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Programmable implants—From pulsatile to controlled release

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Abstract

The aim of this study was to develop programmable implants with a reproducible delayed onset of release followed by several weeks of controlled release. For this purpose, a drug-loaded core was embedded into a drug-free bulk-eroding poly(D,L lactic-co-glycolic acid) or poly(D,L lactic acid) mantle. The manufacturing procedure was established and optimized for three mantle materials, which showed delay times ranging from 7 to 83 days. Triglycerides with fatty acid chain lengths from C12 to C18 were investigated as core materials, producing release periods from 2 to 16 weeks. Concomitantly, applying a convolution/deconvolution model showed the possibility of theoretical prediction of the resulting release profiles.

Keywords: Implants; Controlled release; Pulsatile release; Triglyceride; Convolution

1. Introduction

In recent years "intelligent" drug delivery systems, such as microchip devices, have been developed (Santini et al., 1999; Sershen and West, 2002). The advantage of such systems is their ability to release a plethora of individual doses of one or even several substances from a multitude of drug reservoirs. Due to the pulsatile release of individual doses, any desirable release profile can be 'generated' by repetitively releasing dose after dose. According to the literature, 'pulsatile drug delivery' denotes the release of drugs, peptides or proteins with high rates within a narrow time interval (Peppas, 1992). Such delivery systems are classified as single-or multiple-pulse systems. They are frequently based on polymeric materials that release a drug almost instantly (Bussemer et al., 2001; Stubbe et al., 2004; Kikuchi and Okano, 2002). Many different delivery systems have been developed, such as microchip based devices (Santini et al., 1999; Richards Grayson et al., 2003) as well as matrices with concentric layers of biodegradable polymer (Goepferich, 1997, 2000).

A disadvantage of these systems, however, is that too many pulses would be needed to create a release profile that stretches over extended periods of time, such as several weeks. To overcome this limitation, programmable implants consisting of a drug-loaded polyanhydride core embedded in a drug-free bulk-eroding polymer mantle were developed (Vogelhuber et al., 2003a,b). This system enables a delayed onset of release adjustable by the choice of the mantle material followed by a pulsatile release. However, due to the fast eroding polyanhydride core it was not possible to release drug over an extended time period from these implants. Therefore, in this study we tested different lipophilic core materials with regard to their ability to control drug release (Vogelhuber et al., 2003a,b; Koennings and Goepferich, 2005). In Fig. 1, a comparison of the intended release profiles of this new generation of programmable implants with conventional pulsatile drug release patterns is shown.

This controlled prolonged release from the drug delivery systems may be of great benefit when highly potent substances, for example growth factors (Gillespie et al., 2003; Ozeki and Tabata, 2002), cytokines (Sharma et al., 2004; Yuyama et al., 2000) or anti-cancer drugs (Storm et al., 2002), have to be administered. Such drugs would rapidly exceed therapeutic concentrations during pulsatile release. Concomitantly, controlled prolonged release may be desirable for an intracranial treatment, since, for example, neurodegenerative diseases or brain tumors frequently require long-term therapy (Benoit et al., 2000; Mc Rae et al., 1994).

The goal of this study was to design programmable implants with a reproducible onset of release and a controlled release once the liberation of the drug has started. Different core and mantle

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Fig. 1. Comparison of release profiles from programmable implants. (a) Pulsatile release as obtained with systems described in Vogelhuber et al. (2003a,b); (b) intended release profile after delayed onset in this study.

materials were tested for this purpose. Finally, a mathematical model based on convolution theory (Stepanek, 1976; Suverkrup, 2000; Langguth et al., 2004) was developed, which allows for the prediction of release profiles, when the release from the core material and the properties of the mantle material are known.

2. Materials and methods

2.1. Materials

Glyceroltrilaurate (Dynasan® 112), glyceroltrimyristate (Dynasan® 114), glyceroltripalmitate (Dynasan® 116) and glyceroltristearate (Dynasan® 118) for matrix preparation were purchased from Sasol GmbH, Witten, Germany. Cholesterol, which served as a further matrix material, was obtained from Sigma–Aldrich (Deisenhofen, Germany). Poly(D,L lactic-co-glycolic acid) (PLGA) and poly(D,L lactic acid) (PLA) were used as mantle materials. Resomer® RG502H (50/50, M_w = 10,500 Da, $PLGA_{10}$, T_g = 46 °C) and Resomer® RG502 (50/50, M_w = 17,000 Da, $PLGA_{17}$, T_g = 44 °C) as well as Resomer® R503 (M_w = 30,000 Da, PLA_{30}, T_g = 48 °C) were kindly provided by Boehringer Ingelheim (Ingelheim, Germany). For release experiments, the highly water-soluble fluorescent dye pyranine (Sigma–Aldrich, Deisenhofen, Germany) served as model drug. Tetrahydrofuran (THF) was purchased from Merck (Darmstadt, Germany).

2.2. Manufacture of programmable implants

Investigations on programmable implants were carried out with glyceroltrilaurate, glyceroltrimyristate, glyceroltripalmitate, glyceroltristearate and cholesterol as core materials. For the preparation of the matrices, the respective core material was first loaded with 10% (w/w) pyranine, which served as model drug. To this end, glyceroltripalmitate was dissolved in tetrahydrofuran and mixed with a solution of the dye in water. The resulting mixture with a THF/water-ratio of 9:1 was frozen in liquid nitrogen and subsequently freeze-dried, using a RV5 two stage oil pump from Edwards (Crawley, Sussex, UK). Afterwards, the obtained powder was ground and mixed in a mortar.

