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Synthesis, Characterization, and Swelling Behavior of New pH-Sensitive Hydrogels Derived from Copolymers of 2-Hydroxyethyl Methacrylate and 2-(Diisopropylamino)ethylmethacrylate

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ABSTRACT: The aim of this work was to synthesize and to characterize new pH-sensitive hydrogels that can be used in the controlled release of drugs, useful for dermal treatments or ophthalmology's therapies. Copolymers containing 2-hydroxyethyl methacrylate (HEMA) with different amounts of 2-(diisopropylamino)ethyl methacrylate (DPA) (10 and 30 wt %) and different amounts of crosslinker agent, ethylene glycol dimethacrylate (EGDMA) (1 and 3 wt %) were prepared by bulk photo-polymerization. The copolymers were fully characterized by using Fourier-transform infrared (FTIR) spectra, differential scanning calorimetry, thermogravimetric analysis, UV–visible spectroscopy, and measuring water content and dynamic swelling degree. The results show that modifications in the amount of DPA and/or crosslinker in the hydrogel produce variations in the thermal properties. When adding of DPA, we observed an increase in the thermal stability and decomposition temperature, as well as a change in the mechanism of decomposition. Also a decrease in the glass transition temperature was observed with regard to the value for pure pHEMA, by the addition of DPA. The water content of the hydrogels depends on the DPA content and it is inversely proportional to both the pH value and the crosslinking degree. Pure poly-HEMA films did not show important changes over the pH range studied in this work. The dynamic swelling curves show the overshooting effect associated with the incorporation of DPA, the pH of the solution, and the crosslinking density. On the other hand, no important variations in the optical properties were observed. The synthesized hydrogels are useful as a drug delivery pH-sensitive matrix. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: stimuli-sensitive polymers; hydrophilic polymers; drug delivery systems

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INTRODUCTION

Hydrogels are crosslinked hydrophilic polymers capable of imbibing large volumes of water, but insoluble in water because of their network structure. In the last decades, chemically and physically crosslinking hydrogels have been used for a wide range of applications because of their biocompatibility. Hence, they became standard material for scaffolds, corneal implants, contact lenses, and intelligent controlled drug release devices for site-specific drug delivery.[1]

Stimuli-sensitive hydrogels are very attractive materials for application in biomaterials science and technology. This material has the characteristic of changing its structure and physical properties in response to external stimuli such as pH, ionic strength, temperature, or specific chemical compounds. Especially, the utilization of a stimuli-sensitive hydrogel system would be important for drug delivery systems.[2,3] Depending on the type of monomers (i.e., ionic or neutral) incorporated in the gels, they can respond to a variety of external environmental changes. pH-sensitive hydrogels are produced by adding pendant acidic or basic functional groups to the polymer backbone. A significant number of ionic (acidic or basic) monomers were incorporated into hydrogels to improve their environmental response behavior. Ionic monomers like *N*-(3-

aminopropyl)methacrylamide, 2-(dimethylamino)ethyl methacrylate, methacrylic acid, 2-aminoethyl methacrylate and neutral hydrophobic monomers, butyl methacrylate, allyl diglycol carbonate, diallyl phthalate, and methyl methacrylate were used.[4–6] Recently, cationic monomers like 2-(diethylamino)ethyl methacrylate and 2-(diisopropylamino)ethyl methacrylate (DPA) were used in pH-sensitive hydrogels.[7] The pK_a of poly(2-(diethylamino)ethyl methacrylate) is known to be close to a neutral pH (7.0−7.3) and for DPA homopolymer, it is $\sim$ 6.[8] Therefore, the swelling properties of copolymers containing DPA as a comonomer will have a different pH-sensitive behavior.

pHEMA shows outstanding mechanical properties, a very good transparency in visible light and good physiological compatibility. Therefore, it is used for example in the preparation of soft contact lenses. The drawback of this material is its relatively poor oxygen permeability, water uptake,[9] and slow response rate[10,11] for use as drug delivery control system. By copolymerizing with DPA monomer, we expect to improve the properties for use as drug delivery control system.

To our knowledge, no work was reported using DPA as comonomer in HEMA co-polymers and in view of the distinctive physical characteristic of DPA monomer; we felt that a detailed investigation of such HEMA-based hydrogels was warranted.

In our case, we propose the use of DPA monomer for the synthesis of copolymers with HEMA that respond to pH variations in the lacrimal range of pH (6.5−8.5, mean 7.4).

