



Characterization and drug release kinetics of polyacrylamide/sodium alginate blend hydrogels synthesized by gamma irradiation

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Abstract

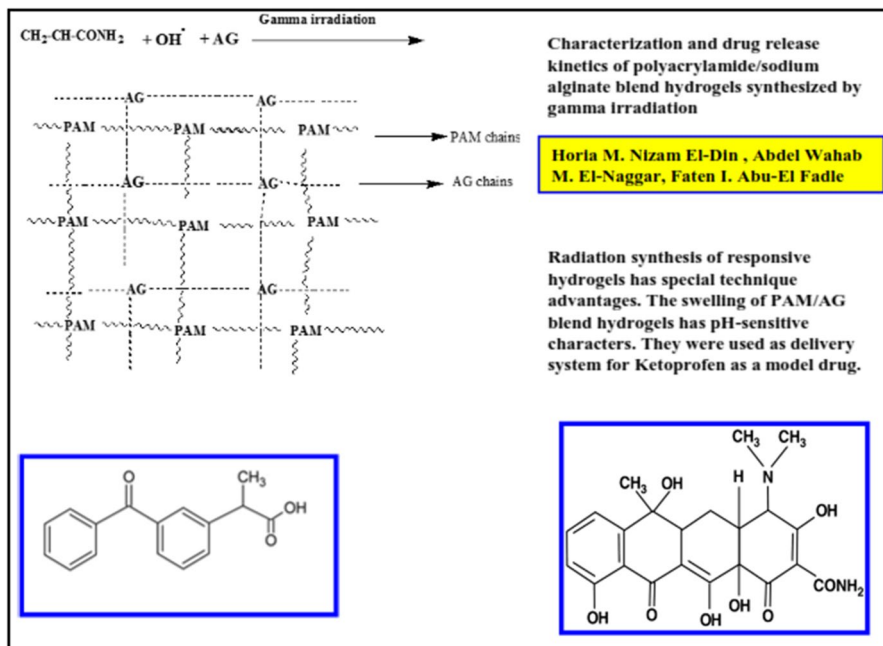
Hydrogels based on polyacrylamide (PAM) and sodium alginate (AG) were fabricated via gamma irradiation. The structure–property behavior of PAM/AG hydrogels was characterized by FTIR spectroscopy, and water absorption measurements. The PAM/AG hydrogels were applied as drug delivery taking chlortetracycline and ketoprofen as drug models. In addition, the water diffusion and drug release kinetics were investigated by applying the Fick’s law, in which the mechanism for water diffusion and drug release was suggested. The results clarified the pH-sensitivity of the PAM/AG blend hydrogels towards the drug-release medium in the case of both drugs.

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Graphical abstract



Keywords Gamma irradiation · PAM/AG blends · pH-sensitive hydrogels · Drug release

Introduction

Hydrogels are three-dimensional network structures, which are capable of swelling and absorbing large amounts of water or biological fluids allowing a wide range of medical applications [1–3]. Drug-delivery hydrogels synthesized by chemical initiation or gamma radiation have been extensively reported. A novel pH-sensitive and macroporous NaAlg-based hydrogels were prepared, in the presence of *N*-methylolacrylamide (NMAAm) and acrylic acid, using *N,N*-methylene-bis-acrylamide (MBA) as a cross-linker, 2,2-dimethoxy-2-phenylacetophenone as a photoinitiator via ultraviolet irradiation [4]. 5-fluorouracil (5-FU) as a model drug was loaded on hydrogel, the drug encapsulation efficiency of products reached to 85.2% and the cumulative release rate of drug was 78.4 and 37% in the intestinal and gastric fluid, respectively. Chemical cross-linking of monomers methacrylic acid (MAA) and itaconic acid (IA) through ethylene glycol dimethacrylate (EGDMA) was carried out for synthesizing robust hydrogel system for oral administration and tuned for targeted release of 5-fluorouracil (5-FU) and leucovorin calcium (LV) at colonic site [5]. PVP hydrogel was synthesized using gamma radiation technique [6]. In the first step, PVP, agar and PEG concentrations were

modified as a function of dose rate. The sample containing 3% of PEG was selected to test its potential as antileishmanial drug carrier. Polyethylene glycol (PEG)-and polyethylene glycol–polycaprolactone (PEG–PCL)—based hydrogels were synthesized with various compositions of prepolymers by using ROP and click chemistry methods [7]. The kinetics of diclofenac sodium release from hydrogels showed similar behavior so that the hydrogels with the highest PCL concentration, the release mechanism fully changed from non-Fickian to Fickian diffusion. Novel colon targeting xanthan gum/polyvinylpyrrolidone-co-poly acrylic acid hydrogels for controlled delivery of 5-fluorouracil at colon-specific site by combining the properties of natural and synthetic polymers was prepared [8]. Drug release kinetics revealed the controlled release pattern of 5-fluorouracil in developed polymeric network. Cross-linked XG/PVP-copoly (AA) hydrogels can be used as promising candidate for controlled delivery of 5-FU for prolonged treatment period at colon-specific site. Chitosan-based hydrogels with poly(ethylene glycol)/polycaprolactone for the controlled release of drugs/growth was studied [9]. A casting/solvent evaporation method was used to obtain films of alginate and gelatin, crosslinked with Ca^{2+} , taking ciprofloxacin hydrochloride as model drug [10]. The results showed a decrease of the ciprofloxacin release with increasing the ratios of gelatin. Ph-sensitive composite hydrogel based on chitosan-g-poly (acrylic acid)/ attapulgitite/sodium alginate (CTS-g-PAA/APT/SA) was fabricated as drug delivery crosslinked by Ca^{2+} [11]. It was found that the rates of accumulative release of diclofenac sodium (DS) from the composite hydrogel beads were 3.76% in pH 2.1 solution and 100% in pH 6.8 solutions within 24 h, respectively. Interpenetrating network (IPN) tablets of diltiazem-HCl (DTZ) based on polyacrylamide-grafted-sodium alginate (PAAm-g-SAL) copolymer and sodium alginate (SAL) to be applied as the drug delivery was investigated [12]. Hydrogels based on alginate-g-poly(itaconic acid) (NaAlg-g-PIA) microspheres as drug delivery matrices of Nifedipine crosslinked by glutaraldehyde (GA) in hydrochloric acid catalyst was prepared [13]. The results indicated that Nifedipine released from grafted microspheres was faster in the pH 7.4 buffer solution than that at pH 1.2 solutions. In addition, it was found that by increasing time, drug amount, GA and NaAlg-g-PIA concentrations, the release of nifedipine from microspheres was decreased. The release characteristics of diclofenac sodium (DS) from poly(vinyl alcohol)/sodium alginate and poly(vinyl alcohol)-grafted-poly(acrylamide)/sodium alginate blend beads were reported [14]. The highest DS release obtained was 92% for 1/1 PVA-g-PAAm/NaAlg ratio beads and that the release results showed that DS release from the beads through the external medium is much higher at high pH (6.8 and 7.4) than that at low pH (1.2). Hybrid alginate hydrogel with shells of porous CaCO_3 microparticles formed by templating water-in-oil emulsion then in situ gelation was used for Brilliant blue (BB) as a drug model [15]. The formation of the shells of CaCO_3 microparticles slowed down the BB released from the colloid some. A drug delivery system for preparing microcapsule by liposome in alginate was used for bovine serum albumin (BSA) as a model drug [16]. The results showed that Ca^{2+} and Ba^{2+} made hydrogels compose easier than Al^{3+} and particle size was uniform, circular. However, the microcapsule prepared by Al^{3+} was flat circular and easily adhere to each other. CaCl_2 as a crosslinking agent was employed to prepare biopolymer microspheres of sodium alginate and starch [17]. The prepared microspheres were loaded with an insecticide; chlorpyrifos, and FTIR and SEM techniques were used to characterize both the

native (unloaded) and loaded microspheres. Fe^{3+} crosslinked alginate-carboxymethyl cellulose in several volume rates was prepared [18]. The vitro release test was used to monitor the controlled release of albumin from hydrogel beads under simulated gastrointestinal conditions over 24 h. The release of protein was protected and controlled by The Fe^{3+} crosslinked AC beads, showing that such beads introduce a promising protein therapeutic carrier for the oral delivery.

