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Biodegradable Pseudolatexes: The Chemical Stability of Poly(D,L-Lactide) and Poly (ε-Caprolactone) Nanoparticles in Aqueous Media

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Pseudolatexes of the biodegradable polyesters poly(D,L-lactide) (PLA) and poly(ε-caprolactone) (PCL) have been developed as potential aqueous coatings for sustained release. Since PLA and PCL are known to hydrolyze, the influence of the surfactant system, temperature, pH, and particle size on the chemical stability of the polymers as aqueous colloidal dispersions was investigated. Pseudolatexes of PLA and PCL formulated with a nonionic surfactant system were the most stable. When these dispersions were stored in unbuffered media for 350 days at 5°C, only small changes in the weight-average molecular weights (M_w) of the polymers were observed. At 37°C there was rapid degradation of both polymers in the dispersions. Arrhenius plots for the degradation of PLA and PCL resulted in a linear relationship for PCL. The nonlinear relationship for PLA was attributed to the polymer being in two different physical states within the 5 to 37°C range which was used for the Arrhenius plots. PCL was in the rubbery state at all temperatures studied. Storage of the pseudolatexes in pH 1.65 buffer at 37°C catalyzed the rates of degradation of both PLA and PCL. However, refrigeration of the pseudolatexes stabilized the polymers even at pH 1.65 for up to 4 months. Particle size had an insignificant effect on PLA and PCL stability in pseudolatexes prepared with either a nonionic or an anionic surfactant system.

KEY WORDS: polylactic acid; polycaprolactone; pseudolatex; degradation; polymer colloid.

INTRODUCTION

Poly(D,L-lactide) (PLA) and poly(ε-caprolactone) (PCL) are biodegradable polyesters that have frequently been used for the preparation of sustained-release drug delivery systems (1–3). These polymers are biocompatible and slowly hydrolyze in the body to water soluble by-products that are either excreted or metabolized in the body. Recently, biodegradable polyesters have been utilized to formulate controlled release delivery systems for peptide drugs (4). The methods to prepare these dosage forms include the use of heat and/or organic solvents, either of which are capable of denaturing peptide drugs (5). Thus, the need for alternative methods of fabricating dosage forms of these labile compounds with biodegradable polyesters is apparent. It is proposed that aqueous pseudolatexes (i.e., colloidal dispersions of polymer spheres in water) of PLA and PCL provide such alternatives as aqueous coating dispersions for preparing sustained-release matrix tablets and coated particles.

For PLA and PCL pseudolatexes to be practical systems for preparing biodegradable controlled drug delivery systems, the polymers must be chemically stable during storage. Poly(D,L-lactide) as a colloidal drug carrier in an aqueous dispersion has been reported to be chemically stable at 25°C for up to 120 days (6). The energy of activation for the ester hydrolysis of PLA in the form of microcapsules has been reported to be 19.9 kcal/mol (7). From these results we have postulated that the degradation of PLA at 5°C should be sufficiently slow for PLA pseudolatexes to be chemically stable. This assumption was extended to PCL because it degrades more slowly than PLA (8). The objective of the present study was to determine the influence of the surfactant system, storage temperature, pH, and particle size on the degradation of PCL and PLA in pseudolatexes.

MATERIALS AND METHODS

Materials

The polymers used in the pseudolatexes included poly(D,L-lactide) (Henley Chemicals, Inc., Montvale, NJ) and poly (ε-caprolactone) (Polysciences, Inc., Warrington, PA). The other chemicals used in this study were polyoxyethylene 20 sorbitan monolaurate and sorbitan sesquioleate (ICI United States Inc., Wilmington, DE), Pluronic F-68 (BASF Corp., Parsippany, NJ), sodium dodecyl sulfate (SDS; Fluka Chemical Corp., Ronkonkoma, NY), potassium oleate (Sigma Chemical Company, St. Louis, MO), and methylene chloride and ethyl acetate (J. T. Baker Inc., Phillipsburg, NJ). All materials were used as received without further purification.

