How Autocatalysis Accelerates Drug Release from PLGA-Based Microparticles: A Quantitative Treatment

Juergen Siepmann,*,[†,‡] Khaled Elkharraz,[†] Florence Siepmann,[‡] and Diana Klose[†]

College of Pharmacy, Freie Universitaet Berlin, Kelchstr. 31, 12169 Berlin, Germany and School of Pharmacy, University of Lille, 3, rue du Professeur Laguesse, 59006 Lille, France

Received March 30, 2005; Revised Manuscript Received April 25, 2005

The major aim of this study was to better understand the importance of autocatalysis in poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles used as controlled drug delivery systems. Upon contact with biological fluids, PLGA is degraded into shorter chain alcohols and acids. An accumulation of the latter can lead to significant drops in micro-pH and subsequent accelerated polymer degradation. The system size, determining the diffusion path lengths, plays a crucial role for the occurrence/absence of autocatalytic effects. Using an oil-in-water solvent-extraction/evaporation process, different-sized drug-free and drug-loaded, PLGA-based microparticles were prepared and physicochemically characterized (SEM, DSC, SEC, optical microscopy, and UV-spectrophotometry) before and upon exposure to simulated biological fluids. Based on these experimental results, an adequate mathematical theory was developed describing the dominating mass transfer processes and chemical reactions. Importantly, a quantitative relationship could be established between the dimension of the device and the resulting drug release patterns, taking the effects of autocatalysis into account.

Introduction

The success of a medical treatment does not only depend on the pharmacodynamic activity of the drug, but to a large extent also to the availability of the active agent at the site of action in the human body. To improve the efficiency of a pharmacotherapy, time-controlled delivery systems can be used.[1,2] The drug can for example be embedded within a polymeric matrix restricting its release. Various types of polymers and dosage form designs (compositions, sizes and shapes) have been studied.[3−6] Poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles (spherical beads, generally 1−100 μm in diameter) offer various important advantages over other controlled drug delivery systems, such as (i) the possibility to accurately control the release rate of the drug over periods of days to months,[7] (ii) good biocompatibility,[8] (iii) easy administration by injection using standard syringes and needles, and (iv) complete biodegradability (avoiding the removal of empty remnants upon drug exhaust). Different types of active agents have been incorporated into this type of advanced drug delivery systems, several products are available on the market.[3,9−11]

Despite of the significant practical importance of PLGA-based microparticles, only little knowledge is yet available on the underlying mass transport mechanisms which are involved in the control of drug release from these systems.[4,12−14] This can be attributed to the complexity of the contributing processes, in particular the occurrence or absence of autocatalytic effects.[12] Poly(lactic-*co*-glycolic acid) (PLGA) is a polyester, which is cleaved into shorter chain alcohols and acids upon contact with water. It has been shown that the diffusion of biological fluids into PLGA-based microparticles is much more rapid than the subsequent ester hydrolysis. Thus, polymer degradation takes place throughout the device upon exposure to aqueous media ("bulk erosion").[15] Due to concentration gradients, the generated acids subsequently diffuse out of the microparticles into the surrounding bulk fluid, where they are neutralized. On the other hand, bases from the surrounding environment diffuse into the system, also neutralizing the generated acids. However, diffusional processes are relatively slow, and depending on the length of the diffusion pathways and mobility of the involved species, the rate at which the acids are generated can be higher than the rate at which they are neutralized. Consequently, the micro-pH within the system can significantly drop.[16]

Electron paramagnetic resonance (EPR) and laser confocal microscopic imaging techniques have been used to monitor such decreases in micro-pH.[17,18] As PLGA degradation is catalyzed by protons, a decrease in pH leads to an acceleration in polymer degradation (autocatalysis)[19,20] and increased drug mobilities. These effects can also be of major importance for other biomedical applications of PLGA, e.g., for the manufacture of tissue engineering scaffolds.[21] Clearly, the dimension of the PLGA-based device plays a major role whether autocatalytic effects occur (determining the length of the diffusion pathways and, thus, the diffusion rates of the involved acids and bases). Recently, Li and Schwende-

---

* To whom correspondence should be addressed. Present address: College of Pharmacy, Université de Lille, 3, rue du Professeur Laguesse, 59006 Lille, France. Phone: +33-3-20964708. Fax: +33-3-20964942. E-mail: jsiepmann@pharma.univ-lille2.fr.

† Freie Universitaet Berlin.

‡ University of Lille.

man[18] experimentally showed that the microparticle size can strongly affect the decrease in micro-pH within the system.

Up to now there is a significant lack of mathematical models taking all relevant physicochemical processes occurring during drug release from PLGA-based devices into account (in particular potential autocatalytic effects).[12,22] For poly(ortho esters), Thombre, Joshi, and Himmelstein[23,24] developed an interesting theory, considering the diffusion of 4 different species and increasing device permeability due to polymer degradation. To quantify the arbitrary chain cleavage in systems based on biodegradable polymers, Monte Carlo simulations have been used.[14,25,26] Charlier et al.[27] and Raman et al.[11] proposed mathematical models considering drug diffusion with a polymer molecular weight dependent diffusivity. However, so far no theory has been reported which quantifies drug release from PLGA-based microparticles, adequately taking autocatalytic effects (and the system size) into account.