Matrices were compressed as described by Vogelhuber et al. (2003a,b). In brief, the core matrices were prepared and subsequently embedded into the drug-free polymer mantle. The last step of the implant manufacture involved the closure of the pores in the mantle, which could otherwise lead to a preliminary release (Vogelhuber et al., 2003a,b), at a temperature above the glass transition point of the respective polymer. Two different methods to heat up the polymer mantle were tested and the results were compared. In the first method, the implants underwent a heat treatment in silicone oil at 110 °C for 3 s, whereas in the second method, the press was heated in a Memmert U40 drying oven (Memmert, Schwabach, Germany) and the implant was subsequently compressed with approximately 25 N for 10 s at 48 °C for $PLGA_{17}$ and $PLGA_{10}$, and 50 °C for PLA_{30}. Fig. 2 shows a schematic of the preparation procedure with the second compression step at higher temperatures.

2.3. In vitro release

Investigation of the in vitro release of pyranine matrices was carried out as follows: the implants were incubated at 37 °C in 50 ml 0.1 M phosphate buffer solution (pH 7.4) in 50 ml tubes (Sarstedt, Nümbrecht, Germany) while subjected to gentle shaking in a GFL 1086 horizontal shaking water bath (GFL, Burgwedel, Germany). To suppress the growth of bacteria and fungi, 0.05% sodium azide were added. The samples of 1.0 ml were replaced by the same volume of fresh buffer solution and the pyranine content of the samples was measured using a RF-1501 fluorescence spectrophotometer (Shimadzu, Duisburg, Germany, extinction wavelength: 403 nm, emission wavelength: 503 nm). Statistical calculations for the investigation of the onset of release were carried out using one-way analysis of variance (ANOVA) in conjunction with Tukey's studentized range test.

2.4. Release model

A convolution/deconvolution model, as described in the literature (Stepanek, 1976; Suverkrup, 2000; Langguth et al., 2004), was applied for describing release profiles:

$$R(t) = F(t) * I(t) \quad (1)$$

The mantle of the programmable implants was handled as a "black box", which reacts on an input function $I(t)$ (e.g. the release of a model drug from a core matrix) with a specific response function $R(t)$ (e.g. the release from embedded core). With the input function being a defined kinetic process (e.g. a bolus release from a core matrix), the system can be characterized by a system function, $F(t)$ (filter function, impulse response). One impulse function is the so-called Dirac's delta-impulse $\delta(t)$, which is a narrow rectangular impulse having the breadth T and the amplitude $1/T$, which results in a value of 1 for the area of the delta-impulse. Consequently, an input function

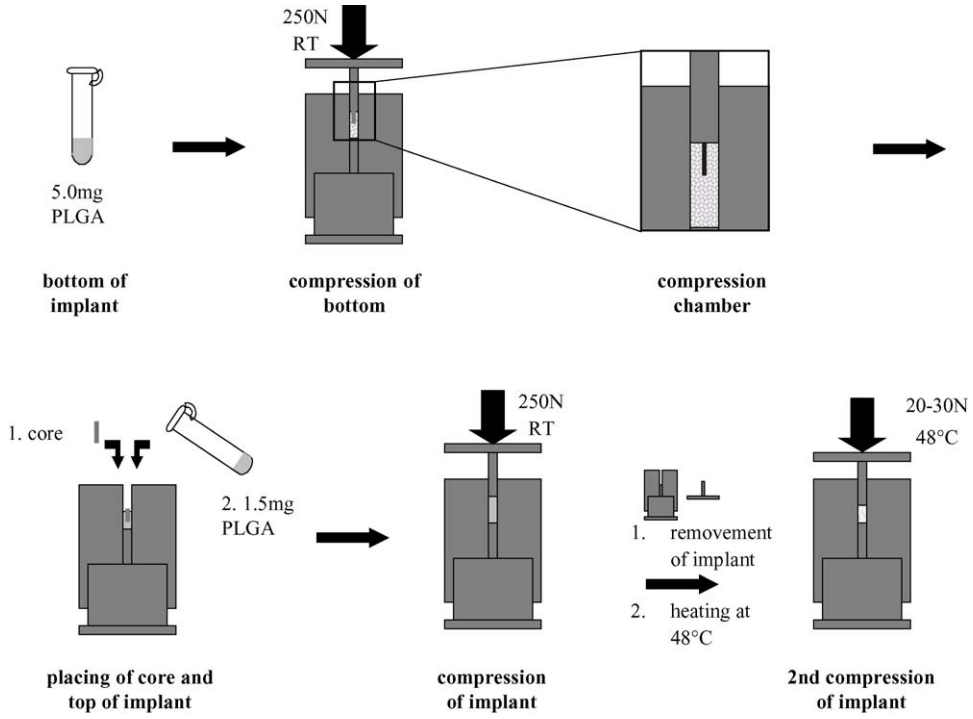

Fig. 2. Schematic illustration of the preparation procedure for programmable implants prior to their incubation in release medium. Closure of pores within the mantle occurred through a second compression step at higher temperatures (here 48 °C for $PLGA_{10}$ and $PLGA_{17}$).

