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Does PLGA microparticle swelling control drug release? New insight based on *single* particle swelling studies

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ABSTRACT

The aim of this study was to better understand the mass transport mechanisms controlling drug release from PLGA microparticles. New insight was gained based on the experimental monitoring of *single* microparticle swelling. An oil-in-water (O/W) solvent extraction/evaporation method was used to prepare ketoprofen-loaded microparticles, varying the initial drug loading from 0.6 to 45.2%. Importantly, the microparticle size was kept about constant. At low ketoprofen loadings, the release patterns were clearly tri-phasic: an initial burst release was followed by a period with an about constant release rate and a final (again rapid) drug release phase. With increasing initial drug content the onset of the third release period was shifted to earlier time points. At even higher drug loadings, the release patterns became more or less bi- or mono-phasic. Interestingly, all types of microparticles showed substantial swelling after a lag-time, which coincided with the onset of the third (and again rapid) drug release phase at low loadings and proceeded it by 1 or 2 d at higher drug loadings. The substantial microparticle swelling set on as soon as a critical PLGA molecular weight was reached (around 20 kDa). Thus, the onset of the third drug release phase from the PLGA microparticles might be explained as follows: once the macromolecules are sufficiently short, substantial amounts of water penetrate into the system, significantly increasing the mobility of the drug within the microparticles and resulting in increased drug release rates.

1. Introduction

Poly(lactic-co-glycolic acid) (PLGA)-based microparticles offer a great potential as parenteral controlled drug delivery systems and are continuously increasing in practical importance [1]. Several products based on PLGA microparticles are available on the market, such as Zoladex, Risperdal Consta, Gonapeptyl, and Decapeptyl (used for the treatment of cancer or disorders of the central nervous system). Importantly, a large variety of drugs can be incorporated into PLGA microparticles, including proteins [2], antigens [3], siRNA [4], antisense oligonucleotides [5] and highly labile drugs [6]. Desired drug release kinetics can for instance be provided by adjusting the composition of the system [7], or by chemical modification of the polymer [8,9].

Different types of drug release patterns can be obtained from PLGA microparticles, in particular mono-, bi-, or tri-phasic drug release kinetics. Generally, an initial rapid drug release phase ("burst release") is followed by a release period with a more or less constant, relatively slow drug release rate, and a final (again rapid) drug release phase. Interestingly, yet the underlying mass transport mechanisms in PLGA microparticles are not fully understood, despite their great practical importance. This can be attributed to the complexity of the involved mass transport mechanisms [10–12]. Upon contact with aqueous body fluids, water penetrates into the system and dissolves the drug [13], which can subsequently diffuse out of the microparticle [14]. Simultaneously, the ester bonds of the macromolecules are randomly cleaved (hydrolytic degradation) and the polymer molecular weight decreases with time, altering the conditions for drug transport. Once the polymer degradation products become water-soluble, they diffuse out into the surrounding bulk fluid. Also, bases from the environment diffuse into the microparticles, due to concentration gradients. However, these diffusional mass transport processes of shorter chain acids out of the system and bases into the microparticles can be relatively slow compared to the rate at which acids are generated due to polymer degradation. Consequently, the local pH in the systems can significantly drop [15]. Since PLGA degradation is catalyzed by protons, this can lead to autocatalytic effects, depending on the size and porosity of the systems [16,17]. The initial burst release phase might be attributable to the release of drug adsorbed to the surface, to the diffusion of drug located close to the surface, and/or to pore closure effects due to PLGA swelling [18,19]. However, the exact reasons for the second and third release phases from PLGA microparticles are yet often only poorly understood.

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The aim of this study was to better understand the mass transport mechanisms controlling drug release from PLGA microparticles. Importantly, new insight was gained based on the experimental monitoring of the swelling kinetics of *single* microparticles.

2. Materials and methods

2.1. Materials

Poly(D,L lactic-co-glycolic acid) (PLGA; Resomer RG 504H; 50:50 lactic acid:glycolic acid; Evonik, Darmstadt; Germany); ketoprofen and polyvinyl alcohol (Mowiol 4–88) (Sigma-Aldrich, Steinheim, Germany); acetonitrile and dichloromethane (VWR, Fontenoy-sous-Bois, France); tetrahydrofurane (HPLC grade; Fisher Scientific, Illkirch, France); Tween 80 (Cooper, Melun, France).

2.2. Microparticle preparation

Ketoprofen-loaded PLGA microparticles were prepared using an oil-in-water (O/W) solvent extraction/evaporation technique: Depending on the theoretical drug loading (which was varied from 1 to 50%), 11–530 mg drug and 523–1035 mg PLGA were dissolved in 6.5–7.7 mL dichloromethane (Table 1) (the volume of the organic solvent was adapted to keep the mean microparticle diameter in the range of 80–90 μm in all cases). This organic phase was emulsified within 2.5 L of an outer aqueous polyvinyl alcohol solution (0.25%, w/w) for 30 min under stirring with a three-blade propeller (2000 rpm), inducing microparticle formation. The particles were hardened by adding 2.5 L of the same outer aqueous polyvinyl alcohol solution and further stirring at 700 rpm during 4 h. The microparticles were subsequently separated by filtration and freeze-dried (Christ Epsilon 2–4 LSC, Martin Christ, Osterode, Germany).