Preparation of the Pseudolatexes

Five percent (w/w) polymer solutions were prepared by dissolving PLA or PCL in a 50% (w/w) solvent mixture of methylene chloride and ethyl acetate. In the nonionic pseudolatexes, sorbitan sesquioleate was dissolved in the solvent system as a stabilizer at a concentration ranging from 0.3 to 1.0% (w/w) of organic solvent. This organic polymer phase was added to an agitated aqueous surfactant phase that contained either the nonionic surfactants polyoxyethylene 20 monolaurate and Pluronic F-68 [their concentrations ranged from 0.4 to 1.3% (w/w) and 0.6 to 1.7% (w/w) of the aqueous phase, respectively] or the anionic surfactants potassium oleate and sodium dodecyl sulfate to form an oil-in-water (o/w) emulsion. This primary o/w emulsion was then passed through a Microfluidizer (Model M-110) four times at a pressure of approximately 6000 psi to reduce the emulsion particle size to the submicron range. The organic solvent was then removed from the microemulsion by evaporation along with a portion of the water until a final solids content of 10% (w/w) was obtained.

Gel Permeation Chromatography (GPC) Analysis

Weight-average molecular weight (M_w) measurements were made using a Waters GPC system that consisted of a

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two-piston pump (Model 510), three Ultrastyragel columns with exclusion limits of 10^4, 10^3, and 10^2 Å and a differential refractometer (Model 410). The operational conditions were as follows: solvent, tetrahydrofuran; column temperature, 31°C; refractometer temperature, 32°C; injection volume, 20 µl; flow rate, 1 ml/min; and solute concentration, 0.3% (w/v). The relative standard deviations of the M_w measurements were less than 8% ($n = 3$). Polystyrene standards, which ranged from 560,000 to 1000 molecular weight, were used to calibrate the GPC system and all values of M_w reported were relative to polystyrene. Samples were prepared by removing an aliquot from each dispersion and driving off the water. The solid residues were then weighed into volumetric flasks and filled to volume with tetrahydrofuran. The polymer solutions were then passed through 0.45-µm nylon filters using a glass syringe. The chromatograms in Fig. 1 are representative of the data used to calculate the M_w's that are reported under Results and Discussion.

Degradation Studies

The pseudolatexes were stored under static conditions. Double-distilled water was the medium used except when the effect of pH on latex stability was studied. The buffers used were (1) hydrochloric acid–citric acid, trisodium salt; (2) hydrochloric acid–citric acid, trisodium salt; and (3) potassium phosphate, monobasic–sodium phosphate, dibasic. The 0.1 *M* buffers had pH values of 1.65, 3.10, and 5.10, respectively. The dispersions were stored at 5°C unless stated otherwise.

Particle Size and pH Measurements

The mean particle diameters of the pseudolatexes were measured using photon correlation spectroscopy (Brookhaven Instruments, Model BI 2030). Measurements were carried out at 20°C at a concentration of 10 µg/ml. The pH values of the pseudolatexes were measured at room temperature with a Corning pH meter (Model 245) using a combination electrode with a silver/silver chloride reference.

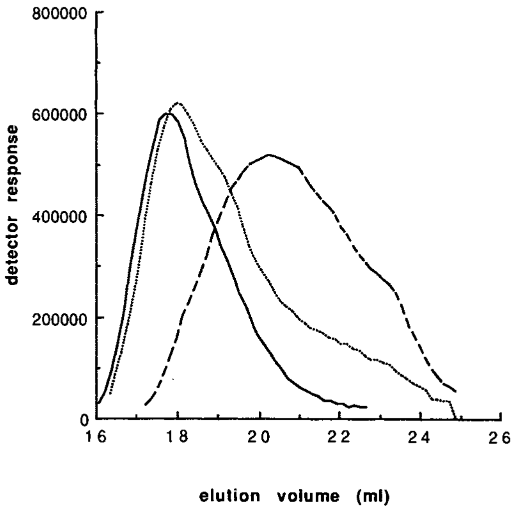


Fig. 1. GPC chromatograms of PLA in pseudolatexes prepared with sodium dodecyl sulfate: (——) initial; (· · · ·) 4 months at 5°C; (- - -) 1 month at 37°C.

