Controlled release of 1-hydroxyethylethidene diphosphonate: in vitro assessment and effects on bioprosthetic calcification in sheep tricuspid valve replacements

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Summary

Calcification (CALC) is the most frequent cause of the clinical failure of bioprosthetic valves (BHV’s). Controlled-release (paravalvar) administration of the anticalcification agent ethanehydroxydiphosphonate (EHDP), as either Na2EHDP or in combination (1:1) with the less soluble CaEHDP, from a silicone rubber matrix (20% w/w EHDP) was studied both in vitro and in vivo for the prevention of BHV CALC. Seventeen sheep (6–7 months old, male, Suffolk) underwent tricuspid valve replacement using Hancock I, 25 mm porcine aortic bioprostheses. BHV explant evaluation after 16–20 weeks revealed that two of the 7 control BHV were calcified (139 ± 20.8 μg Ca2+/mg of tissue), while none of the 9 BHV retrieved from animals receiving controlled release EHDP demonstrated CALC (4.41 ± 1.09 μg Ca2+/mg of tissue). No adverse effects of EHDP on bone or calcium metabolism were noted. The cumulative percent of EHDP released per electron microprobe analysis was 40.4% ± 9.68 (Na, CaEHDP) to 79.0% ± 4.82 (Na2EHDP) in vivo compared to 35.7% ± 7.72 and 78.6 ± 11.1 in vitro, respectively. Assessment of the Young’s modulus (Y) using thermomechanical analysis (TMA) revealed a 1.5-fold (Silastic Q7-4840) to 9.5-fold (Silastic 382) increase in Y following drug loading. The Y for explanted, Silastic Q7-4840 polymer matrices ranged from 2.84 × 10⁴ to 5.57 × 10⁵ dyne/cm². In vitro osmotic related matrix swelling of the Na2EHDP loaded, unsealed matrices (20% w/w) after 75 days was minimized to a 35.8% increase in weight due to coincorporation of CaEHDP with Na2EHDP in a 1:1 ratio and was further reduced (22.2% increase in weight) by sealing 76% of the releasing surface, compared to Na2EHDP matrices which demonstrated a 414% and 141% increase in weight, respectively.

Introduction

Bioprosthetic heart valves (BHV) fabricated from either glutaraldehyde-preserved porcine aortic valve leaflets or pericardium have been
widely used as replacements for diseased cardiac valves since 1970 (Barnhart et al., 1982a; Schoen and Levy, 1984; Schoen, 1987). However, the principal failure mode of BHV is sterile degeneration due to calcification (CALC) (Schoen and Levy, 1984; Schoen, 1987; Milano et al., 1984; Schoen and Hobson, 1985a). Despite the importance of this problem, the pathophysiology of BHV calcification is incompletely understood (Schoen et al., 1985b), and there are no satisfactory means for its prevention.

BHV CALC has been investigated in experimental animals using orthotopic valve replacements or conduit-mounted valves in sheep and calves (Barnhart et al., 1982b; Levy et al., 1983a; Thurbrikar et al., 1983; Gallo et al., 1987), and subcutaneous implants in mice (Levy et al., 1983b), rats (Levy et al., 1983c and 1985a), and rabbits (Fishbein et al., 1982). The subcutaneous and circulatory models simulate many of the pathologic features of long-term clinical implants.

Ethanehydroxydiphosphonate (EHDP) has been shown to effectively inhibit experimental BHV CALC (Levy et al., 1985b and c) but s.c. administration of EHDP to rats at doses greater than 15 mg/kg/day (Levy et al., 1987a) resulted in adverse effects on overall somatic growth, bone development, and serum Ca$^{2+}$ levels. However, controlled release of EHDP from polymeric matrices coimplanted with BHV subdermally in rats prevented CALC without adverse effects by using minimal local doses [> 0.1 mg/kg/24 h] (Levy et al., 1985b and c).

The purpose of the present study was to formulate EHDP controlled release matrices for implantation with orthotopic BHV in the circulation, assess their in vitro release, and in vivo efficacy and function. Thus, these experiments assessed: (1) the efficacy of the polymer–drug formulation with regard to inhibition of BHV CALC following tricuspid valve replacements in sheep, (2) the release profile of EHDP from the implanted matrix comparing in vitro to in vivo release, (3) the changes in viscoelastic properties of the polymer matrix resulting from drug loading and circulatory implantation, and (4) the magnitude of osmotic-induced matrix expansion.

