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Poly(lactic acid) Controlled Drug Delivery

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Abstract Various drug delivery systems are being rapidly developed for controlled drug release, improved efficacy, and reduced side effects with the goal of improving quality of life for patients and curing disease. Poly(lactic acid) (PLA) possesses numerous advantages compared with other polymers, including biocompatibility, biodegradability, low cost, environmental friendliness, and easily modified mechanical properties. These properties make PLA a promising polymer for biomedical applications. This review introduces the specific characteristics of PLA that enable its application for controlled drug delivery and describes different forms of PLA used for drug delivery, including nanoparticles, microspheres, hydrogels, electrospun fibers, and scaffolds. Previous work is summarized and future development is discussed.

Keywords Controlled drug release • Electrospun fiber • Hydrogel • Microparticle • Nanoparticle • Poly(lactic acid) • Scaffold

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1 Introduction

There are serious problems associated with the therapeutic use of small molecule drugs (SMDs), including insolubility, instability (e.g., rapid degradation in physiological environments), sequestration within the blood space by endothelial barriers, and poor uptake by tissues and cells [1–3]. A wide variety of drug delivery systems (DDSs) have been designed to overcome these challenges, which are of crucial importance in healthcare and clinical applications [3–7]. Drug delivery is a process, by which specific drugs are delivered to a target area in the organism (i.e., animals or humans) to achieve a therapeutic effect [8]. Controlled DDSs can be specially designed to increase the solubility of SMDs, improve stability by preventing SMD degradation under physiological conditions, reduce side effects by targeting the lesion regions without affecting healthy sites, and maintain sustained drug release at optimal doses [9, 10]. Moreover, the use of DDSs removes the need for frequent administration, which is the primary cause of various degrees of bodily injury. As a result, DDSs have shown significant efficacy in improving quality of life in patients. Packaging an existing clinically approved drug into an effective delivery system as an advanced formulation can also reduce the economic cost and time required for new drug development.

In controlled DDSs, the carriers are as important as the bioactive drugs. Successful delivery of drugs to target tissues requires that the carriers sustain good stability during administration. Additionally, these carriers should be biocompatible. A variety of polymers, including natural and synthetic polymers, can serve as drug carriers, but few can meet the requirements of acceptable biocompatibility, biodegradability, and absorbability [9, 11]. Recently, the field has begun to pay more attention to the use of biodegradable polymers as drug carriers because of their extraordinary performance [9, 12]. Many forms of carriers, including nanoparticles (NPs), microspheres, hydrogels, electrospun fibers, and scaffolds, have been investigated for the delivery of different types of drugs or for adaptation to different situations in in vivo microenvironments.

Among the numerous biodegradable polymers that have been used as drug carriers, poly(lactic acid) (PLA) is one of the most promising candidates (Fig. 1).

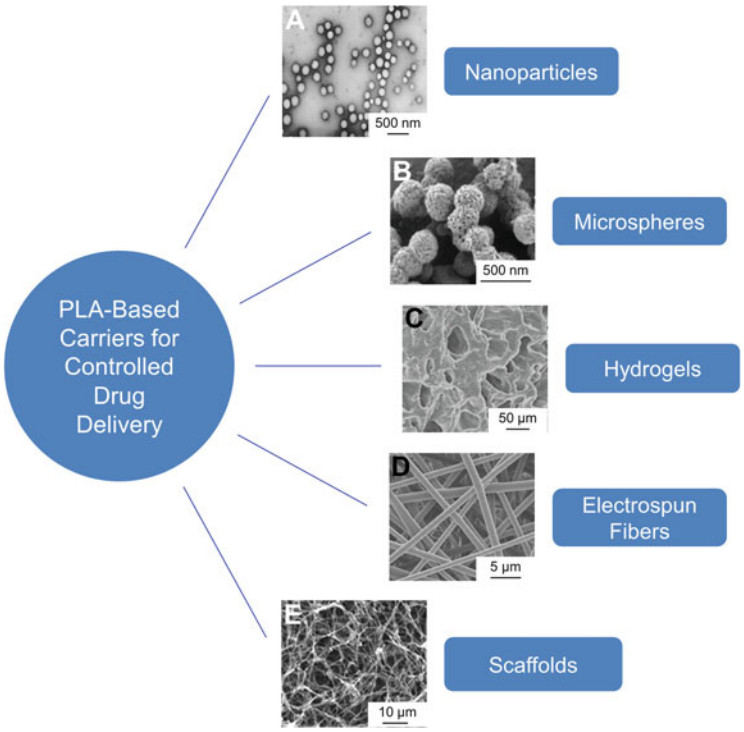

Fig. 1 PLA-based carriers for controlled drug delivery. (**a**) TEM image of PLA nanoparticles [13]. (**b**–**e**) SEM images of (**b**) microspheres [15], (**c**) hydrogels [119], (**d**) electrospun fibers [17], and (**e**) scaffolds [18]. Reproduced from [13] with permission of Springer, from [15, 119] with permission of Elsevier, from [17] with permission of American Chemical Society, and from [18] with permission of John Wiley and Sons, respectively

PLA can be fabricated into various forms for controlled drug release, including NPs [13, 14], microspheres [15], hydrogels [16], electrospun fibers [17], and scaffolds [18]. Its various advantages include being environmentally friendly, existing in multiple forms, exhibiting good biocompatibility and biodegradability, sustaining long drug retention times, having easily modified mechanical properties, and being low cost [19, 20].

PLA is derived from renewable sources, such as sugar, maize, potato, sugarcane, and beet [21]. It is prepared by different polymerizations of lactic acid, which is in turn typically produced by bacterial fermentation [22] or glycolysis [23], with little environmental pollution. Furthermore, lactic acid, the degradation product of PLA, can be removed completely in vivo. Therefore, PLA is a green biomaterial.

Lactic acid is a chiral molecule existing as L and D isomers (Fig. 2). PLA exists primarily in three forms: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), and poly(D,L-lactic acid) (PDLLA) [22, 24, 25]. Of these, PLLA has attracted the most attention in DDSs as a result of its favorable mechanical properties. However,

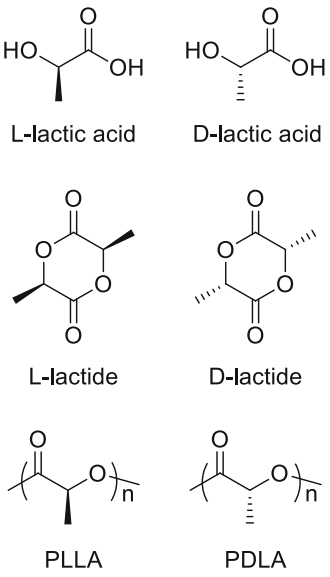

Fig. 2 Chemical structures of L-lactic acid, D-lactic acid, L-lactide, D-lactide, PLLA, and PDLA

because PLLA has a long degradation time and is therefore likely to cause inflammatory responses in vivo, it is often used in combination with polymerization of D, L-lactide monomers [22, 26].

