Synthesis and Erosion Studies of Self-Catalyzed Poly(ortho ester)s

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ABSTRACT: A new variation of poly(ortho ester)s prepared by the addition of diols to the diketene acetal 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane is described. In this variation, a short segment of a glycolic acid dimer is built into the polymer backbone. Such a material does not require the addition of acidic excipients to control polymer hydrolysis rate, as was necessary in previous systems, and excellent control over erosion rate without attendant problems of loss of excipient by diffusion has been achieved.

Introduction

Poly(ortho ester)s are a versatile family of biodegradable polymers that have been under development since the early 1970s and to date, three distinct families of such polymers have been prepared. A comprehensive review of poly(ortho ester)s has been published.[1]

The most successful synthesis of poly(ortho ester)s involves the addition of polyols to a diketene acetal. In our initial work, we have used the diketene acetal 3,9-dimethylene-2,4,8,10-tetraoxaspiro[5.5]undecane. However, this diketene acetal has two electron donor groups attached to a double bond and is thus extremely susceptible to a cationic polymerization. Because the polymerization is an acid-catalyzed reaction, special catalysts such as iodine in pyridine must be used to prevent cross-linking due to a cationic polymerization of the diketene acetal double bonds.[2] However, when a hydrogen of this diketene acetal is replaced with a methyl group, sufficient steric hindrance is introduced to prevent a cationic polymerization, and the new monomer, 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]-undecane, is quite stable and can be prepared in large quantities; linear polymers can be readily prepared using *p*-toluenesulfonic acid catalysis.[3]

We now wish to report the synthesis and erosion studies of a new variation of polymers prepared by addition of diols to 3,9-diethylidene-2,4,8,10-tetraoxaspiro-[5.5]undecane, where a glycolic acid dimer segment is incorporated into the polymer. In addition, we show that by varying the concentration of this segment in the polymer, polymer erosion rate can be reproducibly controlled.

Experimental Section

General Synthesis of Diols Containing a Glycolide Segment. The following represents a typical preparation. In a drybox, 15.07 g (100 mmol) of triethylene glycol and 11.06 g (100 mmol) of glycolide were weighed into a 50 mL flask. The flask was sealed with a rubber septum and heated overnight at 180 °C in an oil bath. Similar reactions were also conducted with *trans*-cyclohexanedimethanol and 1,10-decanediol. The resulting oils were not purified and used directly in the polymerization reactions.

Polymerization. The following represents a typical preparation. Under anhydrous conditions 13.515 g (90 mmol) of triethylene glycol and 2.663 g (10 mmol) of the triethylene glycol monoglycolide described above were weighed into a 250 mL flask, and the mixture was dissolved in 50 mL of tetrahydrofuran. Then 19.103 g (90 mmol) of 3,9-diethylidene-2,4,8,-10-tetraoxaspiro[5.5]undecane was added. After the exothermic reaction subsided, the solution was first concentrated on a rotoevaporator and the remaining solvent removed in a vacuum oven at 40 °C.

Polymer Characterization. Molecular weights were determined by gel permeation chromatography (GPC) using tetrahydrofuran as the solvent, polystyrene molecular weight standards, and a Turbochrome software package. Polymer-softening temperatures were determined by using a melting stage apparatus.

Determination of Erosion Rates. Weighed polymer samples were incubated at 37 °C in pH 7.4, 0.05 M phosphate buffer, and at selected time intervals, samples were removed and dried to constant weight for mass loss determination.

Results and Discussion

Polymer Erosion Studies. Because poly(ortho ester)s based on 3,9-diethylidene-2,4,8,10-tetraoxaspiro-[5.5]undecane are highly hydrophobic materials with saturated water sorption ranging between 0.3 and 0.75 w/w %,[5] the polymers are stable for long periods of time in a pH 7.4 and 37 °C buffer, despite the relatively facile hydrolysis of ortho ester linkages. This stability is demonstrated in Figure 1 which shows weight loss as a function of time for a polymer prepared from 3,9-dimethylene-2,4,8,10-tetraoxaspiro[5.5]undecane and 1,6-hexanediol.[6]

Therefore, to achieve useful rates of polymer hydrolysis, it is necessary to use small amounts of acidic excipients that are physically incorporated into the polymer.[7] Then, the rate of hydrolysis can be manipulated by varying the pK_a and/or concentration of the acidic excipient.

