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Novel Dual-Stimuli-Responsive Polymers Derived from Ethylpyrrolidine

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ABSTRACT: This paper describes the synthesis and characterization of the new stimuli-responsive polymer poly(*N*-ethylpyrrolidine methacrylate), PEPyM. The polymer exhibits a phase separation transition temperature in water at 15 °C, being also sensitive to pH changes. The phase transition temperature can be modulated up to 80 °C by copolymerizing EPyM with different amounts of *N,N′*-dimethylacrylamide (DMA). EPyM was cross-linked with low amounts of bisacrylamide (B-Aam), and PEPyM gels were also sensitive to temperature and pH, showing a pulsatile behavior in response to both stimuli. The water sorption process (swelling kinetics) of the hydrogels at different temperature and pH was also studied in distilled water and in different buffer solutions.

Introduction

In the recent years, stimuli-responsive polymers have attracted a great interest due to their potential applications in areas such as drug delivery,[1] tissue engineering,[2,3] biosensors,[4] and separation processes.[5] These types of polymers respond with dramatic property changes to small variations of the environment such as temperature, pH, electric field, etc., provoking fast changes in their microstructure from a hydrophobic to a hydrophilic state (sol to gel or collapsed to expanded morphology). These changes can be also reversible as the systems return to their initial state when the stimulus is removed. Many of these polymeric systems are soluble in water[6] but undergo phase transition in response to temperature changes (becoming insoluble when increasing temperature), a transition known as lower critical transition temperature (LCST). When slightly cross-linked polymeric systems are considered (for example, poly(*N*-isopropylacrylamide) cross-linked with small quantity of bisacrylamide), a well-defined first-order transition temperature of the swollen (low temperature) to shrunken or collapsed (high temperature) phase has been observed. This phenomenon has been associated with a LCST by many authors.[7−10]

In general, temperature-sensitive polymers are based on the amphiphilic character, which induces changes in the efficiency of hydrogen bonding. On the other hand, pH-sensitive polymers are usually based on ionisable units which induce neutralization of opposite charges. In this sense, it has to be pointed out that polymers that respond to more than one stimuli, in particular to temperature and pH, are prepared usually by copolymerization reactions[11] of monomers sensitive to temperature such as *N*-isopropylacrylamide (NIPAm)[12,13] and ionizable monomers such as acrylic acid (AA)[14,15] which also have been deeply studied and have found applications in the controlled drug delivery field.[16,17] As far as we know, the only polymer systems described in the literature sensitive to dual stimulus (pH and temperature) are poly((dimethylamino)ethyl methacrylate) (polyDMAEMA)[18] and poly(*N*-acryloyl-*N′*-propylpiperazine).[10]

This article describes the synthesis and characterization of a novel but single methacrylic dual-stimulus (temperature and pH)-sensitive polymer derived from ethylpyrrolidine, PEPyM.

Experimental Section

Materials. *N*-(2-Hydroxyethyl)-2-pyrrolidine (EPy) (Fluka) was used as received. Methacryloyl chloride (Fluka) and triethylamine (Scharlau) were distilled and freshly used (bp = 99 and 89 °C, respectively). 2,2′-Azobis(isobutyronitrile) (AIBN) was purified by fractional crystallization from ethanol (mp = 104 °C). *N,N′*-Dimethylacrylamide (DMA) was vacuum-distilled. *N,N′*-Dimethylformamide (DMF) was distilled (bp = 154 °C) and dried over molecular sieves. Other reagents were used without purification.

