POLYMERS AS BIOMATERIALS

Edited by

Shalaby W. Shalaby
ETHICON, Inc.
A Johnson & Johnson Company
Somerville, New Jersey

Allan S. Hoffman
Buddy D. Ratner
and
Thomas A. Horbett
University of Washington
Seattle, Washington

PLENUM PRESS • NEW YORK AND LONDON

A Division of Plenum Publishing Corporation
233 Spring Street, New York, N.Y. 10013

POLYMER BASED DRUG DELIVERY:

MAGNETICALLY MODULATED AND BIOERODIBLE SYSTEMS

E.R. Edelman[ab], R.J. Linhardt[c], H. Bobeck,

J. Kost[bd], H.B. Rosen, and R. Langer[bde]

a Medical Engineering and Medical Physics Program, Harvard-MIT, Division of Health Sciences and Technology Cambridge MA 02139, USA

b Department of Surgical Research, Children's Hospital Medical Center, Boston MA 02115, USA

c Division of Medicinal Chemistry, College of Pharmacy University of Iowa, Iowa City, IA 52242, USA

d Department of Food and Nutrition, Massachusetts Institute of Technology, Cambridge MA 02139, USA

e To whom correspondence should be adressed at MIT

INTRODUCTION

Polymer based drug delivery systems have been considered for many applications to supplement standard means of medical therapeutics. Currently nitroglycerin, scopolamine, progesterone, and pilocarpine [1] are being administered on a chronic basis from such devices. These delivery systems are less complex than mechanical pumps and smaller because drug can be stored as a dry powder within the polymer matrix. Recent advances have shown that polymeric devices may be utilized for very large molecular weight drugs [2], for drugs that must be delivered in minute quantities [3], and at zero order kinetics [4]. None-the-less two very important problems remain to be

answered. First, virtually all of these systems display rates of release that decay with time or are at the very best a constant function of time. None of them allows for control of drug release once the device has been implanted and release intiated. Second, after implantation and depletion of incorporated drug, these systems must be removed, as they are for the most part not biodegradable. Those polymers that have been proposed for biodegradable drug delivery systems generally progessively loosen because erosion is from the entire matrix bulk instead of just the surface. The result is that neither the rate of drug release nor polymer biodegradation is constant or predictable. This paper discusses ongoing research in our laboratory in these two areas.

REGULATION OF DRUG RELEASE FROM POROUS POLYMERS BY OSCILLATING MAGNETIC FIELDS

Ethylene-vinyl acetate copolymer (EVAc) is already used as the basis of polymeric delivery devices for low molecular weight drugs such as pilocarpine and progesterone. The material has been shown to be highly biocompatible [6] and suitable for use with macromolecules [2,5]. Recent investigators [7] have used them to formulate insulin delivery systems, and have controlled the blood sugars of diabetic rats for 120 days with an implant of 0.06 cc. Earlier studies showed that release rates from these systems could be regulated by the application of an oscillating magnetic field [8]. We now report on some of the important factors controlling modulated release of a macromolecule, bovine serum albumin (BSA), from such matrices.

Methods

The procedure for preparing the matrices was modified from earlier methods [8]. Polymer casting solution was made by dissolving EVAc in methylene chloride to achieve a 10% (w/w) solution. Powdered protein which had been seived to contain particles between 149 and 250 micrometers, was mixed with ten ml. of the casting solution. The suspension was poured onto a leveled glass mold which had been previously cooled by placing it on dry ice for five minutes. The mold remained on the dry ice throughout the procedure. Immediately following the pouring of the polymer-protein mixture, magnetic stainless steel spheres or beads were arrayed on the already cast layer using a specially constructed device. The beads were an alloy containing 79.17% iron, 17% chromium, 1% carbon, 1% manganese, 1% silicone, 0.75% molybdenum, 0.4% phospohrus, and 0.4% sulfur (Permag Northeast, Billerica, MA).

The loading device consisted of two rectangular plates of

plexiglass with identical arrangements of 131 holes, 1.8 mm in diameter spaced three mm apart. When the plates were shifted with respect to each other such that the upper and lower holes were offset, the magnetic beads rested in the holes of the top plate against the bottom. The plates could then be positioned over the mold and aligned such that the spheres fell in uniform array through the now aligned holes. Fifteen to 30 seconds after the magnetic beads were added, a top layer of polymer-protein mixture identical to the first layer was cast in the mold, as well. The mixture was left to solidify for ten minutes and then transferred to a -20°C freezer for 48 hours followed by drying at 20°C under houseline vacuum (600 millitorr) for an additional 24 hours. Final samples, one x one x 0.2 cm squares, were cut from the larger unit such that they contained nine magnetic spheres each. Paraffin (Fischer Scientific, paraplast) was melted then applied with a glass pipette to all but one face of the samples. Additional paraffin was used to mount each sample to the end of a polyvinylchloride rod (World Plastics, Waltham, MA) which passed through the cap of a twenty ml. glass scintillation vial. The depth of the rod within the vial was adjustable but was usually set so that the polymer slab face was one cm from the bottom of the vial. Ten ml. of 0.15 M sodium chloride or 0.1 M phosphate buffer was added and release media. Both solutions were made with double glass distilled water adjusted to pH 7.4 .

