REVIEW PAPER

Synthesis of Polylactic Acid Nanoparticles for the Novel Biomedical Applications: A Scientific Perspective

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ABSTRACT

Nanotechnology is an extended investigation field, based on the materials including a size ranging 1-1000 nm. Numerous polymers are used for the production of nanoparticles. Polylactic acid (PLA), its streo-isomers, such as PLLA and PLDA, and its famous co-polymer polylactic-co-glycolic (PLGA) are among the biocompatible synthetic polymers widely used to produce nanoparticles. These chmeicals are of particular impotance, beacuse they are biocompatible and biodegradable, despite their synthetic nature. A biodegradable polymer is a polymer which is submitted to the degrading procedures in-vivo. The polymeric nanoparticles commonly propose an extended surface area, high drug loading capability, feasibility of functionalization with ligands, controlled drug releasing capacity, minimal toxicity, biocompatibility, storage stability, and flexibility in the management methods. Furthermore, these nanostructure materials signify unique groundbreaking non-invasive methods for delivery structures in biomedical fields such as wound dressing materials, tissue scaffolds, gene-delivery materials, and drug delivery systems for cancer chemo-therapy.
This reviwe focuses on the synthesis methods of polylactic acid and its copolymeric nanoparticles for novel bioclinical appliacations. The manufacturing parameters will be exhibited to offer a comprehensive view of this object. Also, the biomedical applications of the nanoparticles will be displayed briefly.

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INTRODUCTION

Nanoparticles describe a specific group of dispersals or solid particles in the size ranging 1-1000 nm[1] [2-4]. Polymeric nanoparticles present a highly attractive platform for a wide array of biological applications [5-7]. The surface and core properties of these systems can be engineered for individual and multimodal applications, including tissue engineering, therapeutic delivery, bio-sensing and bio-imaging [6, 8, 9]. The nanoparticles in drug delivery systems, due to their diminutive size, can penetrate across barriers through small capillaries into individual cells to allow efficient drug accumulation at the targeted locations in the body. Fig. 1 shows a schematic view and transmission electron microscopy images of nanoparticles [8, 10-12]. The biopolymer nanoparticles have been widely used as carriers for non-water-soluble drugs [2, 13, 14]. Indeed, the nanoparticles can be loaded with drugs either with adsorption, dispersion within the polymer-matrix, or encapsulation. Accordingly, an obvious distinction can be drawn between nanospheres and nanocapsules [5, 6, 8, 15, 16].

PREPARATION OF POLYMERIC NANOPARTICLES

The polymeric nanoparticles have been synthesized using various methods according to their application (Fig. 2)[16, 18-20]. The selected

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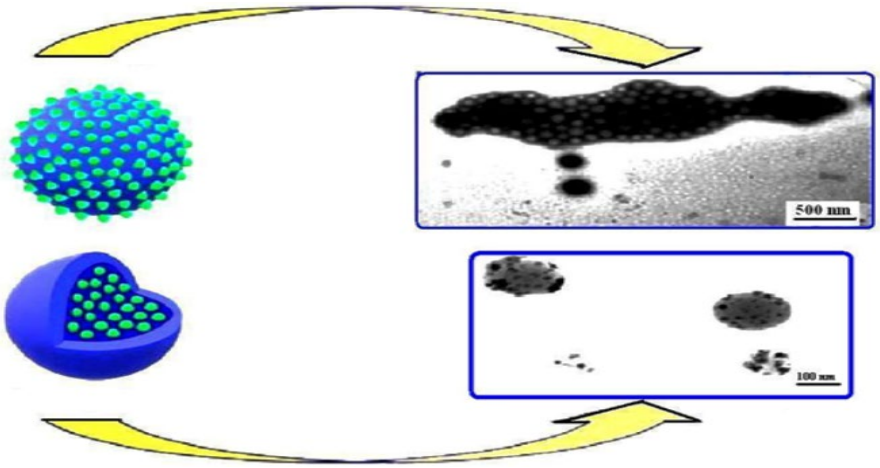

Fig. 1. Scheme of nanoparticle structures with TEM images.

