Pharm Res (2010) 27:2414–2420
DOI 10.1007/s11095-010-0232-5

RESEARCH PAPER

PLGA Erosion: Solubility- or Diffusion-Controlled?

Martin Körber

Received: 2 June 2010 / Accepted: 27 July 2010 / Published online: 3 August 2010

ABSTRACT

Purpose To calculate the degradation time-dependent formation of water-soluble PLGA oligomers and to evaluate the relation between calculated oligomer formation and actual erosion of a PLGA-based delivery system. A proper model of the erosion process would be expected to facilitate forecasting of drug release profiles from PLGA matrices due to the close relationship of erosional mass loss and drug release described in the literature.

Methods The molecular weight distribution (MWD), degradation and erosion behaviour of PLGA were characterized by gel permeation chromatography.

Results PLGA was characterized by a lognormal distribution of mass fractions of individual molecular weights. Implementation of the pseudo-first-order reaction kinetics into the MWD function facilitated calculating the formation of water-soluble oligomers during degradation. The calculated soluble oligomer formation agreed excellently with measured erosional mass loss of a PLGA matrix in aqueous buffer, which suggested that the bulk erosion process was solely controlled by the kinetic of the formation of soluble oligomers and thus solubility-controlled and not diffusion-limited as conventionally assumed.

Conclusion The accurately calculated formation of soluble PLGA oligomers was in excellent agreement with the actual erosional mass loss of a PLGA matrix, suggesting that bulk erosion of PLGA represents a degradation-controlled dissolution process.

KEY WORDS bulk erosion · erosion model · *in-situ* forming implant · molecular weight distribution · PLGA erosion

M. Körber (✉)
College of Pharmacy, Freie Universität Berlin
Kelchstrasse 31
12169 Berlin, Germany
e-mail: koerberm@zedat.fu-berlin.de

INTRODUCTION

Although a number of biodegradable materials have been approved for use in medical devices (1), there are only a few biodegradable polymers in approved parenteral products used as drug release controlling matrices (2), among which the polyesters PLA and PLGA provide the longest safety record of about 40 years. The biodegradable polyesters are characterized by a backbone that can be hydrolyzed under physiological conditions. The hydrolysis results in a cleavage of main-chain bonds producing shorter oligomers and finally monomers (3). PLGA erosion is a consequence of the hydrolytic degradation process of the polyester, characterized by the formation of fragments, which are able to dissolve into the aqueous surrounding. The importance of the erosion process for the release of a number of highly potent drugs from PLGA-based parenteral delivery systems has been shown, e.g. fluphenazine (4), testosterone and proteins like BSA (5) or recombinant human growth hormone (6), or it can be deduced from typically sigmoidal patterns of the release profiles (e.g. risperidone) (7). Therefore, an appropriate description of PLGA erosion could lead to a predictive model for the release of relevant drugs from corresponding biodegradable depot formulations.

Conventional models for PLGA erosion based on so-called "diffusion/reaction" equations treat polymer erosion as a diffusion process of polymer chains coupled to a source term, which assumes an influence of the chemical reaction kinetic on the diffusivity of the chains (8–10). This approach, however, was actually derived from surface-eroding matrices (11), where accessibility and thus diffusion of water molecules is a rate-limiting step for the hydrolysis. For a bulk eroding polymer like PLGA, however, the "diffusion/reaction" approaches might overestimate the role of oligomer diffusion and underestimate the role of

the oligomer solubility as a rate-limiting factor for the erosion kinetic, whereby the importance of the latter aspect has been indicated previously (12). To investigate whether solubility would be the rate-limiting parameter of PLGA erosion, the hydrolytic degradation of the entire PLGA sample has to be described accurately, since each individual chain contributes to the formation of soluble oligomers. Existing models, however, lack an accurate description of PLGA in terms of its molecular weight distribution. This limitation applies to all empirical approaches, which basically represent mathematical fittings of erosion-controlled drug release profiles to modified Gamma (13), Erlang (9), Weibull (14), Prout-Tompkins (15) or normal distribution functions (10,16). Although these models can naturally approximate sigmoidal shapes of erosional release patterns, they were not properly linked to the actual molecular weight distribution and thus not linked to the hydrolysis of PLGA.

