



Thermal and pH dual responsive polyurethane/2-(diisopropylamino)ethyl methacrylate hybrids: Synthesis, characterization, and swelling behavior

Francisco M. Pardini^{a,b}, Paula A. Faccia^{a,b}, Oscar R. Pardini^{a,c}, and Javier I. Amalvy^{a,c,d}

^aGrupo (Nano) Materiales Poliméricos, Instituto de Investigaciones Físicoquímicas Teóricas y Aplicadas (INIFTA), CCT La Plata CONICET, Universidad Nacional de La Plata, La Plata, Argentina; ^bConsejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina; ^cComisión de Investigaciones Científicas de la Provincia de Buenos Aires (CICPBA), La Plata, Argentina; ^dFacultad Regional La Plata, Centro de Investigación y Desarrollo en Ciencia y Tecnología de Materiales (CITEMA), Universidad Tecnológica Nacional, Berisso, Argentina

ABSTRACT

This article describes the synthesis and characterization of stimuli-sensitive hybrid films using 2-(diisopropylamino)ethyl methacrylate (DPA), and a polyurethane (PU) base on isophorone diisocyanate. Hybrid films with different amounts of DPA present good film and physicochemical properties. Characterization techniques such as Fourier transform infrared, UV-visible, modulate differential scanning calorimetry, and thermogravimetric analysis reveal chemical interactions between PU and DPA groups. Swelling behavior of films shows a dependence on DPA content, pH, and temperature and different mechanisms of water uptake in response to pH and temperature variations. Hybrid systems would allow controlling water absorption not only through pH or temperature but also from the chosen PU/DPA proportion.

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Introduction

Synthetic polymers are being used as drug delivery systems as a polymeric drug itself or in combination with small-molecule drugs or with biomacromolecules such as proteins and poly(nucleic acids).^[1] There is an extensive list of criteria that a polymer must fulfill to be applied safely as a polymer therapeutic or as an agent in tissue regeneration and repair. In this field, stimuli-sensitive polymers are very attractive materials for their use as drug delivery systems.^[2,3] They can vary their shapes, structure, or properties in response to external stimuli such as heat, pH, electricity, light, and water. This behavior offers the possibility of localizing the drug at the specific site of action and supplying the required amount for the necessary time, to improve bioavailability and decrease undesirable effects.^[4] Furthermore, responsive polymers can release the drug at a specific rate to maintain constant therapeutic concentration in the body, to prolong its remedial effects, and to prevent fluctuations in their plasma levels.

Within biomedical applications, stimulus-sensitive polymers have to show their response properties in the setting of biological conditions and should be able to respond to changes such as the electric field,^[5] light,^[6] pH^[7], or temperature,^[8] among others. From a biomedical point of view, the most important systems are those sensitive to temperature and/or pH of the environment. The human body exhibits variations of pH in some specific areas like the tumor tissue (pH of

CONTACT Javier I. Amalvy  jamalvy@gmail.com  Grupo (Nano) Materiales Poliméricos, Instituto de Investigaciones Físicoquímicas Teóricas y Aplicadas (INIFTA), CCT La Plata CONICET, Universidad Nacional de La Plata, Diag. 113 y 64, B1904DPI, La Plata, Argentina; Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CICPBA), Argentina; Facultad Regional La Plata, Centro de Investigación y Desarrollo en Ciencia y Tecnología de Materiales (CITEMA), Universidad Tecnológica Nacional, 60 y 124, 1900, Berisso, Argentina.

6.5–7.2),^[9] gastrointestinal tract (pH between 2.0 and 8.0),^[10] and subcellular compartments (pH of 4.5–6.2).^[11,12] Also, chronic wounds have been reported to have pH values between 5.4 and 7.4.^[13] In this way, cationic pH-responsive polymers offer many possibilities of application.^[14]

Thermoresponsive materials are of particular interest for cell culture technologies because the volume phase transition has to occur within the settings of the physiological conditions (20–40°C).^[15] In this way, thermosensitive polymers offer many possibilities in biomedicine due to the sensitive response to small temperature changes around a lower critical solution temperature (LCST). Such response makes chains collapse or extends, responding to modifications of the hydrophobic and hydrophilic interactions between the polymer chains and the aqueous medium.^[15–17]

Thus, temperature-sensitive polymers undergo a sharp change in volume as the temperature of the medium is varied from above or below the LCST.^[18] These unique characteristics make thermoresponsive polymers especially useful in biomedical applications like controlled release of drugs and tissue engineering.^[8,18–20]

Depending on the types of monomers (i.e., ionic or neutral) incorporated in the polymer backbone, smart polymer systems can respond to a variety of external environmental changes.^[21,22] For example, pH-sensitive systems are usually produced by adding pendant acidic or basic functional groups to the polymer backbone. In particular, polymeric systems based on tertiary amine methacrylates have pH- and also temperature-responsive behaviors due to the presence of hydrophobic *N*-alkyl groups and ionizable amine groups.^[23–25] The combination of a pH-responsive system with a thermoresponsive polymer can further alter the hydrophilic/hydrophobic balance. This allows a polymer to become membrane active at a specific temperature^[26] and/or a specific pH.^[27]

In a previous work,^[28] we prepared hybrid acrylic/polyurethane systems, where the acrylic component poly(2-(diethylamino)ethyl methacrylate) (pDEA), was the stimuli-sensitive part of the polymers, while the polyurethane was the structural part of the polymer that improves among other things, water-resistant, chemical, and mechanical properties. The chemical bond between the acrylic and polyurethane components produces a homogeneous, versatile, and stable hybrid polymer in an aqueous media system, enhancing the individual properties of the components.

In polyurethane/2-(diethylamino)ethyl methacrylate (PU/DEA) hybrid systems, the pH-responsive behavior was observed in a wide pH interval (4.0–9.0) but no thermal response was appreciated in the range of studied temperatures (25–37°C).^[28] This behavior was due to the relatively high value for the LCST of pDEA (about 37°C).^[29] To lower the critical transition temperature, we propose the use of 2-(diisopropylamino)ethyl methacrylate (DPA) as a functional monomer, for the synthesis of a dual thermal- and pH-responsive hybrid polymer. The comportment of Poly(2-(diisopropylamino)ethyl methacrylate) (pDPA) in aqueous medium has strong temperature dependence and its pKa is about 6.0.^[30,31] It is well known that ionizable polymers with a pKa value between 3.0 and 10.0 are good candidates for pH-responsive systems.^[32] In addition, it was reported that the larger the dialkylamino ethyl group, the lower the temperature required to observe the LCST behavior.^[25] Also, if we compare structurally both analogous monomers (DEA and DPA), the isopropyl groups in the DPA are more hydrophobic than the ethyl groups in the DEA. In the polymer structure, an increased steric congestion at the nitrogen atom is expected in pDPA compared with pDEA. In other words, the replacement of ethyl by isopropyl group in the tertiary amine methacrylate in the acrylic–polyurethane hybrid should modify the hydrophilic-to-hydrophobic balance resulting in a dual thermal- and pH-responsive polymer.^[33]

To our knowledge, no work was reported using DPA, as the acrylic monomer, in combination with a polyurethane, to obtain a dual responsive hybrid polymer. In view of the distinctive physical characteristic of DPA monomer compared to DEA one, we felt that a detailed investigation of such PU/DPA hybrid polymers was warranted.

Therefore, in this work, polyurethane/acrylic hybrids containing different amounts of DPA monomer were prepared; and their properties and the influence of DPA proportion were thermal (by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)); and spectroscopic (by Fourier transform infrared (FTIR) and UV–visible) characterized. pH- and thermal-responsive behaviors were evaluated by swelling degree studies at different pH values and temperatures.

