Molecular Weight Changes in Polymer Erosion

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We report a study of the effects of polymer molecular weight on the erosion of polyanhydride copolymer matrices composed of 1,3-bis(*p*-carboxyphenoxy)-propane (CPP) and sebacic acid (SA) in aqueous solution. The erosion profile characteristically displays an induction period during which the erosion rate is relatively slow. The length of this period depends on the initial molecular weight of the polymer. The induction period may be characterized as a time during which a rapid decrease in polymer molecular weight occurs, the end of this period correlating with the time required for the polymer molecular weight to decrease to below a value of approximately 5000 (MW).

KEY WORDS: drug delivery system; erodible polymers; polyanhydrides; induction period; molecular weight.

INTRODUCTION

Copolymers have been employed frequently to tailor the properties of degradable polymers and to control release characteristics when these polymers are used in applications such as drug delivery (1–4). Examples where this approach has been successful include the polyanhydrides (1) and lactic/glycolic acid copolymers (5). Previous studies in our laboratory have shown that polyanhydrides can be used in controlled drug delivery systems (6). Degradation of these materials is a result of the hydrolysis of anhydride linkages between monomers. These polymers display a near-zero-order release of incorporated materials over periods ranging from days to years, depending on the choice and ratio of comonomers, with the degradation product having been shown to be noncytotoxic and biocompatible (1,7). These favorable properties have led to the approval of a copolymer of 1,3-bis(*p*-carboxyphenoxy)propane (CPP) and sebacic acid (SA) for experimental use in humans to treat glioblastoma multiforme (6).

The erosion of polyanhydride devices has been studied (8); however, molecular weight changes within the polymer have been examined only in organic solution (9). We believe this to be the first study to examine molecular weight changes during the erosion of polyanhydrides in aqueous solution, thus yielding some insight into the *in vivo* degradation of these polymers. In this paper, erosion is defined as the appearance of monomers in the degradation medium. In this study, molecular weight changes during erosion of polyanhydride devices are correlated with the induction period. The induction period is a characteristic lag time that occurs in the early part of the erosion of polyanhydride devices, the nature of which was previously unknown (10,11). In the present study, the induction period is shown to be a period during which the polymer molecular weight decreases rapidly to below a value of approximately 5000 (MW), with the length of the induction period being dependent on the initial polymer molecular weight.

MATERIALS AND METHODS

Materials

The synthesis and purification of p(SA) and p(CPP:SA) 20:80 copolymer, received as gifts from Nova Pharmaceuticals (Baltimore, MD), have been described previously (1). For the studies with p(CPP:SA) 20:80, 100-mg devices were prepared by the hot melt method (12). The devices were 8 mm in diameter and 1.6 mm thick. For the studies with p(SA), 100-mg devices were prepared by compression molding of spray-dried p(SA) powder at room temperature. The p(SA) devices were 14 mm in diameter and 0.65 mm thick. Water used in these studies was freshly obtained from a Milli-Q water purification system (Millipore Corp., Bedford, MA).

Measurement of Device Erosion

Studies of erosion kinetics of the polymers were performed by monitoring the appearance of CPP and SA in the buffer solution (13). Devices were placed in glass vials containing 60 ml of pH 7.4 phosphate buffer at 37°C. The containers were agitated on a Clinical Rotator (Thomas Scientific, Swedesboro, NJ) set at 120 rpm. The buffer was periodically changed to approximate sink conditions. Buffer solutions were changed every 4 hr at the beginning of the study and once a day toward the end of the study. Samples were analyzed by an HPLC assay, using a PRP-1 hydrophobic interaction column (Hamilton Co.), with a mobile phase containing tetrabutylammonium phosphate ion-pairing agent in the form of PIC A (Waters, Milford, MA) and acetonitrile (Aldrich, HPLC grade), with detection at 210 nm for SA and 246 nm for CPP. The experiments were performed in triplicate for the p(CPP:SA) 20:80 copolymers.