2.3. Microparticle characterization

Microparticle sizes were determined by optical microscopy: Pictures were taken using an Axiovision Zeiss Scope-A1 microscope, equipped with an AxioCam ICc1 camera and Axiovision Zeiss Software (Carl Zeiss, Jena, Germany). Each measurement included 200 microparticles. The mean values +/− standard deviations are reported.

The practical drug loading of the microparticles was determined by dissolving accurately weighed amounts of samples in acetonitrile, subsequent filtering and drug content analysis by UV-spectrophotometry ($\lambda = 258$ nm; UV-1650 PC, Shimadzu, Kyoto, Japan). Each experiment was conducted in triplicate.

X-ray powder diffraction was performed with a Panalytical X'pert Pro diffractometer (λ Cu, Kα = 1.54 Å) in Bragg–Bretano θ–θ geometry (PANalytical, Almelo, the Netherlands) to study the physical state of the drug, polymer and drug-loaded microparticles. Powder samples were placed in a spinning flat sample holder.

In vitro drug release was measured as follows: Fifty milligrams of microparticles was placed in 12 mL glass tubes filled with 10 mL phosphate buffer pH 7.4 (USP 35), containing 0.02% Tween 80. The tubes were horizontally shaken at 80 rpm at 37 °C (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, 3 mL samples were withdrawn and replaced with fresh medium. The samples were filtered and analyzed by UV-spectrophotometry ($\lambda = 258$ nm; UV-1650 PC). Each experiment was conducted in triplicate.

The glass transition temperature (Tg) of the polymer was measured using differential scanning calorimetry (DSC 1 Star System; Mettler Toledo, Greinfensee, Switzerland). Approximately 3 mg samples (drug, polymer or freeze-dried microparticles) were heated in sealed aluminum pans from room temperature to 140 °C, cooled to 0 °C and reheated to 140 °C at a rate of 10 °C/min. The reported Tg was determined during the second heating cycle. Each experiment was conducted in triplicate.

The decrease in polymer molecular weight (Mw) of PLGA during drug release was measured by gel permeation chromatography (Separation Modules e2695 and e2695D, 2419 RI Detector; Waters, Guyancourt, France) (column: PLgel 5 μm MIXED-D, 7.5 × 300 mm, Polymer Laboratories, Varian, Les Ulis, France). Tetrahydrofurane was used as mobile phase at a flow rate of 1 mL/min. Microparticles were treated as described for the in vitro drug release studies. At predetermined time points, samples were withdrawn, filtered and freeze-dried. Three mg microparticles were dissolved in 1 mL tetrahydrofurane. Fifty microliter samples were injected. Molecular weights were calculated using the Empower GPC software and polystyrene standards (Polymer Laboratories).

The swelling of individual microparticles was monitored using 96-well standard microplates: Approximately 50–200 microparticles were introduced into each well, filled with 100 μL phosphate buffer pH 7.4 (USP 35), containing 0.02% Tween 80. The well plates were kept at 37 °C in a horizontal shaker (80 rpm, GFL 3033). To minimize water evaporation, the well plates were closed and surrounded with Parafilm. However, partial evaporation of the medium could not completely be avoided and once a week fresh phosphate buffer pH 7.4 (containing 0.02% Tween 80) was added to assure about 100 μL liquid in each well during the entire observation period. At pre-determined time points, pictures were taken using an Axiovision Zeiss Scope-A1 microscope, as described above.

Table 1
Composition of the inner organic phase used for microparticle preparation.

Theoretical loading, %	1.1	3.3	7.3	10.6	15.4	20.6	30.3	40.3	50.3
CH_2Cl_2, mL	7.7	7.5	7.3	7.1	7.0	7.0	6.9	6.8	6.5
PLGA, mg	1035	1014	972	941	889	836	732	629	523
Drug, mg	11	35	77	112	162	217	318	425	530

3. Results and discussion

3.1. Key properties of the microparticles

Table 2 shows the impact of the theoretical drug loading on the practical ketoprofen content of the microparticles, as well as the corresponding encapsulation efficiency. Clearly, the latter substantially increased (from about 50 to 90%) when increasing the theoretical drug content from 1 to 50%. This can at least partially be explained by saturation effects of the external aqueous phase during microparticle preparation. Importantly, a wide spectrum of initial practical drug loadings could be provided: ranging from 0.6 to 45.2% (w/w), while keeping the mean microparticle size in the range of 80–90 μm.

The impact of the initial drug loading of the PLGA microparticles on the resulting ketoprofen release kinetics in phosphate buffer pH 7.4

Table 2
Impact of theoretical drug loading on the practical drug loading, encapsulation efficiency and mean size of the investigated microparticles (mean values +/− SD).

Theoretical drug loading, %	1.1	3.3	7.3	10.6	15.4	20.6	30.3	40.3	50.3
Practical drug loading, %	0.6 ± 0.0	1.9 ± 0.0	5.2 ± 0.0	8.3 ± 0.1	11.7 ± 0.1	18.0 ± 0.2	26.3 ± 0.2	35.0 ± 0.6	45.2 ± 0.3
Encapsulation efficiency, %	51.7 ± 1.1	57.7 ± 0.0	71.0 ± 0.7	78.7 ± 1.1	76.0 ± 0.9	87.3 ± 0.9	86.9 ± 0.6	86.9 ± 1.4	89.9 ± 0.7
Microparticle diameter, μm	86 ± 28	87 ± 38	86 ± 33	89 ± 31	87 ± 31	87 ± 31	82 ± 26	86 ± 24	86 ± 24

