Biodegradable Polyester Blends for Biomedical Application

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SYNOPSIS

A new family of bioabsorbable materials suitable for biomedical applications was designed and prepared by means of blending of some available polyesters to develop new biodegradable materials tailored for different requirements. Multiphase polymer blends containing poly(d, l-lactide) (PLA), poly(ε-caprolactone) (PCL), poly(d, l-lactide-co-poly(ethylene glycol) (PELA), poly(ε-caprolactone)-co-poly(ethylene glycol) (PECL), and poly(β-hydroxybutyrate) (PHB), PLA/PCL, PELA/PECL, PHB/PLA, PHB/PELA, PHB/PCL, and PHB/PECL blends were respectively investigated. It was found that PLA/PCL, PHB, and PHB/PLA and PHB/PCL blends were seemingly immiscible, with their morphology and hydrolytic behavior were determined by the composition of the blends. On the other hand, the miscibility of PELA/PECL, PHB/PELA, and PHB/PECL blends was improved by using PELA and/or PECL block copolymers that contained poly(ethylene glycol) (PEG) as compatibilizer. The blends showed to a certain extent miscibility, fine phase morphology, and fast hydrolysis. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

Biodegradable polymers are being used in an increasingly large number of biomedical applications, such as bioabsorbable surgical sutures, drug delivery systems, and temporary internal fixation of many different kinds of tissue damage.[1] Generally, as such a material, several demands must be satisfied. These requirements are mostly biological ones that all implanted biodegradable materials must fulfill, especially mechanical properties and biodegradation kinetics. However, only a few kinds of polymers are suited for all these requirements. Naturally the search for new improved biodegradable polymers has piqued a growing interest.

Considering the structure–morphology–property relationship, the main factors determining the properties of biodegradable polymers include chemical and phase structure of the material.[2] To achieve the desired applications, many efforts have been made. One of the effective methods is molecular architecture by which tailored mechanical as well as

biodegradation properties can be obtained, e.g., copolymers and polymer blends are all derived from this method.

Today aliphatic polyesters derived from glycolic acid, d,l- and l-lactic acid, β-hydroxybutyrate, and ε-caprolactone, are the most important biodegradable polymers. These have found frequent applications as biodegradable matrices for prosthetics and controlled drug delivery.[3-7] The optimization of the key properties of these biomaterials, i.e., the permeability, the rate of biodegradation, and the tensile properties, has generally been achieved by copolymerization, such as the copolymers of polyesters[8-13] and poly(ester-ether)s.[14-17] Blending of the homo- and copolymers represents an alternative but less exploited means of tailoring the material properties.[18-23]

Our objective was to design and prepare a series of polyesters or poly(ester-ether)s blends, where the multiphase nature of the system affords the required versatility, in terms of both mechanical as well as biodegradation properties. This approach allowed us to vary, quite independently, various parameters of the system. Consequently, the properties of different materials could be adjusted and balanced by the modification of their components and blend ratio.

Focusing on the degradation property, this article will discuss the effect of blend composition on the miscibility, phase structure, and hydrolytic behavior.

EXPERIMENTAL

Materials

Poly(d,l-lactide) (PLA) and poly (d,l-lactide)-co-poly(ethylene glycol) (PELA) were synthesized by the ring-opening polymerization of d,l-lactide or copolymerization of d,l-lactide and poly(ethylene glycol) (PEG, $\bar{M}_n$ 4,000) with Al(i-Bu)$_3$-H$_2$O-H$_3$PO$_4$ complex catalyst. The resulting copolymers were PELA10 and PELA15, containing 10 and 15% (wt/wt) PEG, respectively. Poly(ε-caprolactone) (PCL) and poly(ε-caprolactone)-co-poly(ethylene glycol) (PECL) with 10% (wt/wt) PEG ($\bar{M}_n$ 4,000) were prepared by the same procedure. Poly(β-hydroxybutyrate) (PHB) sample (kindly supplied by Chengdu Institute of Biology, Academia Sinica) was synthesized by bacterial fermentation using methanol as the carbon source.

Preparation of Blends

Blends were prepared according to the method of[23,24] slowly casting films from chloroform solution (3%

wt/v). Solvent evaporation was conducted at room temperature for 24 h; to ensure complete removal of the solvent, the films were finally kept under vacuum for 24 h. Blends with weight ratios of 20/80, 40/60, 60/40, 80/20, or 50/50 were obtained. The blends prepared by using other methods were also conducted. The comparison of casting blend with precipitated blend and melting blend has been discussed.[25]

Differential Scanning Calorimetry (DSC)

A Perkin–Elmer (PE) DSC-7 apparatus, equipped with a PE 3700 data station was used to study the influence of blend composition on crystallization behavior of crystal components. The miscibility of the blends was investigated according to glass-transition temperature (T_g)-composition dependence for some blends if possible.

