Progress in Polymer Science 35 (2010) 338–356

Contents lists available at ScienceDirect

Progress in Polymer Science

journal homepage: www.elsevier.com/locate/ppolysci

Poly(lactic acid) modifications

Rahul M. Rasal[a,b], Amol V. Janorkar[c], Douglas E. Hirt[a,b,*]

[a] Department of Chemical and Biomolecular Engineering, Clemson University, Clemson, SC 29634, United States
[b] Center for Advanced Engineering Fibers and Films, Clemson University, Clemson, SC 29634, United States
[c] Department of Biomedical Materials Science, School of Dentistry, University of Mississippi Medical Center, Jackson, MS 39216, United States

ARTICLE INFO

Article history:
Received 17 September 2008
Received in revised form 8 September 2009
Accepted 8 December 2009
Available online 14 December 2009

Keywords:
Poly(lactic acid)
Bulk and surface-modifications
Mechanical properties
Degradation

ABSTRACT

Poly(lactic acid) or polylactide (PLA) is the most extensively researched and utilized biodegradable and renewable thermoplastic polyester, with potential to replace conventional petrochemical-based polymers. In recent times, several PLA-based technologies have emerged with an emphasis on achieving chemical, mechanical, and biological properties equivalent or superior to conventional polymers. The frequent need for a chemical or physical modification of PLA to achieve suitable properties for its intended consumer and biomedical applications, however, has demanded significant attention in the last decade. In the first part of this review, we briefly discuss the advantages, limitations, production methods, and applications of unmodified PLA. The second part, the major objective of this paper, focuses on the various bulk and surface-modification strategies used to date and their basic principles, drawbacks, and achievements.

Contents

* Corresponding author at: Department of Chemical and Biomolecular Engineering, Clemson University, Clemson, SC 29634, United States. Tel.: +1 864 656 0822; fax: +1 864 656 4557/0784.
E-mail address: hirtd@clemson.edu (D.E. Hirt).

0079-6700/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.progpolymsci.2009.12.003

1. Introduction

The extensive dependence on polymers drives considerable scientific and engineering efforts devoted to the discovery, development, and modifications of these materials. U.S. production of polyethylene (PE), polypropylene (PP), and related resins is greater than 100 billion pounds per year [1], and is expected to increase as polymers replace other conventional materials, such as glass, metals, etc. Recently, biodegradable and renewably derived polymers have attracted much attention due to the environmental concerns and sustainability issues associated with petroleum-based polymers [2,3]. One such polymer is PLA, a biodegradable and bioabsorbable, renewably derived thermoplastic polyester extensively investigated over the last several decades [4–10].

PLA development initiated with the lactide production formulas published by Bischoff and Walden in 1893. In 1932, Carothers and coworkers produced low molecular weight PLA. E.I. DuPont de Nemours and Ethicon, Inc. began marketing PLA in medical applications for sutures, implants, and drug-delivery systems in 1954. Shimadzu Corporation and Kanebo Gohsen Ltd., Japan produced PLA fibers by melt spinning in the laboratory in 1992 and Kanebo Gohsen Ltd., Japan started commercial production of PLA fibers under the trade name Lactron in 1994. Fiberweb France S.A., France started commercial production of PLA fibers under the trade name Deposa in 1997. Cargill Dow LLC, USA started commercial production of PLA from starch under the trade name NatureWorks at a capacity of 140,000 tons/year in 2002. In 2003, Cargill Dow LLC introduced PLA fiber Ingeo™ spun from the NatureWorks™ polymer. Dow sold its share to Cargill in 2005, which renamed their PLA business NatureWorks LLC [11,12].

1.1. PLA advantages

1) *Eco-friendly*—Apart from being derived from renewable resources (e.g., corn, wheat, or rice), PLA is biodegradable, recyclable, and compostable [13,14]. Its production also consumes carbon dioxide [15]. These sustainability and eco-friendly characteristics make PLA an attractive biopolymer.
2) *Biocompatibility*—The most attractive aspect of PLA, especially with respect to biomedical applications, is its biocompatibility. A biocompatible material should not produce toxic or carcinogenic effects in local tissues. Also, the degradation products should not interfere with tissue healing [16]. PLA hydrolyzes to its constituent α-hydroxy acid when implanted in living organisms, including the human body. It is then incorporated into the tricarboxylic acid cycle and excreted [16,17]. Moreover, PLA degradation products are non-toxic (at a lower composition) making it a natural choice for biomedical applications [2,16]. Table 1 provides a chronological list of PLA *in vivo* studies conducted over last four decades, demonstrating its satisfactory biocompatibility. The Food and Drug Administration (FDA) has also approved PLA for direct contacting with biological fluids [12].
3) *Processibility*—PLA has better thermal processibility compared to other biopolymers such as poly(hydroxy alkanoates) (PHAs), poly(ethyele glycol) (PEG), poly(ε-caprolactone) (PCL), etc. It can be processed by injection molding, film extrusion, blow molding, thermoforming, fiber spinning, and film forming, with PLA resins for these methods commercialized by NatureWorks LLC [18].
4) *Energy savings*—PLA requires 25–55% less energy to produce than petroleum-based polymers and estimations show that this can be further reduced to less than 10% in the future [19]. Lower energy use makes PLA production potentially advantageous with respect to cost as well.

Although PLA is an eco-friendly bioplastic with excellent biocompatibility, processibility, and less energy dependence, it has drawbacks as well, which limit its use in certain applications.

1.2. PLA limitations

1) *Poor toughness*—PLA is a very brittle material with less than 10% elongation at break [20,21]. Although its tensile strength and elastic modulus are comparable to poly(ethylene terephthalate) (PET) [18], the poor toughness limits its use in the applications that need plastic deformation at higher stress levels (e.g., screws and fracture fixation plates [22]).
2) *Slow degradation rate*—PLA degrades through the hydrolysis of backbone ester groups and the degradation rate depends on the PLA crystallinity, molecular weight, molecular weight distribution, morphology, water diffusion rate into the polymer, and the stereoisomeric content [23]. The degradation rate is often considered to be an important selection criterion for biomedical applications [24]. The slow degradation rate leads to a long *in vivo* life time, which could be up to years in some cases [25]. There have been reports of a second surgery almost 3 years after implantation to remove a PLA-based implant [25,26]. The slow degradation rate is

Table 1
PLA *in vivo* biocompatibility testing (adapted, in part, from Ref. [16]).

Application	Results	Reference
Sutures in guinea-pigs and rats	Non-toxic and non-tissue reactive	[184]
Sutures in rat muscle	Degraded suture induced giant cell reaction	[185]
Bone repair of rat tibia	No adverse tissue host responses	[186]
Fracture fixation in dogs, sheep	Uneventful bone healing that proceeded without callus formation or inflammation signs	[187]
Subcutaneous implants in rats	Mild foreign body reaction	[188]
Drug release in rat soft tissue	PLA is tissue compatible	[189]
Bone fixation in rat	No inflammation or foreign body reaction	[190]
Articular defects in rabbit	Well tolerated, minimal inflammatory response	[191]
Soft tissue/rabbit cornea	Non-toxic and safe	[192]
Fracture fixation of rabbit femur	Insignificant inflammatory response	[193]
Ankle fracture fixation in human	Found safe and effective, no complications	[194]
Implants in the repair of goat osteochondral defects	No obvious histological abnormalities	[195]
Fracture fixation of dog femur	No inflammatory reaction	[196]
Fixation of osteochondral fractures of the femoral condyle	Complete bony healing without clinically relevant complications	[197]
Bone defect coverage in sheep	Good biocompatibility	[198]

a serious problem with respect to disposal of consumer commodities as well.

3) *Hydrophobicity*—PLA is relatively hydrophobic, with a static water contact angle of approximately 80°. This results in low cell affinity, and can elicit an inflammatory response from the living host upon direct contact with biological fluids [27,28].
4) *Lack of reactive side-chain groups*—PLA is chemically inert with no reactive side-chain groups making its surface and bulk modifications a challenging task.

The successful implementation of PLA in consumer and biomedical applications relies not only on mechanical properties being better than or comparable to conventional plastics, but also on controlled surface properties (e.g., hydrophilicity, roughness, and reactive functionalities). PLA has been bulk modified mainly to improve toughness and degradation rate. The surface modification of PLA has been attempted to control hydrophilicity, roughness, and to introduce reactive groups. The toughness improvement is a crucial necessity for many consumer applications, while the improvements in hydrophilicity and introduction of reactive groups are beneficial for biomedical applications. The improvements in degradation rate could be important in both consumer and biomedical applications. This review describes several PLA bulk and surface-modification strategies that have been employed to date. This review also tracks recent advances in these strategies and highlights how they play a crucial role in modifying PLA surface and bulk properties.

2. PLA production and applications

Lactic acid, the monomeric building block of PLA, is produced by converting sugar or starch obtained from vegetable sources (e.g., corn, wheat, or rice) using either bacterial fermentation or a petrochemical route. Lactic acid exists as two optical isomers, L- and D-lactic acid (Fig. 1). The L-lactic acid rotates the plane of polarized light clockwise, and D-lactic acid rotates it counterclockwise. Lactic acid produced by petrochemical routes is an optically inactive 50/50 mixture of the D and L forms. Since the fermentation approach is more eco-friendly, it has been used more extensively since the 1990 [12].

An optimized strain of *Lactobacillus* is used to convert corn starch into lactic acid in the bacterial fermentation process [29]. Fermentation derived lactic acid exists almost exclusively in the L form (99.5% of the L-isomer and 0.5% of the D-isomer) [12,19]. Polymerization of lactic acid to PLA can be achieved by a direct condensation process that involves solvents under high vacuum. Alternatively, in a solvent-free process, a cyclic dimer intermediate called lactide is formed followed by catalytic ring opening polymerization of the cyclic lactide [11]. These schemes are shown in Fig. 2. Due to the optical activity of lactic acid, lactide can be found in three different versions, i.e., D,D-lactide, L,L-lactide, and D,L-lactide (*meso*-lactide) [30]. The stereochemical composition of lactide monomers determines the final properties of the polymer [14]. With the direct condensation route, only low molecular weight (M_w ~2–10 kDa [31]) polymers can be produced, mainly due to the presence of water and impurities. Typically, low molecular weight PLA has substandard mechanical properties. Therefore, it suffers from the need for solvent (water) removal, use of solvents under high vacuum and temperature, and also increased color and racemization of PLA [19]. Because of these disadvantages of direct polycondensation, the commercial manufacture of PLA commonly involves lactide ring opening polymerization [19].

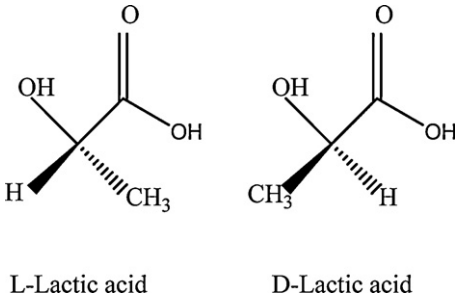


Fig. 1. Lactic acid optical monomers [12].

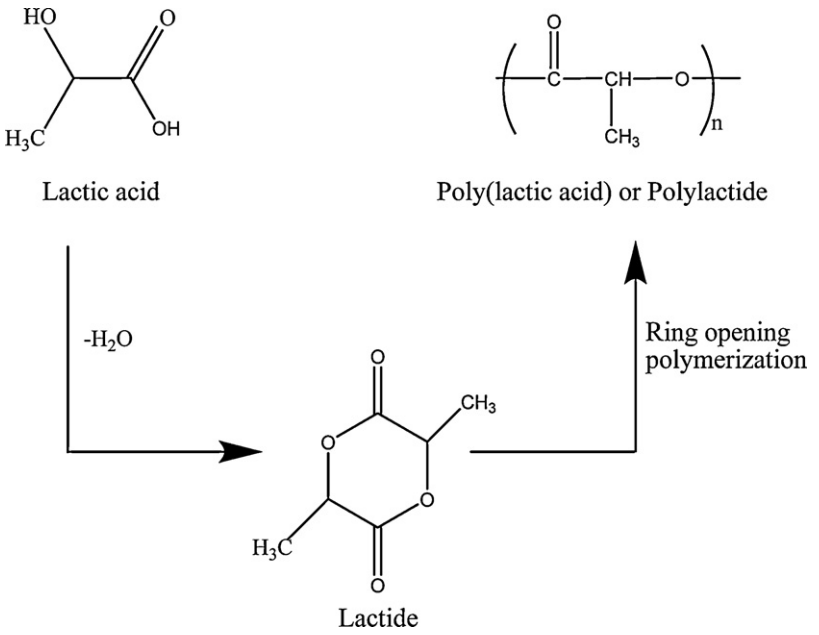


Fig. 2. Reaction schemes to produce PLA [11].

Due to its bioresorbability and biocompatibility in the human body, lactic acid-based polymers have been used for resorbable sutures and prosthetic devices [18]. PLA has been finding increasing consumer applications mainly due to its renewability, biodegradability, transparency, processibility, and mechanical properties. Although PLA has been shown to be a practically feasible packaging material, its higher cost has confined its use to limited packaging application only [18]. Dannon and McDonald's (Germany) pioneered the use of PLA as a packaging material in yogurt cups and cutlery [18]. NatureWorks LLC polymers have been used for a range of packaging applications such as high-value films, rigid thermoformed containers, and coated papers. BASF's Ecovio®, which is a derivative of petrochemical-based biodegradable Ecoflex® and contains 45 wt% PLA, has been used to make carrier bags, compostable can liners, mulch film, and food wrapping. Commercially available PLA films and packages have been found to provide mechanical properties better than polystyrene (PS) and comparable to PET [18]. The extensive utilization of PLA in consumer and biomedical applications will be dictated mainly by cost reductions as well as fine control over PLA bulk and surface properties.

3. Bulk modification of PLA

The major drawback of PLA (with respect to bulk-modification design goals) is its poor ductility and slow degradation rate. Several bulk-modification methods have been employed to improve mechanical properties (mainly toughness), degradation behavior, processibility, and crystallinity of PLA.

3.1. Stereochemical and processing manipulation

Lactide has three stereoisomers: L-lactide, D-lactide, and *meso*-lactide. The stereochemical composition of the PLA has a significant effect upon its melting point, crystallization rate, extent of crystallization, and mechanical properties [14].