Biocompatibility is a highly desirable trait in DDSs and has been the focus of much research. PLA is biodegradable with high biocompatibility and does not circulate in vivo for extended periods of time. Although PLA is hydrophobic, it can undergo scission, primarily by hydrolysis, to monomeric units of lactic acid in vivo even in the absence of enzymes [21]. This degradation process leaves no foreign or toxic substances because lactic acid is a natural intermediate of carbohydrate metabolism [27, 28]. As a result, PLA is highly biocompatible, biodegradable, and bioresorbable in vivo.

Another advantage of biodegradable PLA DDSs is their long retention time. Compared with other polymers, PLA possesses better biodegradability, which is relatively moderate and can be properly controlled. This biodegradability mainly relies on the crystallinity, morphology, and relative molecular mass of the polymer [20]. PLA tends to be crystalline when the PLLA content is higher than 90%, whereas the less optically pure form is amorphous [22]. Auras et al. [29] reported that the densities of solid PLLA, PDLLA, crystalline PLA, and amorphous PLA are 1.36, 1.33, 1.36, and 1.25 g cm^{-3}, respectively. PLA of low molecular weight is preferred for use as a drug carrier because it has a shorter degradation time, giving better release properties [30]. For drug carriers composed of nondegradable polymers, the drug release rate slows gradually with a reduction in the amount of encapsulated drug. PLA systems avoid this problem because the structure of PLA gradually loosens with continued degradation in vivo. As a result, the resistance to drug diffusion out of the PLA carrier is reduced, and the drug release rate is

upregulated. Because the increased drug release rate counteracts the reduced drug concentration, a long-term constant release of drug from the carrier can be achieved [31].

The chemical and physical properties of PLA, especially its biocompatibility and biodegradability, are easily influenced by adding different surfactants or changing the molecular weight, size, shape, temperature, and moisture [21, 22, 29]. This enables the creation of desired DDSs under specific conditions with different formulations [32–38]. It is also possible to control the distribution and release behavior of drugs in the PLA devices. As a typical example, Fernandez et al. [39] extracted proanthocyanidins from grapes and stabilized them with PDLA using an emulsion-evaporation method. They evaluated three factors in the formulation: sonication time for the emulsion process, loading of grape extracts, and concentration of stabilizing agent. They concluded that the extract load and stabilizer concentration were closely related to the properties of this drug model. Wei et al. [25] loaded oxaliplatin (OXA) into NP and compared the drug delivery characteristics of poly(ethylene glycol) (PEG)−PLA NP with that of PLA-only NP. They found that the OXA concentration in the tumor in the PEG−PLA NP group was higher than that in the PLA NP group. Furthermore, less OXA accumulated in the liver and lungs after PEG−PLA NP was administered. The results indicated that the PEG-modified platform possessed good drug retention ability and could deliver more drugs to the target sites. Many others have demonstrated that PEG can resist nonspecific absorption of proteins in the blood [40–44]. However, PEG has some limitations as a coating for PLA DDSs, particularly in achieving effective PEG surface densities [45, 46]. To combat this problem, Deng et al. [47] applied hyperbranched polyglycerol (HPG) as an alternative coating of PLA NP. They found that the antitumor agent camptothecin (CPT) had a longer blood circulation time, higher stability, less accumulation in the liver, and better therapeutic effectiveness against tumors in the HPG−PLA NP group than that in the PEG−PLA NP group. They concluded that HPG is a better surface coating for NPs than PEG for applications in drug delivery. In a study performed by Yamakawa et al. [48], neurotensin analogue-loaded PDLLA microspheres with different PLA molecular weights were prepared. The authors found that when the molecular weight changed, the rate of initial burst and the length of time, over which the drug was released, varied. Zeng et al. [49] examined the influence of surfactants on the diameter of electrospun PLLA fibers by adding cationic, anionic, and nonionic surfactants, that is, triethyl benzyl ammonium chloride, sodium dodecyl sulfate, and aliphatic PPO−PEO ether, respectively. Rifampin (RIF; a drug for tuberculosis) and paclitaxel (PTX; an anticancer drug) were used as model drugs and loaded into PLLA fibers. It was revealed that the addition of each of the three types of surfactant could reduce the diameter and narrow the distribution of electrospun fibers. Furthermore, RIF contained in these fibrous mats could be released constantly with no burst release behavior.

All the advantages of PLA make it a popular drug carrier matrix, and it has been approved by the Food and Drug Administration (FDA) for in vivo applications in humans [21]. The next section gives details on different forms of PLA for

controlled drug delivery, including NPs, microspheres, hydrogels, electrospun fibers, and scaffolds.

2 PLA-Based Carriers for Drug Delivery

With the assistance of DDSs, it is possible to achieve a much greater therapeutic effect for many clinical applications, including a reduced pain burden and improved quality of life. It is also possible to limit side effects by controlling drug release rate and specifically transporting drugs to target sites [50]. A variety of advanced delivery systems have been developed to achieve high efficiency and safety in drug delivery and overcome the disadvantages of traditional formulations [24, 25]. The biomedical applications of PLA-based drug carriers discussed in this section are summarized in Table 1.

2.1 Nanoparticles

NPs are spherical skeletons composed of polymer matrix, with diameters ranging from 1 to 500 nm.

2.1.1 Properties

Of the various categories of drug carrier systems, NPs have attracted the most attention because of their unique properties [34, 51]. NPs have many advantages compared with other DDS formulations. First, NPs have a high drug retention rate, which can prevent inactivation in vivo; second, NPs allow well-controlled drug distribution by delivering drugs to disease sites with few side effects in other areas; and third, NPs allow long-term drug release [52, 53]. A variety of biocompatible and biodegradable biomaterials, especially PLA, have been used as raw materials for NPs, thereby increasing their clinical utility.

