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## Polymer erosion in PLGA microparticles produced by phase separation method

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### Abstract

This article deals with polymer erosion in biodegradable microparticles produced using the phase separation method. Poly(lactic-co-glycolic acid) copolymers with different compositions and molecular weights were employed. The microparticles were stored in phosphate buffer for 6 months. The molecular weight of the polymers was determined by size exclusion chromatography, and the weight loss was monitored gravimetrically. No weight loss was measured in the first weeks, although the molecular weight decreased significantly already from the start. After a certain storage period which was found to be specific for the type of polymer, the weight of the microparticles decreased rapidly. The start of this weight loss occurred when the molecular weight of the polymer in the degrading microparticles reached a threshold of approximately 15,000. This critical molecular weight was found to be identical for all investigated polymers, i.e. it was independent of the initial molecular weight of the polymer and of the lactic-glycolic ratio. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Erosion; Microparticles; Critical molecular weight

Aliphatic polyesters such as poly(lactic acid) and its copolymers with glycolic acid have received considerable interest for controlled release formulations such as microparticles in the pharmaceutical field. The reason for that is the biodegradability and biocompatibility of these synthetic polymers, which degrade into lactic acid

and glycolic acid by simple hydrolysis of the ester bonds. Polymer erosion in microparticles is the degradation of the polymer to water-soluble fragments, accompanied by progressive weight loss of microparticles. In general, two erosion mechanisms are described, namely surface erosion and bulk erosion (Göpferich, 1996). Investigations of these erosion processes are essential for the understanding of drug release from microparticles, as reported in several papers (e.g. Göpferich and Langer, 1995; Shah et al., 1992).

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Erosion mechanism has to be scrutinised for a given microparticle formulation to understand the release behaviour. In the present study, the polymer erosion was investigated using microparticles produced by a phase separation method.

*Poly(lactic-co-glycolic acid)* PLGA 85/15 ( $M_w$  96,000 and 149,000) and PLGA 50/50 ( $M_w$  60,000) were obtained from Alkermes, Cambridge (USA). PLGA 75/25 ( $M_w$  60,000 and 89,000) was purchased from Boehringer Ingelheim (Germany). *Silicone oil* (Dow Corning® Medical Fluid), *propylenglycol octanoate decanoate (PGOD)*, *acetone*, *methylene chloride* and *2-propanol* were of analytical grade. Microparticles were produced by a phase separation method (Donbrow, 1991). Briefly, a solution of PLGA (4 wt%) in methylene chloride was prepared. Afterwards, silicone oil as a non-solvent for PLGA was added while continuously stirring the solution. The microparticles formed were stabilised by a subsequent hardening process using PGOD. Finally, the microparticles were rinsed with 2-propanol and dried.

The *in vitro* degradation of the microparticles was investigated applying the following conditions: 200 mg of the microparticles was dispersed in 50 ml phosphate buffer solution with 0.02% sodium azide and 0.1% polysorbate 80 (pH 7.4) in flasks which were stored at 37 °C. The flasks were gently shaken once a week. Sampling was performed every week during the first 2 months, followed by a 14 day and a final monthly sampling interval. Total storage time was 6 months. Sampling was done by filtering the total content of the flask through a Duran® filter funnel (porosity 4) purchased from Schott, Mainz (Germany), followed by rinsing with water. Afterwards, the samples were dried under vacuum until a constant weight ( $\pm 0.5$ mg) was reached.

The weight loss of the microparticles was determined gravimetrically using the following equation:

$$\text{weight loss \%} = \frac{M - M_i}{M},$$

where  $M$  is the initial weight and  $M_i$  is the final weight of the microparticle samples at a certain sampling time  $i$ .

Afterwards, the samples were prepared for the determination of molecular weight of the polymers. Molecular weight was determined by size exclusion chromatography (SEC) using tetrahydrofuran as solvent. SEC was equipped with a refraction index detector. The polydispersity was calculated by dividing the weight average molecular weight  $M_w$  with the number average molecular weight  $M_n$ .

SEC elution chromatogram of the microparticles showed a polydisperse monomodal molecular weight distribution. The mean molecular weight was similar to the data given by the suppliers of the polymers. A polydispersity between 1.7 and 2.1 was measured for the investigated microparticle formulations. The polydispersity of PLGA remained nearly constant for the first 14 weeks of the study followed by a slight decrease.

Fig. 1 depicts the weight loss of the microparticles as a function of the storage time. The shape of the curves was found to be similar for the investigated polymers. An initial period of no weight loss was followed by a rapid decline in weight of the remaining microparticles. For instance, microparticles consisting of PLGA 50/50 showed no significant weight loss over a period of 5 weeks, whereas microparticles with PLGA 75/25 and PLGA 85/15 showed no significant weight loss over a storage period of 8 and 12 weeks, respectively.

