In vivo versus *in vitro* degradation of controlled release polymers for intracranial surgical therapy

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Intracranial studies to analyze the degradation kinetics of the bioerodible polymer poly[*bis*(*p*-carboxyphenoxy)propane-sebacic acid] [*p*(CPP-SA) 20:80] copolymer wafers were conducted in a rat model. Rats were separated into four groups: those receiving 1) polymer, 2) polymer loaded with the chemotherapeutic agent BCNU, 3) drug-loaded polymer with previous tumor implantation, and 4) polymer and an absorbable hemostatic material. A polymer wafer was surgically implanted into the brain of each animal. Residual polymer was harvested at varying times for chromatographic analysis. *In vitro* effects of pH, mixing, and water availability on degradation were also studied. The results of *in vitro* and *in vivo* studies were compared to understand the behavior of polymers in a clinical setting. We found that degradation of *p*(CPP-SA) initially occurred more slowly *in vivo* than *in vitro*. The presence of BCNU, tumor, and absorbable hemostatic material did not affect the ultimate time of polymer degradation *in vivo*, and the intrinsic polymer degradation time of 1 mm thick *p*(CPP-SA) 20:80 disks *in vivo* was 6–8 weeks.

INTRODUCTION

Controlled release polymers have been developed for a novel approach to the treatment of surgical diseases. Implantable polymers are being evaluated for *in vivo* use in controlled release drug delivery for the treatment of malignant gliomas,[1–3] Alzheimer's disease,[4] Parkinson's disease,[5,6] and peritumoral edema.[7–9] Controlled release has been achieved with dopamine,[10–12] bethanechol,[4] dexamethasone,[7–9] acetylcholine,[13] antibiotics,[14] LH-RH agonist,[15] and several antineoplastic agents.[16–19] Polymers have been used to release heparin[20] and cortisone acetate.[21] Minocycline[22] is currently used to inhibit rat brain tumor angiogenesis, and antibiotics have been used to treat osteomyelitis.[14] Polymers are being evaluated *in vivo* for the treatment of glaucoma[23–25] and for drug delivery into the vitreous humor.[26–28] Controlled release of chemotherapeutic agents are in clinical trials to treat head and neck cancers.[29] Sustained release of nerve growth factor from polymer microspheres has recently been demonstrated,[30,31] and in the future, this may provide a means for peripheral nerve regeneration and improved graft survival.

In many of these applications, substance delivery is enhanced by implanting a polymer device directly at the surgical site. For antineoplastic drugs, potentially toxic agents can then be delivered in high concentrations directly to the tumor site at a controlled rate. This approach increases the efficacy of drugs directed against brain tumors by bypassing the blood brain barrier and minimizing the systemic exposure. The polymer implants are currently being used in the first FDA-supervised clinical trials of a surgically implanted polymer delivery system.[1]

Extensive research has been performed on the degradation kinetics of the bioerodible polymer poly-[*bis*(*p*-carboxyphenoxy)propane-sebacic acid], *p*(CPP-SA), *in vitro*. This polymer was developed for clinical application, and its degradation rates with varying proportions of sebacic acid copolymer have been established *in vitro*.[32] The pH dependence of the erosion rates[32,33] and drug release rates from the loaded

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Journal of Biomedical Materials Research, Vol. 28, 387–395 (1994)

CCC 0021-9304/94/030387-09

polymer[34,35] have also been documented. However, the factors that influence polymer degradation rates *in vivo* are not well understood.

In vivo factors that influence polymer degradation rates become important in clinical trials. Results from early clinical trials suggest that polymer remnants are occasionally found in patient brains at autopsy or reoperation.[1] Although no correlation has been found between the presence of the polymer remnants and specific neurologic findings in patients,[1] the possibility that a foreign material could remain in the body for an extended period of time may be of concern. Reports to date on the occurrence of polymer remnants have been anecdotal, and are therefore difficult to analyze quantitatively.

The current study therefore seeks to determine whether slowed polymer degradation *in vivo* is due to intrinsic *in vivo* conditions, or to conditions of surgical implantation. It also seeks to document the expected time course of *in vivo* polymer degradation.

We hypothesized that various intrinsic parameters might affect polymer degradation in the setting of intraoperative brain tumor therapy, and designed experiments to test these *in vivo* parameters. Four variables were specifically evaluated: 1) the influence of brain tissue; 2) the influence of a chemotherapeutic drug on brain tissue; 3) the influence of a growing tumor, which may recur clinically within 2 cm of the initial tumor margin;[36] and 4) the influence of oxidized regenerated cellulose (Surgical®; Johnson & Johnson) used clinically as a hemostatic agent.