In this work, copolymers containing HEMA polymerized with different amounts of DPA monomer (10 and 30 wt %) and different amounts of crosslinker agent (1 and 3 wt %) were prepared and characterized by using Fourier-transform infrared (FTIR) spectra, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA-DTA), UV–visible spectroscopy, while measuring water content (WC) and the dynamic swelling degree of water. The influence of DPA on swelling behavior, optical transmittance, thermal properties, and pH sensitivity was evaluated.

Previous work in our laboratory has shown that the copolymerization of HEMA and DPA produce good film-forming systems, but by changing the HEMA/DPA ratio we observed that 60/40 ratio and 0.5 wt % of EDGMA were not suitable compositions in terms of film quality, so in this work the maximum amount of DPA used was 30 wt % and the minimum amount used of EDGMA was 1 wt %.

EXPERIMENTAL

Materials

2-hydroxyethyl methacrylate (HEMA, 97%) and the crosslinker, ethylene glycol dimethacrylate (EGDMA, 98%), were purchased from Sigma-Aldrich, while DPA were purchased from Scientific Polymers Products. The chemical structures of the monomers are shown in Figure 1. The monomers were treated with basic alumina to remove the inhibitor and verify that it was completely removed by ^{1}H-RMN and FTIR. Darocur TPO (97%) from Sigma-Aldrich was used as the initiator (Figure 1). The initiator and the crosslinker agent were used without further purification. The phosphate-buffered solutions (PBS) were prepared from standard chemicals.

Polymer Synthesis

The synthesis was performed in bulk by free radical polymerization using the photoinitiator Darocur TPO [diphenyl(2,4,6-trimethylbenzoyl)-phosphine oxide]. Different ratios of HEMA/DPA and crosslinker (EGDMA) were mixed with 1% w/v of photoinitiator (see Table I). The mix was purged with bubbling nitrogen for 20 min and then injected into a mold composed of two thick glass plates (90% transmission at 350–370 nm) separated by a Teflon spacer 0.2 mm thick (Figure 2). The polymerization was carried out by irradiating with UV light at 350 nm during 55 min using a Rayonet RPR3500 lamp. The film samples were denoted by using a short-hand notation H/D-n, where H/D denoted the HEMA and DPA ratio and n the amount of crosslinker. After polymerization the films were immersed in distilled water for 7 days to remove unreacted chemicals. The water was changed every 24 hr and the washing process was

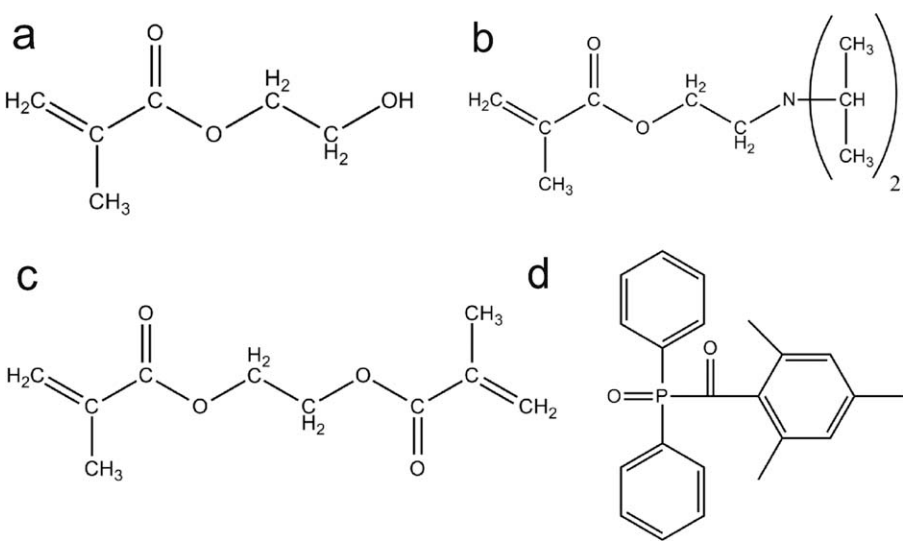

Figure 1. Chemical structures of HEMA (a), DPA (b), EGDMA (c), and Darocur TPO (d).

Table I. Composition of *p*(HEMA-*co*-DPA) Films Prepared in This Work

Name	HEMA wt %	DPA wt %	EGDMA wt %[a]
HD100/0-1	100	0	1
HD100/0-3	100	0	3
HD90/10-1	90	10	1
HD90/10-3	90	10	3
HD70/30-1	70	30	1
HD70/30-3	70	30	3

[a]Relative to the whole monomer.

followed by UV–visible spectroscopy (190–300 nm). The films were cut into circular pieces (∼ 13-mm diameter) with a cork borer and dried at 25°C for 48 h and then stored in desiccators with silica gel until used for the experiments.

