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# Effect of the macromolecular architecture of biodegradable polyurethanes on the controlled delivery of ocular drugs

**Gisele Rodrigues da Silva · Armando da Silva Cunha Jr. · Eliane Ayres · Rodrigo L. Oréfice**

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**Abstract** Controlled delivery of drugs is a major issue in the treatment of ocular diseases, such as in the treatment of uveitis. In this study, dexamethasone acetate, an important type of corticoid used in the treatment of some uveitis, was incorporated into biodegradable polyurethanes (PU) having different macromolecular architectures. The biodegradable polyurethanes were obtained by preparing PU aqueous dispersions having poly(caprolactone) and/or poly(ethylene glycol) as soft segments. The drug was incorporated into the polymer by dissolving it in the PU aqueous dispersion. FTIR results showed the presence of the drug in the polymer with its original chemical structure. Small angle X-ray scattering (SAXS) results were explored to show that the incorporation of dexamethasone acetate led to the modification of the nanostructure of the polyurethane having only poly(caprolactone) as the soft segment, while the drug did not change significantly the microphase separated structure of PU having both poly(caprolactone) and poly(ethylene glycol) as soft segments. The evaluation of the release of the drug in vitro demonstrated that the obtained biodegradable polyurethanes were well succeeded in delivering dexamethasone acetate at an almost constant rate for 53 weeks. The presence of poly(ethylene glycol) together with poly(caprolactone) as soft segment in biodegradable PU was able to increase the rate of dexamethasone acetate release when compared to the rate of drug release from PU having only poly(caprolactone).

G. R. da Silva · A. da Silva Cunha Jr.
School of Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil

E. Ayres · R. L. Oréfice (✉)
Department of Metallurgical and Materials Engineering, Federal University of Minas Gerais, Belo Horizonte, Brazil
e-mail: rorefice@demet.ufmg.br

## 1 Introduction

Special polyurethanes can undergo degradation by hydrolysis of polar groups inserted on its macromolecular architecture [1, 2]. Biodegradable polyurethanes with high mechanical properties can be prepared by using high molar mass polyesters (such as poly(caprolactone)) as the main component for the soft segments. On the other hand, the rate of biodegradation is reduced whenever the length of poly(caprolactone) (PCL) is increased. Poly(ethylene glycol) (PEG) can be used as a comonomer in the synthesis of biodegradable polyurethanes or biodegradable block copolymers since this component can tailor the rate of biodegradation by controlling the water absorption of the polymer [3–5]. Biomedical applications of biodegradable polyurethanes have been tested for polyurethanes derived from PCL and PEG [6, 7]. Results showed that cells have lower rates of proliferation when cultivated on polyurethane containing only PCL than when they were cultivated on polyurethanes having both PCL and PEG.

One of the most interesting biomedical applications that biodegradable polyurethanes can fit is related to the use of this type of material to control the release of drugs. In the field of ophthalmology, for example, biodegradable implants containing drugs are very useful since they can allow a more well succeeded treatment of diseases such as uveitis. Uveitis is a type of inflammation that usually is observed in the posterior segment of eye and frequently leads to blindness. The most common way to treat uveitis is by using eye drops containing drugs such as corticoids. However, drugs in the eye drops have very poor penetration into the posterior part of the eye, leading to the necessity of frequent instillations that still are not totally successful. Oral administration of drugs to treat uveitis is also not effective, since the eye has natural barriers that

avoid the penetration of drugs through the bloodstream. In order to allow the penetration of ocular drugs into the eye, large amounts of them need to be orally used—a procedure that can damage other organs. Therefore, due to the reasons described above, implants that can release drugs inside the eye are a very interesting approach to treat uveitis [8, 9].