MATERIALS AND METHODS

Rats have been used extensively in preclinical testing of *p*(CPP-SA) polymer safety, drug distribution, and efficacy, and were therefore chosen as an animal model in the current study. Rats were divided into four groups for the *in vivo* studies: 1) those receiving empty polymer: 2) those receiving polymer 20% loaded with the chemotherapeutic agent, carmustine (BCNU); 3) those receiving polymer 20% loaded with BCNU 4 days after 9-L-gliosarcoma implantation; and 4) those receiving empty polymer and a piece of an absorbable hemostatic material (Surgicel®).

In vivo protocol

Polymer wafers of *p*(CPP-SA) 20:80 (mole percent CPP to SA) were obtained (Scios-Nova Pharmaceutical Corporation, Baltimore, MD). The synthesis of these polymers is described elsewhere,[37] and the biocompatibility of the polymer *in vivo* has been established.[38–40] Polymer wafers were surgically implanted into the rat brain by the following procedure: polymer wafers were weighed and sterilized for about 2 h by ultraviolet radiation immediately before implantation (1 h each side). Wafers weighed approximately 12 mg each, 3 mm in diameter by 1 mm in thickness. Male rats (Fisher 344 rats; Charles River Breeding Laboratories, Wilmington, MA) were obtained and housed a minimum of 3 days before surgical operation. NIH guidelines for the care and use of laboratory animals were observed. Rats weighed about 250 g and were anesthetized intraperitoneally with xylaket, an anesthetic cocktail consisting of 25% v/v ketamine (Ketaset 100 mg/ml; Aveco Co., Inc.) 2.5% v/v xylazine (Rompun, 100 mg/ml; Mobay Corporation), 14.2% absolute ethanol, and 58.3% or 0.9% saline. The scalp of each rat was shaved and scrubbed several times with 70% ethyl alcohol and surgical scrub (Betadine Surgical Scrub; Purdue Frederick Co.) using sterile swabs. Surgical solution (Betadine Solution [Povidone-iodine, 10%]; Purdue Frederick Co.) was applied before incision. The operative procedure was carried out using sterile surgical technique. The scalp of the rat was draped. A midsagittal incision was made, and the skin was retracted to expose the calvaria. Using a drill (Foredom Electric Co., Bethel, CT), a 3 mm burr hole was made in the calvaria 5 mm posterior and 3 mm to the left of the coronal suture. When the drill bit neared the dura (determined visually through a microscope [Zeiss]), drilling was stopped, and the remaining bone was removed with forceps. Bone powder and blood from the procedure were removed by gentle vacuum suction to clear the visual field during surgery. Surgical absorbent spears (Weck-Cel surgical spears; Edward Weck and Company, Inc.) were also used to clear oozing. The underlying dura was nicked with a 15° microsurgical knife (Weck, Research Triangle Park, NC). The polymer was gently inserted vertically into the brain, and the incision was closed with 9 mm surgical staples (Clay-Adams, Parsippany, NJ). For rats receiving the absorbable hemostat/empty polymer combination, implantation procedures were similar, except that 1.5 in × 2 in sheets of sterile absorbent hemostatic material (Surgicel®) were cut into 1 cm × 1.5 cm strips, UV-sterilized, and wrapped around the polymer wafer before implantation.

In the rats receiving a 9-L-gliosarcoma tissue implant, tumor was excised from the flank of a donor rat on the day of surgery and placed in a sterile Petri dish. The tumor was kept moist with 0.9% saline for irrigation, and was kept on ice during the day. A 3 mm burr hole was made in the calvaria as described above. A sterile Pasteur pipette attached to a vacuum line was used to carefully suction and resect brain tissue through the burr hole, through the white matter, and into the grey matter of the brain until cerebrospinal fluid was viewed. At that depth, a 1 mm^3 piece of

tumor tissue from the source tumor was placed in the site of resection. The incision was again closed with surgical staples, and the tumor was allowed to grow for 4 days before surgical implantation of the polymer. At that time, the staples were removed and the incision was reopened with tissue forceps. Tumor growing above the level of the calvaria was excised, and a microsurgical knife was used to incise an opening in the growing tumor. The polymer was placed vertically into this site, and the incision was restapled.

In all *in vivo* studies, the rat was maintained in accordance with the MIT Committee on Animal Care, with free access to rat chow and water for a predetermined length of time (days to months) before sacrifice. The animal was sacrificed by carbon dioxide inhalation. The skin was reincised, and the calvaria was carefully removed using bone rongeurs. Removal was initiated at the occipital notch, well away from the site of polymer implantation. The residual polymer and adhering cellular material were removed and kept frozen under nitrogen for further analysis. The brain was removed and preserved in 10% neutral formalin for histologic studies. Histologic analysis was provided by Arthur D. Little, Inc.