Synthesis of EPyM. 2-Ethyl-2-pyrrolidine methacrylate (EPyM) was synthesized by using the following procedure: to a solution of 10 g of 2-hydroxyethylpyrrolidine (0.087 mol) in chloroform (75 mL) with 12.1 mL (0.087 mol) of triethylamine, a solution of 8.3 g (0.13 mol) of methacryloyl chloride in 25 mL of chloroform was added dropwise at 0 °C under a N_2 atmosphere with magnetic stirring.[19] After 6 h of reaction solution was washed four times with aqueous NaOH (5 wt %), dried over anhydrous Na_2SO_4, and then removed the solvent at reduced pressure. The isolated product was purified by column chromatography using tetrahydrofuran as eluent. The yield was 70%. The synthesized monomer EPyM was characterized by the spectroscopic techniques ^1H (see Figure 1) and ^{13}C NMR. EPyM ^{13}C NMR ($CDCl_3$): (CH_2=) δ 127, (=C) 134, (αCH_3) 19, (C=O) 167, (OCH_2) 63, (CH_2N) 63, (NCH_2 cycle) 53, (CH_2CH_2 cycle) 23. PEPyM ^{13}C NMR ($CDCl_3$): (CH_2 main chain) δ 44, (quaternary C) 53, (αCH_3) 18, (C=O) 176, (OCH_2) 63, (CH_2N) 53, (NCH_2 cycle) 53, (CH_2CH_2 cycle) 23.

Synthesis of Polymers. EPyM was homopolymerized at 60 °C by free radical polymerization reaction, using AIBN ([I] = 1.5×10^{-2} mol L^{-1}) as initiator and DMF as solvent ([M] = 1.0 mol L^{-1}). Copolymerization reactions of EPyM with DMA were performed using the same experimental conditions. The monomers solutions were prepared with weight percent feed compositions of EPyM/DMA = 10/90 up to 70/30, and the reaction time was adjusted to reach total conversion. All experiments were carried out in Pyrex glass ampules under oxygen-free N_2 atmosphere and after desired time were precipitated in a large excess of diethyl ether, filtered off, and vacuum-dried at room temperature over phosphorus pentoxide. The synthesized monomer EPyM and its corresponding homopolymer and copolymers were characterized by NMR spectroscopy. Average molecular weight and molecular weight distributions were determined by size exclusion chromatog-

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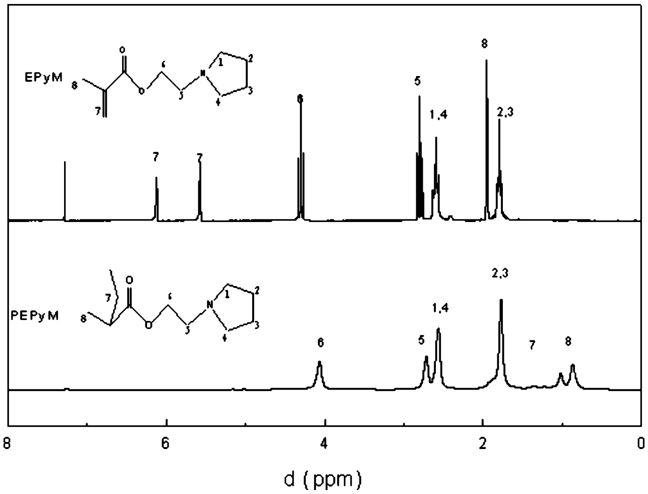

Figure 1. ^{1}H NMR spectra of monomer EPyM and homopolymer PEPyM and their respective chemical structures.

raphy (SEC) using polymer solutions (5 mg/mL) in *N,N′*-dimethylformamide (DMF). Measurements were carried out at 1 mL/min flow with Ultrastyragel columns of 500, 10^4, and 10^5 Å (Polymer Laboratories) at 70 °C and using a differential refractometer as detector. The calibration was performed with poly(methyl methacrylate) (PMMA) standards in the range of 2990 and 1 400 000 Da and polydispersity values lower than 1.1. Poly-EPyM average molecular weight was found to be M_n = 39 000 with polydispersity of 2.4 and symmetric SEC diagram approaching a Gaussian distribution.

Synthesis of Cross-Linked Gels. The films preparation of the cross-linked poly-EPyM was performed in circular Teflon molds with 15 mm diameter. The bulk polymerization of EPyM was carried out in the presence of 1% of *N,N′*-methylenebisacrylamide (BAam) and ammonium persulfate as free radical initiator. Films were washed with water and vacuum-dried, showing an average thickness of 400 μm.

