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Bioerodible implants with programmable drug release[1]

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Abstract

Taking advantage of polymer surface erosion a polymer matrix was developed that allows to release either one drug in two phases or two drugs one after another. The first period of drug release from these implants lasts between one and two weeks and is followed by a second period of similar duration. The matrices consist of several layers of surface eroding polymer. As these polymers erode in general fast, it was necessary to incorporate also bulk eroding polymers to obtain implants with the desired release characteristics and yet keep the dimensions of the implant small. The polymers used for the manufacture are p(CPP-SA) 20:80, a polyanhydride, and poly(D,L-lactic acid). Both are biocompatible and have been used for the manufacture of FDA-approved devices before. Theoretical erosion models were used to support the design of implants as well as to investigate some of the problems involved with drug release.

Keywords: Polymer; Erosion; Implant; Pulsatile release; Programmable release

1. Introduction

Controlled drug delivery research focuses to a large extent on systems for the delivery of drugs at constant rates to the body to generate constant plasma levels. This approach is not necessarily beneficial for all therapies. When pharmakokinetic and pharmacodynamic parameters change periodically, for example [1], one might rather apply variable drug release rates rather than constant ones. For the therapy of bacterial infections or cancer the continuous administration of drugs may cause a loss of sensitivity against antibiotics or cytostatics if same drug is administered continuously over long periods of time. To avoid such a loss of sensitivity during systemic chemotherapy, for example, several chemotherapeutic agents are administered one after another [2]. For vaccination it was found that the discontinuous administration of an antigen might enhance the immune response [3]. These examples illustrate that there is a need for drug delivery devices that release one or even several drugs discontinuously out of a dosage form.

The intention of this study was to develop an erodible polymer matrix that can release drugs or antigens in two phases with a first drug release period of 1–2 weeks and a second period lasting another week. Such systems could be beneficial for the local treatment of cancer because they allow to switch from one drug to another or for vaccination to release antigens twice during a month. To achieve such release behavior with matrix-type implants, the

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[1]Dedicated to Prof. Stricker on the occasion of his 65th birthday.

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use of surface eroding polymers has been proposed before [4]. Loading different layers of laminated matrices with drugs, surface erosion releases the drug out of these layers one after another. In contrast to devices that have been developed for pulsatile or programmable delivery before [5–10] it was the intention in this study to use only degradable and biocompatible polymers. Therefore, poly(1,3 bis[p-carboxy phenoxypropane]-co-sebacic acid) (p(CPP-SA) 20:80), a polyanhydride, and poly(D,L-lactic acid) were selected as polymer materials because they were used for the manufacture of FDA approved parenteral devices for the use in humans before. Concomitantly production techniques that are inexpensive and allow the mass production of such implants were applied.

2. Materials and methods

2.1. Materials

Poly(1,3 bis[p-carboxy phenoxypropane]-co-sebacic acid), p(CPP-SA) 20:80 with molecular weight 70 000 was obtained from Scios-Nova-Pharmaceutical, Baltimore, MD. Poly(D,L-lactic acid) with molecular weight 1900 (Resomer 104®) and 17 400 (Resomer 202®) was a gift from Boehringer Ingelheim, Ingelheim am Rhein, Germany. Brilliant blue and carboxyfluorescein served as model compounds and were purchased from Fluka, Buchs, Switzerland.

2.2. The incorporation of dyes into the polymer

The polymers were loaded with brilliant blue and carboxyfluorescein by melting the polymer at 110°C in an agate mortar and dispersing the dyes in the melt. Drug loading was 5 and 30%. After solidification the polymer was ground in a mortar until a free flowing powder with a particle size smaller than 500 μm was obtained.

2.3. Compression of discs

The polymer was compressed to discs of 4, 6 and 8 mm diameter using an Exacta 1 single punch tablet press, from Fette GmbH, Schwarzenbek/Hamburg, Germany. The machine was used in a manual mode. For the manufacture of composite implants a mantle had to be compressed around an already existing smaller implant. This was achieved by compressing polymer powder to a base plate, on which the smaller core implant was centered. An appropriate amount of ground polymer was added and the composite implant was finally obtained by compression.

2.4. Coating of implants

Implants were coated by dipping them into a 20% polymer solution of poly(D,L-lactic acid) in methylene chloride. The dipping was repeated 5 times. Between the individual coating steps the samples were dried on Teflon plates. After the last layer had been added the samples were dried at room temperature for 48 h.