In vitro protocol

Empty *p*(CPP-SA) 20:80 polymer wafers, 3 mm in diameter (Scios-Nova Pharmaceutical Corporation, Baltimore, MD), were weighed and placed in 10 ml of pH 7.4, 0.1 M phosphate-buffer solution at 37°C. The solution was kept moderately agitated by placing solution vials on a rotator (Orbit Shaker, Lab-Line) throughout the course of each experiment. At specified sampling times, the buffer was aspirated from the sample vial and refrigerated for chromatographic analysis (HPLC). Fresh buffer was added to the polymer sample, and the procedure was repeated for each sampling point.

The pH dependent buffer experiments were run with the following additional buffer solutions: 1) pH 6.4 buffer (0.067 M monopotassium phosphate with 0.067 M disodium phosphate in a 2.7:1 volumetric ratio), 2) pH 4 buffer (410 ml of 0.2 M acetic acid, 90 ml of 0.2 M sodium acetate, made up to 1,000 ml), and 3) pH 2 buffer (250 ml of 0.2 M KCl, 65 ml of 0.2 M HCl, with 685 ml Milli-Q water).

Sample preparation

Polymer remnants from the rat brain were completely dissolved in 20 ml of a pH 7.4 phosphate-buffer solution (0.1 M Na_2HPO_4, 0.02 M $NaHPO_4 \cdot H_2O$) by stirring on a hot plate for several days. A potassium phosphate-buffer solution was used for polymer wafers 20% loaded with BCNU. The solution was prefiltered (Millipore, type HV, 0.45 μm), and chromatographic analysis (HPLC) was performed (see subsequent details) using a hydrophobic column and a preset gradient [85% Pic A in water, 15% acetonitrile [95% solution]).[41] Standards were run with the polymer sample, and levels of the monomers sebacic acid (SA) and CPP were compared and quantified to determine the amount of polymer remnant that remained undegraded in the rat brain. Knowledge of the polymer composition and weight of each polymer before implantation then permitted determination of the amount of polymer that had degraded *in vivo* by a simple mass balance.

For the *in vitro* studies, buffer samples were also analyzed by HPLC for the amount of polymer degraded.

Chromatographic method

Sebacic acid (stated purity 99%) monomer (Aldrich Chemical Co., Inc., Milwaukee, WI) was obtained. Purified CPP monomer prepared according to the method described by Conix[42] was received as a gift from Scios-Nova Pharmaceuticals. Tetrabutylammonium phosphate was obtained in the form of UV PIC A from Waters (Milford, MA) and prepared as a 0.005 M solution. The solution was filtered through a 0.45 μm filter before being used. Acetonitrile (HPLC grade) was also obtained (Mallinckrodt, Inc., Paris, KY). Purified water was used in these studies (Milli-Q water; Mallinckrodt, Inc.). All other chemicals used were of analytical reagent purity.

The instrumentation used for this work consisted of two solvent pumps (Model 510 solvent pumps; Waters), an autoinjector (WISP 712 autoinjector; Waters), and a programmable multiwavelength detector (490 Programmable Multiwavelength Detector; Waters), all controlled by a data station (Dec 350 data station; Digital Equipment Corporation, Maynard, MA). The chromatographic separations were performed at ambient temperatures on a 5 μm PRP-1 polymeric reversed-phase column (150 × 4.1 mm I.D.; Hamilton Co., Reno, NV). The HPLC column was preceded by a PRP-1 cartridge guard column (Hamilton Co.). A gradient system was employed, with the flow rate of the mobile phase maintained at 1.7 ml/min. The initial mobile phase composition was 95% acetonitrile/5% water and 0.005 M tetrabutylammonium phosphate in water in the ratio of 16:84. This ratio was maintained for 4 min, then increased from 16:84 to 30:70 over a period of 6 min using a convex gradient. The 30:70 ratio was maintained for 3 min, then linearly returned to 16:84 over a period of about 6 seconds. The 16:84 ratio was maintained for about 7 min to re-equilibrate

the column for the next injection. Injection volumes were 100 μl. Two channels were used on the UV detector: a wavelength of 210 nm to detect SA and 246 nm to detect CPP.

Six standard solutions were prepared from stock solutions. The standards contained CPP in the concentration range of 3–24 μg/ml and SA in the concentration range of 20–307 μg/ml. The solutions were prepared in pH 7.4 phosphate buffer. Each standard was injected 6 times, and a calibration curve was constructed to quantitate the percentage of erosion.