The major aims of the present study were as follows: (i) to prepare and physicochemically characterize drug-loaded and drug-free, PLGA-based microparticles before and upon exposure to simulated biological fluids, (ii) to develop, based on the experimental results, a novel mathematical theory quantitatively describing drug release, and (iii) to get new insight into the underlying physicochemical processes, in particular into the importance of autocatalytic effects as a function of the system size.

Experimental Section

Chemicals. Poly(D,L-lactic-*co*-glycolic acid) (PLGA; Resomer RG 504H; PLGA 50:50; containing 25% D-lactic units, 25% L-lactic units, and 50% glycolic units; Boehringer Ingelheim Pharma KG, Ingelheim, Germany) and lidocaine (free base; Sigma-Aldrich Chemie GmbH, Steinheim, Germany) were used as received.

Microparticle Preparation. Lidocaine-loaded, PLGA-based microparticles were prepared with an oil-in-water (O/W) solvent extraction/evaporation technique: 46 mg of drug were dissolved within 9 g of dichloromethane. A total of 1 g of PLGA was added to this solution, which was shaken at room temperature to allow complete polymer dissolution. This organic phase was emulsified into 2.5 L of an outer aqueous poly(vinyl alcohol) solution (0.5% w/w) under stirring with a three-blade propeller for 30 min (2000 rpm). Upon contact with the outer aqueous phase, the organic solvent diffused into the water. Due to convection (and diffusion), the dichloromethane was distributed throughout the aqueous phase and evaporated at its surface. Thus, the dichloromethane concentration in the inner organic phase decreased with time, and the polymer concentration increased. At a certain time point, the PLGA precipitated and encapsulated the drug: the microparticles were formed. The latter were hardened by adding 2.5 L further outer aqueous phase. The particles were separated by filtration and subsequently freeze-dried to minimize the residual solvents' content. Different size fractions were obtained by sieving (average pore sizes of the sieves: 200, 125, 100, 63, and 40 μm; Retsch, Haan, Germany). Drug-free microparticles were prepared accordingly without lidocaine.

Particle Size Analysis. Particle size distributions and mean diameters of the complete batch and of each sieve fraction were determined using an optical microscope (Axioskop; Carl Zeiss Jena GmbH, Jena, Germany) equipped with an optical imaging system (EasyMeasure; INTEQ Informationstechnik GmbH, Berlin, Germany) (each measurement included at least 100 particles).

Determination of the Initial Drug loading. The initial, practical drug loading was determined by dissolving accurately weighed amounts of microparticles (approximately 15 mg) in 5 mL of acetonitrile and subsequent UV drug detection at $\lambda = 261.7$ nm (UV-2101PC; Shimadzu, Kyoto, Japan).

In Vitro Drug Release Studies. Lidocaine-loaded microparticles (approximately 400 mg) were placed within 40 mL of phosphate buffer pH 7.4 (USP XXVII) in 50 mL glass bottles. The latter were horizontally shaken at 37 °C (80 rpm; GFL 3033; Gesellschaft für Labortechnik GmbH & Co. KG, Burgwedel, Germany). At predetermined time intervals, 1 mL samples were withdrawn (replaced with fresh medium) and analyzed UV-spectrophotometrically at $\lambda = 261.7$ nm (UV-2101PC). Each experiment was conducted in triplicate.

Monitoring of Changes in the Physicochemical Properties of the Microparticles upon Exposure to the Release Medium. To monitor changes in the physicochemical properties of the delivery systems occurring during drug release, microparticles were treated as described in the section "In Vitro Drug Release Studies". At predetermined time intervals, the contents of the glass bottles were filtered (0.45 μm), and the obtained microparticles were freeze-dried and stored at 4 °C for further analysis.

The average polymer molecular weight of PLGA was determined by size exclusion chromatography (SEC). Microparticles were dissolved in chloroform (2% w/w), and 50 μL of this solution was injected into a SEC apparatus [SCL-10A (Shimadzu, Tokyo, Japan); column: PLgel 5 μm MIXED-D; 7.5 × 300 mm (Polymer Laboratories Ltd, Church Stretton, Shropshire, UK); mobile phase: chloroform containing 0.1% w/w triethanolamin; flow rate: 1 mL/min; column temperature 40 °C; detector: refractometer]. All indicated molecular weights are weight-average molecular weights (M_w), calculated using the Cirrus GPC software (Polymer Laboratories Ltd, Church Stretton, Shropshire, U.K.) and polystyrene standards (580-299400 Da) (Polymer Laboratories GmbH, Darmstadt, Germany).

Scanning electron microscopy (SEM) was used to characterize the internal and external morphology of the microparticles (S-4000; Hitachi High-Technologies Europe GmbH, Krefeld, Germany). Samples were covered under an argon atmosphere with a fine gold layer (10 nm; SCD 040; Baltec GmbH, Witten, Germany). Cross-sections of the microparticles were obtained after inclusion into water-based glue and cutting with a razor blade.