FTIR Spectroscopy

The FTIR spectra were measured in transmission mode using a FTIR Nicolet 380 spectrometer, Thermo Scientific, USA. Samples were powdered mixed with KBr and disks were formed by pressing. The FTIR spectra were obtained by recording 64 scans between 4000 and 400 cm^{-1} with a resolution of 4 cm^{-1}. Spectra processing was performed using the software EZ Omnic.

TGA-DTA

TGA-DTA was performed using a DTG-60, Shimadzu Scientific Instrument, USA. Approximately 5 mg of dry sample was sealed into an aluminum pan. The sample was heated at a rate of 10°C min^{-1} from 40 to 500°C under a nitrogen flow rate of 50 mL min^{-1}.

Modulated DSC

The glass-transition temperature, T_g, of the polymeric materials was measured with a modulated differential scanning calorimeter (Modulated DSC Q 200, TA Instruments, USA). Nitrogen was used as a purge gas at a flow rate of 30 mL min^{-1}. An empty hermetic aluminum pan was used as a reference and the heating/cooling rate was 2.5°C min^{-1}, modulated by a sinusoid with amplitude 1°C and period 60 s. The temperature range was −30°C to 200°C. All glass-transition temperatures were determined from the inflection point in the reversing heat flow (RHF) signal with the TA Instrument Analyzer Software.

Light Transmission of Films

Hydrogel films fully hydrated in PBS at different pH values (between 6.5 and 8.5) were mounted on one side of the outer surface of a quartz cuvette.[12] The transmittance from 350 to 700 nm was measured using a Fluorat-02-Panorama spectrophotometer, Lumex, Russia.

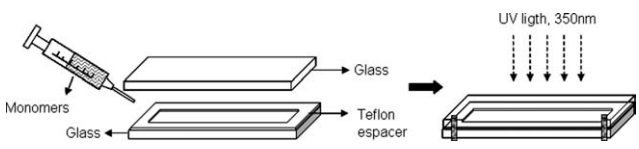

Figure 2. Schematic representation of the polymerization system.

Water Content

The WC of the films was determined by immersing the samples (13.0-mm diameter disk and 200-μm thickness) in a phosphate buffer solution (PBS, ∼ 0.1*M*) at the desired pH (ranging from 6.0 to 8.5) and a temperature of 25°C until reaching the swelling equilibrium. The WC was determined using eq. (1).

$$WC = \left[\left(W_{s,\infty} - W_d\right)/W_{s,\infty}\right] \times 100 \quad (1)$$

where $W_{s,\infty}$ is the weight of swollen film at equilibrium and W_d is the weight of dry film.

Dynamic Swelling Degree

For the determination of the dynamic swelling degree, dry samples were immersed in PBS (0.1*M*) at the desired pH (ranging from 6.0 to 8.5) at 25°C. At regular periods of time, the samples were removed from the aqueous solution, blotted with filter paper to remove surface liquid, weighed and returned to the same container until weight stabilization was observed.

The degree of swelling (Q_t) at time t, was calculated using the following equation:

$$Q_t = \left[\left(W_{s,t} - W_d\right)/W_d\right] \times 100 \quad (2)$$

where W_d and $W_{s,t}$ are the weights of the dry and swollen film at time t, respectively.

The equilibrium swelling degree (Q_∞) was calculated using the following equation:

$$Q_\infty = \left[\left(W_{s,\infty} - W_d\right)/W_d\right] \times 100 \quad (3)$$

RESULTS AND DISCUSSION

Characterization of the Poly(HEMA-*co*-DPA)

Figure 3 shows the FTIR spectrum of pHEMA. The most important bands are at ∼ 3431 [ν(OH)], 2987 [ν (CH_3)as, ν (CH_2)as], 2952 [ν (CH_2)s, ν (CH_3)s], 2887 [δ(CH_3)], 1728 [H-bonded ν (C=O)], 1745 [free ν (C=O)] 1486 [δ (CH_2)], 1454 [δ (CH_2), δ (CH_3)as], 1390 [δ (CH_3)s], 1366 [ω (CH_2)], 1276 [ω (CH_2), δ (CH)], 1252 [ν (C—O)], 1160 [γ(CH_3), τ(OH)], 1076 [ν (O—C), alcohol], 1023 [ν (C—O), ester], 966–800 [ν (C—C), γ (CH_3), γ (CH_2)], and 750 [δ (O=C—O] cm^{-1},[13,14]

