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FEATURE ARTICLE

Polylactic acid (PLA) synthesis and modifications: a review

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This article reviews various methods of synthesizing polycondensation and ring-opening polymerization and modifying properties of polylactic acid (PLA), which may be used as biomaterials, such as a drug carrier in a drug delivery system, as a cell scaffold and suture in tissue engineering, and as packaging materials in packaging engineering field. Copolymerization of lactide with other monomers or polymers such as malic acid, polyethylene glycol (PEG), polyglycolic acid (PGA), or dextran, as well as blending polylactide with natural derivatives and other methods of modification are discussed. Surface modifications of PLA-type copolymers, such as surface coating, chemical modification, and plasma treatment are described.

Keywords polylactic acid, synthesis, modification, copolymerization, surface coating, plasma treatment

1 Introduction

Biomaterials and biodegradable materials represent two of the most interesting areas of material science, in which chemical, medical, and environmental scientists are contributing to human health care, improving quality of life, protecting environment from white pollution, and reducing dependence on fossil fuels. A great number of polymers have been developed as potential biomaterials and biodegradable packaging materials due to their various compositions, special structures, and excellent properties that cover a wide range of applications [1–3].

Biodegradable polymers are widely used in the medical and packaging engineering fields. Since aliphatic polyesters contain flexible ester bonds and they can degrade into nontoxic matters in different pH solutions, they might be the most promising biodegradable polymers for medical and packaging applications. With their excellent biocompatibility, polylactones such as polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolactone (PCL), as well as their copolymers are becoming the most commonly used synthetic biodegradable polymers in the medical field. With their inherent and important renewable feature, biodegradability, and other important properties like transparency, excellent film-forming properties via casting for coatings, good thermal, permselective, mechanical, and processing properties, they can also be used in packaging engineering field [2]. PLA was approved by the US Food and Drug Administration as far back as in the 1970s and has since been widely utilized in sutures, clips, plates and screws, in drug delivery devices, and in food packaging applications. However, if we consider the practical requirements of packaging engineering and medical systems, PLA also has many obvious disadvantages: its degradation rate cannot meet a wide range of application-specific requirements; and there are no cell recognition sites that are important for tissue compatibility on the surface of PLA application on tissue engineering. On the other hand, in the case of using PLA directly as a packaging material, brittle breakage has often occurred. It is, therefore, of industrial interest to improve the mechanical performance of PLA in order to strengthen its 'value-added' arguments. In this context, the functional and eco-harmless modifications that have a significant potential to enhance mechanical and bioproperties of PLA and provide controlled release of functional (antimicrobial, antioxidant, bioactives, etc.) substances will be introduced. The modifying hydrophilicity, degradability, and breaking elongation of PLA were reviewed [3–5]. To do this, modifying the bulk and surface of PLA by introducing hydrophilic and biocompatible components and by adjusting the surface energy, surface charge, and surface roughness were described [4–8].

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2 PLA synthesis

The synthetic routes to obtain PLA are basically through direct condensation of the free acid or ring opening polymerization of esters of the acid (Figure 1) [9].

Direct condensation polymerization includes solution polycondensation and melt condensation. It was reported that the Mitsui Toatsu Chemical Company [9] polymerized poly-*DL*-lactic acid (PDLLA) using direct solution polycondensation, in which lactic acid, catalysts, and organic solvent with high boiling point were mixed in a reactor. The reaction would last 2 h at 140°C, then the high boiling point solvent and water were evaporated at 130°C and dehydrated for 20–40 h in 3A molecular sieve until the water is less than 3 ppm in solvent. The resultant product shows a molecular weight (MW) of about 300000 [10]. Sung et al. studied the influence of different catalysts on melt condensation and found that tin oxide and chloride could efficiently increase the PLA molecular weight [11]. The reaction temperature is at 180°C, which is a little higher than poly-*L*-lactic acid's (PLLA) melting point. Protonic acid was added as a cocatalyst into the system to improve polarity of the reaction system, which is related to the catalysts' activity and can reduce by-products lactide and depigment when the reaction is at high temperature and lasts long time. The result shows that the MW was about 100000 [11]. Moon et al. successfully obtained high molecular weight PLLA through the melt/solid polycondensation catalyzed by a tin chloride dehydrate/p-toluenesulfonic acid binary system [12]. The whole process was divided into three steps including dehydration, polycondensation, and crystallization (Figure 2). The results showed that the molecular weight of PLLA reached over 20000 in a relatively short reaction time.