The glass transition temperature of the polymer (T_g) was analyzed by differential scanning calorimetry (DSC; DSC821e; Mettler Toledo, Giessen, Germany). Approximately 10 mg samples were heated in sealed aluminum pans (investigated temperature range: −10 to +80 °C, heating rate: 5 °C/min, two heating cycles).
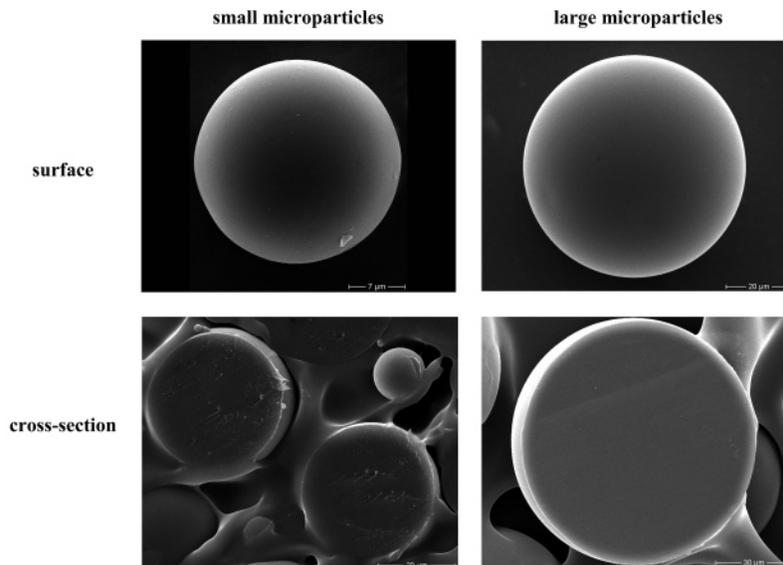
Figure 1. SEM pictures of small and large, lidocaine-loaded, PLGA-based microparticles before exposure to phosphate buffer pH 7.4 (surfaces and cross-sections, as indicated in the figure).

Table 1. Particle Size and Practical Drug-Loading of the PLGA-Based Microparticles (s = Standard Deviation)

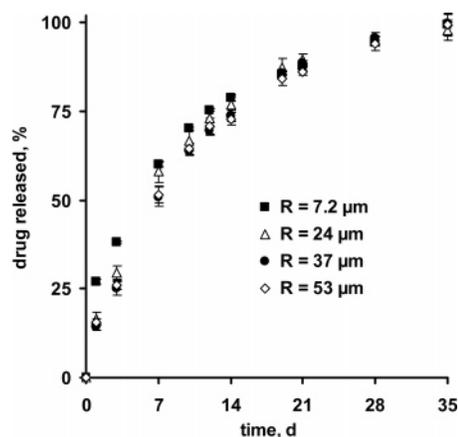| drug-loaded			drug-free	
mean radius, μm	s, μm	practical loading, % w/w	mean radius, μm	s, μm
7.2	1.2	4.0	7.9	4.0
24	5.1	4.0	26	3.1
37	3.0	4.0	38	5.9
53	5.2	3.9	55	3.9

Figure 2. Experimentally determined in vitro drug release kinetics from PLGA-based microparticles in phosphate buffer pH 7.4: Effects of the system size (the microparticle radius is indicated in the figure).

Results and Discussion

Microparticle Size, Morphology, and Drug Loading. As it can be seen in Figure 1, the obtained PLGA-based microparticles were spherical in shape and exhibited a smooth surface, irrespective of their size. Importantly, also their inner structure was homogeneous and nonporous. Only the results obtained with lidocaine-loaded systems are shown. However, the morphology of drug-free microparticles was very similar (data not shown). Furthermore, no drug crystals, amorphous aggregates, or nonencapsulated drug were visible (Figure 1).

Importantly, different-sized microparticles with very similar drug loadings could be obtained (Table 1). As the practical loading was rather low (around 4% w/w), the drug is molecularly dispersed within the polymeric matrix [monolithic solution; DSC measurements showed no evidence for drug melting events (data not shown); scanning electron microscopy showed smooth, homogeneous internal and external structures (Figure 1)].

In Vitro Drug Release. The effects of the microparticle size on the resulting drug release kinetics in phosphate buffer pH 7.4 are illustrated in Figure 2. Interestingly, varying the average particle diameter from 7.2 to 53 μm (thus, by a factor of 7) had no significant impact on the resulting relative lidocaine release rate. Neither the shape nor the slope of the curves was markedly affected. This is surprising, because diffusion is known to play a major role in the control of drug release from this type of drug delivery system.[12] Thus,

with increasing system dimension, the relative drug release rate should decrease (due to the increasing diffusion pathways). To better understand these observations, the effects of the microparticle size on the degradation kinetics of the polymer were studied using SEC, DSC, and SEM analysis.

