Advanced Drug Delivery Reviews 107 (2016) 47–59

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Poly(lactic acid) blends in biomedical applications☆

P. Saini [1], M. Arora [1], M.N.V. Ravi Kumar *

Department of Pharmaceutical Sciences, Texas A&M Health Sciences Center, College Station, TX 77845, USA

ARTICLE INFO

Article history:
Received 31 December 2015
Received in revised form 23 May 2016
Accepted 17 June 2016
Available online 29 June 2016

Keywords:
Biocompatible
Biodegradable
Blends
Drug delivery
Tissue engineering

ABSTRACT

Poly(lactic acid) (PLA) has become a "material of choice" in biomedical applications for its ability to fulfill complex needs that typically include properties such as biocompatibility, biodegradability, mechanical strength, and processability. Despite the advantages of pure PLA in a wider spectrum of applications, it is limited by its hydrophobicity, low impact toughness, and slow degradation rate. Blending PLA with other polymers offers a convenient option to enhance its properties or generate novel properties for target applications without the need to develop new materials. PLA blends with different natural and synthetic polymers have been developed by solvent and melt blending techniques and further processed based on end-use applications. A variety of PLA blends has been explored for biomedical applications such as drug delivery, implants, sutures, and tissue engineering. This review discusses the opportunities for PLA blends in the biomedical arena, including the overview of blending and postblend processing techniques and the applications of PLA blends currently in use and under development.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "PLA biodegradable polymers".

* Corresponding author.
E-mail address: mnvrkumar@tamhsc.edu (M.N.V.R. Kumar).

[1] Equal contribution.

http://dx.doi.org/10.1016/j.addr.2016.06.014
0169-409X/

1. Introduction

Recently bio-based or biodegradable polymers have found a niche in the polymer industry because of increasing environmental concerns as well as their adaptability to be used in a variety of applications such as biomedical products, packaging, and consumer items. Poly(lactic acid) (PLA) is a commercially available bio-based polymer used in a variety of applications because of its high strength, modulus, and biodegradability [1].

PLA is a thermoplastic polymer belonging to the α-hydroxy acid family. Lactic acid is obtained as a product of fermentation of starch from plants such as corn, sugarcane, potatoes, and beets. The polymer is then synthesized by direct polycondensation of lactic acid or ring-opening polymerization of lactide dimer using a suitable catalyst [2]. More recently, enzymatic synthetic processes using lipases have also been reported for the production of PLA, eliminating the use of metallic catalysts [3,4]. However, such green processes are in their stage of infancy, and the major production of PLA still rests with traditional condensation techniques. Because PLA contains two stereoisomers of lactic acid, it can be synthesized as PLLA, PDLA, or PDLLA. The two enantiomerically pure homopolymers (PLLA and PDLA) and an array of racemic PDLLA polymers with varying ratios of *d* and *l* monomers present a range of physical properties [5]. In addition, thermal and mechanical properties of PLA vary with molecular weight [6]. Table 1 lists the physical properties of the PLA polymers [7].

In general, PLA boasts high mechanical strength and modulus, but it has low impact toughness, low use temperature, and a relatively small window for processability. Most of the commercially available PLA polymers comprise mainly PLLA with a small amount of PDLA added to increase the processing window by inducing melting point depression. This also causes a considerable decrease in crystallinity [8]. In addition, PLA has a high hydrophobicity and low degradation rate, which may be undesirable for certain biomedical applications.

Various approaches have been employed to overcome the limitations of physical properties of existing PLA or to attune them for target applications. Some of the commonly employed techniques for PLA bulk modification include copolymerization, cross-linking, composition, and blends [9].

Polymer blending is a convenient physical modification technique to blend the properties of different polymers or to generate novel properties. Blending eliminates the requirement to develop new polymers or copolymers and can tailor a material with the desired properties through a thermodynamically driven mixing of two or more polymers. Many polymers from biological and petrochemical sources have been explored for PLA blends for use in a variety of applications such as biomedical, packaging, textiles, and consumer products. The synthesis, properties, degradation profile, and applications of PLA have been extensively reviewed in the literature [10–13]. This review covers the current state of research and the commercial scenario of physical PLA blends for potential biomedical applications.

Table 1
The physical properties of PLA polymers.
(Reproduced from Ref. [7]).

Physical properties of PLA	
Crystallinity	Semicrystalline (PDLA) 0–37% (PLLA) Amorphous (PDLLA)
Glass transition temperature, T_g	50–64 °C
Melting temperature, Tm	145–186 °C
Tensile strength	28–50 MPa
Young's modulus	1.2–3 GPa
Elongation-at-break	2–6%

2. Opportunities for PLA blends

PLA is an attractive choice for applications involving human interface because of its biocompatibility and biodegradability [13]. The superior tensile properties of PLA make it an ideal candidate for load-bearing applications [14]. Low impact toughness, however, has an impeding effect on its usability in mechanically intense applications such as implants and bone grafts [15]. In addition, the high level of hydrophobicity of PLA is unsuitable for use in biological systems. Nevertheless, the useful properties of PLA outweigh the limitations, which can be eliminated or masked by a variety of aforementioned bulk modification techniques, including polymer blending. For instance, blending PLA with polymers with higher wettability can enhance the hydrophilicity of PLA in the blend. Similarly, PLA blends have been developed with increased crystallinity, enhanced mechanical properties such as toughness and elongation-at-break, and tailored hydrolytic or enzymatic degradation [16,17].

The superior properties of PLA are also used to enhance the existing properties of other polymers in blends. Natural polymers such as chitosan, collagen, elastin, and hyaluronic acid are preferable for biomedical applications such as tissue engineering, since they simulate the native materials found in biological systems [18]. However, poor mechanical properties of such natural polymers limit their use in mechanically demanding environments. Synthetic polyesters such as PLA are often blended with natural polymers to generate hybrid materials with optimal thermomechanical properties for processing and use in biomedical applications [19]. PLA blends with other polymers for biomedical applications have also been developed with novel properties such as shape memory and morphology, which are not present in any of the parent polymers. PLA blends can be formed into a variety of structures, including films, porous scaffolds, fibers, and particles, based on target application. Table 2 presents a list of some of the polymers used for blending with PLA with properties tuned to be used in different biomedical applications.

While blending PLA with other polymers can develop materials with desired properties for a particular application, it should be noted that it only offers limited flexibility in tailoring material properties. Being a physical method, it does not alter the chemical fingerprint of the constituents. Blends are often prepared for specific applications before or during processing. Although blending offers a convenient method to enhance the performance of existing polymers, their application is restricted to the few areas for which they are tailored. The polymer modification method of choice remains copolymerization to cater to a wider range of applications with enhanced properties while maintaining the influence of the constituent monomers on the properties. Hence, copolymers of PLA, specifically PLGA, find more use in biomedical applications. Not only do the copolymers provide a ready-to-use range of materials with an array of properties to adapt based on requirement, they also eliminate the blending step in the processing. Nonetheless, blends are still a cheaper, quicker, and more convenient option to develop a product with altered mechanical and thermal properties, degradation profile, and bio-interaction, while retaining the chemical nature of the constituents.

3. End-use modifications

As mentioned earlier, polymer blending provides a faster and more economical means to alter or enhance the properties of a polymer, thereby eliminating high cost and efforts involved in research and the development of new polymers or copolymers. Blends provide the means by which the required properties for the end product can be generated by mixing of two pre-existing polymers. They are often tailored according to the specifications for the applications of the product. Being a thermodynamically driven process, the blending of polymers is facilitated by the knowledge of thermodynamic parameters of the constituent polymers. This section covers the thermodynamics involved

Table 2
Examples of polymers used for PLA blends, the techniques used, applications, and the effects of blending on existent properties or generation of new ones.

Polymer	Technique	Application	Properties affected	References
Polyhydroxybutyrate (PHB)	Melt extrusion	Packaging	Enhanced ductility, elongation-at-break, barrier properties	[20]
Thermoplastic polyurethane	Melt extrusion	Actuators, tissue engineering	Shape memory, enhanced tensile strength, elongation-at-break	[21,22]
	Foaming	Tissue engineering	Shape memory, porous morphology, higher crystallinity	[23]
Polycaprolactone (PCL)	Electrospinning	Tissue engineering, grafts	Increased elasticity, fiber orientation, decreased hydrophilicity	[24]
	Solvent cast film	Nerve conduits	PLA provides decreased crystallinity and increased degradation than PCL alone, introduced surface porosity for cell attachment	[25]
Polyglycolic acid (PGA)	Electrospinning	Soft tissue engineering	Similar mechanical properties to structural materials of soft tissues	[26]
Poly(ethylene glycol) (PEG)	Nanoparticles/microparticles	Drug delivery	Increased hydrophilicity, tuned degradation	[27]
	Foaming	Scaffolds	Decreased viscoelasticity, increased crystallinity and hydrophilicity	[28]
Hyaluronic acid (HA)	Melt blending/compression molding	Bone grafts, wound healing, tissue engineering	PLA provides higher mechanical strength and elongation-at-break than HA alone	[29]
Chitosan (CHI)/PCL	Solution blended PLA/PCL emulsified into CHI solution/solution cast film	Antimicrobial, hemostatic wound dressing	Combination of mechanical strength of PLA, flexibility of PCL, and swelling behavior of CHI	[30]
Lignin	Melt extrusion/compressed film	Food packaging	Introduction of anti-oxidant and barrier properties by lignin	[31]

in polymer blends, the effects of blending on the properties of the final polymer blend, and the processing of PLA blends into defined structures for end-use.

3.1. Thermodynamics of blends

Polymer blends involve the mixing of polymers within the constraints of free energy and entropy of the system. The blending thermodynamics are dictated by the Gibbs free energy equation.

$$\Delta G_M = \Delta H_M - T\Delta S_M \quad (1)$$

where ΔG_M, ΔH_M, and ΔS_M are energy, enthalpy, and entropy of mixing, respectively. ΔG_M must be less than 0 for two or more polymers to be miscible. In the case of low-molecular-weight compounds, solubility/miscibility of the blend increases with the increase in temperature due to more negative value of $T\Delta S$, thus driving more negative ΔG_M. In contrast, for high-molecular-weight components such as polymeric blends, the following equation determines miscibility (Eq. (2)):

$$\left(\frac{\partial^2 \Delta G_m}{\partial \phi_i^2}\right)_{T,p} > 0 \quad (2)$$

To assess the miscibility of polymer blends, Flory–Huggins developed the following Eq. (3),

$$\Delta G_m = kTV\left[\frac{\phi_1}{V_1}\ln\phi_1 + \frac{\phi_2}{V_2}\ln\phi_2\right] + \phi_1\phi_2\chi_{12}kTV/\upsilon_r \quad (3)$$

in which V = total volume, V_i = molecular volume of component i, Φ_i = volume fraction of component i, k = Boltzman's constant, χ_{12} = Flory–Huggins interaction parameter, and υ_r = interacting segment volume (a repeat unit volume), also referred to as reference volume.

The Flory–Huggins equation presents an explanation for the decrease in the miscibility of solvent–polymer mixtures compared to solvent–solvent mixtures with the decrease in combinatorial entropy of mixing. The combinatorial entropy of mixing in polymer–polymer mixtures approaches insignificant values for high-molecular-weight polymer mixtures. Therefore, achieving miscibility is dependent on negative heat of mixing (i.e., $\chi_{12} < 0$). A study by Zhong and Al-Saigh [32] reports the use of a series of derivative calculations from the original Flory–Huggins equation to determine the polymer–polymer interaction parameters and deduce the compatibility of different weight ratios of PLA and amylopectin (AP) in various organic solvents. They found exothermic interaction parameter at all weight ratios. The authors followed their thermodynamic calculations with an inverse gas chromatography technique to analyze the morphology of PLA/AP blends and observed the most favorable blending ratio as 75AP–25PLA, which has the most negative interaction parameters. Other studies to evaluate thermal resistance and durability of PLA have been performed on stereocomplex-poly(L- and D-lactide) (sc-PLA)/poly(methylmethacrylate) (PMMA) blends by using PMMA loadings varying from 20 to 80 mass%. The isothermal and nonisothermal studies performed on these blends prove miscibility at molecular levels with a negative value of the Flory–Huggins interaction parameter [33,34].

During blend formation, phase separation is often observed in initially miscible polymer mixtures subjected to the removal of either temperature or solvent [35]. The degree of separation in blends greatly affects the resulting morphology. The two common processes involved in blending are nucleation and growth and spinodal decomposition. The spinodal region is the most favored area of interest for material development to tailor a particular blend for different commercial applications. With the knowledge of thermodynamics and kinetics of the blends, they can be tuned for target mechanical and electrical properties while avoiding the adverse effects of demixing, metastable, and unstable stages. Fig. 1 shows how phase separation occurs with variation in temperature and composition [36].