Erosion Studies by UV Spectrophotometry During the Induction Period

A feature of the kinetics of polyanhydride erosion is an induction period, during which the rate of erosion is lower than during the majority of the lifetime of the device (1,10). The length of this induction period varies according to the type of polyanhydride, with the more hydrophobic materials exhibiting a longer induction period. The effects of initial polymer molecular weight on the kinetics of erosion during the induction period of polyanhydride devices were examined in detail. In order to do this, a flow-through system

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composed of a custom built jacketed glass cell and a UV spectrophotometer (DU-65, Beckman Instruments, Inc., Fullerton, CA) was implemented. Fifty milliliters of pH 7.4 phosphate buffer was pipetted into the cell and circulated through the spectrophotometer at a flow rate of 5.4 ml/min using a peristaltic pump (Rabbit-Plus, Rainin Instrument Co., Inc., Woburn, MA). The dead volume of the system was 4.3 ml. The effect of flow rate was examined by comparing the erosion profile of a control device with that of a device where the flow rate was varied in three increments at 2-hr intervals from 4.3 to 6.8 ml/min. No differences were found in the profiles, indicating that the flow rate used provided adequate mixing. The temperature of the buffer was maintained at 37°C using a constant-temperature water circulator (RTE-210, NESLAB Instruments, Inc., Dublin, CA). The appearance of CPP was monitored at 246 nm. Prior to experiments, the buffer was pumped through the system for at least 30 min to establish a baseline. To examine the baseline stability of the spectrophotometer, buffer alone and buffer containing approximately 0.01 mg/ml CPP were pumped through the system. In both cases no significant baseline drift was found over a period of 16 hr. Experiments were performed by placing a device in the cell and monitoring the erosion kinetics during the induction period. Experiments were performed in triplicate for a series of polymers with different initial molecular weights, ranging from 10,000 to 65,000.

Molecular Weight Studies

The molecular weight changes during the early phase of polymer erosion, particularly the induction period, were determined. Polymer devices were incubated in 50 ml of pH 7.4 buffer at 37°C and removed from the buffer solution at predetermined intervals. After removal, the devices were rinsed with distilled water to remove buffer salts and dried under vacuum overnight. The buffer solution was replaced daily during the study to approximate sink conditions. The surface layer (<0.5 mm) of devices was scraped off and the core was crushed using a mortar and pestle. The powdered device core was dissolved in chloroform (<10 mg/ml). The molecular weight of the polymer was determined relative to polystyrene standards (Polysciences, Warrington, PA) by gel permeation chromatography (GPC). A Perkin–Elmer GPC system (Perkin–Elmer, Norwalk, CT) consisting of the Series 10 pump, an LKB 2140 Rapid Spectral Detector (Pharmacia LKB, Gaithersburg, MD) at 254 nm, and a PE 3600 Data Station was used. The samples were eluted with chloroform through a 30 × 0.75-cm PL Gel column with a particle size of 5 μm (Polymer Laboratories Inc., Amherst, MA) at a flow rate of 0.9 ml/min. Experiments were performed in triplicate for a series of polymers with different initial molecular weights, ranging from 10,000 to 65,000.

RESULTS AND DISCUSSION

Device Erosion

The cumulative erosion profiles of CPP and SA from p(CPP:SA) 20:80 of initial molecular weights of approximately 20,000, 50,000, and 60,000 and p(SA) from disks of initial molecular weights of approximately 6100, 9450, and 35,750 are shown in Fig. 1. Material balances were calculated from the initial weights of the devices, accounting for the change in mass caused by the addition of H_2O to the polymer. The profiles have been normalized by the cumulative experimental monomer erosion. The profiles are characterized by an induction period followed by a period during which the erosion rate is almost constant, then finally, the rate decays toward the end of the device life. When considered over the course of the entire 10-day period for p(CPP:SA) or 3-day period for p(SA), the overall erosion profile in these systems is not greatly affected by the initial polymer molecular weight. However, careful examination of the early period in the erosion profiles reveals that the initial molecular weight has an effect on the induction period. Results of experiments to study this effect in detail are discussed in the next section.