In this work, polyurethanes derived from PCL and PEG were produced based on a water dispersion of the polymer. Dexamethasone acetate, an important drug used in the treatment of uveitis, was incorporated into the polyurethanes by dissolving it in the polymer water dispersion. The structure of the polymer was studied by analytical techniques to determine how the drug can interact with the polymer and affects its morphology. The analyzed structures of the materials were also useful in understanding the measured kinetics of drug release.

## 2 Experimental

### 2.1 Materials

Poly(ethylene glycol) (PEG, $\overline{M_n}$ = 1500 g mol$^{-1}$) and dexamethasone acetate were purchased from Sigma-Aldrich. Polycaprolactone-diol (PCL 1000) (Tone Polyol 2221, $\overline{M_n}$ = 1000 g mol$^{-1}$) and polycaprolactone-diol (PCL 2000) (Tone Polyol 0249, $\overline{M_n}$ = 2000 g mol$^{-1}$) were provided by Dow (USA). Isophorone diisocyanate (IPDI) was obtained from Bayer (Brazil). Dibutyl tin dilaurate (DBDLT) and hydrazine (HZ, solution 64%) were obtained from Miracema Nuodex (Brazil) and Arch Química (Brazil) respectively. All these chemicals were employed throughout this work without any treatment. Triethylamine (TEA, 98%, Vetec) and 2, 2- bis(hydroxymethyl) propionic acid (DMPA, 98.3%, Fluka) were purchased and used as received.

### 2.2 Synthesis of the aqueous polyurethane dispersions (PUD)

Aqueous polyurethane dispersions were prepared by the prepolymer mixing process, using a 250 ml three-neck glass flask equipped with a heating mantel, a mechanical stirrer, a thermometer under nitrogen atmosphere. The macrodiol components (PEG, PCL 1000, PCL 2000), DMPA and IPDI (NCO/OH ratio of 2.3) were added to the reactor in the presence of DBDLT and the reaction was carried out at 70–75°C under nitrogen atmosphere for 4 h. The amount of free NCO groups on a percentage basis was determined by the standard di-butyl amine back titration method. After titration, the prepolymer temperature was allowed to drop to 40°C. The carboxylic acid groups were neutralized by the addition of TEA. The mixture was stirred for further 40 min to ensure the reaction was completed. All samples were dispersed by adding deionized water to the neutralized prepolymer which was stirred vigorously. After the dispersion, the amount of HZ, enough to react with free NCO groups, was added to the reactor with a small amount of water, and stirring was continued for further 30 min. This chemical procedure was well succeeded in producing polyurethane dispersions with solid content about 25% (PUD). A schematic representation of the chemical reactions and processing steps used to produce the polyurethane dispersion is shown in Fig. 1. The compositions of the samples that were prepared are shown in Table 1**.** Films were produced by casting the dispersions in a Teflon mould and allowing then to dry and cure at room temperature for one week. Afterwards the films were placed in an oven at 60°C for 24 h for post-curing. Two types of polyurethane were produced: (1) PUD5, that contains only PCL as the soft segment; and (2) PUD6 that has PEG and PCL as soft segments.

### 2.3 Incorporation of dexamethasone acetate

Dexamethasone acetate was incorporated into the polyurethanes by dissolving it into the polyurethane water dispersions prior from casting the films to yield materials having 5 wt.% of the drug.

### 2.4 Characterization

Infrared spectra were collected in a Fourier transform infrared spectrophotometer (FTIR; Perkin Elmer, model Spectrum 1000). Measurements were carried out using the attenuated total reflectance (ATR) technique. Each spectrum was a result of 32 scans with a resolution of 4 cm$^{-1}$.

Wide angle X-ray diffraction (WAXR) was performed in a Philips PW 3710 diffractometer with a copper target ($\lambda = 1.54$ Å) and Ni filters. Scans were performed from $2\theta = 3.50$ at rates of 0.01° min$^{-1}$.

