Incorporation of Triclosan into Polydioxanone Monofilaments and Evaluation of the Corresponding Release

M. G. Blanco, L. Franco, J. Puiggalí, A. Rodríguez-Galán

Departament d'Enginyeria Química, Escola Tècnica Superior d'Enginyeria Industrial, Universitat Politècnica de Catalunya, Diagonal 647, Barcelona E-08028, Spain

Received 3 March 2009; accepted 22 April 2009
DOI 10.1002/app.30651
Published online 12 August 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Poly(*p*-dioxanone) monofilaments were loaded with triclosan, a drug with a well-known antimicrobial effect. Two different procedures were considered: loading by molecular diffusion with a swelling solvent such as dichloromethane and loading by means of a coating based on polycaprolactone or polycaprolactone/magnesium stearate mixtures. Triclosan release was studied in different media by high-performance liquid chromatography. The kinetics of loading by diffusion and the release from both kinds of preparations were evaluated with well-established models. In general, the first stages of the loading process fit with the Higuchi approximation, whereas the final stages fit with the first-order model. The last model could be applied to predict the release behavior. A sustained release over a period that could reach 400 h was attained when ethanol was added to the release medium, whereas equilibrium conditions were reached when Sörensen's hydrophilic medium was used. Significant differences in the release profiles of a Sörensen's/ethanol medium were observed, which depended on the loading methodology. Thus, an 80% release was attained after 36 h for a polycaprolactone-coated sample and after 80–100 h for a sample loaded by diffusion. Degradation studies of the triclosan-loaded samples were also performed because the increase in the hydrophobicity of the samples could hinder the hydrolytic degradation. The weight-average molecular weight of unloaded and loaded (29,075 μg/g) sutures dropped to 220.000 and 110.000 after 45 days of exposure to the medium at 37°C, respectively. J Appl Polym Sci 114: 3440–3451, 2009

Key words: degradation; drug delivery systems; polyesters

INTRODUCTION

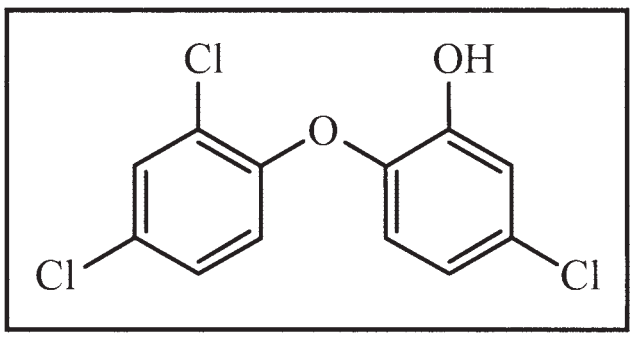
Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether; Scheme 1) is a hydrophobic drug with a well-demonstrated antimicrobial effect[1] that has received much attention for topical applications such as soaps, deodorants, and toothpastes. Indeed, the controlled release of triclosan from microspheres has also recently been investigated for application to the oral cavity[2,3] and malaria treatment.[4]

Preventing bacterial attachment and growth on implanted sutures is a strategy that has recently been proposed to improve the performance of such materials.[5] It is well known that synthetic absorbable sutures can be classified into monofilament and braided sutures on the basis of their filament structure. The former group is advantageous if factors such as tissue drag,[6] knot tie down,[7] and risk of infection[8] are considered. Tissue drag can be minimized in braided sutures with a coating based on a degradable polymer with a sticky nature. This coating can also be useful to incorporate a drug with pharmacological activity. Thus, triclosan has been deposited on the surface of a commercial suture composed of glycolide (90%) and lactide (10%, Vicryl), and the indicated antimicrobial effect has been demonstrated. *Staphylococcus,* one of the most common organisms associated with infection,[9] was inhibited by triclosan at levels below parts per million.[10] Moreover, the release profiles of polyglycolide threads with triclosan incorporated into or deposited over a coating copolymer have recently been studied and compared.[11] This release was strongly dependent on the interactions between the drug and the coating and on the hydrophobicity of the release medium. The results indicate that elution was enhanced when a serum medium was used because the presence of proteins and lipids increased the solubility and elution of triclosan. In this way, serum seems an appropriate elution medium for testing materials that must be in contact with blood. Sörensen's/ethanol

Correspondence to: A. Rodríguez-Galán (alfonso.rodriguez-galan@upc.es).

Contract grant sponsor: Centro de Investigación Científica y Tecnológica.

Contract grant sponsor: Fundo Europeu de Desenvolvimento Regional; contract grant number: MAT 2006-02406.



Scheme 1 Structure of triclosan.

mixtures, where the volume percentage of ethanol is close to 25%, have a hydrophobicity that has also been revealed to be adequate for simulating triclosan release in serum media.[11]

Monofilaments can be coated in a similar way to braided sutures, but in this case, the lubricant function of the coating copolymer is no longer necessary. Thus, it seems also alternatively interesting to consider the direct incorporation of the drug after the melt-spinning process.

Poly(*p*-dioxanone) (PPDO) is a synthetic poly(ester–ether) that was processed in the form of a monofilament surgical suture in the early 1980s[12] and is nowadays commercialized under different trademarks (PDSII by Ethicon, Inc., and Monoplus by B. Braun). This longest lasting absorbable suture is indicated for use where cell growth is expected. The polymer slightly swells in some organic solvents such as dichloromethane or chloroform, a feature that is usually considered for undying commercial samples (0.2 w % D&C Violet no. 2 is frequently added to aid visualization). Thus, small organic compounds could alternatively be loaded into the polymer by diffusion when it is exposed to a dichloromethane solution of the corresponding drug. This approach has recently been studied to incorporate an anti-inflammatory drug such as ibuprofen into PPDO monofilaments. In addition, the kinetics of both the loading and release processes have been evaluated.[13] Furthermore, the results were highly promising because the load through that exposure to a dichloromethane solution did not have a relevant impact on the mechanical properties of the monofilament.[13]

The aim of this work was to study the incorporation of a hydrophobic drug such as triclosan into a PPDO monofilament suture and to evaluate the corresponding release. Two loading processes based on the use of a coating or direct diffusion from an organic solvent were considered. In any case, the amount of triclosan-loaded was enough to guarantee an antimicrobial effect against *Staphylococcus aureus*, as has been previously demonstrated with braided polyglycolide sutures.[14] Recent studies revealed that a polydioxanone suture with triclosan had activity *in vitro* against gram-positive and gram-negative bacteria and also inhibited *in vivo* colonization by *S. aureus* and *Escherichia coli*.[15]

EXPERIMENTAL

Materials

Commercial PPDO monofilaments (PDSII) of USP size 1 (diameter = 0.53 mm) were purchased from BBraun, Rubi (Barcelona, Spain) (weight-average molecular weight = 296,000, number-average molecular weight = 114,000). Undyed samples were obtained by exposure to dichloromethane for 24 h. Triclosan, magnesium stearate, and polycaprolactone (weight-average molecular weight = 65,000 g/mol) were purchased from Aldrich (St. Louis, MO).

Sörensen's buffer (pH 7.4) was prepared by the dissolution of $Na_2HPO_4 \cdot 12H_2O$ (12.968 g) and KH_2PO_4 (1.796 g) in distilled water (1 L). The buffer contained 0.01% (w/v) NaN_3 to prevent bacterial growth.

Incorporation of triclosan into the PPDO monofilaments

Different amounts of triclosan were dissolved in dichloromethane to prepare solutions with drug concentrations ranging from 2 to 10% w/v. PPDO monofilaments 5 cm in length were immersed in these solutions for 0–24 h. After this treatment, the monofilaments were dried in air for 24 h and then dried *in vacuo* for another 6 h to follow the Food and Drug Administration recommendation regarding organic content (<500 ppm). Triclosan particles deposited over the fiber surface were removed before the final drying process by washing in an ethyl acetate bath, a usual bath treatment commercially used for coating braided sutures.

