Preparation and Release Profiles of Cyclophosphamide from Segmented Polyurethanes

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ABSTRACT: Supermolecular structure of drug delivery system on the basis of segmented polyurethane (SPU) has been determined to control the release of anticancer drug, cyclophosphamide (CPh). It has been established that the phase separation in SPU is essentially intensified by means of both the increase of molecular weight for SPU's soft segments and CPh incorporation in the monolithic systems of polyethylene glycol-based polyurethane. Infrared and proton NMR data indicate that CPh is hydrogenicly associated with a urethane group of hard segments. It has been determined that the drug-concentrated domains of hard segments are microheterogeneously dispersed in the amorphous soft segments. These results indicate that a supermolecular structure design of SPU allows for control of the CPh release from the polymer matrix. Medical-biological tests of the prepared polyurethane device have shown reduced toxic action of the cytostatic drug compared with injections. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 75: 35–43, 2000

Key words: segmented polyurethane; cyclophosphamide; drug delivery system; diffusion of anticancer drug; rhabdomyoma

INTRODUCTION

Controlled release systems are being successfully developed because of a number of advantages: they provide uniform drug concentrations over a prolonged period, decrease total dosage, eliminate undesirable side effects, and improve pharmaceutical action.[1–4] One of the peculiarities of a drug delivery system is its ability to regulate the drug release from polymeric material to the body.

Segmented polyurethanes (SPUs) are widely used as biomedical material because of their excellent mechanical properties.[5–7] Moreover, the phase separation where one of the phases is a drug reservoir and another is a transport channel allows regulation of the release profile of a drug.[8,9] The most dominant factors in this microdomain formation are the incompatibility of soft (polyethylene glycol) with hard (urethane) segments, as well as the presence of intermolecular hydrogen bonding. In addition, any hydrogen bonding in which the drug takes part changes the release mechanism from microdomain-structured polymers.[10,11]

In order to clarify the release profile of a drug from SPUs in detail, the supermolecular structure of a microdomain-containing polymer and the interaction between the drug and the polymer have been studied.[12,13] The present investigation has been carried out to demonstrate the wide-ranging regulation of the release profile that can be provided by series of SPUs with polyethylene glycol (PEG) soft segments of varying molecular weights, as well as to discuss the design of such segmented polymers with a required release rate.

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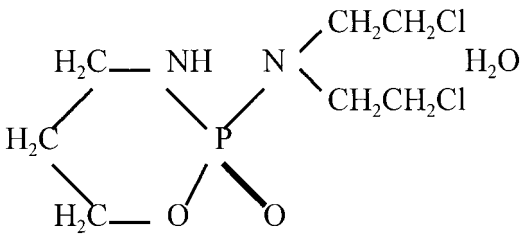

Figure 1 Structure of cyclophosphamide.

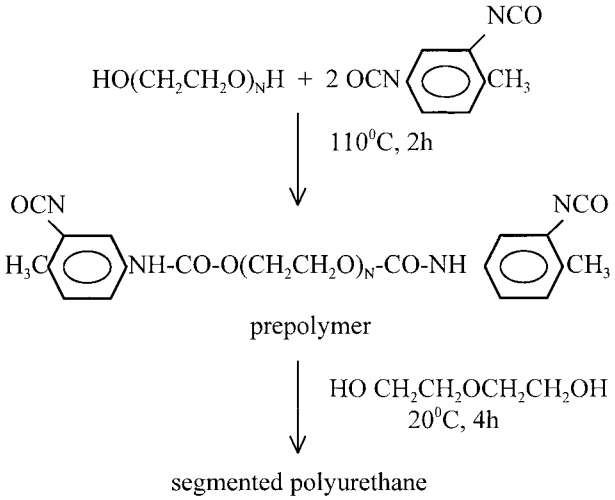

Figure 2 Scheme of SPU synthesis.

MATERIALS AND METHODS

Materials

PEG, with molecular weight from 600 to 4000 Dalton, purchased from Fluka, were previously dried under vacuum at 80°C for 3–4 h. Tolylene-2,4-diisocyanate (TDI), purchased from Aldrich, was vacuum distilled and stored under dry conditions in a refrigerator prior to use. Diethylene glycol (DEG), purchased from Sigma, was dried over calcium hydride for 3 days and distilled under nitrogen. Dimethylsulphoxide (DMSO) from Aldrich was dried over calcium hydride for 2 days and then vacuum distilled to use fraction (boiling point 86 ± 1°C, 20 mm Hg) only. Cyclophosphamide was commercial Cytoxan from Bristol-Myers as fine crystals. Cyclophosphamide or tetrahydro-*N,N*-bis(2-chloroethyl)-2H-1,2,3-oxazaphosphorin-2-amine 2-oxide is represented in Figure 1.