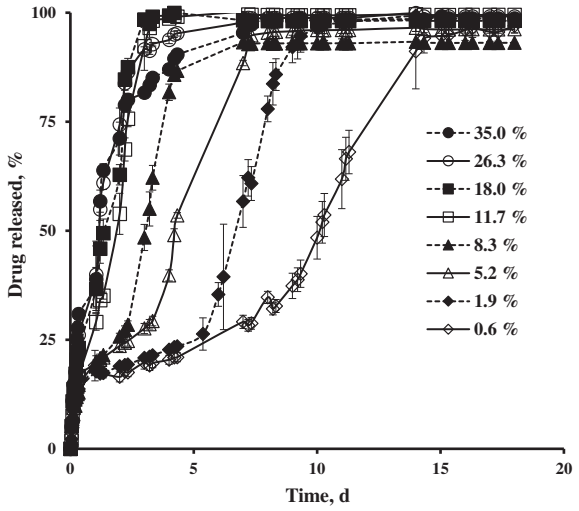

Fig. 1. Effects of the practical drug loading (indicated in the diagram) on ketoprofen release from PLGA-based microparticles upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80).

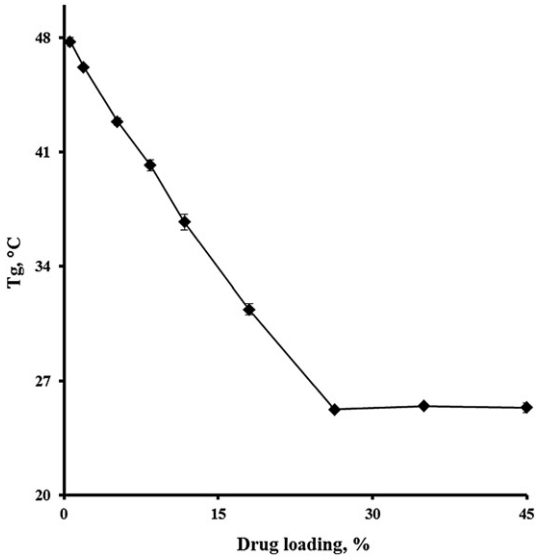

Fig. 3. Impact of the initial drug loading on the glass transition temperature of ketoprofen-loaded PLGA microparticles (measured in the dry state) (mean values +/− SD).

(containing 0.02% Tween 80) is shown in Fig. 1. Interestingly, the initial drug loading did not only substantially affect the resulting drug release *rate* (= the slope of the curves), but also the *shape* of the drug release profiles. At low drug loadings, tri-phasic drug release patterns were observed: After an initial rapid release phase ("burst release"), a release period with a more or less constant drug release rate was observed, followed by a third (and again rapid) drug release phase. With increasing drug loadings the onset of this third release phase was shifted to earlier time points. At high drug loadings, it was difficult to clearly distinguish different drug release phases, the profiles were more or less bi- or mono-phasic.

To better understand why these pronounced differences in the drug release patterns were observed and in order to elucidate the underlying mass transport mechanisms controlling ketoprofen release from these PLGA microparticles, the latter were thoroughly characterized before and after exposure to the release medium. Fig. 2 shows for example the X-ray powder diffraction patterns of the different types of drug-loaded PLGA microparticles before exposure to the release medium. The practical ketoprofen loading is indicated in the diagram. For reasons of comparison, also the pure drug (as received) and PLGA powder (as received) were studied. Clearly, the ketoprofen powder as received was highly crystalline, whereas neither the PLGA powder (as received), nor any of the ketoprofen-loaded PLGA microparticles showed X-ray diffraction peaks indicating crystallinity. This can serve as an indication for the fact that the ketoprofen, which was dissolved in the organic phase during microparticle preparation, did not re-crystallize upon solvent evaporation, but was probably molecularly dispersed in the PLGA matrix (dissolved) and optionally partially precipitated in an amorphous form within the system (depending on the practical drug loading).

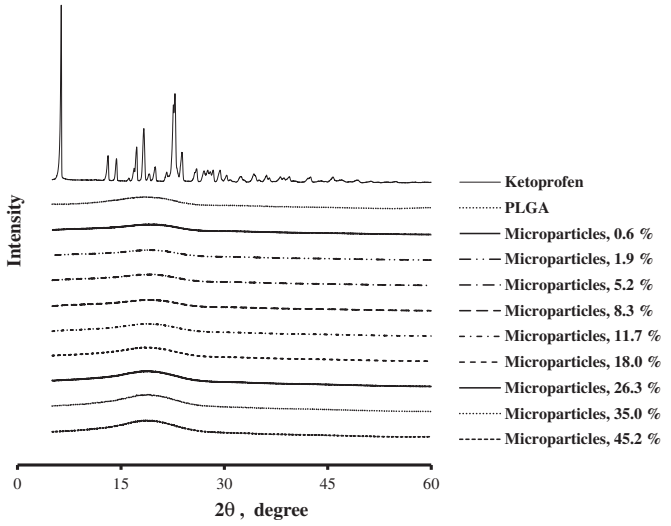

Fig. 2. X-ray diffraction patterns of ketoprofen (powder, as received), PLGA (powder, as received) and drug-loaded microparticles (the practical drug loading is indicated in the diagram).