Pure poly(D-lactide) or poly(L-lactide) have an equilibrium crystalline melting point of 207 °C [32,33]. However, due to small and imperfect crystallites, slight racemization, and impurities, typical PLA melting points are 170–180 °C [31]. A 1:1 mixture of pure poly(L-lactide) and poly(D-lactide) exhibited a higher melting temperature (230 °C) and better mechanical properties than either pure polymer (the ultimate tensile strength for the 1:1 stereocomplex was 50 MPa while that for pure poly(L-lactide) was 31 MPa [31,34,35]). Although stereochemical composition had a

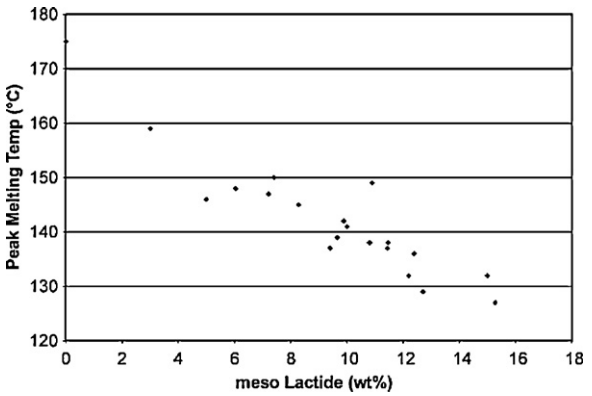


Fig. 3. Peak melting temperature as a function of *meso*-lactide content (reproduced with permission from Ref. [14]).

significant effect on melting point (Fig. 3), glass transition temperature was not as significantly affected (e.g., glass transition temperature of pure poly(L-lactide) was found to be 55–60 °C for M_v ~23–66 kDa and that of poly(D,L-lactide) was found to be 49–52 °C for M_v ~47.5–114 kDa) [36].

With respect to structure–property relationships, crystallinity is an important characteristic that affects PLA degradation rate [23] and mechanical properties [36]. Kolstad [37] observed approximately 40% increase in the crystallization half time for every 1 wt% increase in the *meso*-lactide content in poly(L-co-*meso*-lactide). He also observed that the addition of 15 wt% or more *meso*-lactide rendered the resulting polymer significantly non-crystallizable (Fig. 3). Huang et al. [38] found that poly(L-co-*meso*-lactide) spherulitic growth rates (as analyzed using the Lauritzen–Hoffman kinetic theory of crystal growth) and equilibrium melting temperature (derived using the Gibbs–Thomson and data-fitting approaches) decreased with increasing *meso* content. Reeve et al. [39] reported a similar behavior for poly(D,L-lactide), where the melting point was observed to decrease from 180 to 138 °C as the %L repeat units decreased from 100 to 92%, signifying a large decrease in crystallinity. Poly(D,L-lactide) with %L content of 15% was found to be amorphous. The stereochemical composition of poly(D,L-lactide) was also observed to affect its enzymatic degradation rate, where proteinase K preferentially degraded [L]-PLA as opposed to [D]-PLA.

Perego et al. [36] studied the effect of molecular weight and crystallinity on the mechanical properties of PLA. Poly(L-lactide) (M_v ~23–66 kDa) and poly(D,L-lactide) (M_v ~47.5–114 kDa) exhibited small changes in the tensile strength at break, which varied from 55 to 59 MPa for poly(L-lactide) and from 40 to 44 MPa for poly(D,L-lactide) in the given molecular weight range. It was also observed that the tensional and flexural moduli of elasticity, Izod impact strength, and heat resistance (the measure of polymer's resistance to distortion under a given load at elevated temperature) increased with crystallinity. Recently, Park et al. [40] found PLA's heat resistance to increase with crystallinity. Amorphous PLA films rapidly crystallized under stress (biaxial orientation) above their glass transition temperature (80 °C) [14]. Crystallinity not only affects the bulk properties but also the surface roughness. Washburn et al. [41] applied a linear temperature gradient to produce a crystallinity gradient across a PLA film and observed that MC3T3-E1 osteoblasts proliferated faster on the smoother regions than on the rougher regions. The critical rms roughness, above which a statistically significant reduction in proliferation rate occurred, was found to be approximately 1.1 nm.

Different processing methodologies have been applied to control orientation and, hence, bulk properties of polymers. These approaches influence the bulk properties without altering the PLA chemistry or introducing additives. Injection molded samples of amorphous PLA showed higher tensile strength at break and notched Izod impact strength upon drawing [42]. An injection molding process that applied an oscillating shear flow to orient the semi-solid melt improved the Charpy impact strength [42]. Bigg [43] observed a substantial increase in % elongation and tensile strength at break of PLA with different ratios of L-lactide to D,L-lactide upon biaxial orientation. For an L-lactide to D,L-lactide copolymer ratio of 80/20, % elongation at break increased from 5.7 to 18.2% and tensile strength at break increased from 51.7 to 84.1 MPa upon biaxial orientation at 85 °C.

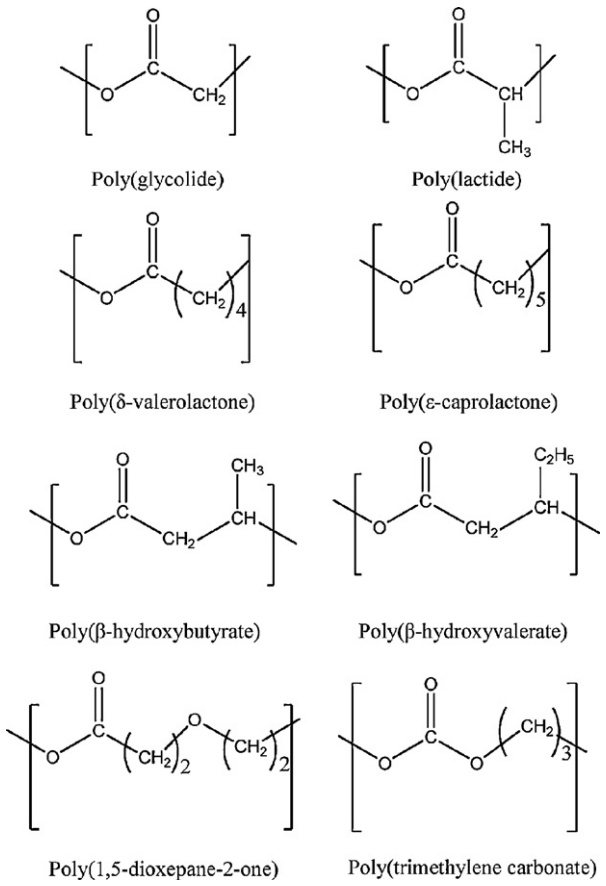


Fig. 4. Common polyester repeat units of PLA-based copolymers [30].

3.2. Copolymerization

PLA has been copolymerized with a range of polyesters (Fig. 4) and other monomers either through polycondensation of lactic acid with other monomers, producing low molecular weight copolymers, or ring opening copolymerization of lactide with cyclic monomers like glycolide, ε-caprolactone, δ-valerolactone, trimethylene carbonate, etc. as well as linear monomers like ethylene glycol [30] producing high molecular weight copolymers.

3.2.1. Polycondensation copolymerization

Acid and hydroxyl groups present in the lactic acid make it feasible to copolymerize through polycondensation. Fukuzaki et al. [44] copolymerized L-lactic acid and ε-caprolactone without any catalyst to produce low molecular weight (M_w ~6.8–8.8 kDa) copolymers for biomedical applications. These copolymers showed excellent *in vitro* (enzymatic) and *in vivo* degradation properties.

L-Lactic acid and ε-caprolactone condensation copolymerization, using stannous octoate as a catalyst, was followed by crosslinking through reaction with diisocyanate to form biodegradable thermoplastic elastomers [45]. L-Lactic acid has also been polycondensed with D,L-mandelic acid [46] and other α-hydroxy acids such as D,L-α-hydroxybutyric acid, D,L-α-hydroxyisovaleric acid, and D,L-α-hydroxyisocaproic acid [47].

A key advantage that condensation copolymerization offers is control over polymer end groups. Lactic acid has been condensation copolymerized with diols or diacids in such a way that the resulting copolymer has either hydroxyl or acid end groups and a particular molecular weight. Although polycondensation produces low molecular weight polymers (M_w < 10 kDa), this control over the end groups is a valuable tool in addition-type chemistry [48]. These low molecular weight lactic acid-based prepolymers have been further polymerized to produce higher molecular weight (M_w as high as 390 kDa) biodegradable polyesters using a chain extender molecule such as diisocyane to produce poly(ester-urethane) [49] or bis(amino-ether) to produce poly(ester-amide) [50].

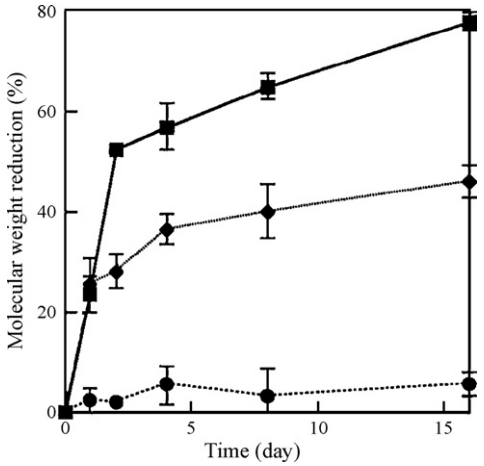


Fig. 5. Degradation behavior of the PLA graft copolymers in 1/15 M KH_2PO_4/Na_2HPO_4 (pH 7.0) at 37 °C: (●) PLA (0 wt% sugar content); (♦) graft copolymer with 1.5 wt% sugar content; (■) graft copolymer with 3.4 wt% sugar content (reproduced with permission from Ref. [68]).

3.2.2. Ring opening copolymerization (ROC)

ROC of L-lactide is a common approach for PLA copolymer synthesis, initiated with hydroxyl groups, such as alcohol or polyol [51]. The ring opening lactide copolymerization route has been used extensively due to its precise chemistry control and resulting favorable copolymer properties [30]. The polymerization mechanism can be ionic, co-ordination, or free radical depending on the type of catalyst system involved [30,52]. The transition metal compounds of tin [53,54], aluminum [55], lead [56], zinc [57], bismuth [56], iron [58], and yttrium [59] have been reported to catalyze lactide ROC.

Grijpma and Pennings [60,61] copolymerized L-lactide with D-lactide, glycolide, ε-caprolactone, and trimethylene carbonate using an ROC approach involving a stannous octoate ($Sn(Oct)_2$) catalyst. This copolymerization strategy resulted in controlled degradation, thermal, and mechanical properties. Glycolide, L-lactide, and ε-caprolactone were copolymerized using a similar ROC approach and resulting copolymers (PGLC) were found to present an amorphous structure over a wide range of compositions with a variable *in vitro* degradation rate. PGLC (10/10/80 molar ratio) was found to have the slowest degradation rate. The degradation rates of three other compositions investigated were in the order of PGLC63/27/10 > PGLC45/45/10 > PGLC27/63/10 initially, but insignificant differences were observed at later stages [62]. The amorphous structure is typically more favored in applications demanding higher toughness and degradation rate. In another example, poly(D,L-lactide)-co-poly(ε-caprolactone) elastic properties were modified by chemically crosslinking the copolymer network. The % elongation at break varied between 50 ± 10% and 350 ± 40% for the composition range investigated. The elastic network formation was confirmed by the absence of a flow region in DMA analyses, increase in the glass transition temperature in DSC, and the full recovery of the sample dimensions after tensile testing [63]. Haynes et al. [64] copolymerized lactide with another commercially available biodegradable and renewably derived thermoplastic polyester, poly(hydroxyalkanoate) (PHA). The resulting copolymer was found to have a lower complex viscosity compared to neat PLA. Also, the storage and loss modulii of this copolymer underwent less change with frequency (0.1–100 radians/s) compared to neat PLA. These researchers also copolymerized lactide with fluorinated polyether oligomers and found these fluoropolyether segments to impart ductility, optical clarity, reduced water wettability, and better melt-processibiltiy with a minimum of fluorine (<20 wt% fluropolyether) incorporation [65]. PHA has also been copolymerized with lactide using a two-step method, where in Step 1, PHA macroinitiator was synthesized and was copolymerized with lactide in Step 2. These copolymers were used as compatibilizers for PLA–PHA melt blends [66]. Ouchi and coworkers synthesized comb-type PLA by means of graft copolymerization of L-lactide onto a depsipeptide–PLA copolymer to control degradation and molding properties [67] and also PLA–polysaccharide graft copolymers to improve hydrolytic degradation behavior. The graft copolymer's hydrolytic degradation rate was dependent on the sugar content in the following order: graft copolymer with 3.4 wt% sugar content > graft copolymer with 1.8 wt% sugar content > neat PLA. The molecular weight reduction of the graft copolymer with 3.4 wt% sugar content was approximately 80%, while that with 1.5 wt% sugar content was approximately 40% and that of neat PLA was less than 10% in 15 days (in 1/15 M $KH_2PO_4/NaHPO_4$ buffer pH 7.0 at 37 °C) (Fig. 5) [68]. Since these methodologies required multiple steps, PLA was copolymerized with a metabolic intermediate DL-mevalonolactone in one step to synthesize branched PLA to control degradation and molding properties [51]. Frick et al. [69] synthesized polylactide–polyisoprene–polylactide thermoplastic elastomers with various compositions and morphologies that exhibited excellent elongation and elastomeric properties.

PLA has been copolymerized extensively with PEG due to PEG's biocompatibility and hydrophilicity. An alternating copolymer of lactic acid and ethylene oxide produced from the ring opening of the cyclic ester monomer 3-methyl-1,4-dioxan-2-one has been used to plasticize PLA [70]. Diblock and triblock PLA-PEG copolymers were also synthesized to improve hydrophilicity and drug-delivery properties of PLA. However, PLA and PEG underwent phase separation leading to poor mechanical properties of the copolymers [71,72]. To improve the compatibility between PLA and PEG components, PLA-PEG copolymers were produced by copolycondensation of PLA-diols and PEG-diacids using carbodiimide-based wet chemistry. The resultant copolymer did not phase separate and exhibited improved mechanical properties [73]. Star- and dendrimer-like PLA–PEG copolymers have also been synthesized to lower glass transition temperature, melting temperature, and crystallinity [74].

3.3. Blending

Blending is probably the most extensively used methodology to improve PLA mechanical properties. PLA has been blended with different plasticizers and polymers (biodegradable and non-biodegradable) to achieve desired mechanical properties.

3.3.1. Plasticizers

PLA is a glassy polymer that has poor elongation at break (<10%) [20]. Different biodegradable as well as non-biodegradable plasticizers have been used to lower the glass transition temperature, increase ductility, and improve processibility [75]. Typically, these aspects have been achieved by manipulating the following plasticizer properties: molecular weight, polarity, and end groups.

