New Polyanhydrides Made from a Bile Acid Dimer and Sebacic Acid: Synthesis, Characterization, and Degradation

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ABSTRACT: New degradable polyanhydrides have been prepared by polycondensation from a dimer of one of the natural bile acid, lithocholic acid, and by copolymerizing the bile acid dimer with different amounts of sebacic acid (50, 80, and 90 wt %). The homo- and copolymers have shown near zero-order kinetics in the degradation and release studies, carried out in a phosphate buffer environment (pH 7.4) at room temperature. The results showed that the degradation and release rates of the polymers could be adjusted by the copolymer composition. The duration of the samples in the pellet form ranged from several weeks to about 5 years (by extrapolation). No apparent toxicity was observed for the polymer when tested in vivo with cells from normal human and pig tissues. The study showed that these new degradable polymers can be potentially used as controlled release systems.

Introduction

Bioerodible polymers have been used for various applications in biomedical and pharmaceutical fields, including tissue replacements[1] and controlled release systems of bioactive compounds.[2−4] The use of biodegradable drug carriers has significant advantages over the conventional systemic administration of medicine. The conventional approach produces a peak in the plasma drug level as the drug enters the body, followed by a rapid decrease as the drug is metabolized, thus requiring repeated drug administrations. The polymer−drug carrier system permits a controlled release of an active principle over a long period of time, i.e., months or even years. These systems can maintain a constant level of drugs in the plasma in a specified therapeutic range. Thus, the unwanted side effects of high plasma drug level and the nontherapeutic low plasma drug level of the conventional administration saw-tooth pattern can be avoided.[5] Furthermore, a polymeric drug-carrier system prevents the patient from being exposed to a massive excess of drugs over the quantity required. It also helps to localize the release of the drug at the desired site of action. Hydrogels can be used as drug carriers for controlled delivery systems and have been extensively investigated for this purpose.[6,7] Degradable polymers offer a significant advantage over the nonerodible system, since the degradation products will eventually be absorbed or metabolized, thus avoiding the necessity to surgically remove the implant.[8]

Bioerodible polymer delivery systems are attractive also in terms of predictability of the release, when the release is controlled only by the degradation process. In many cases, however, once the diffusion of the active principle through polymer matrix takes place, the release process becomes difficult to control. Diffusion of the active principle occurs as the matrix starts to erode in a homogeneous manner. This leads to a progressive loosening of the matrix which change its permeability and then the diffusion of the active principle becomes increasingly faster. Many factors may affect the erosion rate: bond lability, hydrophobicity, crystallinity, dissolution of degradation products and porosity. To achieve a surface erosion of zero-order kinetics, the ideal polymer should have a hydrophobic backbone, to prevent bulk erosion and diffusion, and very labile bonds, to ensure that the hydrolytic degradation is much faster than the penetration of water into the matrix. Many types of polymers have been studied for their degradation properties, such as polyesters,[9] polyamides,[10] polyurethanes,[11] and polyphosphazenes,[12] but only polyorthoesters[13] and polyanhydrides[14] have been shown to achieve a zero-order degradation rate. Because of the backbone stability of polyorthoesters, excipients must be added in the matrix to promote degradation. These excipients, usually water-soluble inorganic salts, tend to swell in aqueous media and thus promote diffusional release. Polyanhydrides may be sufficiently labile in hydrolysis to produce heterogeneous erosion, without the addition of any excipient.

Polyanhydrides were first synthesized by Hill and Carothers in the 1930s[15,16] as a substitute of polyester in the textile industry, but were discarded because of their hydrolytic instability. Erosion rate of polyanhydrides can be changed several 1000-fold only by changing the monomers or the composition of the copolymers.[17−19] There are many ways to polymerize a diacid into a polyanhydride. The use of dehydrative coupling agents, such as phenyl *N*-phenylphosphoroamidochloridate or bis[2-oxo-3-axazolidinyl]phosphinic chloride, yields only impure oligomers, since the salt formed cannot be removed.[20] Phosgene or the less toxic diphosgene can be used to prepare polyanhydrides of low molecular weights, but the toxicity of the reagents restricts their uses.[21] High molecular weight polyanhydrides can be obtained via melt polycondensation of the mixed anhydride prepolymers.[22]