Synthesis of Segmented Polyurethane

Polyurethane was synthesized by a prepolymer method using tolylene-2,4-diisocyanate, polyethylene glycol with various molecular weight from 600 to 4000 Dalton, and diethylene glycol as a chain extender. The scheme of SPU synthesis is represented in Figure 2. Polyethylene glycol was placed in a three-necked flask equipped with a stirrer, a thermometer, and a tube for argon supply and then tolylene-2,4-diisocyanate was added dropwise. The molar ratio of polyol and diisocyanate was 1 : 2.2. The reaction proceeded at 110–115°C for 2 h in the argon flow. A prepolymer with isocyanate end groups was obtained where the percentage of isocyanate was determined, as mentioned elsewhere.[14]

Polyurethane films were prepared by a reaction between the isocyanate terminal groups of prepolymer and diethylene glycol as a chain extender. A 1.0-g shot of the prepolymer, 0.06 g diol (NCO : OH molar of 1 : 1.2), and the drug substance as fine crystals containing 20 mg of the drug/1 g polyurethane (20 mg/g) were successively dissolved in dimethyl sulphoxide solvent. The solvent was gradually vaporized from the solution placed in a Teflon dish under vacuum at 50°C. In addition, the obtained films were dried under vacuum at 50°C for 48 h till they attained a constant weight by the removal of DMSO traces. The obtained polyurethane films contained a homogeneously dissolved pharmaceutical agent. The structure of the resulting polymers is shown in Figure 3 and SPU compositions are presented in Table I.

Thermal Analysis

The glass transition temperature and melting point were measured using a Derivatograph Q-1000 (MOM, Paulik, Paulik & Erdey System).

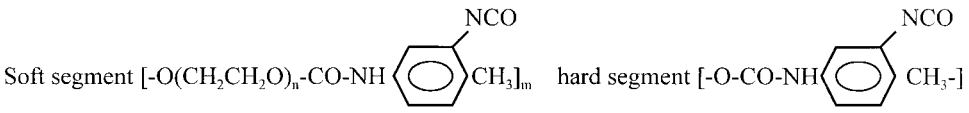

Figure 3 Structure of segments in polyethylene oxide or polypropylene oxide-based SPU.

Table I Chemical Composition of Polyethylene Glycol-Based SPU

Code and Molecular Weight	Content (wt %)			Content of Urethane (%)
	PEG	TDI	DEG	
PEG-600	58.7	37.5	3.8	40.0
PEG-1500	76.9	19.7	3.4	28.9
PEG-3500	87.4	9.6	3.0	21.1
PEG-600 + 1500	70.6	25.7	3.7	29.4
PEG-1500 + 3500	84.0	12.9	3.1	16.0

Two hundred milligrams of polymer was dissolved in 20 ml of DMSO, then precipitated in 500 mL of water, and centrifuged, and the precipitate was dried under vacuum at 50°C for at least 2 days to obtain a powder of a constant weight. The polymer powder was heated twice at a rate of 10°C/min. Aluminium oxide was used as a reference material for a differential thermal analysis. The temperature range was from 0 to +250°C.

Infrared Study

The IR spectra of polyurethane films were recorded with a microattenuated total reflectance attachment (MATR-81) of a Jasco IR-810 spectrometer (Japan). In addition, the 5% polyurethane solution in DMSO was coated directly onto a KRS optical crystal, with a thin film of polyurethane being formed on the KRS after rapid evaporation of DMSO under vacuum at 50°C. Afterwards, the KRS-coated polyurethane film was held in a vacuum oven at 50°C for 1 week to remove all traces of DMSO. In the total reflection method, the 10 × 30-mm polymer sample was held between a KRS-5 prism and a silicon rubber plate. In the crystal coated with polymer film, the spectra were recorded in reference to a pure KRS-5 crystal.

