Cyclic Swelling as a Phenomenon Inherent to Biodegradable Polyesters

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ABSTRACT: The aim of this study is to evaluate and describe the phenomenon and mechanism of the spontaneous cyclic swelling and deswelling of linear and branched aliphatic polyesters in the aqueous medium. The fluctuation of gel volume in one or several cycles as an inherent property of biodegradable and bioerodible materials has not yet been described. We have observed the process at linear and branched polyesters of aliphatic α-hydroxy acids. The period of duration of cycles was in order of hours to days, as influenced by the size of the bodies ranging from 25 to 1000 mg, the temperature in the range of 7°C–42°C, ionic strength, and pH value. The results demonstrated that swelling is accompanied by hydrolysis of ester bonds with the development of small water-soluble osmotically active molecules. After reaching a higher degree of swelling, the obstruction effect of the gel decreases and the diffusion of soluble degradation products from the body to the environment prevails. A decrease in osmotic pressure inside the body and a decrease in the hydrophilic character of the gel matrix result in deswelling by a collapse of the structure, probably due to hydrophobic interactions of nonpolar polyester chains. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3560–3566, 2014
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INTRODUCTION

Polyesters derived from aliphatic α-hydroxy acids (AHAs) are the most important biodegradable material in medicine, pharmacy, and tissue engineering. The main reason for the long-term interest in AHA is its biodegradability and biocompatibility.[1] It is possible to affect the course of the degradation processes by a modification of the structure and/or by composition, whereas the biocompatibility can be increased by surface modification.[2] Copolymers of the lactic and glycolic acids have been used in practice as surgical suture for more than four decades. Since then, there has been intensive research on and development of highly sophisticated materials based on the structure of the aliphatic polyesters. Of the nanocomposite blends of poly(DL-lactide-co-glycolic acid) PLGA and gelatin, three-dimensional nanofiber scaffolds have been fabricated, by the method of electro spinning, showing improved biocompatibility in bone regeneration.[3] It is possible to modify superficially PLGA particles, incorporate a combination of the different drugs in the form of molecular dispersion or nanoparticles, and target this composite system at organs and cells. Increased therapeutic effect is thereby achieved.[4] A three-dimensional stable porous structure of large surface was created by electrostatic interaction of two oppositely charged alginate- and chitosan-coated submicroscopic particles of PLGA, into which bioactive substances were intercalated.[5] Monolithic *in situ* forming implants applied by syringe into muscle find application opportunities in different biomedical applications.[6] They represent an attractive option to the commercial preformed implants for they do not require surgery when applied.[7]

In a biological environment, AHA degradation proceeds heterogeneously, that is, in the surface layer, or homogeneously, that is, in whole content. Homogeneous degradation is characterized by swelling. Swelling by covalent bonds of cross-linked nonbiodegradable elastomers as the result of two contrary-acting energies of elasticity of the gel network and mixing with solvent have been reported in a great detail.[8] A new wave of interest in this process has originated in connection with marked oscillation changes in the volume of some hydrogels, the so-called stimuli responsive polymers, after external interventions, such as chemical[9] or physical ones.[10,11] A marked change in the volume of gel may also be stimulated by autonomous oscillation chemical reaction[12] or biochemical interaction.[13] Swelling of gels, which are stabilized by physical bonds, takes a different course; it may end in pseudoequilibrium, or it may also continue by a process of dissolution.[14] Another type of nonequilibrium gels may be emerged in the aqueous medium from an insoluble polymer with its simultaneous degradation. These are mainly biodegradable materials, which are employed in pharmacotherapy or the production of scaffolds in tissue engineering.

In this communication, we demonstrate the cyclic swelling of poly-α-hydroxy acids with linear or branched constitution as new phenomenon. Here, we describe the influence of polymeric body size, temperature, pH, and ionic strength of aqueous medium on the process of swelling. Depending on these conditions, changing of swelling and deswelling phases took place in various intensity and duration. On the basis of similarity of course of changes in concentration of end carboxyl groups, glass transition temperature, and degree of swelling, we comment on the mechanism of cyclic swelling. We are convinced that this is the first report explaining this mechanism at a molecular level.

MATERIALS AND METHODS

Polyesters Synthesis and Characterization

Linear copolymer of DL-lactic acid and glycolic acid (PLGA) was synthesized by melt condensation polymerization from

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equimolecular mixture of glycolic acid and DL-lactic acid. For branched terpolymers, both acids with 3% tripentaerythritol were used. The reagent charge was 5 kg. All the chemicals were obtained from Sigma–Aldrich Chemical Company, St. Louis, MO. The synthesis of linear PLGA and branched PLGA with lower molar mass was carried out at 160°C and 550 Pa for 75 h. The reaction period of branched PLGA with higher molar mass lasted for 90 h. No catalyst was used.