Experimental

Materials

2-(diisopropylamino)ethyl methacrylate (97%) was purchased from Scientific Polymers Products. The monomer was treated with basic alumina to remove the inhibitor. Isophorone diisocyanate (IPDI, 98%, Aldrich), 2-hydroxy ethyl methacrylate (HEMA, 97%, Aldrich), poly(propylene glycol) diacrylate (PPGDA, 98%, Aldrich), ammonium persulfate (APS, 98%, Fisher), ethylene diamine (EDA, 99%, Aldrich), dibutyltin dilaurate (DBTDL, 95%, Aldrich), and sodium dodecyl sulfate (SDS, 90%, Anedra) were of analytical grade and were used as received. Monomethoxy-capped poly(ethylene glycol) methacrylate (PEGMA) macromonomer ($M_n = 2000 \text{ g mol}^{-1}$; $M_w/M_n = 1.10$) was supplied by Cognis Performance Chemicals (Hythe, UK) as a 50 wt% aqueous solution. Polypropylene glycol 1000 (PPG1000, Voranol 2110) was of technical grade and triethylamine (TEA, 99%) was provided by ADELFA S.A. PPG1000 was dried and degassed at 80°C at 1–2 mm Hg before used. Dimethylol propionic acid (DMPA, 98%, Aldrich) was dried at 100°C for 2 h in an oven. TEA was also dried before use. Buffer solutions for fixing the medium pHs were prepared from standard chemicals.

Polymer synthesis

Synthesis of PU/DPA hybrid dispersions

In a 1000-mL six-neck separable flask, PPG1000 and DMPA were charged and the mixture heated to 90°C and bubbled the dried air for approximately 60 min, followed by increasing the temperature to 98°C and adding a mixture of IPDI and DBTDL catalysts. After 2 h of reaction, the prepolymer was cooled to 45°C and HEMA dissolved in acetone was added slowly and allowed to react for approximately 90 min. Then, the temperature was raised to 60°C and kept constant until the isocyanate (NCO) content reached the desired value (approximately for 90 min). The free isocyanate content was determined using the conventional dibutylamine backtitration method.^[34] Upon obtaining the theoretical NCO value (ca. 4.7%), the mixture was cooled to 55°C and TEA (in acetone) was fed in slowly over 50 min. After neutralization, the temperature was lowered to room temperature. An aqueous dispersion of PU was obtained by adding the PU prepolymer to water containing the appropriate amount of EDA to perform the chain extension reaction. The dispersion was performed at about 300 rpm in an ordinary glass reactor at 30°C over a period of 45 min. The resulting product was a stable dispersion with a solid content of about 30 wt% and it was divided into several parts and added different amounts of DPA, PPGDA as the cross-linking agent and PEGMA as the steric stabilizer. The polymerization of PU-DPA/PPGDA/PEGMA mixtures was performed in batch mode using a glass reactor (1000 mL) with a water jacket for temperature control. The mixture was degassed with nitrogen gas and then dispersion polymerized at 80°C using APS (0.015 wt% on DPA monomer base) as an initiator. The polymerization leads to the formation of PU/DPA hybrids having a chemical bond between polyurethane and DPA moieties. The resulting product was a stable dispersion with a solid content of approximately 30 wt%. A shorthand notation is used in this paper to describe the hybrid systems. Thus, “H90/10” denotes a hybrid system containing 90 wt% of PU and 10 wt% of DPA monomer.

Synthesis of polyurethane-polymerized dispersion

Polyurethane-polymerized dispersion (PU) was prepared in the same way as the hybrid systems without the addition of DPA/PPGDA/PEGMA mixture, and it was used as a reference material for comparison with the hybrid systems. For more experimental details, refer the work done by Pardini and Amalvy.^[28]

Synthesis of dispersion of the homopolymer of DPA

The pDPA was carried out in a 100-mL, round-bottomed flask fitted with a nitrogen gas inlet, water condenser, and overhead mechanical stirrer operating at 250 rpm. For batch reactions with the APS

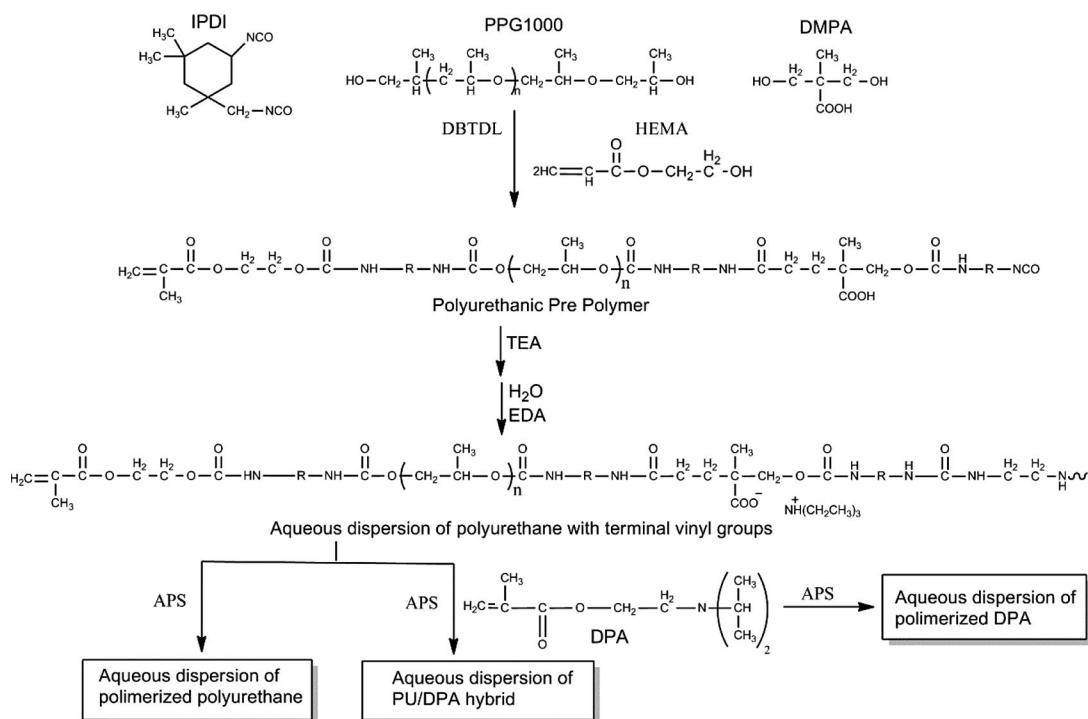


Figure 1. Synthesis of polymer dispersions. *Note:* APS, ammonium persulfate; DBTDL, dibutyltin dilaurate; DMPA, dimethylol propionic acid; DPA, 2-(diisopropylamino)ethyl methacrylate; EDA, ethylene diamine; HEMA, 2-hydroxy ethyl methacrylate; IPDI, isophorone diisocyanate; PPG, poly(propylene glycol); PU, polyurethane; TEA, triethylamine.

initiator, the required amount of water and SDS (1.0 wt% based on the DPA monomer) and a mixture of DPA and PPGDA cross-linker (2.0 wt% based on the DPA monomer) were added to the flask, and the solution was stirred for 30 min under a nitrogen flow at 60°C. The polymerization began with the addition of a previously degassed aqueous solution of the initiator (1.0 wt% based on the DPA monomer). The reactive macromonomer stabilizer PEGMA (10.0 wt% based on the DPA monomer) was added to the aqueous solution before the addition of monomer and cross-linker. The reaction solution turned milky white within 5 min and was stirred for about 18–20 h at 60°C under the nitrogen atmosphere.

Figure 1 shows the synthesis of polymer dispersions used in this work and Table 1 presents a typical base formulation used in this article.

Film formation

Films were prepared by casting the aqueous dispersions on Petri dish. After drying at 30°C for 24 h, the films were cut into circular pieces (about 22 mm diameter) with a cork borer and cured at 60°C

Table 1. Typical recipe to prepare 100 g (wt%) of PU, pDPA, and hybrid dispersions.

System	DPA content (wt%)	PU (g) ^a	DPA/PPGDA/PEGMA monomers (g)	Water (g)
PU	0	94.84	0	5.16
H90/10	10	85.46	2.82/0.05/0.51	11.42
H70/30	30	66.67	8.46/0.15/1.52	23.95
H50/50	50	47.89	14.10/0.25/2.54	36.49
pDPA	100	0	24.68/4.82/0.5	70.0

^a30 wt% aqueous dispersion.