Polymer Degradation. The effects of the microparticle size on the degradation kinetics of lidocaine-loaded and drug-free microparticles in phosphate buffer pH 7.4 at 37 °C are illustrated in Figure 3. As it can be seen, in both cases the degradation rate increases with increasing system size. This can be attributed to the increasing importance of autocatalytic effects with increasing device dimension. PLGA-based microparticles are known to be bulk eroding, because water penetration into the systems is much faster than the subsequent polymer chain cleavage.[15] Being a polyester, PLGA is cleaved into shorter chain alcohols and acids. Due to concentration gradients, the latter diffuse out of the microparticles into the surrounding bulk fluid. On the other hand, bases from the release medium (phosphate buffer pH 7.4) diffuse into the microparticles (also due to concentration gradients). Both types of mass transfer processes lead to the neutralization of the generated acids. However, diffusional
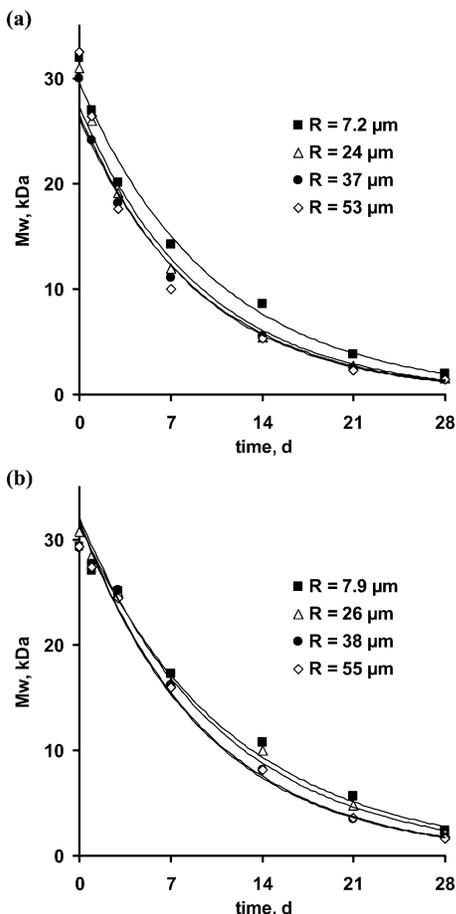
(a)

(b)

Figure 3. Effects of the size of PLGA-based microparticles on polymer degradation upon exposure to phosphate buffer pH 7.4: (a) lidocaine-loaded systems and (b) drug-free devices. Symbols indicate experimentally determined results, solid curves fitted pseudo-first-order kinetics [eq 1].

processes are relatively slow. Thus, the rate at which the acids are generated within the device can be higher than the rate at which they are neutralized.

This is especially true for the center of the microparticles, because here the diffusion pathways are the longest. A subsequent drop in the microenvironmental pH leads to accelerated PLGA degradation because the ester bond cleavage is catalyzed by protons. With increasing microparticle size, the diffusion pathways for the acids and bases increases. Thus, the diffusion rates decrease and the drop in micro-pH and acceleration of polymer degradation become more pronounced.

As PLGA degradation is known to follow pseudo-first-order kinetics, the following equation was fitted to the experimental results:

$$M_w(t) = M_{w0} \exp(-k_{degr}t) \qquad (1)$$

where $M_w(t)$ and M_{w0} are the average polymer molecular weight at time t and $t = 0$ (before exposure to the release medium), respectively, and k_{degr} denotes the degradation rate constant of the polymer. As it can be seen in Figure 3, good agreement between theory and experiment was obtained for lidocaine-loaded as well as drug-free microparticles, irrespective of the system size. Table 2 shows the exponential relationships for each type of microparticle, together with

Table 2. Pseudo-First-Order Equations Describing PLGA Degradation in the Investigated Lidocaine-Loaded and Drug-Free Microparticles[a]

radius, μm		R^2
	Lidocain-Loaded	
7.2	Mw[kDa] = 29.6 e$^{-0.6767t[weeks]}$	1.00
24	Mw[kDa] = 27.4 e$^{-0.7498t[weeks]}$	0.99
37	Mw[kDa] = 26.3 e$^{-0.7574t[weeks]}$	0.99
53	Mw[kDa] = 26.7 e$^{-0.7753t[weeks]}$	0.98
	Drug-Free	
7.9	Mw[kDa] = 31.5 e$^{-0.6058t[weeks]}$	0.99
26	Mw[kDa] = 32.2 e$^{-0.6479t[weeks]}$	1.00
38	Mw[kDa] = 31.9 e$^{-0.7199t[weeks]}$	1.00
55	Mw[kDa] = 31.8 e$^{-0.7280t[weeks]}$	1.00

[a] The coefficient of determination, R^2, serves as a measure for the goodness of the fittings.
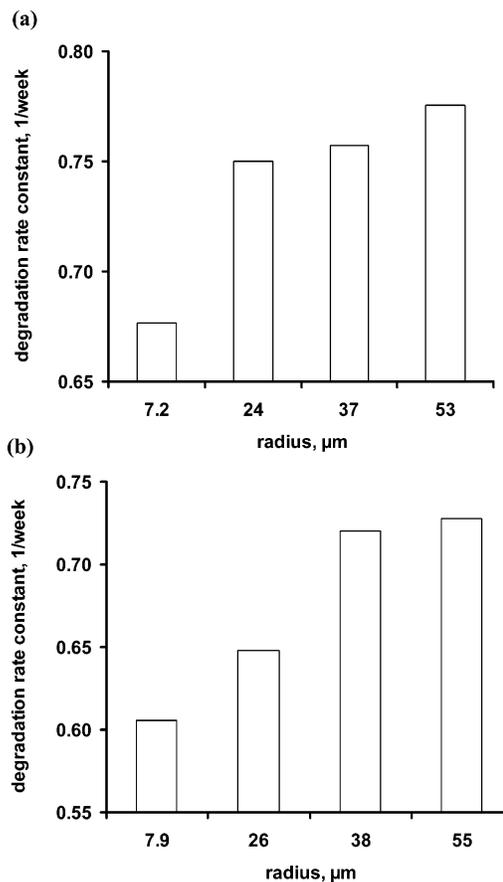
(a)

