11

Poly(Lactic Acid)-Based Biomaterials: Synthesis, Modification and Applications

Lin Xiao[1,2], Bo Wang[1,2], Guang Yang[*1,2] and Mario Gauthier[3]
[1]College of Life Science and Technology, Huazhong University of Science and Technology,
[2]National Engineering Research Center for Nano-Medicine,
Huazhong University of Science and Technology,
[3]Department of Chemistry, University of Waterloo,
[1,2]China
[3]Canada

1. Introduction

Social and economic development has driven considerable scientific and engineering efforts on the discovery, development, and utilization of polymers. Widespread reliance in everyday life on conventional polymeric materials such as polyolefins has resulted in serious pollution which cannot be resolved in a straightforward fashion. Sustainable development and a green economy both require brand new materials which can avoid the occurrence of these problems.

Poly(lactic acid) (PLA), an aliphatic polyester, has outstanding advantages over other polymers, and may thus be part of the solution. As early as the 1970's, PLA products have been approved by the US Food and Drug Administration (FDA) for direct contact with biological fluids. Four of its most attractive advantages are renewability, biocompatibility, processability, and energy saving (Rasal, 2010). First of all, PLA is derived from renewable and degradable resources such as corn and rice, which can help alleviate the energy crisis as well as reduce the dependence on fossil fuels of our society; PLA and its degradation products, namely H_2O and CO_2, are neither toxic nor carcinogenic to the human body, hence making it an excellent material for biomedical applications including sutures, clips, and drug delivery systems (DDS). Furthermore, PLA can be processed by film casting, extrusion, blow molding, and fiber spinning due to its greater thermal processability in comparison to other biomaterials such as poly(ethylene glycol) (PEG), poly(hydroxyalkanoates) (PHAs), and poly(ε-caprolactone) (PCL) (Rhim et al., 2006). These thermal properties contribute to the application of PLA in industry in fields such as textiles and food packaging. Last but not least, PLA production consumes 25-55% less fossil energy than petroleum-based polymers. Cargill Dow has even targeted a reduction in fossil energy consumption by more than 90% as compared to any of the petroleum-based polymers for the near future, which will surely also lead to significant reductions in air and water pollutant emissions. It is also noteworthy that the total amount of water required for PLA production is competitive with the best performing petroleum-based polymers. This energy-saving feature perfectly caters to the

---

[*] Corresponding author

new concept of "low-carbon economy" which emerged recently in response to the global warming and energy crisis concerns, and makes investment in PLA a necessary and wise strategy in the future (Vink et al., 2003). Fig. 1 shows the cycle of PLA in nature.
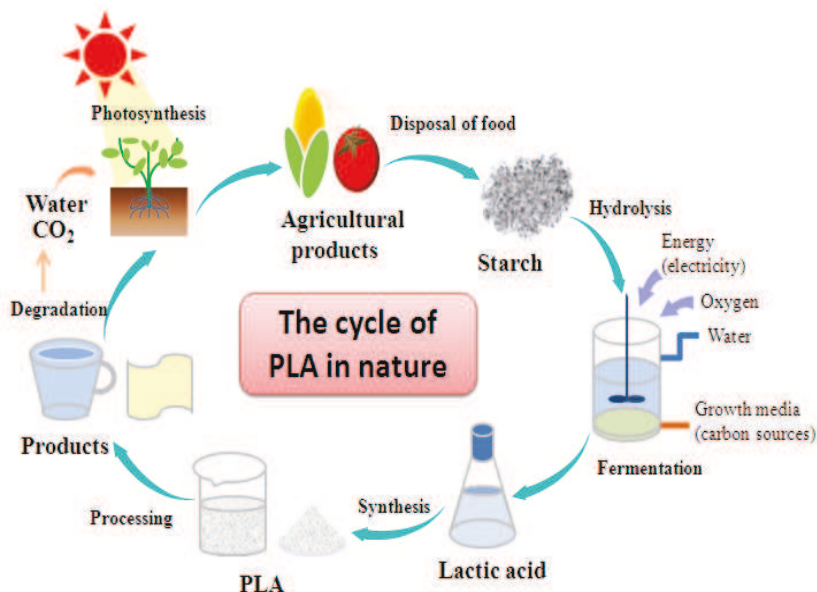

Fig. 1. The cycle of PLA in nature.

While PLA can be considered an eco-friendly biomaterial with excellent properties, it also has many obvious drawbacks when confronted with requirements for certain applications: 1) Its degradation rate through hydrolysis of the backbone ester groups is too slow. This process sometimes takes several years, which can impede its biomedical and food packaging applications (Bergsma et al., 1995). 2) PLA is very brittle, with less than 10% elongation at break, thus it is not suitable for demanding mechanical performance applications unless it is suitably modified (Rasal & Hirt, 2009). 3) PLA is strongly hydrophobic and can elicit an inflammatory response from the tissues of living hosts, because of its low affinity with cells when it is used as a tissue engineering material. 4) Another limitation of PLA towards its wider industrial application is its limited gas barrier properties which prevent its complete access to industrial sectors such as packaging (Singh et al., 2003). Considering the disadvantages of PLA stated above and its high cost (another shortcoming of that material), it is not surprising that PLA has not received the attention it deserves. Nevertheless, researchers have examined different methods for the bulk or surface modification of PLA, the introduction of other components, or the control of its surface energy, surface charge and surface roughness, depending on the requirements of specific applications.

Previous reviews have examined different aspects of PLA chemistry and engineering. Thus Maharana et al. (Maharana et al., 2009) presented a review on the melt-solid polycondensation of lactic acid (LA). Gupta et al. (Gupta et al., 2007) presented an overview of the production of PLA fibers by various methods, along with correlations between the

structure and the properties of the fibers. Butterwick et al. (Butterwick et al., 2009) discussed the applications of PLA in Europe and the United States with respect to practitioner experiences and techniques to optimize the outcomes. Rasal et al. (Rasal et al., 2010) examined the chemical modification of PLA, while Graupner et al. (Graupner et al., 2009) assessed the production and the mechanical characteristics of composites prepared from PLA and renewable raw materials including cotton, hemp, kenaf, and man-made cellulose fibres (Lyocell) by compression molding.

In this chapter we will underline novel ideas or technologies introduced over the last 5-10 years, emphasizing some ambitious work which, even though it appears less successful than other mature methods, introduces concepts that may prove extremely positive in the near future. We will also attempt to foretell developmental trends on the basis of social demands and the progress achieved so far. More traditional topics including the synthesis, modification, and applications of PLA in biomedical field will be introduced mainly to provide a more comprehensive picture of PLA as a biomaterial.

2. Physical and chemical properties of PLA

L-lactic acid and D-lactic acid, the two isomers of lactic acid, are shown in Scheme 1. Pure L-lactic acid or D-lactic acid, or mixtures of both components are needed for the synthesis of PLA.

L-Lactic acid   *D*-Lactic acid
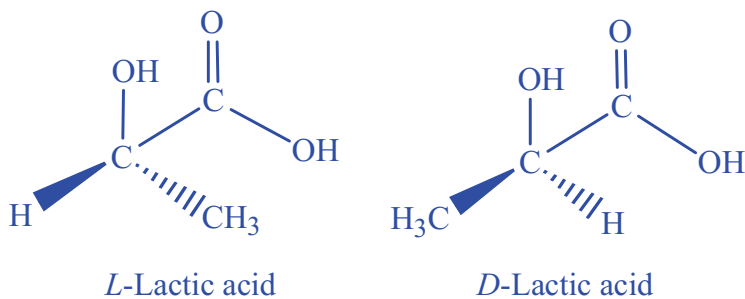
Scheme 1. The stereoisomers of lactic acid.

The homopolymer of LA is a white powder at room temperature with T_g and T_m values of about 55°C and 175°C, respectively. High molecular weight PLA is a colorless, glossy, rigid thermoplastic material with properties similar to polystyrene. The two isomers of LA can produce four distinct materials: Poly(*D*-lactic acid) (PDLA), a crystalline material with a regular chain structure; poly(*L*-lactic acid) (PLLA), which is hemicrystalline, and likewise with a regular chain structure; poly(*D,L*-lactic acid) (PDLLA) which is amorphous; and *meso*-PLA, obtained by the polymerization of *meso*-lactide. PDLA, PLLA and PDLLA are soluble in common solvents including benzene, chloroform, dioxane, etc. and degrade by simple hydrolysis of the ester bond even in the absence of a hydrolase. PLA has a degradation half-life in the environment ranging from 6 months to 2 years, depending on the size and shape of the article, its isomer ratio, and the temperature. The tensile properties of PLA can vary widely depending on whether it is annealed or oriented, or its degree of crystallinity (Garlotta et al., 2001). Some of the physical and chemical properties of PLA are summarized in Table 1.

| Properties	PDLA	PLLA	PDLLA
Solubility	All are soluble in benzene, chloroform, acetonitrile, tetrahydrofuran (THF), dioxane etc., but insoluble in ethanol, methanol, and aliphatic hydrocarbons		
Crystalline structure	Crystalline	Hemicrystalline	Amorphous
Melting temperature (T_m)/ °C	~180	~180	Variable
Glass transition temperature (T_g)/ °C	50-60	55-60	Variable
Decomposition temperature/°C	~200	~200	185-200
Elongation at break/ (%)	20-30	20-30	Variable
Breaking strength/ (g/d)	4.0-5.0	5.0-6.0	Variable
Half-life in 37°C normal saline	4-6 months	4-6 months	2-3 months

Table 1. Selected physical and chemical properties of PLA.

3. Synthesis of PLA

Two main synthetic methods are used to obtain PLA: Direct polycondensation (including solution polycondensation and melt polycondensation), and ring-opening polymerization (ROP).

3.1 Direct polymerization

Since the LA monomer has both –OH and –COOH groups, necessary for polymerization, the reaction can take place directly by self-condensation (Scheme 2):
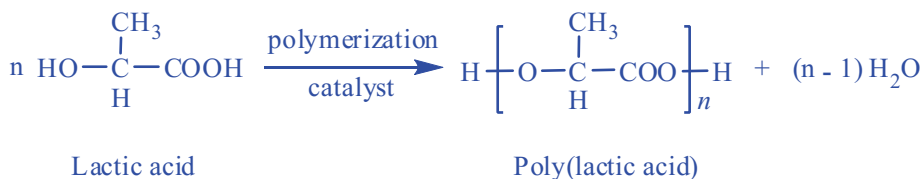
Scheme 2. Direct polymerization.

Direct polymerization includes solution and melt polycondensation, depending on whether a solvent is used in the reaction to dissolve the PLA or not.

3.1.1 Solution polycondensation

In this case an organic solvent capable of dissolving the PLA without interfering with the reaction is added, and the mixture is refluxed with removal of the water generated in the polycondensation process, which is beneficial to achieve a high molecular weight. Many procedures yield PLA with a weight-average molecular weight (M_w) of over 200,000 by this method (Ohta et al., 1995; Ichikawa et al., 1995). This approach was developed by Carothers and is still used by Mitsui Chemicals. The resultant polymer can be coupled with isocyanates, epoxides or peroxides to produce a range of molecular weights (Lunt et al.,

1998). The reaction proceeds smoothly, however solution polymerization suffers from certain disadvantages such as being susceptible to impurities from the solvent and various side reactions including racemization and trans-esterification. It also consumes large volumes of organic solvents, which are potential pollutants to the environment.

Under optimized conditions, Ajioka et al. obtained PLA with M_w > 300,000 by this method (Ajioka et al., 1995). Characterization data have shown that the glass transition temperatures (T_g) of PLA and polylactide synthesized by the conventional lactide process are essentially identical (T_g = 58°C and 59 °C, respectively), but PLA has a lower melting point (T_m = 163 °C) than polylactide (T_m = 178°C). The mechanical properties of the two polymers are also very similar.

3.1.2 Melt polycondensation

In contrast to solution polycondensation, the melt polycondensation of monomers can proceed without any organic solvent, but only if the temperature of the reaction remains above the T_m of the polymer (Gao et al., 2002). Moon et al. discovered that high M_w PLLA [M_w ≥ 100,000] could be produced in this way in a relatively short reaction time (≤ 15 h) (Moon et al., 2000). This method can lower the cost of the synthesis significantly due to the simplified procedure, but major problems still need to be solved before it can be applied industrially because of its sensitivity to reaction conditions (Maharana et al., 2009). Thus Moon et al. worked to develop a melt/solid polycondensation technique using a binary catalyst system (tin dichloride hydrate and *p*-toluenesulfonic acid) (Moon et al., 2001). Simply put, thermal oligocondensates of LA were first subjected to melt polycondensation to obtain a melt polycondensate, which was then subjected to solid state polycondensation at 105°C. As a consequence, the molecular weight of the PLA was as high as 600,000 after a short reaction time under optimized conditions.

In summary, these one-step polymerization processes are relatively economical and easy to control, but they are equilibrium reactions affected by numerous parameters such as the temperature, the reaction time, catalysts, pressure, and so on. These factors can strongly influence the molecular weight of the products obtained. Besides, the water generated in this process can cause high molecular weight PLA to break down at high reaction temperatures. Thus the polymer resulting from these reactions usually has an unsatisfactorily low molecular weight. Attention must be paid to three aspects of the reaction to obtain a high molecular weight, namely controlling the reaction kinetics, removing the water formed, and preventing the degradation of the PLA chains.

3.2 Ring-opening polymerization

Considering the drawbacks of direct polymerization, PLA is typically synthesized by ring-opening polymerization (ROP) (Scheme 3), an important and effective method to manufacture high molecular weight PLA. This reaction requires strict purity of the lactide monomer, obtained by dimerization of the lactic acid monomer. PLA is obtained by using a catalyst with the monomer under vacuum or an inert atmosphere. By controlling the residence time and the temperatures in combination with the catalyst type and concentration, it is possible to control the ratio and sequence of *D*- and *L*-lactic acid (LA) units in the final polymer (Lunt et al., 1998). The polymerization mechanism involved can be ionic, coordination, or free-radical, depending on type of catalyst employed (Penczek et al.,

2000). Most of the researchers are now exploring new and effective catalysts. Köhn et al. (Köhn et al., 2003) first reported that the ROP of *D,L*-lactide could be catalyzed by bis(trimethyl triazacyclohexane) praseodymium triflate [(Me$_3$TAC)$_2$ Pr(OTf)$_3$] (Cat), while Pr(OTf)$_3$ by itself had a poor catalytic activity. Cat was found to catalyze the polymerization of *D,L*-lactide in various solvents (THF, dichloromethane, ethyl acetate, and toluene) without any additional reagents. The optimal polymer yield (95%) and molecular weight (18,000) were obtained after 18 h at 170°C, with a ratio of [LA]:[Cat] = 1000. John et al. (John et al., 2007) produced one of the few reports on lactide polymerization with a Cu-based catalyst. ROP of *L*-lactide catalyzed by {2-[1-(2,6-diethylphenylimino)ethyl]phenoxy}$_2$Cu(II) yielded the highest M_w (26.3 × 10^3) with a monomer conversion of 57%. Two other copper complexes, {2-[1-(2,6-dimethylphenylimino)ethyl]phenoxy}$_2$Cu(II) and {2-[1-(2-methylphenylimino)ethyl]phenoxy}$_2$Cu(II), also catalyzed the reaction under solvent-free melt conditions (160°C) but produced polylactides of moderate molecular weights (M_w = 12.0 × 10^3 and 15.9 × 10^3, respectively).