Derivatives of natural compounds such as fatty acids have already been used in the preparation of degradable polyanhydrides.[23,24] Bile acids are natural, amphiphilic

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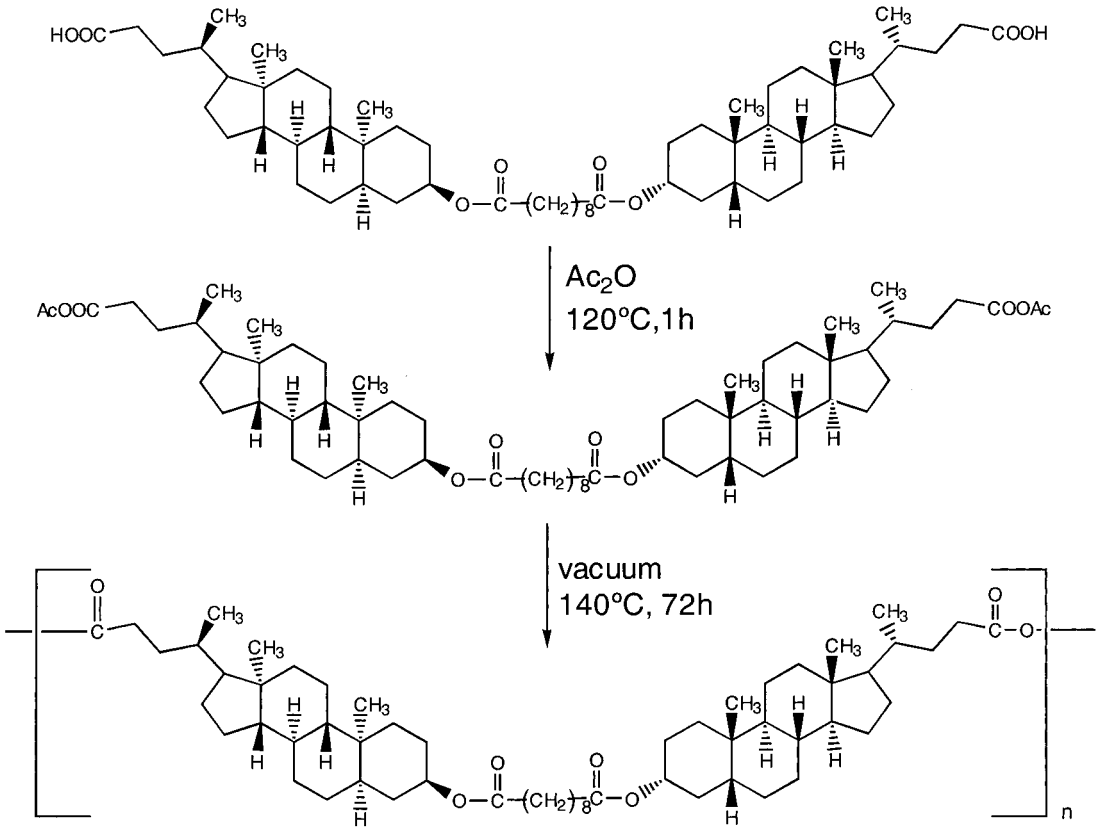

Figure 1. Synthetic scheme of polyanhydride from dimers of lithocholic acid.

compounds stored in the gallbladder and serve as emulsifiers for the solubilization of fats and lipids in food. When such biocompounds are used in the preparation of polymer materials, they should be better tolerated in the biological environment, especially in the gastrointestinal tract. The preparations of polymers containing bile acids as side chain pendants,[25−30] in the main chain,[31,32] or as end groups[33] have been reported. Previously, we have synthesized new polymers that contain bile acids and can be used in the preparation of hydrogels.[26−29] We have reported the synthesis of new 3α- and 3β-dimers of selected bile acids with spacers of different lengths[34] that could be used as monomers for the synthesis of new biodegradable polymers based on anhydride link.

