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Synthesis and Characterization of (Methyl Methacrylate/Phenyl Acrylamide) Hydrogel for Biomedical Applications

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Abstract

The basic explorations of structure property correlations and the variety of commercial and biological applications all attest to the fact that amphiphilic is highly useful. In this work, the monomer phenyl acrylamide was synthesized by reacting acrylamide with chloro benzene in the presence of pyridine. Two series of Poly (phenyl acrylamide-co-methyl methacrylate) (poly(PAAm-co-MMA)) hydrogels have been prepared, series 1 composed of PAAm/MMA copolymers covering a range of composition (60-90% PAAm) while series 2 composed of 90PAAm/10MMA copolymer containing 1, 2, 3, and 4 wt% of N,N'-methylenebisacrylamide (MBAA) as crosslinker. Fourier transform infrared spectroscopy (FT-IR) was used to characterize the resulting monomer and polymers. The effects of the monomer ratio and added crosslinker on the swelling behavior and mechanical properties of poly (PAAm-co-MMA) hydrogels were investigated. Swelling parameters such as volume fraction of polymer (φ_2), weight loss during swelling were determined. Depending on shear and Young's modulus (G and E), network parameters such as polymer-solvent interaction (χ), cross-link density (v_e), and molecular mass between cross-links (Mc) were calculated. The ability of series 1 hydrogels for use in controlled release of drugs such as ciprofloxacin was also studied. Results revealed that during the first 10 hours, most of the drug load is released.

Keywords: Phenyl acrylamide-co-methyl methacrylate; controlled load and release; swelling parameters; mechanical properties; crosslinking density.

1. Introduction

New scientifically and commercially relevant materials can be obtained when two distinct monomers with various physical and or chemical attributes are incorporated in the same polymer molecule at different ratios [1, 2]. Hydrophilicity, softness and oxygen permeability are the qualities that polymeric materials must fulfil to permit their use in certain medical application fields [3, 4]. The usefulness of a range of polymeric materials in applications related to medical fields (e.g. contact lenses) has already been demonstrated [5]. However, despite their properties that make them suitable for different medical applications, polymeric materials also have features that constrict their use. For example, the Poly methylmethacrylate (PMMA) material employed in contact lenses lacks sufficient oxygen permeability and hydrophilicity, despite possessing the qualities of rigidity and durability [6]. On the other hand, the Poly hydroxyl ethylmethacrylate (PHEMA) material used in hydrogel contact lenses does possess hydrophilicity and softness, but it is not durable or dimensionally stable and lacks sufficient oxygen permeability [7, 8]. Similarly, another polymeric material popular in medical applications is silicone rubber, which displays softness, durability and high oxygen permeability, although it lacks hydrophilicity [9].

It is obvious that combining a hydropholic and a hydrophilic group in a polymer can result in a biomedical material with desirable qualities such as transparency, chemical stability, soft when absorbs high water amount, a moderate elastic modulus, and oxygen permeability [10-12].

Based on what has been reported before, two types of monomers have been chosen to prepare hydrogels for biomedical applications: Phenyl acrylamide (PAAm) was synthesized as the

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hydrophilic component. Its high water content causes mechanical instability, but it is transparent and oxygen-permeable. Methyl methacrylate (MMA) was chosen as the hydrophobic component, PMMA has transparency and low wettability. However, a copolymer of these two chemicals exhibits a wide range of incompatibilities. This is interphase with a third component, N,N'-methylenebisacrylamide (MBAA), besides of its main function as a cross-linking agent.

2. Materials and Methods

2.1. Materials

The raw materials were all obtained from Aldrich-oma chemical Co. Phenyl acrylamide monomer was prepared by combining chloro benzene with acrylamide in the presence of pyridine at 40°C for four hours until a white precipitate appeared. The result was then poured onto a watch glass, filtered, and recrystallized with methanol before being dried at 40°C. The initiator (BPO) was recrystallized from chloroform; it is filtered and dried under reduced pressure in the presence of calcium chloride. The crosslinker N,N'-methylenebisacrylamide (MBAA), dichlorodimethylsilane (DMDCS), and all solvents have been used as received.