Scheme 3. Ring-opening polymerization.

Numerous studies have examined the influence of different factors such as the concentration and type of catalyst, monomer purity, and temperature on the polymerization of lactide. Special attention has been paid to the catalyst. Currently tin octoate is the most widely used catalyst for the ring-opening polymerization of lactides, but numerous novel efficient metal-free catalytic systems are emerging as valuable alternatives (Jérôme & Lecomte, 2008). The heavy metal-based catalysts are indeed very likely to contaminate the product, which complicates the purification of the PLA obtained and also limits the applications of PLA in the fields of food packaging and biomedicine. Some of the means developed to solve this problem will be addressed later.

3.3 New approaches

The inherent disadvantages of the traditional synthetic methodology have led some researchers to explore solutions such as the development of nontoxic catalysts, unusual polymerization conditions, or other polymerization pathways (Lassalle & Ferreira, 2008).

To solve the potential pollution problems caused by heavy metal catalysts, many nontoxic catalysts derived from magnesium (Wu et al., 2005), calcium (Zhong et al., 2003), zinc (Sarazin et al., 2004), alkali metals (Chisholm et al., 2003), and aluminum (Nomura et al., 2002) have been developed for the ROP of lactides (Deng et al., 2000; Ejfler et al., 2005). For example, Chen et al. (Chen et al., 2007) tested a series of β-diketiminate zinc complexes as initiators for the ROP of lactide and they were all highly active, however the M_w attained was unsatisfactory. It is worth noting that a variety of rare earth derivatives are usually highly reactive, which entitles them to be very promising initiators for the ROP of lactide (Agarwal et al., 2000).

With respect to unusual reaction conditions, supercritical CO_2 ($scCO_2$) technology has attracted much attention because this environmentally friendly, chemically inert, inexpensive, non-toxic, and nonflammable solvent can be substituted for organic solvents (Nalawade et al., 2006). Yoda et al. (Yoda et al., 2004) thus carried out the synthesis of PLLA from an *L*-lactic acid oligomer in $scCO_2$ with dicyclohexyldimethylcarbodiimide (DCC) as an esterification promoter and 4-dimethylaminopyridine (DMAP) as a catalyst. PLLA with a number-average molecular weight M_n reaching 13,500 was obtained in 95% yield after 24 h at 3500 psi and 80°C. The molecular weight distribution of the products was also narrower than for PLLA prepared by melt–solid phase polymerization under conventional conditions. Not only can $scCO_2$ be used as a medium to synthesize polymers, but it can also serve in the purification and processing of the polymer micro-particles obtained (Kang et al., 2008).

The direct polycondensation of lactic acid has been considered to have a promising future due to its low cost; however it is hard to increase the molecule weight due to the difficulty in removing the water from the system under these conditions. One way to solve this problem is a chain-extension method, although the properties of the PLA obtained in this way can be somewhat affected by the procedure. Simply put, hydroxyl- or carboxyl-terminated low molecular weight PLA obtained by direct polymerization can be linked together through a chain extender, which is a bifunctional compound carrying highly reactive functional groups. Many achievements have been reported in this area, hexamethylene diisocyanate (HDI) being the most widely used chain extender for hydroxyl-terminated prepolymers since the work done by Woo and coworkers (Woo et al., 1995). Finding new and satisfactory chain extenders will remain a major goal in the near future, since HDI is toxic and subject to side reaction in this process.

In addition, LA-polymerizing enzymes functioning in replacement of metal catalysts should enable the biosynthesis of PLA, even though it is enormously challenging both in terms of research and industrial implementation. The best solution could be the development of a PLA-producing microorganism, but this has not been reported so far. Taguchi et al. (Taguchi et al. 2008) have nonetheless obtained encouraging results by developing a recombinant *Escherichia coli* strain allowing the synthesis of LA-based polyesters by introducing the gene encoding polyhydroxyalkanoate (PHA) synthase. This is illustrated in Fig. 2. They thus achieved the one-step biosynthesis of a copolymer with 6 mol% of lactate and 94 mol% of 3-hydroxybutyrate units, having a molecular weight of 1.9×10^5. This extremely important result represents a milestone towards the biological synthesis of PLA and confirms that the work is moving in the right direction. At present, the LA fraction in the copolyesters has been enriched up to 96 mol% (Shozui et al., 2011), so the synthesis of homopolymers of LA represents a major goal. To that end, the current microbial cell factory ought to be improved with further evolved LA-polymerizing enzymes (LPE) and metabolic engineering-based optimization (Taguchi, 2010). Matsumura et al. (Matsumura et al., 1997) likewise reported the lipase PC-catalyzed polymerization of cyclic diester-D,L-lactide at a temperature of 80-130°C to yield poly(lactic acid) with molecular masses of up to 12,600. Other novel methods (e.g. metal-free catalysts, non-catalytic systems) are also under development (Zhong et al., 2003; Achmad et al., 2009). The advantages and disadvantages of the PLA synthesis methods mentioned above are summarized in Table 2.
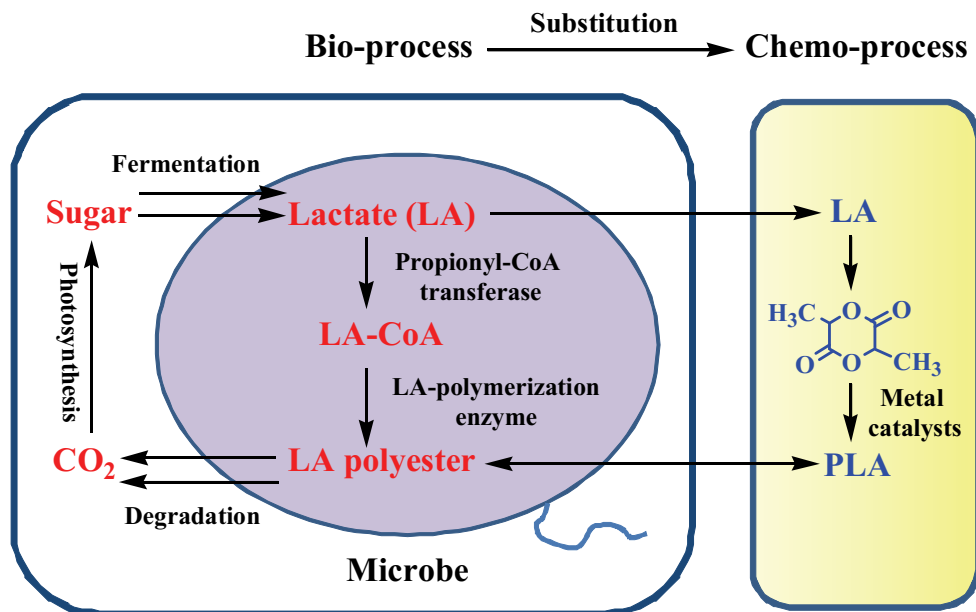
Bio-process ──── Substitution ────▶ **Chemo-process**

Fig. 2. Mechanism for the bio-synthesis of LA polyester. In the bio-process, the LA monomer is converted into LA-CoA ,which is recognized by the LA-polymerizing enzyme recruited from microbial PHA synthase (Tajima et al., 2009).

Synthesis methods	Advantages	Disadvantages
Solution polycondensation	One-step, economical and easy to control	Impurities, side reactions, pollution, low molecular weight PLA
Melt polycondensation		High reaction temperature, sensitivity to reaction conditions, low molecular weight PLA
Ring-opening polymerization	High molecular weight PLA	Requires strict purity of the lactide monomer, related high cost
New solutions (new catalysts, polymerization conditions, etc)	Efficient, non-toxic, no pollution , high molecular weight PLA, etc.	Under development
Biosynthesis	One-step, efficient, non-toxic, no pollution, low cost, etc.	Under development

Table 2. Comparison of PLA synthesis methods.

4. Modification of PLA

The major drawbacks of PLA limiting its applications are its poor chemical modifiability and mechanical ductility, slow degradation profile, and poor hydrophilicity. In order to be suitable for specific biomedical applications, the PLA has been modified mainly concerning two aspects: Bulk properties and surface chemistry. To achieve this, both chemical modification and physical modification have been tried, involving the incorporation of functional monomers with different molecular architectures and compositions, the tuning of crystallinity and processibility via blending and plasticization, etc., which are described in the following sections.

4.1 Bulk modification

Biomaterials must possess bulk properties, particularly hydrophilic and mechanical properties, meeting special requirements. Critical factors affecting these characteristics include chemical additives, composition, and morphological structure. At present considerable research focuses on a variety of hydrolytic groups, controlling the flexibility and crystallinity of the molecular chains, and the presence of hydrophilic groups.

4.1.1 Physical modification

Blending, plasticization, and composition variations belong to this category.

Blending

Polymer blending is an effective, simple, and versatile method to develop new materials with tailored properties without synthesizing new polymers (Peesan et al., 2005). The properties of different polymers (biodegradable and non-biodegradable) can be combined by blending with PLA, or even new properties can arise in the products due to interactions between the components. Biodegradable components blended with PLA include poly(ethylene glycol) (PEG), poly(β-hydroxybutyrate) (PHB), poly(ε-caprolactone) (PCL), poly(butylene adipate-*co*-terephthalate) (PBAT), chitosan, and starch (Sheth et al., 1997). While blends of PLA and non-biodegradable polymers have not been as extensively studied, low-density polyethylene (LDPE), poly(vinyl acetate) (PVA), and polypropylene (PP) have been examined. Reddy et al. (Reddy et al., 2008) found that PLA in blends obtained from five ratios of PLA/PP had substantially better resistance to biodegradation and hydrolysis, and improved dyeability with dispersed dyes. However most of these blends are immiscible (phase-separated) and display poor mechanical properties due to low interfacial adhesion between the polymer phases.

To improve the processing and mechanical properties of PLA without sacrificing its degradability and biocompatibility, Xu et al. (Xu et al., 2009) blended PLA with a new degradable thermoplastic derived from konjac glucomannan (TKGM), synthesized by graft copolymerization of vinyl acetate and methyl acrylate onto konjac glucomannan (KGM). Dynamic mechanical analysis (DMA) and scanning electron microscopy (SEM) measurements showed that the PLA/TKGM system was miscible due to specific interactions between PLA and TKGM. This led to a maximum elongation at break of 520% for the blend (20/80), as compared to 14% for neat PLA. The impact strength also increased from 11.9 kJ/m^2 for neat PLA to 26.9 kJ/m^2 for the 20/80 blend. The synthesis of new polymers, biodegradable or non-biodegradable, to be compatibly blended with PLA, will represent a major task in the future.

Plasticization

PLA is a glassy polymer with poor elongation at break (typically less than 10%). The modification of PLA with different biodegradable and non-biodegradable plasticizers,

having a low molecular weight but a high boiling point and a low volatility, has been explored as a mean to lower the T_g and increase the ductility and softness of PLA. This has been achieved by varying the molecular weight, the polarity and functional groups of the plasticizers. Biocompatible molecules such as oligomeric lactic acid, oligomeric citrate ester, oligomeric PEG, and glycerol are all plasticizers of choice for PLA (Martin & Averous, 2001; Ljungberg et al., 2005). Ljungberg et al. (Ljungberg & Wesslén, 2002) have blended PLA with five plasticizers (triacetine, tributyl citrate, triethyl citrate, acetyl tributyl citrate, and acetyl triethyl citrate) and found that triacetine and tributyl citrate were more effective as plasticizers than the others to obtain a significant decrease in T_g for PLA.

Wang et al. (Wang et al., 2009) found that diisononyl cyclohexane-1,2-dicarboxylate (DINCH), a new plasticizer obtained by the hydrogenation of the benzene ring of o-phthalates, had limited compatibility with PLA when compared with tributyl citrate ester (TBC). PLA samples plasticized with 10 and 20 phr DINCH gave a constant T_g of 50°C. They were stiff materials displaying elevated values of elongation at break (129% and 200%, respectively) and impact strength (41.1 MPa and 30.1 MPa, respectively). On the other hand, TBC significantly decreased the T_g and increased the crystallinity of PLA, the PLA/TBC (20 phr TBC) blend being a soft material with a T_g of 24°C. Results from thermogravimetric and thermal analysis also indicated that PLA plasticized with DINCH had good mechanical properties and excellent water resistance (as reflected in time-dependent weight loss data in phosphate buffer) and aging resistance (characterized by the mechanical and thermal properties of specimens exposed to ambient conditions for 4 months).

Composition

Fibers can serve as fillers in the formation of PLA composites processable by compression or injection molding, to enhance the thermal stability, the hydrolysis resistance, or the mechanical properties of PLA. Several investigations on PLA composites prepared from natural and modified cellulose fibers have shown that their mechanical properties scale with the mass fraction of added fibers (Wan et al., 2001; Mathew et al., 2005). Optimization of the natural fiber-reinforced PLA composites, in terms of mechanical and other properties, is critical to minimize their cost, tailor their biodegradability, and broaden their areas of application. Inorganic fillers can also contribute to property modification. Table 3 provides a comparison of some of the organic and inorganic materials tested as PLA fillers.

Graupner et al. (Graupner et al., 2009) prepared composites from different types of natural fibers (cotton, hemp, kenaf) and modified cellulose fibers (Lyocell), with a fiber mass fraction of 40%, by compression molding. The mechanical properties of these composites are summarized in Table 4. Tomé et al. (Tomé et al., 2011) prepared composites from PLA and acetylated bacterial cellulose by mechanical compounding. The composites displayed significant increases in both elastic and Young moduli, as well as in tensile strength (increments of about 100, 40, and 25%, respectively, as compared with neat PLA) at 6% filler loading. Some surface modifiers can enhance adhesion between the fibers and the PLA matrix. For example, 3-aminopropyltriethoxysilane (APS) hydrolyzes in water or solvents to produce silanol groups that are capable of bonding to -OH groups on the kenaf fiber surface (Huda et al., 2008). The $-NH_2$ groups from APS can also bond with $-CO_2^-$ sites formed on the PLA surface by treatment with a sodium hydroxide solution. Thus APS effectively functions as a coupling agent. Yang et al. (Yang et al., 2011) produced a composite from PLA and microcrystalline cellulose modified by *L*-lactic acid. The tensile strength and the elongation at break of the composite were higher than for neat PLA. The surface modification of the cellulose substrates was considered a key element of the mechanical reinforcement.