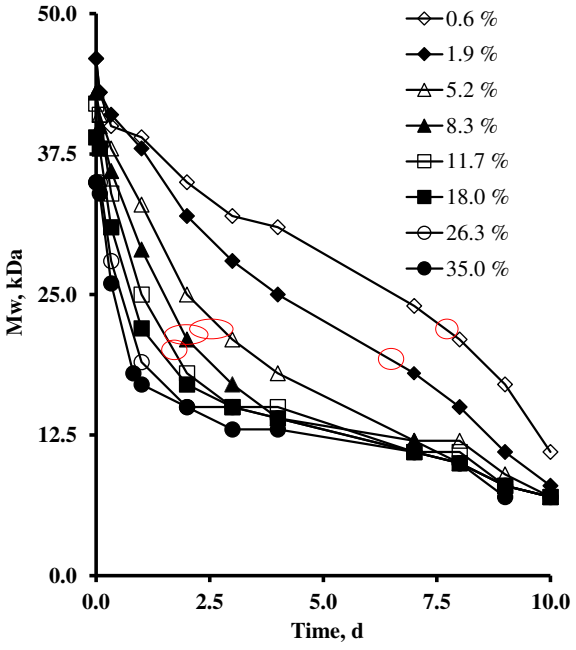

Fig. 4. Effects of the initial drug loading (indicated in the diagram) on PLGA degradation in ketoprofen-loaded microparticles upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80). The red ellipses indicate the periods for the onset of substantial microparticle swelling.

DSC measurements with dry, ketoprofen-loaded microparticles confirmed this hypothesis: The pure ketoprofen powder (as received) showed a sharp melting peak at about 95 °C, whereas none of the investigated ketoprofen-loaded PLGA microparticles showed any thermal event in this temperature range (supplementary Fig. S1). This is also in good agreement with data reported by Ricci et al. [20]. Furthermore, the DSC studies revealed that ketoprofen is an efficient plasticizer for PLGA: Fig. 3 shows how the glass transition temperature (Tg) of the polymer significantly decreased upon addition of up to around 25% ketoprofen. Blasi et al. attributed these plasticizing effects to hydrogen bonding [21]. Importantly, the glass transition temperature remained about constant at higher initial ketoprofen loadings. This is an indication for the fact that up to approximately 25% drug loading, the ketoprofen is likely to be molecularly dispersed within the PLGA matrix ("monolithic solution") and acts as an efficient plasticizer for the polymer. The addition of an excess amount of ketoprofen leads to the precipitation of the drug in an amorphous form within the PLGA matrix (which is saturated with the drug). Note that the DSC measurements were performed with *dry* microparticles and that water has been reported to be an efficient plasticizer for PLGA: For instance, PLGA microparticle exposure to phosphate buffer pH 7.4 decreases the glass transition temperature of the polymer by about 10 °C [22]. Since water penetration into PLGA microparticles is generally much more rapid than subsequent drug release [11], the PLGA can be expected to be in the rubbery state during virtually the entire time periods of drug release in the investigated PLGA microparticles, irrespective of their initial drug loading. Thus, at drug loadings below about 25%, the microparticles consist of a monolithic solution of ketoprofen in PLGA, whereas at higher drug loadings, amorphous ketoprofen is dispersed within a polymeric phase which is saturated with the drug.

For the underlying drug release mechanisms in PLGA microparticles, not only the physical states of the drug and polymer are of utmost importance, also dynamic changes in the polymer molecular weight upon exposure to the release medium can be decisive [10]. Once in contact with water, the ester bonds of the macromolecules are randomly cleaved. Fig. 4 illustrates the impact of the initial practical ketoprofen loading on PLGA degradation in the investigated microparticles upon exposure to the release medium. As it can be seen, the polymer degradation rate substantially increased with increasing initial drug content. This can be attributed to the fact that ketoprofen is an acid and PLGA degradation is catalyzed by protons [12]. Importantly, the polymer molecular weight can be expected to be potentially decisive for key properties of the microparticles, such as their mechanical stability and swelling behavior.

3.2. Swelling kinetics of individual microparticles and correlation with drug release

The microscopic pictures in Fig. 5 show ensembles of microparticles, which were exposed to phosphate buffer pH 7.4 (containing 0.02% Tween 80) at 37 °C for 7, 10 and 14 d, respectively. The particles were placed into the wells of 96-well standard microplates, which were filled with 100 μL release medium and agitated in a horizontal shaker at 80 rpm (as the glass tubes used for the drug release measurements). Importantly, the spatial arrangements of the microparticles in the wells remained about constant, so that it was possible to follow the changes