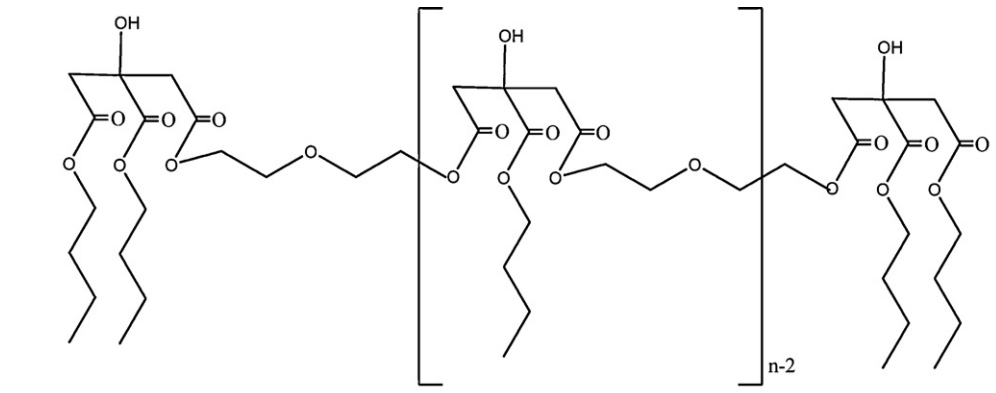
Lactide is a natural choice to plasticize PLA. Lactide-plasticized PLA showed a significant increase in elongation at break [76] but underwent stiffening with time due to low molecular weight lactide migration toward the surface [77]. Oligomeric plasticizers that would not tend to migrate toward the surface due to their relatively higher molecular weight have also been utilized. Martin and Avérous [78] used glycerol, citrate ester, PEG, PEG monolaurate, and oligomeric lactic acid to plasticize PLA and found that oligomeric lactic acid and low molecular weight PEG (M_w ~400 Da) gave the best results while glycerol was found to be the least efficient plasticizer. Citrate esters (molecular weight 276–402 Da) derived from naturally occurring citric acid were found to be miscible with PLA at all compositions. For these blends with citrate esters, elongation at break was significantly improved accompanied with considerable loss of tensile yield strength [79].

Ljungberg and Wesslén plasticized PLA using triacetine and tributyl citrate, successfully lowering T_g to ~ 10 °C at 25 wt%, after which phase separation occurred [80]. Triacetine- or tributyl-citrate-plasticized PLA films underwent crystallization, and plasticizer molecules migrated toward the surface with storage time due to their low molecular weight [81]. To overcome the aging problem, tributyl citrate oligomers (Fig. 6a) were synthesized by trans-esterification of tributyl citrate and diethylene glycol. However, these oligomeric tributyl citratre plasticizers also underwent phase separation with storage time [82]. To achieve better stability, these researchers used diethyl bishydroxymethyl malonate (DBM) and its oligomer (Fig. 6b), synthesized through an esterification reaction between DBM and dichloride. When DBM alone was used as a plasticizer, it showed a tendancy to phase separate and migrate toward the surface. DBM-oligomer-plasticized PLA demonstrated morphological stability with storage time [83]. Oligomeric polyesters and esteramides (Fig. 6c) have also been used to plasticize PLA, showing better plasticizing properties due to an increased number of polar amide groups [84].

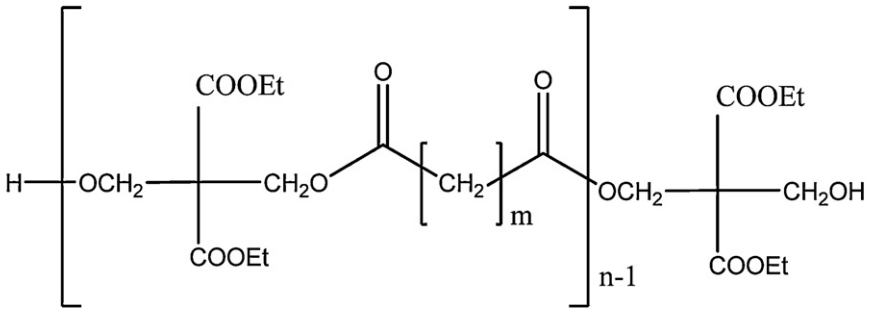
Baiardo et al. [85] used acetyl tri-*n*-butyl citrate and PEGs with different molecular weights (M_w ~ 0.4–10 kDa) to plasticize PLA. Acetyl tri-*n*-butyl citrate miscibility limit was found to be 50 wt% while PEG miscibility decreased with increasing molecular weight. These researchers also observed a significant increase in elongation at break at the expense of strength and tensile modulus. Apart from plasticizer molecular weight and polarity, the effect of plasticizer end groups might significantly affect PLA bulk properties and has been investigated. PLA was plasticized with PEGs (M_w ~0.4–0.75 kDa) having hydroxyl and ether end groups. The thermal and mechanical properties were significantly dependent on PEG composition, while the PEG end groups had very little effect [86]. Lai et al. [87] found that the PEG end groups (hydroxy and methyl) influenced the miscibility and crystallization behavior when added to PLA. These researchers did not investigate the effect of more polar end groups, such as acid and amine. Multiple plasticizers (low molecular weight triacetin [TAC] and oligomeric poly(1,3-butylene glycol adipate) [PBGA]) have also been used to plasticize PLA, significantly improving the elastic properties at the cost of tensile strength [88]. Pillin et al. [89] also reported PEG as the most efficient for T_g reduction when compared with poly(1,3-butanediol), dibutyl sebacate, and acetyl glycerol monolaurate. Poly(propylene glycol) (PPG) was recently used to plasticize PLA since it does not crystallize, has a low T_g, and is miscible with PLA. PPG successfully plasticized PLA and influenced the crystallization behavior less that PEG did [90]. High molecular weight PEG (M_n ~20 kDa)-PLA blends cast from chloroform solution (40 wt% PEG) were found to be very ductile [91]. Melt processed PLA–PEG bends (PEG M_n ~20 kDa) were found to be miscible, showed improved ductility, and reduced tensile strength for concentrations up to 50 wt% PEG. However, above 50 wt% PEG, blend crystallinity was found to increase significantly and resulted in an increased modulus and decreased ductility [92].

3.3.2. PLA–non-biodegradable polymer/filler blends and composites

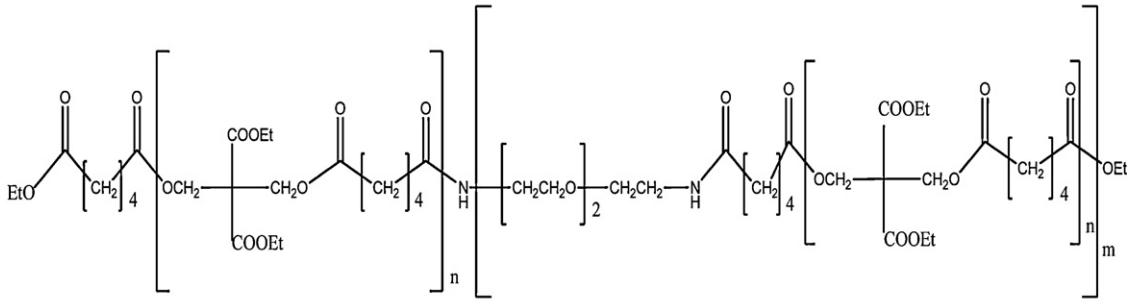
Hillmyer et al. [93,94] blended PLA with low density poly(ethylene) (LDPE) to improve the toughness. PLA crystallinity was found to significantly impact the blend toughness. Amorphous PLA blends with LDPE needed PLA–LDPE diblock copolymer compatibilization, however, semi-crystalline PLA blends with LDPE showed toughening even in the absence of the block copolymer. PLA–poly(vinyl acetate) (PVAc) blends were found to be miscible, exhib-



(a) Oligomeric tributyl citrate [82].



(b) Oligomeric diethyl bishydroxymethyl malonate (DBM) [83].



(c) Oligomeric esteramide [84].

Fig. 6. Chemical structures of oligomeric plasticizers.

ited improved tensile strength between 5 and 30 wt% PVAc, and improved elongation at break with 5 wt% PVAc [95]. Zhang et al. [96] studied crystallization and phase behavior of poly(methyl methacrylate) (PMMA)–poly(DL-lactide) blends and found that blends prepared by a solution/precipitation method were miscible while those prepared by a solution casting were partially miscible. They also found that the crystallization of poly(DL-lactide) was greatly restricted by amorphous PMMA.

Recently, DuPont has commercialized Biomax® Strong PLA additives to improve toughness without significant transparency loss. These additives are designed to have "special chemistry" for PLA, so even small amounts (1–5 wt%) provide significant toughness benefits [97]. NatureWorks LLC studied different commercial toughening agents for PLA [1]. In their work, Blendex™ 338, an acrylonitrile–butadiene–styrene terpolymer containing 70% butadiene rubber, was found to significantly improve notched Izod impact strength and elongation at break of PLA. Another additive, Pellethane™ 2102-75A (a commercial grade polyurethane from Dow Chemical Company), was also found to significantly improve these properties [1].

Another approach to improve the mechanical properties of PLA is through the incorporation of organic/inorganic fillers. For example, PLA–clay solvent cast blends exhibited improved Young's modulus [98]. PLA blends with β-$Ca(PO_3)_2$ exhibited a modulus of elasticity similar to

that of natural bone (>5 GPa) [99]. PLA has also been blended with metal oxides, such as alumina and titania, to improve mechanical properties suitable for orthopedic applications [100–103]. Carbon-fiber-reinforced PLA composites showed improved mechanical properties on nitric acid surface treatment of the fibers [104]. Additionally, PLA has been melt blended with inorganic fillers, such as $9Al_2O_3{\cdot}2B_2O_3$ and $CaCO_3$, to improve its mechanical and thermal properties [105]. PLA-nano-sized precipitated calcium carbonate (NPCC) composites showed a strain at break increase from less than 5% for neat PLA to 5.1% at 2.5 wt% NPCC content to 13% at 5 and 7.5 wt% NPCC contents. PLA-organically modified montmorillonite (MMT) clay composites showed a strain at break increase to 15.9% at 2.5 wt% MMT content. The tensile strength of PLA–NPCC composites decreased monotonically with NPCC content from 65 MPa for neat PLA to 57 MPa at 7.5 wt% NPCC content, whereas that of PLA–MMT composites increased to 67 MPa at 5 wt% MMT content and then decreased to 55 MPa at 7.5 wt% MMT content. The extent of increase in strain at break and decrease in tensile strength was not significant in that study [106].

3.3.3. PLA-biodegradable/renewable-resource polymer blends

PLA–non-biodegradable polymer/filler blends and composites are not as extensively studied as PLA–biodegradable polymer blends, probably due to the incorporation of non-biodegradable component into the blend. However, PLA blends with biodegradable polymers have been extensively investigated because they offer property improvements without compromising biodegradability. For example, PHA is a bacterially produced family of biodegradable aliphatic homo or copolyesters with more than 150 different types consisting of different monomers [107]. Poly(3-hydroxy butyrate) (PHB) and its copolymers with 3-hydroxyvalerate (PHBHV), 3-hydroxyhexanoate (PHBHHx), and 3-hydroxyoctanoate (PHBHO) units are among the most commonly used PHAs [108–110]. Metabolix and Archer Daniels Midland (ADM) Company are commercializing PHAs (under trade name Mirel) through a joint venture called Telles [111].

PHB homopolymer has a very high crystallinity resulting in a hard and brittle material, not very suitable to blend with PLA. Also, its melt temperature is high (>170 °C) and close to the thermal degradation temperature of PHB, making its processing relatively difficult. Procter & Gamble had introduced a family of PHAs under registered trademark Nodax. These PHAs primarily contained 3-hydroxy butyrate units and a small amount of 3-hydroxyalkanoate units, which served to reduce melting temperature and crystallinity of the final copolymer (see Fig. 7). Addition of a small amount (typically <20 wt%) of Nodax copolymer to PLA remarkably improved the toughness of the resultant blend without significantly affecting the optical clarity [110].

PLA/PHBHV solvent cast blends were found to be non-compatible and showed minimal elongation at break improvement [112]. Although Takagi et al. [113] found PLA/poly(3-hydroxyoctanoate) (PHO) blends to be immiscible, they exhibited enhanced impact toughness. In our laboratory, we found that the PLA phase in PLA–PHBHHx blends (90 wt% PLA) underwent rapid physical aging resulting in significant toughness loss with storage time [20]. A similar observation has been reported for PLA/starch blends, where blends lost their toughness with physical aging [114].

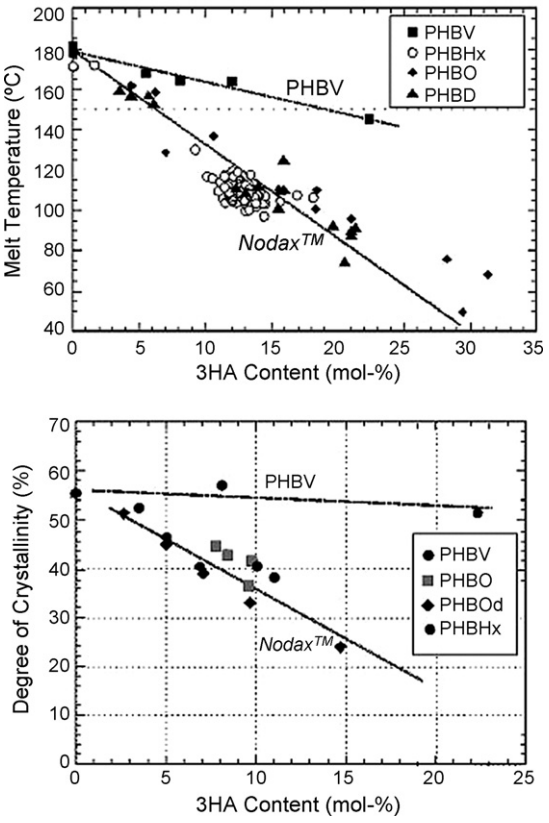


Fig. 7. The effect of 3-hydroxyalkanoate (3-HA) content on the melting temperature and crystallinity of the PHA copolymers (reproduced with permission from Ref. [110]).