Compared with ring opening polymerization, direct condensation polymerization has fewer manufacturing steps and lower cost, and is easier to manipulate and commercialize. The primary disadvantage of this method is the low molecular weight of the resultant polymer, which is due to the equilibrium among the free acid, the oligomers, and the water produced during the reaction or some special treatment. Thus, some conventional method-ring opening polymerization was developed.

The ring opening polymerization of PLA is an important method to obtain high molecular weight products, in which using high purity lactide is the most important step in the whole process. Lactide can be prepared through a decompression method in which the water is separated from the system, and then, some catalysts are added into the reactor. After reacting for several hours, lactide is obtained. Then, the lactide opens its ring to polymerize. Many papers described this process [9–12].

The ring-opening polymerization requires the use of heavy-metals-based catalysts, such as oxides of Zn and Sn, chlorides of zinc and tin, or stannous octoate, which commonly contaminate the obtained polymer. This contamination of PLA could limit some specific applications on food packaging engineering and medical system. In addition, high-purity monomers for PLA ring opening polymerization are needed, and severe conditions of temperature and vacuum must be used.

Based on the above disadvantages of the ring opening

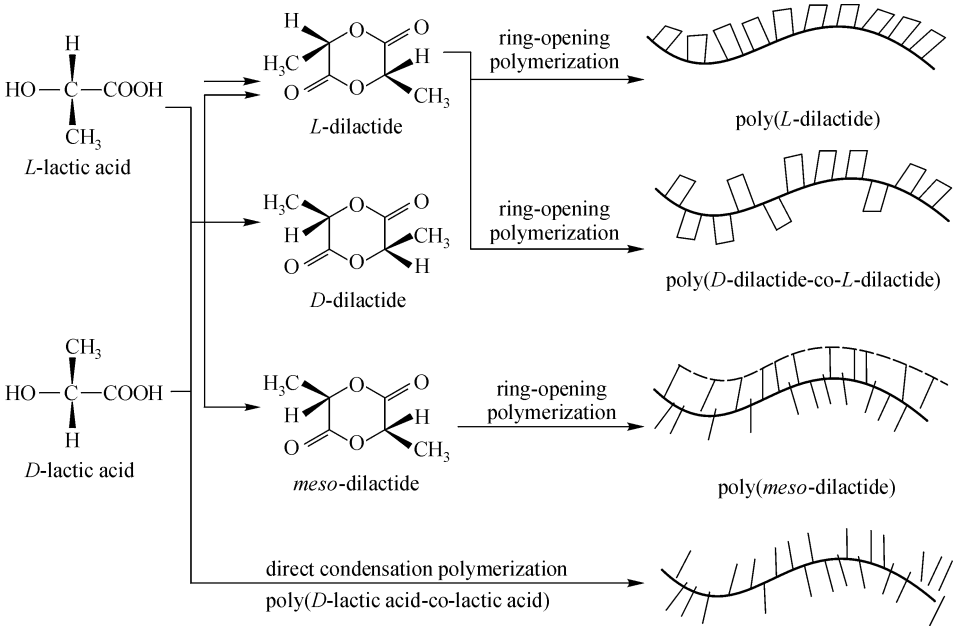

Figure 1 Polymerization scheme of copolymers from *L*-lactic acid and *D*-lactic acid.