**Materials and Methods**

Polydimethylsiloxane (Silastic 382), Silastic Q7-4840 and reinforced dacron Q7-4840 sheeting (plain weave, 0.007 in thick) were provided by Dow Corning (Midland, MI). Disodium 1,1-hydroxyethylidene diphosphonate (Na$_2$EHDP) was provided by Norwich Eaton (Norwich, NY). The Na$_2$[1$^{14}$C]EHDP (spec. act. = 48.9 μCi/mmol) and the calcium salt of EHDP were provided by Procter and Gamble, Inc. (Cincinnati, OH). Atom light scintillation solution was obtained from New England Nuclear (Billerica, MA).

**Controlled release matrices**

Carrier-free radiolabelled Na$_2$[1$^{14}$C]EHDP, appropriately diluted with unlabelled Na$_2$EHDP to yield a specific activity of 1830 dpm/μmol EHDP, was levigated into polymer formulations for determining in vitro release of Na$_2$EHDP. For implants with calcium EHDP incorporated with Na$_2$EHDP, a 1 : 1 ratio of the two salts was used at the same total weight percentages as below. Circular (i.d. = 25 mm, o.d. = 31 mm) controlled release matrices were formulated by levigating disodium EHDP (90–106 μm particle size) into either Silastic 382 or Silastic Q7-4840 at a 20 or 30 wt. % concentration.

A typical circular controlled release matrix is shown in Fig. 1. Each circular implant was fabricated with a wall thickness of 3 mm. The height of the polymer–drug ring was 3.5 mm, and sealing of all the surfaces (76% of total available surface area) except the internal circumference with a non-drug-containing layer (500 μm) of Silastic Q7-4840 or 382 resulted in a total initial releasing surface area of 2.75 cm$^2$. Formulations fabricated from Silastic 382 were catalyzed by adding 2 drops of the catalyst (stannous octanoate) to 2 g of total formulation and then compression-molded under 2000 p.s.i. at room temperature in stainless-steel molds on a Carver Press equipped with heated platens (model C, Fred S. Carver, Inc., Menomonee Falls, WI). Controlled release matrices fabricated from Silastic Q7-4840 or 382 were compression-molded as above and heat-cured at 120°C Dacron-reinforced sheeting was thermally bonded (T = 120°C) to the top and bottom surface of the
Fig. 1. A silicone rubber-EHDP controlled-release matrix positioned at the circumferential support of a porcine aortic bioprosthesis. Reproduced with permission from *Replacement Cardiac Valves*, Bodnar E. and Frater, R. (Eds.) Pergamon, Elmsford, NY, 1988.

polymer ring with plain polymer base. A typical matrix prior to implantation contained 149 ± 8.69 mg of EHDP.

**In vitro release of EHDP**

The release profiles of EHDP from silicone rubber drug delivery matrices were determined by calculating the diphosphonate-associated phosphorus (P) depleted from the polymer matrix as a function of time using electron microprobe analysis. Electron microprobe analysis was conducted using a Super 8000 Analyst equipped with a Kevex (Foster City, CA) system for elemental localization which was coupled with a scanning electron microscope (Hitachi, Model S-570, Santa Clara, CA). The Super 8000 Analyst and scanning electron microscope were acquired under Grant No. BSR-83-14092 from the National Science Foundation.

Matrices were incubated at 37°C in 20 ml of a physiologic buffer (0.10 M NaCl in 0.05 M HEPES, pH = 7.4) and a center, cross-sectional cut of the matrix was obtained at 0, 1, 2, 3, 4, and 5 months. The samples taken at the various time points were allowed to dry at room temperature before the analysis. The samples were mounted on stainless-steel stubs and sputter-coated with carbon. Samples were analyzed for phosphorus and silicon. Emitted X-rays for each element were collected for 1.5 min. The counts associated with the area under a peak for each element were calculated by a deconvolution routine contained in the software program Quantex 1 (Mykelbust et al., 1979).

The amount of silicon in the silicone based polymers was used to normalize the phosphorus depletion by computing the ratio of the counts associated with the phosphorus peak to the counts observed for the silicon (Si) peak for each sample at the above specified time points and were compared with a series of precisely formulated standards of known composition (5%, 10%, 15%, 20%, and 30% w/w EHDP in silicone rubber). The results obtained by microprobe analysis were also correlated with data obtained from parallel radioactive in vitro release studies using Na₂[^14]C]EHDP and additional studies in which the decrease in weight of the polymer rings was observed with time. The solubilized Na₂[^14]C]EHDP was counted for radioactivity on a Beckman liquid scintillation counter (model 3801, Berkeley, CA).