2.1.2 Applications

PLA NPs have been the subject of much interest as DDSs to access the central nervous system (CNS) [54]. The blood–brain barrier (BBB) is a significant challenge for drug delivery to the CNS, because it is composed of special endothelial cells that form tight junctions, blocking drug transport into the CNS [34, 52]. Drugs are typically unable to pass through the BBB in free form [34]. However, by varying the molecular weight of PLA and using surfactants or surface modifications, the PLA NPs loaded with different drugs can be successfully delivered to the CNS. For example, Liu et al. [13] prepared the breviscapine (BVP)-loaded PDLLA NPs of different sizes and investigated the distribution of BVP in rats. The mean

Table 1 PLA-based carriers for drug delivery

Category	Polymer	Drug	Application	Reference
NPs	PDLLA	BVP	Penetrating BBB	[13]
	PLLA	Ritonavir (RIT)	Penetrating BBB	[55]
	PLA	MTX	Intranasal delivery	[61]
	PLA	Endostar	Cancer therapy	[63]
	PEG−PDLLA	IFF	Cancer diagnosis	[64]
	PEG−PDLLA	PTX and RAP	Cancer therapy	[65]
	PLA	BF_2dbmPLA	Cell imaging	[72]
	PEG−PLA	TNFα	Inflammatory bowel disease	[73]
	PEG−PLA	TNFα	Inflammatory bowel disease	[73]
	PLA	TC	Antibacterial	[74]
	PEG−PLA	Minocycline (MC)	Periodontitis	[44]
	PLA/PLGA	TC	Periodontitis	[76]
	PLA	Bone morphogenic protein 2 (BMP-2)	Bone repair	[77]
	PLA	Betamethasone phosphate (BMS)	Autoimmune uveoretinitis	[79]
	PEG−PLA	Bis-triazole DO870	Chagas disease	[80]
Microspheres	PLLA−PEG−PLLA	MTX	Cancer therapy	[97]
	Dextran/ PLGA−PLA	rIL-2	Cancer therapy	[98]
	PDLLA	Epirubicin (EPI)	Cancer therapy	[99]
	PLLA	5-FU	Cancer therapy	[100]
	PDLLA	CDDP	Cancer therapy	[101]
	PLLA	PTX	Cancer therapy	[103]
	PLA	5-FU	Cancer therapy	[104]
	PLA	5-FU	Cancer therapy	[106]
	PEG–PLA	Amphotericin B (AmB)	Local antibiotic delivery	[108]
	PLA	Gentamicin (GEN)	Local antibiotic delivery	[109]
	PLA	Piroxicam (PIR)	Anti-inflammation	[112]
	PLA	IL-1β	Vaccine	[113]
	PLA	TV and FEP proteins	Vaccine	[114]
	PLA/PLGA	IFN-γ	Vaccine	[116]
	PLLA	HBsAg	Vaccine	[117]
Hydrogels	PEG−PLCPHA	CEF	Antibacterial	[125]
	PLA/PEO/PLA	Bovine serum albumin (BSA) and fibrinogen (Fib)	Drug release	[126]
	PEG−PLA	CDDP	Drug release	[128]
	PLEOF	Stromal derived factor-1α (SDF-1α)	Tissue engineering	[127]

(continued)

Table 1 (continued)

Category	Polymer	Drug	Application	Reference
	PLA−L64−PLA	DTX and LL-37 peptide	Colorectal peritoneal carcinomatosis	[129]
	PLA−DX−PEG	siRNA	Bone repair	[130]
	PLA	FGF and IGF-1	Cardivascular engineering	[131]
Electrospun fibers	PLLA	5-FU	Cancer therapy	[140]
	PLLA	DOX	Cancer therapy	[137]
	PEG−PLA/PLGA	Cefoxitin (CFX)	Adhesion prevention	[142]
	PLLA	Silver NP	Antibacterial and anti-adhesion	[144]
	PLLA	IBU	Anti-inflammation and anti-adhesion	[145]
	PELA	Celecoxib (CEL)	Adhesion prevention	[146]
	PELA	IBU	Adhesion prevention	[147]
	PLLA	bFGF	Adhesion prevention	[148]
	PLLA	Bone marrow MSCs	Vascular tissue engineering	[149]
	PLLA	TGF	Annulus fibrosus repair and regeneration	[152]
	PDLLA	2,3-Dihydroxybenzoic acid (DBC)	Antibacterial	[153]
	PLA	Polybiguanide (PBG)	Antibacterial	[154]
	PLA/PCL	KGF	Wound healing	[158]
	PLA/PGA	IBU	Wound healing	[159]
Scaffolds	PLA	VEGF	Bone repair	[163]
	Chitosan/PLLA	BMP-2-derived peptide	Bone repair	[165]
	PLLA	Tranilast (TRA)	Local drug delivery	[167]
	PLA	EGF	Nerve engineering	[168]
	PLLA	Retinoic acid (RA)	Nerve engineering	[171]
	PLLA	β-Tricalcium phosphate (β-TCP)	Bone repair	[170]
	PLLA	ALK	Wound healing	[172]
	PLA	CUR	Wound healing	[173]
	PLA/PCL	KGF	Wound healing	[158]
	PLA	IBU, ALK, and CUR	Wound healing	[174]

diameters of these NPs were 177 and 319 nm. The BVP-loaded PDLLA NPs could not only avoid capture by the reticuloendothelial system (RES), but also penetrated the BBB and enhanced accumulation of BVP in the brain. Additionally, a larger NP could deliver more BVP to the CNS. In another study, the PLLA NP loaded with ritonavir (a protease inhibitor) was attached to a trans-activating transcriptional activator (TAT) peptide [55]. The results indicated that TAT increased the transport of NPs across the BBB. In addition, the TAT-conjugated NPs were able to maintain a therapeutic drug level in the brain, which could be effective in controlling viral replication in the CNS. In a recent study, Sun et al. [56] demonstrated that the coating was necessary for drug delivery across the BBB. Compared with the modified PLA NP, the unmodified platform was able to deliver only a small amount of drug to the brain [34, 57–59]. However, in all cases, less than 1% of the administered dose reached the CNS, far less than enough to achieve a significant therapeutic effect.

By-passing the BBB is another efficient way of achieving drug delivery for CNS diseases. Intranasal delivery is one such method for circumventing the BBB and not only provides rapid access to the CNS, but also avoids first-pass hepatic clearance and tends to avoid systemic side effects [60]. Unfortunately, the brain concentration of drugs delivered intranasally is often still too low to achieve a desired therapeutic effect. NPs may help to solve this problem: loading drugs into NPs can protect them from degradation in the nasal enzymatic microenvironment. For example, Jain et al. [61] delivered methotrexate (MTX) by designing the thermosensitive PLA NP that exhibited enhanced residence time in the nasal cavity and by-passed the BBB. The results indicated that more NP was detected in the brain than free drug. Xia et al. [62] applied low molecular weight protamine (LMWP) to decorate the surface of methoxy poly(ethylene glycol) (mPEG)−PLA NP and determined the percentage of drug delivered to the brain after intranasal administration. Their results showed that the LMWP-modified mPEG−PLA NP could be more effectively delivered to the CNS than the unmodified one.