PLA/PCL is another extensively studied biodegradable PLA blend system. PCL is a rubbery polymer with low T_g and degrades by hydrolytic or enzymatic pathways. Broz et al. [115] tuned modulus, strain at break, and ultimate tensile strength through the blend composition. For these binary blends, a strain at break increase occurred only above 60 wt% PCL content. However, this strain at break improvement was not significant and was accompanied with significant modulus and tensile strength loss. Addition of a small amount of surfactant (copolymer of ethylene oxide and propylene oxide) did not offer any significant strain at break improvement for PLA/PCL blends [116]. However, addition of a small amount of PLA–PCL–PLA triblock copolymer (~4 wt%) to PLA/PCL (70/30, w/w) blends improved the dispersion of PCL in PLA and enhanced the ductility of the resultant ternary blend. The dimension (as calculated from the SEM micrographs of liquid nitrogen fractured surfaces of the blend) of dispersed PCL domains decreased from 10–15 to 3–4 μm on addition of the triblock copolymer (4 wt%), resulting in an increase in elongation

at break from 2% for PLA/PCL (70/30, w/w) blend to 53% for the ternary blend [117]. PLA/PLA-PCL block copolymer blends (80 wt% PLA) exhibited better miscibility and greater elongation at break than PLA/PCL blends (80 wt% PLA). % elongation at break increased from 1.6 ± 0.2% for neat PLA to greater than 100% for PLA/PLA-PCL blends (80 wt% PLA) [21]. In order to induce better interaction between PLA and PCL components, these blends were prepared through reactive blending. Semba et al. improved the strain at break and impact strength without significantly affecting tensile modulus and tensile stress at break of PLA/PCL blends by crosslinking induced by dicumyl peroxide. % elongation at break increased from around 10% for neat PLA to around 150% for injection molded PLA/PCL (70/30, w/w) samples compatibilized with 0.2 and 0.3 phr (parts per hundred) DCP. The tensile modulus decreased from approximately 1500 MPa for neat PLA to 1250 MPa for the compatibilized blend and tensile strength reduced from 70 MPa for neat PLA to 55 MPa for the compatibilized blend [118]. Wang et al. [119] compatibilized PLA/PCL blends through a trans-esterification reaction and found that the compatibilized blends were more ductile than physical blends with faster enzymatic degradation rate. The elongation at break for PLA/PCL blend (80 wt% PLA) increased to 120% for reactive compatibilized blends from 28% for physical blends and 3% for the neat PLA.

Jiang et al. [120] blended PLA with a biodegradable thermoplastic poly(butylene adipate-co-terephthalate) (PBAT) to improve toughness and processibility of PLA. Addition of a small amount of biodegradable poly(ester amide) to PLA improved ductility and reduced melt viscosity of the resultant blend [121]. PLA/poly(tetramethylene adipate-co-terephthalate) (PTAT) solvent cast blend membranes exhibited greater elongation at break and lesser tensile strength at break compared to neat PLA. % elongation at break was 97% and tensile strength at break was 25 MPa for PLA–PBAT blend membranes (75 wt% PLA), and 285% and 11 MPa for PLA–PBAT blend membranes (25 wt% PLA). Tensile strength at break was 28 MPa and % elongation at break was 19% for neat PLA [122].

PLA has also been blended with chitosan, a naturally occurring biodegradable, biocompatible, edible, and nontoxic biopolymer, to improve wettability [123]. Suyatma et al. [124] prepared PLA/chitosan blends by solution mixing and found these blends to be non-compatible. The tensile strength increased from 52.5 ± 5.9 MPa for neat PLA to 72.7 ± 1.8 MPa for PLA/chitosan blends containing 90 wt% chitosan. The % elongation at break was not significantly improved. Recently, PLA/chitosan blend fibers have also been electrospun [125]. Although PLA/collagen blends had reduced tensile and bending strengths compared to neat PLA, they underwent faster degradation under enzymatic conditions. The weight decreased to half the original weight of a PLA/collagen blend (30 wt% collagen) after 5 weeks, but neat PLA and PLA/collagen blends (10 wt% collagen) did so after 8 and 6 weeks, respectively [126]. PLA/starch blends have also exhibited a similar behavior [127,128]. Ke and Sun [129] studied melting behavior and crystallization kinetics of PLA/starch blends. The starch was observed to effectively increase the crystallization rate, even at a concentration of 1%. PLA/dextran blend scaffolds were found to be more hydrophilic and biocompatible compared to neat PLA but had lower tensile strength (13 MPa for the blend compared to 39 MPa for neat PLA) [130]. PLA has also been blended with other biodegradable polymers like poly(*para*-dioxanone) [131], poly(propylene carbonate) [132], poly(butylene succinate), and derivatives [133,134] to improve mechanical properties, especially toughness.

The loss of toughness with physical aging still remains a challenge for PLA-based blends. PLA bulk modifications that offer durable toughness and processibility improvements without significantly affecting biodegradability and transparency are critical.

4. Surface modification of PLA

PLA surface interactions with other materials play an important role in numerous consumer and biomedical applications. Special surface chemical functionalities, hydrophilicity, roughness, and topography are often required and need to be controlled. A variety of synthetic polymers, natural polymers, and biomacromolecules have been used to tailor these properties on PLA substrates through a variety of techniques.

Surface-modification methods can be classified as non-permanent (non-covalent attachment of functional groups) or permanent (covalent attachment). While, undoubtedly, there has been work done to surface modify PLA for commodity applications (e.g., packaging films), there is a scarcity of data in the literature related to such things as friction modification, adhesion, and anti-fogging. However, there is abundant research reported in the literature, a surface modification for biomedical applications, so this portion of the review will focus on those investigations with the notion that some of the approaches could also be suitable for other applications.

4.1. Non-permanent surface-modification methods

4.1.1. Coating

Surface coating involves the deposition/adsorption of the modifying species onto the polymer surface. Typically, PLA has been coated with biomimetic apatite [135]; extra cellular matrix (ECM) proteins like fibronectin, collagen, vitronectin, thrombospondin, tenascin, laminin, and entactin [71,136]; RGD peptides [137]; and PLA–PEG block copolymers [138,139] to control PLA–cell interactions.

Chen et al. [135] produced PLA scaffolds coated with bonelike apatite or apatite/collagen composites. Saos-2 osteoblast-like cell compatibility of these scaffolds was greatly enhanced with these coatings. Atthof and Hilborn [136] studied the collagen adsorption onto PLA discs. The adsorbed protein layer became structured showing clear fibrous networks on PLA. It was also demonstrated that the protein adsorption increased 3T3 mouse fibroblast cell attachment to the PLA surface. Quirk et al. [140] used poly(L-lysine)-RGD coatings to improve the spreading of bovine aortic endothelial cells on PLA. It was also demonstrated that the control over cell-spreading inhibition could be achieved by altering the ratio of poly(L-lysine)/RGD components. Kubies et al.

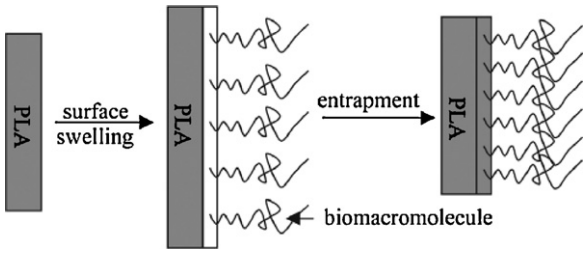


Fig. 8. Schematic diagram of the entrapment process (reproduced with permission from Ref. [145]).

[138] deposited Langmuir–Blodgett films of several AB and ABA type block copolymers on PLA film surfaces to improve hydrophilicity (where A = PLA and B = PEO, α-methoxy-ω-hydroxy PEO, α-carboxy-ω-hydroxy PEO, or poly(L-aspartic acid)). This study showed that the phase separation between the hydrophilic and hydrophobic domains was more favorable in the case of AB copolymers than ABA copolymers, resulting in more hydrophilic surfaces. Spatially selective adsorption of proteins and cells on PLA scaffolds is important with respect to biomedical applications such as medical implants [141], biosensors [142], and bioassays [143]. Lin et al. microcontact printed poly(oligoethyleneglycol methacrylate) (poly-OEGMA) on PLA film to create micron-size protein- or cell-resistant areas. Proteins or cells adsorbed only on the unprinted regions [144].

Although coating is a simple and convenient surface-modification protocol, passive adsorption could induce competitive adsorption of other materials in the system and change the configuration of adsorbed species [71].

4.1.2. Entrapment

Biomacromolecules such as alginate [145], chitosan [145], gelatin [145], poly(L-lysine) (PLL) [146], PEG [146–148], and poly(aspartic acid) [149] have been entrapped during the reversible swelling of the PLA surface region upon exposure to a solvent/non-solvent mixture. This methodology incorporates molecules that do not adsorb onto PLA and does not require reactive side-chain groups. It requires a miscible mixture of a solvent and non-solvent for PLA, with the surface-modifying molecules being soluble in the mixture and the non-solvent [146]. Zhu et al. [145] have entrapped alginate, chitosan, and gelatin into PLA sub-surface regions. As shown schematically in Fig. 8, PLA exposure to a solvent/non-solvent mixture results in a rapid polymer gelation at the surface allowing biomacromolecules to diffuse into the swollen PLA. This swelling was reversed upon exposure to a non-solvent. Results showed that the depth of penetration of surface-modifying molecules was 10–20 μm and the hydrophilicity of the modified PLA films was greatly improved. The water contact angle (sessile drop method) decreased from 88° for neat PLA to 49°, 40°, and 55° for PLA films modified with alginate, chitosan, and gelatin, respectively. Quirk et al. have demonstrated the entrapment of PEG and PLL [146] and studied the cell interactions with surface-modified PLA [147]. The authors successfully controlled the species entrapment by varying the solvent/non-solvent ratio, treatment time, and/or concentration of the surface-modifying molecules [146]. Also, these researchers successfully demonstrated the performance of PEG-entrapped PLA in a cell/serum environment to repel proteins or cells [147]. Cai et al. [149] modified PLA surfaces by entrapping poly(aspartic acid) (PASP) in order to enhance their cell affinity. Rat osteoblasts were seeded onto the modified surfaces to examine their effects on cell adhesion and proliferation. The findings showed that PASP-modified PLA surfaces may enhance the cell-surface interactions.

The solvent/non-solvent mixtures used in these entrapment protocols consisted of acetone or 2,2,2-trifluroethanol as a solvent for PLA. Typically, most of the good solvents for PLA are not biocompatible. These studies have not reported on the amounts of the residual solvent in surface-modified films. We have recently reported that PLA films solvent cast from chloroform solution retained approximately 13 wt% chloroform [150]. From a biocompatibility standpoint, surface-modification protocols should involve more benign solvents or removal of non-biocomptible solvents from the film bulk without affecting surface properties.

4.1.3. Migratory additives

Migratory additives, carrying specific functional groups, are blended with PLA as a way to tailor PLA surface properties. Irvine et al. [151] investigated surface segregation creating nanoscale ligand clusters of poly(methyl methacrylate-*r*-polyoxyethylene methacrylate) (p(MMA-*r*-POEM)) comb polymers modified with Arg-Gly-Asp (RGD) peptide ligands by blending these comb polymers with PLA. It was observed that the molecular weight, number of ligands per modified comb, and the ratio of ligand-bearing to unmodified combs in the blend influenced the cluster size and density. The surface of these PLA-based films showed an increase in fibroblast attachment with an increased surface density of the RGD-modified combs. Kiss et al. [152] blended PLA with poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (Pluronic) at concentrations of 1, 2, 3.85, 6.5, and 9.1% (w/w) with the aim to improve the biocompatibility and wettability of the resultant film surface. The water contact angle decreased with increasing amounts of Pluronic. X-ray photoelectron spectroscopy (XPS) analyses revealed the considerable accumulation of Pluronic in the surface layer of the blend films. Yu et al. [153] blended poly(D,L-lactic acid)-block-poly(ethylene glycol) (PLE) copolymer and RGD derivatives with PLA to engineer the surface properties of the resultant blend to promote chondrocyte attachment and growth. The blends prepared by this methodology showed enhanced hydrophilicity compared to neat PLA. The water contact angle decreased from 76° for neat PLA to 50° for PLA/PLE blends (75 wt% PLA). The chondrocyte cultures showed significant improvement of chondrocyte attachment and viability on the PLA films modified with PLE and RGD derivatives.

4.1.4. Plasma treatment

The term "plasma" refers to a mixture of positive ions and electrons produced by ionization [154]. Plasma surface treatment of polymers began in the 1960s [155] and, within the last decade, has been applied to improve PLA surface hydrophilicity and cell affinity. Hirotsu et al. [156] treated melt extruded PLA sheets with oxygen, helium, and nitrogen plasmas to improve the wettability. They observed that the plasma treatment did not affect PLA biodegradation rate in soil. Yang et al. [157] used anhydrous ammonia (NH_3) plasma treatment to improve hydrophilicity and cell (human skin fibroblast) affinity of complex shapes like porous PLA scaffolds prepared using a particulate leaching technique. The NH_3 plasma created reactive amine groups on PLA scaffolds that anchored collagen through polar and hydrogen bonding interactions. These surface-modified scaffolds showed enhanced cell adhesion [158]. O_2 plasma treatment has been used to improve wettability and nerve cell adhesion of PLA films [159].

Although plasma treatment has been successfully used to improve PLA wettability and cell affinity, the main disadvantage of this technique is that the effectiveness of the surface modification is partially lost due to surface rearrangement [160]. The surface-modifying species rearrange by thermally activated macromolecular motions to minimize the interfacial energy, making the effect of plasma treatment non-permanent [157,160–162]. Yang et al. [157] found that the modifying effects could be maintained by preserving samples at a low temperature (0–4 °C). The mobility of surface molecular chains was significantly decreased at temperatures much less than the T_g of PLA (55 °C). Since this temperature range (0–4 °C) is much lower than physiological as well as room temperature, this stabilization approach might not be practical. Apart from the rearrangement tendency of the modifying species introduced using plasma treatment, the treatment can also affect degradation of PLA. The NH_3 plasma-modification depth increased with treatment time, while the plasma power (20–80 W) influenced the depth only slightly. It was observed that the PLA degradation increased with an increase of plasma power and treatment time [163]. Although plasma treatment has been used to improve wettability and cell affinity of PLA, the issues related to non-permanent surface modification potentially make it unsuitable for certain biomedical and consumer applications.

4.2. Permanent surface-modification methods

4.2.1. Chemical conjugation using wet chemistry

PLA dissolves in many common organic solvents such as benzene, chloroform, dichloromethane, dioxane, ethyl acetate, toluene, trichloromethane, and *p*-xylene, but it does not dissolve in water, alcohols, and unsubstituted hydrocarbons. Racemic poly(D,L-lactic acid) dissolves in acetone, dimethylformamide, and tetrahydrofuran [30]. Additionally, PLA does not have any reactive side-chain groups. Both of these features present a challenge in PLA surface modification using environmentally benign solvents. Alkaline surface hydrolysis is a simple way to create reactive functional groups, e.g., carboxylic acids (–COOH) and hydroxyls (–OH), on PLA [71]. The resulting carboxylic acid groups on PLA can readily be conjugated with surface-modifying species containing amine ($-NH_2$) or hydroxyl (–OH) groups. Typically acid groups are first activated with phosphorous pentachloride (PCl_5) [164], thionyl chloride ($SOCl_2$) [165], or water soluble carbodiimides [166] and subsequently conjugated with amines or hydroxyls (Fig. 9).

Chitosan was covalently attached to PLA surfaces through alkaline surface hydrolysis (generating acid groups) followed by acid-chitosan conjugation. Rat osteoblast attachment and proliferation were significantly improved as a result of this treatment [167]. Yang et al. [168] hydrolyzed PLA surfaces by treating with a mixture of 0.25 M NaOH/ethanol for improving its hydrophilicity and cell affinity. The low concentration of alkali solution was applied to avoid any significant bulk degradation. Ethanol was found to assist the hydroxide nucleophilic attack on PLA's ester bonds.