Type	Filler	Result	Reference
Organic	Jute	Tensile stress and modulus increase with fiber volume fraction	Khondkeret al., 2006
	Flax fibers	Composite strength about 50% higher than for PP/flax composites	Oksman et al., 2003
	Kenaf fibers	Greatly improved crystallization rate, tensile and storage moduli	Pan et al., 2007
	Bamboo fibers	Increased bending strength and improved thermal properties	Tokoro et al., 2008
	Silkworm silk fibers	Good wettability, increased elasticity modulus and ductility	Cheung et al., 2008
	Microcrystalline cellulose	Poor mechanical properties and adhesion; increased storage modulus	Mathew et al., 2005
	LA-modified microcrystalline cellulose	Higher tensile strength and elongation at break than neat PLA	Yang et al., 2011
	Acetylated bacterial cellulose	Considerable improvement in thermal and mechanical properties	Tomé et al., 2011
Inorganic	Calcium metaphosphate	Narrow pore size distribution and high tensile strength	Jung et al., 2005
	Calcium carbonate	No brittle fracture behavior and comparably high bending strength	Kasuga et al., 2003
	Montmorillonite	Good affinity and improved thermal stability of the nanocomposites	Pluta et al., 2002
	HAP	Improved elastic modulus and unchanged bending strength	Kasuga et al., 2001
	Carbon nanotubes	Dramatic enhancement in thermal and mechanical properties	Wu & Liao, 2007
	Nano/Micro-silica	Increased tensile strength, thermal stability, and hydrolysis resistance	Huang et al., 2009

Table 3. Organic and inorganic fillers for the preparation of PLA composites.

	Tensile strength/ (N/mm^2)	Young's modulus/ (N/mm^2)	Elongation at break/ (%)	Charpy impact strength/ (kJ/mm^2)
Pure PLA sample	30.1	3820.2	0.83	24.4
Cottom-PLA	41.2	4242.3	3.07	28.7
Kenaf-PLA	52.9	7138.6	1.05	9.0
Hemp-PLA	57.5	8064.2	1.24	9.5
Lyocell-PLA	81.8	6783.8	4.09	39.7
Hemp/kenaf-PLA	61.0	7763.8	1.22	11.8
Hemp/Lyocell-PLA	71.5	7034.9	1.65	24.7

Table 4. Mechanical properties of composites and a pure PLA sample (mean values; all the specimens were tested at 0°C; adapted in part from (Graupner et al., 2009).

Kim et al. (Kim et al., 2010) prepared a series of PLA/exfoliated graphite (EG) nanocomposites and confirmed that the graphite nanoplatelets could be dispersed homogeneously within the PLA matrix. Thermogravimetric analysis also showed that the thermal stability of the nanocomposites was improved with incremental amounts of EG up to 3 wt %. For example, the temperature corresponding to a 3% weight loss for a composite with 3.0 wt % EG increased by 14 degrees to ~364 °C vs. pure PLA. Additionally, the Young's modulus of the composites increased with their graphite content and their electrical resistivity was dramatically lowered. Poly(lactic acid)/hydroxyapatite (PLA/HAP) composite scaffolds processed by foaming with supercritical CO_2 were shown to be promising for bone replacement, because their mechanical characteristics closely matched the properties of bone in terms of viscoelasticity and anisotropy (Mathieu et al., 2006).

4.1.2 Chemical modification

The chemical modification of PLA has been achieved mainly through copolymerization and cross-linking.

Copolymerization

The carboxyl and hydroxyl groups of LA make it possible to copolymerize it with other monomers through polycondensation with lactone-type monomers such as ε-caprolactone, which generally leads to low molecular weight copolymers, or alternately through the ring-opening copolymerization of lactide with other cyclic monomers including glycolide, δ-valerolactone, and trimethylene carbonate, as well as with monomers like ethylene oxide (EO) to produce high molecular weight copolymers. The hydrophobicity and crystallinity of the copolymers can be increased for low to moderate comonomer contents. Besides, poly(ethylene oxide) (PEO) and PEG have been most commonly copolymerized with PLA to prepare copolymers on account that it is highly biocompatible, hydrophilic and non-toxic, non-immunogenic and non-antigenic (Metters et al., 2000). Such properties reduce protein adsorption and enhance resistance to bacterial and animal cell adhesion.

Block copolymers are composed of long sequences (blocks) of the same monomer unit, covalently bound to sequences of a different type. The blocks can be connected in a variety of ways. Fig. 3 shows examples of block copolymer structures. Diblock PLA-PEG copolymers and triblock PLA-PEG-PLA copolymers allow modulation of the biodegradation rate, the hydrophilicity, and the mechanical properties of the copolymers, while phase separation can be tailored with PLA-PEG multi-block copolymers of predetermined block lengths (Wang et al., 2005). Star- and dendrimer-like PLA-PEG copolymers have also been synthesized to lower the T_g, T_m, and the crystallinity of the materials (Zhang et al., 2004).

Riley et al. (Riley et al., 2001) prepared a range of PLA-PEG copolymers incorporating a PEG block of constant molecular weight (Mn = 5,000) and varying PLA segment lengths (Mn = 2,000-110,000) by ROP of *D,L*-lactide catalyzed by stannous octoate; all the dispersions were stable under physiological conditions. In 2003, Li and Vert (Li & Vert, 2003) prepared series of diblock and triblock copolymers by ring-opening polymerization of *L(D)*-lactide from mono- and dihydroxyl PEO, using zinc metal as a catalyst under vacuum. The copolymers were semicrystalline, their composition and molar mass being determining factors affecting their solubility in water. Fu et al. (Fu et al., 2008) prepared series of LA-based polyurethanes modified by castor oil with controllable mechanical properties. In this work, hydroxyl-terminated prepolymers were synthesized by copolymerization of L-LA and 1, 4-butanediol.
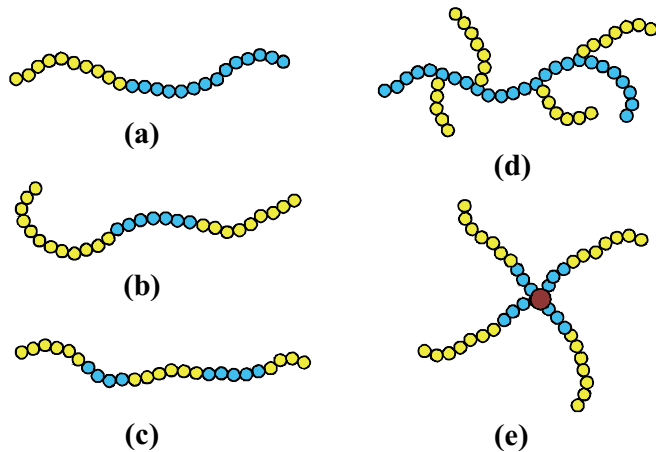
Fig. 3. Schematics of block copolymer structures: (a) diblock; (b) triblock; (c) alternating multiblock; (d); dendrimer-like copolymer; (e) star-like copolymer.

Cross-linking

Cross-linked PLA structures can be formed either by irradiation or through chemical reactions. Electron beam and γ-irradiation have been widely applied to cross-linking PLA in the presence of small amounts of cross-linking agents such as triallyl isocyanurate (TAIC) (Quynh et al., 2008; Phong et al., 2010). The thermal stability of PLA-based materials can be significantly improved in this way (Quynh et al., 2007). Quynh et al. (Quynh et al., 2009) obtained stereocomplexes by cross-linking blends of PLLA and low molecular weight PDLA. Alkaline hydrolysis and enzymatic degradation of the stereocomplex could be controlled by radiation cross-linking, because the alkaline solution as well as proteinase hardly attacked the cross-linked polymer network. Unfortunately, irradiation equipment is expensive and the PLA samples must be processed as thin plates to absorb enough energy from the radiation to initiate cross-linking reactions, which significantly limits its practical application.

Modified PLA with different gel fractions and cross-linking densities can also be obtained through chemical reactions between linking agents and the polymer chains without irradiation (Agrawal et al., 2010). Yang et al. (Yang et al., 2008) thus induced cross-linking via treatment of the PLA melt with small amounts of TAIC and dicumyl peroxide (DCP). The results obtained for samples with different gel fractions and cross-link densities showed that the cross-linking of PLA was initiated at low contents of either TAIC or DCP. The crystallinity of cross-linked PLA samples obtained with 0.5 wt% TAIC and 0.5 wt% DCP decreased from 32% for pure PLA to 24%. Significant increases in tensile modulus from 1.7 GPa to 1.9 GPa, and in tensile strength from 66 GPa to 75 GPa were also observed, and the thermal degradation initiation and completion temperatures were both increased relatively to neat PLA. Additional advantages of this method are that it requires neither extra purification steps nor specialized equipment, since the reaction is carried out in the molten state with only small amounts of cross-linking agent. It is thus economically very advantageous over irradiation, which requires expensive equipment. An increase in brittleness was nevertheless observed following the formation of highly cross-linked structures, which remains a problem to be solved.

4.2 Surface modification

The surface properties of materials play a key role in determining their applications. The presence of specific surface chemical functionalities, hydrophilicity, roughness, surface energy, and topography is crucial for biomedical applications of PLA and its interactions with biomacromolecules. Pure PLA causes a mild inflammatory response if it is implanted into human tissues. It is therefore important to design biomaterials with the required surface properties. The different surface modification strategies examined include physical methods, including surface coating, entrapment and plasma treatment, and chemical methods. Both types of approaches are reviewed.

4.2.1 Physical methods

Surface coating

This is one of the simplest surface modification methods and has been applied to various polymers, but particularly to PLA nanoparticles used for drug delivery. For instance, PEG coating delayed the phagocytosis of PLA nanoparticles and prolonged the circulation time of the nanoparticles in vivo (Gref et al., 1994). Unfortunately the PEG-coated PLA nanoparticles cannot provide specific targeting, which influences their delivery efficiency. One of the most promising alternatives to PEG in this respect is the use of polysaccharides. These materials provide steric protection to the nanoparticles against non-specific interactions with proteins and thereby insure particle stability in the blood circulation system (Ma et al., 2008). Additionally, ligands to achieve active targeting can be conjugated on the surface of these nanoparticles, because many reactive groups are available on the polysaccharides and their derivatives (Gu et al., 2007). Another option is coating of the surface with extracellular matrix (ECM) proteins such as fibronectin, laminin, vitronectin, and collagen, which are conducive to cell adhesion and can greatly improve biocompatibility as well (Lin et al., 2010).

Innovative work was accomplished by Cronin et al. (Cronin et al., 2004), who tested a PLLA fiber scaffold as a substrate for the differentiation of human skeletal muscle cells. Cell attachment (the number of cells attached to the films counted along the center, from one edge to the opposite edge of the film within the field of view) increased significantly on PLLA films coated with ECM gel, fibronectin, or laminin as compared to uncoated or gelatin-coated PLLA films. Myoblasts were able to differentiate into multinucleated myofibers on the ECM gel-coated PLLA fibers and expressed muscle markers such as myosin and α-actinin, as demonstrated by western blot and oligonucleotide microarray analysis.

Entrapment

The entrapment of modifying species (e.g. PEG, alginate, gelatin, etc.) can be achieved through reversible swelling of the PLA surface as illustrated in Fig. 4. This is a simple yet effective method for surface modification requiring no specific functional groups in the polymer chains, as the modifying molecules accumulate merely on the surface of the material without modifying its bulk properties (Lu et al., 2009). Additionally, entrapment can be used to generate different morphologies and thicknesses of 3D scaffolds, which cannot be achieved by other surface modification methods. Finally, entrapment allows the modification of the surface in a controlled fashion because various parameters (e.g. solvent ratio, gelatin concentration, immersion time, and chemical cross-linking) can be varied to tailor the process (Zhu et al., 2003).
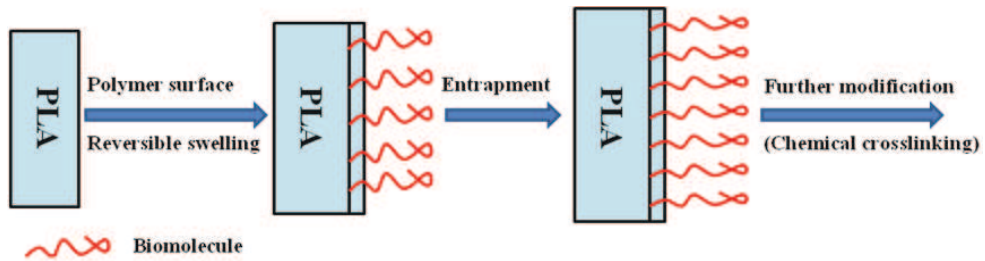
Fig. 4. Schematic illustration of entrapment process.

PEG (M_w = 18,500) and poly(*L*-lysine) (PLL) (M_w = 29,300) have been trapped on PLA surfaces using 2,2,2-trifluoroethanol (TFE)/water as solvent/nonsolvent mixtures (Quirk et al., 2002). A new entrapment process has also been reported by Liu et al. (Liu et al., 2005), through chemical cross-linking of gelatin with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) HCl and *N*-hydroxysuccinimide (NHS) (97%) in {2-[N-morpholino] ethanesulfonic acid} (MES) hydrate buffer, after the pretreated PLLA films were immersed in the gelatin solution for a set time. Results in comparison to the control scaffolds have shown that the surface hydrophilicity increased with the amount of entrapped gelatin and that cell attachment and proliferation, the deposition of collagen fibers, and other cell excretion (extracellular matrix, etc.) were also significantly improved.

Plasma treatment

Tests with plasma treatment were initiated in the 1960s and have been since then widely utilized to improve the hydrophilicity and cell affinity of PLA surfaces. The obvious advantages of plasma treatment as compared to other surface modification methods include its ability to control the surface structure, energy and charge, and to uniformly modify the surface without impacting bulk properties (Chu et al., 2002). Functional groups such as –NH$_2$, –COOH, and –OH, which are apt to form covalent bonds with other materials for further modification, are most frequently introduced by plasma treatment (Favia et al., 1998).

Liu et al. thus investigated the influence of the main operation parameters, namely the plasma power, the treatment duration (number of treatment cycles) and the electrode gap on a dielectric barrier discharge (DBD) plasma treatment of PLA films in terms of changes in surface wettability and chemistry (Liu et al., 2004). They further developed equations relating the surface properties (water contact angle and oxygen enrichment, as observed by XPS analysis) to these operational parameters. It was determined that the magnitude of the electrode gap played a dominant role in the treatment of PLA, and the observed wettability improvements were attributed to changes in both surface chemistry and microstructure. Chaiwong and coworkers (Chaiwong et al., 2010) investigated the influence of SF$_6$ plasma on the hydrophobicity and barrier properties of PLA. It was found that the SF$_6$ plasma enhanced the hydrophilicity and increased the water absorption time of PLA two-fold. Plasma treatment did not have any significant influence on the water vapor permeability of PLA, however, since the bulk structure controlling the transport properties are unaffected by the treatment. Other types of plasmas such as oxygen, helium, and nitrogen plasmas have also been investigated (Hirotsu et al., 2002).

