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# SYNTHESIS AND *IN VITRO* CHARACTERIZATION OF HYDROXYPROPYL METHYLCELLULOSE- GRAFT-POLY(ACRYLIC ACID/2-ACRYLAMIDO-2-METHYL-1-PROPANESULFONIC ACID) POLYMERIC NETWORK FOR CONTROLLED RELEASE OF CAPTOPRIL

FURQAN MUHAMMAD IQBAL, MAHMOOD AHMAD* and AYSHA RASHID

Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, 63100, Punjab, Pakistan

**Abstract:** A super-absorbent hydrogel was developed by crosslinking of 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) and acrylic acid with hydroxypropyl methylcellulose (HPMC) for controlled release drug delivery of captopril, a well known antihypertensive drug. Acrylic acid and AMPS were polymerized and crosslinked with HPMC by free radical polymerization, a widely used chemical crosslinking method. N,N'-methylenebisacrylamide (MBA) and potassium persulfate (KPS) were added as cross-linker and initiator, respectively. The hydrogel formulation was loaded with captopril (as model drug). The concentration of captopril was monitored at 205 nm using UV spectrophotometer. Equilibrium swelling ratio was determined at pH 2, 4.5 and 7.4 to evaluate the pH responsiveness of the formed hydrogel. The super-absorbent hydrogels were evaluated by FTIR, SEM, XRD, and thermal analysis (DSC and TGA). The formation of new copolymeric network was determined by FTIR, XRD, TGA and DSC analysis. The hydrogel formulations with acrylic acid and AMPS ratio of 4 : 1 and lower amounts of crosslinker had shown maximum swelling. Moreover, higher release rate of captopril was observed at pH 7.4 than at pH 2, because of more swelling capacity of copolymer with increasing pH of the aqueous medium. The present research work confirms the development of a stable hydrogel comprising of HPMC with acrylic acid and AMPS. The prepared hydrogels exhibited pH sensitive behavior. This superabsorbent composite prepared could be a successful drug carrier for treating hypertension.

**Keywords**: composite, superabsorbent, polymerization, acrylic acid, 2-acrylamido-2-methyl-1-propanesulfonic acid, hydroxypropyl methylcellulose, initiator, cross linker, hydrogel

Drug delivery systems have been known for enhancing therapeutic efficacy, minimizing side effects, and improving patient compliance. Among drug delivery systems, hydrogels have attracted the interest of biomaterial scientists due to their hydrophilic character and biocompatibility (1). Due to their softness and pliable nature, they have tendency to absorb higher amounts of water and physiological solutions, these absorbed aqueous solutions are capable of retaining water even if subjected to pressure. They have numerous applications as drug carriers, water-absorbents and food additives (2).

Superabsorbent hydrogels have an ability to absorb water from 10% to thousands times of their dry weight (3). Due to special characteristics, these materials have gained attention in the fields of: agriculture, waste water treatment (4-6), pharmaceuticals and biomedical (7, 8) and biotechnology (9, 10). Polysaccharide based hydrogels are currently attracting much interest for their unique properties, which are their better biocompatibility, biodegradability, renewability, and nontoxicity. Various polysaccharides, such as starch (11), chitosan (12), carrageenan (13), alginate (14), cellulose and cellulose derivatives (15-17) have been used for superabsorbent hydrogel formulation.

In this work, a super-absorbent hydrogel was synthesized by copolymerization of two monomers (acrylic acid and AMPS) and their crosslinking with HPMC using potassium persulfate to initiate the reaction and MBA as crosslinking agent. Hydroxypropyl methylcellulose (HPMC), the cellulose derivative, is a semisynthetic, inert and viscoelastic polymer found in a variety of commercial products. Depending on the grade, HPMC is widely utilized in oral solid dosage forms (tablets and capsules) as well as an ophthalmic lubricant (18, 19). HPMC comprises of repeated units of glucose, linked with

* Corresponding author: e-mail: ma786_786@yahoo.com; phone: 00923009682258

one another by 1,4-glycosidic bonds, while the polymer chains are attached together by hydrogen bonding (20).

Acrylic acid (AA) has been extensively used as monomer in hydrogel synthesis due to relatively economical advantage, crosslinking ability as well as rapid polymerization by various formulation techniques. It possesses a pH and electrically responsive behavior due to ionic repulsion between anionic charged carboxylate groups. It polymerizes to polyacrylic acid (PAA) - an established vehicle in controlled release drug delivery (21, 22).

2-Acrylamido-2-methyl-1-propanesulfonic acid (AMPS) has attracted an attention in hydrogel formation due to the presence of sulfonate groups. Strongly ionizable sulfonate groups increase the hydrophilicity and ultimately swelling capability of hydrogels. The polymeric network comprising of AMPS have ability to swell at all pH ranges, therefore it does not impart a pH-sensitive behavior to its hydrogel formulation. As stated in the literature, it swells rapidly in acidic medium and relatively slower at pH higher than 5. AMPS contains both nonionic and anionic groups; whereas AA is an anionic monomer (23). Due to these characteristics, acrylic acid was combined with AMPS, to release the drug loaded in a controlled manner. The hydrogels prepared were observed for their swelling behavior at different pH (2, 4.5 and 7.4). They were loaded with captopril and its release was studied by dissolution process at pH 2 and 7.4. Moreover, FTIR, SEM, XRD, DSC and TGA analyses were performed for *in vitro* characterization of superabsorbent composite.

## MATERIALS AND METHODS

### Chemicals

Hydroxypropyl methylcellulose (2600-5600 cps) and acrylic acid were from Sigma Aldrich, Netherlands. AMPS, (99%, Aldrich, product of Germany) N,N-methylene-bis-acrylamide (98%, Fluka, Switzerland), potassium persulfate (Analar, BDH, England) and potassium dihydrogen phosphate (Merck, Germany) were purchased through local commercial sources. Distilled water from laboratory and solvents of analytical grades were used.