Upper critical solution temperature (UCST) behavior studies of poly(L-lactide) blended with poly(methyl methacrylate) (PLLA/PMMA)

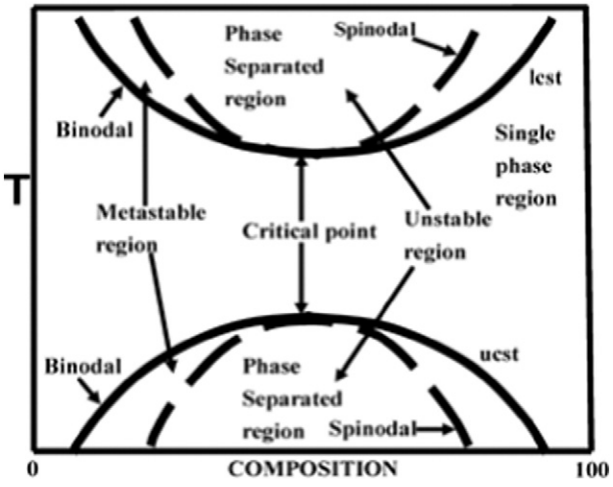

Fig. 1. Phase diagram for a binary blend in terms of lower critical solution temperature and upper critical solution temperature.
(Reproduced from Ref. [36]).

by Li and Woo [37] demonstrated phase reversibility and transition between the miscible and immiscible regions in PLA/PMMA. The polymers, immiscible at room temperature, became miscible at higher temperatures with a UCST of 230 °C, but reverted to a quasi-miscible state on temperature removal. The authors report the interaction parameters at this quasi-miscible state to be −0.15 to −0.19, indicative of the existence of weak interactions between the ester and carbonyl groups of PLA and PMMA, respectively.

Because of semicrystalline nature of the polymers used in the blends, the turbidity measurements aided by light-scattering techniques are often unable to detect the extent of miscibility or heterogeneity. Thermal analysis is employed to determine the miscibility of polymers with glass transition temperature (T_g) less than 10 °C apart. Thermograms of miscible blends show single T_g, intermediate to T_gs of constituent polymers. In contrast, elongated single or two separate transitions reflect partial miscibility and phase separation or immiscibility of polymers, respectively. The comparison between the thermal behaviors of different polymer blends with variable mixing is presented in Fig. 2 [38].

In a study to analyze the miscibility of PLA and poly(butylene adipate-co-terephthalate) (PBAT), Dil and coworkers [39] used modulated DSC to determine one-way partial miscibility of PBAT in PLA-rich phases, which declines when a higher molecular weight PBAT is used in the blend. The thermal behavior of the polymeric blends also varies with the mode of preparation [40]. During blending, the molecular mobility of the polymer changes, which eventually impacts T_g, crystallization and corresponding enthalpies [41]. Thus, extensive thermodynamic and morphological studies have been conducted on diversely tailored PLA blends with other polymers to obtain specific required properties [42]. For instance, annealing technique has been successfully employed to PLA/starch blend to overcome a certain degree of depolymerization of PLA during material processing and for better thermodynamic stability and crystallinity [43].

3.2. Effects of PLA blending on polymer properties

As discussed in the previous sections, polymer blending generates physical properties that are different from those of the parent polymers, with the extent of alteration depending on the amount of each constituent polymer. The blend morphology, phase dispersion, and processing conditions have a significant influence on the thermomechanical properties and degradation of the final material. This section discusses the manner in which the properties of polymers can be tailored by blending techniques.

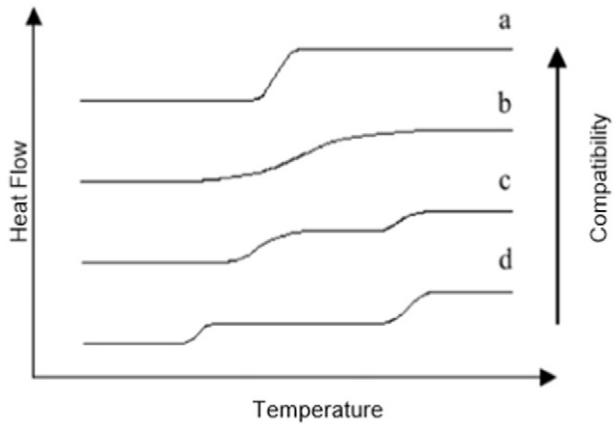

Fig. 2. Differential scanning calorimetry (DSC) thermograms for (a) a miscible blend, (b) miscible blend close to phase separation, (c) partially miscible blend close to complete immiscibility, and (d) immiscible blend.
(Reproduced from Ref. [38]).

3.2.1. Thermal and mechanical properties

Despite being a material with high strength and modulus, PLA lacks application in mechanically demanding environments because of low impact toughness, brittle nature, and low elongation-at-break. At the same time, blending PLA with other polymers with low strength can enhance the tensile strength and modulus of the polymers with inferior properties. Hence, PLA is often blended with other polymers to either blend properties of two or more polymers or enhance thermomechanical properties either of PLA or the other constituent polymers. As mentioned in the previous section, the alteration in thermal behavior of PLA blends is dictated by the extent of miscibility of the constituent polymers. Polymer blends can be tailored by varying the polymer composition to achieve a combination of thermal and mechanical properties as required for specific applications. Anakabe et al. [44] studied the effect of melt blending PLA and poly(methylmethacrylate) to determine a single T_g for the blends after heating them to 250 °C in a DSC apparatus, with a value intermediate to those for individual polymers and impact toughness similar to the neat polymer in which they were rich. The authors also noted the effect of processing temperature on the final T_g of the blend, since they discovered that the blends processed at 215 °C showed dual T_g transitions due to polymer immiscibility below the UCST of 230 °C [37]. In another study by Jing et al. [45], blending PLA with thermoplastic polyurethane (TPU) enhanced toughness and elongation-at-break of PLA, imparted by TPU. They further noted that the blend with 80% PLA has shape-memory behavior, which the authors attribute to the crystalline regions of PLA, that cause retention of shape by acting as cross-linking points within the blend. Poly(ε-caprolactone) (PCL) has also been reported to increase the elongation-at-break and thermal stability of PLA in a blend, accompanied by a decrease in the tensile strength and modulus compared with neat PLA because of the lower values of these properties in PCL [46,47]. The addition of PCL also changes the failure behavior of the blend from brittle, as in the case of neat PLA, to ductile. As mentioned earlier, PLA is often blended with natural polymers with lower mechanical strength to enhance their performance. Starch/PLA blends have been reported where PLA enhances the tensile strength of the blend, while it decreases the moisture uptake compared to starch alone [48–51]. Wootthikanokkhan et al. [52] report PLA/maleated thermoplastic starch blends, which show an increase in tensile strength, elongation-at-break, modulus, and toughness with an increase in the amount of PLA from 60% to 80%. They also note the effect of blending temperature and time on the mechanical properties of the blend, where the strength and modulus increase while elongation-at-break and toughness decrease with an increase in the blending time and temperature. Zhang et al. [53] blended PLA with soy protein to increase the tensile strength with respect to the amount of PLA in the blend, which further increased with the addition of poly(2-ethyl-2-oxazoline) as a compatibilizing agent.

Compatibilizers are added to polymer mixtures to increase the interfacial adhesion between polymers, which in turn improves the mechanical properties of the blend. Imre and Pukanszky [54] present a detailed review about the nature and use of compatibilization in the blends of biodegradable polymers. The use of various compatibilizers has been explored to improve the properties of PLA blends with other polymers, especially those with lower levels of miscibility with PLA [5]. Yu et al. [55] studied the effect of methyldiisocyante (MDI) compatibilizer on PLA/cornstarch blends. They found an increase in modulus, strength, and impact toughness with an increase in the MDI concentration from 0.5% to 1%, with further improvement in properties when MDI is distributed in the PLA phase. Presence of MDI in the PLA phase also enhances cold crystallization in the PLA/corn starch blends, which the authors attribute to starch acting as a nucleating agent for PLA. Hence, the interfaces between the two polymers are improved.

According to the desired application, polymers are often subjected to plasticization to make the material more flexible. Plasticizers induce a decrease in T_g, tensile strength, and solution viscosity of the polymer,

but increase its elongation, impact toughness, and processability [56]. There have been reports of PLA blended with plasticizers alone to enhance the properties of the polymer and of the introduction of plasticizers in blends of PLA with other polymers, either to make them more processable or to further improve their properties. Polyethylene glycol (PEG) and PEG derivatives or copolymers are common plasticizers used to blend with PLA to increase toughness and flexibility and have been widely reported in the literature [57–60]. Poly(vinyl alcohol) (PVA)/PLA blends, with PVA plasticized with an esterification product of lactide and glycerol (lacti-glyceride), have been reported by Li et al. [61]. The authors observed improved thermal processability and flexibility with relatively lower T_g in the blend as expected upon plasticization. The authors also reported a compatibilizing effect of lacti-glyceride on PVA/PLA blends when catalyzed using Stannous Octoate, which they attribute to in situ transesterification between PVA and PLA. Along the same lines, Clasen et al. [62] describe the use of maleic anhydride (MA) to serve the dual purpose of plasticizer and compatibilizer in thermoplastic starch (TPS)/PLA blends, where the presence of free or grafted MA in the blend increases its toughness and flexibility but decreases the modulus compared to the blends devoid of MA.

3.2.2. Degradability

Many applications of PLA, including biomedical, compostable packaging, benefit from its biodegradable nature. Blending PLA with other polymers generates a new degradation profile that depends on the amount of each polymer in the blend and the blend morphology. The degradation products of each polymer remain the same as the parent polymers, but the rate and level of degradation of the blend are dictated by its composition and morphology. Thus, the degradation profile of a blend can be tuned by altering its composition and processing conditions to suit the needs of different applications. Jaso et al. [63] studied the biodegradation of blends of PLA with TPU at an elevated temperature of 58 °C in simulated compost conditions for 70 days. They found that the degradation of PLA/TPU blends is dictated by the polymer in which they are rich. They report that the blends rich in TPU show rapid initial degradation followed by a plateau phase, similar to neat TPU, which underwent fast initial degradation followed by a slow degradation and only 30% mineralization at the end of 70 days. In contrast, the blends rich in PLA exhibit an initial lag in degradation, but achieve a higher degree of degradation at the end. This is similar to pure PLA, which starts to degrade after 20 days and is almost completely degraded by the end of 70 days. The authors also note that morphology plays an important role in the degradation process in which co-continuous blends degrade at a higher rate initially than those with globular morphology.

In addition to blend composition and phase dispersion, further thermal processing of blends and the introduction of additives can have a dramatic effect on the rate of degradation of a blend. Malwela and Ray [64] investigated enzymatic degradation of PLA/poly(butylene succinate-co-adipate) (PBST) blends in Tris–HCl buffer with proteinase K. They report an enhanced degradation rate of the blend compared to that of the individual polymers due to phase-separated morphology of the blend owing to immiscibility of PLA and PBST. Annealing the PLA/PBST films at 70 °C decelerates the degradation rate due to the increased crystallinity of the PBST phase and is further decreased by the addition of nanoclay fillers that enhances the crystallinity of PBST. Degradation is even more dramatically decelerated when the films are annealed at 120 °C at which point the crystallinity of the PLA phase is enhanced. This is further pronounced by the addition of nanoclay.

Degradation of PLA under physiological conditions for biomedical applications is well evidenced and has been extensively reported and reviewed in the literature [13,65–67]. An important design consideration to achieve optimal performance in vivo for the end product is to maintain the degradation of PLA blends within the physiological constraints, while tuning the degradation profile for specific biomedical applications such as drug delivery and scaffolds. Tuning the blend composition not only alters the rate of degradation but also modifies the pattern to allow the material to degrade in a complex fashion. This can be particularly beneficial to design release profiles for drug-delivery applications and compatibilize scaffold degradation to tissue recovery in tissue engineering or graft applications [68–70]. PLA blends with one or more polymers or copolymers can yield complex degradation patterns; this may not be possible in the case of copolymers alone, such as PLGA, which, despite having a deviated degradation profile from the parent polymers, undergo a predetermined degradation profile. For instance, Zhu et al. [71] developed a tissue-engineering scaffold using a blend of PLA, PEG, and a PLA—PEG copolymer, which show an initial rapid loss in simulated physiological conditions, followed by a slow degradation over 100 h. This is faster than the degradation for a neat PLA scaffold, which shows significantly slower degradation over 200 h. The authors also compared the degradation pattern with that of a PLA/PEG binary, which shows an initial rapid degradation due to PEG dissolution followed by the degradation rate similar to that of neat PLA.

3.3. Processing of PLA blends

Polymer blends can be prepared by two methods: (i) solvent blending involving dissolution of polymer mixture in a cosolvent and (ii) melt blending by mechanical mixing of molten polymer mixture [72]. In the case of solvent blending, the polymers are dissolved in a cosolvent and processed to form the end product, followed by evaporation of the solvent. Polymer blends prepared by dissolution in a solvent can be cast into films and porous materials, spun (wet, dry, or electrospun), and subjected to particulating techniques (e.g., emulsion–diffusion–evaporation, phase separation, spray-drying) to form particles of different-sized profiles. Because of the solvated state of polymers and the presence of large amounts of solvent, solution blending is not an applicable method for compression molding [73]. The melt blending technique employs a melt extruder, e.g., a twin-screw extruder, to blend the molten mixture of polymers. Melt-blended polymers can then be cast into films by compression, melt spun, electrospun, injection, and blow molding and subjected to foaming techniques to form porous structures.