Polarizing Optical Microscope

The shape of PHB spherulites in the blends was observed by a polarizing optical microscope. The sample was first heated to 200°C and kept at this temperature for 1 min. The temperature was then lowered to the desired crystallization temperature
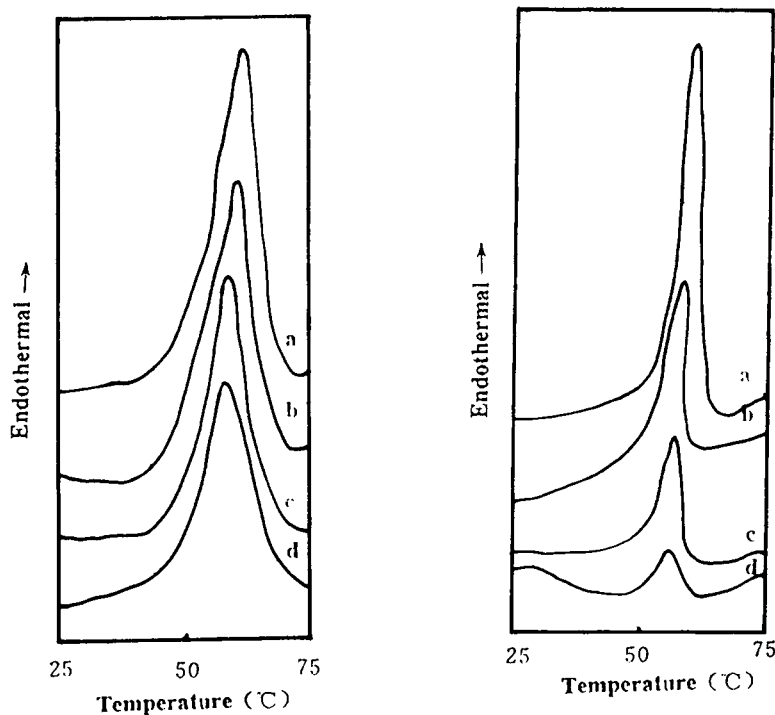

Figure 1   DSC peaks of PCL in (left) PLA/PCL and (right) PHB/PCL blends with various blend ratios: (a) 20/80; (b) 40/60; (c) 60/40; (d) 80/20.

(T_c) and PHB allowed to crystallize isothermally. An ORTHOLUX II POL-PK polarizing optical microscope equipped with a hot stage was used.

Scanning Electron Microscope (SEM)

SEM evaluation was carried out to examine the phase morphology of the blends. The blend films were first extracted with toluene to remove PLA, PELA, PCL, or PECL components selectively. After drying, SEM observation was conducted using AM-RAY-1000B equipment. Before observation, the sample was coated with a thin layer of gold by vacuum deposition.

Hydrolytic Degradation

The hydrolytic degradation of the blends was performed at 37°C, and pH 7.4 buffer solution. Duplicate samples were withdrawn at different time intervals and water absorption was determined gravimetrically, prior to the weighing to remove the excess surface water. The water content is expressed as percentage water of the dry sample. Molecular weights were determined by gel permeation chromatograph (GPC) in tetrahydrofuran (THF). Surface morphology of hydrolysis degraded films was attained by means of SEM.
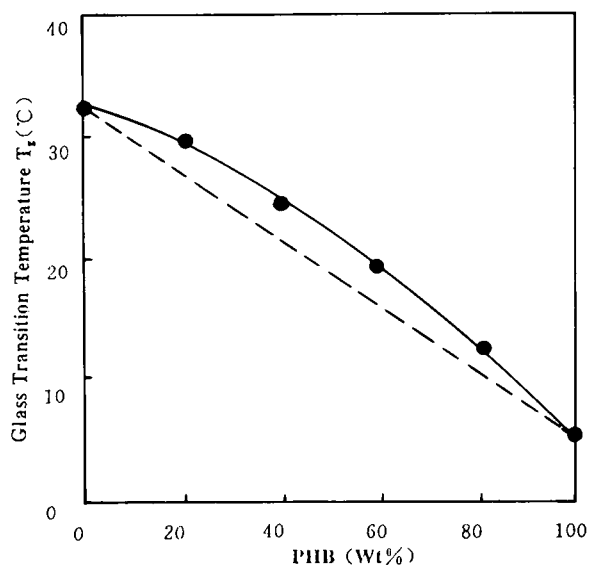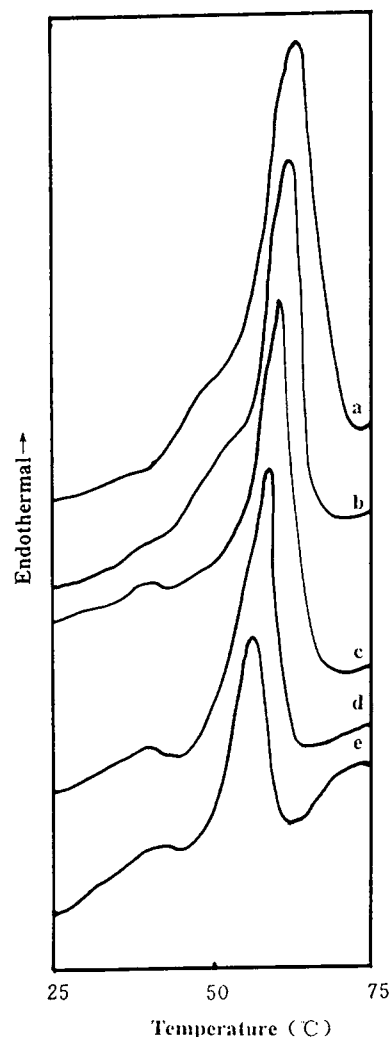