Incorporation of triclosan into the coating of the PPDO monofilaments

PPDO monofilaments 5 cm in length were immersed for 30 s in dichloromethane solutions containing different percentages (5 and 10% w/v) of triclosan and 3% w/v of either the coating polycaprolactone or the coating polycaprolactone/magnesium stearate mixture (15/85 w/w). The samples were then dried and stored *in vacuo*. Coating percentages were selected to obtain a very thin film surface that would not interfere with later absorption processes. Note that this percentage was also similar to that used in braided commercial sutures.

Measurements

The concentration of triclosan-loaded into a PPDO monofilament was determined by total extraction in

dichloromethane (after washing in an ethyl acetate bath when triclosan deposited on the surface was not considered). Extraction was performed with 15 mL of dichloromethane for an exposure period of 1 day and then with 15 mL of renewed dichloromethane for 1 week. Subsequently, both solutions were mixed and rotavaporated *in vacuo*. The residue was dissolved in 2 mL of the high-performance liquid chromatography (HPLC) mobile phase (ethanol 96%). The data correspond to an average of five measurements.

The thermal properties (glass-transition temperature, melting enthalpy and melting temperature) of the triclosan-loaded PPDO monofilaments were obtained via differential scanning calorimetry (DSC) with a TA Instruments (New Castle, DE) Q100 series equipped with a refrigerated cooling system, which operated from −90 to 550°C. Indium was used for calibration, and the experiments were carried out under a flow of dry nitrogen. Heating runs were performed at 20°C/min with the original samples or with samples previously quenched from the melt state, where they were kept for 5 min to erase the thermal history of the material.

Hydrolytic degradation assays of loaded and undyed PPDO monofilaments were carried out in a pH 7.4 phosphate-buffered solution and under accelerated conditions provided by distilled water at 37 and 50°C, respectively. Each assay was performed with two 5 cm long filaments that were introduced in a bottle filled with 30 mL of degradation medium and sodium azide (0.03 wt %) to prevent microbial growth. After exposure, the samples were thoroughly rinsed with distilled water, dried to a constant weight *in vacuo,* and stored over $CaCl_2$ before analysis. The degradation data correspond to an average of five measurements for each experimental condition.

The molecular weights were determined by size exclusion chromatography with a liquid chromatograph (Shimadzu, Kyoto, Japan, model LC-8A) and processed with an Empower computer program (Waters, New Castle, DE). The average molecular weights were calculated with poly(methyl methacrylate) standards. A PL HFIPgel column (Polymer Lab, Darmstadt, Germany) and a refractive-index detector (Shimadzu RID-10A) were used. The polymers were dissolved and eluted in hexafluoroisopropanol containing CF_3COONa (0.05*M*) at a flow rate of 0.5 mL/min (injected volume = 100 μL, sample concentration = 1.5 mg/mL).

Changes in the pH at 37 and 50°C were determined with a GLP21 Crison pH-meter with water used as a degradation media in both cases.

The mechanical properties of the sutures were determined with a Zwick (Ulm, Germany) Z2.5/TN1S testing machine in stress–strain experiments, which were carried out at a deformation rate of 200 mm/min.

Controlled release measurements were performed with PPDO monofilaments that were 5 cm in length. They were weighed and incubated at 37°C in an orbital shaker at 60 rpm in vessels with either 30 mL of Sörensen's release medium or 30 mL of a Sörensen's/ethanol (75/25 v/v) solution. The experiments were conducted in triplicate with a single monofilament in each vessel.

Evaluation of the triclosan concentration in the release or extraction media was carried out by HPLC with a Shimadzu LC-6A model. A tracer extrasil ODS1 3-μm 10 × 0.4 cm column (Teknokroma) and a UV detector (Shimadzu SPD-6A) were used. We obtained the calibration curves by plotting the absorbance measured at 281 nm against the triclosan concentration. Samples were drawn from the release medium at predetermined intervals and eluted in ethanol (96%) at a flow rate of 0.8 mL/min (injected volume = 20 μL). All of the drug-release tests were carried out in triplicate to control the homogeneity of the drug release, and the results obtained from the samples were averaged.

Scanning electron microscopy (JEOL, Tokyo, Japan, model JSM-6400) was used to examine the texture of the loaded samples before and after the release experiments. The samples were coated with a gold layer by sputtering to avoid charging under the electron beam with a Balzers (Liechteinstein) SCD-004 sputter coater.

RESULTS AND DISCUSSION

Triclosan load of the PPDO monofilaments

Table I summarizes the amounts of triclosan-loaded into the PPDO monofilaments when they were exposed to dichloromethane baths containing triclosan percentages of 2, 5, and 10% w/v. The values were measured after the drug particles deposited on the fiber surface were removed by immersion in an ethyl acetate. The corresponding loading profiles for the studied bath concentrations of triclosan are shown in Figure 1(a). In each case, the triclosan load tended toward a maximum value (at 24 h; M_0), which depended on the bath concentration. Thus, it seemed that equilibrium conditions could be reached after an exposure time not longer than 24 h. A good correlation was found [Fig. 1(b)] between the triclosan concentration in the dichloromethane bath and the amount of loaded triclosan after an exposure time of 24 h.

Different mathematical equations could be assayed to fit the experimental loading profiles over the indicated 0–24 h period. We obtained a reasonable agreement (Table II) with a combined model that required two different equations. The early and late approximations that described the first (0–60%) and the last part of the drug uptake (40–100%), respectively, were

TABLE I
Amount of Triclosan Incorporated into the PPDO Filaments

Triclosan in the loading bath (% w/v)	Exposure time (h)	Incorporated triclosan	
		μg/g	μg/cm
2	0.5	1,790 ± 50	5.2 ± 0.15
2	1	2,150 ± 80	6.2 ± 0.23
2	2	2,900 ± 30	8.4 ± 0.09
2	4	4,200 ± 80	12.2 ± 0.23
2	8	4,700 ± 80	13.6 ± 0.23
2	16	5,200 ± 100	15.1 ± 0.09
2	24	5,500 ± 60	16.0 ± 0.18
5	0.5	2,800 ± 50	8.1 ± 0.15
5	1	3,800 ± 40	11.0 ± 0.12
5	2	5,425 ± 20	15.7 ± 0.06
5	4	7,775 ± 50	22.5 ± 0.15
5	8	10,155 ± 70	29.4 ± 0.02
5	16	11,600 ± 80	33.6 ± 0.23
5	24	12,600 ± 50	36.5 ± 0.15
10	0.5	7,000 ± 50	20.3 ± 0.15
10	1	9,645 ± 50	28.0 ± 0.15
10	2	13,250 ± 40	38.4 ± 0.12
10	4	17,000 ± 60	49.3 ± 0.18
10	8	22,000 ± 70	63.8 ± 0.02
10	16	27,000 ± 80	78.3 ± 0.23
10	24	29,075 ± 60	84.3 ± 0.18

$$M_t/M_0 = k_H t^{1/2} \quad (0 \le M_t/M_0 \le 0.6) \tag{1}$$

$$\ln(1 - M_t/M_0) = \ln[(8/\pi^2) - k_1 t] \quad (0.4 \le M_t/M_0 \le 1.0) \tag{2}$$

where k_H is the Higouchi rate constant, k_1 is the first order rate constant for first-order models, and the M_t and M_0 terms correspond to the amount of triclosan loaded at time t and 24 h, respectively.

These approximations were based on the Higouchi[16,17] and first-order[18,19] models and have been well described for the study of *in vitro* drug release.[20] There, a diffusion coefficient (D) was related to the constants k_H and k_1 under the assumption of a film geometry with a uniform thickness (l):

$$k_H = 4(D/\pi l^2)^{1/2} \tag{3}$$

$$k_1 = \pi^2 D/l^2 \tag{4}$$

Figure 1 clearly shows the simulated loading profiles fit with the experimental data. Moreover, profiles based only on the first-order [$\ln(1 - M_t/M_0) = -k_1 t$] or Higouchi ($M_t/M_0 = k_H t^{1/2}$) equations were plotted to indicate the advantages of the combined approximation.