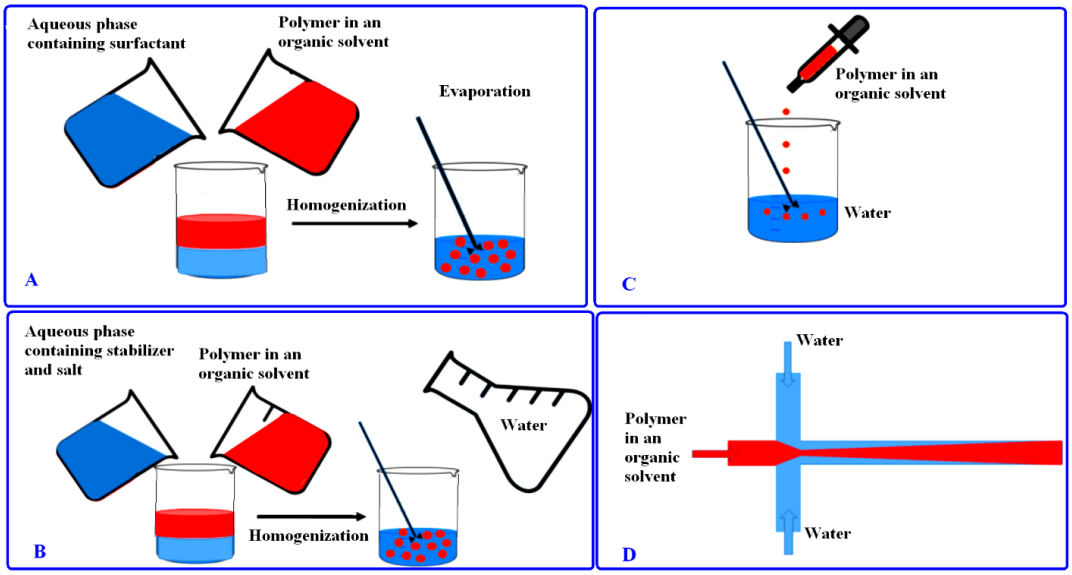

Fig. 2. Scheme of polymeric nanoparticle manufacture procedures : A) emulsification/evaporation technique, B) salting-out technique, C) nano-precipitation technique, D) microfluidic-assisted technique[17].

method determines the characteristics of spheres, including the size, as the most important property [21-24]. Another property affecting the preparation process is the ability to interact with active principles contained in the formulation [14, 25-27]. The most common method based on the dispersion of preformed polymers is the emulsification-solvent- evaporation method[10, 13, 28].

Polymeric nanoparticle properties

The polymeric nanoparticles have been used frequently as carriers due to their grand bio-availability, better encapsulation, and control-release with less toxic-property [27, 29-32]. Particle size and size distribution are the most important characteristics determining the performance of the nanoparticles, including biological activity, toxicity and the targeting ability of nanoparticles *in-vivo* [33-35]. Drug loading, drug release and stability of nanoparticles are also influenced by the particle size and size distribution [9, 13, 36-38]. Many studies have demonstrated that submicron size particles have a number of benefits over micro-particles as a drug delivery system[39-41]. Nanoparticles have

a relatively higher intracellular uptake compared to microparticles. Polymer degradation can also be affected by the particle size [20, 32, 42-44].

POLYLACTIC ACID

Polylactic Acid (PLA) is a bio-based polymer [45, 46] with helix structure containing an orthorhombic unit cell that is produced from 100% renewable resources like corn, starch, wheat , rice and sweet potato[47-50]. PLA holds stereo-isomers like poly(L-lactide) (PLLA), poly(D-lactide) (PDLA), and Poly(DL-lactide) (PDLLA)[51-53]. PLA has a famous co-polymer namely poly(lactic-*co*-glycolide) (PLGA). PLA structures are seen in Fig. 3 [51, 52, 54-56].

The PLA nanoparticles are a kind of polymeric nanoparticles, often applied as nanomedicines that have benefits over metallic nanoparticles such as the capability for maintaining the beneficial drug molecules for sustained phases of time[58-60]. The PLA nanoparticles are considered biocompatible materials, indicating that they are biologically non-toxic in human body and have suitable interactions with host cells[61-63].

All methods for synthesizing of PLA, PLLA, PLDA and PLGA nanoparticles for novel bio-medical applications, such as drug delivery systems, cancer chemo-therapy, gene-delivery structures, encapsulating growth factors, anti-bacterial agent, magnetic resonance imaging, and wound healing process will be described in the next section.

ALL SYNTHESIS ROUTS OF PLA NANOPARTICLES FOR THE BIOMEDICAL USES

In a novel work in 2020, PLGA-tazarotene nanoparticles were successfully prepared using the emulsification-volatilization method. Tazarotene ($C_{21}H_{21}NO_2S$) is an ethyl ester of tazarotenic acid. This medication is applied for healing psoriasis, acne, and sun injured skin (photo-damage)[64]. These novel PLGA nanoparticles accelerated wound healing of deep tissue pressure injuries[65].

