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Research Article

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Effect of tertiary amine methacrylate structure on the pH-responsive release behavior of polyurethane/acrylic hybrid films

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Abstract: Smart polymers with pH-responsive behavior are attractive materials for controlled drug delivery. In this work, hybrid systems based on polyurethane and two tertiary amine methacrylates—2-diethylaminoethyl methacrylate (PU/DEA) and 2-(diisopropylamino)ethyl methacrylate (PU/DPA)—were synthesized and evaluated using Rhodamine 6G (R6G) as a model drug. The pH-responsiveness of both hybrids was characterized through swelling studies and scanning electron microscopy (SEM). Drug–matrix interactions were analyzed by Fourier Transform Infrared (FTIR) spectroscopy. In addition, the optimal loading pH was also evaluated. Release kinetics were studied at acidic and basic pH, and the transport mechanism was determined using the Korsmeyer–Peppas model model. Both polyurethane/acrylic (PU/A) hybrid systems exhibited reversible morphological changes and a marked pH-dependent release behavior. PU/DEA showed higher surface drug localization and stronger ionic interactions, while PU/DPA displayed lower hydrophilicity and slower release in most proportions. These results highlight the influence of the tertiary amine structure on the responsive behavior of polyurethane-based hybrids and their potential as tunable matrices for controlled drug delivery.

Keywords: Hybrid polymer materials; Polyurethane; 2-diethylaminoethyl methacrylate; 2-(diisopropylamino)ethyl methacrylate; pH-responsive polymers; Drug delivery systems.

1. Introduction

Stimuli-responsive polymers constitute an important class of functional materials whose physicochemical properties can be reversibly altered by environmental stimuli, including pH, ionic strength, temperature, and specific chemical compounds. [1, 2]. Owing to these unique properties, they have attracted considerable attention for applications including drug delivery, biomedical therapies, industrial coatings, separation technologies, sensors, oil exploration, membrane science, colloidal stabilization, and water remediation [3-8].

Among responsive materials, pH-sensitive polymers have attracted particular interest for drug delivery applications because they can regulate both the location and the timing of drug release in response to changes in the surrounding environment[5, 9]. Recent advances in responsive polymeric systems have demonstrated their potential for improving drug bioavailability and modulating release kinetics in response to environmental changes [10].

A common strategy for producing pH-responsive polymers consists of introducing ionizable acidic or basic groups into the polymer structure during synthesis.[11]. In particular, polyurethane (PU)-based responsive systems can be obtained by combining PU with functional monomers such as N-(3-aminopropyl)methacrylamide, 2-(dimethylamino)ethyl methacrylate, methacrylic acid, 2-aminoethyl methacrylate, and 2-hydroxyethyl methacrylate [12]. Polyurethanes (PUs) are are versatile materials whose final properties can be adjusted through the selection of suitable polyols, polyisocyanates, and functional comonomers.[13, 14]. Due to their excellent mechanical properties, biocompatibility, and structural versatility, PUs have been extensively explored for biomedical applications, particularly in drug delivery systems [1, 15, 16].

One of the most widely used approaches for incorporating functional monomers into PU systems is the blending of polymer dispersions in selected proportions to achieve the desired material properties.[17]. However, another effective approach is the formation of chemically integrated polyurethane/acrylic hybrid systems through covalent interactions between both polymeric phases [12, 18]. These hybrid structures offer improved compatibility and allow modulation of the physicochemical properties of the resulting materials [19]

In previous studies, we reported the synthesis and characterization of pH-responsive polyurethane/poly(2-(diethylamino)ethyl methacrylate) (PU/DEA) hybrid polymers , which exhibited

suitable film-forming ability, tunable mechanical properties depending on acrylic content, and potential applications in drug delivery and metal uptake systems [8, 20].

In the present work, we propose a comparative study of pH-responsive polyurethane hybrids prepared using two different tertiary amine methacrylate monomers: 2-(diethylamino)ethyl methacrylate (DEA) and 2-(diisopropylamino)ethyl methacrylate (DPA). Hybrid films containing different acrylic contents were synthesized and evaluated as smart pH-responsive materials for controlled drug delivery applications.

The proportion of the acrylic phase plays a key role in the structure and performance of polyurethane/acrylic hybrids. Several studies have shown that increasing acrylic content modifies chain mobility, particle coalescence, and film formation, directly affecting both mechanical properties and mass transport phenomena within the polymer matrix [13]. Recent studies on polyurethane/acrylic systems have demonstrated that higher degrees of grafting generate stiffer materials with improved thermal stability, although they may also restrict the mobility of the soft segments [11] Similarly, analyses of UV-curable polyurethane/acrylate systems have reported a significant increase in storage modulus as the acrylic fraction increases, attributed to greater conformational restrictions within the polymer network. In addition, not only the acrylic content, but also the chemical nature of the acrylic monomer strongly influences the material response. Different tertiary amine methacrylates, exhibit distinct pKa values, hydrophilicity, steric effects, and protonation behavior, leading to differences in swelling capacity and ionic interactions within the polymer matrix [21]. This structure–response relationship demonstrates that modifying both the type and proportion of acrylic monomers constitutes an effective strategy for tuning the pH responsiveness and drug release behavior of polymer systems [22].

The performance of drug delivery systems depends on several factors, including the loading method, the strength of the interactions between the drug and the polymer matrix, and the molecular characteristics of the active compound [23]. Consequently, drug release from polymeric films may vary from rapid release to prolonged and sustained delivery [24]. In particular, the incorporation method of the drug plays a critical role in determining release efficiency and transport kinetics [25].

Although a wide variety of pH-responsive polymeric carriers have been reported, considerably less attention has been devoted to understanding how subtle structural variations in tertiary amine methacrylates influence swelling, polymer–drug interactions, and release kinetics in polyurethane/acrylic hybrid matrices. In particular, the influence of structurally related monomers such as DEA and DPA on transport mechanisms and pH-responsive release behavior has not been systematically investigated [26]. Understanding these structure–response relationships is essential for the rational design of tunable polymeric drug delivery materials.

Accordingly, this study aims to compare the release performance of pH-responsive PU/DEA and PU/DPA hybrid systems using Rhodamine 6G chloride (R6G, MW = 479.01) as a model active compound.R6G was selected as a model compound because of its high solubility in both aqueous and organic media, excellent chemical stability, and straightforward quantification by UV–visible and fluorescence techniques.. Furthermore, its structural and physicochemical similarities to several pharmaceutical compounds make it a suitable model for studying diffusion and release phenomena in responsive polymeric systems [27].

Drug-loaded films can be prepared by either immersion or dispersion techniques. In a previous study, we evaluated the effect of the loading method on release performance and found that immersion loading provided more controlled and reproducible release profiles [20]. For this reason, the immersion approach was adopted in the present work. 00 Particular attention was devoted to the mechanisms controlling drug loading and release. FTIR spectroscopy was used to evaluate the interactions established between R6G and the polymer network, while swelling studies and SEM characterization provided information on the pH-induced structural changes of the hybrid matrices. Together, these analyses allow a comprehensive discussion of how the chemical structure and content of the acrylic component influence the responsiveness and transport behavior of the systems.

2. Experimental Section

2.1. Materials

2-(diethylamino)ethyl methacrylate (DEA) and 2-(diisopropylamino)ethyl methacrylate (DPA, 97%) were purchased from Scientific Polymers Products. The monomers were treated with basic alumina to remove the inhibitor. Isophorone diisocyanate (IPDI, Aldrich), 2-hydroxy ethylmethacrylate (HEMA, Aldrich), poly(propylene glycol) diacrylate (PPGDA, Aldrich), ammonium persulfate (APS, Fisher Scientific), ethylene diamine (EDA, 99%, Aldrich), dibutyltin dilaurate (DBTDL, Aldrich) and sodium dodecyl sulfate (SDS, Anedra) were of analytical grade and were used as received. Monomethoxy-capped poly(ethylene glycol) methacrylate (PEGMA) macromonomer (M_n = 2000; M_w/M_n = 1.10) was supplied by Cognis Performance Chemicals (Hythe, U.K.) as a 50 wt. % aqueous solution. Polypropylene glycol 1000 (PPG1000, Voranol 2110) was of technical grade and was dried and degassed at 80 °C at 1-2 mm Hg before being used. Triethylamine (TEA) was provided by ADELFA S.A and was also dried before use. . Dimethylol propionic acid (DMPA, Aldrich) was dried at 100 °C for 2 h in an oven. . The phosphate buffer solutions used for drug loading and release were prepared from standard chemicals. Rhodamine 6G Chloride (R6G, Sigma-Aldrich, MW = 479.01) was used as a model drug and without additional purification.

