FORMULATION-ASSISTED BIODEGRADABLE POLYMER MATRICES

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A method is proposed to control degradation rates of biodegradable polyester matrices for DDS and medical implantable materials. The degradation rates of poly(lactic acid), poly β-hydroxybutyrate and β-hydroxybutyrate-valerate copolymer matrices, which have poor degradability, could be accelerated by incorporating basic compounds, such as cinnarizine and clonidine, as a hydrolysis accelerator. The rates could be controlled by changing the loading amount and the basicity of the basic compounds.

KEYWORDS biodegradable polymer; poly(lactic acid); poly β-hydroxybutyrate; β-hydroxybutyrate-valerate copolymer; degradation rate; degradation-control; drug delivery system

Biodegradable polyesters, such as poly(glycolic acid), poly(lactic acid) (PLA), and poly- β-hydroxybutyrate (PHB), have been increasingly used in the matrices of drug delivery systems (DDS) and implantable medical materials. Although these applications were intended to take advantage of the biodegradability of these polymers, little has been reported on the degradation rates of the polymer matrices.[1-3] In designing a DDS, a certain polymer with suitable properties is selected so that the polymer matrix gives a required release rate of therapeutic agents. The degradation rates of the matrices are determined inherently, so some matrices remain for a long time after the drug release has been completed. The polymers used for medical implantation are chosen to suit the initial mechanical properties, such as tensile strength and toughness. Thus the degradation rates of the polymer matrices can not be intentionally designed. For both DDS and implantable materials, it is desirable to control the degradation rates.

We studied a method to control the degradation rates of biodegradable polyesters, in which basic chemicals are incorporated in polymer matrices as hydrolysis accelerators. PHB, β-hydroxybutyrate-valerate copolymer (PHB-PHV) and relatively high-molecular-weight PLA, which have poor degradability, were selected in order to clarify the effect of the basic compounds. PHB and PHB-PHV were purchased from ICI Biopolymers and the weight average molecular weights (Mw) were determined to be 220,000. PLA (Mw:780,000) was polymerized from l-lactic acid by the ring opening polymerization method.[4] Cinnarizine, thioridazine, indenorol and clonidine were used as model hydrolysis accelerators in this study, though basic compounds without pharmacological activity are preferable. The polymer (100 mg) and 42.2 mg of basic compound (25 mg for indenorol) were dissolved in 3 ml of methylene chloride, which was then removed under atmospheric pressure for 18 h at 4°C to get a film. The polymer hydrolysis in the films stored in the air and in 0.1 M phosphate buffer (pH 7.4) was followed by measuring the molecular weight of the polymer. The data analysis software for gel permeation chromatograph-low angle laser light scattering system which we developed previously[5] was used to determine the molecular weight distribution.

The molecular weights of the PHB and PHB-PHV films without basic compounds did not

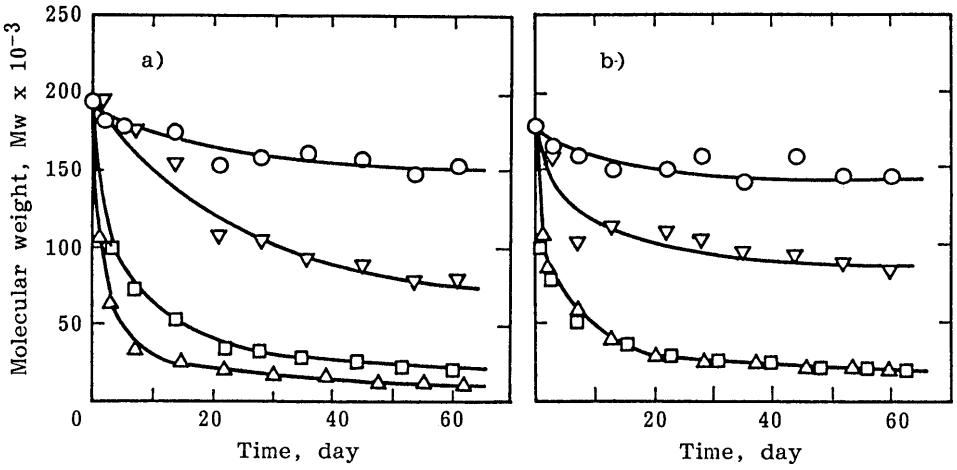

Fig. 1. Effect of Basic Compounds on Hydrolysis of PHB-PHV (a) and PHB (b) in Films Stored in the Air