Both solvent and melt blending procedures are used to prepare PLA blends. The process adapted to prepare PLA bends depends on the miscibility of the polymers and the physical structure and mechanical properties of the end product. For instance, PLA fibers have been reported to possess different mechanical properties and degradation rates when prepared using melt blending and solution spinning techniques [74]. According to the end-use requirements, PLA blends are further processed into different structures, e.g., films, fibers, particles, and porous structures, and molded into shapes like those for implants.

3.3.1. Films

The first use of PLA films in biomedical applications was reported by Yolles and Colleagues [75,76] for slow release of narcotic antagonists. PLA and PLA blends have been employed to cast films using a variety of techniques with or without the use of solvents. In the early 1990s, the Langer group [77] reported a method to blend PLA with pluronic surfactant with and without polyethyleneimine (PEI) coating. The PLA/pluronic blends were cast onto petri dishes by the solvent evaporation method, and the films were further coated with PLA by compression molding followed by PEI treatment in water and dried; films without PEI served as a control. The PEI coating formed ionic links with the proteins trapped in the films, minimized the burst effects, and modulated the release profiles. Boonkong et al. [30] reported films cast from a chitosan (60%), PLA (28%), and PCL (12%) blend using glycerin (Gly) or PEG as an emulsifier. Glycerin or PEG was used to reduce surface tension between the organic and aqueous phases and to increase their miscibility. Films with glycerin had better mechanical properties, transparency, and ease of peeling than the ones with PEG.

Ljungberg and Wesslen [78] report a solvent-free melt extrusion/hot-press technique to form films of PLA blended with monomeric and oligomeric plasticizers for enhanced flexibility and morphological stability over time. Electrospun fiber mats were prepared using PLA and poly(ethylene-co-vinyl acetate) (PEVA) blend, where PEVA facilitated chain entanglements to produce fibers [79]. The mats spun from a 50:50 PLA/PEVA blend were stiffer than those of PEVA, thus confirming the role of PLA in enhancing the mechanical strength of the mats, which is necessary for drug-delivery applications.

Bie et al. [80] report antimicrobial films prepared from a PLA/starch/chitosan blend by film extrusion using a twin-screw extruder. Starch provides hydrophilicity to the blend to facilitate diffusion of water and initial burst release of chitosan, while the slow degrading PLA maintains sustained release over a longer time. Shirai et al. [49] describe another approach to prepare biodegradable films of PLA blends with TPS and PBAT by using blown film extrusion technique. PLA, in these blends, contributes to the enhancement of the modulus, strength, and barrier properties of the films, but it decreases transparency and elongation-at-break at higher weight percentages.

3.3.2. Fibers

The first recognized biomedical applications of PLA involved its use as a bio-absorbable suture [81]. Since then, advancement in science and technology has led to the manufacture of high performance, reliable, and eco-friendly PLA or PLA-blend fiber products for various biomedical applications [82–84]. Fibers are advantageous in applications that require a large surface area. This makes them ideal for various applications such as scaffolds, wound dressings, and biosensors. Peesan et al. [84] studied fibers of hexanoyl chitosan/PLA blend prepared by electrospinning, which possessed distinct characteristics from those of the individual polymers. The solvents used in electrospinning played a significant role in determining the end morphology; dichloromethane leads to the formation of polymer beads, which are not present in the case of chloroform. The size of fibers decreases with the increase in hexanoyl chitosan content from 0% to 50% due to a decrease in viscosity.

In another study by Xiong et al. [85], soluble eggshell membrane protein (SEP) was co-electrospun with poly(propylene carbonate) (PPC) and PLA in various compositions in 1, 1, 1, 3, 3, 3-hexafluoro-2-propanol (HFIP) solutions. These fibers exhibit better mechanical properties with either PPC or PLA in the blend. The presence of SEP on the fiber surface contributes to improved surface hydrophilicity and biocompatibility. He et al. [86] evaluated the potential of mono or multi-fibers composed of poly(3 hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx), poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), and PLA as medical sutures. The two fibers, PHBHHx and PHBV/PLA, show high tensile strength, elasticity, biocompatibility, and processability that are appropriate for use as medical sutures.

As mentioned earlier, compatibilizing agents are often employed to tune the microstructure of immiscible polymer blends. In one such approach, cellulose nanowhiskers (CNWs) extracted from ramie fibers were used as substrates to compatibilize binary polyester blends containing 50:50 polycaprolactone (PCL)/PLA [87]. In this study, CNW grafted with a copolymer of PCL and PLA, CNW-g-P(CL-*b*-LA), showed the potential to serve as a suitable nanofiller to tune the compatibility and microstructure of PCL/PLA.

PLA blends are also applicable to tune degradation for optimal release of drugs from fiber-based mats or membranes. Valarezo et al. [88] blended PLA and PCL to achieve an optimal release of amoxicillin by attaining an intermediate degradation behavior, compared to the fast degradation of PCL and slow degradation of PLA. As discussed in Section 3.2.2, different degradation behaviors and the amount of constituent polymers in a blend along with blend morphology determine its degradation profile and hence the release of an incorporated drug.

3.3.3. Particulates

The biocompatibility and safety of degradation products of PLA in biological systems, along with its superior mechanical properties, have been leveraged to encapsulate various agents into micro- and nanoscale particulates for in vivo use. Particles based on PLA and PLA blends have applications in various biomedical arenas, e.g. drug delivery, diagnostics, and tissue engineering. They have been used to encapsulate a variety of agents, including but not limited to drugs, diagnostic molecules, genes, proteins, and nucleic acids [89–92]. The size profile and structure of the particles are determined by the methods used in their preparation and are tailored based on the target application. PLA blends with a variety of natural and synthetic polymers and lipids have been developed with tailored mechanical integrity to form a matrix to entrap the encapsulants and tune the degradation profile for controlled release [93–96].

The emulsion–diffusion–evaporation technique is the most widely used method to prepare particles for the delivery of drugs and bioactives. This is because of its adaptability to encapsulate a variety of materials with different physico-chemical attributes. For instance, nanoparticles of PLA blend with poly(D,L-lactide-co-caprolactone) (PLC) loaded with tamoxifen (TMX), a hydrophobic anticancer drug, prepared using the double emulsion–evaporation method and PVA as a stabilizer were investigated for antitumor activity in MCF-7 and HeLa cells [97]. The nanoparticles show initial burst release in the first 3 h followed by sustained release over 63 days in vitro. The cells exhibit time- and concentration-dependent uptake of nanoparticles with a slower decrease in cell viability compared to that with TMX solution at the same concentration, indicative of sustained release of the drug over time.

In addition to drug delivery, particles of PLA blends are also used to fabricate tissue-engineering scaffolds, where they can be employed to either sustain the release of growth factors or differentiation agents in a scaffold composed of other materials or can form the physical structure themselves. Porous PLA microparticles with chitosan or polyvinyl alcohol (PVOH) in their internal matrix have been developed using modified double emulsion–evaporation method with the incorporation of sucrose as additive in the primary aqueous phase [98]. MCF-7 breast cancer cells seeded onto the porous microparticulates were reported to have adhered to the scaffolds within 24 h and proliferated to form 3D tissue-like structures over a period of 5 days.

Recently, attempts have been made to automate the emulsion–diffusion technique using microfluidic innovations. Min et al. [99] report uniform anisotropic microparticles of PLA blends with PMMA and polystyrene (PS), using a microfluidic capillary device for controlled dispersion of emulsion drops of polymer blends in aqueous surfactant solution. Phase separation of polymers occurs upon diffusion of the organic solvent. Dimpled core–shell, spherical core–shell, and acorn-shaped janus microparticles can be prepared by varying the polymer pair in the blend and surfactant. The phase separation and the bulk structure of particles in this case determine their degradation rate and pattern and hence drug-release profiles.

In addition to the emulsion–diffusion process, spray-drying techniques have also been explored for the preparation of particles of PLA blends. Sacchetin et al. [100] developed PLA/PCL particles loaded with androgen hormone 17α-methyltestosterone (MT) using the carbon dioxide (CO_2) supercritical fluid anti-solvent method, where supercritical CO_2 was purged into the flowing solution of polymer blend and MT, causing mutual diffusion of CO_2 and organic solvent at the droplet interface followed by supersaturation to induce nucleation to form fine particles. The microparticles with MT:polymer mass ratio between 0.029 and 0.378 were stable in simulated gastrointestinal conditions and released the majority of entrapped MT over a 10-h period in vitro. Takami and Murakami [101] developed a model spray-drying system for potential pulmonary delivery applications. This system generates PLA–PEG/PLGA microparticles by emulsification of polymer solution in an organic solvent in aqueous solution followed by nebulization of emulsion and subsequent drying by heating while using nitrogen as the carrier gas.

3.3.4. Porous structures

Porosity of materials is an important design criterion for certain applications, for example, scaffolds for tissue engineering, drug-delivery substrates, and membranes. Different methods can be employed to induce porosity in polymers and polymer blends. PLA blends are heavily used in tissue engineering, which requires a porous structure for optimal proliferation of cells and the development of microvasculature. Particle-leaching technique is one of the methods used to induce porosity in polymeric materials, which involves casting of polymer solution dispersed with a salt, followed by leaching of salt particles using an appropriate solvent, for example, water in the case of inorganic salts. The kind and size of salt grains used as porogen affect the structure and size range of porosity obtained by the particle leaching method. Cai et al. [102] report a porous scaffold composed of a PLA/dextran blend by the solvent casting of a solution of PLA and trimethylsilyl-protected dextran in methylene chloride/benzene mixture with a dispersion of sodium chloride, followed by leaching of salt particles in water to create micro and macropores in the range of 5–10 μm and 100–200 μm, respectively. Sadiasa et al. [103] used a similar solvent casting/particle-leaching technique to form porous PLA/PCL scaffolds by casting the polymer solution in chloroform and using sodium bicarbonate as the porogen, resulting in the porosity ranging between 100 and 300 μm.

Another approach to create a porous polymer structure is phase extraction, where one of the phase-separated polymers is extracted after melt blending and setting of the polymer mixture. Xiang et al. [104] report a porous PLA substrate with a pore size of 1.5 μm obtained through quenching of melt-blended PLA/PS, followed by the solvent extraction of the PS phase to create a porous structure. The porous substrate was devised for controlled release of bovine serum albumin (BSA) loaded into the porous substrate following the layer-by-layer deposition of polyelectrolytes to tune the amount of open areas and hence the release profile of BSA.

Melt-blended polymers can also be subjected to foaming with a supercritical gas, usually CO_2, under a high-pressure environment to induce porosity [105]. Porous scaffolds of PLA/PEG with interconnected porosity have been developed by foaming of compressed plates prepared from melt-blended polymers using supercritical CO_2 as the foaming agent [106].

The density, shape, and size of the pores can be further tuned by combining two or more pore-forming techniques. Zhou et al. [107] used a combination of solid-state gas foaming and phase-extraction techniques to devise a porous scaffold of PLA/PS blend with 20- to 70 μm-sized pores. The polymer mixture was melt blended, compression molded, and subjected to solid-state foaming with CO_2, followed by extraction of the PS phase to further increase the porosity.

4. Applications

As mentioned in the above sections discussing end-use modifications, PLA blends have been explored in a variety of biomedical applications. Most research involving PLA blends revolves around drug delivery and tissue engineering. Diagnostic and theranostic usage of blends of PLA, first modified at the synthetic level, is also being explored because of the specific need for the incorporation of moieties for targeting, stimuli response, or stealth. In addition to developing PLA blends with a predetermined fate, material development in search for better biomaterials from a compatibility, biodegradability, and mechanistic point of view is also being explored by many researchers. Blending PLA with other natural or synthetic polymers with established biocompatibility such as PCL, PLGA, and chitosan ensures its applicability as biomaterials. The following sections briefly cover the current status of PLA blends in drug delivery, tissue engineering, implants, and biomaterial development for potential biomedical applications.

4.1. Drug delivery

While there are many reasons for high drug-attrition rates [108,109], lack of appropriate dosage form is considered one of the major bottlenecks. To address the new drug development needs, the pharmaceutical industry is turning toward drug repurposing, where innovative delivery strategies hold the key to success. However, the application of nonconventional drug-delivery strategies requires careful consideration of the 4Ds: drug, destination, delivery, and disease [110]. The choice of the delivery system and route of administration, in turn, largely depend on drug potency, where many options exist for low-dose drugs, typically <10 mg [111]. Drugs are most useful when orally bioavailable. However, the discovery program aimed at identifying physicochemical properties that correlate with this characteristic often leads to limited success, [112] and novel delivery technologies may be useful. Despite better understanding and success of drug absorption, the oral route remains restricted to small molecules. Significant literature is available on novel delivery strategies addressing a range of issues in pharmaceutical product development that includes, but is not limited to, (a) life-cycle management, (b) new indications for existing drugs, (c) alternate route of administration to meet compliance or new indication, (d) reduce/minimize toxicity, and (e) alter pharmacokinetics.