2.2. Methods

2.2.1. Hybrids Synthesis

PPG1000 and DMPA were introduced into a 1000 mL six-neck separable flask and heated to 90 °C while dry air was bubbled through the mixture for approximately 60 min. The temperature was then increased to 98 °C, and a mixture of IPDI and DBTDL catalyst was added. After 2 h of reaction, the resulting prepolymer was cooled to 45 °C and a solution of HEMA in acetone was slowly incorporated. The reaction was allowed to proceed for a further 90 min, after which the temperature was raised to 60 °C and maintained until the theoretical isocyanate (NCO) content (ca. 4.7%) was reached, which required approximately 90 min.

The reaction mixture was subsequently cooled to 55 °C, and TEA dissolved in acetone was added dropwise over 50 min. Following neutralization, the system was allowed to cool to room temperature. The polyurethane dispersion was then prepared by dispersing the prepolymer into water containing the appropriate amount of EDA for chain extension. This step was carried out in a glass reactor at 30 °C under mechanical stirring (300 rpm) for 45 min. A stable aqueous PU dispersion with a solids content of approximately 30 wt.% was obtained.

The dispersion was then divided into several portions, and different amounts of acrylic monomer were added together with PPGDA as crosslinking agent and PEGMA as steric stabilizer. The PU/acrylic/PPGDA/PEGMA mixtures were polymerized in a 1000 mL glass reactor equipped with a water jacket for temperature control. Prior to polymerization, the reaction mixture was purged with nitrogen and subsequently dispersion-polymerized at 80 °C using APS (0.015 wt.% relative to the acrylic monomer content) as initiator. Under these conditions, chemically integrated PU/DEA and PU/DPA hybrid systems were obtained through covalent linkage between the polyurethane and acrylic phases (Fig. 1). The resulting products were stable aqueous dispersions with a solids content of approximately 30 wt.%.

Three hybrid formulations containing 10, 30, and 50 wt.% of the acrylic component were prepared. For clarity, a simplified nomenclature based on the PU/acrylic ratio is adopted throughout the manuscript. Thus, H_{DEA}90/10 designates a PU/DEA hybrid containing 90 wt.% polyurethane and 10 wt.% DEA, while H_{DPA}90/10 designates the corresponding PU/DPA hybrid with the same composition.

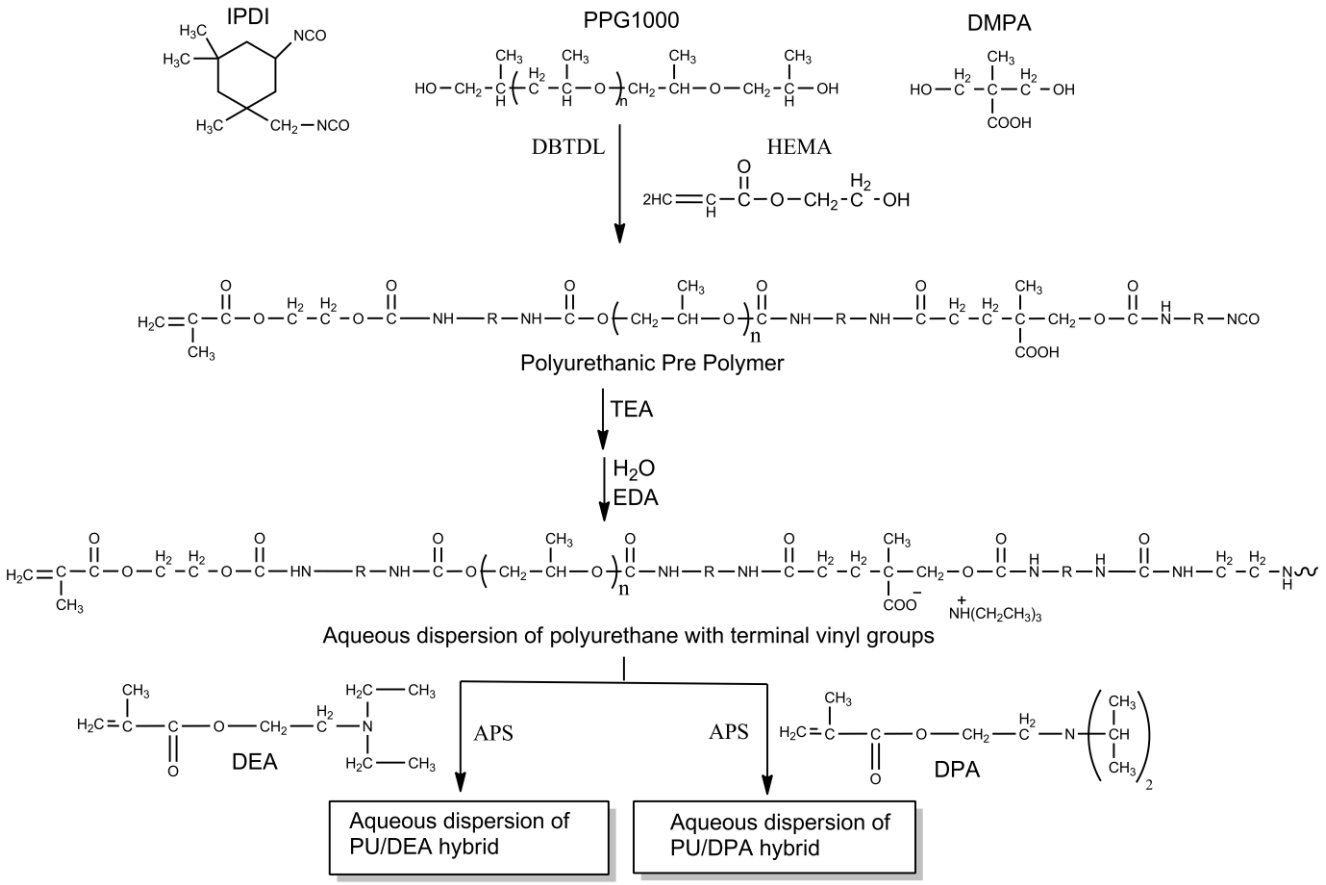


Fig. 1 Synthesis of polymer dispersions. Note: APS (ammonium persulfate); DBTDL (dibutyltin dilaurate); DMPA (dimethylol propionic acid); DEA (2-(diethylamino)ethyl methacrylate); DPA, 2-(diisopropylamino)ethyl methacrylate; EDA (ethylene diamine); HEMA (2-hydroxy ethyl methacrylate); IPDI (isophorone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

2.2.2. Preparation of Hybrid Films

Films were obtained by casting the aqueous dispersions onto Petri dishes and drying them at 30 °C for 24 h. After drying, circular samples with a diameter of 22 mm were prepared using a cork borer and cured at 60 °C for 48 h. The cured films were subsequently stored in silica gel desiccators until required for further characterization and release experiments

2.2.3. Swelling studies

The equilibrium swelling behavior of the films was evaluated by immersing disk-shaped samples (22.0 mm diameter, 292 ± 16 μm thickness) in phosphate-buffered saline (PBS, ca. 0.1 M, pH 8.0) and in a dihydrogen phosphate/phosphoric acid buffer solution (ca. 0.1 M, pH 4.0). The samples were maintained at 37 °C until equilibrium swelling was reached.

The equilibrium swelling degree (Q_∞) was determined using Equation (1):

$$Q_{\infty} = \frac{(W_{s,\infty} - W_d) \times 100}{W_d} \quad (1)$$

where Ws,∞ represents the mass of the swollen film at equilibrium and Wd corresponds to the initial dry mass of the sample. All experiments were performed in triplicate and the average values are reported.