In this paper, we report the synthesis of new biodegradable polyanhydrides derived from dimers of lithocholic acid, one of the bile acids. The new polymers have been characterized and their degradation and release profiles have been determined.

Experimental Section

Materials and Instruments. Lithocholic acid (LCA), acetic anhydride, and sebacic acid and its chloride were purchased from Aldrich and used as received. The probe molecule used in the release studies, *p*-nitroaniline, was purchased from Kodak and used as received. The solvents were also purchased from Aldrich. Chloroform and petroleum ether were dried over molecular sieves 4A (Aldrich) and redistilled. THF was refluxed with sodium and redistilled.

Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrophotometer with KBr pellets. Nuclear magnetic resonance (NMR) spectra were recorded at 23 °C on a Bruker AMX-300 spectrometer operating at 300.1 MHz for ^{1}H in deuterated chloroform, which also served as an internal reference (7.27 ppm for ^{1}H). The chemical shifts are given in ppm and coupling constants (*J*) in Hz. The molecular weight of the polymers were determined by size exclusion chromatography (SEC) at 33 °C using a 5 wt % solution in THF on a Waters 410 system (Waters) with polystyrene as the standard. The glass transition temperatures of the polymers were determined on a differential scanning calorimeter (DSC 2910, TA Instrument) with a heating rate of 20 °C/min from −100 to +300 °C. The concentration of the probe molecule in the degradation buffer was determined by UV absorbance on a Varian DMS 100 UV−visible spectrophotometer at 455 nm.

Preparation of Polymers. Prepolymer. The preparation of the polyanhydrides is shown schematically in Figure 1. The prepolymer of sebacic acid (PreSA) was prepared according to the literature.[22] The dimer, bis(5β-cholan-24-oic-3α-yl) sebacate, used in this study was synthesized as described in a previous paper.[28] A solution of 1 g of the lithocholic acid dimer in 6 mL of acetic anhydride was heated to 120 °C in an oil bath for 1 h. The solvent was partially removed, and the mixed anhydride prepolymer was allowed to crystallize at −10 °C. The product was filtered out, washed with a small amount of cold acetic anhydride, and dried under vacuum at room temperature for 2 days. The prepolymer was obtained with a yield of 50%.

Prepolymer of Bis(5β-cholan-24-oic acid 3α-yl) Sebacate (PreLCA). IR: 2927 and 2865 (C−H), 1820 (C═O, anhydride) 1730 (C═O, ester). ^{1}H NMR (selected signals): 4.72 (2H, m, 3-CH of LCA), 2.23 (4H, t, CH_2 of sebacate), 2.15 (6H, s, acetic CH_3), 1.32 (4H, CH_2 of sebacate), 0.96 (6H, d, J = 6, 21-CH_3 of LCA), 0.91 (6H, s, 19-CH_3 of LCA), 0.71 (6H, s, 18-CH_3 of LCA).

Homopolymer. The polymerization was achieved by melt polycondensation of PreLCA under an inert gas. The prepolymer (PreLCA) was placed in a polymerization tube equipped with a capillary inlet tube for gas and a sidearm for the vacuum. The prepolymer was then heated in an oil bath to 140 °C under a flow of nitrogen. After the prepolymer was molten the polymerization was allowed to proceed in a vacuum for 72 h. The polymer was then purified by precipitation from petroleum ether.

Polyanhydride of Bis(5β-cholan-24-oic acid 3α-yl) Sebacate (PLCA). IR: 2920 and 2870 (C−H), 1820 (C═O, anhydride) 1735 (C═O, ester). ^{1}H NMR (selected signals): 4.70 (2H, m, 3-CH of LCA), 2.20 (4H, t, CH_2 of sebacate), 1.32 (4H, CH_2 of sebacate), 0.98 (6H, s, 21-CH_3 of LCA), 0.90 (6H, s, 19-CH_3 of LCA), 0.73 (6H, s, 18-CH_3 of LCA).