### Preparation of hydrogel

The hydrogel was prepared by free radical polymerization, where the polymer (HPMC) in varying quantities was added in distilled water and stirred at 80$^{o}$C for 1 h. Then, the HPMC solution was subjected to nitrogen purging for about 30 min and potassium persulfate (0.5% w/w) was added to initiate the reaction by generating free radicals. After that, the reactants were cooled down to 30$^{o}$C and MBA as cross-linking agent dissolved in acrylic acid (AA) was added under magnetic stirring. Then, AMPS previously dissolved in small quantity of water was added to above mixture and final volume was adjusted by addition of deionized distilled water. After that, the above mixture was poured in test tubes and heated in water bath at 50, 55, 65 and 75$^{o}$C for 30 min, 1, 2 and 3 h, respectively. Then, the glass tubes were cooled to 25$^{o}$C and hydrogels were taken out and cut in the form of discs of nearly 8 mm long diameter. They were then thoroughly treated with ethanol and distilled water mixture (50 : 50, v/v) for removing catalysts and uncross-linked monomer, till the pH of solutions after washing became nearly the same as before being used. After washing process, the hydrogel discs were air dried for overnight and then transferred to oven at 45$^{o}$C for 4 to 5 days until they attained a constant weight.

### *In vitro* evaluation

#### Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectrophotometer (Bruker, Tensor 27) was used to record the spectra of hydrogel, HPMC, acrylic acid and AMPS. The hydrogel samples were ground by the help of cutter as well as pestle and mortar. The components and crushed hydrogel samples were then analyzed in wavelength range from 4000 to 500 cm$^{-1}$.

#### Scanning electron microscopy (SEM)

SEM images were taken to investigate the surface morphology of super-absorbent hydrogels using a scanning electron microscope (Quanta 250, FEI). Both drug free formulations and drug loaded samples were ground and scanned at different magnifications to observe the microscopic surface of dried hydrogels. It was done to assess the capability to adsorb and entrap the drug into their polymeric network.

#### X-ray diffraction (XRD)

X-ray diffraction analysis determines the crystalline and amorphous properties of the substances. It investigates the interaction of components or polymers and drug. Xpert Pro diffractometer (Panalytical) was used to record x-ray diffraction. The XRD patterns of pure drug and drug loaded formulations were measured at room temperature by scanning at angle 5-50$^{o}$ (2θ), at scanning speed of 20/min.

**Thermal analysis**

Thermal analysis was recorded by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) using Q5000 series (TA instruments) and Q2000 series (TA instruments), respectively. The hydrogel samples were crushed into powder form using pestle and mortar and passed through a mesh no. 50.

***TGA***

For measuring TGA, 1-4 mg of ground sample was placed in platinum pan connected to microbalance and heated till 500°C at a rate of 20°C/min in nitrogen atmosphere.

***DSC***

To record DSC, hydrogel samples (1 to 3 mg) along with HPMC, AMPS and acrylic acid were placed in aluminum pan crimped with an aluminum lid and heated from 0 to 500°C at the same rate as used for TGA.

**Swelling study**

The swelling of hydrogels was measured at different pH (2, 4.5 and 7.4) at room temperature. Dried discs of hydrogels were accurately weighed and immersed in swelling medium i.e., 0.1 M USP phosphate buffer solution. Hydrogel discs were weighed at regular intervals of time and before

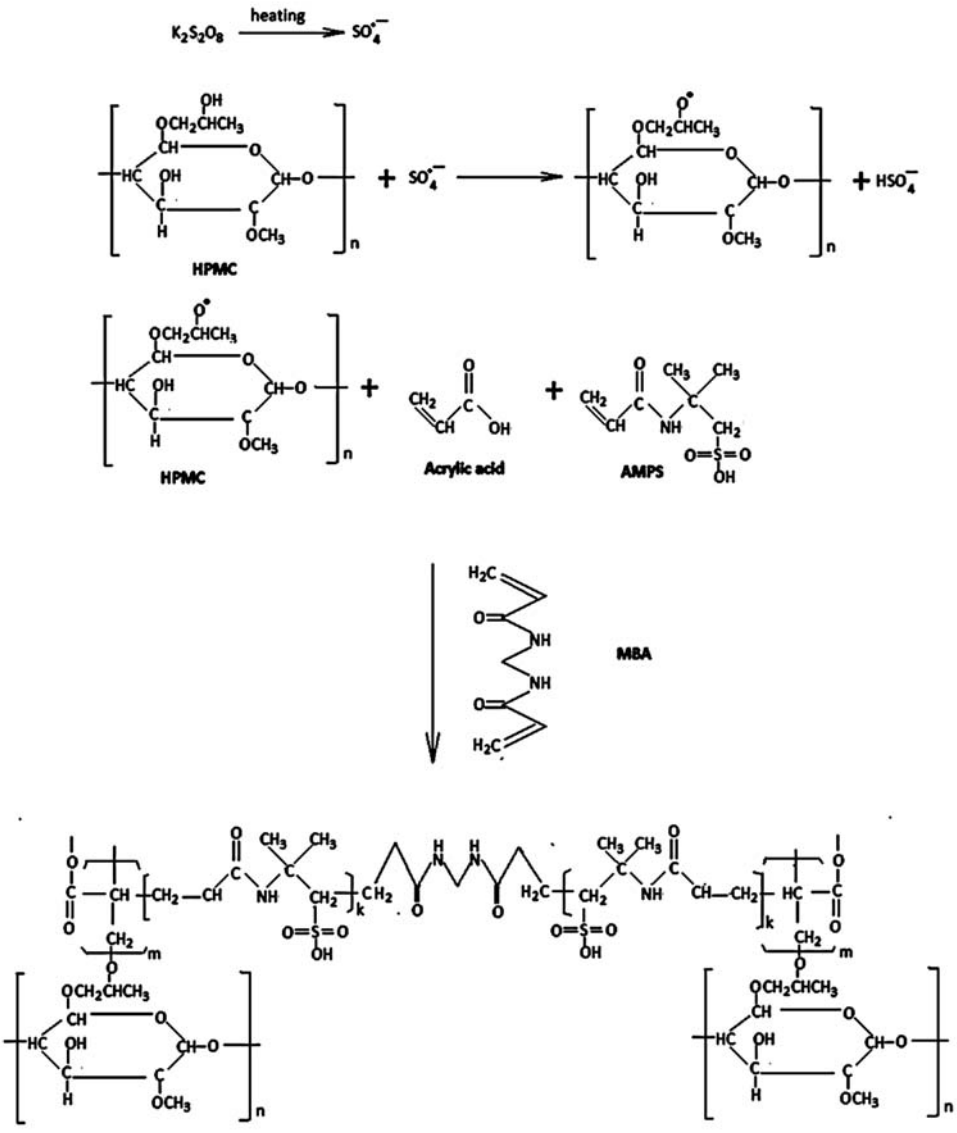



Figure 1. Crosslinked HPMC-g-poly(AA-co-AMPS) hydrogels

weighing they were placed on filter paper to remove excess of solution from the surface. The hydrogels were weighed for a period until they attain equilibrium. The swelling ratio was calculated as:

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

where, $W_s$ is the weight achieved after swelling and $W_d$ denotes the weight of dry hydrogel discs. The percentage equilibrium swelling was determined by equation:

$$\%ES = \frac{W_{eq} - W_d}{W_{eq}} \quad (2)$$

where, $W_{eq}$ is the equilibrium weight and $W_d$ is the initial weight of hydrogels before swelling study.