The measurements of Synchrotron Small Angle X-ray Scattering (SAXS) were performed using the beam line of the National Synchrotron Light Laboratory (LNLS, Campinas, Brazil). The photon beam used in the LNLS SAXS beamline comes from one of the 12 bending magnets of the electron storage ring. The white photon beam is extracted from the ring through a high-vacuum path. After passing through a thin beryllium window, the beam is monochromatized ($\lambda = 1.608$ Å) and horizontally focused by a cylindrically bent and asymmetrically cut silicon single crystal. The focus is located at the detection plane. The X-ray scattering intensity, I(q), was experimentally determined as a function of the scattering vector "q" whose modulus is given by $q = (4\pi/\lambda)\sin\theta$ where $\lambda$ is the

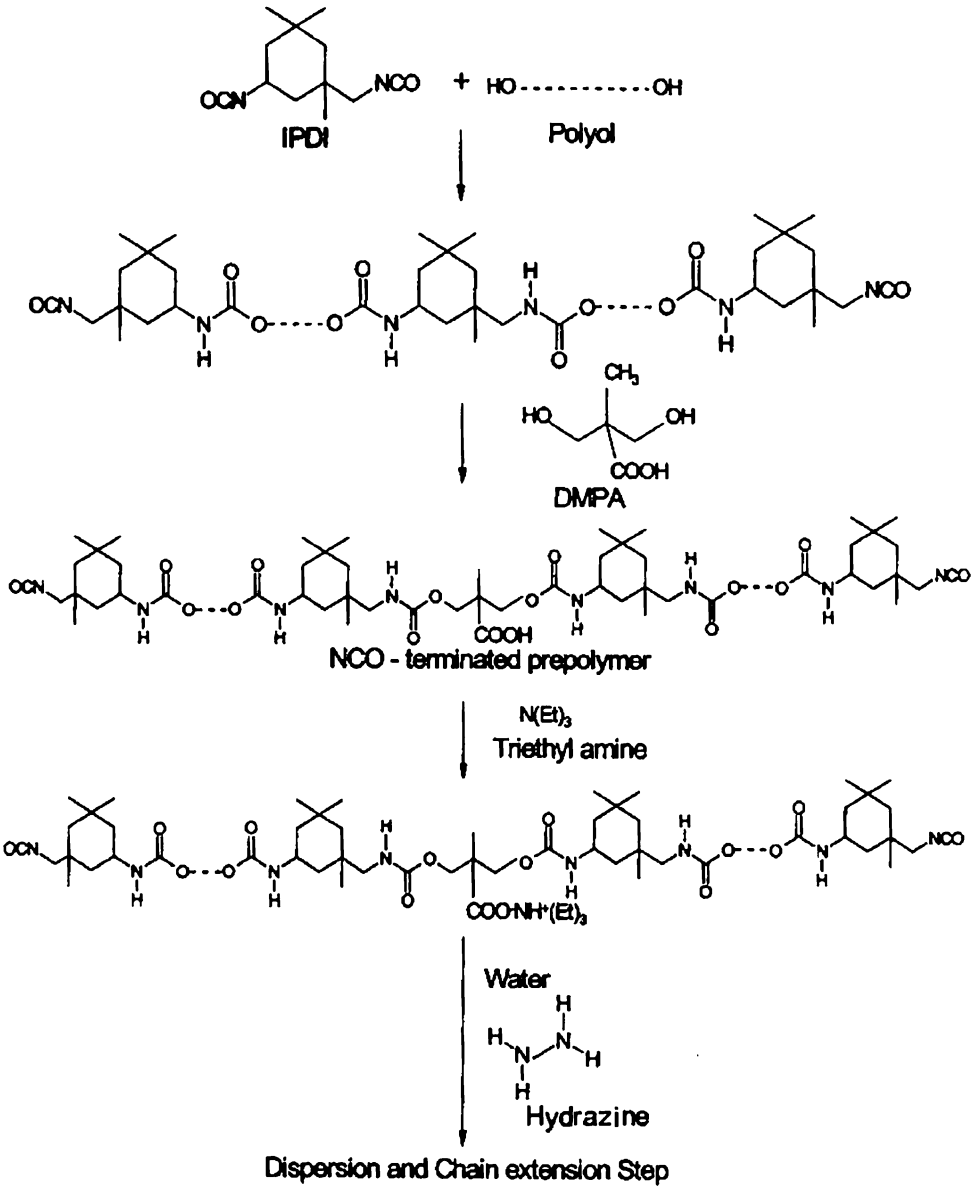


**Fig. 1** Schematic representation of the polyurethane preparation process

**Table 1** Proportion of the reagents (wt. %) used to produce the aqueous polyurethane dispersions[a]

| | IPDI | PCL 1000 | PCL 2000 | PEG 1500 | DMPA | TEA | $H_2O$ | HZ |
|---|---|---|---|---|---|---|---|---|
| PUD-5 | 8.58 | 4.85 | 9.09 | – | 0.97 | 0.73 | 74.70 | 1.08 |
| PUD-6 | 8.58 | 4.85 | 8.36 | 0.73 | 0.97 | 0.73 | 74.70 | 1.08 |

[a] 0.01% of DBDLT based on the amounts of IPDI, PEG and DMPA

X-ray wavelength and $\theta$ being half the scattering angle. Each SAXS pattern corresponds to a data collection time of 300 s. From the experimental scattering intensity produced by all the studied samples, the parasitic scattering intensity produced by the collimating slits was subtracted. All SAXS patterns were corrected for the non-constant sensitivity of the detector, for the time varying intensity of the direct synchrotron beam and for differences in sample thickness. Because of the normalization procedure, the SAXS intensity was determined for all samples in the same arbitrary units so that they can be directly compared.

