Controlled Drug Release from Ureasil−Polyether Hybrid Materials

C. V. Santilli,*,† L. A. Chiavacci,‡ L. Lopes,† S. H. Pulcinelli,† and A. G. Oliveira‡

Instituto de Química, Universidade Estadual Paulista, 14800-900 Araraquara, São Paulo, Brazil, and Faculdade Ciências Farmacêuticas, Universidade Estadual Paulista, 14801-902 Araraquara, São Paulo, Brazil

Received July 11, 2008. Revised Manuscript Received November 27, 2008

Flexible, transparent, and insoluble urea-cross-linked polyether−siloxane hybrids presenting a tunable drug delivery pattern were prepared using the sol−gel method from PEO (poly(ethylene oxide)) and PPO (poly(propylene oxide)) functionalized at both chain ends with triethoxysilane. Different polyether chain lengths were used to control the urea/siloxane (named ureasil) node density, flexibility, and swellability of the hybrid network. We herein demonstrate that the drug release from swellable hydrophilic ureasil−PEO hybrids can be sustained for some days, whereas that from the unswellable ureasil−PPO hybrids can be sustained for some weeks. This outstanding feature conjugated with the biomedically safe formulation of the ureasil cross-linked polyether-siloxane hybrid widens their scope of application to include the domain of soft and implantable drug delivery devices.

1. Introduction

Controlled release technology has received increasing attention in many applied scientific fields including medicine, pharmaceutics, agriculture, chemistry, and materials science, as it offers numerous advantages over the conventional routes of delivering drugs, agrochemicals, and other biologically active agents.[1−5] These advantages include high delivery efficiency, precise control of the dose for prolonged time periods (i.e., days, weeks, or months) and reduced toxicity. Temporal controlled drug delivery systems often use either synthetic or natural hydrophilic homopolymers or amphiphilic copolymers as drug carriers in the form of micro/nanospheres, micro/nanocapsules, dendrimers, micelles, liposomes, and hydrogels.[3−5] Typically, these devices are designed to operate under static conditions, which requires a constant rate of drug transport from the carrier to the live environment. This may be achieved by controlling the dissolution, the diffusion, and the relaxation processes, using polymers that dissolve at a lower rate than the drug, insoluble polymers, and swellable hydrogels, respectively.[6]

The suitability of polymers as a biomedical material and their performance in a delivery device depend, to a large extent, on their bulk structure and their interface properties with biological systems.[5] In this context, poly(ethylene oxide) (PEO) and its inclusions in block copolymers or in cross-linked networks (hydrogels) represents a good standard of biointerfacial compatibility.[3,5] The hydrophilic nature of PEO inhibits protein adsorption, cell adhesion, and provides its own full excretion, but its aqueous solubility allows unpredicted bulk erosion of drug delivery devices.[3] Because of such a limitation, an amphiphilic triblock copolymer with a hydrophobic poly(propylene oxide) (PPO) midblock or a poly(lactide) (PLA) end-block and a hydrophilic PEO block with different architectures have generated wide interest for use in biomedical applications.[7−9] Another emerging approach to circumvent this problem is to cross-link PEO chains each other to form an insoluble network able to absorb large amounts of water, resulting in a swollen hydrogel.[5,6] Typically, such hydrogels are prepared by simultaneous copolymerization and cross-linking by means of one or two vinyl groups. However, these cross-linking agents are generally recognized as therapeutically unsafe, because the vinyl monomers are either highly toxic, carcinogenic or teratogenic.[5] Furthermore, these conventional organic cross-linked polymers present substantial structural inhomogeneity, such as heterogeneous aggregation of cross-linking points and a broad distribution of inter-cross-link chain lengths, resulting in poor optical transparency.[10] Thus, recent work in this area points to the development of new approaches to solves these problems, such as to replace the vinyl function by polyurethane or inorganic clay-based cross-linking or to promote the cross-linking by radiation methods.[10−12]