Figure 3 DSC curves of pure PECL and PELA/PECL blends: (a) PECL; (b) 20/80; (c) 40/60; (d) 60/40; (e) 80/20.

RESULTS AND DISCUSSION

Blend Miscibility

As the DSC results showed, PLA/PCL and PHB/PCL blends display only a slight shift of melting endotherm of PCL in the blends (Fig. 1); and the endothermal peaks of PHB in PHB/PCL blends present no shift with variation in the blend composition. The results indicate that the blends are immiscible. A similar conclusion was drawn for PHB/PCL and poly(β-hydroxybutyrate-co-β-hydroxyvalerate) P(HB-HV)/PCL blends.[22,23] For PHB/PLA blends, the peak melting temperature (T_m) of PHB remains at 175°C; moreover, two glass transitions were observed over the entire composi-
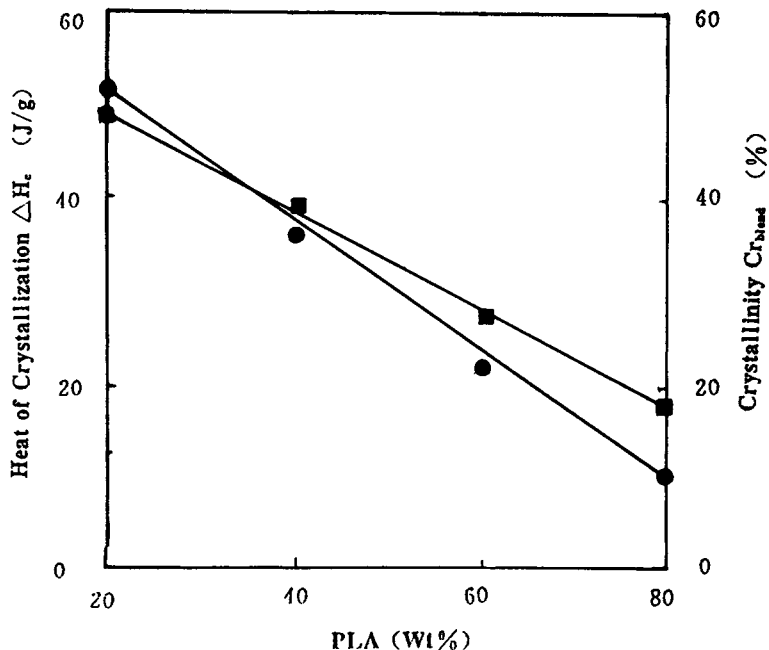

Figure 2 (—) Experimental and (from Fox equation - - -) theoretical glass-transition temperature (T_g) for PHB/PELA15 blends.

Figure 4 (●) Heat of crystallization ΔH_c and (■) crystallinity Cr_{blend} of PLA/PCL blends vs. blend composition.

tion range studied. The position of transitions was found to be independent of composition, at 10 and 53°C, respectively, close to the values observed for pure components. Therefore, PHB/PLA blends are also immiscible.

It is interesting to note that the miscibility of PELA/PECL, PHB/PELA, and PHB/PECL blends, however, are improved by the addition of poly(ester-ether) block copolymers that contain PEG as compatibilizer. Consequently, the blends
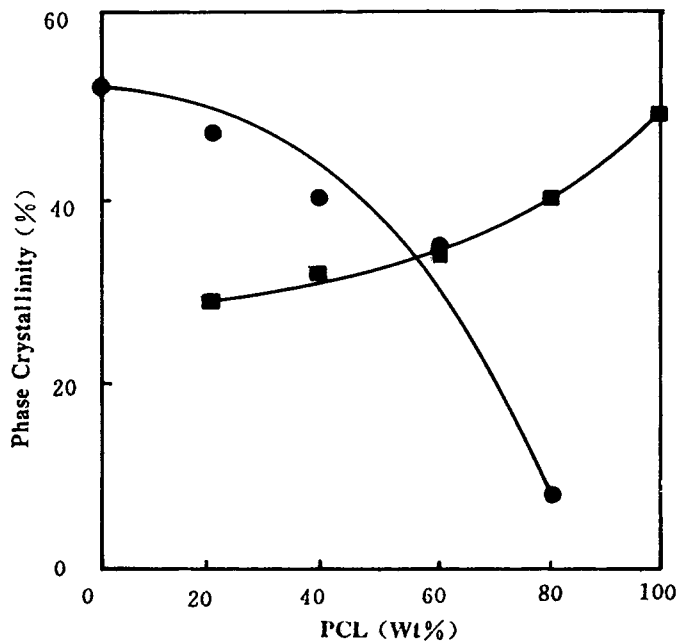