Thermal Analysis

A computer-interfaced differential scanning calorimeter (Model DSC-2C) with a Thermal Analysis Data System (Perkin-Elmer Corp.) was used to obtain thermograms of films ($n = 3$) cast from solutions of PLA and PCL with or without sorbitan sesquioleate in a 50% (w/w) methylene chloride/ethyl acetate solution. The glass transition temperatures of the PLA samples were obtained after quenching while the heats of fusion of the PCL samples were measured on the first heating. The scanning temperature range was from −23 to 150°C at a heating rate of 20°C/min.

RESULTS AND DISCUSSION

The weight-average molecular weights (M_w) of PLA in unbuffered pseudolatexes as a function of time, storage temperature, and surfactant system are shown in Fig. 2. It is apparent from the data that at 37°C there was extensive degradation of PLA in all three formulations. At this temperature the anionic surfactants facilitated the degradation of PLA as evidenced by the M_w of PLA decreasing to less than 30,000 after 28 days at 37°C in the potassium oleate and sodium dodecyl sulfate formulations. In the nonionic formulation, the M_w of PLA was nearly 100,000 after 28 days at 37°C. At 5°C the rate of decrease in the M_w of PLA was much slower in each dispersion. The nonionic formulation showed no appreciable drop in M_w after 4 months at 5°C, indicating that PLA in the colloidal dispersion was chemically stable during this period of time. In the formulations containing the anionic surfactants, the M_w of PLA dropped to less than 100,000 after 4 months at 5°C and suggested that hydrolysis of the PLA was occurring.

Representative chromatograms of PLA in the SDS formulation, from which some of the M_w values in Fig. 2 were calculated, are shown in Fig. 1. These samples were taken from the initial dispersions, 1-month samples at 37°C and

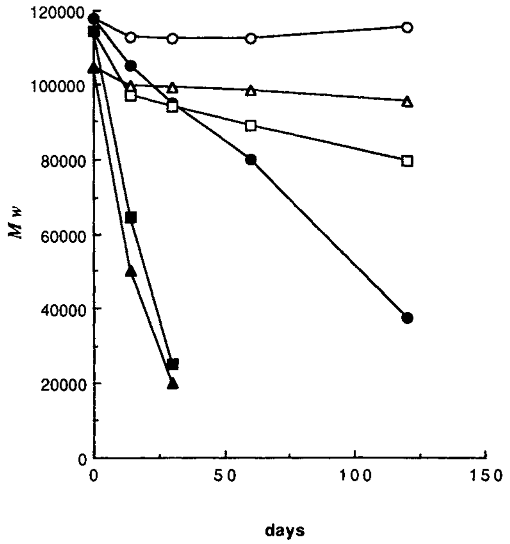


Fig. 2. Effect of the pseudolatex surfactant system and temperature on the degradation of PLA in unbuffered pseudolatexes: (○) nonionic, 5°C; (●) nonionic, 37°C; (△) potassium oleate, 5°C; (▲) potassium oleate, 37°C; (□) sodium dodecyl sulfate, 5°C; (■) sodium dodecyl sulfate, 37°C.

4-month samples at 5°C. These GPC traces indicate that very substantial degradation had occurred in the 37°C sample and to a much lesser extent at 5°C. For comparison, it should be pointed out that the GPC traces of the 5°C, 4-month samples for the nonionic formulations were virtually perfect layovers of their initials, which confirms the greater chemical stability of these dispersions. The chromatograms in Fig. 1 also suggest that hydrolysis of the polymer chains occurs through a two stage process. First, the formation of the shoulder and tail in the 5°C sample shows that the intermediate and low molecular weight chains are hydrolyzed first. The position of the shoulder correlates well with a previous report (7) that a M_w of 60,000 represents a stable fraction in PLA. This enhanced stability is due to some structural order in this portion of the polymer. The appearance of shoulders and tails in the chromatograms was followed by overall shifting of the traces which resulted from the hydrolysis of the high molecular weight chains.