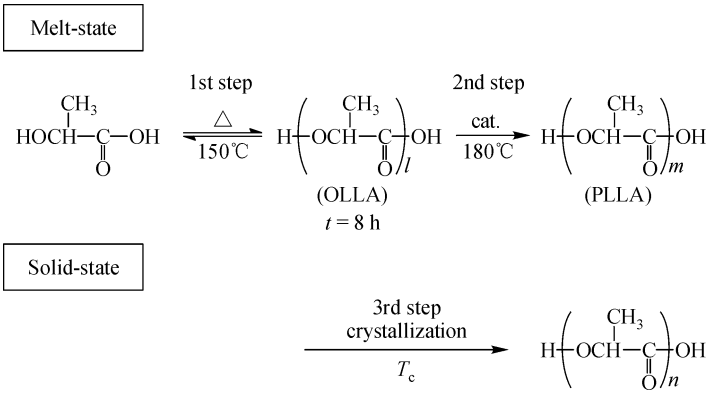

Figure 2 The melt/solid polycondensation of PLA.

polymerization methods, some researchers have focused on choosing nontoxic catalysts, using some special treatment, or exploring other polymerization ways [13]. Enzymatic polymerization emerges as one of the most viable alternatives to avoid these difficulties. Enzymatic synthesis is an environmentally benign method that can be carried out under mild conditions and can provide adequate control of the polymerization process. The reaction temperature and water content on the stability of the enzyme were studied. Specifically, the recovery of PLA after the reaction, the interaction of lipase with the solvent, and the potential mistakes in measurement of the conversion by titration (due to the presence of nonfree lactic acid (LA)) were explored [13]. In addition, some modifications and surface treatments of PLA were conducted in order to improve PLA properties and widen its application on some specific fields.

3 PLA modification

The critical factors that influence the properties of polymers include chemical components, compositions, morphological structure and so on. In PLA synthesis, most studies [14] focus on the variety and amount of hydrolytic groups, the flexibility and crystallinity of the molecular chains, and the hydrophilic groups. The modification of PLA includes the copolymerizing of the lactide with other lactone-type monomers, a hydrophilic macromonomers (polyethylene glycol (PEG)), or other monomers with functional groups (such as amino and carboxylic groups, etc.), and the blending PLA with other materials.

The copolymerization of lactide with other lactone-type monomer polyglycolide can improve PGA's high crystallinity, high melting point, and poor solubility. Thus, the copolymerization product (poly-lactic-glycolic acid (PLGA)) exhibits better properties (lower crystallinities and melting temperature (T_m)) than PLA and PGA. The degradation characteristic of PLGA could be adjusted by controlling the ratio of LA to glycolic acid (GA) in the feeding dose. The PLGA composed of 50:50 (LA:GA) is entirely amorphous. The degradation rate of PLGA is faster than that of PLA and can be increased by increasing the GA content [14]. However, the solubility and toughness of the copolymer are also limited by the composition.

In order to further adjust the degradation rate of PLGA and the flexibility of the polymeric chain, a third component – caprolactone (CL) was introduced into PLGA. The poly(glycolide-co-lactide-co-caprolactone) tri-component copolymer (PGLC) was synthesized by ring-opening copolymerization of glycolide, *L*-lactide, and ε-caprolactone in the presence of stannous octoate. By adjusting the component ratio of the three monomers, copolymers with different degradation rates could be obtained. Also, as the glass temperature (T_g) of PCL is getting lower, the T_g of PGLC decreases as the CL and GA content increase. The mechanical property measurement showed that the increasing of the CL content resulted in the toughness reduction but enhanced the flexibility of the copolymers. The break elongation ratio of the PGLC increased significantly with the introduction of the CL content. Based on this principal, a series of copolylactides with different degradation ratio ranging from several weeks to more than two years, as well as various physical appearances and mechanical properties, could be gained by adjusting the component ratio of lactide to the other lactone-type monomers and the molecular weights of the copolymers [14–17].

However, the hydrophilicity of the copolymer using this method could not be improved significantly. The use of PEG is hence necessary. PEG is a highly biocompatible, nontoxic, nonimmunogenic, and nonantigenic polymer with excellent hydrophilicity. It is known to decrease the attractive forces between solid surfaces and proteins because of its highly hydrated polymer chains, steric stabilization forces, as well as chain mobility. Such properties can make a surface highly resistant to biological fouling and reduce protein adsorption

and resistance to bacterial and animal cell adhesion. Since PEG is very soluble in water and many organic solvents, it can also be easily removed from the tissue. In addition, since it has two hydroxyl groups with reactive ends, the using PEG as the macromonomer to improve the hydrophilicity and the biocompatibility of PLA is a good choice [18].