2.2.4. Scanning electron microscopy (SEM)

The morphology of the swollen films was examined by Scanning Electron Microscopy (SEM) using an FEI Quanta 200 microscope (The Netherlands) operated in high-vacuum mode at an accelerating voltage of 15–20 kV. Prior to analysis, PU, PU/DEA, and PU/DPA films were equilibrated for 24 h in the corresponding buffer solutions, frozen at −40 °C in an alcoholic medium and subsequently freeze-dried under vacuum for 24 h. To minimize charging effects during SEM analysis, fractured film sections were mounted on aluminum specimen stubs and sputter-coated with a thin gold layer before imaging.

2.2.5. R6G loading studies

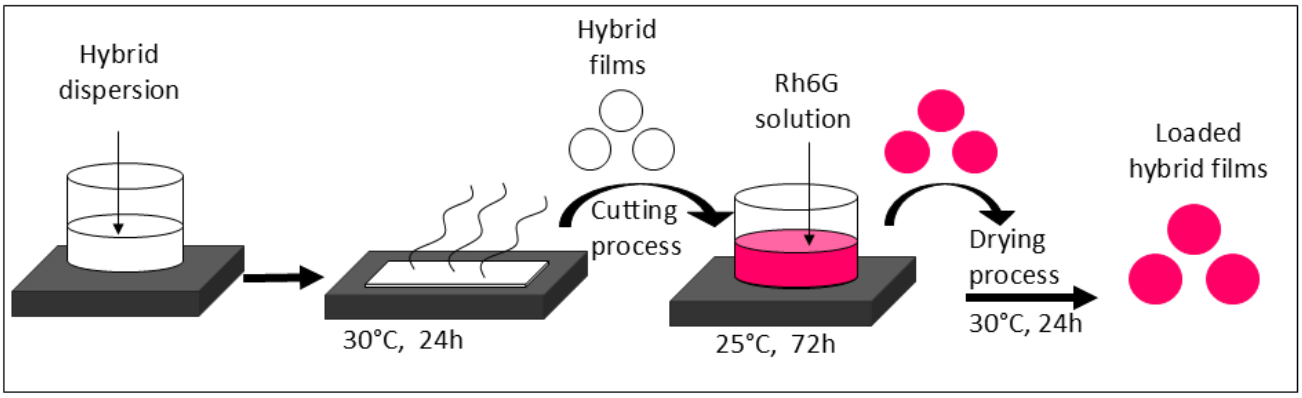


Fig. 2 Schematic preparation of drug loaded films by immersion method

R6G loading was conducted by immersing the films in an aqueous solution containing 100 mg/L of the dye. To evaluate the influence of the loading medium, experiments were performed at three different pH values (4.0, 7.0, and 8.0). Based on preliminary loading studies, a contact time of 72 h was selected for all systems to ensure equilibrium conditions and allow direct comparison among samples.

The amount of R6G incorporated into the films was determined indirectly by monitoring the decrease in dye concentration in the loading solution using a Thermo Genesys 10S UV–visible spectrophotometer (USA). Absorbance measurements were performed at 348 nm for concentrations ranging from 10 to 120 mg/L and at 526 nm for concentrations between 0.15 and 10 mg/L. The

corresponding calibration curves were used to calculate both the amount of R6G incorporated into the films and the amount subsequently released during the release experiments.

After the loading step, the films were carefully rinsed with distilled water to remove residual solution from the surface and then dried at 30 °C for 24 h prior to the release studies and further characterization.

2.2.6. FTIR Spectroscopy

Fourier Transform Infrared (FTIR) spectra were acquired using a Nicolet 380 spectrometer (Thermo Scientific, USA) equipped with a MIRacle™ Single Reflection attenuated total reflectance (ATR) accessory (Pike Technologies, USA). Spectral data were collected over the 4000–500 cm^{-1} range by averaging 64 scans at a resolution of 4 cm^{-1}. The resulting spectra were subsequently processed and corrected using the Advanced ATR Correction tool available in EZ Omnic software.

2.2.7. R6G Release Studies

Drug release experiments were carried out using R6G-loaded films under two different pH conditions (pH 8.0 and 4.0). Each film was immersed in 80 mL of buffer solution (0.1 M) maintained at 37.0 °C under continuous magnetic stirring (400 rpm). Initially, the samples were placed in the pH 8.0 medium until a constant release value was reached. The films were then removed, gently washed with distilled water, and transferred to a pH 4.0 buffer solution to evaluate the effect of acidification on the release behavior.

The concentration of R6G released into the medium was determined spectrophotometrically by monitoring the absorbance at 526 nm at predetermined time intervals [28]. All experiments were performed in triplicate.

The release data were analyzed using the Ritger–Peppas power-law model [29,30]:

(2)

$$\frac{M_t}{M_e} = kt^n \tag{2}$$

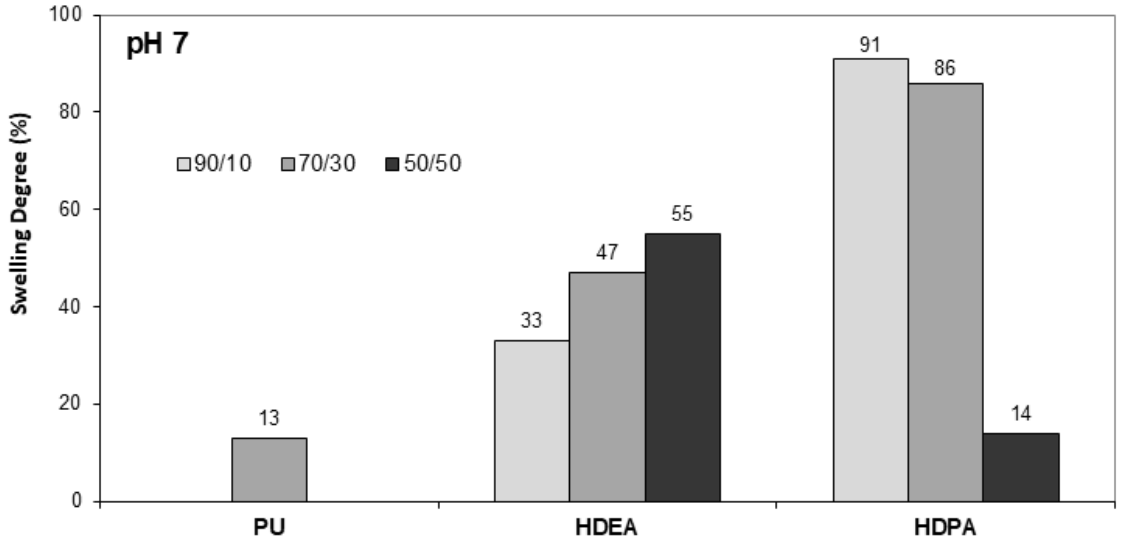
where Mt and Me represent the cumulative amount of drug released at time t and at equilibrium, respectively. The constant k is associated with the kinetic characteristics of the system and experimental conditions, whereas n corresponds to the diffusional exponent related to the release mechanism. To ensure the validity of the model, only the initial portion of the release curves, corresponding to drug release values below 60%, was considered for fitting. The parameters k and n were obtained from the intercept and slope of the linearized form of Equation (3):

$$ln(M_t / M_e) = ln k + n ln t \quad (3)$$

3. Results and Discussion

3.1. Swelling behavior

In pH-responsive systems the release rate of the drug is regulated by several factors such as swelling degree, drug-matrix interaction, water content and the initial drug concentration as extensively reported for smart polymeric delivery systems [10, 28]. However, swelling behavior as a function of pH plays a major role in drug release regulation, which makes this technique to be an important tool for predicting the rate of drug release.