**Tricuspid valve replacement in sheep**

Twenty-one sheep (6–7 ± 3 months, male, Suffolk, 42–46 kg) underwent tricuspid valve replacement with Hancock I (25 mm) bioprosthetic heart valves (Johnson & Johnson Cardiovascular, Anaheim, CA). Autoclaved silicone rubber matrices were coimplanted with the BHV (Johnson et al., 1988). The matrices contained Na₂EHDP, Na₂EHDP:CaEHDP (1:1), or no drug. Data from two previous control animals were also compared with these implants (Levy, 1987b). Each matrix ring was placed around the stent posts of the bioprosthesis directly under the sewing cushion. Thus, perianular sewing ring sutures also secured the matrix to the prosthesis.

**Retrieval analysis**

At necropsy, the BHV’s were removed and examined grossly, photographed, and then radiographed. A representative section of the valve cusp from the free edge to the point of attachment on the stent post was immediately fixed in a cacodylate-buffered 2.5% glutaraldehyde-2% paraformaldehyde solution buffered at pH 7.2 (Karnovsky, 1965) for 24 h and then dehydrated
in graded ethanol solutions prior to embedding in glycolmethylmethacrylate (JB-4, Polysciences, Warrington, PA). Sections (2–3 μm) were stained with hematoxylin and eosin for overall morphologic analyses and von Kossa’s reagent for calcium phosphate (Levy et al., 1985b). The remaining portion of each cusp was prepared for quantitative analysis of calcium using atomic absorption spectroscopy (Levy et al., 1980 and 1983c). The polymeric drug delivery ring was detached from the sewing ring of the Hancock I bioprosthetic heart valve, weighed, and frozen until electron microprobe analysis.

Representative specimens of lung, liver, kidney, spleen, and myocardial tissue adjacent to the implant valves were also obtained at necropsy. Since systemically administered diphosphonates at doses of 15 mg/kg/day or more cause bone toxicity in rats (Levy et al., 1985b and 1987a), the proximal femoral head was removed from all control and treated sheep at necropsy. All specimens were stored in 10% neutral buffered formalin until the time of histologic analysis by light microscopy.

Osmotic-mediated matrix expansion

EHDP matrices of various compositions were formulated to study the effects on swelling of sealing 76% of the surface area of the matrices with drug-free polymer base, incorporating varying initial amounts of EHDP (20% w/w vs 30% w/w), and varying the content of the less soluble calcium EHDP coincorporated with Na₂EHDP. The percent weight increase was monitored as a function of time with incubations at 37°C in a physiologic buffer (0.10 M NaCl in 0.05 M HEPES, pH = 7.4) and weighing the rings on a laboratory balance (Galaxy, Model G400, Florham Park, NJ).

Thermomechanical analysis of polymeric implants

A Metler thermomechanical analyzer (TMA) (Model TMA-40, Heightstown, NJ) was used to assess elastic properties of the various matrix formulations by applying standardized loads to linear segments of the polymer matrices. The Young’s modulus (Y) was calculated for Silastic polymer (Silastic Q7-4840 and Silastic 382), with and without dispersed drug, as well as samples of explanted polymeric formulations retrieved after 5 months of circulatory implantation as part of sheep tricuspid valve replacements.

Results and Discussion

The present study demonstrated an absence of CALC in all EHDP controlled-release treated BHV’s after 120–150 days (Table 1). However, only 2 of 7 non-treated explants were calcified, indicating deficiencies in the CALC model for testing this approach. Nevertheless, there was comparable EHDP release in vitro and in vivo, and matrix swelling was minimized through sealing 76% of the releasing surface with drug-free polymer and coincorporation of the poorly soluble calcium salt of EHDP. In addition, the Young’s moduli for explanted matrices containing Na₂EHDP dispersed in Silastic Q7-4840 (20% w/w) were noted to be less than non-drug containing Silastic Q7-4840.