The radiation synthesis of hydrogels in aqueous solution based on natural and synthetic water-soluble polymers has been a special interest and widely used as drug delivery systems. In this contest, pH sensitive hydrogels based on acrylamides and their swelling and diffusion characteristics with drug delivery behavior taking 5-fluorouracil as a model drug [14].

In previous studies, we were interested with the radiation synthesis of drug-delivery responsive hydrogels from natural polymers. In this regard, the temperature and pH responsive behavior of carboxymethyl cellulose/acrylic acid hydrogels prepared by electron beam irradiation was reported [19]. The properties of swelling and drug release of acrylamide/carboxymethyl cellulose networks composed by gamma irradiation were studied [20]. Gamma irradiated concentrated aqueous solutions of chitosan/sodium alginate blends were characterized and their drug uptake-release characters were investigated [21]. The radiation synthesis of pH-sensitive hydrogels from carboxymethyl cellulose/poly(ethylene oxide) blends as drug delivery systems was studied [22]. The physico-chemical and drug release properties of poly(vinyl alcohol)/gum arabic/ TiO_2 nanocomposite hydrogels formed by gamma radiation [23] and radiation synthesis and drug delivery properties of interpenetrating networks (IPNs) based on poly(vinyl alcohol)/ methylcellulose blend hydrogels [24] were investigated. Recently, the biological applications of nanocomposite hydrogels prepared by gamma-radiation copolymerization of acrylic acid (AAc) onto plasticized starch (PLST)/montmorillonite clay (MMT)/chitosan (CS) blends was reported [25].

As seen above, most of the drug delivery hydrogels prepared by gamma irradiation or ionizing radiation was based on using acrylamide, sodium alginate and cross-linked PVP as a single component and network of xanthan gum and poly(vinyl pyrrolidone) prepared by a chemical method. All those hydrogels were investigated taking 5-fluorouracil as a drug model. In the present study, gamma radiation was used for the preparation of a drug delivery hydrogels from polyacrylamide (PAM) and sodium alginate (AG) blends taking new drugs such as Tetracycline and Keto-profen as drug models. The importance of choosing PAM and AG is due the presence of many hydrophilic groups capable of forming covalent bonds with those on the drugs. The study of the pH-sensitivity of swelling and applying PAM/AG as pH-responsive hydrogels as drug delivery systems is an important objective.

Experimental

Materials

A laboratory grade chemicals sodium alginate (AG) used in this work was obtained from Aldrich Chemical Co. (Milwaukee, WI). A laboratory grade of polyacrylamide

(PAM) was purchased from Merck, Germany. Calcium chloride, pure grade chemicals was used as a crosslinking agent for sodium alginate. Tetracycline, antibiotic drug, and Ketoprofen were purchased from Sigma Chemical Co., USA. All chemicals used such as, citrate, phosphate buffer were of analytical reagent grade and were purchased from El-Nasr Co. for Chemical Industries, Egypt, and used as received.

Preparation of PAM/AG blend hydrogels

Films of PAM/AG blends were first prepared by solution casting. In this procedure, aqueous solutions with different concentrations of AG were prepared using CaCl_2 (1 wt%) as a crosslinking agent in distilled water. PAM was dissolved in distilled water. The solutions of PAM and AG were then mixed with continuous stirring to obtain homogenous solutions to obtain PAM/AG compositions of 80/20, 50/50 and 20/80 wt%. The blend solutions were put into Petri dishes, and made free of air by purging nitrogen for 5 min at least and sealed. The films were then exposed to gamma irradiation at a dose rate of 6.92 kGy/h. The hydrogel films were first washed with excess distilled water to remove unreacted materials, extracted with distilled water using a Soxhlet system for 6 h to remove homopolymers and finally dried in a vacuum oven at 80 °C to constant weight to get films with thickness of ~0.5 mm.

The gamma irradiation procedure was carried out in a cobalt-60 gamma cell (made in Russia) installed at the National Center for Radiation Research and Technology, Egyptian Atomic Authority, Cairo, Egypt.

Characterization

FT-IR spectroscopic analysis

The IR spectra were performed on a FT-IR spectrometer model Mattson 100, Unicam, and were recorded over the range 500–4000 cm^{-1} .

Swelling characters

A dry weight of the Pam/AG hydrogel (W_0) was immersed in distilled water for different periods up to 24 h at room temperature and at pH of 7.4 (10 mM NaH_2PO_4 – Na_2HPO_4 buffered solution). At each period, the sample was removed and blotted on filter paper to remove the excess water on the surface and weighed (W_s). The swelling ratio was calculated according to Eq. 1:

$$\text{Swelling ratio} = [(W_s - W_0)] / W_0 \quad (1)$$

The pH-sensitivity of swelling was determined by the same procedure but in buffer solutions with various pH values (2.1, 5, and 8) at room temperature for 12 h to reach equilibrium swelling. The different solutions of NaH_2PO_4 , Na_2HPO_4 , NaCl and NaOH were combined to form buffer solutions with various pH values. All experiments were done in triplicates.

Tensile mechanical properties

The tensile mechanical properties were tested in the form of stripes (1 cm in width and 3 cm in length). The tensile strength and elongation at break point were determined at a crosshead speed of 10 mm/min on a testing machine, Mecmesin, multi Test 25-I (United Kingdom).

Scanning electron microscopy (SEM)

The surface morphology of the PAM/AG hydrogels was examined by scanning electron microscopy (SEM). The SEM micrographs were taken on a JSM-5400 instrument (Joel, Japan). A sputter coater was used to pre-coat conductive gold onto the fracture surfaces at 30 kV.

Preparation of the hydrogels (PAM/AG) loaded with the drug (tetracycline and ketoprofen)

In order to determine the amount of tetracycline and ketoprofen drugs uptake or release, a standard calibration curves representing the absorbance of different concentrations of tetracycline and ketoprofen drugs were first constructed. From this relation, a concentration of unknown sample can be determined. A dry weight PAM/AG hydrogel (W_0) was immersed into different concentrations of drug solutions at room temperature for 12 h until complete sorption (W_1). UV spectrophotometer model UV2 series made by Unicam was used at the specific wavelength of drugs. The drug uptake (%) was calculated using the Eq. 2:

$$\text{Drug uptake (\%)} = \left[\frac{W_1}{W_0} \right] \times 100 \quad (2)$$

Drug release characters of PAM/AG blend hydrogels

Release profiles of the drugs tetracycline and ketoprofen were carried out by placing drug-loaded blend hydrogels into 20 ml of buffer solutions at pH 2.1, 5 and 8 and allowed to complete release. The release experiment was performed three times for every sample and the average value was used to plot the release profiles.