(b)

Figure 4. Dependence of the polymer degradation rate constant in the investigated PLGA-based microparticles on the system size: (a) lidocaine-loaded devices and (b) drug-free particles.

the coefficient of determination, being a measure for the goodness of the fit. The obtained values for k_{degr} are of the same order of magnitude as those reported previously in the literature for related systems.[27,28] The dependence of the obtained PLGA degradation rate constant on the system size for lidocaine-loaded and drug-free microparticles is illustrated in Figure 4. Importantly, the degradation rate constant monotonically increases with increasing microparticles size, irrespective of the presence/absence of drug.

In addition, changes in the glass transition temperature (T_g) of the polymer upon exposure of the microparticles to the release medium were monitored (Figure 5). These changes
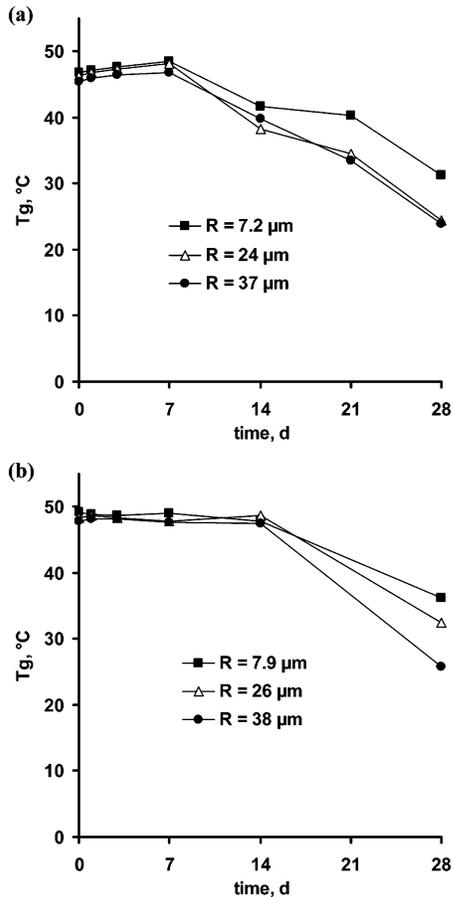
(a)

(b)

Figure 5. Decrease in the glass transition temperature (T_g) of the polymer in PLGA-based microparticles upon exposure to phosphate buffer pH 7.4: (a) lidocaine-loaded systems and (b) drug-free devices.

can be used as a measure for the degradation of PLGA: with decreasing polymer molecular weight the degree of polymer chain entanglement decreases and the mobility of the macromolecules increases, thus, the T_g decreases. Furthermore, the knowledge whether the matrix former is in the glassy or rubbery state is of major importance when studying drug release mechanisms. Macromolecules in the rubbery

state are much more mobile and allow significantly higher drug diffusion rates than those in the glassy state. As it can be seen in Figure 5, the decrease in the T_g of the polymer is more rapid in larger microparticles than in smaller ones (especially at late time points), irrespective of the presence/absence of the drug. This is a further indication for an increasing importance of autocatalytic effects with increasing system size.

It has to be pointed out that the DSC measurements were conducted with freeze-dried microparticles. Upon exposure to aqueous release media, water diffuses into the system, acting as a plasticizer for PLGA. As previously shown, the T_g subsequently significantly decreases, attaining values below 37 °C (body temperature).[13] Thus, the matrix former is in the rubbery state during drug release, allowing much higher diffusion rates than in the glassy state.

The effects of the microparticle size on the degradation behavior of the polymer were also monitored using scanning electron microscopy. Figure 6 shows surfaces and cross-sections of small and large, PLGA-based microparticles after 7 d exposure to phosphate buffer pH 7.4. Only results obtained with lidocaine-loaded systems are illustrated, the morphology of drug-free devices was very similar (data not shown). Clearly, the external and internal porosity was much higher in the case of large microparticles compared to smaller ones, confirming the increasing importance of autocatalytic effects with increasing system dimension.

These experimental results were used to get further insight into the underlying drug release mechanisms from PLGA-based microparticles. In particular, the consequences of autocatalysis for the resulting drug release kinetics were to be elucidated, because this is the most important aspect from a practical point of view (determining the drug concentration−time-profiles at the site of action in the human body and, thus, the success of the medical treatment).