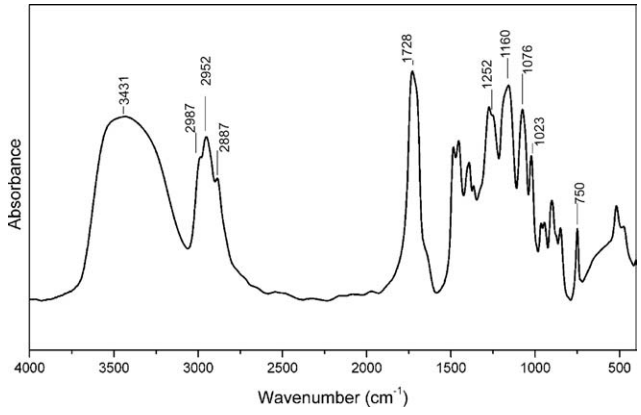

Figure 3. FTIR spectrum of pHEMA.

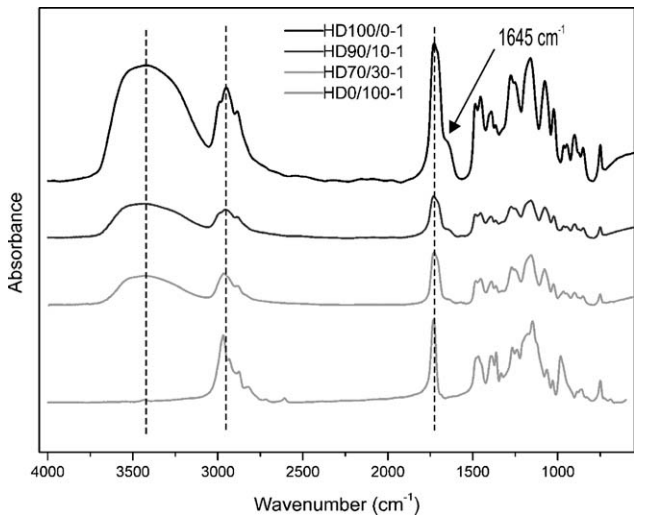

Figure 4. FTIR spectra of pHEMA, HD90/10, HD70/30, and pDPA, all with 1 wt % of crosslinker.

where ν is the stretching vibration; δ, the bending; ω, the wagging; γ, the rocking; and τ, the torsion modes.

Figure 4 shows the FTIR spectra of p(HEMA-*co*-DPA) films with 1 wt % of EGDMA. A progressive change in the bands of the FTIR spectra is observed when increasing the amount of DPA monomer. The most important feature when going from pure pHEMA to p(HEMA-*co*-DPA) is the decrease in intensity of the band centered at 3430 cm^{-1} (decrease of OH groups from HEMA and water) and the shoulder at 1645 cm^{-1} due to a loss of hydrogen-bond interactions with the carbonyl group.

A close examination in the C—H stretching region also shows the contribution of the DPA monomer: the characteristic peak of the methine group in the isopropyl moiety, $(CH_3)_2$—C*H*—, at 2968 cm^{-1} and those at 2821 and 2718 cm^{-1} for the —CH_2— group close to the nitrogen atom.[15]

Characterization by TGA-DTA

The thermograms (weight loss) of pHEMA and p(HEMA-*co*-DPA) with different HEMA/DPA and crosslinker ratios are shown in Figure 5. The TGA measurements show that these polymers lose water at temperatures in the range of 106–116°C for 1 wt % of crosslinker and in the range of 105–120°C for 3 wt %. All the samples showed residual WC, entrapped inside the network; 6.08 wt % for HD 100/0-1, 5.06 wt % for HD90/10-1, 4.13 wt % for HD70/30-1, 6.63 wt % for HD 100/0-3, 6.43 wt % for HD90/10-3, and 4.96 wt % for HD70/30-3. By increasing DPA content, the residual water decreases, as expected, due to the hydrophobic nature of the neutral DPA (fewer numbers of hydrophilic sites). If we compare the amount of residual water between the samples of differing proportions of crosslinker, we can see that as the crosslinker concentration increases, the residual WC increases. This is probably because, at a high crosslinking density, the mobility of polymer chains during the drying process are limited, which in turn limits the diffusion of water molecules leaving the hydrogel.