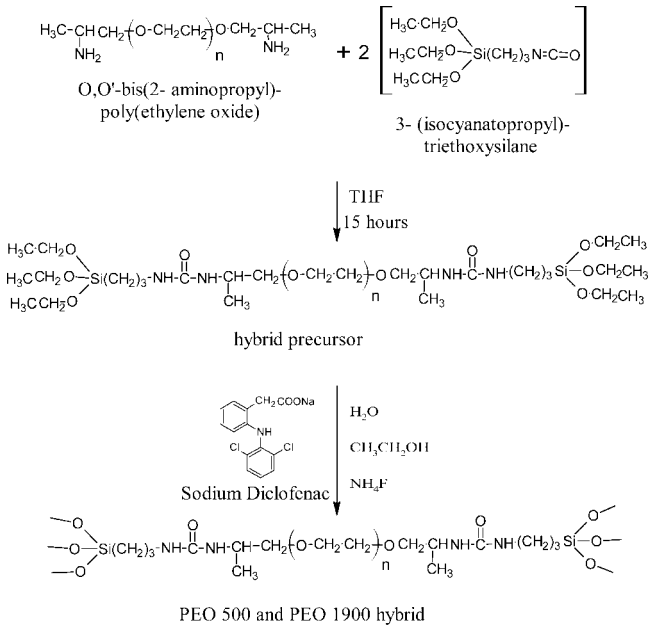
Here, we make use of a biomedically safe formulation to synthesize rubbery, flexible, transparent and insoluble ureasil cross-linked polyether (PEO and PPO) material presenting

* Corresponding author. Phone: 55 16 33016645. Fax: 55 16 33016692. E-mail: santilli@iq.unesp.br.
† Instituto de Química, UNESP.
‡ Faculdade Ciências Farmacêuticas, UNESP.

(1) Belting, M.; Sandgren, S.; Wittrup, A. *Adv. Drug Delivery Rev.* **2005**, *57*, 505–527.
(2) Nori, A.; Kopecek, J. *Adv. Drug Delivery Rev.* **2005**, *57*, 609–636.
(3) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181–3198.
(4) Orive, G.; Hernández, R.; Gascón, M. A. R.; Pedraz, J. L. *Cancer Ther.* **2005**, *3*, 131–138.
(5) Peppas, N. A.; Hilt, J. Z.; Khademhosseini, A.; Langer, R. *Adv. Mater.* **2006**, *18*, 1345–1360.
(6) Kim, S. W.; Bae, Y. H.; Okano, T. *Pharm. Res.* **1992**, *9*, 283–290.
(7) Jeong, B.; Bae, Y. H.; Doo Sung Lee, D. S.; Kim, S. W. *Nature* **1997**, *388*, 860–862.
(8) Kabanov, A. V.; Batrakova, E.V.; Alakhov, V. Y. *J. Controlled Release* **2002**, *82*, 189–212.
(9) Bromberg, L.; Temchenko, M.; Alakhov, V.; Hatton, T. A. *Int. J. Pharm.* **2004**, *282*, 45–60.
(10) Haraguchi, K.; Takehisa, T. *Adv. Mater.* **2002**, *14*, 1120–1123.
(11) Shekunov, B. Y.; Chattopadhyay, P.; Tong, H. H. Y.; Chow, A. H. L.; Grossmann, J. G. *J. Pharm. Sci.* **2007**, *96*, 1320–1331.
(12) Abd El-Rehim, H. A.; Hegazy, E. A.; Abd El-Mohdy, H. L. *Polym. Adv. Technol.* **2004**, *15*, 544–550.

10.1021/cm801899u CCC: $40.75
Published on Web 01/02/2009

Scheme 1. Schematic Representation of the Synthesis of PEO500 (n= 8) and PEO1900 (n = 40) Hybrids; Analogous Process Was Adopted in the Synthesis of PPO300 (n = 6) and PPO2000 (n = 33) Hybrid Matrices



a tunable drug-release rate. This set of properties is attractively convenient for the pharmaceutical formulation of ophthalmic (contact lenses), trans-dermal (patches) and implantable (soft tissue) drug delivery systems. Moreover, we report the possibility to fine-tune the sodium diclofenac (SDCF), deliver rate during short (days) and prolonged (weeks) periods by the judicious choice of PEO- and PPO-chain molecular weights, respectively. SDCF, 2-[(2,6-Dichlorophenyl)amino] benzeneacetic acid sodium salt, an antipyretic, analgesic, and nonsteroidal anti-inflammatory agent, was chosen as the model drug because of its limited solubility in acidic medium, especially in gastric juice.[13]