The release of dexamethasone acetate was monitored by immersing the samples into a phosphate buffer solution (PBS, pH = 7.4) at 37°C for 53 weeks (371 days). The presence of the dexamethasone acetate in the PBS solution was detected and quantified by HPLC [10]. The weight of the samples was also measured and compared with the initial weight to indicate the percentage of the material that has been hydrolyzed. The average of at least three measurements with $P < 0.05$ was reported as the overall result of the tests.

## 3 Results and discussion

Figure 2 shows the infrared spectrum of the polyurethane containing only PCL as soft segment (PUD5, Fig. 2a), the spectrum of dexamethasone acetate (Fig. 2b) and PUD5 containing dexamethasone acetate (Fig. 2c). Typical infrared absorptions bands observed in polyurethanes can be detected in spectra of Fig. 2a and c, such as: 3300 $cm^{-1}$—stretching vibration of primary amines; 2994–2857 $cm^{-1}$—stretching vibration of the $–CH_2$ group; ~1450 $cm^{-1}$—bending vibration of the $–CH_3$ group; 1730 $cm^{-1}$—stretching vibration due to the carbonyl group. The result of a spectral subtraction performed between spectra c and a is also exhibited in Fig. 2d to show clearly the presence of absorption bands due to the dexamethasone acetate that can be readily compared to the bands of pure dexamethasone acetate (Fig. 2b). The same type of result for polyurethanes containing both PCL and PEG (PUD6) was obtained (spectra not shown). These results indicate that the drug was successfully incorporated into the polymer and also that the main chemical aspects of the drug were preserved during the whole manufacture process, since no changes in absorption bands of the drug were observed.