of impulse $\delta(t)$, results in the following response function:

$$\delta(t) * F(t) = F(t) \tag{2}$$

With an amplitude of, for example, the value A, which differs from $1/T$, the area of the impulse equals $A{\cdot}T$. Such an impulse can generally be treated in the same manner as a Dirac-impulse, whose input and response functions are described as $AT\delta(t)$ and $ATF(t)$, respectively, which results in Eq. (3):

$$A \cdot T\delta(t) * F(t) = A \cdot T \cdot F(t) \tag{3}$$

A function $I(t)$, which can be integrated, can be taken to pieces having the form $A{\cdot}T\delta(t)$, whereby the amplitude-value A is replaced by the value of the function $I(iT)$. Considering the time-related shifting of the respective impulse, each of them becomes $I(iT){\cdot}T\delta(t - iT)$, which results in Eq. (4):

$$I(iT) \cdot T\delta(t - iT) * F(t) = I(iT) \cdot T \cdot F(t - iT) \tag{4}$$

The response function $R(t)$ now results from the overlapping of each single input function. Since $F(t)$ generally is not as short as the delta-impulse and can be maintained for longer time periods, the previous intervals have to be taken into account. Considering an overlapping of all parameters results in

$$R(nT) = T\sum_{i=0}^{n} I(iT)F(t - iT) \tag{5}$$

With the intervals being very small, an integral can be formulated and the discrete time values iT can be replaced by the variable τ:

$$R(t) = \int_0^t I(\tau)F(t - \tau)\,\mathrm{d}\tau \tag{6}$$

This integral is called convolution integral. A schematic of the relationship between the input function, filter function and response function is depicted in Fig. 3.

Generally, for such systems, it is true that when two of the depicted functions are known, the third function can be calculated from the others. For the mathematical modeling in the investigations of programmable implants, the numerical solution of the convolution integral was applied. Thereby, the input function or the filter function is considered to be constant within the respective time interval $0 \le T \le t$. Starting with Eq. (5) for the numerical convolution, $F(t)$ becomes the value $F(nT)$ of the function. Thus, it can be formulated that: $I(iT) = I_i$, $F(nT - iT) = F_{n-i}$,

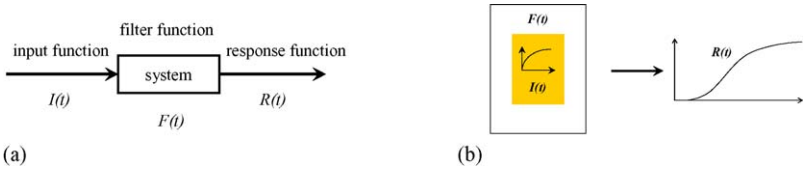

Fig. 3. (a) Schematic for a linear system, on which a convolution operation can be applied. For a known filter function, one special response function can be calculated for each known input function (adapted from Langguth et al. (2004)). (b) Visualization for the transfer of convolution theory to programmable implants.

which leads from Eq. (6) to

$$R_n = T\sum_{i=1}^{n} I_i F_{n-i} \tag{7}$$

Thus, the numerical algorithm depicted in Eqs. (8)–(11) can be formulated as solution of the convolution integral. This algorithm replaces the integration by multiplication and addition of numbers:

$$R_0 = (I_0 \cdot F_0) \cdot T \tag{8}$$

$$R_1 = (I_0 \cdot F_1 + I_1 \cdot F_0) \cdot T \tag{9}$$

$$R_2 = (I_0 \cdot F_2 + I_1 \cdot F_1 + I_2 \cdot F_0) \cdot T \tag{10}$$

$$R_n = (I_0 \cdot F_n + I_1 \cdot F_{n-1} + \cdots + I_{n-1} \cdot F_1 + I_n \cdot F_0) \cdot T \tag{11}$$

Applying this algorithm, constant values for the input function and the filter function within the respective time intervals were considered. Thus, the values change at the transition to the next time interval (staircase algorithm).

Values for the filter function were then calculated as follows:

$$F_0 = \frac{R_0}{T \cdot I_0} \tag{12}$$

$$F_1 = \frac{R_1}{T \cdot I_0} - \frac{I_1 \cdot F_0}{I_0} \tag{13}$$

$$F_2 = \frac{R_2}{T \cdot I_0} - \frac{I_1 \cdot F_1}{I_0} - \frac{I_2 \cdot F_0}{I_0} \tag{14}$$

$$F_n = \frac{R_n}{T \cdot I_0} - \frac{1}{I_0} \cdot \sum_{i=1}^{n} I_i \cdot F_{n-i} \tag{15}$$

Transferred to the programmable implants, convolution means the mathematical modeling of expected theoretical release profiles (=response function) when a core with known release properties (=input function) is embedded into a polymeric mantle (=filter function). Hence, the effect of the respective polymeric mantle material was calculated by the use of data gained from core matrices made of cholesterol and embedded cholesterol cores, which showed pulsatile release. For PLA_{30}, the calculation of the filter function was carried out using release data elaborated with a fast releasing polyanhydride by Vogelhuber et al. (2003a,b). Time intervals of $T = 1$ day were chosen for the calculations.