It was therefore the purpose of this study, to (a) determine the actual molecular weight distribution of PLGA, (b) develop a model for the hydrolytic degradation of PLGA, which facilitates the accurate calculation of the degradation time dependent formation of water-soluble PLGA oligomers and (c) compare the calculated mass fractions of soluble oligomers with actual mass loss of a PLGA-based delivery system.

MATERIALS AND METHODS

Materials

Uncapped, short-chain 50:50 poly(lactic-co-glycolic acid) (PLGA) (RG 502H, lot. 1005072 and 1036003, Boehringer-Ingelheim, Germany); dimethyl sulfoxide (DMSO), tetrahydrofurane (THF, stabilized HPLC grade) and sodium hydroxide (Carl Roth GmbH & Co, Karlsruhe, Germany); sodium azide and acetic acid (Merck KGaA, Darmstadt, Germany).

Experimental Methods

Degradation Study

PLGA hydrolysis under conservation of mass was studied at 40°C/75%RH and in aqueous buffer medium. Twenty milligram powder samples ($n=2$ for each time-point) were weighed into Eppendorf vials. The open vials were covered with a cloth and incubated at 40°C/75%RH in a climate chamber (Sanyo Gallenkamp PLC, Sanyo E&E Europe BV, Loughborough, UK). Each week two samples were withdrawn, dissolved in THF and analyzed by gel permeation chromatography (GPC).

Degradation in aqueous buffer was studied with a 40% PLGA solution in DMSO (*in-situ* implant). The polymer solution was prepared by dissolving 5 g polymer in 7.5 g DMSO, and about 450 mg of the solution was injected into 16 ml of the aqueous buffer (33 mM sodium acetate buffer, pH 5.0 with 0.01% sodium azide) and subjected to horizontal shaker (Gemeinschaft für Labortechnik, Burgwedel, Germany) at 80 rpm and 37°C. At predetermined sampling time-points (1 d, 4 d, 7 d, 10 d, 12 d, 14 d, 21 d, 35 d, 43 d) two samples were withdrawn and the buffer in the other samples completely replaced by fresh medium. The buffer medium of all withdrawn samples was decanted, and the residual polymer material was carefully rinsed with 10 ml DI-water before they were subjected to freeze-drying for 24 hours (Alpha, Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany). The samples were then stored at −70°C until GPC analysis.

Molecular Weight Determination

GPC analysis was carried out using a Shimadzu (Shimadzu, Tokyo, Japan) LD-10 liquid chromatograph equipped with degasser, pump, auto-injector and column oven in combination with a Viscotek triple detector (TDA-300, Viscotek, Malvern Instruments Ltd., Malvern, UK) operated in dual mode (refractive index, viscosimetry). A column with a linear range from 500 g/mol to 18,000 g/mol (Mesopore 7.5 µm×300 mm; Varian Inc., Darmstadt, Germany) was used as stationary and THF as mobile phase. The sample concentration was either 2% or 4% with the corresponding injection volumes of 50 µl and 25 µl, respectively. Column and detector were operated at 30°C, and the flow rate was 1 ml/min.

A universal calibration method (third-order polynomial fit, R^2: 0.99996) was applied to determine the true molecular weights of PLGA, which was obtained from polystyrene standards with peak molecular weights of 580 g/mol, 1,260 g/mol, 2,360 g/mol, 4,920 g/mol, 9,920 g/mol, 19,880 g/mol (Varian Inc., Darmstadt, Germany). Data acquisition was performed using Ominisec software Version 4.5.6.268 (Viscotek, Malvern Instruments Ltd., Malvern, UK), which accounts for peak broadening during elution (sigma: 0.093; tau: 0.072). Non-linear regression of data was conducted using WinCurveFit software (Kevin Raner Software, Mt. Waverley, Australia) to derive mean values, standard deviations, areas and regression coefficients.

