gel fraction values were given in table 6.

Porosity.

Table 6 shows the porosity of different formulations of AA/HPMC hydrogels. From figures 11 to 13, it was observed that by increasing AA and HPMC concentrations porosity also increases. It can be explained as by increasing the concentration of polymer and monomer viscosity of solution increased, which prevented the bubbles from escaping from solution thus forming interconnected channels thus porosity increased. By increasing the concentration of EGDMA (C_1 to C_3) porosity was decreased. As molecular entanglements between AA and HPMC increased by increasing crosslinking density, so there was decrease in mesh size of hydrogel and less pore formation which resulted in decreased porosity.

Table 6: Porosity and Gel fraction of AA/HPMC hydrogels

Sample code	Porosity (%)	Gel fraction (%)
A_1	56.98	89.97
A_2	64.26	90.67
A_3	74.58	92.70
B_1	56.74	92.08
B_2	63.33	90.92
B_3	66.14	88.60
C_1	82.39	90.84
C_2	65.62	91.06
C_3	46.37	92.66

Table 7: Effect of acrylic acid concentration on release kinetics of AA/HPMC hydrogel using EGDMA as crosslinking agent (0.4 wt% of AA)

Sample code	Acrylic acid content (%)	pH	Zero order kinetics		First order kinetics		Higuchi Model	
			K_o (h^{-1})	r	K_1 (h^{-1})	r	K_2 (h^{-1})	r
A_1	16.25	1.2	2.165	0.993	0.026	0.997	0.0918	0.980
		6.5	4.117	0.979	0.060	0.996	0.1771	0.995
		7.5	4.887	0.978	0.088	0.994	0.2103	0.995
A_2	21.25	1.2	2.251	0.993	0.027	0.997	0.0955	0.982
		6.5	4.312	0.986	0.066	0.996	0.1843	0.988
		7.5	5.333	0.986	0.104	0.989	0.2282	0.992
A_3	26.25	1.2	2.368	0.993	0.029	0.997	0.1005	0.983
		6.5	4.744	0.987	0.075	0.996	0.2021	0.983
		7.5	5.857	0.982	0.128	0.982	0.2514	0.994

Table 8: Effect of acrylic acid concentration on release mechanism of AA/HPMC hydrogel using EGDMA as crosslinking agent (0.4 wt% of AA)

Sample code	Acrylic acid content (%)	pH	Release exponent (n)	r	Order of release
A_1	16.25	1.2	0.6352	0.9746	Non-fickian
		6.5	0.7132	0.9945	Non-fickian
		7.5	0.5810	0.9971	Non-fickian
A_2	21.25	1.2	0.6292	0.9778	Non-fickian
		6.5	0.6478	0.9834	Non-fickian
		7.5	0.5708	0.9916	Non-fickian
A_3	26.25	1.2	0.6360	0.9805	Non-fickian
		6.5	0.6726	0.9721	Non-fickian
		7.5	0.5867	0.9941	Non-fickian

Drug release mechanism

The drug release is closely related to the swelling characteristic of the hydrogels, which in turn, is a key parameter of chemical architecture of the hydrogels. The method that best fits the release data was evaluated by the regression coefficient (r). Criteria for selecting the most appropriate model was based on the ideal fit indicated by the values of regression coefficient (r) near to 1. Values of regression coefficient (r) for zero order and first order obtained from drug loaded AA/HPMC hydrogels at varying contents of AA and HPMC are given in the table 7 and 9. For most of samples, the value of regression co-efficient (r) obtained for first order release rate constants were found higher than those of zero order. It is therefore attributed to the fact that drug release from the samples of varying

monomeric and polymeric compositions are according to first order release. In Higuchi model the value of regression coefficient (r) at different monomeric and polymeric composition indicated that the drug release mechanism is diffusion controlled. As for diffusion controlled system, the plot of drug released versus the square root of time is linear, which indicates diffusion controlled system. Effects of acrylic acid and HPMC on release exponent "n" values are given in table 8 and 10 respectively. The value of 'n' for the release of isosorbide mononitrate at different pH has been evaluated from the slope and intercept of the plot ln M_t/M_∞ versus lnt and the results presented that the values of 'n' are between 0.5 and 1.0 which indicates a non-Fickian or anomalous diffusion mechanism. It also clarifies that the rate of polymer chain relaxation and the rate of drug diffusion from these hydrogels are comparable.