Since this mathematical method can only be applied to linear systems, the beginning of the mathematical modeling was fitted to the onset day of release. During the delay time, erosion of the polymeric mantle occurred and thus the filter would not have been linear. Changes within the mantle, taking place after the onset of release, were considered to be negligible in comparison to that occurring during the delay period, which led to linearity of the system. Due to this alignment, the first value for the input function (I_0 in Eqs. (8)–(11)) had to be the summarized release of the model drug until the day of the onset of release. Time-invariance, which is a second prerequisite, was taken for granted.

Since programmable implants do not exactly fit into the theory of convolution, due to the erosion of the mantle during the delay time, the mathematical model was applied, starting with the onset point of the release. Otherwise, calculation of the theoretical release curve would implicate that the mantle was intact throughout the release period, although erosion of the polymer occurred during the delay time. Changes within the mantle after the onset of release were considered to be tolerable, compared to the processes occurring before. The commencement of release was defined as the time point when 1.25% of the total dye content was liberated from the programmable implant. This value represents the 10-fold standard deviation of all values determined for time points at which no release occurred.

3. Results

3.1. In vitro release

First, the release of pyranine from the lipid core matrices without the polymer mantle was investigated (Fig. 4). Cholesterol showed the fastest release within 1.5 h, whereas glyceroltrilaurate (C12) and glyceroltristearate (C18) released the incorporated dye over a period of 14 days. The triglycerides with the intermediate fatty acid chains showed continuous release of the model compound over approximately 10 weeks for glyceroltripalmitate (C16) and 16 weeks for glyceroltrimyristate (C14).

The first steps to embed the cores into a bulk-eroding polymer mantle made of $PLGA_{17}$ were carried out using the manufacturing procedure with the heat treatment at 110 °C. Unfortunately, the resulting implants prematurely released their contents in an unpredictable manner, due to incomplete pore closure (data not shown). In addition to this irreproducible onset of release, DSC investigations showed that the heating step might additionally cause an alteration of the modification of the crystalline lipid core materials (data not shown).

A perfectly delayed release with a reproducible onset of all investigated core and mantle materials (Fig. 5) was obtained by applying a second compression step to the finished implants at temperatures above the glass transition temperature of the respective mantle polymer (Fig. 2). For all investigated groups, reproducible onset of the release after the degradation of the

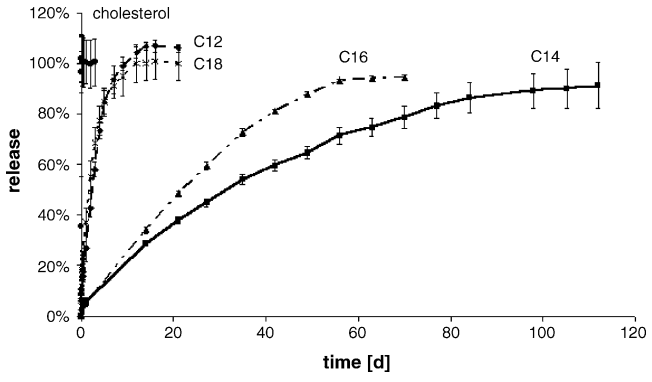

Fig. 4. In vitro release profiles of pyranine as model drug from variable lipophilic core materials; for different triglycerides the number of C-atoms of the fatty acid chains is given; data show mean ± S.D., ($n = 5$).

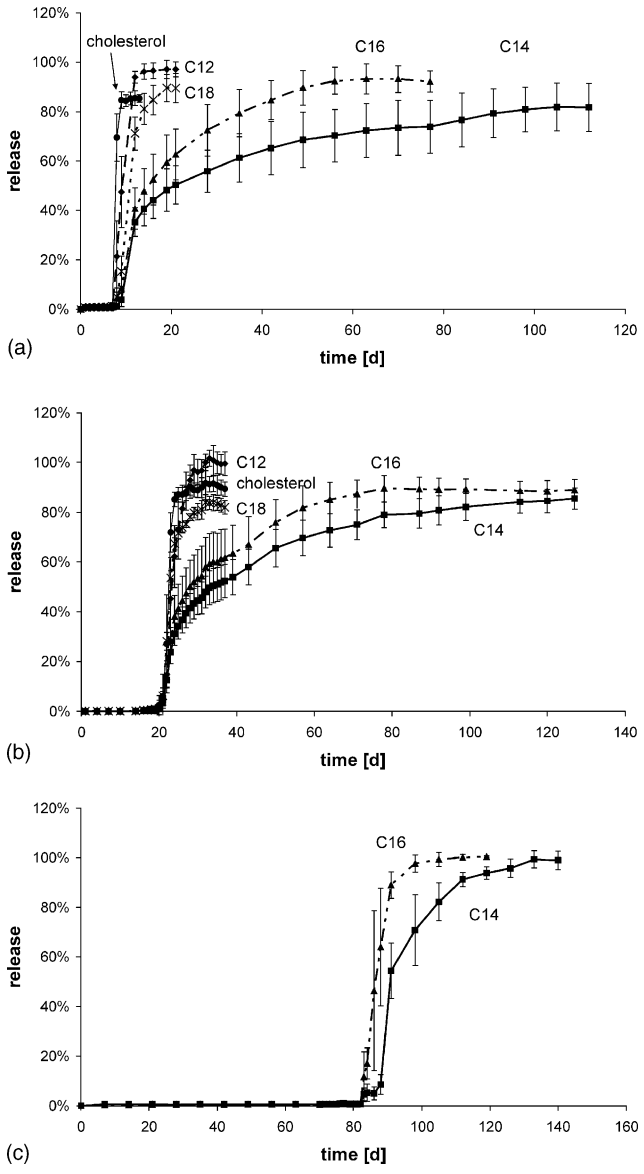

Fig. 5. In vitro release from programmable implants with different core and mantle materials; for different triglycerides the number of C-atoms of the fatty acid chains is given; values are expressed as mean ± S.D. (a) $PLGA_{10}$, $n = 4$; (b) $PLGA_{17}$, $n = 4$; (c) PLA_{30}, $n = 3$.