Mass Loss

Mass loss of PLGA-based *in-situ* implant formulations in aqueous medium was determined by GPC through quantification of the residual polymer mass at each sampling point. The refractive index detector served as concentration

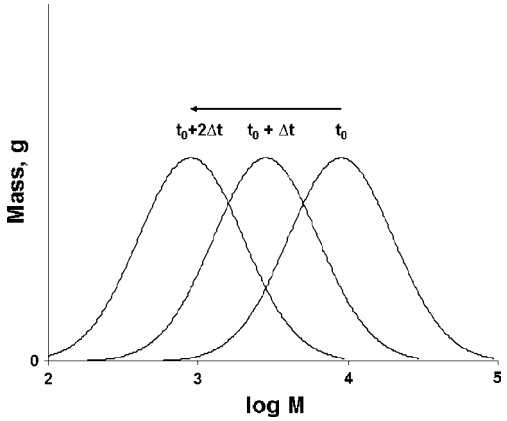

Fig. 1 Schematic representation of the time-dependent shift of the molecular weight distribution of PLGA during hydrolysis under conservation of mass.

detector, with a calibration constant of the differential refractive index detector k_{cal} of 30.588 mV, a refractive index of the mobile phase n_0 of 1.405 and a refractive index increment dn/dc of 0.054 ml/mg. The refractive index increment was thereby constant in the linear range of the column (500–18,000 g/mol).

Erosion Modeling

The lognormal distribution of molecular weights was integrated up to the critical molecular weight for each time-point with conventional spreadsheet software (MS Excel: normdist). The erosion of PLGA was thus calculated at predetermined time-points using the initial peak molecular weight, the pseudo-first-order reaction rate constant and the standard deviation of the lognormal distribution obtained from the degradation study.

RESULTS AND DISCUSSION

The Molecular Weight Distribution of PLGA

The molecular weight distribution of a polymer depends on the type of its polymerization reaction. Molecular weight distributions of polymers are often approximated with generalized exponential distributions. For polycondensation products like polyesters, however, the distribution tends to possess a lognormal character (17), which can be expressed in the form of Eq. 1 (18), where *f(M)* is the fraction by which the mass *m(M)* of a polymer chain of molecular weight M contributes to the total mass m_{total}, where σ_{logM} is the multiplicative standard deviation of the distribution on *log M* scale, and where M_p is peak molecular weight. Conversion of such a distribution from a linear to a logarithmic expression of the x-axis leads to the corresponding normal distribution (Eq. 2), whereby the weight fractions of a polymer chain of the molecular weight M_i are maintained [$f(M_i)=f(log(M_i)$ (19)]. The advantage of the lognormal expression is that an entire polymer sample can be described by only two variables, the peak molecular weight and the standard deviation of the distribution, which both are accessible by conventional gel permeation chromatography.

$$f(M) = \frac{m(M)}{m_{total}} = \frac{\log e}{M \cdot \sigma_{\log M}\sqrt{2\pi}} e^{-\frac{(\log M - \log M_p)^2}{2\sigma^2_{\log M}}} \quad (1)$$

$$f(\log M) = \frac{m(\log M)}{m_{total}} = \frac{1}{\sigma_{\log M}\sqrt{2\pi}} e^{-\frac{(\log M - \log M_p)^2}{2\sigma^2_{\log M}}} \quad (2)$$