The chemical stability of PCL in the three pseudolatex formulations is depicted by the plots of M_w versus time shown in Fig. 3. There was rapid degradation of the polymer at 37°C in each formulation and much slower degradation at 5°C as was observed in the PLA dispersions. However, it is apparent that PCL was very susceptible to hydrolysis by SDS at 5°C as evidenced by its M_w decreasing to 50,000 after 4 months. The initial M_w of PCL in the SDS pseudolatex was lower than in the other two formulations. This was due to the 1-week lag time which resulted from removal of the organic solvent and some of the water. The precise mechanism for the catalysis of PCL hydrolysis by SDS was not clear. The pH values of the SDS and nonionic PCL pseudolatexes were in the range of pH 4 to pH 6, where pH has been reported to have no effect on the degradation of PCL (8). The potassium oleate dispersions had pH values of approximately 9 initially, where the base-catalyzed hydrolysis of polyesters has been reported (9). Therefore, pH-dependent catalysis did not seem plausible and leads these investigators to believe that the sulfate anion may have catalyzed the degradation by nucleophilic attack of the PCL ester bonds. Nucleophilic attack of the carbonyl groups on PCL–PLA copolymers by basic drugs and subsequent catalysis of its degradation rate has been reported (3). The amorphous regions of PCL would have been more susceptible to such an attack at 5°C than PLA because of PCL's low T_g (T_g = −65°C). The inducement of PLA hydrolysis by SDS at 5°C was likely inhibited by steric hindrance (10) and/or the glassy state of the polymer (T_g of PLA = 57°C). At 37°C, it is reasonable to assume that sufficient energy was available to overcome the steric barrier, thus leading to the very rapid decrease in the M_w of PLA at 37°C in the SDS formulation.

The data in Fig. 4 show the long-term stability of the PLA and PCL pseudolatexes that had been prepared using the nonionic surfactant system. The change in M_w's of PLA and PCL at 5°C was insignificant after 350 days and indicated that very little cleavage of the ester bonds of the polymers occurred during this period of time. The stability data at 25°C were rather surprising, since PCL has been reported to hydrolyze more slowly than PLA (8). The 8-month data showed that PCL in the pseudolatex stored at 25°C had degraded from a M_w of 108,000 to approximately 45,000, while PLA still measured a M_w of nearly 90,000. The faster degradation of PCL could have been due to the high levels of nonionic surfactants which were used to stabilize the PLA and PCL pseudolatexes. The surfactants may have increased the percentage of amorphous regions in PCL, which are known to degrade more rapidly than the crystalline regions in PCL (12). Thermal analysis of sorbitan sesquioleate:PCL films failed to reveal that effect though, even when film levels of stabilizer exceeded 20%, as shown in Table I. At 37°C, PLA and PCL both showed very large decreases in M_w after 60 days of storage, degrading to a M_w of 77,000 and 66,000, respectively. The M_w measurements of PCL at 37°C were discontinued after 60 days since the pseudolatex had agglomerated and the PCL nanoparticles had formed a cake that could not be redispersed.

Arrhenius plots for the degradation of PLA and PCL in

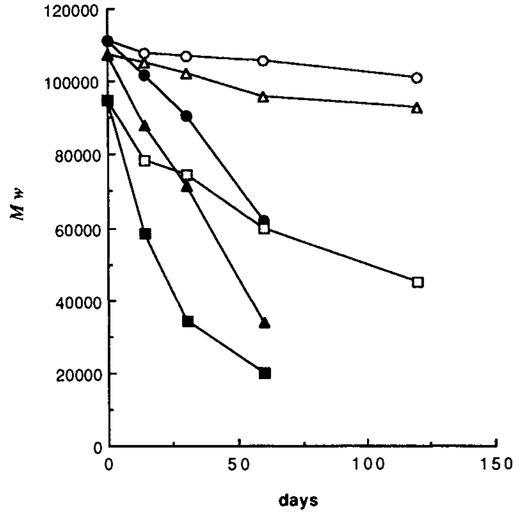


Fig. 3. Effect of the pseudolatex surfactant system and temperature on the degradation of PCL in unbuffered pseudolatexes; (○) nonionic, 5°C; (●) nonionic, 37°C; (△) potassium oleate, 5°C; (▲) potassium oleate, 37°C; (□) sodium dodecyl sulfate, 5°C; (■) sodium dodecyl sulfate, 37°C.