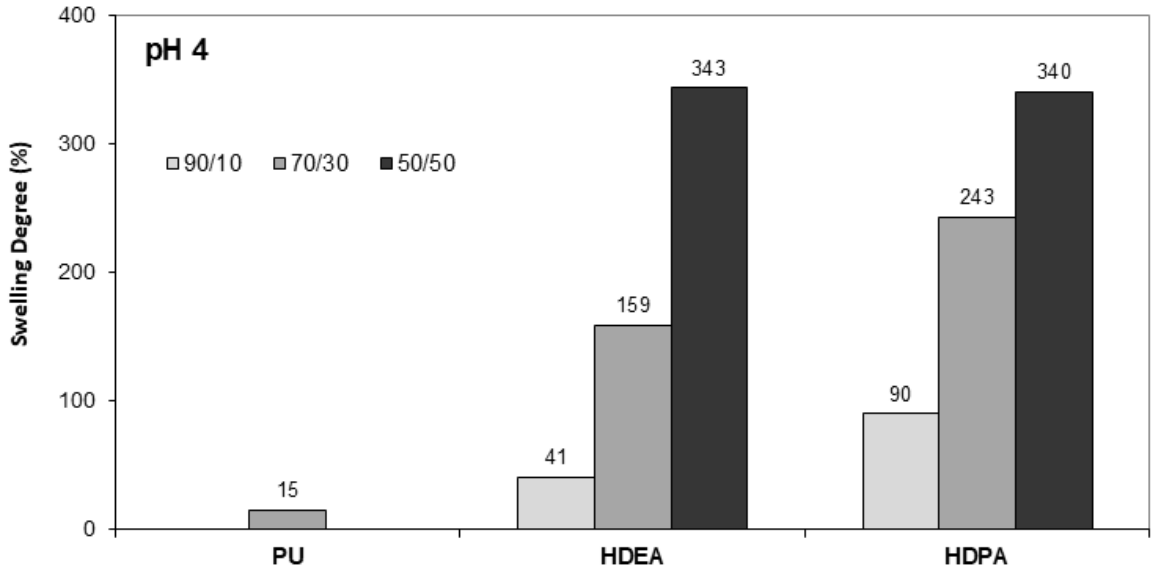


Fig. 3 Swelling degree (%) of PU and hybrid films at two different pH values. **a** pH 7.0; **b** pH 4.0

At pH 4 for hybrid films, an increase in DEA and DPA content led to an increase in SD. This effect was attributed to the protonation of amino groups of acrylic moieties and to an increase of the electrostatic repulsive force between ionized groups. This behavior is characteristic of tertiary amine-containing pH-responsive polymers, where protonation induces electrostatic repulsion and expansion of the polymer network [29]. The expansion of the polymeric network facilitates water penetration into the matrix, thereby increasing the swelling degree. Similar swelling behavior has been reported in other cationic methacrylate-based responsive systems [29]. For the PU system, the SD at pH 4 was lower than in hybrid systems because the carboxylic groups of the matrix are protonated.

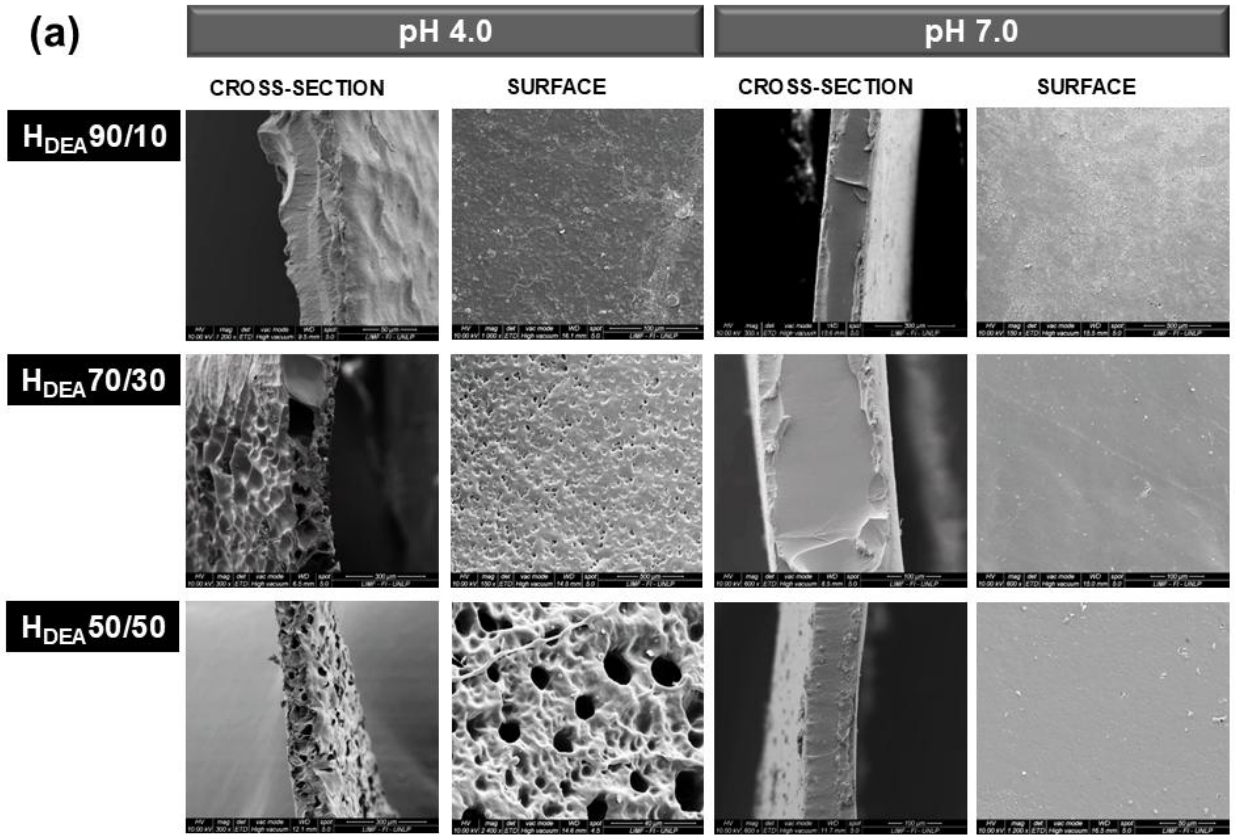
At neutral pH, the SD values for hybrid films decrease due to the reduced degree of protonation of the amino groups. When incorporating DEA monomer into the polymer chain a new ionizable group is introduced. The pK_a for the swollen-to-non swollen transition in linear PDEA homopolymer is around 7.3 [30] and in the hybrid polymers the critical pH for this transition is close to that value and around pH 6.5[31]. When the pH of the solution is around 7.0 about half of $-NR_2$ groups are therefore in non-ionized state. In the H_{DEA}90/10 hybrid the $-NR_2$/-C(O)OH molar ratio (where R = $-CH_2CH_3$) is close to 2 and the swelling is due to the partially ionized –C(O)OH groups with a low contribution from the DEA moiety. When increasing DEA content, the $-NR_2$/-C(O)OH ratio is about 7 and the total number of ionic groups increases and therefore the SD value.

The pDPA block has a pKa around 6.0, so above pH 6.0 this polymer becomes deprotonated and insoluble [30]. This lower pKa explains the reduced protonation degree of DPA-containing systems at neutral pH. In this situation, by increasing the amount of DPA in the system, the protonated groups decrease and so does the SD. Additionally, the carboxylic groups of PU proportion begin to ionize and there is an increase in SD (at pH 7.0), especially in compositions with a higher amount of polyurethane (90/10 and 70/30).

Consistent with previous swelling studies in PU/A systems, increasing the acrylic fraction enhanced the responsiveness of the hybrid matrix. The increase in swelling at acidic pH of both PU/A hybrid systems, facilitates the formation of additional diffusion pathways within the hybrid matrix, which may promote faster transport of R6G molecules toward the external medium.

3.2. SEM characterization

SEM is widely used to characterize responsive polymeric matrices because it provides valuable information about surface morphology, porosity, phase separation, and structural changes associated with swelling behavior [21, 32]. Morphologic changes of lyophilized pH-responsive films, after exposure to aqueous solutions of different pH values (4.0 and 7.0), were examined by SEM technique and the images are shown in Figure 4.