Results and discussion

Synthesis of PAM/AG copolymer hydrogels via gamma radiation

Sodium alginate is a natural non-toxic polysaccharide available in the brown algae. It is a water soluble salt of alginic acid. Sodium alginate has a tendency to undergo crosslinking in the presence of multivalent cations, such as calcium ions in aqueous

media [26]. On the other hand, the crosslinking of vinyl polymers in solutions by gamma radiation was established [27]. The crosslinking of PAM in aqueous solution by gamma radiation may be briefly summarized as follows:

- (1) Gamma radiation is absorbed by the polymer PAM and the solvent H₂O, the radicals $-(\text{C}\dot{\text{H}}-\text{C}\dot{\text{H}}-\text{CONH}_2-)_n$, HO[•] and H[•] are formed. The radicals resulted from the radiolysis of water transfer to PAM polymer and thus increase the concentration of PAM radicals and increase the rate of crosslinking.
- (2) Two PAM polymer radicals with n and m repeat units combine to form a crosslinked point. It is expected that the formed PAM/AG blend hydrogel represents an interpenetrating polymer network (IPN). These kinds of network structure contain an entangled combination of two crosslinked polymers not bonded to each other as shown in Fig. 1. However, the possible formation of hydrogen bonding between PAM and AG still exist.

FT-IR Spectroscopic analysis

Figures 2 and 3 show The FT-IR spectra of unirradiated PAM and AG polymers and PAM/AG blend hydrogels at different rates before and after gamma irradiation at different doses, respectively. The IR spectrum of unirradiated AG showed a broad peak at 3355 cm⁻¹ due to -OH group, two peaks at 1576 and 1412 cm⁻¹ due the -COO⁻ group, and one sharp peak at 1036 cm⁻¹, due to the C-O group. The characteristic band of AG can be seen at 819 cm⁻¹. The IR spectrum of unirradiated PAM

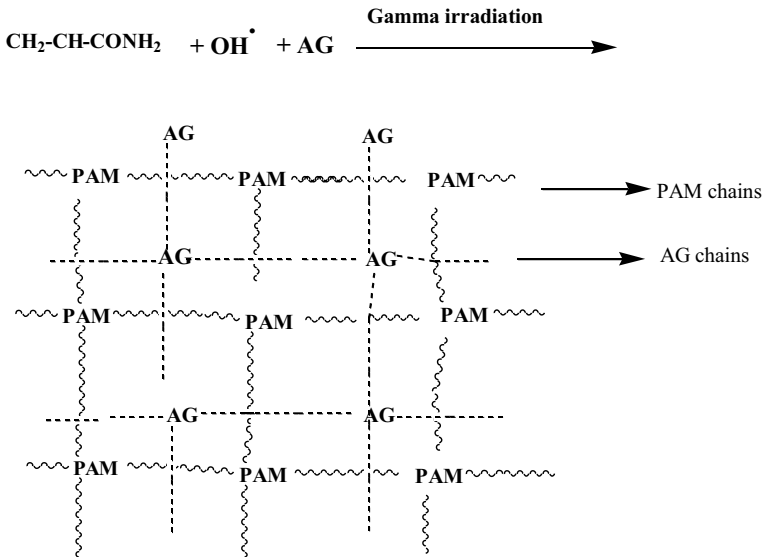


Fig. 1 Proposed schematic diagram of the proposed interpenetrating network structure (IPN) of PAM/AG blend hydrogels, formed by gamma irradiation

showed bands at 3408 cm^{-1} and 3116 cm^{-1} , assigned to the stretching vibration of N–H, 1676 cm^{-1} (C–O stretching) and 1567 cm^{-1} (N–H bending). Also bands at 2940 cm^{-1} (CH stretching) and $1515\text{--}1370\text{ cm}^{-1}$ (various CH bending) can be observed. The IR spectra of the unirradiated PAM/AG blends are characterized by the absorption bands typical of the pure components. However, the AG characteristic band appeared at 819 cm^{-1} was not observed in all the IR spectra of PAM/AG blends. For the unirradiated PAM/AG blends at different ratios, the absorption band seen at 1576 cm^{-1} is due to the asymmetric stretching vibration of --COO^- groups coupled with the PAM band at 1676 cm^{-1} were shifted to 1562 cm^{-1} . These findings suggest the existence of new hydrogen bonds formed between --COO^- groups of alginate and --CONH_2 groups of PAM. The PAM bands at $3408\text{--}3116\text{ cm}^{-1}$ are due to the stretching vibration of --NH_2 groups are coupled with --OH band of AG at 3506 cm^{-1} indicating the formation of hydrogen bonds between --OH groups of AG and --NH_2 groups of PAM molecules [28, 29].

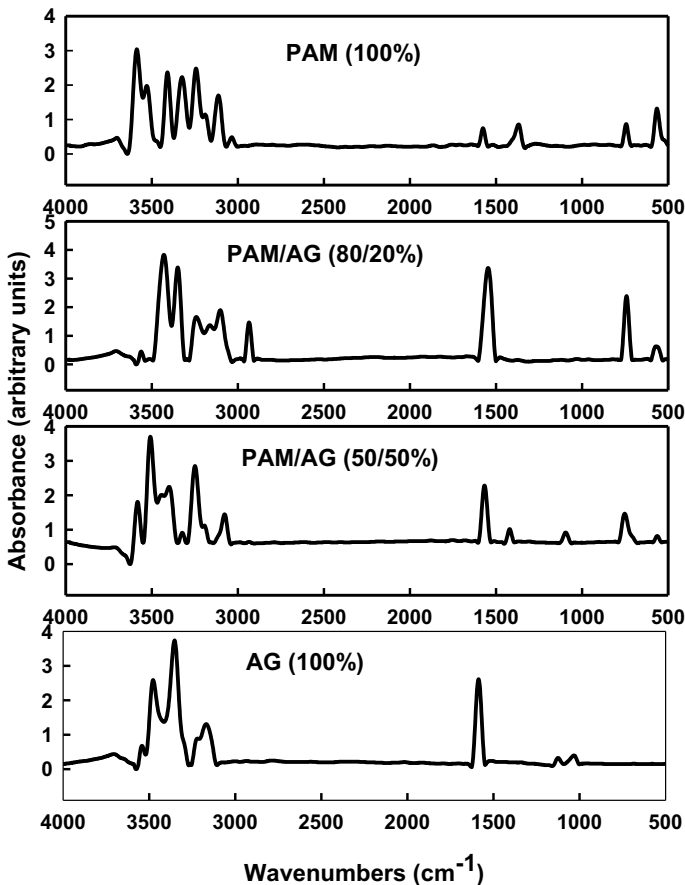


Fig. 2 FT-IR spectra of unirradiated PAM, AG, PAM/AG blends at different ratios

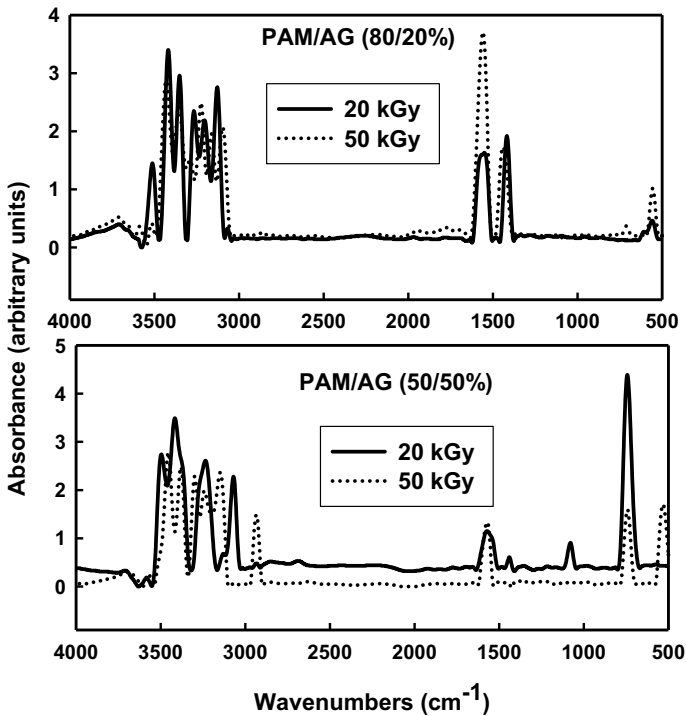


Fig. 3 FT-IR spectra of PAM/AG copolymer hydrogels of different ratios, prepared by gamma irradiated to different doses