In vivo results

Six of the 21 sheep were excluded from the study because of perioperative death. However,

<table>
<thead>
<tr>
<th>Drug/polymer formulation</th>
<th>% EHDP released in vitro</th>
<th>% EHDP released in vivo</th>
<th>Tissue Ca²⁺ (μg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>139 ± 20.8 c</td>
</tr>
<tr>
<td>Calified</td>
<td>-</td>
<td>-</td>
<td>2.07 ± 0.27</td>
</tr>
<tr>
<td>Na₂EHDP/silicone rubber</td>
<td>78.6 ± 11.1</td>
<td>79.0 ± 4.82</td>
<td>5.74 ± 1.35 d</td>
</tr>
<tr>
<td>Na-CaEHDP (1:1)/silicone</td>
<td>35.7 ± 7.72</td>
<td>40.4 ± 9.68</td>
<td>2.74 ± 0.64</td>
</tr>
</tbody>
</table>

Numbers of determinations in parentheses.

a Determined by electron microprobe analysis, Na₂[14C]EHDP release, and reduction in matrix weight.
b Determined by electron microprobe analysis.
c From Levy et al. (1987b); values are mean ± S.E.M.
d Includes 2 cases of bacterial endocarditis at 16 weeks.
none of the sheep died as a result of prosthetic valvular dysfunction. Two additional sheep died suddenly at 16 weeks and were noted to have bacterial endocarditis. One additional animal was excluded from the EHDP controlled-release group due to sudden death and subsequent contamination of the explant. All of the remaining 12 animals (7 treatment, 5 control (2 of the 5 control animals are from Levy et al., 1987b)) were electively euthanized at 20 weeks.

None of the explanted BHV with drug delivery matrices had detectable CALC as determined by radiography, light microscopy, and leaflet Ca$^{2+}$ analysis with atomic absorption spectroscopy (Table 1). However, only two of the 7 non-treated valves, from previous control animals, were calcified. Nevertheless, animals implanted with EHDP matrices demonstrated no detectable diphosphonate-related adverse effects, as determined by light microscopy of the femoral epiphyseal bone biopsies.

Although previous work (Levy et al., 1985b and c; Golomb et al., 1986a and b) had demonstrated that the controlled release of approximately 10–30 \( \mu \text{g EHDP/day/tissue leaflet} \) (avg. tissue weight = 8 mg) was sufficient to inhibit CALC of bovine pericardial or porcine aortic tissue implanted subdermally in rats, it would be expected that larger amounts of EHDP would be required when delivered locally in the circulation. Although the amount (550–775 \( \mu \text{g EHDP/day} \)) of EHDP delivered in vivo in the present study was sufficient to inhibit BHV CALC (Levy et al., 1987a), efficacy could not be definitely assessed due to the sporadic calcification noted in the control group (Table 1). The present study confirms the large variability in the measured calcium leaflet concentration observed by others (Barnhart et al., 1982a) following tricuspid valve replacement in sheep.

Furthermore, the hemodynamic stresses affecting the orthotopic valve replacements in the tricuspid position in the present study might have contributed to lack of BHV CALC observed in explanted valves. Mitral valve replacements, which experience greater circulatory stresses, have been shown to calcify more extensively than tricuspid bioprostheses following implantation into the circulation of juvenile sheep (Jones et al., 1986; Shemin et al., 1988).

**Osmotic-mediated matrix expansion**

Time-dependent matrix expansion due to osmosis-related fluid uptake was reduced in vitro by sealing 76% of the surface area of each matrix, and was further limited with coinorporation of CaEHDP as shown in Fig. 2.

The characteristic matrix swelling and deswelling stages reported by others (Di Colo et al., 1980, 1984, 1986; Carelli et al., 1986) were observed in the polymeric implants in the present study. Previous work by others has demonstrated that for water-soluble drugs dispersed in PDMS polymers, the extent of matrix swelling, \( \gamma \), defined as the ratio of swollen to dry weight of a matrix containing a water-soluble additive, has been used to characterize stages of matrix swelling and matrix deswelling (Di Colo et al., 1980, 1984, and 1986; Carelli et al., 1986) (Fig. 2). Initially, as buffer, water, or physiologic fluids are osmotically taken up by the matrix, \( \gamma \) increases. At some point in time, the value of \( \gamma \) plateaus and then begins to decrease resulting in a parabolic curve when plotted against time of fluid uptake (Di Colo et al., 1980, 1984, and 1986; Carelli et al., 1986). The time for the value of \( \gamma \) to reach a maximum value...
in the present in vitro studies ranged from 4 to 29 days (Fig. 2).