RESULTS

Empty polymer degradation

The *p*(CPP-SA) 20:80 polymer wafers degraded slightly more slowly in the rat brain than in agitated *in vitro* buffer solutions (Fig. 1). Moreover, there was a marked lag in the *in vivo* CPP degradation profile for about a week before any significant erosion was observed. Although the SA eroded from the wafer more slowly *in vivo* as compared with *in vitro,* the degradation profiles were otherwise similar. In the rat brain, the polymer degraded completely, and no polymer remnants were found by 6 weeks.

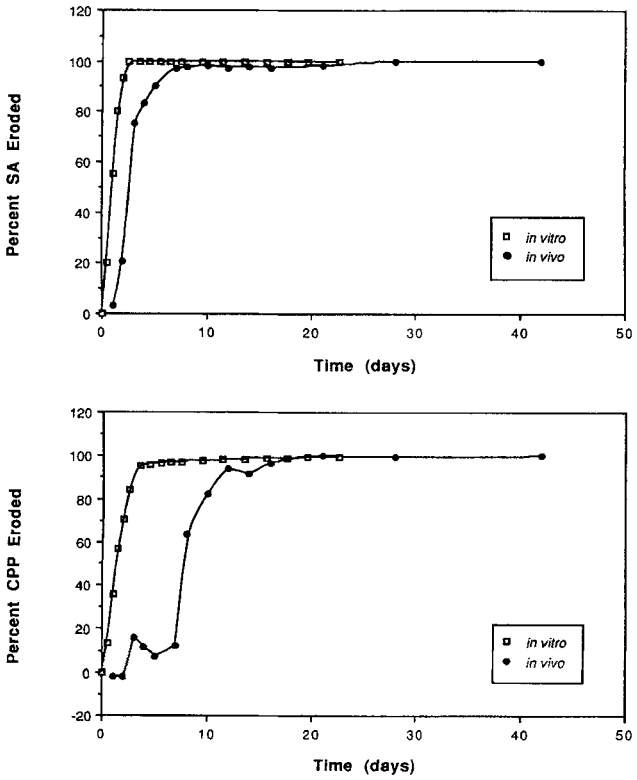

Figure 1. Erosion of *p*(CPP-SA) 20:80 polymer wafers in rat brain compared to erosion into pH 7.4 0.1 M phosphate buffer. Polymer initially eroded more slowly in the rat brain than in agitated *in vitro* buffer solutions. By 42 days *in vivo,* no polymer remnants remained.

BCNU-loaded polymer degradation

Polymers that were 20% BCNU-loaded also degraded slightly more slowly *in vivo* than *in vitro* at pH 7.4. Erosion patterns for both monomers were similar to those observed for empty polymer wafers (Fig. 2).

BCNU-loaded polymer degradation with previous tumor implantation

The BCNU-loaded polymer that degraded in the environment of previous tumor implantation eroded within about 5 weeks. Although the wafer in the initial 2 days of *in vivo* erosion displayed a larger percentage of erosion than the empty polymer, long-term degradation was similar to that of the empty polymer (Fig. 3), and complete erosion was observed.

Empty polymer degradation with Surgicel® wrap

One absorbable strip of hemostatic agent (Surgicel®) was immersed in 5 ml of pH 7.35 potassium phosphate buffer at 37°C and allowed to degrade for 1 week. The pH of the solution was then measured and found to be approximately pH 3.5. The *in vivo* effect of the hemostatic agent on polymer degradation was subsequently investigated. Wafers of *p*(CPP-SA), prewrapped in the low pH absorbable hemostatic agent, were allowed to degrade for various times in the rat brain before removing the remnants. Remnants were analyzed at seven different time intervals, beginning at 1 week after implantation. In every case, polymer degradation was more than 90% complete at the time of removal (Fig. 4). No polymer or hemostatic material (Surgicel®) remnants were found by 8 weeks.

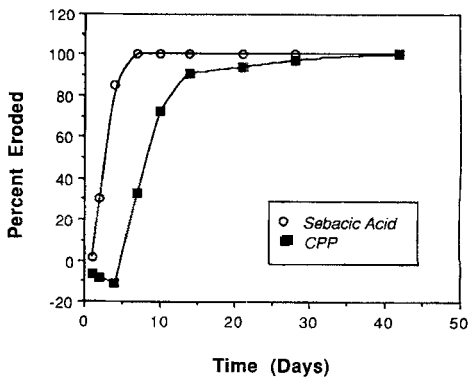

Figure 2. Erosion of 20% BCNU loaded *p*(CPP-SA) 20:80 wafers in rat brain. Polymer wafer completely eroded by 42 days.