Aminolysis is another way to introduce reactive amine groups onto PLA surfaces. 1,6-Hexanediamine has been used for aminolysis followed by conjugation with biocompatible macromolecules like gelatin, chitosan, or collagen [169]. The aminolysis reaction was performed by immersing PLA in hexanediamine–propanol solution (0.06 g/mL) at 50 °C (below PLA's T_g) for 8 min. PLA surface hydrophilicity (as measured using a sessile drop method) decreased slightly after aminolysis and further after biomacromolecule immobilization. Aminolysis and the incorporation of biocompatible macromolecules on the PLA surface were observed to have a positive effect in accelerating endothelium regeneration *in vitro*. Janorkar et al. [170] introduced amine groups on the PLA film surface by photoinduced grafting of 4,4′-diaminobenzophenone followed by wet chemistry to create branched architectures containing amine functionalities on the periphery of the grafted layers. The grafted branched architectures were created by subsequent carbodiimide mediated reactions with succinic acid and tris(2-aminoethyl) amine. MC3T3 fibroblast attachment and viability improved with the grafting of amine terminated branched architectures.

4.2.2. Photografting

Photografting has been used extensively to tailor PLA surface properties primarily due to the advantages it offers: low cost of operation, mild reaction conditions, selectivity of UV light, and permanent alteration of surface chemistry [171]. This approach relies on PLA photoactivation to create reactive groups associated with or followed by grafting of selected functionalities. Since PLA does not have any reactive side-chain groups, this approach is useful for PLA surface modification. Typically, these methods are classified as "grafting to" or "grafting from" approaches. Polymer chains of known molecular weight, composition, and architecture are covalently attached to the surface in a "grafting to" approach, which is very convenient for preliminary studies [172]. However, it is difficult to achieve high grafting densities with a "grafting to" approach because of steric hindrance and diffusion limitations [173]. The "grafting from" approach, which involves growing polymer chains from the surface, overcomes the limitations of the "grafting to" approach. In "grafting from", photoinitiators are

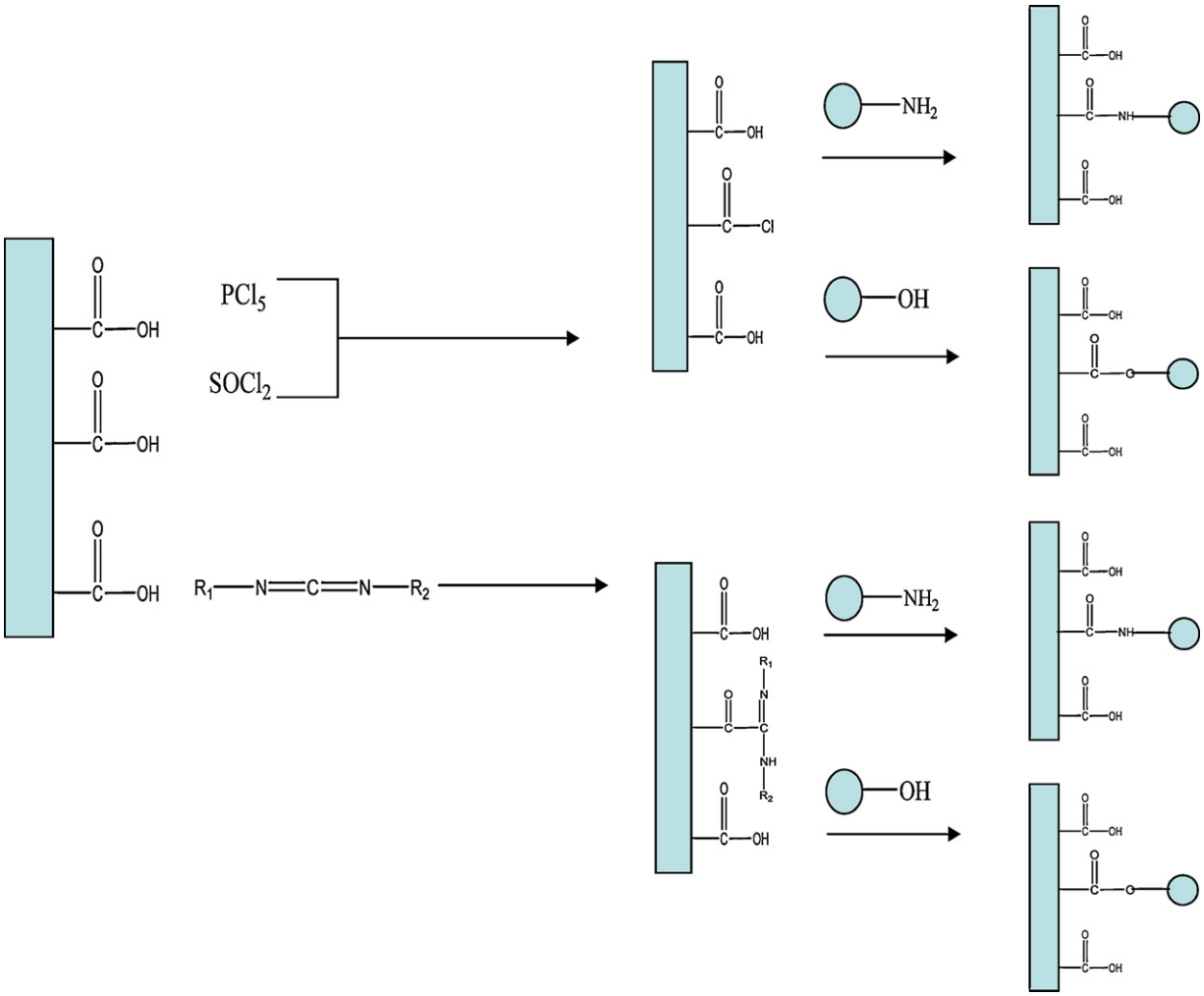


Fig. 9. Generalized reaction scheme for carboxylic acid activation using PCl_5, $SOCl_2$, or water soluble carbodiimides followed by chemical conjugation with amine ($-NH_2$) or hydroxyl (–OH) functionalities.

immobilized onto the substrate to initiate subsequent polymerization of vinyl or acrylic monomers from the surface. Photografting reactions have been carried out either in liquid or vapor phases.

4.2.2.1. Liquid phase photografting. Zhu et al. [174] used a "grafting to" approach to immobilize chitosan chains onto PLA film surfaces using a hetero-bifunctional crosslinking reagent, 4-azidobenzoic acid. The 4-azidobenzoic acid was bonded to chitosan by reaction between the acid group of the crosslinking reagent and a free amine group of chitosan. When the modified chitosan was solvent cast on the PLA film surface and exposed to UV irradiation, the free azide groups of 4-azidobenzoic acid underwent an insertion reaction with the underlying PLA creating a grafted chitosan layer.

The "grafting from" approach has been used more extensively than the "grafting to" approach for PLA surface modification. Typically, either plasma treatment or photoinitiator is used to activate the PLA surface followed by photopolymerization of vinyl or acrylic monomers from the surface. Argon-plasma-activated PLA films were immersed in aqueous acrylic acid solution and exposed to UV to produce chains of poly(acrylic acid) [175]. This was followed by conjugation of acids with amine groups of proteins using water soluble carbodiimide chemistry. They reported immobilized proteins in amounts of micrograms per square centimeter. Ma et al. [176] used a liquid phase, two-step "grafting from" approach to introduce hydrophilic groups like hydroxyls (–OH), carboxyls (–COOH) or amides ($-CONH_2$) onto PLA to study the effect of PLA surface functional groups on chondrocyte cell cultures. Briefly, the PLA substrate was activated by immersing it in hydrogen peroxide solution followed by exposure to UV irradiation at 50 °C for 40 min in Step 1. The photo-oxidized PLA substrate was subsequently immersed in monomer solution and exposed to UV light for another 60 min at 50 °C. This protocol improved the hydrophilicity (sessile drop method) from 82° for unmodified PLA to 65° for polyacrylamide (PAAm) grafted PLA and 51° for poly(methacrylic acid) (PMAA) and poly(hydroxyethyl methacrylate) (PHEMA) grafted PLA surfaces. It was also observed that surfaces

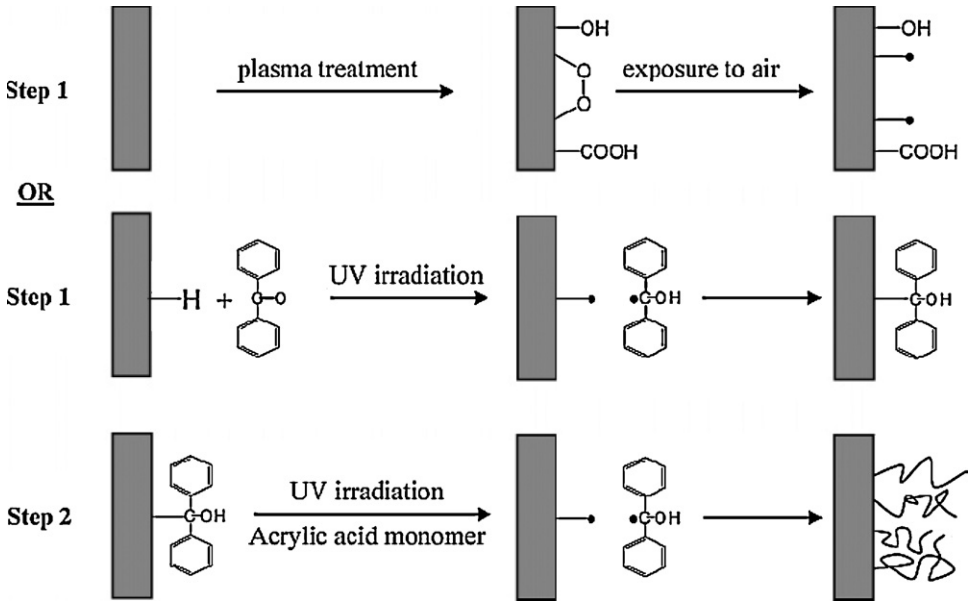


Fig. 10. Reaction scheme for the photoinduced graft polymerization of acrylic acid onto a polymer film surface (adapted from Ref. [171]).

containing hydroxyl and amide groups had better cytocompatibility, while surfaces containing acid groups did not. We have used an analogous sequential, two-step photografting method using benzophenone as a photoinitiator to graft several hydrophilic and reactive polymers from PLA film surfaces to control wettability [23,150,166,177,178]. Benzophenone abstracts hydrogen (preferentially tertiary hydrogen atoms) from the PLA to generate surface radicals and semipinacol radicals, which combine to form surface initiators in the absence of monomers. These surface initiators remain photo-labile under the UV irradiation. Subsequently, when the monomer solution is added onto the activated surface, polymerization is initiated from the surface [171]. Janorkar et al. [23] successfully created bioactive PLA surfaces using this approach (Fig. 10). The PLA film grafted with poly(acrylic acid) (PAA) and poly(acrylamide) (PAAm) exhibited improved wettability. Another positive outcome of this research was that PLA films grafted with PAA underwent faster *in vitro* degradation, which was attributed to PAA chains migrating into the film bulk. For the given grafting conditions, the "optimum grafting time" (step 2) was shorter when films were activated using benzophenone (photoactivation) than using plasma treatment. Janorkar et al. [177] have also used single-monomer and mixed-monomer systems of AA, AAm, and vinyl acetate (VAc) to produce surface-confined homopolymers and copolymers to yield a spectrum of hydrophilicities, ranging from 82° for unmodified PLA to 12° for PLA grafted with PAAm.

Recently, we have used a similar two-step photografting protocol to polymerize PAA and PAAm from PLA film surfaces using water as the reaction solvent [150]. Although the reaction solvent (water vs. ethanol) did not have significant effect on surface properties, bulk properties were significantly affected. We have conducted photografting experiments in ethanol and water, and found that films lost their toughness after surface modification, the extent of loss being more prominent when ethanol was used as the reaction solvent (toughness, as reflected by the area under an engineering stress vs. strain curve, reduced from 70 ± 15 MPa for neat solvent cast PLA to less than 10 MPa for surface-modified PLA films). This toughness loss was attributed to the PLA crystallization and loss of residual chloroform on surface modification (the PLA film specimens were cast from a chloroform solution). Also, there was significant monomer and/or homopolymer penetration into the bulk when ethanol was used as the reaction solvent.

4.2.2.2. Vapor phase photografting. In order to avoid detrimental solvent effects on PLA, Edlund et al. [179] used a single-step vapor phase photografting route to covalently attach poly(acrylamide), poly(maleic anhydride), and poly(*N*-vinylpyrrolidone) to PLA-film surfaces. PLA film was exposed to the vapor phase mixture of monomer and benzophenone (photoinitiator) under UV irradiation at 50 °C. These reactions were carried out below PLA's glass transition temperature to avoid any significant bulk changes. The extent of grafting and wettability increased with UV irradiation time. The static water contact angle values of PLA changed from 80° to 50° for poly(maleic anhydride) grafting, to 35° for poly(acrylamide) grafting, and to 25° for poly(*N*-vinylpyrrolidone) grafting for 30 min. Källrot et al. [180] observed that PLA films grafted with poly(N-vinylpyrrolidone) using the single-step vapor phase photografting protocol provided a good substrate for normal human cells of two types, keratinocytes and skin fibroblasts, to adhere and proliferate.

One of the major drawbacks of PLA is its slow degradation rate, which is considered to be a disadvantage in many applications [181]. Källrot et al. [182] attempted to tune the *in vitro* PLA degradation rate using the single-step vapor

phase covalent grafting of one of the following hydrophilic monomers: acrylamide, *N*-vinyl pyrrolidone, or acrylic acid. The films were degraded *in vitro* in 0.1 M phosphate buffered saline solution at pH 7.4 and 37 °C. It was observed that the grafted surface layers remained attached to the PLA surface upon incubation. The degradation rate was faster for the poly(acrylamide) grafted PLA films during the initial degradation (approximately less than 40 days degradation time), poly(*N*-vinyl pyrrolidone) grafted and neat PLA films had a similar degradation rate. The researchers could not investigate the degradation of poly(acrylic acid) grafted PLA films using size-exclusion chromatography (SEC) because of their insolubility in the commonly used SEC solvents ($CHCl_3$, THF, DMF, and H_2O). The polydispersity index (PDI) of the unmodified PLA increased almost linearly with degradation time. The poly(acrylamide) and poly(*N*-vinyl pyrrolidone) grafted PLA films showed an increase in PDI with a maximum at 119 days of degradation followed by a PDI decrease. This observation was attributed to the greater wettability of grafted PLA films leading to a greater extent of water uptake compared to unmodified PLA. The authors speculated that this may have been the result of degradation of longer chains to shorter chains at the end of degradation and/or the shortest chains may have been lost to a greater extent by erosion in the case of the grafted samples.