Diffusion coefficients close to 3.7×10^{-13} and 3.0×10^{-13} m^2/s were derived from the early and late approximations, respectively, with the assumption of a sample thickness equivalent to the suture radius (0.265 mm) and the constants deduced for samples loaded from 5 and 10% concentrated baths. The

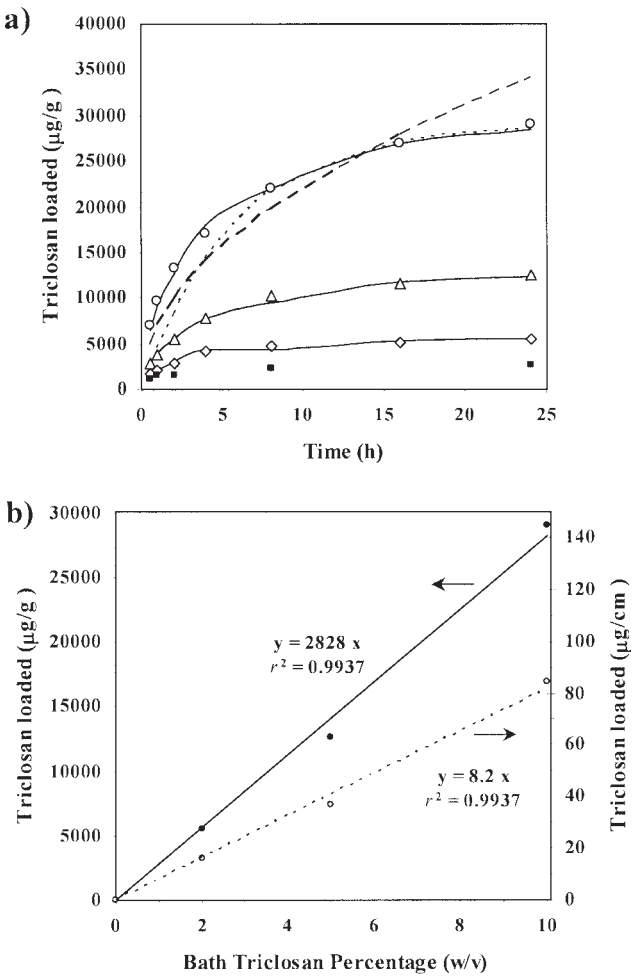


Figure 1 (a) Plots of the total amount of loaded triclosan versus the time of exposure for dichloromethane solutions containing triclosan at concentrations of (◇) 2, (△) 5, and (○) 10 wt %. Theoretical values calculated according to the combined, first-order, and Higouchi models are represented by solid, dotted, and dashed lines, respectively. For the sake of completeness, the reported data[13] on ibuprofen loading from a 10% dichloromethane solution containing 10% ibuprofen are indicated by the ■ symbol. (b) Plot of the (○) weight/length and (●) weight/weight ratios of triclosan incorporated into the PPDO sutures as a function of the triclosan concentration in the dichloromethane bath where the sutures were immersed for a period of 24 h.

TABLE II
Correlation Coefficient (r) and Loading Rate Constant (k_H or k_1) Values for the Fitting to the Combined Mathematical Model of the Triclosan Load Profiles

Triclosan in the loading bath (% w/v)	Early approximation		Late approximation	
	r	k_H (h$^{-0.5}$)	r	k_1 (h^{-1})
2	0.93	0.39	0.84	0.18
5	1	0.31	0.93	0.15
10	0.98	0.31	1	0.15

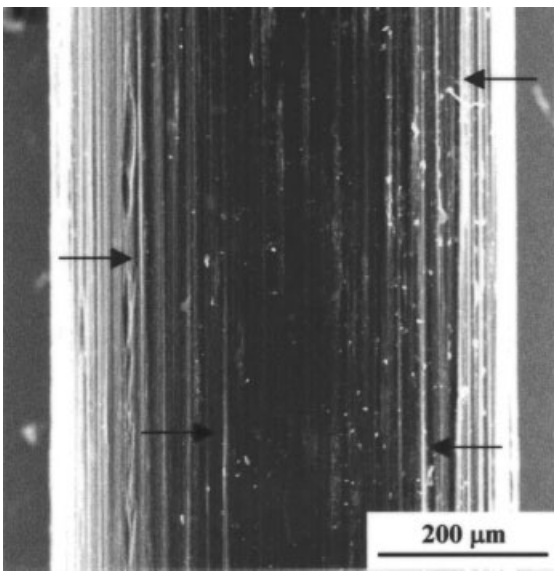


Figure 2 Scanning electron micrograph of a monofilament of PPDO loaded with triclosan by immersion in a dichloromethane bath with a triclosan drug concentration of 10% for 24 h. The arrows indicate characteristic striations produced during the melt-spinning process.

results were clearly consistent with those of previous studies[13] that indicated a slightly lower diffusion constant (1.5×10^{-13} m^2/s) when a more hydrophilic drug such as ibuprofen was loaded into the PPDO monofilaments. A comparison between the triclosan and ibuprofen loading processes is also given in Figure 1(a), which clearly shows the higher affinity of the polymer matrix toward the hydrophobic triclosan drug.

The electron micrographs of the loaded PPDO monofilaments (Fig. 2) did not show noticeable morphological changes with respect to the commercial sutures. Thus, only some remaining triclosan crystals were detected on the filament surface when the washing with ethyl acetate was incomplete. Striations caused by the melt-spinning process were observed but no pores or fissures that might have been caused by exposure to the swelling dichloromethane medium.

Thermal behavior of the triclosan-loaded PPDO monofilaments

The thermal properties of the loaded PPDO monofilaments were not significantly affected by the incorporation of triclosan molecules. Thus, the first heating scan was practically identical for the undyed monofilaments and samples with the maximum triclosan load (2.9 wt % was attained after exposure for 24 h to a bath containing 10% triclosan). In both cases, a double melting peak, indicative of a crystal reorganization before fusion, was detected. These peaks were observed at 100 and 106°C with a total enthalpy close to 83 J/g. The second peak, which was associated with the more perfect lamellae formed during the heating process, always had the lowest enthalpy.

In contrast, the crystallization behavior was influenced by the incorporation of triclosan, as revealed by the DSC heating scans performed with the melt-quenched samples (Fig. 3). Thus, the undyed samples could crystallize during the fast cooling run, as deduced from the absence of a cold crystallization peak and the presence of a single melting peak during the heating run [Fig. 3(b)]. This melting peak, which corresponded to the previously indicated melt-reorganized crystals, appeared at 106°C and had an enthalpy of 50 J/g, which was slightly lower than that measured in the initial melt-processed samples. However, the triclosan-loaded samples showed a clear cold crystallization peak around 52°C with an enthalpy of 52 J/g and a trace of a hot crystallization peak around 95°C [Fig. 3(c)]. The final melting enthalpy of 54 J/g demonstrated that the triclosan molecules prevented the crystallization of the polymer during the fast cooling rate. For comparative purposes, Figure 3(a) also shows the heating

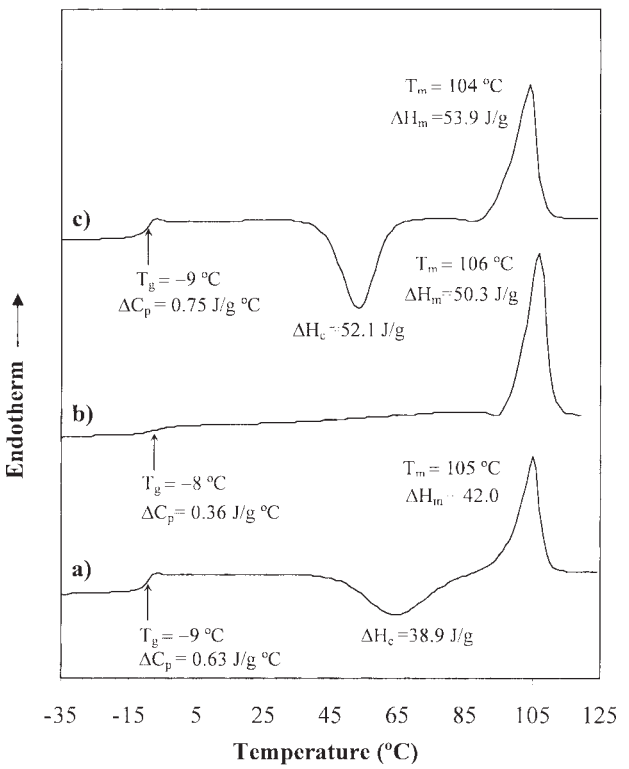


Figure 3 DSC heating scans of (a) commercial, (b) undyed, and (c) triclosan-loaded PPDO sutures. All samples were previously quenched from the melt state. Loading was performed by immersion in a dichloromethane bath containing 10% triclosan for a period of 24 h. ΔC_p = change in the specific heat capacity; ΔH_c = crystallization enthalpy; ΔH_m = melting enthalpy; T_g = glass-transition temperature; T_m = melting temperature.