DPA, 2-(diisopropylamino)ethyl methacrylate; pDPA, poly(2-(diisopropylamino)ethyl methacrylate); PEGMA, poly(ethylene glycol) methacrylate; PPGDA, poly(propylene glycol) diacrylate; PU, polyurethane.

for 48 h, and finally stored in desiccators with silica gel until they were ready to be used for the experiments.

Characterization experiments

FTIR spectroscopy

Fourier transform infrared spectra were measured in transmission mode using an FTIR Nicolet 380 spectrometer, Thermo Scientific, USA. Samples were freestanding films or powdered mixed with KBr and pressing to form disks. FTIR spectra were obtained by recording 64 scans between 4000 and 400 cm^{-1} with a resolution of 4 cm^{-1} . Spectrum processing was performed using the software EZ Omnic.

UV-visible spectroscopy and light transmission

UV-visible spectra were determined on dried free-standing films and were normalized by the thickness of films. The transmittance from 200 to 800 nm was measured with a Nicolet Genesys 10 spectrophotometer, USA.

Thermogravimetric analysis

Thermogravimetric analysis was performed using a DTG-60, Shimadzu Scientific Instrument, USA. About 5 mg of dry sample was sealed into an aluminum pan. The sample was heated at a rate of 10 $^{\circ}\text{C min}^{-1}$ from 40 to 550 $^{\circ}\text{C}$ under a nitrogen flow rate of 30 mL min^{-1} .

Modulate differential scanning calorimetry

Glass transition temperature (T_g) of the polymeric materials was measured with a DSC Q 200 (TA Instruments, USA). Nitrogen was used as a purge gas at a flow rate of 30 mL min^{-1} . As a reference, an empty hermetic aluminum pan was used. The heating/cooling rate was 2.5 $^{\circ}\text{C min}^{-1}$, the temperature range was from -80 to 100 $^{\circ}\text{C}$. Glass transition temperatures were determined using the TA Instrument Analyzer Software.

Swelling degree

Swelling degree (SD) was determined by immersing polymer films (22.0-mm-diameter disk and thickness of $150 \pm 50 \mu\text{m}$) in a phosphate buffer solution (ca. 0.1 M) of desired pH (ranging from 5.0 to 8.0) and at different temperatures (25 and 37 $^{\circ}\text{C}$), until they reached the swelling equilibrium. A buffer solution of sodium dihydrogen phosphate/phosphoric acid (ca. 0.1 M) was used for pH 4.

The equilibrium swelling degree (SD_{eq}) was calculated with the following equation:

$$\text{SD}_{\text{eq}} = \frac{W_{s,\infty} - W_d}{W_d} \times 100 \quad (1)$$

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

Dynamic swelling degree

For the determination of dynamic swelling degree, dry films were immersed in a buffer solution of the desired pH (4.0 and 7.0) at 37 $^{\circ}\text{C}$. At regular periods of time, the samples were removed from the aqueous solution, blotted with filter paper to remove the surface liquid, weighed, and returned to the same container until weight stabilization was observed. The degree of swelling at time t (SD_t) was calculated with the following equation:

$$\text{SD}_t = \frac{W_{s,t} - W_d}{W_d} \times 100 \quad (2)$$

where $W_{s,t}$ is the weight of the swollen film at time t .

SD_t was adjusted to a power law-type relationship^[35,36] using the equation of Ritger–Peppas (Equation (3)):

$$\frac{M_t}{M_e} = kt^n \quad (3)$$

Here, M_t and M_e are the cumulative amount of water absorbed after a time t and at infinite time, respectively, while k is a constant related to kinetic behavior and experimental conditions and n is the exponent depending on the mechanism of the swelling process. Data were fitted only up to 60% of water absorbed to apply Equation (3). Parameters k and n were calculated from the intercept and the slope of Equation (4):

$$\ln \frac{M_t}{M_e} = \ln k + n \ln t \quad (4)$$

Scanning electron microscopy

Changes in the morphology of polymers were observed by scanning electron microscopy (SEM) with an FEI-Quanta 200 (The Netherlands) instrument, in high-vacuum mode and operated at 15–20 kV acceleration voltage. PU and PU/DPA films were equilibrated during 24 h in different buffer solutions and then were frozen at -40°C in an alcoholic solution followed by lyophilization under vacuum for 24 h. To prevent sample charging effects during the observation, fractured pieces of samples were previously mounted onto the surface of an aluminum SEM specimen holder and sputter coated with a thin overlayer of gold.

Results and discussion

Characterization by FTIR spectroscopy

Fourier transform infrared spectroscopy was performed to study the presence of chemical interactions between PU and DPA and to analyze the changes in the spectra produced by the incorporation of different proportions of DPA into the polymer backbone.

In our previous work, we discussed in detail the FTIR spectrum of PU^[28] and pDPA films.^[37] Briefly, the most important bands described for PU were 3340 cm^{-1} (hydrogen bonding N–H stretching vibration), 1534 cm^{-1} (combination of C–N stretching and NH bending, amide II band), 1712 cm^{-1} (free C=O and H-bonded C=O stretching), 1655 cm^{-1} (disordered urea C=O), 1305 cm^{-1} (combination of NH bending and C–N stretching), 1242 cm^{-1} (combination of NH bending and C–N stretching, Amide IV band), and 1110 cm^{-1} (C–O–C stretching vibration of the polyetherdiol). While the main bands mentioned for pDPA were observed at 3435 cm^{-1} (N–H, stretching), 2970 cm^{-1} (C–H stretching of the methine H of isopropyl group), 1729 cm^{-1} (C=O, stretching vibration), and 1140 cm^{-1} (C–O stretching vibration).

In **Figure 2**, it can be seen a progressive change in the absorption bands of the hybrids when increasing the amount of DPA monomer. The most important features when going from pure PU to PU/DPA are a decrease in intensity of the band centered at 3340 cm^{-1} (decrease in amount of NH groups from urethane moieties), a higher intensity of the characteristic peak of methine group in the isopropyl moiety, $(\text{CH}_3)_2\text{-CH-}$, at 2970 cm^{-1} , and a lower intensity of the signal at 1549 cm^{-1} assigned to the amide II band.

A shift to higher wave numbers in the NH stretching band is also observed ($3460\text{--}3330\text{ cm}^{-1}$ region) as the DPA content is increased. This behavior is due to the rupture of the hydrogen-bonding interactions between the urethane-ether and urethane-ester groups^[38] present in the polymer chain. By including more DPA (50/50 hybrid), the amount of NH groups is reduced, and the intensity decreases as mentioned before.

In C–H stretching region, the intensity and width of the band centered at 2930 cm^{-1} were higher, due to the contribution of the characteristic peak of the methine group in the isopropyl $(\text{CH}_3)_2\text{-CH}$

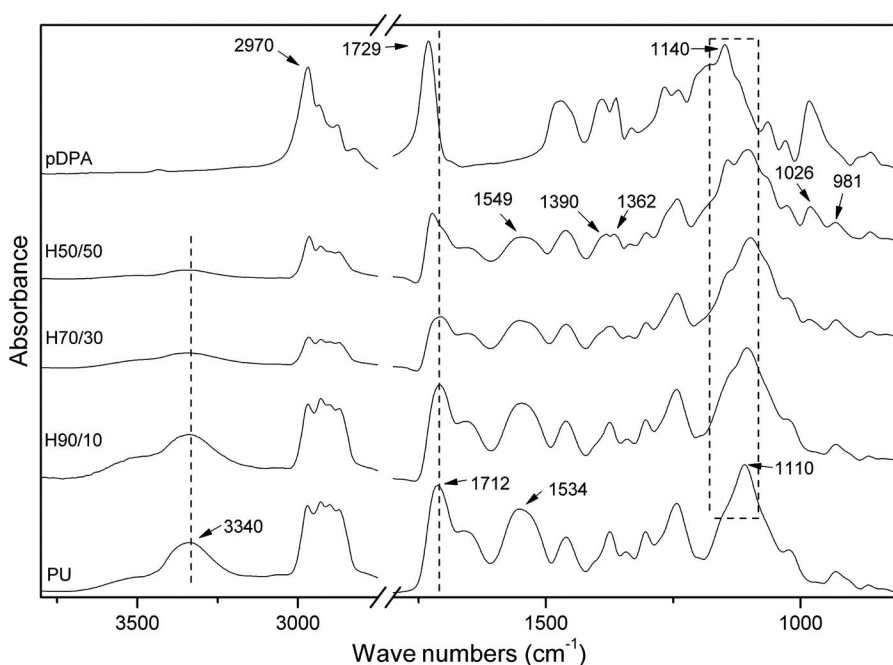


Figure 2. FTIR absorption spectra of pure PU, pDPA, and hybrid systems. Note: FTIR, Fourier transform infrared.

moiety. A shoulder at 2820 cm^{-1} and a weak band at 2720 cm^{-1} of the CH_2 group next to the nitrogen atom are also observed.