2. Experimental Section

Synthesis of the Hybrid Materials. To preserve the flexibility and nearly random conformation of the polymer chains, we covalently bonded the ureasil cross-link agent to both ends of the macromer polyether (Scheme 1) by reacting the terminal amino-propyl groups of the functionalized PEO or PPO (O,O′-bis(2-aminopropyl)-poly(ethylene oxide) or O,O′-bis(2-aminopropyl)-poly(propylene oxide) with 3-(isocyanatopropyl)-triethoxysilane in a molar ratio of 1:2. These commercially available reagents (Fluka, Aldrich) were stirred together in tetrahydrofuran (THF) under reflux for 15 h. Following this, the THF solvent was eliminated by evaporation at 60 °C, leading to the hybrid precursor $(EtO)_3Si$-$(CH_2)_3NHC(=O)NHCHCH_3CH_2$-(polyether)-$CH_2CH_3CHNH(O=)$-$NHC(CH_2)_3Si(OEt)_3$. This well-known synthesis[14] was adopted for the PEO with average molecular weights (M_w) of 500 and 1900 g mol^{-1} (labeled PEO500 and PEO1900 hybrids) and also for PPO with M_w of 300 and 2000 g mol^{-1} (labeled PPO300 and PPO2000 hybrids). The second step comprised the hydrolysis of $Si(OEt)_3$ to generate silanol moieties, followed by condensation reactions to form ureasil cross-linking nodes (Figure 1a), and water or alcohol as byproducts. Hydrolysis was initialized by adding 3 mL of a water/ethanol mixture (0.03 V/V) containing 110 mg Kg^{-1} of NH_4F catalyst (oral toxity limit 200 mg Kg^{-1}) and the desired proportion of the sodium diclofenac (SDCF) to 1.5 g of the precursor. Finally, monolithic xerogels were obtained after drying under vacuum at 70 °C for 24 h.

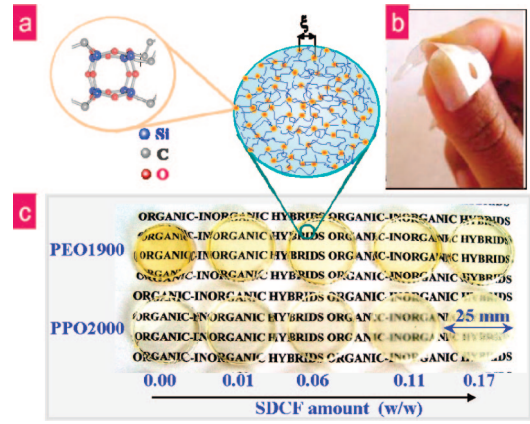


Figure 1. Network structure and macroscopic aspects of ureasil cross-linked polyether: (a) schematic representation of the uniform distribution of ureasil cross-link nodes; (b) image of flexible transparent film of PEO1990 hybrids; (c) images of PEO1900 (upper row) and PPO2000 (lower row) hybrids loaded with different amounts of SDCF.

In vitro Drug Release and Swelling Study. Six-tenths of a gram of monolithic xerogel was immersed in 500 mL of deionized water at 37 ± 0.5 °C and was stirred with a UPS paddle at a speed of 110 rpm. At a given time intervals, 2 mL of filtered release medium was removed for analysis and replaced with the same volume of deionized water. The SDCF amount in the extracted solutions was analyzed by UV−vis absorbance at 276 nm, using a HP Diode Array Spectrophotometer. The cumulative percentage of drug release was calculated from the average of three parallel monitorings. For the swell test, the monolithic hybrid was placed under the same conditions used for the drug release assay. The swollen disks were lifted from the aqueous medium, patted dry, and the weight and thickness were accurately measured at regular intervals until equilibrium was attained.

SAXS Measurements. The nanoscopic structure of the hybrids before and during drug release was studied by small-angle X-ray scattering (SAXS) measurements. Data collection was done at the synchrotron SAXS beam line of the LNLS (Campinas, Brazil), which is equipped with an asymmetrically cut and bent Si(111) monochromator that yields an horizontally focused beam (λ = 0.1608 nm). A vertical position-sensitive X-ray detector and a multichannel analyzer were used to record the SAXS intensity, I(q), as a function of the modulus of the scattering vector q, $q = (4\pi/\lambda)\sin(\varepsilon/2)$, ε being the scattering angle. The parasitic scattering produced by slits was subtracted from the total scattering intensity. The scattering intensity was recorded in relative units but for a quantitative comparison, they were normalized to same experimental conditions and equivalent sample thickness. Because the incident X-ray beam has a point-like cross-section at the detection plane and the width of the resolution detector slit was small, no mathematical desmearing of the scattering curves was done.