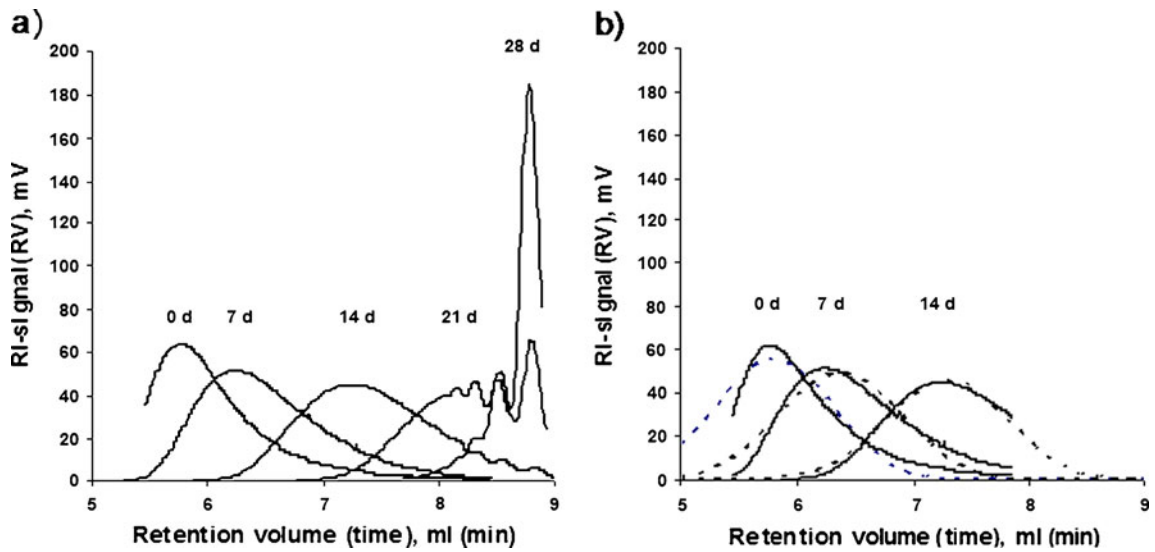

Fig. 2 GPC-chromatograms of PLGA powder incubated at 40°C/75%RH as function of incubation time (**a**) and with approximated normal distributions for 0 d, 7 d and 14 d (**b**).

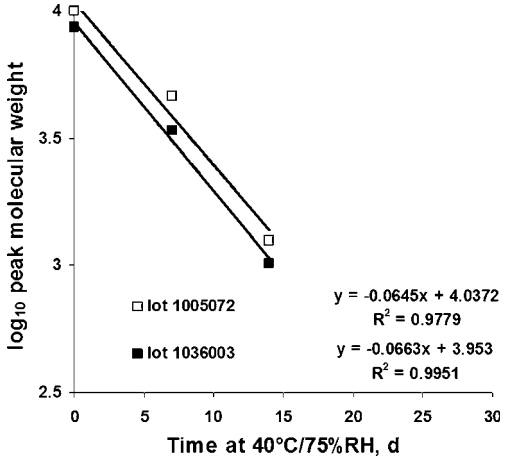

Fig. 3 Semi-log plot of the peak molecular weight of two lots of low molecular weight 50:50 PLGA as function of incubation time at 40°C/75% RH.

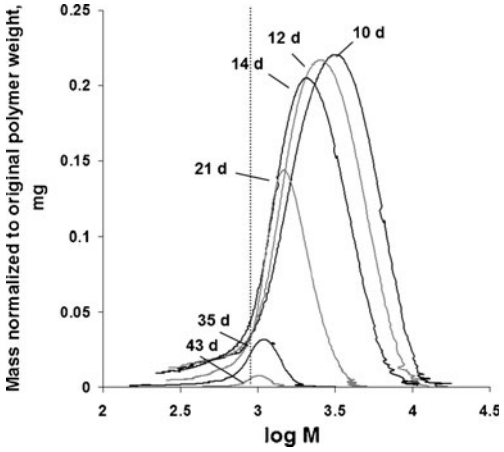

Fig. 5 Effect of polymer erosion on RI-signal (normalized for concentration) over log molecular weight plots of samples incubated in aqueous buffer medium.