While plasma treatment has been successfully applied to improving PLA wettability and cell affinity, its main disadvantage is that surface rearrangements caused by thermally activated macromolecular motions, to minimize its interfacial energy, can also influence the surface modification. Moreover, the potential influence of plasma on the degradation of PLA cannot be ignored.

4.2.2 Chemical modification

PLA does not carry reactive side-chain functional groups. Consequently, the first step of chemical modification is typically a simple surface hydrolysis (with an alkali) or an aminolysis treatment. The hydrophilic –COOH and –OH or reactive –NH$_2$ groups introduced by cleavage of the ester bonds can be used to bind bioactive molecules such as arginine-glycine-aspartic acid (RGD)-containing peptides, chitosan (CS), arginine and lysine, PEG, collagen, and so on to regulate cell adhesion or protein adsorption.

The synthetic RGD-containing peptides could be immobilized on PLA after treatment by hydrolysis or aminolysis (Stupack et al., 2001). Materials prepared by this method provide suitable recognition sites for cell adhesion receptors and biodegradation rates, making them suitable for various applications in fields such as tissue engineering and implant technology. It has also been determined that RGD-conjugated poly(lactic acid-*co*-lysine)(arginine-glycine-aspartic acid) nanoparticles (PLA-PLL-RGD NP) are non-toxic and bind more efficiently to human umbilical vein endothelial cells (HUVECs) as compared to bare PLA-PLL NP in vitro. Targeted imaging results obtained in vivo showed that PLA-PLL-RGD can selectively bind to BACP-37 breast cancer cells. Lieb et al. also demonstrated largely increased cell densities and cell proliferation on surfaces modified with RGD-anchored monoaminated poly(ethylene glycol)-*block*-poly(*D,L*-lactic acid) (H$_2$N-PEG-PLA), mediated through RGD–integrin interactions (Lieb et al., 2005).

Chitosan (CS) is a biopolymer displaying good biocompatibility, non-toxicity and biodegradability, produced by the alkaline *N*-deacetylation of chitin. The immobilization of this polymer on PLA has been accomplished by coating the surface with chitosan, modified with the photosensitive hetero-bifunctional cross-linking reagent 4-azidobenzoic acid, and irradiation with ultraviolet light to photolyze the azide groups and covalently link the two polymers (Zhu et al., 2002). The -OH and -NH$_2$ groups of chitosan provide further opportunities to introduce a wide range of functional groups on the surface. Thus CS molecules immobilized on PLA were modified with a heparin (Hp) solution to form a polyelectrolyte complex on the surface, which inhibited platelet adhesion and activation, and enhanced cell adhesion.

4.3 Outlook of PLA surface modification

The surface attributes of PLA can be tailored to enhance its hydrophilicity and biocompatiblity through various methods. Unfortunately, all these established methods for surface modification are inherently flawed to some extent. For example, a single plasma treatment can merely improve cell adhesion but cannot accelerate cell growth; non-covalent attachment of a functional material onto a PLA surface is not stable and permanent. An excellent method suggested to solve the second issue is the use of 1,6-hexanediamine for surface aminolysis, followed by conjugation with biocompatible macromolecules such as gelatin, chitosan, or collagen (Zhu et al., 2004). Hong et al. have

shown that chondrocyte cells could attach, proliferate, and spread on PLA microspheres coated with collagen in the same way as described above, in particular those having high collagen contents (Hong et al., 2005). It appears that the surface modification of PLA would be best achieved with a combination of distinct approaches, to benefit from the advantages of all the methods. Polysaccharide polyelectrolyte multilayers, including chitosan and dextran sulfate-stabilized silver nano-sized colloids developed by Yu et al. (Yu et al., 2007), were successfully deposited on an aminolyzed PLA membrane in a layer-by-layer self-assembly manner. This seemingly easy process resulted in significant improvements in hydrophilicity, antibacterial activity, hemocompatibility, and cytocompatibility for the PLA membrane, thanks to the different attributes of $-NH_3^+$ (positive charge), chitosan (biocompatibility), and silver nanoparticles (antibacterial activity). The radiation-induced methods are emerging as powerful surface modification techniques, particularly when relying on PLA photoactivation to create reactive groups or moieties useful to graft specific chemical functionalities. The irradiation of PLA with UV (ozone can be generated from molecular oxygen irradiated with UV in this process), for example, is known to increase fiber adhesion to high surface energy components due to the introduction of photo-oxidized polar groups on the surface (Koo & Jang, 2008). Irradiation followed by grafting has also been used extensively to alter PLA surface characteristics, mainly due to the advantages it offers, namely a low operation cost, mild reaction conditions, selectivity to UV light, and the permanent surface chemistry changes induced (Ma et al., 2000).

5. Applications of PLA in the biomedical field

Due to its bioresorbability and biocompatibility in the human body, PLA has been employed to manufacture tissue engineering scaffolds, delivery system materials, or covering membranes, different bioabsorbable medical implants, as well as in dermatology and cosmetics.

5.1 Tissue engineering

Since the introduction of the concept in 1988, tissue engineering, a technique invented to reconstruct living tissues by associating the cells with biomaterials that provide a scaffold on which they can proliferate three-dimensionally and under physiological conditions, has emerged as a potential alternative to tissue or organ transplantation and has thus attracted great attention in science, engineering, and medicine. To meet the diverse needs of tissue engineering, scaffolds made from various materials have been tested in this field. Although certain metals are somewhat good choices for medical implants due to their superior mechanical properties, their lack of degradability in a biological environment makes them disadvantageous for scaffold applications (Liu & Ma, 2004). Inorganic/ceramic materials such as HAP or calcium phosphates, being studied for mineralized tissue engineering with good osteoconductivity, are also limited due to poor processability into porous structures (Ilan & Ladd, 2002). In contrast, polymers have great design flexibility because their composition and structure can be tailored to meet specific needs (Huang et al., 2007). Degradable polymers frequently used for tissue engineering applications are linear aliphatic polyesters such as PGA, PLA, and their copolymers (PLGA), which are fabricated into

scaffolds. These polymers are among the few synthetic polymers approved by the FDA for human clinical applications. The drawbacks of these polyesters include their hydrophobicity and lack of functional groups, which limits cell adhesion, an important factor when constructing polymeric scaffolds. Another drawback is their slow hydrolytic degradation (Iwata & Doi, 1998).

An ideal scaffold used for tissue engineering should possess the following properties: 1) Be biocompatible, so that the scaffold can be well integrated into host tissues without resulting in any immune response; 2) It should be porous with appropriate pore size, size distribution and mechanical function, to allow cell or tissue growth and the removal of metabolic waste; 3) It must be mechanically able to withstand local stress and maintain the pore structure for tissue regeneration; 4) Very importantly, the scaffold should be biodegradable (Ma, 2004). Synthetic scaffolds are considered important components of a successful tissue engineering strategy (Wang, 2007). Hybrid three dimentional porous scaffolds of synthetic and naturally derived biodegradable polymers are particularly promising because they combine the advantages of the two types of materials. They should maintain sufficient mechanical strength while providing specific cell-surface receptors during the tissue remodeling process that stimulate both in vitro and in vivo cell growth (Chen et al., 2002). PLA-based hybrid materials have been successfully tested clinically for that purpose so far, and tests on other tissues including bladder (Engelhardt et al., 2011), cartilage (John et al., 2003), liver (Lv et al., 2007), adipose (Mauney et al., 2007), and bone tissues (Mathieu et al., 2006) have also been reported.

Jiang et al. (Jiang et al., 2010) functionalized chitosan/PLGA by heparin immobilization with controlled loading efficiency. One of the main benefits of introducing chitosan into PLGA microspheres is that chitosan imparts functionality due to its reactive amino groups, so that biomolecules such as heparin could be attached (Jiang et al., 2006). The compressive strength and modulus remained in the range of human trabecular bone after the heparinization process. More importantly, heparinized chitosan/PLGA scaffolds with a low heparin loading (1.71 g/scaffold) showed a stimulatory effect on cell differentiation, as indicated by enhanced osteocalcin expression as compared with a non-heparinized chitosan/PLGA scaffold. Based on these results, Jiang et al. (Jiang et al., 2006) continued to evaluate the novel scaffolds for bone regeneration in vivo. In the rabbit ulnar critical-sized-defect model created, successful bridging of the critical-sized defect on the sides both adjacent to and away from the radius occurred using chitosan/PLGA-based scaffolds. However, the addition of chitosan to PLGA led to somewhat higher inflammation and lower mineralization than for the PLGA counterpart, which is a major problem that remains to be solved.

Three-dimensional (3D) electrospun fibrous scaffolds have been suggested as a potential tissue engineering tool for bone regeneration. Shim et al. (Shim et al., 2010) thus reported a 3D microfibrous PLLA scaffold fabricated using electrospinning techniques with a subsequent mechanical expansion process. The use of these 3D scaffolds for the proliferation of osteoblasts was examined. The 3D scaffolds led to a 1.8-fold higher level of osteoblast proliferation than generally achieved for electrospun 2D nanofibrous membranes. In vivo results further showed that 3D electrospun microfibrous matrices provided a favorable substrate for cell infiltration and bone formation after 2 and 4 weeks when using a rabbit calvarial defect model.

3D printing technology has rapidly expanded in the tissue engineering field since it was first developed at the Massachusetts Institute of Technology. Ge et al. (Ge et al., 2009) developed 3D-printed poly(lactic acid-co-glycolic acid) (PLGA) scaffolds which could support the proliferation and osteogenic differentiation of osteoblasts. Based on their in vitro study, they also evaluated PLGA scaffolds for bone regeneration within a rabbit model (Ge et al., 2009). In both the intra-periosteum and the iliac bone defect models, the implanted scaffolds facilitated new bone tissue formation and maturation over a time period of 24 weeks.

The current clinical use of PLA-based scaffolds nevertheless remains very limited (Iwasa et al., 2009), mainly because of the risk of disease transmission and immune response. This can be illustrated by taking cartilage tissue engineering as an example. Traditional autologous chondrocyte implantation (ACI), first introduced by Brittberg et al. in 1994 (Brittberg et al., 1994), has yielded good clinical results (Bentley et al., 2003). To date, none of the short- or mid-term clinical and histological results using scaffolds were reported to be better than ACI. As for the scaffolds, collagen and hyaluronan-based matrices are among the most popular scaffolds in clinical use nowadays, since they offer substrates which are normally essential elements in native articular cartilage (Iwasa et al., 2009). Among the very few cases of scaffolds in clinical use is the copolymer of PGA/PLA (polyglactin, vicryl) and polydioxanone, which is used for cartilage repair under the trade name of BioSeed®-B and BioSeed®-C (Biotissue Technologies AG, Freiburg, Germany).

In summary, tissue engineering is one of the most exciting interdisciplinary fields today and is growing rapidly with time. The inclusive criteria for studies on scaffolds capable of clinical application were in vivo or clinical studies and thus certain artificially designed scaffold features (such as pore size, interpore connectivity, etc.) are necessary for optimal tissue engineering applications (accelerated tissue regeneration). Suggestions for future directions include the use of designer scaffolds with in vivo experimentation, and coupling scaffold design with cell printing to create designer material/biofactor hybrids to optimize tissue engineering treatments (Hollister, 2005).

5.2 Delivery systems

There has long been a desire to achieve the targeted delivery of bioactive compounds to areas in the body to maximize therapeutic potential and minimize side-effects. Many types of particles have been tested as delivery tools for biomedical applications such as liposomes, solid lipid nanoparticles, and biodegradable polyesters like PLA and PLGA (Torchilin, 2006). With its excellent biocompatibility, biodegradability, mechanical strength, heat processability, and solubility in organic solvents, PLA can be used to produce dosage forms such as pellets, microcapsules, microparticles (MP), nanoparticles (NP), etc. MP and NP of PLA, modified or unmodified, are increasingly investigated for sustained release and targeted drug, peptide/protein, and RNA/DNA delivery applications because of their small size enabling their permeation through biological barriers such as the blood-brain barrier (Roney et al., 2007).

Although PLA-based materials such as PLGA have been FDA-approved and are clinically available, they lack chemical functionalities to facilitate specific cell interactions. Furthermore, their potential for the sustained release of hydrophilic molecules (e.g. proteins) is often limited (Fahmy et al., 2005). Frequent undesired effects include low

encapsulation efficiency and high burst release of the encapsulated biomolecule within the first few hours or days, which is mainly due to the desorption of surface-associated hydrophilic molecules having weak interactions with the polymer (Fahmy et al., 2005). To circumvent these limitations and establish therapeutic efficacy, large doses or site-specific administration are often required for devices comprised of polyester biomaterials. In an attempt to address these problems, numerous groups have introduced functional groups (such as amine functionalities) on these materials, either through direct conjugation or device fabrication with additives (Betram et al., 2009).

As for drug release from MPs or NPs, it is generally controlled by both drug diffusion and polymer degradation. To ensure the efficacy of drug delivery, control over the particle size and particle size distribution is critical, since smaller particles and narrower size distributions facilitate the design of targeted drug delivery systems. These involve binding fragments specific to a tumor-associated surface antigen, with a ligand binding to its corresponding receptor on the tumor cell surface, which can be attached on the surface of the PLA-based materials. Furthermore, polymers that display a physicochemical response to changes in their environment are being intensively explored as potential drug and gene delivery systems. The use of stimuli-responsive nanocarriers offers an attractive opportunity for targeted delivery, in which the delivery system becomes an active participant rather than a passive vehicle. The advantage of stimuli-responsive nanocarriers becomes obvious when the stimuli are unique to disease pathology, allowing the nanocarrier to respond specifically to the pathological characteristics. For instance, in solid tumors, the extracellular pH decreases significantly from 7.4 (the pH value under normal physiological conditions) to about 6.5 (Vaupel et al., 1989; Haag, 2004). In addition, the pH ranges from 4.5 in lysosomes to about 8.0 in mitochondria. Given these pH shifts, therapeutic compounds with a pK$_a$ between 5.0 and 8.0 are able to exhibit dramatic changes in physicochemical properties (Ganta et al., 2008). Another option is thermo-sensitive polymeric micelles, containing a hydrophobic core and a thermo-sensitive shell, the later changing from a hydrophilic nature at body temperature to a collapsed hydrophobic polymer at a hyperthermic condition of 42°C (Na et al., 2006). Investigations concerned with this theme include responses induced by chemical substances, changes in temperature (Tyagi et al., 2004) or pH (Sethuraman & Bae, 2007), electric signals (Sawahata et al., 1990) or other environmental conditions (Qiu & Park, 2001).