PLA and PLGA are the most widely used polymers for nonconventional dosage form design that are applied in a wide range of pathologies, for example, alcohol dependency, cancer, diabetes, and wound healing. PLA and PLA blends have been explored for many drug-delivery strategies, including nanosystems, hydrogels, films, and fibrous matrices.

Particle-based delivery systems such as micro and nanoparticles, vesicles, and polymerosomes have been developed for therapy, diagnosis, and imaging. For instance, nanoparticles of methoxy poly(ethylene glycol)/PLA (mPEG/PLA) blends for paclitaxel delivery were produced as an alternative to conventional Cremophor EL (now renamed Kolliphor EL)-based Taxol®. By varying the ratios of mPEG–PLA component in the blend, a range of properties such as drug loading, particle size, and release profiles can be controlled [113]. With the intent of developing materials for antifungal and antibacterial activity, blends of chitosan, PVA, and PLA mixed in varying ratios were developed, where PVA facilitates the blendability of the two immiscible components chitosan and PLA [114].

The rapid removal of nanoparticles upon injectable administration from the circulation by the reticuloendothelial system (RES) prompted the incorporation of PEG chains in the polymers. PEG confined to the surface of the particles improves circulation time in vivo and site-specific targeting [115,116]. Novel delivery technologies can be beneficial for drugs with narrow therapeutic index for which small changes in systemic concentration can lead to significant changes in pharmacodynamic response or toxicity [117].

While research activity continues to utilize PLA blends to develop delivery systems, physical blending falls short of incorporating properties such as target identification, binding, stimuli response, and stealth in biological systems. As mentioned earlier, PEG is chemically incorporated into a polymer backbone or at terminus to provide stealth in the biological environment by evading protein adsorption, macrophagial response, and accumulation in RES of delivery vehicles in the circulation [118,119]. Nottelet et al. [120], in their review on polyester-based imaging and theranostic agents, discuss the benefits of conjugating imaging modalities to the polymer as opposed to encapsulation where synthetic coupling not only prevents the leakage of contrast agent from the carrier but also allows the control of its structure for optimal imaging. This exemplifies another case in which physical blending fails to deliver, and synthetic modifications are required to serve the purpose.

Targeted and stimuli-responsive drug-delivery polymer-particulate systems have been garnering attention because of the added advantages of specificity for diseased cells or biological barriers, thus enhancing the

efficacy of encapsulated drugs [121,122]. The polymer, however, has to be synthetically/chemically modified pre- or postfabrication of the delivery system to incorporate the targeting or stimuli-responsive moiety. Hence, PLA-based blends used for active delivery systems usually involve the use of modified PLA or its copolymer such as PLGA [123–128]. In addition, multifunctionality can play an important role in receptor-mediated delivery to attain maximum interaction and avidity of delivery vehicles with the available receptors. Simple physical blending of two linear chain polymers cannot cater to this requirement, and one has to depend on the modification of the polymer at the synthetic level. Where PLA and its blends with other polymers fail to cater to the needs to modern drug-delivery systems, commercially available pre-modified copolymers of PLA such as PLGA find a niche in the field of particulate drug delivery.

Hydrogels based on PLA and its blends have been explored for biomedical applications such as contact lens, tissue engineering, and drug-delivery vehicles. Recently, PLA/poly(N-isopropyl acrylamide)-co-acrylamide blend hydrogels with silver nanoparticles were developed by Prabhakar et al. [129], which exhibited antimicrobial activity against *Escherichia coli* and thermoresponsive-sustained release of 5-fluoroucil drug. Often, blends of neat PLA with other polymers do not successfully achieve the desired characteristics and optimal gelation of the blend and hence have to be synthetically modified before blending with other polymers. Zong et al. [130] copolymerized PLA with PEG to form a PLA–PEG–PLA copolymer to be blended with *Bombyx mori* silk fibroin to form hydrogels capable of holding drugs or growth factors within their nanoglobules. The authors report that the use of PLA–PEG–PLA polymer accelerates the hydrogelation of the blend and improves the modulus and rigidity of the hydrogel.

PLA blends have also been explored for film- [131–134] and nanofiber- [88,135–137] based drug-delivery approaches. Liu et al. [138] investigated the effect of blending ethylene vinyl acetate copolymer (EVA) with PLA to develop paclitaxel-eluting stent coatings, where the rate and amount of drug release can be modulated by varying the amount of PLA in the blend. Chitrattha et al. [139] report PLA/PEG-based porous matrix films for the delivery of gentamicin sulfate or metronidazole for wound dressing application. Compared to films of neat PLA, PLA/PEG-based films are more amorphous and exhibit enhanced porosity and pore size, which in turn increase the rates of water vapor and oxygen transmission, degradation rate, and total drug release. For a fiber-based transdermal delivery approach, PLA/poly(butylene adipate) (PBA) blend electrospun nanofibers were developed by Panoraia Siafaka et al. [140] for sustained delivery of teriflunomide, an anti-rheumatoid agent, to correlate with the degradation of the nanofibrous matrix.

Recently, gene therapy has emerged as a field with high-research activity. PLA has been explored in gene transfection applications after subjection to synthetic modification. The literature has numerous examples in which PLA has been modified by copolymerization or grafting to develop gene transfection agents with or without blending [141–145].

4.2. Tissue engineering

The prerequisites for vascular grafts and tissue-engineering scaffolds include biocompatibility, anti-thrombogenecity, application-specific degradation profile, and appropriate mechanical properties to match native blood vessels or tissues. Owing to their biocompatibility and superior mechanical properties, PLA and its blends with other polymers have been explored to develop porous scaffolds using different techniques such as electrospinning, particle leaching, and foaming as described in Section 3. For instance, electrospun grafts of PLA/PCL and PCL/PLA/PEG blends have been investigated for their endothelialization support using human placental endothelial cells [146]. Scaffolds of PLA blends show enhanced endothelialization, cell viability and physiological cobblestone morphology in cells compared to conventional poly(tetra-fluoroethylene) grafts. The rigid nature of PLA was blended with flexible mechanical properties of TPU in different ratios by using twin-screw extrusion and microcellular injection molding [22]. The elongation-at-break of the blend improves dramatically as the TPU content is increased. PLA/TPU blends also exhibit better cell viability than pure PLA. Kramschuster and Turng [147] report a solvent-free combinatorial injection molding/supercritical fluid processing/particle-leaching technique to prepare porous scaffolds of PLA-blended hydrophilic PVOH using NaCl as a porogen. Another study presents a rapid protyping technique to prepare 3D scaffolds of PLA/PEG with a well-defined structure, enhanced hydrophilicity, elastic modulus, and tuned degradation [148]. Shabna et al. [149] report that *Pseudomonas* sp. derived poly 3-[hydroxy propionate (15%)–hydroxy octa decanoate (85%)] (PHA) blended with biodegradable polymers such as PLA improves the polymer processability and enhances viability and proliferation of cells grown on the resultant scaffolds. Biomimetic scaffolds of poly(glycerol sebacate) (PGS)/PLLA blend were developed by Martin Frydrych et al. [150] for adipose tissue engineering by solvent casting followed by freeze drying and curing. Compared to scaffolds of neat PLA, PGS/PLA scaffolds possess better hydrophilicity, more optimal porosity, and mechanical properties for soft tissue engineering and provide enhanced cell penetration into the scaffold and tissue growth. Tissue-engineering scaffolds using PLA as one of its constituents bank upon its ideal mechanical properties for structural integrity and ease of processing. Blending PLA with other natural or synthetic polymers with better wettability and faster degradation provides a feasible means to tune its biodegradability to be compatible with the time taken for tissue growth and/or recovery. Thus, PLA blends with different polymers offer the opportunity to tailor tissue-specific scaffolds.

4.3. Implants

The optimal performance of implants is contingent upon the material's biocompatibility, superior mechanical properties, and corrosion and creep resistance. PLA and its blends have been used for implants for over three decades [10,151–154]. For instance, ocular implants were developed using PLA/polyvinyl pyrrolidone (PVP) for fluorometholone delivery in which the release rate increased with the increase in PVP and followed first-order kinetics. Subsequently, a good in vitro–in vivo correlation was established using rabbit as a model [155]. Blends of biodegradable PLLA and PDLLA or PCL along with the surfactant, a copolymer of ethylene oxide and propylene oxide, were prepared in different weight percentages [156]. Solution-blended PDLLA/PLLA in the presence of a surfactant enhances toughness, making it suitable for potential use in dental or orthopedic implants.

In drug-releasing implants such as drug-eluting stents, the drug is either incorporated into the matrix during processing or is adsorbed on the composite. Exploration of PLA and PLA blends for use in drug-eluting stents has been ongoing in commercial medical device companies, with many products already on the market. Garg et al. [157] present the current commercial status of PLA/PLA blends in stent technology in their comprehensive review of drug-eluting stents. Further research at the academic level has also continued in this direction. Drug-eluting nanofibers of PLA/PCL have been developed by embedding 5-fluorourasil into the polymer matrix. PLA/PCL (80:20) nanofibers exhibit a controlled degradation profile and considerable cell apoptosis under the influence of the drug [158]. Liu et al. [138] report two polymer blends, EVA/PLA and EVA/PEG, as coating film materials for paclitaxel-eluting stents. McConville et al. [159] developed vaginal rings of PEVA blend for tenofovir delivery.

4.4. Biomaterials for potential biomedical applications

Research activity in materials science and engineering often revolves around generating polymers with enhanced properties without delving into application-specific requirements. Numerous PLA blends have been

Table 3
A nonexhaustive list of PLA blends developed for biomedical applications.

Type of blend	Process	Suggested application	References
PLA/natural rubber	Dynamic vulcanization using dicumyl peroxide(DCP) as a cross-linking agent		[160]
PLA/HDI-grafted starch/castor oil	Interphase layer toughening technique		[48]
PLA/PEGDA(poly(ethylene glycol)diacylate	Melt blending		[161]
PLA/PHBHHx (poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)	Melt blending using twin-screw extruder	Artificial vascular grafts	[162]
PLA/EPO(epoxidized palm oil)	Melt blending	Alternate to conventional plastics	[163]
PLA/TPS blends using water as a foaming agent	Foam extrusion		[164]
PLA/PPGs(poly(propylene glycol))	Melt blending		[165]
PLA/PBAT(poly(butylene adipate-co-terephthalate))	Melt blending using twin-screw extruder		[166]
PLA/poly(butylene adipate-co-terephthalate) in the presence of chain extender	Melt blending		[167]
PLLA(poly(L-lactide))/PDLA(poly-D-lactide))/PMMA(poly(methyl methacrylate)	Melt extrusion		[168]
PLA/PBSA(poly(butylene succinate-co-adipate) in the presence of TPP (triphenyl phosphite	Melt blending	Environment-friendly packaging material	[169]
PLA/poly(ω-hydroxyfatty acid) bioplastic (PCL14)	Reactive extrusion		[170]
PLA/starch with epoxide soybean oil as a plasticizer	Melt blending using twin-screw extruder		[48]
PLA/EPO (epoxide palmolein)	Melt blending	Flexible films for food packaging material	[163]
PLA/starch with tung oil anhydride as a plasticizer	Melting using twin-screw extruder		[48]
PLA/soy proteins	Melt blending using twin-screw extruder		[53,171]
PLA/PHBV(poly(3-hydroxybutyrate–co-hydroxyvalerate)/ PBS(poly(butylene succinate))	Melt blending		[172]
PLA/PCL using CNW (cellulose nanowhiskers) as a compatibilizer	Melt blending	Biomedical and industrial applications	[87]
PLA/PBSA(poly(butylene succinate)-co-adipate))	Melt blending		[169]
PLA/poly(ether-b-amide)/ethylene–methylacrylate–glycidyl methacrylate	Melt bending using twin-screw extruder		[173]

reported with potential applications in biomedical field because of the biocompatibility and biodegradability of the constituent polymers. Table 3 lists examples of PLA blends developed for use as potential biomaterials with/without any targeted application at present.

5. Commercial scenario of PLA blends

The demand for bio-based biodegradable polymers has been increasing due to growing environmental concerns and pressure on finite petrochemical resources. The bio-based plastics market is projected to increase to about 3.45 million tons by 2020, in which PLA alone is estimated to account for about 800,000 tons [174]. A research report published by the Agricultural Utilization Research Institute gives information about the major PLA manufacturers in the world as of 2013 with their projected capacities by 2020 (Table 4) [175].

The utility of modified PLA in different plastics industries is a major contributing factor to its increasing market demand. PLA blends are being developed for commercial use, spanning a variety of applications. The majority of PLA blends market is dominated by packaging applications, for which a number of PLA blends with enhanced mechanical, thermal, and optical properties are already in the market. While packaging still remains the largest market segment, ongoing heavy research activity in biomedical fields is expected to increase the demand for PLA and PLA blends for biomedical and possible consumer goods applications. PLA and PLA blends boast a higher global production capacity and market share than other biodegradable polymers. However, they lag behind bio-sourced nondegradable polymers such as Bio-PET, which are heavily consumed in the packaging industry. Fig. 3 presents the market data for bioplastics in 2014 as published by European Bioplastics [176].