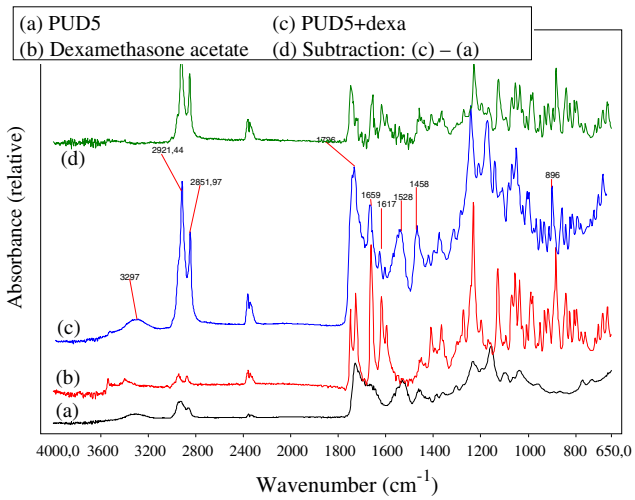


**Fig. 2** FTIR spectra of PUD5 (a), dexamethasone acetate (dexa) (b), PUD5 containing dexamethasone acetate (c) and d the result of a spectral subtraction between spectrum (c) and spectrum (a)

The X-ray diffraction curve of PUD6 is displayed in Fig. 3. Broad diffraction bands at $2\theta = 20°$ and $2\theta = 40°$ are an indication of a polymer structure having only short range order. The detection of an amorphous structure by WAXR suggests that the poly(caprolactone) segments were too short ($\overline{M_n}$ = 1,000 and 2,000 g $mol^{-1}$) to be able to lead to crystallization as often seen when high molar mass poly(caprolactone) is used. In Fig. 3, the WAXR curves of PUD6 containing dexamethasone acetate (DEXA) (Fig. 3b) together with the pure dexamethasone acetate (Fig. 3c) are also shown. No diffraction peaks due to dexamethasone acetate can be seen within the diffraction curve of PUD6 (Fig. 3c), suggesting that no crystalline clusters of the drug were present within the polymer and indicating that the drug was well dispersed and dissolved throughout the polymer matrix. The same type of WAXR result was also observed for PUD5 (WAXR curves not shown).

Small Angle X-ray Scattering (SAXS) is one of the most useful characterization techniques to study the morphology of polymer nanocomposites, block copolymers and segmented polymers [11, 12]. SAXS applied to polyurethanes, for example, has provided a series of information regarding the chemical reactions related to the polymer synthesis, kinetics of phase separation and the effect of some

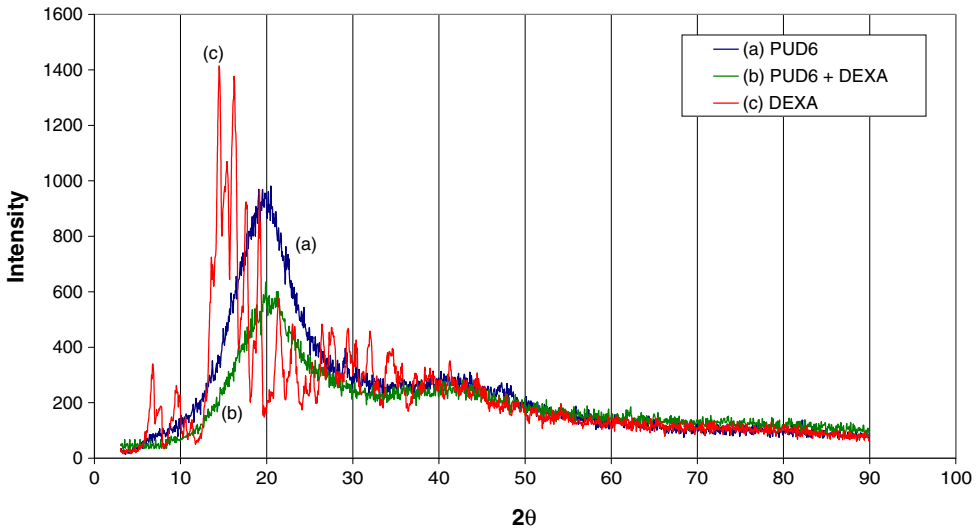


**Fig. 3** WAXR curves of PUD6 (a), PUD6 containing dexamethasone acetate (dexa) (b) and pure dexa (c)

parameters such as temperature and mechanical deformation on phase morphology [13, 14].