Table 9: Effect of polymer (HPMC) concentration on release kinetics of AA/HPMC hydrogels using EGDMA as crosslinking agent (0.4 wt% of AA)

Sample code	HPMC content (%)	pH	Zero order kinetics		First order kinetics		Higuchi Model	
			K_0 (h^{-1})	r	K_1 (h^{-1})	r	K_2 (h^{-1})	r
B_1	1.25	1.2	2.7787	0.9918	0.0363	0.9977	0.1182	0.9859
		6.5	4.6199	0.9933	0.0732	0.9949	0.1961	0.9826
		7.5	5.8245	0.9860	0.1228	0.9828	0.2493	0.9924
B_2	2.5	1.2	2.4857	0.9927	0.0315	0.9976	0.1056	0.9840
		6.5	4.6199	0.9933	0.0768	0.9942	0.1961	0.9826
		7.5	6.2603	0.9908	0.1499	0.9634	0.2667	0.9876
B_3	3.75	1.2	2.2514	0.9935	0.0279	0.9976	0.0955	0.9821
		6.5	5.2187	0.9875	0.0926	0.9952	0.2220	0.9818
		7.5	6.4947	0.9905	0.1784	0.9404	0.2768	0.9880

Table 10: Effect of polymer (HPMC) concentration on release mechanism of AA/HPMC hydrogels using EGDMA as crosslinking agent (0.4 wt% of AA)

Sample code	HPMC content (%)	pH	Release exponent (n)	r	Order of release
B_1	1.25	1.2	0.5724	0.9805	Non-fickian
		6.5	0.6624	0.9816	Non-fickian
		7.5	0.6101	0.9942	Non-fickian
B_2	2.5	1.2	0.5562	0.9752	Non-fickian
		6.5	0.5831	0.9747	Non-fickian
		7.5	0.5903	0.9852	Non-fickian
B_3	3.75	1.2	0.5414	0.9694	Non-fickian
		6.5	0.6128	0.9668	Non-fickian
		7.5	0.5669	0.9841	Non-fickian

Fourier transform infrared spectroscopy

Figure 14 shows the FTIR spectra of pure HPMC (A), AA/HPMC hydrogel (B) and AA/HPMC hydrogel loaded with isosorbide mononitrate (C). From the spectra of pure HPMC (A), it shows the strong absorption band at 3421.48 cm^{-1} due to the stretching frequency of the OH group. The band at 2918.10 cm^{-1} is the result of C–H stretching vibration. The bands around 1456.16 and 1377 cm^{-1} are assigned to –CH2 scissoring and –OH bending vibration, respectively. The band at 1063.57 cm^{-1} is due to C–O stretching vibration [47]. In the spectra of AA/HPMC hydrogels, the absorption peak at 1699 cm^{-1} indicating intermolecular hydrogen bond formed between AA and HPMC at the expense of partial detachment of intramolecular hydrogen bond among the carboxylic groups of AA. The peak at 1708 cm^{-1} was assigned to the associated carboxylic acid groups of AA [44], suggesting that most of the carboxylic acid groups were associated with intramolecular hydrogen bonding. Changes in the hydroxyl stretching region were also observed. For pure HPMC, the absorption band of hydroxyl group at 3421.48 cm^{-1} shifts to 3325 cm^{-1} in AA/HPMC hydrogels. Two peaks at 3446 and 2921 cm^{-1} can be observed. These two peaks are attributable to the free hydroxyl groups in AA and the hydroxyl groups suffering from hydrogen bonds, respectively [45]. In AA/HPMC hydrogels, the intensity of the band at 2921 cm^{-1} decreases significantly, and the band at 3446 cm^{-1} shifts to a lower wave number (3325 cm^{-1}). The intensity decrease in the band at 2921 cm^{-1} is caused by the hydrogen bonding between HPMC and AA. From the spectra of AA/HPMC hydrogel loaded with isosorbide mononitrate (C), it shows the organic nitrate peaks at 860 cm^{-1} (NO symmetric stretch), 1280 cm^{-1} (NO_2 symmetric stretch) and 1635 cm^{-1} (NO_2 asymmetric stretch). Similar results showed in reference [46].

CONCLUSION

In the present work, series of crosslinked acrylic acid/hydroxypropyl methylcellulose (AA/HPMC) hydrogels have been developed by free radical polymerization in the presence of ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent and benzyl peroxide as initiator. Swelling of polymeric network was affected by composition and pH of the swelling medium. It was observed that swelling of hydrogel increased by increasing the concentration of AA and HPMC and decreased with the increased concentration of EGDMA. As pH of medium increased, swelling coefficient was increased. Swelling coefficient of AA and HPMC was decreased at lower pH. Porosity and solgel analysis were investigated and it was reported that porosity and gel fraction was increased by increasing the concentration of AA but gel fraction decreased by increasing the concentration of HPMC. It was examined that release of isosorbide mononitrate increased with increase of AA and decreased with increase in concentration of EGDMA. At low pH, drug release rate was decreased by increasing the concentration of HPMC but increased at high pH. Swelling characterization of AA/HPMC hydrogel was studied by measuring diffusion coefficient, volume fraction of polymer, solvent interaction parameters, molecular weight between crosslinks and crosslinked density. AA/HPMC hydrogel was characterized by FTIR to study the network structure of hydrogel. Mostly drug loaded AA/HPMC hydrogels followed first order kinetics. Drug release mechanism was non-fickian. The result confirms that AA/HPMC hydrogels can be effectively used in pH sensitive controlled released vehicle for drug delivery due to rate controlling and swellability nature of hydrophilic HPMC.