Copolymers. PreLCA and PreSA were mixed together in the polymerization tube in various desired weight fractions, 50:50, 20:80 and 10:90. The copolymers, P(LCA-*co*-SA), have been prepared in the same manner as for the homopolymer.

Degradation and Release Kinetics. To study the degradation and release kinetics of the polymers, devices in the pellet form were prepared. PLCA or P(LCA-*co*-SA) was mixed with *p*-nitroaniline and then pressed between two aluminum pellets at room temperature with a force of 8 metric tons/m^2. The device was cylindrical with a height of approximately 1 mm. The total apparent surface area of the matrices was 1.32 cm^2, and the sample weighed from 120 to 150 mg.

In vitro release studies were performed by placing the PLCA or P(LCA-*co*-SA) devices in glass scintillation vials containing 10 mL of phosphate buffer (pH 7.4) at room temperature. To simulate the constant flow of biological liquid in the body, the buffer was periodically changed before 33% of the saturation concentration of *p*-nitroaniline is reached for a perfect sink effect, by removing the device from the vials and placing it in a vial containing fresh buffer. The sink conditions were based on the solubility of *p*-nitroaniline since the degradation products were much more soluble in water than *p*-nitroaniline and the saturation concentration of the probe is reached before the saturation concentration of the degradation products. The absorbance of the collected buffer solution was measured at a wavelength of 455 nm. The concentration was determined from a standard curve constructed by measuring the absorption at 455 nm of pure *p*-nitroaniline at concentrations ranging from 0.01 to 0.4 mg/mL. In vitro erosion was studied in a parallel experiment by weighing the device periodically after it had been dried at 60 °C for 24 h under vacuum.

To determine if the polymer degradation products were toxic, cells derived from normal human and pig tissues were grown in the presence of the polymer for 10 days. The origin and culture of the cell lines (normal human dermal fibroblasts, pig fibroblasts, pig smooth muscle cells, and pig aortic endothelial cells) has been described elsewhere.[35] Cells (1×10^4) were plated in 12 well plates grown to confluence in approximately 10 days. When powdered polymer was suspended in the medium (2 mg/mL), there was no difference in the rate of growth of any of the cell lines nor in the cell density at confluence. The morphology of cells in the exponential or confluent phase of growth was unchanged by the addition of polymer to the medium.

In other experiments, cells were grown attached to the polymer surface as described by Leong et al.[18] Cells (1×10^5) were plated directly onto the surface of polymer disks (1 cm diameter, 1 mm thickness) in 0.25 mL of medium and allowed to attach for 2 h. The disk was then transferred to 10 mL of medium in a 10-mL Petri dish, and the cells were allowed to grow for 10 days with daily medium changes. Disks with attached cells were fixed with formaldehyde, stained with crystal violet and examined at 20× magnification by reflected light. All the cell lines were found to have attached to the polymer disks and to have proliferated to near-confluency during the incubation period.

Results and Discussion

Two techniques can be used to polymerize the diacids into polyanhydride: dehydrative coupling and melt polycondensation. The first method yields oligomers. The purification of the product is difficult since the anhydrides decompose quite easily. The second technique involves the preparation of a prepolymer and the melt polycondensation of the prepolymer (Figure 1). This method requires very pure products to obtain the polymer. It does not require strict stoichiometry as in other forms of polycondensation, since it is a self-polycondensation reaction.

Table 1. Glass Transition (T_g), Crystallization (T_c) and Melting (T_m) Temperatures of the Homo- and Copolymers as Measured by DSC

	transition temperatures		
polymer[a]	T_g (°C)	T_c (°C)	T_m (°C)
PLCA	85		>250
P(LCA-SA) (50:50)	30	42	63
P(LCA-SA) (20:80)	15	59	79
P(LCA-SA) (10:90)	13	71	77

[a] For the copolymers, the ratios indicated are weight percentages.