A second phase of colloidal dimensions dispersed in a matrix of constant electronic density presents small angle X-ray scattering if there are differences in electronic densities between the phases. For a two-phase system, as in microphase separated polymer systems, the invariant $Q$ describes the electron density variation throughout the polymer and can be a good approximation to estimate the overall degree of phase separation [15]. The invariant $Q$ of overall mean-square electron density variation can be obtained by integrating $q^2I(q)$ over the range of scattering angles. The invariant $Q$, therefore, can be defined as in equation 1.

$$Q = \int_0^\infty I(q)q^2dq = 2\pi^2V(\Delta\eta)^2\varphi(1-\varphi), \quad (1)$$

where $I(q)$ is scattering intensity, $q$ is the scattering vector as defined previously, $\Delta\eta$ is the average electron density contrast, $\varphi$ is the volume fraction of the dispersed phase and $V$ is the irradiated volume.

In this work, SAXS technique was used to provide information regarding the effect of the polyurethane macromolecular architecture on the morphology of the polymer and on the microphase separation phenomenon. SAXS was also used to study how the incorporation of dexamethasone acetate within the polymer network affected the morphology. Moreover, SAXS was also useful in analyzing the structure of the nanoscaled domains created by the microphase separation derived from the low compatibility between hard and soft segment in polyurethane chains and how these domains were modified by the incorporation of the drug.

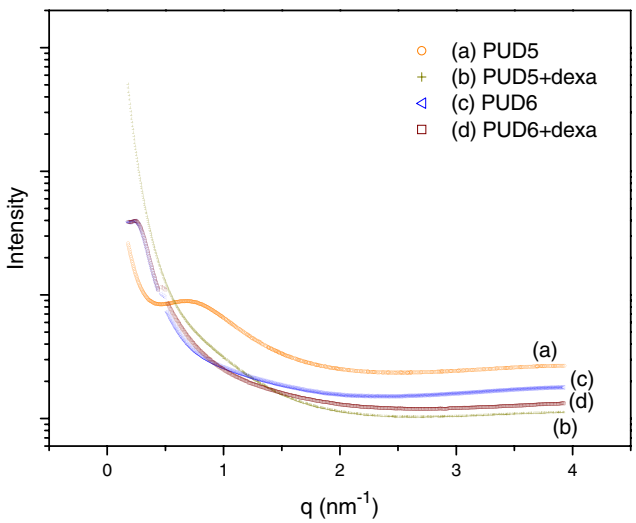


**Fig. 4** SAXS scattering data for PUD5 and PUD6 containing dexamethasone acetate (dexa)

Representative scattering data as a function of the scattering vector ($q$) for systems based on PUD5 (having only PCL as soft segment) and PUD6 (having both PCL and PEG as soft segments) is shown in Fig. 4. The scattering curve of pure PUD5 (Fig. 4a) shows a small and broad scattering peak at q values close to 0.72 $nm^{-1}$. This value of $q$ at the maximum height of the peak ($q_{max}$) can be converted to distance between phases ($L$) by using the Bragg's law ($L = 2\pi/q_{max}$, $L \approx 8.7$ nm for PUD5). This scattering peak is related to the phase separated structure typical of polyurethanes, in which hard domains based on urethane bonds were not compatible with soft domains based on polyol units. The shape of the scattering curve for PUD5 became different when dexamethasone acetate was incorporated into the polymer (Fig. 4b). The scattering peak due to the phase separation process in polyurethanes became less visible for PUD5 with dexamethasone acetate. Otherwise, the scattering intensities at low values of $q$ tended to increase when dexamethasone was incorporated into PUD5. These facts can be associated with the presence of new scattering sites and less defined structures with different sizes. Dexamethasone acetate can interact with soft and hard PU segments to change the course of the microphase separation process, leading to the stabilization of a new nanostructure for the systems. In order to reveal with more details SAXS peak positions hidden underneath the scattering background, a mathematical procedure was used to filter the scattering information due to Bragg