trace of a commercial sample after quenching. In this case, a cold crystallization peak was also observed despite the low content (0.2 wt %) of D&C Violet No. 2 dye molecules. Indeed, the shift of the cold crystallization peak toward higher temperatures and the lower melting enthalpy (42 J/g) indicated greater difficulty in crystallizing when these larger molecules were added. Triclosan caused a very small shift in the glass-transition temperature with respect to the undyed sample (−9 vs −8°C) and an increase in the change in calorific capacity, as expected from the increase in the amorphous phase content. This behavior was very similar to that observed for the commercial dyed samples.

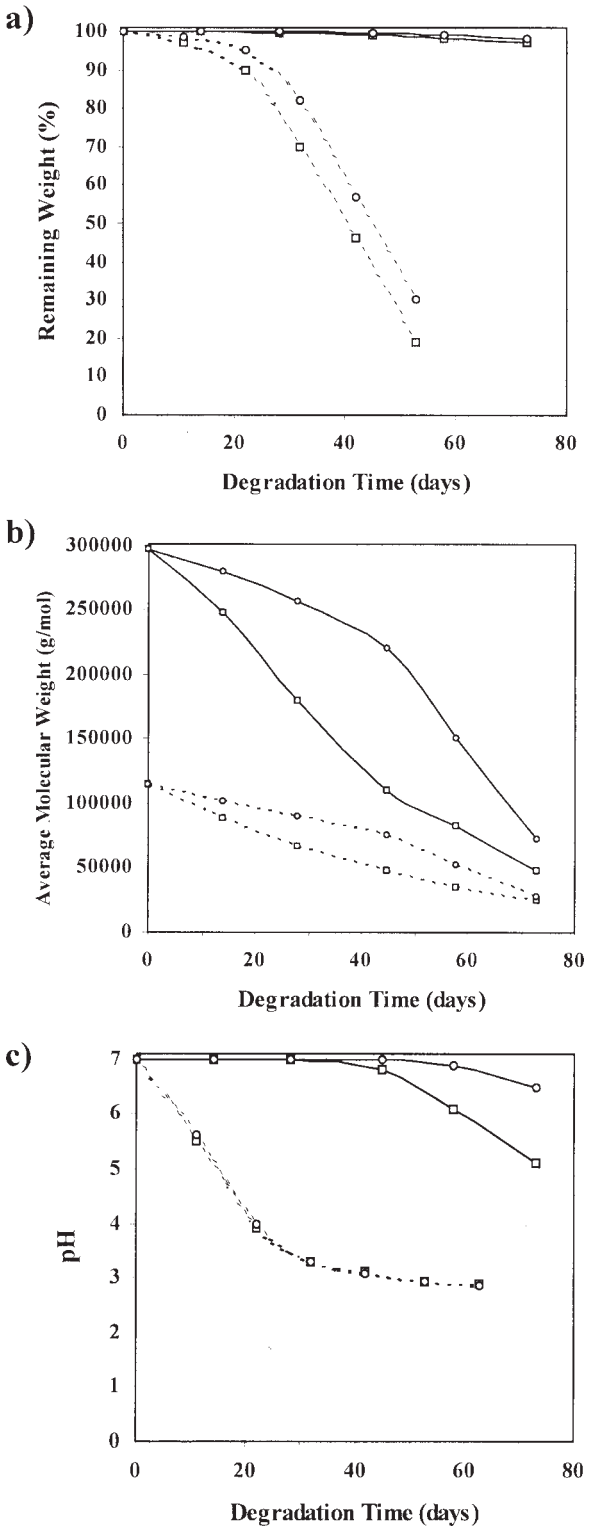


Figure 4 (a) Remaining weight percentages of (□) undyed and (○) triclosan-loaded PPDO sutures versus exposure time in a pH 7.4 buffered solution at 37°C (solid lines) and in distilled water at 50°C (dotted lines). Loading was performed by immersion in a dichloromethane bath containing 10% triclosan for a period of 24 h. (b) Weight-average (solid lines) and number-average (dotted lines) molecular weights of (□) undyed and (○) triclosan-loaded PPDO sutures versus exposure time in a pH 7.4 buffered solution at 37°C. Loading was performed by immersion in a dichloromethane bath containing 10% triclosan for a period of 24 h. (c) pH of a distilled water degradation medium at 37°C (solid lines) and 50°C (dotted lines) during the exposure of undyed (□) and triclosan-loaded (○) PPDO sutures. Loading was performed by immersion in a dichloromethane bath containing 10% triclosan for a period of 24 h.

Degradation of the triclosan-loaded PPDO monofilaments

The hydrolytic degradability of the undyed and triclosan-loaded PPDO monofilaments was evaluated at different temperatures by measurement of the weight loss and the changes in molecular weight during exposure to the selected media (pH 7.4 phosphate-buffered solution and distilled water). The low-temperature data during exposure to pH 7.4 phosphate-buffered solution were especially relevant because they showed the behavior under physiological conditions. Data from the accelerated conditions provided by a high temperature were also interesting because they allowed the degradability of both samples to be clearly differentiated. In this case, distilled water was used to follow the change of the pH of the medium during degradation.

The slow degradation rate of PPDO at 37°C resulted in minimal differences in weight loss between both samples after 70 days of exposure [Fig. 4(a)]. However, a slightly greater stability was detected for the triclosan-loaded samples, a feature that was clearly evident when the temperature of the medium was raised to 50°C [Fig. 4(a)]. It seemed that triclosan increased the hydrophobicity of the sample, which became less exposed to the water molecules and, consequently, to hydrolytic degradation.

The degradation process can be easily envisaged by the evaluation of molecular weight changes. Thus, Figure 4(b) shows that the weight average dropped to approximately one third of the initial

TABLE III
Change in the Knot Strength of the PPDO Monofilaments Loaded with Different Amounts of Triclosan During Hydrolytic Degradation in a pH 7.4 Buffered Solution at 37°C

Degradation time (days)	Triclosan load (μg/g)	Knot strength (N)
0	0	63
0	5500[a]	59
0	5425[b]	59
0	7000[c]	57
20	0	51
20	5500[a]	49
20	5425[b]	49
20	7000[c]	47
40	0	36
40	5500[a]	34
40	5425[b]	34
40	7000[c]	33
55	0	10
55	5500[a]	11
55	5425[b]	10
55	7000[c]	11

[a] By exposure to a 2% loading bath for 24 h.
[b] By exposure to a 5% loading bath for 2 h.
[c] By exposure to a 10% loading bath for 0.5 h.

value after 70 days of exposure to the medium at 37°C. The triclosan-loaded sample showed a lower decrease, in agreement with the indicated greater protection against hydrolysis.

Figure 4(c) shows that the degradation process led to a decrease in the pH of the medium because of an increase in carboxylic acid end groups. Undyed and triclosan-loaded samples showed a similar pH evolution with time when the experiments were performed at 50°C. For this reason, a new set of measurements was made with distilled water at 37°C. In this case, the differences were significant, and it was possible to verify again that triclosan reduced the degradability of the sample because fewer acid terminal groups were generated.