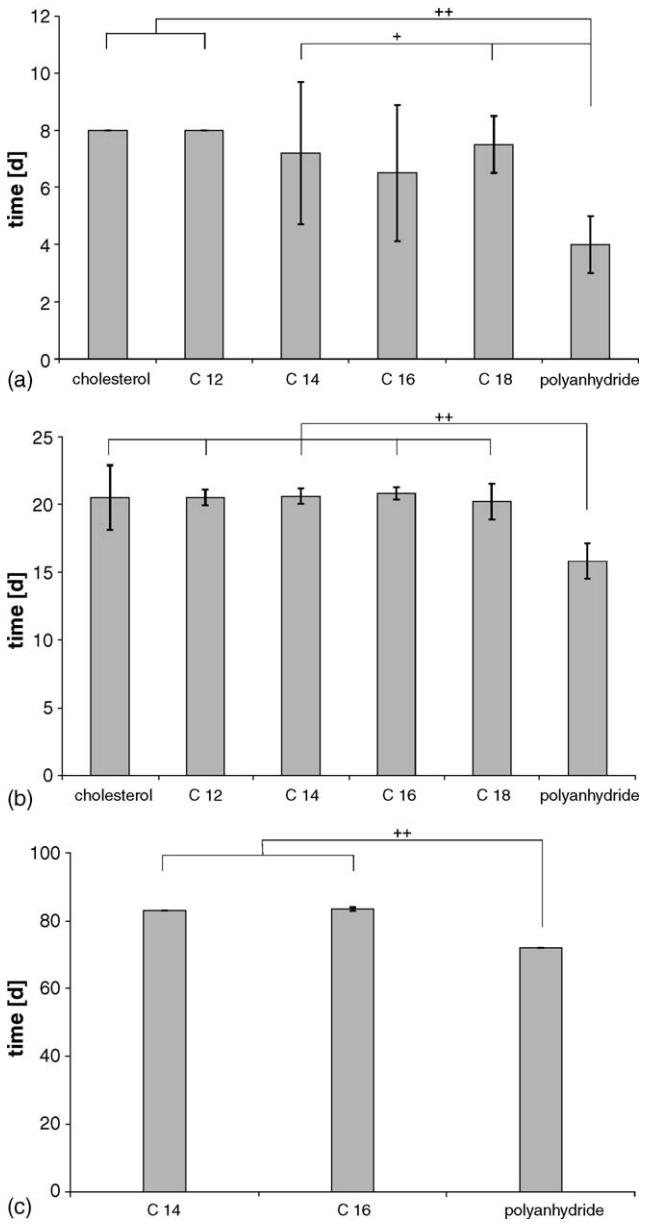

Fig. 6. Delay times for the onset of release observed for programmable implants prepared with varying core and mantle materials; data represent mean ± S.D., ++ indicates statistical significance with $p < 0.01$; + indicates statistical significance with $p < 0.05$. (a) $PLGA_{10}$, $n = 4$; (b) $PLGA_{17}$, $n = 4$; (c) PLA_{30}, $n = 3$.

polymer mantle was achieved (Fig. 6). Delay times were 8 days for $PLGA_{10}$, 21 days for $PLGA_{17}$ and 83 days when the PLA_{30} was used as mantle material (Fig. 6). Concomitantly, the desired prolonged release from the programmable implants over periods from 2 weeks (glyceroltrilaurate (C12) and glyceroltristearate (C18)) up to several months (glyceroltrimyristate (C14) glyceroltripalmitate (C16)) was achieved.

3.2. Mathematical modeling

For the design of programmable implants, it would be desirable to be able to predict the resulting release profile when a core with known release properties is embedded into a polymer mantle. Thus, a convolution model was applied to investigate whether a sensible prediction is possible. For the above-described mathematical modeling, the release of pyranine from a cholesterol core matrix was used as unit impulse function for the matrix materials $PLGA_{10}$ and $PLGA_{17}$. For the investigations carried out with PLA_{30} as polymeric mantle material, release data from polyanhydride cores gathered by Vogelhuber et al. (2003a,b) were used as the unit impulse function. Both core materials showed complete release of the incorporated pyranine within 1 day and can thus be used as unit impulse functions. The release profiles are shown in Fig. 7.