**Drug loading**

Hydrogels were loaded with drug (captopril) using absorption method by immersing the dry discs of hydrogels in 100 mL of captopril solution (1% w/v) comprising of phosphate buffer solution and methanol (50 : 50, v/v). The hydrogels were swollen till they achieved equilibrium, then taken out and dried in oven at 40°C to their constant weights. The amount of drug loaded in hydrogels was measured by extracting them with the methanol/phosphate buffer solution in the same ratio used for drug loading. The extraction was done repeatedly at regular intervals and each time with freshly prepared solution until no drug remained in the extracting solution. All samples of drug solutions used during extraction procedure were analyzed for drug contents. The calibration curve of captopril was drawn by preparing its various dilutions to determine the drug concentration spectrometrically at $\lambda_{max}$ of 205 nm.

**Drug release**

Drug release measurement was carried out by dissolution process using 0.1 M USP phosphate buffer solutions of lower and higher pH values (pH

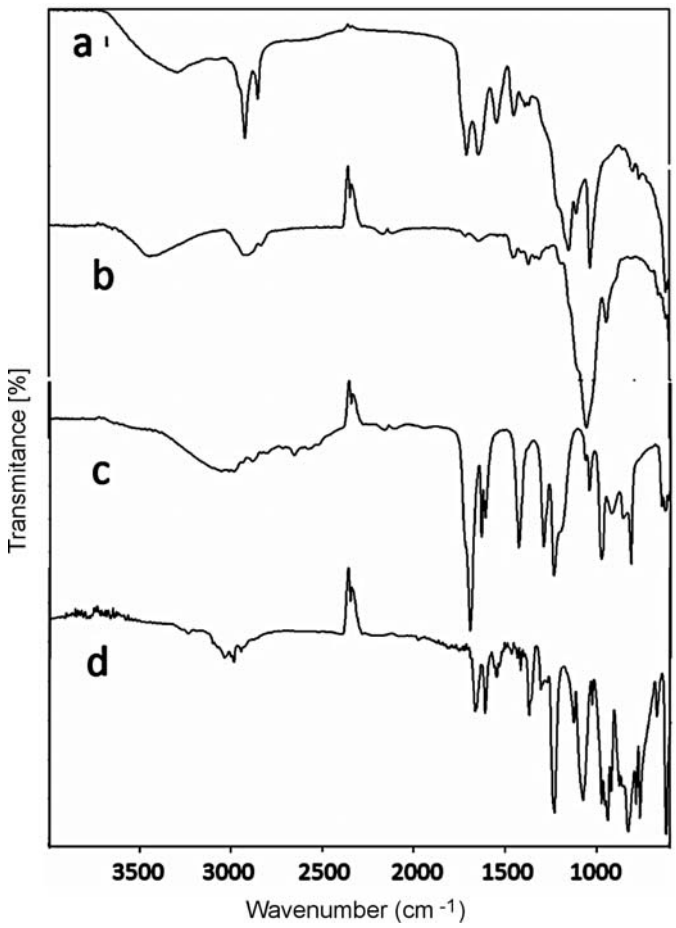



Figure 2. FT-IR spectra of HPMC-g-poly(AA-co-AMPS) (a), HPMC (b), acrylic acid (c) and AMPS (d)

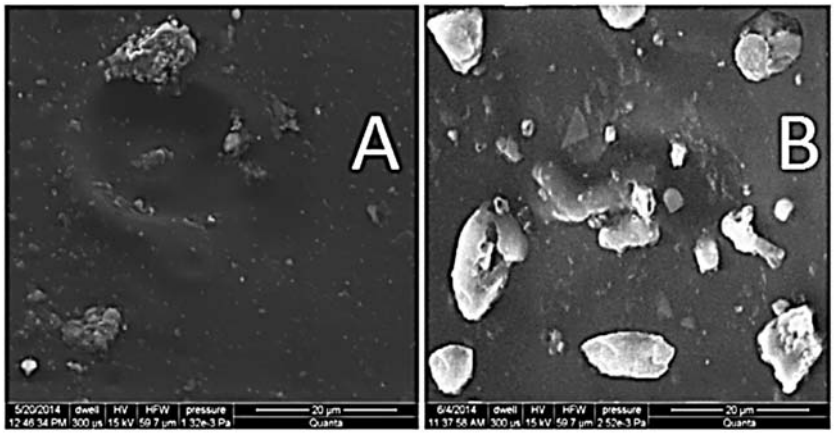



Figure 3. SEM images of HPMC-g-poly(AA-co-AMPS) hydrogels, without drug (A) and loaded with drug (B)

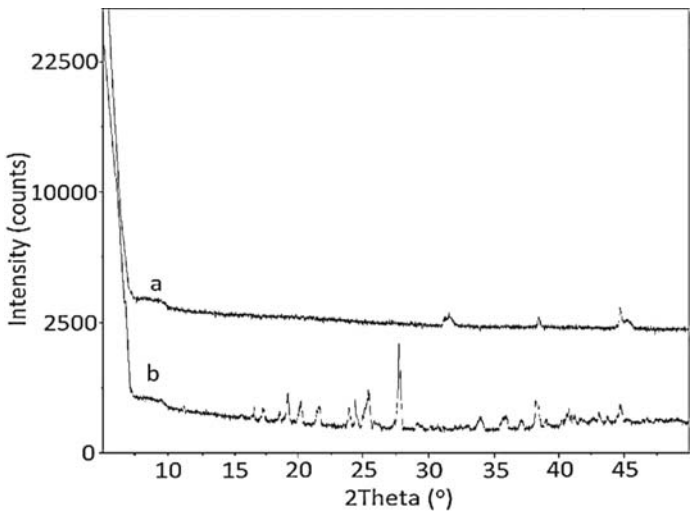



Figure 4. XRD patterns of captopril (a) and HPMC-g-poly(AA-co-AMPS) hydrogels (b)

2 and 7.4). The dried hydrogel discs loaded with captopril were placed in 500 mL buffer solution (dissolution medium) maintained at 37°C and agitated by a paddle stirrer at a speed of 50 rpm. Then, the samples were taken at specific time intervals and drug released was measured by UV spectrophotometer at $\lambda_{max}$ of 205 nm.