Sealed matrices explanted from sheep demonstrated osmotic-related swelling comparable to the in vitro results. The percent increase in weight of explanted sealed polymers were 162% ± 34.5 (Na₂EHDP) and 69.5% ± 1.35 (Na,CaEHDP) compared to 141% (Na₂EHDP) and 22.2% (Na, CaEHDP) for sealed polymer matrices studied in vitro, respectively.

**Controlled release of EHDP**

Matrices containing Na₂EHDP and CaEHDP (1 : 1) released in vitro less EHDP after 20 weeks than did those matrices containing only Na₂EHDP as determined by electron microprobe analysis, matrix weight change, and release of Na₂[^14C]EHDP.

A typical profile of the cumulative percent of drug (Na, CaEHDP in Silastic 382 (30% w/w)) released in vitro over a 20 week period as determined by electron microprobe analysis is shown in Fig. 3. The 3 sealed areas of an individual cross-sectional specimen examined in vitro by electron microprobe analysis for EHDP release demonstrated background phosphorus levels versus time for all EHDP matrix formulations. Thus, EHDP release from the matrix formulations proceeded in one dimension only.

In formulations where a 1 : 1 ratio of Na₂[^14C]EHDP:CaEHDP was incorporated in the polymer, the cumulative percent of Na₂[^14C]EHDP released from the matrix following 20 weeks incubation was in close agreement with the total percent of EHDP (Na₂EHDP and CaEHDP) released as determined by electron microprobe analysis. This would suggest that the less soluble CaEHDP undergoes a delayed dissolution and hence, negligible release from the matrix interior in the 20 week period. However, although no attempt was made in the present study to precisely quantitate the relative ratios of the Na₂EHDP and CaEHDP that had been released, it can be noted in Fig. 3 that Na₂EHDP was the salt form primarily released from the 1 : 1 matrix formulations; the CaEHDP acting as a relatively less soluble coexcipient [Na₂EHDP's aqueous solubility is approximately 1000 times that of CaEHDP (Golomb, G., Smith, M., unpublished data)]. The relative release rates of sodium EHDP and calcium EHDP in the formulation used in the present study have been previously described in detail (Golomb et al., 1987).

Previous research has shown that the mechanism of release for EHDP from silicone rubber occurs by absorption of a solvent/fluid into the matrix interior resulting in dissolution of the drug particles and subsequent diffusion of the drug from the polymeric matrix via a network of tortuous channels and pores created by dissolved drug particles (Golomb et al., 1986a; Levy et al., 1985c; Bawa et al., 1985). Neither Na₂EHDP nor CaEHDP are soluble in the hydrophobic silicone rubbers used in the present study (Golomb et al., 1986b and 1987; Levy et al., 1985b and c). Determination of the cumulative percent of EHDP released after 20 weeks by calculation of the decrease in matrix weight after drying to a constant weight, resulted in an approximate 7–10% underestimation of total drug released compared to the percent EHDP released as determined by electron microprobe analysis (Fig. 3). Furthermore, it was assumed that the reduction in the initial weight of the ring, following oven-drying to a constant weight to remove buffer, was due to release of the

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**Fig. 3.** Typical in vitro release profiles of EHDP from a silicone rubber-EHDP circular drug delivery matrix [30% w/w Na, CaEHDP (1 : 1)] ( ), Determination by electron microprobe analysis; ( ), determination by incorporation of Na₂[^14C]EHDP; ( ), determination by following overall matrix weight.
dispersed active agent(s) and not due to deterioration or destruction of the cured silicone rubber polymer matrix.

In vivo explant analysis of EHDP matrices using electron microprobe analysis revealed 79.0 ± 4.82 cumulative percent EHDP released for Na$_2$EHDP matrices and 40.4 ± 9.68 cumulative percent EHDP released for matrices containing Na-CaEHDP (1:1) after 120–150 days. These results were comparable to the in vitro data (Table 1). However, as emphasized above and previously (Johnston et al., 1988), matrix CaEHDP would be expected to have continued to release for more than 2 years using the present formulation.