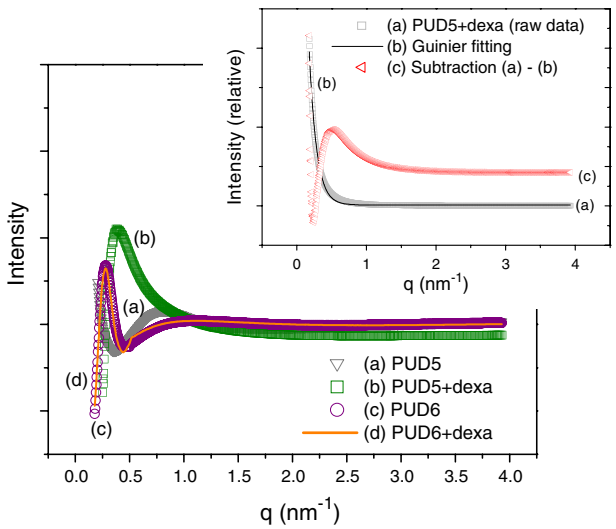


**Fig. 5** SAXS data processed by the mathematical treatment described in the text to enhance the resolution of small scattering peaks. SAXS scattering data shown in Fig. 4 for PUD5 and PUD6 containing dexamethasone acetate (dexa). At the top of the figure: example of how SAXS data was explored in this work to enhance resolution of small scattering peaks: (a) raw SAXS data; (b) Guinier fitting of the raw data; (c) result of the subtraction between raw data and Guinier fitting

diffraction within a background due to Guinier type of scattering [16]. This mathematical procedure involved fitting the experimental scattering data to a combination of an exponential decay function (Guinier scattering) and a Gaussian function (capable of identifying Bragg diffraction peaks). Figure 5 shows the usefulness of this mathematical procedure to enhance the resolution of scattering peaks for PUD5 and PUD6 systems. It is possible to see in Fig. 5 that the main scattering peak for PUD5 shifted to lower values of q when dexamethasone acetate was introduced into the polymer. This shift to lower $q$ may mean that the ions from dexamethasone acetate had interacted with the segments of the polyurethane leading mainly to densification of the more polar hard domains and consequently to chain stretching of the soft domains [17]. Figure 4 shows also scattering curves due to PUD6 (Fig. 4c) and PUD6 containing dexamethasone acetate (Fig. 4d). It can be observed