The band at 1712 cm^{-1} assigned to $\text{C}=\text{O}$ stretching modes of PU exhibits a systematic drift toward higher wave numbers and an increase in its intensity with the rise of the amount of DPA. This indicates the presence of free $\text{C}=\text{O}$ groups. In addition, the contribution of DPA absorption on the spectra can be appreciated from a wider signal centered at 1723 cm^{-1} , between the values of individual components. The maximum of this band is moved from 1712 cm^{-1} (PU) to 1723 cm^{-1} (H50/50).

In the low-wave number zone, new bands are observed at 1026 and 981 cm^{-1} corresponding to the $\text{C}-\text{N}$ stretch and to the CH_3 groups from DPA, respectively. The doublet of the isopropyl group is clearly evident in H50/50 (1390 and 1362 cm^{-1}).

In conclusion, the observed changes in FTIR spectra are mostly due to the rupture of the hydrogen-bonding interactions between the carbonyl and ether groups in the PU chain. By increasing the DPA content, the two asymmetric bulky isopropyl groups opposed to the formation of new hydrogen-bonding interactions of the mentioned PU's groups. This behavior was observed in other polymer systems with amino groups.^[39] The observed changes reveal the interactions between the DPA and PU chains.

Characterization by UV-visible spectroscopy

The carbonyl absorption band in the UV-visible electromagnetic spectrum is sensitive to the chemical environment, so information about symmetry in the polymer network can be obtained from UV spectra.

In the visible region ($350\text{--}700\text{ nm}$), films with a thickness of $200 \pm 50\ \mu\text{m}$ showed very high transmission (higher than 93%) for different DPA contents. In some applications, such as therapeutic contact lenses, ocular drug delivery, and the monitoring of wound healing (for making it easy to see the instruments in the working area during application), transparency is an important issue.^[37] On the other hand, interesting differences in the UV-visible spectra were observed as the composition was varied from 10 to 50 wt% of DPA (Figure 3).

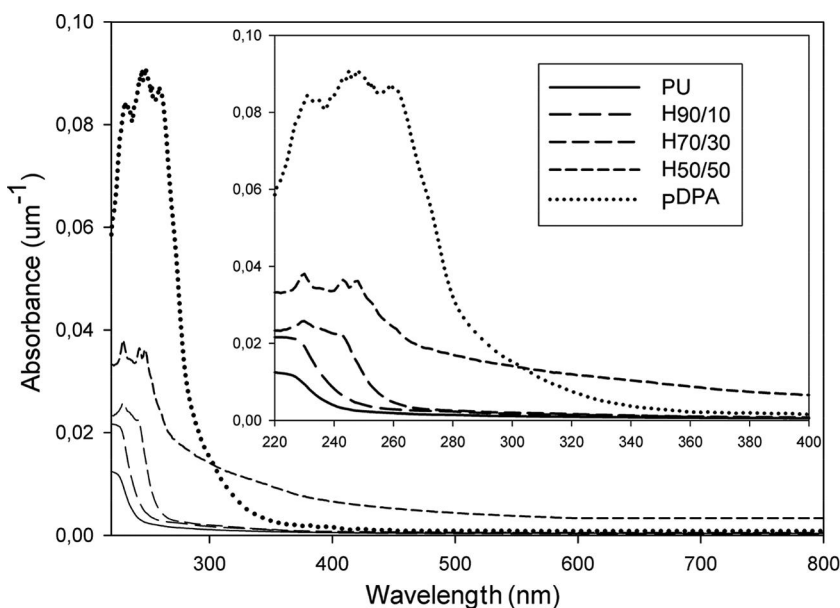


Figure 3. UV-visible absorption spectra of PU, pDPA, and PU/DPA hybrid films. Enlargement shows the UV region (220–400 nm). Note: DPA, 2-(diisopropylamino)ethyl methacrylate; pDPA, poly(2-(diisopropylamino)ethyl methacrylate); PU, polyurethane.

Pure PU displays an important absorption at around 220 nm due to electronic transitions of the urethane carbonyl group. The absorption in the 200–280 nm region increases when increasing DPA content (and also PPGDA and PEGMA content). The absorption comes from the C=O transition $n \rightarrow \pi^*$ of the carbonyl of the ester groups of DPA moiety. The intensity of spectra which arise from the $n \rightarrow \pi^*$ transition is comparatively low. However, in polymeric systems compared with that of the single molecules, a difference in molar extinction coefficients arises because of the perturbation of electronic states, as a consequence of the stereostructure of macromolecules. The increasing intensity of absorbance of the C=O band indicates the loss of symmetry around carbonyl groups, related probably to the steric effect of isopropyl group that prevents the formation of a more symmetric packing.

Characterization by TGA

Thermal stability of hybrids polymers was studied with TGA, and the results are shown in Figure 4. The initial degradation temperature (IDT) of the PU is at 224°C and the temperature where the 50 wt% of the polymer is loosed (T_{50}) is at 355°C. The PU degradation occurs in two principal steps, where about 90 wt% of polymer is degraded in the first step, probability owing to the urethane bond breaking.^[40]

Poly(2-(diisopropylamino)ethyl methacrylate) degradation also occurs in two definite steps, with a polymer weight loss of 59 wt% in the first step and 39 wt% in the second one. These results are consistent with those obtained by Cervantes et al. for acrylic with similar structure (pDEA).^[41] In this case, the authors describe a process of degradation of two main stages, where the first corresponds to the rupture of the ester bonds eliminating the tertiary amine and alcohols and the formation of structure of anhydride type, and the second one to the degradation of the polyanhydride formed in the prior step with the removal of various compounds including monomers and oligomers. IDT and T_{50} of pDPA were 191 and 339°C, respectively. T_{50} value indicates a decrease in thermal stability for pDPA compared to PU.

Thermogravimetric analysis curves of PU/DPA hybrids showed two well-defined decomposition stages as well as their respective homopolymers (PU and DPA), and a high thermal stability in the analyzed range. Table 2 summarized temperatures and percentages of weight loss of the different decomposition stages of the mentioned systems together with other relevant data of the process.

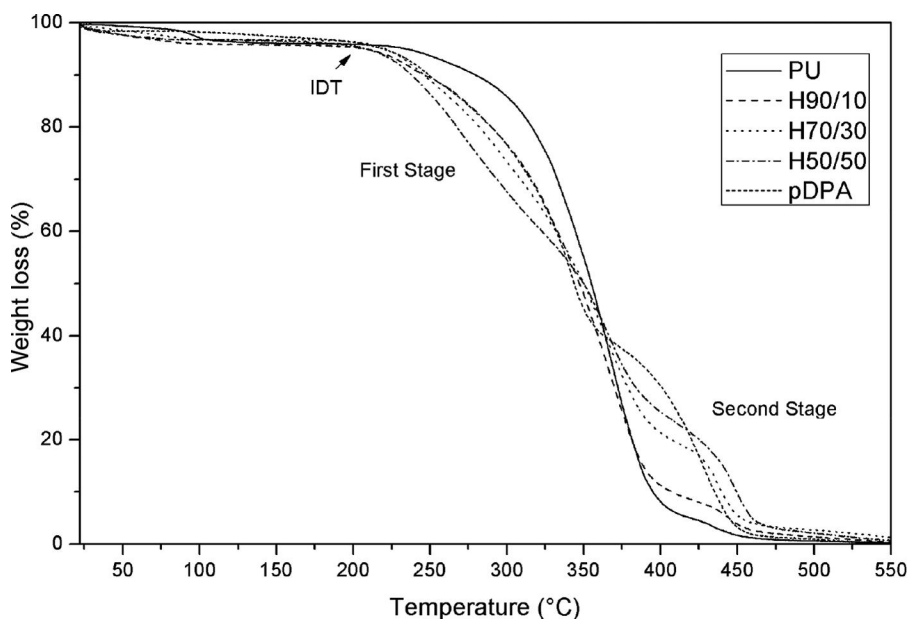


Figure 4. TGA curves for PU, pDPA, and hybrid polymers. Note: DPA, 2-(diisopropylamino)ethyl methacrylate; IDT, initial degradation temperature; pDPA, poly(2-(diisopropylamino)ethyl methacrylate); PU, polyurethane; TGA, thermogravimetric analysis.