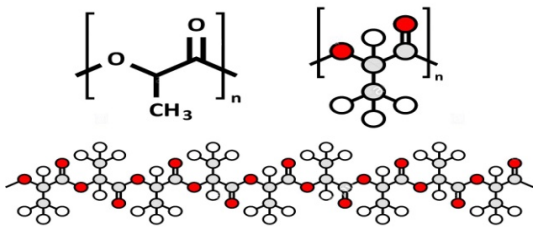

Fig. 3. Chemical structure of PLA[57].

In another exploration in 2020, PLA nanoparticles were successfully coated with a cyclic peptide. These new nanoparticles displayed a high encapsulation efficiency of liraglutide molecules. Liraglutide is a medicine applied for treating the diabetes type 2[66].

Protein loaded PLGA nanoparticles were synthetized with a fast and scalable procedure by means of micro-fluidics[67]. Szcze *et al.*[68] prepared PLA core-shell nanoparticles via spontaneous emulsification solvent evaporation way and functionalized them using a layer-by-layer process.

In a different research in 2020, poly (D,L-lactic-co-glycolic acid) nanoparticles having proper drug molecules were used for treating chondrocyte injury[69].

Khoee *et al.*[70] prepared PLA-Berberine nanoparticles using co-axial electrospray method for cancer treatment. Berberine, broadly found in medicinal plants, has a major application in pharmacological therapy as an anti-cancer drug. In another research in 2020, PLGA nanoparticles containing platelet lysate were synthesized for wound healing process in an animal model (mice)[71]. Human platelet lysate is a proper supplement for fetal-bovine-serum in bio-clinical cells cultivation[72]. It is a turbid, light-yellow liquid which is gained from human blood platelets after freeze-thaw period of time[73]. Sezer *et al.*[74] prepared PLGA nano-particles holding transforming growth factor beta 1 (TGF-β1) for wound treatment. TGF-β1 is a poly-peptide member of the transforming growth factors . It is a secreted protein which performs various cell's roles such as controlling the cellgrowth, cell-proliferation, cell-differentiation, and apoptosis[74].

Osteo-arthritis is a main problematic ilness in older people. So, in 2020, Elkasabgy *et al.*[75] syntethized PLA nanoparticles holding etoricoxib molecules as an intra-articular injection for the healing process of osteo-arthritis. Etoricoxib ($C_{18}H_{15}ClN_2O_2S$) is an anti-inflammatory medicine [76]. Daunorubicin ($C_{27}H_{29}NO_{10}$) is a synthetic drug medication which is applied in chemo-therapy for treating human cancers (especially for leukemia) [77, 78]. PLA-poly vinyl alcohol nanoparticles were manufactured by means of solvent-evaporation process. These nanostructures carries daunorubicin molecules [79].

Borges *et al.*[80] stated that PLA nanoparticle size extremely affects the toxicity profile. They

also displayed that by reduction of poly(D,L-lactic acid) nanoparticle size, their immuno-toxicity will increase[80]. Corrêa Leite *et al.*[81] reported that PLA nanoparticles help to the biological alterations in lung epithelial cells (A549 cells) [81].

Researchers in 2019 designed nanoparticles with an innovative structure including core section and outer section for delivery of doxorubicin molecules. PLGA-doxorubicin nanoparticles were constructed as a core segment and dendrimer/cationized/albumin was considered put as an outer layer [3]. Chitosan ($C_{56}H_{103}N_9O_{39}$) is a linear polysaccharide which has various biomedical applications[82, 83]. Zulfiqar *et al.* [84] fabricated PLA mediated chitosan nano-particles for enhancing anti-microbial properties of cotton fabrics against *S. aureus* and *E. Coli* in wound dressing. Amarnath *et al.*[85] manufactured PLA-chitosan nanoparticles as a strong antitumor nanomedicine.

The PLA-PEG-PLA nanoparticles with three various PLA/PEG ratios were manufactured for encapsulating recombinant human growth hormone (rhGH). The structural analysis of the co-polymers revealed that they were positively produced, furthermore, the size of nanoparticles was improved by means of increase in quantities of PLA/PEG ratio [86].

The PLA-tocopheryl polyethylene glycol succinate co-polymers were applied for nanoparticle preparation. The PLA-tocopheryl polyethylene glycol succinate nanoparticles have the size around 300 nm. The results demonstrated that PLA:TPGS composition ratio has a slight influence on the particle size and size distribution[87]. The poly(D,L-lactic-*co*-glycolic acid) nanoparticles were prepared and coated with tuftsin-pluronic[88]. Tuftsin ($C_{21}H_{40}N_8O_6$) is a tetra-peptide which particularly binds macrophages and leukocytes, and potentiates their biological killer performance against tumors[89, 90]. The outcomes displayed that these nanoparticles dramatically act against *Mycobacterium tuberculosis* Bactria[88].