**Drug release kinetics**

Various drug release models were used to determine the mechanism of drug release as given below:

***Zero order kinetic model***

It relates the drug delivery systems, where the rate of drug release does not exhibit concentration dependency. It is represented as:

$$M_0 - M_t = Kt \quad (3)$$

where, $M_0$ is the initial quantity of drug, $M_t$ is the fraction of drug released at time $t$ and $K$ is the proportionality constant.

***First order kinetic model***

The first order kinetics describes the concentration dependent release of drug and is represented by the following equation:

$$Log\ M_0 - Log\ M_t = K_1\ t/2.303 \quad (4)$$

where, $M_0$ is the initial amount of drug, $M_t$ is the drug concentration released at time t and $K_1$ is the release constant.

***Higuchi model***

Higuchi model can be presented by a simplified equation as:

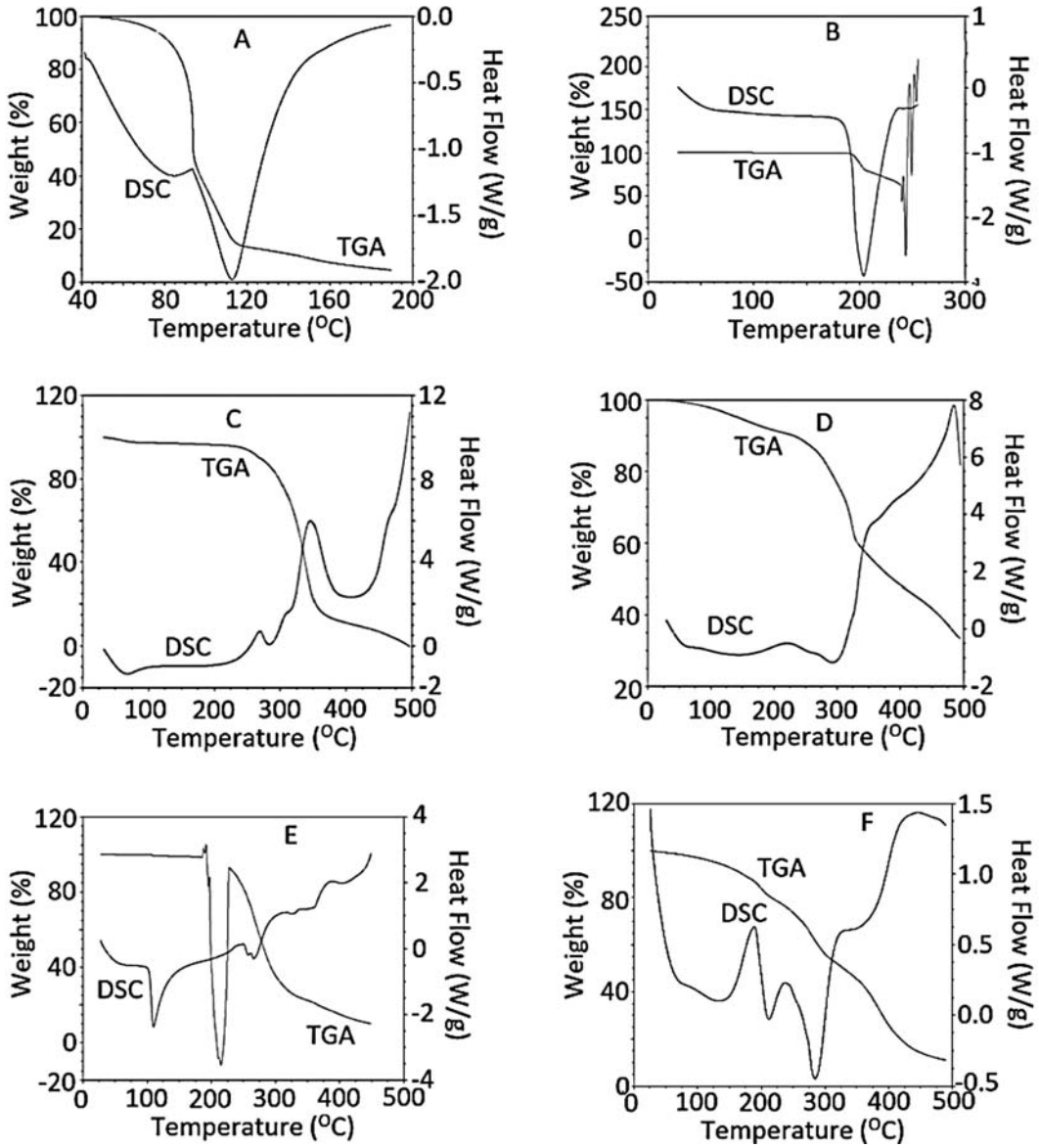



Figure 5. DSC and TGA thermograms of acrylic acid AA (A), AMPS (B), HPMC (C), drug free hydrogel (D), captopril (E) and drug loaded hydrogel (F)

$$Q = K_H\, t^{1/2} \quad (5)$$

where, Q represents the fraction of drug released at time $t$ and $K_H$ is the Higuchi constant.

***Weibull model***

The dissolution and release process was described by an equation expressing the fraction of drug accumulated 'M' in dissolution medium at time $t$ given as:

$$M = 1 - \exp[\frac{-(t - T_i)^b}{a}] \quad (6)$$

where, $a$ defines the dependency on time, $b$ denotes the shape parameter of dissolution curve and the other parameter "$T_i$" represents the lag time before dissolution process.

***Korsmeyer-Peppas model***

Korsemeyer-Peppas model is described by a simple empirical equation to describe the Fickian and non-Fickian drug release from polymeric drug carriers, given as following:

$$M_t/M_\infty = K\, t^n \quad (7)$$

where, "K" is the kinetic constant that incorporates the geometric and structural properties of the hydrogels and other drug carriers. $M_t/M_\infty$ represents the drug fraction released at time $t$ and $n$ is the release

exponent. When the value of n is 0.45, it indicates Fickian release order and for n = 1, represents case II transport mechanism. On the other hand, n value between 0.45 and 1 corresponds to non-Fickian diffusion.