The oscillating magnetic field was generated from two five cm x five cm x 2.5 cm "Crucore-18" permanent magnets (Permag Northeast, Billerica, MA) mounted to a 1/4 inch thick plexiglass plate. This material is a complex alloy of the rare earth metal samarium cobalt which possesses a high residual induction, coercive force and maximum energy product. The magnetic moment was oriented though the top and bottom faces. The plate was attached to a motor and rotated beneath samples suspended in vials which were secured in holes in a second plexiglass plate.

BSA release from the polymer matrices was followed by absorbance at 220 or 280 nm. The media was changed before and after each field exposure and the duration noted. Rates of release were then determined by dividing the amount of protein released by this elapsed time. The ratio of the release rate under an applied field to the release rate when the field was withdrawn provided an assesment of the extent of modulation.

Results and Discussion

To assure that changes in absorbance of the release media were due to BSA alone, all of the materials involved in the experimental procedure was placed in the release media alone and then together, and then changes in absorbance determined. To

determine whether the presence of the magnetic beads within the polymer matrix would alter normal release kinetics in the absence of an applied magnetic field, only half of the samples made from the same casting contained any beads. Release kinetics were followed for over a month and found to be identical ($p<0.0001$), and fit ($R^2 = 0.998$) linearly to the square root of cumulative time, suggesting that diffusion is the predominant release determinant. Finally, to show that modulation could only be achieved when there was both an applied alternating field and embedded magnetic particles, kinetic analysis was performed in the following experiments. 1) Slabs without any beads or embedded with 1.4 mm nonmagnetic stainless steel beads were exposed to magnetic fields alternating at frequencies ranging from 0.866 to 11 Hz, and 2) slabs with magnetic beads were examined in the absence of applied fields or in the presence of DC fields [9]. None of these groups exhibited any significant modulation.

Several sets of experiments were conducted to assess the affect of different system parameters on release. In one set, release was studied from identical slabs exposed to magnetic fields at different frequencies. The frequency was altered by increasing the rotational speed of the disc on which the permanent magnets were mounted. Frequencies of either 155, 200, 290 or 325 rotations per minute were used representing magnetic fields of 5.0, 6.6, 9.5, and 11.0 Hz. The frequency strongly affected the rate of protein release. After 180 hours of release at these four frequencies increases over baseline of 133%, 150%, 450% and 733% were obtained. The average ratio of the release rates obtained in the presence and absence of applied magnetic fields reveals a linear relationship with frequency ($R^2 = 0.996$), (figure 1). The magnetic particles probably move within the elastic environment of the EVA copolymer matrix. At very low frequencies the field is not alternating fast enough to create the optimum motion and alteration of the matrix. As the oscillation frequency increases so does the frequency of motion of the beads. At some critical frequency the visco-elastic properties of the copolymer material will probably no longer allow the bead full freedom of movement. We are currently investigating modulated release in the higher frequency ranges.

The force on an object in a magnetic field is proportional to the magnetic moment of the object and the strength of the magnetic field or its spatial gradient. Therefore, we expected this system to be sensitive to changes in these parameters. When the strength of the magnetic field was decreased 43.5%, from 2000 Gauss to 870 Gauss, by increasing the distance between the field source and the samples, the release rates during the field exposed periods fell 35% . When the amplitude was returned to

its original strength the release rates returned, as well. Likewise, when a single 1.4 mm high, 1.4 mm diameter samarium cobalt permanently magnetized cylinder replaced the nine magnetic beads there was a sigificant difference in the release rates obtained in the presence and absence of magnetic fields ($p<0.0001$) (figure 2). The average ratio of the rates of release for the field exposure and field absent periods was 1.55 ± 0.35 for the beads and 12.4 ± 2.5 for the magnetized cylinders. The dependence on frequency and strength of the applied field provide two separate means of controlling the release rates from a device once implanted. In this manner, the same device could be used to deliver different amounts of drug in varying fashions, as required.