In the case of blend hydrogels prepared by gamma irradiation, the absorption bands typical of the pure components were also observed. In this regard, the AG characteristic band, appeared at 819 cm^{-1} , was absent in all the spectra of PAM/AG blend hydrogels. It is clear that all the characteristic bands for pure components exist in the different PAM/AG blend hydrogels. In general, it is believed that the peak near 1129 cm^{-1} originated from glycosidic linkages in polysaccharides is due to asymmetric α -(1–4) stretching mode of the glycosidic [30, 31]. It is clear that, the AG band shifted from 1129 to 1095 cm^{-1} after blending with PAM for the blend 50/50%. Upon exposure of the blends to gamma irradiation at 20 to 50 kGy, this band was shifted to 1071 cm^{-1} in case of the PAM/AG (50/50) blend composition. It was proposed that based on the proposal that the 1124 cm^{-1} band is assigned to C–O stretching vibrations, which may have appeared due to the C–OH group at the C6 position [32].

Swelling characters

The swelling in buffer solutions of various pH values and at different temperature for PAM/AG blend hydrogels of different ratios, prepared at the dose of 20 kGy of gamma irradiation is illustrated in Fig. 4. Few points may be indicated:

- (1) The swelling was suddenly increased after to 5 h and then reached the equilibrium stat up to 12 h, regardless of hydrogel composition and pH value however, the swelling ratio was found to increase with the increase of the pH value up to 8.
- (2) The swelling ratio increases with increasing temperature from 25 to 50 °C.
- (3) At all, values of pH and temperature, the swelling ratio increases with increasing the AG component.
- (4) It is evident that the PAM/AG hydrogels displayed pH-sensitive swelling behavior. This sensitivity resulted from the existence of the hydrophilic carboxylic acid and amide groups along the hydrogels chains. At higher pH values than the pKa, the carboxylic acid groups became ionized, leading to swollen networks due to the electrostatic repulsion between charged groups [33]. The low swelling ratio within the pH values 2–5, is due to electrostatic interaction. On increasing the pH to 8, the hydrogen bonds broke as the carboxylic acid groups ionized.

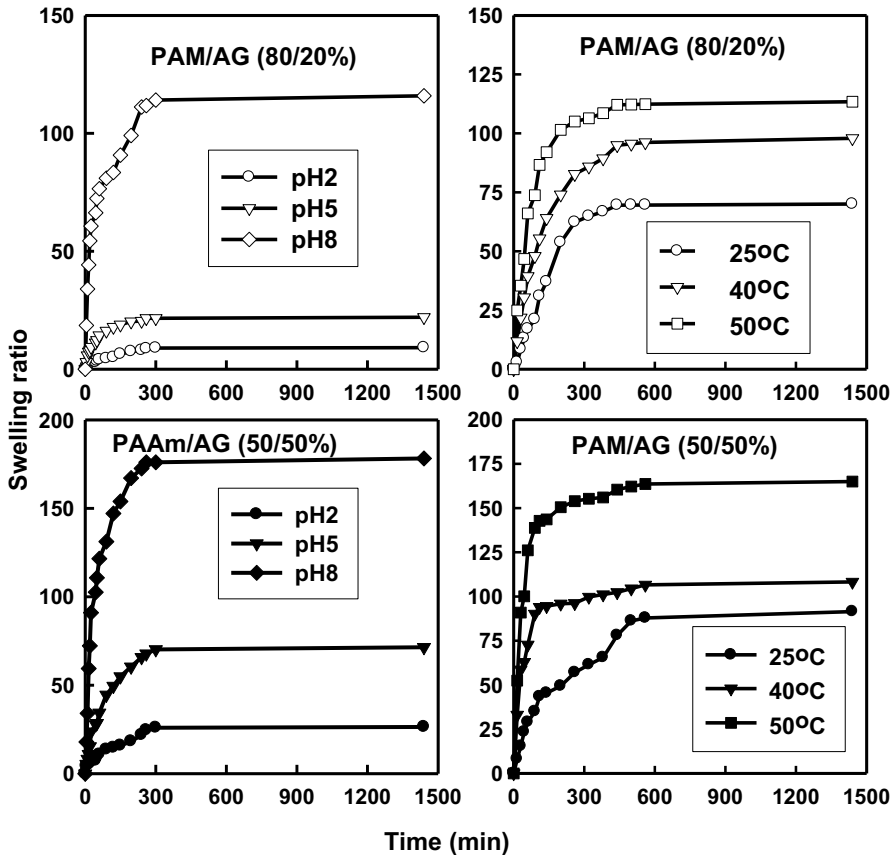


Fig. 4 Swelling in buffer solutions of various pH values and at different temperature for PAM/AG copolymer hydrogels of different ratios, prepared by gamma irradiation to a dose of 20 kG

Meanwhile electrostatic repulsion caused the network to expand; therefore, the swelling ratio reached a relatively larger value.

- (5) The increase of swelling ratio with increasing the AG ratio has a direct relation with the gel fraction of PAM/AG blend hydrogels, in which it was found that the crosslinking degree (gel content) was decreased by increasing the ratio of AG. Thus, as the gel content decreases, the hydrogel structure becomes compact and hence facilitates the diffusion of water molecules.
- (6) The increase of temperature would increase the mobility of chains and hence facilitate the diffusion of water molecules from the surroundings.

The mechanism of diffusion into hydrophilic polymeric systems has been paid great attention due to the important biomedical, pharmaceutical and environmental applications [34]. The nature of water diffusion into PAM/AG hydrogels was determined by applying Fick's law according to the following equation [35]:

$$F = W_t / W_e = kt^n$$

or

$$\ln F = \ln k + n \ln t$$

where W_t is the amounts of water absorbed by the hydrogel at time t and W_e is the amounts of water absorbed by the hydrogel at equilibrium, k represents a constant characteristic of the networks structure and n is the exponent determining the mode of water diffusion. When $\ln F$ is plotted against $\ln t$, it gives a straight line from which the constant k is determined by the intercept and the slope gives the number n . In this concern, a value of $n = 0.5$ implies a Fickian diffusion mechanism, in which the sorption is diffusion controlled, while a value of $0.5 < n < 1$ implies an anomalous non-Fickian type diffusion and adds to the water-sorption process.

Figure 5 shows the plots of $\ln F$ against $\ln t$ for the swelling in buffer solutions of different pH values and different temperatures for PAM/AG blend hydrogels of different ratios, prepared at the dose of 20 kGy of gamma irradiation. Table 1 presents the kinetic parameters calculated for the PAM/AG hydrogels of different compositions. The data indicated that all the hydrogels represented a non-Fickian type of diffusion. Thus, it may be concluded that the water diffusion into the hydrogel networks is not controlled but it depends on the water sorption process, which in turn depends on the structure and pathways of water through the networks. This result indicates that the relatively high crosslinking density restricts the water pathways diffusion onto the hydrogels.