The method used in the synthesis of prepolymers from lithocholic acid dimers and sebacic acid was adapted from the procedure developed by Conix[22] for the polycondensation of diacids. A long crystallization time was needed for a high yield and an acceptable purity. In the case of the lithocholic acid dimer prepolymer, we found that 1 week is necessary for a yield of 50% and that longer crystallization time improves the yield only slightly. The complete conversion of the acid group into anhydride in the prepolymer is crucial to obtain the final polymer. If some acid group remains, water will be produced during the melt polycondensation and oligomers may be formed. It is difficult to verify the complete conversion of the acid group by proton NMR technique since the methyl proton peak of the acetic anhydride group (2.15 ppm) is overlapped with the proton signals of the steroid skeleton. FT-IR spectrophotometry is more useful to determine the completion of the reaction. The O−H absorption band at 3500 cm^{-1} disappears when the conversion of the acid group is complete.

The molecular weights of all the polymers synthesized have been evaluated by size exclusion chromatography (SEC) in comparison with polystyrene as the standard. This technique gave a relative molecular weight since no suitable standards were available. A correction of the calibration curve obtained with polystyrene standards was made by the use of the lithocholic acid dimer, which has a known molecular weight. Molecular weight of the polymer was then evaluated by assuming a perfect sigmoidal calibration curve profile, and the number-average molecular weight (M_n) was found to be 18 000 with a polydispersity of 5.

The glass transition (T_g), crystallization (T_c), and melting (T_m) temperatures of the homopolymer and copolymers, shown in Table 1, have been determined by DSC. Previous thermal history of the samples was erased by a preliminary heating cycle from −100 to +250 °C at 20 °C/min. The transition temperatures were determined by heating the sample at 20 °C/min from −100 to +300 °C for the homopolymer and from −100 to +250 °C for the copolymer, since the sebacic acid copolymers were prone to thermal degradation. The T_g values of the polymers were found to depend on the chemical composition of the copolymers. Since sebacic acid is more flexible than lithocholic acid dimer, a higher composition of sebacic acid in the copolymer leads to a lower T_g. When the proportion of sebacic acid in the different polymers increased from 0 to 90 wt %, the T_g dropped from 85 to 13 °C. The thermograms (Figure 2) show a strong melting peak for all the copolymers, indicating that the copolymers are quite crystalline. Since perfect crystalline samples could not be obtained for the polymers, the percentage of crystallinity could not be estimated. However, it is clear that the degree of crystallinity increases with the content of sebacic acid

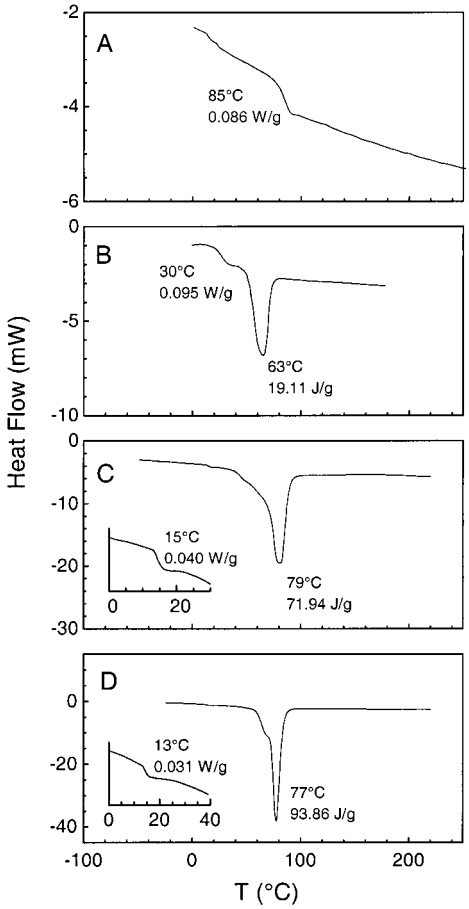

Figure 2. Thermograms of selected homo- and copolyemrs: (A) PLCA; (B) P(LCA-*co*-SA) 50:50; (C) P(LCA-*co*-SA) 20:80; (D) P(LCA-*co*-SA) 10:90.

in the copolymers. The heat of fusion increased from 19 to 93 J/g as the content of sebacic acid increased from 50 to 90%. The homopolymer of lithocholic acid dimer does not show a melting peak and the degradation temperature is over 300 °C. Obviously, the chains of this polymer are not very flexible, and thus the polymer is difficult to crystallize.