Table III shows the changes in the knot strength, taken as a representative mechanical parameter, of the PPDO monofilaments loaded with different amounts of triclosan during hydrolytic degradation in a pH 7.4 buffered solution at 37°C. The results indicated that the knot strength decreased when triclosan was incorporated, although this variation was not highly significant for moderate amounts of loaded triclosan. The knot strength reached similar values for the loaded and unloaded samples after some time of exposure to the degradation medium. This feature was a logical consequence of the slower degradation rate observed for the triclosan-loaded samples.

Figure 5 shows the first DSC heating run performed for the undyed and triclosan-loaded samples that had been exposed to hydrolytic degradation at 37 and 50°C. The corresponding melting data (temperature and enthalpy), together with the estimated degree of crystallinity, are summarized in Table IV. The heat of fusion for a 100% crystalline material (200.8 J/g) was estimated from the group contribution theory[21] (4, 5, and 3.5 kJ/mol for the methylene, ester, and ether groups, respectively) and used to evaluate the indicated degrees of crystallinities. These estimated values were only approximate but were useful for comparison purposes and also for

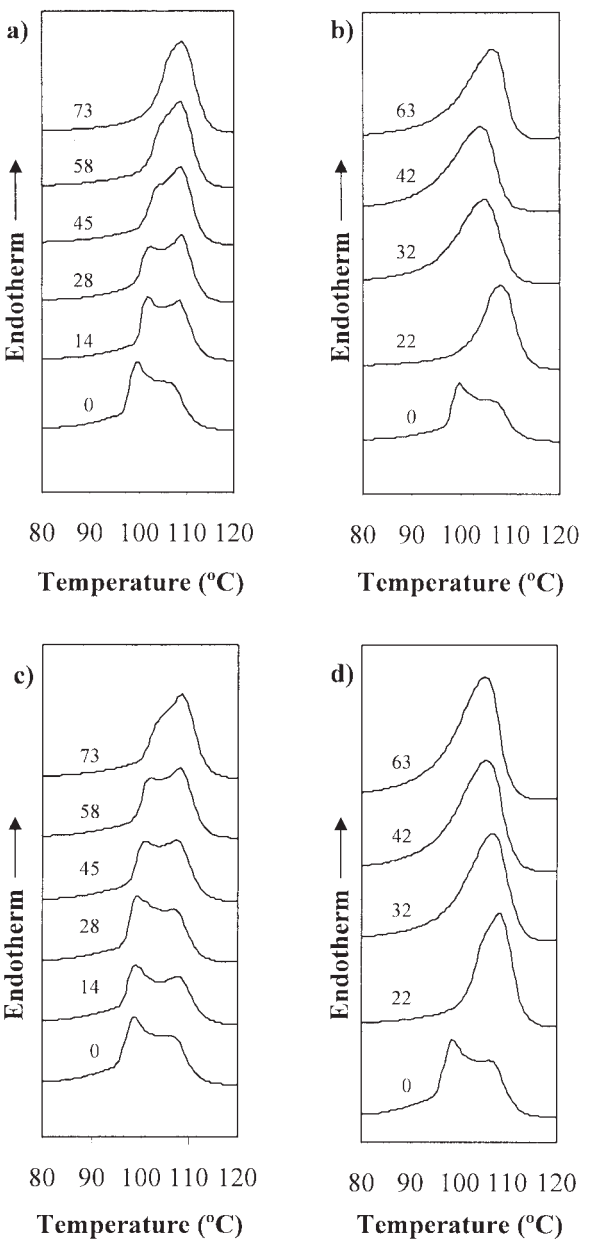


Figure 5 DSC heating scans of (a,b) undyed and (c,d) triclosan-loaded PPDO sutures after the indicated days of degradation in (a,c) a pH 7.4 buffered solution at 37°C and (b,d) distilled water at 50°C. Loading was performed by immersion in a dichloromethane bath containing 10% triclosan for a period of 24 h.

TABLE IV
Values of the Melting Enthalpy (ΔH_f) and Estimated Crystallinity (χ) of the Undyed and Triclosan-Loaded PPDO Filaments After Exposure to the Degradation Media at 37 and 50°C

	37°C[a]					50°C[b]			
	Undyed		Triclosan-loaded			Undyed		Triclosan-loaded	
Time (days)	ΔH_f (J/g)	χ (%)	ΔH_f (J/g)	χ (%)	Time (days)	ΔH_f (J/g)	χ (%)	ΔH_f (J/g)	χ (%)
0	82.4	41.0	82.4	41.0	0	82.4	41.0	82.4	41.0
14	84.4	42.0	82.4	41.0	22	106.5	53.0	94.5	47.0
28	87.4	43.5	84.4	42.0	32	120.6	60.0	102.9	51.2
45	90.4	45.0	86.4	43.0	42	130.6	65.0	114.2	56.8
58	91.4	45.5	88.4	44.0	53	129.6	64.5	124.2	61.8
73	92.5	46.0	89.4	44.4	—	—	—	—	—

A load of 29,075 μg/g was attained by exposure to the dichloromethane solution with a triclosan concentration of 10 % w/v for 24 h.
[a] Phosphate-buffered solution (pH 7.4).
[b] Distilled water.

the determination of the influence of degradation on crystalline morphology.

A double melting peak indicative of a lamellar reorganization process during heating was observed in the heating traces of samples before exposure to the degradation media. The relative areas of these two peaks indicated that the less perfect lamellae, which were associated with the lowest melting temperature, were the predominant ones in both samples. During degradation at 37°C, the melting temperature corresponding to the reorganized crystals was practically constant, as expected, whereas the temperature of the first peak increased slightly with the exposure time. An increase in the global melting enthalpy (i.e., in the degree of crystallinity) and in the relative area of the peak associated with the reorganized crystals, which became progressively predominant, was also detected. Degradation mainly affected the amorphous phases, as is well established for commercial PPDO sutures,[22,23] but had also a clear influence on the lamellar morphology, probably affecting the chain-folded surfaces and enhancing the melt reorganization process. The increase in the degree of crystallinity was lower for the triclosan-loaded samples, which was in agreement with their lower degradation rate (Table IV and Fig. 6).

Similar trends were observed for samples degraded under accelerated conditions. However, in this case, the first melting peak quickly disappeared (at 32 and 22 days for the triclosan-loaded and undyed samples, respectively), and the increase in the degree of crystallinity was more pronounced. The undyed sample degraded again faster, and an attack on its crystalline phase was deduced because the melting enthalpy started to decrease after 53 days of exposure to the degradation media. The melting temperature of the single peak decreased slightly during degradation, with the exception of the most degraded sample (i.e., the undyed monofilament after 53 days of exposure).

Finally, no significant degradation was detected at 37°C during the first 20 days of exposure, as revealed by the assays we performed. This feature demonstrated that drug release would not be influenced by the degradation processes under physiological conditions.

Release of triclosan from the PPDO monofilaments loaded by diffusion

Figure 7 shows the release profiles of the PPDO monofilaments with different triclosan loads

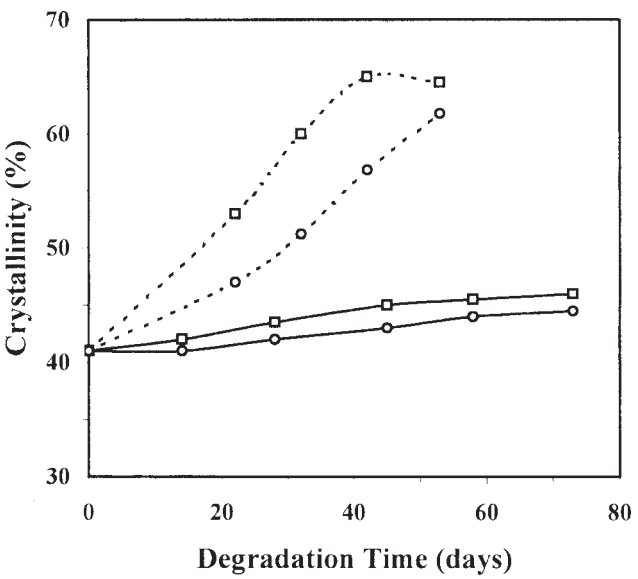


Figure 6 Degree of crystallinity (%) of (□) undyed and (○) triclosan-loaded PPDO sutures versus exposure time in a pH 7.4 buffered solution at 37°C (solid lines) and in distilled water at 50°C (dotted lines). Loading was performed by immersion in a dichloromethane bath containing 10% triclosan for a period of 24 h.