2.2. Copolymers Preparation

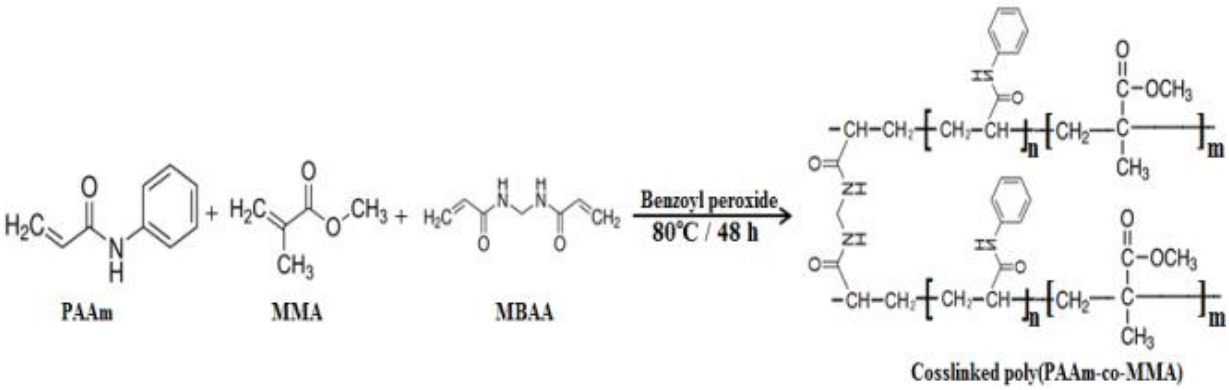
The isothermal condition during the polymerization was achieved by using sample ampoules with appropriate surface area and a diameter of 13 mm. To facilitate removing polymer rods, the ampoules were siliconized using a 2% solution of (DMDCS) in chloroform and stored in an air oven for one day at 75 °C. For each composition, the appropriate amounts of PAAm, MMA, MBAA, and BPO were dissolved in 80% aqueous ethanol, the initiator used (0.5% (w/w)) is based on the total weight of the mixture. The copolymers xerogels containing 60, 70, 80 and 90% PAAm molar ratio were designated P_1, P_2, P_3, and P_4, respectively. To produce xerogels with varied cross-linking density, different cross-linking agent ratios were used to synthesize copolymers xerogels prepared by 90% PAAm to 10% MMA feed ratios. The xerogels containing 1.0, 2.0, 3.0, and 4.0% cross-linking agent were designated P_{1a}, P_{1b}, $P_{1c,}$ and P_{1d}, respectively; the compositions of series 1 and series 2 are listed in Table 1. Copolymers were prepared as follow: The mixture was stirred for 15 minutes before being put to previously siliconized glass ampoules. Prior to the process and to remove all oxygen, the contents of the tubes were purged with nitrogen for 15 minutes. The glass ampoules were placed in an 80°C water bath for a specific period of time to polymerize (48 h). The temperature is then increased to 90°C, and the tubes are kept for 24 hours in an oven. Polymerization is generally finished at the end of this time, and the polymerized rods are pulled from the tubes. After that, the rods were post-cured at 90°C for 12 hours to finish the polymerization process and remove any mechanical tensions. The rods were cut as discs and dried to a constant weight in a 35 °C oven. All the prepared xerogel discs were of the same diameter and thickness, approximately 0.8–0.9 mm and 2.20–2.25 mm, respectively. The polymerization reaction is described in Scheme 1.

Table 1: Feed compositions of cross-linked (methyl methacrylate-co-phenyl acrylamide) xerogels (series 1 and series 2)

Sample Cod.	Monomer feed ratio PAAm/MMA	Benzoyl peroxide (g) (w/w)	MBAA (g)	Solvent 80% aq. Ethanol,
P_1	90/10	0.051	0.088	15 ml
P_2	80/20	0.043	0.087	15 ml
P_3	70/30	0.055	0.079	15 ml
P_4	60/40	0.042	0.091	15 ml
P_{1a}	90/10	0.061	0.167 (4%)	15 ml
P_{1b}	90/10	0.068	0.125 (3%)	15 ml
P_{1c}	90/10	0.059	0.083 (2%)	15 ml
P_{1d}	90/10	0.073	0.044 (1%)	15 ml

2.3. Fourier Transform Infrared (FTIR) characterization

FTIR Spectra was recorded at room temperature by a Perken Elmer-1650 spectrometer using KBr Pellets in the wavenumber range of 200-4000 cm^{-1}.