The use of nucleic acids as therapeutic agents for genetic diseases has been extensively studied (Torchilin, 2008). However, a major limitation of this technique lies in the low delivery efficiency of the therapeutic DNA to the diseased site. To address this issue, various strategies have been explored including vectors engineered from viruses (Brun et al., 2008) and PLGA in NP formulations. PLGA NP have shown particular promise in improving the delivery efficacy (Kocbek et al., 2007). Besides, the physical characteristics of the nanoparticles can be manipulated to escape the degradative endosomal lumen, resulting in cytosolic localization. To develop novel administration paths, hybrid versions of research have been conducted on this subject, yet the results are mostly based on animal models or in vitro results, making it difficult to draw final conclusions. From clinical trials, substantial obstacles to their use, such as immunogenicity and inflammatory potential, have also been demonstrated (Nafee et al., 2007). Therefore, there is still a long way to go before real clinical applications come through.

Some examples of delivery systems incorporating PLA are provided in Table 5 and in Fig. 5 (Chen et al., 2007; Sethuraman & Bae, 2007). Sethuraman et al. (Sethuraman & Bae, 2007) developed a novel drug delivery system for acidic tumors consisting of two components: 1) A polymeric micelle with a hydrophobic core of PLLA and a hydrophilic shell of PEG conjugated to TAT (a cell-penetrating peptide in HIV), and 2) a highly pH-sensitive copolymer of poly(methacryloyl sulfadimethoxine) (PSD) and PEG (PSD-b-PEG). The final carrier, which was able to shield the micelles and expose them at slightly more acidic tumor pH levels, was achieved by complexing PSD with the TAT of the micelles. The results obtained showed significantly higher uptake of TAT micelles at pH 6.6 in comparison with pH 7.4, and that TAT not only translocated into the cells but it was also traced to the surface of the nucleus [see Fig. 5].
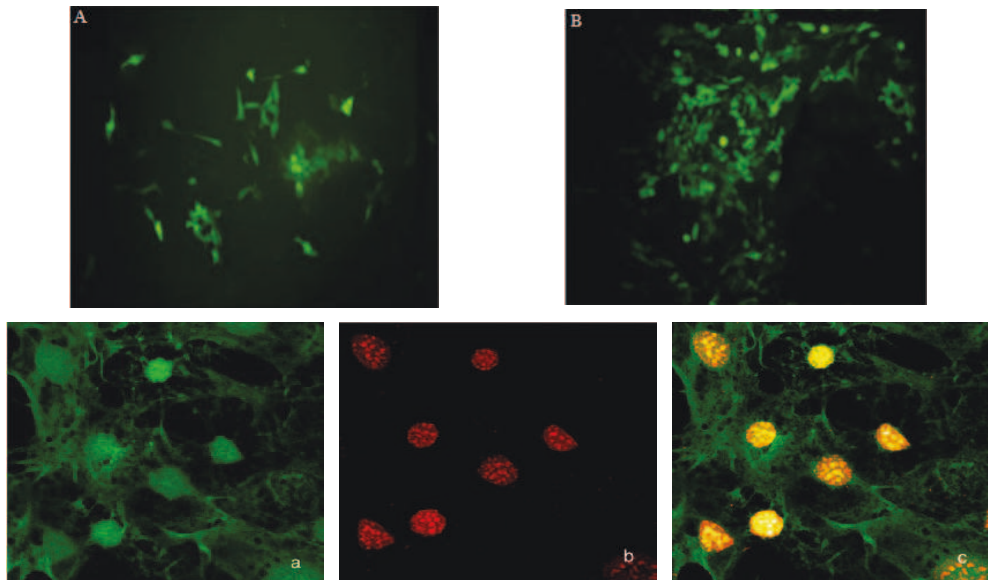
Fig. 5. Test results for PLA-based drug delivery materials. Fluorescent microscopy images are shown on top for COS7 cells transfected by plasmid encoding enhanced green fluorescence protein (EGFP) with different carriers: (A) lipofectamine, (B) methoxypolyethyleneglycol-PLA-chitosan nanoparticles (MePEG-PLA-CS NP); the transfection efficiency, as detected by flow cytometry, is higher in (B) than in (A) (Reproduced with the permission from Chen, J. et al. (2007). Preparation, characterization and transfection efficiency of cationic PEGylated PLA nanoparticles as gene delivery systems, Journal of Biotechnology, Vol.130, No.2, pp.107. Copyright (2007) Elsevier) At the bottom are dual label confocal micrographs for MCF-7 cells incubated with TAT micelles: (a) Cells stained with fluorescein isothiocyanate (FITC) attached to TAT in the micelles; (b) the same nuclei as in (a) were stained with TOPRO-3; (c) superimposed images of (a) and (b); the yellow color shows the localization of TAT within the nuclei (Reproduced with the permission from Sethuraman, V. A. & Bae, Y. H. (2007). TAT peptide-based micelle system for potential active targeting of anti-cancer agents to acidic solid tumors. Journal of Controlled Release, Vol.118, No.2, pp.216. Copyright (2007) Elsevier).

Material	Application	Results	Reference
PLA-PEG particles	Carrier for tetanus toxoid	Enhanced transport across the rat nasal mucosa	Vila et al., 2005
PEG-PLA NP	Conjugated with lactoferrin (Lf)	Increased uptake of the Lf-NP by bEnd.3 cells	Hu et al., 2009
PLA-b-Pluronic-b-PLA	Carrier for oral insulin	Good control over blood glucose concentration	Xiong et al., 2007
PLA NP	Carrier for HIV p24 proteins	Induced seric and mucosal antibody production	Aline et al., 2009
Surfactant-free PLA NP	Carrier for HIV p24 proteins	Elicited strong CTL response and cytokine release	Liggins et al., 2004
PLA microspheres	Carrier for paclitaxel	Reduced inflammation of arthritis rabbit model	Jie et al., 2005
PEO-PLA copolymers	Carrier for 5-FU and paclitaxel	Complete drug release	Zhang & Feng, 2006
PLA-TPGS copolymers	Carrier for paclitaxel	Initial burst followed by sustained release	Freitas et al., 2005
PLA microspheres	Carrier for nimesulide	Initial burst followed by an exponential decrease	Chen et al., 2007
PEGylated PLA NP	Gene delivery systems	Improved transfection activity	Ataman-Önal et al., 2006
PLA-PEG-PLA copolymer	Carrier for 5-FU and paclitaxel	Good control over the release	Venkatraman et al., 2005
AP-PEG-PLA/MPEG-PAE	Drug carrier for cancer therapy	Presented high tumor-specific targeting ability	Wu et al., 2010
PLGA/PEI NP	Carrier for luciferase siRNA	Effective silencing of the gene in cells	Patil & Panyam, 2009
cNGR-PEG-PLA NP	Carrier for DNA	Rapid and efficient nanoparticle internalization	Liu et al., 2011
DMAB coated PLGA NP	Loaded with plasmid DNA	Significantly improved transfection efficiencies	Fay et al., 2010

Table 5. Investigations on PLA-based material as drug delivery systems. AP: peptide, CRKRLDRN; MPEG: methyl ether poly(ethylene glycol); PAE: poly(β-amino ester); PEI: polyethylenimine; cNGR: Cyclic Asn-Gly-Arg; DMAB: dimethyldidodecylammonium bromide.

In summary, some problems still remain to be tackled for this promising novela dministration method. A major issue is the presence of surfactants such as SDS or stabilizers such as PVA in the microparticles, necessary to achieve antigen binding and colloidal stability. Although present only at low concentrations, the acceptability of such components in human vaccines depends on the results of extensive and costly toxicological studies. Biodegradable polymers used for drug delivery to date have mostly been in the form of injectable microspheres or implant systems requiring complicated fabrication processes with organic solvents. In such systems, the organic solvents can denature components such as protein drugs being encapsulated. Besides, these delivery systems have relatively low transfection efficiencies in vitro as compared with reagents commercialized for cell transfection. The last problem concerns the lack of test results for these delivery systems

using animal models or in clinical trials, which is of fundamental importance for real applications in biomedical therapy.

5.3 Other fields

Due to its versatility, PLA has been investigated for membrane applications (e.g. wound covers), implants and medical devices (fixation rods, plates, pins, screws, sutures, etc.), and dermatological treatments (e.g. facial lipoatrophy and scar rejuvenation).

With respect to wound treatment, bacterial infections are one of the main factors impacting the healing process. One of the best approaches to treat wound infections is by the immobilization of drugs or antibacterial agents within the nanofibers by electrospinning, or the electrospinning of polymers with intrinsic antibacterial and wound-healing properties. Dozens of patents have been issued on that topic so far (Ghosh et al., 2007; Robinson et al., 2009). Silver nanoparticles (nAg) and the natural polysaccharide chitosan (as well as its quaternized derivatives) are most commonly used as antibacterial agents with a high intrinsic activity against a broad spectrum of bacteria (Rujitanaroj et al., 2008; Ignatova et al., 2009).

Metals are still the most popular materials for fracture fixation, but their disadvantages include stress shielding, accumulation in tissues, hypersensitivity, growth restriction, pain, corrosion, and interference with imaging techniques. Consequently, the focus of research is increasingly shifted to biomaterials like PLA, which offers satisfactory strength during the healing of bone tissue and then degrades over time (Mavrogenis et al., 2009). A commercial product with a proven track record in clinical applications is the VICRYL™ suture material, based on PGA/PLA copolymers (Mehta et al., 2005). The number of applications of PLA as fixation rods, plates, pins, screws, sutures, etc. in orthopaedics and dentistry is also increasing (Raghoebar et al., 2006).
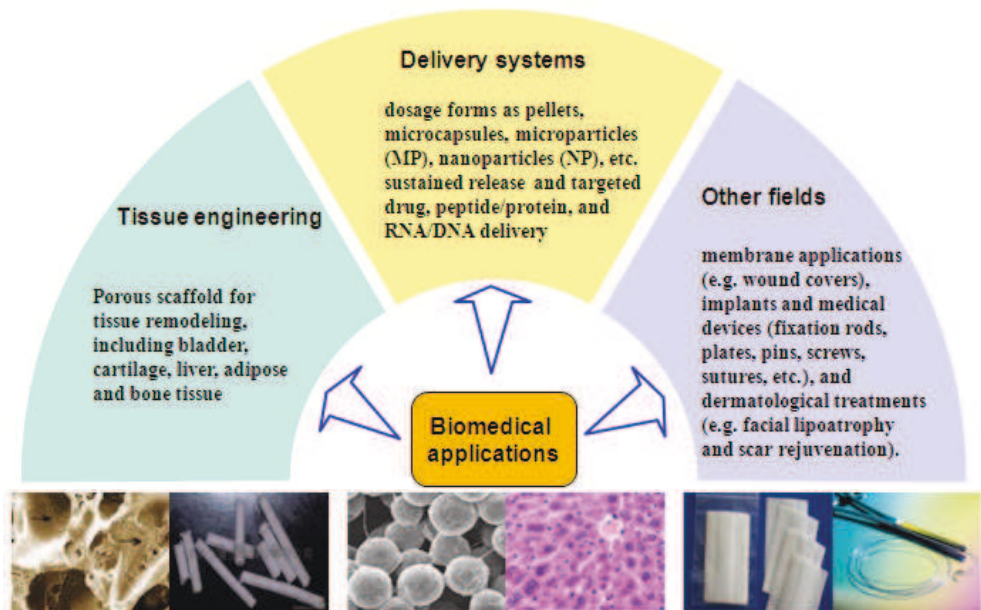

Fig. 6. Applications of PLA in the biomedical field.

In 2004, Sculptra™ [poly(*L*-lactic acid)] was approved by the FDA as the first injectable facial "volumizer" in the treatment of lipoatrophy due to its significant therapeutic effectiveness (Burgess & Quiroga, 2005). The lipodystrophy syndrome is associated with the usage of highly active antiretroviral therapy (HAART) containing protease inhibitors or nucleoside reverse transcriptase inhibitors for HIV patients. The action mechanism of Sculptra™ is via stimulation of the fibroblastic activity with generation of collagen and other connective tissue fibers. In addition, it acts as dermal matrix adding support by thickening the dermis (Vleggaar & Bauer, 2004). Moreover, PLA can help improve the appearance of scars due to acne, surgery, trauma, or suture (Lowe & Beer, 2005, as cited in Beer & Rendon, 2006).

6. Conclusions

Due to the multiple desirable characteristics of PLA including renewability, biocompatibility, transparency, and thermoplasticity, it is being used or is a potential candidate for many consumer and biomedical applications (Jamshidian et al., 2010). Ever increasing environmental concerns associated with conventional polymers derived from petrochemicals lead to constantly expanding applications for PLA since its discovery in 1932 by Carothers at DuPont.

In previous years, the most negative point of PLA was its higher price as compared with petrochemical-based polymers. Today, by optimizing the LA and PLA production processes, and with increasing PLA demand, a reduction in its price can be achieved. The price of PLA is currently much lower than in previous years. Meanwhile, PLA is mainly synthesized in the industry by ROP employing tin(II) bis(2-ethylhexanoate) (SnOct$_2$) as a catalyst, which has been approved as a food additive by the FDA, but the potential toxicity associated with most tin compounds cannot be ignored for biomedical applications. Scientists all over the world are now exploring novel, well-defined catalysts with good biocompatibility, high catalytic activity, low toxicity, and excellent stereoselectivity. This should remain an everlasting interest area. Finally, the possibility of obtaining 100% bio-sourced opens the way for PLA to become more independent from petrochemical-based polymers, free of environmental and health concerns.

However, the major disadvantages of PLA such as its poor ductility, slow degradation rate, and poor hydrophilicity somewhat limit its applications. The modification of PLA bulk and surface properties has thus become crucial to increase its applicability. Many of the bulk and surface modification strategies discussed above have been designed to tune the PLA surface properties according to the demands of biomedical applications. Unfortunately, all these established methods for surface modification are somewhat deficient and while they provide control over the wettability, degradation rate, and functionality, it is still compulsory to minimize their negative impact on PLA bulk properties. Thus a combined modification strategy (e.g. irradiation followed by grafting) or a better balance of PLA surface and bulk properties should be sought. Ideally, with respect to a better balance of properties and shorter modification times, one-step approaches need to be developed because it is time-consuming to carry out surface and bulk modifications separately, and the solvents and reagents involved in multiple modification steps tend to affect PLA properties significantly.