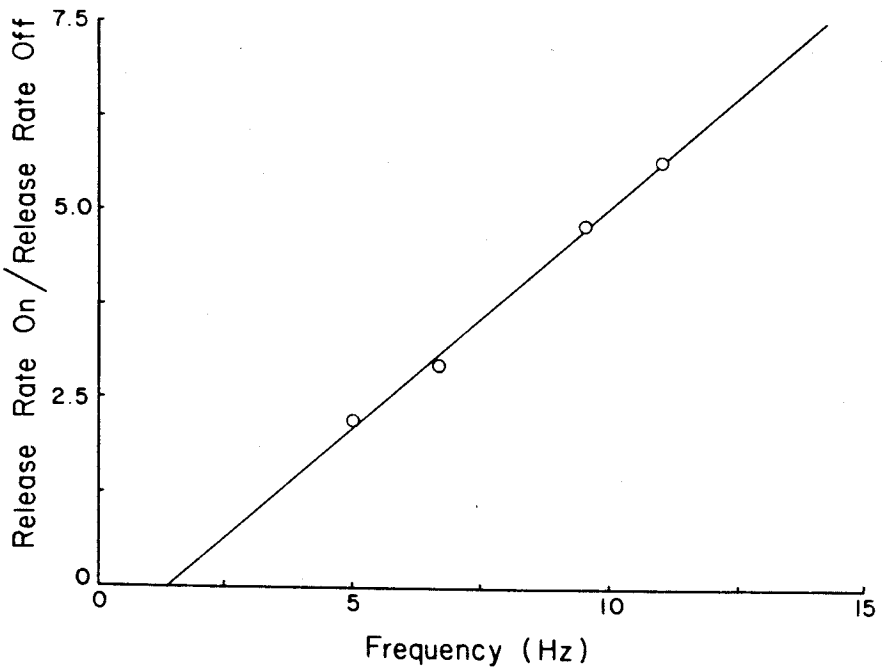

Figure 1: The average ratio of the rates of bovine serum albumin release from EVAc matrices during field applied and field absent periods plotted versus the frequency of magnetic field oscillation reveals a linear fit ($R^2 = 0.996$) with a slope of 0.59 . At 5.0 Hz the average ratio is 2.19 ± 0.46, at 6.67 Hz, 2.93 ± 1.0, at 9.5 Hz, 4.77 ± 0.63 and at 11.0 Hz, 5.62 ± 1.25 .

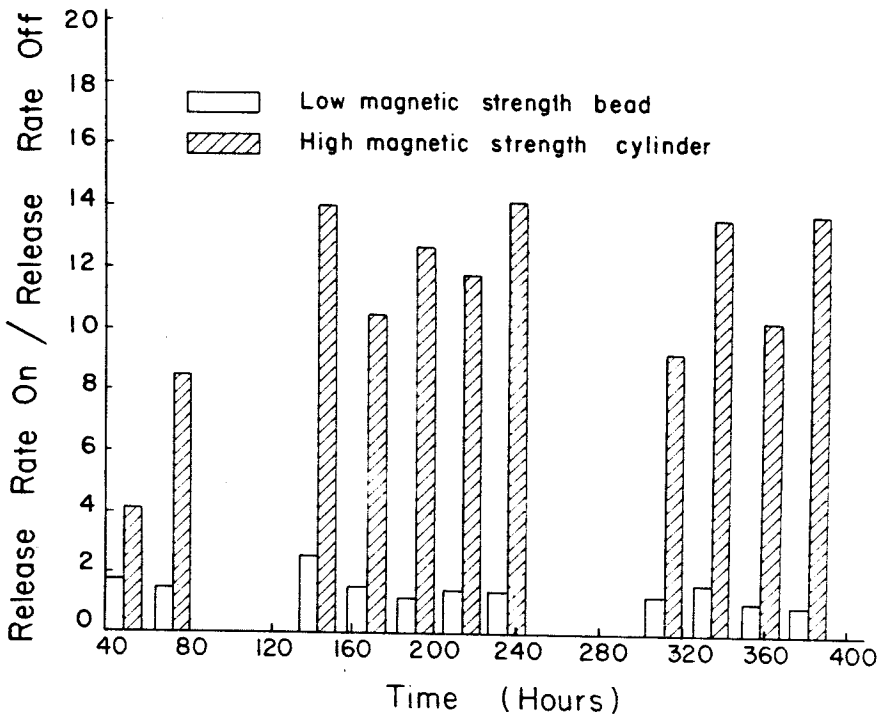

Figure 2: Ratio of rates of BSA release (averaged over all samples at a given time period) from EVAc matrices embedded with magnetic spheres (clear bars) and magnetized cylinders (hatched bars). Over the course of the entire experiment the average of this ratio was, 1.55 ± 0.35 for the bead embedded matrices and 12.4 ± 2.5 for those containing magnetized cylinders.