3. Results and Discussion

As a result of the nanostructural uniformity of the network produced by the organic−inorganic hybrid approach (Figure 1a), different shaped, transparent, and rubbery xerogels (b

(13) Llina's, A.; Burley, J. C.; Box, K. J.; Glen, R. C.; Goodman, J. M. *J. Med. Chem.* **2007**, *50*, 979–983.
(14) Dahmouche, K.; Santilli, C. V.; Pulcinelli, S. H.; Craievich, A. F. *J. Phys. Chem. B* **1999**, *103*, 4937–4942.

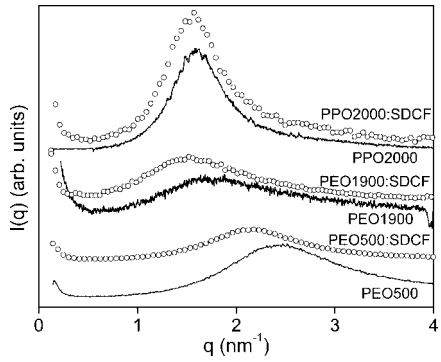


Figure 2. SAXS curves of unloaded (continuous lines) and 0.01 w/w SDCF loaded ureasil cross-linked polyether xerogels (symbol).

and c in Figure 1) were obtained after drying under a vacuum at 70 °C. Despite the fact that the same sol volume was used to produce the disk-shaped tablet, an expansion of ∼28 and 15% in diameter occurred upon adding 0.01 w/w SDCF to the PEO1900 (Figure 1c) and PEO500 hybrids, respectively. This effect indicates the preferential dissolution of SDCF at the flexible PEO moieties of the hybrid matrices. In contrast, any remarkable expansion was observed by loading PPO300 and PPO2000 (Figure 1c) with SDCF. Moreover, the increasing opacity of the PPO2000 hybrid observed by loading it above 0.06 w/w reveals the demixion of the SDCF crystals from the hybrid matrix. Although a similar behavior was observed for the PPO300 hybrids at a higher SDCF loading limit, for both ureasil-PPO matrices, the demixion became remarkable below the same urea/SDCF molar ratio (urea/SDCF < 4). This finding reveals the extraordinary role of the urea moieties (−NHC(═O)NH−) on the solubility of the sodium diclofenac in the ureasil-PPO matrices.

The nanostructural homogeneity and the swellability of the ureasil cross-linked network were analyzed by SAXS measurements performed for dried samples and also during the swelling-drug release experiment carried out at 37 °C. Figure 2 shows some illustrative SAXS curves corresponding to unloaded and 0.01w/w SDCF loaded ureasil-PPO and uresil-PEO matrices. The single broad peak observed in SAXS patterns gives evidence of a strong spatial correlation between the regular spaced cross-link nodes.[14] For both the PPO2000 (Figure 2) and PPO300 (not shown) hybrids, the average correlation distance between two adjacent nodes, given by $\xi = 2\pi/q_{max}$ (q_{max} is the modulus of the scattering vector at the peak's maximum), is essentially unaffected by the SDCF loading. This agrees closely with the invariance of the macroscopic size of the monolithic xerogel with the amount of loaded SDCF (Figure 1c). This feature suggests again that the incorporated SDCF interacts mainly with the hard moieties of the hybrid network, such as the siloxanes and urea (−NHC(═O)NH−). In fact, the preferential interaction of ionic species with the urea groups at the ureasil−PPO interface was successfully demonstrated in a recent work.[15] On the other hand, the average correlation distance shifts from 3.6 to 4.2 nm (PEO1900) and from 2.5 to 2.9 nm (PEO500) when ureasil−PEO matrices are 0.01 w/w SDCF

