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How porosity and size affect the drug release mechanisms from PLGA-based microparticles

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Abstract

Porous, poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles were prepared using a water-in-oil-in-water (W/O/W) solvent extraction/evaporation technique. Lidocaine was used as a model drug and different-sized particle fractions were obtained by sieving. The physicochemical properties of the devices and changes thereof upon exposure to phosphate buffer pH 7.4 were studied using optical and scanning electron microscopy, size exclusion chromatography (SEC), differential scanning calorimetry (DSC), gravimetric analysis and in vitro drug release measurements. In contrast to non-porous microparticles of identical composition, the relative drug release rate was found to decrease with increasing system size. SEC, DSC and gravimetric analysis showed that the degradation rate of the polymer increased with increasing microparticle dimension, indicating that autocatalytic effects play an important role even in small and highly porous PLGA-based microparticles. However, these effects were much less pronounced than in non-porous devices. Importantly, they were overcompensated by the effects of the increasing diffusion pathway lengths with increasing system dimension. Thus, high initial microparticle porosities do not only lead to increased drug mobilities, but can also fundamentally alter the underlying mass transport mechanisms.

Keywords: Porosity; Autocatalysis; PLGA; Controlled release; Microparticle

1. Introduction

Poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles offer various advantages compared to other controlled drug delivery systems, including: (i) the possibility to accurately control the resulting drug release kinetics over periods of days to months; (ii) complete biodegradability (avoiding the removal of empty remnants upon drug exhaust); (iii) good biocompatibility, even if directly administered into brain tissue (Fournier et al., 2003); (iv) easy administration using standard syringes and needles. Thus, this type of controlled drug delivery system can be very helpful to optimize the therapeutic efficiency of medical treatments and to reduce serious side effects (Benoit et al., 2000; Ravivarapu et al., 2000).

Despite of the steadily increasing practical importance of PLGA-based microparticles, only limited knowledge is yet available on the physicochemical processes, which are involved in the control of drug release from these systems (Siepmann and Göpferich, 2001; Raman et al., 2005). This can at least partially be attributed to the complexity of the occurring phenomena (Faisant et al., 2002; Siepmann et al., 2002). Upon contact with aqueous media water imbibes into the microparticles, and PLGA (being a polyester) starts to be degraded. It is well known that the rate at which water imbibes into PLGA-based microparticles is much higher than the rate at which the ester bonds are hydrolytically cleaved (von Burkersroda et al., 2002). Thus, the entire particle is rapidly wetted and polymer degradation occurs throughout the device ("bulk erosion"). If the drug is not already molecularly dispersed within the system, drug crystals and/or amorphous aggregates dissolve. Due to concentration gradients the dissolved drug molecules subsequently diffuse out of the microparticles into the surrounding bulk fluid.

In addition to these processes, autocatalytic effects might occur in PLGA-based drug delivery systems (Grizzi et al., 1995; Lu et al., 1999; Grayson et al., 2005). PLGA is hydrolytically

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cleaved into shorter chain alcohols and acids. As PLGA-based microparticles are bulk-eroding, acids are generated throughout the devices and (similar to the drug) diffuse out into the surrounding release medium or human body fluids, where they are neutralized. In addition, bases from the bulk fluid diffuse into the microparticles, neutralizing the generated acids. However, diffusional mass transport is relatively slow, especially in polymer-based matrices. Thus, the rate at which the acids are generated within the microparticles can be higher than the rate at which they are neutralized. Consequently, the pH within the system can significantly drop (Brunner et al., 1999; Li and Schwendeman, 2005). As the ester bond cleavage is catalyzed by protons, such decreases in micro-pH can lead to accelerated polymer degradation (autocatalysis) (Grizzi et al., 1995; Lu et al., 1999). There are two potential important consequences of this phenomenon: (i) drug stability might be affected (especially in the case of protein-based drugs) and (ii) the mobility of the drug molecules can significantly increase (due to the accelerated decrease in the average polymer molecular weight), resulting in increased drug release rates. It has recently been shown in a quantitative way that these autocatalytic effects are of major importance in non-porous, PLGA-based microparticles (Siepmann et al., 2005).

Different strategies can be used to avoid/reduce autocatalytic effects in PLGA-based microparticles, including a decrease in the length of the diffusion pathways for the acids and bases (reduced microparticle size) (Dunne et al., 2000), the addition of bases to the formulation (Kang and Schwendeman, 2002), and an increase in the mobility of the involved diffusing species. One possibility to increase the diffusivity of water-soluble molecules in polymeric matrices is to increase the porosity of the system (Fan and Singh, 1989). Using adequate preparation techniques [e.g. water-in-oil-in-water (W/O/W) solvent extraction/evaporation methods], highly porous PLGA-based microparticles can be obtained.

The major aims of the present study were: (i) to prepare highly porous, drug-loaded and drug-free, PLGA-based microparticles of different size; (ii) to physicochemically characterize the systems before and upon exposure to phosphate buffer pH 7.4; (iii) to study the effects of the porosity and size of the microparticles on the resulting drug release kinetics and polymer degradation behavior; (iv) to better understand the underlying drug release mechanisms, in particular the importance of autocatalytic effects.

2. Materials and methods

2.1. Materials

Poly(D,L-lactic-*co*-glycolic acid) (PLGA; Resomer RG 504H; PLGA 50:50; containing 25% D-lactic units, 25% D-lactic units and 50% glycolic units) (Boehringer Ingelheim Pharma KG, Ingelheim, Germany), lidocaine (free base; Sigma–Aldrich Chemie GmbH, Steinheim, Germany) and polyvinyl alcohol (Mowiol 4–88; Kuraray Specialities Europe GmbH, Frankfurt am Main, Germany) were used as received.