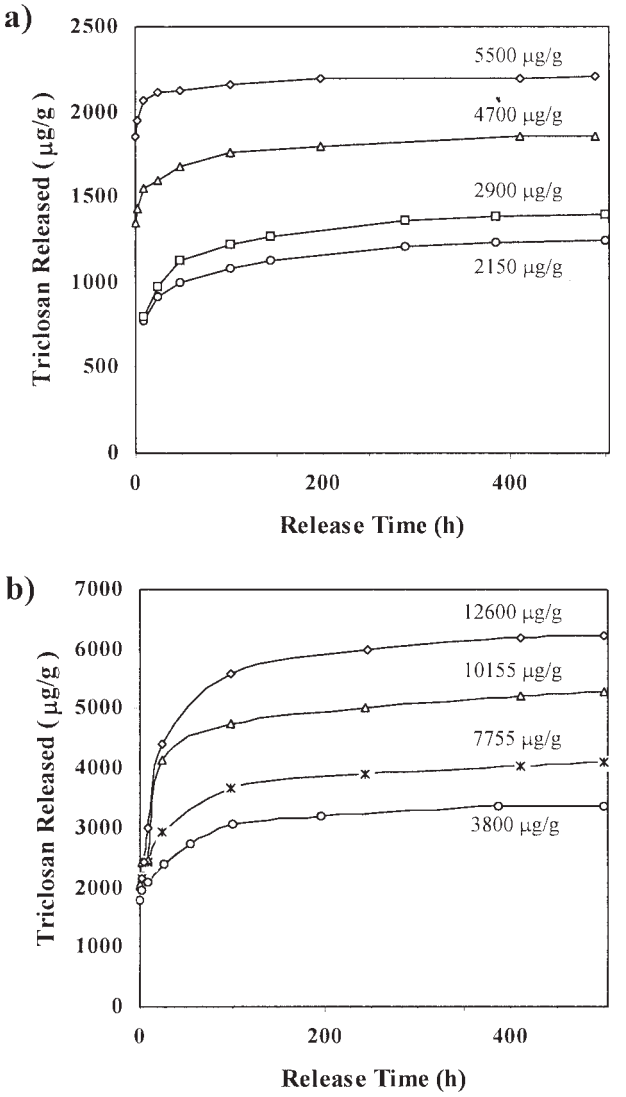


Figure 7 Release of triclosan from PPDO monofilaments in Sörensen's medium at 37°C. Samples were previously loaded by exposure to a dichloromethane solution containing triclosan weight percentages of (a) 2 and (b) 5% (b) for (○) 1, (□) 2, (×) 4, (△) 8, and (◇) 24 h. The amount of triclosan incorporated is indicated in each profile.

immersed in Sörensen's medium at 37°C. In all cases, the amount of released triclosan reached an asymptotic value that was significantly lower than the amount previously loaded into the monofilament. These asymptotic values were dependent on the loading amounts and logically increased with them. The concentration of released triclosan was always lower than the corresponding solubility limit (10–17 mg/L); this suggested an equilibrium defined by a partition coefficient between the drug concentration in the aqueous medium (m_{am}/V_{am}) and that inside the monofilament (m_m/monofilament volume); where m_{am} is mass (triclosan weight) dissolved in aqueous medium, V_{am} is aqueous medium volume, and m_m is mass (triclosan weight) inside the monofilament. This feature was observed previously in the release study of triclosan from coated polyglycolide threads.[11] The real monofilament volume where the hydrophobic drug was distributed depended on the loading time. Thus, it should only have corresponded to the volume of the suture after the time necessary to reach the asymptotic loading concentration (more than 15 h according to Fig. 1). Partition coefficients ranging from 2.5 10^{-4} to 4 $\times$ 10^{-4} were estimated for samples loaded for 15 h in baths containing 2 and 5% triclosan, respectively. These equilibrium conditions could be avoided by frequent changing of the release medium.

Both ethanol[24] and its mixtures[11] with Sörensen's aqueous solution have been demonstrated to be adequate media to obtain a sustained and complete triclosan release from polymer matrices. In our case, the solvent mixture was considered more appropriate to simulate the aqueous physiological medium.

The release profiles in Sörensen's/ethanol (75/25 v/v) medium at 37°C from monofilaments with different amounts of loaded triclosan (from dichloromethane baths with 2, 5, and 10% triclosan content) are shown in Figure 8. In all cases, monofilaments were washed with ethyl acetate before these release experiments were performed. The release always tended to an asymptotic value that was close to the total load determined by the extraction with dichloromethane. For the higher loading amounts (i.e., in baths containing 10% triclosan) some molecules seemed to be trapped in the polymer matrix because of the lower swelling capability of the Sörensen's/ethanol mixture. Thus, the cumulative release profiles (Fig. 9) showed that approximately 5 and 3% of the drug remained in the monofilament after exposure to the release medium for 400 h when the loaded triclosan amounts were 24,075 and 12,600 μg/g, respectively. Also, as shown in Figure 8, this value increased up to 51% (for a triclosan load of 12,600 μg/g) when Sörensen's release medium was used because of the previously explained equilibrium conditions.

The release profiles (Fig. 8) showed a small burst effect and a sustained release, which extended over a period between 100 and 300 h and increased with the loading time. This means that triclosan molecules reached the inner parts of the monofilaments when loading was performed for longer exposure times in the dichloromethane bath. In general, 80% release was attained in a period that ranged between 80 and 100 h (Fig. 9).

A first-order equation [$\ln(1 - M_t/M_0) = -k_1 t$, where M_t and M_0 correspond to the amount of triclosan released at time t and at the end of the release process] was found appropriate to fit the experimental release data because reasonable correlation coefficients were attained (Table V). This equation is adequate when the drug released at each