However, excipients such as suberic acid, while effective in catalyzing polymer erosion, can, and in fact do, diffuse from the polymer matrix, particularly if long erosion times are desired. Clearly, diffusion of an acidic excipient from the polymer is undesirable and represents a significant problem in drug delivery applications because the varying excipient concentration not only complicates kinetics of drug release but, more importantly, results in an excipient-depleted polymer that will remain in the tissues for a significant length of time. Diffusion of acidic excipients from poly(ortho ester)s has been mathematically modeled.[8,9]

Control of Polymer Hydrolysis Rates without the Need To Use Acidic Excipients. Some time ago, we investigated the catalytic effect of pendant carboxylic acid groups by the use of 9,10-dihydroxystearic acid as one of the diols used in the synthesis and demonstrated that it is possible to control the release of a marker compound, *p*-nitroacetanilide, from the polymer by

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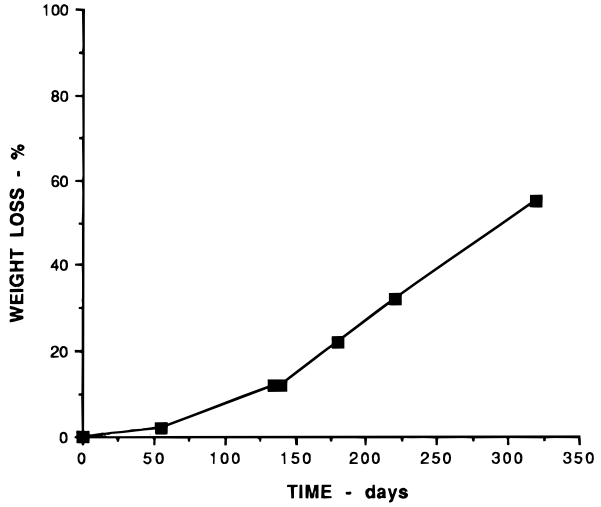
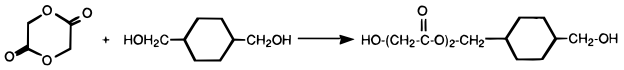


Figure 1. Weight loss as a function of time for a polymer prepared from 3,9-dimethylene-2,4,8,10-tetraoxaspiro[5.5]-undecane and 1,6-hexanediol (0.05 M phosphate buffer, pH 7.4, 37 °C).

Scheme 1



varying the concentration of 9,10-dihydroxystearic acid.[10] However, no actual erosion studies were carried out, and a significant effect could only be achieved when the polymer had a certain degree of hydrophilicity.

Subsequent to that study, we have found that carboxylic acid groups react with ketene acetals to form carboxy−ortho ester linkages, which are extremely unstable and rapidly hydrolyze to carboxylic acids and pentaerythritol propionate. Thus, the use of this monomer complicates the synthesis because 9,10-dihydroxystearic acid is actually a trifunctional monomer which unbalances the stoichiometry and produces a transiently cross-linked material.

For this reason, we have now investigated another approach, in which a catalytically active material is produced as a consequence of the uncatalyzed hydrolysis of the polymer. The synthesis of such a material is achieved by using a diol containing a glycolide dimer segment, prepared, for example, by using *trans*-cyclohexanedimethanol as shown in Scheme 1. It is recognized that a 2/1 stoichiometry of glycolide to diol will not produce a pure monomer as shown in Scheme 1, and instead a mixture of monosubstituted, disubstituted, and unsubstituted diols will be obtained. However, for the purposes of this polymer synthesis use of a pure monosubstituted diol is not essential since the only important parameters are total concentration of a glycolic acid dimer segment in the final polymer and strict bifunctionality of the diol reaction products.