In another research in 2018, cholic acid functionalized poly(ε-caprolactone-ran-lactide) nanoparticles were produced through a novel synergistic chemo-photo-thermal approach aiming at delivery of docetaxel molecules for cancer chemo-therapy[23]. Docetaxel ($C_{43}H_{53}NO_{14}$) is a chemo-therapy medicine applied for treating various kinds of cancer such as breast, stomach, prostate and lung cancers[91, 92]. Also, in 2011, poly(lactide-co-caprolactone)-docetaxel nanoparticles were synthetized for healing the prostate cancer[93]. Furthermore, PLGA-TGPS nanoparticles were prepared by Jin *et al.*[94] for delivery of docetaxel molecules for breast cancer treatment.

Amani *et al.* [95] designed different nanoparticles with poly-ethyl enimine (PEI) and tri bloc polylactic acid/polyethylene-glycol/polylactic acid co-polymer as nanocarriers. The results display that increasing the mass ratio of PEI:(PLA/PEG/PLA) (w/w%) in the nanoparticles results in an improvement in zeta-potential[95]. Andima *et al.* [7] used PLGA and PEG-block-PLA nanoparticles for encapsulating of ß-Sitosterol [7]. ß-Sitosterol ($C_{29}H_{50}O$) is a main phytosterol in plants having the capacity of prevention and therapy for human cancers.

In an investigation in 2018, docetaxel loaded nanoparticles were formulated via PEG-PLA-PEG, as an anticancer nanomedicine. These structures presented a particle-size less than 150 nm after reconstitution[96]. Dai *et al.*[97] fabricated PLA nanoparticles as the nanocarriers of doxorubicin molecules and attached Mn-porphyrin on the nanoparticles with covalent bonds for magnetic resonance imaging[97].

The PEG-coated PLA nanoparticles were fabricated as a delivery nanostructure for hexadecafluoro zinc phthalocyanine for treatment of EMT-6 mouse mammary tumors[98]. Pieper *et al.*[21] formulated PLA-doxorubicin nanoparticles via solvent-displacement and emulsion-diffusion methods as anticancer drugs. The nano-particles had a size-range in 73-246 nm and showed sustained-release kinetics[21]. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) with chemical formulation of $C_{21}H_{20}O_6$ is an anticancer herbal drug[99]. Chauhan et al.[100] constructed PLGA-curcumin nanoparticles for advanced therapeutic properties in metastatic cancer cells.

Researchers, in 2017, prepared the PLA-PEG-catechin nanoparticles. Catechin ($C_{15}H_{14}O_6$) is a type of natural phenol and antioxidant. Results signify that PLA-PEG nanoparticles were appropriate for catechin encapsulation [33]. The PLGA nanoparticles were constructed via merging the polymer with Pluronic-F127 leading to homogeneous nanoparticles[101]. Sibeco *et al.* [102] synthesized PLA-methacrylic acid nanoparticles as nanocarrier structures for methotrexate (Fig. 4). The nanoparticles with particle size of 211.0-378.3 nm were manufactured[102].

The PLGA-curcumin nanoparticles were

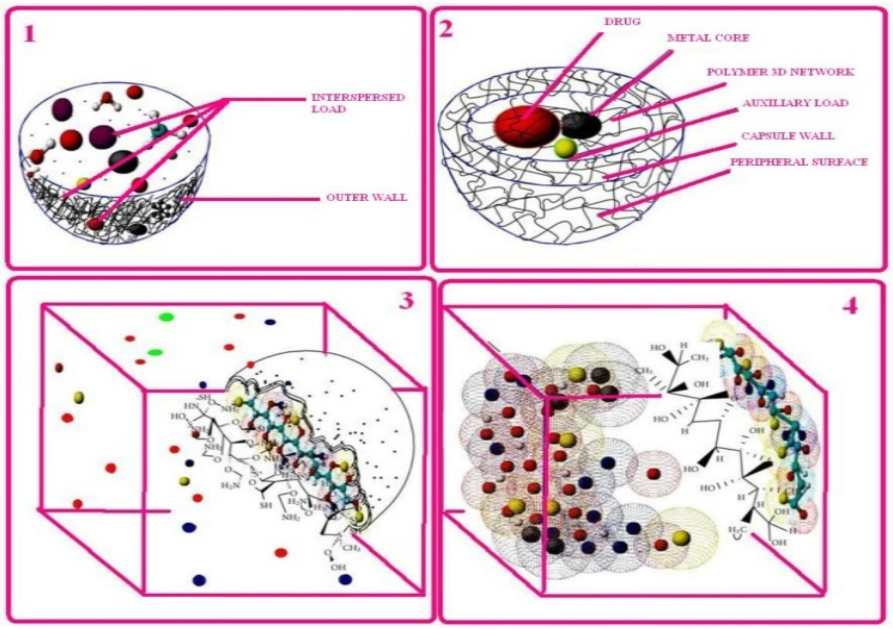

Fig. 4. (1) Polymer composite, (2) PLA-MAA- MTX bond depicted in a stereo-orientation design, (3) 3D representation of PLA-MAA surface embedding MTX, (4) neighboring intermediate in an unhydrated phase[102].