BIODEGRADABLE POLYANHYDRIDES

Although controlled release of drugs can be accomplished by several mechanisms [1], biodegradation of an insoluble polymer carrier to soluble monomer units offers the advantage of eliminating the need for surgical removal of the device. Controlled release matrices composed of hydrophilic biodegradable polymers such as poly(lactic acid), poly(glycolic acid), and their copolymers generally erode in a homogenous manner from the entire matrix and not just from the matrix surface [10,11]. This leads to a progressive loosening of the matrix which causes changes in both the permeability and mechanical strength of the devices during bioerosion [10,12]. It would be far more desirable if a matrix were to erode heterogeneously, from the surface first. Such erosion will lead to zero-order drug release provided that diffusional release is minimal and the overall shape of the device remains nearly constant; thus maintaining constant surface area [13]. To obtain a device that erodes heterogeneously, the polymer used should be hydrophobic yet contain water labile linkage. The only polymers designed for this purpose have been poly(orthoesters) [14]. However, because of the stability of the backbone bonds, these polymers erode slowly and require additives to promote biodegradation. The delivery systems containing additives, such as water soluble salts, swell considerably leading to diffusional release. It is possible that poly(anhydrides), which were originally synthesized as fiber forming polymers in the textile industry [15], but rejected because of their hydrolytic instability compared to polyesters of similar structure [15], might be sufficiently hydrolytically labile to produce heterogeneous erosion at rates suitable for controlled release applications.

Methods

Poly[bis(p-carboxyphenoxy) methane] (PCPM), was selected as a prototype poly(anhydride) because its erosion rate in NaOH [16] suggested to us sufficient hydrolytic labilty for drug delivery application. PCPM was synthesized by the method of Conix [16] from the mixed anhydride of bis(p-carboxyphenoxy)methane and acetic acid. The polycondensation was performed *in vacuo* at 195-210°C [16,17]. The Tg and Tm of the melt pressed polymer were determined on a Perkin-Elmer DSC-2 differential scanning colorimeter.

To formulate drug-free matrices, PCPM was ground using a Fisher Scientific Micro Mill and the resulting particles sized using sieves. PCPM particles (150-300 micrometer diameter) were melt-pressed between sheets of aluminum foil at 121.1°C and 8000

lbs. (representing from 22-81 kpsi) on a Carver Laborotory Press using shims to regulate device thickness. The matrix dimensions examined ranged from having face areas of 0.2 to 0.8 cm^2 and having thicknesses of 0.05 to 0.10 cm.

To incorporate a drug, unlabelled cholic acid from Sigma Chemical Co. (15mg) was dissolved in ten ml of ethanol. Titrated cholic acid from New England Nuclear, in 125 microliters of ethanol (2.42×10^8 DPM, S.A. = 3.72×10^{10} DPM/mg) was added to the unlabeled solution and the solution was dried in vacuo. The drug powder (10.5 wt %) was mixed with the PCPM particles and melt-pressed as above. The drug containing device was then sandwiched between two very thin (<1 wt %) drug free layers of ground PCPM to eliminate the presence of surface exposed drug particles and then repressed.

Erosion and drug release studies were performed by placing the PCPM devices weighing from 10-50 mg in glass scintillation vials containing 10 ml of 0.2 M sodium phosphate buffer (pH 7.4) at 37°C or 60°C. The buffer was periodically changed by removing the device from the vial and placing it in a vial of fresh buffer. The absorbance of the collected buffer solutions was measured on a Gilford spectrophotometer at 243 nm to detect the diacid monomer, bis(p-carboxyphenoxy) methane. Concentrations were determined from a standard curve constructed by measuring the absorbance at 243 nm of the pure diacid monomer at concentrations from 0 to 0.02 mg/ml. The polymer devices containing titrated cholic acid were eroded and the buffer solutions were analyzed on a Beckman scintillation counter.

Results and Discussion

The erosion curves for drug-free PCPM slabs at 37°C and 60°C are shown in figure 3. Both curves are characterized by an induction period followed by a linear region of mass loss at a nearly constant rate. Throughout the erosion, the devices decreased in size while maintaining their structural integrity [17] suggesting that only surface erosion is occurring.