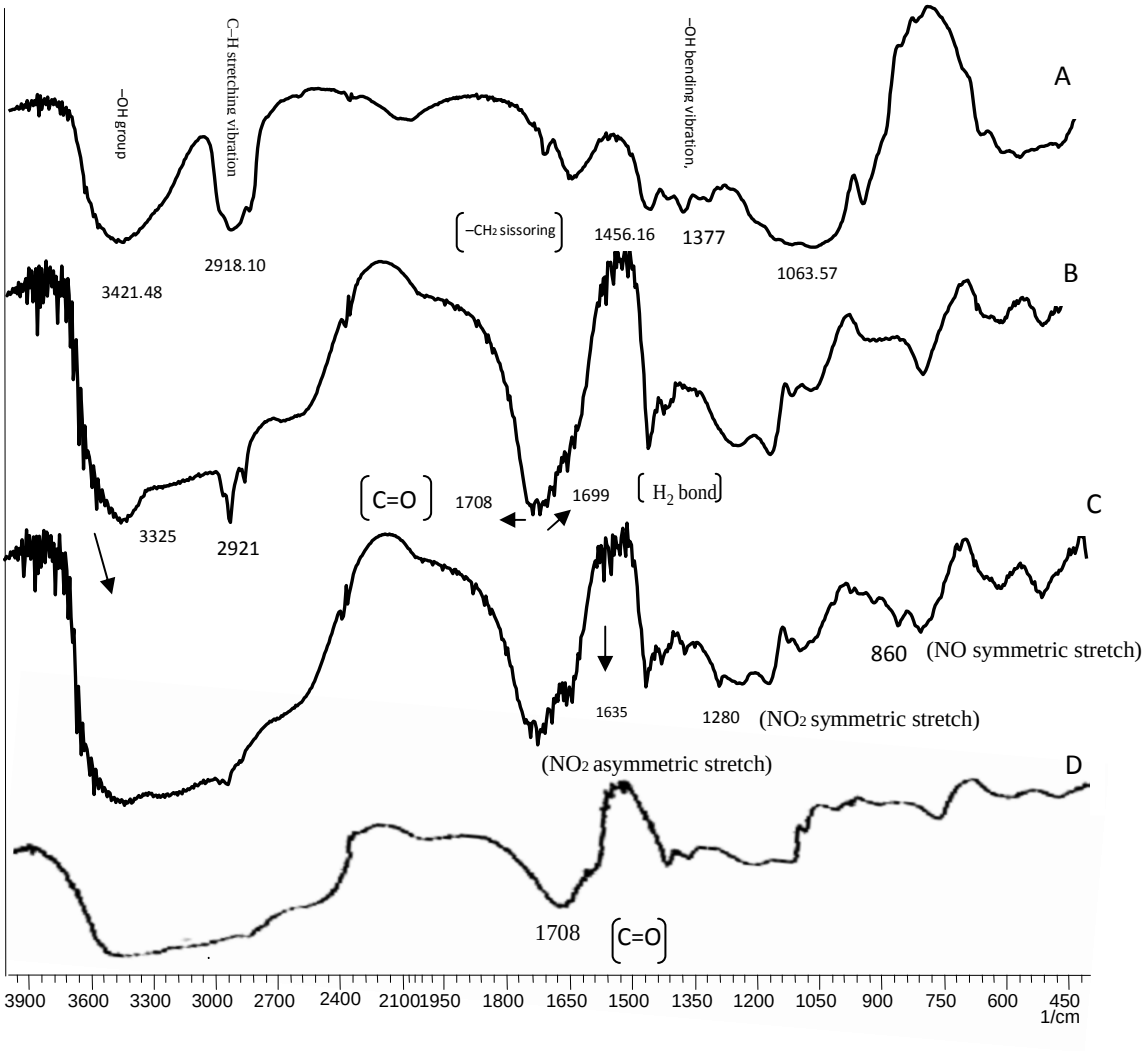

Fig.14: FTIR spectrums of pure HPMC (A): AA/HPMC hydrogel (B): AA/HPMC hydrogel loaded with isosorbide mononitrate (C): acrylic acid (D)

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