2.2. Microparticle preparation

Lidocaine-loaded, PLGA-based microparticles were prepared by a water-in-oil-in-water (W/O/W) solvent extraction/evaporation technique: 0.5 g de-mineralized water was emulsified into a solution of lidocaine (46.5 mg) and PLGA (1 g) in methylene chloride (9 g) using an Ultra-Turrax® (60 s, 13,000 rpm; T25 basic, IKA-Werke, Staufen, Germany). This primary water-in-oil (W/O) emulsion was dispersed within 2.5 l of an outer aqueous polyvinyl alcohol solution (0.5%, w/w) under stirring with a three-blade propeller for 30 min (2000 rpm), inducing microparticle formation. 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. Drug-free microparticles were prepared accordingly without lidocaine. Different size fractions were obtained by sieving (average pore sizes of the sieves: 200, 125, 100, 63 and 40 μm for lidocaine-loaded systems; 315, 200, 150 and 50 μm for drug-free devices; Retsch, Haan, Germany).

2.3. 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 imaging system (EasyMeasure; INTEQ Informationstechnik GmbH, Berlin, Germany) (each measurement included at least 100 particles).

2.4. 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 acetonitrile and subsequent UV drug detection at $\lambda = 261.7$ nm (UV-2101PC; Shimadzu, Kyoto, Japan).

2.5. In vitro drug release studies

Lidocaine-loaded microparticles (approximately 400 mg) were placed within 40 ml phosphate buffer pH 7.4 (USP XXVII) (assuring perfect sink conditions) 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 pre-determined 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.

2.6. Monitoring of changes in the physicochemical properties of the microparticles upon exposure to the release medium

Microparticles were treated as described in the Section 2.5. At predetermined time intervals, the contents of the glass bottles was filtered (0.45 μm), the obtained microparticles freeze-dried, weighed [dry weight (t)] and stored at 4 °C for further analysis.

The relative dry weight of the microparticles at time t was calculated as follows:

$$\text{dry weight}\,(\%)(t) = \frac{\text{dry weight}\,(t)}{\text{dry weight}\,(t=0)} \cdot 100 \quad (1)$$

where dry weight ($t=0$) denotes the initial dry weight of the microparticles (before exposure to the release medium).

The average polymer molecular weight of PLGA was determined by size exclusion chromatography (SEC). Microparticles were dissolved in chloroform (2%, w/w); 50 μl of this solution were injected into a SEC apparatus [SCL-10A (Shimadzu, Tokyo, Japan); column: PLgel 5 μm MIXED-D; 7.5 mm × 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 polymer molecular weights are weight-average molecular weights (Mw), calculated using the Cirrus™ GPC software (Polymer Laboratories Ltd., Church Stretton, Shropshire, UK) and polystyrene standards (580–299,400 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 determined 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).

2.7. Mathematical modeling of drug release

As previously described in detail (Siepmann et al., 2005), the following analytical solution of Fick's second law of diffusion can be used to describe drug release from lidocaine-loaded, PLGA-based microparticles (of identical composition as those investigated in the present study, but in contrast to the latter being non-porous):

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left(-\frac{n^2 \cdot \pi^2}{R^2} \cdot D \cdot t\right) \quad (2)$$

where M_∞ and M_t denote the absolute cumulative amounts of drug released at infinite time and time t, respectively; R represents the radius of the microparticles and D the apparent diffusion coefficient of the drug within the polymeric system.

This equation can be derived from Fick's second law, assuming that drug diffusion is the solely release rate controlling mechanism and considering the following initial and boundary conditions:

(i) At $t=0$ (before exposure to the release medium), the drug is homogeneously distributed throughout the microparticles.
(ii) The initial drug concentration is below the solubility of the drug (molecular dispersion, monolithic solution).
(iii) The diffusional resistance for drug release within the unstirred liquid boundary layers surrounding the microparticles is negligible compared to the diffusional resistance within the polymeric systems under the given experimental conditions.
(iv) Perfect sink conditions are provided throughout the experiment.

3. Results and discussion

3.1. Drug loading, size, shape and morphology of the microparticles

As it can be seen in Fig. 1, spherical drug-loaded microparticles of different size were obtained. Surfaces (lower and higher magnification) and cross-sections (lower magnification) of small, medium-sized and large, PLGA-based microparticles before exposure to the release medium ($t=0$) are illustrated. Importantly, the systems are highly porous, irrespective of their dimension. This is in contrast to microparticles of identical composition previously prepared by an oil-in-water (O/W) solvent extraction/evaporation technique (Siepmann et al., 2005). The difference in porosity is due to the presence of the inner aqueous phase during microparticle formation in the present study [water-in-oil-in-water (W/O/W) method]. Upon organic solvent extraction/evaporation, the polymer concentration in the organic phase continuously increases. At a certain methylene chloride concentration, the PLGA starts to precipitate and encapsulates the drug as well as the inner water droplets. Upon elimination of the water during drying, empty holes remain. Interestingly, these holes were uniformly distributed throughout the microparticles, irrespective of their size. [Remark: in some of the cross-sections the holes have (partially) been closed during microparticle cutting]. Only pictures of lidocaine-loaded systems are illustrated, the inner and outer morphology of drug-free devices was very similar (data not shown).