Degradation Under Conservation of Mass

The hydrolytic degradation of PLGA is usually characterized by a pseudo-first-order reaction kinetic (6). Correspondingly, logarithms of molecular weights *log M(t=0)* decrease linearly with time t at a constant degradation rate k (Eq. 3).

$$\log M(t) = \log M(t=0) - kt \tag{3}$$

Implementation of the pseudo-first-order degradation kinetic into the lognormal molecular weight distribution (Eq. 2) by substitution of *log* M_p results in the mathematical description of the hydrolytic degradation of PLGA (Eq. 4 and Fig. 1).

$$f(\log M, t) = \frac{m(\log M, t)}{m_{total}} = \frac{1}{\sigma_{\log M}\sqrt{2\pi}} e^{-\frac{(\log M - \log M_p(0) + kt)^2}{2\sigma^2_{\log M}}} \tag{4}$$

The suitability of the degradation model relies on (a) the applicability of the lognormal molecular weight distribution to PLGA, (b) a molecular weight-independent pseudo-first-order reaction rate constant and (c) a degradation time-independent standard deviation. To test the applicability of the model, PLGA samples incubated at 40°C/75%RH were analyzed by gel permeation chromatography.

Peaks in the chromatograms of incubated PLGA samples were Gaussian up to day 14, where accumulation of short oligomers (≤ pentamer) led to a loss of the lognormal character and to the presence of discrete oligomer peaks (Fig. 2a and b). Accordingly, the differen-

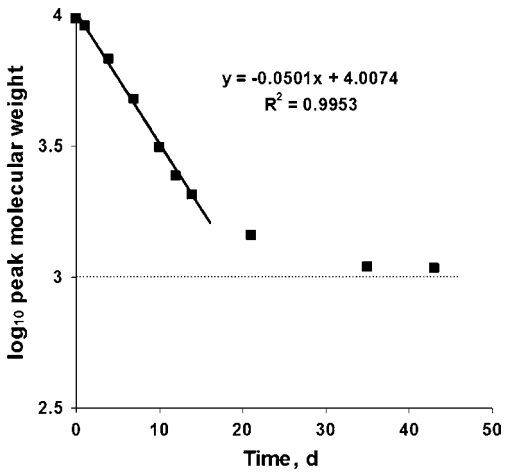

Fig. 4 Semi-log plot of the decrease of the peak molecular weight of PLGA (30% solution in DMSO) incubated in aqueous medium as function of incubation time.

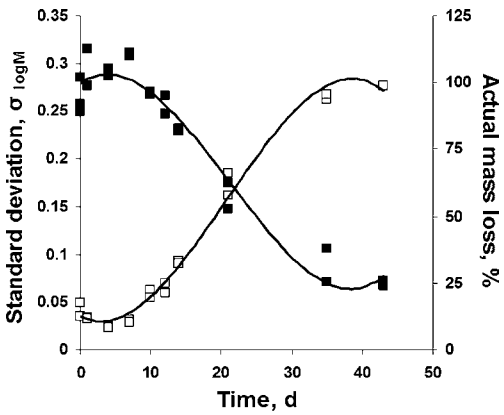

Fig. 6 Standard deviations of the lognormal molecular weight distributions and actual mass loss data of a PLGA based *in situ* implant (40% in DMSO) as function of incubation time in aqueous buffer at 37°C (polynomial trend lines).