Scraping the face of the polymer matrix did not eliminate the

BIODEGRADABLE POLYANHYDRIDES

Although controlled release of drugs can be accomplished by several mechanisms [1], biodegradation of an insoluble polymer carrier to soluble monomer units offers the advantage of eliminating the need for surgical removal of the device. Controlled release matrices composed of hydrophilic biodegradable polymers such as poly(lactic acid), poly(glycolic acid), and their copolymers generally erode in a homogenous manner from the entire matrix and not just from the matrix surface [10,11]. This leads to a progressive loosening of the matrix which causes changes in both the permeability and mechanical strength of the devices during bioerosion [10,12]. It would be far more desirable if a matrix were to erode heterogeneously, from the surface first. Such erosion will lead to zero-order drug release provided that diffusional release is minimal and the overall shape of the device remains nearly constant; thus maintaining constant surface area [13]. To obtain a device that erodes heterogeneously, the polymer used should be hydrophobic yet contain water labile linkage. The only polymers designed for this purpose have been poly(orthoesters) [14]. However, because of the stability of the backbone bonds, these polymers erode slowly and require additives to promote biodegradation. The delivery systems containing additives, such as water soluble salts, swell considerably leading to diffusional release. It is possible that poly(anhydrides), which were originally synthesized as fiber forming polymers in the textile industry [15], but rejected because of their hydrolytic instability compared to polyesters of similar structure [15], might be sufficiently hydrolytically labile to produce heterogeneous erosion at rates suitable for controlled release applications.

Methods

Poly[bis(p-carboxyphenoxy) methane] (PCPM), was selected as a prototype poly(anhydride) because its erosion rate in NaOH [16] suggested to us sufficient hydrolytic labilty for drug delivery application. PCPM was synthesized by the method of Conix [16] from the mixed anhydride of bis(p-carboxyphenoxy)methane and acetic acid. The polycondensation was performed *in vacuo* at 195-210^{o}C [16,17]. The Tg and Tm of the melt pressed polymer were determined on a Perkin-Elmer DSC-2 differential scanning colorimeter.

To formulate drug-free matrices, PCPM was ground using a Fisher Scientific Micro Mill and the resulting particles sized using sieves. PCPM particles (150-300 micrometer diameter) were melt-pressed between sheets of aluminum foil at 121.1^{o}C and 8000

lbs. (representing from 22-81 kpsi) on a Carver Laborotory Press using shims to regulate device thickness. The matrix dimensions examined ranged from having face areas of 0.2 to 0.8 cm^2 and having thicknesses of 0.05 to 0.10 cm.

To incorporate a drug, unlabelled cholic acid from Sigma Chemical Co. (15mg) was dissolved in ten ml of ethanol. Titrated cholic acid from New England Nuclear, in 125 microliters of ethanol (2.42×10^8 DPM, S.A. = 3.72×10^{10} DPM/mg) was added to the unlabeled solution and the solution was dried in vacuo. The drug powder (10.5 wt %) was mixed with the PCPM particles and melt-pressed as above. The drug containing device was then sandwiched between two very thin (<1 wt %) drug free layers of ground PCPM to eliminate the presence of surface exposed drug particles and then repressed.

Erosion and drug release studies were performed by placing the PCPM devices weighing from 10-50 mg in glass scintillation vials containing 10 ml of 0.2 M sodium phosphate buffer (pH 7.4) at 37°C or 60°C. The buffer was periodically changed by removing the device from the vial and placing it in a vial of fresh buffer. The absorbance of the collected buffer solutions was measured on a Gilford spectrophotometer at 243 nm to detect the diacid monomer, bis(p-carboxyphenoxy) methane. Concentrations were determined from a standard curve constructed by measuring the absorbance at 243 nm of the pure diacid monomer at concentrations from 0 to 0.02 mg/ml. The polymer devices containing titrated cholic acid were eroded and the buffer solutions were analyzed on a Beckman scintillation counter.

Results and Discussion

The erosion curves for drug-free PCPM slabs at 37°C and 60°C are shown in figure 3. Both curves are characterized by an induction period followed by a linear region of mass loss at a nearly constant rate. Throughout the erosion, the devices decreased in size while maintaining their structural integrity [17] suggesting that only surface erosion is occurring.

Scraping the face of the polymer matrix did not eliminate the

undesired induction period. However, when the samples were pre-eroded for 50 hours at 60°C, removed, vacuum dried, and returned to fresh buffer solutions at either 37°C or 60°C, near zero-order erosion of the matrices began almost immediately (figure 4). This suggests that two rate constants might control the rate of device erosion. The first is the rate of hydrolysis of the anhydride linkage and the second the rate of polymer dissolution. In order to begin to measure monomer units in the buffer it seems likely that many anhydride linkages on the polymer's surface must first be cleaved. This non-productive hydrolysis corresponds to the observed induction time. Pre-erosion of the device presumably decreases the surface polymer's chain length and in the subsequent erosion the anhydride hydrolysis rate and device dissolution rate become equivalent. Alternatively the observed induction period and its elimination by pre-erosion may be the result of an initially hydrophobic surface becoming increasingly hydrophilic as hydrolysis occurs. The rate of erosion would increase up to the point were it becomes limited by both the rate of hydrolysis and the rate of water penetration into the polymer.