A similar single-step vapor phase photografting strategy followed by wet chemistry has been used to immobilize osteoinductive growth factor to PLA to create a bone-graft material. A single-step vapor phase protocol was used to graft PAAm to PLA film surfaces. Amide groups were further reduced to amine groups using $LiAlH_4$ chemistry. The amine groups were conjugated with heparin via a Schiff base formation. The recombinant human bone morphogenetic protein 2 (rhBMP-2) has a high affinity towards heparin, resulting in ionic bonding. The rhBMP-2 immobilized PLA provided a more biocompatible surface for mesenchymal stem cells (MSC) to grow and proliferate compared to unmodified PLA [183].

5. Summary

PLA is being used or is a potential candidate for consumer and biomedical applications. With increasing environmental and sustainability concerns associated with conventional petrochemical-based polymers, PLA applications will continue to increase. Modifying PLA bulk and surface properties has become crucial to increase its applicability. Surface and bulk modifications of PLA for consumer as well as biomedical applications have been reviewed in this article.

The primary aim of most of the bulk-modification strategies has been to make PLA tougher, but PLA toughening is often associated with tensile strength and/or modulus loss. The major challenge for future toughening strategies would be to achieve durable toughening without compromising tensile strength, modulus, and degradability. Moreover, toughened PLA showed a tendency to lose toughness with physical aging.

Many surface-modification strategies discussed in this review have been designed to tune PLA surface properties in accordance with biomedical application demands. Reactive groups such as –COOH, –OH, and $–NH_2$ as well as non-reactive groups such as –C–O–C– are typically introduced onto PLA using permanent or non-permanent surface-modification strategies. Although many surface-modification strategies achieved controlled wettability, degradation rate, and functionality, there is still an unfulfilled need to have minimal negative impact of these surface modifications on PLA bulk properties. For example, monomer migration into the film bulk is often observed when UV-induced photografting is used for PLA surface modification for an extended period of time (~2–3 h). To minimize such monomer migration, the grafting times should be significantly reduced (on the order of a few minutes). This could be achieved by using a high-power UV lamp for the photografting process. However, care should be taken, such as the use of a Pyrex container, to minimize PLA degradation under such high-power UV irradiation. In addition to minimizing the monomer migration into the film bulk, a faster photografting holds promise for the surface-modification process to be viable on a commercially relevant time scale.

Most of the surface- and bulk-modification strategies developed to date have been designed to modify a given property, and the impact of the modification methodology on other crucial properties has often been neglected. A better balance of PLA surface and bulk properties is needed. Surface- and bulk-modifications have often been carried out separately. This is more time consuming and solvents and reagents involved in these multiple steps tend to significantly affect PLA bulk properties. Ideally, with respect to the better balance of properties and shorter modification times, one step approaches that can give a better control of the final surface and bulk properties need to be developed.

Finally, the efficacy of bulk- and surface-modification approaches on 3-dimensional (3D) scaffolds of commonly used thermoplastic polyesters, such as PGA, PLGA, poly(hydroxy alkanoates) (PHA), and blends of PLA/PHA, remains a fruitful area of research. Therefore, the modification approaches discussed in this review should be transformed to PLA nanoparticles and 3D microporous scaffolds. The development of "PLA-nanocomposites" is another emerging area that relies on nanoparticles of different sizes, shapes, and materials used to tune PLA properties. Nanoparticles can be used to improve PLA bulk properties (e.g., modulus and barrier properties) and processing (extrudability and mixing properties). With the success of nanoparticles with conventional petrochemical-based plastics, it would not be surprising to see extensive future work on PLA-nanocomposites. Another interesting field that needs more work is PLA shape memory properties (the ability of a material to change shape according to the applied stimulus). Since PLA is an implantable biomaterial, better control over PLA shape memory properties is important for the development of minimally invasive surgeries.

Acknowledgements

The Engineering Research Centers Program of the National Science Foundation under NSF Award Number EEC-9731680 supported this research. Any opinions, find-

ings, conclusions, or recommendations expressed in this material are those of the authors and do not necessarily reflect those of the National Science Foundation.

References

[1] Anderson KS, Schreck KM, Hillmyer MA. Toughening polylactide. Polym Rev 2008;48:85–108.
[2] Eling B, Gogolewski S, Pennings AJ. Biodegadable materials of poly(L-lactic acid). 1. Melt-spun and solution spun fibers. Polymer 1982;23:1587–93.
[3] Schmack G, Tändler B, Vogel R, Beyreuther R, Jacobsen S, Fritz H-G. Biodegradable fibers of poly(L-lactide) produced by high-speed melt spinning and spin drawing. J Appl Polym Sci 1999;73:2785–97.
[4] Rasal RM, Hirt DE. Micropatterning of covalently attached biotin on poly(lactic acid) film surfaces. Macromol Biosci 2009;9:989–96.
[5] Ray SS, Okamoto M. Biodegradable polylactide and its nanocomposites: opening a new dimension for plastics and composites. Macromol Rapid Commun 2003;24:815–40.
[6] Zhang Z, Feng SS. The drug encapsulation efficiency, in vitro drug release, cellular uptake and cytotoxicity of paclitaxel-loaded poly(lactide)-tocopheryl polyethylene glycol succinate nanoparticles. Biomaterials 2006;27:4025–33.
[7] Gottschalk C, Frey H. Hyperbranched polylactide copolymers. Macromolecules 2006;39:1719–23.
[8] Zhu KJ, Xiangzhou L, Shilin Y. Preparation, characterization, and properties of polylactide (PLA)–poly(ethylene glycol) (PEG) copolymers: a potential drug carrier. J Appl Polym Sci 1990;39:1–9.
[9] Schugens C, Grandfils C, Jerome R, Teyssie P, Delree P, Martin D, et al. Preparation of a macroporous biodegradable polylactide implant for neuronal transplantation. J Biomed Mater Res 1995;29:1349–62.
[10] Okada M. Chemical syntheses of biodegradable polymers. Prog Polym Sci 2002;27:87–133.
[11] Linnemann B, Sri Harwoko M, Gries T. Polylactide fibers (PLA). Chem Fibers Int 2003;53:426–33.
[12] Gupta B, Revagade N, Hilborn J. Poly(lactic acid) fiber: an overview. Prog Polym Sci 2007;32:455–82.
[13] Sawyer DJ. Bioprocessing—no longer a field of dreams. Macromol Symp 2003;201:271–81.
[14] Drumright RE, Gruber PR, Henton DE. Polylactic acid technology. Adv Mater 2000;12:1841–6.
[15] Dorgan JR, Lehermeier HJ, Palade LI, Cicero J. Polylactides: properties and prospects of an environmentally benign plastic from renewable resources. Macromol Symp 2001;175:55–66.
[16] Athanasiou KA, Niederauer GG, Agrawal CM. Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers. Biomaterials 1996;17:93–102.
[17] Kimura Y, Shirotani K, Yamane H, Kitao T. Ring-opening polymerization of 3(S)-[(Benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione: a new route to a poly(a-hydroxy acid) with pendant carboxyl groups. Macromolecules 1988;21:3338–40.
[18] Auras R, Harte B, Selke S. An overview of polylactides as packaging materials. Macromol Biosci 2004;4:835–64.
[19] Vink ETH, Rábago KR, Glassner DA, Gruber PR. Application of life cycle assessment to NatureWorks™ polylactide (PLA) production. Polym Degrad Stab 2003;80:403–19.
[20] Rasal RM, Hirt DE. Toughness decrease of PLA–PHBHHx blend films upon surface-confined photopolymerization. J Biomed Mater Res Part A 2008;88A:1079–86.
[21] Hiljanen-Vainio M, Varpomaa P, Seppälä J, Törmälä P. Modification of poly(L-lactides) by blending: mechanical and hydrolytic behavior. Macromol Chem Phys 1996;197:1503–23.
[22] Grijpma DW, Nijenhuis AJ, Van Wijk PGT, Pennings AJ. High impact strength as-polymerized PLLA. Polym Bull 1992;29:571–8.
[23] Janorkar AV, Metters AT, Hirt DE. Modification of poly(lactic acid) films: enhanced wettability from surface-confined photografting and increased degradation rate due to an artifact of the photografting process. Macromolecules 2004;37:9151–9.
[24] Tokiwa Y, Calabia BP. Biodegradability and biodegradation of poly(lactide). Appl Microbiol Biotechnol 2006;72:244–51.
[25] Bergsma JE, De Bruijn WC, Rozema FR, Bos RRM, Boering G. Late degradation tissue response to poly(L-lactide) bone plates and screws. Biomaterials 1995;16:25–31.
[26] Incardona SD, Fambri L, Migliaresi C. Poly-L-lactic acid braided fibers produced by melt spinning: characterization and in vitro degradation. J Mater Sci Mater Med 1996;7:387–91.
[27] Ratner BD. Surface modification of polymers: chemical, biological and surface analytical challenges. Biosens Bioelectron 1995;10:797–804.
[28] Burg KJL, Holder Jr WD, Culberson CR, Beiler RJ, Greene KG, Loebsack AB, et al. Parameters affecting cellular adhesion to polylactide films. J Biomater Sci Polym Ed 1999;10:147–61.
[29] Dorgan JR, Lehermerier H, Mang M. Thermal and rheological properties of commercial-grade poly(lactic acid)s. J Polym Environ 2000;8:1–9.
[30] Södergård A, Stolt M. Properties of lactic acid based polymers and their correlation with composition. Prog Polym Sci 2002;27:1123–63.
[31] Garlotta D. A literature review of poly(lactic acid). J Polym Environ 2001;9:63–84.
[32] Gilding DK, Reed AM. Biodegradable polymers for use in surgery polyglycolic/poly(actic acid) homo- and copolymers. 1. Polymer 1979;20:1459–64.
[33] Kricheldorf HR, Kreiser-Saunders I, Boettcher C. Polylactones. 31. Sn(II)octoate-initiated polymerization of L-lactide: a mechanistic study. Polymer 1995;36:1253–9.
[34] Ikada Y, Jamshidi H, Tsuji H, Hyon SH. Stereocomplex formation between enantiomeric poly(lactides). Macromolecules 1987;20:904–6.
[35] Tsuji H, Horii F, Hyon SH, Ikada Y. Stereocomplex formation between enantiomeric poly(lactic acid)s. 2. Stereocomplex formation in concentrated solutions. Macromolecules 1991;24:2719–24.
[36] Perego G, Cella GD, Bastioli C. Effect of molecular weight and crystallinity on poly(lactic acid) mechanical properties. J Appl Polym Sci 1996;59:37–43.
[37] Kolstad JJ. Crystallization kinetics of poly(L-lactide-co-meso-lactide). J Appl Polym Sci 1996;62:1079–91.
[38] Huang J, Lisowski MS, Runt JP, Hall ES, Kean RT, Buehler N, et al. Crystallization and microstructure of poly(L-lactide-co-meso-lactide) copolymers. Macromolecules 1998;31:2593–9.
[39] Reeve MS, McCarthy SP, Downey MJ, Gross RA. Polylactide stereochemistry: effect on enzymatic degradability. Macromolecules 1994;27:825–31.
[40] Park SD, Todo M, Arakawa K, Koganemaru M. Effect of crystallinity and loading-rate on mode I fracture behavior of poly(lactic acid). Polymer 2006;47:1357–63.
[41] Washburn NR, Yamada KM, Simon Jr CG, Kennedy SB, Amis EJ. High-throughput investigation of osteoblast response to polymer crystallinity: influence of nanometer scale roughness on proliferation. Biomaterials 2004;25:1215–24.
[42] Grijpma DW, Altpeter H, Bevis MJ, Feijen J. Improvement of the mechanical properties of poly(D,L-lactide) by orientation. Polym Int 2002;51:845–51.
[43] Bigg DM. Polylactide copolymers: effect of copolymer ratio and end capping on their properties. Adv Polym Technol 2005;24:69–82.
[44] Fukuzaki H, Yoshidat M, Asano M, Kumakura M, Mashimo T, Yuasa H, et al. Synthesis of low-molecular-weight copoly(L-lactic acid/e-caprolactone) by direct copolycondensation in the absence of catalysts, and enzymatic degradation of the polymers. Polymer 1990;31:2006–14.
[45] Kylmä J, Seppälä JV. Synthesis and characterization of a biodegradable thermoplastic poly(ester-urethane) elastomer. Macromolecules 1997;30:2876–82.
[46] Fukuzaki H, Aiba Y. Synthesis of biodegradable poly(L-lactic acid-co-D,L-mandelic acid) with relatively low molecular weight. Macromol Chem 1989;190:2407–15.
[47] Fukuzaki H, Aiba Y, Yoshida M, Asano M, Kumakura M. Low-molecular-weight copolymers composed of L-lactic acid and various m-hydroxy acids as biodegradable carriers. Macromol Chem 1989;190:2571–7.
[48] Hiltunen K, Härkönen M, Seppälä JV, Väänänen T. Synthesis and characterization of lactic acid based telechelic prepolymers. Macromolecules 1996;29:8677–82.
[49] Hiltunen K, Seppälä JV, Härkönen M. Lactic acid based poly(ester-urethanes): use of hydroxyl terminated prepolymer in urethane synthesis. J Appl Polym Sci 1997;63:1091–100.
[50] Tuominen J, Seppälä JV. Synthesis and characterization of lactic acid based poly(ester-amide). Macromolecules 2000;33:3530–5.
[51] Tasaka F, Ohya Y, Ouchi T. One-pot synthesis of novel branched polylactide through the copolymerization of lactide with mevalonolactone. Macromol Rapid Commun 2001;22:820–4.
[52] Penczec S, Duda A, Szymanski R, Biela T. What we have learned in general from cyclic esters polymerization. Macromol Symp 2000;153:1–15.