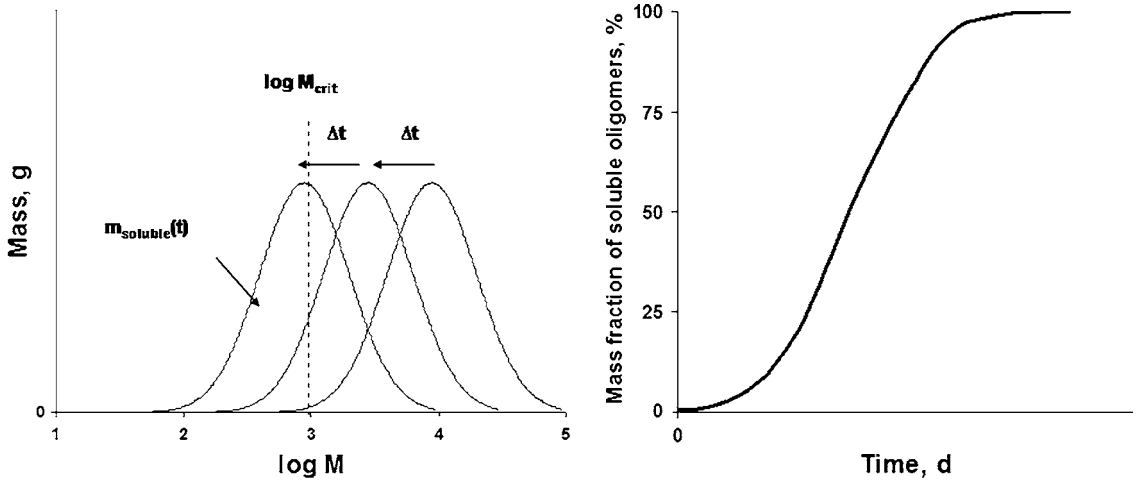

Fig. 7 Schematic representation of the time-dependent shift of the molecular weight distribution of PLGA during hydrolysis against the critical molecular weight (*left*) and the corresponding time-dependent mass fraction of soluble oligomers (*right*).

tial refractive index detector signal *RI_signal(RV)* up to day 14 could be well approximated to normal distributions according to Eq. 5 (R^2: 0.923–0.990), based on the retention volume at peak (RV_p), the area under the chromatogram (*RI_area* in mV × ml) and the standard deviation on retention volume scale (σ_{RV}).

$$RI\_signal(RV) = RI\_area \cdot \frac{1}{\sigma_{RV}\sqrt{2\pi}} e^{-\frac{(RV-RV_p)^2}{2\sigma^2}} \tag{5}$$

In the molecular weight range between 500 g/mol and 18,000 g/mol the retention volume and *log M* were linearly related to each other (R^2: 0.998) with a slope d*logM*/d*RV* of -0.575 ml^{-1}. Hence, the retention volume could be transformed to the corresponding *log M* scale by substitution with Eqs. 6 and 7, which convert the approximated GPC data (Eq. 5) into the corresponding lognormal molecular weight distributions (Eq. 2) at the individual time-points 0 days, 7 days and 14 days.

$$\frac{RI\_signal(RV)}{RI\_area} = \frac{d\log M}{dRV} \cdot \frac{m(\log M)}{m_{total}} \tag{6}$$

$$\sigma_{RV} = \left(\frac{d\log M}{dRV}\right)^{-1} \cdot \sigma_{\log M} \tag{7}$$

The logarithm of the peak molecular weight decreased linearly with time, according to a pseudo-first-order degradation kinetic with a constant degradation rate (Fig. 3). The degradation rates of two different lots of the same PLGA type were thereby comparable (0.0645 d^{-1} and 0.0663 d^{-1}). The standard deviation, which relates to the polydispersity of the lognormal molecular weight distributions (Eq. 8) (17), was thereby constant during degradation (σ_{logM}: 0.30±0.03; PD: 1.63±0.16), which corresponds to a molecular weight-independent degradation rate over the entire molecular weight distribution. Therefore, the changes of the molecular weight distribution of PLGA were in accordance with the hydrolytic degradation model (Eq. 4 and Fig. 1).

$$\sigma^2_{\log M} = \log PD \cdot \log e = \log\left(\frac{M_w}{M_n}\right) \cdot \log e \tag{8}$$