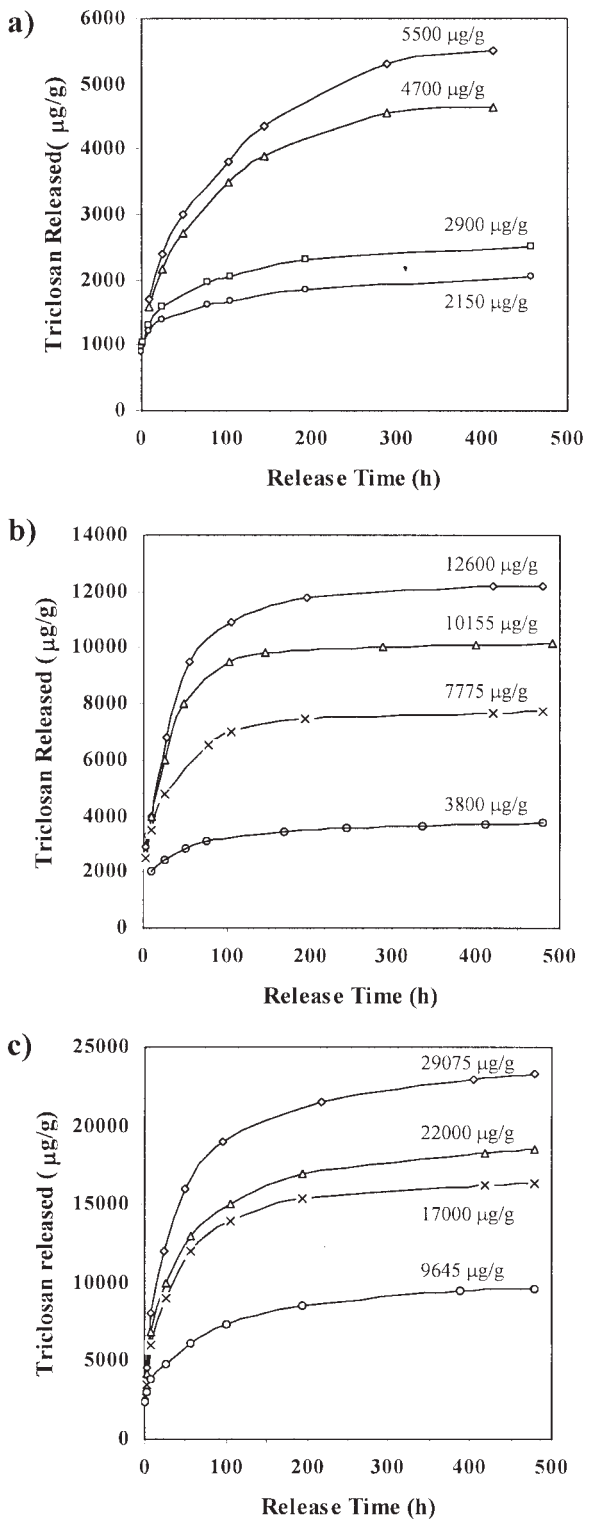


Figure 8 Release of triclosan from PPDO monofilaments in Sörensen's/ethanol (75/25 v/v) medium at 37°C. Samples were previously loaded by exposure to a dichloromethane solution containing triclosan weight percentages of (a) 2, (b) 5, and (c) 10% for (○) 1, (□) 2, (×) 4, (△) 8, and (◇) 24 h. The amount of triclosan incorporated is indicated in each profile.

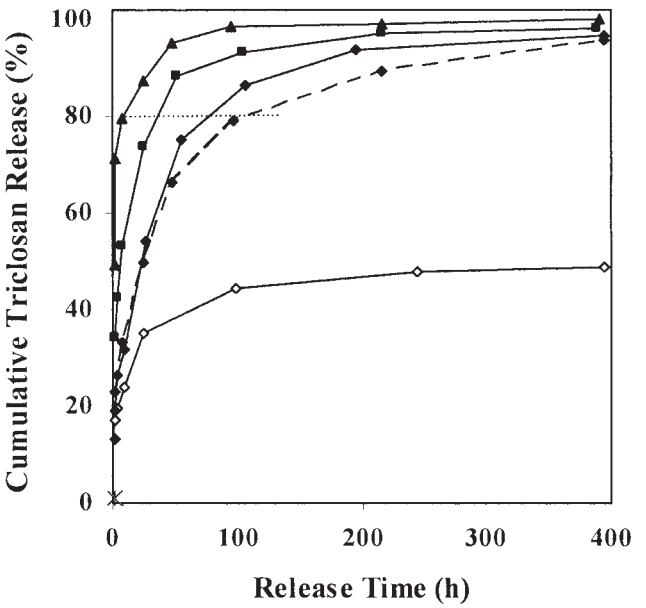


Figure 9 Cumulative triclosan release in (◇) Sörensen's and (◆) Sörensen's/ethanol (75/25 v/v) media at 37°C from monofilaments loaded by exposure to a dichloromethane solution containing triclosan weight percentages of 5% (solid line) and 10% (dashed line) and (■) monofilaments coated with polycaprolactone or (▲) a mixture of polycaprolactone and magnesium stearate. The triclosan concentration in the coating bath was 5%.

time was proportional to the residual drug inside the dosage form. In this case, the improvement caused by the use of a combined model was not highly significant. The release constant rates were always in the 0.012–0.019 h^{-1} range with a mean value of 0.016 h^{-1} and were allowed to estimate a diffusion constant that varied between 3.8×10^{-14} and 2.4×10^{-14} m^2/s when the equation relating the constant rate and the diffusion constant was applied ($k_1 = \pi^2 D/l^2$). The diffusion constants determined

TABLE V
Correlation Coefficient (r) and Release Rate Constant (k_1) Values for the Fitting to the Mathematical Models of the Triclosan Release Profiles of the PPDO Monofilaments in the Sörensen/Ethanol (75/25 v/v) Medium at 37°C

Triclosan in the loading bath (% w/v)	Exposure time (h)	Amount of loaded triclosan (μg/g)	First order	
			r	k_1 (h^{-1})
2	1	2,150	—	0.014
2	2	2,900	0.72	0.015
2	8	4,700	0.98	0.013
2	24	5,500	0.98	0.012
5	1	3,800	0.80	0.013
5	4	7,775	0.95	0.016
5	8	10,155	0.90	0.015
5	24	12,600	0.96	0.019
10	1	9,645	0.98	0.013
10	4	17,000	0.96	0.013
10	8	22,000	0.96	0.012
10	24	29,075	0.96	0.012

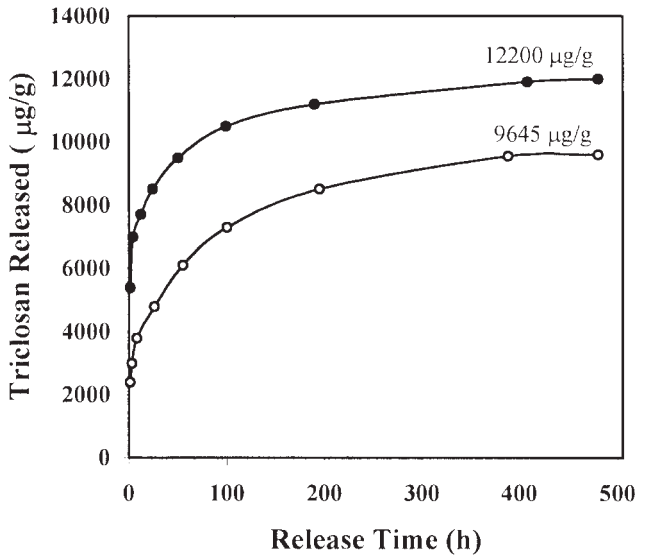


Figure 10 Release of triclosan in Sörensen's/ethanol (75/25 v/v) medium at 37°C from PPDO monofilaments (○) after and (●) without washing with ethyl acetate. Samples were previously loaded by exposure to a dichloromethane solution containing a triclosan weight percentage of 10% for 1 h. The amount of triclosan incorporated is indicated in each profile.

for the release were considerably lower than that found for the loading process, where a solvent with a higher swelling capability was used.

All these experiments corresponded to monofilaments where triclosan deposited on the surface was removed by immersion in an ethyl acetate bath. However, it may be also interesting to keep this surface-attached material to increase the burst effect and, consequently, the amount of initially released triclosan. Figure 10 compares the profiles of samples after and without washing with ethyl acetate and demonstrates that the surface-attached material only represents a small percentage of the total load. A very short loading time was chosen to reduce the amount of drug diffused inside the monofilament. Furthermore, a loading bath with a high triclosan content was used to increase the material directly deposited on the surface, which corresponded to approximately 25% of the triclosan that diffused into the sample.

Finally, it should be pointed out that the surface morphology was similar to that shown in Figure 2. Thus, it was not substantially affected by the release experiments performed at 37°C for 15–20 days.

Release of triclosan from the coated PPDO monofilaments

Triclosan could also be incorporated into a coating of the PPDO monofilament. In this case, the loading process was clearly simplified because it was only necessary to immerse the monofilament in a bath containing both the coating and the triclosan drug for a short period. Polycaprolactone, a polyester with a hydrophobic character, and its mixture with magnesium stearate, which are compounds commonly used as coating lubricants in braided sutures,[25] were considered adequate to interact with the triclosan molecules. Scanning electron micrographs of the coated monofilaments (not shown) indicated a homogeneous surface similar to that of the uncoated sutures.