Tensile mechanical properties

The tensile strength and elongation at break parameters are indicative for the handling properties and mechanical performance of the hydrogel films. The tensile strength and elongation at break of PAM/AG blend hydrogels of different ratios are shown in Fig. 6. From the data in Fig. 6, few points may be indicated:

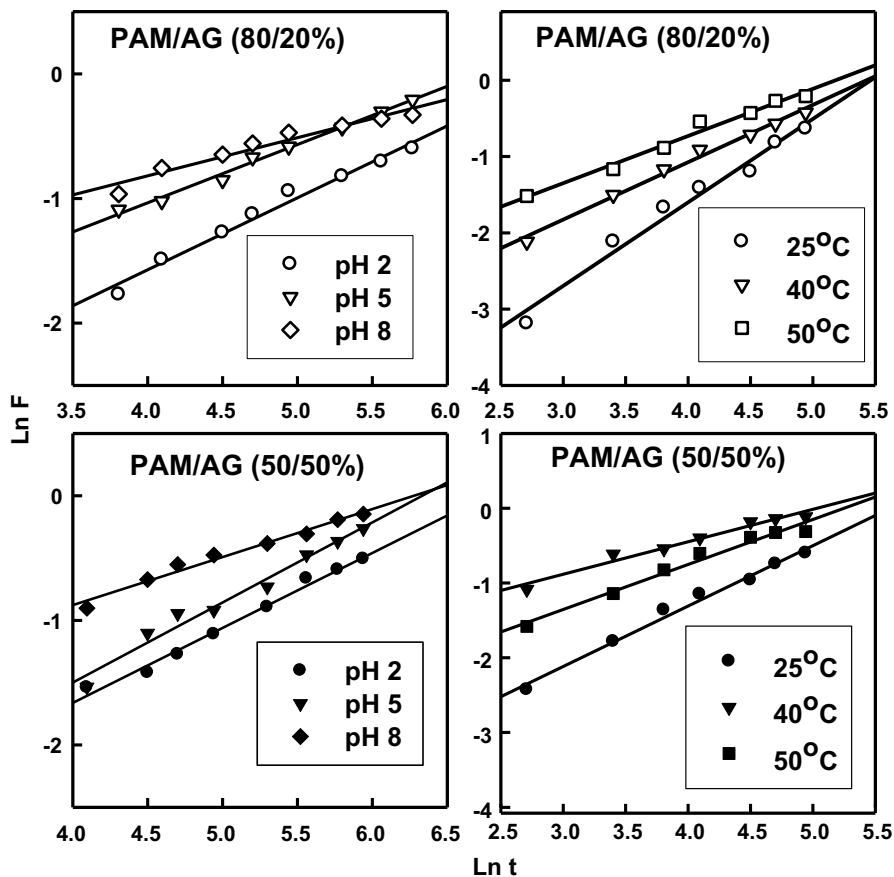


Fig. 5 Plots of $\ln F$ versus $\ln t$ for the swelling in buffer solutions of different pH values and different temperatures for PAM/AG copolymer hydrogels of different ratios, prepared at the dose of 20 kGy of gamma irradiation

Table 1 Kinetic parameters of water diffusion, in different pH values and at different temperatures, for PAM/AG blend hydrogels at different ratios, prepared by gamma irradiation to a dose of 40 kGy

PMA/AG (%)	Kinetic parameters of water diffusion							
	pH sensitivity				Temperature sensitivity			
	pH	n	k	r^2	Temp (°C)	n	k	r^2
80/20%	2	0.60	0.0188	0.98004	25	1.09	0.0025	0.97729
	5	0.60	0.0213	0.97469	40	0.75	0.0169	0.99016
	8	0.52	0.0388	0.98063	50	0.62	0.0407	0.98104
50/50%	2	0.63	0.0145	0.99140	25	0.81	0.0107	0.98802
	5	1.18	0.0005	0.96758	40	0.43	0.1123	0.96795
	8	0.66	0.0150	0.98727	50	0.60	0.0425	0.97546

- (1) The tensile strength and elongation at break of either unirradiated or gamma irradiated PAM/AG blend hydrogels was found to decrease with increasing the ratio of AG polymer is due to the brittle nature of the natural AG.
- (2) It is obvious that the tensile strength of PAM/AG blend hydrogels increased with increasing irradiation dose and decreased with the increase of AG ratio, regardless of blend composition. This finding is due the crosslinking occurred to the PAM component. These findings are true for the PAM/AG blend hydrogels up to the 75/25%. This behavior could be attributed to the occurrence of degradation to the AG component.

Scanning electron microscopy (SEM)

Figure 7 shows the SEM micrographs of pure PAM and AG polymers and PAM/AG (50/50%) blend hydrogels, before and after gamma irradiation to a dose of 20 kGy. The SEM micrograph of the fracture surface of unirradiated AG polymer is smooth

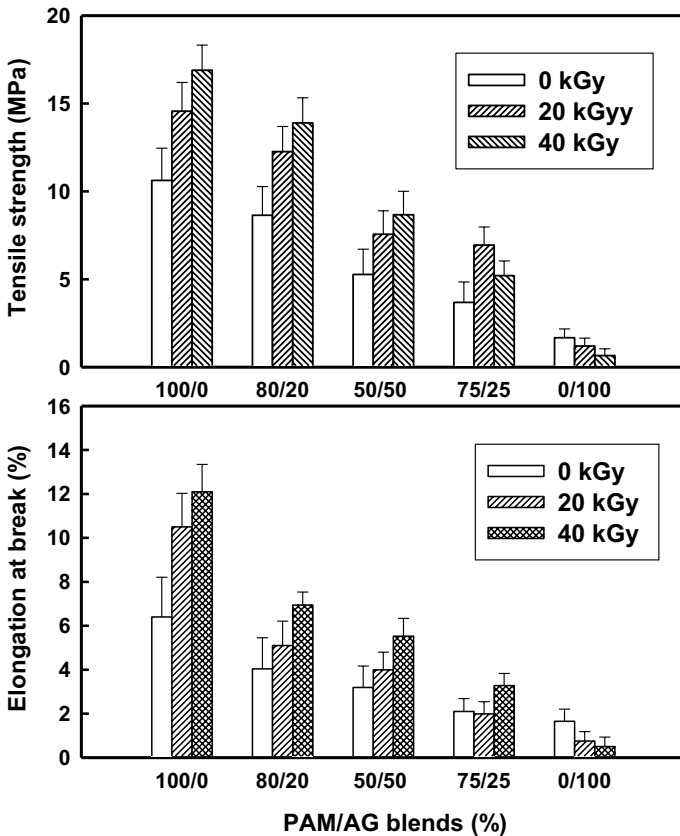


Fig. 6 Tensile strength and elongation at break (%) properties of PAM/AG copolymer hydrogels of different ratios, prepared by gamma irradiation to different doses

while the fracture surface of unirradiated PAM polymer showed a number of small particles dispersed along the micrograph. The fracture surface of the unirradiated PAM/AG (50/50%) is full of cavities, small particles and small holes spread all over the surface. Gamma irradiation improved greatly the surface. It became smoother, in which the cavities and small particles were almost disappeared and were replaced by very small particles spread homogeneously all over the surface. These findings indicate the occurrence of crosslinking.