All these modification strategies aim at tailoring the properties of PLA-based materials for certain applications. Fortunately, more and more encouraging results have been reported,

but the present conclusions from most of these reports cannot be directly generalized to truly biomedical applications since most of the experiments were carried out in vitro. Nevertheless, these findings offer some clues for further improvements. The increasing number of functional PLA-based polyesters provides the opportunity to study the relationships between structure and functionality of these polymers such as cell adhesion and degradability in vitro and in vivo, as well as to develop applications of these materials for delivery system in the form of micro- and nanoparticles or scaffolds for tissue engineering. Finally, cancers and acquired or inherited genetic diseases represent one of the most serious threats to the health of human beings, but no effective therapies are available so far. It is suggested that the development of effective and ideal tools for drug, peptide/protein, and RNA/DNA delivery will represent a good alternative in drug development. It therefore appears that it would be best to focus future research work on the rational design of novel carriers for biomedical uses and targeted delivery systems. Obviously, this requires plenty of relevant experiments on animal model and enough clinical trials before they are widely utilized.

Even though countless studies have focused on the synthesis and the modification of PLA and remarkable progresses has been achieved over the last two decades, vast opportunities as well as challenges remain in terms of exploring the characteristics of PLA-based materials and expanding their domains of applications.

7. Acknowledgement

8. References

Achmad, F. et al., (2009). Synthesis of polylactic acid by direct polycondensation under vacuum without catalysts, solvents and initiators. *Chemical Engineering Journal,* Vol.151, No.1, (August 2009), pp. 342-350, ISSN 1385-8947

Agrawal, S. K. et al., (2000). Rare earth metal initiated ring-opening polymerization of lactones. *Macromolecular Rapid Communications*, Vol.21, No.5, (March 2000), pp. 195-212, ISSN 1022-1336

Agrawal, S. K. et al., (2010). Energetics of association in poly(lactic acid)-based hydrogels with crystalline and nanoparticle-polymer junctions. *Langmuir,* Vol.26, No.22, (October 2010), pp. 17330-17338, ISSN 0743-7463

Ajioka, M. et al. (1995). The basic properties of poly(lactic acid) produced by the direct condensation polymerization of lactic acid. *Journal of Polymers and the Environment,* Vol.3, No.4, (October 1995), pp. 225-234, ISSN 1566-2543

Aline, F. et al., (2009). Dendritic cells loaded with HIV-1 p24 proteins adsorbed on surfactant-free anionic PLA nanoparticles induce enhanced cellular immune

responses against HIV-1 after vaccination. *Vaccine,* Vol.27, No.38, (August 2009), pp. 5284-5291, ISSN 0264-410X

Ataman-Önal, Y. et al., (2006). Surfactant-free anionic PLA nanoparticles coated with HIV-1 p24 protein induced enhanced cellular and humoral immune responses in various animal models. *Journal of Controlled Release,* Vol.112, No.2, (May 2006), pp. 175-185, ISSN 0168-3659

Bentley, G. et al., (2003). A prospective, randomized comparison of autologous chondrocyte implantation versus mosaicplasty for ostechondral defects of the knee. *Journal of Bone and Joint Surgery-British Volume,* Vol.85, No.2, (March 2003), pp. 223-230, ISSN 0301-620X

Bergsma, J. E. et al., (1995). Late degradation tissue response to poly(L-lactide) bone plates and screws. *Biomaterials,* Vol.16, No.1, (1995), pp. 25-31, ISSN 0142-9612

Bertram, J. P. et al., (2009). Functionalized poly(lactic-co-glycolic acid) enhances drug delivery and provides chemical moieties for surface engineering while preserving biocompatibility. *Acta Biomaterialia,* Vol.5, No.8, (October 2009), pp. 2860-2871, ISSN 1742-7061

Brittberg, M. et al., (1994). Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *New England Journal of Medicine,* Vol.331, No.14, (October 1994), pp. 889-895, ISSN 0028-4793

Brun, A. et al., (2008). Antigen delivery systems for veterinary vaccine development. Viral-vector based delivery systems. *Vaccine,* Vol.26, No.51, (December 2008), pp. 6508-528, ISSN 0264-410X

Burgess, C. M. & Quiroga, R. M. (2005). Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *Journal of the American Academy of Dermatology,* Vol.52, No.2, (February 2005), pp. 233-239, ISSN 0190-9622

Butterwick, K. & Lowe, N. J. (2009) Injectable poly-L-lactic acid for cosmetic enhancement: Learning from the European experience. *Journal of the American Academy of Dermatology*, Vol.61, No.2, (August 2009), pp. 281-293, ISSN 0190-9622

Chaiwong, C. et al., (2010). Effect of plasma treatment on hydrophobicity and barrier property of polylactic acid. *Surface and Coatings Technology,* Vol.204, No.18-19, (June 2010), pp. 2933-2939, ISSN 0257-8972

Chen, G.; Ushida, T. & Tateishi, T. (2002). Scaffold design for tissue engineering. *Macromolecular Bioscience,* Vol.2, No.2, (February 2002), pp. 67-77, ISSN 1616-5187

Chen, H. Y. et al., (2011). Comparative study of lactide polymerization by zinc alkoxide complexes with a β-diketiminato ligand bearing different substituents. *Journal of Molecular Catalysis A: Chemical,* Vol.339, No.1-2, (April 2011), pp. 61-71, ISSN 1381-1169

Chen, J. et al., (2007). Preparation, characterization and transfection efficiency of cationic PEGylated PLA nanoparticles as gene delivery systems. *Journal of Biotechnology,* Vol.130, No.2, (June 2007), pp. 107-113, ISSN 0168-1656

Cheung, H. Y. et al., (2008) A potential material for tissue engineering: Silkworm silk/PLA biocomposite. *Composites Part B: Engineering,* Vol.39, No.6, (September 2008), pp. 1026-1033, ISSN 1359-8368

Chisholm, M. H. et al., (2003). Binolate complexes of lithium, zinc, aluminium, and titanium; preparations, structures, and studies of lactide polymerization. *Dalton Transactions,* No.3, (July 2003), pp. 406-412, ISSN 1477-9226

Chu, P. K. et al., (2002). Plasma-surface modification of biomaterials. *Materials Science and Engineering: R: Reports,* Vol.36, No.5-6, (March 2002), pp. 143-206, ISSN 0927-796X

Cronin, E. M. et al., (2004).Protein-coated poly(L-lactic acid) fibers provide a substrate for differentiation of human skeletal muscle cells. *Journal of Biomedical Materials Research Part A,* Vol.69A, No.3, (June 2004), pp. 373-381, ISSN 1549-3296

Deng, X. et al., (2000). Polymerization of lactides and lactones VII. Ring-opening polymerization of lactide by rare earth phenyl compounds. *European Polymer Journal,* Vol.36, No.6, (June 2000), pp. 1151-1156, ISSN 0014-3057

Ejfler, J. et al., (2005). Highly efficient magnesium initiators for lactide polymerization. *Dalton Transactions,* No.11, (June 2005), pp. 2047-2050, ISSN 1477-9226

Engelhardt, E. M. et al., (2011). A collagen-poly(lactic acid-co-caprolactone) hybrid scaffold for bladder tissue regeneration. *Biomaterials,* Vol.32, No.16, (June 2011), pp. 3969-3976, ISSN 0142-9612

Fahmy, T. M. et al., (2005). Surface modification of biodegradable polyesters with fatty acid conjugates for improved drug targeting. *Biomaterials*, Vol.26, No.28, (October 2005), pp. 5727–5736, ISSN 0142-9612

Favia, P. & d'Agostino, R. (1998). Plasma treatments and plasma deposition of polymers for biomedical applications. *Surface and coatings Technology,* Vol.98, No.1, (January1998), pp. 1102-1106, ISSN 0257-8972

Fay, F. et al., (2010). Gene delivery using dimethyldidodecylammonium bromide-coated PLGA nanoparticles. *Biomaterials,* Vol.31, No.14, (May 2010), pp. 4214-4222, ISSN 0142-9612

Freitas, M. N. & Marchetti, J. M. (2005). Nimesulide PLA microspheres as a potential sustained release system for the treatment of inflammatory diseases. *International Journal of Pharmaceutics,* Vol.295, No.1-2, (May 2005), pp. 201-211, ISSN 0378-5173

Fu, B. et al., (2008). Preparation of lactic acid based polyurethanes modified by castor oil. *Advanced Materials Research,* Vols. 47-50, (June 2008), pp. 1458-1461, ISSN 1022-6680

Ganta, S. et al., (2008). A review of stimuli-responsive nanocarriers for drug and gene delivery. *Journal of Controlled Release,* Vol.126, No.3, (March 2008), pp. 187-204, ISSN 0168-3659

Gao, Q. W. et al., (2002). Direct synthesis with melt polycondensation and microstructure analysis of poly(L-lactic acid-co-glycolic acid). *Polymer Journal,* Vol.34, No.11, (November 2002), pp. 786-793, ISSN 0032-3896

Garlotta, D. (2001). A literature review of poly(lactic acid). *Journal of Polymers and the Environment,* Vol.9, No.2, (April 2001), pp. 63-84, ISSN 1566-2543

Ge, Z. et al., (2009). Proliferation and differentiation of human osteoblasts within 3D printed poly-lactic-co-glycolic acid scaffolds. *Journal of Biomaterials Applications*, Vol.23, (May 2009), pp.533-547, ISSN 1530-8022

Ge, Z. et al., (2009). Histological evaluation of osteogenesis of 3D-printed poly-lactic-co-glycolic acid (PLGA) scaffolds in a rabbit model. *Biomedical Materials*, Vol. 4, No. 2, (April 2009), 021001, ISSN 1748-6041

Ghosh, D. et al., (2007). Interactive wound cover. US Patent 0,258,958, filed February 12, 2007, issued November 8, 2007

Graupner, N.; Herrmann, A. S. & Müssig, J. (2009). Natural and man-made cellulose fibre-reinforced poly(lactic acid) (PLA) composites: An overview about mechanical characteristics and application areas. *Composites Part A: Applied Science and Manufacturing,* Vol.40, No.6-7, (July 2009), pp. 810-821, ISSN 1359-835X

Gref, R. et al., (1994). Biodegradable long-circulating polymeric nanospheres. *Science,* Vol.263, No.5153, (March1994), pp. 1600-1603, ISSN 0036-8075

Gu, M. et al., (2007). Surface biofunctionalization of PLA nanoparticles through amphiphilic polysaccharide coating and ligand coupling: Evaluation of biofunctionalization and drug releasing behavior. *Carbohydrate Polymers,* Vol.67, No.3, (February 2007), pp. 417-426, ISSN 0144-8617

Gupta, B.; Revagade, N. & Hilborn, J. Poly(lactic acid) fiber: An overview. *Progress in polymer science,* Vol.32, No.4, (April 2007), pp. 455-482, ISSN 0079-6700

Haag, R. (2004). Supramolecular drug-delivery systems based on polymeric core–shell architectures. *Angewandte Chemie International Edition,* Vol.43, No.3, (January 2004), pp. 278-282, ISSN 1433-7851

Hirotsu, T. et al., (2002). Plasma surface treatments of melt-extruded sheets of poly(L-lactic acid). *Polymer Engineering and Science,* Vol.42, No.2, (February 2002), pp. 299-306, ISSN 0032-3888

Hollister, S. J. (2005). Porous scaffold design for tissue engineering. *Nature Materials,* Vol.4, (July 2005), pp. 518-524, ISSN 1476-1122

Hong, Y. et al., (2005). Collagen-coated polylactide microspheres as chondrocyte microcarriers. *Biomaterials,* Vol.26, No.32, (November 2005), pp. 6305-6313, ISSN 0142-9612

Hu, K. et al., (2009). Lactoferrin-conjugated PEG-PLA nanoparticles with improved brain delivery: In vitro and in vivo evaluations. *Journal of Controlled Release,* Vol.134, No.1, (February 2009), pp. 55-61, ISSN 0168-3659

Huang, J. W. et al., (2009), Polylactide/nano and microscale silica composite films. I. Preparation and characterization. *Journal of Applied Polymer Science,* Vol.112, No.3, (May 2009), pp. 1688-1694, ISSN 0021-8995

Huang, L. et al., (2007). Synthesis and characterization of electroactive and biodegradable ABA block copolymer of polylactide and aniline pentamer. *Biomaterials*, Vol.28, No.10, (April 2007), pp. 1741-1751, ISSN 0142-9612

Huda, M. S. et al., (2008). Effect of fiber surface-treatments on the properties of laminated biocomposites from poly(lactic acid)(PLA) and kenaf fibers. *Composites Science and Technology,* Vol.68, No.2, (February 2008), pp. 424-432, ISSN 0266-3538

Ichikawa, F. et al., (1995). Process for preparing polyhydroxycarboxylic acid. US Patent 5,440,008, filed May 19, 1994, issued August 8, 1995

Ignatova, M. et al., (2009). Electrospun non-woven nanofibrous hybrid mats based on chitosan and PLA for wound-dressing applications. *Macromolecular Bioscience,* Vol.9, No.1, (January 2009), pp. 102-111, ISSN 1616-5187

Ilan, D. I. & Ladd, A. L. (2002). Bone graft substitutes. *Operative Techniques in Plastic and Reconstructive Surgery,* Vol.9, No.4, (November 2002), pp. 151-160, ISSN 1071-0949

Iwasa, J. et al., (2009). Clinical application of scaffolds for cartilage tissue engineering. *Knee Surgery, Sports Traumatology, Arthroscopy,* Vol.17, No.6, (June 2009), pp. 561-577, ISSN 0942-2056

Iwata, T. & Doi, Y. (1998). Morphology and enzymatic degradation of poly(L-lactic acid) single crystals. *Macromolecules,* Vol.31, No.8, (April 1998), pp. 2461-2467, ISSN 0024-9297

Jamshidian, M. et al., (2010). Poly-lactic acid: Production, applications, nanocomposites, and release studies. *Comprehensive Reviews in Food Science and Food Safety,* Vol.9, No.5, (September 2010), pp. 552-571, ISSN 1541-4337

Jiang, T. et al., (2006). In vitro evaluation of chitosan/poly(lactic acid-glycolic acid) sintered microsphere scaffolds for bone tissue engineering. *Biomaterials,* Vol.27, No.28, (November 2006), pp. 4894-4903, ISSN 0142-9612

Jiang, T. et al., (2010). Functionalization of chitosan/poly(lactic acid-glycolic acid) sintered microsphere scaffolds via surface heparinization for bone tissue engineering. *Journal of Biomedical Materials Research Part A,* Vol.93A, No.3, (June 2010), pp. 1193-1208, ISSN 1549-3296

Jiang, T. et al., (2010). Chitosan-poly(lactide-co-glycolide) microsphere-based scaffolds for bone tissue engineering: In vitro degradation and in vivo bone regeneration studies. *Acta Biomaterialia,* Vol.6, No.9, (September 2010), pp. 3457-3470, ISSN 1742-7061

