CONTROLLED RING-OPENING POLYMERIZATION OF LACTONES AND LACTIDES

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SUMMARY: 1,5-dioxepan-2-one (DXO) is presented as a versatile component in biodegradable polymers for biomedical applications. Copolymerization of DXO and L-lactide yielded a semi-crystalline, yet flexible, material where the extent of crystallinity and erosion characteristics were controlled by an appropriate choice of copolymer composition. Crosslinked PDXO was polymerized as a novel biodegradable elastomer. The degradation behavior of these materials were explored *in vitro*. Microspheres from poly(DXO-co-L-LA) were prepared and shown to be promising candidates for controlled release. The polymer composition and drug solubility provided effective means of controlling the drug delivery pattern.

Introduction

Biomaterials are defined as a non-viable material, used in a medical device for the replacement of living material, to repair, restore, or replace damaged or diseased tissue or to interact with biological systems. The use of non-sustainable materials, degradable by hydrolysis into products resorbed by the body with a minimal tissue response, minimizes the number of surgical operations. Degradable synthetic polymers such as aliphatic polyesters, especially those derived from lactide (LA), glycolide (GA), and polyanhydrides have been thoroughly investigated [1,2]. Both homo- and copolymers of synthetic poly(hydroxy acid)s are important degradable materials on the market today due to adjustable degradation rate and at the same time good initial mechanical properties. This study presents 1,5-dioxepan-2-one (DXO), as a component in L-lactide copolymers or as a crosslinked biodegradable elastomer, as versatile and very promising bioresorbable materials in the field of surgery and pharmaceuticals.

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Over the years we have developed the controlled ring-opening polymerization (ROP) of lactones, lactides and cyclic anhydrides to prepare polymers where the elasticity, degradability and biocompatibility are regulated. The ROP provides a versatile way to achieve pure and well defined structures. Homopolymers, random and crosslinked copolymers with different complex molecular architecture are prepared using ROP with multifunctional initiators, crosslinkers or termination agents[3]. The work involves the synthesis of monomers, studies of the polymerization kinetics and mechanism[4], and characterization of the polymers to form materials suitable for pharmaceutical applications such as drug delivery[5], or as surgical devices like sutures.

The interest and use of biodegradable polymers in controlled drug delivery systems is constantly growing. The incorporation of therapeutic agents in a polymeric matrix serves two main purposes; the protection of the drug from physiological degradation and the sustained release of drug to the patient. Microspheres from poly(DXO-co-L-LA) were prepared by a solvent evaporation technique. The polymer composition, molecular weight and stereochemistry offer important tools to tailor-make different release profiles for specific applications.

Experimental

Polymerization. Copolymers of 1,5-dioxepan-2-one and L-lactide were prepared by bulk copolymerization with stannous octoate as catalysts at 120°C[6]. After the desired reaction time, the reaction vessel was cooled and the content was dissolved in chloroform and precipitated in cold methanol. Crosslinked poly(1,5-dioxepan-2-one) (X-PDXO) was prepared by transesterification between the poly(DXO) and the crosslinker 2,2-Bis((ε-caprolactone-4-yl)-propane) (BCP) or bis(ε-caprolactone-4-yl) (BCY)[3]. Transesterification was conducted in bulk at 140°C with stannous octoate as catalyst.

***In vitro* hydrolysis.** Hydrolysis studies were performed with melt-pressed films of the copolymers, 0.5 mm in thickness. Circular disks with a diameter of 13 mm were immersed in a phosphate buffer of pH=7.4. Degradation was carried out at 37°C without shaking or stirring motions. *In vitro* studies of the X-PDXO were conducted with

polymer films or rods and agitated gently on a mechanical shaker under otherwise equal conditions.

Preparation of microspheres. Microspheres from poly(DXO-co-L-LA) having a DXO:L-LA ratio of 30:70 and 15:85 respectively were prepared and drugs were incorporated using an oil-in-water solvent evaporation technique. A homogenous solution of polymer and drug in methylene chloride was added dropwise to a water phase containing 1% (w/v) poly(vinyl alcohol) under vigorous stirring. Dropsize was reduced by sonication. After precipitation at ambient temperature, the microspheres were recovered by centrifugation, washing in destilled water and drying under vacuum. A hydrophilic (timolol maleate) and a hydrophobic (amitryptiline) model drug were studied.