Importantly, the practical drug loading was almost identical in all cases (4.0–4.1%, w/w), indicating uniform and relatively high drug encapsulation efficiencies (85–88%), irrespective of the microparticle size (Table 1). As the solubility of the drug

Table 1
Particle size and practical drug loading of the investigated porous, PLGA-based microparticles (s = standard deviation)

Lidocaine-loaded			Drug-free	
Mean radius (μm)	s (μm)	Practical loading (%, w/w)	Mean radius (μm)	s (μm)
7.3	4.1	4.0	12	5
26	3	4.0	48	15
39	5	4.1	85	14
54	3	4.1	114	13
73	8	4.1		

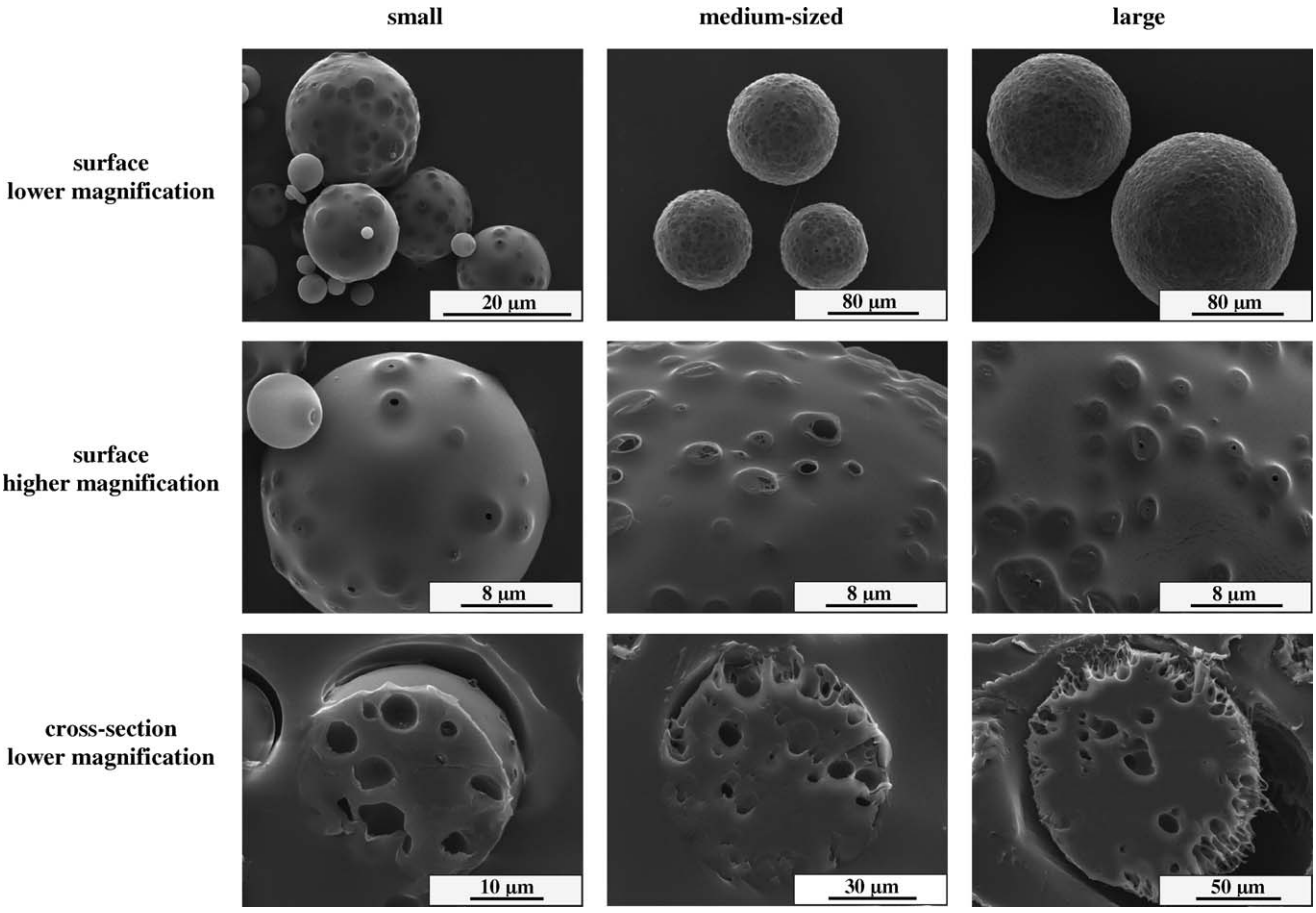

Fig. 1. Morphology of the investigated small, medium-sized and large, lidocaine-loaded, PLGA-based microparticles before exposure to phosphate buffer pH 7.4 ($t = 0$): SEM pictures of surfaces (lower and higher magnification) and cross-sections (lower magnification) (as indicated in the figure).

within the polymeric matrix can be expected to be >4% (w/w), lidocaine is likely to be molecularly dispersed within the PLGA (monolithic solution). Also DSC measurements showed no evidence for drug melting events (data not shown), and no drug crystals or amorphous aggregates were visible on scanning electron microscopy pictures (Fig. 1). As it can be seen in Table 1, also different-sized drug-free, PLGA-based microparticles were obtained.

3.2. *In vitro drug release kinetics*

The effects of the size of the porous, PLGA-based microparticles on the resulting drug release kinetics in phosphate buffer pH 7.4 are illustrated in Fig. 2a. Clearly, the relative lidocaine release rate decreased with increasing system dimension. This is in contrast to microparticles of identical composition with an initially non-porous internal and external structure (Fig. 2b). The latter particles were prepared by an oil-in-water (O/W) solvent extraction/evaporation technique and did not show any significant effect of the system size on the resulting relative drug release kinetics, as reported previously (Siepmann et al., 2005).