Table 4
List of major PLA manufacturers with their current and projected production capacities from the 2014 bioplastics market report published by the Agricultural Utilization Research Institute.
(Reproduced from Ref. [175]).

Company	Location	2013 capacity (tons)	2020 projected capacity (tons)
NatureWorks LLC	USA/Thailand	150,000	450,000
Purac/Corbion	EU/Thailand	75,000	150,000
Zhejiang Hisun	China	5000	20,000
Nantong Jiuding Biologic	China	5000	5000
Shenzhen Bright China	China	10,000	10,000
Shanhai Tong-Jie-Liang	China	3000	10,000
Futerro (Galactic/Total)	EU	1500	5000
Teijin	Japan	1200	5000
Pyramid	Germany	3000	60,000
Total		255,700	715,000

The increasing demand of PLA blends in biomedical applications is prompting bioplastic manufacturers to commercialize pre-formed PLA blends. Some of the key players in PLA blends market are companies such as NatureWorks-BioAmber joint venture (AmberWorks), Corbion, Arkema (Biostrength), Sukano (Bio-loy), and BASF [177–181]. In addition to the PLA blends marketed by plastic companies, biomedical companies and academia are actively filing patents for novel PLA blends for an array of biomedical applications. Table 5 presents examples of patents issued in the recent past for biomedical applications involving PLA blends.

6. Conclusions and future prospective

PLA is an ideal polymer for biomedical applications given its excellent biocompatibility and safe degradation products. The ability to modify PLA with other polymers through blending has been widely employed to impart the properties required for target applications. Various companies in bioplastics and biomedical businesses are developing new PLA blends for applications including packaging, fabrics, tissue engineering, and implants. As indicated by the generation of new intellectual property by industry and academia and joint ventures between companies manufacturing different natural and synthetic polymers, the demand for PLA blends is expected to grow in the near future.

While certain applications such as packaging can benefit from pre-blended polymers to fabricate their end products, most of the other products require custom blending based on end-use requirements. As such, platform blends for application such as scaffolds and grafts for in vivo applications are not practical, as their development is dictated by subjective measures varying from patient to patient. For in vivo use, the hydrophobicity of PLA can be decreased to some extent by blending with more hydrophilic polymers, but the immiscibility of certain polymers can compromise the mechanical properties of the blends.

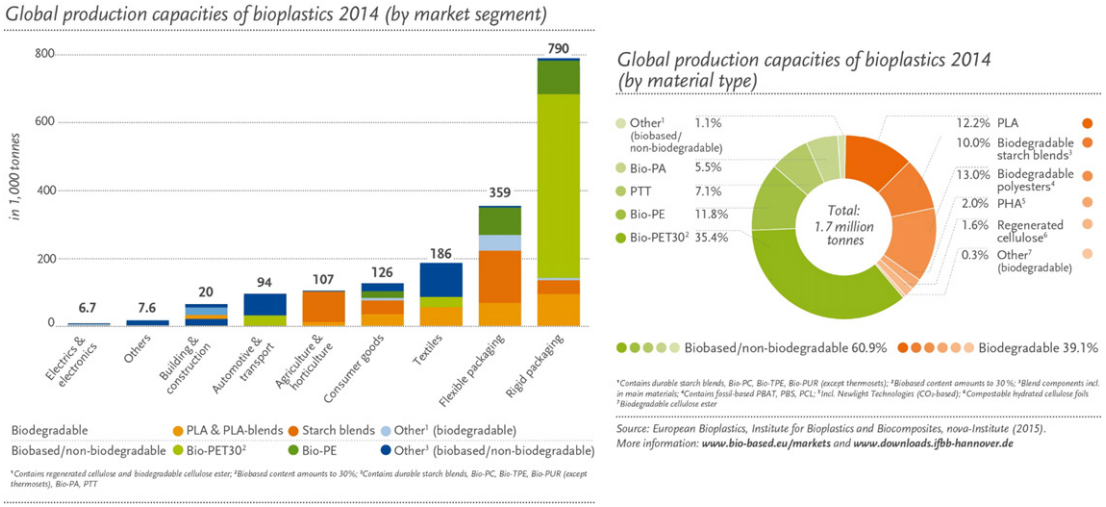

Fig. 3. Global production capacities of bioplastics by market segment and material type in 2014. (Reproduced from Ref. [176]).

Hence, copolymers of PLA with more hydrophilic constituents in the polymer backbone, such as PLGA, are more suitable for the applications that require enhanced wettability with superior mechanical properties. However, the mechanical properties and crystallinity of the PLA cannot be undermined for load-bearing applications such as implants and sutures. Blends provide an easy means to mold implants and spin fibers with the addition of reinforcements or plasticizers, if required, for such applications.

In the field of drug delivery, where the inclination toward active delivery systems is increasing, physical PLA blends cannot be employed, since they require a more synthetic approach to modify the polymer backbone or end groups with molecules of choice to introduce targeting ability in the delivery vehicles. Receptor-mediated active drug delivery or diagnostics benefit from the multifunctionality of polymers forming the delivery systems. This is because a higher ligand density on the surface results in higher affinity to the receptors and higher cumulative force of avidity to the receptor, preventing the premature shedding of the delivery system. PLA is limited by the single terminal functionality for the conjugation of active molecules of interest. Thus, pre-blending synthetic modification of PLA becomes necessary.

Despite the limitations of unmodified PLA, the promising attributes of compatibility, degradability, processability, and mechanical strength will continue to keep its status as a polymer of choice for biomedical blends. While commercial PLA blends have found a niche in the packaging industry and are growing in use in the biomedical industry, most of the work in this field is still confined to the exploratory zone at the laboratory scale. In addition to developing PLA blends, research also needs to focus on developing strategies to manufacture devices that allow for customization of blends on-demand and as-needed in biomedical applications driven by patient conditions. In the current scenario, PLA blends are still a long way from scale-up and translation to medical market.

Table 5
Some of the recent patents filed for PLA blends for biomedical applications.

Application	References
Controlled-release drug delivery	[182–184]
Tissue engineering	[185,186]
Implants	[187–189]
Drug-eluting stents	[190]
Wound healing	[191]
Gene delivery	[192]
Shape memory	[193]

References

[1] R.E. Conn, J.J. Kolstad, J.F. Borzelleca, D.S. Dixler, L.J. Filer Jr., B.N. LaDu Jr., M.W. Pariza, Safety assessment of polylactide (PLA) for use as a food-contact polymer, Food Chem. Toxicol. 33 (1995) 273–283.

[2] A. Sodergard, M. Stolt, Properties of lactic acid based polymers and their correlation with composition, Prog. Polym. Sci. 27 (2002) 1123–1163.

[3] S. Chanfreau, M. Mena, J.R. Porras-Domingues, M. Ramirez-Gilly, M. Gimeno, P. Roquero, A. Tecante, E. Barzana, Enzymatic synthesis of poly-L-lactide and poly-L-lactide-co-glycolide in an ionic liquid, Bioprocess Biosyst. Eng. 33 (2010) 629–638.

[4] D. Omay, Y. Guvenilir, Synthesis and characterization of poly(D,L-lactic acid) via enzymatic ring opening polymerization by using free and immobilized lipase, Biocatal. Biotransform. 31 (2013) 132–140.

[5] J.B. Zeng, K.A. Li, A.K. Du, Compatibilization strategies in poly(lactic acid)-based blends, RSC Adv. 5 (2015) 32546–32565.

[6] W. Zhang, Y. Wang, Synthesis and properties of high molecular weight poly(lactic acid) and its resultant fibers, Chin. J. Polym. Sci. 26 (2008) 425–432.

[7] L. Lu, A.G. Mikos, Poly(lactic acid), in: J.E. Mark (Ed.), Polymer Data Handbook, Oxford University Press, New York 1999, pp. 627–633.

[8] D. Garlotta, A literature review of poly(lactic acid), J. Polym. Environ. 9 (2001) 63–84.

[9] L. Xiao, B. Wang, G. Yang, M. Gauthier, Modification of PLA, in: D.N. Ghista (Ed.), Biomedical Science, Engineering and Technology, InTech, Rijeka, Croatia 2012, pp. 255–259.

[10] R.P. Pawar, S.U. Tekale, S.U. Shisodia, J.T. Totre, A.J. Domb, Biomedical applications of poly(lactic acid), Recent Pat. Regen. Med. 4 (2014) 40–51.

[11] L. Averous, Polylactic acid: synthesis, properties and applications, in: M.N. Belgacem, A. Gandini (Eds.), Monomers, Polymers and Composites From Renewable Resources, Elsevier, Oxford 2008, pp. 433–450.

[12] R.A. Auras, L.T. Lim, S.E.M. Selke, H. Tsuji, Poly(lactic acid): synthesis, structures, properties, processing and applications, in: R.F. Grossman, D. Nwabunma (Eds.), Wiley Series in Polymer Engineering and Technology, John Wiley & Sons, Hoboken, 2010.

[13] A.J. Lasprilla, G.A. Martinez, B.H. Lunelli, A.L. Jardini, R.M. Filho, Poly-lactic acid synthesis for application in biomedical devices — a review, Biotechnol. Adv. 30 (2012) 321–328.

[14] K.A. Athanasiou, C.M. Agrawal, F.A. Barber, S.S. Burkhart, Orthopaedic applications for PLA–PGA biodegradable polymers, Arthroscopy 14 (1998) 726–737.

[15] G. Kfoury, J.M. Raquez, F. Hassouna, J. Odent, V. Toniazzo, D. Ruch, P. Dubois, Recent advances in high performance poly(lactide): from "green" plasticization to super-tough materials via (reactive) compounding, Front. Chem. 1 (2013) 32.

[16] N.R. Nair, K.M. Nampoothiri, A. Pandey, Preparation of poly(L-lactide) blends and biodegradation by *Lentzea waywayandensis*, Biotechnol. Lett. 34 (2012) 2031–2035.

[17] T. Takayama, M. Todo, H. Tsuji, Effect of annealing on the mechanical properties of PLA/PCL and PLA/PCL/LTI polymer blends, J. Mech. Behav. Biomed. Mater. 4 (2011) 255–260.

[18] X. Tang, S.K. Thankappan, P. Lee, S.E. Fard, M.D. Harmon, K. Tran, X. Yu, Natural polymers in tissue engineering and regenerative medicine, in: S.G. Kumar, C.T. Laurencin, M. DEng (Eds.), Natural and Synthetic Biomedical Polymers, Elsevier, Burlington, MA 2014, pp. 352–358.

[19] A. Sionkowska, Introduction, in: S. Dumitriu, V. Popa (Eds.), Polymeric Biomaterials: Structure and Function, CRC Press, Boca Raton, FL 2013, p. 311.

[20] I. Armentano, E. Fortunati, N. Burgos, F. Dominici, F. Luzi, S. Fiori, A. Jimenez, K. Yoon, J. Ahn, S. Kang, J.M. Kenny, Processing and characterization of plasticized PLA/PHB blends for biodegradable multiphase systems, Express Polym Lett 9 (2015) 583–596.