PLA NPs are also widely used for the diagnosis and treatment of cancers. Li et al. [63] first fabricated PLA NP encapsulating Endostar, then conjugated the near-infrared (NIR) dye IRDye 800CW and GX1 peptide onto NP (IGPNE). With NIR, fluorescence molecular imaging, and bioluminescence imaging, they were able to use this composite to attain a real-time image of U87MG tumor. Furthermore, IGPNE accumulated in the tumor site and had an antiangiogenic therapeutic effect. Miller et al. [64] incorporated dechloro-4-iodo-fenofibrate (IFF) into the core of PEGylated PDLLA (PEG−PDLLA) micelle and investigated its effect on tumor targeting, as shown in Fig. 3a. The results showed that the separation process of the drug from the carrier was extremely fast and that the drug accumulated more in the tumor than did the carrier (Fig. 3b, c). Mishra et al. [65] investigated the angiogenesis inhibition effect of mPEG-*b*-PDLLA micelle loaded with PTX and rapamycin (RAP). The results indicated that the PTX−RAP dual drug micelle had an enhanced antiangiogenesis effect that was promising for cancer chemotherapy. Other studies have also reported the anticancer effects of PLA DDSs loaded with chemotherapy drugs [66–71].

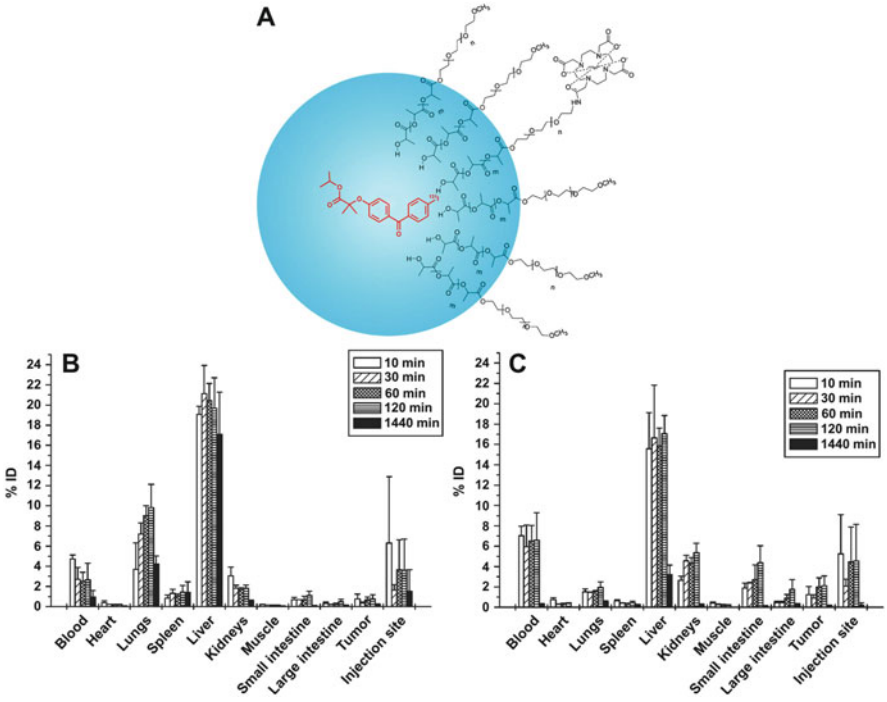

Fig. 3 Micelle composition and metabolism in vivo [64]. (**a**) The core component consists of PDLLA, which hosts the radioactively labeled drug ^{131}IFF or ^{125}IFF. The particle shell is covered with PEG. The surfaces show a mixture of ^{111}In-DOTA-HN-PEG and H_3CO-PEG. (**b**) Biodistribution (%ID) of polymer carrier and (**c**) IFF drug payload (%ID). All statistical data are presented as mean ± standard deviation (SD; $n = 3$). Reproduced from [64] with permission of Elsevier

PLA NPs also play an important role in other areas, such as live cell imaging and treatment, and diagnosis of various other diseases. For instance, Contreras et al. [72] prepared the PLA NP based on difluoroboron dibenzoylmethane dye (BF_2dbmPLA). They found that the BF_2dbmPLA NP could be internalized into cultured HeLa cells by endocytosis and that the NP retained its fluorescence property, suggesting that the unique optical property of this complex could be harnessed for live cell imaging. In another study, the Fab′-bearing siRNA tumor necrosis factor α (TNFα)-loaded PEG−PLA NP was prepared and studied for use in inflammatory bowel disease [73]. The in vivo experiment indicated that colitis was inhibited efficiently as the TNFα-siRNA-loaded NP was released to and accumulated in the diseased area. Babak et al. [74] prepared PLA DDSs for long-term antibacterial applications. They designed the composite platforms of poly(ε-caprolactone) (PCL) with different concentrations of the triclosan (TC)-loaded PLA NPs and investigated their drug release properties and antibacterial effects. Because of the advantages of PLA, including its higher glass transition temperature (T_g) and lower flexibility,

this biocomposite showed reduced burst release of TC and an antibacterial effect that lasted approximately 2 years.

Various other studies have shown the therapeutic effect of drugs loaded into PLA NPs against many diseases, including hearing loss by cisplatin (CDDP) chemotherapy [75], periodontitis [44, 76], colitis [73], acute hepatic failure [73], bone fracture [77], dermatitis [78], autoimmune uveoretinitis [79], and Chagas disease [80].

2.2 Microspheres

Microspheres are another kind of fine particle dispersion system in which drug molecules are dispersed or adsorbed. The diameters of microspheres range from 1 to 250 μm, and the main difference between NPs and microspheres is their size [81]. Because microspheres are larger than NPs in size, they are unlikely to cross biological barriers. Furthermore, microspheres tend to stay in place if injected into certain tissues. Additionally, microspheres can be only taken up by phagocytosis, whereas NPs can be taken up by both phagocytosis and pinocytosis [81]. For these reasons, microspheres are most widely used in cancer treatment as DDSs. However, NPs can be applied in many medical areas, as discussed in Sect. 2.1.

2.2.1 Properties

The drug-loaded microspheres can disperse specifically to target tissues in vivo, improving local drug concentrations and reducing systemic side effects. As a result of their excellent biocompatibility and biodegradability, PLA and its copolymers are the most frequently used polymers for DDSs. However, discovering which factors affect the rate of microsphere degradation and achieving more appropriate degradation behaviors is extremely important. Previous studies have found that the degradation of microspheres is associated with molecular weight, polymer crystallinity, microsphere size, and the presence of drugs [82]. Li et al. [83] found that a copolymer with 50% lactic acid and 50% glycolic acid (50:50 PLGA) has a shorter half-life period than 75:25 PLGA, and degrades faster than PLA.

The PLA-based microspheres loaded with different drugs are primarily delivered by intravascular injection, subcutaneous injection, in situ injection, and oral administration. Various types of drugs have been loaded into microspheres for medical applications, including anticancer drugs, antibiotics, antituberculosis drugs, antiparasitic drugs, asthma drugs, and vaccines. Of these, anticancer therapeutics have been most studied.