## RESULTS AND DISCUSSION

### FT-IR spectroscopy

The structure and formation of cross-linkage among the polymers were investigated by spectra recorded using FT-IR spectroscopy. The spectrum of HPMC (b) shows an absorption band at 3444.60 $cm^{-1}$ assigned to stretching frequency of the hydroxyl (-OH) group. Another band at 1373.63 $cm^{-1}$ is due to bending vibration of -OH. Other stretching vibration bands related to C-H and C-O were observed at 2929 $cm^{-1}$ and 1055.52 $cm^{-1}$, respectively. The spectrum of HPMC-g-poly(AA-co-AMPS) suggests the formation of intermolecular hydrogen bonding due to carboxylic acid groups of acrylic acid as observed by the appearance of an absorption peak at 1710.75 $cm^{-1}$. In Figure 2, the hydrogel spectrum (a) indicates the shifting of -OH vibration band of HPMC from 3444.60 $cm^{-1}$ to 3292.58 $cm^{-1}$ due to formation of hydrogen bonds. Hence, it confirms the crosslinking of HPMC with acrylic acid involving the reaction of -OH (of HPMC) with -COOH (of acrylic acid). In addition, characteristic bands at 1547.30 $cm^{-1}$ (C=O stretching vibration of –CONH groups) and at

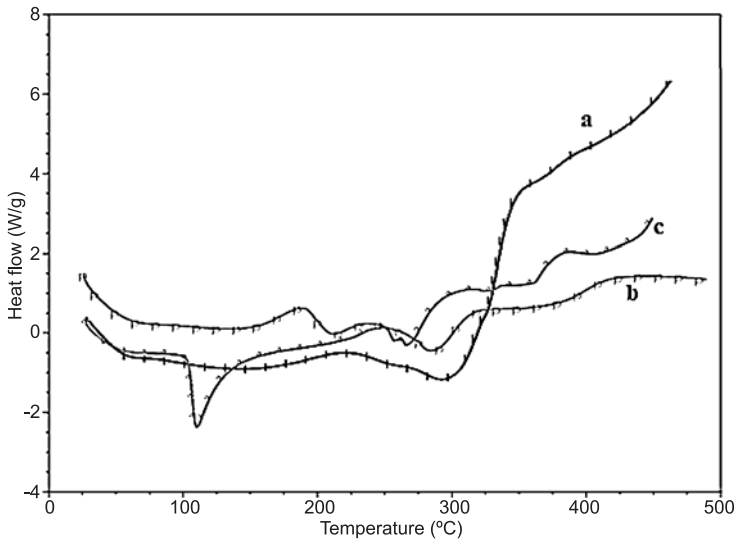



Figure 6. DSC thermograms of a) drug free and b) drug loaded and c) pure drug

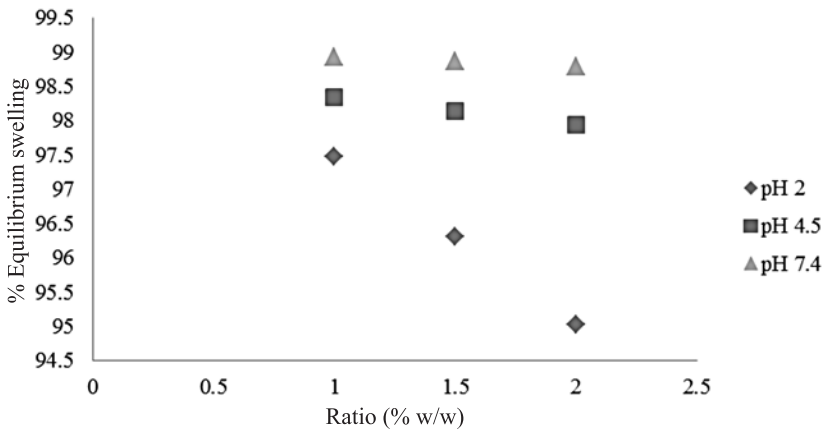



Figure 7. Percent equilibrium swelling (%ES) of formulations at different pH containing different concentrations of HPMC

1153.14 $cm^{-1}$ attributed to stretching vibration of sulfonate ($–SO_3H$) groups of AMPS monomer were observed. Consequently, it is concluded that the AA and AMPS monomers were successfully grafted onto the HPMC backbones.

**SEM**

In order to determine the microstructure and surface morphology of the hydrogel formulations, SEM images were taken. Scanning electron microscopy is one of the preferred methods to characterize the hydrogels in terms of porosity and water retention. The micrographs recorded, as shown in Figure 3 (A and B), show the surface of the drug free and drug loaded hydrogels.

As could be clearly seen from the SEM images in Figure 3, hydrogel surface was rough along with micro spaces for water retention and entrapment of solutes. Figure 3 (A) presents drug free hydrogel formulation with voids and spaces for accommodation of biological fluids as well as drug particles. They had tendency to exhibit remarkable swelling because of their water absorption capability.

Moreover, due to the presence of these voids and roughness of surface of hydrogels, the captopril was loaded into these regions as shown in Figure 3 (B). It was concluded from the prepared grafted polymeric network that HPMC-g-poly (AA-co-AMPS) had ability to act as suitable drug carrier for drug delivery.

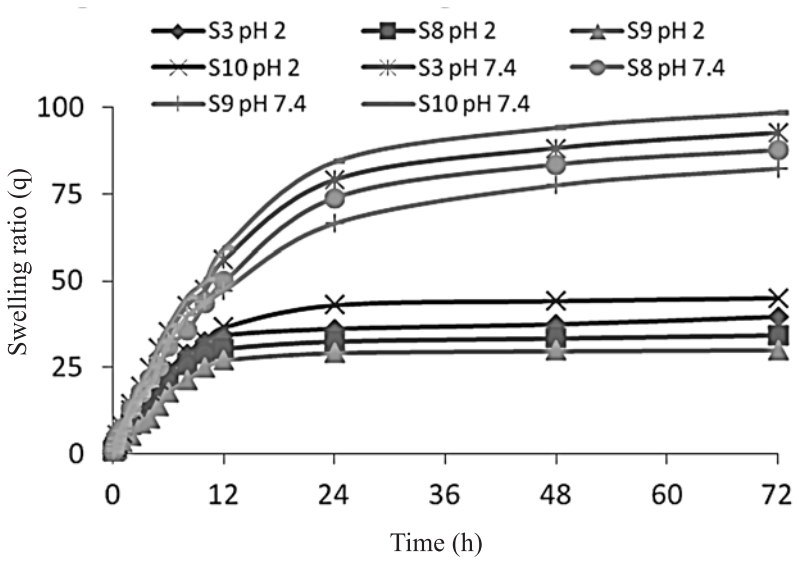



Figure 8a. Comparative swelling ratios of the hydrogels with different concentrations of crosslinking agent