[21] J.J. Song, H.H. Chang, H.E. Naguib, Biocompatible shape memory polymer actuators with high force capabilities, Eur. Polym. J. 67 (2015) 186–198.
[22] H.Y. Mi, M.R. Salick, X. Jing, B.R. Jacques, W.C. Crone, X.F. Peng, L.S. Turng, Characterization of thermoplastic polyurethane/polylactic acid (TPU/PLA) tissue engineering scaffolds fabricated by microcellular injection molding, Mater. Sci. Eng. C Mater. Biol. Appl. 33 (2013) 4767–4776.
[23] J.J. Song, H.H. Chang, H.E. Naguib, Design and characterization of biocomaptible shape memory polymer (SMP) blend foams with a dynamic structure, Polymer 56 (2015) 86–92.
[24] K.K. Sankaran, U.M. Krishnan, S. Sethuraman, Axially aligned 3D nanofibrous grafts of PLA–PCL for small diameter cardiovascular applications, J. Biomater. Sci. Polym. Ed. 25 (2014) 1791–1812.
[25] M. Sun, P.J. Kingham, A.J. Reid, S.J. Armstrong, G. Terenghi, S. Downes, In vitro and in vivo testing of novel ultrathin PCL and PCL/PLA blend films as peripheral nerve conduit, J. Biomed. Mater. Res. A 93 (2010) 1470–1481.
[26] L.I. Ramdhanie, S.R. Aubuchon, E.D. Boland, D.C. Knapp, C.P. Barnes, D.G. Simpson, G.E. Wnek, G.L. Bowlin, Thermal and mechanical characterization of electrospun blends of poly(lactic acid) and poly(glycolic acid), Polym. J. 38 (2006) 1137–1145.
[27] R.M. Mainaedes, N.M. Khalil, M.P.D. Gremiao, Intranasal delivery of zidovudine by PLA and PLA–PEG blend nanoparticles, Int. J. Pharm. 395 (2010) 266–271.
[28] B.Y. Chen, H.Y. Mi, H. Zhao, W.H. Zhang, X.F. Peng, Fabrication of polylactic acid/polyethylene glycol (PLA/PEG) porous scaffold by supercritical CO_2 foaming and particle leaching, Polym. Eng. Sci. 55 (2015) 1339–1348.
[29] C.S. Wu, H.T. Liao, A new biodegradable blends prepared from polylactide and hyaluronic acid, Polymer 46 (2005) 10017–10026.
[30] W. Boonkong, A. Petsom, N. Thongchul, Rapidly stopping hemorrhage by enhancing blood clotting at an opened wound using chitosan/polylactic acid/polycaprolactone wound dressing device, J. Mater. Sci. 24 (2013) 1581–1593.
[31] S. Domenek, A. Louaifi, A. Guinault, S. Baumberger, Potential of lignins as antioxidant additive in active biodegradable packaging materials, J. Polym. Environ. 21 (2013) 692–701.
[32] B. Zhong, Z.Y. Al-Saigh, Characterization of biodegradable polymers by inverse gas chromatography. III. Blends of amylopectin and poly(L-lactide), J. Appl. Polym. Sci. 123 (2012) 2616–2627.
[33] Q. dong, Y. Bian, Y. Li, C. Han, L. Dong, Miscibility and crystallisation behaviors of stereocomplex-type poly(L- and D-lactide)/poly(methyl methacrylate) blends, J. Therm. Anal. 118 (2014) 359–367.
[34] X. Hao, J. Kaschta, X. Liu, Y. Pan, D.W. Shubert, Entanglement network formed in miscible PLA/PMMA blends and its role in rheological thermo-mechanical properties of the blends, Polymer 80 (2015) 38–45.
[35] P. van de Witte, P.J. Dijkstra, J.W.A. van den Berg, J. Feijen, Phase separation processes in polymer solutions in relation to membrane formation, J. Membr. 117 (1996) 1–31.
[36] L. Robeson, Historical perspective of advances in the science and technology of polymer blends, Polymers 6 (2014) 1251–1265.
[37] S.H. Li, E.M. Woo, Immiscibility–miscibility phase transitions in blends of poly(L-lactide) with poly(methyl methacrylate), Polym. Int. 57 (2008) 1242–1251.
[38] V. Arrighi, J.M.G. Cowie, S. Furhman, Y. Abdelsallem, Miscibility criterion in polymer blend and its determination, in: A.I. Isayev (Ed.), Encyclopedia of Polymer Blends, Wiley-VCH Verlag GmbH & Co., Weinheim, Germany 2010, p. 158.
[39] E.J. Dil, P.J. Carreau, B.D. Favis, Morphology, miscibility and continuity development in poly(lactic acid)/poly(butylene adipate-co-terephthalate) blends, Polymer 68 (2015) 202–212.
[40] N. Hashim, K. Rerenam, S. Somderam, K. Yousoh, Effect of processing method on thermal behavior in PLA/PEG melt blending, Adv. Mater. Res. 1134 (2016) 185–190.
[41] P. Miuller, B. Imre, J. Bere, J. Moczo, B. Pukanszsky, Physical ageing and molecular mobility in PLA blends and composites, J. Therm. Anal. 122 (2015) 1423–1433.
[42] G. Zhang, J. Zhang, S. Wang, D. Shen, Miscibility and phase structure of binary blends of polylactide and poly(methyl methacryalte), J. Polym. Sci. B Polym. Phys. 41 (2003) 23–30.
[43] S. Lu, J. Gu, J. Cao, H. Tan, Y. Zhang, Effect of annealing on the thermal properties of poly(lactic acid)/starch blends, Int. J. Biol. Macromol. 74 (2015) 297–303.
[44] J. Anakabe, A.M.Z. Huici, A. Eceiza, A. Arbelaiz, Melt blending of polylactide and poly(methylmethacrylate): thermal and mechanical properties and phase morphology characterization, J. Appl. Polym. Sci. 132 (2015) 42677–42685.
[45] X. Jing, H.Y. Mi, X.F. Peng, L.-S. Turng, The morphology, properties, and shape memory behavior of polylactic acid/thermoplastic polyurethane blends, Polym. Eng. Sci. 55 (2015) 70–80.
[46] H. Zhao, G. Zhao, Mechanical and thermal properties of conventional and microcellular injection molded (lactic acid)/poly(ε-caprolactone) blends, J. Mech. Behav. Biomed. Mater. 53 (2016) 59–67.
[47] J.M. Ferri, O. Fenollar, A. Jorda-Vilaplana, D. Garcia-Sanoguera, R. Balart, Effect of miscibility on mechanical and thermal properties of poly(lactic acid)/polycaprolactone blends, Polym. Int. 65 (2016) 453–463.
[48] Y. Yang, Z. Tang, Z. Xiong, J. Zhu, Preparation and characterization of thermoplastic starches and their blends with poly(lactic acid), Int. J. Biol. Macromol. 77 (2015) 273–279.
[49] M.A. Shirai, J.B. Olivato, P.S. Garcia, C.M. Muller, M.V. Grossmann, F. Yamashita, Thermoplastic starch/polyester films: effects of extrusion process and poly(lactic acid) addition, Mater. Sci. Eng. C Mater. Biol. Appl. 33 (2013) 4112–4117.
[50] M.A. Shirai, M.V. Grossmann, S. Mali, F. Yamashita, P.S. Garcia, C.M. Muller, Development of biodegradable flexible films of starch and poly(lactic acid) plasticized with adipate or citrate esters, Carbohydr. Polym. 92 (2013) 19–22.
[51] D. Preechawong, M. Peesan, P. Supaphol, R. Rujiravanit, Preparation and characterization of starch/poly(L-lactic acid) hybrid foams, Carbohydr. Polym. 59 (2005) 329–337.
[52] J. Wootthikanokkkan, N. Wongta, N. Sombatsompop, A. Kositchaiyong, J. Wong-On, S.I.n. Ayutthaya, N. Kaabbuathong, Effect of blending conditions on mechanical, thermal, and rheological properties of plasticized poly(lactic acid)/maleated thermoplastic strach blends, J. Appl. Polym. Sci. 124 (2012) 1012–1019.
[53] J. Zhang, L. Jiang, L. Zhu, Morphology and properties of soy protein and polylactide blends, Biomacromolecules 7 (2006) 1551–1561.
[54] B. Imre, B. Pukanszky, Compatibilization in bio-based and biodegradable polymer blends, Eur. Polym. J. 49 (2013) 1215–1233.
[55] L. Yu, E. Petinakis, K. Dean, H. Liu, Q. Yuan, Enhancing compatibilizer function by controlled distribution in hydrophobic polylactic acid/hydrophilic starch blends, J. Appl. Polym. Sci. 119 (2011) 2189–2195.
[56] G. Wypych, Expectations from plasticizers, in: G. Wypych (Ed.), Handbook of Plasticizers, ChemTec Publishing, Toronto 2012, pp. 2–4.
[57] K. Sungsanit, N. Kao, S.N. Bhattacharya, Properties of linear poly(lactic acid)/polyethylene glycol blends, Polym. Eng. Sci. 52 (2011) 108–116.
[58] P. Byung-Sik, J.C. Song, D.H. Park, K.-B. Yoon, PLA/chain extended PEG blends with improved ductility, J. Appl. Polym. Sci. 123 (2011) 2360–2367.
[59] A. Zubrowska, E. Piorkowska, A. Kowalewska, M. Cichorek, Novel blends of polylactide with ethylene glycol derivatives of POSS, Colloid Polym. Sci. 293 (2015) 23–33.
[60] Z. Jia, J. Tan, C. Han, Y. Yang, L. Dong, Poly(ethylene glycol-co-propylene glycol) as a macromolecular plasticizing agent for polylactide: thermomechanical properties and aging, J. Appl. Polym. Sci. 114 (2009) 1105–1117.
[61] H.Z. Li, S.C. Chen, Y.Z. Wang, Thermoplastic PVA/PLA blends with improved processability and hydrophobicity, Ind. Eng. Chem. Res. 53 (2014) 17355–17361.
[62] S.H. Clasen, C.M.O. Muller, A.T.N. Pires, Maleic anhydride as a compatibilizer and plasticizer in TPS/PLA blends, J. Braz. Chem. Soc. 26 (2015) 1583–1590.
[63] V. Jaso, G. Glenn, A. Klamczynski, Z.S. Petrovic, Biodegradability study of polylactic acid/thermoplastic polyurethane blends, Polym. Test. 47 (2015) 1–3.
[64] T. Malwela, S.S. Ray, Enzymatic degradation behavior of nanoclay reinforced biodegradable PLA/PBSA blend composites, Int. J. Biol. Macromol. 77 (2015) 131–142.
[65] A.F.C. Vieira, Modeling hydrolytic degradation of PLA devices: chemistry, research and applications, in: V. Piemonte (Ed.), Polylactic Acid: Synthesis, Properties and Applications, Nova Science Publishers, 2012.
[66] C. Shasteen, Y. Choy, Controlling degradation rate of poly(lactic acid) for its biomedical applications, Biomed. Eng. Lett. 1 (2011) 163–167.
[67] H. Tsuji, Poly(lactide) stereocomplexes: formation, structure, properties, degradation, and applications, Macromol. Biosci. 5 (2005) 569–597.
[68] A.C. Viera, R.M. Guedes, V. Tita, Damage-induces hydrolyses modelling of biodegradable polymers for tendons and ligaments repair, J. Biomech. 48 (2015) 3478–3485.
[69] Q. Cai, J. Bei, S. Wang, In vitro study on the drug release behavior from polylactide-based blend matrices, Polym. Adv. Technol. 13 (2002) 534–540.
[70] Y. Kim, P. Dalhaimer, D.A. Christian, D.E. Discher, Polymeric worm micelles as nano-carriers for drug delivery, Nanotechnology 16 (2005) S484–S491.
[71] X. Zhu, T. Zhong, R. Huang, A. Wan, Preparation of hydrophilic poly(lactid acid) tissue engineering scaffold via (PLA)–(PLA-β-PEG)-(PEG) solution casting and thermal induced surface structural transformation, J. Biomater. Sci. Polym. Ed. 26 (2015) 1286–1296.
[72] M. Yue, K.S. Chian, Polymer blending, in: N.P. Cheremisinoff (Ed.), Multiphase Reactor and Polymerization System Hydrodynamics, Gulf Publishing Company, Houston, TX 1996, p. 749.
[73] M.T. Shaw, Casting from common solvents, in: D.J. Walsh, J.S. Higgins, A. Maconnachie (Eds.), Polymer Blends and Mixtures, Martinus Nijhoff, Dordecht 1985, p. 60.
[74] L. Famri, C. Migliaresi, Fibers, in: R. Auras, L.T. Lim, S.E.M. Selke, H. Tsuji (Eds.), Poly(lactic acid): Synthesis, Properties, Processing and Application, John Wiley & Sons Inc., Hoboken, NJ 2010, pp. 119–121.
[75] S. Yolles, T.D. Leafe, J.H. Woodland, F.J. Meyer, Long acting delivery systems for narcotic antagonists II: release rates of naltrexone from poly(lactic acid) composites, J. Pharm. Sci. 64 (1975) 348–349.
[76] J.H. Woodland, S. Yolles, D.A. Blake, M. Helrich, F.J. Meyer, Long-acting delivery systems for narcotic antagonists, J. Med. Chem. 16 (1973) 897–901.
[77] T.G. Park, S. Cohen, R. Langer, Controlled protein release from polyethyleneimine-coated poly(L-lactic acid)/pluronic blend matrices, Pharm. Res. 9 (1992) 37–39.
[78] N. Ljungberg, B. Wesslen, Preparation and properties of plasticized poly(lactic acid) films, Biomacromolecules 6 (2005) 1789–1796.
[79] R. Kenawy el, G.L. Bowlin, K. Mansfield, J. Layman, D.G. Simpson, E.H. Sanders, G.E. Wnek, Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend, J. Control. Release 81 (2002) 57–64.
[80] P. Bie, P. Liu, L. Yu, X. Li, L. Chen, F. Xie, The properties of antimicrobial films derived from poly(lactic acid)/starch/chitosan blended matrix, Carbohydr. Polym. 98 (2013) 959–966.
[81] R.K. Kulkarni, E.G. Moore, A.F. Hegyeli, F. Leonard, Biodegradable poly(lactic acid) polymers, J. Biomed. Mater. Res. 5 (1971) 169–181.
[82] H.W. Kim, H.S. Yu, H.H. Lee, Nanofibrous matrices of poly(lactic acid) and gelatin polymeric blends for the improvement of cellular responses, J. Biomed. Mater. Res. A 87 (2008) 25–32.
[83] K.M. Hossain, M.S. Hasan, D. Boyd, C.D. Rudd, I. Ahmed, W. Thielemans, Effect of cellulose nanowhiskers on surface morphology, mechanical properties, and cell adhesion of melt-drawn polylactic acid fibers, Biomacromolecules 15 (2014) 1498–1506.
[84] M. Peesan, R. Rujiravanit, P. Supaphol, Electrospinning of hexanoyl chitosan/polylactide blends, J. Biomater. Sci. Polym. Ed. 17 (2006) 547–565.
[85] X. Xiong, Q. Li, J.W. Lu, Z.X. Guo, Z.H. Sun, J. Yu, Fibrous scaffolds made by co-electrospinning soluble eggshell membrane protein with biodegradable synthetic polymers, J. Biomater. Sci. Polym. Ed. 23 (2012) 1217–1230.