The microspheres composed of biocompatible and biodegradable polymers like PLA can also increase the stability and bioavailability of drugs, reduce gastrointestinal irritation, prolong the duration of drug release, and deliver drugs to target sites [84, 85]. Guan et al. [86] formulated the PLA microspheres loaded with

lovastatin (LVT) for oral administration, and evaluated the in vitro and in vivo characteristics of the microspheres. They concluded that PLA microspheres could significantly prolong the circulation time of LVT in vivo and also significantly increase the relative bioavailability of LVT. Ding et al. [15] evaluated the drug loading ability and drug release behavior of amorphous calcium phosphate (ACP) microspheres containing mPEG–PDLLA. The ACP porous hollow microspheres were found to have a high docetaxel (DTX) loading capacity, thus causing more damage to tumor cells. Lu et al. [87] prepared the RIF-loaded PLA microspheres using the electrospray technique and showed that drug release from the microspheres lasted for more than 60 h in vitro. In another study, Chen et al. [88] formulated the emodin (ED)-loaded PLA microspheres and studied their lung-targeting effect. Apart from determining the optimal parameters for formulation and sustained drug release, this research also indicated that ED was mainly delivered to lung tissue without causing toxicity to the liver and kidneys. Mirella et al. [89] compared PLLA microspheres with poly(lactide-*co*-glycolide) (PLGA) microspheres prepared by the same technique. They concluded that the PLLA microspheres had the best physical properties, the highest drug loading content, and the most efficient drug release behavior without any burst effect. Other studies have similarly shown that PLA microspheres increase drug release time, stability, and bioactivity, all of which increase their medical applicability [90–96].

2.2.2 Applications

PLA microspheres are primarily used for delivering anticancer drugs to target sites. In a study conducted by Chen et al. [97], the in vitro and in vivo antitumor efficacy of magnetic composite microspheres of the MTX-loaded Fe_3O_4-PLLA-PEG-PLLA (MMCMs) was investigated. The results from experiments at the cellular, molecular, and integrated level indicated that MMCMs with magnetic induction possess the ability to accumulate MTX in tumor tissue, leading to apoptosis of the tumor cells. Zhao et al. [98] investigated the antitumor efficacy of dextran/PLGA−PLA core/shell microspheres loaded with recombinant interleukin-2 (rIL-2), as depicted in Fig. 4. They injected a single dose of microspheres intratumorally in a subcutaneous colon carcinoma BALB/c mouse model and demonstrated that the antitumor effect of the microspheres was promising. Tumor growth was significantly suppressed in the rIL-2-loaded microsphere group (Fig. 4). Zhou et al. [99] explored the use of epirubicin (EPI)-loaded PDLLA microspheres for treating hepatocellular carcinoma (HCC) in mice. Compared with the blank microsphere group and the normal saline control group, the group treated with the EPI-loaded PDLLA microspheres had the longest survival time, which indicated that the PLA microspheres combined with EPI are highly effective in treating HCC in mice. In another study, the PLLA microspheres containing 5-fluorouracil (5-FU) were prepared [100]. The authors found that the microspheres were primarily located in the liver and were more efficient than free 5-FU in prolonging the survival time of rats with liver tumors. In a study performed by Kuang et al. [101], the PDLLA microspheres

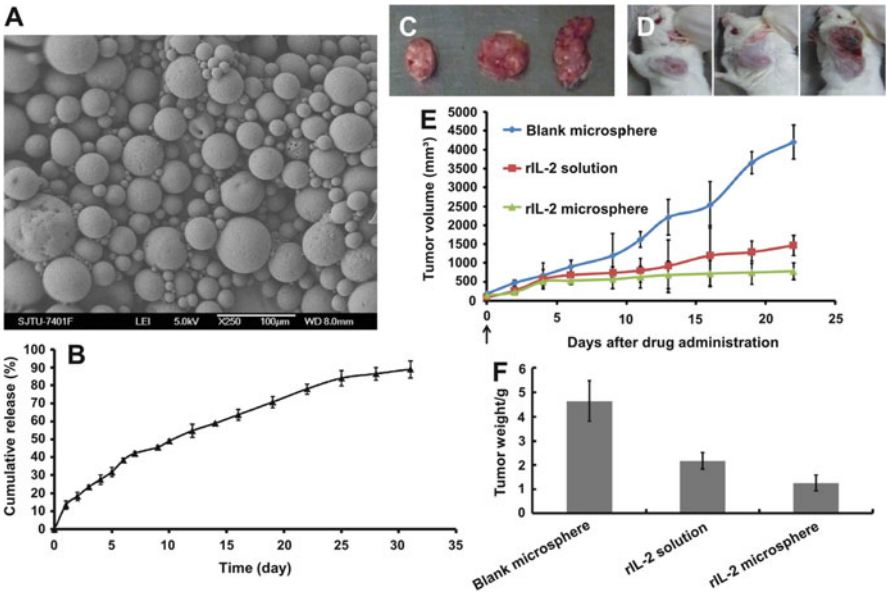

Fig. 4 Properties and antitumor efficacy of rIL-2-loaded dextran/PLGA−PLA core/shell microsphere [98]. (**a**) SEM image of drug-loaded microsphere. (**b**) In vitro cumulative rIL-2 release profile of loading microsphere in phosphate-buffered saline (PBS) of pH 7.4 at 37 °C. Error bars represent the SD ($n = 3$). (**c**–**f**) In vivo antitumor efficacy of rIL-2-loaded dextran/PLGA−PLA core/shell microsphere toward BALB/c mice bearing colon carcinoma. All mice were euthanized on day 22, and tumors were stripped, weighed, and photographed. (**c**) Representative photographs of tumors. (**d**) Representative photographs of BALB/c mice bearing tumors. (**e**) Tumor volumes in the different groups (blank microsphere, rIL-2 solution, and rIL-2-loaded microsphere) as a function of days post-treatment. *Arrow* represents the day that each formulation was administrated for the first time. (**f**) Tumor weights after euthanizing on day 22. Data are expressed as mean ± SD ($n = 4$). Reproduced from [98] with permission of Elsevier

loaded with CDDP were injected into mammary tumors in rats. These microspheres had a similar antitumor effect as aqueous CDDP solution in that the tumor became significantly smaller or disappeared 16 days after treatment. Fascinatingly, the CDDP-loaded PDLLA microspheres showed less nephrotoxicity than the aqueous CDDP solution. Other studies have also revealed the anticancer effects of drug-loaded PLA microspheres and provided an experimental basis for further therapies [102–106].

In addition to anticancer drugs, other kinds of drugs, including antibiotics [107–109], anti-TB drugs [110], asthma drugs [111, 112], and vaccines [113–118] have been loaded into PLA microspheres. Consequently, PLA microspheres are another widely used DDS for medical applications.