In PU/DPA hybrids, IDT values slightly decreased, from 191 to 188°C, as the amount of DPA increased. This behavior is due to the lower IDT value of the DPA homopolymer compared to PU. Also, T_{50} values were within the range of PU and pDPA values.

The percentage of degradation decreased in the first stage and increased in the second one, as the amount of DPA of the hybrid is higher. These changes are a consequence of the presence of anhydride structures formed during the degradation of pDPA fraction. By increasing the proportion of acrylic, the number of anhydride structures formed increased and therefore more energy will be needed to degrade the compound. In all samples, a weight loss was observed at the beginning of the essay corresponding to the evaporation of residual water. These values are given in Table 2.

Characterization by MDSC

Modulate differential scanning calorimetry (MDSC) allows separating reversible and kinetic (nonreversible) phenomena facilitating the T_g determination in complex polymers.^[37] Reverse heat flow (RHF)–MDSC curves for PU/DPA hybrids and pure components (PU and pDPA) are shown in Figure 5.

Polyurethane curve showed a glass transition temperature of soft segments (T_g) at -33.6°C . The RHF–MDSC curve for the DPA homopolymer (pDPA) showed a T_g of 23.5°C . This value is related to

Table 2. Relevant data obtained from the TGA curves of PU, pDPA, and hybrid films.

System	First stage			Second stage		Residual polymer (wt%)	Residual water (wt%)
	IDT ($^\circ\text{C}$)	Degradation (wt%)	T_{50} ($^\circ\text{C}$)	T_2^* ($^\circ\text{C}$)	Degradation (wt%)		
PU	224	89.7	355	420	4.4	0.24	3.0
H90/10	197	84.0	347	402	4.4	0.38	4.1
H70/30	194	74.2	350	396	18.6	0.39	3.2
H50/50	188	67.9	350	389	24.9	1.47	3.2
pDPA	191	59.0	339	350	39.0	5.46	1.9

T_2^* , initial degradation temperature of the second stage.

DPA, 2-(diisopropylamino)ethyl methacrylate; IDT, initial degradation temperature; pDPA, poly(2-(diisopropylamino)ethyl methacrylate); PU, polyurethane; TGA, thermogravimetric analysis.

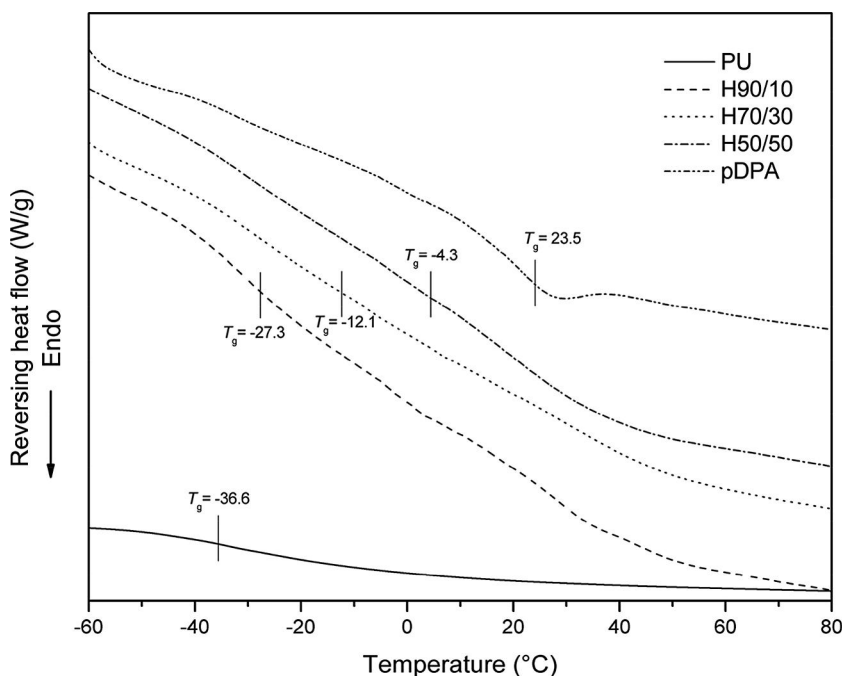


Figure 5. RHF–MDSC curves for PU, pDPA, and hybrid systems. Note: DPA, 2-(diisopropylamino)ethyl methacrylate; MDSC, modulate differential scanning calorimetry; pDPA, poly(2-(diisopropylamino)ethyl methacrylate); PU, polyurethane; RHF, reverse heat flow.

the flexibility of the main chain (formed by $-\text{CH}_2-$); the presence of isopropyl groups, which increase the free volume of the polymer favoring movement between the segments of the chain; and by the fact that the pDPA has limited ability to form intermolecular bonds of the hydrogen bond type, as already seen by FTIR, by the steric hindrance of the tertiary amine group. The signal at about 28–30°C observed in Figure 5 for pDPA could be assigned to the hydrophilic–hydrophobic transition (LCST). For this homopolymer, a range of values was reported.^[25] For the acrylic content of 30 wt% or higher (H70/30 and H50/50), almost a single-phase transition was observed. This fact indicates that both compounds (PU–acrylic) are miscible with each other and have a random distribution in these systems.

T_g values are located in the range of values corresponding to PU and homopolymer (see Table 3).

In the case of binary miscible mixtures of polymers, the dependence of T_g on the composition can be described by several equations. One of the most widely used models is Fox,^[42] where this equation is symmetrical with respect to the two components and allows a prediction based on the properties only of the pure components. Its main application was in copolymers but then extended to the analysis of polymer blends.^[43]

Table 3. Glass transition temperatures for PU, pDPA, and PU/DPA systems obtained experimentally from RHF–MDSC curves and using Gordon–Taylor equation (5).

System	Experimental T_g (°C)	Gordon–Taylor equation T_g (°C)
PU (100/0)	–33.6	–33.6
H90/10	–27.3	–26.9
H70/30	–12.1	–14.2
H50/50	–4.3	–2.5
pDPA (0/100)	23.5	23.5

DPA, 2-(diisopropylamino)ethyl methacrylate; MDSC, modulate differential scanning calorimetry; pDPA, poly(2-(diisopropylamino)ethyl methacrylate); PU, polyurethane; RHF, reverse heat flow; TGA, thermogravimetric analysis.

Brostow et al.^[44] suggest that in the ideal behavior of miscible systems, the Fox equation may be sufficient to describe the process; but when the complexity of the system increases, this equation, based on the rules of additivity, may not adequately fit the experimental data. Similar concluding points have been reported by other authors.^[45] In this case, the complexity of the systems is given by the presence of cross-linker (PPGDA), which modifies the free volume of the polymer, and the interaction between HS and SS of the polymer chains.