2.5. The investigation of composite implants by light microscopy

Cross sections of composite polyanhydride cylinders were investigated for the regular arrangement of the polymer layers by light microscopy. For preparation the matrices were cooled to −25°C and broken, using flat tweezers. The cross sections were investigated using a stereomicroscope from Zeiss, Oberkochen, Germany.

2.6. The investigation of composite implants by scanning electron microscopy (SEM)

The polymers were investigated before and after erosion by scanning electron microscopy using a model 1810T scanning electron microscope from Amray Inc., Bedford, MA. Samples were prepared in the same way as for the light microscopy investigations. The polymer pieces were fixed on the sample holders using conductive carbon cement from Neubauer Chemikalien, Münster, Germany. The samples were finally gold sputtered for 2.5 min at 20 mA on a Hummer IR sputtercoater from Technics, Alexandria, VA.

2.7. Erosion of implants and drug release

Implants were eroded at 37°C in 10 ml·1M phosphate buffer solution (pH 7.4). The buffer was changed daily and analyzed photometrically for drug release. Brilliant blue and carboxyfluorescein served as model compounds. To determine their concentration in mixtures the extinction of solutions was measured at 490 nm and 630 nm which are the absorption maxima of both dyes using an Uvikon 810 spectrophotometer from Kontron Instruments, Neufahrn, Germany. The values were corrected for the presence of the second dye according to equation 1 and 2.

$$E_{C490} = \frac{k_C \cdot E_{490} - k_B \cdot k_C \cdot E_{630}}{k_C - k_B} \quad (1)$$

$$E_{B630} = \frac{k_C \cdot E_{630} - E_{450}}{k_C - k_B} \quad (2)$$

Equation 1 calculates the extinction of carboxyfluorescein at 490 nm and equation 2 the extinction of brilliant blue at 630 nm. E_{490} and E_{630} are the experimentally measured values, k_C and k_B the ratio of the extinctions at 490 and 630 nm in the UV-VIS spectra of carboxyfluorescein and brilliant blue. To exclude any interaction between the two dyes, the content of solutions containing both dyes in various ratios was determined using the described method. Deviations from the true concentrations were found to be less than 2%. This indicates that the method is suited for the quantitative investigation of solutions containing mixtures of brilliant blue and carboxyfluorescein.

2.8. Erosion simulation

Programs for erosion simulation were written in PASCAL using a PASCAL compiler from Symantec, Cupertino, CA. Programs were run on a Macintosh IIsi from Apple Computer Inc., Cupertino, CA.

3. Results and discussion

3.1. The prediction of drug release from composite cylinders made of surface eroding polymers

For the manufacture of implants with programmable drug release, surface eroding polymers have previously been proposed as drug carriers [4]. In this study it was first investigated if it was possible to use polyanhydrides to manufacture implants that release two drugs one after another by incorporating the drugs into different parts of the implant as shown in Fig. 1a. If both layers are made of surface eroding polymers erosion affects first the mantle of the matrix then its core. If core and mantle are loaded with two different drugs, they should be released one after another.

Prior to proof this hypothesis experimentally it was investigated theoretically using polymer erosion models. Recently, a theoretical model was developed to predict the erosion of surface eroding polymers [11] which was expanded to allow simulations for three dimensional polymer matrices and to predict drug release from such matrices [12]. Preliminary studies showed that these models might also be used to predict drug release from composite polymer cylinder matrices such as the one in Fig. 1a [13]. This model was first expanded to allow for detailed simulations such as to predict erosion and drug release for more complicated geometries (Fig. 1b). Polymer cylinder cross sections were, therefore, represented by a two-dimensional computational grid as shown in Fig. 2. The grid takes into account two aspects. First, it divides the cylinder into a core and a mantle. The gray area indicates the location of the

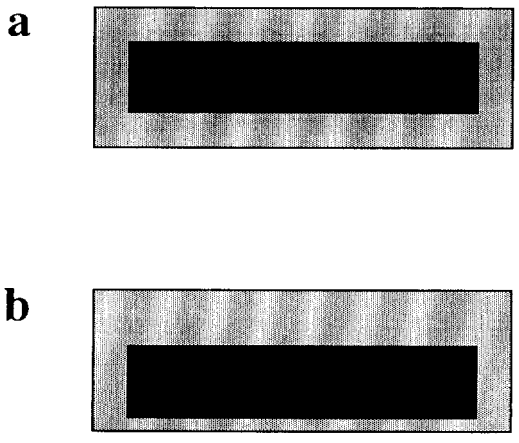

Fig. 1. Schematic illustration of cylinder cross sections that can be investigated for erosion and drug release using theoretical models. (a) composite cylinder with coinciding cylinder axes, (b) composite cylinder with non-coinciding cylinder axes.

