An Important Biodegradable Polymer — Polylactone-Family Polymer

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Summary: Systemic investigation on the synthesis and properties of aliphatic polylactones were carried out. And various materials were obtained with different degradation rates and mechanical properties. Two in vivo experiments were presented in this study to envision the biomedical applications of this kind of aliphatic polylactones.

Keywords: biodegradable; drug delivery; polylactone; tissue engineering

Introduction

The application of degradable polylactones for medical purposes is growing very fast. It has found applications in such diverse fields as tissue engineering, implantation of medical devices and artificial organs, prostheses, ophthalmology, dentistry, bone repair and many other medical fields[1,2].

Tissue engineering is a new emerging field, where matrices play a central role. Although a variety of synthetic biodegradable polymers can be utilized to fabricate tissue engineering matrices, the ester bond-containing aliphatic polyesters are the most attractive because of their outstanding biocompatibility and versatility regarding physical, chemical and biological properties[3,4]. Polymers and copolymers deriving from lactide (LA), glycolide (GA) and ε-caprolactone (CL) are by far the most commonly used synthetic polymers in tissue engineering[5]. These polylactones are also extensively utilized in other biomedical applications such as drug delivery, preferably for the formulation can disappear completely from the site of injection after drug was completely delivered[2, 6].

The properties of degradable polyesters, especially their degradation behaviors, depend on many factors, including composition, structure, morphology, hydrophilicity/hydrophobicity, molecular weight, even size and porosity of the matrix[7,8], so far, it is possible to adjust and govern the properties of polylactone to fit various desired applications.

In this study, we have summarized the research work of our laboratory on the synthesis and properties of various polylactones. Thereafter, some applications are presented to demonstrate the potential application of the polylactones in drug delivery, tissue engineering and other fields.

 CCC 1022-1360/00/$ 17,50+.50/0

Preparation and Characterization of Polymers

Several di- and tri-components polylactones, such as poly(lactide-co-glycolide) (PLG), poly(lactide-co-caprolactone) (PLC), and poly(glycolide-co-lactide-co-caprolactone) (PGLC), were synthesized by the ring-opening homo- and copolymerization of lactide, glycolide and/or caprolactone, usually using stannous ocotoate as catalyst. The polymerization temperature primarily depended on the polymer components[9, 10]. Briefly, temperature will be high to ensure the polymerization of random copolymers, e.g. above 160°C, if the reaction system contained high content of glycolide. Because the reactivities of the lactones were in the order of glycolide > lactide > caprolactone, and the difference of reactivity between them will decrease at an elevated temperature. However, the most common polymerization temperature is around 120-140°C to avoid transesterification and thermal degradation. On the other hand, control of molecular weight was achieved by using a chain-transfer agent, such as compounds containing hydroxyl groups.

For the sake of simplicity, the copolymers were identified in this paper by the acronyms like PLG(y/x) and PGLC(x/y/z), where x, y and z are the molar percentage of glycolidyl, lactidyl and caproyl units in the copolymer, respectively. Besides, random or block copolymers are named as r- or b-, e.g. r-PGLC and b-PGLC.

The polymers have been characterized by gel permeation chromatography, nuclear magnetic resonance, and differential scanning calorimetry to define the distribution of co-monomers. Besides, mechanical properties of the polylactones were measured, as shown in Table 1, which strongly depended on components and compositions, as well as different chain architectures of polymers.

Unlike PLA homopolymers, PCL is an elastic polymer with large elongation around 1500%. By copolymerization of lactide with caprolactone, the toughness of PLA chains was decreased to lead to the elongation of PLC reaching around 500% in comparison with brittle

Table 1. In vitro degradation rates and properties of part of polylactones.