As diffusion is known to play a major role in the control of drug release from PLGA-based microparticles (Siepmann and Göpferich, 2001), an increase in system size is a priori expected to result in reduced relative release rates (due to the increased length of the diffusion pathways and, thus, decreased drug concentration gradients). The absence of this "increased diffusion pathway length effect" in the case of non-porous, PLGA-based microparticles can be attributed to accelerated polymer degradation (Siepmann et al., 2005). Upon water imbibition the polyester is hydrolytically cleaved into shorter chain alcohols and acids throughout the system ("bulk erosion"). Due to concentration gradients, the latter diffuse into the surrounding bulk fluid, where they are neutralized. In addition, bases from the release medium diffuse into the microparticles, neutralizing the generated acids. However, diffusional processes in polymeric systems are relatively slow and the rate at which the acids are generated can be higher than the rate at which they are neutralized. Consequently, the pH within the microparticles can significantly drop (Brunner et al., 1999; Li and Schwendeman, 2005). As the ester bond cleavage is catalyzed by protons, significant decreases in micro-pH lead to accelerated polymer degradation (autocatalysis) and, thus, increased drug mobilities and release rates. In the case of non-porous lidocaine-loaded microparticles this "autocatalysis effect" was found to compensate the "increased diffusion pathway length effect", resulting in almost unaltered drug release kinetics with increasing microparticle size (Fig. 2b).

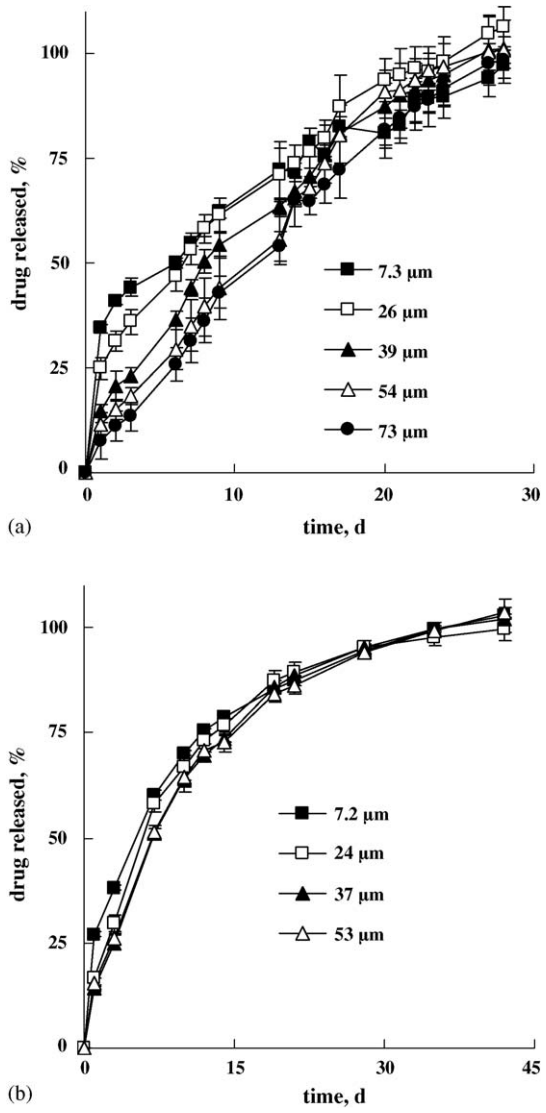

Fig. 2. Effects of the microparticle size on lidocaine release from PLGA-based microparticles in phosphate buffer pH 7.4: (a) porous systems and (b) non-porous devices (the mean microparticle radii are indicated in the figures; please note the different scaling of the *x*-axes).

In porous PLGA-based microparticles the diffusion of water-soluble acids and bases can be expected to be much more rapid than in non-porous devices (Fan and Singh, 1989). Thus, autocatalytic effects should be much less important in this type of systems. They should be reduced or even completely suppressed (depending on the degradation rate of the polymer and the mobility of the involved species). As it can be seen in Fig. 2a, potentially occurring autocatalytic effects are not able to compensate the "increased diffusion pathway length effect" in the present system: The relative lidocaine release rate decreased with increasing microparticle dimension. However, this decrease is not very pronounced. Increasing the length of the diffusion pathways by a factor of 10 (from 7.3 to 73 μm) results only in a moderate decrease in the release rate. To better understand these phenomena, the degradation behavior of the polymer within the porous, PLGA-based microparticles upon exposure to the release medium was studied in more detail.

3.3. Polymer degradation

The decrease in the average polymer molecular weight (Mw) of (a) lidocaine-loaded and (b) drug-free, porous microparticles upon exposure to phosphate buffer pH 7.4 is shown in Fig. 3. Clearly, the PLGA degradation rate increased with increasing microparticle dimension, irrespective of the presence/absence of the drug. This might be attributable to the following phenomena:

(1) Autocatalytic effects. With increasing microparticle dimension the length of the diffusion pathways for the generated