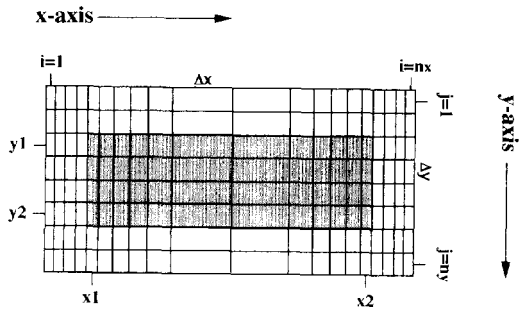

Fig. 2. Computational grid that allows for the simulation of composite cylinder erosion.

core that carries for example a dose of drug that is intended to be released in the second stage of erosion and is surrounded by a mantle containing a dose of drug that is to be released first. Second, the grid divides the cross section into individual polymer pixels of the same volume. This is achieved by decreasing the stepsize Δx in radial direction with the root of the increasing radius. The 4 corners of the core $P_1(x_1|y_1)$, $P_2(x_2|y_1)$, $P_3(x_2|y_2)$ and $P_4(x_1|y_2)$ can freely be chosen to allow for the existence of non-symmetric geometries. In contrast to previous studies this area can now vary in size and position. To simulate erosion using such grids, the erosion algorithm described in [11] was applied with some modification. In brief: each pixel is assigned at random either the quality crystalline or amorphous depending on the crystallinity, χ, of the polymer material. Erosion is simulated by assuming that only those pixels can erode that have contact to the buffer medium. These pixels are assigned a lifetime at random so that the lifetimes of all pixels are distributed according a first order Erlang distribution:

$$e(t) = \lambda \cdot e^{-\lambda \cdot t} \tag{3}$$

The lifetime t is, thereby, on the average higher for crystalline pixels because of their smaller erosion rate constant λ. Erosion proceeds by removing the pixels from the grid in the sequence of their lifetimes. The release of drugs was predicted assigning to each amorphous pixel a relative amount of drug $1/(n_x \cdot n_y)$. In contrast to other approaches [14–16] it was assumed that whenever a pixel erodes an appropriate amount of drug is spontaneously released which was found sufficiently accurate for hydrophilic drugs [12]. With this assumption, drug release can be predicted using this erosion model if the erosion rate constants of the polymer are known.

3.2. The prediction of drug release out of composite cylinders

To investigate if the release of drugs in 2 phases from implants as the one shown in Fig. 1a is feasible, the erosion of a device made of p(CPP-SA) 20:80, a polyanhydride, was simulated. The erosion rate constants λ for amorphous (λ_a) as well as crystalline (λ_c) p(CPP-SA) 20:80 as well as the polymer crystallinity (χ) were taken from the literature [11,17]. Fig. 3a shows an example for the erosion of a composite polyanhydride cylinder. At early times, erosion is confined to the surface of the implant. After 1.5 days the typical picture of an eroding p(CPP-SA) 20:80 polymer cylinder is obtained. Erosion fronts separate the eroded surface from a non-eroded polymer core and move towards the implant center. Fig. 3b shows the erosion of a cylinder the core of which is not perfectly centered inside the cylinder. Such simulations are relevant because it could happen that a device is not perfectly symmetric with respect to both cylinder axes. From such simulations the effect of the arrangement and dimensions of the two polymer layers on drug release can be simulated. Fig. 4 shows an example for the simulated drug release profiles that are obtained when core and mantle are loaded with two different drugs. These simulations predict that the sequential release of two drugs is possible as the release of drug out of the core is postponed substantially.

Next the effect of geometry on drug release was investigated. Although both polymer layers can be drug-loaded, only the release out of the inner cylinder was simulated as it is obvious that drug contained in the mantle would be released right from the beginning of erosion. First, the effect of the mantle thickness on the onset of drug release was investigated. Fig. 5a shows that the onset of drug release can be postponed by increasing the thickness of the mantle via decreasing the dimensions of the core. The dimensions of the cylinder can, therefore, be used to move the onset to a desired value. Next the