Mathematical Modeling of Drug Release. As the investigated PLGA-based microparticles were spherical in shape (Figure 7a gives an overview on an ensemble of devices),

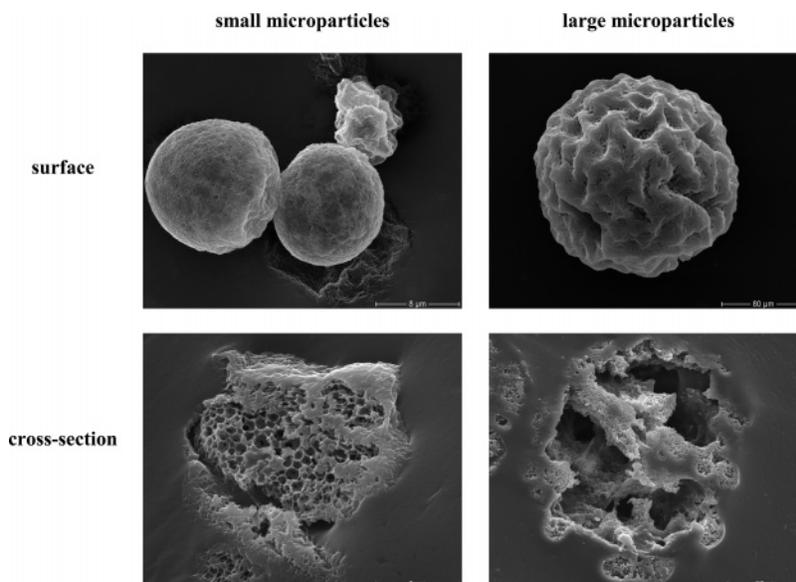**small microparticles**　　　**large microparticles**

Figure 6. SEM pictures of small and large, lidocaine-loaded, PLGA-based microparticles after 7 d exposure to phosphate buffer pH 7.4 (surfaces and cross-sections, as indicated in the figure).
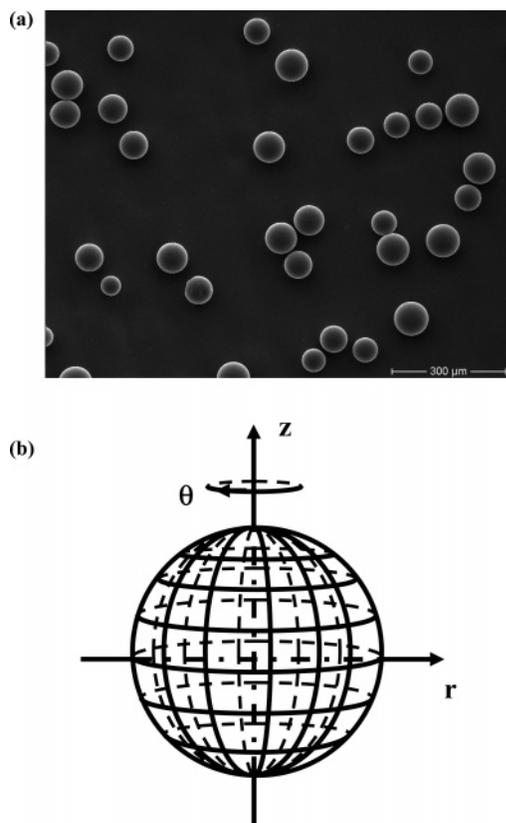
(a)

(b)

Figure 7. Spherical geometry of the investigated PLGA-based microparticles: (a) SEM picture of an ensemble of lidocaine-loaded systems and (b) schematic presentation of a single microparticle for mathematical analysis.

the mathematical analysis was based on this geometry (Figure 7b). Drug release from spherical dosage forms being controlled by diffusion can be described using Fick's second law of diffusion:[29]

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r}\right) \quad (2)$$

where c denotes the concentration of the drug, t represents time, D is the diffusion coefficient, and r is the radial coordinate.

This partial differential equation was solved considering the following initial and boundary conditions (which are based on the experimental results and the setup for the in vitro drug release measurements):

(i) At $t = 0$ (before exposure to the release medium), the drug is homogeneously distributed throughout the spherical dosage forms.

(ii) The initial drug concentration is below the solubility of the drug (molecular dispersion, monolithic solution).

(iii) The rate at which the drug leaves the device is always equal to the rate at which the drug is brought to the surface by internal diffusion (no drug accumulation at the surface). The constant of proportionality is called mass transfer coefficient in the boundary layer, k:

$$-D\left(\frac{\partial c}{\partial r}\right)_R = k(c_{surface} - c_\infty) \quad (3)$$

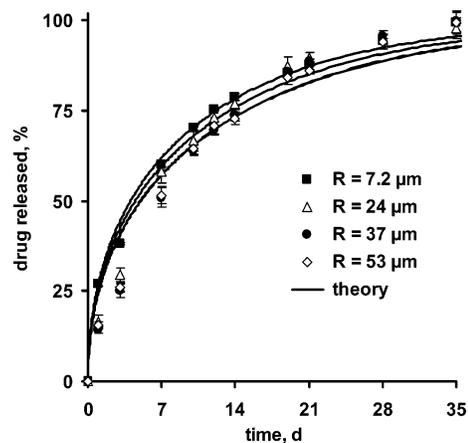where $c_{surface}$ is the actual drug concentration at the surface

Figure 8. Mathematical modeling of drug release from different-sized, PLGA-based microparticles in phosphate buffer pH 7.4 [solid curves: theory (curves for $R = 37$ μm and $R = 53$ μm are very similar); symbols: experimental results (indicated for reasons of comparison)].

at time t, and c_∞ is the corresponding concentration which is at equilibrium with the liquid; R represents the radius of the sphere.