In Figs. 8–10, results of predicted release curves are compared with the experimental release data. When glyceroltrilaurate (C12) core matrices were embedded into a $PLGA_{10}$ mantle (Fig. 8a), a slower release was determined experimentally, com-

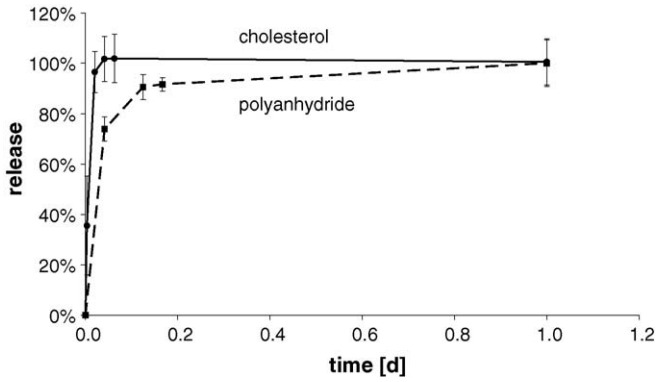

Fig. 7. Unit impulse functions used for mathematical modeling. Release from cholesterol cores was used for $PLGA_{10}$ and $PLGA_{17}$. Release from polyanhydride cores (Vogelhuber et al., 2003a,b) was used for PLA_{30}.

pared to the theoretical profiles. For glyceroltristearate (C18) cores embedded into this polymeric mantle material, the same effect was observed (Fig. 8b). Again in vitro release occurred slightly slower than predicted by the convolution model.

Differences between theoretical and experimental release profiles were also observed for the programmable implants prepared with glyceroltrimyristate (C14) as core material and $PLGA_{10}$ as polymer mantle (Fig. 8c). In this case, programmable implants released the model drug faster than predicted by the model. Deviations between the profiles were higher in the first period of release, but disappeared afterwards. Only minimal differences were observed between theoretically predicted and experimentally determined release profiles after 6–7 weeks and, as could have been expected for the end of the release experiment, good agreement was seen from day 70 to day 112. Fig. 8d shows similar results for glyceroltripalmitate (C16) cores. The again visible but less distinctive differences between predicted and in vitro determined release profiles of pyranine from the programmable implants were only visible within the first period of release, but not from day 35 to day 77, which was here the last time point of the experiment.

Concerning the results observed for programmable implants made with $PLGA_{17}$ as a polymeric mantle material, comparable findings were obtained for the two faster releasing core materials glyceroltrilaurate (C12) and glyceroltristearate (C18) as seen for $PLGA_{10}$. In these groups again the mathematically predicted release was slightly faster than experimentally determined (Fig. 9a and b). For the slower releasing core materials, glyceroltrimyristate (C14) and glyceroltripalmitate (C16), good correlations between the theoretically predicted release curves and the experimental data were achieved (Fig. 9c and d) when these matrix materials were embedded into a mantle of $PLGA_{17}$.

When the slowest eroding mantle material (PLA_{30}) was used for the embedding of glyceroltrimyristate (C14) and glyceroltripalmitate (C16), again a faster theoretically predicted release was observed compared to the in vitro findings (Fig. 10).

4. Discussion

4.1. In vitro release

All three of the mantle materials tested produced programmable implants with a reproducible onset of release. This confirms the suitability of the preparation method with a second compression step at a temperature above the T_g of the respective

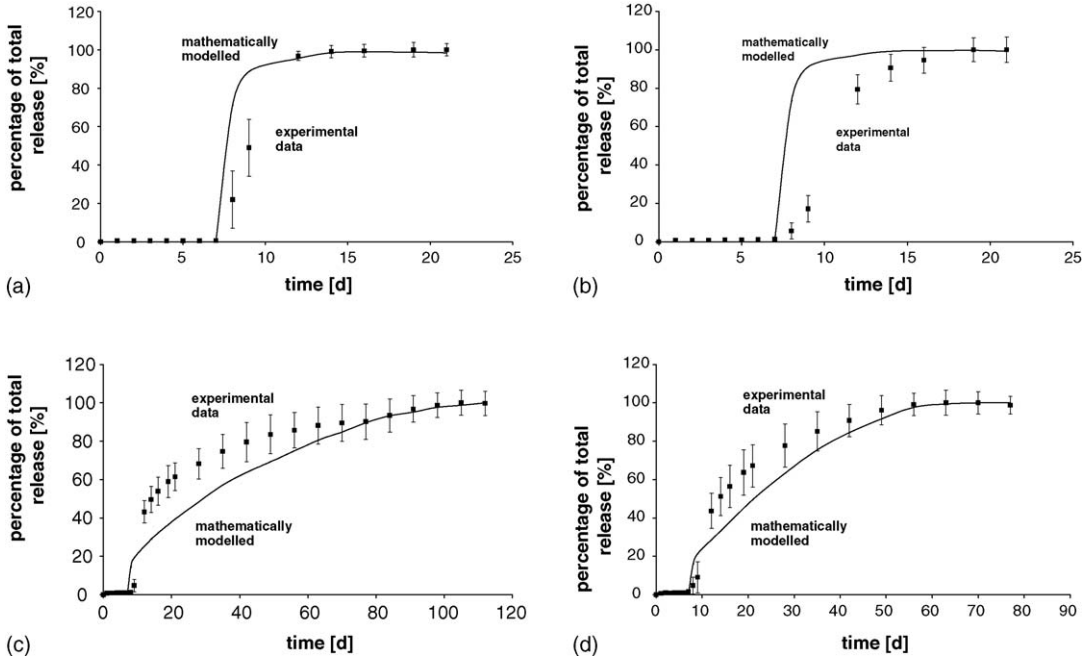

Fig. 8. Release profiles from programmable implants prepared with $PLGA_{10}$ as mantle material and different core materials. (■) Values of experimental release data are expressed as mean ± S.D.; (—) theoretical release calculated with mathematical model of convolution theory by the use of release data from cholesterol cores as unit impulse function. (a) Glyceroltrilaurate (C12) was used as core material, ($n = 5$); (b) glyceroltristearate (C18) was used as core material, ($n = 4$); (c) glyceroltrimyristate (C14) was used as core material, ($n = 5$); (d) glyceroltripalmitate (C16) was used as core material, ($n = 4$).