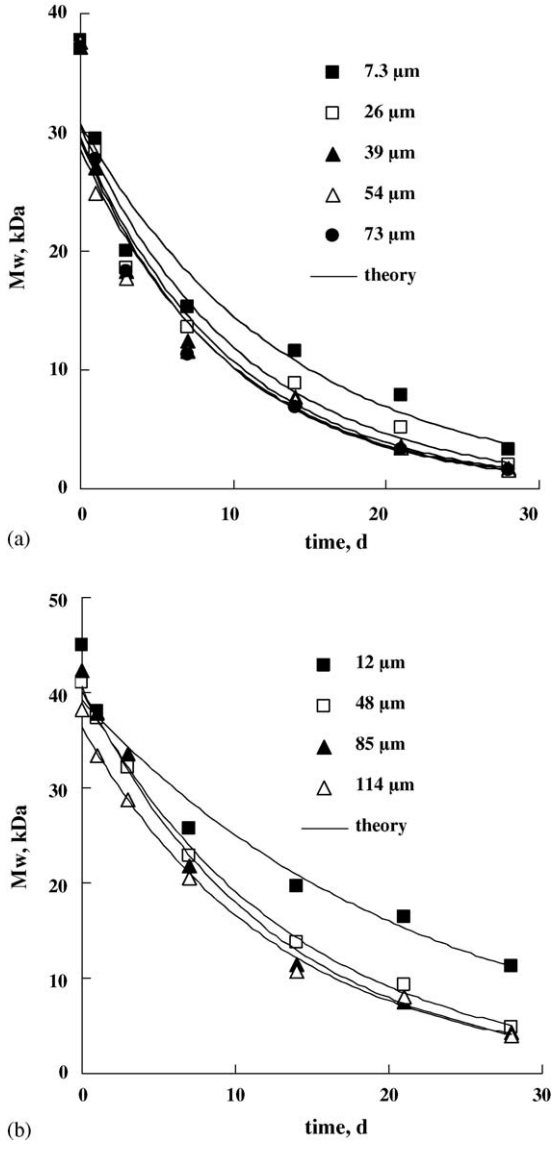

Fig. 3. Decrease in polymer molecular weight of porous, different-sized, PLGA-based microparticles upon exposure to phosphate buffer pH 7.4: (a) lidocaine-loaded systems and (b) drug-free devices (the mean microparticle radii are indicated in the figures). Symbols indicate experimentally determined results, solid curves fitted pseudo-first-order kinetics [Eq. (3)].

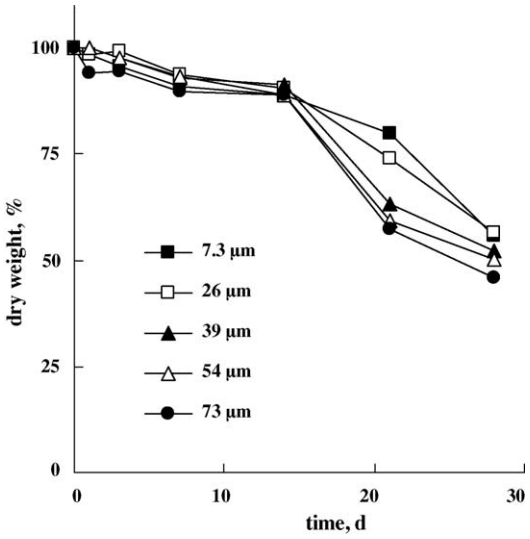

Fig. 4. Effects of the size of porous, lidocaine-loaded, PLGA-based microparticles on the decrease in relative dry weight upon exposure to phosphate buffer pH 7.4 (the mean microparticle radii are indicated in the figure).

acids (and bases from the release medium) increases. Thus, the decrease in micro-pH becomes more pronounced and ester bond cleavage is accelerated.

(2) Altered release rates of shorter chain PLGA fractions. With increasing microparticle dimension the length of the diffusion pathways for shorter chain degradation products increases. Thus, the release rate of these compounds from the microparticles decreases. Consequently, the average polymer molecular weight in large devices decreases more rapidly than in small ones (from which short chain degradation products are rapidly released).

To be able to distinguish between these two phenomena, changes in the dry weight of the microparticles upon exposure to phosphate buffer pH 7.4 were monitored. As it can be seen in Fig. 4, the dry weight loss of larger microparticles was more rapid than that of smaller ones. Thus, altered release rates of shorter chain degradation products cannot explain the above described microparticle size-dependent polymer degradation kinetics. In contrast, autocatalytic effects can be expected to be of significance even in small and highly porous microparticles.

As PLGA degradation is known to follow pseudo-first-order kinetics (Kenley et al., 1987; Charlier et al., 2000), the following equation was fitted to the experimentally determined results:

$$\mathrm{Mw}\,(t) = \mathrm{Mw}\,(t=0)\cdot\exp(-k_{\mathrm{degr}}\cdot t) \quad (3)$$

where Mw (t) and Mw ($t=0$) are the average polymer molecular weights at time t and $t=0$ (before exposure to the release medium), respectively; k_{degr} denotes the degradation rate constant of the polymer.

Table 2
Pseudo-first-order equations describing PLGA degradation in the investigated lidocaine-loaded and drug-free microparticles (the coefficient of determination, R^2, serves as a measure for the goodness of the fitting)

Radius (μm)		R^2
Lidocaine-loaded		
7.3	$\mathrm{Mw\ [kDa]} = 30.8e^{-0.52t\ [\mathrm{weeks}]}$	0.96
26	$\mathrm{Mw\ [kDa]} = 30.5e^{-0.66t\ [\mathrm{weeks}]}$	0.97
39	$\mathrm{Mw\ [kDa]} = 29.6e^{-0.71t\ [\mathrm{weeks}]}$	0.98
54	$\mathrm{Mw\ [kDa]} = 28.6e^{-0.72t\ [\mathrm{weeks}]}$	0.98
73	$\mathrm{Mw\ [kDa]} = 27.8e^{-0.72t\ [\mathrm{weeks}]}$	0.99
Drug-free		
12	$\mathrm{Mw\ [kDa]} = 39.2e^{-0.31t\ [\mathrm{weeks}]}$	0.97
48	$\mathrm{Mw\ [kDa]} = 40.1e^{-0.52t\ [\mathrm{weeks}]}$	1.00
85	$\mathrm{Mw\ [kDa]} = 40.6e^{-0.57t\ [\mathrm{weeks}]}$	0.99
114	$\mathrm{Mw\ [kDa]} = 36.4e^{-0.55t\ [\mathrm{weeks}]}$	0.99