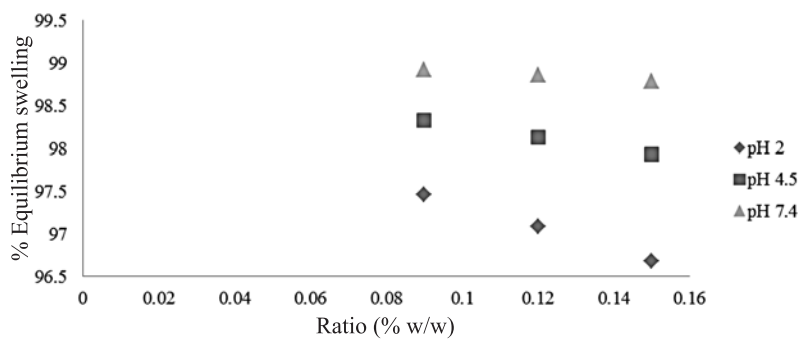
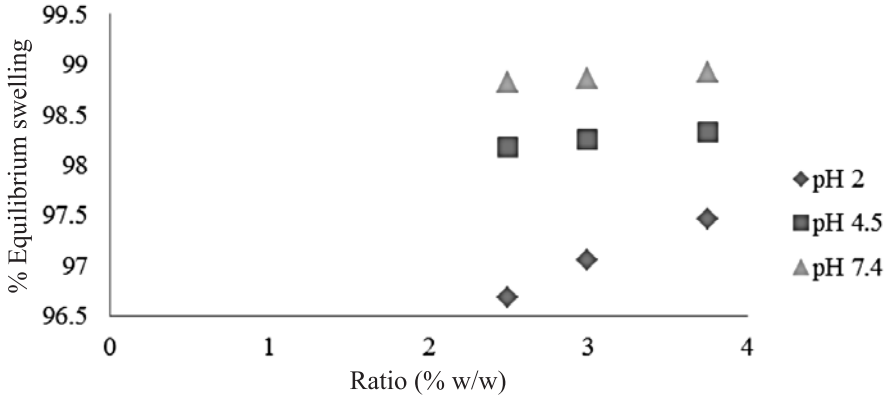
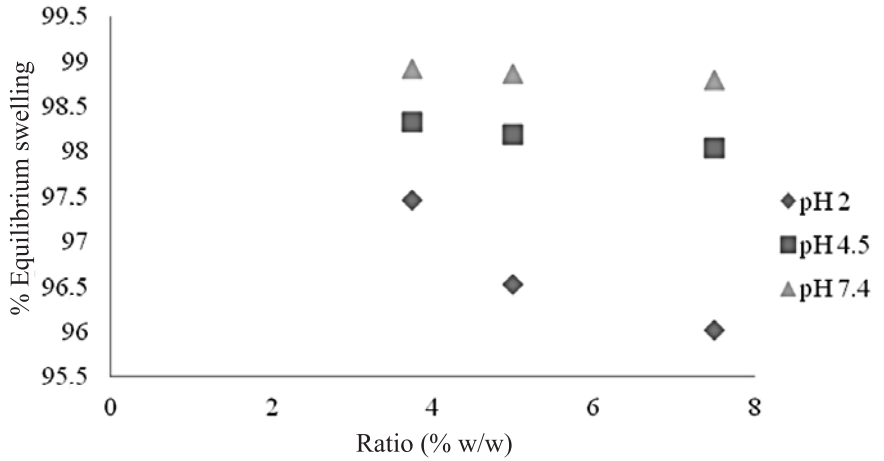



Figure 8b. Percent equilibrium swelling (%ES) of formulations at different pH containing different concentrations of MBA




(i) - Increase in percent equilibrium swelling with increase in AMPS concentration




(ii) - Decrease in percent equilibrium swelling with increase in AMPS concentration above 3.75 g (with AA/AMPS ratio 4 :1 )
Figure 9 (i and ii). Percent equilibrium swelling (%ES) of formulations at different pH containing different ratios of AA/AMPS

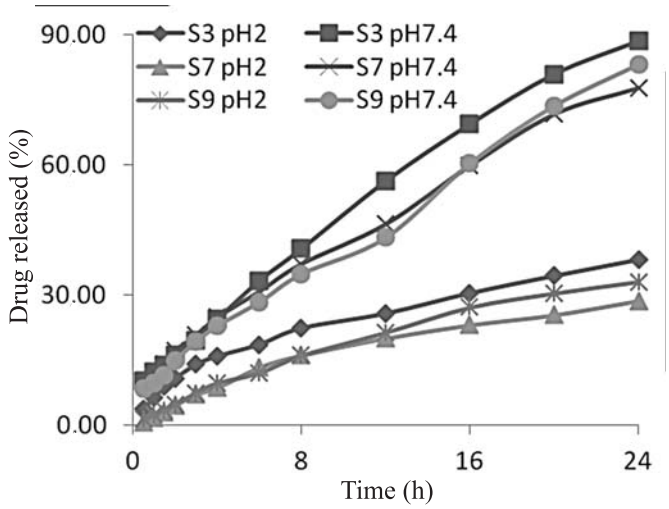



Figure 10. Captopril released up to 24 h from HPMC-g-poly(AA-co-AMPS) hydrogels (S3, S7, and S9) in dissolution media of pH 2 and pH 7.4

**XRD**

X-ray diffractograms of pure captopril and captopril loaded hydrogel formulation are presented in Figure 4. The diffraction patterns of hydrogels loaded with drug were compared with pure drug. The XRD scan of plain captopril had characteristic sharp and intense peaks between $0^o$ and $50^o$ ($2\theta$), which were appeared due to its crystalline nature as shown in Figure 4, diffraction pattern (a).

The appearance of a sharp peak at $2\theta = 27.79^o$ is the characteristic of captopril. The diffractogram of drug loaded hydrogel was not showing any notable sharp peak, which was due to amorphous characteristics of the formed polymeric network. Therefore, in comparison to pure captopril, the captopril loaded formulations had low intensity and dense peaks suggesting the amorphous distribution of drug into polymeric network, as it could be observed from Figure 4 diffractogram (b).