(a)
pH 4.0
pH 7.0
CROSS-SECTION
SURFACE
CROSS-SECTION
SURFACE
HDEA90/10
HDEA70/30
HDEA50/50

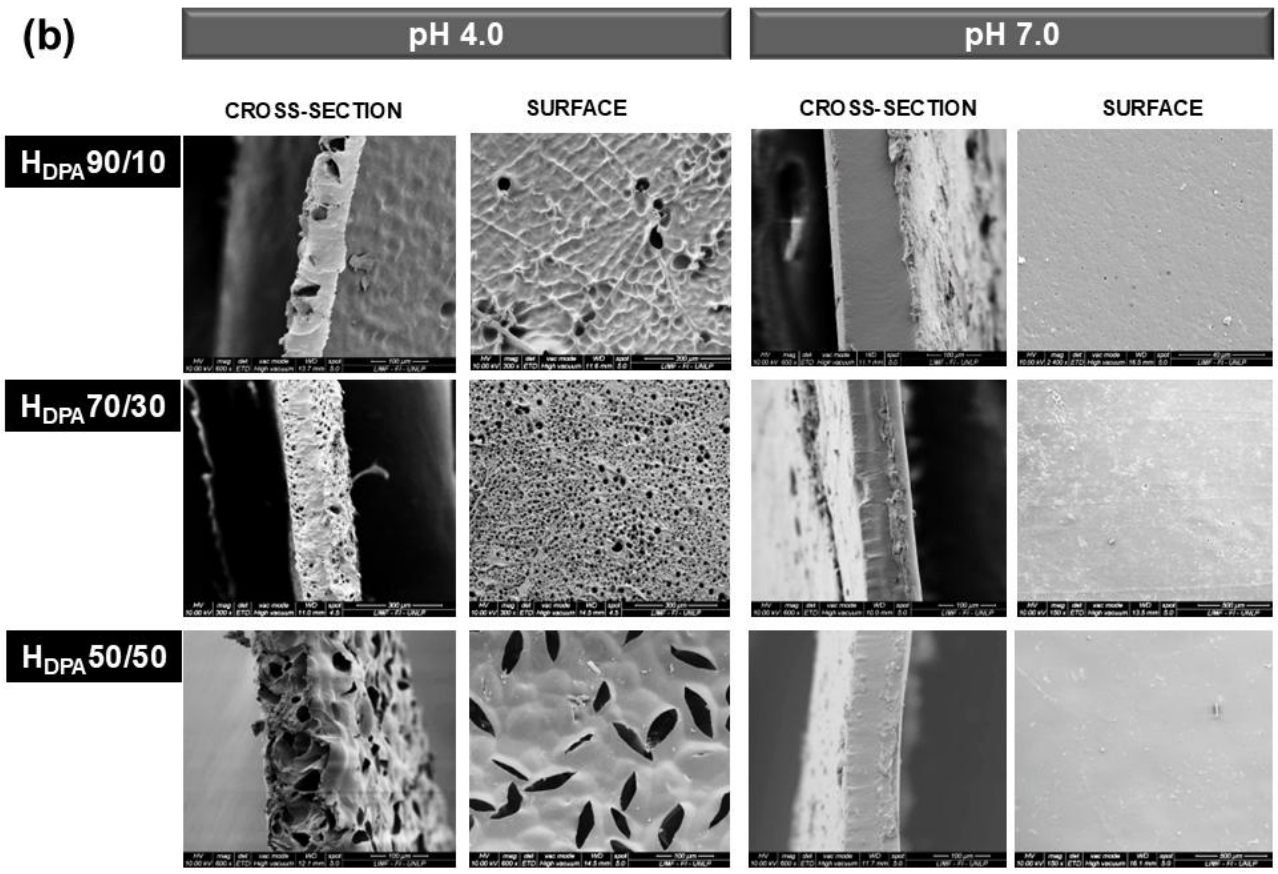

(b)
pH 4.0
pH 7.0
CROSS-SECTION
SURFACE
CROSS-SECTION
SURFACE
HDPA90/10
HDPA70/30
HDPA50/50

Fig. 4 SEM images of hybrid films at two pH values (4.0 and 7.0). **a** PU/DEA; **b** PU/DPA

In PU/DEA systems at pH 7.0 a compact and non-porous surface was observed due to lower swelling degree and a more hydrophobic polymer characteristic. At pH 4.0 the surface of H_{DEA}90/10 film shows a morphologic change and an increment in the surface roughness. In addition. in H_{DEA}70/30 and H_{DEA}50/50 systems, the surface shows an open morphology state with a porous structure, and void regions due to the matrix expansion. When DEA content is higher, at pH 4.0, the equilibrium swelling degree increases and it results in an open morphology state due to ionization of the amine groups.

At pH 4.0 the surface of H_{DPA}90/10 presents undulations and a certain roughness with small pores visible in the studied area in accordance with what was observed in the H_{DEA}90/10 film and in the swelling tests. It can be deduced that the greater amount of water incorporated by this system results in a more altered morphology compared to the H_{DEA}90/10 system. In systems with a higher proportion of DPA, the appearance of pores, predominantly oval (especially in H_{DPA}50/50), can be observed, distributed throughout the surface, as well as a rougher and more open morphology.

Therefore, the incorporation of DEA and DPA imparts pH-responsive behavior to the polymer matrix, producing reversible changes not only in film volume but also in surface morphology.

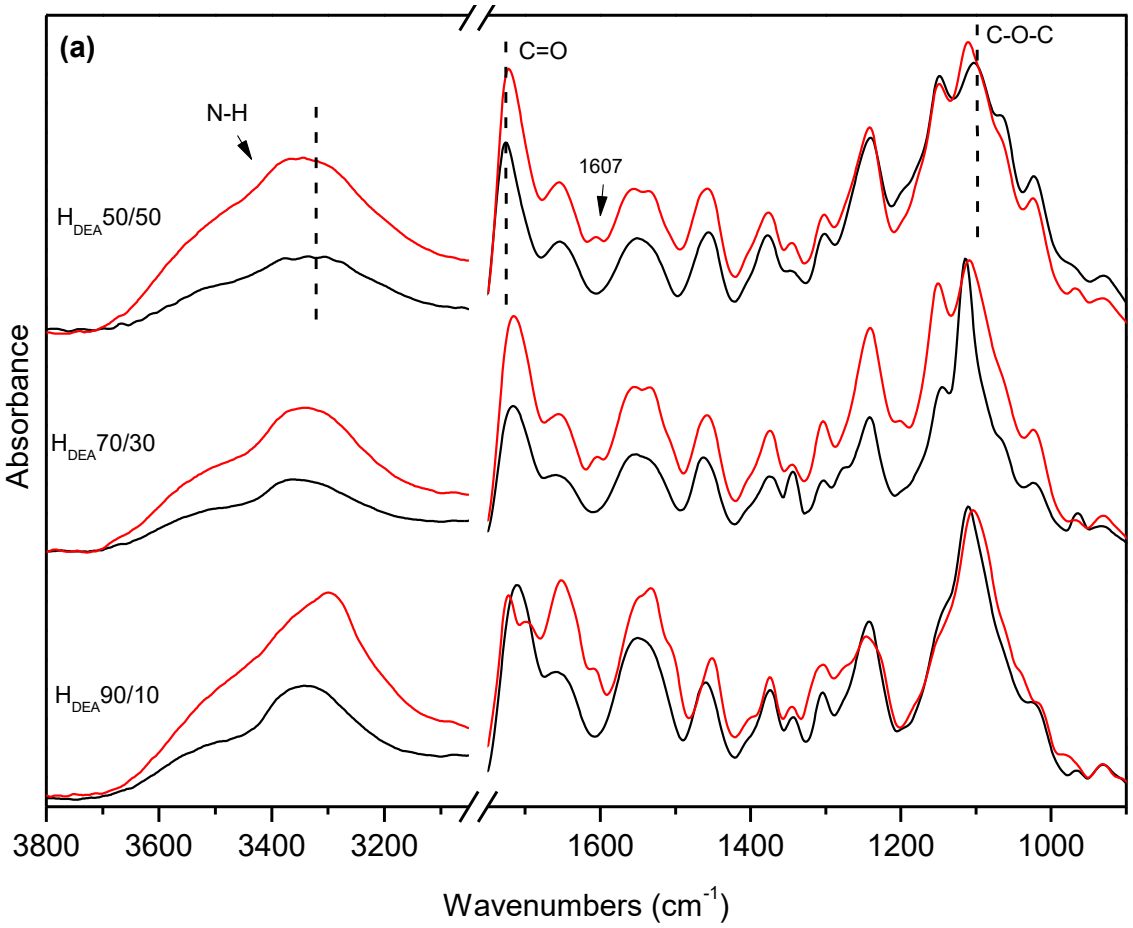
3.3. FTIR analysis

In the R6G spectrum, the main band with high wavenumbers at 3229 cm^{-1} is assigned to the N-H stretching and the weak bands observed at 3000 cm^{-1} region are assigned to the C-H stretching. In the low wavenumbers region below 2000 cm^{-1} the main bands are observed at 1717 cm^{-1} (C=O stretching vibration); and at 1647, 1606 cm^{-1} (vibrational modes of xanthene ring) [33].