Figure 5 Phase crystallinity of (●) PHB Cr_{PHB} and (■) PCL Cr_{PCL} as a function of blend composition.

show miscibility to a certain extent. Unlike PHB/ PLA blends, PHB/PELA blends are characterized by only one T_g, composition-dependent and intermediate between that of plain PHB and PELA. As Figure 2 shows, the experimental values of T_g approximately agree with those calculated theoretically from the Fox equation: $1/T_g = W_1/T_{g1} + W_2/T_{g2}$, where T_g is the glass-transition temperature of the blend, T_{g1} and T_{g2} are those of two blend components, respectively, and W_1 and W_2 are the corresponding weight fractions. Similarly, PELA/PECL and PHB/PECL blends were also found to have a composition-dependent T_g in spite of their classification, the reason for which is not quite clear so far. Further, the T_m of PECL in its blends is slightly depressed, as shown in Figure 3.

The PEG chains in PELA and PECL block copolymers act as a "bridge" between the PELA and PECL phase in PELA/PECL blends, which causes a homogeneous intermediate phase contributing to the blend miscibility. Because the specific interactions involve the carbonyl groups of PHB and the hydrogen of the CH_2 group in PEG, it is not unexpected that PHB/PELA and PHB/PECL blends show better miscibility. Unlike the compatibilization of the addition of the third component to the blends, the compatibilizer PEG is connected with PLA or PCL by chemical bond. Hence, the action of PEG on the block copolymers in the blends can be called "internal compatibilization."

Crystallization Behavior

The crystallinity of the polymers has significant effect on the rate of polymer hydrolysis that will decrease as the crystallinity increases.[2] Taking advantage of this factor, we can control the rate of degradation. The crystallization of PCL, PECL, and PHB is affected by the addition of the second components, amorphous PLA, PELA or crystal PCL, PECL, and PHB. To all systems investigated, the heat of crystallization of the crystal components in the blends (ΔH_c) in the nonisothermal DSC run decreases with the increase of the content of the second components. Therefore, this results in a low crystallinity (Cr_{blend}) characterized by the ratio of the apparent enthalpy of fusion per gram blend, ΔH_f, to the apparent enthalpy of fusion per gram plain component, $\Delta H_{f100\%}$, or thermodynamic enthalpy, ΔH_f^0, as shown in Figure 4.

It is worth noting that the phase crystallinity of PECL in PELA/PECL blends, Cr_{PECL} calculated by Cr_{blend}/W_{PECL} where W_{PECL} is the weight fraction of PECL in the blends, also decreases with the increase

of the content of PELA, especially when the content is above 40%. Similarly, the $\Delta H_c/W_{PECL}$ means the heat of crystallization per gram PECL in the blends, that also shows a drastic decrease due to better blend miscibility.

In PHB/PLA and PHB/PELA blends, the PHB crystallization exothermic peaks are affected by the presence of the second components to cause a low T_c. The results indicate that the crystallization of PHB in the blends is restricted by both PLA and PELA; the rate of nonisothermal crystallization of PHB in the blends is slower than that of pure PHB. Nevertheless, the effect of PELA is more evident: it causes a sharp depression of T_c.

In PHB/PLA and PHB/PECL blends in which both components can crystallize are more interesting. Figure 5 shows the phase crystallinity of PCL; Cr_{PCL} decreases with the increase of PHB content. Such a result is probably accounted for by assuming that a fraction of PCL is not allowed to crystallize, being trapped in the interlamellar regions of PHB spherulites. Likewise, the phase crystallinity of PHB, Cr_{PHB}, also shows a notable decrease.
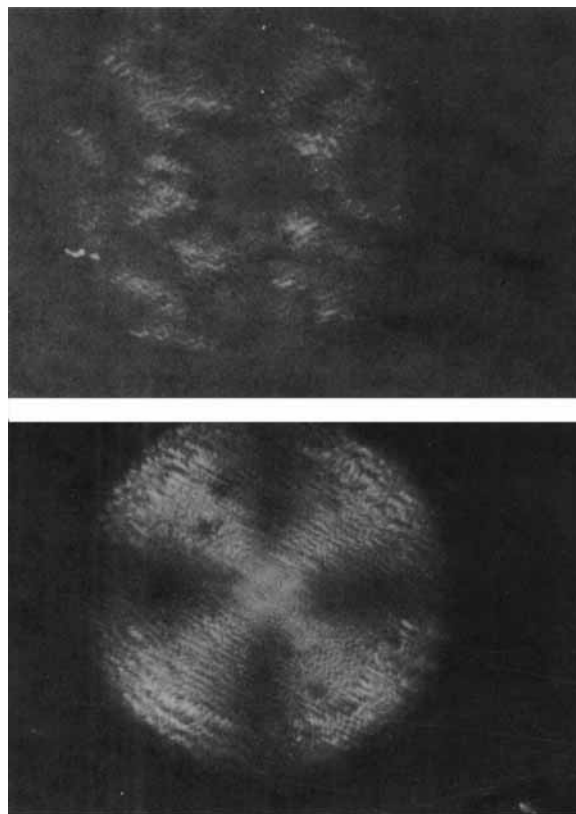