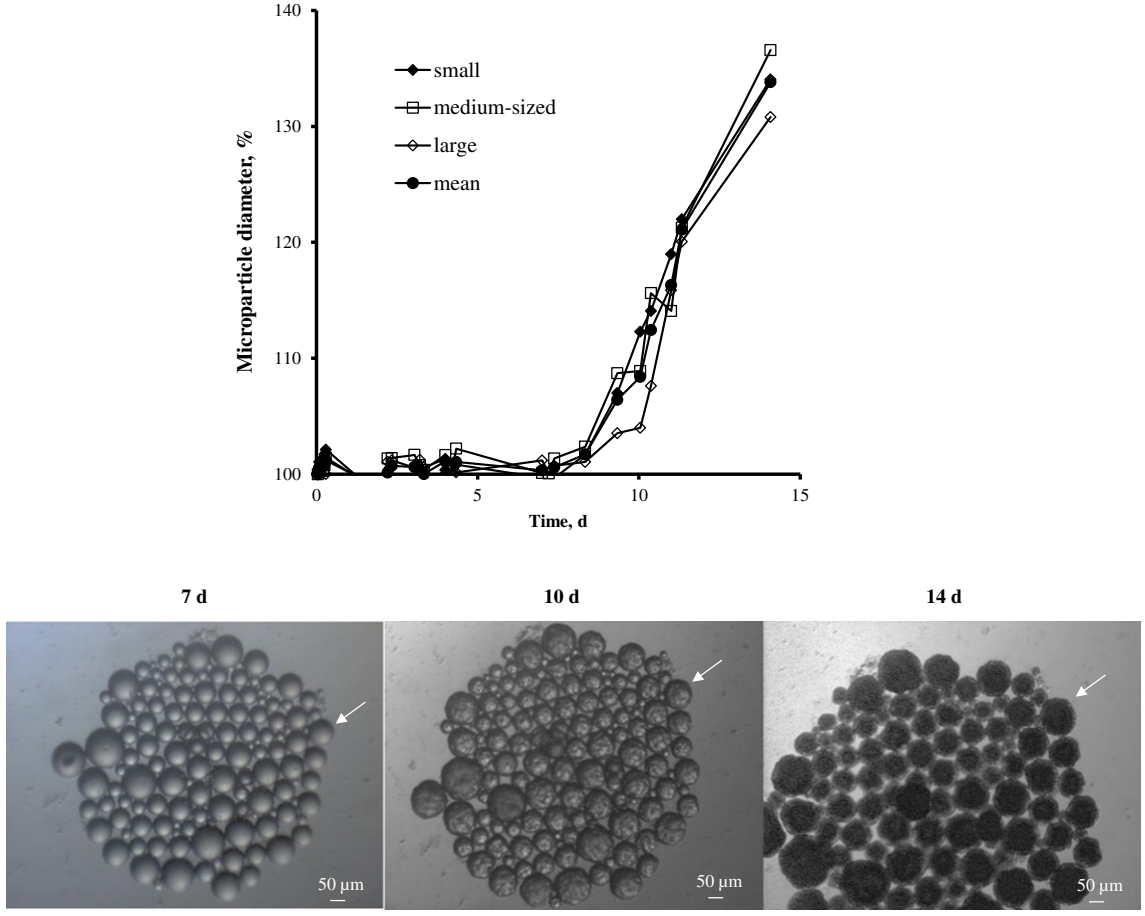

Fig. 5. Dynamic changes in the diameter of individual PLGA-microparticles (loaded with 0.6% ketoprofen) upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80): Small (55 μm), medium-sized (83 μm) and large (109 μm) microparticles were studied. Also the mean values are indicated. Optical microscopy pictures of microparticles after 7, 10 and 14 d exposure to the release medium are shown at the bottom. The arrows mark the same microparticle on each picture.

in the size of individual microparticles during the entire drug release period. For example, the arrows in the microscopic pictures in Fig. 5 highlight the same microparticle, observed at different time points. Clearly, also the other microparticles can be followed individually over time. This is very important: This method, thus, allows monitoring the dynamic changes in the diameter of individual PLGA microparticles during the entire drug release period, offering highly valuable new insight into the underlying drug release mechanisms.

For each ketoprofen loading, 200 microparticles (covering all sizes) were monitored. The diagram in Fig. 5 shows 3 examples: The swelling kinetics of a small microparticle (initially 55 μm in diameter), of a medium-sized microparticle (initially 83 μm in diameter) and of a large microparticle (initially 109 μm in diameter) are illustrated. Clearly, the microparticle size remained about constant during the first 7 d, and then substantially increased, irrespective of the microparticle size. This is likely attributable to the fact that after a certain lag-time, a critical PLGA molecular weight is reached, at which polymer swelling is less hindered. Initially, the degree of polymer chain entanglement is very high and effectively prevents substantial microparticle swelling. Upon contact with water, the polyester chains are more and more cleaved by hydrolysis and as soon as the degree of macromolecular entanglement becomes insufficient to prevent substantial particle swelling, the PLGA matrix can increase in volume. Also, the degradation products are creating a steadily increasing osmotic pressure within the system, attracting more and more water into the microparticles. Importantly, the observed dramatic changes in the microparticles' size result in tremendous changes in the systems' composition: the water content of the polymeric particles fundamentally increases. This can be expected to have major impact on the conditions for drug transport in the systems: The mobility of dissolved ketoprofen molecules is likely to substantially increase with the onset of significant microparticle swelling. Interestingly, the swelling behavior of the microparticles was very similar for all the investigated sizes (filled diamonds versus open squares versus open diamonds in Fig. 5; the filled circles show the respective mean values). Furthermore, the changes in microparticle size were accompanied by morphological changes: The particles' surface was initially smooth, but became more and more irregular over time. Also, the transparency for visible light substantially changed during the observation period (Fig. 5).

The diagram in Fig. 6 shows both: the in vitro drug release kinetics (filled diamonds, left y-axis) and the swelling kinetics (open triangles, right y-axis) of PLGA microparticles, loaded with 0.6% ketoprofen upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80). Very interestingly, the onset of the swelling of the microparticles coincided with the onset of the third (and again rapid) drug release phase. Thus, the swelling of the PLGA particles might control the resulting drug release rate: As long as microparticle swelling is very limited (due to the high degree of polymer chain entanglement), drug diffusion through the system is effectively hindered and ketoprofen release is relatively slow: The release rate during the second release period is more or less constant and much lower than during the other drug release phases (note that the reasons for the initial "burst release" phase are not addressed in this study). However, once the particles start to significantly swell, their water content substantially increases and, thus, the mobility of the drug molecules increases. In other words, the degree of microparticle swelling determines the mobility of the drug molecules in the system and, thus, the drug release rate. The images at the bottom of Fig. 6 show examples of microscopic pictures of microparticles after 8.3 and 10 d exposure to the release medium: As it can be seen, substantial changes in the microparticle morphology and size start during this time period, coinciding with the onset of the third (and again rapid) drug release phase.