Jie, P. et al.,(2005). Micelle-like nanoparticles of star-branched PEO-PLA copolymers as chemotherapeutic carrier. *Journal of Controlled Release,* Vol.110, No.1, (December 2005), pp. 20-33, ISSN 0168-3659

John, A. et al., (2007) Ni (II) and Cu (II) complexes of phenoxy-ketimine ligands: Synthesis, structures and their utility in bulk ring-opening polymerization (ROP) of L-lactide. *Polyhedron,* Vol.26, No.15, (April 2007), pp. 4033-4044, ISSN 0277-5387

Jung, Y. et al., (2005). A poly(lactic acid)/calcium metaphosphate composite for bone tissue engineering. *Biomaterials*, Vol.26, No.32, (November 2005), pp. 6314-6322, ISSN 0142-9612

Jérôme, C. & Lecomte, P. (2008). Recent advances in the synthesis of aliphatic polyesters by ring-opening polymerization. *Advanced drug delivery reviews,* Vol.60, No.9, (June 2008), pp. 1056-1076, ISSN 0169-409X

Kang, Y. et al., (2008). Preparation, characterization and in vitro cytotoxicity of indomethacin-loaded PLLA/PLGA microparticles using supercritical CO_2 technique. *European Journal of Pharmaceutics and Biopharmaceutics,* Vol.70, No.1, (September 2008), pp. 85-97, ISSN 0939-6411

Kasuga, T. et al., (2001). Preparation and mechanical properties of polylactic acid composites containing hydroxyapatite fibers. *Biomaterials,* Vol.22, No.1, (January 2001), pp. 19-23, ISSN 0142-9612

Kasuga, T. et al., (2003). Preparation of poly(lactic acid) composites containing calcium carbonate (vaterite). *Biomaterials,* Vol.24, No.19, (August 2003), pp. 3247-3253, ISSN 0142-9612

Khondker, O. A. et al., (2006). A novel processing technique for thermoplastic manufacturing of unidirectional composites reinforced with jute yarns. *Composites Part A: Applied Science and Manufacturing,* Vol.37, No.12, (December 2006), pp. 2274-2284, ISSN 1359-835X

Kim, I. H. & Jeong, Y. G. (2010). Polylactide/exfoliated graphite nanocomposites with enhanced thermal stability, mechanical modulus, and electrical conductivity.

Journal of Polymer Science Part B: Polymer Physics, Vol.48, No.8, (April 2010), pp. 850-858, ISSN 0887-6266

Kocbek, P. et al., (2007). Targeting cancer cells using PLGA nanoparticles surface modified with monoclonal antibody. *Journal of Controlled Release,* Vol.120, No.1-2, (July 2007), pp. 18-26, ISSN 0168-3659

Koo, G. H. & Jang, J. (2008). Surface modification of poly(lactic acid) by UV/Ozone irradiation. *Fibers and Polymers,* Vol.9, No.6, (December 2008), pp. 674-678, ISSN 1875-0052

Köhn, R. D. et al., (2003). Ring-opening polymerization of,-lactide with bis (trimethyl triazacyclohexane) praseodymium triflate. *Catalysis Communications,* Vol.4, No.1, (January 2003), pp. 33-37, ISSN 1566-7367

Lassalle, V. L. & Ferreira M. L. (2008). Lipase-catalyzed synthesis of polylactic acid: An overview of the experimental aspects. *Journal of Chemical Technology and Biotechnology,* Vol.83, No.11 , (October 2008), pp. 1493-1502, ISSN 0268-2575

Li, S. & Vert, M. (2003). Synthesis, characterization, and stereocomplex-induced gelation of block copolymers prepared by ring-opening polymerization of L (D)-lactide in the presence of poly(ethylene glycol). *Macromolecules,* Vol.36, No.21, (September 2003), pp. 8008-8014, ISSN 0024-9297

Lieb, E. et al., (2005). Mediating specific cell adhesion to low-adhesive diblock copolymers by instant modification with cyclic RGD peptides. *Biomaterials,* Vol.26, No.15, (May 2005), pp. 2333-2341, ISSN 0142-9612

Liggins, R. T. et al., (2004). Intra-articular treatment of arthritis with microsphere formulations of paclitaxel: Biocompatibility and efficacy determinations in rabbits. *Inflammation Research,* Vol.53, No.8, (August 2004), pp. 363-372, ISSN 1023-3830

Lin, Y. M. et al., (2010). Tissue engineering of lung: The effect of extracellular matrix on the differentiation of embryonic stem cells to pneumocytes. *Tissue Engineering Part A,* Vol.16, No.5, (April 2010), pp. 1515-1526, ISSN 1937-3341

Liu, C. et al., (2004). Effects of DBD plasma operating parameters on the polymer surface modification. *Surface and Coatings Technology,* Vol.185, No.2-3, (July 2004), pp. 311-320, ISSN 0257-8972

Liu, C. X. et al., (2011). Enhanced gene transfection efficiency in CD13-positive vascular endothelial cells with targeted poly(lactic acid)-poly(ethylene glycol) nanoparticles through caveolae-mediated endocytosis. *Journal of Controlled Release,* (in press), ISSN 0168-3659

Liu, P. et al., (2010). The research of RGD-conjugated PLA-PLL nanoparticles carriers on targeted delivery to tumor, *Proceedings of Nanoelectronics Conference (INEC), 2010 3rd International,* 978-1-4244-3543-2, Hong Kong, January 2010

Liu, X, & Ma, P. X. (2004). Polymeric scaffolds for bone tissue engineering. *Annals of Biomedical Engineering,* Vol.32, No.3, (March 2004), pp. 477-486, ISSN 0090-6964

Liu, X.; Won, Y. & Ma, P. X. (2005). Surface modification of interconnected porous scaffolds. *Journal of Biomedical Materials Research Part A,* Vol.74A, No.1, (July 2005), pp. 84-91, ISSN 1549-3296

Ljungberg, N. & Wesslén, B. (2002). The effects of plasticizers on the dynamic mechanical and thermal properties of poly(lactic acid). *Journal of Applied Polymer Science,* Vol.86, No.5, (October 2002), pp. 1227-1234, ISSN 0021-8995

Ljungberg, N.; Colombini, D. & Wesslén, B. (2005). Plasticization of poly(lactic acid) with oligomeric malonate esteramides: Dynamic mechanical and thermal film properties. *Journal of Applied Polymer Science,* Vol.96, No.4, (March 2005), pp. 992-1002, ISSN 0021-8995

Lowe, N. & Beer, K. (2005). A new material in subdermal sculpting, In: *Procedures in Cosmetic Dermatology Series; Soft Tissue Augmentation,* Carruthers, J. & Carruthers, A., pp. 143-146, Elsevier Saunders, 1-4160-4214-8, Oxford

Lu, J. W. et al., (2009). Surface engineering of poly(D, L-lactic acid) by entrapment of soluble eggshell membrane protein. *Journal of Biomedical Materials Research Part A,* Vol.91A, No.3, (December 2009), pp. 701-707, ISSN 1549-3296

Lunt, J. (1998). Large-scale production, properties and commercial applications of polylactic acid polymers. *Polymer Degradation and Stability,* Vol.59, No.1, (January 1998), pp. 145-152, ISSN 0141-3910

Lv, Q. et al., (2007). Preparation and characterization of PLA/fibroin composite and culture of HepG2 (human hepatocellular liver carcinoma cell line) cells. *Composites Science and Technology,* Vol.67, No.14, (June 2007), pp. 3023-3030, ISSN 0266-3538

Ma, H.; Davis, R. H. & Bowman, C. N. (1999). A novel sequential photoinduced living graft polymerization. *Macromolecules,* Vol.33, No.2, (January 2000), pp. 331-335, ISSN 0024-9297

Ma, P. X. (2004). Scaffolds for tissue fabrication. *Materials Today,* Vol.7, No.5, (May 2004), pp. 30-40, ISSN 1369-7021

Ma, W. et al., (2008). Evaluation of blood circulation of polysaccharide surface-decorated PLA nanoparticles. *Carbohydrate Polymers,* Vol.72, No.1, (April 2008), pp. 75-81, ISSN 0144-8617

Maharana, T.; Mohanty, B. & Negi, Y. S. (2009). Melt-solid polycondensation of lactic acid and its biodegradability. *Progress in Polymer Science,* (January 2009), Vol.34, No.1, pp. 99-124, ISSN 0079-6700

Martin, O. & Averous, L. (2001). Poly(lactic acid): Plasticization and properties of biodegradable multiphase systems. *Polymer,* Vol.42, No.14, (June 2001), pp. 6209-6219, ISSN 0032-3861

Mathew, A. P.; Oksman, K. & Sain, M. (2005). Mechanical properties of biodegradable composites from poly lactic acid (PLA) and microcrystalline cellulose (MCC). *Journal of applied polymer science,* Vol.97, No.5, (September 2005), pp. 2014-2025, ISSN 0021-8995

Mathieu, L. M. et al., (2006). Architecture and properties of anisotropic polymer composite scaffolds for bone tissue engineering. *Biomaterials,* Vol.27, No.6, (February 2006), pp. 905-916, ISSN 0142-9612

Matsumoto, K. & Taguchi, S. (2010). Enzymatic and whole-cell synthesis of lactate-containing polyesters: Toward the complete biological production of polylactate. *Applied microbiology and biotechnology,* Vol.85, No.4, (December 2009), pp. 921-932, ISSN 0175-7598

Matsumura, S.; Mabuchi, K. & Toshima, K. (1997). Lipase-catalyzed ring-opening polymerization of lactide. *Macromolecular Rapid Communications,* Vol.18, No.6, (April 2003), pp. 477-482, ISSN 1022-1336

Mauney, J. R. et al., (2007). Engineering adipose-like tissue in vitro and in vivo utilizing human bone marrow and adipose-derived mesenchymal stem cells with silk fibroin

3D scaffolds. *Biomaterials,* Vol.28, No.35, (December 2007), pp. 5280-5290, ISSN 0142-9612

Mavrogenis, A. F. et al., (2009). Early experience with biodegradable implants in pediatric patients. *Clinical Orthopaedics and Related Research,* Vol.467, No.6, (June 2009), pp. 1591-1598, ISSN 0009-921X

Mehta, R. et al., (2005). Synthesis of poly(lactic acid): A review. *Journal of Macromolecular Science, Part C: Polymer Reviews,* Vol.45, No.4, (October 2005), pp. 325-349, ISSN 1532-1797

Metters, A. T.; Anseth, K. S. & Bowman, C. N. (2000). Fundamental studies of a novel, biodegradable PEG-b-PLA hydrogel. *Polymer,* Vol.41, No.11, (May 2000), pp. 3993-4004, ISSN 0032-3861

Moon, S. I. et al., (2000). Melt polycondensation of L-lactic acid with Sn(II) catalysts activated by various proton acids: A direct manufacturing route to high molecular weight Poly(L-lactic acid). *Journal of Polymer Science Part A: Polymer Chemistry,* Vol.3, No.89, (May 2000), pp. 1673-1679, ISSN 0887-624X

Moon, S. I. et al., (2001). Synthesis and properties of high-molecular-weight poly(L-lactic acid) by melt/solid polycondensation under different reaction conditions. *High Performance Polymers,* Vol.13, No.2, (June 2001), pp. 189-196, ISSN 0954-0083

Moran, M. J.; Pazzano, D. & Bonassar, L. J. (2003). Characterization of polylactic acid-polyglycolic acid composites for cartilage tissue engineering. *Tissue Engineering,* Vol.9, No.1, (February 2003), pp. 63-70, ISSN 1076-3279

Na, K. et al., (2006). Biodegradable thermo-sensitive nanoparticles from poly(L-lactic acid)/poly(ethylene glycol) alternating multi-block copolymer for potential anti-cancer drug carrier. *European Journal of Pharmaceutical Sciences,* Vol.27, No.2–3, (December 2006), pp. 115–122, ISSN 0928-0987

Nafee, N. et al., (2007). Chitosan-coated PLGA nanoparticles for DNA/RNA delivery: Effect of the formulation parameters on complexation and transfection of antisense oligonucleotides. *Nanomedicine,* Vol.3, No.3, (September 2007), pp. 173-183, ISSN 1743-5889

Nalawade, S. P.; Picchioni F. & Janssen L. P. B. N. (2006). Supercritical carbon dioxide as a green solvent for processing polymer melts: Processing aspects and applications. *Progress in Polymer Science,* Vol.31, No.1, (January 2006), pp. 19-43, ISSN 0079-6700

Nomura, N. et al., (2002). Stereoselective ring-opening polymerization of racemic lactide using aluminum-achiral ligand complexes: Exploration of a chain-end control mechanism. *Journal of the American Chemical Society,* Vol.124, No.21, (May 2002), pp. 5938-5939, ISSN 0002-7863

Ohta, M.; Obuchi, S. &Yoshida, Y. (1995). Preparation process of polyhydroxycarboxylic acid. US Patent, 5,444,143, filed December 21, 1993, issued August 22, 1995

Oksman, K.; Skrifvars, M. & Selin J. F.. (2003). Natural fibres as reinforcement in polylactic acid (PLA) composites. *Composites Science and Technology,* Vol.63, No.9, (July 2003), pp. 1317-1324, ISSN 0266-3538

Pan, P. et al., (2007). Crystallization behavior and mechanical properties of bio-based green composites based on poly(L-lactide) and kenaf fiber. *Journal of Applied Polymer Science,* Vol.105, No.3, (Auguest 2007), pp. 1511-1520, ISSN 0021-8995

Patil, Y. & Panyam, J. (2009). Polymeric nanoparticles for siRNA delivery and gene silencing. *International Journal of Pharmaceutics.* Vol.367, No.1-2, (February 2009), pp. 195-203, ISSN 0378-5173

Peesan, M.; Supaphol, P. & Rujiravanit R. (2005). Preparation and characterization of hexanoyl chitosan/polylactide blend films. *Carbohydrate Polymers,* Vol.60, No.3, (March 2005), pp. 343-350, ISSN 0144-8617

Penczek, S. et al., (2000). What we have learned in general from cyclic esters polymerization. *Macromolecular Symposia,* Vol.153, No.1, (March 2000), pp. 1-15, ISSN 1022-1360

Phong, L. et al. (2010). Properties and hydrolysis of PLGA and PLLA cross-linked with electron beam radiation. *Polymer Degradation and Stability,* Vol.95, No.5, (May 2010), pp. 771-777, ISSN 0141-3910

Pluta, M. et al., (2002) Polylactide/montmorillonite nanocomposites and microcomposites prepared by melt blending: Structure and some physical properties. *Journal of Applied Polymer Science,* Vol.86, No.6, (November 2002), pp. 1497-1506, ISSN 0021-8995