Scheme 1. Synthesize of crosslinked PPAA/MMA copolymer from PAAm, MMA and MBAA

2.4. Procedure of Swelling

The discs were swollen at room temperature 25°C. Dry discs of known diameter and weight were placed in containers with (50 ml) volume. The swelling time was measured from the time the vial was filled with deionized water. The swollen discs were removed with tweezers at regular intervals, and the excess water on the discs' surface was removed by wiping with the edge of Whitman No. 1 qualitative filter paper. They were promptly weighed and reverted to their containers. The volume fraction of polymer (ϕ_2), extension ratio (ER), weight loss of xerogels during swelling, and water content (EWC) were calculated as [13]:

$$EWC\ \% = \frac{(W_s - W_d)}{W_s} \times 100 \quad (1)$$

$$Weight\ loss = \frac{(W_0 - W_d)}{W_0} \times 100 \quad (2)$$

Where W_0, W_s and W_d are the weights of the xerogel, swollen sample after 30 days fully hydrated, and after drying in an oven at 40 °C for (48 h), respectively.

$$ER = \frac{d}{d_0} \quad (3)$$

$$\phi_2 = \left(\frac{d_0}{d}\right)^3 \quad (4)$$

Where, d and d_0 are the diameters of fully hydrated and dry discs, respectively. As a result, at equilibrium, the volume fraction of water (ϕ_1) in the hydrogel equals $(1 - \phi_2)$.

2.5. Mechanical Properties Studies

For compression strain–stress testing, an Instron 3366 machine analyzer was used. The samples were sliced into strips with dimensions of ~ (2 mm in thickness, 5 mm in width and 25 mm in length). The load was run at a constant speed of 2 mm/min until the strips were broken. The hydrogels' Young's modulus (E) was calculated from the slopes of plotting the strain (λ-1) versus stress (τ), as shown below:

$$\tau = E(\lambda - 1) \quad (5)$$

Where λ is the ratio of the hydrogel's deformed length (l) to its undeformed length (l_0), and τ is the applied force per unit area of hydrogel. The compression-strain measurements from kinetic theory of rubbery elasticity can be used to calculate the effective crosslinking density (ν_e) [14].

$$\tau = G\ (\lambda - \lambda^{-2}) \quad (6)$$

$$G = R\ T\ \nu_e \phi_2^{1/3} \quad (7)$$

The slope of the stress (τ) versus $(\lambda - \lambda^{-2})$ can be used to calculate (G). In Equation (7), T is the absolute temperature, R is the gas constant (8.314 J K^{-1} mol^{-1}), and ϕ_2 is the volume polymer fraction. The Flory-Rehner equation can be used to determine the polymer/solvent interaction parameter (χ), which describes the specific interaction between water and polymers [15].

$$In(1 - \phi_2) + \phi_2 + \chi\phi_2^2 + \nu_e V_1\left(\phi_2^{1/3} - 2\ \phi_2 f^{-1}\right) = 0 \quad (8)$$

In which f is the functionality of MBAA and V_1 is the molar volume of water (18.05×10^{-3} dm^3 / mol at 298° K) [16]. Equation (10), in which ρ is the density of the xerogel, can be used to determine the molecular mass between cross-links, Mc.

$$M_c = \rho/\nu_e \quad (9)$$

The following relationship was used to determine the theoretical cross-linking density v_t:

$$v_t = C\ f/2 \quad (10)$$

Where, C is the concentration of MBAA. Because f = 4 for MBAA [16], equation (10) is reduced to:

$$v_t = 2C \quad (11)$$

The weight concentration of MBAA was used to determine the values of C by calculating the densities of the xerogels and dividing by the molar mass of MBAA (154.169 gm mol^{-1}).

2.6. Procedure of Drug Loading and Release

0.1 g of xerogel discs were obtained by polishing them with a smooth surface tool and then sunken in 100 mL of ciprofloxacin solution (5 mg/mL) at 37 ^{0}C. Similarly to the swelling procedure, the weight of submerged discs were checked regularly until equilibrium was reached, the discs then dried at room temperature during a week until constant weight. The weight of loaded drug was calculated from the difference between the weight of discs before and after loading.