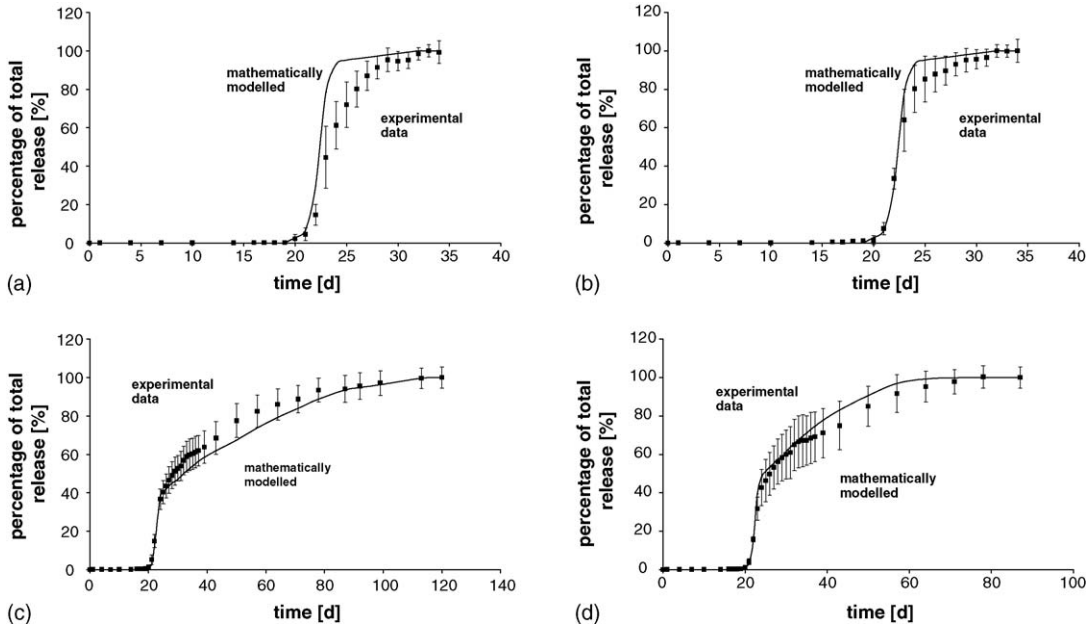

Fig. 9. Release profiles from programmable implants prepared with $PLGA_{17}$ as mantle material and different core materials. (■) Values of experimental release data are expressed as mean ± S.D., ($n = 5$); (—) theoretical release calculated with mathematical model of convolution theory by the use of release data from cholesterol cores as unit impulse function. (a) Glyceroltrilaurate (C12) was used as core material, ($n = 4$); (b) glyceroltristearate (C18) was used as core material, ($n = 4$); (c) glyceroltrimyristate (C14) was used as core material, ($n = 5$); (d) glyceroltripalmitate (C16) was used as core material, ($n = 5$).

mantle material to completely close pores, which occur within the polymer mantle. Additionally, the goal of the controlled release after the onset was achieved. Programmable implants containing glyceroltrilaurate (C12) or glyceroltristearate (C18) released the model drug over 2 weeks, whereas programmable implants prepared with glyceroltrimyristate (C14) or glyceroltripalmitate (C16) as matrix materials showed release periods extending over months. This is identical to the results for non-embedded core matrices (Fig. 4).

Vogelhuber et al. reported shorter delay times before the start of release for the three polymer materials (see bars of polyanhydride cores in Fig. 6), which is due to the different core materials used (Vogelhuber et al., 2003a,b). The degradation of a polyanhydride core, as it was used previously (Vogelhuber et al., 2003a,b) most likely led to an acidic microclimate, which worked as a catalyst and thus accelerated the degradation of the mantle polymer. This effect did not occur when lipid core materials were used and thus the delay time for the onset of the programmable implants increased significantly in most cases. Only for the group of glyceroltripalmitate cores embedded into $PLGA_{10}$ as mantle material, significance was not reached due to relatively high standard deviations.