In hybrid films with R6G, progressive changes are observed as the proportion of acrylic increases and, consequently, the amount of incorporated R6G.

By comparing the spectra of the hybrid, it can be appreciated that the intensity of the corresponding bands of R6G at 1605 cm^{-1}, assigned to the stretching vibration of C=O, and those at 1528 and 1498 cm^{-1}, assigned to the xanthene ring movements are different. The C=O band at 1714 cm^{-1} of the loaded hybrids shifts to lower wavenumbers (1705 cm^{-1}) indicating interaction between the R6G and the polymer matrix through the carboxylic groups of PU.

It can be observed that the intensity of the band corresponding to the N-H stretches, located at 3344 cm^{-1}, increases considerably. Furthermore, a shift in this band is observed upon incorporation of the R6G. In this sense, both the shift and the increase in intensity indicate the existence of hydrogen bonds between the R6G functional groups and the polymer matrix. In addition, changes in the wavenumbers of C-O-C (1102 to 1110 cm^{-1}) groups, corroborate the existence of specific interactions between the hybrids and R6G.


(a)
N-H
C=O
1607
C-O-C
H_DEA50/50
H_DEA70/30
H_DEA90/10
Absorbance
3800
3600
3400
3200
1600
1400
1200
1000
Wavenumbers (cm-1)

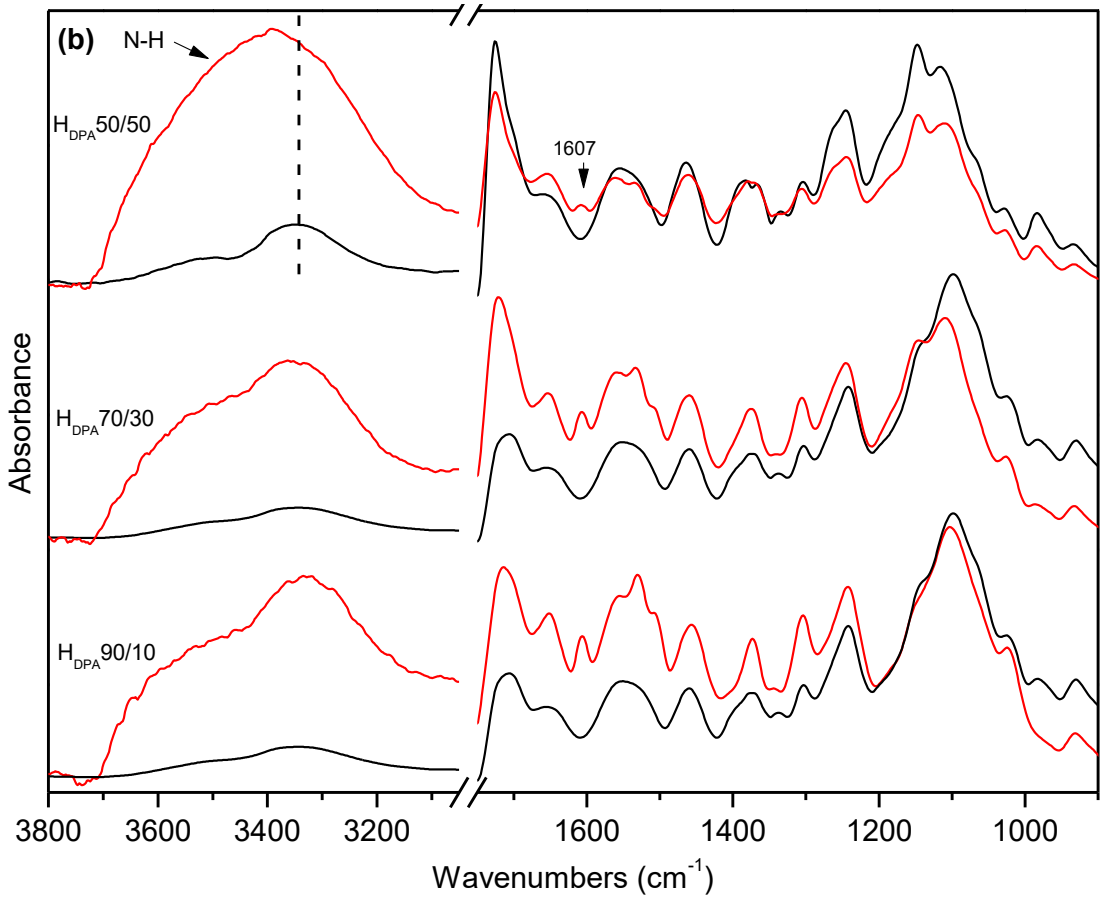

(b)
N-H
1607
H_DPA50/50
H_DPA70/30
H_DPA90/10
Absorbance
3800
3600
3400
3200
1600
1400
1200
1000
Wavenumbers (cm-1)

Fig. 5 ATR-FTIR spectra of hybrid films with (red) and without (black) R6G. **a** PU/DEA; **b** PU/DPA

In PU/DPA systems with R6G, progressive changes are also observed as the proportion of acrylic increases. An increase in the width of the NH band (zone 3730 to 3070 cm^{-1}) and a shift of the peak centered at 3347 cm^{-1} towards higher wavenumbers (3400 cm^{-1}) were observed. These modifications indicate interactions between the polymer and R6G via hydrogen bonding. The shift of the C=O band from 1721 to 1724 cm^{-1} corroborates these interactions.

As in the PU/DEA films with R6G, the appearance of the small peak characteristic of R6G, corresponding to the ring vibration modes, is observed at 1607 cm^{-1}, indicating the presence of PA in different regions of the polymer matrix. These spectral modifications indicate specific interactions between R6G and the polymer matrix through hydrogen bonding and electrostatic interactions.

3.4. R6G loading efficiency

In previous work we have shown that drug loading efficiency depends on the pH and composition of the film [20]. In this work, the amount of R6G loaded at three different pHs (8.0, 7.0 and 4.0) was evaluated to determine the optimal loading pH. The concentration of R6G in the loading solution was 100 mg/L in all cases and the optimal loading time was set at 72 hours (the time required to reach equilibrium in all systems). Results indicated that the loading of R6G was more efficient at pH 8.0 for all the systems (see Table 1).

Table 1 Mass of R6G incorporated in PU/DEA hybrid films and in PU at pH 4.0, 7.0 and 8.0

System	R6G (mg/g polymer)		
	pH 4	pH 7	pH 8
PU	10,65 ± 0,8	13,65 ± 1,0	19,28 ± 0,6
H_{DEA} 90/10	7,31 ± 1,1	10,99 ± 0,9	19,35 ± 0,5
H_{DEA} 70/30	10,44 ± 1,2	16,64 ± 1,1	24,36 ± 1,0
H_{DEA} 50/50	14,86 ± 1,5	20,84 ± 2,1	32,48 ± 1,6

In the case of PU, at pH 4, the incorporation of R6G is explained by hydrogen bonding interactions between the urethane groups of PU and the secondary amine groups of R6G. As pH increases, the ionization of the negatively charged carboxylic groups increases, allowing them to interact with the positively charged molecules of R6G and facilitating their entry into the matrix. At pH 8.0, this process is maximized, resulting in maximum R6G incorporation.