A polymer using this monomer and another diol, in this case *trans*-cyclohexanedimethanol, is then prepared as shown in Scheme 2. This polymer contains glycolic acid dimer segments which, unlike poly(ortho ester) segments, are not stable at pH 7.4 and 37 °C and as shown in Scheme 3, when placed in an aqueous environment, will hydrolyze to generate glycolic acid which will then catalyze hydrolysis of the ortho ester linkages in the polymer backbone. The poly(ortho ester) linkages will then hydrolyze as shown in Scheme 4.[11]

Erosion of a polymer based on *trans*-cyclohexanedimethanol and *trans*-cyclohexanedimethanol glycolide, as a function of glycolic acid dimer segment concentration, is shown in Figure 2. Clearly, incorporation of glycolic acid dimer segments into the polymer not only results in excellent erosion behavior which proceeds to completion by close to zeroth-order kinetics but also allows an accurate control over erosion rate within very wide limits.

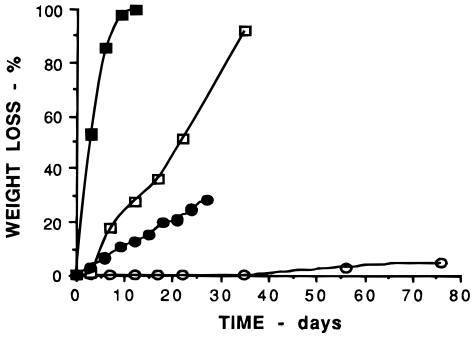
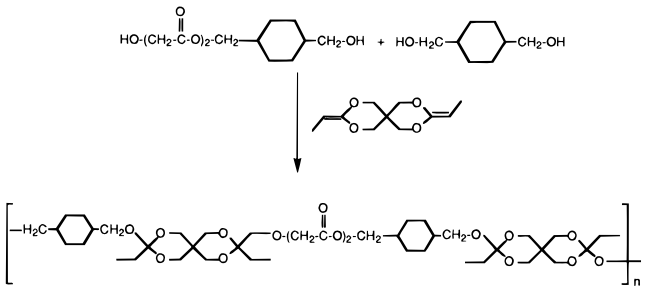
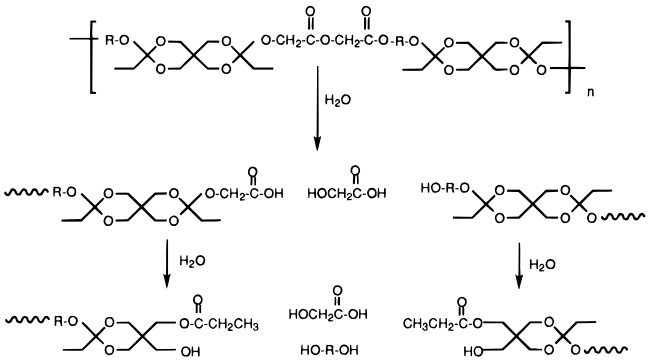


Figure 2. Weight loss as a function of poly(glycolic acid) dimer content for a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol glycolide (tCDM-Gly), and *trans*-cyclohexanedimethanol (tCDM): (■) 75/25 tCDM/tCDM-Gly, (□) (50/50 tCDM/CDM-Gly, (●) 25/75 tCDM/tCDM-Gly, and (○) 10/90 tCDM/tCDM-Gly (0.05 M phosphate buffer, pH 7.4, 37 °C.

Scheme 2



Scheme 3



Scheme 4

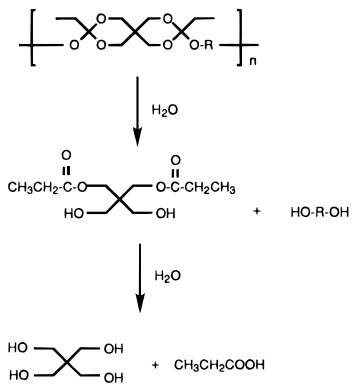


Figure 3 shows weight loss and changes in number-average molecular weight as a function of time for a 50/

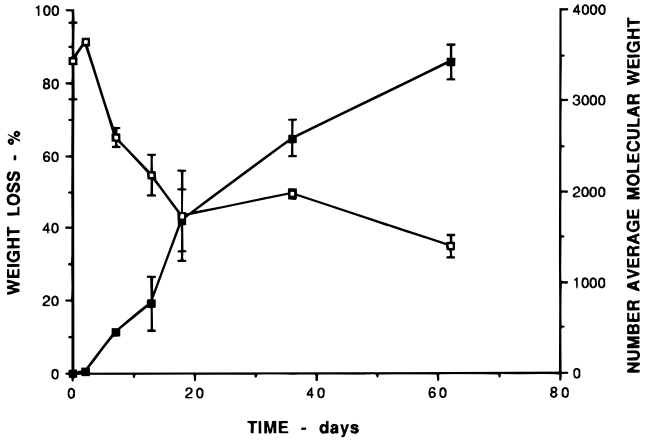


Figure 3. Weight loss (■) and changes in number-average molecular weight (□) as a function of time for a polymer prepared from 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]-undecane and a 50/50 mixture of *trans*-cyclohexanedimethanol glycolide and *trans*-cyclohexanedimethanol (0.05 M phosphate buffer, pH 7.4, 37 °C).