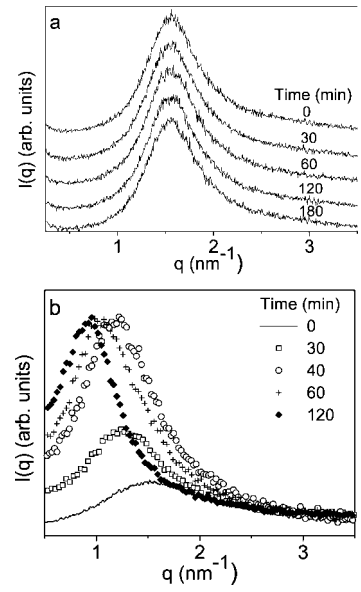


Figure 3. Time dependence of SAXS curves during in vitro drug release in water at 37 °C from (a) PPO2000 and (b) PEO1900 hybrids loaded with 0.01 w/w SDCF.

loaded. This finding sugests that the SDCF molecules are mainly incorporated in the soft segment of the PEO, leading to a chain extension and to a consequent macroscopic expansion of the xerogel (Figure 1c). These claims are in complete agreement with the reconfiguration of the PEO segments observed when salts of different natures are incorporated into the ureasil-PEO matrices.[16−18]

The time evolution of selected SAXS curves recorded during the swelling-drug release experiments are represented in Figure 3. As expected from the hydrophobic nature of the PPO, the average correlation distance between the cross-link nodes is time-invariant for both PPO2000 (Figure 3a) and PPO300 (not shown) ($\xi = 3.7$ and 2.5 nm for PPO2000 and PPO300, respectively). Opposed to this, the hydration of the PEO1900 hybrid matrix during the swelling-drug release experiment leads to a shift in the peak position to low q-values and to an increase of the peak intensity (Figure 3b). The former is an evidence of the increase of the electronic-density contrast between the ureasil nodes and the polymeric matrix, whereas the later reveals the expansion of the average distance between adjacent nodes from 4.2 to 6.5 nm. This feature, which was also observed for the PEO500 hybrids, successfully demonstrated the swellability of the ureasil cross-linked PEO network.

Motivated by the effect of water swelling of the ureasil-PEO hybrids observed on the nanoscopic-scale, we examined the macroscopic dimensional change and the water uptake of monolithic disks (Figure 1c) immersed in deionized water at 37 °C. The water uptake ($\Delta w/w_d$) and the expansion factor

(15) Chaker, J. A.; Santilli, C. V.; Pulcinelli, S. H.; Dahmouche, K.; Briois, V.; Judeinstein, P. *J. Mater. Chem.* **2007**, *17*, 744–757.

(16) Gonçalves, M. C.; Silva, N. J. O.; Bermudez, V. D. Z.; Ferreira, R. A. S.; Carlos, L. D.; Dahmouche, K.; Santilli, C. V.; Ostrovskii, D.; Vilela, I. C. C.; Craievich, A. F. *J. Phys. Chem. B* **2005**, *109*, 20093–20104.

(17) Chiavacci, L. A.; Dahmouche, K.; Briois, V.; Santilli, C. V.; Bermudez, V. D.; Carlos, L. D.; Jolivet, J. P.; Pulcinelli, S. H.; Craievich, A. F. *J. Appl. Crystallogr.* **2003**, *36*, 405–409.

(18) Molina, C.; Dahmouche, K.; Santilli, C. V.; Craievich, A. F.; Ribeiro, S. J. L. *Chem. Mater.* **2001**, *13*, 2818–2823.