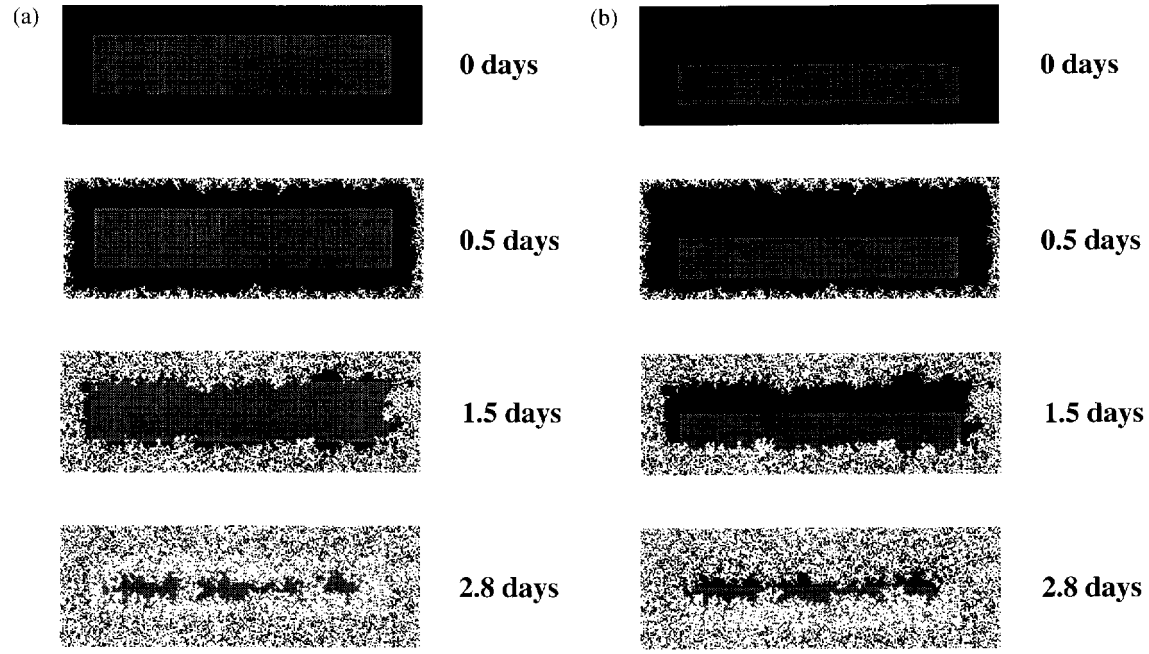

Fig. 3. (a) Polymer erosion for a symmetric composite cylinder ($n_x = 300$, $n_y = 100$, $P_1(33|33)$, $P_2(266|33)$, $P_3(266|66)$, $P_4(33|66)$, $\chi = 0.35$, $\lambda_a = 7.32 \cdot 10^{-7}$ s^{-1}, $\lambda_c = 8.75 \cdot 10^{-9}$ s^{-1}), (b) Polymer erosion for a composite cylinder ($n_x = 300$, $n_y = 100$, $P_1(33|50)$, $P_2(266|50)$, $P_3(266|83)$, $P_4(33|83)$, $\chi = 0.35$, $\lambda_a = 7.32 \cdot 10^{-7}$ s^{-1}, $\lambda_c = 8.75 \cdot 10^{-9}$ s^{-1}).

effect of a non-centered core caused by a displacement along the y-axis was examined which might happen during the manufacturing of such a device. Fig. 5b shows this has effects similar to increasing the size of the core implants. The release of drugs sets in earlier if the core is closer to the surface of the implant. Furthermore the release profiles can be divided into 2 phases which differ by the slope of the release curve. This can be explained with the movement of erosion fronts in y-direction. These fronts move from top and bottom at the same speed. If the core is perfectly centered, they hit it at the same time. If in contrast the core is displaced, it will be reached by one front first as shown in Fig. 3b after approximately 1.5 days of erosion. The release rate at that time is only half of the rate that is obtained after the second front has also reached the core. Accordingly the slope of the two phases in simulation 5b differ by a factor of 2.

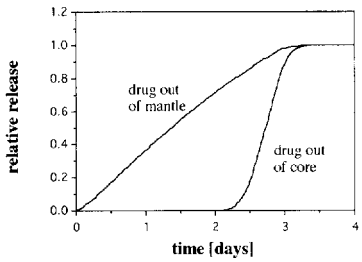

Fig. 4. Simulated drug release profiles for the sequential release of 2 drugs out of a composite cylinder ($n_x = 600$, $n_y = 200$, $P_1(80|80)$, $P_2(520|80)$, $P_3(520|120)$, $P_4(80|120)$, $\chi = 0.35$, $\lambda_a = 7.32 \cdot 10^{-7}$ s^{-1}, $\lambda_c = 8.75 \cdot 10^{-9}$ s^{-1}).