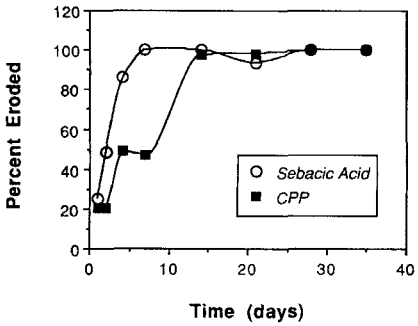

Figure 3. Erosion of 20% BCNU loaded *p*(CPP-SA) 20:80 polymer wafers in rat brain with previous 9-L-gliosarcoma implantation. By 42 days, no polymer remnants remained.

Water availability

Wafers of *p*(CPP-SA) 20:80 were allowed to erode into sodium phosphate-buffer solutions with two different amounts of monomer saturation in the buffer solution. Wafers were placed in buffer such that the initial mass of polymer per volume of buffer solution was 1 and 20 mg/ml. The wafer in the 20 mg/ml system degraded at a rate slower than that of the 1 mg/ml system (Fig. 5). This suggests that low water availability may lead to saturation of the surrounding buffer with monomer, and thereby lower the driving force for dissolution. Such a phenomenon may also occur in the brain.

pH dependence

Poly[*bis*(*p*-carboxyphenoxy)propane-sebacic acid] 20:80 polymer wafers were allowed to degrade in buffer solutions of pH 7.4, 6.4, 4, and 2 (Fig. 6). Both CPP and SA eroded from the wafers significantly more slowly with decreasing pH.

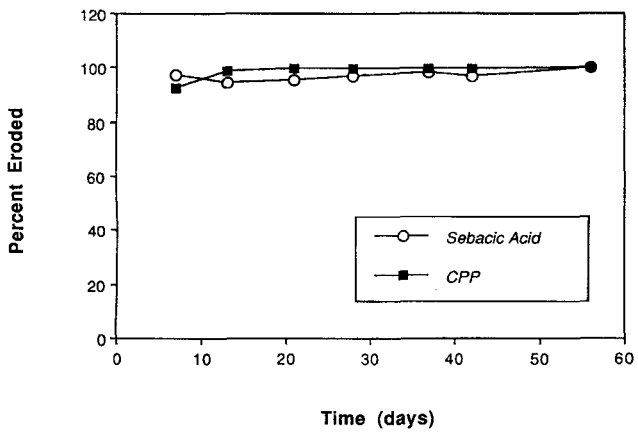

Figure 4. Erosion of unloaded *p*(CPP-SA) 20:80 polymer wafers prewrapped with Surgicel® in rat brain. The presence of Surgicel® did not significantly slow polymer erosion.

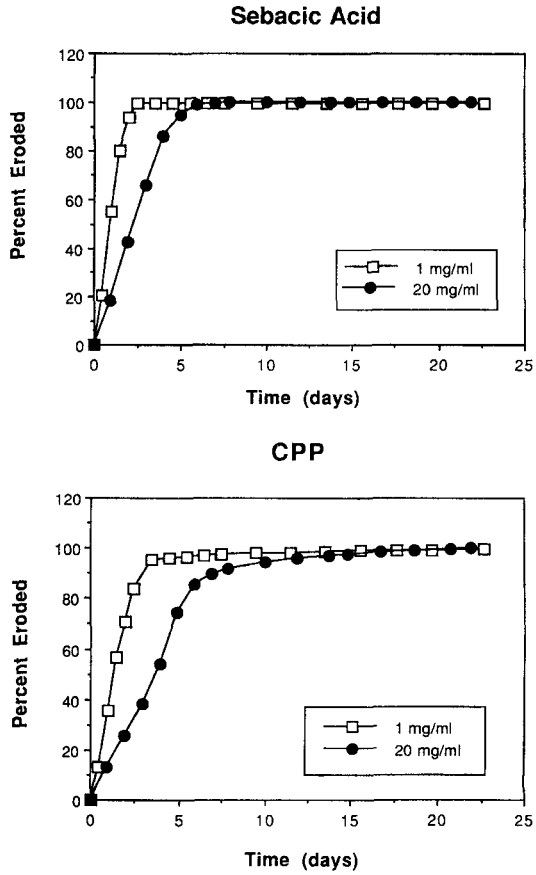

Figure 5. Erosion of *p*(CPP-SA) wafers into 0.1 M phosphate-buffer solutions with different amounts of monomer saturation in the buffer solution.