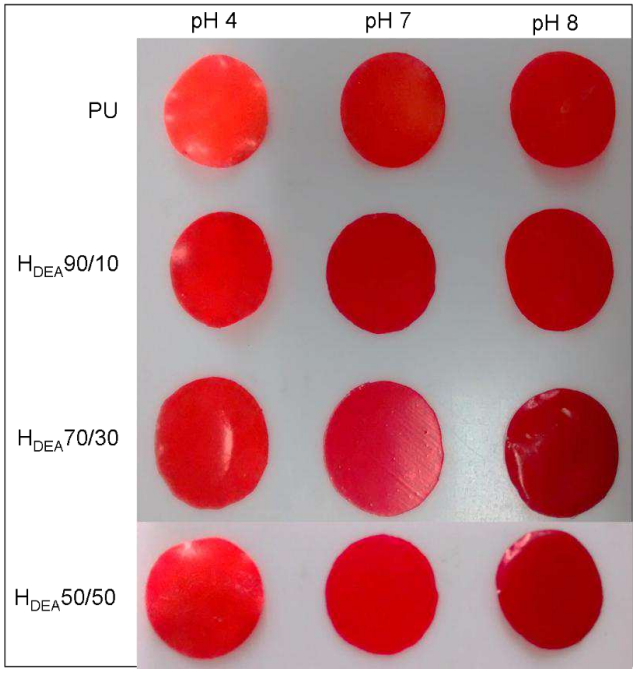


Fig. 6 PU and hybrid films of PU/DEA with R6G loaded at pH 4.0, 7.0 y 8.0

In the case of the hybrids, it is also observed that incorporation increases with pH. At acidic pH, charge repulsion occurs between the protonated amino groups of DEA and the positively charged molecules of R6G, hindering its incorporation. As the pH increases, the electrostatic repulsion decreases due to the reduced degree of ionization of the matrix, and therefore, R6G incorporation increases, with higher values observed in the cases containing 30% and 50% of the acrylic component. Furthermore, the incorporation of DEA introduces ester and amino groups that contribute to the interaction with R6G through hydrogen bonds. At pH 4.0, the R6G content in the H_{DEA}90/10 hybrid is lower than in pure PU. In the H_{DEA}70/30 hybrid, the contribution of the functional groups of DEA compensates for the electrostatic interactions, and the charge level is similar to the PU. In the H_{DEA}50/50 hybrid, the interactions provided by DEA outweighed the contribution of electrostatic repulsions, resulting in increased R6G incorporation. The mass values of R6G incorporated at pH 8.0 in the PU/DPA systems were similar to those obtained for the PU/DEA hybrids and followed the same trend (increasing the DPA ratio led to greater R6G incorporation). Incorporation efficiency values were greater than 80% in all cases (Table 2).

It can be concluded that PA incorporation is governed by the interactions between R6G and the polymer matrix and depends on the PU/A ratio of the system and the pH of the loading medium. Therefore, it is possible to modify the final PA incorporation by varying the pH of the loading medium or the PU/A ratio. This would also allow for regulating the amount of drug incorporated into the polymer depending on the required dose.

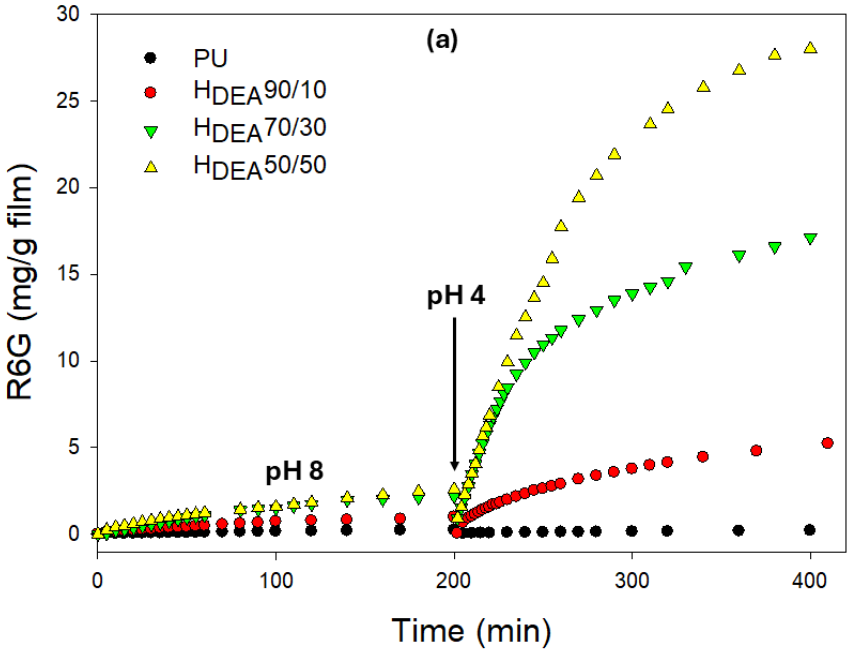
Table 2 R6G incorporated into hybrid films at pH 8.0

R6G loaded	Hybrid films		
	H90/10	**H70/30**	**H50/50**
	DEA / DPA	**DEA / DPA**	**DEA / DPA**
R6G (mg/g polymer)	19,35 ± 0,5 / 20,04 ± 0,8	24,36 ± 1,0 / 23,00 ± 1,0	32,48 ± 1,6 / 33,91 ± 1,5
R6G (%)	85,5 / 85,0	90,5 / 91,0	92,0 / 92,5

3.5. R6G release performance

In this section the results of the *in vitro* studies of pH-responsive hybrid polymers PU/DEA are discussed at extreme pH conditions (8.0 and 4.0) to characterize their drug release behavior and to evaluate the pH sensitivity of polymers at those pHs .

The amount of drug release with time at pH 8.0 and 4.0 for the PU and hybrid films is shown in Figure 7.



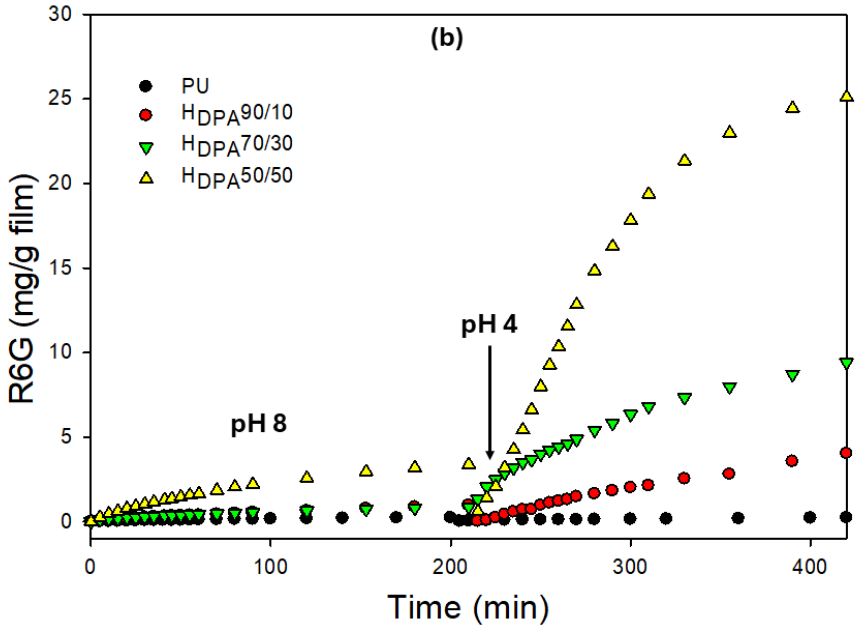


Fig. 7 Kinetics of R6G released from **a** PU/DEA and **b** PU/DPA systems. PU was used as reference system

All hybrid films exhibited a similar release behavior at pH 8.0. After approximately 200 min, all samples reached a plateau, indicating a limited release of R6G under basic conditions. When the medium was subsequently adjusted to pH 4.0, a marked change in the release profile was observed, demonstrating the pH-responsive character of the hybrid films. This response became progressively more pronounced as the acrylic content increased, whereas pure PU exhibited only a negligible release. The differences observed are directly associated with the increasing concentration of amino and carboxylic groups introduced by the DEA or DPA monomers. Consequently, the highest release rates and release percentages were obtained for the hybrids containing the highest acrylic fraction. Similar composition-dependent release behavior has been described in other pH-responsive polyurethane and methacrylate-based systems [34, 35].