3.3. Composite implants: manufacture and drug release

After having shown theoretically that the release of 2 drugs one after another out of the same implant should be feasible, composite implants as the one shown in Fig. 1a were manufactured to prove this hypothesis experimentally. The implants were made of a 5% carboxyfluorescein loaded p(CPP-SA) 20:80 core and a 5% brilliant blue loaded p(CPP-SA) 20:80 mantle. The dyes served as low molecular weight model compounds because they are easily detectable.

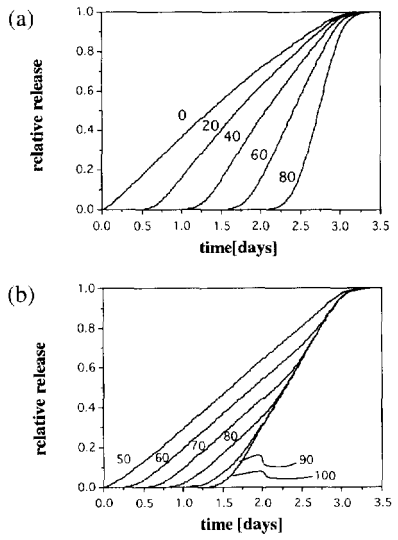

Fig. 5. Simulation of drug release out of the inner cylinder of composite implants. (a) release depending on the thickness of the inner cylinder (various values x_1) ($n_x = 600$, $n_y = 200$, $x_1 = x_2 = y_1 = y_2$, $\chi = 0.35$, $\lambda_a = 7.32 \cdot 10^{-7}$ s^{-1}, $\lambda_c = 8.75 \cdot 10^{-9}$ s^{-1}). (b) release depending on the distance of the inner cylinder to the surface in y-direction (various values y_1) ($n_x = 600$, $n_y = 200$, $x_1 = 150$, $x_2 = 450$, $y_2 = y_1 + 100$, $\chi = 0.35$, $\lambda_a = 7.32 \cdot 10^{-7}$ s^{-1}, $\lambda_c = 8.75 \cdot 10^{-9}$ s^{-1}).

To decrease the porosity of the matrices, they were melted and solidified again. To preserve the shape during this process the implants were mounted into cylindrical Teflon molds. The molds consisted of a cylindrical die of the same diameter as the implants and 2 punches that held the matrix in place and allowed to push it out of after solidification. Fig. 6 shows the release of dyes from such composite implants. The core was loaded with carboxyfluorescein and the mantle with brilliant blue. Both dyes are released one after another. Brilliant blue is released immediately while carboxyfluorescein is released with a 2 day delay. These results show that it is possible to release drugs out of the same implant one after another using surface eroding polymers.

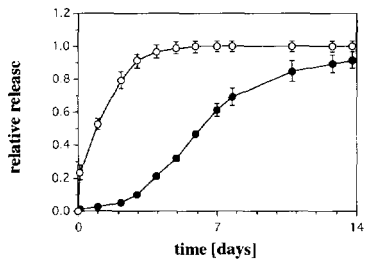

Fig. 6. Release of brilliant blue (○) and carboxyfluorescein (●) from a composite p(CPP-SA) 20:80 cylinder (inner cylinder: 5% carboxyfluorescein loaded, 4 mm diameter, outer cylinder: 5% brilliant blue loaded, 6 mm diameter).

3.4. Improved composite implants: manufacture and structural investigations

The simple composite implants have two major disadvantages:

1. To postpone the onset of the release of the second drug, the mantle thickness has to be increased. According to Fig. 5a this is, however, subject to severe limitations because the size of the cylinder increases if the drug release phases need to be separated longer times. To postpone the onset of the release of the second drug to 2 weeks a mantle thickness of at least 6 mm would be required around the implant which would lead to a total height of more than 12 mm.
2. The implants have to be heat treated after manufacturing to close pores that would lead to an early release of the second dose.

Both problems can be overcome by changing the design of the matrices in such a way, that the core containing the second drug or dye is protected against premature release of the second dose by an additional polymer layer of slow eroding polymer such as poly(D,L-lactic acid). Fig. 7 shows schematically the structure of such a composite polymer matrix (implant 4) and its precursors during manufacturing (implant 1–3). The composition of the individual implants is listed in Table 1. Implant 1 is a monolithic device made of p(CPP-SA) 20:80 loaded with a dose of drug to be released later during erosion. In order to protect the drug loaded core in the subsequent coating step against the loss of drug, implant 2 has a protective drug free mantle of p(CPP-SA) 20:80. Implant 3 is obtained by coating implant 2 with poly(D,L-lactic acid) that protects the core from early erosion and drug release. Around implant 3, a mantle of p(CPP-SA) 20:80 was finally compressed that contains the dose of drug that is