Determination of molar mass, polydispersity, and branching degree was carried out by the HPLC–multiangle light scattering (HPLC–MALS) method (Wyatt Technology). A configuration of liquid chromatograph, scattering photometer Helios (Wyatt Technology Corporation), ViscoStar viscometer (Wyatt Technology Corporation), and a differential refractometer 2410 (Waters) was used. Liquid chromatograph consisted of a pump 1100 (Agilent) and an autosampler 717 (Waters). Two columns PLgel Mixed-C were used for separation. Tetrahydrofuran was used as the mobile phase at the flow rate of 1 mL/min. The volume of samples was 100 μL and the polyester concentration was 4% (w/v).

The degree of branching was determined as the ratio of the intrinsic viscosity of the branched compound to the intrinsic viscosity of the linear molecule with the same molar weight. For each measured branched polymer, a linear polymer PLGA with a close molar weight, determined by the size-exclusion chromatography (SEC) method, was used. The measurement is affected by different polydispersity of the compared polymers.

Differential scanning calorimetry (DSC) was performed using DSC 200 F3 Maia® (Netzsch, Germany). The glass transition temperature (T_g) values of synthesized polyesters are given in Table 1. DSC scans were acquired under nitrogen at a rate of 20°C/min. Samples were first heated from 20°C to 90°C (first heating), then cooled down to –60°C and heated (second heating) and cooled again. The T_g values were obtained from the second heating at the inflection point. The measurements were made in triplicate.

Polymeric Matrices Preparation and Testing

Matrices were prepared by the melt molding method at 90°C–150°C in the vacuum. Oligoesters and polyesters were drawn into tubes made of silicon rubber under negative pressure. Firm rods were removed from the molds, divided into cylinders of the appropriate length by razor blade, and then adjusted to a certain weight by emery grinding. Prepared matrices were placed into vials, phosphate buffer pH 7.0 *Ph. Eur. 8.0* was added, and changed everyday. The changes in the liquid medium pH value were monitored before each replacement. In set time intervals, matrices were removed from the medium and after soft drying of the surface, matrices were dried and weighted. These swollen bodies were intensively dried at 25°C and 100 Pa for a period of at least 7 days and weighed. The characteristics of the degree

of swelling (Sw) and erosion (Er) were calculated according to the following equations:

$$\text{Sw} = \left(\frac{m_s - m_d}{m_d} \right) \times 100 \qquad (1)$$

$$\text{Er} = \left[1 - \left(\frac{m_0 - m_d}{m_0} \right) \right] \times 100 \qquad (2)$$

where m_0 is the initial mass of matrices, m_s is mass in the swollen state, and m_d is mass in the dried state.

Neutralization number (named also acid number) was determined by titration of a solution of polyesters in dimethyl ketone with a solution of 0.01 mol L⁻¹ potassium hydroxide (KOH), the amount of KOH in milligrams necessary to neutralize carboxyls in 1 g of polyester. The concentration of carboxyl groups in the fraction soluble in water related to 1 g of polyester was determined by titration of the aqueous extract of a chloroform polyester solution.

RESULTS AND DISCUSSION

Polyesters and Their Degradation

Our syntheses of polyester carriers are applicable on a laboratory scale. With a reagent charge of 5 kg, the reaction yield was over 85%. The long period of the polycondensation reaction is influenced by a slow increase in the temperature of reagents under vacuum (6.5°C/h) and running of the reaction without any catalyst. Even though the product was not purified, no cyclic dimers were detected in it. It is also possible to expect linear structures in the products of polycondensation reaction marked as branched, but with respect to values of the degree of branching, it is possible to assume their small share.

Linear PLGA has been used in medicine for more than four decades (Fig. 1a). The simplified formula of the eight-branched terpolymer of PLGA star-branched on
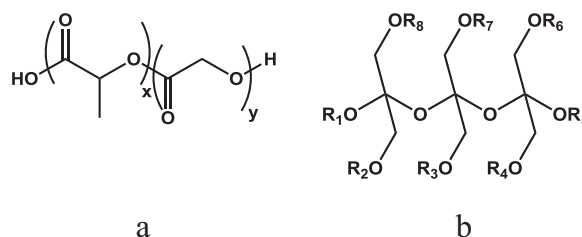
Figure 1. Formula of (a) linear poly(lactide-co-glycolic acid) (PLGA) and (b) star-like branched terpolymer of lactic acid, glycolic acid, and tripentaerythritol. R_1–R_8 are the branches of PLGA.

Table 1. Characteristics of Tested Polyesters

Polyester	M_n (g/mol)	M_w (g/mol)	$[\eta]_w$ (mL/g)	g'	T_g (K)	Label
Linear PLGA	4600	7100	11.7	1.00	311.2	PLGA
Branched terpolymer of high molar mass	8600	18,400	8.4	0.33	305.9	T- h
Branched PLGA of low molar mass	3400	13,500	6.0	0.31	294.9	T- l

M_n and M_w molar weights; η_w intrinsic viscosity, g' branching degree, T_g glass transition temperature.