In these cases, it is necessary to use other equations that allow a correct description of the systems, such as Gordon–Taylor's equation^[44] (GT):

$$T_g = \frac{x_1 T_{g,1} + k_{GT} x_2 T_{g,2}}{x_1 + k_{GT} x_2} \quad (5)$$

where x_i ($i = 1, 2$) is the weight fraction of component i , T_{gi} ($i = 1, 2$) is the glass transition temperature of component i , and T_g is the glass transition temperature of a mixture. k_{GT} is a curve-fitting factor representing the miscibility of the system, with $k_{GT} = 1$ indicating the complete miscibility of the polymers and the lower/higher values of k_{GT} indicating poor miscibility.^[46]

In this work, the agreement between the experimental data obtained in RHF–MDSC curves and the description through the Gordon–Taylor equation was satisfactory (Table 3). This shows an adequate miscibility of the components during the polymerization, in the range of compositions studied. Also, the value of k_{GT} obtained was 1.2, indicating a strong interaction between the components of the polymer.^[45]

Swelling degree (SD) behavior

The water absorption by a hydrogel is one of the most important properties influencing the permeability, mechanical, surface, and other characteristics of the polymer that are related with controlled drug release behavior.^[47] It is known that the responsive polymers undergo a modification in their structure, from a collapsed state to a swollen state, in the presence of a suitable stimulus such as a change in pH or temperature of the medium. Bearing this in mind, the effect of pH and temperature on SD of PU/DPA hybrid films is discussed in this section.

Figure 6 shows the variation of SD as a function of pH value for PU and hybrid systems at 25°C.

It can be observed how the variation of pH and composition of the polymer modify the swelling behavior of films. PU film has the lowest SD at pH 4.0 to 7.0 with values between 20 and 30 wt%. At pH higher than 7.0, SD values of PU film increase because the carboxylic groups of the DMPA moiety became ionized. In contrast, SD values of hybrids films were higher than the PU, in the pH range between 4.0 and 7.0.

H90/10 system has SD values greater than PU between pH 4.0 and 7.0; however, it did not show a clear responsive behavior with the pH at this temperature.

For H70/30 and H50/50 systems, the situation changes and a clear pH-responsive behavior can be appreciated, especially at pH 4.0 where hybrids swelled more than 300 wt%. This is attributed to the protonation of amino groups of DPA and to the consequently electrostatic repulsion between them. The mentioned electrostatic force increases the network space, and in turn, allows water to get into the matrix. At pH 4.0, a linear relationship (R^2 of 0.99) between the amount of DPA in the film and the SD was observed (not shown) indicating a proportional dependency of the amino groups with the water molecules inside the matrix.

At pH above 6.0, SD values decrease when DPA proportion is higher. The pDPA block has a pKa around 5.8–6.6, so above pH 6.0 this polymer became deprotonated and insoluble.^[48,49] In this situation, by increasing the amount of DPA in the system, the protonated groups decrease and so does the SD.

To evaluate the swelling response of hybrid systems at body temperature, in Figure 7 it can be appreciated the variation of SD as a function of PU/DPA ratio, in the pH range from 4.0 to 8.0 and at 37°C.

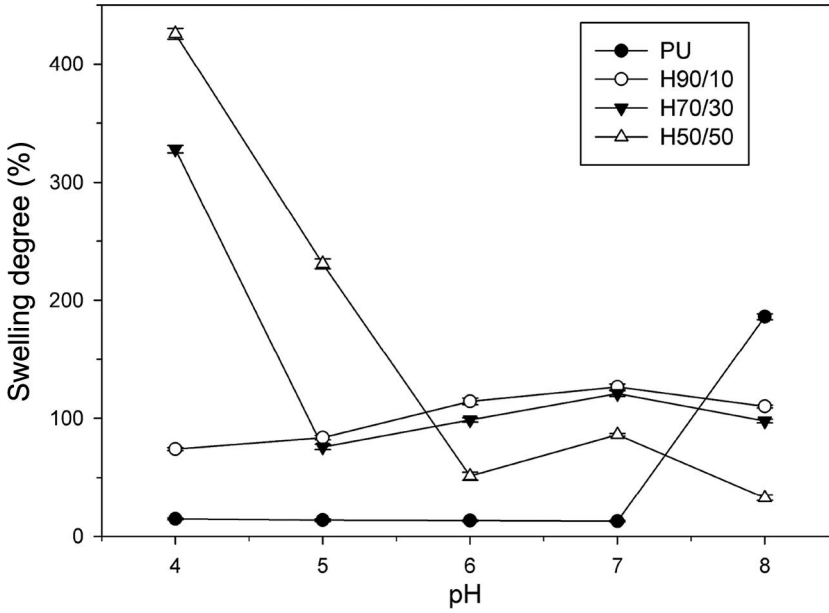


Figure 6. Equilibrium swelling degree values for PU and hybrid systems in a pH range from 4.0 to 8.0 and at 25°C. Note: PU, polyurethane.

Temperature modification (from 25 to 37°C) changes the pH response of hybrid systems. At pH 4.0, although the SD is lower than at 25°C, the tendency is the same, and SD increases with the DPA content in the polymer. However, at higher pH values the situation is different in hybrid systems, and the H50/50 system presents the lowest SD, indicating that the intermolecular forces are changing due

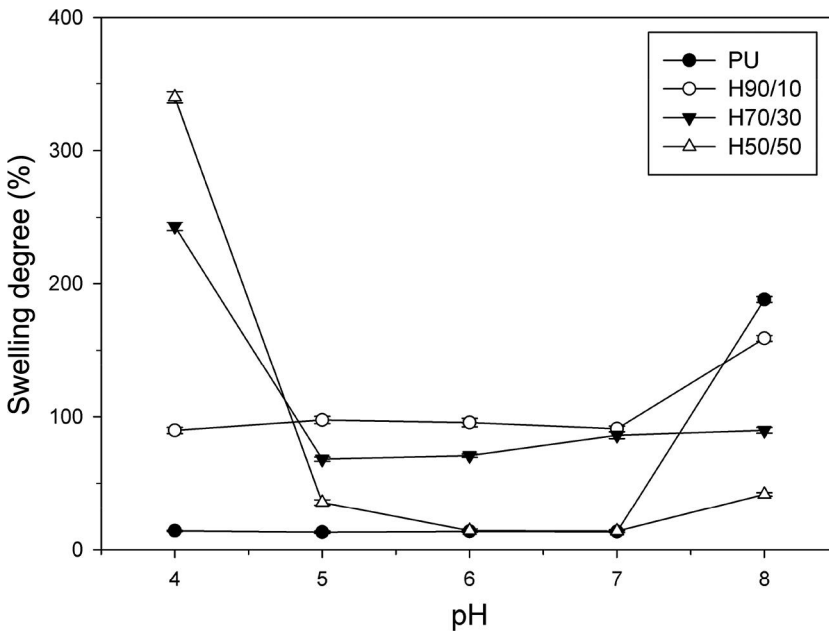


Figure 7. Equilibrium swelling degree values for PU and hybrid systems in a pH range from 4.0 to 8.0 and at 37°C. Note: PU, polyurethane.

to the hydrophilic–hydrophobic transition of the DPA moieties at that temperature. The rise in medium temperature produces a decrease in the SD value which is related to the amount of DPA in the polymer and is well marked in H70/30 films and even more in H50/50 ones.

Pearson et al.^[30] studied the effect of temperature on poly(2-(methacryloyloxy)ethyl phosphorylcholine)–poly(2-(diisopropylamino)ethyl methacrylate) diblock copolymers (PMPC–pDPA) and found that the pKa of PDPA block had a strong temperature dependence, with a maximum value of 7.60 at 5°C and of a minimum value of 5.75 at 50°C. Using the equation derived from that work, we can then estimate the pKa values of pDPA located at 6.55 and 6.25 for 25 and 37°C, respectively. Therefore, when raising the temperature from 25 to 37°C, the pKa value decreases and the amount of unprotonated state of tertiary amine group increases, decreasing in this way the SD.

At pH 5.0, when going from 25 to 37°C, an abrupt decrease in SD is observed in H50/50 (mostly) and in H70/30 hybrids. This is because the unprotonated–protonated ratio changes rapidly in the transition region between pH 4.0 and 5.0.

At pH 6.0 and 7.0, no major changes were observed; however, at pH 8.0, an increase in the SD is observed due to the ionization of carboxyl groups of PU.

