

SYNTHESIS AND CHARACTERIZATION OF NOVEL BIODEGRADABLE COPOLYMER COMPOSED OF RICINOLEIC ACID AND L-LACTIC ACID

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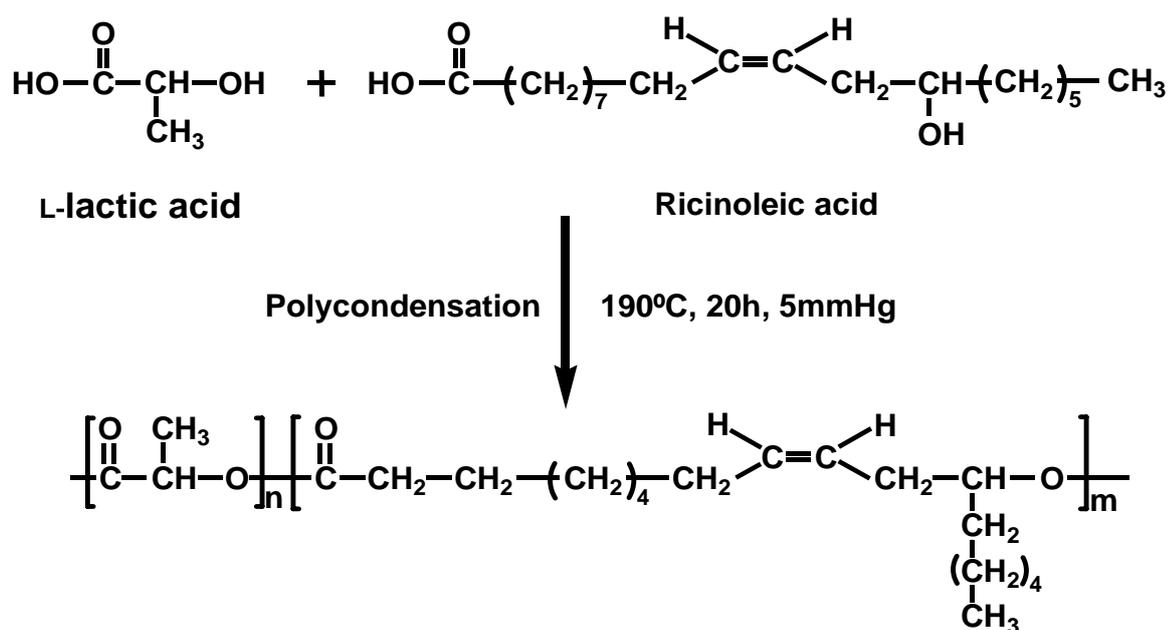
Introduction

Biodegradable polymers are used in a wide variety of areas as suture materials, bone fixation materials, drug delivery systems and environmental materials(1-4). Among these polymers, poly(α -hydroxy acid)s, poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers are the most common biodegradable polymers. PLA is particularly well adapted for orthopedic applications, because the mechanical properties, biodegradability and biocompatibility of this polymer are fairly good. The good mechanical properties are attributed to high crystallinity which results in a simple chemical structure composed of lactic acid and glycolic acid, and lacking reactive side chains. Novel applications of biodegradable polymers are a growing area of interest. For example, the formation of biodegradable scaffolds for tissue engineering is one of the most desirable applications, and PLA and PGA have been successfully utilized for this purpose. Further application of these novel biodegradable polymers requires development of special characteristics such as chemical reactivity, photoreactivity and radical reactivity.

A lot of studies have been reported in answer to these demands. For example, we have reported the synthesis and properties of the polyester of D,L-lactic acid and 4-hydroxycinnamic acid for the purpose of introducing reactive groups to the main PLA chain(5). The copolymers of 4HCA and DLLA had a double bond, suggesting potential applications as a novel biodegradable photoreactive and radicalreactive substance. Ohya et al. synthesized polydepsipeptides which are copolymers of α -amino acids and α -hydroxy acids(6). This polymer is known to be biodegradable and has a reactive side chain. Mikos et al. has prepared poly(propylene fumarate) (PPF), which is an unsaturated functional biodegradable polymer(7). Hubbell et al. has prepared poly(ethylene glycol)-PLA hydrogels for the prevention of postoperative adhesions(8).

In this study, we attempted to synthesize the polyester of L-lactic acid (LA) and ricinoleic acid(RA) for the purpose of introducing reactive groups to the main PLA chain. RA, being the principal constituent of castor oil, is a kind of fatty acid and has an unsaturated bound, a hydroxyl group, and long alkyl side chain. RA is good candidates for preparing biodegradable polymers. The copolymers of RA and LA have a double bond, suggesting potential applications as a novel biodegradable photoreactive and radicalreactive substance. RA-LA is not an alternating copolymer. As such, the bulk properties of RA-LA copolymers could potentially be alternated by changing RA content and molecular weight. In this preliminary study, the synthesis and characterization of this copolymer are described.

Experimental Part



Scheme 1. Synthesis of Poly(L-lactic acid-*r*-ricinoleic acid).