Rotational speed dependence

Poly[*bis*(*p*-carboxyphenoxy)propane-sebacic acid] wafers were allowed to dissolve in a pH 7.4 phosphate-buffer solution at two different rotational speeds for agitation (Fig. 7). Negligible differences in degradation rates were observed over the speeds tested.

Correlation with inflammation

Rat brains harvested from the blank polymer implantations were placed in 10% neutral formalin (Sigma) and preserved for histology. Specimens were sent for pathologic examination and sectioned at three areas (anterior, center, and posterior) in the polymer implant site. Specimens were scored for inflammation as follows: 1 = minimal; 2 = mild; 3 = moderate; and 4 = marked. The inflammation scores from all three sites were summed for each rat brain, and the percentage of maximal inflammation was plotted based on the highest score for the series. Results are shown in Figure 8, with the CPP degradation. The time at which CPP degradation markedly increased

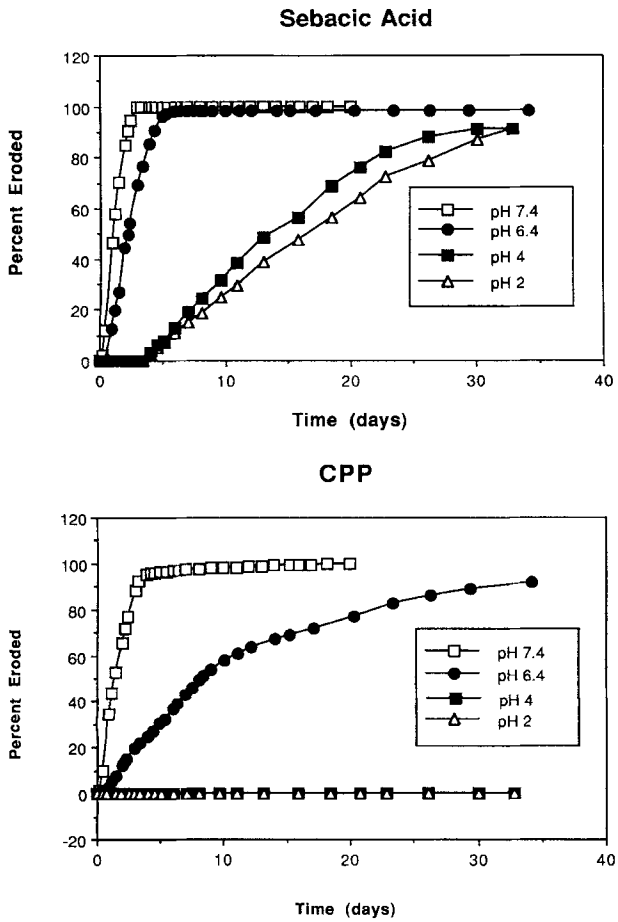

Figure 6. Erosion of *p*(CPP-SA) 20:80 wafers into buffer solutions of varying pH. Polymer erosion is markedly slowed only at low pH ranges.

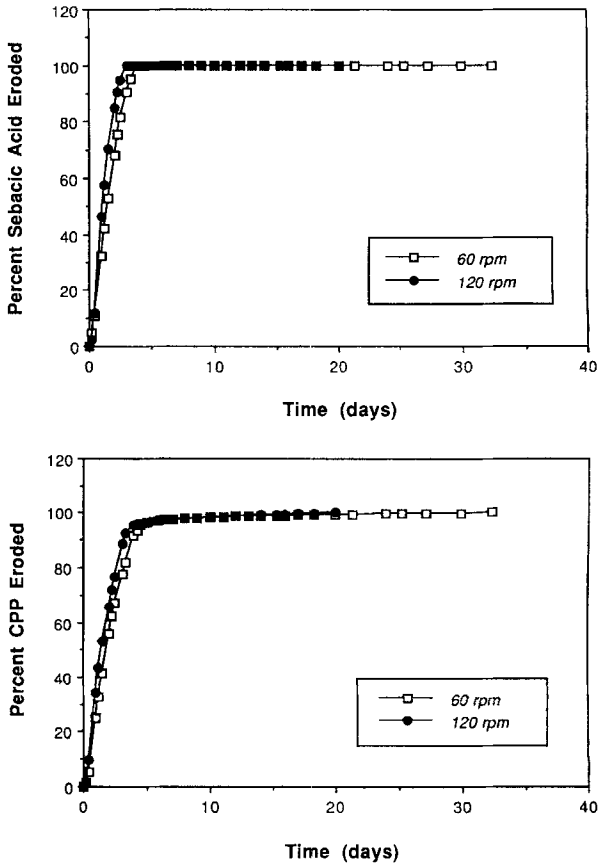

Figure 7. Erosion of *p*(CPP-SA) 20:80 wafers into 0.1 M phosphate buffer solutions at different rotational speeds for agitation. Differences in rates of erosion are insignificant.

seemed to coincide with the time at which the inflammatory process dissipated.