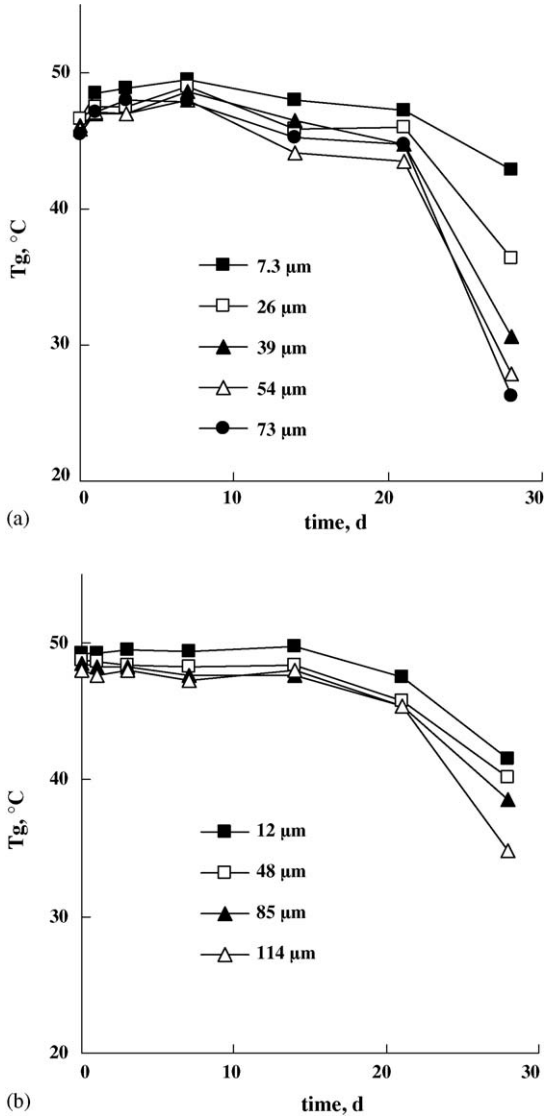

Fig. 5. Changes in the glass transition temperature (T_g) of PLGA in different-sized, porous microparticles upon exposure to phosphate buffer pH 7.4: (a) lidocaine-loaded systems and (b) drug-free devices (the mean microparticle radii are indicated in the figures).

As it can be seen in Fig. 3, rather good to very good agreement was obtained in all cases ($R^2 = 0.96$–1.00). The determined pseudo-first-order equations for the different-sized, lidocaine-loaded and drug-free microparticles are given in Table 2. Clearly, the degradation rate constant k_{degr} increased with increasing system dimension, irrespective of the absence/presence of drug. This indicates that autocatalysis is of significance in these microparticles, despite of their high porosity. However, the determined k_{degr} values are much smaller than those observed with non-porous microparticles of identical composition (Siepmann et al., 2005). The latter were in the range of 0.68–0.78 week^{-1} (lidocaine-loaded systems) and 0.61–0.73 week^{-1} (drug-free devices), respectively. Thus, autocatalysis is less important in the investigated, porous microparticles compared to non-porous ones, but it is not suppressed.

Also changes in the glass transition temperature (T_g) of the polymer can be used as a measure for the degradation of PLGA. With decreasing average molecular weight the degree of entanglement of the macromolecules decreases and, thus, the polymer chain mobility increases and the T_g decreases. Fig. 5 illustrates how the glass transition temperature of PLGA in the investigated porous microparticles decreases upon exposure to the release medium: (a) lidocaine-loaded and (b) drug-free systems. Irrespective of the absence/presence of the drug, the T_g decreased more rapidly in larger microparticles than in smaller ones. This is a further indication for the fact that autocatalytic effects play a major role in the investigated microparticles despite of their porosity.

Changes in the morphology of (initially porous) lidocaine-loaded microparticles upon 3 and 7 days exposure to the release medium are illustrated in Figs. 6 and 7, respectively. Surfaces (lower and higher magnification) as well as cross-sections (lower magnification) of small, medium-sized and large microparticles are shown. Clearly, the internal and external porosity of the systems increased with increasing exposure time due to polymer degradation. In addition to the (already initially present) relatively large pores, also numerous very small pores were visible after 3 days, irrespective of the system size (Fig. 6). After 7 days, also several very large cavities can be seen, again irrespective of the size of the microparticles (Fig. 7). Based on these SEM pictures, it is not possible to conclude whether or not the microparticle dimension affects the importance of autocatalytic effects. This is in contrast to the results obtained with non-porous systems of identical composition (Siepmann et al., 2005). The porosity in initially non-porous microparticles increased much more rapidly in larger systems than in smaller ones. Only