Polylactones	[η]	Half life	σ	Elongation	T_g
	dl/g	weeks	MPa	%	°C
PCL	0.5~6.0	> 110	10 ~ 35	~ 1500	-60
PLLA	0.7~8.0	110	10~200	/	70
PDLLA	1.13	10	~ 30	/	65
PLG(90/10)	1.57	> 50	34	250	58
PLG(70/30)	0.95	10	29	310	52
PLG(50/50)	0.63	3	21	360	46
PGLC(27/63/10)	1.53	9	26	570	22
PGLC(45/45/10)	1.12	5	25	600	17
PLC(50/50)	1.41	40	34	550	22

break behaviors of PLA. With the introduction of caproyl units into the PLG copolymers, even being of similar molar ratio of glycolidyl to lactidyl units (e.g. PLG(70/30) and PGLC(27/63/10), PLG(50/50) and PGLC(45/45/10)), the PGLC copolylactones showed higher elasticity.

More importantly, the glass transition temperature (T_g) of amorphous PGLC copolylactones was very sensitive to caproyl units content, and it decreased with the content of caprolactidyl units increasing. The materials, which have Tg lower than or near body temperature, had a potential to be made into temperature depending drug delivery devices on the basis of different drug diffusion coefficients in glass and rubbery state. These elastic materials could also be good scaffold materials for skin tissue engineering or guides for nerve regeneration.

Degradation Studies

Degradation behavior of a biodegradable polymer is a critical factor in determining its biomedical applications. Therefore, a systemic investigation on the degradation characteristics of various aliphatic homo- and copolylactone films under comparable conditions was performed in vitro at pH7.4 under 37°C, and the degradation rate was expressed as half life on the basis of 50% weight loss as listed in Table 1.

The chemical compositions and the ratio of monomers used in the polymerization reaction strongly influence the degradation characteristics of the copolylactone. By altering the components and adjusting the compositions, materials with different degradation rates that the half life varied from 3 weeks to more than 2 years could be obtained. PCL and PLLA are the most stable members of the series, however, their random copolymers had accelerated degradation rates due to the weakened crystallinity and amorphous structure.

The copolymers containing glycolidyl units all have faster degradation rates than corresponding homopolymers, and the degradation rate was significantly accelerated with the content of glycolidyl units in the copolymers increasing. One reason is the improved hydrophilicity of the copolymer due to the hydrophilic nature of glycolidyl units. Another reason is the amorphous structure resulting from random copolymerization. And the third possible reason might be the decreased intrinsic viscosity of copolymers containing higher content of glycolidyl units that lead to faster degradation rate.

Application of Polylactone in Tissue Engineering

Many strategies in tissue engineering have focused on using synthetic biodegradable polymers as temporary scaffolds to stimulate isolated cells to regenerate tissues with defined size and shape. The temporary scaffold should have a three-dimensional porous structure and

its porosity should be at least 90% in order to provide a high surface area for maximizing cell seeding and attachment, sufficient space for extracellular matrix regeneration and minimal diffusion constraints during the in vitro culture. By means of various foam forming methods, including particle leaching, phase separation, emulsion freeze drying and 3-D printing technique, scaffolds with different porous structures were prepared (Figure 1). After surface modification by plasma treating or/and collagen coating[11], the cell affinity of polylactones was remarkably improved. Preliminary researches on tissue engineered skin, cartilage, bone, heart valve and nerve have been performed.

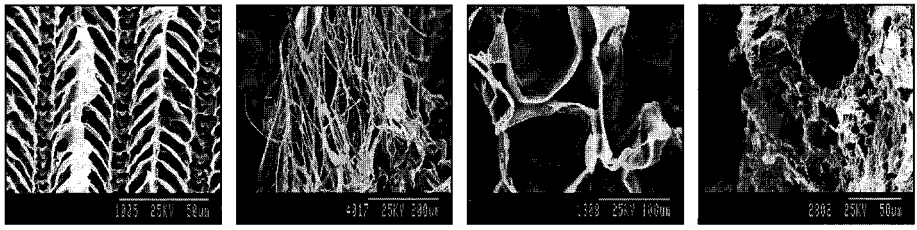

Figure 1. Scaffolds with different porous structures made by different techniques.