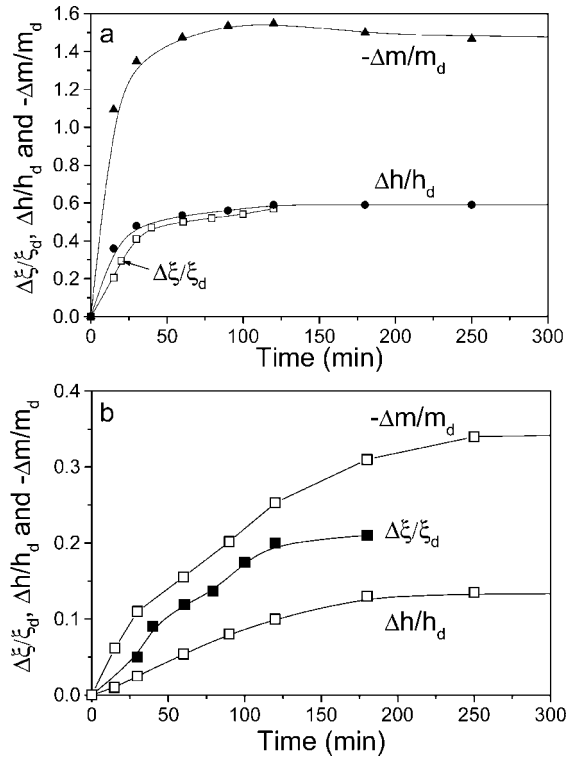


Figure 4. Time dependence of water uptake ($\Delta m/m_d$) and macroscopic ($\Delta h/h_d$) and nanoscopic ($\Delta\xi/\xi_d$) expansion ratio for hybrids loaded with 0.01 w/w SDCF: (a) PEO1900 hybrid; (b) PEO500 hybrid.

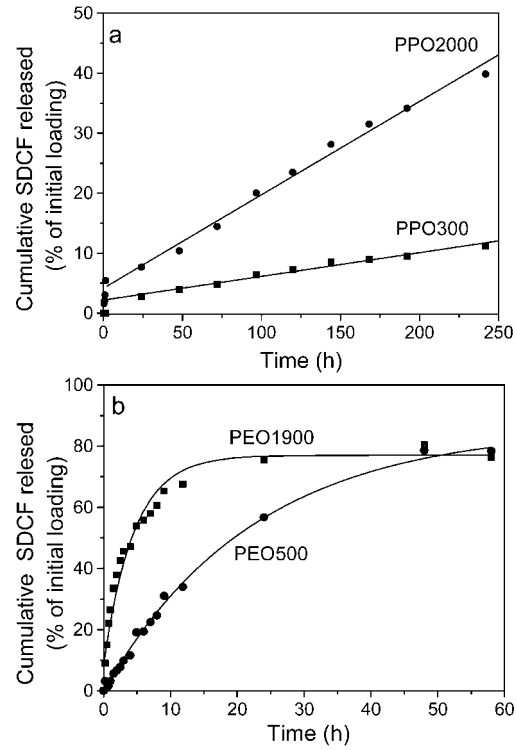


Figure 5. Cumulative percentage of an initial SDCF loading released from ureasil cross-liked polyether: (a) unswellable PPO300 and PPO2000 hybrids; (b) swellable PEO500 and PEO1900 hybrids.

($\Delta h/h_d$ or $\Delta\xi/\xi_d$), calculated from the swollen (w_s, h_s, or ξ_s) and dried weight (w_d), thickness (h_d), or average distance between nodes (ξ_d), are displayed as a function of the immersion time in Figure 4. The excellent agreement between the nanoscopic and the macroscopic dynamic of expansion gives evidence of the uniformity of the hydration process and the quick formation of a fully water-embedded PEO1900 matrix. This is presumably because the fast flux of water through the hydrophilic hybrid network is provided by the segmental motion of the rubber PEO backbone (glass transition temperature about −60 °C). This prompt uniform hydrogel formation is very different from the slow penetration of the swollen layer reported for many glassy networks and this is also true for a hydrophobic polymer loaded with water-soluble solute.[5,6] The swelling equilibrium was attained in a few hours for ureasil-PEO hydrogels (∼1 h for PEO1900 and ∼3 h for PEO500), whereas it was achieved after a few days or weeks in the large majority of glassy cross-linked polymer networks potentially explored as controlled delivery devices.[5,6] Furthermore, as the cross-link node density always increases by decreasing the polymer chain lengths, both the swelling equilibrium expansion factor and the water uptake are higher for PEO1900 ($\Delta h/h_d \approx 0.59$ and $\Delta w/w_d \approx 1.47$) when compared to PEO500 ($\Delta h/h_d \approx 0.13$ and $\Delta w/w_d \approx 0.35$). As expected from the hydrophobic nature of PPO, all the studied ureasil-PPO matrices showed a very low water uptake ($\Delta w/w_d \approx 0.06$) and an undetectable expansion in water at 37 °C.