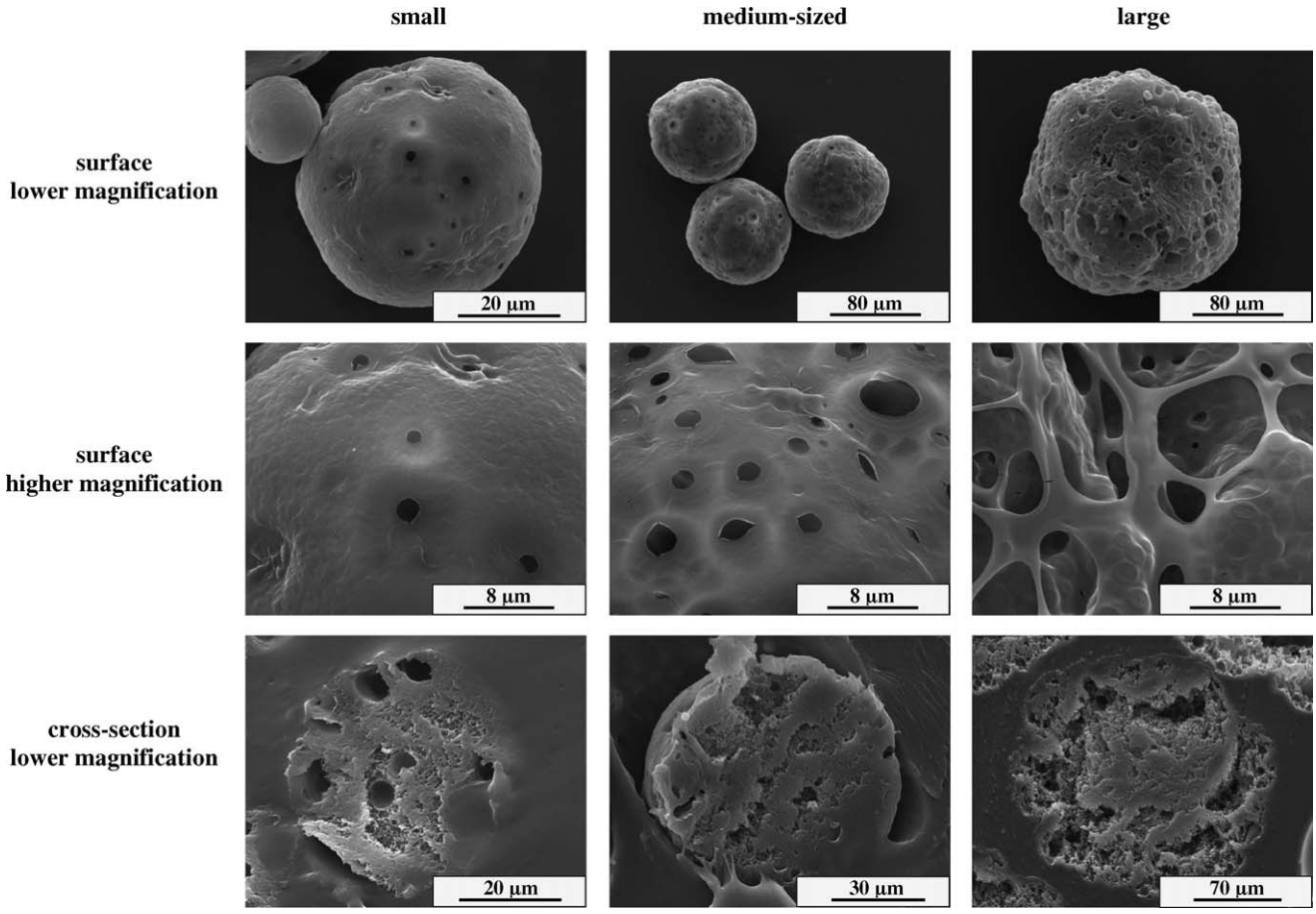

Fig. 6. Morphology of small, medium-sized and large, lidocaine-loaded, PLGA-based microparticles after 3 days exposure to phosphate buffer pH 7.4: SEM pictures of surfaces (lower and higher magnification) and cross-sections (lower magnification) (as indicated in the figure).