**Thermal analysis**

The grafting of HPMC-g-poly (AA-co-AMPS) polymeric network was also determined by thermogravimetric analysis (TGA). The pure acrylic acid decomposition starts at nearly $80^oC$ and complete mass loss was observed at $189.50^oC$ as shown in Figure 5, thermogram (A). Similarly, the degradation of other monomer AMPS had taken less time as can be seen in Figure 5, thermogram (B). The TGA thermogram (C) of HPMC shows decomposition at $265^oC$ which then continued till $350^oC$. During that period 78% of loss in weight was observed because of polymer degradation. In comparison to the individual components, thermogram of the grafted product (D) was recorded, where three stages of decomposition from 30 to $500^oC$ were observed. In the first stage of degradation, loss of weight started from $114^oC$ to $250^oC$, there was about 12% weight loss during this stage due to loss of absorbed and bound water. Then, the second stage of weight loss started at $250^oC$ and continued to $331.88^oC$, corresponding to 40% weight loss. Finally, the third stage beginning from $332^oC$ till $500^oC$ caused the degradation of hydrogel's structure. In case of HPMC, there was complete removal at $490^oC$, whereas the hydrogel had 67% weight loss and 33% still remaining at that temperature. A greater thermal stability of the formed polymeric network was observed as compared to its individual polymer and monomers (HPMC, acrylic acid and AMPS). Hence, the hydrogels prepared were more stable and resistant to higher temperatures.

The alterations in heat capacity as well as enthalpy changes are measured using differential scanning calorimetry (DSC). It is a well-known and established technique adopted for quantitative assessment of physicochemical variations in heat capacity of crystalline drugs, when loaded into hydrogels. The DSC endothermic peaks of pure HPMC, AA, AMPS and cross-linked polymeric network were in accordance with TGA thermal patterns. The thermal behavior of pure captopril drug loaded S3 hydrogel was characterized using DSC, as shown in Figure 5 (F).

The disappearance of characteristic peaks and appearance of other peaks suggests some sort of interaction of drug with polymers. In thermogram (E) of pure captopril, the appearance of sharp peak at $106^oC$ indicates its melting point. This peak of drug was not appeared in DSC thermogram of the drug loaded formulation, whereas two peaks were observed at $225^oC$ and $292^oC$. It could be clearly suggested that the drug loaded hydrogels showed an increase in the exothermic peak temperature (Fig. 6). The extra obvious peak of the drug ($106^oC$) was not observed in the drug loaded hydrogels. It suggests that captopril was molecularly dispersed in different hydrogel matrix without changing its thermal behavior.

**Swelling study**

Swelling ratios of the gels synthesized were measured gravimetrically at the pH 1.2, 4.5 and 7.4 in phosphate buffer. The swelling of hydrogels is dependent upon the presence of hydrophilic groups. Hydroxypropyl methylcellulose interact with water due to its –OH groups. The hydrogel swelling is enhanced by increasing the amount of AMPS. This high swelling property of AMPS is attributed to the presence of strongly ionizable sulfonate groups that create charge repulsion among the grafted chains. The sulfonate groups present have better hydrophilicity than carboxylate groups. The carboxylic groups associated with acrylic acid impart a pH responsiveness that prevents the abrupt swelling of copolymeric system due to AMPS. Increasing the pH of the buffer solution made ionization of carboxylic groups, which ultimately generates repulsive forces responsible for the swelling behavior of hydrogels containing acrylic acid.

***Effect of polymer concentration***

Hydrogels containing higher amount of polymer show less comparative swelling ratios As shown in Figure 7, the S3 formulation comprising lower amount of polymer swells more as compared to the S6 and S7 formulations. As the quantity of polymer increases in the hydrogels, the value of their swelling ratio decreases.

***Effect of crosslinking agent***

The graphic presentation of swelling ratios in Figure 8(a) and percent equilibrium swelling in Figure 8(b) elaborates the effect of different concentrations of MBA on swelling behavior. By increasing the amount of crosslinking agent there was decrement in swelling ratio. Increasing the crosslinker amount leads to increment of crosslinking density due to higher interaction among the components and ultimately reduces the porosity. Hence, the structure of hydrogels becomes dense having less spaces to accommodate aqueous solutions. On the other hand, the hydrogels comprising less amounts of MBA were able to swell more due to lower crosslinking density. The formulation S10 containing the lower quantity of crosslinker exhibited the highest swelling ratio among other formulations.

Various quantities of MBA, 0.09% w/w, 0.12% w/w and 0.15% w/w were added for S3, S8 and S9 formulations, respectively. Formulation S3 containing less amount of crosslinking agent exhibited higher percent equilibrium swelling (% ES) as shown in Figure 8 (b).

**Effect of AMPS concentration**

The result of varying the ratio of acrylic acid to AMPS was demonstrated in Figure 9 (i) and 9 (ii). Increasing the amount of AMPS in formulation had enhanced the swelling, which reached maximum as the mass ratio of AA to AMPS was 4 : 1. Further increase of AMPS content led to a decrement of

Table 1. Hydrogels formulations using different amounts of HPMC, AMPS and MBA.

| Formulation code | Polymer (HPMC) g/100g | Monomers, g/100g | | | Crosslinking agent, mol % of each monomer's concentration |
|---|---|---|---|---|---|
| | | AA | AMPS | AA/AMPS ratio | |
| S1 | 1 | 15 | 2.5 | 6 : 1 | 0.6 |
| S2 | 1 | 15 | 3 | 5 : 1 | 0.6 |
| S3 | 1 | 15 | 3.75 | 4 : 1 | 0.6 |
| S4 | 1 | 15 | 5 | 3 : 1 | 0.6 |
| S5 | 1 | 15 | 7.5 | 2 : 1 | 0.6 |
| S6 | 1.5 | 15 | 3.75 | 4 : 1 | 0.6 |
| S7 | 2 | 15 | 3.75 | 4 : 1 | 0.6 |
| S8 | 1 | 15 | 3.75 | 4 : 1 | 0.8 |
| S9 | 1 | 15 | 3.75 | 4 : 1 | 1 |
| S10 | 1 | 15 | 3.75 | 4 : 1 | 0.4 |

Table 2. Amount of captopril loaded and percentage of drug released at pH 2 and pH 7.4.

| Formulation code | Amount of captopril loaded (mg) per 0.3 g of dry hydrogel discs | % release of captopril | |
|---|---|---|---|
| | | pH 2 | pH 7.4 |
| S1 | 113.5 | 32.83 | 82.57 |
| S2 | 118.81 | 34.75 | 86.28 |
| S3 | 124.28 | 38.22 | 88.50 |
| S4 | 117.5 | 33.29 | 84.39 |
| S5 | 109.7 | 30.84 | 81.56 |
| S6 | 112.55 | 32.63 | 82.12 |
| S7 | 104.15 | 28.65 | 77.68 |
| S8 | 119.56 | 35.16 | 87.07 |
| S9 | 114.31 | 33.08 | 83.16 |
| S10 | 127.78 | 44.40 | 90.01 |