Erosion Profile and Molecular Weight Changes During the Induction Period

Figure 2 shows the effect of initial device molecular

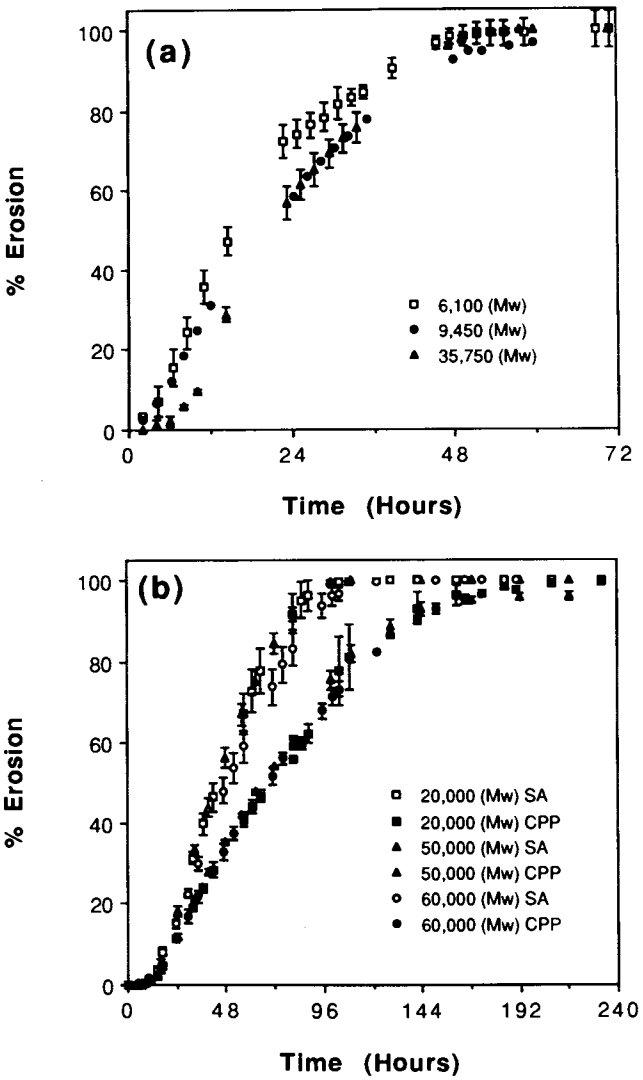

Fig. 1. (a) Cumulative erosion from 100-mg devices of p(SA) over a 3-day period. (b) Cumulative erosion for sebacic acid and CPP from 100-mg devices of p(CPP:SA) 20:80 copolymer over a 10-day period.

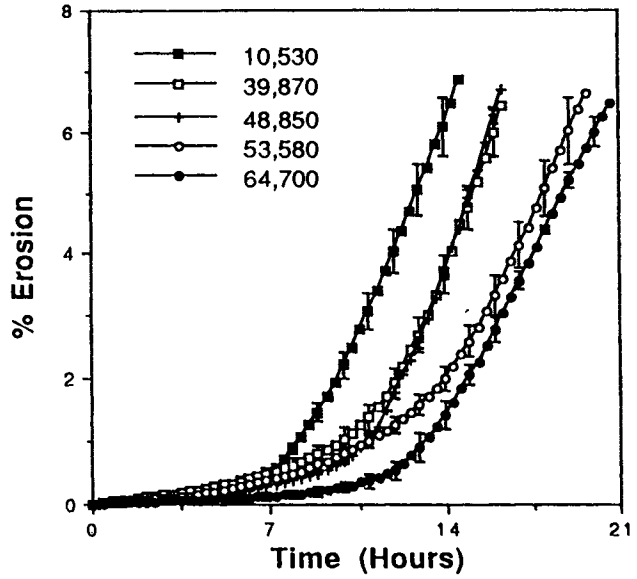

Fig. 2. Effect of initial device molecular weight on erosion kinetics during the early stages of device erosion.

weight on the erosion profiles of polyanhydride devices during the early stages of device lifetime. The profiles are all characterized by an induction period. As can be seen, the length of the induction period depends on the initial molecular weight of the polymer, increasing molecular weight leading to a longer induction period. In general, the induction period for all polymers of different molecular weights is complete before 2% of a device has eroded (calculated by monomer appearance).

Figure 3 shows the relationship between the decrease in polymer molecular weight and device erosion for a range of devices with different initial molecular weights. In all cases, the molecular weight of the devices decreased rapidly during the first 12 hr of immersion in the buffer solution, indicating rapid degradation of the polymer. The loss in molecular weight could also be correlated with the induction period in all cases. The induction period correlates with the time required for the polymer molecular weight to decrease to below a value of approximately 5000.

If the linear portion of the profile after the induction period is extrapolated to the X axis, a lag time may be determined. A plot of initial device molecular weight versus lag time (Fig. 4) indicates that the lag time is related to the initial molecular weight of the polymer. Thus with a knowledge of the initial molecular weight, the length of the induction period may be predicted.