Phase Transition Temperatures. The phase transition temperatures, associated with a LCST in the case of soluble linear PEPyM homopolymer and DMA-EPyM non-cross-linked copolymers and with a swollen to shrunken transition in the case of cross-linked polymeric systems, were determined in deionized water by turbidimetry measurement on a UV−vis spectrophotometer connected to a temperature controller at 2 °C/min. The polymer concentration was 1 wt % and the absorbance at 450 nm in all cases. For cross-linked gels the transition temperature was determined by differential scanning calorimetry (DSC) at a heating rate of 1 °C/min using swollen samples at its equilibrium hydration degree in distilled water recording the maximum of the endothermic peak and also from the swelling experiments.

Titrations. The pK_b value of PEPyM was determined by acid−base titration of a polymer solution (100 mg in 25 mL of 0.1 M aqueous NaCl). About 1−3 mL of 0.1 N HCl was added to ensure the complete ionization of the polymer amino groups. An aqueous basic solution of NaOH (0.1 N) was employed to carry out the titration using small volumes without modifying the solution ionic strength. The pH changes were measured using a Schott GC841 pHmeter at 37 °C in a thermostatic bath.

Swelling Studies. Equilibrium hydration or swelling degree (H%) is defined in eq 1:

$$H\,(\%) = \frac{W - W_0}{W_0} \times 100 \qquad (1)$$

where W_0 is the weight of the dried sample and W is the weight at time t of immersion. H% was determined at different temperatures and pH by immersing the cross-linked PEPyM films in different buffer solutions with the same ionic strength, 0.1 M. Samples weight was registered at different temperatures and immersion times until constant weight was attained.

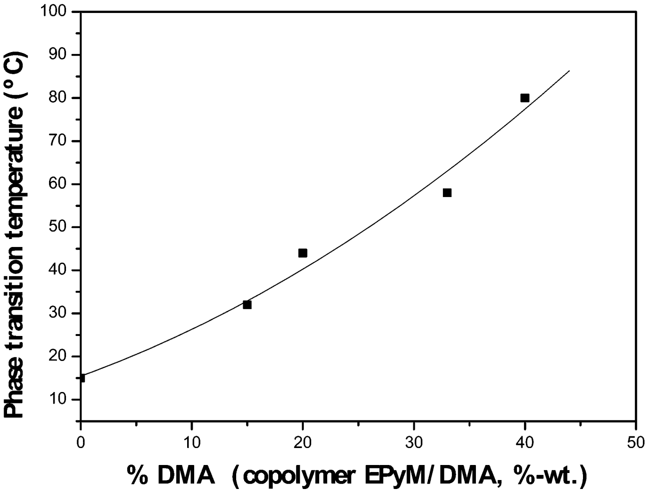

Figure 2. Diagram of phase transition temperature vs wt % of DMA in the prepared DMA−EPyM copolymers.

Results and Discussion

Phase Transition Temperatures. The chemical structure of PEPyM is based on the presence of nonpolar (methylene units) and polar groups (cyclic amine), which confers a dipolar amphiphilic-like character to the system and the ability to be sensitive to temperature changes. In this sense, the phase transition temperature, associated with a LCST in deionized water of the homopolymer, determined by turbidimetry measurement on a UV−vis spectrophotometer, was found to be 15 °C. When incorporating more hydrophilic units in the macromolecular chain by copolymerization reactions of the monomer EPyM with the hydrophilic monomer DMA, the transition temperature was increased and found to be dependent on the copolymer composition as has been observed in NIPAm−acrylamide copolymers.[20] Figure 2 shows the phase transition temperature dependence on the EPyM−DMA copolymer's composition. It can be observed that as the DMA content increases, the transition temperature of copolymers also increases up to 80 °C when the DMA content is 40 wt %, and it is not detected at temperatures below the boiling point of water for copolymers with DMA content higher than 40 wt %. The phase transition modulation is a very important aspect when considering these types of materials to be applied in the biomedical field when the LCST is found to be near the physiological temperature, i.e., 37 °C.