[53] Nijenhuis AJ, Grijpma DW, Pennings AJ. Lewis acid catalyzed polymerization of L-lactide. Kinetics and mechanism of bulk polymerization. Macromolecules 1992;25:6419–24.
[54] Kowalski A, Duda A, Penczek S. Kinetics and mechanism of cyclic esters polymerization initiated with tin(II) octoate. 3. Polymerization of L,L-dilactide. Macromolecules 2000;33:7359–70.
[55] Dubois P, Jacobs C, Jérôme R, Teyssié P. Macromolecular engineering of polylactones and polylactides. 4. Mechanism and kinetics of lactide homopolymerization by aluminum isopropoxide. Macromolecules 1991;24:2266–70.
[56] Kricheldorf HR, Serra A. Polylactones. 6. Influence of various metal salts on the optical purity of poly(L-lactide). Polym Bull 1985;14:497–502.
[57] Bero M, Kasperczyk J, Jedlinski ZJ. Coordination polymerization of lactides. 1. Structure determination of obtained polymers. Macromol Chem 1990;191:2287–96.
[58] Stolt M, Södergård A. Use of monocarboxylic iron derivatives in the ring-opening polymerization of L-lactide. Macromolecules 1999;32:6412–7.
[59] Chamberlain BM, Jazdzewski BA, Pink M, Hillmyer MA, Tolman WB. Controlled polymerization of DL-lactide and e-caprolactone by structurally well-defined alkoxo-bridged di- and triyttrium(III) complexes. Macromolecules 2000;33:3970–7.
[60] Grijpma DW, Pennings AJ. (Co)polymers of L-lactide. 1. Synthesis, thermal properties and hydrolytic degradation. Macromol Chem Phys 1994;195:1633–47.
[61] Grijpma DW, Pennings AJ. (Co)polymers of L-lactide. 2. Mechanical properties. Macromol Chem Phys 1994;195:1649–63.
[62] Cai Q, Bei J, Wang S. Synthesis and degradation of a tricomponent copolymer derived from glycolide, L-lactide, and epsilon-caprolactone. J Biomater Sci Polym Ed 2000;11: 273–88.
[63] Helminen AO, Korhonen H, Seppälä JV. Cross-linked poly(e-caprolactone/D,L-lactide) copolymers with elastic properties. Macromol Chem Phys 2002;203:2630–9.
[64] Haynes D, Abayasinghe NK, Harrison GM, Burg KJ, Smith Jr DW. In situ copolyesters containing poly(L-lactide) and poly(hydroxyalkanoate) units. Biomacromolecules 2007;8: 1131–7.
[65] Haynes D, Naskar AK, Singh A, Yang CC, Burg KJ, Drews M, et al. Poly(L-lactic acid) with segmented perfluoropolyether enchainment. Macromolecules 2007;40:9354–60.
[66] Schreck KM, Hillmyer MA. Block copolymers and melt blends of polylactide with Nodax™ microbial polyesters: preparation and mechanical properties. J Biotechnol 2007;132:287–95.
[67] Tasaka F, Miyazaki H, Ohya Y, Ouchi T. Synthesis of comb-type biodegradable polylactide through depsipeptide–lactide copolymer containing serine residues. Macromolecules 1999;32:6386–9.
[68] Ohya Y, Maruhashi S, Ouchi T. Graft polymerization of L-lactide on pullulan through the trimethylsilyl protection method and degradation of the graft copolymers. Macromolecules 1998;31:4662–5.
[69] Frick EM, Zalusky AS, Hillmyer MA. Characterization of polylactide-b-polyisoprene-b-polylactide thermoplastic elastomers. Biomacromolecules 2003;4:216–23.
[70] Bechtold K, Hillmyer MA, Tolman WB. Perfectly alternating copolymer of lactic acid and ethylene oxide as a plasticizing agent for polylactide. Macromolecules 2001;34:8641–8.
[71] Wang S, Cui W, Bei J. Bulk and surface modifications of polylactide. Anal Bioanal Chem 2005;381:547–56.
[72] Lee SH, Kim SH, Han YK, Kim YH. Synthesis and characterization of poly(ethylene oxide)/polylactide/poly(ethylene oxide) triblock copolymer. J Polym Sci Polym Chem 2002;40:2545–55.
[73] Luo WJ, Li SM, Bei JZ, Wang SG. Synthesis and characterization of poly(L-lactide)–poly(ethylene glycol) multiblock copolymers. J Appl Polym Sci 2002;84:1729–36.
[74] Li YX, Kissel T. Characteristics and in vitro degradation of star-block copolymers consisting of L-lactide, glycolide and branched multiarm poly(ethylene oxide). Polymer 1998;39:4421–7.
[75] Mascia L, Xanthos M. A overview of additives and modifiers for polymer blends: facts, deductions, and uncertainties. Adv Polym Technol 1992;11:237–48.
[76] Sinclair RG. The case for polylactic acid as a commodity packaging plastic. J Macromol Sci Pure Appl Chem 1996;A33:585–97.
[77] Jacobsen S, Fritz HG. Plasticizing polylactide—the effect of different plasticizers on the mechanical properties. Polym Eng Sci 1999;39:1303–10.
[78] Martin O, Avérous L. Poly(lactic acid): plasticization and properties of biodegradable multiphase system. Polymer 2001;42: 6209–19.
[79] Labrecque LV, Kumar RA, Dave V, Gross RA, McCarthy SP. Citrate esters as plasticizers for poly(lactic acid). J Appl Polym Sci 1997;66:1507–13.
[80] Ljungberg N, Wesslén B. The effects of plasticizers on the dynamic mechanical and thermal properties of poly(lactic acid). J Appl Polym Sci 2002;86:1227–34.
[81] Ljungberg N, Andersson T, Wesslén B. Film extrusion and film weldability of poly(lactic acid) plasticized with triacetine and tributyl citrate. J Appl Polym Sci 2003;88:3239–47.
[82] Ljungberg N, Wesslén B. Tributyl citrate oligomers as plasticizers for poly(lactic acid): thermo-mechanical film properties and aging. Polymer 2003;44:7679–88.
[83] Ljungberg N, Wesslén B. Thermomechanical film properties and aging of blends of poly(lactic acid) and malonate oligomers. J Appl Polym Sci 2004;94:2140–9.
[84] Ljungberg N, Colombini D, Wesslén B. Plasticization of poly(lactic acid) with oligomeric malonate esteramides: dynamic mechanical and thermal film properties. J Appl Polym Sci 2005;96:992–1002.
[85] Baiardo M, Frisoni G, Scandola M, Rimelen M, Lips D, Ruffieux K, et al. Thermal and mechanical properties of plasticized poly(L-lactic acid). J Appl Polym Sci 2003;90:1731–8.
[86] Kulinski Z, Piorkowska E. Crystallization, structure and properties of plasticized poly(L-lactide). Polymer 2005;46:10290–300.
[87] Lai WC, Liau WB, Lin TT. The effect of end groups of PEG on the crystallization behaviors of binary crystalline polymer blends PEG/PLLA. Polymer 2004;45:3073–80.
[88] Ren Z, Dong L, Yang Y. Dynamic mechanical and thermal properties of plasticized poly(lactic acid). J Appl Polym Sci 2006;101:1583–90.
[89] Pillin I, Montrelay N, Grohens Y. Thermo-mechanical characterization of plasticized PLA: is the miscibility the only significant factor? Polymer 2006;47:4676–82.
[90] Kulinski Z, Piorkowska E, Gadzinowska K, Stasiak M. Plasticization of poly(L-lactide) with poly(propylene glycol). Biomacromolecules 2006;7:2128–35.
[91] Kim KS, Chin IJ, Yoon JS, Choi HJ, Lee DC, Lee KH. Crystallization behavior and mechanical properties of poly(ethylene oxide)/poly(L-lactide)/poly(vinyl acetate) blends. J Appl Polym Sci 2001;82:3618–26.
[92] Sheth M, Kumar RA, Davé V, Gross RA, McCarthy SP. Biodegradable polymer blends of poly(lactic acid) and poly(ethylene glycol). J Appl Polym Sci 1997;66:1495–505.
[93] Wang Y, Hillmyer MA. Polyethylene-poly(L-lactide) diblock copolymers: synthesis and compatibilization of poly(L-lactide)/polyethylene blends. J Polym Sci Part A Polym Chem 2001;39:2755–66.
[94] Anderson KS, Lim SH, Hillmyer MA. Toughening of polylactide by melt blending with linear low-density polyethylene. J Appl Polym Sci 2003;89:3757–68.
[95] Gajria AM, Davé V, Gross RA, McCarthy SP. Miscibility and biodegradability of blends of poly(lactic acid) and poly(vinyl acetate). Polymer 1996;37:437–44.
[96] Zhang G, Zhang J, Wang S, Shen D. Miscibility and phase structure of binary blends of polylactide and poly(methyl methacrylate). J Polym Sci Part B Polym Phys 2003;41:23–30.
[97] E.I. du Pont de Nemours and Company DuPont™ Biomaz® Sheet, Resins and Modifiers. http://www2.dupont.com/Biomax/en_US/ (Accessed June 15, 2008).
[98] Ogata N, Jimenez G, Kawai H, Ogihara T. Structure and thermal/mechanical properties of poly(L-lactide)–clay blend. J Polym Sci Part B Polym Phys 1997;35:389–96.
[99] Kasuga T, Fujikawa H, Abe Y. Preparation of polylactic acid composites containing β-$Ca(PO_3)_2$ fibers. J Mater Res 1999;14:418–24.
[100] Kasuga T, Ota Y, Nogami M, Abe Y. Preparation and mechanical properties of polylactic acid composites containing hydroxyapatite fibers. Biomaterials 2001;22:19–23.
[101] McManus AJ, Doremus R, Siegel R, Bizios R. Evaluation of cytocompatibility and bending modulus of nanoceramic/polymer composites. J Biomed Mater Res 2005;72A:98–106.
[102] Durucan C, Brown PW. Low temperature formation of calcium-deficient hydroxyapatite–PLA/PLGA composites. J Biomed Mater Res 2000;51:717–25.
[103] Hiroi R, Ray SS, Okamoto M, Shiroi T. Organically modified layered titanate: a new nanofiller to improve the performance of biodegradable polylactide. Macromol Rapid Commun 2004;25:1359–64.
[104] Wan YZ, Wang YL, Li QY, Dong XH. Influence of surface treatment of carbon fibers on interfacial adhesion strength and mechanical properties of PLA-based composites. J Appl Polym Sci 2001;80:367–76.

[105] Urayama H, Ma C, Kimura Y. Mechanical and thermal properties of poly(L-lactide) incorporating various inorganic fillers with particle and whisker shapes. Macromol Mater Eng 2003;288:562–8.
[106] Jiang L, Zhang G, Wolcott MP. Comparison of polylactide/nano-sized calcium carbonate and polylactide/montmorillonite composites: reinforcing effects and toughening mechanisms. Polymer 2007;48:7632–44.
[107] Steinbüchel A, Lütke-Eversloh T. Metabolic engineering and pathway construction for biotechnological production of relevant polyhydroxyalkanoates in microorganisms. Biochem Eng J 2003;16:81–96.
[108] Bluhm TL, Hamer GK, Machessault RH, Fyfe CA, Veregin RP. Isodimorphism in bacterial poly(β-hydroxybutyrate-co-β-hydroxyvalerate). Macromolecules 1986;19:2871–6.
[109] Doi Y, Kunioka M, Nakamura Y, Soga K. Nuclear magnetic resonance studies on unusual bacterial copolyesters of 3-hydroxybutyrate and 4-hydroxybutyrate. Macromolecules 1988;21:2722–7.
[110] Noda I, Satkowski MM, Dowrey AE, Marcott C. Polymer alloys of nodax copolymers and poly(lactic acid). Macromol Biosci 2004;4:269–75.
[111] DiGregorio BE. Biobased performance bioplastic: Mirel. Chem Biol 2009;16:1–2.
[112] Iannace S, Ambrosio L, Huang SJ, Nicolais L. Poly(3-hydroxybutyrate)-co-(3-hydroxyvalerate)/poly-L-lactide blends: thermal and mechanical properties. J Appl Polym Sci 1994;54:1525–35.
[113] Takagi Y, Yasuda R, Yamaoka M, Yamane T. Morphologies and mechanical properties of polylactide blends with medium chain length poly(3-hydroxyalkanoate) and chemically modified poly(3-hydroxyalkanoate). J Appl Polym Sci 2004;93:2363–9.
[114] Wang H, Sun X, Seib P. Properties of poly(lactic acid) blends with various starches as affected by physical aging. J Appl Polym Sci 2003;90:3683–9.
[115] Broz ME, VanderHart DL, Washburn NR. Structure and mechanical properties of poly(D,L-lactic acid)/poly(e-caprolactone) blends. Biomaterials 2003;24:4181–90.
[116] Chen CC, Chueh JY, Tseng H, Huang HM, Lee SY. Preparation and characterization of biodegradable PLA polymeric blends. Biomaterials 2003;24:1167–73.
[117] Maglio G, Migliozzi A, Palumbo R, Immirzi B, Volpe MG. Compatibilized poly(1-caprolactone)/poly(L-lactide) blends for biomedical uses. Macromol Rapid Commun 1999;20:236–8.
[118] Semba T, Kitagawa K, Ishiaku US, Hamada H. The effect of crosslinking on the mechanical properties of polylactic acid/polycaprolactone blends. J Appl Polym Sci 2006;101:1816–25.
[119] Wang L, Ma W, Gross RA, McCarthy SP. Reactive compatibilization of biodegradable blends of poly(lactic acid) and poly(e-caprolactone). Polym Degrad Stab 1998;59:161–8.
[120] Jiang L, Wolcott MP, Zhang J. Study of biodegradable polylactide/poly(butylene adipate-co-terephthalate) blends. Biomacromolecules 2006;7:199–207.
[121] Lin Y, Zhang KY, Dong ZM, Dong LS, Li YS. Study of hydrogen-bonded blend of polylactide with biodegradable hyperbranched poly(ester amide). Macromolecules 2007;40:6257–67.
[122] Liu TY, Lin WC, Yang MC, Chen SY. Miscibility, thermal characterization and crystallization of poly(L-lactide) and poly(tetramethylene adipate-co-terephthalate) blend membranes. Polymer 2005;46:12586–94.
[123] Wan Y, Wu H, Yu A, Wen D. Biodegradable polylactide/chitosan blend membranes. Biomacromolecules 2006;7:1362–72.
[124] Suyatma NE, Copinet A, Tighzert L, Coma V. Mechanical and barrier properties of biodegradable films made from chitosan and poly(lactic acid) blends. J Polym Environ 2004;12:1–6.
[125] Peesan M, Rujiravnit R, Supaphol P. Electrospinning of hexanoyl chitosan/polylactide blends. J Biomater Sci Polym Ed 2006;17:547–65.
[126] Yang X, Yuan M, Li W, Zhang G. Synthesis and properties of collagen/polylactic acid blends. J Appl Polym Sci 2004;94:1670–5.
[127] Ke T, Sun SX, Seib P. Blending of poly(lactic acid) and starches containing varying amylose content. J Appl Polym Sci 2003;89:3639–46.
[128] Garlotta D, Doane W, Shogren R, Lawton J, Willett JL. Mechanical and thermal properties of starch-filled poly(D,L-lactic acid)/poly(hydroxy ester ether) biodegradable blends. J Appl Polym Sci 2003;88:1775–86.
[129] Ke T, Sun X. Melting behavior and crystallization kinetics of starch and poly(lactic acid) composites. J Appl Polym Sci 2003;89:1203–10.
[130] Cai Q, Yang J, Bei J, Wang S. A novel porous cells scaffold made of polylactide-dextran blend by combining phase-separation and particle-leaching techniques. Biomaterials 2002;23:4483–92.
[131] Pezzin APT, Alberda van Eckenstein GOR, Zavaglia CAC, ten Brinke G, Duek EAR. Poly(*para*-dioxanone) and poly(L-lactic acid) blends: thermal, mechanical,and morphological properties. J Appl Polym Sci 2003;88:2744–55.
[132] Ma X, Yu J, Wang N. Compatibility characterization of poly(lactic acid)/poly(propylene carbonate) blends. J Polym Sci Part B Polym Phys 2006;44:94–101.
[133] Shibata M, Inoue Y, Miyoshi M. Mechanical properties, morphology, and cryastallization behavior of blends of poly(L-lactide) with poly(butylene succinate-co-L-lactate) and poly(butylene succinate). Polymer 2006;47:3557–64.
[134] Chen GX, Kim HS, Kim ES, Yoon JS. Compatibilization-like effect of reactive organoclay on the poly(L-lactide)/poly(butylene succinate) blends. Polymer 2005;46:11829–36.
[135] Chen Y, Mak AFT, Wang M, Li J, Wong MS. PLLA scaffolds with biomimetic apatite coating and biomimetic apatite/collagen composite coating to enhance osteoblast-like cells attachment and activity. Surf Coat Technol 2006;201:575–80.
[136] Atthof B, Hilborn J. Protein adsorption onto polyester surfaces: is there a need for surface activation? J Biomed Mater Res Part B Appl Biomater 2007;80B:121–30.
[137] Eid K, Chen E, Griffith L, Glowacki J. Effect of RGD coating on osteocompatibility of PLGA-polymer disks in a rat tibial wound. J Biomed Mater Res 2001;57:224–31.
[138] Kubies D, Machová L, Brynda E, Lukás J, Rypácek F. Functionalized surfaces of polylactide modified by Langmuir–Blodgett films of amphiphilic block copolymers. J Mater Sci Mater Med 2003;14:143–9.
[139] Black FE, Hartshorne M, Davies MC, Roberts CJ, Tendler SJB, Williams PM, et al. Surface engineering and surface analysis of a biodegradable polymer with biotinylated end groups. Langmuir 1999;15:3157–61.
[140] Quirk RA, Chan WC, Davies MC, Tendler SJB, Shakesheff KM. Poly(L-lysine)–GRGDS as a biomimetic surface modifier for poly(lactic acid). Biomaterials 2001;22:865–72.
[141] Healy KE, Thomas CH, Rezania A, Kim JE, McKeown PJ, Lom B, et al. Kinetics of bone cell organization and mineralization on materials with patterned surface chemistry. Biomaterials 1996;17:195–208.
[142] Gross GW, Rhoades BK, Azzazy HME, Wu MC. The use of neuronal networks on multielectrode arrays as biosensors. Biosens Bioelectron 1995;10:553–67.
[143] Wang Y, Lai HH, Bachman M, Sims CE, Li GP, Allbritton NL. Covalent micropatterning of poly(dimethylsiloxane) by photografting through a mask. Anal Chem 2005;77:7539–46.
[144] Lin CC, Co CC, Ho CC. Micropatterning proteins and cells on polylactic acid and poly(lactide-co-glycolide). Biomaterials 2005;26:3655–62.
[145] Zhu H, Ji J, Shen J. Surface engineering of poly(DL-lactic acid) by entrapment of biomacromolecules. Macromol Rapid Commun 2002;23:819–23.
[146] Quirk RA, Davies MC, Tendler SJB, Shakesheff KM. Surface engineering of poly(lactic acid) by entrapment of modifying species. Macromolecules 2000;33:258–60.
[147] Quirk RA, Davies MC, Tendler SJB, Chan WC, Shakesheff KM. Controlling biological interactions with poly(lactic acid) by surface entrapment modification. Langmuir 2001;17:2817–20.
[148] Zhang J, Roberts CJ, Shakesheff KM, Davies MC, Tendler SJB. Micro- and macrothermal analysis of a bioactive surface-engineered polymer formed by physical entrapment of poly(ethylene glycol) into poly(lactic acid). Macromolecules 2003;36:1215–21.
[149] Cai K, Yao K, Hou X, Wang Y, Hou Y, Yang Z, et al. Improvement of the functions of osteoblasts seeded on modified poly(D,L-lactic acid) with poly(aspartic acid). J Biomed Mater Res 2002;62:283–91.
[150] Rasal RM, Bohannon BG, Hirt DE. Effect of the photoreaction solvent on surface and bulk properties of poly(lactic acid) and poly(hydroxyalkanoate) films. J Biomed Mater Res Part B Appl Biomater 2008;85B:564–72.
[151] Irvine DJ, Ruzette AG, Mayes AM, Griffith LG. Nanoscale clustering of RGD peptides at surfaces using comb polymers. 2. Surface segregation of comb polymers in polylactide. Biomacromolecules 2001;2:545–56.
[152] Kiss É, Bertóti I, Vargha-Butler EI. XPS and wettability characterization of modified poly(lactic acid) and poly(lactic/glycolic acid) films. J Colloid Interface Sci 2002;245:91–8.
[153] Yu G, Ji J, Zhu H, Shen J. Poly(D,L-lactic acid)-block-(ligand-tethered poly(ethylene glycol)) copolymers as surface additives for promot-