In addition to the copolymerization technique, the bulk properties of PLA could also be modified by blending with other materials. By blending PLA with naturally derived dextran, a new kind of biodegradable material, could be obtained. Moreover, a sponge-like scaffold could be fabricated using solvent-casting and particle-leaching techniques. In order to obtain a uniform blend of PLA and dextran, hydroxyls of dextran were protected via trimethylsilyl (TMS) groups to make dextran soluble. A homogeneous solution of PLA and TMS-protected dextran could be obtained using a mixed solvent of dichloroform and benzene. The hydrophilicity and cell affinity of the PLA-dextran blend was improved significantly compared with pure PLA [19].

Chitosan is a promising natural cationic polymer with good biocompatibility, nontoxicity, and biodegradability. It is produced by alkaline N-deacetylation of chitin, the most abundant natural polymer after cellulose. Chitosan has been shown to be useful as a chelating agent, drug carrier, membrane, water treatment additive, biodegradable pressure-sensitive adhesive tape, wound healing agent, nerve repair, and in other important applications. However, such biomedical properties of chitosan must be improved for the adsorption of drugs and proteins and the adhesion of cells to biomedical materials. Thus, in order to improve the properties of chitosan, a hydrogel was synthesized through grafting *D*,*L*-lactic acid onto the amino groups of chitosan. Because the $-NH_2$ groups of the chitosan were substituted randomly along the chain, the regularity between chitosan chains was destroyed and the crystallinity of chitosan hence gradually decreases after grafting. A brush-like copolymer of poly *D*,*L*-lactide-g-chitosan was prepared in this way [20–22].

4 PLA surface modification

The surface properties of materials play a critical role in determining their applications, especially for biomaterials in biocompatibility. Hence, it is important to design biomaterials with the right surface properties. Biomaterials must also possess bulk properties that meet other requirements, especially physical and mechanical properties, in order to function properly in biological environments. As it is difficult to design biomaterials fulfilling both requirements, a common approach is to fabricate biomaterials with adequate bulk properties followed by modification of its surface to render desirable surface properties. Different surface modification strategies, such as physical, chemical, plasma, and radiation-induced methods, have been employed to create desirable surface properties of PLA biomaterials. Modifications based on the deposition of plasma polymers and plasma treatments are highly substrate independent. Plasma polymerization has unique practical advantages, which include (i) confirmative ultra thin film deposition, (ii) good adhesion to the substrate material, and (iii) formation of chemically and physically durable surfaces [22–24].

Surface modification with plasma treatment of poly(lactic-co-glycolic acid) (50:50) (PLGA) was investigated by Lee et al. to induce cell affinity on the polymer surface [3]. In recent years, many studies have focused on coating or grafting bioactive molecular on the polymer surface in order to mediate the cell attachment and cell growth. For example, the (1→6)ranched (1→3)-β-glucans, mainly constructed in the outer cell wall of fungi, have wound healing activities. The study of Lee et al. is to enhance the cell affinity of PLGA by grafting β-glucan with plasma treatment. The plasma treated film and untreated film were coated with β-(1→3)(1→6)-glucan. The amount of β-(1→3)(1→6)-glucan in each sample was indirectly determined by the phenol–sulfuric acid method. The result showed that the plasma-modified groups exhibited more amount of the β-glucan than the nonplasma-treated groups. The human dermal fibroblast (HDF) was seeded on each group at an initial cell density of 2×10^5 cells/film. Cell proliferation was significantly enhanced in the HDF attachment for experimental group after six days of incubation (pb0.05) due to the improved hydrophilicity of PLGA film by plasma treatment. Surface modification of PLGA film with plasma treatment has an effect on β-(1→3)(1→6)-glucan coating and cell affinity to the film [3].