Effect of Both Stimuli. The presence of an ionizable cyclic amine group in PEPyM structure (see Figure 1) makes this polymer also sensitive to pH changes. This is an example of ionizable polymers that pH values where they are not ionized, the hydrophobic character predominates being insoluble in aqueous solutions, whereas hydrophilic becomes dominant forming a polyelectrolyte solution at pH where the polymer is ionized.[21] PEPyM is ionized at pH lower than its pK_b, the presence of positive charges being responsible for its solubility at acidic pH. The pK_b of the monomer EPyM and its respective homopolymer PEPyM were determined by acid−base titration to be 5.0 and 6.5, respectively. The different solubility of PEPyM when it is more or less ionized can modify phase transition conditions in different buffer solutions as has been observed in the case of poly((*N,N*-dimethylamino)ethyl methacrylate).[22] Moreover, it can be said that at each pH the different polymer ionization degree (α) leads to different temperature

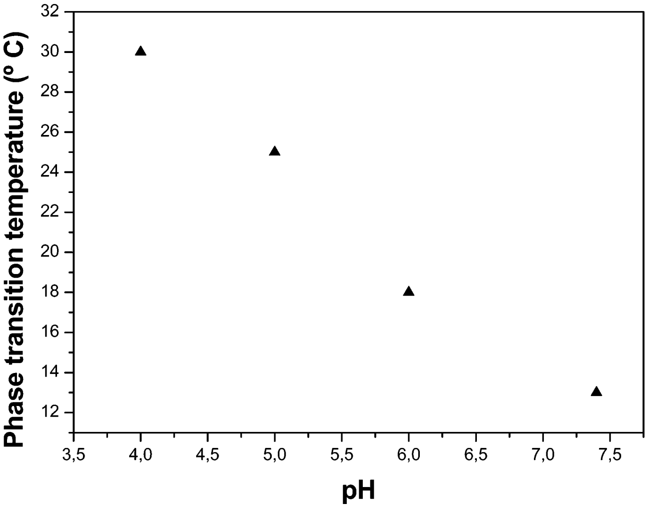

Figure 3. Variation of PEPyM phase transition temperature with the pH.

sensitivity. In this sense, PEPyM α has been determined for each pH from the Henderson−Hasselbalch equation:

$$\alpha = 1/(1 + 10^{(\mathrm{pH}-\mathrm{p}K_\mathrm{b})}) \qquad (2)$$

The effect of the pH on the phase transition temperature is shown in Figure 3. At acidic pH (0−3) the polymer is totally ionized ($\alpha > 0.99$) as the amino group is protonated, leading to electrostatic repulsion that causes the polymer to be more soluble, a pH interval where the phase transition is not observed as the ionic interactions are predominant. At pH = 4 some turbidity started to be observed at 30 °C. At higher pH the α decreases (less protonation) to about 0.1 at physiological pH (7.4) and to practically nonionized polymer at pH 10, the phase transition being 13 °C and lower than 10 °C, respectively. In this pH interval (7.4−10) the polymer interactions become dominated by electrostatics at acidic pH.

Swelling Studies. PEPyM was cross-linked with a small amount (1 wt %) of *N,N*′-methylenebisacrylamide (BAam), and the obtained polymer films were used to study the temperature sensitivity of the prepared gels in aqueous solutions. The sensitivity was reflected on the variations of the swelling degree (*H*%), from the expanded state below the phase transition temperature to a shrunken or collapsed state above it. The transition temperature of the swollen to shrunken phases in water was determined by DSC to be 17 and 22 °C from the swelling experiments, considering the inflection point of the diagram equilibrium swelling degree vs temperature (Figure 4a). From this diagram it can be observed that the *H*% at lower temperatures (10−15 °C) is about 300% whereas at higher (50 °C) is 130%, giving a wide transition from 15 to 35 °C. PEPyM exhibits a reversible thermoshrinking ability, also called on−off or pulsatile behavior, as is shown in Figure 4b, where this was studied above (50 °C) and below (10 °C) the phase transition temperature, the times being very similar in all cases to reach the equilibrium for swelling and deswelling.