For release measurement, the loaded discs were placed in 300 ml saline solution under magnetic stirring; the pH and temperature were adjusted to 7.3 and 37 °C, respectively. During 48 h, aliquots of 1 ml were withdrawn and replaced with fresh saline solution. After that, each removed sample was diluted and analyzed at 270 nm using a double-beam UV-Vis spectrophotometer. To estimate drug concentration at each time, the absorbance of each sample was compared to a calibration curve. Differences in the solubility parameter or Hildebrand parameter (δ), estimated from equation 12, can be used to measure the interaction between CPR (drug model) and the hydrogels:

$$\delta = \frac{\sqrt{Ecoh}}{V} \quad (12)$$

where, V represents the molar volume (cm^3/mol) and E_{coh} is the cohesive energy (J/mol). Both parameters can be calculated using various tabulated values. Since then, E_{coh} has been regarded as an additive characteristic. The group contribution theory can be used to estimate for a particular molecule.

3. Results and Discussion:

3.1. Characterization

The structure of PAAm and PAAm-co-MMA are confirmed by FITR as shown in Figure 1a and Figure 1b, respectively. PAAm-co-MMA: the carbonyl absorption of MMA observed at 1730 (ester C=O), 1680 (amide C=O). A broad band at 3400 cm^{-1} corresponded to the N-H asymmetrical stretching vibration of the second amide. A band at 1330 cm^{-1} corresponded to C-N and N-H stretching vibration. The sharp band at 1430 cm^{-1} is attributed to the C-N stretch vibration. A peak at 3210 cm^{-1} is attributed to the C-H stretching vibration on the benzene ring. The peaks at 2850 cm^{-1} are attributed to C-H symmetrical stretching on CH_2 group. The multiple bands between 1050-1250 cm^{-1} belong to C-O-C in MMA. A band at 780 cm^{-1} is ascribed to C-H out-of-plane wagging vibration from the substituted benzene ring and a band at 620 cm^{-1} is attributed to C-C twisting vibration of the phenyl ring. Furthermore, absence of olefinic double bond peak in PAAm-co-MMA (Figure 2b) while its presence in respective monomer PAAm (Figure 1a) at about 1590 cm^{-1} supports the formation of polymers.

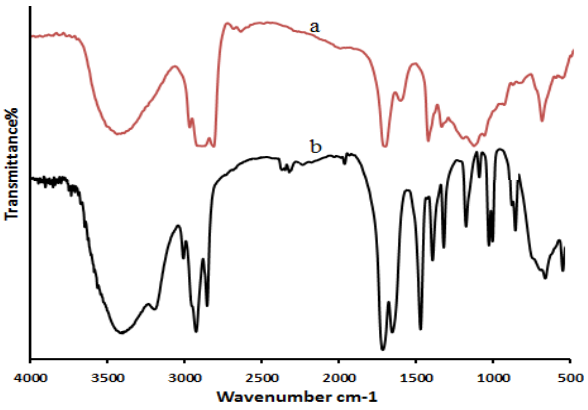


Fig. 1. FT-IR spectrum of (a) phenyl acrylamide monomer (b) PAAm-co-MMA

3.2. Results of Series 1 (P1-P4)

3.2.1. Swelling Parameters

Table 2 summarizes the swelling properties of series 1 polymers. Within the concentration range of 10 – 40 wt % MMA, the effect of increasing the amount of the hydrophobic monomer in the feed mixture on the swelling of the hydrogel was evaluated. Because of the decreasing hydration degree of the gel, an increased amount of MMA lowers the swelling capacity of the hydrogels. The amount of weight loss during swelling in the prepared xerogels decreases, with increasing MMA contents. This is a common results that has been reported in a number of different investigations [17].

Table 2: Swelling parameters of PAAm/MMA hydrogels of different copolymer composition

PAAm/MMA	EWC%	ER	ϕ_2	ϕ_1	Weight loss%
90/10	71.31	1.66	0.279	0.721	22.11
80/20	68.01	1.51	0.399	0.601	18.47
70/30	64.78	1.37	0.423	0.577	14.95
60/40	61.88	1.29	0.509	0.491	13.88

3.2.2. Loading of Ciprofloxacin Drug

Figure 2 shows the loaded amount of ciprofloxacin drug in the (poly(PAAm-co-MMA) with different monomer ratios (60-90% PAAm). The results reveal that an increase of loaded ciprofloxacin drug is observed with the increase in methyl methacrylate mole ratio in the feed composition. This result could be explained in term of a preferred ciprofloxacin drug interaction with poly methyl methacrylate over poly phenyl acrylamide for. This behavior is supported by the fact that the difference between the values of solubility parameters (δ) for the pair ciprofloxacin/poly methyl methacrylate (34.8 J/cm^3) is lower than for the pair ciprofloxacin/poly phenyl acrylamide (171.6 J/cm^3) [18].