A number of previous theories as to the nature of the induction period have been proposed based on studies with polymers of 1,3-bis(*p*-carboxyphenoxy) methane (10). One suggestion was that the induction period may be the result of an initially hydrophobic surface becoming increasingly hydrophilic as hydrolysis occurs. The theories were based on the findings that scraping the surface of devices prior to immersion into buffer had no effect on the induction period. The induction period could, however, be eliminated by preeroding the samples for 50 hr, drying them, and returning them to the buffer solution (10). The present findings corroborate those findings which show that the induction period is a time during which a rapid loss in polymer molecular weight occurs.

The type of induction period described here has been found with other polymers. It has been reported that the degradation profile of copolymers of L-lactic acid and DL-hydroxyisocaproic acid depends strongly on molecular weight (14). A parabolic erosion profile changes into an S-type profile (due to a lag period) as the molecular weight is increased. Although no explanation was given, it may be speculated that the induction period is due to the time required for the polymer molecular weight to decrease below a certain level, as found with the polyanhydrides in the present study. A study of the erosion and molecular weight changes of microbial polyesters composed of butyrates and valerates showed that, after 58 days of erosion, although only 2% of the polymer had eroded (calculated by weight loss), significant losses in molecular weight had occurred (15). Insufficient data were presented to determine whether this period represents a lag period. Another study on the degradation of hydroxybutyrate–hydroxyvalerate copolymers also commented on erosion profiles which showed an initial slow rate followed by a secondary enhanced erosion phase, the lag phase increasing with an increase in molecular weight (16). The same authors also note that a major loss in molecular weight occurs during the initial lag period (17). A recent study on the degradation of poly(ester) microspheres described an initial phase of polymer degradation during which they found that polymer molecular weight decreased significantly, with no detectable polymer weight loss and without the detection of soluble monomeric products (18). Poly(ε-caprolactone) also displays an induction period during which significant polymer molecular weight losses are not accompanied by a loss in polymer weight (19). A tailing-off in the loss of molecular weight was characterized with the onset of weight loss, as found in the present study. This was attributed to the increased probability that chain scission of a low molecular weight polymer will produce a fragment small enough to diffuse out of the polymer bulk. The findings in all these studies are consistent with the present detailed study of the induction period. One possible practical implication of a lag period is that delayed or pulsed release may be achieved. A careful selection of polymer molecular weight may allow a lag period before which there is no release of drugs from a polymer matrix. Additionally, this lag period may be decreased if required by the external application of ultrasound (12). To achieve longer lag periods, either higher molecular weight p(CPP:SA) or other polymers might be considered.

It is also apparent from this study that there needs to be a careful distinction in the use of the terms erosion (appearance of monomers in medium) and degradation (breakdown of polymer into monomers/oligomers). (Analogously, surface degradation and surface erosion are not necessarily equivalent.) As demonstrated with the polyanhydrides, one would expect the different parameters used to describe kinetic studies of degradation (e.g., molecular weight loss, device weight loss, and monomer appearance) to produce different values. Additionally, the mechanisms occurring during erosion are not continuous, and distinct phases may be identified as shown in this study. These phases require char-