manufactured as a nanomedicine for the wound treatment. The PLGA nanoparticles presented numerous profits for the encapsulated curcumin such as protection from light degradation and improved water-solubility[103].

Oleanolic acid ($C_{30}H_{48}O_3$) is a natural compound with anticancer and apoptotic activities[104, 105]. Researchers prepared PLGA-(D-α-tocopheryl polyethylene glycol succinate) nano-particles holding oleanolic acid for healing the liver cancer[106, 107]. Honokiol ($C_{18}H_{18}O_2$) is a lignan compound prepared from the bark, seed cones, and leaves of trees in the genus Magnolia [108]. Qian *et al.* [109] fabricated PLA-MPEG nanoparticles as the potential delivery systems for honokiol molecules in cancer treatment.

In another research, a different PLA nanoparticle was designed as a gene-delivery system for RNA encapsulation. Ribonucleic acid (RNA) is a polymeric molecule vital in different biotic characters in coding, decoding, regulation and expression of genes[1, 110, 111]. These nanoparticles were produced by means of double emulsion-solvent-evaporation method[112]. In an innovative exploration in 2020, Kim *et al.*[113] prepared poly(D,L-lactic-co-glycolic acid) nanoparticles holding miRNA for treating the neuropathic healing process in the rats having neuropathic damage on thier back section[113]. A miRNA (microRNA) is a class of small endogenous RNA molecule (holding approximately 21-25 nucleotides) found in plants, animals and a few infections which play a crutial role in controlling gene-expression[114].

Zou *et al.* [115] formulated cationic PLA-PEG nanoparticles as a delivery structure for DNA(deoxyribonucleic acid). RNA and DNA are nucleic acids, and together with lipids, proteins and carbohydrates establish four main macro-molecules vital for all procedures of life [4, 116]. The nano-particles with high binding efficiency(>95%) could keep DNA from the degradation with plasma[115].

PLA-monomethoxy polyethylene glycol was produced with ring opening polymerization process, and fabricated to nanoparticles for carring honokiol molecules for cancer treatment. The nanoparticles were manufatured by means of solvent extract tecnique[109]. Honokiol ($C_{18}H_{18}O_2$) is a lignan compound isolated from the bark, seed cones, and leaves of trees in the genus Magnolia area[117]. Dexamethasone is a kind of corticosteroid medicine ($C_{22}H_{29}FO_5$) [118]. The PLGA-dexamethasone nanoparticles were prepared with emulsification-solvent-evaporation process for healing choroidal neo-vascularization(CNV).