Drug uptake-release characters of PAM/AG hydrogels

The crosslinking affected directly the swelling of PAM/AG and reducing the permeability of different solutes. Consequently, the release of loaded drugs onto PAM/AG matrices will eventually allowing these systems to be used in drug-controlled release [36]. The drug release mechanisms and the resulting release patterns are determined by the physicochemical nature of the matrix. Several processes, i.e. drug dissolution and diffusion, swelling and erosion of the matrix or a combination of two or more of these processes are related to the overall control of drug release [37, 38].

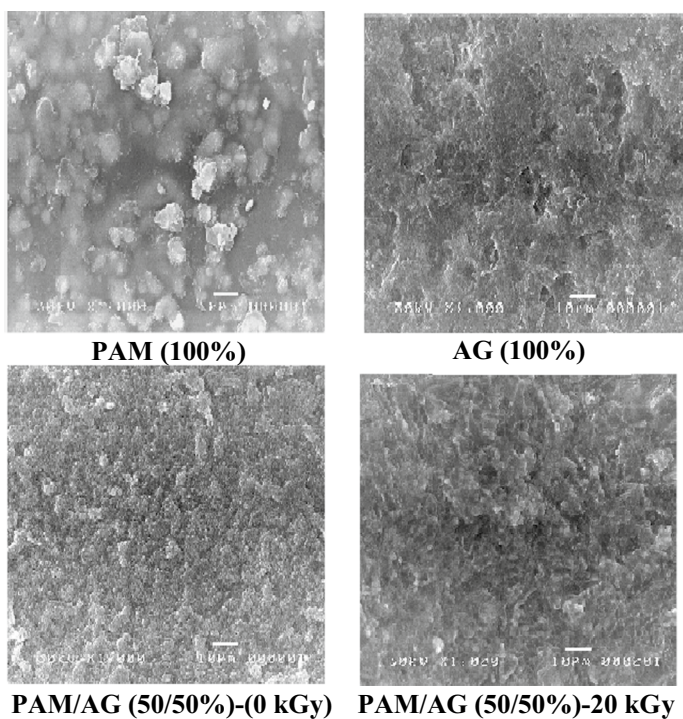
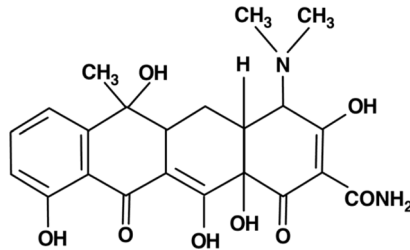


Fig. 7 SEM micrographs of pure PAM and AG polymers and PAM/AG (50/50%) blend hydrogels, before and after exposed to a dose of 20 kGy of gamma irradiation. **A** PAM/AG (100/0%)-0 kGy, **B** PAM/AG (0/100%)-0 kGy, **C** PAM/AG (50/50%)-0 kGy, **D** PAM/AG (50/50%)-20 kGy

Uptake and release of tetracycline drug

The chemical structure of tetracycline drug (shown below) contains many active groups capable of forming covalent and hydrogen bonding with the chains of PAM/AG blends hydrogels. The uptake of tetracycline by PAM/AG (%) hydrogels at different ratios was at room temperature and pH 7 to the equilibrium state is shown in Fig. 8. It can be seen that the uptake (%) was increased with increasing drug concentration and with increasing AG ratio. It seems that the bonding of drug with AG through hydrogen bonding was favorable than with PAM chains.



The tetracycline release profiles at room temperature and in buffer solutions of different pH values and the equilibrium drug release at various pH values from

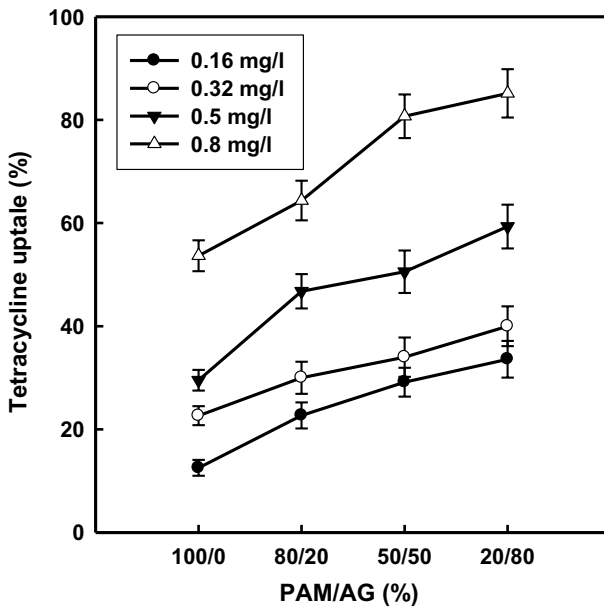
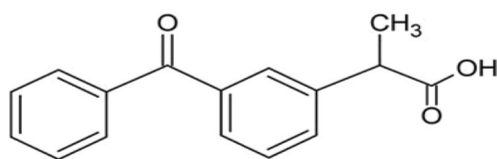


Fig. 8 Uptake at room temperature and at a pH value of 7 from different concentrations of Tetracycline drug by PAM/AG copolymer hydrogels at different ratios prepared by gamma irradiation to a dose of 20 kGy

PAM/AG blend hydrogels at different compositions, prepared by gamma irradiation to a dose of 20 kGy. It is clear that the release process of tetracycline depends largely on the pH of the medium. The highest release was reached at pH 8.0 while the lowest release was at pH 2.0, depending on hydrogel composition. The release however was found to increase with increasing the ratio of AG in the hydrogel composition. It seems that the release is greatly related to the swelling in water of non-loaded PAM/AG hydrogel films at different pH values as shown in Fig. 4. At lower pH value, the amount of COO⁻ on alginate is almost equal to the amount of NH³⁺ on PAM, and hence the macromolecular chains in the hydrogel film matrix attract each other causing a shrink and therefore, the lowest value of water swelling of blank matrix film at pH 2.0. At higher pH, the equilibrium ratio between the amount of COO⁻ and NH³⁺ was broken and the macromolecules chains of the film matrix take each other apart, which increased the swelling of water and thus decrease the drug release (Fig. 9).

Release of Ketoprofen drug

Ketoprofen is a non-steroidal anti-inflammatory drug having a 4.94 pKa and its chemical structure name is shown below. It is clear that the chemical structure contains -COOH and C=O groups. Thus, it is expected that when the drug is loaded onto the PAM/AG hydrogels networks, it would form hydrogen bonding with the available groups along the PAM/AG hydrogels networks. The Ketoprofen release profiles at room temperature and in buffer solutions at different pH values are shown in Fig. 10. The drug release at equilibrium from PAM/AG blend hydrogels at different pH values for the same hydrogels is shown in Fig. 10. It is evident that the ketoprofen releases gradually and then reaches the equilibrium release state after ~3 h depending on the medium pH. However, the release (%) of ketoprofen at The equilibrium state of ketoprofen from the PAM/AG hydrogel of compositions 80/20 and 50/50% at pH 8 was found to be 85.5 and 40.8%, respectively.