The decrease in device thickness throughout the erosion [17] and the maintenance of the matrice's structural integrity, as well as, the nearly zero-order erosion kinetics suggests that the heterogeneous surface erosion predominates.

Drug release from PCPM was investigated using cholic acid which because of its low u.v. absorption at 234 nm did not interfere with the matrix erosion measurement. The erosion and release profiles were nearly zero-order, had similar slopes and both the drug and the polymer had completely disappeared at nearly identical times (figure 5); though initially, polymer erosion lagged behind drug release. This might be explained by one of two possible mechanisms. First, cholic acid which adheres to the surface of the polymer sample may be released upon contact with the buffered media, even before erosion occurs. Second, when a portion of the polymer slab does erode, cholic acid escapes and is immediately dissolved in the buffer solution. While the polymer material which breaks needs time to completely hydrolyze and dissolve to a point where it can be detected by our assay [17].

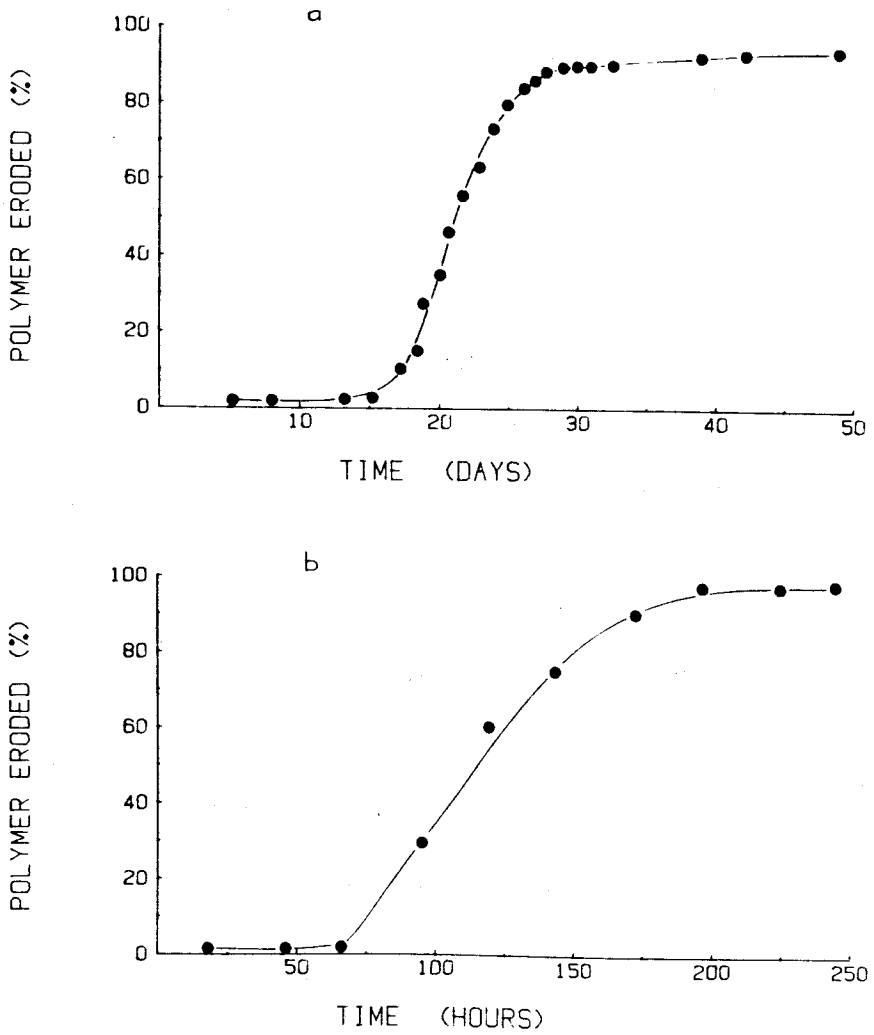

Figure 3: Erosion curves for the drug-free PCPM matrices in phosphate buffer at (a) 37°C and (b) 60°C. Percent polymer eroded is 100x the cumulative mass eroded at each sample point divided by the total mass of the matrices eroded. The PCPM matrices eroded at 37°C and 60°C weighed 23 and 18 mg and had dimensions of 0.24 cm^2 face area x 0.08 cm thick and 0.33 cm^2 face area x 0.05 cm thick, respectively.