Sensitivity to pH was studied at constant temperature (37 °C) in buffer solutions. Hydrogels were found to be swollen up to more than 750% at pH 2, about 5.3 times more than at neutral and basic pH (around 140%) as is exhibited in Figure 5a. It can be observed that in polyelectrolytes the *H*% changes with pH are more pronounced than those caused by temperature. In this case polymer swelling is mainly due to its ionization as the electrostatic repulsions increase the swelling degree with respect to nonionizable polymers.[23] The theoretical ionization diagram was estimated at pK_b = 5, lower than the polymer pK_b from the non-cross-linked polymer water solutions (Figure 5a). The lower pK_b can be attributed to diffusion and ionic repulsions phenomena that make more difficult the polymer ionization when the polymer is cross-linked. From Figure 5a can be observed that experimental swelling degrees adjust to theoretical ionization diagram, and the transition is observed between pH 3−6. Pulsatile behavior was also detected when pH changes were performed from acidic to basic pH at 37 °C as is reflected in Figure 5b, where the experimental times to reach swelling and deswelling were 24 h in all cases, the deswelling process being slower than the swelling as equilibrium at pH 10 was not attained after 24 h of deswelling.

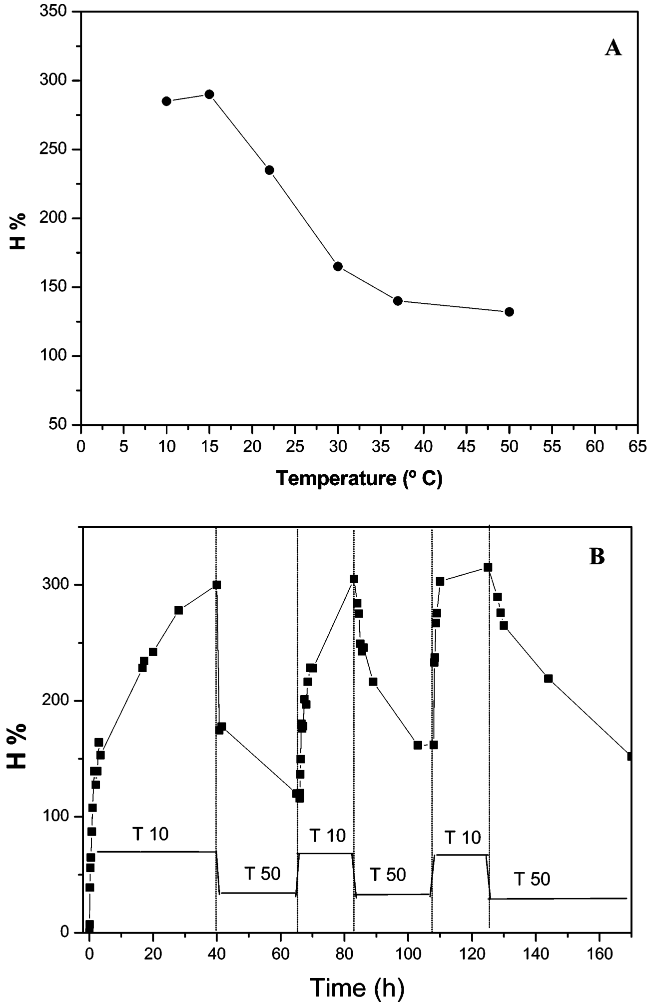

Figure 4. (A) Hydration degree (H %) vs temperature of cross-linked PEPyM in distilled water. (B) Pulsatile swelling vs time of cross-linked PEPyM at different temperatures, 10 and 50 °C in distilled water.