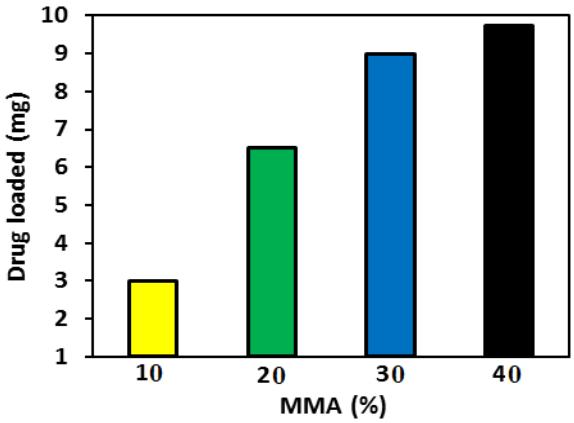


Fig. 2. Ciprofloxacin content loaded as a function of MMA feed ratio

3.2.3. Release of Ciprofloxacin Drug

The concentration of released ciprofloxacin was measured at λ = 270 nm by UV-vis spectroscopy. Based on the data of solubility parameters (δ) which have been reported before, ciprofloxacin would prefer to interact with the poly methyl methacrylate segments of the hydrogel than with the solvent itself (see the scheme in Figure 3c). Figure 3b shows the dependence of cumulative ciprofloxacin release on the methyl methacrylate amount in the feed composition. The results reveal that there is an increasing in the concentration of ciprofloxacin release as the relative quantity of methyl methacrylate decreases, having a minimum for the composition 60PAAm/40MMA hydrogel. In the case of composition 90PAAm/10MMA hydrogel, the cumulative release is close to 82 %, indicating that

the ciprofloxacin has been completely released. 70PAAm/30MMA and 80PAAm/20MMA hydrogels, on the other hand, presented an incomplete release with 61 and 68%, respectively. At the same time, the cumulative drug release isotherm for 90PAAm/10MMA shows a steady increase in ciprofloxacin concentration until it reaches equilibrium after around 10 hours. The cumulative drug release isotherm depicted for 90PAAm/10MMA presents a sustained increase of ciprofloxacin concentration until the equilibrium is reached after approximately 10 h (Figure 3a). These are common findings and have been frequently reported in many other investigations, in which similar release behavior of ciprofloxacin drug has been obtained for other systems [19-21].

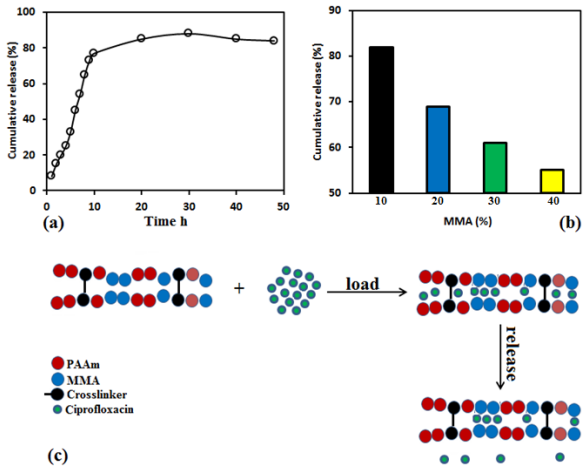


Fig. 3. (a) Cumulative Ciprofloxacin release using 90PAAm/10MMA copolymer as drug carriers. (b) Cumulative Ciprofloxacin release as function of the weight proportion of MMA in the feed (c) Schematic of Ciprofloxacin loading and releasing from the hydrogel.