***In vitro* degradation and drug release.** Degradation and drug release studies were conducted at 37 °C by immersing pre-weighed samples in 0.1 M phosphate-buffered saline (pH 7.4). Duplicate samples were removed at selected times and the microspheres were isolated by filtration on pre-weighed AcetatePlus supported filters, dried under vacuum and analyzed. Mean values were calculated and used. The saline buffer was periodically analyzed for the release of drug by measuring the extinction at 294 nm using a 8451A Diode Array UV-VIS Spectrophotometer from Hewlett Packard.

Instrumentation. ^{1}H-NMR spectra were obtained by a Bruker Avance DMX 500 NMR spectrometer. Molecular weight was monitored by size exclusion chromotography using a Waters equipment consisting of a Waters 6000A pump with five Ultrastyralgel® columns (10^5, 10^4, 10^3, 500 and 100Å pore sizes) and a Polymer Labs evaporative light scattering detector. Chloroform was used as eluent and polystyrene standards with narrow molecular weight distributions (M_w/M_n=1.06) were used to calibrate the system. DSC thermograms were recorded on a Mettler Toledo DSC 820 connected to a RP100 cooling unit from Labplant, England. A JEOL JSM 5400 scanning electron microscope was employed to examine the surface morphology of films. Samples were mounted on metal stubs and sputter coated with gold-palladium (Denton Vacuum Desc II).

Results and discussion

Polymerization. Extensive research is performed by our research group to develop degradable polymers with properties that can be altered for different applications. The materials obtained have been shown to exhibit adjustable properties by different kinds of modifications, by copolymerization, crosslinking or surface treatment. The copolymerization between DXO and L-LA was conducted to produce materials suitable for drug delivery.

Due to the difference in reactivity ratio for the two monomers, $r_{(L\text{-lactide})}=10$ and $r_{(DXO)}=0.1$, the polymer formed was not a true random copolymer but rather a semi-block copolymer.

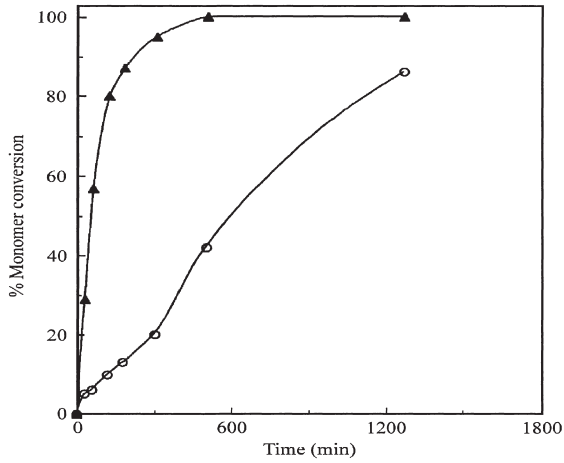


Figure 1. The monomer conversion as a function of the reaction time for the copolymerization of L-lactide (▲) and 1,5-dioxepan-2-one (○).

Figure 1 shows that the L-lactide monomer was consumed predominantly during the first part of the polymerization, the DXO monomer was incorporated in the macromolecule during the later stages of reaction. The copolymers were analyzed with NMR spectroscopy, which revealed that the polymer composition were in agreement with the feed ratios. ^{13}C-NMR studies showed that transesterification reactions had taken place and redistributed the monomer sequence. Only shorter homopolymer

segments with an average length of about 3 to 5 units could be detected. This feature made the resulting material semi-crystalline, exhibiting thermal properties that could be adjusted by changing the polymer composition. Figure 2 shows the crystallinity as a function of the amount of DXO. The crystallinity decreases with increasing amount of DXO up to a DXO content of 40% after which no crystallinity is detectable.