When considering the effect of both stimuli, the swelling degree was studied at different temperatures in different buffer solutions, as is shown in parts a and b of Figure 6 where the equilibrium hydration degree (*H*%) is plotted vs temperature and pH, respectively. Again, PEPyM ionization (at acidic pH) causes higher *H*% as the polymer is solvated by more water molecules in comparison to nonionized hydrogel (neutral and basic pH) due to the ionic repulsion of the protonated amine

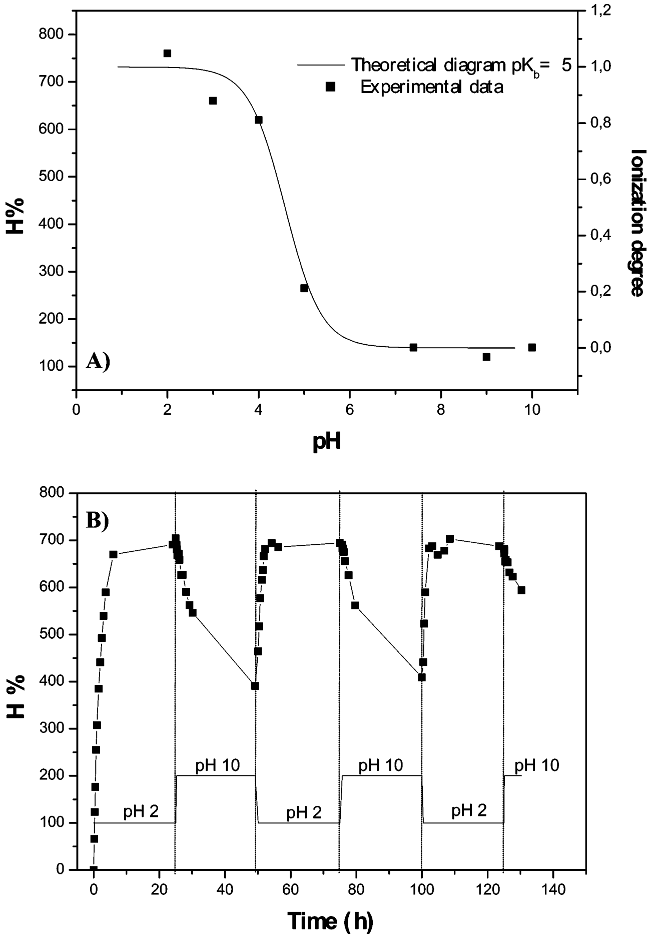

Figure 5. (A) Variation of the swelling degree (*H%*) and the ionization degree with the pH at 37 °C of cross-linked PEPyM. (B) Pulsatile swelling vs time of cross-linked PEPyM at different pH, 2 and 10 at 37 °C.

groups which collapses at higher pH because of the unprotonated amine groups. This aspect can be observed in Figure 6a,b where the H% of the PEPyM hydrogels has a maximum value at acidic pH (1−4) (ionized polymer), which varies from about 680 at pH = 4 and 40 °C to about 830 at pH = 1 and at 12 °C. In the case of pH from 5 to 10 (less or nonionized polymer) *H%* moves from about 120 at pH = 10 and at 40 °C to about 590 at pH = 5 at 10 °C. In terms of temperature it can be observed that the sensitivity to this stimuli at acidic pH (1−4) is very much lower than at neutral and basic pH with the exception at pH = 9 and 10 (*H%* goes from 80 to about 120) as can be observed in Figure 6b. This can be explained by the predominance at low pH of the ionic interactions in the swelling degree over the hydrophobic/hydrophilic interactions (responsible for temperature sensitivity), whereas at higher pH (non-ionized hydrogels) temperature sensitivity prevails over pH, suggesting that the hydrogels are more hydrophobic at high temperatures.