(iv) Perfect sink conditions are provided throughout the experiment.

The initial value problem described by eq 2 and conditions (i) to (iv) can be solved leading to[30]

$$\frac{M_\infty - M_t}{M_\infty} = \sum_{n=1}^{\infty}\frac{6S^2}{\beta_n^2(\beta_n^2 + S^2 - S)}\exp\left(-\frac{\beta_n^2}{R^2}Dt\right) \quad (4)$$

where M_∞ and M_t denote the absolute cumulative amounts of drug released at infinite time and time t, respectively; the β_ns are the roots of

$$\beta_n \cot\beta_n = 1 - S \quad (5)$$

with the dimensionless number

$$S = \frac{kR}{D} \quad (6)$$

The values of β_n are given in tables for various values of S.[29,30]

When fitting eqs 4−6 to the experimentally measured drug release kinetics, good agreement between theory and experiment was obtained in all cases (Figure 8). Based on these calculations, the apparent diffusion coefficients in the polymeric matrix, D, as well as the mass transfer coefficients within the liquid boundary layers, k, could be determined. Importantly, the latter were found to be very high (with $kR/D > 100$) for all types of microparticles. Thus, the diffusional resistance within the unstirred liquid boundary layers was negligible compared to the diffusional resistance within the polymeric matrixes under the given experimental conditions. Consequently, instead of eqs 4−6 also the following (simplified) solution of Fick's second law can be used to describe drug release and to determine the apparent diffusion coefficients of the drug

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{n^2 \pi^2}{R^2} Dt\right) \qquad (7)$$

The obtained drug diffusivities were in the range of 4.6×10^{-14} to 2.0×10^{-12} cm²/s, thus, in the same order of magnitude as those reported in the literature on related systems.[11,31,32] Their dependence on the microparticle size is illustrated in Figure 9.

Clearly, the diffusivity (being a measure for the mobility of lidocaine in the PLGA-based devices) significantly increased with increasing microparticle dimension. This can be explained by the increasing importance of autocatalytic effects as discussed above. Interestingly, these phenomena play an important role even in very small microparticles (radius < 10 μm) (Figure 9). The following quantitative relationship between the diffusion coefficient of the drug, D, and the radius of the microparticles, R, could be established ($R^2 = 1.00$)

$$D[\text{cm}^2/\text{s}] = 1.1 \times 10^{-15} R[\mu\text{m}]^{1.887} \qquad (8)$$

This tremendous dependence of the mobility of the drug within the polymeric matrix on the radius of the microparticles clearly demonstrates the fundamental importance of autocatalytic effects in this type of controlled drug delivery system.

For reasons of comparison, eq 7 was also used to calculate the resulting drug release kinetics from the investigated microparticles, assuming the absence of autocatalytic effects (considering the same diffusion coefficient for all microparticle sizes, e.g., the one for $R = 7.2$ μm). The theoretical lidocaine release patterns for microparticles with a radius of 7.2, 24, 37, and 53 μm are shown in Figure 10. Clearly, the relative release rate significantly decreases with increasing system dimension (due to the increasing length of the diffusion pathways). Comparing these theoretical drug release profiles with the experimentally determined ones (Figure 2), it becomes evident that autocatalytic effects must properly be taken into account when developing and optimizing this
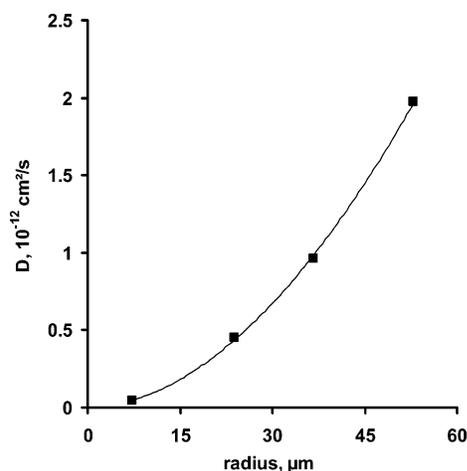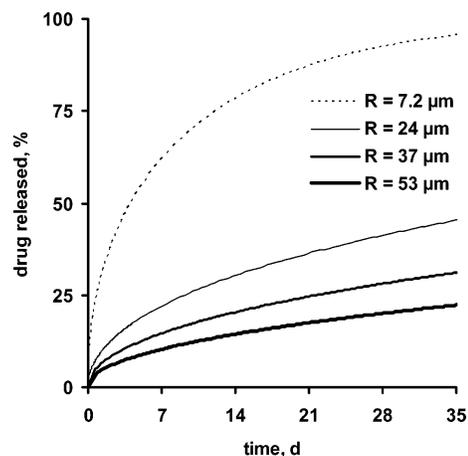

Figure 10. Theoretically calculated lidocaine release from different-sized, PLGA-based microparticles assuming the absence of auto-catalytic effects (the microparticle radii are indicated in the figure; $D = 4.6 \times 10^{-14}$ cm²/s was assumed for all systems).

type of controlled drug delivery system. Importantly, even very small-sized microparticles (radius < 10 μm) are affected.