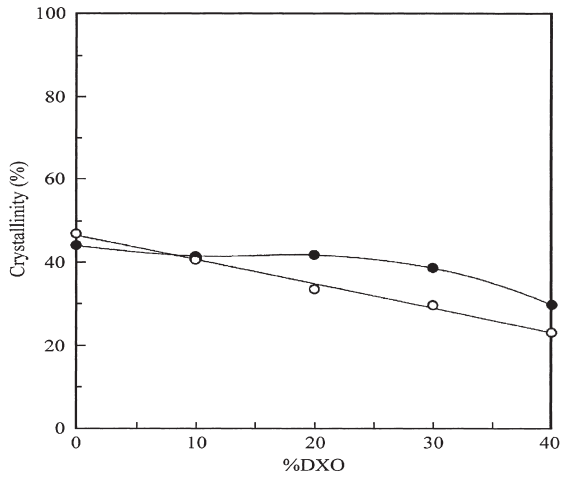


Figure 2. The crystallinity as a function of the amount of DXO in the copolymer. Open circles denote crystallinity determined by DSC, filled circles crystallinity determined by X-ray diffraction.

Microspheres, *in vitro* drug delivery A oil-in-water solvent evaporation technique was employed to prepare microspheres with encapsulated drug from poly(DXO-co-L-LA)[5]. Figure 3 shows that the obtained particles were smooth and dense without visible pores on the sphere surface. The average diameter was 65 μm. The internal structure was slightly polarized with a greater porosity in the bulk than on the external face.

Molecular weight loss was apparent immediately after incubation, whereas the mass loss was characterized by a lag period of 2 weeks followed by a gradual loss of material. This degradation pattern is typical of a bulk eroding polymer and well consistent with the classical theory of polyester hydrolysis.

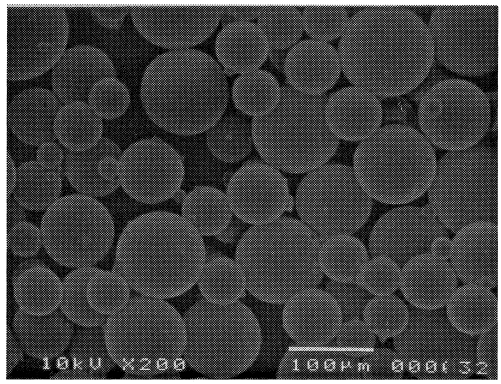


Figure 3. Scanning electron micrograph of poly(DXO-co-L-LA) microspheres.

^{1}H-NMR analysis of copolymer composition revealed the enrichment of lactide units over degradation time. The crystalline lactide regions were more resistant to water penetration and diffusion and were thus preserved in the structure although being more hydrolytically susceptible than the amorphous DXO units.

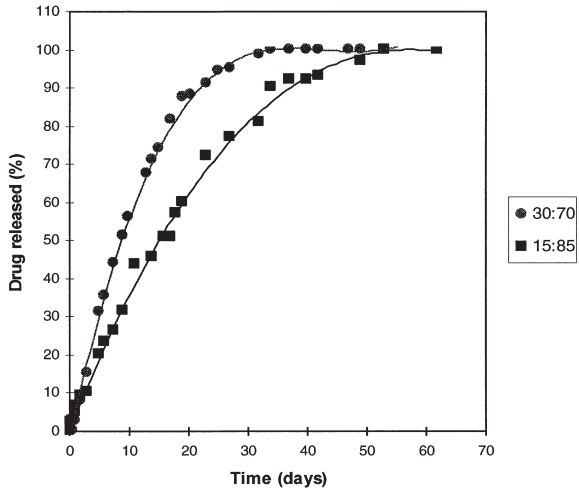
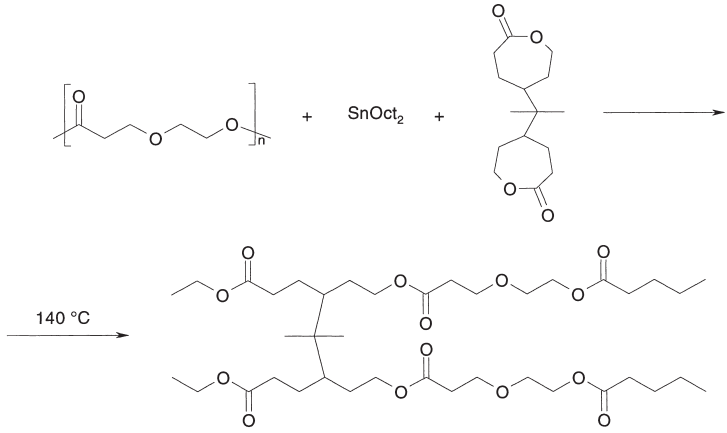