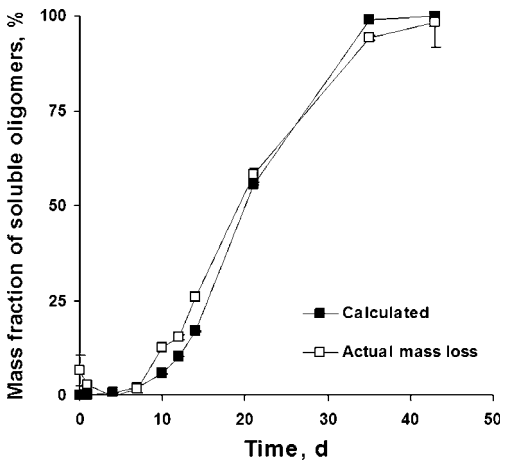

Fig. 8 Actual mass loss of PLGA (30% solution in DMSO) as function of time *vs.* the fraction of soluble oligomers calculated for the same time-points.

Degradation in Aqueous Buffer

PLGA hydrolysis in aqueous buffer was investigated with an *in situ* implant formulation consisting of a 40% PLGA solution in DMSO. In contrast to PLGA degradation at 40°C/75% RH, incubation in aqueous buffers

facilitates the erosion of polymer due to loss of soluble oligomers.

The peak molecular weight decreased according to a pseudo-first-order kinetic the first 14 days with a pseudo-first-order reaction rate constant k of 0.0501 d^{-1} (Fig. 4). Such a loss of the pseudo-first-order characteristic was recently attributed to a decreased reaction rate due to the loss of auto-catalytically active oligomers (20). Consideration of the lognormal (R^2: 0.929–0.992) molecular weight distributions at each individual time-point, however, depicts another scenario. If the measured molecular weight distributions of PLGA samples, which reside in the erosion period (10–43 d), were normalized to the initial polymer mass (Fig. 5), a time-dependent decrease of the area under the curve becomes evident, which represents the erosional mass loss. The shift of the molecular weight distribution to lower *log M* values, however, appeared to stop after reaching a molecular weight of about 1,000 g/mol. This molecular weight was in perfect agreement with the upper limit for soluble PL(G)A oligomers reported elsewhere (21). Hydrolysis did therefore not stop but turned into a dissolution process of oligomers.

As a consequence of hydrolysis on one and mass loss on the other side, the standard deviation of the molecular weight distributions measured at each individual time-point decreased with time (Fig. 6). Thus, only σ_{logM} values before the commencement of mass loss (0–7 d) would be representative of the entire PLGA mass in the original *in situ* implant.

The above-mentioned points indicated that erosion of the polymer matrix was in close relationship to the kinetic at which water-soluble oligomers were formed during hydrolysis. Based on the hydrolysis model, the fraction of soluble oligomers formed up to a certain time-point could be obtained from integration of Eq. 4 up to the critical molecular weight M_{crit} where PLGA oligomers become soluble (Eq. 9), which corresponds to the scheme depicted in Fig. 7.

$$f_{soluble}(t) = 1 - \int_{\log M_{crit}}^{\infty} \frac{1}{\sigma_{\log M}\sqrt{2\pi}} e^{-\frac{\left(\log M - \log M_p(0) + kt\right)^2}{2\sigma_{\log M}^2}} \cdot d(\log M) \tag{9}$$

The degradation time-dependent soluble polymer fraction $f_{soluble}(t)$ of the original sample was calculated using the obtained values for $logM_p(t=0)$ of 4.0, σ_{logM} of 0.32, k of 0.05 d^{-1} and M_{crit} of 1,000 g/mol (Figs. 4, 5, 6). Interestingly, the calculated profile was in excellent agreement with the actual mass loss pattern of the PLGA implant (Fig. 8). This suggested that the erosion of PLGA from the *in situ* forming implant was a solubility-controlled process solely controlled by the kinetic of the formation of soluble oligomers and thus without any indication for a rate-limitation by diffusion.

CONCLUSIONS

A theoretical model for the hydrolytic degradation of PLGA based on the entire molecular weight distribution was developed, verified, and applied to calculate the degradation time-dependent formation of water-soluble PLGA oligomers in an *in situ* implant formulation. The calculated results were in excellent agreement with actually measured mass loss pattern, which suggested that the erosion of PLGA from the *in situ* forming implant was a solubility-limited process without any indication for a rate-limitation by diffusion. This opens up the opportunity to forecast the erosion-controlled release of drugs with PLGA-based *in situ* implant formulation on the basis of raw material properties of the ingoing polymer (peak molecular weight and polydispersity) and the pseudo-first-order degradation rate.