Figure 6 Polarizing optical micrographs of PHB spherulites in PHB/PCL (upper) (40/60) and (lower) (60/ 40) blends (crystallized isothermally at 90°C).
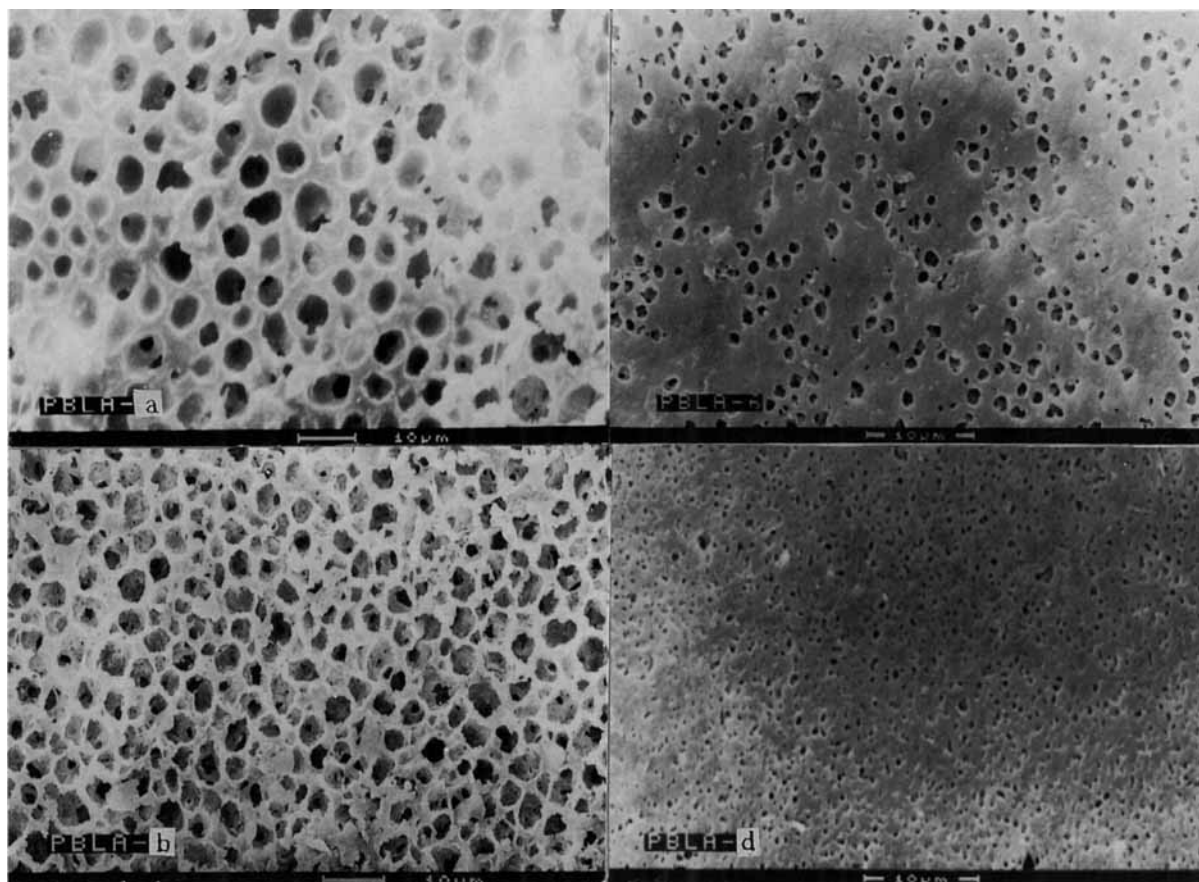
Figure 7   Scanning electron micrographs of PHB/PLA blend films extracted with toluene:
(a) 20/80; (b) 40/60; (c) 60/40; (d) 80/20.

The polarizing optical micrographs of PHB/PCL blends in Figure 6 display PHB spherulites growing under isothermal conditions. It is found that PHB is able to crystallize according to a spherulitic morphology when its content is above 20%. Under this content, the crystallization of PHB is hardly observed because the major component, PCL, fills PHB lamellae.

Morphological Structure

SEM studies were performed on toluene extracted samples to discern the macrostructure of PHB in the blends. Being a good solvent to PLA, PELA, PCL, and PECL, but relatively poor to PHB, toluene can remove PLA, PELA, PCL, or PECL components from their blends selectively. Thus, the micrographs of the blends may clearly represent the phase character of PHB blends.