Sensitivity and drug release kinetics

Sensitivity of drug release

A useful parameter in the in the field of drug delivery applications is to measure the sensitivity of drug delivery character of PMA/AG copolymer hydrogel by plotting the initial part of the release profiles of the drugs tetracycline and ketoprofen against time on a linear regression plots, as shown in Fig. 11. The calculated slopes (rate of

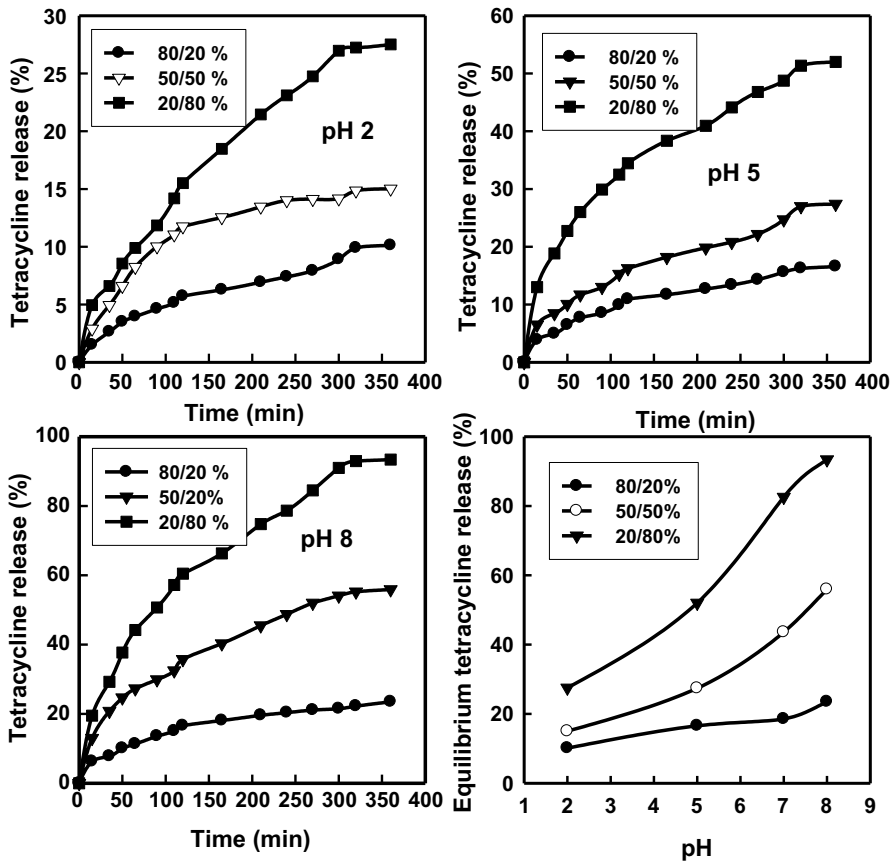


Fig. 9 Tetracycline release profiles at room temperature and in buffer solutions of various pH values and the effect of pH on the equilibrium drug release from PAM/AG copolymer hydrogels at different ratios prepared by gamma irradiation to a dose of 20 kGy

release) are listed in Table 2. The data show that the ketoprofen release rate, in different buffer solutions of various pH values, from PAM/AG hydrogels is ~3–5 times higher than the release rate of tetracycline under the same conditions. This finding may be referred to the relatively weak hydrogen bonding of ketoprofen through the carboxylic groups in PAM/AG hydrogels and the relatively smaller the size of ketoprofen.

Drug release kinetics

The nature of drug release was studied by applying Fick’s law. The application of this law on the present system is by plotting $\ln F$ versus $\ln t$ for drugs release profiles of tetracycline and ketoprofen at room temperature and in buffer solutions of various pH values from PAM/AG blend hydrogels at different ratios, prepared

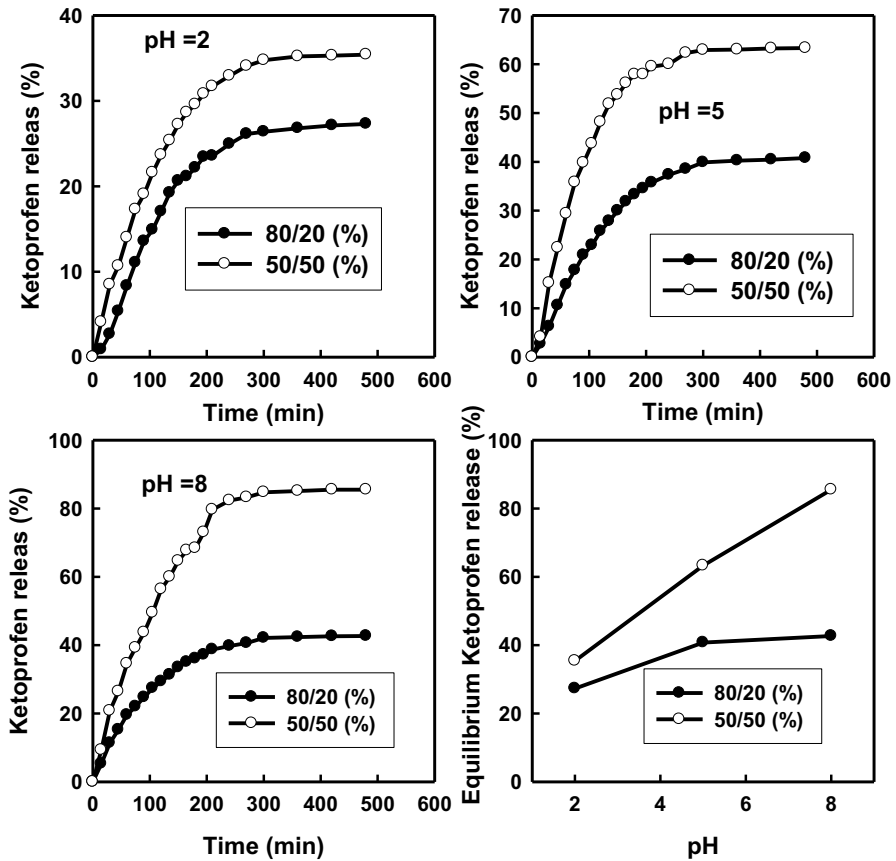


Fig. 10 Ketoprofen release profiles at room temperature and in buffer solutions of various pH values and the effect of pH on the equilibrium drug release from PAM/AG copolymer hydrogels, prepared by gamma irradiation to a dose of 20 kGy

by gamma irradiation to a dose of 20 kGy in illustrated in Fig. 12. The calculated data parameters for " n " and " k " are presented in Table 2. Based on the data on Table 2, few conclusions may be outlined:

- (1) The " n " values for the drug delivery of Tetracycline from PAM/AG blend hydrogels was calculated to be ~ 0.5 indicating a Fickian release mechanism, where the drug delivery diffusion is controlled, regardless of the pH value or blend hydrogel composition.
- (2) The " n " values for the drug delivery of Ketoprofen from PAM/AG blend hydrogels were calculated to be $0.5 < n < 1$ indicating anomalous non-Fickian type release [39]. It may be deduced that the drug release of Ketoprofen from the