4.2. Mathematical modeling

Matrices made by embedding glyceroltrilaurate (C12) and glyceroltristearate (C18) in $PLGA_{10}$ displayed slower release profiles experimentally than was predicted using the mathematical modeling (Fig. 8a and b). This can be explained by the percentage of dye released in the experiment from glyceroltrilaurate and glyceroltristearate core matrices into the polymer mantle during the delay time of the programmable implants and the fact that the onset day of release from programmable implants was chosen as starting point for the mathematical modeling, due to the above mentioned reasons. Regarding the algorithm depicted in Eq. (11), the consequence for the theoreti-

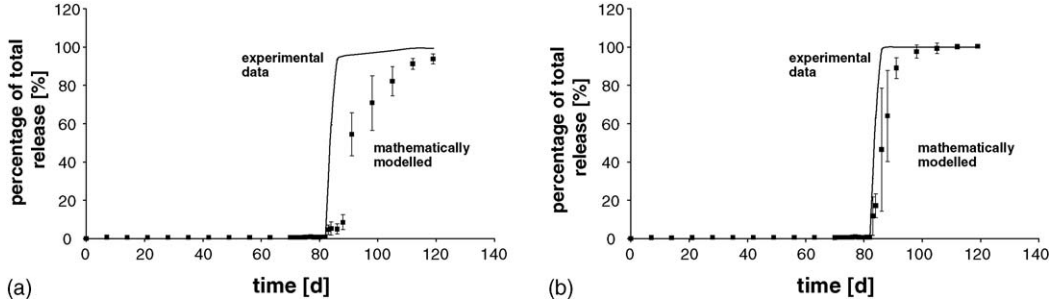

Fig. 10. Release profiles from programmable implants prepared with PLA_{30} as mantle material and different core materials. (■) Values of experimental release data are expressed as mean ± S.D., ($n = 3$); (—) theoretical release calculated with mathematical model of convolution theory by the use of release data from polyanhydride cores as unit impulse function. (a) Glyceroltrimyristate (C14) was used as core material; (b) glyceroltripalmitate (C16) was used as core material.

cal prediction can be briefly described as follows: the calculated amount of dye released from the core matrix until the onset (=I_0 in Eq. (11)) is treated in the mathematical model as if it was released in the experiment at day 1 (=I_0 of the unit impulse function). Thus, for example when a core matrix would show complete release of the model drug within 7 days or less experimentally, the predicted release profile for the programmable implants would always be exactly the same as it was obtained for the unit impulse function. But since release from the glyceroltrilaurate (C12) and glyceroltristearate (C18) core matrices in fact occurred over a longer period of time (Fig. 4), less diffusion of the model drug within the polymer mantle occurred during the delay time and thus explaining the slower in vitro release from the programmable implants compared to the theoretical prediction.

Release of the core matrices had reached approximately 87% at day 7 in the case of glyceroltrilaurate (C12) and glyceroltristearate (C18) core matrices released 91% of the dye within the first 7 days (Fig. 4), which was the delay time for $PLGA_{10}$. Thus, differences between the two release profiles were slightly higher in case of the C18 triglyceride compared to glyceroltrilaurate (C12).

But despite the alignment of the calculation method, the modeling resulted in a rather acceptable agreement between predicted and experimentally observed release curves.

The deviations in the first release period when glyceroltrimyristate (C14) was used as core material and $PLGA_{10}$ served as polymer mantle (Fig. 8c) may be explained by the relatively unsteady onset of release in this group, which was observed by slightly higher standard deviations, compared to the other investigated groups (Fig. 6). Since a slightly unsteady onset of release was also observed for glyceroltripalmitate cores (Fig. 6), the deviations in the early period after the onset (Fig. 8d) may be explained. Considering these results, a rather acceptable agreement between theory and experiment was observed for $PLGA_{10}$ as mantle material.

Programmable implants made with $PLGA_{17}$ as polymeric mantle material and the two faster releasing core materials, glyceroltrilaurate and glyceroltristearate, lead to slower release of the implants than predicted (Fig. 9a and b), due to the above described reasons. Nevertheless, when glyceroltrilaurate was used as core material, an acceptable prediction was obtained by convolution and in the glyceroltristearate group two release profiles even showed rather good agreement. Concerning the slower releasing core materials glyceroltrimyristate and glyceroltrilaurate, measured release profiles fitted nearly perfectly into the mathematically modeled prediction of release.

Concerning PLA_{30}, release of pyranine from glyceroltrimyristate cores was approximately 85% at day 83 (Fig. 4), which was the onset of the release from programmable implants with this mantle material. Glyceroltripalmitate cores show a complete release of 100% of the dye within an even shorter time period of 70 days (Fig. 4). However, the observed deviations between predicted and determined release profiles, which can be explained as aforementioned, were only minute and convolution again resulted in acceptable agreement between theory and experiment.

These results showed that it is possible to make sensible predictions for the release from programmable implants with the three investigated polymeric mantle materials when release from the core material is known. Concomitantly, convolution results calculated for PLA_{30} were obtained by using data from a polyanhydride core as unit impulse function. These release data for the pulsatile releasing core material were detailed by Vogelhuber 2 years ago (Vogelhuber et al., 2003a,b), but, nevertheless, a rather good fitting of the theoretical release curves and the experimental profiles obtained for investigations on triglycerides was observed. This additionally demonstrated the suitability of convolution for the modeling of theoretical release profiles from programmable implants. The prediction of the expected release profile is of great benefit for the design of programmable implants with desired release properties. When release from a core matrix is known, convolution alleviates the need for further in vitro release experiments with programmable implants, due to the possibility to sensibly predict the expected resulting release profile.

5. Conclusions

The goal of controlled release after the onset was realized by using triglycerides as core materials. Concomitantly, it was shown that applying a model based on convolution leads to a sensible prediction of the release of a drug from the programmable implants when release rate from the core material is known. This facilitates the design of programmable implants and offers a powerful tool for the adjustment of the resulting drug release to desired profiles.

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