In Park et al.'s study [25], the biodegradable polymers poly (*L*-lactic acid) (PLLA) was dissolved in proper solvents and then subjected to electrospinning process in order to make nanofibrous scaffolds. The surfaces were then chemically modified using oxygen plasma treatment and *in situ* grafting of hydrophilic acrylic acid (AA). The ultimate tensile strength of PLLA was about 2 MPa on average. The elongation-at-break was 100%–130% for the nanofibrous scaffolds. When the surface properties of AA-grafted scaffolds were examined, higher ratios of oxygen to carbon, lower contact angles, and the presence of carboxylic (–COOH) groups were identified. The properties were significantly different from those of the unmodified nanofibrous scaffolds. This study showed that, with the use of plasma treatment and AA grafting, the hydrophilic functional groups could be successfully adapted on the surface of electrospun nanofibrous scaffolds [25]. Those surface-modified scaffolds made significant improvement on cell attachment and proliferation *in vitro*.

Attachment to and proliferation on the substrate are deemed

important considerations when Schwann cells (SCs) are to be seeded in synthetic nerve grafts. Hence, the surface properties of artificial materials are the dominating factor influencing the interactions between cells and synthetic nerve grafts. Huang et al. investigated the surface effects of laminin modified PLGA and chitosan membranes after plasma treatment [26]. Laminin, the extracellular matrix protein, is a permissive protein for SCs adhesion used in neural regeneration. Results showed that laminin was covalently bonded onto the surface of both PLGA and chitosan membranes by oxygen plasma treatment. The cell affinity of the laminin modified membranes was verified by SCs culturing. The results also indicate that oxygen plasma is indeed a better method to incorporate laminin onto the surface of membrane. Laminin-modified chitosan membrane significantly increases SCs attachment and affinity for directing peripheral nerve regeneration [26].

Gutierrez-Villarreal et al. also chose the photoinduced grafting process to modify PLA for its low operation cost, weak penetration of absorbed UV light, and the required mild reaction conditions that do not affect the bulk polymer [27].

N-vinylpyrrolidone (NVP) has seldom been used in surface photografting, although some researchers have used X-ray or other initiation methods to graft it onto different substrates [27].

Albertsson et al. grafted NVP over PLA surface on a single-step under solvent-free conditions. Polyvinylpyrrolidone (PVP) is a versatile synthetic polymer that is soluble in water and has different applications depending on its molecular weight. NVP was easily photografted onto PLA film surfaces. The wettability of the PLA surface was improved, and it can be manipulated by changing the irradiation time [28].

5 Summary

Although the PLA-type polymers have many good properties, their hydrophilicities, biocompatibilities, and cell affinities are still not suitable for some tissue engineering and other biotechnology applications. Focusing on the application of PLA-type polymers for medical use, we have reviewed methods of modifying PLA-type polymers by bulk modification and surface modification. Using bulk modification, such as copolymerization with other lactone-type monomers, PEG, monomers with functional groups, and blending with other materials, the degradation rates, hydrophilicities, mechanical properties, and surface properties of PLA-type polymers can be significantly improved. Moreover, surface modifications of the polymers, such as surface coating and plasma treatment, can improve the cell affinities of PLA-type polymers. This ability to improve the properties of PLA-type polymers, giving them excellent biocompatibilities, biodegradabilities, and cell affinities, points to a promising future for their applications in medical science and particularly in tissue engineering, packaging engineering, and other human health care fields.

Roger RUAN currently serves as the director of the Center for biorefining and a professor at the Department of Bioproducts and Biosystems Engineering and Department of Food Science and Nutrition in the University of Minnesota. His research interests include nuclear magnetic resonance and other imaging and spectroscopy and microscopy technology development and application in moisture and fat management, shelf stability, structure-function relationships of biological and food materials, and nonthermal processing. He is also interested in refining renewable biomass into fuels, chemicals, materials, food and feed, energy crop such as algae production, refining, and conversion, biopolymer and food process improvement, quality enhancement, and safety assurance.