Table 1. Different methods for manufacturing the PLA nanoparticles

PLA Nano-particle	Preparation Method		Application Field	Ref.
	Technique	Organic Phase		
PLA—Bevacizumab	Solvent—Emulsification—Evaporation(based on a w—o—w Double—Emulsion method)	Ethyl-acetate	Anti-angiogenic Ttherapy	[120]
PLA—PVA	Solvent—Evaporation	PLA+ PVA	leukemia Cancer Treatment	[79]
PLA—PEG PLGA/ß-Sitosterol PLA—PEG/ß-Sitosterol CA/(PCL—ran—PLA) Apt/pD/CA/[PCL—ran—PLA] CA/(PCL—ran—PLA)— DTX Apt/pD/CA/[PCL—ran—PLA]—DTX	Emulsion—Diffusion—Solvent Evaporation Modified Nano-Precipitation	PVA Acetone	Breast Cancer Treatment Breast Cancer Treatment	[7] [23]
PLA/PEG/PLA PLA/PEG/PLA/PEI PLA/PEG/PLA—DNA PLA/PEG/PLA/PEI—DNA	Double-Emulsion Solvent Evaporation	BSA + plasmid pEGFP-N1 + chloroform + PVA	Gene Delivery System	[95]
PLA—PEG—Catechin	Double—Emulsion Solvent —Evaporation	DCM + PVA + water-oil-water Emulsion	Cancer Treatment	[96]
PLA/TPGS	Modified Solvent—Extraction—Evaporation	DCM	Cancer Treatment	
PLA	Emulsion—Diffusion	Dichloro Methane	Cancer Treatment	[21]
PLGA	Emulsion—Diffusion	Ethyl Acetate	Cancer Treatment	[21]
PLGA—PEG	Emulsion—Diffusion	Ethyl Acetate	Cancer Treatment	[21]
PLA—block—PEG	Solvent—Evaporation—Suspension	Tetrahydrofuran	Oxidative Medicine	[121]
PLGA—PEG—Disulfiram		Folic acid	Breast Cancer Treatment	[122]
PLGA—Curcumin	Anti/Solvent Method , Flash Precipitation	DMF	Skin Treatment (Imiquimod / Induced Psoriasis/like Mouse Model.)	[42]
PLGA	Emulsion Solvent Evaporation	DCM	Healing of Diabetic wounds	[123]
PLGA— VEGF	Emulsion Solvent Evaporation	DCM + VEGF	Healing of Diabetic wounds	[123]
Cationic PLA—PEG	Nano-precipitation	Acetone	Gene Therapy	[115]
PLA—PEG—DNA	Electrostatic Attraction between the Anionic Plasmid DNA and the Blank Cationic Nano-particles	Acetone + DNA	Gene Therapy	[115]
PLGA	Emulsion Solvent Evaporation	DCM + PVA	Skin Wound Healing	[103]
PLGA—Curcumin	Emulsion Solvent Evaporation	DCM + PVA	Skin Wound Healing	[103]
PLA—MAA	Double—Emulsion Solvent Evaporation	PEG + NaOH + DMSO + Isopropyl Alcohol + DCM	chemo—therapy of central nervous system lymphoma	[102]
PLA—MAA—MTX	Double—Emulsion Solvent Evaporation	PEG + NaOH + DMSO + Isopropyl Alcohol + DCM	chemo—therapy of central nervous system lymphoma	[102]
mPEG—PLA	Water in oil in water (W/O/W) Double—Emulsion Solvent Evaporation	DCM + 2% w/v co-polymer + 1% w/v PVA	Delivery of recombinant human Growth Hormone (rhGH)	[86]
PLA—PEG—PLA	Water in oil in water (W/O/W) Double—Emulsion Solvent Evaporation	DCM + 2% w/v co-polymer + 1% w/v PVA	Delivery of recombinant human Growth Hormone (rhGH)	[86]
PLA—MPEG	Solvent—Extract	Acetone	Delivery of Honokiol	[109]

CNV includes the growth of new blood vessels. CNV is a main reason for visual damage[119].

Table 1 summarizes the preparation methods for manufacturing PLA nanoparticles and Table 2 gives some information about different PLA nanoparticles discussed so far.