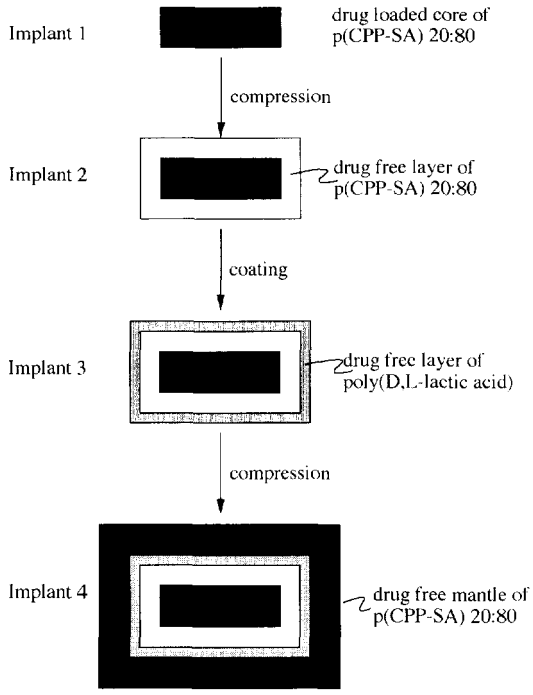

Fig. 7. Structure and manufacture of a composite polymer matrix cylinder that allows to postpone the release of the second dose of drug for 2 weeks.

intended to be released initially. This last step yields implant 4 which is the final product.

Prior to release studies the cross sections of implants were investigated by light microscopy and scanning electron microscopy. Fig. 8 shows the picture of a cross section through implant 4 obtained by light microscopy. The core and the outermost mantle which carry dye appear dark. The drug-free polyanhydride layer is clearly visible but cannot be

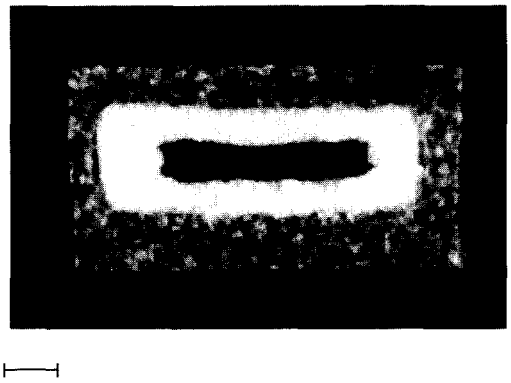

Fig. 8. Light microscopic picture of a cross sections through implant 4 (cf Fig. 7 and Table 1). Scale bar = 1 mm.

distinguished from the poly(D,L-lactic acid)-layer. The picture proves that a regular arrangement of layers can be achieved using the proposed manufacturing procedure and that these layers are sharply separated from one another. SEM investigations revealed that the poly(D,L-lactic acid) layer is intact and has a thickness of approximately 100 μm.

3.5. Drug release studies with implant 1–4

To analyze the effect of the various polymer layers on drug release from the developed implants, the release of drug from implant 1–4 was tested. This allowed to investigate the effect of each individual polymer layer on drug release.

The release profiles for implant 1 are typical for drug release from polyanhydride matrices (Fig. 9). The release of brilliant blue is faster than the release of carboxyfluorescein which is due to the better solubility of brilliant blue compared to

Table 1
Survey on the composition of implants with a 14 day delay of the release of the second dose (implant 4) and its precursors (implant 1–3)

Implant	Composition			
	Layer 1	Layer 2	Layer 3	Layer 4
1	30% drug-loaded p(CPP-SA)20:80	—	—	—
2	30% drug-loaded p(CPP-SA)20:80	Drug-free p(CPP-SA)20:80	—	—
3	30% drug-loaded p(CPP-SA)20:80	Drug-free p(CPP-SA)20:80	Drug free poly- (D,L-lactic acid)	—
4	30% drug-loaded p(CPP-SA)20:80	Drug-free p(CPP-SA)20:80	Drug free poly- (D,L-lactic acid)	5% drug-loaded p(CPP-SA)20:80

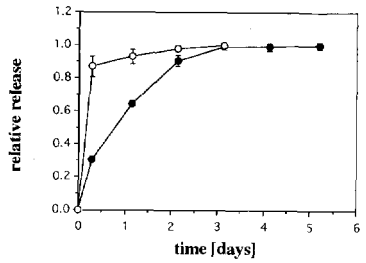

Fig. 9. Release of brilliant blue (○) and carboxyfluorescein (●) from implant type 1 (cf Fig. 7) (5% drug loading, 4 mm diameter).

carboxyfluorescein. The solubility of carboxyfluorescein is pH dependent and decreases in the acidic environment that prevails inside the pores of eroding p(CPP-SA) 20:80. Values were found to be between 4 and 5 despite the erosion of the matrices in a pH 7.4 buffer. This can be explained by the massive release of degradation products with an acid functionality into the pores during erosion [18,20]. Therefore, brilliant blue is released faster than carboxyfluorescein.