[86] Y. He, Z. Hu, M. Ren, C. Ding, P. Chen, Q. Gu, Q. Wu, Evaluation of PHBHHx and PHBV/PLA fibers used as medical sutures, J. Mater. Sci. Mater. Med. 25 (2014) 561–571.
[87] A.L. Goffin, Y. Habibi, J.M. Raquez, P. Dubois, Polyester-grafted cellulose nanowhiskers: a new approach for tuning the microstructure of immiscible polyester blends, ACS Appl. Mater. Interfaces 4 (2012) 3364–3371.
[88] E. Valarezo, L. Tammaro, O. Malagon, S. Gonzalez, C. Armijos, V. Vittoria, Fabrication and characterization of poly(lactic acid)/poly(epsilon–caprolactone) blend electrospun fibers loaded with amoxicillin for tunable delivering, J. Nanosci. Nanotechnol. 15 (2015) 4706–4712.
[89] F. Mohamed, C.F. Van der Walle, Engineering biodegradable polyester particles with specific drug targeting and drug release properties, J. Pharm. Sci. 97 (2008) 71–87.
[90] V. Lassalle, M.L. Farreira, PLA nano- and microparticles for drug delivery: An overview of methods of preparation, Micromol. Biosci. 7 (2007) 767–783.
[91] A. Salerno, R. Levato, M.A. Mateos-Timoneda, E. Engel, P.A. Netti, J.A. Planell, Modular polylactic acid microparticle-based scaffolds prepared via microfluidic emulsion/solvent displacement process: fabrication, characterization, and in vitro mesenchymal stem cells interaction study, J. Biomed. Mater. Res. A 101 (2013) 720–732.
[92] G. Ma, Microencapsulation of protein drugs for drug delivery: strategy, preparation, and applications, J. Control. Release 193 (2014) 324–340.
[93] K. Hadinoto, A. Sundaresan, W.S. Cheow, Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review, Eur. J. Pharm. Biopharm. 85 (2013) 427–443.
[94] W. Wang, S. Chen, L. Zhang, X. Wu, J. Wang, J.F. Chen, Y. Le, Poly(lactic acid)/chitosan hybrid nanoparticles for controlled release of anticancer drug, Mater. Sci. Eng. C Mater. Biol. Appl. 46 (2015) 514–520.
[95] G.S. Das, G.H. Rao, R.F. Wilson, T. Chandy, Colchicine encapsulation within poly(ethylene glycol)-coated poly(lactic acid)/poly(epsilon–caprolactone) microspheres-controlled release studies, Drug Deliv. 7 (2000) 129–138.
[96] R. Lindner Gda, L.F. Dalmolin, N.M. Khalil, R.M. Mainardes, Influence of the formulation parameters on the particle size and encapsulation efficiency of resveratrol in PLA and PLA-PEG blend nanoparticles: a factorial design, J. Nanosci. Nanotechnol. 15 (2015) 10173–10182.
[97] E. Perez, M. Benito, C. Teijon, R. Olmo, J.M. Teijon, M.D. Blanco, Tamoxifen-loaded nanoparticles based on a novel mixture of biodegradable polyesters: characterization and in vitro evaluation as sustained release systems, J. Microencapsul. 29 (2012) 309–322.
[98] S.K. Sahoo, A.K. Panda, V. Labhasetwar, Characterization of porous PLGA/PLA microparticles as a scaffold for three dimensional growth of breast cancer cells, Biomacromolecules 6 (2005) 1132–1139.
[99] N.G. Min, B. Kim, T.Y. Lee, D. Kim, D.C. Lee, S.H. Kim, Anisotropic microparticles created by phase separation of polymer blends confined in monodisperse emulsion drops, Langmuir 31 (2015) 937–943.
[100] P.S. Sacchetin, R.F. Setti, T. Rosa Pde, A.M. Moraes, Properties of PLA/PCL particles as vehicles for oral delivery of the androgen hormone 17-alpha-methyltestosterone, Mater. Sci. Eng. C Mater. Biol. Appl. 58 (2016) 870–881.
[101] T. Takami, Y. Murakami, Development of PEG-PLA/PLGA microparticles for pulmonary drug delivery prepared by a novel emulsification technique assisted with amphiphilic block copolymers, Colloids Surf. B: Biointerfaces 87 (2011) 433–438.
[102] Q. Cai, J. Yang, J. Bei, S. Wang, A novel porous cells scaffold made of polylactide–dextran blend by combining phase-separation and particle-leaching techniques, Biomaterials 23 (2002) 4483–4492.
[103] A. Sadiasa, T.H. Nguyen, B.T. Lee, In vitro and in vivo evaluation of porous PCL–PLLA 3D polymer scaffolds fabricated via salt leaching method for bone tissue engineering applications, J. Biomater. Sci. Polym. Ed. 25 (2014) 150–167.
[104] Z. Xiang, P. Sarazin, B.D. Favis, Controlling burst and final drug release times from porous polylactide devices derived from co-continuous polymer blends, Biomacromolecules 10 (2009) 2053–2066.
[105] M. Bhamidipati, A.M. Scurto, M.S. Detamore, The future of carbon dioxide for polymer processing in tissue engineering, Tissue Eng. B Rev. 19 (2013) 221–232.
[106] W. Zhang, B. Chen, H. Zhao, P. Yu, D. Fu, J. Wen, X. Peng, Processing and characterization of supercritical CO_2 batch foamed poly(lactic acid)/poly(ethylene glycol) scaffold for tissue engineering application, J. Appl. Polym. Sci. (2013) 3066–3073.
[107] C. Zhou, L. Ma, W. Li, D. Yao, Fabrication of tissue engineering scaffolds through solid-state foaming of immiscible polymer blends, Biofabrication 3 (2011) 045003.
[108] I. Kola, J. Landis, Can the pharmaceutical industry reduce attrition rates, Nat. Rev. Drug Discov. 3 (2004) 711–716.
[109] M.J. Waring, J. Arrowsmith, A.R. Leach, P.D. Leeson, S. Mandrell, R.M. Owen, G. Pairaudeau, W.D. Pennie, S.D. Pickett, J. Wang, O. Wallace, A. Weir, An analysis of the attrition of drug candidates from four major pharmaceutical companies, Nat. Rev. Drug Discov. 14 (2015) 475–486.
[110] S.S. Davis, L. Illum, Drug delivery systems for challenging molecules, Int. J. Pharm. 176 (1998) 1–8.
[111] K.R. Horspool, C.A. Lipinski, Enabling strategies: advancing new drug delivery concepts to gain the lead, J. Drug Deliv. Sci. Technol. 3 (2003) 34–46.
[112] D.S. Tan, Diversity-oriented synthesis: exploring the intersections between chemistry and biology, Nat. Chem. Biol. 1 (2005) 74–84.
[113] Y. Dong, S.S. Feng, Nanoparticles of poly(D,L-lactide)/methoxy poly(ethylene glycol)-poly(D,L-lactide) blends for controlled release of paclitaxel, J. Biomed. Mater. Res. A 78 (2006) 12–19.
[114] R. Grande, A.J. Carvalho, Compatible ternary blends of chitosan/poly(vinyl alcohol)/poly(lactic acid) produced by oil-in-water emulsion processing, Biomacromolecules 12 (2011) 907–914.
[115] T. Betancourt, J.D. Byrne, N. Sunaryo, S.W. Crowder, M. Kadapakkam, S. Patel, S. Casciato, L. Brannon-Peppas, PEGylation strategies for active targeting of PLA/PLGA nanoparticles, J. Biomed. Mater. Res. A 91 (2009) 263–276.
[116] R. Gref, Y. Minamitake, M.T. Peracchia, V. Trubetskoy, V. Torchilin, R. Langer, Biodegradable long-circulating polymeric nanospheres, Science 263 (1994) 1600–1603.
[117] J.L. Italia, V. Bhardwaj, M.N.V. Kumar, Disease, destination, dose and delivery aspects of ciclosporin: the state of the art, Drug Discov. Today 11 (2006) 846–854.
[118] S. Mitragotri, P.A. Burke, R. Langer, Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies, Nat. Rev. Drug Discov. 13 (2014) 655–672.
[119] P. Aggarwal, J.B. Hall, C.B. McLeland, M.A. Dobrovolskaia, S.E. McNeil, Nanoparticle interaction with plasma proteins as it relates to particle biodistribution, biocompatibility and therapeutic efficacy, Adv. Drug Deliv. Rev. 61 (2009) 428–437.
[120] B. Nottelet, V. Darcos, J. Coudane, Aliphatic polyesters for medical imaging and theranostic applications, Eur. J. Pharm. Biopharm. 97 (Part B) (2015) 350–370.
[121] N. Kamaly, Z. Xiao, P.M. Valencia, A.F. Radovic-Moreno, O.C. Farokhzad, Targeted polymeric therapeutic nanoparticles: design, development and clinical translation, Chem. Soc. Rev. 41 (2012) 2971–3010.
[122] Q. Zhang, N.R. Ko, J.K. Oh, Recent advances in stimuli-responsive degradable block copolymer micelles: synthesis and controlled drug delivery applications, Chem. Commun. (Camb.) 48 (2012) 7542–7552.
[123] J. Zhao, Y. Mi, Y. Liu, S.S. Feng, Quantitative control of targeting effect of anticancer drugs formulated by ligand-conjugated nanoparticles of biodegradable copolymer blend, Biomaterials 33 (2012) 1948–1958.
[124] J. Pan, S.S. Feng, Targeted delivery of paclitaxel using folate-decorated poly(lactide)-vitamin E TPGS nanoparticles, Biomaterials 29 (2008) 2663–2672.
[125] A. Cunningham, N.R. Ko, J.K. Oh, Synthesis and reduction-responsive disassembly of PLA-based mono-cleavable micelles, Colloids Surf. B: Biointerfaces 122 (2014) 693–700.
[126] Y. Yu, C.K. Chen, W.C. Law, E. Weinheimer, S. Sengupta, P.N. Prasad, C. Cheng, Polylactide-graft-doxorubicin nanoparticles with precisely controlled drug loading for pH-triggered drug delivery, Biomacromolecules 15 (2014) 524–532.
[127] S. Mura, J. Nicolas, P. Couvreur, Stimuli-responsive nanocarriers for drug delivery, Nat. Mater. 12 (2013) 991–1003.
[128] C.J. Cheng, G.T. Tietjen, J.K. Saucier-Sawyer, W.M. Saltzman, A holistic approach to targeting disease with polymeric nanoparticles, Nat. Rev. Drug Discov. 14 (2015) 239–247.
[129] M.N. Prabhakar, P. Sudhakara, M.C.S. Subha, K.C. Rao, J.I. Song, Novel thermoresponsive biodegradable nanocomposite hydrogels for dual function in biomedical applications, Polym.-Plast. Technol. Eng. 54 (2015) 1704–1714.
[130] T. Zhong, C. Deng, Y. Gao, M. Chen, B. Zuo, Studies of in situ-forming hydrogels by blending PLA–PEG–PLA copolymer with silk fibroin solution, J. Biomed. Mater. Res. A 100 (2012) 1983–1989.
[131] E.-R. Kenawy, G.L. Bowlin, K. Mansfield, J. Layman, D.G. Simpson, E.H. Sanders, G.E. Wnek, Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend, J. Control. Release 81 (2002) 57.
[132] W. Boonkong, A. Petsom, N. Thongchul, Rapidly stopping hemorrhage by enhancing blood clotting at an opened wound using chitosan/polylactic acid/polycaprolactone wound dressing device, J. Mater. Sci. Mater. Med. 24 (2013) 1581–1593.
[133] C.J. Taylor, Paclitaxel attachment to PLA–PHA blend films, Technical Papers, Regional Technical Conference — Society of Plastics Engineers 2008, pp. 912–916.
[134] T. Gwan Park, S. Cohen, R. Langer, Controlled protein release from polyethyleneimine-coated poly(L-lactic acid)/pluronic blend matrices, Pharm. Res. 9 (1992) 37–39.
[135] H.J. Haroosh, Y. Dong, G.D. Ingram, Synthesis, morphological structures, and material characterization of electrospun PLA:PCL/magnetic nanoparticle composites for drug delivery, J. Polym. Sci. B Polym. Phys. 51 (2013) 1607–1617.
[136] H. Haroosh, Y. Dong, K. Lau, Tetracycline hydrochloride (TCH)-loaded drug carrier based on PLA:PCL nanofibre mats: experimental characterisation and release kinetics modelling, J. Mater. Sci. 49 (2014) 6270–6281.
[137] E. Valarezo, L. Tammaro, S. Gonzalez, O. Malagon, V. Vittoria, Fabrication and sustained release properties of poly(ε-caprolactone) electrospun fibers loaded with layered double hydroxide nanoparticles intercalated with amoxicillin, Appl. Clay Sci. 72 (2013) 104–109.
[138] X. Liu, L. Lei, J.W. Hou, M.F. Tang, S.R. Guo, Z.M. Wang, K.M. Chen, Evaluation of two polymeric blends (EVA/PLA and EVA/PEG) as coating film materials for paclitaxel-eluting stent application, J. Mater. Sci. Mater. Med. 22 (2011) 327–337.
[139] S. Chitrattha, T. Phaechamud, Porous poly(DL-lactic acid) matrix film with antimicrobial activities for wound dressing application, Mater. Sci. Eng. C 58 (2016) 1122–1130.
[140] P.I. Siafaka, P. Barmbalexis, D.N. Bikiaris, Novel electrospun nanofibrous matrices prepared from poly(lactic acid)/poly(butylene adipate) blends for controlled release formulations of an anti-rheumatoid agent, Eur. J. Pharm. Sci. 88 (2016) 12–25.
[141] H.W. Lu, Q.L. Nie, G.Q. Liu, H. He, Synthesis of biodegradable chitosan-poly(D,L-lactide) hybrid amphiphiles via ring opening graft polymerization for efficient gene carrier, J. Macromol. Sci. A 50 (2013) 738–746.
[142] C. Fu, X. Sun, D. Liu, Z. Chen, Z. Lu, N. Zhang, Biodegradable tri-block copolymer poly(lactic acid)-poly(ethylene glycol)-poly(L-lysine)(PLA–PEG–PLL) as a non-viral vector to enhance gene transfection, Int. J. Mol. Sci. 12 (2011) 1371–1388.
[143] V. Nadeau, P. Hildgen, AFM study of a new carrier based on PLA and salen copolymers for gene therapy, Molecules 10 (2005) 105–113.
[144] X. Qian, L. Long, Z. Shi, C. Liu, M. Qiu, J. Sheng, P. Pu, X. Yuan, Y. Ren, C. Kang, Star-branched amphiphilic PLA-b-PDMAEMA copolymers for co-delivery of miR-21 inhibitor and doxorubicin to treat glioma, Biomaterials 35 (2014) 2322–2335.