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References

1. Okada, M., *Prog. Polym. Sci*. **2002**, *27*, 87
2. Cava, D.; Giménez E.; Gavara R.; Lagaron, J. M., *J. Plast. Film Sheeting* **2006**, *22*, 265
3. Lee, S. G.; An, E. Y.; Lee, J. B.; Park, J. C.; Shin, J. W.; Kim, G. K., *Surf. Coat. Technol*. **2007**, *201*, 5128
4. Ogaki, R.; Green, F.; Li, S.; Vert, M.; Alexander, M. R.; Gilmore, I. S.; Davies, M. C., *Appl. Surf. Sci*. **2006**, *252*, 6797
5. Sasatsu, M.; Onishi, H.; Machida, Y., *Int. J. Pharm*. **2006**, *317*, 167
6. Majerska, K.; Duda, A.; Penczek, S., *Macromol. Rapid Commun*. **2000**, *21*, 1327
7. Kowalski, A.; Duda, A.; Penczek, S., *Macromol. Rapid Commun*. **1998**, *19*, 567
8. Filachione, E. M.; Fisher, C. H., *Ind.. Eng. Chem*. **1944**, *36*, 223
9. Zhang, S.; Li, F.; Wei, D., *ACI Mater. J*. **2007**, *5*, 227
10. Ajioka, M.; Enomoto, K.; Suzuki, K., *Bull.Chem.Soc. Jpn*, **1995**, *68*, 2125
11. Sung, I. M.; Chan, W. L.; Masatoshi, M., *Polym. Sci. Polym. Chem.*, **2000**, *38*, 1673

12. Moon, S. I.; Lee, C. W.; Taniguchi, I.; Miyamoto, M.; Kimura, Y., *Polymer* **2001**, *42*, 5059
13. Lassalle, V. L.; Ferreira, M. L., *Chem. Technol. Biotechnol*. **2008**, *83*, 1493
14. Mooney, D. J., Breuer, M. D., Mcnamara, K., Vacanti, J. P., *Langer. R. Tissue Eng*. **1995**, *1*, 107
15. Qian, H. T.; Bei, J. Z.; Wang, S. G., *Polym. Degrad. Stab*. **2000**, *68*, 423
16. Cai, Q.; Bei, J. Z.; Wang, S. G., *Biomed. Sci. Polym. Ed*. **2000**, *11*, 273
17. Wang, S. G.; Wan, Y. Q.; Cai, Q.; He, B.; Chen, W. N., *Chem. Res. Chin. Univ*. **2004**, *20*, 191
18. Yang, J.; Gao, J. C., *Mater. Sci. Technol*. **2008**, *24*, 261
19. Cai, Q.; Yang, J.; Wang, S. G., Bei, J. Z., *Biomaterials* **2002**, *23*, 4483
20. Xu, J.; McCarthy, S. P.; Gross, R. A., *Macromolecules* **1996**, *29*, 3436
21. Huang, Y. C.; Huang, Y. Y.; Huang, C. C.; Liu, H. C., *Biomed. Mater. Res. B Appl. Biomater*. **2005**, *74*, 659
22. Huang, Y. C.; Huang, C. C.; Huang, Y. Y.; Chen, K. S., *J. Biomed. Mater. Res., Part A*, **2007**, 842
23. Khorasani, M. T.; Mirzadeh, H.; Irani, S., *Radiat. Phys. Chem*. **2008**, *77*, 280
24. Hirotsu, T.; Tagaki, C., *Thin Solid Films* **2004**, *457*, 20
25. Park, K.; Ju, Y. M.; Son, J. S.; Ahn, K. D.; Han, D. K., *Biomater. Sci. Polymer. Edn*. **2007**, *18*, 369
26. Huang, Y. C.; Huang, C. C.; Huang, Y. Y.; Chenet, K. S., *Biomed. Mater. Res*. **2007**, *8A*, 842
27. Gutierrez-Villarreal, M. H.; Ulloa-Hinojosa, M. J.; Gaona-Lozano, J. G, *J. Appl. Polym. Sci*. **2008**, *110*, 163
28. Edlund, U.; Kallrot, M.; Albertsson, A. C., *J. Am. Chem. Soc*. **2005**, *127*, 8865