2.3 Hydrogels

Hydrogels, a type of three-dimensional (3D) polymer network containing significant amounts of water [119, 120], have received increasing attention in the fields of drug delivery and tissue engineering [121, 122].

2.3.1 Properties

The environmentally sensitive hydrogels are widely studied because of their biocompatibility and resemblance to biological tissues [123]. As a result of its biocompatibility, PLA has gained favor for the construction of hydrogels. The most attractive feature of PLA hydrogels is their thermal sensitivity: the PLA copolymer is soluble at room temperature and changes into a gel at body temperature. In addition, PLA hydrogels have good controlled drug release properties and can maintain drug release for over a month. However, crystallization and subsequent precipitation in solution is a major challenge for PLA use in hydrogel fabrication. To solve this problem, PLGA−PEG systems are often chosen. The PLGA−PEG solution is liquid at room temperature and immediately forms a hydrogel at body temperature. Furthermore, its mechanical properties are superior to those of PLA-only hydrogels [124].

Compared with hydrophobic materials, hydrogels interact less strongly with immobilized biomolecules. Because of the biocompatibility of PLA and the high water content of hydrogels, the use of PLA hydrogels is ideal for sustained drug release. Various studies have demonstrated this idea: for example, Lai et al. [125] developed a thermosensitive methoxy poly(ethylene glycol)-*co*-poly(lactic acid-*co*-aromatic anhydride) (mPEG−PLCPHA) hydrogel for cefazolin (CEF) delivery that exhibited long-term antibacterial effects. Wang et al. [119] studied the safety of a pH-sensitive hydrogel consisting of mPEG, PLA, and itaconic acid, and concluded that it might be used as a safe method for drug delivery. Other studies have also provided convincing evidence that PLA hydrogels can serve as efficient DDSs [126–128].

2.3.2 Applications

PLA hydrogels have already shown great potential as DDSs for medical applications. In one study, researchers dispersed NPs of DTX and LL-37 peptide into a PLA−L64−PLA thermosensitive hydrogel and evaluated the intraperitoneal effect of this composite in a colorectal peritoneal carcinomatosis HCT116 model [129]. They found that the hydrogel showed significant antitumor efficacy both in vitro and in vivo. Manaka et al. [130] evaluated the bone formation effect of a PDLLA−*p*-dioxanone−PEG hydrogel carrier for siRNA delivery. The hydrogel was found to be safe and efficient for siRNA delivery, and could promote new bone

formation (Fig. 5). Devin et al. [131] synthesized a degradable methacrylate PLA hydrogel loaded with bioactive basic fibroblast growth factor (bFGF) and insulin-like growth factor-1 (IGF-1). This hydrogel loaded with growth factors was injected into infarcts in Lewis rats and found to improve cardiac function and geometry compared with the saline control. The results indicated that PLA hydrogel can act as a carrier of growth factors to influence cardiac remodeling. In another study, a diblock hydrogel of mPEG−PLA was studied for adhesion prevention [122]. The

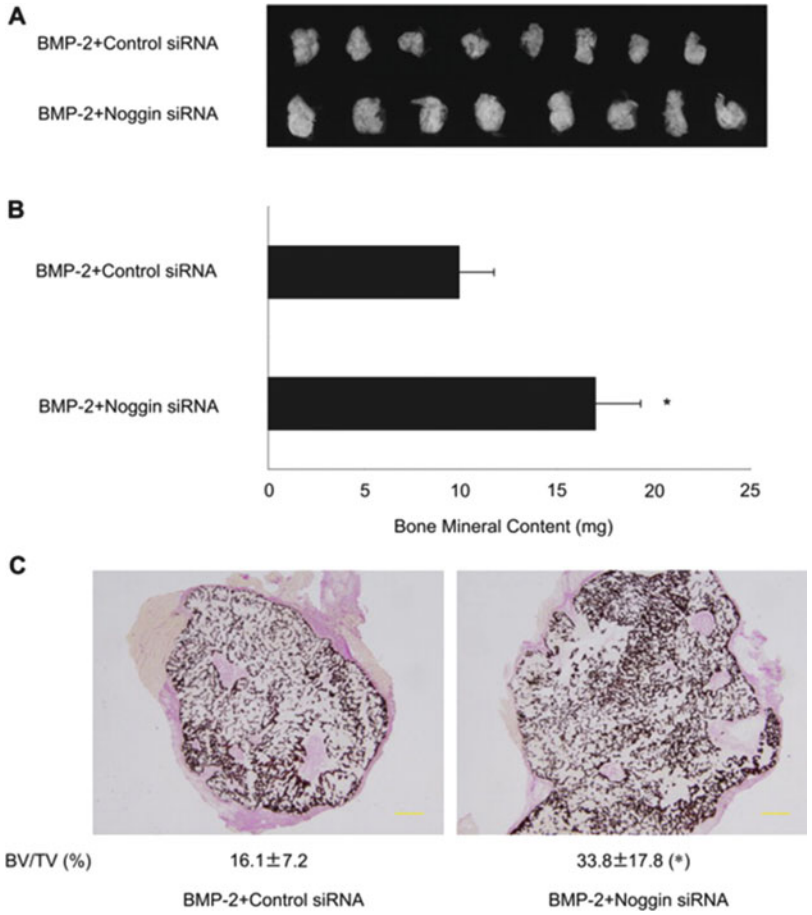

Fig. 5 Characterization of ectopic bone formation [130]. (**a**) Soft X-ray examination of newly formed ectopic bone induced by hydrogel containing 2.5 mg rhBMP-2 without Noggin siRNA [BMP(+)siRNA(−)] or with Noggin [BMP(+)siRNA(+)] for 2 weeks. (**b**) Bone mineral contents of ossicles measured by dual-energy X-ray absorptiometry (DXA). $*P < 0.05$, compared with control group. (**c**) Von Kossa and van Gieson staining of sections of undercalcified BMP-induced ectopic bone without or with Noggin siRNA. Bone volume per tissue volume (BV/TV) is expressed as mean. $*P < 0.05$ compared with control group. Reproduced from [130] with permission of Elsevier

results showed that the hydrogel system was equally effective compared with the commercial anti-adhesion product. Furthermore, this hydrogel system could be more promising for adhesion prevention if it were loaded with antifibrosis and anti-inflammatory drugs.

Even though PLA hydrogels are not as widely used as PLA NPs and microspheres, they still play an important role in controlled drug delivery.

2.4 Electrospun Fibers

Electrospinning is a facile and economic technique for producing nanoscale or microscale fibers from different polymers. The fibers can then be used for a variety of biomedical applications [132–137].