Application of Polylactone in Drug Delivery Systems

In vivo release of cyclosporine (CS) was given here as a example to envision the application of polylactone as drug carriers. Corneal transplantation is one of the most common allografts performed, however, immune graft rejection is a major cause of graft failure. CS has been found to be an effective immunosuppressive agent and is widely used in organ transplantation in human. Using a polymer matrix, it is possible to obtain sustained therapeutically effective levels of CS to the anterior chamber to prolong corneal transplant survival by implanting the drug delivery systems in the grafted eyes, which would also minimize the side effects of CS. PGLC copolylactones were used in this study, which were in a rubbery state at body temperature for their low glass temperatures and thus it would not cause mechanical damages to the eyes. The drug delivery devices were shaped into small cylinders containing different dosage of CS. By transplanting these polymeric cylinders in rabbit's eyes, sustained release of CS could be detected by measuring the CS concentration in anterior chamber (Figure 2). More importantly, it was found that the median survival time was 17.5±5.15 days for untreated allografts, and >90 days for grafts given CS-polymer implants in the anterior chamber.

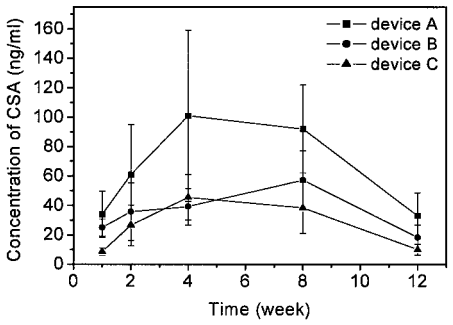

Figure 2. Changes of cyclosporine concentration in aqueous humor of rabbit's anterior chamber with time: A-1.2mg of CS; B-0.8mg of CS; C-0.4mg of CS.

Application of Polylactone in Orthopedic

The treatment of bone defection is one of the most important subjects in orthopaedics. Because traditional methods such as autografting and allografting have some shortcomings, people have been searching the bone substitutes. Complex of PLLA and β–tricalcium phosphate (β-TCP) was conceived as a potential substitute, and it could be prepared by a three-dimension printing with a rapid forming machine, moreover, recombinant human bone morphogenetic protein (rhBMP) could be loaded to obtain a bioactive bone substitute.

Good results had been obtained by using this PLLA-TCP-BMP composite to repair a 2.0cm radius defect in dogs. As shown in Figure 3, there was no callus formed in 24 weeks postoperation and the defect has not been repaired in controlled groups, whereas, the defect was connected by callus within 12 weeks postoperation, and the callus rebuilt well in 24 weeks if the bioactive substitute was implanted into the defect.

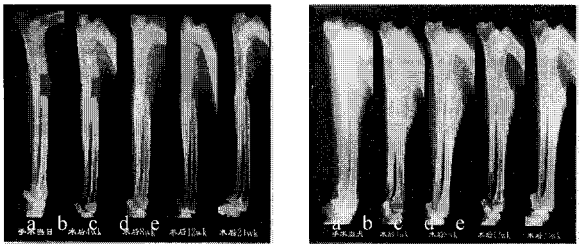

Figure 3. 2.0cm of radius's defect of dog recovering by itself (left) and repaired by PLLA-TCP-BMP substitute: (a) exactly after operation; (b) 4 weeks; (c) 8 weeks; (d) 12 weeks; (e) 24 weeks.

Conclusion

A series polylactones with various biodegradability, mechanical properties, hydrophilicity and cell affinity could be synthesized by copolymerization of various lactones, which provided a wide choice for different biomedical applications.

Acknowledgement

The authors are indebted to Basic Science Research and Development Grants (973) (Project G1999054305 and G1999054306) for financial supports, and the kind cooperation of Prof. Yunyu Hu from Xijing Hospital, Prof.. Yongnian Yan from Qinghua University, and Prof. Lixin Xie from Shandong Academy of Medical Science.

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