DISCUSSION

In vivo versus *in vitro* correlations

The current study documents the *in vivo* erosion profile of *p*(CPP-SA) 20:80 polymer under a variety of conditions, including polymer degradation in the presence of BCNU, 9-L-gliosarcoma, and an absorbable hemostatic agent. In all cases, polymer wafers completely degrade within 6–8 weeks.

The approximate time of polymer degradation has been visualized through computerized tomography scanning and magnetic resonance imaging[43] in monkeys. Similarly, radiologic images in clinical studies[1] have been helpful in providing an indication of polymer degradation. Although not providing the quantitation of the current study, these observations are consistent with the results presented in this article, in that polymer wafers were generally no longer visualized by 2 months.

We found that the initial degradation of *p*(CPP-SA) 20:80 polymer wafers occurred more slowly in the rat brain than *in vitro* at pH 7.4. The phase of early slowing was particularly marked in the release of CPP monomer from the vicinity of the polymer matrix (Fig. 1). This phenomenon was found under a variety of experimental conditions, including loading the polymer with the anti-neoplastic drug BCNU (Fig. 2), and implanting the drug-loaded polymer in the presence of 9-L-gliosarcoma (Fig. 3). The reasons for the slowed degradation of CPP *in vivo* are not clear. However, this lag in degradation occurred only in the first week following implantation. It had no bearing on the ultimate time by which polymers completely degraded when compared with *in vitro* studies at physiologic pH ranges. In all conditions tested, the polymer *p*(CPP-SA) 20:80 degraded completely by 6–8 weeks *in vivo*.

Clinical implications

Our results suggest that long-term polymer erosion rates are insignificantly affected by drug loading, the presence of 9-L-gliosarcoma, and the use of a low

pH absorbable hemostat (Surgicel®). These findings suggest that, intrinsically, the polymer *p*(CPP-SA) 20:80 should completely degrade within 6–8 weeks *in vivo*. In the rat model, biologic factors, such as local tissue necrosis induced by BCNU and an altered microenvironment secondary to products of tumor metabolism, seem to have had no effect on the time of complete polymer degradation when compared with *in vitro* studies; we suspect this also to be the case in the clinical setting.

The *in vitro* effects of pH on polymer degradation have been well documented in the current study, and both CPP and SA were found to erode from the wafers more slowly with increasing acidity (Fig. 6). The pH dependence of polymer degradation have been previously reported, including pH dependence of polyCPP (pCPP) at high pH ranges (pH 7.4–10.0)[32]; *p*(CPP-SA) degradation characteristics for various ratios of the CPP and sebacic acid monomers at pH 7.4[32]; and *p*(CPP-SA) 30:70 degradation at pH 2, 5, 7.4, and 11.[33] However, in these studies, degradation kinetics followed only the degradation of the CPP monomer. Simultaneous degradation of CPP and SA monomers had been documented previously only at pH 7.4,[41] but had not been well characterized in the low pH ranges of potential clinical interest. Although *p*(CPP-SA) clearly erodes much more slowly in acidic solutions *in vitro*, our data suggest that the buffering capacity of the brain is capable of keeping local pH within an adequately narrow range so that polymer degradation rates are essentially unaffected. Such conclusions are made based on our observations that, in rats, the presence of a very low pH absorbable hemostatic agent (Surgicel®) frequently used in the clinical implantations did not markedly slow the rate of polymer degradation.

Although tumor interstitial fluid may be produced by human brain tumors, our results based on the 9-L-gliosarcoma rodent tumor suggest that the small changes in pH attributed to tumor metabolism are probably not significant in long-term polymer degradation. This is consistent with an *in vivo* measurement of brain tumor pH in patients, using [^{11}C]dimethyloxazolidinedione and positron emission tomography, which demonstrated that the pH microenvironment of brain tumors was not more "acidic" than that of normal grey or white matter.[44]

In vivo versus *in vitro* differences in degradation

Further investigation is required to elucidate the cause for slowed *in vivo* CPP erosion in the days immediately following polymer implantation, and the technical causes for slowed polymer erosion noted occasionally in clinical trials.