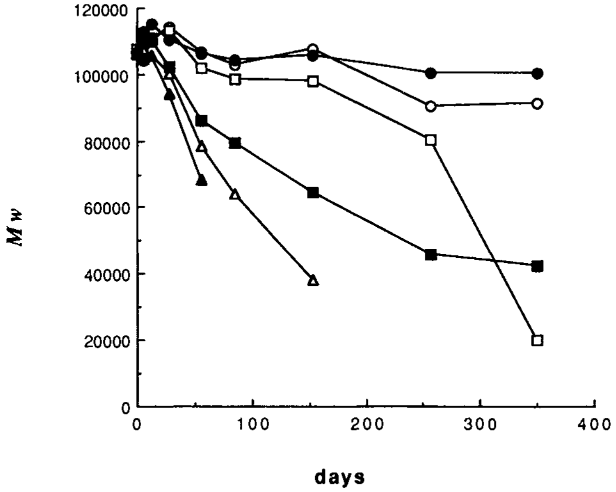


Fig. 4. Effect of temperature on the degradation of PLA and PCL in unbuffered pseudolatexes formulated with the nonionic surfactant system: (○) PLA, 5°C; (□) PLA, 25°C; (△) PLA, 37°C; (●) PCL, 5°C; (■) PCL, 25°C; (▲) PCL, 37°C.

Table I. The Influence of Sorbitan Sesquioleate on the Heat of Fusion of PCL

Sorbitan sesquioleate (%, w/w)	Onset (°K)		ΔH_f (cal/g)	
	Mean	SD	Mean	SD
0.0	329.6	0.15	22.6	0.16
3.0	329.5	2.48	21.6	0.33
11.0	329.5	0.47	21.4	0.58
20.8	330.0	1.62	20.1	0.71

unbuffered, nonionic pseudolatexes are shown in Fig. 5. The Arrhenius plot for the degradation of PCL was linear as compared to that for the degradation of PLA, which was unexpectedly nonlinear. A possible explanation for nonlinearity may be derived from the physical states of PLA and PCL at the temperatures studied. Sorbitan sesquioleate was used as a stabilizer in the pseudolatexes and was codissolved with the polymers into the organic solvent system. The thermograms in Fig. 6 demonstrate that sorbitan sesquioleate lowered the T_g of PLA. Concentrations of 1 and 5% (w/w) sorbitan sesquiloleate decreased the T_g of PLA from 57 to approximately 30°C. Poly(ε-caprolactone) was in the rubbery state at all temperatures studied. Poly(D,L-lactide) was, however, in the rubbery state at 37°C and in the glassy state at 5°C. An Arrhenius plot that crosses the glassy and rubbery states of a polymer would not be expected to be linear over the entire temperature range that was studied because the rubbery state of a polymer is at a higher free energy level than its glassy state and thus, is much more reactive. These differences in physical states of the polymers over the range of temperatures used in this study provide a logical explanation for the more rapid of degradation of PCL at 25°C relative to that obtained for PLA. Reed and Gilding (11) have shown that the rate of tensile strength loss is a linear function of temperature above and below the T_g of polyglycolic acid. However, the slope of the rate loss function was seven times greater at temperatures above the T_g of the polymer. Therefore, if PLA was in the rubbery state at 37°C and in the glassy state at 25°C, then the rate of degradation of the polymer at 25°C would be much lower than that predicted from the data obtained at 37°C.

The pH of the PLA and PCL nonionic pseudolatex dispersions was also followed as a function of time and temperature. The results in Fig. 7 reveal that the pH data for the PLA pseudolatex were in good agreement with the M_w results obtained from GPC. The pH of the pseudolatex decreased rapidly at 37°C from pH 6.0 to pH 3.3 after 115 days. At 5°C, the pH of the PLA pseudolatex was essentially unchanged and confirmed the M_w data which showed that PLA was stable in a pseudolatex at these temperatures. At 25°C, the pH of the pseudolatex was unchanged for a time period up to 115 days. It then began to drop and reached pH 4.0 after 250 days. This decrease in pH at 25°C can be ascribed to the generation of the low molecular weight polymer chains that do not appreciably influence the M_w of the PLA. The drop in pH was a precursor to degradation that was detected by GPC analysis at the 350-day time point. The hydrolysis of PLA has been described as autocatalytic (7). The mechanism of autocatalysis may be due either to a decrease in the pH of the polymer's microenvironment or to plasticization of the bulk polymer by the low molecular weight chains produced by hydrolysis (13). In general, the pH of the PLA pseudolatex was a good measure of PLA stability, since as the polymer degraded, more carboxyl groups were created. For every hydrolysis reaction that occurred, an additional carboxyl group was produced. The pH values of the PCL pseudola-