First, the blend composition affects the morphological structure of the blends. For example, all PHB/PLA blends show two-phase structure, how-

ever, there are some differences in their morphologies. As shown in Figure 7, in the blend films with various blend ratios extracted with toluene at a constant time, the distributive size of PLA component enlarges with the increase of its content in the blends. For PHB/PLA (20/80) blend film, if treatment time in toluene solvent is too long, the sample would fail to remain a continuous film.

Second, the second component is most important to the phase structure of PHB blends, in other words, the miscibility of the blend systems determines their phase structure. So, the morphological structure differs from the components in the blend systems containing different second components, but at the same blend ratio. A fine phase structure is obtained when PELA or PECL is used as the second component instead of PLA or PCL in PHB blends.

Finally, the composition of the second component plays an important role in the phase structure of the blends. For instance, in the same blend system at a constant blend ratio, the morphological structure of PHB/PELA (40/60) blends presents differ-
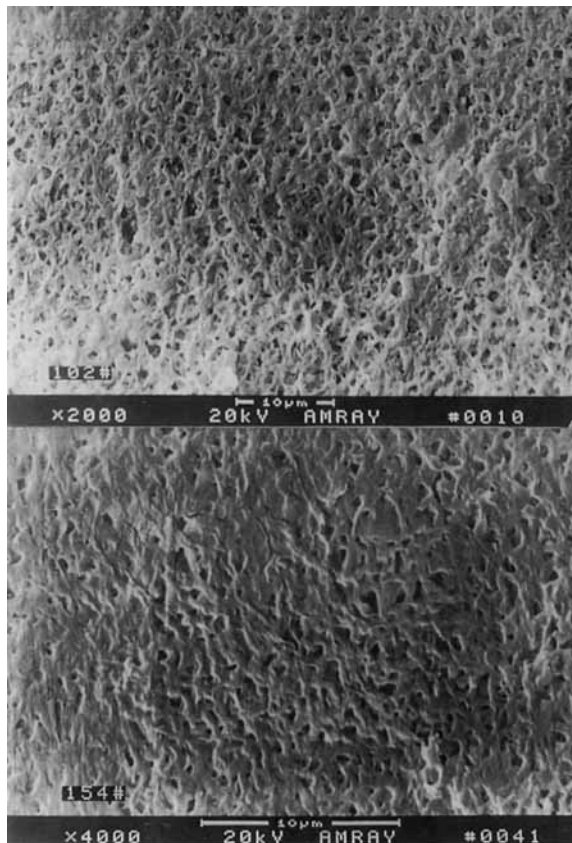
Figure 8 Morphology of (upper) PHB/PELA10 (40/60) and (lower) PHB/PELA15 (40/60) blend films extracted with toluene.

ent features because of their different content of PEG in PELA block copolymers. From the micrographs of Figure 8, we can find out that the PHB/PELA15 blend shows finer dispersion of the two phase than PHB/PELA10 blend.

Hydrolytic Degradation

Water absorption of pure PLA, PCL and PLA/PCL, or PELA/PECL blend films during hydrolytic degradation is shown in Figure 9. As expected, crystal PCL is more hydrophobic than amorphous PLA, and the water content of PLA/PCL (25/75 and 50/50) blends is between that of plain PCL and PLA during the entire hydrolysis process studied. Curiously, the PLA/PCL (75/25) blend displays higher water content than the PLA component, presumably due to higher amorphous phase content and its two-phase nature.

On the other hand, the change of the water content during hydrolysis reflects the surface features of the blend films. The more hydrophilic the blend surface is, the higher the water contained, which causes fast hydrolysis; further, the degraded surface brings about an increase of the water content again. The results described in Figure 10 agree with the tendency presented in Figure 9 and the data of GPC in Table I. It shows a notable decrease of molecular weight $(\bar{M}_n)$ and a wide molecular weight distribution (D) after 65-days degradation.
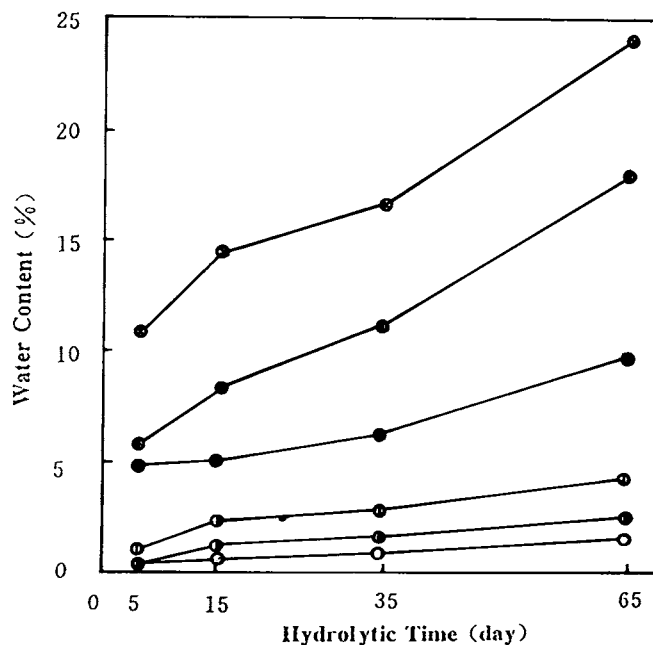