REFERENCES

1. Middleton JC, Tipton AJ. Synthetic biodegradable polymers as orthopedic devices. Biomaterials. 2000;21:2335–46.
2. Whittlesey KJ, Shea LD. Delivery systems for small molecule drugs, proteins, and DNA: the neuroscience/biomaterial interface. Exp Neurol. 2004;190:1–16.
3. Edlund U, Albertsson AC. Degradable polymer microspheres for controlled drug delivery. Adv Polym Sci. 2002;157:67–112.
4. Ramtoola Z, Corrigan OI, Barrett CJ. Release kinetics of fluphenazine from biodegradable microspheres. J Microencapsulation. 1992;9:415–23.
5. Shah SS, Cha Y, Pitt CG. Poly(glycolic acid-co-DL-lactic acid): diffusion or degradation controlled drug delivery? J Control Release. 1992;18:261–70.
6. Tracy MA, Ward KL, Firouzabadian L, Wang Y, Dong N, Quian R, *et al.* Factors affecting the degradation rate of poly(lactide-co-glycolide) microspheres *in vivo* and *in vitro*. Biomaterials. 1999;20:1057–62.
7. Lyons SL, Ramstack MJ, Wright SG. Preparation of microparticles having a selected release profile, EP 1140029, 1999.
8. Göpferich A, Langer R. Modeling monomer release from bioerodible polymers. J Control Release. 1995;33:55–69.
9. Goepferich A. Polymer bulk erosion. Macromolecules. 1997;30:2598–604.
10. Soares JS, Zunino P. A mixture model for water uptake, degradation, erosion and drug release from polydisperse polymeric networks. Biomaterials. 2010;31:3032–42.
11. Joshi A, Himmelstein KJ. Dynamics of controlled release from bioerodible matrices. J Control Release. 1991;15:95–104.
12. de Jong SJ, Arias ER, Rijkers DTS, van Nostrum CF, Kettenes-van den Bosch JJ, Hennink WE. New insights into the hydrolytic degradation of poly(lactic acid): participation of the alcohol terminus. Polymer. 2001;42:2795–802.
13. Batycky RP, Hanes J, Langer R, Edwards DA. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J Pharm Sci. 1997;86:1464–77.

14. D'Souza S, DeLuca PP. Methods to assess *in vitro* drug release from injectable polymeric particulate systems. Pharm Res. 2006;23:460–74.
15. Dunne M, Corrigan OI, Ramtoola Z. Influence of particle size and dissolution conditions on the degradation properties of polylactide-co-glycolide particles. Biomaterials. 2000;21:1659–68.
16. Rothstein SN, Federspiel WJ, Little SR. A unified mathematical model for the prediction of controlled release from surface and bulk eroding polymer matrices. Biomaterials. 2009;30:1657–64.
17. Sanayei RA, Suddaby KG, Rudin A. Characterization of non-homogeneous polymers with size-exclusion chromatography by implementing an on-line viscometer. Makromol Chem. 1993;194:1953–63.
18. Shortt DW. Differential molecular weight distributions in high performance size exclusion chromatography. J Liq Chromatogr. 1993;16:3371–91.
19. Limpert E, Stahel WA, Abbt M. Log-normal distributions across the sciences: keys and clues. BioScience. 2001;51:341–52.
20. Antheunis H, van der Meer J-C, de Geus M, Kingma W, Koning CE. Improved mathematical model for the hydrolytic degradation of aliphatic polyesters. Macromolecules. 2009;42:2462–71.
21. Park TG. Degradation of poly(D, L-lactic acid) microspheres: effect of molecular weight. J Control Release. 1994;30:161–73.