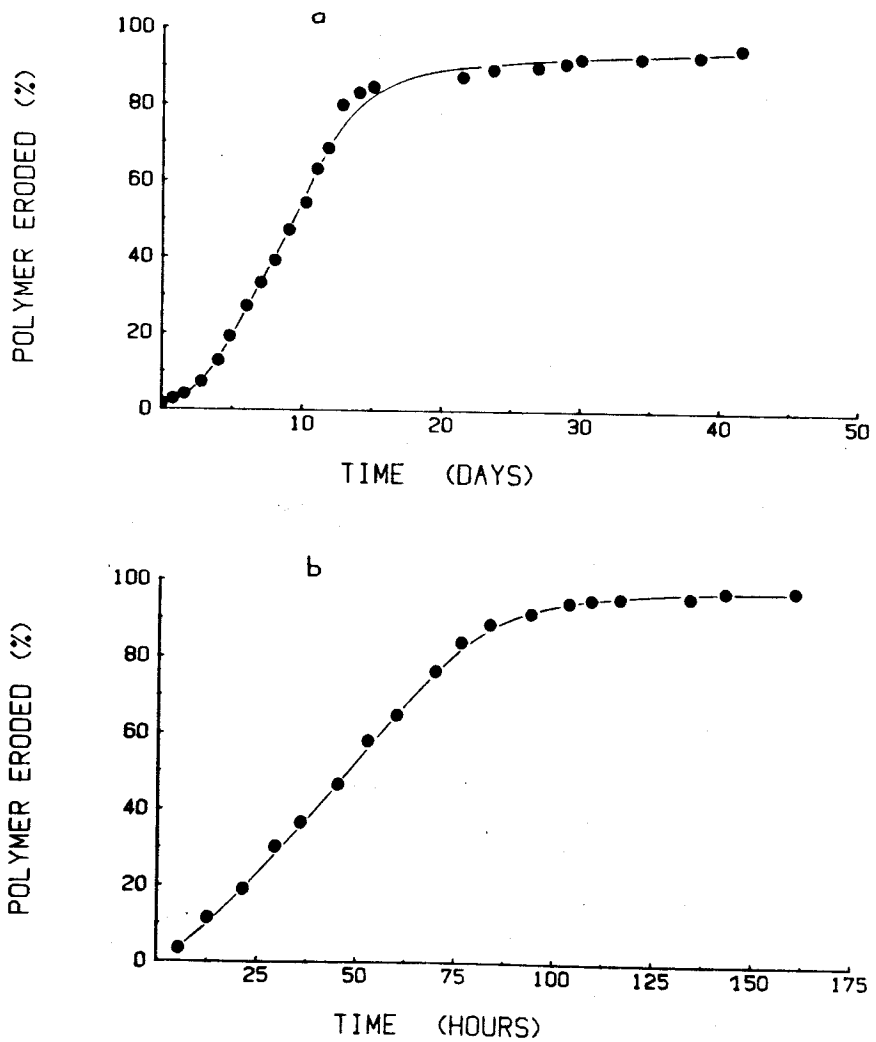

Figure 4: Erosion curves for the for the drug-free PCPM matrices which had been pre-eroded at 60°C for 50h, at (a) 37°C and (b) 60°C. The matrices weighed 74 and 25 mg and had dimensions of 0.57 cm^2 face area x 0.06 cm thick and 1.13 cm^2 face area x 0.05 cm thick, respectively.

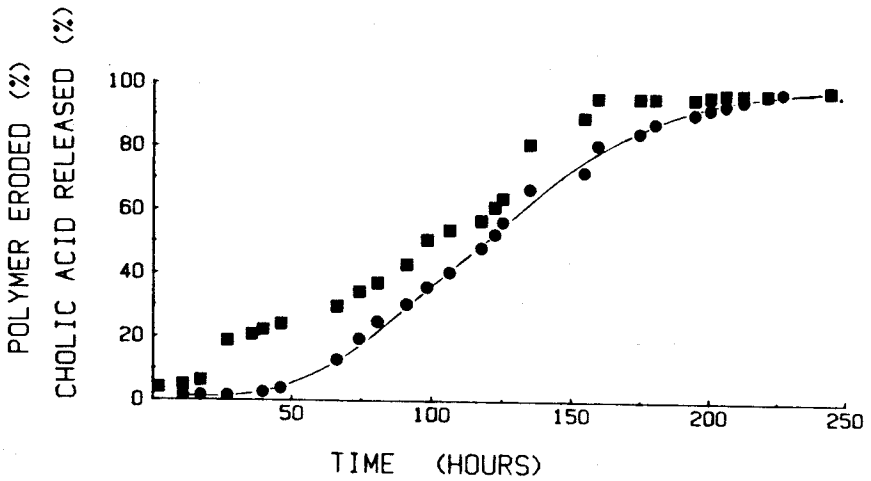

Figure 5: Erosion and release curves for a 25 mg PCPM matrix containing cholic acid at 10.5 wt.%, 0.5 cm^2 face area x 0.006 cm thick, eroded in phosphate buffer at 60°C. PCPM erosion (circles) is plotted as percent polymer erosion which equals 100x the cumulative mass eroded at each sample point divided by the total mass of the matrix. Cholic acid release (squares) is plotted as the percent cholic acid released which equals 100x the cumulative counts per minute at each sample point divided by the total number of counts per minute within the polymer matrix.