The kinetics of the loss of this residual water is similar for all samples as judged by the DTA curves (Figure 6). However, the maximums of the DTA curves shifted toward higher temperatures. The incorporation of DPA causes an increase in the viscosity of the less hydrated network, resulting in a more difficult diffusion through it. The values are 72.3°C for HD 100/0-1, 78.1°C for HD90/10-1, and 79.5°C for HD70/30-1. On the other hand, the maximum temperature for losing water is lower for the higher crosslinking density with a similar composition, indicating a weaker interaction between the water molecules and the polymer matrix. As the crosslinking density increases, there is a subsequent increase in the hydrophobicity.

By incorporating DPA, the thermal stability of hydrogel increases (Figure 6). The initial degradation temperatures are 201.6°C for HD100/0-3, 237.5°C for HD90/10-3, and 250.9°C for HD70/30-3. However, no significant differences are noted in

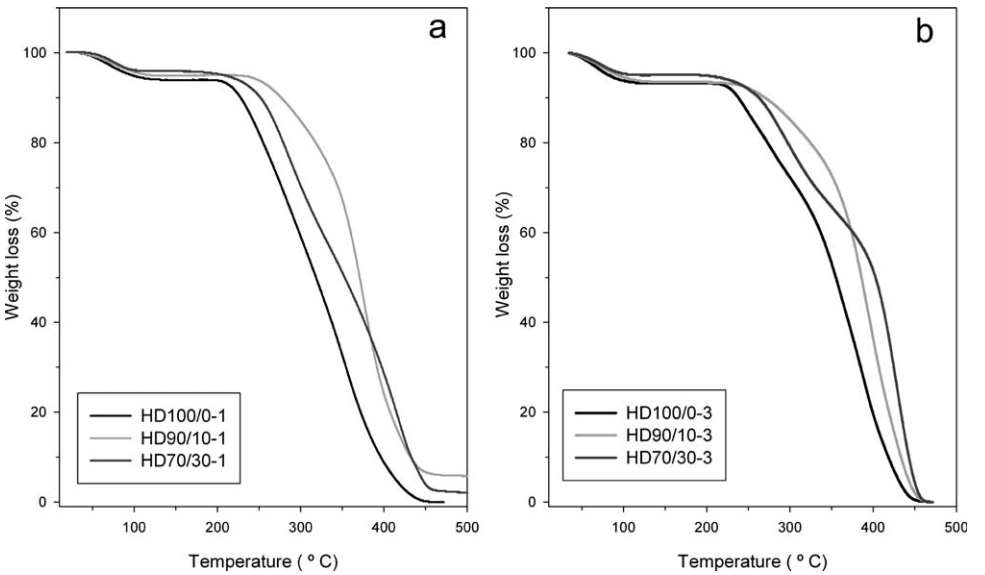

Figure 5. TGA curves of HD100/0, HD90/10, and HD70/30 with 1 wt % (a) and 3 wt % (b) of crosslinker.

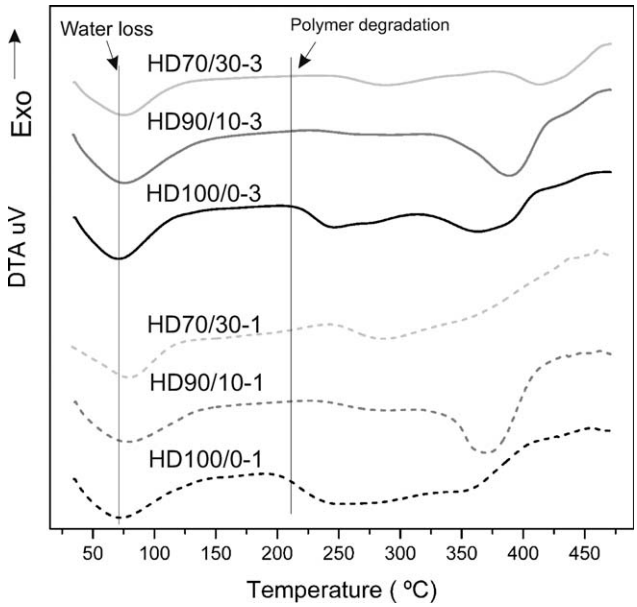

Figure 6. DTA curves of HD100/0, HD90/10, and HD70/30 with 1 wt % and 3 wt % of crosslinker.

the stability of copolymers by changing the crosslinking degree. At higher DPA content, the thermal decomposition mechanism seems to change from a three-step process to a one- or two-step process, and the temperature for the last decomposition step increases in all cases.