Conclusions

New insight into the importance of autocatalytic effects in PLGA-based microparticles could be gained. In particular, the effects of the system dimension on the resulting drug release kinetics could (for the first time) be described in a quantitative way considering accelerated polymer degradation and increased drug mobility within the matrix. This knowledge can help to facilitate the development of new pharmaceutical products and to optimize existing ones. In addition, the obtained experimental and theoretical results can be useful also for other PLGA applications, such as for the manufacture of biodegradable tissue engineering scaffolds.

References and Notes

(1) Langer, R. S. *Nature* **1998**, *392*, 5−10.
(2) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181−3198.
(3) Ravivarapu, H. B.; Burton, K.; DeLuca, P. P. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 263−270.
(4) Siepmann, J.; Peppas, N. A. *Adv. Drug Delivery Rev.* **2001**, *48*, 139−157.
(5) Lee, K. E.; Kim, B. K.; Yuk, S. H. *Biomacromolecules* **2002**, *3*, 1115−1119.
(6) Csaba, N.; Caamano, P.; Sanchez, A.; Dominguez, F.; Alonso, M. J. *Biomacromolecules* **2005**, *6*, 271−278.
(7) Benoit, J. P.; Faisant, N.; Venier-Julienne, M. C.; Menei, P. *J. Controlled Release* **2000**, *65*, 285−96.
(8) Fournier, E.; Passirani, C.; Montero-Menei, C. N.; Benoit, J. P. *Biomaterials* **2003**, *24*, 3311−3331.
(9) Woo, B. H.; Jiang, G.; Jo, Y. W.; DeLuca, P. P. *Pharm. Res.* **2001**, *18*, 1600−1606.
(10) Na, D. H.; Youn, Y. S.; Lee, S. D.; Son, M. W.; Kim, W. B.; DeLuca, P. P.; Lee, K. C. *J. Controlled Release* **2003**, *92*, 291−299.

Figure 9. Dependence of the apparent diffusion coefficient of the drug on the size of the PLGA-based microparticles (the solid curve indicates an exponential relationship between the diffusivity and the radius of the system).

(11) Raman, C.; Berkland, C.; Kim, K. K.; Pack, D. W. *J. Controlled Release* **2005**, *103*, 149−158.

(12) Siepmann, J.; Göpferich, A. *Adv. Drug Delivery Rev.* **2001**, *48*, 229−247.

(13) Faisant, N.; Siepmann, J.; Benoit, J. P. *Eur. J. Pharm. Sci.* **2002**, *15*, 355−366.

(14) Siepmann, J.; Faisant, N.; Benoit, J. P. *Pharm. Res.* **2002**, *19*, 1885−1893.

(15) von Burkersroda, F.; Schedl, L.; Göpferich, A. *Biomaterials* **2002**, *23*, 4221−4231.

(16) Kang, J.; Schwendeman, S. P. *Biomaterials* **2002**, *23*, 239−245.

(17) Brunner, A.; Mäder, K.; Göpferich, A. *Pharm. Res.* **1999**, *16*, 847−853.

(18) Li, L.; Schwendeman, S. P. *J. Controlled Release* **2005**, *101*, 163−173.

(19) Grizzi, I.; Garreau, S. L.; Vert, M. *Biomaterials* **1995**, *16*, 305−311.

(20) Lu, L.; Garcia, C. A.; Mikos, A. G. *J. Biomed. Mater. Res.* **1999**, *46*, 236−244.

(21) Croll, T. I.; O'Connor, A. J.; Stevens, G. W.; Cooper-White, J. J. *Biomacromolecules* **2004**, *5*, 463−473.

(22) Lemaire, V.; Bélair, J.; Hildgen, P. *Int. J. Pharm.* **2003**, *258*, 95−107.

(23) Thombre, A. G.; Himmelstein, K. J. *AIChE J.* **1985**, *31*, 759−766.

(24) Joshi, A.; Himmelstein, K. J. *J. Controlled Release* **1991**, *15*, 95−104.

(25) Göpferich, A. *Biomaterials* **1996**, *17*, 103−114.

(26) Zygourakis, K.; Markenscoff, P. A. *Biomaterials* **1996**, *17*, 125−135.

(27) Charlier, A.; Leclerc, B.; Couarraze, G. *Int. J. Pharm.* **2000**, *200*, 115−120.

(28) Kenley, R. A.; Lee, M. O.; Mahoney, T. R.; Sanders, L. M. *Macromolecules* **1987**, *20*, 2398−2403.

(29) Crank, J. *The Mathematics of Diffusion*; Clarendon Press: Oxford, 1975.

(30) Vergnaud, J. M. *Controlled Drug Release of Oral Dosage Forms*; Ellis Horwood: Chichester, U.K., 1993.

(31) Pitt, C. G.; Jeffcoat, A. R.; Zweidinger, R. A.; Schindler, A. *J. Biomed. Mater. Res.* **1979**, *13*, 497−507.

(32) Kang, J.; Schwendeman, S. P. *Macromolecules* **2003**, *36*, 1324−1330.