2.4.1 Properties

Electrospun fibers have attracted increasing attention as DDSs because of their specific advantages, including a high surface to area ratio, which can lead to high drug loading capacity, variable pore size, and mechanical flexibility [135, 136, 138]. Electrospinning is an efficient and simple method of rapidly and reproducibly manufacturing fiber networks incorporating different kinds of drugs [139]. However, hydrophilic water-soluble drugs cannot be directly mixed into solutions of PLA. Fortunately, the techniques of emulsion electrospinning and coaxial electrospinning can be used to encapsulate hydrophilic drugs in the core of the fibers to mitigate the initial burst release of drug [137]. Furthermore, the characteristics of electrospun fibers as DDSs can be modified by biological, chemical, optical, thermal, magnetic, and electric stimuli [139]. As a result, electrospun fibers can be designed to achieve the desired drug transport properties for medical application. PLA electrospun fibers play a significant role in this area.

2.4.2 Applications

Like other PLA DDSs, electrospun PLA fibers are widely used in cancer therapy. Zhang et al. [140] manufactured the PLLA electrospun fibers loaded with 5-FU and OXA for treatment of colorectal cancer. They found that the PLLA electrospun fiber loaded with chemotherapy drugs significantly suppressed tumor growth and prolonged mouse survival time. In another study (Fig. 6), researchers prepared the electrospun PLLA fibers loaded with multiwalled carbon nanotubes (MWCNTs) and doxorubicin (DOX) [141]. As demonstrated in Fig. 6, the combination of photothermal therapy using MWCNTs and chemotherapy induced with DOX greatly suppressed tumor growth, with less damage to nearby normal tissue.

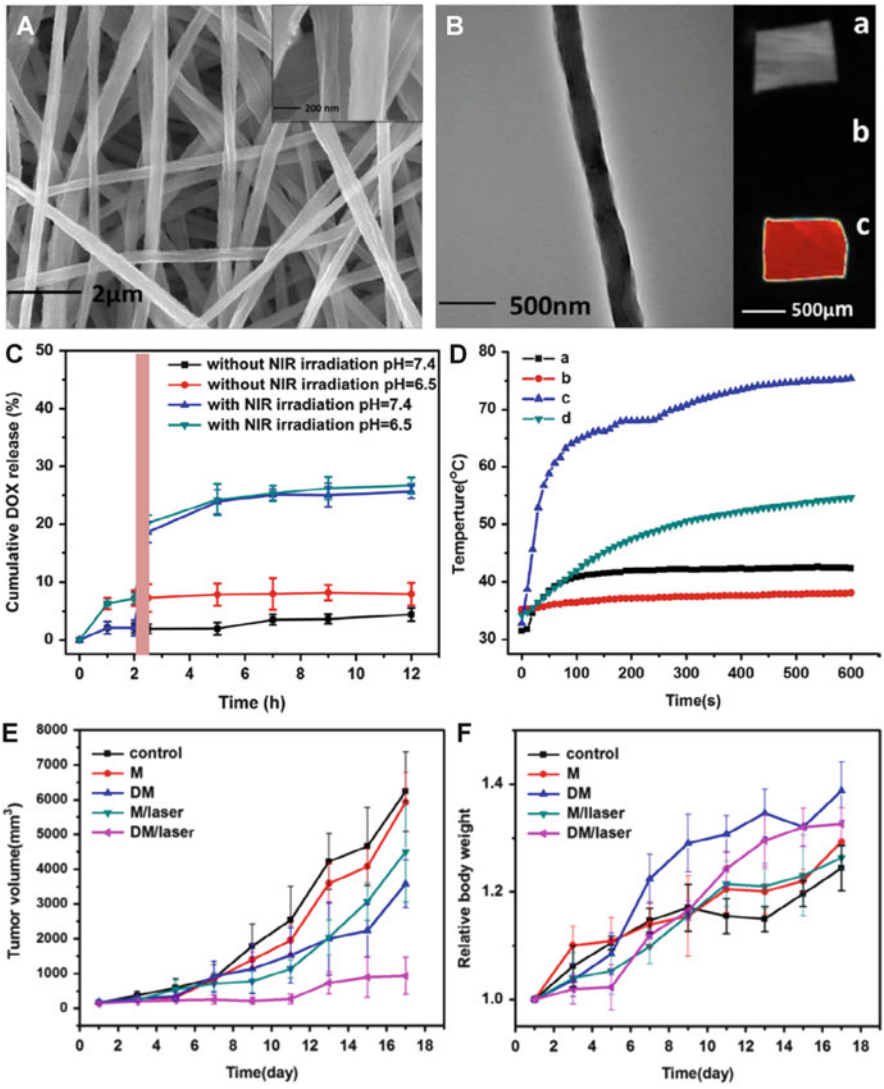

Fig. 6 Fabrication of DOX/MWCNT co-loaded electrospun PLA fibers for treatment of U14 cervical cancer in mice [141]. (**A**) SEM image of co-loaded fibers. (**B**) TEM of co-loaded fiber, and fluorescence image of (*a*) PLA fiber, (*b*) MWCNT-loaded PLA fiber, and (*c*) co-loaded PLA fiber. (**C**) Release profiles of DOX from co-loaded fiber in PBS at 37°C without or with NIR irradiation of 2 W/cm^2. The column zone indicates when the NIR irradiation was applied. (**D**) Temperature of tumor region at different time points under NIR irradiation of 1.5 W/cm^2. Control group: (*a*) tumor surface, (*b*) 3 mm inside tumor. Fiber dressing group: (*c*) tumor surface, (*d*) 3 mm inside tumor. (**E**) Evolution of U14 tumor volumes of KM mice as a function of time. (**F**) Relative body weight changes with time of U14 tumor-bearing mice. All the fibers were implanted only once in the beginning at an equivalent DOX dose of 0.1 mg and MWCNT dose of 0.1 mg. In groups of M/laser and DM/laser, tumor regions were exposed to NIR irradiation (1.5 W/cm^2) for 10 min after fiber dressing for 24 h. Reproduced from [141] with permission of Elsevier

The electrospun PLA fibers loaded with various kinds of drugs are also used for adhesion prevention [137]. Tissue adhesion is one of the most common postoperative complications, in most cases requiring a second operation to remove the adhesions [142]. Electrospun PLA membranes not only act as a physical barrier, but can also be loaded with many kinds of drugs to prevent post-surgical adhesions. Because of the excellent biocompatibility and biodegradability of PLA, antibacterial drugs [142–144], anti-inflammatory drugs [145–147], drugs that facilitate healing [148], and synergistic combinations [149] have also been loaded into electrospun PLA fibers.