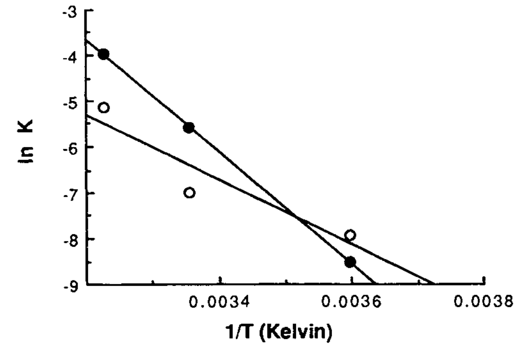


Fig. 5. Arrhenius plots for the degradation of PLA (○) and PCL (●) in unbuffered pseudolatexes formulated with the nonionic surfactant system. $K = dM_w/dt$.

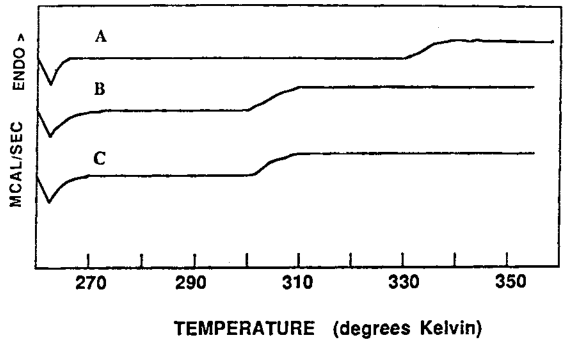


Fig. 6. DSC thermograms of (A) PLA without sorbitan sesquioleate; (B) PLA with 5% sesquioleate; (C) PLA with 1% sorbitan sesquioleate.

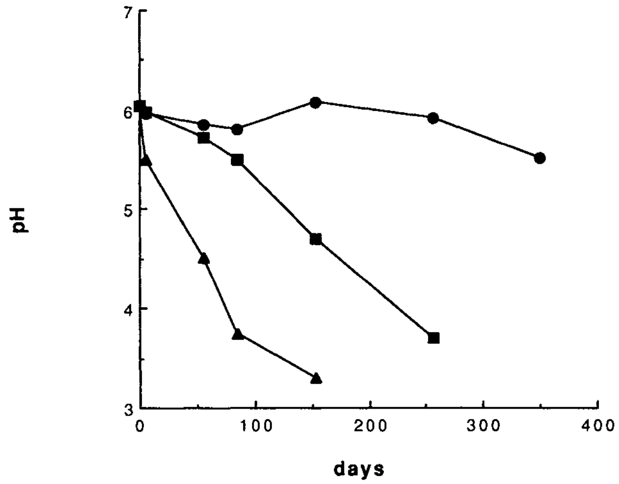


Fig. 7. Effect of temperature on the pH of unbuffered PLA pseudolatexes formulated with the nonionic surfactant system: (●) 5°C; (■) 25°C; (▲) 37°C.

texes were relatively constant at all storage temperatures and time points.

Nonionic pseudolatexes of PLA and PCL were buffered at pH 1.65, 3.1, and 5.1. This range of pH values was chosen because the maximum stability of PLA has been reported to be in the range of pH 3.0 to 5.0, while catalysis occurs at pH 1.65 (7). The aqueous dispersions were stored at 5 and 37°C to determine if a reduction in storage temperature to 5°C would be sufficient to stabilize the polymers even at very low pH values where catalytic degradation would occur. The data in Fig. 8 reveal that storage of the pseudolatexes at 5°C effectively retarded the rate of polymer hydrolysis at all pH values studied. The decreases in M_w of PLA and PCL at 5°C in each buffer were within the relative standard deviations of the measurements. In addition, the data in Fig. 8 corroborated that catalysis occurred at pH 1.65 and 37°C as the M_w's of PLA and PCL decreased from 115,000 and 108,000, respectively, to approximately 30,000. Comparatively, the M_w's of PLA and PCL decreased to only 60,000 at pH 3.1 and pH 5.1 at 37°C. The degradation profiles of PLA and PCL at pH 3.1 and pH 5.1 in Fig. 8 were very similar to those shown in Fig. 4, which were obtained from the degradation of the polymers in the unbuffered pseudolatexes. Approximately equal degradation rates were anticipated because the pH of the unbuffered latexes was in the range of pH 4.0 to 6.0, which is near the pH range of maximum stability for PLA. In addition, the higher ionic strength of the buffered pseudolatexes was expected to be inconsequential, as previous investigators have shown ionic strength to have only a very minor effect on polymer hydrolysis (7).