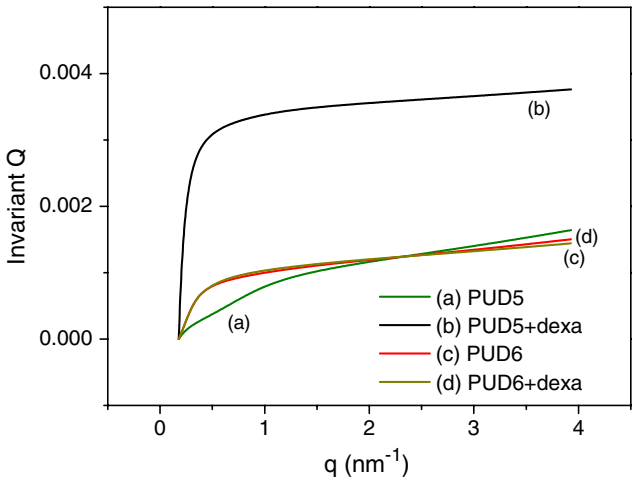


**Fig. 6** Invariant $Q$ extracted from SAXS scattering data for PUD5 and PUD6 containing dexamethasone acetate (dexa)

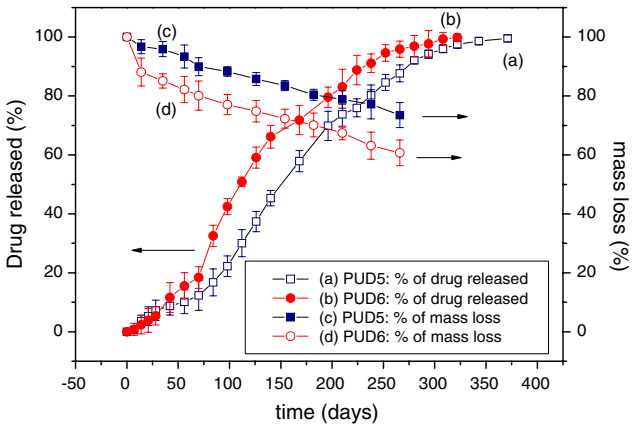


**Fig. 7** Kinetics of dexamethasone acetate release and rate of hydrolysis of PUD5 and PUD6

in these curves that the introduction of dexamethasone acetate did not change significantly the scattering profile of the samples, suggesting that no major alteration of the PU morphology had been induced by the incorporation of the drug. The scattering data associated with PUD6 and PUD6 with the ocular drug was also mathematically converted to allow the identification of weak scattering peaks, such as a peak at 0.28 nm$^{-1}$ ($L = 22$ nm).

The degree of microphase separation in polyurethanes can be studied more effectively by calculating the invariant Q (Eq. 1) [15]. Figure 6 shows the result of this type of calculation as a function of the scattering vector q for PUD5 and PUD6 systems. Higher values of the invariant $Q$ were obtained for the PUD5 polyurethane having dexamethasone acetate, as an indication that this type of sample has phases with more different electron densities that scatter X-rays very successfully. This result suggests that the incorporation of dexamethasone acetate into PUD5 led to a rearrangement of the phases to yield a phase separated system in which the ions of the drug would be located preferentially close to the more polar hard domain (and therefore increasing the electron density difference), while the presence of dexamethasone acetate in PUD6 did not change the phase separated structure of the pure PUD6, possibly because the ions of the dexamethasone acetate were more uniformly distributed along polar soft segments containing PEG.

Figure 7 shows that the ocular drug was released almost constantly from PUD5 and PUD6 during the 53 weeks period of evaluation. Figure 7 also shows that the insertion of hydrophilic segments (PEG in PUD6) within the macromolecular structure of biodegradable polyurethanes led to an increase in the overall rate of dexamethasone acetate release possibly because these polar segments are more effective in allowing water penetration that would improve the rate of hydrolysis of the ester bonds in poly(caprolactone) segments and the rate of diffusion of the water soluble drug. Figure 7 shows also that the rate of hydrolysis (loss of mass) in PUD6 is higher than in PUD5.

## 4 Conclusions

The macromolecular architecture of biodegradable polyurethanes based on poly(caprolactone) was modified by the introduction of hydrophilic poly(ethylene glycol) soft segments. An important corticoid (dexamethasone acetate) used in the treatment of ocular diseases, such as uveitis, was incorporated into the polymers by dissolving it in a dispersion of the polymer in water. This procedure of drug incorporation avoided the use of organic solvents usually associated with toxic effects. FTIR results showed that the incorporation of the drug into the polymer did not change chemical aspects of the molecule. Small angle X-ray

scattering (SAXS) results allowed the identification of the effect of the incorporated drug on the morphology of the polymer. The incorporation of dexamethasone acetate in polyurethanes containing only poly(caprolactone) soft segments (PUD5) led to a phase separated system with a new morphology, while the drug did not change significantly the nanostructure of the biodegradable polyurethane modified with PEG segments (PUD6). The biodegradable polyurethanes produced in this work were able to release dexamethasone acetate for long period of time at almost constant rates. The presence of PEG segments in polyurethane was successful in increasing the rate of the ocular drug release, as an indication that the presence of hydrophilic segments enhances water penetration and hydrolysis of the ester bonds in poly(caprolactone) segments.

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