The proposed hydrogels are intended to be used for drug delivery, which will normally take place at the physiological temperature of 37°C, so the hydrogels are thermally stable in the vicinity of that temperature and up to the usual temperature of sterilization of 120°C.

Characterization by MDSC

MDSC allows separating reversible and kinetic (non-reversible) phenomena facilitating the T_g determination in hydrogels.[16] The MDSC curves (RHF) for pDPA polymer with 1 wt %, 3 wt % and without crosslinker are shown in Figure 7(a), and for HD100/0-1, HD90/10-1, and HD70/30-1 are shown in Figure 7(b).

The RHF of the MDSC curve of pure pDPA shows a glass transition at $\sim$ 22.5°C [Figure 7(a)]. By addition of EDGMA, the T_g shifted to higher temperatures as a consequence of the restricted motion of chains.[17] The T_g for pHEMA with 1 wt % of crosslinker (HD100/0-1) is observed at 122.5°C, higher than 105.5°C for pure pHEMA reported by Russell et al.[18] As expected, the T_g for copolymers decreases when increasing the DPA content (T_g pDPA = 22.5°C) from 122.5°C to 116°C and 106.3°C for HD90/10-1 and HD70/30-1, respectively. The glass transition of copolymers increases from 115.5°C to 119.4°C for HD90/10 when increasing the crosslinker from 1 to 3 wt %.

Light Transmission of Films

The films have very high transmission in the visible light region which is important for ophthalmic applications. In the range of 350 to 700 nm, the observed transmission is higher than 93% for a film thickness of $\sim$ 200 μm for differing pH values. No differences were observed as the composition and crosslinker quantities were varied. The values obtained are similar to the values published for commercial contact lenses,[19] indicating that those systems are suitable for contact lens application.

Water Content

The water absorbed by a gel network is the most important property influencing the permeability, mechanical, surface, and other properties of the hydrogel.[20] Several characteristics of the polymer are going to influence the WC of hydrogels, such as cross linking density, type of ionic groups in the polymers, pK_a of the ionizables groups and also several factors of the solution, such as ionic strength, pH, and temperature.[21,22] The effect of the composition, crosslinking density, and pH on WC of p(HEMA-*co*-DPA) film at 25°C is discussed in this section. Figure 8 shows the variation of WC for hydrogels as a function of HEMA/DPA ratio, with 1 and 3 wt % of crosslinker agent for pH 6.5 and 7.5 (PBS, 0.1*M*).

At pH 7.5, the increase in DPA content causes an increase in the WC, disregarding the crosslinking concentration. However, the increase is lower for 3 wt % of crosslinker. The WC increase

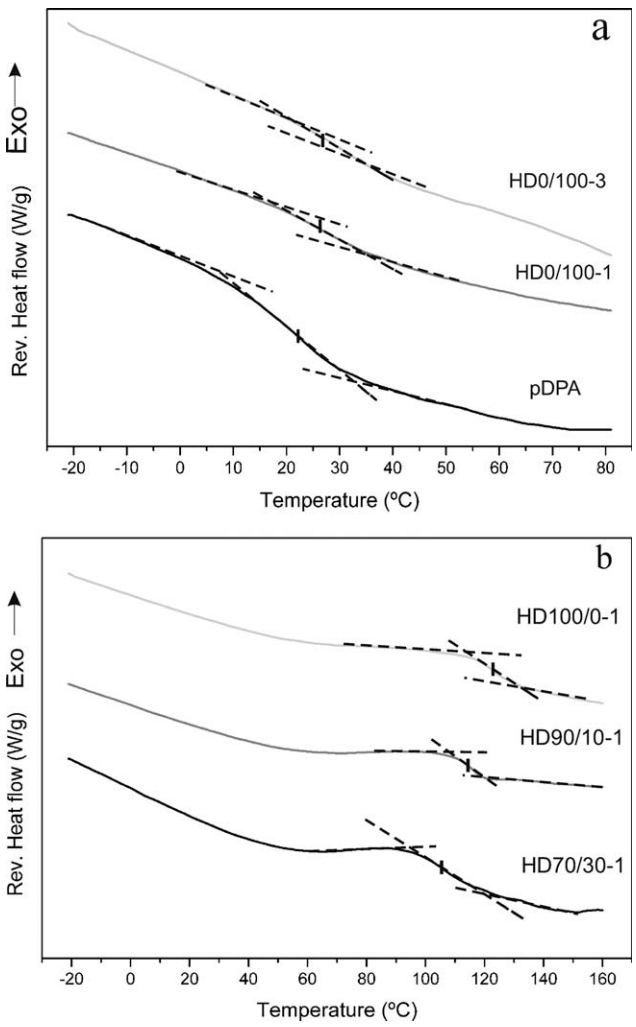

Figure 7. MDSC curves: (a) pDPA, HD0/100-1, and HD0/100-3; (b) HD70/30-1, HD90/10-1, and HD100/0-1 (reversing-heat-flow).