Table 2. Different properties of the PLA nanoparticles

PLA Nano-particle	Zeta Potential (mV)	Particle Size (nm)	Polydispersity Index(PI)	Loading Content (%) (LC)	Encapsulation Efficiency (%) (EE)	Ref.
PLGA—Platelet lysate	—17.6	318	0.29	—	—	[71]
PLA—MPEG	—10	95	—	—	—	[109]
PLA/PEG/PLA/PEI—DNA PEI: (PLA-PEG-PLA) 0:300	—20±2.0	280±3.0	—	—	48±2.5	[95]
PLA/PEG/PLA/PEI—DNA PEI: (PLA-PEG-PLA) 1:300	—5±2.0	320±3.0	—	—	68±2.5	[95]
PLA/PEG/PLA/PEI—DNA PEI: (PLA-PEG-PLA) 5:300	15±2.0	360±3.0	—	—	80±2.5	[95]
PLA/PEG/PLA/PEI—DNA PEI: (PLA-PEG-PLA) 10:300	18±2.0	380±3.0	—	—	85±2.5	[95]
PLA/PEG/PLA/PEI—DNA PEI: (PLA-PEG-PLA) 15:300	20±2.0	420±3.0	—	—	90±2.5	[95]
PLGA—PEG + S,S-2-(3-[5-amino-1-carboxypentyl]- ureido)-Pentanedioic Acid + Irinotecan + Cisplatin	—	55 ± 1.0	—	—	—	[124]
PLA 10%wt + PVA 10%wt	—	—	—	1.36 ± 0.04	—	[79]
PLA 70%wt + PVA 10%wt	—	—	—	1.29 ± 0.19	—	[79]
PLA 10%wt + PVA 70%wt	—	—	—	1.18 ± 0.01	—	[79]
PLA 30%wt + PVA 30%wt	—	—	—	1.24 ± 0.07	—	[79]
PLA 40%wt + PVA 10%wt	—	—	—	1.29 ± 0.17	—	[79]
PLA10%wt + PVA 40%wt	—	—	—	1.45 ± 0.24	—	[79]
PLA 40%wt + PVA 40%wt	—	—	—	0.84 ± 0.12	—	[79]
PLGA—PEG + Folic acid + DOX Drug		160 ± 2.0	—	—	—	[125]
PEG–PLA–PEG+ DTX 10 %wt	—	125 ± 2.7	0.24 ± 0.01	7.4	81.9	[96]
PEG–PLA–PEG+ DTX 20 %wt	—	84 ± 2.0	0.26 ± 0.02	10.9	65.3	[96]
PEG–PLA–PEG+ DTX 30 %wt	—	83 ± 4.2	0.29 ± 0.02	12.4	53.5	[96]
PLGA—PEG + Disulfiram Drug	—	165. 204	—	—	—	[122]
CA/(PCL—ran—PLA)	—17.8 ± 3.9	103.4±3.3	0.126	10.02 ±0.28	95.01 ± 2.16	[23]
CA/ pD /(PCL—ran—PLA)— DTX	—18.6 ± 3.6	120.3 ±4.6	0.115	9.98 ± 0.39	94.31 ± 1.98	[23]
Apt/pD/CA/[PCL—ran—PLA]— DTX	—19.2 ± 5.2	124.6±5.1	0.123	9.73 ±0.46	94.18 ± 2.76	[23]
PLGA—PEG + (VEGFR-C) + PTX Drug	—	710 ± 3.0	—	—	—	[126]
PLA—TPGS 93:7	—30.7±5.2	320±28	0.18±0.02	—	83.4±5.0	[87]
PLA—TPGS 89:11	—31.4±4.2	325±18	0.22±0.03	—	90.3±4.5	[87]
PLA—TPGS 84:16	—31.6±3.2	330±11	0.29±0.04	—	82.0±3.6	[87]
PLA—TPGS 80:20	—31.7±2.6	320±13	0.20±0.06	—	80.0±5.2	[87]
PLGA (Surfactant : TPGS)	—32.7±3.1	338±30	0.25±0.04	—	79.9±8.7	[87]
PLGA (Surfactant : PVA)	—13.0±2.3	311±12	0.19±0.02	—	59.0±6.2	[87]
PLGA—Curcumin	—	150 ±2.0	—	—	92.48 ± 0.14	[42]
PLA (Emulsion Diffusion Method)	—	250±2.0	—	2.6 ± 0.2	41.6 ± 2.0	[21]
PLA (Solvent Displacement Method)	—	180±2.0	—	6.3 ± 0.1	32.7±3.1	[21]
PLGA (Emulsion Diffusion Method)	—	150 ±2.0	—	6.7 ± 0.3	53.5± 2.0	[21]
PLGA (Solvent Displacement Method)	—	170± 2.8	—	5.1 ± 0.2	48±2.5	[21]
PLGA (Surfactant : unmodified PVA solution)	-41.6 ± 2.0	177.9 ± 1.0	0.039 ± 0.031	—	—	[21]
PLGA (Surfactant : PVA Solution adjusted to pH 7)	-43.8 ± 3.7	174.1 ± 2.8	0.057 ± 0.030	—	—	[21]
PLGA + 0.5 mg DOX(Surfactant : unmodified PVA solution)		180		—		[21]
PLGA + 2.5 mg DOX(Surfactant : unmodified PVA solution)		180		—		[21]
PLGA + 5 mg DOX(Surfactant : unmodified PVA solution)		180		—		[21]
PLGA + 7.5 mg DOX(Surfactant : unmodified PVA solution)		190		—		[21]
PLGA+ Boron—CUR complex	—	149 ± 3.0				[37]
PLGA-PEG (Emulsion Diffusion Method)	—	230±2.0	—	—	23.2 ± 3.8	[21]
PLGA-PEG (Solvent Displacement Method)	—	80±2.0	—	—	32.7±3.1	[21]
PLGA + 0.5 mg DOX(Emulsion Diffusion Method)	—	180 ±2.0	0.07± 0.040	5.1 ± 0.2	42.7± 2.0	[21]