The modification of SD values with temperature and DPA content can be attributed to the existence of a hydrophilic → hydrophobic transition,^[50] which in this case occurs between 28 and 30°C.

This hydrophilic–hydrophobic transition has been observed in matrices with hydrophobic compounds in their structure, which undergo reversible swelling–deflating in response to changes in temperature.^[15] This transition is controlled by the balance between the hydrophobic and hydrophilic groups of the polymer; and by the temperature dependence of certain molecular interactions that contribute to this type of phase separations such as hydrogen bonds and hydrophobic interactions.^[51]

In the polymers presented in this work, the hydrophilic–hydrophobic transition occurs as a consequence of the modification of the nature of the interactions between the PU hydrophilic COOH groups, and the hydrophobic diisopropyl groups of the DPA, with water molecules.^[52] When the transition temperature is exceeded, water molecules are ejected from the matrix with the consequent reduction of the aqueous content which leads to the collapse of polymer chains.

Dynamic swelling behavior

A kinetic analysis of the swelling degree is very interesting for the design of controlled drug delivery systems based on polymer matrices with swellability, since it can be used to predict the rate of release of pharmacologically active substances. In the case of drugs incorporated into a polymer in the vitreous state, it depends on the diffusion of water to improve its mobility in the matrix. An adequate design of the polymer matrix will allow the development of very specific control systems. For this, a deep knowledge of the parameters that determine the equilibrium and dynamics of polymer swelling is essential.^[51]

The influence of acrylic content on the hydration kinetics can be appreciated. The SD of PU slightly increases in the first minutes and then remains constant in all pH range in correlation to the response observed in [Figure 7](#). While in hybrid systems, the situation is clearly different and other behavior can be appreciated in function of pH and DPA proportion.

At pH 4.0, both the rate and degree of swelling increased with DPA content. Swelling kinetics at this pH value indicates a good hydration performance of the systems.^[53,54]

At pH 5.0 and higher, the swelling rate for hybrid systems decreased mostly for H50/50 and H70/30, due to the nonionized state of the amino groups. H50/50 system SD, for example, drops from 300 to 30% when the pH goes from 4.0 to 5.0. Also, as discussed above, at this temperature (37°C) a hydrophilic → hydrophobic transition occurs upon passing the LCST of the polymer (28–30°C), so the hydrophobic–hydrophilic equilibrium is displaced having a more hydrophobic nature at pH 5.0, compared with the results obtained at 25°C (see [Figure 6](#)).

These results indicate a direct dependence of the SD kinetic with the amount of protonated amine groups, and the proportion of DPA present, which would allow controlling the swelling kinetics of the films not only through pH but also from the chosen PU/DPA proportion. The selection of both pH and PU/DPA ratio to be used will ultimately depend on the needs and objectives presented in each case.

Also in Figure 8, swelling curves (H90/10, and H70/30, clearly; and H50/50, to a lesser extent), at pH 5.0, 6.0, and 7.0 mainly, present an abnormal trend, where the curve reaches a maximum of SD and then decreases until reaching the equilibrium value. This phenomenon is described in the literature as an effect of overshooting^[51,55] and consists of a first stage where the film swells to a maximum value (SD_{max}), which is followed by a second step of gradual deflating until finally reaching an equilibrium condition, SD_{eq} . Once the SD_{max} is reached, an internal reorganization occurs in the matrix that causes the expulsion of water from the inside. This internal reorganization does not change the value of the swelling equilibrium obtained under normal conditions and is considered by different authors as a “physical interlocking.”^[51,55] For example, in the case of hydrophilic systems with nonionizable side chains, several authors^[56] have proposed that water diffuses into the network before the chains have time to relax, and the curve reaches a maximum. When the chains finally relax, they force the water to leave the net, and the system reaches equilibrium. Therefore, from what is observed in Figure 8 at pH 6.0 and 7.0 mainly, the rate of diffusion of water would be higher than that of relaxation of polymer chains, thus producing a short time, overshooting effect in H90/10 and H70/30 hybrids.

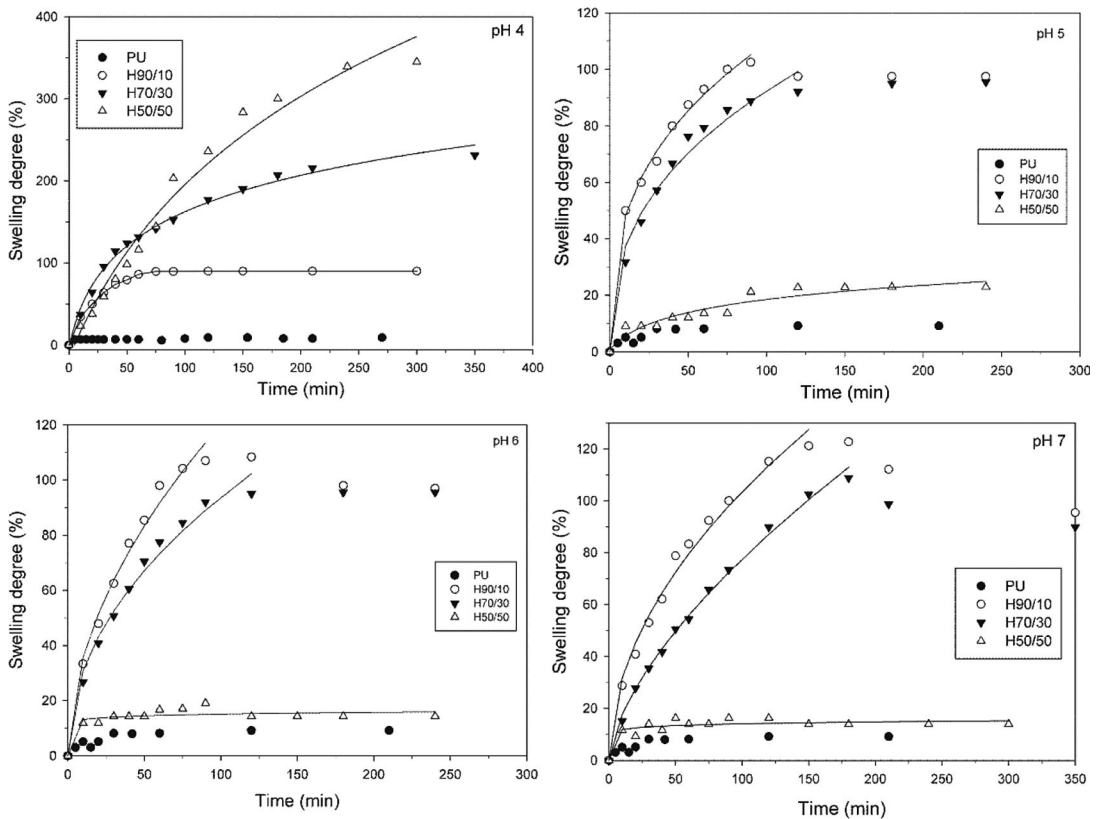


Figure 8. Curves of dynamic swelling for PU and hybrid systems at different pH values (from 4.0 to 7.0) and at 37°C. Straight lines were obtained from the fit of Equation (3). Note: PU, polyurethane.

No overshooting effect was observed at pH 4.0 probably because the relaxation rate of polymer chains is greater than the rate of water diffusion.^[37]

At 25°C, dynamic swelling curves (not shown in this work) have not presented the overshooting effect, indicating that modifying temperature conditions also affects this phenomenon.

Water uptake mechanism

To analyze the mechanism of water uptake, in Table 4 are presented the kinetic parameters (k and n) of the experimental data obtained from dynamic swelling curves, calculated using Equation (4).

At 25°C, n values of H90/10 system indicate the Fickian diffusion from pH 4.0 to 7.0 in correlation to the results observed in Figure 6.

Furthermore, for hybrid systems with more than 10 wt% of DPA, the n values are between 0.60 and 0.88, indicating anomalous transport, and a domination of relaxation process over diffusion at 25°C and overall range of pH studied. This is attributed to the electrostatic repulsion between ionized amino groups which increase in the network space, and in turn, allows water to get into the polymer.