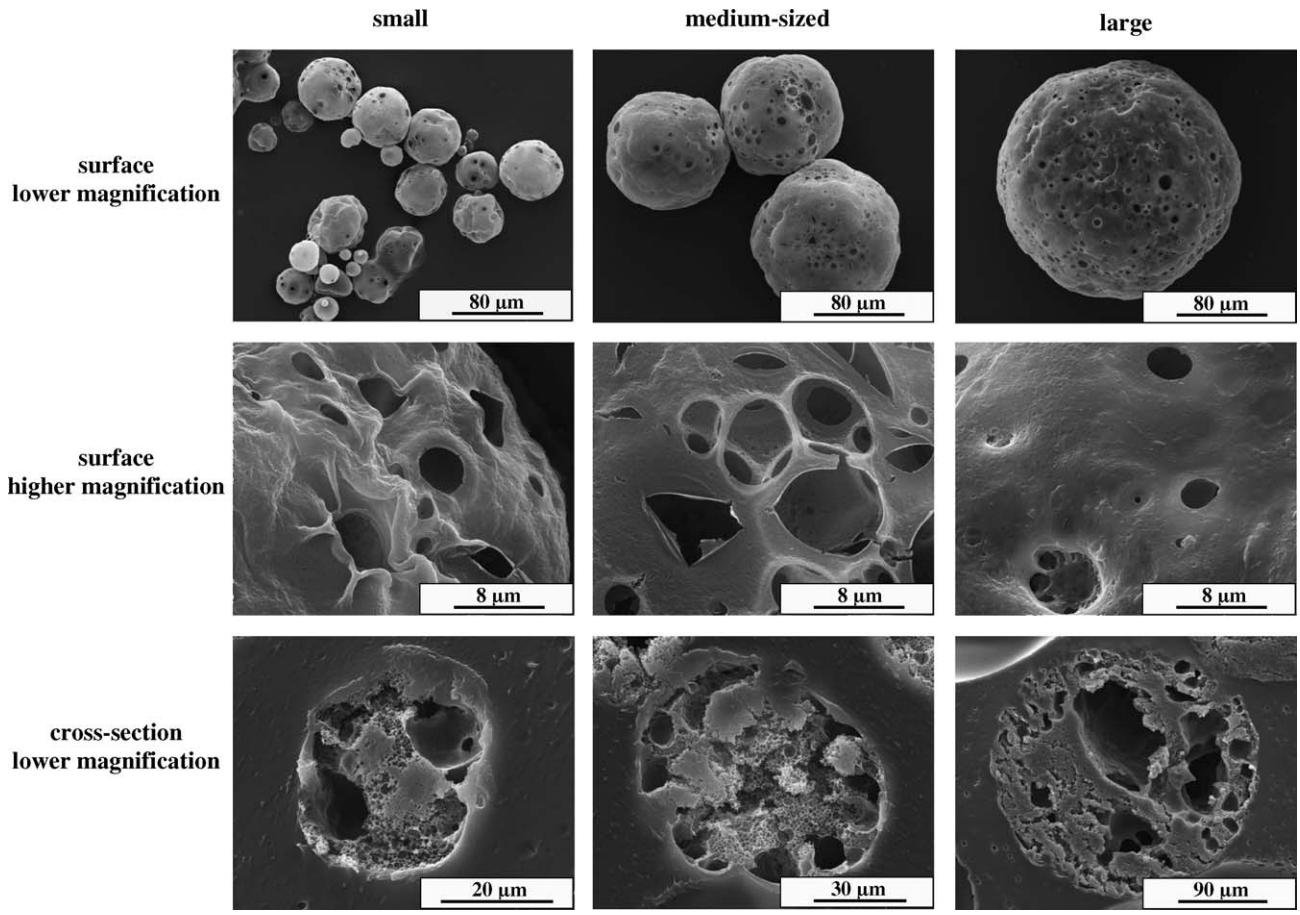

Fig. 7. Morphology of small, medium-sized and large, lidocaine-loaded, PLGA-based microparticles after 7 days exposure to phosphate buffer pH 7.4: SEM pictures of surfaces (lower and higher magnification) and cross-sections (lower magnification) (as indicated in the figure).

SEM pictures of lidocaine-loaded microparticles are shown, the internal and external morphology of drug-free devices was very similar (data not shown).

3.4. Drug release mechanism

To better understand which physicochemical processes are involved in the control of drug release from the investigated porous, PLGA-based microparticles, Eq. (2) was fitted to the experimentally determined in vitro drug release kinetics (Fig. 8). The mathematical model is based on the assumption that drug diffusion through the polymeric matrix is the solely release rate controlling mechanism. As previously shown, good agreement between this theory and experimentally determined drug release kinetics was obtained in the case of non-porous microparticles of identical composition (Siepmann et al., 2005). In contrast, systematic deviations were observed in the present case, irrespective of the microparticle size (Fig. 8): Lidocaine release is overestimated at early time points and underestimated at late time points. This clearly indicates that the high porosity of the PLGA-based microparticles is of fundamental importance for the underlying drug release mechanisms. Obviously, not only lidocaine diffusion is of significance in this type of delivery system, but also other phenomena play a major role. Thus, the presence of pores in PLGA-based microparticles (before

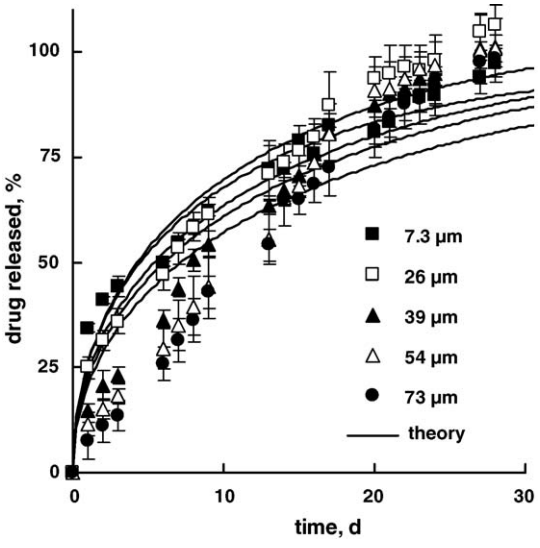

Fig. 8. Theory and experiment: fittings of Eq. (2) to the experimentally measured in vitro drug release kinetics of lidocaine from different-sized, porous, PLGA-based microparticles (the mean microparticle radii are indicated in the figure) (symbols, experimental results; curves, fitted theory).

exposure to the release medium) does not only increase the mobility of the involved diffusing species (drug molecules, acids and bases), but it fundamentally alters the contributions of the involved physicochemical processes to the overall control of drug release. These phenomena have to be carefully taken into account when developing and optimizing this type of controlled drug delivery systems.

4. Conclusion

Even in small and highly porous, PLGA-based microparticles autocatalytic effects play an important role for the control of drug release and must be considered when optimizing existing and developing new controlled drug delivery systems of this type. However, the effects are much less pronounced than in non-porous microparticles of identical composition and an increase in the system size results in a decrease in the relative drug release rate. Importantly, the presence of the pores does not only increase the mobility of the involved species (drug molecules, acids and bases), but fundamentally alters the underlying drug release mechanisms.

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