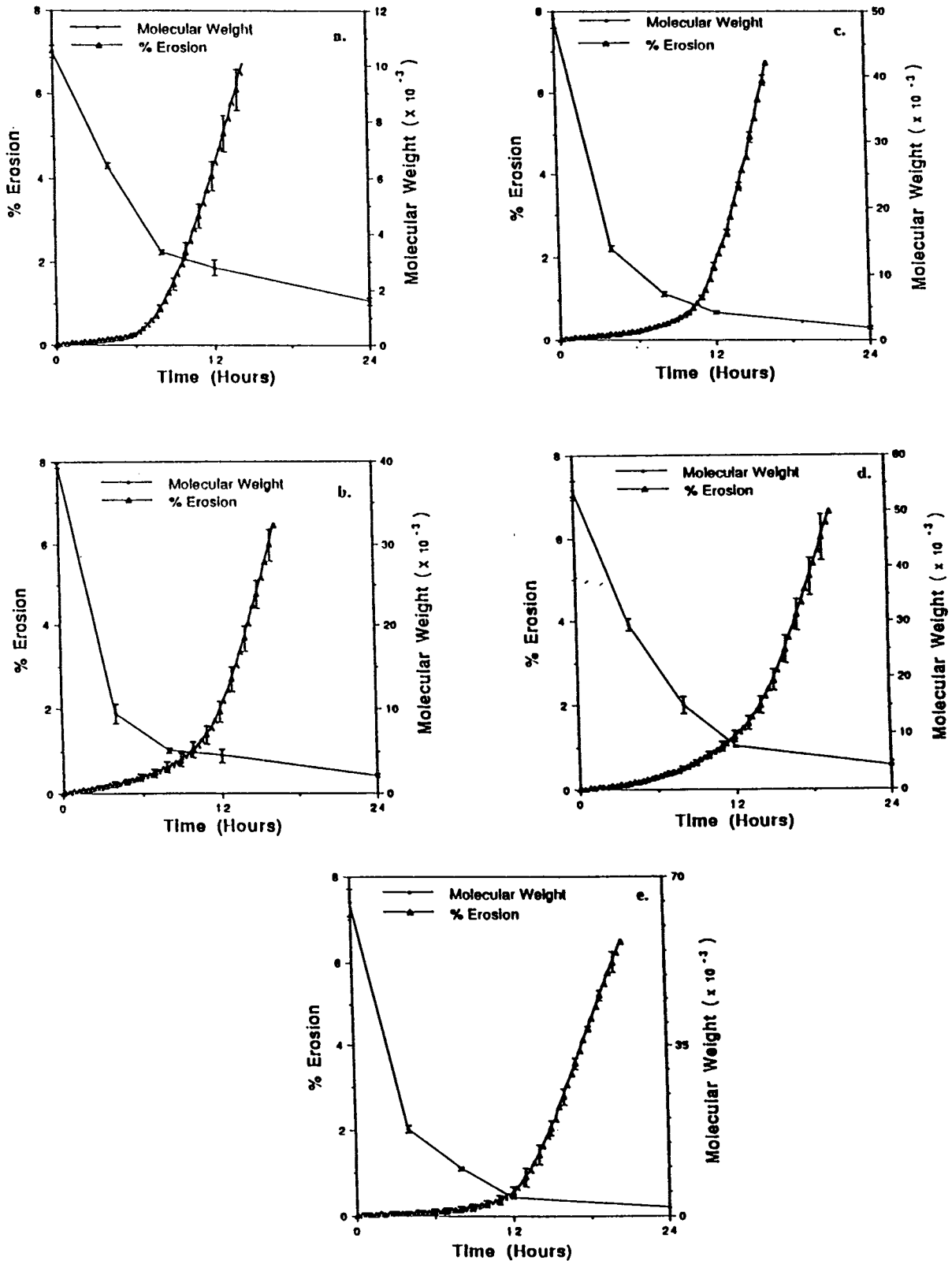

Fig. 3. The relationship between the decrease in polymer molecular weight and device erosion in the early stages of erosion for devices with various initial molecular weights: (a) 10,530, (b) 39,873, (c) 48,855, (d) 53,582, and (e) 64,744.

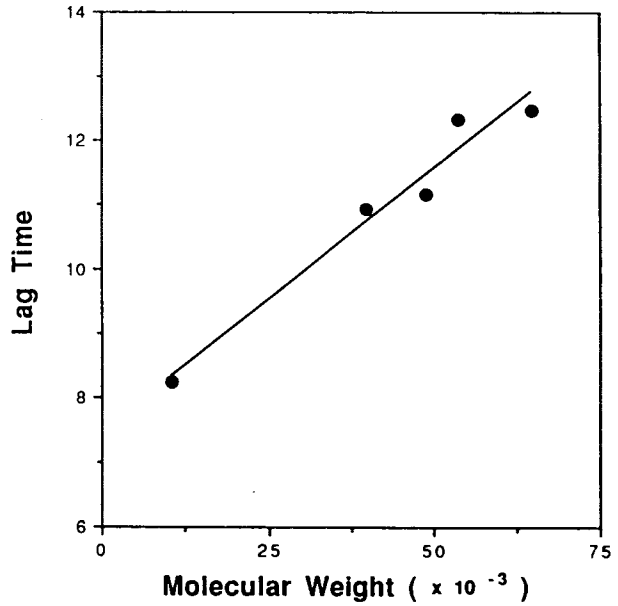

Fig. 4. The relationship between initial polymer molecular weight and lag time of erosion.

acterization by more than one parameter including molecular weight changes, weight losses, and solubility of the monomers/oligomers produced.

CONCLUSIONS

The erosion of polyanhydride matrices is characterized by an induction period during which the rate of erosion is relatively slow. It was found that during this period significant molecular weight losses occur within polymeric matrices, without significant device erosion (>20%). The length of the induction period depends on the initial polymer molecular weight and can be estimated if the polymer molecular weight is known. This effect may be applied to the development of systems which produce pulsed or delayed release profiles.

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