On the other hand, at 37°C we observe some changes in the mechanism of water diffusion of hybrids films. For H90/10 systems, n values (between 0.56 and 0.60) indicate an anomalous transport from pH 4.0 to 7.0 unlike observed at 25°C. For H70/30 and H50/50 hybrids, when pH value of the solution was 5.0, these hybrid systems change their mechanism from anomalous to Fickian one (n values around 0.5).^[57] The same behavior was appreciated at pH 6.0 for the H50/50 system. Finally, at pH 4.0 for H50/50 hybrid, n value (around 1.0) indicates a time-independent swelling mechanism.

These results indicate that the hydrophilic \rightarrow hydrophobic transition that occurs upon passing polymers' LCST not only affects SD values of hybrid films but also the water uptake mechanism. This behavior shows the potential ability of hybrid systems to achieve a control of drug released as a function of the pH and temperature of the medium.

Structure characterization by SEM

The freeze-drying process associated with the SEM technique allows studying the characteristic structural changes that occur in responsive polymers.^[37] From SEM images present in Figure 9, we can see the morphologic structure of the samples previously swelled at two pH values, 4.0 and 8.0.

As expected, PU SEM images show a compact, close, and homogeneous structure (both on its surface and inside) at pH 4.0, while at pH 8.0, the morphology changes visibly in agreement with SD results. An important increase in roughness with higher terminations and sharp edges can be observed. In addition, the images corresponding to the cross section showed the appearance of pores, characteristic of an open-state morphology, due to the high hydration obtained by the film at that pH value. The observed behaviors are consistent with the results obtained in the SD analysis, where the water absorption of the PU films is given by the ionization of OH groups of DMPA at pH above 7.0.

On the other hand, hybrid films also show structural changes with the pH of the surrounding media. Both H70/30 and H50/50 systems show at pH 8.0 a collapsed and homogeneous matrix without visible presence of pores as a result of the low hydration of this hybrid at alkaline pH. However, at

Table 4. Parameters (k , n) calculated from the fit of Equation (4) for the dynamic swelling curves of hybrid systems.

System	Temperature (°C)	pH4		pH5		pH6		pH7	
		n	$k \cdot 10^2 (\text{cm}^{-1})$	N	$k \cdot 10^2 (\text{cm}^{-1})$	n	$k \cdot 10^2 (\text{cm}^{-1})$	n	$k \cdot 10^2 (\text{cm}^{-1})$
H90/10	25	0.54	1.0	0.53	6.3	0.53	5.0	0.53	6.0
H70/30		0.60	4.0	0.71	7.1	0.69	2.7	0.74	3.0
H50/50		0.70	4.5	0.88	8.8	0.64	7.0	0.63	3.2
H90/10	37	0.56	1.0	0.57	2.2	0.59	5.5	0.60	5.6
H70/30		0.68	3.6	0.53	8.9	0.57	9.3	0.70	2.9
H50/50		0.98	6.4	0.54	7.6	0.45	5.7	0.46	6.4

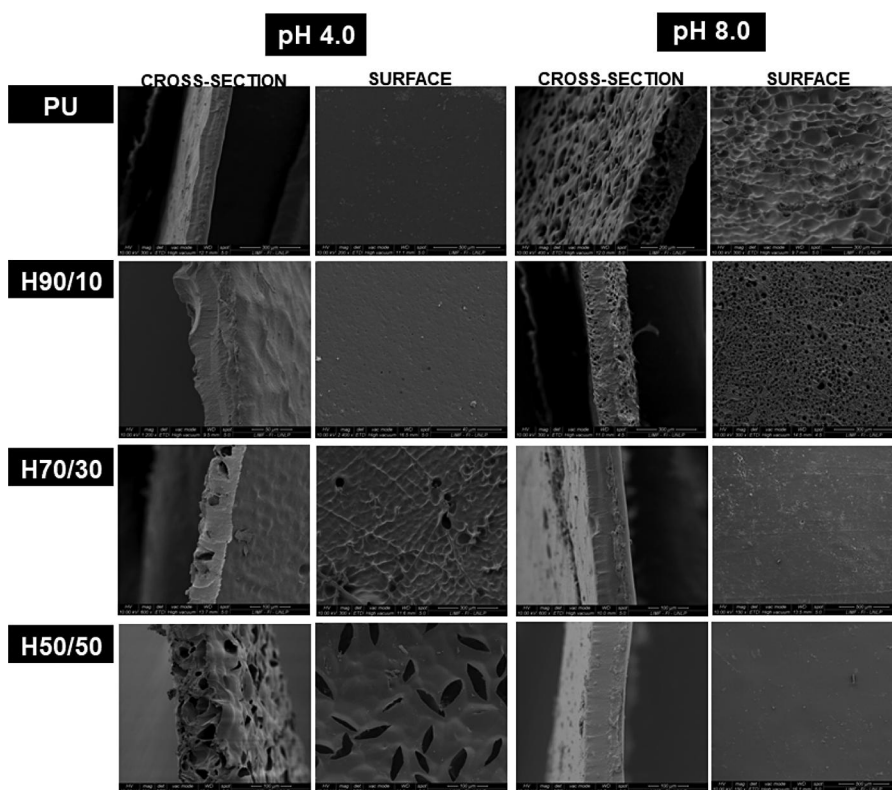


Figure 9. Surface and cross-sectional SEM images from PU and hybrid systems previously swelled at two pH values (4.0 and 8.0). Note: PU, polyurethane; SEM, scanning electron microscope.

pH 4.0 the matrix undergoes well-marked changes. In H70/30, it can be seen the appearance of some pores as well as an increase in roughness on both cross section and surface, while in H50/50, it can be observed a rougher and open morphology as well as the appearance of pores, with predominantly oval form distributed throughout the surface due to the high SD (425.8%). These changes are associated with the increase of the free space in the network because of the electrostatic repulsion that occurs in the matrix at this pH. Finally, the H90/10 system has the same behavior as PU, the images present a rather porous structure both on the surface and inside with a homogeneous distribution at pH 8.0. This behavior is related to the high SD value of this hybrid (110%), where this interstitial network space of the matrix allowed water to get into the polymer, whereas at pH 4.0, the situation changes, and although the morphology presents undulations and some roughness, the film appears more compact with only some small pores visible in the studied area. The results were consistent with the decrease in the SD at pH 4.0 for this hybrid.

Based on these results, it is expected that hybrid polymers will have the ability to modify the release of an active principle (AP), as a consequence of observed morphological changes when modifying the pH. In this way, and if there are no other predominant factors such as interaction forces or effects associated with the solubility of the AP, systems with larger pore size will have a higher release rate of the AP, whereas for those with a more compact morphology they will have lower values of release rate.

Conclusion

Dual pH- and thermal-responsive hybrid films of PU and DPA were satisfactorily synthesized and characterized. Systems showed good film and physicochemical properties. TGA studies indicated that

thermal degradation occurs in two principal steps and MDSC experiments showed a single-phase transition (in H70/30 and H50/50 systems), with good miscibility between PU and DPA polymers. The incorporation of DPA monomer modifies the interactions inside polyurethane chains and causes the water uptake process to become pH and temperature dependent.

H70/30 and H50/50 systems presented pH-responsive behavior between pH 4.0 and 7.0., where these hybrids swelled more than 300 wt% at pH 4.0. This is attributed to the protonation of amino groups of DPA fraction and to the consequently electrostatic repulsion between these ionized groups which increase the network space, and in turn, allows water to get into the matrix. SEM images agree with swelling results where H70/30 and H50/50 systems show at pH 8.0 a collapsed and homogeneous matrix without visible presence of pores. However, when the pH changes to 4.0, systems presented a rough and open morphology with the consequent appearance of pores.

The increment of temperature not only affects SD values of hybrid films but also the water uptake mechanism. These changes in the swelling mechanism were attributed to the hydrophilic → hydrophobic transition that occurs upon passing the LCST of the polymer (28–30°C).

The dependence of SD with the protonated amine groups would allow controlling the swelling of the films not only through pH or temperature but also from the chosen PU/DPA proportion.

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