NMR Study

Proton NMR spectra were recorded in DMSO-D_6 using tetramethyl silane (Me_4Si) as an internal standard, by Varian spectrometer of Mercury-300 by means of 300 MHz proton frequency. Twenty milligrams of SPU sample as a powder were dried over calcium hydride for 3 days, dissolved in 1 mL of DMSO-D_6, and then cast in Pyrex NMR tubes. The number of scans performed was 16, and proton chemical shifts were expressed by using the line of DMSO residual proton at 2.5 ppm as an external reference. The chemical shifts are expressed in terms of the parameter δ in ppm, with $\delta = (\upsilon - \upsilon_{Me4Si})$ being the resonance field in cps for sample and Me_4Si, respectively.

Solubility Determination

CPh solubility was determined in several solvents with different solubility parameters by dissolving of 10 mg of drug in 1 mL of each solvent at 25°C. Water, ethanol, ethyleneglycol, and methanol (as strong hydrogen bonding solvents), as well as *N,N*-dimethylformamide, dimethylsulphoxide, dimethylacetamide, acetone, and methylethylketone (as moderate hydrogen bonding solvents) were used as extra pure substances purchased from Merck to determine the CPh solubility. The mixture was stirred for 1 h and filtered under vacuum, and then the precipitate was dried under vacuum at 50°C for 24 h to extract the insoluble drug. A dissolved drug quantity was determined as the difference between the initial and extracted amounts of a drug. The solubility parameter of the hard segment, poly(ethyleneoxide) was taken from ref. 15, where this parameter was based on the functional group contributions of dispersion, polar, and hydrogen bonding components.

In Vitro Release Experiments

In order to record the release behavior of CPh, the disc-shaped devices of 0.30 ± 0.02 mm thickness and 10.0 ± 0.1 mm diameter were prepared from each of the SPU films. The disc was immersed in 100 mL of phosphate buffer (0.01*M,* pH 7.4) at 37°C upon constant stirring. To maintain the same release conditions, the buffer was thermostated. The release of drug was determined by ultraviolet spectrometry (Jasco UV/VIS 7850), using a flow cell and a calibration curve at an absorption wave length of 245 nm.

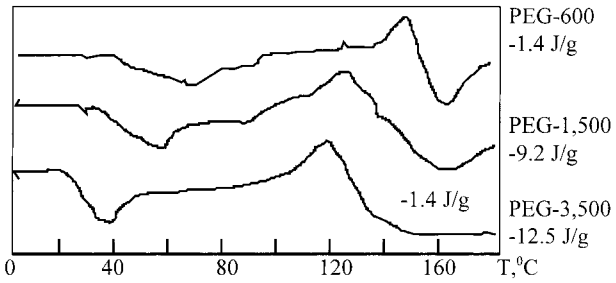

Figure 4 Glass temperature of series of polyethylene glycol-based SPU.

In Vivo Experiments

A malignant *Rhabdomyoma* strain was injected into the tail vein of rats at a dose of 10,000 cells. A total of 120 rats were divided into three groups: control; a group for polymer device implantation in peritoneum, and a third group for daily intramuscular injection of CPh into the tail vein. The polyurethane implant (slab of 10 × 10-mm size) was placed in the abdominal wall 7 days after the strain infection. On the 10th and 17th days, 20 animals of each group were sacrificed, and the device was removed for morphological/histological study. The quantity of clones of myoma cells was calculated using magnetic resonance tomography.

RESULTS AND DISCUSSION

In order to determine what influence the SPU structure exerts upon the release profile of drug, the supermolecular structure of polyurethane with various molecular structures, as well as drug/polymer interactions were studied.

Thermal Properties of SPU

Thermoanalysis measurements were carried out to obtain the glass transition point (T_g) and the heat absorption capacity around T_g (ΔC_p) of SPUs with various molecular structure of soft segments, as shown in Figure 4. There are endothermal peaks attributed to the glass transition of segments; for polyethylene glycol with M_w = 3500, the clear phase transition at 45°C was identified. This transition is interpreted as crystallization of the hard segment domains whose structure improves with increasing the soft segment content. A higher temperature of glass transition was detected only in samples of higher urethane content. This result can be explained by the fact that the segment mobility of polyethylene glycol is restricted by the urethane groups of SPU.