After the implants are covered with a mantle drug-free p(CPP-SA) 20:80, the drug release profiles change substantially (Fig. 10). The release of carboxyfluorescein out of implant 2 shows now a lag time of 4 days. The release profile is sigmoid which is caused by the drug-free polymer layer that functions as a diffusion barrier. Brilliant blue shows a burst release of 35% during the first day. Thereafter its release profile has also a sigmoid shape. The differences in both release profiles are probably due to differences in the solubility of both model dyes. Because of the porosity of the polymer matrix which is made by compression, water can enter the implants via capillaries. Due to its high water solubility,

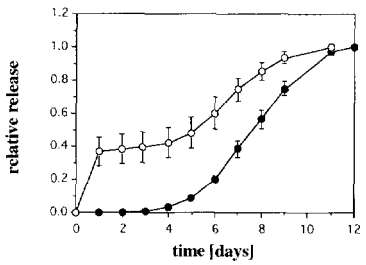

Fig. 10. Release of brilliant blue (○) and carboxyfluorescein (●) from implant type 2 (cf Fig. 7) (5% drug loading, 6 mm diameter).

brilliant blue inside the core of implant 2 is dissolved and released by diffusion. At later times, the polymer has to erode before more brilliant blue can be released because even though the mantle is porous it seals the core of these implants from the erosion medium.

To suppress the early release of hydrophilic drugs, the diffusion of water into the polymer has to be suppressed. Therefore the implants were coated with poly(D,L-lactic acid). Fig. 11a,b show the release of drugs from implant 3 and prove that the burst release is substantially suppressed after the coating and that the profiles have the desired lag-time of 10–14 days. Brilliant blue is again released faster than carboxyfluorescein. The drug release mechanism is now more complicated than for implant 1 and 2. During early times of erosion the poly(D,L-lactic acid) layer swells but allows only small amounts of water to pass into the core of the implant. As a consequence small amounts of both dyes may leak out by diffusion. During the following days, poly(D,L-lactic acid) starts to erode. When the film is eroded to a critical value, large amounts of water can enter the implant start the degradation of the polyanhydride core and trigger the massive release of drug which is

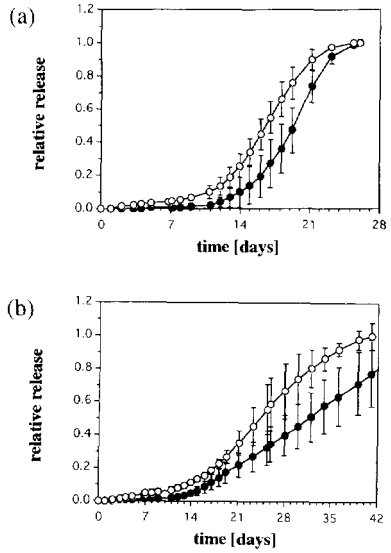

Fig. 11. Release of brilliant blue (○) and carboxyfluorescein (●) from implant type 3 (cf Fig. 7) (5% drug loading): (a) poly(D,L-lactic acid) MW 1900 as coating polymer, (b) poly(D,L-lactic acid) MW 17 400 as coating polymer.

then controlled by the erosion of the anhydride core. The molecular weight of poly(D,L-lactic acid) becomes a tool for regulating the release rate. The high molecular weight polymer retains the drug for a longer period of time which might be due to the slower erosion of polylactides with increasing molecular weight [19].

Of implant 4 first the release from devices that contained brilliant blue in their core and carboxyfluorescein in the outer mantle was investigated. Fig. 12a shows, that carboxyfluorescein is released as seen before from implant one. Its release profile is again similar to those of monolithic devices. The release of brilliant blue can be divided into 2 phases. During phase 1 small amounts of dye leak out of these implants. The release during the first 10 days is, however, less than 5%. The massive release sets in after 2 weeks. Compared to the mantle-free implants (implant 3), brilliant blue is released with slightly higher lag time and at a slightly lower speed compared to the mantle-free implants. In a control experiment, core and mantle were loaded with the opposite type of dye. Fig. 12b shows that brilliant blue is released almost instantaneously. Carboxyfluorescein in contrast has a lag period of approximately 2 weeks which agrees very well with the release profiles of implant 3. This proves that the release of the second dose does not depend on the type of drug incorporated into the core.