ing chondrocyte attachment and growth. J Biomed Mater Res Part B Appl Biomater 2006;76B:64–75.
[154] Hall JR, Westerdahl CAL, Devine AT, Bodnar MJ. Activated gas plasma surface treatment of polymers for adhesive bonding. J Appl Polym Sci 1969;13:2085–96.
[155] Wang CX, Ren Y, Qiu YP. Penetration depth of atmospheric pressure plasma surface modification into multiple layers of polyester fabrics. Surf Coat Technol 2007;202:77–83.
[156] Hirotsu T, Nakayama K, Tsujisaka T, Mas A, Schue F. Plasma surface treatments of melt-extruded sheets of poly(L-lactic acid). Polym Eng Sci 2002;42:299–306.
[157] Yang J, Shi GX, Wang SG, Bei JZ, Cao YL, Shang QX, et al. Fabrication and surface modification of macroporous poly(L-lactic acid) and poly(L-lactic-co-glycolic acid) (70/30) cell scaffolds for human skin fibroblast cell culture. J Biomed Mater Res 2002;62:438–46.
[158] Yang J, Bei JZ, Wang SG. Enhanced cell affinity of poly(D,L-lactide) by combining plasma treatment with collagen anchorage. Biomaterials 2002;23:2607–14.
[159] Khorasani MT, Mirzadeh H, Irani S. Plasma surface modification of poly(L-lactic acid) and poly(lactic-co-glycolic acid) films for improvement of nerve cells adhesion. RadPhys Chem 2008;77:280–7.
[160] Ximing X, Gengenbach TR, Griesser HJ. Changes in wettability with time of plasma modified perfluorinated polymers. J Adhes Sci Technol 1992;6:1411–31.
[161] Occhiello E, Morra M, Morini G, Garbassi F, Humphrey P. Oxygen-plasma-treated polypropylene interfaces with air, water, and epoxy resins. Part I. Air and water. J Appl Polym Sci 1991;42:551–9.
[162] Safinia L, Datan N, Höhse M, Mantalaris A, Bismarck A. Towards a methodology for the effective surface modification of porous polymer scaffolds. Biomaterials 2005;26:7537–47.
[163] Wan Y, Tu C, Yang J, Bei J, Wang S. Influences of ammonia plasma treatment on modifying depth and degradation of poly(L-lactide) scaffolds. Biomaterials 2006;27:2699–704.
[164] Luo N, Stewart MJ, Hirt DE, Husson SM, Schwark DW. Surface modification of ethylene-co-acrylic acid copolymer films: addition of amide groups by covalently bonded amino acid intermediates. J Appl Polym Sci 2004;92:1688–94.
[165] Zhang P, He C, Craven RD, Evans JA, Fawcett NC, Wu Y, et al. Subsurface formation of amide in polyethylene-co-acrylic acid film: a potentially useful reaction for tethering biomolecules to a solid support. Macromolecules 1999;32:2149–55.
[166] Janorkar AV, Luo N, Hirt DE. Surface modification of an ethylene-acrylic acid copolymer film: grafting amine-terminated linear and branched architectures. Langmuir 2003;20:7151–8.
[167] Cai K, Yao K, Cui Y, Lin S, Yang Z, Li X, et al. Surface modification of poly(D,L-lactic acid) with chitosan and its effects on the culture of osteoblasts *in vitro*. J Biomed Mater Res 2002;60:398–404.
[168] Yang J, Wan YQ, Wang SG, Tu CF, Cai Q, Bei JZ, et al. Enhancing the cell affinity of macroporous poly(L-lactide) cell scaffold by a convenient surface modification method. Polym Int 2003;52:1892–9.
[169] Zhu YB, Gao CY, Liu XY, He T, Shen JC. Immobilization of biomacromolecules onto aminolyzed poly(L-lactic acid) toward acceleration of endothelium regeneration. Tissue Eng 2004;10:53–61.
[170] Janorkar AV, Fritz EW, Burg KJL, Metters AT, Hirt DE. Grafting amine-terminated branched architectures from poly(L-lactide) film surfaces for improved cell attachment. J Biomed Mater Res Part B Appl Biomater 2007;81B:142–52.
[171] Ma H, Davis RH, Bowman CN. A novel sequential photoinduced living graft polymerization. Macromolecules 2000;33:331–5.
[172] Rahane SB, Kilbey II SM, Metters AT. Kinetics of surface-initiated photoiniferter-mediated photopolymerization. Macromolecules 2005;38:8202–10.
[173] Zhao B, Brittain WJ. Polymer brushes: surface-immobilized macromolecules. Prog Polym Sci 2000;25:677–710.
[174] Zhu A, Zhang M, Wu J, Shen J. Covalent immobilization of chitosan/heparin complex with a photosensitive hetero-bifunctional crosslinking reagent on PLA surface. Biomaterials 2002;23:4657–65.
[175] Steffens GCM, Nothdurft L, Buse G, Thissen H, Höcker H, Klee D. High density binding of proteins and peptides to poly(D,L-lactide) grafted with polyacrylic acid. Biomaterials 2002;23:3523–31.
[176] Ma Z, Gao C, Gong Y, Shen J. Chondrocyte behaviors on poly-L-lactic acid (PLLA) membranes containing hydroxyl, amide or carboxyl groups. Biomaterials 2003;24:3725–30.
[177] Janorkar AV, Proulx SE, Metters AT, Hirt DE. Surface-confined photopolymerization of single- and mixed-monomer systems to tailor the wettability of poly(L-lactide) film. J Polym Sci Part A Polym Chem 2006;44:6534–43.
[178] Janorkar AV, Metters AT, Hirt DE. Degradation of poly(L-lactide) films under ultraviolet-induced photografting and sterilization conditions. J Appl Polym Sci 2007;106:1042–7.
[179] Edlund U, Källrot M, Albertsson AC. Single-step covalent functionalization of polylactide surfaces. J Am Chem Soc 2005;127:8865–71.
[180] Källrot M, Edlund U, Albertsson AC. Surface functionalization of degradable polymers by covalent grafting. Biomaterials 2006;27:1788–96.
[181] Tsuji H, Ikada H. Blends of crystalline and amorphous poly(lactide). III. Hydrolysis of solution-cast blend films. J Appl Polym Sci 1997;63:855–63.
[182] Källrot M, Edlund U, Albertsson AC. Covalent grafting of poly(L-lactide) to tune the in vitro degradation rate. Biomacromolecules 2007;8:2492–6.
[183] Edlund U, Dànmark S, Albertsson AC. A strategy for the covalent functionalization of resorbable polymers with heparin and osteoinductive growth factor. Biomacromolecules 2008;9:901–5.
[184] Kulkarni RK, Pani KC, Neuman C, Leonard F. Polylactic acid for surgical implants. Arch Surg 1966;93:839–43.
[185] Cutright DE, Hunsuck EE. Tissue reaction to the biodegradable polylactic acid suture. J Oral Surg 1971;31:134–9.
[186] Hollinger JO. Preliminary report on the osteogenic potential of a biodegradable copolymer of polylactide (PLA) and polyglycolide (PGA). J Biomed Mater Res 1983;17:71–82.
[187] Leenslag JW, Pennings AJ, Bos RRM, Rozema FR, Boering G. Resorbable materials of poly(L-lactide). VI. Plates and screws for internal fracture fixation. Biomaterials 1987;8:70–3.
[188] Schakenraad JM, Nieuwenhues P, Molenaar I, Helder J, Dykstra PJ, Feijen J. In vivo and in vitro degradation of glycine/DL-lactic acid copolymers. J Biomed Mater Res 1989;23:1271–88.
[189] Schakenraad JM, Hardonk MJ, Feijen J, Molenaar I, Nieuwenhuis P. Enzymatic activity toward poly(L-lactic acid) implants. J Biomed Mater Res 1990;24:529–45.
[190] Majola A, Vainionpla S, Vihtonen K, Mero M, Vasenius J, Tormala P, et al. Absorption, biocompatibility and fixation properties of polylactic acid in bone tissue: an experimental study in rats. Clin Orthop Relat Res 1991;268:260–9.
[191] Von Schroeder HP, Kwan M, Amiel D, Coutts RD. The use of polylactic acid matrix and periosteal grafts for the reconstruction of rabbit knee articular defects. J Biomed Mater Res 1991;25:329–39.
[192] Kobayashi H, Shiraki K, Ikada Y. Toxicity test of biodegradable polymers by implantation in rabbit cornea. J Biomed Mater Res 1992;26:1463–76.
[193] Päivärinta LJ, Böstman O, Majola A, Toivonen T, Törmälä P, Rokkanen P. Intraosseous cellular response to biodegradable fracture fixation screws made of polyglycolide polylactide. Arch Orthop Trauma Surg 1993;112:71–4.
[194] Bucholz RW, Henry S, Henley MB. Fixation with bioabsorbable screws for the treatment of fractures of the ankle. J Bone Joint Surg Am 1994;76A:319–24.
[195] Athanasiou KA, Korvick DL, Schenck RC. Biodegradable implants for the treatment of osteochondral defects in goat model. Tissue Eng 1997;3:363–73.
[196] An YH, Friedman RJ, Powers DL, Draughn RA, Latour Jr RA. Fixation of osteotomies using bioabsorbable screws in the canine femur. Clin Orthop 1998;355:300–11.
[197] Prokop A, Jubel A, Hahn U, Dietershagen M, Bleidistel M, Peters C, et al. A comparative radiological assessment of polylactide pins over 3 years in vivo. Biomaterials 2005;26:4129–38.
[198] Schmidmaier G, Baehr K, Mohr S, Kretschmar M, Beck S, Wildemann B. Biodegradable polylactide membranes for bone defect coverage: biocompatibility testing, radiological and histological evaluation in a sheep model. Clin Oral Impl Res 2006;17:439–44.