Several processing methods have been tried to prepare the device used in the degradation and release kinetic studies: solvent evaporation, microparticle formation, and compression molding. The first two techniques were not practical or led only to porous and fragile samples. Therefore, compression molding appears to be best suited for the processing of the polymers. The polymer and the chosen molecular probe (*p*-nitroaniline) were mixed together and ground into fine powder. The polymer was then placed between two clean pellets of aluminum and pressed at 8 metric tons/m^2 at room temperature. Compression molding above glass transition temperature confers better mechanical properties to the device. To avoid any possible reactions between *p*-nitroaniline and the anhydride at high temperatures, compression molding was carried out at room temperature for all the polymers. The devices formed at room temperature were more fragile to handle, but they were still suitable for the degradation and release studies.

All the polymers studied here displayed near zero-order erosion kinetics over a period of several weeks. Figure 3 shows the degradation and release profiles for the samples. The decrease in the device thickness throughout the erosion, the structural integrity of the

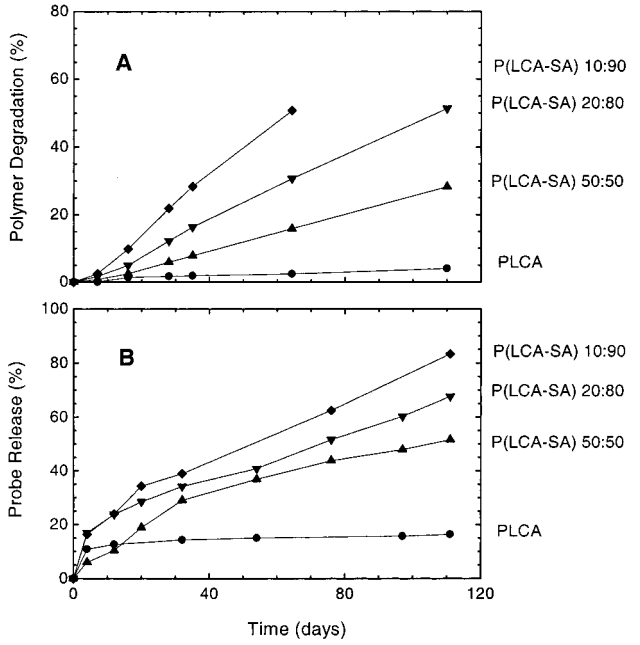

Figure 3. (A) Degradation of polymers and (B) release profiles of *p*-nitroaniline for homo- and copolyemrs with 5 wt % probe loading: PLCA, circles; P(LCA-*co*-SA) 50:50, upward triangles; P(LCA-*co*-SA) 20:80, downward triangles; P(LCA-*co*-SA) 10:90, diamonds.

Table 2. Release and Degradation Rates of Homo- and Copolymers

wt % of SA in the polymer	wt % of *p*-nitroaniline	release rate (mg/d cm^2)	degradation rate (mg/d cm^2)
0	20	0.007	0.061
0	5	0.004	0.068
50	5	0.012	0.194
80	5	0.022	0.509
90	5	0.030	0.752

matrix and the near zero-order degradation kinetics suggest that heterogeneous surface erosion predominates. It can be estimated by extrapolation that a 150 mg sample of PLCA of this geometry and size can be degraded completely in 5 years, which seems longer than that for common degradable polymers of a comparable size reported in the literature. The degradation rates were evaluated by a linear regression of the degradation profile shown in Figure 3. The degradation rates were found to be enhanced by copolymerization with sebacic acid. As shown in Table 2, the degradation rate increased from 0.068 to 0.752 mg d^{-1} cm^{-2} as the proportion of sebacic acid in the polymer increased from 0 to 90 wt %. An increase of nearly 20 times in degradation rate was observed when the sebacic acid content reaches 90 wt %. The dependence of the degradation rate on the sebacic acid content in the polymer is shown in Figure 4. The increase in the degradation rate is due to the increase in the hydrophilicity of the polymer, as explained by Leong et al.,[17−19] since infiltration of water in hydrophilic polymers is faster than in hydrophobic ones. The more hydrophilic copolymers tend to crumble toward the final stages of degradation. No bulk degradation was observed; the hydrolysis of anhydride links of the polymer backbone seems to proceed in a controlled manner. Carboxylic acid is produced upon degradation, which lowers the pH, and at low pH, the polymer degrades slowly. This is one of the intrinsic advantage of polyanhydrides, in addition to their very hydrolytically reactive linkage. The samples have shown a wide range