Table 1. Changes in Weight-Average and Number-Average Molecular Weight as a Function of Time for a Polymer Prepared from 3,9-Diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane and a 50/50 Mixture of *trans*-Cyclohexanedimethanol and *trans*-Cyclohexanedimethanol Glycolide

days	M_w	M_n	polydispersity
0	7442	3440	2.16
2	6440	3645	1.77
7	6897	2599	2.65
13	7256	2178	3.33
18	3662	1736	2.10
36	4887	1970	2.48
62	3418	1396	2.45

50 copolymer of *trans*-cyclohexanedimethanol glycolide and *trans*-cyclohexanedimethanol. The points represent weights of lost polymer and molecular weights of the remaining polymer. There is a slight induction time of about 2 days where no weight loss, nor molecular weight decrease, is detected, after which the molecular weight decreases steadily until about day 20, after which it remains relatively constant at about one-half of the original value. Rate of weight loss remains relatively constant throughout the entire study carried out over 60 days.

In view of the relatively high concentration of glycolic acid dimer segments in the polymer backbone, it is clear that these segments hydrolyze gradually since rapid hydrolysis of all segments would result in a cleavage of the backbone at the glycolic acid dimer segments with a consequent decrease of polymer molecular weight to a value of about 350. Thus, the linearity of weight loss and the slow changes in molecular weights are consistent with a process that occurs predominantly in the surface layers of the device with a gradual production of glycolic acid. At this point the discontinuity in the rate of molecular weight change that occurs at day 20 is not understood.

Table 1 shows weight-average molecular weights, number-average molecular weights, and polydispersity at each time point. Since production of small molecules such as glycolic acid would significantly lower the number-average molecular weight of the remaining polymer with consequent significant changes in the polydispersity index, these data confirm that there is no rapid production of glycolic acid.

Control over Mechanical Properties. By proper choice of diols and their ratios, it is possible to prepare materials that at room temperature have an ointment-like consistency or that are relatively rigid solids. Of particular interest are materials that at temperatures at or below 37 °C, the body temperature, are highly viscous materials that do not deform, even when subjected to fairly strong shear forces, but at temperatures above 37 °C, but below about 45 °C, are viscous fluids. Such slightly warmed materials can be injected into an appropriate body site, where they will solidify into a well-defined and nondeformable depot. Another important application for such materials is the delivery of sensitive therapeutic agents, especially proteins or antigens, because they can be incorporated into the gently warmed polymer by a simple mixing procedure without the need to use solvents and without exposure to water.

Table 2. Softening Points of Poly(ortho ester)s Prepared from Triethylene Glycol Monoglycolide (TEG/GLY) and Triethylene Glycol (TEG)

TEG/GLY	TEG	softening point (°C)
100	0	35
50	50	40
10	90	45

One such polymer is based on the flexible diol triethylene glycol and triethylene glycol glycolide. A typical melting behavior for this polymer as a function of diol compositions is shown in Table 2.

Conclusion

Poly(ortho ester)s containing glycolic acid dimer segments in the polymer backbone offer significant advantages over poly(ortho ester)s that require the addition of acidic excipients to control erosion rate. Using these new materials, erosion rates can be accurately controlled by varying the amount of the glycolic acid dimer segments in the polymer, and erosion proceeds by good zeroth-order kinetics to completion.

By using flexible diols, materials having controllable erosion rates and that are nondeformable semisolids at body temperature and injectable semisolids at temperatures below 45 °C have been prepared. Such materials should allow the incorporation of sensitive therapeutic agents without loss of activity as well as the formation of well-defined depots by a simple injection thus obviating the need for an invasive procedure.

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