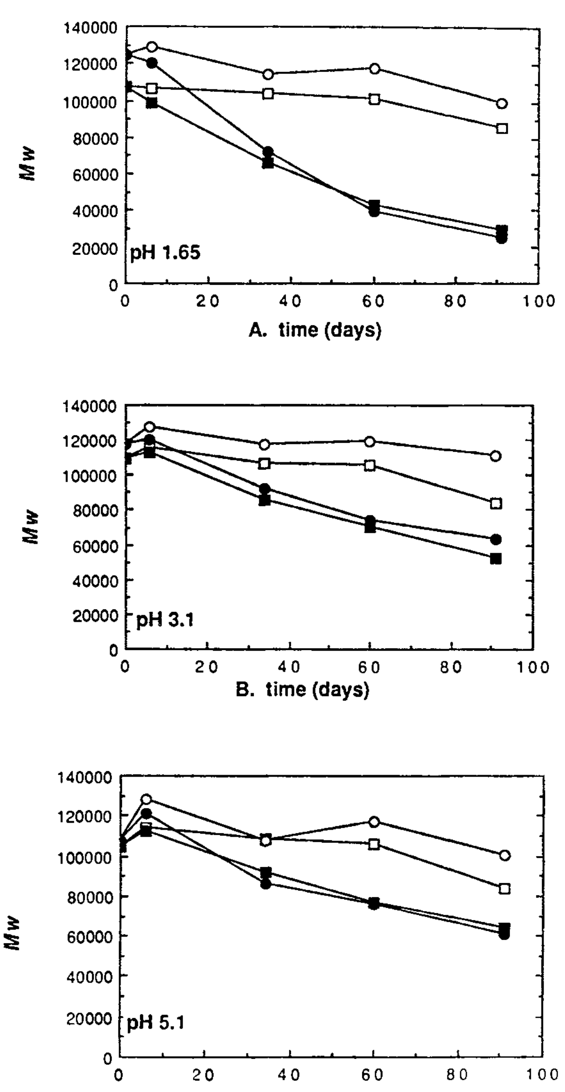


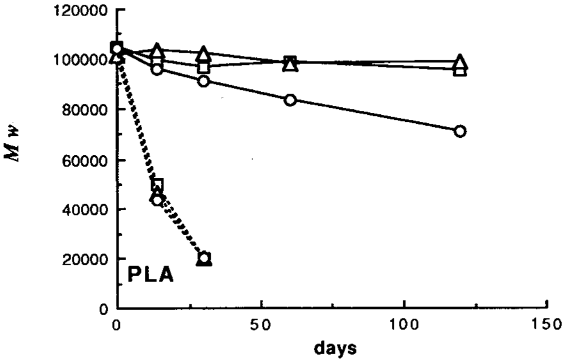
Fig. 8. Degradation of PLA and PCL in nonionic surfactant stabilized pseudolatexes at pH 1.65, 3.1, and 5.1. (○) PLA at 5°C; (●) PLA at 37°C; (□) PCL at 5°C; (■) PCL at 37°C.