CONCLUSION

Reproducible regulation of macromolecule (bovine serum albumin) release from biocompatible polymer systems has been demonstrated. Small magnetic particles were embedded within the polymer matrix which was then subjected to an oscillating magnetic field. Parameters critical to the regulation of this release included the pole strength of the embedded particles and the amplitude and frequency of the applied magnetic field. A second polymer system, based on bioerodible polyanhydrides, displayed heterogeneous erosion and near zero-order release of a model drug (cholic acid).

ACKNOWLEDGEMENTS

The authors would like to thank Pamela Brown for assistance in preparing this manuscript and Dr. Larry Brown for his helpful comments in reviewing this paper. These studies were supported by N.I.H. grant no. GM 26698 and a grant from the Juvenile Diabetes Foundation.

REFERENCES

1 R. Langer and N.A. Peppas, Present and Future Applications of Biomaterials in Controlled Drug Release, Biomaterials , 2:201-214 (1981)

2 W. Rhine, D. Hsieh, and R. Langer, Polymers for Sustained Macromolecule Release: Procedures to Fabricate Reproducible Delivery Systems and Control Release Kinetics. J. Pharm. Sci., 69:265-270 (1980)

3 J. Murray, L. Brown, M. Klagsburn and R. Langer, A Micro System for Sustained Release of Epidermal Growth Factor, In Vitro, 19:743-750, (1983)

4 D. Hsieh, W. Rhine and R. Langer, Zero-Order Controlled Release Polymer Matrices for Micro- and Macromolecules, J. Pharm. Sci., 72:17-22 (1983)

5 R. Langer and J. Folkman, Polymers for the Sustained Release of Macromolecules and Other Proteins, NATURE, 263:797 (1976)

6 R. Langer, H. Brem, and D. Tapper, Biocompatability of Polymeric Drug Delivery Systems for Macromolecules, J. Biomed. Mat. Res., 15:267-277 (1981)

7 L. Brown, C. Munoz, L. Siemer, E. Edelman, J. Kost, and R. Langer, Sustained Insulin Release from Implantable Polymers Diabetes 32, Supplement #1, Abstract 137, June (1983)

8 R. Langer, E. Edelman and D. Hsieh, Magnetically Controlled Polymeric Delivery Systems, Chapter 25, pp 585-596 in "Biocompatible Polymers, Metals, and Composites", M. Szycher ed., Technomic Pub. Co. (1983)

9 D. Hsieh, R. Langer and J. Folkman, Magnetic Modulation of Release of Macromolecules From Polymers, Proc. Natl. Acad. Sci. USA, 78:1863-1867 (1981)

10 J. Heller and R.W. Baker, Theory and Practice of Controlled Drug Delivery from Bioerodible Polymers, pp 1-17, in "Controlled Release of Bioactive Materials", R.W. Baker ed., Academic Press, NYC (1980)

11 C.G. Pitt, M.M. Gratzl, G.L. Kummel, J. Surles and A. Schindler, Aliphatic Polyesters II. The degradation of poly(DL-lactide), poly(ϵ-caprolactone), and their copolymers in vivo, Biomaterials, 2:215-220 (1981)

12 C.C. Chu, Hydrolytic Degradation of Polyglycolic Acid: Tensile Strength and Crystallinity Study, J. Appl. Poly. Sci., 26(5),1727-24 (1981)

13 H.B. Hopfenberg, Controlled Release from Erodible Slabs, Cylinders and Spheres, in "Controlled Release Polymeric Formulations", D.R. Paul and F.W. Harris eds., ACS Symposium Series No. 33, pp 26-32 (1976)

14 J. Heller, D.W.H. Penhale, R.F. Helwing, and B.K. Fritzinger, Release of Norethindrone from Polyacetals and Poly(OrthoEsters), Polym. Eng. Sci., 21:727-731 (1981)

15 A. Conix, Aromatic Polyanhydrides A New Class of High Melting Fiber-Forming Polymers, J. Polym. Sci., 29:343-353 (1958)

16 A. Conix, Poly[1,3-Bis(p-caorboxy-phenoxy)propane anhydride], Macromolecular Synthesis, pp 95-99, Vol. 2, J.R. Elliot ed., Wiley, NYC (1966)

17 H.B. Rosen, J. Chang, G.E. Wnek, R.J. Linhardt and R. Langer, Bioerodible Polyanhydrides for Controlled Drug Delivery, Biomaterials, 4:131-133 (1983)