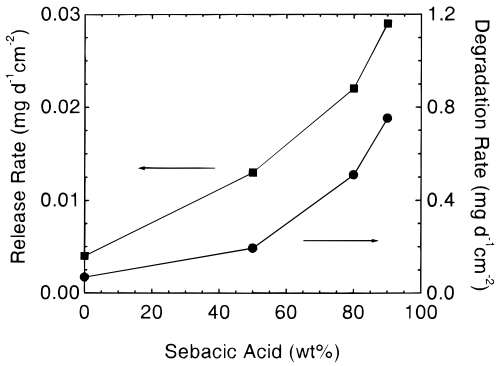

Figure 4. Dependence of release and degradation rates on the proportion of SA in the copolymers with 5 wt % probe loading: release rate of *p*-nitroaniline, squares; degradation rate of polymers, circles.

of degradation rates. With copolymerization, lifetimes of several weeks to several years with the 150 mg pellets have been obtained. This wide range of lifetimes is very important for the potential utilization of the polymers in pharmaceutical applications.

For the release kinetic studies, *p*-nitroaniline was used as a probe since it is a stable compound that can mix well with the polymers. It is slightly soluble in water and absorbs strongly in UV at 455 nm. It is remarkable to observe a close correlation between the degradation and the release kinetics for the device loaded at 5 wt % of the probe. The devices release the probe in a near zero-order manner almost parallel with the degradation profile. A zero-order profile indicates a constant release of solute with time, which is desirable because it ensures a constant drug plasma level when used in controlled release systems. Table 2 shows the release rates and the degradation rates of the homopolymer and the copolymers. Release rates of the probe by the polymers have been calculated by a linear regression of the linear portion of the release profile in Figure 3. The later linear portion of the release profile was used for the linear regression, and the R^2 value was at least 0.968 for all the analysis. Table 2 shows that the release rates increased from 0.004 to 0.030 mg d^{-1} cm^{-2} as the weight content of sebacic acid in the polymers increased from 0 to 90 wt %. Dependence of the release rate on sebacic acid content in the polymer is not linear, as shown in Figure 4, but seems to follow the same trend as the degradation rate as a function of the sebacic acid content.

The disk loaded with 20 wt % of *p*-nitroaniline displays a much more rapid release of the probe during the first stage and then a zero-order release kinetic nearly parallel with the degradation rate of the polymer (Table 2). The degradation rate was not as much affected by the percentage of loading. For the more hydrophilic polymers, the crumbling of the device does not seem to affect the release rate of the probe. There is no sudden burst during the crumbling, usually shown by a visible inflection in the release profile. In addition, no apparent toxicity was observed for the copolymer when tested in vivo with cells from normal human and pig tissues.

Conclusion

The new degradable polymers developed in this study have been shown to be interesting and potentially useful as controlled release systems, since the polymers can have long lifetimes and nearly zero-order kinetic profiles for degradation and release. Polymers with predictable release rate, closely related to the degradation rate, have been obtained. The properties of the polymers would allow the use of the materials for the release of active principles at a constant rate for a long period of time, avoiding the saw-tooth patterns of conventional systemic administration. Different release rates can be obtained by adjusting the comonomer contents during the copolymerization of the lithocholic dimer with sebacic acid. These new polymers have the added advantage since they also contain a natural compound, a character that may enhance the biocompatibility of the polymers.

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