An increase in the polyethylene glycol content has led to an increase of the heat depression, which can be explained as heat emission as result a decrystallization of hard segments. Apparently the hard segment domain contains some amount of the solubilized soft segment, but a higher content of soft segment in SPU causes a phase segregation between the soft and hard segments of SPU. ΔC_p of SPU segments increases with an increase in the polyethylene glycol content essentially. The observed behavior also can be explained the phase separation in SPU. Polyethylene glycol with low molecular weight may be dissolved in the hard segment domains to a marked degree. On the basis of ΔC_p data, the contents of urethane group have been calculated (Table II) taken the heat emission of polyurethane on the basis of diethylene glycol and TDI as 100% of urethane group content. The resulting data agree with the content of urethane groups for synthesis (Table I).

Infrared Study

Since polyurethanes are found to be extensively hydrogen bonded, an analysis of the IR spectra

Table II Characteristic Properties of Polyethylene Glycol-Based SPU

Basis of SPU	Content of Urethane by Thermoanalysis (%)	Content of Associated NH Group (%)	Content of Associated Carbonyl Group (%)	Swelling Degree (%)
PEG-600	34.8	34.8	36.1	30.5
PEG-1500	25.1	50.2	42.5	110
PEG-3500	13.9	76.4	49.8	400
PEG-600 + 1500	21.1	39.8	37.7	330
PEG-1500 + 3500	10.4	53.5	43.8	750

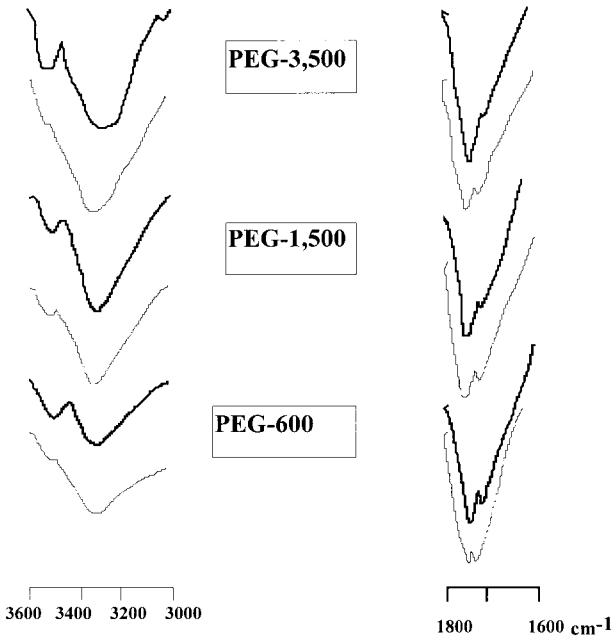

Figure 5 Spectra of NH and carbonyl bands for polyethylene glycol-based SPU.

provides a more detailed understanding of the relation between composition, transition behavior, and properties. It is well known that a band near 3300 cm^{-1} is caused by the H-bonded NH-group, while the non-H-bonded NH-group appears near 3460 cm^{-1}.[16] MacKnight et al.[17] have reported an integrated extinction coefficient $E_f = 3.44 \times 10^3$ l/(mol · cm^2) for the free NH-group and $E_b = 1.19 \times 10^4$ l/(mol · cm^2) for the H-bonded NH-groups. These values for the extinction coefficient were used to calculate the fraction of H-bonded NH-groups for the polyurethanes on the basis of tolylene-2,4-diisocyanate.

However, the carbonyl region shows splitting of the absorption band into two peaks at 1740 cm^{-1} for the free carbonyl of SPU and near 1700 cm^{-1} for the H-bonded carbonyl of the polyurethanes on the basis of tolylene-2,4-diisocyanate. It is well known that the extinction coefficients of H-bonded and free carbonyl do not differ. Table II reviews the characteristic properties and composition of the polymers that were studied. Figure 5 shows the IR spectra for SPU in the two regions, characteristic for the NH and carbonyl groups.

In all series the NH band in the region of 3200–3500 cm^{-1} indicates hydrogen bonding of 80–90%. A peak at 3320 cm^{-1} is visible only, whereas free NH peak at 3450 cm^{-1} is almost negligible. Moreover, the free NH band disappears, as shown in Figure 5, in the samples with the drug incorporated. It was noted that hydrogen bonding of the NH groups also slightly increases with an increase in a molecular weight of the SPU soft segments.

The fraction of bonded carbonyl is calculated to be in the range of 35–60% in the SPU series. The majority of NH-groups are hydrogen bonded with carbonyl groups, with the remainder of NH-groups bonded with the ether oxygen of the SPU soft segments. It is important to note that the content of both the H-bonded NH-groups and the H-bonded carbonyl groups increases in the samples with the drug incorporated.