The cumulative drug released from 0.01 w/w SDCF loaded ureasil-PPO and ureasil-PEO hybrids are shown in Figure 5, in parts a and b, respectively. As expected, the release from swellable ureasil-PEO matrices is faster than that of unswellable ureasil-PPO, the latter having a sustained drug release pattern over the entire monitoring period. The amount released after 10 days from PPO300 and PPO2000 matrices reaches about 10% and 40%, respectively. Because the hydrophilicity of these hybrid matrices is very low, the water accessibility does not change significantly during the drug release period, so that the equilibrium conditions are not achieved. Therefore, the drug diffusion through the ureasil-PPO matrices is much faster than the drug dissolution rate, allowing a linear release profile as shown in Figure 5a. Thus, the release pattern can be predicted by assuming a zero-order or a linear model. The zero-order rate constant (k_o) corresponding to the SDCF release from the PPO300 hybrid ($k_o = 0.04\%\ h^{-1}$) is four times lower than that from the PPO2000 ($k_o = 0.16\%\ h^{-1}$). This is an overall consequence of the increase of the network rigidity as the cross-link density increases, which hampers the drug diffusion assisted by the segmental motion of the PPO chains. It has to be noted that the SDCF concentration in the tested environment increases very fast during the initial time period because of the release of molecules onto the surface of the tablet. This burst effect is lower for hybrids containing higher ureasil cross-linking density, i.e., prepared with small PPO chains (PPO300). This shows again that the hydrophilic groups, like silanol and urea (−NHC(═O)NH−), present in the cross-linking node interfaces facilitate the adsorption of drug molecules within the hybrid matrices.

For the hydrophilic ureasil-PEO matrices, the drug molecules can easily diffuse to the release medium through the free volume of the swollen network. Under these conditions, the diffusion of dissolved drug molecules to the liquid environment is a time-dependent process that can be

predicted by assuming a pseudo first-order kinetic. The first-order rate constant (k_1) determined from the fit of an exponential decay function (continuous line in Figure 5b) is about five-times lower for the PEO500 hybrid ($k_1 \approx 0.05$ h^{-1}) when compared to that of the SDCF released from the PEO1900 matrix ($k_1 \approx 0.23$ h^{-1}). It is also noticeable that the previously mentioned swelling-equilibrium expansion factor for PEO1900 hybrids is about five times higher than that of PEO500 hybrids. This clearly demonstrates that the drug release profile is mainly dependent on the swellability of the ureasil-PEO hybrids.

Finally, it must be stressed that these ureasil-polyether hybrids material matrices can be used to incorporate and to release different medicines such as the anti-inflammatories piroxicam and naproxen, the antihelminthic praziquantel and the antitumorals doxorrubicin, carboplatinum and cysplatinum (see, for instance, Figure S1 in the Supporting Information). Moreover, we believe that the behaviors emerging from the different release and swelling patterns of PEO and PPO based hybrid, combined with the simplicity and flexibility of their sol−gel synthesis, can inspire the design of advanced drug delivery devices such as nanocapsules with an ureasil-PEO core and an ureasil-PPO skin. This core−shell type structure should generate new sustained and controlled drug-release profiles arising from the osmotic transport through the less hydrophilic PPO skin. Furthermore, we propose that the different properties reported for PEO- and PPO-based hybrids may be conjugated by blending ureasil-PEO and ureasil-PPO networks or by fabricating heteropolymers such as PEO-ureasil-PPO diblock copolymers in order to design new functional materials.

4. Conclusions

Transparent, rubbery, flexible, and water insoluble monolithic xerogels presenting controlled swellability and a tunable drug-release kinetic were produced from a simple sol−gel synthesis of ureasil cross-linked polyether (PEO and PPO) hybrid materials. The constant drug-release rate achieved over long time periods (weeks) combined with the dimensional stability of ureasil-PPO hybrids in aqueous media provides a set of properties desired for the pharmacological formulation of ophthalmic (contact lenses), trans-dermal (patches), and implantable (soft tissues) drug delivery devices. Moreover, we also report here the possibility to fine-tune the rate of drug release by controling the swellability of the ureasil-PEO network achieved through by the judicious choice of the PEO chain length. The different behaviors emerging from the release and swelling kinetics of PEO and PPO based hybrid, combined with the simplicity and flexibility of their sol−gel synthesis, can inspire the design of the new advanced drug delivery devices.

Acknowledgment. This work has been financially supported by CAPES/COFECUB, CNPQ, and FAPESP.

Supporting Information Available: Optical photography of hybrids loaded with different medicines (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

CM801899U