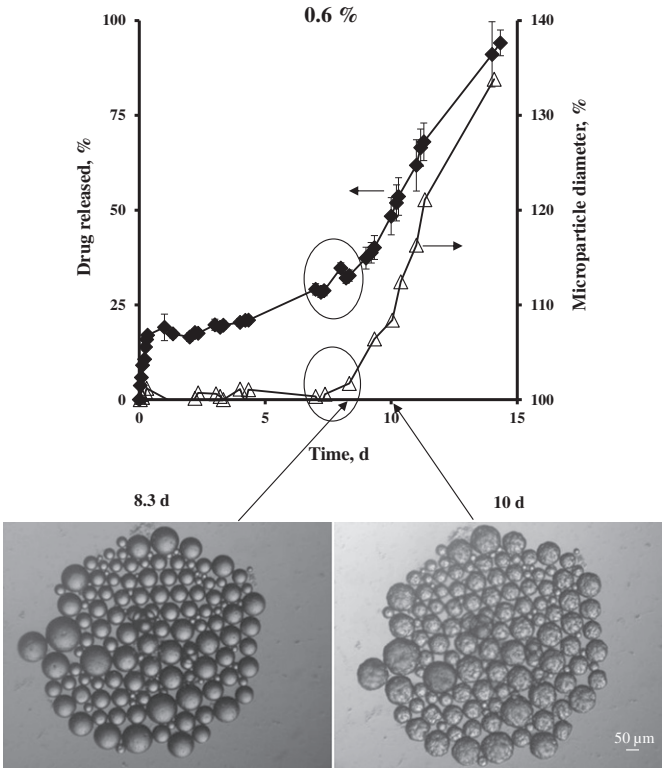

Fig. 6. Drug release from and swelling of PLGA microparticles loaded with 0.6% ketoprofen upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80) (upper diagram). Optical microscopy pictures of microparticles after 8.3 and 10 d exposure to the release medium (pictures at the bottom).

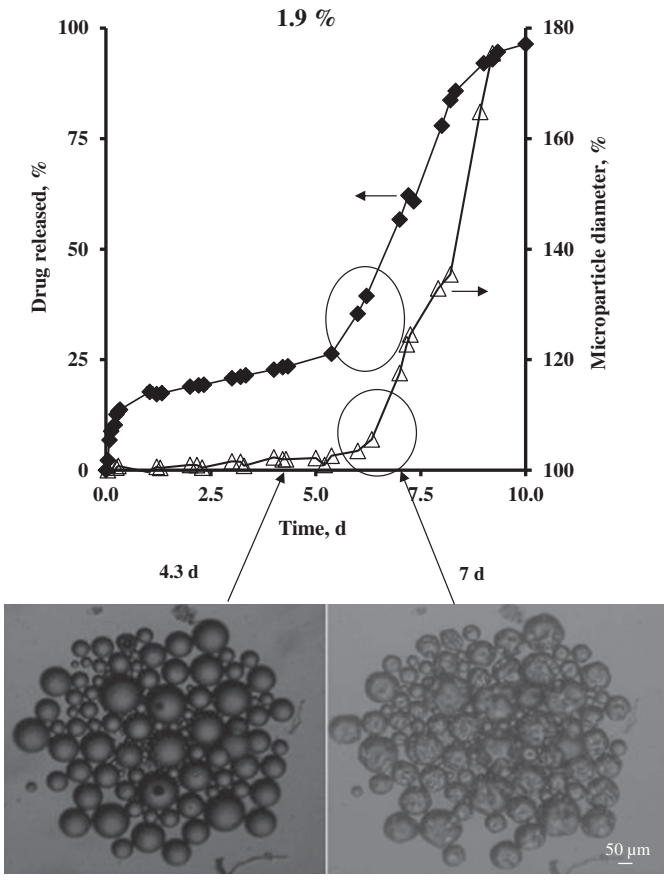

Fig. 7. Drug release from and swelling of PLGA microparticles loaded with 1.9% ketoprofen upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80) (upper diagram). Optical microscopy pictures of microparticles after 4.3 and 7 d exposure to the release medium (pictures at the bottom).

Fig. 7 shows the drug release kinetics, swelling behavior and microscopic pictures of PLGA microparticles initially loaded with 1.9% ketoprofen (instead of 0.6%, as in Fig. 6) upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80). Again, the filled diamonds show the drug release kinetics, whereas the open triangles illustrate the dynamic changes in microparticle diameter. Clearly, also in this case the onset of microparticle swelling coincides with the onset of the third (and again rapid) drug release phase. Also, substantial changes in the microparticle morphology are visible during this time period (pictures at the bottom of Fig. 6). This is further evidence for the hypothesis that PLGA microparticle swelling plays a dominant role in the control of ketoprofen release from the investigated systems.