Since a part of the NH-group is bonded to acceptors of the soft segments, we can assume that the mixing of hard segments in the soft segment phase is likely to occur. However, it has been shown that an increase in the polyethylene glycol molecular weight intensified the phase separation. The phase mixing was negligible in SPU on the basis of $M_w = 3800$ polyethylene glycol, and it was confirmed by the disappearence of the free carbonyl shoulder in Figure 5. At the same time, drug incorporation into SPU results in an intensification of the phase separation. As shown in Figure 5, the IR spectra shoulders of the free NH and carbonyl groups become negligible, but the shoulders of the H-associated groups increase. Thus, the drug molecule is hydrogen-bonded to hard segments, being a hydrogen-active substance. Therefore, we can assume that the drug incorporation enhances the phase separation, and the drug mainly resides in the hard segments of SPU.

Proton NMR Study

The structure of the SPUs obtained was analyzed by 300 MHz proton NMR. Figure 6 shows the principal bands of proton NMR spectra of SPU. Protons attached to benzene nuclei are not identified here. The polyurethane obtained from tolylene-2,4-diisocyanate shows resonance signals of equal intensity that are separated by 1,2 ppm from each other. Considering the inductive effect due to the methyl group, the high-field signal was assigned to the *ortho*-NH proton and the low-field signal to the *para*-NH proton. On the other hand, the NH proton of the SPU derived from tolylene-2,6-diisocyanate resonates at the magnetic field just between those for the 2,4-isomer. All signals of NH protons show sharp resonance, as compared with hydrocarbon protons, at the place of the lower magnetic field. This might be explained by the hydrogen bonding of NH protons of the urethane group.

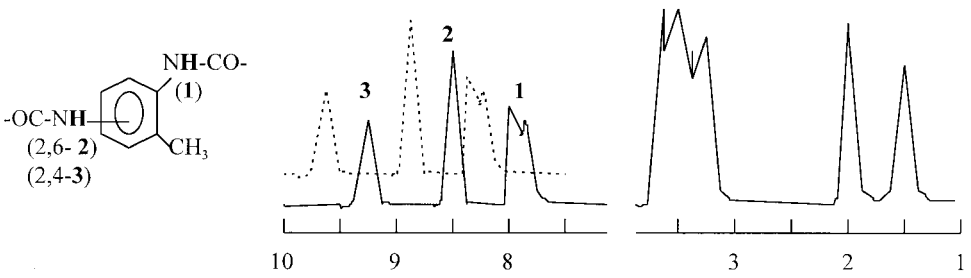

Figure 6 Proton NMR spectra of the polyurethane device.

The dotted line in Figure 4 shows the proton NMR spectra of SPU after incorporation of the drug. It is well known that the proton participating in the stronger hydrogen bonding shows the NMR at the lower field. Incorporation of the drug in the polymer causes intensification of hydrogen bonding. Thus, CPh with hydrogen-active centers takes part in an intermolecular association of urethane groups.

Drug Location in SPU Devices

The SPU used in this study contains the urethane fragment hard segments and polyethylene glycol soft segments, which have different solubility parameters. Hence, it can be expected that the drug is better dissolved in one of the phases than elsewhere.

The solubility parameter of CPh has been established to be equal to the solubility parameter of the solvent in which the drug is completely dissolved. On the basis of the results obtained, it may be concluded that the solubility parameter of CPh is equal to that of methanol, which is equal to 14.5 $[\text{cal/cm}^3]^{1/2}$. The solubility parameter for each solvent has been cited from van Krevelen.[15] It is known that the solubility of a drug with a solubility parameter δ in the given polymer, with a solubility parameter δ_s is a maximum when the $(\delta - \delta_s)^2$ value is zero.[15]

In general we can conclude that the cyclophosphamide preferentially dissolves in the hard segment domains and to a lesser extent in the soft phase of SPU. This can be theoretically estimated by using the Flory-Huggins interaction parameter, which is 0.06 for the drug/hard segment interaction, but 1.04 for the drug/soft segment one.