Electrospun PLA fibers can be applied in many other medical fields, including tissue engineering [150–152], antibiotic therapy [144, 153–155], bone repair [156, 157], and wound healing [158, 159]. For example, Screerekha et al. [150] developed a fibrin-based electrospun composite scaffold that provided a natural environment for cell attachment, migration, and proliferation. The results indicated that the electrospun-based composite was promising for myocardial tissue engineering. In another study, Spasova et al. [155] prepared PLA stereocomplex fibers using an amphiphilic block copolymer and demonstrated good antibacterial properties in experiments on blood cells and pathogenic microorganisms. Ni et al. [156] developed an electrospun PEG/PLA fibrous scaffold to provide an interconnected porous environment for attachment of mesenchymal stem cells (MSCs). The results showed good cell response, excellent osteogenic ability, and outstanding biocompatibility of the electrospun PEG/PLA fibrous composite for bone repair. Kobsa et al. [158] developed a PLA-based electrospun scaffold integrating nucleic acid delivery and studied its effect in the treatment of full thickness wounds. They found that the scaffold could serve as a protective barrier in the early stages of wound healing, as well as induce cell migration and growth.

2.5 Scaffolds

Tissue engineering scaffolds, especially those prepared from biocompatible and biodegradable polymers, are increasingly widely used. The scaffolds loaded with different drugs are crucial for the regeneration of large defects.

2.5.1 Properties

PLA has also become a popular scaffold for tissue engineering, again due to its outstanding biocompatibility and biodegradability. PLA scaffolds can be designed to match the mechanical properties of native tissues [160]. Furthermore, because the concentration of degradation products is reduced with increased porosity, PLA is a favorable material for scaffold fabrication [160].

2.5.2 Applications

PLA is promising for tissue engineering applications, not only as a scaffold material, but also for its drug delivery properties [24, 25, 161]. PLA scaffolds can be implanted at injured sites to support injured tissues and enhance the repair process. By loading drugs into the scaffolds, it is also possible to generate multifunctional PLA scaffolds for various applications [162]. However, release properties are important when scaffolds are also harnessed as DDSs. Many parameters, such as loading method, scaffold properties, and choice of polymer, can all play an important role in the mechanism of drug release, which occurs primarily via desorption, degradation, and diffusion in the electrospun PLA scaffolds [160].

The PLA scaffolds loaded with various agents have been the subject of much research in bone, vascular, and other tissue engineering applications. As a typical example, Zhou et al. [163] exploited a calcium phosphate−PLA composite as a coating for a tantalum porous scaffold (Fig. 7). Vascular endothelial growth factor (VEGF) and transforming growth factor (TGF) were loaded into the scaffold and used for bone defect repair. Their results indicated that the scaffold provided growth factors, physical support, structural guidance, and interfaces for new bone growth, and was therefore useful to guide new bone regeneration. Other studies have also reported the superior effects of various PLA scaffolds for tissue engineering [158, 164–173]. For example, Hu et al. [166] fabricated a nanofibrous PLLA scaffold for blood vessel regeneration. The results showed that the scaffold preferentially supported the reconstruction of tissue-engineered vascular graft. In another study, Niu et al. [165] developed a microencapsulated chitosan (CM), nanohydroxyapatite/collagen (nHAC), and PLLA-based microsphere–scaffold delivery system. Bone morphogenetic protein-2 (BMP-2)-derived synthetic peptide

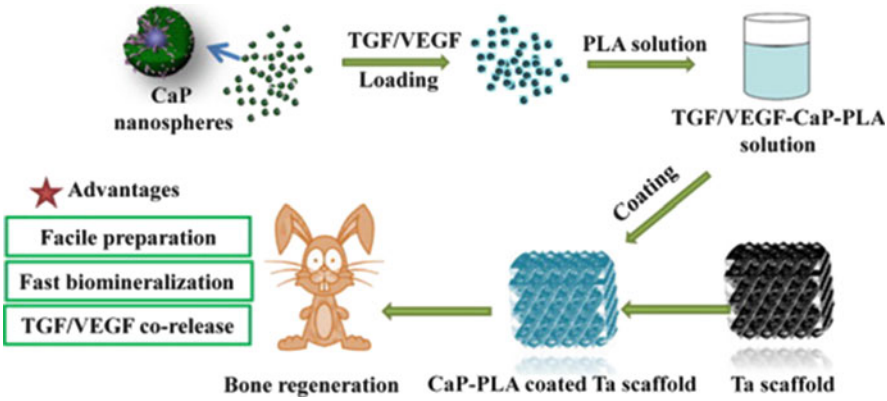

Fig. 7 Strategy for preparation and bone defect repair application of porous tantalum scaffold coated with a composite of calcium phosphate and PLA. Reproduced from [163] with permission of Elsevier

was incorporated into the synthesized composite. The results showed that the CM/nHAC/PLLA composite can accelerate the regeneration of cancellous bone defect with controlled release of the incorporated peptide. Haddad et al. [168] developed a 3D PLA scaffold with polyallylamine to introduce amine groups, followed by grafting of epidermal growth factor (EGF) onto the scaffold. They found that neural stem-like cells were able to proliferate on the EGF-grafted substrates and might be promising for repair of the CNS. The PLA scaffolds loaded with drugs, such as ibuprofen IBU, alkannin ALK, and curcumin (CUR), are also used for promoting cutaneous wound healing [160]. However, a detailed discussion is beyond the scope of this review on DDSs.

3 Conclusions and Perspectives

This review introduces the characteristics of PLA as a promising matrix for DDSs in its five most commonly used forms: NPs, microspheres, hydrogels, electrospun fibers, and scaffolds. The PLA DDSs can effectively deliver drugs to the target sites, reduce drug toxicity, and increase the therapeutic effect. In addition, PLA can be modified to achieve various desired properties in DDSs. As a result, PLA has great potential for DDS development.

The PLA DDSs loaded with different drugs can be used for the treatment of many diseases. For example, the PLA DDSs loaded with anticancer agents like PTX can directly deliver drugs to tumor sites, thereby increasing drug accumulation and retention time in the tumor while reducing systemic side effects. Meanwhile, the PLA DDSs loaded with different cytokines, such as BMP, can control drug release via degradation and play an important role in bone repair. The PLA DDSs loaded with other drugs, including anti-inflammatory agents [107, 108], antihypotensors [174], painkillers [158], and vaccines [113, 114, 118], can also be used for other medical applications.

With the development of biotechnology, peptide and protein drugs have become increasingly prevalent. However, the short retention time of these drugs limits their application, as continuous administration is often impractical. PLA DDSs may be able to improve the application of peptide- and protein-based therapeutics. Furthermore, PLA DDSs can be engineered to be intelligent drug delivery vehicles. For example, a smart PLA glucose monitor may be engineered to be inserted into body tissue and release the proper dose of insulin according to glucose fluctuations.

Although some aspects of PLA DDSs still need to be improved, further research will allow PLA to play an increasingly important role as a matrix promising material for DDSs and provide more efficacious treatment methods for many diseases.

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