Figure 4. The release of TM from (●) poly(DXO-co-L-LA)(30:70) and (■) poly(DXO-co-L-LA)(15:85) microspheres.

Whilst a hydrophilic substance was released within 4 weeks, a hydrophobic drug required up to 3 months for depletion. In the former case, diffusion was the dominating release mechanism whereas the release of hydrophilic substance was mainly erosion controlled. Sustained release of an incorporated hydrophilic drug was obtained, as shown in Figure 4. The difference in morphology between copolymers with different DXO:L-LA ratios had a marked effect upon the rate of drug delivery, thus providing an excellent tool for controlling the release behavior.

Crosslinked poly(1,5-dioxepan-2-one). A novel polymer under evaluation as a potential material for medical applications is the crosslinked poly(1,5-dioxepan-2-one). Studies showed that crosslinked poly(DXO) was easily formed by exposing the poly(DXO) to stannous octoate and crosslinker at 140°C[3] (Scheme 1). The formed material were elastic and totally amorphous with a Tg of –35°C for the BCP crosslinked films and –21°C for the BCY crosslinked ones. Analysis of the molecular weight between the crosslinks by swelling experiments, indicated that homogeneous crosslinking had taken place.



Scheme 1. Formation of crosslinked poly(DXO) by transesterification between poly(DXO) and BCP at 140°C with stannous octoate as catalyst.

The material was subjected to various kinds of surface treatments, e.g. electron beam irradiation and surface grafting with acryl amide. The degradation of crosslinked and modified poly(DXO) is shown in Figure 5. During the initial stages of hydrolysis the untreated samples showed a bigger mass loss than the irradiated and surface grafted.

Both the irradiated and the surface grafted samples exhibited a plateau in mass loss up to 16 weeks after which the rate of degradation was comparable for all samples. A total weight loss was achieved after about 300 to 350 days *in vitro*.

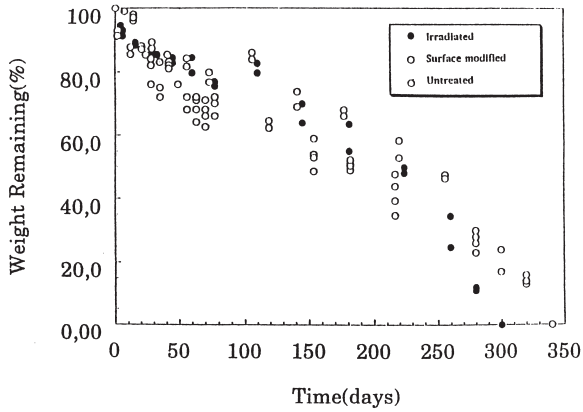


Figure 5. Weight loss in crosslinked poly(DXO) with a crosslinking density of 16% BCP, degradation in saline buffer 37°C.

Conclusions

It is possible to prepare a wide range of materials, varying from physically crosslinked copolymers of L-lactide and DXO, to strong and tough crosslinked poly(DXO) networks by ring-opening polymerization. Copolymerization of L-lactide and 1,5-dioxepan-2-one were studied and the material formed was used as a novel matrix for sustained drug delivery. Smooth and dense microspheres were successfully prepared by an oil-in-water technique. Sustained release of incorporated drugs was obtained. The polymer composition and the drug solubility were proven effective instruments of modifying the rate of hydrolytically degradation, erosion, and drug release.

References

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