In Vitro Release of Drug

The CPh release results from the monolithic devices of SPU are shown in Figure 7 and the drug release rate is presented in Figure 8. Proceeding from the data, we can state that the release rate of the drug considerably increases with the enhancing of the polyethylene glycol content (or molecular length) in the polymer. SPUs with various content of polyethylene glycol demonstrate different behaviors to release the CPh. If the diffusion of drug from the polymer film is limited by the time required to reach a surface of film, the conditions for the solution of the first Fick's equation follows these conditions: $t = 0$; $C = C_0$ at $0 < x < l$ and $t > 0$; $C = 0$ at $x = 0$ and $x = l$. The release behavior, in our case for the SPU based on polyethylene glycol of $M_w = 2500$ and higher, can be generally expressed as drug diffusion from a fully swollen material:

$$M_t/M_\infty = 1.0 - 8/\pi^2 \sum 1/(2n+1)^2 \times \exp[-D(2n+1)^2\pi^2 t/l^2] \quad (1)$$

where l is a thickness of the sheet.[18,19]

If the drug diffusion is limited by the time required to move the drug from polymer to surrounding media, the concentration is proportional to the square of time: $t = 0$; $C = C_0$ at $0 < x < l$ and $t > 0$; $C = C(\sqrt{t})$ at $x = 0$ and $x = l$, and drug release for the SPU based on polyethylene glycol with $M_w = 2500$ and lower is likely to diffuse as from a partially swollen polymer:

$$M_t/M_\infty = 4.0(Dt/\pi l^2)^{1/2} \quad (2)$$

where l is a thickness of the sample.[18–20]

The results of the experimental study are satisfactorily described by the Fickian equations (Table III). Thus, we can conclude that the content of the soft phase influences the release profile of CPh from SPU materials where drug diffusion is controlled by a swelling of the polymer.

The amount of CPh released from each of SPU device during the first 2 and 10 h (M_t/M_∞) was

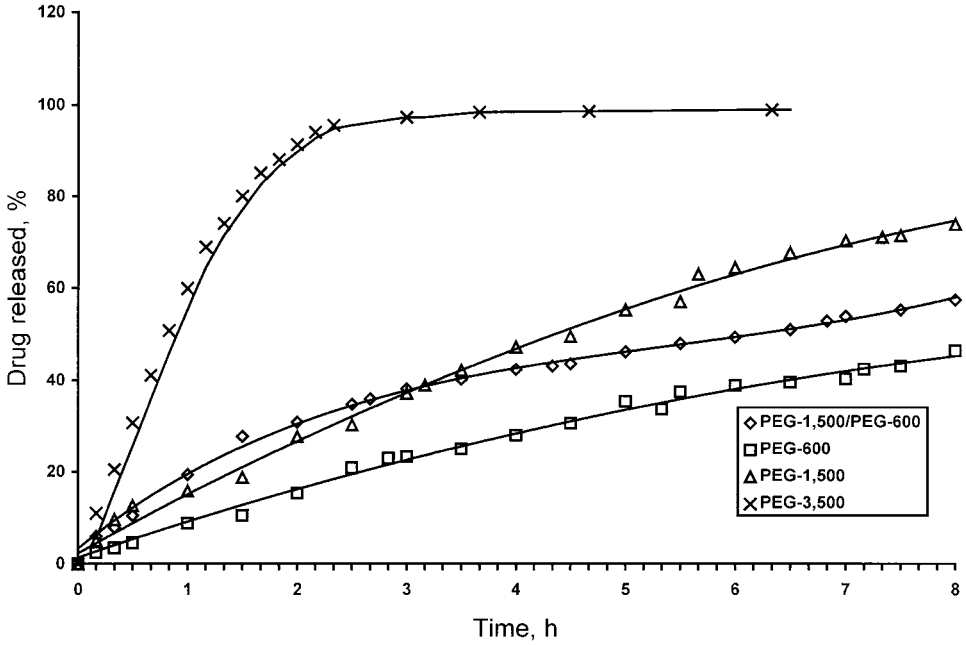

Figure 7 CPh release from polyethylene glycol-based SPU.

plotted against polyethylene glycol wt % in soft segment in Figure 9, as well as against polyethylene glycol molecular weight in Figure 10. The drug release increases with an increase in the polyethylene glycol content (molecular weight) up to about 85 wt % ($M_w \approx 4000$), but further on it decreases. It can be probably explained by a disappearance of the physical intermolecular cross-linkage and an intensification of segmental mobility.