The hydrogels phase transition temperature at different pH was determined considering the inflection point of the swelling diagrams, whose transition profiles are somewhat different in the different buffer solutions. At acidic pH (1−4) no clear phase transition is observed, and *H%* softly decreases when increasing the temperature, the polymer being ionized and showing the highest *H%*, behaving as a superabsorbent polymer material. In the interval pH 5−7.4 the phase transition can be clearly observed, becoming lower when increasing the pH as was detected in non-cross-linked PEPyM (see Figure 2). At basic pH 9 and 10 the sensitivity to temperature is very low in comparison to other pH as the phase transition is lower than 10 °C, the hydrogel at these pH and temperature range being in a collapsed state. Figure 6b shows that as the temperature increases the degree of the volume phase transition becomes sharper and the transition profiles shift to lower pH, which is the same behavior of the non-cross-linked homopolymer in water and also the behavior that has been observed in polyDMAEMA hydrogels.[24] To illustrate the PEPyM dual sensitivity, in Figure 7 is represented a 3-dimensonal diagram of swelling vs pH (6−10) and temperature (40−10 °C), showing the dual sensitivity of PEPyM and how *H%* varies at pH = 7.4 and at 25 °C (bold lines).

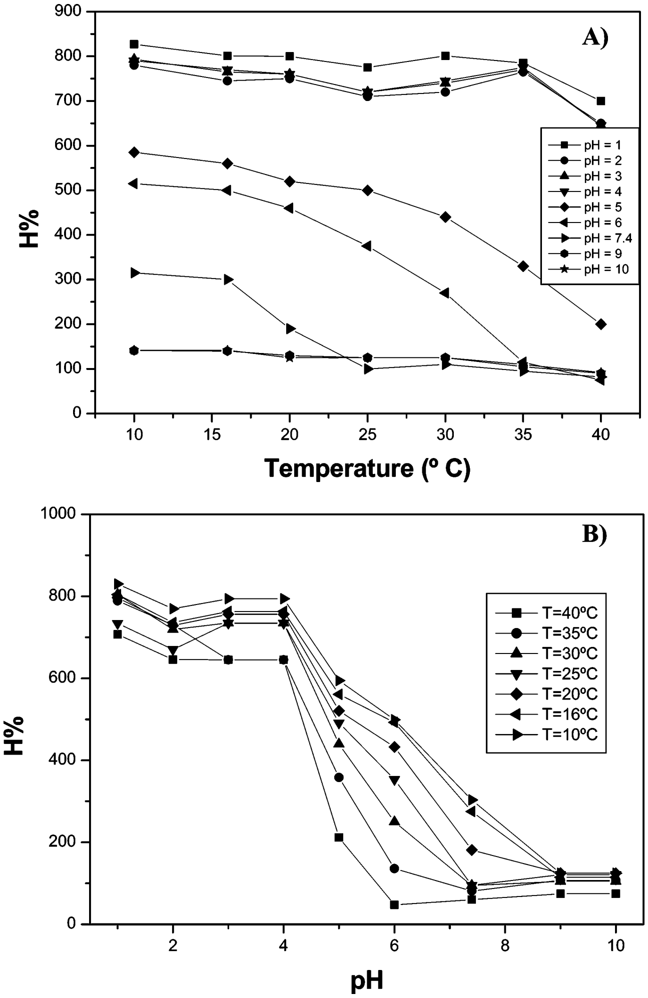

Figure 6. Cross-linked PEPyM equilibrium hydration degree (*H%*) vs (A) temperature at different pH and (B) pH at different temperatures.

Water Sorption Characteristics. Water sorption kinetic studies were performed on the cross-linked PEPyM at different temperatures and pH. The kinetics of the hydrogels water sorption was analyzed by fitting the swelling data to the equation proposed by Ritger and Peppas[25] according to Fick's law:[26]

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t and M_∞ are the mass of water absorbed at time *t* and infinite time respectively, *k* is a characteristic