L-lactic acid (90% aqueous solutions) and ricinoleic acid (technically 80% pure) were purchased from Wako Pure Chemical CO. (Tokyo, Japan) and Tokyo Chemical Industry CO. (Tokyo, Japan), respectively, and used without further purification. Benzoyl peroxide (BPO) (70% Remainder Water) was purchased from Aldrich CO. (Milwaukee, WI, USA) and used without purification. All other reagents were purchased from Wako Pure Chemical CO. and used as received. Synthesis of Poly(L-lactic acid-*r*-ricinoleic acid). Random copolymers composed of ricinoleic acid and L-lactic acid were synthesized by direct polycondensation (Scheme 1). The reaction yield was calculated from the weight of the dried products and the total mass of LA and RA in feed. A series of copolymers with different composition were prepared by changing ratio of RA to LA in feed. In vitro hydrolytic degradation testing. The copolymers were dissolved in chloroform (4 wt%), and the resulting copolymer solution was deposited onto sample bottles. PLA ($M_n = 18500$) was used as a reference polymer. After dried in vacuum, the cast films formed on the bottom of the bottle were incubated in 1/15M $\text{KH}_2\text{PO}_4/\text{NaHPO}_4$ buffer (pH = 7.0) at 37°C for 28 days. After 1, 2, 4, 8, 14, and 28 days, the films were washed with distilled water and dried in vacuum at room temperature over night. The molecular weights of the polymers were measured by GPC. The degradation rates were estimated by the molecular weight reduction (%) calculated. Radical reactivity testing. Random Copolymer (RA content = 55 mol%) and BPO were dissolved in chloroform at a concentration of 7.1×10^{-2} wt/vol %. After removal of oxygen, the solution was heated at 45°C for 5h and 10h. The radical reactivity of random copolymer was evaluated by the change of UV adsorption.

Results and Discussion

Synthesis of Poly(L-lactic acid-*r*-ricinoleic acid): The characterization of the products obtained by the direct polycondensation was done by $^1\text{H-NMR}$, FT-IR, and GPC analysis. The results of FT-IR and $^1\text{H-NMR}$ indicate that RA was introduced into the copolymer, and the unsaturated group of the copolymer was preserved through the polycondensation. The GPC elution profiles were unimodal, and

the elution profile detected by RI detector was compatible with the one detected by UV detector. This means that the copolymer obtained was not a mixture of the respective homopolymers. From these results, it was confirmed that the polymer prepared here was the poly(L-lactic acid-r-ricinoleic acid) having an unsaturated group in main chain. The obtained copolymers with high RA content were viscous fluid. The copolymer with lower RA content formed film. The example is shown in Figure 1. That film was very soft even 90% of content was LA.



Figure 1. Casted film of Poly(LA-r-RA) (RA content = 10%)

In vitro hydrolytic degradation testing and radical reactivity testing:

The degradation rate of the copolymer having lower RA content was larger than PLA (Figure 2), while the copolymer having higher RA content degraded slower than PLA (Data not shown). These results suggest that the degradation rate of the copolymer can be controlled by changing not only the crystallinity but also the hydrophobicity due to RA moiety. As compared with UV adsorption before and after the radical reactivity testing, the adsorption peak arising from double bond at ca. 200nm decreased with an increase in reaction time. This result suggests that the random copolymer has the radical reactivity.

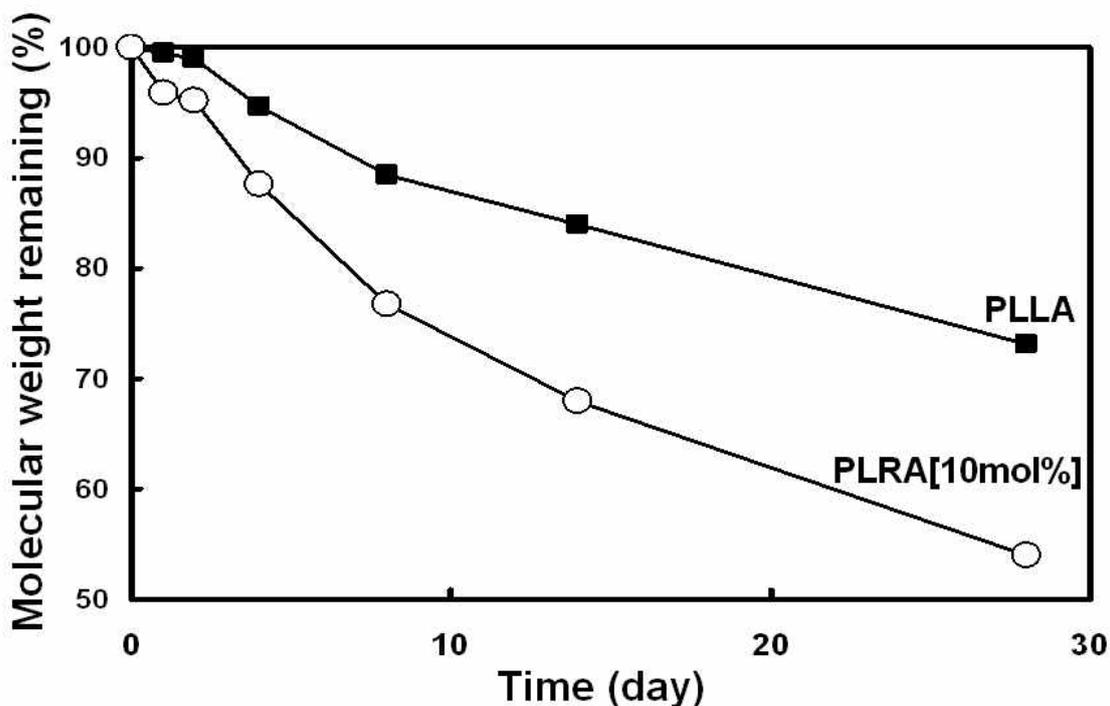


Figure 2. Degradation profile of PLA and Poly(LA-r-RA). (RA content =10 %)

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