Continued Table 2. Different properties of the PLA nanoparticles

PLA Nano-particle	Zeta Potential (mV)	Particle Size (nm)	Polydispersity Index(PI)	Loading Content (%) (LC)	Encapsulation Efficiency (%) (EE)	Ref.
PLGA + 2.5 mg DOX(Emulsion Diffusion Method)	—	180 ±2.0	0.06± 0.040	33.8 ±3.1	57.9±8.7	[21]
PLGA + 5.0 mg DOX(Emulsion Diffusion Method)	—	180 ±2.0	0.05± 0.040	52.7± 2.0	45.7± 2.0	[21]
PLGA + 7.5 mg DOX(Emulsion Diffusion Method)	—	180 ±2.0	0.06± 0.040	55.7± 2.0	38.7±3.1	[21]
PLGA + 12.5 mg DOX(Emulsion Diffusion Method)	—	250±2.0	0.15± 0.040	42. 2 ± 2.0	21.2 ± 3.8	[21]
PLGA + 25.0 mg DOX(Emulsion Diffusion Method)	—	320±2.0	0.22± 0.040	43. 2 ± 2.0	10.02 ±0. 44	[21]
PLA—block—PEG	28.73 ± 1.44	911.4 ± 117.6	—	—	—	[121]
PLGA	−30 ± 2.0	203 ± 9	0.07 ± 0.02	1.26 ± 0.06	75.8 ± 4.7	[123]
PLGA— VEGF	−21 ± 3.5	163 ± 2	0.15 ± 0.05	NA	NA	[123]
PLGA—Cyclic Penta Peptide (cRGDfK) + Gemcitabine Drug	—	90±2.0	—	—	—	[127]
PLGA—PEG + EGFR-targeting Peptide + Scrambled Peptide + Tylocrebrine Drug	—	350 ± 2.0	—	—	—	[126]
PLGA	−18.2 ± 2.5	150.0 ± 3.2	0.175 ± 0.051	—	—	[42]
PLGA—Curcumin	−23.2 ± 3.8	176.5 ± 7.0	0.105 ± 0.025	—	89.2 ± 2.5	[42]
mPEG113—PLA90	−6.54 ± 0.02	165.7	0.295 ± 0.03	—	40.6	[86]
mPEG113—PLA222	−6.9 ± 0.13	176.5	0.148 ± 0.014	—	45.9	[86]
mPEG113—PLA375	−8.78 ± 0.05	192.5	0.243 ± 0.022	—	50.3	[86]
PLA55—PEG91—PLA55	−4.56 ± 0.39	202.1	0.314 ± 0.0014	—	31.9	[86]
PLA130—PEG91—PLA130	−3.91 ± 0.32	209.6	0.295 ± 0.037	—	39.5	[86]
PLA205—PEG91—PLA205	−9.1 ± 0.47	224.5	0.382 ± 0.017	—	51	[86]
mPEG—PLA (2%) + 2 mg rhGH	—	192.4 ± 6.5	0.243 ± 0.022	—	50.3	[86]
mPEG—PLA (4%) + 2 mg rhGH	—	194.7 ± 9.2	0.178 ± 0.045	—	45.8	[86]
mPEG—PLA (6%) + 2 mg rhGH	—	201.1 ± 8.1	0.133 ± 0.021	—	39.3	[86]
mPEG—PLA (8%) + 2 mg rhGH	—	211.2 ± 16.7	0.158 ± 0.039	—	44.8	[86]
mPEG—PLA (2%) + 1 mg rhGH	—	188.7 ± 14.3	0.098 ± 0.026	—	47.2	[86]
mPEG—PLA (2%) + 3 mg rhGH	—	184.9 ± 0.8	0.21 ± 0.06	—	34.9	[86]
PLA—PEG—PLA (2%) + 2 mg rhGH	—	224.2 ± 15.6	0.38 ± 0.017	—	51	[86]
PLA—PEG—PLA (4%) + 2 mg rhGH	—	223.9 ± 10.3	0.295 ± 0.012	—	39.9	[86]
PLA—PEG—PLA (6%) + 2 mg rhGH	—	234.3 ± 12.1	0.283 ± 0.021	—	46.3	[86]
PLA—PEG—PLA (8%) + 2 mg rhGH	—	254.1 ± 4.8	0.29 ± 0.011	—	31.7	[86]
PLA—PEG—PLA (2%) + 1 mg rhGH	—	219 ± 4.5	0.298 ± 0.015	—	49.4	[86]
PLA—PEG—PLA (2%) + 3 mg rhGH	—	211.3 ± 6.8	0.341 ± 0.012	—	42.3	[86]
Cationic PLA—PEG	28.9	89.7	0.185	—	—	[115]
PLA—PEG—DNA	16.8	128.9	0.161	—	—	[115]

CONCLUSION

The latest developments in synthesis and the use of PLA nanoparticles have been reviwed here. Various types of PLA nanoparticles have been developed to be used in biomedical fields. Many studies (more than 120 articles) have been reported in this review for indicating the enormous potential of PLA nanoparticles in biomedical applications.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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