Figure 9 Water absorption of pure PLA, PCL and PLA/PCL, and PELA/PECL blend films during hydrolytic degradation: (⊗) PELA/PECL (50/50); (◐) PLA/PCL (75/25); (●) PLA; (◑) PLA/PCL (50/50); (◖) PLA/PCL (25/75); (○) PCL.
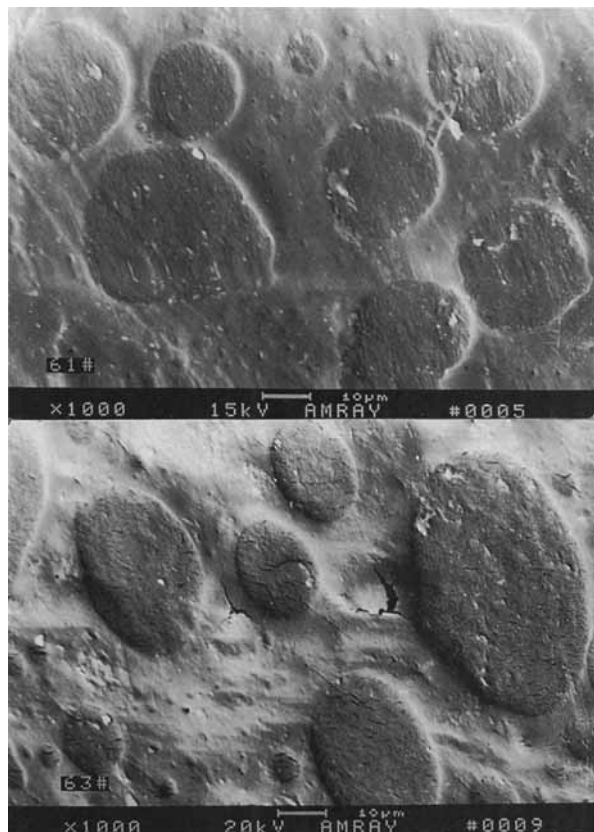
Figure 10 Scanning electron micrographs of PLA/PCL (75/25) blend film after (upper) 5 days and (lower) 35 days hydrolysis.

Also, the increase of D during the hydrolytic degradation *in vitro* has been found in both PLA homopolymer and its copolymers with PEG. After a few month hydrolysis, a broad distribution ($D > 2.0$) was often observed, because in the early degradation of the sample films, the main pattern, diffusion-controlled hydrolysis occurred. The surface contained more water than the bulk, hence degraded rapidly. The difference in water content and hydrolytic rate between surface and bulk resulted in the increase of molecular weight distribution. Yasin et al. presented the same result in other biodegradable polymers.[21]

The water content of PLA/PCL blends increases with the increase of PLA content in the blends at all time intervals during degradation; hence, the rate of hydrolysis increases. After 65-days degradation, the $\bar{M}_n$ of PLA/PCL (25/75, 50/50, 75/25) blends decreases from 6.5×10^4 at the beginning to 5.9×10^4, 4.9×10^4, 1.6×10^4, respectively; the D increases from 1.92 to 2.1, 2.4, and 3.7 in turn.

The data presented in Figure 9 clearly show that the PELA/PECL blend exhibits markedly enhanced

hydrophilicity, partly because of the hydrophilic nature of the PEG chain in the block copolymers. The change of $\bar{M}_n$ and D of PELA/PECL blend is similar to that of the PLA/PCL blend. It is worth noting that because of poor efficiency of the GPC column, the peaks of PLA, PCL or PELA, and PECL are overlapped in GPC analysis, so the results only represent an approximate quantity.

Just as the morphological structure, the hydrolytic behavior of PHB blends is reasonably affected by the second components at the same blend ratio. The water content of the PHB blends decreases in turn for PELA, PLA, PECL, and PCL. Two main factors, the phase structure and hydrophilicity of the second component, are most important to water content. The amorphous components, such as PLA and PELA, make the blends show high water content; the hydrophilic components, such as PELA and PECL, raise the water content. Figure 11 shows the comparison of PHB/PLA and PHB/PELA blends during hydrolysis: the more the water contains, the faster the hydrolysis.

CONCLUSIONS

Biodegradable polyester blends are a new approach to achieve the desired properties of biomaterials. A series of polyester blends that contain various components and with different blend ratios show a wide range of properties. The blend composition has shown a significant effect on the phase structure to produce quite different degradation behavior. Moreover, the blend components with different chemical structure determine the blend miscibility, crystallization behavior, and morphological structure; thus adjustable properties can be acquired.