Figure 11 shows the release profiles obtained from monofilaments loaded in dichloromethane baths containing 3% polycaprolactone and 10 or 5% triclosan. Although the final amount of released triclosan was comparable to that found when the monofilaments were loaded by the diffusion process from baths containing the same proportion of triclosan, some differences were indicated. First, loading by diffusion required a longer time to incorporate a similar amount of triclosan (ca. 24 h), and second, the release of the diffusion-loaded samples also took longer, which in this case may be an interesting feature. For instance, 110 h were required to attain a release of 95% from the coated samples from baths with a 5% triclosan content, whereas 200 h were necessary when the corresponding diffusion-loaded samples were considered (Fig. 8). Moreover, an 80% release was attained after 36 h for the coated sample and after 78 h for the sample loaded by diffusion.

The release rate constant was again evaluated with the assumption of a first-order model that

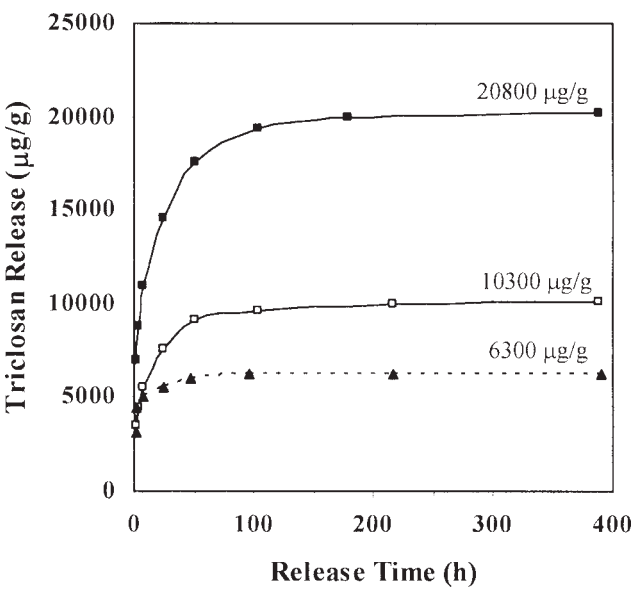


Figure 11 Release of triclosan in Sörensen's/ethanol (75/25 v/v) medium at 37°C from PPDO monofilaments coated with (■, □, solid lines) polycaprolactone or (▲, dotted line) a mixture of polycaprolactone and magnesium stearate. Samples were previously loaded by immersion in a dichloromethane solution containing 3% polycaprolactone or 0.45 and 2.55% polycaprolactone and magnesium stearate, respectively, for 30 s. The triclosan concentration in the baths was (□, ▲) 5 and (■) 10%. The amount of triclosan incorporated is indicated in each profile.

rendered a value of 0.029 h^{-1} and a correlation coefficient close to 0.94 for the two studied samples. This constant became about twice the previous values deduced for the diffusion-loaded samples. In the case of coated monofilaments, the diffusion constant could be evaluated because of the lack of precision concerning the thickness of the polycaprolactone layer. However, it was clear that this constant must have been lower than that determined for the diffusion-loaded samples, as expected from the higher hydrophobicity of polycaprolactone, which should have allowed better interactions with triclosan molecules to be established.

Figure 11 also shows the release profile of a monofilament coated from the polycaprolactone/magnesium stearate (15/85 w/w) mixture. In this case, the release took place almost immediately because an 80% release was attained after only 8 h of exposure. This feature suggests that magnesium stearate has less ability to trap triclosan molecules. Furthermore, the triclosan amount loaded into this coating was significantly lower (ca. by 40%) than the amount incorporated into the polycaprolactone coating when identical bath conditions were used. In this way, it seems possible to obtain a tailored triclosan release by a simple change in the ratio between the two indicated coating components.

CONCLUSIONS

Triclosan can be loaded into PPDO monofilaments by molecular diffusion from a swelling solvent such as dichloromethane. The amount of triclosan incorporated into the monofilament reached an asymptotic value at a time that was dependent on the triclosan concentration in the loading bath (24 h of exposure when the concentration was close to 10%). The loading process followed a combined Higuchi/first-order model, which allowed the estimation of a diffusion coefficient close to 3.7–3.0 $\times 10^{-13}$ m^2/s for the sample with a higher triclosan load (29,075 μg/g).

The thermal properties were influenced by the incorporation of triclosan in such a way that triclosan-containing samples crystallized with more difficulty from the melt than the undyed samples. The incorporation of triclosan increased the hydrophobic nature of the monofilaments and gave rise to a greater stability toward hydrolytic degradation.

Equilibrium conditions were found in the release of triclosan when the hydrophilic Sörensen's medium was used. On the contrary, a sustained release over a period that could reach 400 h was observed when Sörensen's/ethanol (75/25 v/v) medium at 37°C was chosen. This release behavior could be predicted by a first-order model, which in addition, allowed the estimation of a diffusion coefficient close to 2.4 $\times 10^{-14}$ to 3.8 $\times 10^{-14}$ m^2/s, a lower value than that calculated for the loading process with a swelling agent.

The release profiles of samples with triclosan incorporated into a coating could be tailored according to its composition. The triclosan loading process could be simplified, but in general, the release proceeded faster than when triclosan was directly incorporated into the monofilament by diffusion.

References

1. Jones, R. D.; Jampani, H. B.; Newman, J. L.; Lee, A. S. Am J Infect Control 2000, 28, 184.
2. Kockish, S.; Rees, G. D.; Young, S. A.; Tsiboukis, J.; Smart, J. D. J Pharm Sci 2003, 9, 1614.
3. Kockish, S.; Rees, G. D.; Young, S. A.; Tsiboukis, J.; Smart, J. D. Eur J Pharm Biopharm 2005, 59, 207.
4. Maestrelli, F.; Mura, P.; Alonso, M. J. J Microencapsulation 2004, 21, 857.
5. Rothenburger, S.; Spangler, D.; Bhende, S.; Burkley, D. Surg Inf 2002, 3, S79.
6. Homsy, C. A.; McDonald, K. E.; Akers, W. W. J Biomed Mater Res 1968, 2, 215.
7. Rodeheaver, G. T.; Thacker, J. G.; Owen, J.; Strauss, M.; Masterson, T.; Edlich, R. F. J Surg Res 1983, 35, 525.
8. Blomstedt, B. Acta Chir Scand 1978, 144, 269.
9. Hirshman, H. P.; Schurman, D.; Kajiyama, G. J Orthopaed Res 1984, 2, 269.
10. Bhargava, H. N.; Leonard, P. A. Am J Infect Control 1996, 24, 209.
11. Zurita, R.; Puiggalí, J.; Rodríguez-Galán, A. Macromol Biosci 2006, 6, 58.
12. Ray, J. A.; Doddi, N.; Regula, D.; Williams, J. A.; Melveger, A. Surg Gynecol Obstet 1981, 153, 497.
13. Zurita, R.; Puiggalí, J.; Rodríguez-Galán, A. Macromol Biosci 2006, 6, 767.
14. Zurita, R. Ph.D. Thesis, Universitat Politècnica de Catalunya, 2008.
15. Ming, X.; Rothenburger, S.; Nichols, M. M. Surg Infect 2008, 9, 451.
16. Higuchi, T. J Pharm Sci 1961, 50, 874.
17. Higuchi, T. J Pharm Sci 1963, 52, 1145.
18. Gibaldi, M.; Feldman, S. J Pharm Sci 1967, 56, 1238.
19. Wagner, J. G. J Pharm Sci 1969, 58, 1253.
20. Baker, R. Controlled Release of Biologically Active Agents; Wiley: New York, 1987; Chapter 4.
21. Davids, D. J.; Misra, A. Relating Materials Properties to Structure; Technomic: Lancaster, PA, 1999.
22. Sabino, M. A.; González, S.; Márquez, L.; Feijoo, J. L. Polym Degrad Stab 2000, 69, 209.
23. Sabino, M. A.; Albuerne, J.; Müller, A. J.; Brisson, J.; Prud'homme, R. E. Biomacromolecules 2004, 5, 358.
24. Chung, D.; Papadakis, S.; Yam, K. Int J Food Sci Technol 2003, 38, 165.
25. Martinello, T.; Kaneko, T. M.; Robles Velasco, M. V.; Santos Taqueda, M. E.; Consiglieri, V. O. Int J Pharm 2006, 322, 87.