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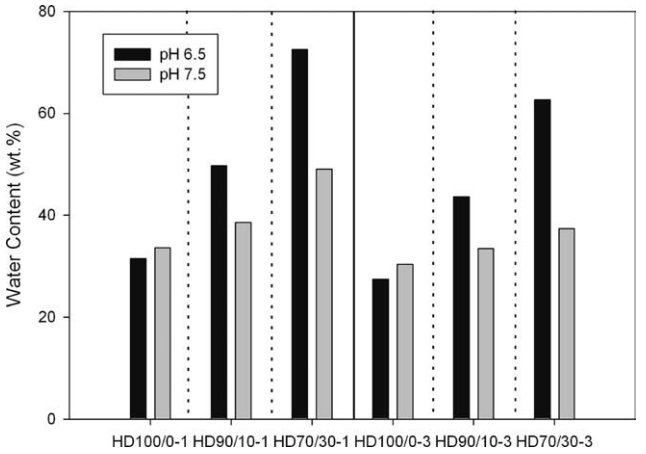

Figure 8. Water content for different HEMA/DPA ratios, with 1 and 3 wt % of crosslinker at pH 6.5 (black bar) and 7.5 (gray bar) at 25°C.

is attributed to the protonation of amino groups and the increase of electrostatic repulsive force between ionized groups. The increase of the network space, in turn, allows water to get into the matrix.[23,24]

The WC at pH 6.5 and 7.5 for pure pHEMA hydrogels is similar (∼ 30 wt %) and slowly increases with the increase of the pH, almost no significant pH-dependence is observed in this pH range. Ferreira et al.[25] reported a pH-dependence but in an ample range from 6.5 to 12.0. Although the p(HEMA-*co*-DPA) shows a very interesting pH behavior. The decrease in the solution pH produces an increase in water swelling due to the increasing degree of protonation of the pendant cationic amine groups of DPA. From swelling experiments (over the pH range of 6.0–8.5), we can estimate that the pK_a of the copolymers are between 7.0 and 7.5. When the pH of the solution became lower than 7.0, the degree of ion groups increased and the effect on the osmotic swelling force by the presence of ions became larger. These characteristics allow the system to control the drug release when the surrounding medium changes.[26]

The effect of the crosslinking density on the WC of pHEMA hydrogels follows the expected trend of decreasing WC with increasing crosslink density.[27,28] For all ratios of HEMA/DPA, the WC decreased when going from 1 to 3 wt % of crosslinker. This effect is due to decrease in the available free space to be occupied by the water and a more rigid three-dimensional structure that limits the mobility of the chains, preventing an increase in the internal volume of the hydrogel. This effect is similar to results reported by other authors.[25,29]

The absolute value of WC is very similar for the equivalent composition of both series of crosslinker copolymers, indicating that the swelling response is more affected by the interaction between both co-monomers than by the crosslinking degree.[30]

Dynamics Swelling

Figure 9 shows the curves of the swelling process of the hydrogels in water at pH 6.5 and 7.5. For sample HD100/0-1 at pH 6.5 and 7.5, the observed curves are similar to those of the typical swelling curves of hydrogels. The swelling process is faster in the first 20 min and then becomes slower until the hydrogel reaches the

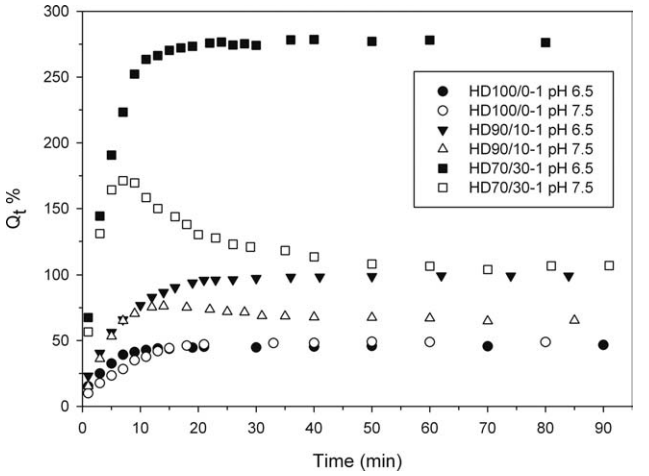

Figure 9. Curves of dynamic swelling HD70/30 and HD90/10, with 1 wt % of crosslinker at pH 6.5 and 7.5.

equilibrium maximum swelling ratio, at about 60 min. At pH 6.5, the initial swelling rate was faster (9 min) than at pH 7.5 (17 min), but there were no differences in the overall kinetic behavior between both of the swelling solutions with different pHs.