The incorporation of DEA or DPA into the PU matrix modifies the interaction between R6G and the polymer network. Upon decreasing the pH to 4.0, the carboxylate groups become protonated, reducing the ionic interactions between R6G and the polymer chains. Simultaneously, protonation of the tertiary amine groups in the DEA and DPA moieties generates electrostatic repulsion between the positively charged polymer segments and the cationic R6G molecules. Therefore, two main driving forces govern the release process under acidic conditions: matrix swelling associated with water uptake and electrostatic repulsion between the protonated polymer network and the dye molecules. Similar behaviors have recently been reported for pH-responsive polyurethane and tertiary amine methacrylate-based systems, where protonation-induced swelling and ionic repulsion strongly enhanced drug diffusion and release kinetics [10, 16, 19, 36].

The release profiles clearly illustrate the pH-dependent behavior of hybrid films. In all cases, the response to pH changes was rapid, with an initial burst release followed by a slower stage in which the

release rate gradually decreased until equilibrium was reached. All systems attained their maximum release value within approximately 10 h. This biphasic release profile is commonly observed in swelling-controlled polymeric delivery systems [23].

Table 3 Results of kinetic analysis of R6G release according to Eq. 2 at pH 4

System	R6G released (%)	t ½ (h)	n coefficient	Transport mechanism	Type of release
H_{DEA}90/10	71,23 ± 2,6	5,0	0,54	Fickian Diffusion	Time-dependent f($t^{-1/2}$)
H_{DEA}70/30	97,08 ± 1,3	1,0	0,78	Non-Fickian Transport (anomalous)	Time-dependent f(t^{n-1})
H_{DEA}50/50	97,86 ± 1,8	0,9	0,88	Non-Fickian Transport (anomalous)	Time-dependent f(t^{n-1})
H_{DPA}90/10	73,82 ± 2,4	15,0	0,68	Non-Fickian Transport (anomalous)	Time-dependent f(t^{n-1})
H_{DPA}70/30	82,77 ± 2,2	3,4	0,84	Non-Fickian Transport (anomalous)	Time-dependent f(t^{n-1})
H_{DPA}50/50	91,80 ± 3,1	1,5	1,20	Super transport case II	Time-dependent f(t^{n-1})

For the PU/DEA hybrids, high release percentages were obtained even at low acrylic contents. The H_{DEA}90/10 system released more than 70% of the loaded R6G, whereas the H_{DEA}70/30 hybrid reached nearly complete release (~100%). Increasing the DEA content significantly enhanced both the release rate and the total amount released. Increasing the DEA fraction from 10 to 30 wt.% reduced the half-release time ($t_{1/2}$) from approximately 5 h to 1 h, while the release percentage increased from 71% to 97%. A similar trend was observed for the PU/DPA systems. The incorporation of only 10 wt.% DPA increased the release from 6.54% for pure PU to values above 70%, while simultaneously reducing the mean release time from 15 h to approximately 1.5 h. Moreover, increasing the DPA content from 10 to 50 wt.% reduced the release time by nearly one order of magnitude, confirming the strong influence of acrylic composition on the release kinetics.

When comparing both hybrid series, the PU/DEA systems exhibited faster release kinetics than the corresponding PU/DPA hybrids, as evidenced by the lower mean release times summarized in Table 3. Although both monomers contain tertiary amine groups, the bulkier diisopropyl substituents in DPA generate a greater steric shielding effect around the protonated amine groups, reducing the electrostatic repulsion between the polymer matrix and the cationic R6G molecules. In addition, Li et al. reported that steric hindrance may promote the formation of thicker polymer domains, increasing the diffusion

path length that the drug must travel to leave the system. The larger steric bulk around the amino groups also increases the hydrophobicity of the polymer chains, strengthening hydrophobic interactions between the matrix and the drug molecules. Consequently, the PU/DPA systems exhibit stronger drug retention and slower release kinetics than the corresponding PU/DEA hybrids. These differences demonstrate that modifying the chemical structure of the acrylic component provides an effective strategy for tuning the release rate and duration of action of the delivery system.

All release profiles were successfully fitted using the Korsmeyer–Peppas model, with correlation coefficients (R^2) higher than 0.99 in all cases. The H_{DEA}90/10 hybrid exhibited an n value close to 0.54, indicating a Fickian diffusion-controlled mechanism. In contrast, the H_{DEA}70/30 and HDEA50/50 systems presented n values between 0.5 and 1.0, characteristic of anomalous transport, where drug release is governed by the combined contribution of passive diffusion and polymer chain relaxation. Similar diffusion–relaxation coupled mechanisms have been reported in pH-responsive polymeric networks and hydrogel-based delivery systems [37, 38].

For the PU/DPA hybrids, anomalous transport was also observed for the H_{DPA}90/10 and H_{DPA}70/30 systems, whereas the H_{DPA}50/50 hybrid exhibited an n value higher than one, corresponding to a Super Case II transport mechanism. This type of behavior has been associated with a significant contribution of polymer relaxation and swelling-driven transport phenomena. Although Super Case II transport is sometimes linked to polymer erosion processes, no detectable erosion or mass loss was observed in the present systems, even after prolonged immersion times. Therefore, the release process in these hybrids is mainly governed by diffusion and polymer chain relaxation associated with the pH-induced swelling of the network. Comparable observations have recently been described for weakly crosslinked pH-responsive polymeric matrices, where swelling-controlled transport predominates in the absence of significant degradation or erosion [39, 40]. This observation is consistent with the structural stability of crosslinked polyurethane/acrylic hybrid networks.

Overall, the release mechanism of these hybrid materials is strongly associated with their ability to reversibly modify their structure in response to environmental pH variations. The protonation/deprotonation processes occurring within the polymer network alter both the swelling degree and the electrostatic interactions with the loaded compound, allowing reversible modulation of the release kinetics through external pH variations. This behavior highlights the potential of these PU/acrylic hybrids as tunable pH-responsive delivery platforms.

4. Conclusions

The synthesized polyurethane/acrylic hybrid films exhibited an evident pH-responsive behavior strongly dependent on both the type and proportion of the acrylic component. Increasing the DEA or DPA content enhanced swelling, accelerated the release rate, and increased the total amount of R6G released under acidic conditions. In all cases, PU/DEA systems showed faster release kinetics than

PU/DPA hybrids, indicating that the chemical structure of the tertiary amine monomer plays a significant role in the transport behavior of the systems.

The release behavior was mainly associated with protonation-induced modifications within the polymer matrix. Under acidic conditions, protonation of the tertiary amine groups and reduction of ionic interactions between the polymer and R6G promoted drug diffusion toward the aqueous phase. Therefore, differences between DEA and DPA systems were attributed to steric and electrostatic effects associated with the bulkier diisopropyl groups present in DPA-containing hybrids. The Korsmeyer–Peppas model successfully described the release behavior of all systems, revealing transport mechanisms governed by diffusion and polymer chain relaxation.

Overall, the results demonstrate that modifications in the chemical structure and proportion of the acrylic phase constitute an effective strategy to tailor swelling behavior, transport properties, and release kinetics in polyurethane-based hybrid materials. These findings provide valuable insights into the design of pH-responsive polymeric systems with potential applications in controlled drug delivery materials. Further studies focused on biocompatibility and biologically relevant active compounds will contribute to expanding the biomedical applicability of these hybrid systems.

Authors contribution

F. Pardini: Conceptualization, Desing, Methodology, Data analysis and interpretation, Writing.
P. Faccia: Data validation, Analysis and Review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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