**Thermomechanical analysis of polymeric implants**

Thermomechanical analysis results revealed that the Young’s moduli (Y), or slopes of the respective stress-strain curves as shown in Fig. 4, of EHDP-Silastic matrices were greater than those measured in the non-drug containing Silastic samples. However, explanted matrices (20% w/w Na$_2$EHDP or Na-CaEHDP in Silastic Q7-4840) were demonstrated to have values of Y less than non-drug loaded Silastic Q7-4840, indicating perhaps, that the matrices explanted after 5 months in the circulation were demonstrating material fatigue.

While the greater stresses applied to the matrices implanted in the circulation were below the ultimate failure stress or yield stress, the continuous, cyclic stress-strain patterns may have resulted in the initiation of cracks or voids in the matrices (Schott, 1983; Sperling, 1986). On repeated stressing, these tiny flaws or cracks might have slowly propagated throughout the entire matrix, representing sites where ultimate failure or rupture of the polymer matrix could potentially occur. Extensive propagation of cracks or voids would result in a low tensile strength or weakening of the polymer matrix (Schott, 1983; Sperling, 1986). Weakening of the drug-loaded polymer matrix due to extensive propagation of cracks could potentially give rise to lower values of Y for explanted specimens.

Propagation of cracks or voids in a polymer matrix (20% w/w Na$_2$EHDP in Silastic Q7-4840) arising from deformation due to osmotic-related swelling of the drug-loaded matrix would be expected to result in a much weaker polymer than a Silastic Q7-4840 matrix incorporating a 1:1 ratio of Na-CaEHDP (20% w/w). It can be noted in Fig. 4 that the explanted polymer matrices containing 20% w/w Na-CaEHDP dispersed in Silastic Q7-4840 had an approximate 20-fold larger value of Y than an explanted polymer specimen containing 20% w/w Na$_2$EHDP in Silastic Q7-4840. Thus, osmotic effects in the latter matrix composition may have contributed to an overall weakening of drug-loaded polymer matrices implanted in the circulation for 5 months as compared to non-implanted, control (non-drug loaded) Silastic Q7-4840 polymer.

**Strategies to inhibit BHV CALC**

Local, controlled release of diphosphonate into BHV implants for use in the circulation represents a novel approach to inhibit BHV CALC. It has been shown that localized, controlled release of diphosphonate (EHDP) using a 2-week osmotic pumping device (ALZET, Alza Inc., Stanford, CA) was effective at inhibiting BHV CALC at a dose of 5 mg/kg/day and was not associated with adverse effects (Levy et al., 1985b).

Once the effectiveness of locally delivered diphosphonate was established, the search for implant materials (biocompatible polymers) that
would achieve a longer therapeutic duration was initiated. It was reported that EVA copolymer could be used for the controlled release (> 600 h) of EHDP in vitro (Levy et al., 1985c). A further prolongation in drug delivery at a controlled rate has been demonstrated by judicious selection of initial drug load and drug solubility by coinocporation of the poorly soluble calcium salt of EHDP in polydimethylsiloxane (Golomb et al., 1986b and 1987). Recent studies have been directed at still furthering drug delivery by appropriate membrane coating with non-drug containing polymer (Golomb et al., 1986b and 1987). All of these strategies have been effective in sustaining release of EHDP from various biocompatible polymeric matrices to inhibit BHV CALC.

Conclusions

The present study has demonstrated the novel use of controlled release EHDP for inhibition of BHV CALC in sheep. Advantage was taken of previous work (Golomb et al., 1986b and 1987) using the poorly soluble calcium salt of EHDP codispersed with Na₂EHDP in Silastic matrices to reduce osmotic-mediated matrix expansion and to potentially increase the duration of EHDP controlled release. Although efficacy could not be definitely assessed, matrix release in vivo corresponded with in vitro results, delivering dosages known to be efficacious in the rat subdermal model of BHV CALC without adverse side effects. Osmosis-related matrix swelling was successfully limited by surface sealing and coinocorporation of CaEHDP. The Young's moduli of the explanted controlled-release matrices formulated with Silastic 382 were intermediate between those of drug-loaded matrices and drug-free Silastic 382, indicating a return to a native viscoelastic state with in vivo release. However, explanted controlled release matrices fabricated using Silastic Q7-4840 appeared to have undergone material fatigue and weakening of the polymer matrix, especially matrices containing 20% w/w Na₂EHDP in Silastic Q7-4840 where osmosis-related matrix swelling might have contributed to the propagation of cracks and voids in the polymer matrix.

Acknowledgments

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References