Medical Biological Tests

In Figure 11 the quantity of tumor clones and the weight of the sensible tissue of spleen are shown for control animals as well as for those who received

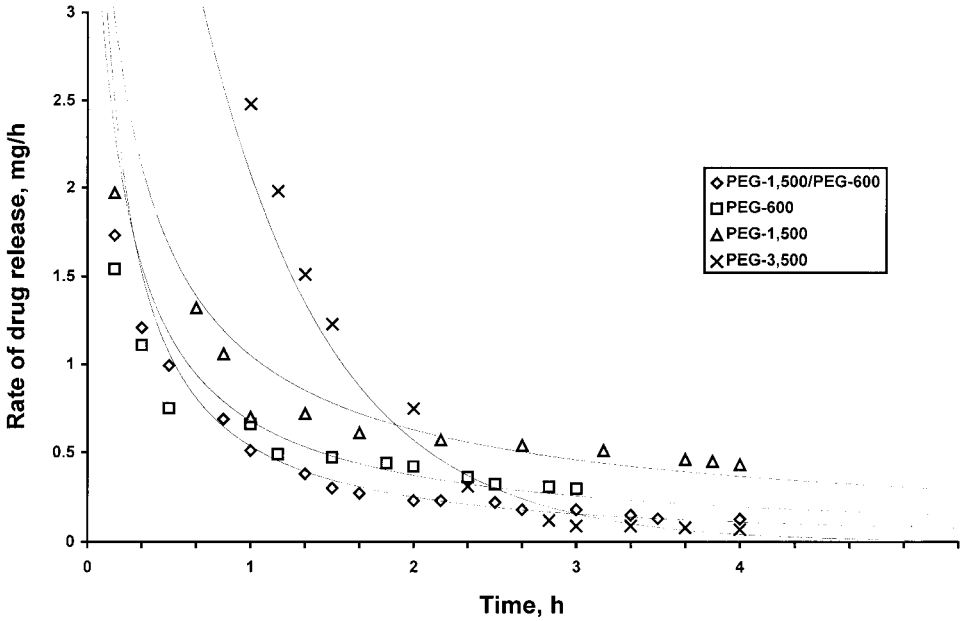

Figure 8 Rate of CPh release from polyethylene glycol-based SPU.

Table III Experimental and Calculated Release Values

Time (min)	PEG-600		PEG-1500		PEG-3500		PEG-1500 + 3500	
	Exp.	Eq 1	Exp.	Eq 1	Exp.	Eq 2	Exp.	Eq 2
10	0.02	0.0543	0.04	0.067	0.11	0.2735	0.13	0.2799
20	0.04	0.0768	0.07	0.0947	0.2	0.3492	0.26	0.3606
30	0.045	0.094	0.11	0.116	0.31	0.417	0.38	0.4322
40		0.1086		0.1339	0.4	0.4777	0.53	0.4958
50		0.1214		0.1497	0.51	0.5321	0.66	0.5523
60	0.09	0.133	0.15	0.164	0.59	0.5808	0.74	0.6025
70		0.1437		0.1771	0.68	0.6245	0.8	0.647
80		0.1536		0.1894	0.74	0.6636	0.82	0.6866
90	0.11	0.1629	0.18	0.2009	0.8	0.6987	0.83	0.7217
100		0.1717		0.2117	0.85	0.73	0.83	0.7529
110		0.1801		0.2221	0.87	0.7582	0.84	0.7806
120	0.16	0.1881	0.27	0.2319	0.91	0.7834	0.84	0.8051
130		0.1958		0.2414	0.94	0.8059	0.85	0.827
140		0.2032		0.2505	0.95	0.8261	0.85	0.8464
150	0.21	0.2103	0.3	0.2593		0.8442		0.8636
160		0.2172		0.2678		0.8605		0.8789
170	0.22	0.2239		0.2761		0.875		0.8924
180	0.23	0.2304	0.37	0.2841	0.96	0.888	0.87	0.9045

implants and injections. The strong antitumor action of both forms of CPh is characterized by a decrease of clone quantity, but the lower toxic action of the implant is expressed by the lower reduction in spleen weight. Morphological analysis of the surrounding tissue after 10 days of implantation shows that the implant is surrounded by a capsule containing histocytes and fibroblasts, as well as a diffusion accumulation of lymphocytes and plasmocytes. After 17 days of implantation the capsule thickens, but the surrounding tissue shows the usual structure. Thus, the implantation of SPU containing CPh appears to reduce the toxic action of cytostatic drug compared with injections.