In a final set of experiments core and mantle were loaded with the same drug. In both cases profiles were obtained in which drug is released in two phases (Fig. 13a,b). There are again the same differences between brilliant blue and carboxyfluorescein as observed before. Brilliant blue is released fast during the first phase and at a slightly lower rate during the second phase. Carboxyfluorescein, in contrast, is again released at the same rate as before. Release periods of up to 4 weeks were achieved using these composite implants.

The release studies reflect some of the properties of the polymers that were used for the manufacture of the composite implants. The polyanhydride layers erode fast which is typical for surface eroding polymers. This can be concluded from the fast release of dyes from the outermost mantle and the core. The erosion of the polylactides is substantially slower and follows a bulk erosion process. It is the erosion of this polymer layer that postpones the release of the second dose. That the erosion of the

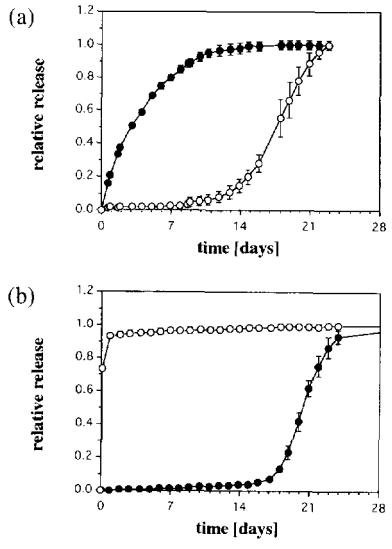

Fig. 12. Release of brilliant blue (○) and carboxyfluorescein (●) from implant type 4 (cf Fig. 7): (a) core containing 30% brilliant blue, mantle containing 5% carboxyfluorescein, (b) core containing 30% carboxyfluorescein, mantle containing 5% brilliant blue.

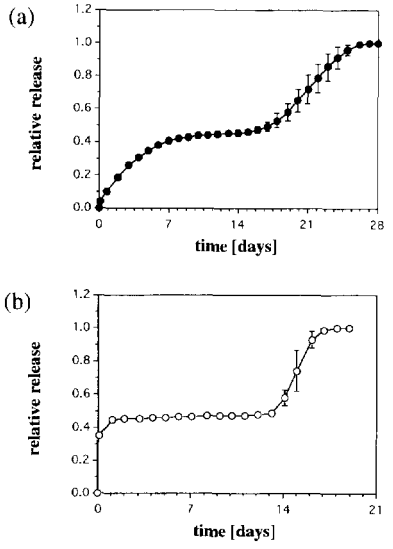

Fig. 13. Release of brilliant blue (○) and carboxyfluorescein (●) from implant type 4 (cf Fig. 7): (a) core containing 30% carboxyfluorescein, mantle containing 5% carboxyfluorescein, (b) core containing 30% brilliant blue, mantle containing 5% brilliant blue.

various polymer layers is responsible for the overall release kinetics becomes obvious when following the crystallinity of the polymer matrices that stems from the partially crystalline polyanhydrides by differential scanning calorimetry or wide angle X-ray spectroscopy. These studies revealed, that erosion proceeds in two phases. The outermost implant mantle is eroded during an initial phase and the two innermost layers towards the end of erosion [21]. The delay is controlled by the bulk eroding polylactide layer which functions as a time fuse This does also explain the slightly better ability of the higher molecular weight polylactide (Resomer 202®) to postpone the release of the second dose. That drug release is not only governed by erosion but also diffusion phenomena becomes obvious when comparing the model compounds that were used. Whilst brilliant blue is always released very quick, carboxyfluorescein is released at lower speed. The reason is the lower solubility of carboxyfluorescein at the pH that exists inside the eroding matrices.

4. Conclusions

Using a combination of fast eroding polyanhydrides and slow eroding poly(D,L-lactic acid), implants were manufactured that release drugs in a preprogrammed way. It is possible to release one drug in two phases or two different drugs one after another. The materials used for the manufacturing are biocompatible and have been used for the manufacture of FDA approved implants before. The methods used for manufacturing allow easy production of the systems. Potential applications for such implants are the local treatment of infections and cancer or vaccination.

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