However, samples containing DPA at pH 7.5 show an anomalous effect previously reported as overshooting.[30,31] At the beginning, the swelling ratio of samples HD70/30-1 and HD90/10-1 increases, reaching a maximum value, and after that, the water is expelled, while a deswelling step takes place until equilibrium is reached. The absolute value of the overshooting depends on the copolymer composition, increasing with the DPA content. According to Peppa and coworkers[28,31] and Díez-Peña et al.,[30] after swelling, a reorganization of the internal structure of the hydrogel takes place and part of the water is expelled out of the matrix. This reorganization is a consequence of an increment of the physical crosslinking by hydrogen bond formation between the amine groups of the DPA and the carbonyl groups of the HEMA moiety.

A similar case of this overshooting effect has been reported in *N*-iPPAm and MAA copolymers.[30] The overshooting effect is

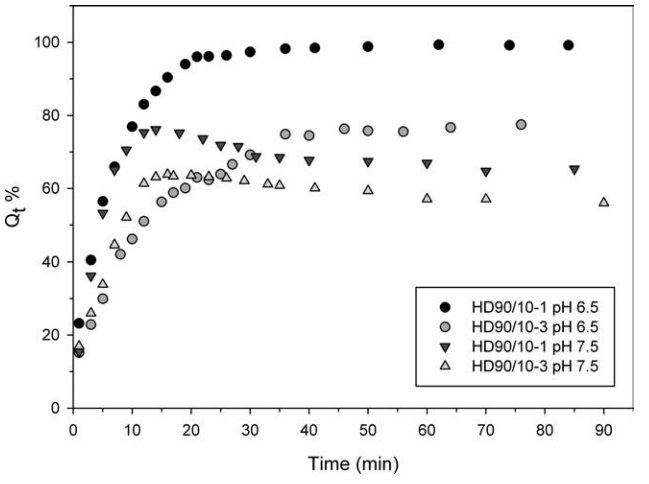

Figure 10. Curves of dynamic swelling. Comparison of crosslinking degree for HD90/10 films with 1 and 3 wt % crosslinker at pH 6.5 and 7.5.

gradually weakened with a decrease of the pH, because the increase of the degree of protonation of the amine groups produces a decrease in the degree of hydrogen bonds. In this way, the capacity of expelling water out of the hydrogels is reduced, and the equilibrium swelling ratio is higher. The same behavior was reported for phospholipid polymers when the solution pH condition turns from carboxyl groups into carboxylate anions, thus avoiding the hydrogen bond formation.[23]

Also the ionization of the pendant groups and the electrostatic repulsion between them, reduce the time required for the relaxation process of the polymer,[24] preventing or decreasing the overshooting effect. The variations of the swelling and overshooting effect as function of the crosslinking degree are show in Figure 10. In the samples, at pH 7.5, the expelled water ($Q_{max} - Q_{\infty}$) is 12.78 wt % for HD90/10-1 and 13.11 wt % for HD90/10-3. These quantities of the overshooting effect are similar when adding crosslinker agent, but the water expelling rates are different. The samples with 1 wt. % of crosslinker expel the water faster than that with 3 wt % of crosslinker. An increase in crosslinking density prevents a rapid mobility of the lateral chains and thereby preventing the consistent formation of hydrogen bonding at short times. On the other hand, for both pH values tested, the swelling rates are slowed down and the equilibrium swelling ratios are reached after a greater amount of time, as crosslinker content is increased.

CONCLUSION

Copolymers of HEMA and DPA, having good film forming and physicochemical properties adequate for ophthalmic drug delivery applications, were prepared and characterized. The incorporation of DPA monomer modifies the interactions between pHEMA chains as revealed by DSC and FTIR analysis, and causes the water uptake process to become pH dependent. At pH 7.5, the copolymers show the overshooting effect at both crosslinker concentrations. The rate of water expelling, to get the equilibrium WC, depends on the DPA content.

The levels of WC in the studied copolymers are adequate for contact lens manufacturing and their release of typical active principles used in ophthalmic therapy are under investigation and the results will be published in due course.

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