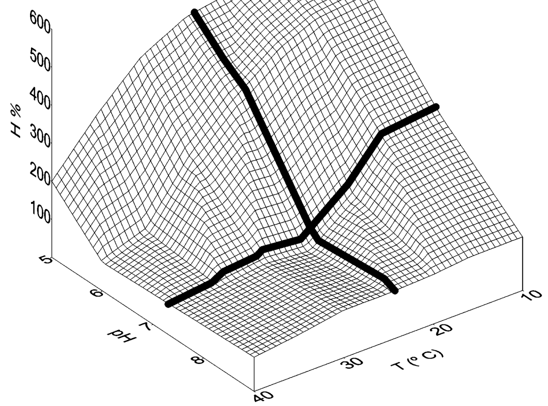

Figure 7. Cross-linked PEPyM 3-dimesional diagram of swelling vs pH and temperature. Bold lines represent the "crossroad" point corresponding to $H\%$ changes at 25 °C and at pH = 7.4.

Table 1. Water Sorption Characteristics of Cross-Linked PEPyM at Different Temperatures in Distilled Water

temp (°C)	W_∞	n	k
10	285	0.75 ± 0.08	0.07
22	235	0.79 ± 0.04	0.05
30	165	0.34 ± 0.09	0.11
37	140	0.38 ± 0.06	0.10
50	132	0.27 ± 0.01	0.14

Table 2. Water Sorption Characteristics of Cross-Linked PEPyM at Different pH at 37 °C

pH	W_∞	n	k
1	622	0.99 ± 0.04	0.04
2	760	0.77 ± 0.14	0.03
3	660	0.68 ± 0.03	0.02
4	620	0.69 ± 0.02	0.04
5	265	0.54 ± 0.04	0.03
7.4	140	0.54 ± 0.02	0.10
9	120	0.44 ± 0.01	0.12
10	140	0.41 ± 0.07	0.17

constant of the hydrogel, and n is the characteristic exponent that indicates the type of water transport. Data were fitted into eq 2 (for $M_t/M_\infty \leq 0.6$), and the n and k values were determined from the slopes and intercepts of the plots of $\log(M_t/M_\infty)$ vs $\log t$, respectively. The value of the exponent $n = 0.5$ indicates Fickian kinetics (water diffusion is rate limiting), whereas $0.5 < n < 1$ indicates the contribution of non-Fickian process as polymer relaxation.

Tables 1 and 2 show the k and n values obtained at different temperatures and pH. When considering changes in temperatures n goes from 0.3 to 0.4, at high temperature interval (30−50 °C), closer to Fickian kinetics at 37 °C (i.e., $n \sim 0.5$), and from 0.7 to 0.8 at lower temperatures, i.e., below the phase transition temperature. This corresponds to a diffusion mechanism when the gel is collapsed, but when moving to lower temperatures, being the gel in the expanded state, the morphological changes of the polymer chains become more important, being the case of anomalous water diffusion. When the swelling kinetics were analyzed at different pH (see Table 2), the behavior was quite similar to that at different temperatures, but more pronounced as the gel expansion is much higher. The n values were also higher and close to 1 at pH = 1 and lower, ∼0.5 (Fickian), near the conditions of the phase transition (pH 5−7.4).

Conclusions

A novel methacrylic polymer derived from ethylpyrrolidine, PEPyM, has been synthesized and characterized. This polymer is sensitive to external stimuli such as temperature and pH. This sensitivity have been observed and discussed in the polymer different solubility at different temperature and pH, on the basis of a phase transition temperature (associated with a LCST) and pK_b. The LCST of the polymer can be modulated by copolymerization reactions with DMA when required for specific applications. Cross-linked PEPyM swelling degree was also analyzed to changes in the external stimuli. At acidic pH (1−4) PEPyM behaves as a superabsorbent hydrogel having low sensitivity to temperature changes, whereas at pH 5−7.4 pH and temperature, the sensitivity is clearly observed. At basic pH PEPyM hydrogels are in a collapsed state (low $H\%$) at the studied temperatures as their phase transition temperatures are lower than 10 °C. Pulsatile (on−off) behavior in the swelling−deswelling ability was also observed when the stimuli was removed or reversed. The water sorption process of the hydrogels was found to be Fickian in temperature and pH physiological conditions (37 °C and pH = 7.4).

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