○, cinnarizine, 30% ; ▽, thioridazine, 30% ;
□, indenorol, 20%; △, clonidine, 30%.
Temp.: 37°C

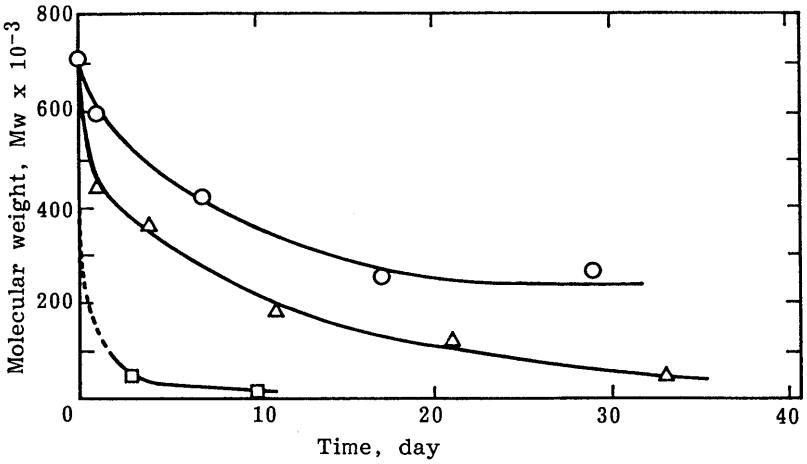

Fig. 2. Hydrolysis of PLA in Thioridazine-Formulated Films Stored in Buffer Solution
The loading amount of thioridazine : ○,0; △,5; □,30%
Temp.: 37°C

decrease either in the air or in the buffer solution, even at 70°C. Incorporating basic compounds accelerated hydrolysis of the polymer as shown in Fig. 1. The hydrolysis rates in the air seem to be related to the basicity of the compounds. The hydrolysis rates increased in order with apparent pKa of the conjugate acid of each basic compound (cinnarizine < thioridazine < clonidine < indenolol), which was determined by a titration method. The hydrolysis in buffer solutions, on the other hand, seemed to depend not only on the basicity but also on the solubility of the compounds in the solution. Figure 2 shows the hydrolysis profile for PLA films in buffer solution. The hydrolysis rate depended on the loading amount of the compounds and it was higher than the PHB and PHB-PHV rates. The effect of temperature on the hydrolysis rate of these polymers in films was studied in a range from -15 to 70°C. The rate depended largely on temperature, and there was no hydrolysis at -15°C. The hydrolysis in vivo was studied by implanting the

films subcutaneously in rats. The hydrolysis was accelerated by the basic compounds in vivo as it was in vitro, but the effect of the accelerators was smaller than in vitro. Apparently the accelerators were removed from the polymer matrices into the biological fluid more easily than into buffer solution.

These results show that the hydrolysis rates of PHB and PHB-PHV in films, which are very low under physiological conditions, can be accelerated by incorporating basic compounds. This is of great interest especially for PHB which has not been known to degrade under such mild conditions (pH 7.4, 37°C). Williams et al. reported on the degradation of PHB after polymer chain scission by gamma-ray sterilization,[6] but the method we propose here is much easier and more effective to accelerate degradation of poorly reactive polymers. Polymer matrices which have the desired degradability can be made by incorporating a proper amount of a certain basic compound with suitable pK_b into polymer matrices. The matrices presented in this paper may be named "formulation-assisted biodegradable matrices" in the sense that the degradation rate of the matrices is controlled by incorporating some ingredient in the formulation. These degradation-controlled matrices seem to be useful for DDS and biomedical materials.

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