Qiu, Y. & Park, K. (2001). Environment-sensitive hydrogels for drug delivery. *Advanced Drug Delivery Reviews*, Vol.53, No.3, (December 2001), pp. 321-339

Quirk, R. A. et al., (2000). Surface engineering of poly(lactic acid) by entrapment of modifying species. *Macromolecules,* Vol.33, No.2, (January2000), pp. 258-260, ISSN 0024-9297

Quynh, T. M. et al., (2007). Properties of crosslinked polylactides (PLLA & PDLA) by radiation and its biodegradability. *European Polymer Journal,* Vol.43, No.5, (May 2007) pp. 1779-1785, ISSN 0014-3057

Quynh T. M. et al., (2008). The radiation crosslinked films based on PLLA/PDLA stereocomplex after TAIC absorption in supercritical carbon dioxide. *Carbohydrate Polymers,* Vol.72, No.4, (June 2008), pp. 673-681, ISSN 0144-8617

Quynh, T. M. et al., (2009). Properties of radiation-induced crosslinking stereocomplexes derived from poly(L-lactide) and different poly(D-lactide). *Polymer Engineering and Science,* Vol.49, No.5, (May 2009), pp. 970-976, ISSN 0032-3888

Raghoebar, G. M. et al., Resorbable screws for fixation of autologous bone grafts. *Clinical Oral Implants Research,* Vol.17, No.3, (June 2006), pp. 288-293, ISSN 0905-7161

Rasal, R. M. & Hirt, D. E. (2009). Toughness decrease of PLA-PHBHHx blend films upon surface-confined photopolymerization. *Journal of Biomedical Materials Research Part A,* Vol.88A, No.4, (March 2009), pp. 1079-1086, ISSN 1549-3296

Rasal, R. M.; Janorkar, A. V. & Hirt, D. E. (2010). Poly(lactic acid) modifications. *Progress in Polymer Science,* Vol.35, No.3, (March 2010), pp. 338-356, ISSN 0079-6700

Reddy, N.; Nama, D. & Yang, Y. (2008). Polylactic acid/polypropylene polyblend fibers for better resistance to degradation. *Polymer Degradation and Stability,* Vol.93, No.1, (January 2008), pp. 233-241, ISSN 0141-3910

Rhim, J. W. et al., (2006). Effect of the processing methods on the performance of polylactide films: Thermocompression versus solvent casting. *Journal of Applied Polymer Science,* Vol.101, No.6, (September 2006), pp. 3736-3742, ISSN 0021-8995

Riley, T. et al., (2001). Physicochemical evaluation of nanoparticles assembled from poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) block copolymers as drug delivery vehicles. *Langmuir,* Vol.17, No.11, (May 2001), pp. 3168-3174, ISSN 0743-7463

Robinson, T. M.; Kieswetter, K. & McNulty, A. (2009). System and method for healing a wound at a tissue site. US Patent 0,216,170, filed February 27, 2009, issued August 27, 2009

Roney, C. et al., (2005). Targeted nanoparticles for drug delivery through the blood-brain barrier for Alzheimer's disease. *Journal of Controlled Release,* Vol.108, No.1-2, (November 2005), pp. 193-214, ISSN 0168-3659

Rujitanaroj, P.; Pimpha, N. & Supaphol, P. (2008). Wound-dressing materials with antibacterial activity from electrospun gelatin fiber mats containing silver nanoparticles. *Polymer,* Vol.49, No.21, (October 2008), pp. 4723-4732, ISSN 0032-3861

Sarazin, Y.; Schormann, M. & Bochmann, M. (2004). Novel zinc and magnesium alkyl and amido cations for ring-opening polymerization reactions. *Organometallics,* Vol.23, No.13, (May 2004), pp. 3296-3302, ISSN 0276-7333

Sawahata, K. et al., (1990). Electrically controlled drug delivery system using polyelectrolyte gels. *Journal of Controlled Release,* Vol.14, No.3, (December 1990), pp. 253-262, ISSN 0168-3659

Sethuraman, V. A. & Bae, Y. H. (2007). TAT peptide-based micelle system for potential active targeting of anti-cancer agents to acidic solid tumors. *Journal of Controlled Release,* Vol.118, No.2, (April 2007), pp. 216-224, ISSN 0168-3659

Sheth, M. et al., (1997) Biodegradable polymer blends of poly(lactic acid) and poly(ethylene glycol). *Journal of Applied Polymer Science,* Vol.66, No.8, (November 1997), pp. 1495-1505, ISSN 0021-8995

Shin, I. K. et al., (2010). Novel three-dimensional scaffolds of poly(L-lactic acid) microfibers using electrospinning and mechanical expansion: Fabrication and bone regeneration. *Journal of Biomedical Materials Research B: Applied Biomaterials*, Vol.95B, No.1, (October 2010), pp.150-160, ISSN 1552-4981

Singh, R. P. et al., (2003). Biodegradation of poly(ε-caprolactone)/starch blends and composites in composting and culture environments: The effect of compatibilization on the inherent biodegradability of the host polymer. *Carbohydrate Research,* Vol.338, No.17, (August 2003), pp. 1759-1769, ISSN 0008-6215

Stupack, D. G. et al. (October 2001). Apoptosis of adherent cells by recruitment of caspase-8 to unligated integrins. *The Journal of Cell Biology,* Vol.155, No.3, (2001), pp. 459-470, ISSN 0021-9525

Taguchi, S. et al., (2008). A microbial factory for lactate-based polyesters using a lactate-polymerizing enzyme. *Proceedings of the National Academy of Sciences,* Vol.105, No.45, (November 2008), pp. 17323-17327, ISSN 0027-8424

Taguchi, S. (2010). Current advances in microbial cell factories for lactate-based polyesters driven by lactate-polymerizing enzymes: Towards the further creation of new LA-based polyesters. *Polymer Degradation and Stability,* Vol.95, No.8, (January 2010), pp. 1421-1428, ISSN 0141-3910

Tajima, K. et al., (2009). Chemo-enzymatic synthesis of poly(lactate-co-(3- hydroxybutyrate)) by a lactate-polymerizing enzyme. *Macromolecules,* Vol.42, No.6, (February 2009), pp. 1985-1989, ISSN 0024-9297

Tokoro, R. et al., (2008). How to improve mechanical properties of polylactic acid with bamboo fibers. *Journal of Materials Science,* Vol.43, No.2, (January 2008), pp. 775-787, ISSN 0022-2461

Tomé, C. L. et al.,(2011). Transparent bionanocomposites with improved properties prepared from
acetylated bacterial cellulose and poly(lactic acid) through a simple approach. *Green Chemistry,* Vol.13, No.2, (February 2011), pp. 419-427, ISSN 1463-9262

Torchilin, V. P. (2006). Multifunctional nanocarriers. *Advanced Drug Delivery Reviews,* Vol.58, No.14, (December 2006), pp. 1532–1555, ISSN 0169-409X

Torchilin, V. P. (2008). Cell penetrating peptide-modified pharmaceutical nanocarriers for intracellular drug and gene delivery. *Biopolymers,* Vol.90, No.5, (September 2008), pp. 604-610, ISSN 0006-3525

Tyagi, P. et al., (2004). Sustained intravesical drug delivery using thermosensitive hydrogel. *Pharmaceutical Research,* Vol.21, No.5, (May 2004), pp. 832-837, ISSN 0724-8741

Vaupel, P.; Kallinowski, F. & Okunieff, P. (1989). Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: A review. *Cancer Research,* Vol.49, No.23, (December 1989), pp. 6449–6465, ISSN 0008-5472

Venkatraman, S. S. et al., (2005). Micelle-like nanoparticles of PLA-PEG-PLA triblock copolymer as chemotherapeutic carrier. *International Journal of Pharmaceutics,* Vol.298, No.1, (July 2005), pp. 219-232, ISSN 0378-5173

Vila, A. et al., (2005). PLA-PEG particles as nasal protein carriers: The influence of the particle size. *International Journal of Pharmaceutics,* Vol.292, No.1-2, (March 2005), pp. 43-52, ISSN 0378-5173

Vink, E. T. H. et al., (2003). Applications of life cycle assessment to NatureWorks™ polylactide (PLA) production. *Polymer Degradation and Stability,* Vol.80, No.3, (2003), pp. 403-419, ISSN 0141-3910

Vleggaar, D. & Bauer, U. (2004). Facial enhancement and the European experience with Sculptra. *Journal of Drugs in Dermatology,* Vol.3, No.5, (September-October 2004), pp. 542-547, ISSN 1545-9616

Wan, Y. Z. et al., (2001). Influence of surface treatment of carbon fibers on interfacial adhesion strength and mechanical properties of PLA-based composites. *Journal of Applied Polymer Science,* Vol.80, No., (April 2001), pp. 367-376, ISSN 0021-8995

Wang, M. (2007). Surface modification of biomaterials and tissue engineering scaffolds for enhanced osteoconductivity, *Proceedings of IFMBE,* 978-3-540-68016-1, Kuala Lumpur, Malaysia, December 2006

Wang, R. Y. et al., (2009). Morphology, mechanical properties, and durability of poly(lactic acid) plasticized with di(isononyl) cyclohexane-1, 2-dicarboxylate. *Polymer Engineering and Science,* Vol.49, No.12, (December 2009), pp. 2414-2420, ISSN 0032-3888

Wang, S.; Cui, W. & Bei, J. (2005). Bulk and surface modifications of polylactide. *Analytical and Bioanalytical Chemistry,* Vol.381, No.3, (February 2005), pp. 547-556, ISSN 1618-2642

Woo, S. I. et al., (1995) Polymerization of aqueous lactic acid to prepare high molecular weight poly(lactic acid) by chain-extending with hexamethylene diisocyanate. *Polymer Bulletin,* Vol.35, No.4, (May1995), pp. 415-421, ISSN 0170-0839

Wu, C. S. & Liao, H.T. (2007). Study on the preparation and characterization of biodegradable polylactide/multi-walled carbon nanotubes nanocomposites. *Polymer,* Vol.48, No.15, (July 2007), pp. 4449-4458, ISSN 0032-3861

Wu, J. C. et al., (2005). Ring-opening polymerization of lactide initiated by magnesium and zinc alkoxides. *Polymer,* Vol.46, No.23, (November 2005), pp. 9784-9792, ISSN 0032-3861

Wu, X. L. et al., (2010). Tumor-targeting peptide conjugated pH-responsive micelles as a potential drug carrier for cancer therapy. *Bioconjugate Chemistry,* Vol.21, No.2, (February 2010), pp. 208-213, ISSN 1043-1802

Xiong, X. Y. et al., (2007). Vesicles from Pluronic/poly(lactic acid) block copolymers as new carriers for oral insulin delivery. *Journal of Controlled Release,* Vol.120, No.1-2, (July 2007), pp. 11-17, ISSN 0168-3659

Xu, C. et al., (2009). Preparation and characterization of polylactide/thermoplastic konjac glucomannan blends. *Polymer,* Vol.50, No.15, (July 2009), pp. 3698-3705, ISSN 0032-3861

Yang, G. et al., (2011). Composite from modified biomass fiber and polylactide (PLA) and the method of preparation. CN Patent 201010510498, filed October 15, 2010, and issued January 26, 2011

Yang, S. L. et al., (2008) Thermal and mechanical properties of chemical crosslinked polylactide (PLA). *Polymer Testing,* Vol.27, No.8, (December 2008), pp. 957-963, ISSN 0142-9418

Yoda, S.; Bratton, D. & Howdle, S. M. (2004). Direct synthesis of poly(L-lactic acid) in supercritical carbon dioxide with dicyclohexyldimethylcarbodiimide and 4-dimethylaminopyridine. *Polymer,* Vol.45, No.23, (October 2004), p. 7839-7843, ISSN 0032-3861

Yu, D. G.; Lin, W. C. & Yang, M. C. (2007). Surface modification of poly(L-lactic acid) membrane via layer-by-layer assembly of silver nanoparticle-embedded polyelectrolyte multilayer. *Bioconjugate Chemistry,* Vol.18, No.5, (September-October2007), pp. 1521-1529, ISSN 1043-1802

Zhang, L. et al., (2004). Camptothecin derivative-loaded poly(caprolactone-co-lactide)-b-PEG-b-poly(caprolactone-co-lactide) nanoparticles and their biodistribution in mice. *Journal of controlled release,* Vol.96, No.1, (April 2004), pp. 135-148, ISSN 0168-3659

Zhang, Z. & Feng, S. S. (2006). Nanoparticles of poly(lactide)/vitamin E TPGS copolymer for cancer chemotherapy: Synthesis, formulation, characterization and in vitro drug release. *Biomaterials,* Vol.27, No.2, (January 2006), pp. 262-270, ISSN 0142-9612

Zhong, Z. et al., (2003). Single-site calcium initiators for the controlled ring-opening polymerization of lactides and lactones. *Polymer Bulletin,* Vol.51, No.3, (November 2003), pp. 175-182, ISSN 0170-0839

Zhu, A. et al., (2002). Covalent immobilization of chitosan/heparin complex with a photosensitive hetero-bifunctional crosslinking reagent on PLA surface. *Biomaterials,* Vol.23, No.23, (December 2002), pp. 4657-4665, ISSN 0142-9612

Zhu, H.; Ji, J. & Shen, J. (2002). Surface engineering of poly(DL-lactic acid) by entrapment of biomacromolecules. *Macromolecular Rapid Communications,* Vol.23, No.14, (October 2002), pp. 819-823, ISSN 1022-1336

Zhu, Y. et al., Immobilization of biomacromolecules onto aminolyzed poly(L-lactic acid) toward acceleration of endothelium regeneration. *Tissue Engineering,* Vol.10, No.1-2, (January-February 2004), pp. 53-61, ISSN 1076-3279
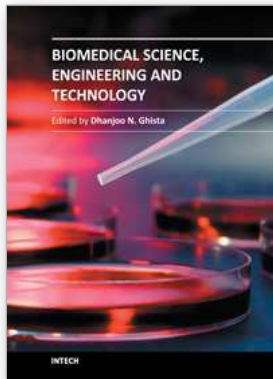
Biomedical Science, Engineering and Technology

Edited by Prof. Dhanjoo N. Ghista

This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytomedicinal plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering coves topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Lin Xiao, Bo Wang, Guang Yang and Mario Gauthier (2012). Poly(Lactic Acid)-Based Biomaterials: Synthesis, Modification and Applications, Biomedical Science, Engineering and Technology, Prof. Dhanjoo N. Ghista (Ed.), ISBN: 978-953-307-471-9, InTech, Available from: http://www.intechopen.com/books/biomedical-science-engineering-and-technology/poly-lactic-acid-based-biomaterials-synthesis-modification-and-applications

INTECH
open science | open minds

www.intechopen.com