Of special interest is the effect of the PEG chain in poly(ester-ether) block copolymers on the blend properties. It probably shows two mainly important functions: first, it acts as an internal compatibilizer, improving the blend miscibility; second, due to its

Table I **Effect of Degradation on Molecular Weight and Molecular Weight Distribution (D) of PLA/PCL (75/25) Blend**

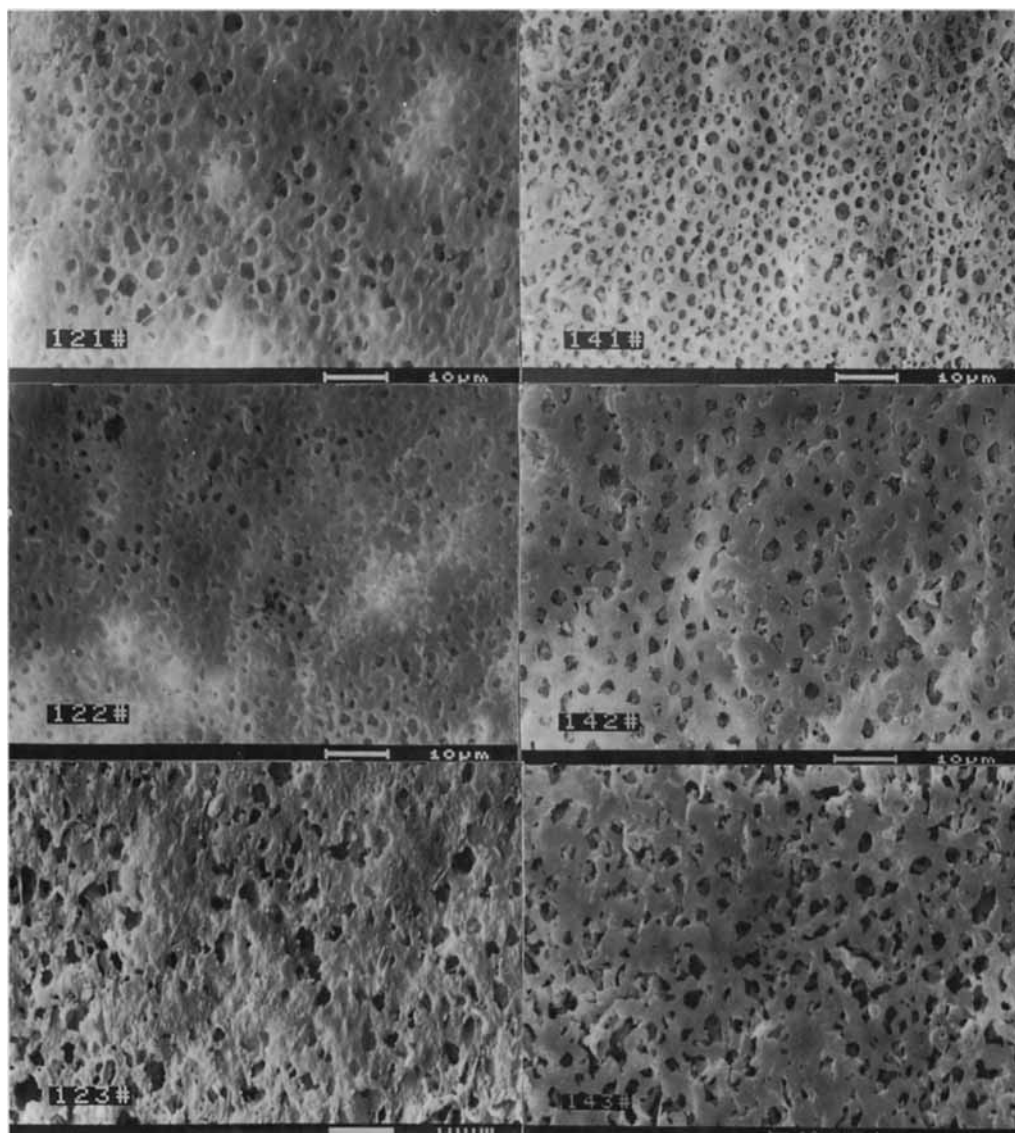|	Hydrolytic TIme (Days)			
	5	15	35	65
$\bar{M}_n \times 10^{-4}$	6.5	5.16	4.43	1.16
$\bar{M}_n \times 10^{-4}$	12.5	10.6	9.2	5.94
$D\ (\bar{M}_w/\bar{M}_n)$	1.92	2.03	2.08	3.69

Figure 11 Surface morphology of (left) PHB/PLA (50/50), (right) (50/50) PHB/PELA blends after 10, 35, and 60 days hydrolytic degradation (from top to bottom).

hydrophilic nature, it contributes to adjust the hydrophilicity/hydrophobicity ratio of the blend systems. Besides these, the PEG soft segment may improve the biocompatibility of the blends because its surface structure changes easily *in vivo*. Further studies will be carried out concerning the biomedical applications of these systems.

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