To date, most studies concerning the degradation of PLA and PCL have used either films (13), rods (14), sutures (15), microspheres, or microcapsules with particle diameters greater than 1 μm (3) as the model system. All of these configurations of the polymers expose significantly less surface area of the polymers to the immediate aqueous environment as compared to pseudolatexes which have mean particle diameters below 300 nm. The influence of particle size on the rate of polymer degradation was investigated to determine if an increase in surface area would increase the rate of polymer degradation. This was thought to be a potential problem because the pH of the microenvironments around the PLA and PCL nanoparticles might be sufficiently low to cause acid catalysis. The data in Table II show the M_w of the PLA and PCL in nonionic pseudolatexes as a function of time at 5°C, with mean particle diameters ranging from roughly 225 to 400 nm. The results verified that at 5°C there were no appreciable differences in the degradation rates of the polymers and indicated that the higher surface area of the polymers as pseudolatexes should not adversely affect the chemical stability of PLA and PCL. The initial increase in M_w seen after 28 days may have been due to the preferential degradation of the low molecular weight fractions of polyesters which are known to degrade more rapidly (16). The influence of particle size was also examined in pseudolatexes prepared using potassium oleate as the surfactant. The results in Fig. 9 again show that particle size had no appreciable effect on the rate of polymer degradation. These results are consistent with those obtained by other investigators that indicate that PLA and PCL degradation is bulk mediated as opposed to surface mediated (17).

In conclusion, the results of this investigation demonstrated that biodegradable pseudolatexes of PLA and PCL will be stable at 5°C for their use in the fabrication of drug

Table II. Effect of Pseudolatex Mean Particle Diameter (MPD) on the Degradation of PCL and PLA at 5°C in Pseudolatexes Formulated with Nonionic Surfactant System

		Weight-average molecular weight (M_w)				
Polymer	MPD (nm)	0 days	28 days	56 days	112 days	250 days
PCL	405	111,000	116,132	111,779	103,884	102,246
PCL	267	107,800	112,802	108,872	98,746	93,109
PCL	242	107,670	111,867	100,784	96,411	92,496
PLA	387	120,355	127,397	125,124	102,203	113,056
PLA	265	119,650	126,586	118,201	112,942	115,207
PLA	227	112,250	121,339	112,840	105,118	115,678



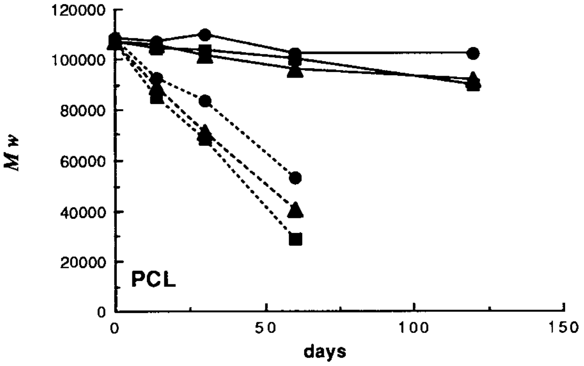


Fig. 9. The effect of particle size on the degradation of PLA and PCL pseudolatexes formulated with potassium oleate as the surfactant at 5°C (solid lines) and 37°C (dashed lines). PLA: (○) 200 nm; (□) 220 nm; (△) 241 nm. PCL: (●) 171 nm; (■) 221 nm; (▲) 240 nm.

delivery devices. The degradation of PLA and PCL was insignificant in nonionic pseudolatexes that were stored at 5°C for 350 days. The hydrolysis of PLA and PCL in these dispersions was very slow even at pH 1.65, where acid catalysis of the reaction occurs, when the temperature of the pseudolatexes was maintained at 5°C. This exemplified the strong dependence of the degradation rate upon temperature. The data also showed that unbuffered pseudolatexes of PLA may be stored for up to 4 months at 25°C with little effect on polymer stability. In addition, studies concerned with the influence of pseudolatex additives, such as the surfactant system, on polymer stability demonstrated that anionic surfactants such as potassium oleate and sodium dodecyl sulfate caused more rapid degradation of PLA and PCL than the nonionic surfactant system. Pseudolatexes with smaller particle sizes and, thus, higher surface areas did not degrade at a faster rate than pseudolatexes with less surface area. Therefore, surface area did not contribute significantly to polymer degradation. The chemical instability of PLA and PCL pseudolatexes was believed to be the major obstacle to be overcome prior to evaluating their potential as aqueous coating dispersions. Future studies will focus on the impact of the molecular weight distribution of these pseudolatexes on the rate of drug release from monolithic and reservoir dosage forms. Once it is known to what extent the molecular weight distributions of PLA and PCL can vary with no impact on drug release, then shelf-life predictions can be made for these biodegradable aqueous dispersions.

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