3.3. Results of Series 2 (P1a-P1d)

3.3.1. Swelling Parameters

Table 3 shows the swelling parameters. As expected, the parameters increase with decreasing amount of MBAA present in series 2 polymers. Generally, a higher MBAA content led to a stronger gel with lower water content. This was expected because of the increasing crosslinker density, which limited the diffusion of water molecules into the gel network. As a result, in the equilibrium swollen state, the hydrogel with a high level of MBAA absorbs less water. Another possibility for the observed result is that as the number of crosslinks in the hydrogel grows, the molecular weights between them fall, reducing the free space between macromolecular chains and making them more accessible to penetrant water [22, 23]. The weight loss in hydrogels (22%) is reduced to almost half its original value (10%) when the crosslinker is increased to 4 wt%.

Table 3: Swelling results of 90PAAm/10MMA samples with various amount of MBAA

MBAA %	EWC%	ER	ϕ_2	ϕ_1	Weight loss%
1.0	72.46	1.66	0.279	0.721	22.11
2.0	63.79	1.45	0.428	0.572	16.45
3.0	58.18	1.19	0.501	0.419	12.79
4.0	52.14	0.93	0.614	0.386	10.01

3.3.2. Mechanical Properties

To study the mechanical properties of synthesized hydrogels, the tensile test was used. Crosslinked density affects not just the swelling of materials but also their mechanical performance in crosslinked materials such as hydrogels. The effect of MBAA concentration on the stress-strain behavior for swollen 90PAAm/10MMA copolymers at equilibrium are represented in Table 4. According to stress-strain tests, an increase in MBAA concentration leads to a continual increase in Young's and shear modulus. The amount of water found on swelling is inversely proportional to the extent of crosslinking in the network, and directly proportional to the Young's modulus, which is substantially smaller for hydrogels that exhibit more swelling. For a small strain, the ratio of E over G for an elastic hydrogel should be equal to 3.0 [24, 25]. The values of E/G for the data sets in Tables 4 do not differ considerably from the average value of 2.791. Thus, the system could be considered as elastic materials and fit with the properties of hydrogel which is used for biomedical applications.

Table 4: Tensile results of 90PAAm/10MMA samples with various amount of MBAA

MBAA content %	Young's moduli (E) (Mm^{-2})	Shear moduli (G) ($MN\ m^{-2}$)	E/G
1.0	0.877	0.301	2.913
2.0	1.893	0.711	2.662
3.0	2.949	1.081	2.728
4.0	4.512	1.521	2.966

3.3.3. Network Structures

Table 3 shows the theoretical and effective crosslinking density. Increased crosslinking agent content improved hydrophilic bonding, resulting in an increase in effective crosslink density. Another structural measure that characterizes the three-dimensional network structure is the average molecular weight between consecutive crosslinks (Mc). It is proportional to the density of crosslinks. Table 4 lists the Mc values determined for each gel system. The results reveal that the concentration of MBAA has an effect on the average molecular weight between crosslinks, and that the average molecular weight between crosslinks decreases significantly as the crosslinking concentration increases. At swelling equilibrium, the polymer-solvent interaction

parameter provides the dominant interaction between water and polymers. Values of $\chi > 0.50$ indicate that the solvent used is thermodynamically inefficient. The values of the polymer-solvent interaction parameter are shown in Table 5; an increase in MBAA content resulted in a decrease in χ. The relative hydrophilicity of the MBAA explains this tendency. All computed values were more than 0.50, indicating that increasing the MBAA concentration reduces the polymer/water interaction.

Table 5: Network parameters of hydrogels with various amount of MBAA

MBAA %	χ	Mc× 10^{-3} (g mol^{-1})	v_t (mol dm^{-3})	v_e (mol dm^{-3})
1.0	0.712	4.861	0.312	0.388
2.0	0.688	4.021	0.471	0.523
3.0	0.611	3.198	0.509	0.577
4.0	0.597	2.766	0.621	0.734

4. Conclusion

In this research, detailed properties of two series of the prepared copolymers, crosslinked (phenyl acrylamide-co-methyl methacrylate), were studied to evaluate their performance as a novel materials used for biomedical applications. The swelling parameters increased, with an increase in the PAAm content whilst decreased with an increase in the crosslinker amount. Stress-strain measurements for 90PAAm-co-10MMA containing different amount of crosslinker yielded polymer-water interaction parameters, effective crosslinking density, and Young's module. The released drug amount decreased with increasing MMA content of the hydrogels. By combination with PMMA beads, the hydrogels of series 1 could be used to overcome the issue of the current bone cement while study the properties of series 2 polymers showed that their hydrogels have potential to be used as contact lens material.

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