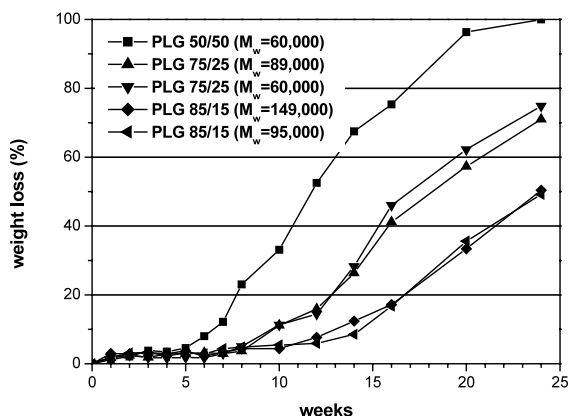


Fig. 1. Weight loss of PLGA microparticles as a function of storage time.

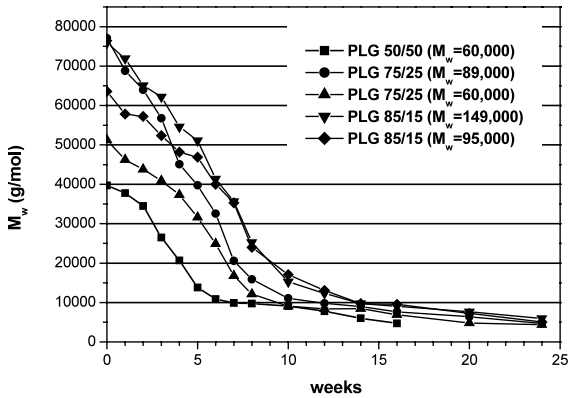


Fig. 2. Molecular weight of PLGA microparticles as a function of storage time.

The molecular weight of the polymers declined rapidly from the beginning (Fig. 2). After a certain storage time, the polymer degradation rate slowed down and the molecular weight decreased slowly. These time-periods were different for each type of polymer.

During the first time of the degradation, the molecular weight of the polymer decreased rapidly without a significant weight loss. Obviously, the polymers had to degrade to a critical molecular weight at which they became water soluble and could be released from the microparticles into the surrounding aqueous medium (Fig. 3). However, the time to reach this critical molec-

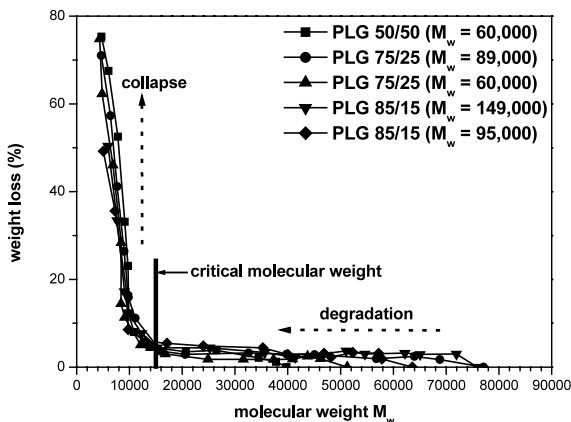


Fig. 3. Weight loss as a function of the molecular weight of microparticles consisting of different types of PLGA copolymers stored in phosphate buffer.

ular weight was characteristic for each polymer. For instance, microparticles based on PLGA 50/50 ( $M_w$  60,000) reached the critical molecular weight after 32 days of storage in the buffer. For particles made from PLGA 75/25 with the same initial molecular weight, this time-period was found to be 50 days. Microparticles consisting of PLGA 75/25 with a higher molecular weight ( $M_w$  89,000) reached the critical molecular weight after 56 days.

The value of the critical molecular weight at which microparticles started to loose weight was found to be identical for all polymers investigated, i.e. the value was independent of the initial molecular weight of the polymer and of the lactic–glycolic ratio (Fig. 3). This finding was not expected since the degradation of the polymer is a random process which can affect each bond in the polymer backbone with equal probability. Consequently, water-soluble fragments of low molecular weight should be created already in the beginning of the degradation process.

Bulk erosion is characterised by the autocatalytically accelerated polymer degradation in the inner part of the microparticles due to the generation of acidic degradation products, whereas a slower degradation at the microparticles' surface is observed (Göpferich, 1996, 1997). Accordingly, the microparticles collapse spontaneously when the polymer at the surface reaches a critical molecular weight. For all investigated microparticles, collapse occurred at an average molecular weight of approximately 15,000. This is in accordance with other publications: For instance, Bodmer et al. (1992) reported a sudden mass loss of cylindrical poly(lactic–co–glycolic acid) implants after the molecular weight was reduced to approximately 10,000, whereas Spenlehauer et al. (1989) observed a dramatic change in the microsphere structure when the polymer molecular weight reached approximately 20,000.

The release characteristic of PLGA microparticles could be divided into two sections. Firstly, a diffusion-controlled release until the critical molecular weight of approximately 15,000 was reached followed by an erosion-controlled release (data not shown).

In summary, poly(lactic-co-glycolic acid) polymers in biodegradable microparticles produced by the phase separation method degraded to a critical molecular weight at which they became water soluble. Significant weight loss of the microparticles was only observed after this critical molecular weight was reached. Consequently, the weight loss of the observed polymeric microparticles was caused by a bulk erosion process. It should be noticed that the critical molecular weight was found to be independent of polymer composition and initial molecular weight. However, the time-period to reach the critical molecular weight was dependent on the polymer characteristics, i.e. molecular weight and composition.

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