[145] V.M. Gaspar, P. Baril, E.C. Costa, D. De Melo-Diogo, F. Foucher, J.A. Queiroz, F. Sousa, C. Pichon, I.J. Correia, Bioreducible poly(2-ethyl-2-oxazoline)–PLA–PEI–SS triblock copolymer micelles for co-delivery of DNA minicircles and doxorubicin, J. Control. Release 213 (2015) 175–191.
[146] D. Pfeiffer, C. Stefanitsch, K. Wankhammer, M. Muller, L. Dreyer, B. Krolitzki, H. Zernetsch, B. Glasmacher, C. Lindner, A. Lass, M. Schwarz, W. Muckenauer, I. Lang, Endothelialization of electrospun polycaprolactone (PCL) small caliber vascular grafts spun from different polymer blends, J. Biomed. Mater. Res. A 102 (2014) 4500–4509.
[147] A. Kramschuster, L.S. Turng, An injection molding process for manufacturing highly porous and interconnected biodegradable polymer matrices for use as tissue engineering scaffolds, J. Biomed. Mater. Res. B Appl. Biomater. 92 (2010) 366–376.
[148] T. Serra, M. Ortiz-Hernandez, E. Engel, J.A. Planell, M. Navarro, Relevance of PEG in PLA-based blends for tissue engineering 3D-printed scaffolds, Mater. Sci. Eng. C Mater. Biol. Appl. 38 (2014) 55–62.
[149] A. Shabna, V. Saranya, J. Malathi, R. Shenbagarathai, H.N. Madhavan, Indigenously produced polyhydroxyalkanoate based co-polymer as cellular supportive biomaterial, J. Biomed. Mater. Res. A 102 (2014) 3470–3476.
[150] M. Frydrych, S. Román, S. Macneil, B. Chen, Biomimetic poly(glycerol sebacate)/poly(L-lactic acid) blend scaffolds for adipose tissue engineering, Acta Biomater. 18 (2015) 40–49.
[151] K. Hamad, M. Kaseem, H.W. Yang, F. Deri, Y.G. Ko, Properties and medical applications of polylactic acid: a review, Express Polym Lett 9 (2015) 435–455.
[152] L. Yu, K. Dean, L. Li, Polymer blends and composites from renewable resources, Prog. Polym. Sci. 31 (2006) 576–602.
[153] I. Armentano, E. Fortunati, S. Mattioli, N. Rescignano, J.M. Kenny, Tissue engineering, in: A. Jimenez, M.A. Peltzer, R.A. Ruseckaite (Eds.), Poly(lactic acid) Science and Technology, Royal Society of Chemistry, Cambridge, UK 2015, p. 266.
[154] S.O. Adeosun, G.I. Lawal, O.P. Gbenebor, Characteristics of biodegradable implants, J. Miner. Mater. Charact. Eng. 2 (2014) 88–106.
[155] Y. Morita, H. Saino, K. Tojo, Polymer blend implant for ocular delivery of fluorometholone, Biol. Pharm. Bull. 21 (1998) 72–75.
[156] C.C. Chen, J.Y. Chueh, H. Tseng, H.M. Huang, S.Y. Lee, Preparation and characterization of biodegradable PLA polymeric blends, Biomaterials 24 (2003) 1167–1173.
[157] S. Garg, C. Bourantas, P.W. Serruys, New concepts in the design of drug-eluting coronary stents, Nat. Rev. Cardiol. 10 (2013) 248–260.
[158] K.K. Gupta, N. Pal, P.K. Mishra, P. Srivastava, S. Mohanty, P. Maiti, 5-Fluorouracil-loaded poly(lactic acid)–poly(caprolactone) hybrid scaffold: potential chemotherapeutic implant, J. Biomed. Mater. Res. A 102 (2014) 2600–2612.
[159] C. Mc Conville, I. Major, D.R. Friend, M.R. Clark, A.D. Woolfson, R.K. Malcolm, Development of polylactide and polyethylene vinyl acetate blends for the manufacture of vaginal rings, J. Biomed. Mater. Res. B Appl. Biomater. 100 (2012) 891–895.
[160] Y. Chen, D. Yuan, C. Xu, Dynamically vulcanized biobased polylactide/natural rubber blend material with continuous cross-linked rubber phase, ACS Appl. Mater. Interfaces 6 (2014) 3811–3816.
[161] H. Fang, F. Jiang, Q. Wu, Y. Ding, Z. Wang, Supertough polylactide materials prepared through in situ reactive blending with PEG-based diacrylate monomer, ACS Appl. Mater. Interfaces 6 (2014) 13552–13563.
[162] Q. Zhao, S. Wang, M. Kong, W. Geng, R.K. Li, C. Song, D. Kong, Phase morphology, physical properties, and biodegradation behavior of novel PLA/PHBHHx blends, J. Biomed. Mater. Res. B Appl. Biomater. 100 (2012) 23–31.
[163] V.S. Silverajah, N.A. Ibrahim, N. Zainuddin, W.M. Yunus, H.A. Hassan, Mechanical, thermal and morphological properties of poly(lactic acid)/epoxidized palm olein blend, Molecules 17 (2012) 11729–11747.
[164] M. Mihai, M.A. Huneault, B.D. Favis, H. Li, Extrusion foaming of semi-crystalline PLA and PLA/thermoplastic starch blends, Macromol. Biosci. 7 (2007) 907–920.
[165] Z. Kulinski, E. Piorkowska, K. Gadzinowska, M. Stasiak, Plasticization of poly(L-lactide) with poly(propylene glycol), Biomacromolecules 7 (2006) 2128–2135.
[166] L. Jiang, M.P. Wolcott, J. Zhang, Study of biodegradable polylactide/poly(butylene adipate-co-terephthalate) blends, Biomacromolecules 7 (2006) 199–207.
[167] W. Dong, B. Zou, Y. Yan, P. Ma, M. Chen, Effect of chain-extenders on the properties and hydrolytic degradation behavior of the poly(lactide)/poly(butylene adipate-co-terephthalate) blends, Int. J. Mol. Sci. 14 (2013) 20189–20203.
[168] C. Samuel, J. Cayuela, I. Barakat, A.J. Muller, J.M. Raquez, P. Dubois, Stereocomplexation of polylactide enhanced by poly(methyl methacrylate): improved processability and thermomechanical properties of stereocomplexable polylactide-based materials, ACS Appl. Mater. Interfaces 5 (2013) 11797–11807.
[169] V. Ojijo, S. Sinha Ray, R. Sadiku, Role of specific interfacial area in controlling properties of immiscible blends of biodegradable polylactide and poly[(butylene succinate)-co-adipate], ACS Appl. Mater. Interfaces 4 (2012) 6690–6701.
[170] S. Spinella, J. Cai, C. Samuel, J. Zhu, S.A. McCallum, Y. Habibi, J.M. Raquez, P. Dubois, R.A. Gross, Polylactide/poly(omega-hydroxytetradecanoic acid) reactive blending: a green renewable approach to improving polylactide properties, Biomacromolecules 16 (2015) 1818–1826.
[171] B. Liu, L. Jiang, J. Zhang, Study of effects of processing aids on properties of poly(lactic acid)/soy protein blends, J. Polym. Environ. 19 (2011) 239–247.
[172] K. Zhang, A.K. Mohanty, M. Misra, Fully biodegradable and biorenewable ternary blends from polylactide, poly(3-hydroxybutyrate-co-hydroxyvalerate) and poly(butylene succinate) with balanced properties, ACS Appl. Mater. Interfaces 4 (2012) 3091–3101.
[173] V. Nagarajan, K. Zhang, M. Misra, A.K. Mohanty, Overcoming the fundamental challenges in improving the impact strength and crystallinity of PLA biocomposites: influence of nucleating agent and mold temperature, ACS Appl. Mater. Interfaces 7 (2015) 11203–11214.
[174] L.T. Sin, A.R. Rahmat, W.A.W.A. Rahman, Market potential of biodegradable polymers and PLA, in: S. Ebnesajjad (Ed.), Handbook of Biopolymers and Biodegradable Plastics: Properties, Processing and Applications, William Andrew, Elsevier, Waltham, MA 2013, p. 20.
[175] J.A. Lunt, Marketplace Opportunities for Integration of Biobased and Conventional Plastics, Agricultural Utilization Research Institute, 2014.
[176] Publications, European bioplastics, European-bioplastics.org2016.
[177] High heat PLA, corbion.com2015.
[178] NatureWorks and BioAmber from joint venture to commercialize new bio-based polymers, natureworksllc.com2012.
[179] Biostrength biopolymer impact mofiers, arkema.com2015.
[180] SUKANO bio-loy, products, sukano.com2015.
[181] Ecovio, product finder, basf.com2015.
[182] J.B. Kohn, D.M. Schachter, Pharmaceutical Formulation Composed of a Polymer Blend and an Active Compound for Time-controlled Release Rutgers, The State University of New Jersey, USA, 2014.
[183] W.L. Hunter, L.S. Machan, A.L. Arsenault, H.M. Burt, J.J. Jackson, S.K. Dordunoo, Anti-Angiogenic Nanoparticle Compositions, Angiotech Pharmaceuticals Inc., USA, 2012.
[184] E. Lavik, Y.H. Kwon, M. Kuehn, S. Saluja, J. Bertram, J. Huang, Sustained Intraocular Delivery of Drugs From Biodegradable Polymeric Microparticles, Yale University, University of Iowa Research Foundation, USA, 2013.
[185] D.G. Simpson, G.L. Bowlin, G.E. Wnek, P.J. Stevens, M.E. Carr, J.A. Matthews, S. Rajendran, Electroprocessed Collagen and Tissue Engineering, Virginia Commonwealth University Intellectual Property Foundation, USA, 2011.
[186] A.M. Mayes, L.G. Griffith, D.J. Irvine, P. Banerjee, T.D. Johnson, Comb Copolymers for Regulating Cell-surface Interactions, Massachusetts Institute of Technology, USA, 2002.
[187] J.H. Contiliano, J.J. Yuan, K.S. Tenhuisen, Polymer-based Orthopedic Screw and Driver System With Increased Insertion Torque Tolerance and Associated Method for Making and Using Same, Ethicon Inc., USA, 2010.
[188] S. McCarthy, J. Weinzweig, Biodegradable Bone Plates and Bonding Systems, University of Massachusetts Lowell, USA, 2014.
[189] M.W.R. Brown, Blend of Bioresorbable Polymers, Smith & Nephew PLC, USA, 2003.
[190] K.-P. Schmitz, D. Behrend, K. Sternberg, N. Grabow, D.P. Martin, S.F. Williams, Polymeric, Degradable Drug-eluting Stents and Coatings, Tepha Inc., USA, 2009.
[191] E.B. Bond, J.-P.M. Autran, L.N. Mackey, I. Noda, H.J. O'Donnell, Fibers Comprising Starch and Biodegradable Polymers, The Procter & Gamble Company, USA, 2005.
[192] E. Mathiowitz, Y.S. Jong, K. Beokelheide, Polymeric Gene Delivery System, Brown University Research Foundation, USA, 2003.
[193] P.T. Mather, C. Liu, C.J. Campo, Blends of Amorphous and Semicrystalline Polymers Having Shape Memory Properties, University of Connecticut, USA, 2008.