Figs. 8 and 9 show the drug release kinetics, swelling behavior and examples of microscopic pictures of PLGA microparticles initially loaded with 5.2 and 8.3% ketoprofen, respectively. As in the case of 0.6 and 1.9% initial drug loading, the ketoprofen release kinetics were clearly triphasic. Compared to Figs. 6 and 7, the onset of the third (and again rapid) drug release phase was shifted to earlier time points with increasing drug loading, probably due to accelerated PLGA degradation in the presence of increasing amounts of this acidic drug (polyester hydrolysis being catalyzed by protons): As it can be seen in Fig. 4, the decrease in the polymer molecular weight of the PLGA is more and more rapid when increasing the initial drug loading. Thus, the critical macromolecular chain length, allowing for substantial particle swelling, is more rapidly reached and the third (and again rapid) drug release phase sets on at earlier time points. The red ellipses in Fig. 4 illustrate the approximate onset time points for substantial microparticle swelling observed in this study: As it can be seen, the critical PLGA molecular threshold value seems to be roughly around 20 k Da. However, in contrast to the above discussed lower initial drug loadings, at 5.2 and 8.3% ketoprofen content there was a short delay after the onset of substantial microparticle swelling and the beginning of the third drug release phase. This might eventually be due to drug precipitation effects in these cases: At higher initial drug loadings, the penetration of substantial amounts of water into the system upon microparticle swelling might lead to the (partial) precipitation of the drug. The latter is much more soluble in the lipophilic PLGA than in water: According to Fig. 3 about 25% of ketoprofen can be dissolved in the dry PLGA matrix, whereas the drug's solubility in water at 25 °C is only about 0.13 mg/mL [23]. Since only dissolved drug is available for diffusion, this leads to slower drug release. In addition, the local pH values within the microparticles might differ between the two set-ups used for microparticle swelling and for the drug release measurements (wells versus glass tubes), leading to potential differences in the PLGA degradation rate.

The drug release kinetics and swelling behavior of microparticles loaded with 11.7, 18.0, 26.3 and 35.0% ketoprofen in phosphate buffer pH 7.4 (containing 0.02% Tween 80) are illustrated in Fig. 10. As it can be seen, the lag-time for microparticle swelling is further reduced with increasing drug loading (probably due to accelerated PLGA degradation, as discussed above). At the same time, it is more and more difficult to clearly distinguish different drug release phases, the profiles might be only bi- or mono-phasic. Since the standard deviations are relatively important and drug release was not continuously measured, the authors prefer not to speculate in this respect based on the available data. In any case, it is clear that already at relatively early time points, the water contents of the microparticles substantially increases, resulting in limited resistance for drug transport in the polymeric

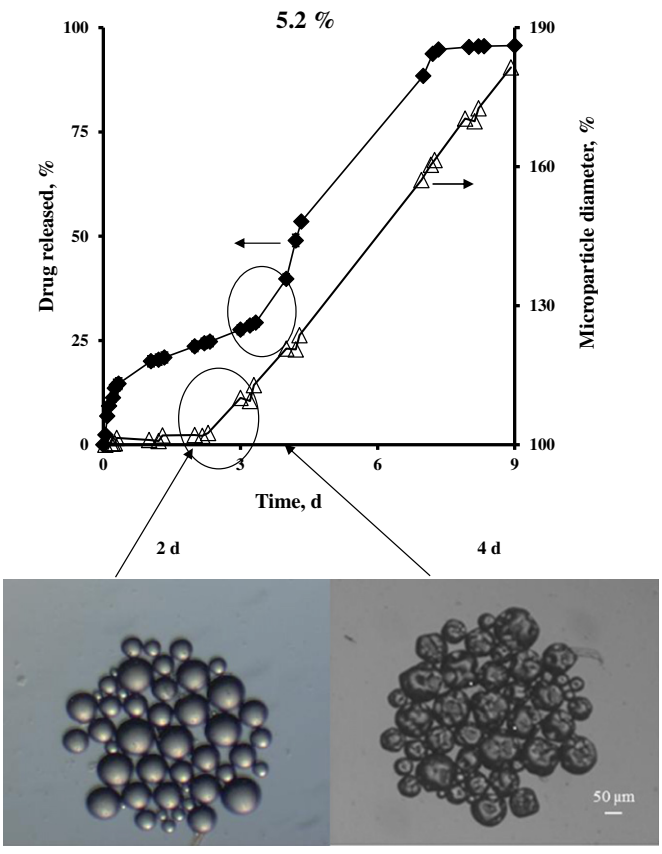

Fig. 8. Drug release from and swelling of PLGA microparticles loaded with 5.2% ketoprofen upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80) (upper diagram). Optical microscopy pictures of microparticles after 2 and 4 d exposure to the release medium (pictures at the bottom).