In the current study, we document the inflammatory response to *p*(CPP-SA) as a function of time (Fig. 8). To our knowledge, there exist few studies that quantitatively document histologic changes over time in parallel with polymer degradation. It is interesting to note here that the inflammatory response to polymer implantation was most marked in the first week, coinciding with the initially slowed erosion of CPP. However, it must be emphasized that these results are strictly correlative. Further work is needed to identify the cause for initial slowing in CPP degradation.

The current studies suggest that the intrinsic degradation process of the *p*(CPP-SA) polymer occurs in a predictable manner *in vivo*. It is therefore likely that extrinsic factors have an important role in occasionally affecting polymer performance in the clinical setting. Our *in vitro* data demonstrate that differences in the rates of wafer dissolution occur with decreased water availability (Fig. 5). In the clinical setting, up to eight polymer wafers (200 mg each) have been implanted into a tumor resection site depending upon the size of the resection cavity, and overlapping has been permitted.[1] In certain patients, the amount of polymer implanted may be excessive for a small cavity, resulting in decreased solubility. However, an adequate number of polymer wafers must be used to ensure that a sufficient amount of BCNU is delivered to prevent tumor recurrence. The balance between these two factors has not been well studied, and further investigation is necessary to determine the minimum amount of drug needed to prevent tumor recurrence and the maximum amount of polymer to be used to prevent lengthy degradation times.

The contents of the cavitary space after resection of tumor also likely influence the rate of polymer degradation in the clinical setting. Although an air–polymer interface is initially present following implantation, by our observation of polymer implantation in clinical trials, four types of fluid can enter the cavity intraoperatively. These are: 1) extracellular fluid from brain tissue; 2) cerebrospinal fluid; 3) blood from minor hemorrhaging; and 4) saline from irrigation, which is frequently used to clear the surgical site. If an air–polymer interface is maintained for a long time after implantation, one would predict degradation to be slower than if fluid contacts the wafers. "Trapped" air in the implantation site can be identified on postoperative scans.[1]

Conclusions

Based on the experimental evidence presented, the polymer *p*(CPP-SA) remains a suitable matrix for drug delivery. A comparison between our *in vivo* and *in vitro* data enables us to suggest that clinical findings of occasional polymer remnants after wafer implantation are not due to intrinsic properties of

the polymer or to the interactive processes occurring between polymer and brain parenchyma. More likely, the apparently slowed degradation of polymer in some clinical cases represents a technical variation that is difficult to predict. Depending upon the conditions of implantation and patient variability, it is possible that these remnants are merely slowly degrading wafers that, given enough time, will eventually erode. Clinical correlations between amounts of polymer implanted, size of tumor cavity, and time of remnant retrieval are needed further to establish reasons for a slower clinical degradation in some patients.

Multiple biologic phenomena could cause a slow initial erosion of CPP monomer from the wafer. However, in the 47 rats sacrificed, no wafers were found beyond 6–8 weeks for all of the parameters evaluated. Although further studies may need to be performed to test the possibility of interspecies differences in degradation, our data suggest that drug loading, tumor presence, and the presence of a low pH hemostatic agent have no effect on slowing wafer dissolution rates. In short, the polymer does degrade appropriately *in vivo*. Further investigation will be required to determine solubility and water availability conditions in the brain, particularly with regard to the amount of polymer loading permissible in a small tumor resection site.

This work was supported by NIH Grant CA 48508 and by a Johnson and Johnson Research Fellowship from the Harvard-M.I.T. Division of Health Sciences and Technology. The authors thank Dr. Abraham Domb for providing polymer wafers, Dr. Robert Marini, Michael Pinn, Betty Tyler, and Sandra Tan for their technical assistance, and Dr. Elizabeth Goad for her assistance with histology.

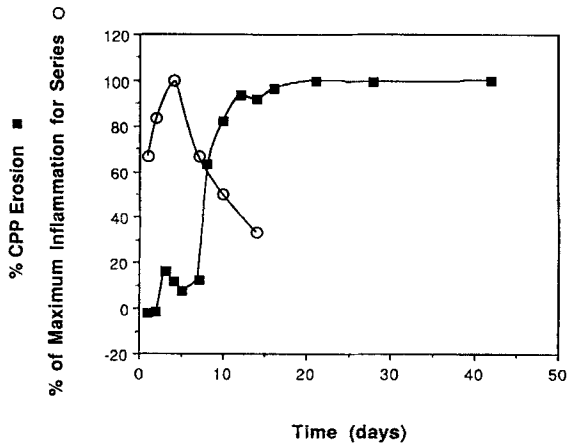

Figure 8. Erosion of p(CPP-SA) 20:80 wafers in the rat brain plotted with corresponding inflammatory reaction. States of inflammation may be correlated with degradation rates.

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Received July 20, 1993
Accepted October 15, 1993