Table 3. Determination coefficient ($R^2$) of various release kinetic models for the prepared superabsorbent hydrogel formulations.

| Sample code | pH | Zero order | First order | Higuchi | Weibull |
|---|---|---|---|---|---|
| S1 | 2 | 0.9815 | 0.7443 | 0.9954 | 0.7489 |
| | 7.4 | 0.9934 | 0.6024 | 0.9673 | 0.8986 |
| S2 | 2 | 0.9629 | 0.6954 | 0.9959 | 0.7257 |
| | 7.4 | 0.9956 | 0.5858 | 0.9659 | 0.9198 |
| S3 | 2 | 0.9484 | 0.5329 | 0.9961 | 0.8081 |
| | 7.4 | 0.991 | 0.5774 | 0.9822 | 0.8989 |
| S4 | 2 | 0.9691 | 0.7125 | 0.9974 | 0.7001 |
| | 7.4 | 0.9945 | 0.5842 | 0.9683 | 0.9133 |
| S5 | 2 | 0.9717 | 0.7269 | 0.9978 | 0.7025 |
| | 7.4 | 0.9855 | 0.5106 | 0.9931 | 0.8856 |
| S6 | 2 | 0.9851 | 0.7503 | 0.9919 | 0.7142 |
| | 7.4 | 0.9912 | 0.5766 | 0.9816 | 0.8894 |
| S7 | 2 | 0.9434 | 0.6957 | 0.9947 | 0.6683 |
| | 7.4 | 0.9917 | 0.5428 | 0.9842 | 0.901 |
| S8 | 2 | 0.9633 | 0.6986 | 0.9941 | 0.7366 |
| | 7.4 | 0.9958 | 0.5912 | 0.9637 | 0.9188 |
| S9 | 2 | 0.9758 | 0.7307 | 0.9938 | 0.7743 |
| | 7.4 | 0.9956 | 0.6003 | 0.9691 | 0.987 |
| S10 | 2 | 0.9359 | 0.4794 | 0.9845 | 0.7975 |
| | 7.4 | 0.994 | 0.5914 | 0.9775 | 0.9071 |

swelling ratio. By increasing the amount of AMPS, number of hydrophilic groups such as -CONH and $-SO_3H$ increased accordingly. As a result, the synergistic effect produced by -CONH and $-SO_3H$ on AMPS, together with that of -COOH on AA increased (24), which brought about great enhancement of absorbency of aqueous solution.

However, when the mass ratio of AA to AMPS was below 4 : 1, which meant that AMPS content was over one-fifth of total monomers, swelling decreased because the electrostatic repulsion between ions weakened and the three-dimensional network compacted. In addition, as AMPS contained quaternary carbon atoms and $-SO_3H$ groups which were of high size, stretching of the polymer chains would be obstructed and absorbency would decrease accordingly. The subsequent decrease in swelling ratio of the hydrogels can be ascribed to the low reactivity of the AMPS monomer (25, 26). This indicates that the monomer grafting onto CMC chains decreases with increasing AMPS/AA molar ratio.

**Drug loading and release studies**

The hydrogel discs exhibiting greater swelling accommodated higher amounts of drug. The release study of captopril was performed at pH 2 and 7.4 as shown in Figure 10. The drug release at both pH (2 and 7.4) was observed for a period of 24 h, while USP phosphate buffer was used as dissolution medium. Drug release measured was in correspondence to swelling studies where relatively higher amount of drug was loaded and ultimately released in formulations exhibiting more swelling.

The drug release kinetics of prepared superabsorbent hydrogels was determined by different kinetic models already mentioned. The values of release coefficient $R^2$ calculated by kinetic models are presented in Table 3. The drug release from hydrogel formulations were best fitted into the kinetic model having value of $R^2$ close to 1.

The release exponent *n* obtained by Korsemeyer-Peppas model for the formulations of HPMC-g-poly(AA-co-AMPS) copolymer containing different components, polymer concentration, AA/AMPS ratio and amount of crosslinker are presented in Table 4.

The mechanism of drug release was indicated by the values of n i.e., release exponent. By fitting of recorded data to Peppas model, it was found that

Table 4. Mechanism of drug release by determination of release exponent 'n'.

| Sample code | pH | n | r |
|---|---|---|---|
| S1 | 2 | 0.59 | 0.9954 |
| | 7.4 | 0.72 | 0.9855 |
| S2 | 2 | 0.47 | 0.9914 |
| | 7.4 | 0.73 | 0.9871 |
| S3 | 2 | 0.56 | 0.9962 |
| | 7.4 | 0.59 | 0.9989 |
| S4 | 2 | 0.55 | 0.9957 |
| | 7.4 | 0.69 | 0.987 |
| S5 | 2 | 0.63 | 0.9957 |
| | 7.4 | 0.58 | 0.9979 |
| S6 | 2 | 0.79 | 0.9977 |
| | 7.4 | 0.64 | 0.9869 |
| S7 | 2 | 0.54 | 0.9795 |
| | 7.4 | 0.63 | 09952 |
| S8 | 2 | 0.46 | 0.991 |
| | 7.4 | 0.78 | 0.9853 |
| S9 | 2 | 0.48 | 0.9956 |
| | 7.4 | 0.78 | 0.987 |
| S10 | 2 | 0.61 | 0.9757 |
| | 7.4 | 0.62 | 0.9991 |

approximately all hydrogel formulations in spite of using different concentrations of polymer, monomers and crosslinking agent were following non-Fickian mechanism of drug release as presented in Table 4. The value of n in all cases were higher than 0.45 but lower than 1.

## CONCLUSIONS

It has been revealed from the entire discussion that the developed superabsorbent hydrogel exhibits remarkable swelling properties, reasonable stability and smart pH responsiveness. The HPMC-g-poly(AA-co-AMPS) polymeric network was successfully crosslinked by a well-established and widely used chemical crosslinking method - free radical polymerization. The formulations prepared by varying amounts of components were then loaded with an antihypertensive drug, captopril. The drug entrapped into these hydrogels remained stable and was compatible with its components. The hydrogel network was also capable to release relatively smaller fraction of drug in acidic medium and more quantity at higher pH. Thus, after oral administration, the hydrogel formulation would be capable of exerting the effects throughout its retention in the stomach and intestine. Therefore, this can prove its worth as a successful and promising drug carrier for the controlled release of captopril, which can be used for treatment of hypertensive patients as well as for the management of cardiac disorders.

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