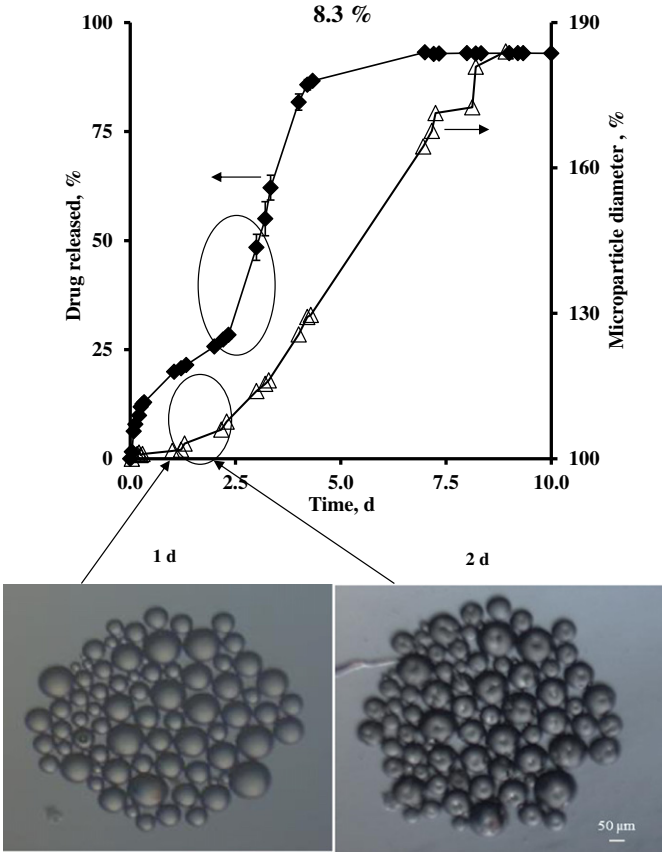

Fig. 9. Drug release from and swelling of PLGA microparticles loaded with 8.3% ketoprofen upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80) (upper diagram). Optical microscopy pictures of microparticles after 1 and 2 d exposure to the release medium (pictures at the bottom).

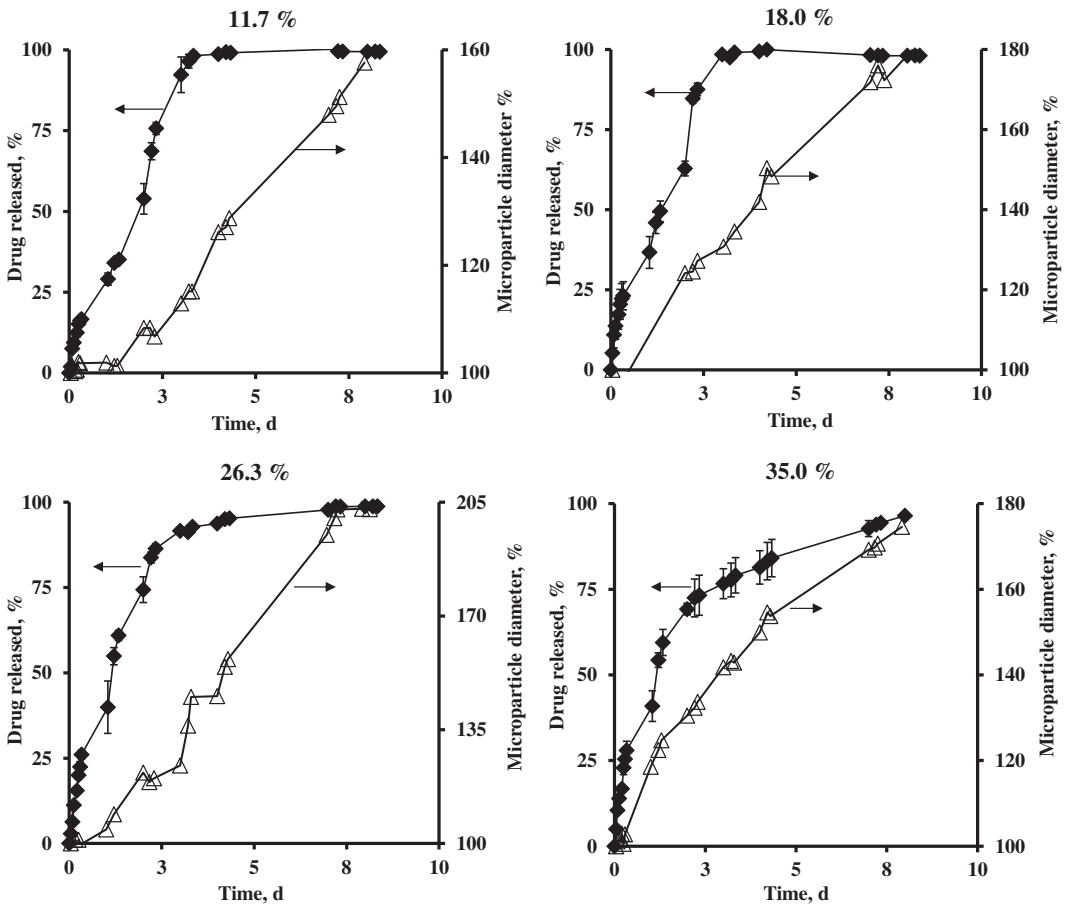

Fig. 10. Drug release from and swelling of PLGA microparticles loaded with 11.7%, 18.0%, 26.3% and 35.0% ketoprofen (as indicated) upon exposure to phosphate buffer pH 7.4 (containing 0.02% Tween 80).

systems. The initial burst release becomes more and more important with increasing initial drug content, because the amount of drug located close to the microparticles' surface (which can be rapidly released) increases.

4. Conclusion

The presented results suggest that the swelling kinetics of PLGA microparticles can play a decisive role in the control of drug release: The onset of the often observed third (and again rapid) drug release phase form these systems might be a consequence of the penetration of substantial amounts of water into the particles, leading to a fundamental increase in drug mobility. During the second drug release phase, the polymer chain entanglement is too high to allow for significant particle swelling and, thus, results in limited water contents and limited drug mobility, resulting in a relatively low drug release rate. In the future, it will be interesting to see whether this type of drug release mechanism is also valid for other types of microparticles, e.g. loaded with different types of drugs, and to study the reasons for the initial burst release in more detail.

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