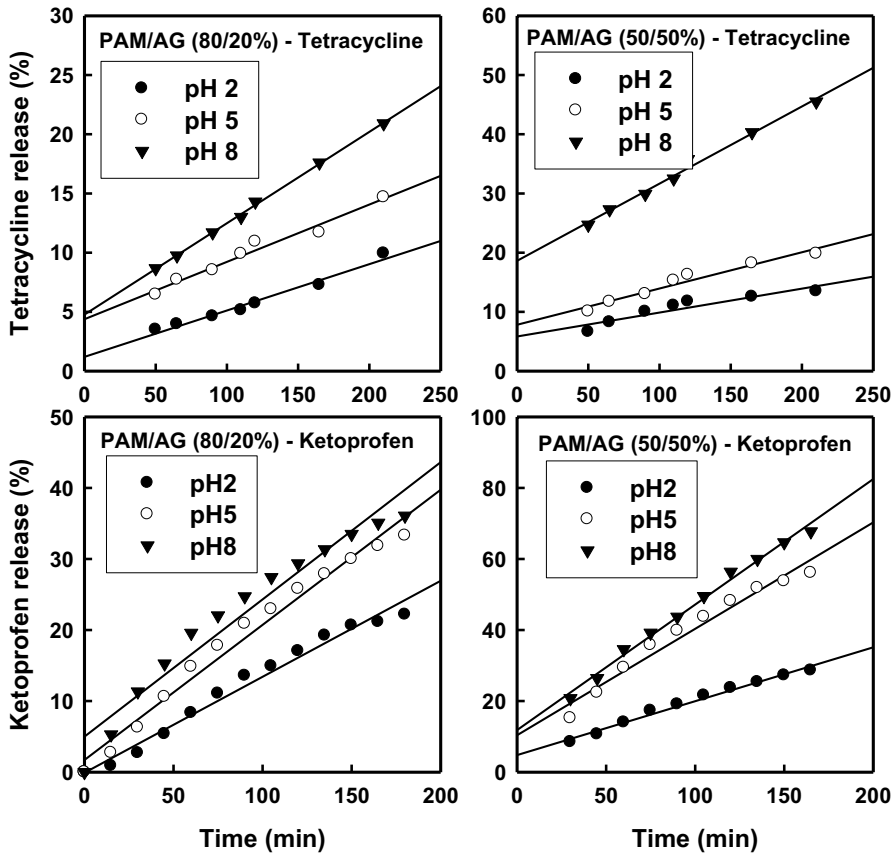


Fig. 11 The rate of release of the tetracycline and ketoprofen drugs from PAM/AG copolymer hydrogel at different ratios, prepared by gamma irradiation to a dose of 20 kGy

hydrogel networks depends on the structure and pathways of water through the networks rather being controlled.

- (3) The lower accumulated release values rate at pH 2 may be explained as follows: Since the blend hydrogel chains would combine via hydrogen bonding and electrostatic interaction at acidic condition, it is hard to relax, and only a part of Tetracycline or Ketoprofen drugs could enter into the buffer solution, which causing a lower release. Thus, the release behaviors of Tetracycline and ketoprofen from the PAM/AG hydrogels would be higher in alkaline medium rather than in acidic medium.

Table 2 Drug release kinetics of the plots of $\ln F$ versus $\ln t$ for Tetracycline and Ketoprofen release profiles at room temperature and in buffer solutions of various pH values from PAM/AG blend hydrogels at different ratios prepared by gamma irradiation to a dose of 20 kGy. In addition, the rate of the release (%/min) of the same drugs from PAM/AG blends hydrogels under the same conditions is presented

PAM/AG (%)	pH	Drug release kinetics					
		Tetracycline			Ketoprofen		
		n	k	R_T	n	k	R_K
80/20	2	0.52	0.0437	0.039	0.82	0.0118	0.135
	5	0.49	0.0563	0.048	0.71	0.0208	0.190
	8	0.46	0.0722	0.077	0.55	0.0483	0.193
50/50	2	0.47	0.0739	0.050	0.64	0.0297	0.152
	5	0.48	0.0572	0.061	0.56	0.0507	0.299
	8	0.45	0.0754	0.130	0.66	0.0266	0.353

The regression factor (r^2) = 0.97638–0.99517 is related to the average regression factor of the straight-line plots of $\ln F$ versus $\ln t$ (Fig. 12). R_T and R_K are the rate coefficient of the release (% release/min) of Tetracycline and Ketoprofen drugs (Fig. 12)

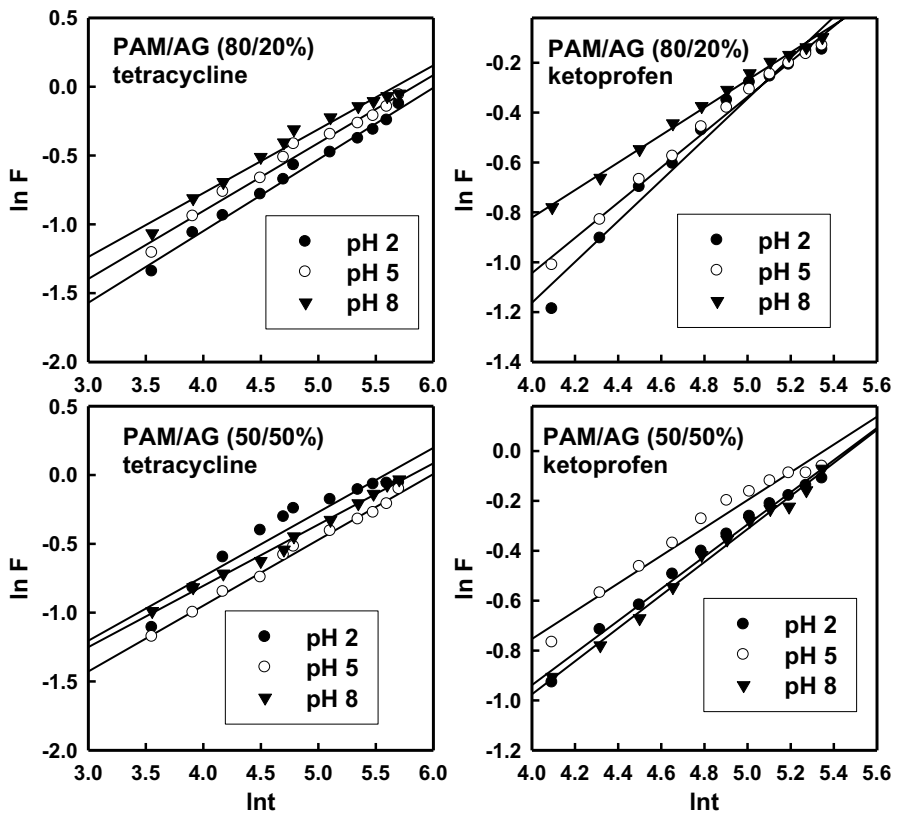


Fig. 12 Plots of $\ln F$ versus $\ln t$ for tetracycline and ketoprofen drugs release profiles at room temperature and in buffer solutions of various pH values from PAM/AG blend hydrogels at different ratios prepared by gamma irradiation to a dose of 20 kGy

Conclusions

In this study, films of a new pH-sensitive blend hydrogel based on polyacrylamide (PAM) and sodium alginate (AG) were successfully prepared by gamma radiation. The results indicated that the pH-sensitivity of PAM/AG hydrogels was greatly affected the swelling in water and the drug release characters. The uptake and release of Tetracycline drug increased with the increase in AG ratio in the blend mixture. At pH range 2.1–5, the drug accumulated release ratio from the hydrogel films is slower than that at pH 7.4–8, and decreased with increasing PAM ratio. These affairs hold true in the case of ketoprofen drug. At pH 7.4–8, the drug release mechanism of the hydrogel films was swelling-controlled. The results indicated that introducing AG in polymeric network might present simple and unique ways to prepare new controlled drug delivery systems.

Author contributions All authors contributed to the study conception and design. Material preparation: FIAEF, Data collection and analysis: HMNED. The first draft of the manuscript: AWMEN, and HMNED. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials The authors declare that the data and materials are available.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Consent for publication The authors declare no conflict of interest regarding the publication of this paper.

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