CONCLUSIONS

It has been determined that the supermolecular structure of polyurethane consists of hard segments associated in microdomains with a continuous phase containing soft segments of polyethylene glycol. The most predominant factors behind microdomain formation are the incompatibility between soft and hard segments and intermolecular hydrogen bonding, typical for urethane segments.

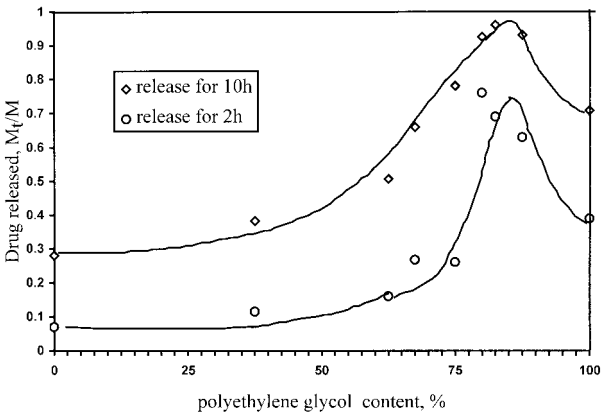

Figure 9 Changes in the CPh release versus polyethylene glycol content in SPU.

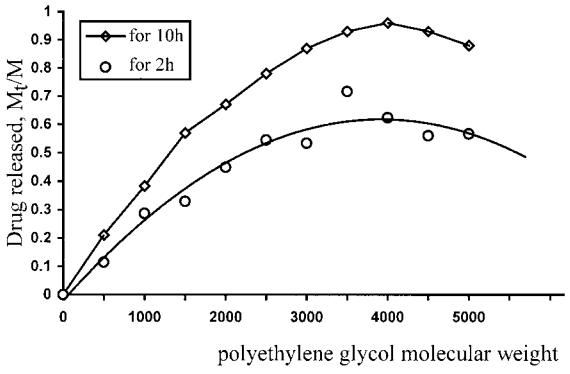

Figure 10 Changes in the CPh release versus polyethylene glycol molecular weight in SPU.

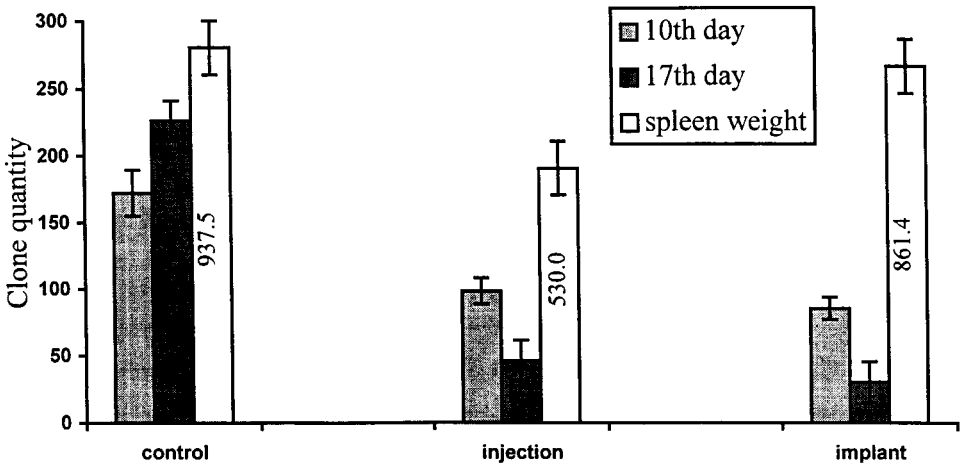

Figure 11 Antitumor and toxic actions of various forms of CPh.

In the case of drug introduction in SPU, the phase separation between microdomain and the continuous phase may be increased, because the proton donors and acceptors of a drug molecule may participate in the hydrogen bonding. Specifically, it can be concluded that CPh is mainly localized in the microdomain of the hard segment.

It has been demonstrated that the release of drug varies widely with changes in the molecular weight of the polyethylene glycol. The molecular weight of the polyethylene glycol segments in SPU influences the transport mode of CPh release, with the release changing from zero-order to Fickian diffusion with a decrease in the polyethylene glycol molecular weight in SPU. Thus, the supermolecular picture of SPU is as follows: the CPh-concentrated domains act as a depot that is microheterogeneously dispersed in the continuous phase, which serves as a transport channel for the drug diffusion. These results indicate that a supermolecular structure design of SPU can allow control of the CPh release from the polyurethane matrix.

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