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Poly (Lactic-co-Glycolic) Acid (PLGA)-Based Compounds for Articular Cartilage Regeneration

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The most famous artificial polymers for cartilage regeneration constructs are poly lactic acid (PLA, which is present in both L and D forms), poly-glycolic acid (PGA), and their copolymer poly-lactic-co-glycolic acid (PLGA). PLGA shows high biocompatibility, a potential to break down into safe monomer units, a beneficial range of mechanical characteristics, and governable degradation time depending on the copolymer ratio. In this review we critically focused on PLGA applications such as scaffolds and carriers for bioactive agents such as drugs, growth factors, and other bioactive molecules in order to safely delivering to cartilage tissue for reconstructing articular cartilage (AC) defects.

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Introduction

TE is a regenerating strategy for repairing tissues or organs[1].AC is a connective tissue with very poor to self-treatment ability of the induced diseases, trauma, or natural degradation, due to its avascular, aneural and low cell density[2]. Nowadays, scaffolds are the promising methodologies for healing damaged cartilage tissue [3]. Polymeric scaffolds play a vital role in TE and they operate similar to the extracellular matrices (ECM) in the body [1]. Moreover, these structures are the best candidates to delivery nutrients, metabolites, and soluble factors to damaged tissues [1]. Two important groups of polymeric materials are natural and synthetic polymers. Proteins and polysaccharides are natural polymers with moderate degradation properties and negligible cell toxicity. However, there are a number of advantages for synthetic polymers as compared with natural ones, including controllable degradation rates and suitable mechanical and physical properties [4, 5]. Toxicity, immunogenicity and favoring infections are biological characteristics that have been observed a few for synthetic polymers[6]. Degradable synthetic polymers as three-dimensional (3D) scaffolds for TE are poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and PLGA copolymers [7,8]. Hydrolytic degradation can be occurred in these polymers through de-esterification. Some of PLA and PGA biomedical applications which have been approved by the FDA were reported in table 1[9, 10]. According to the degradation tests reports, PGA degrades faster than PLA because the former is a hydrophilic and less crystalline polymer. Chemical, physical, and mechanical properties of PLA are considerably different form PGA because of methyl group's presence in its molecular chains structures. PLGA is a copolymer of PLA and PGA with superior degradation properties which can be controlled by altering monomers ratio [10]. Despite being pure PLGA is a biocompatible material, it shows low cell attachment affinity. Hence, using other materials such as bioceramics (e.g., bioactive glasses (BGs) nanoparticle) as fillers in PLGA matrix can be able to intensify its potential in tissues (e.g, AC and bone) regeneration [11-14]. In this review, we described the application of PLGA based compounds for AC applications. Therefore, PLGA compounds for AC have been categorized according to their physical configurations: scaffolds, fibers, hydrogels or injectable microspheres. Because of its diversity, the review focuses on the scaffolds and microspheres made of PLGA. Finally, the new current trends in the development of PLGA compounds were also been reviewed.

PLGA Fabrication

PLGA is a copolymer of lactic acid (LA) and glycolic acid (GA) with different ratio of the monomers.

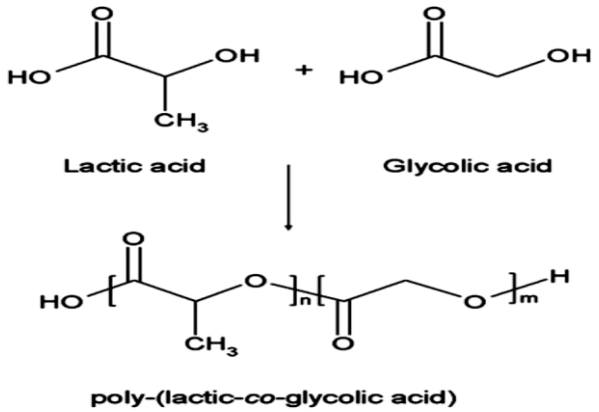


Fig. 1. Chemical structure of poly(lactic-co-glycolic) acid. (Reproduced from [ref. 54], with permission from [Pub med]).

Many types of PLGA can be fabricated depending on the LA/ GA monomers ratio (i.e., PLGA 50:50 recognizes a polymer composed of 50% glycolic acid and 50% lactic acid). There are different mechanisms for PLGA synthesis that could influence on the physicochemical characteristics of the final product. Nowadays, numerous techniques have been utilized in order to produce low molecular weight (MW< 10 kDa) of PLGA such as solution poly-condensation, direct poly condensation, melt and melt/solid poly condensation, enzymatic polymerization and so on [15-18].

Table1. PLGA and their co-polymers application in cartilage abnormalities.

Polymer	References
PLGA(75/15)	[, 19,20, 22, 60]
PLGA (50/50)	[11,12,21,23]
PLGA (85/15)	[24,25]
PLLA	[,26,27, 28]
PGA	[29]

One of the enzymatic polymerization is ring-opening mechanism that occurs in controllable reaction conditions (temperature, pressure, and pH) with a long reaction time to produce low molecular weight PLGA [30]. Dechy-cabaret reported that the cited ring-opening polymerization technique can produce atactic or syndiotactic PLGA conformations [31]. Literatures reported that the repeat units sequence and the synthesizing mechanism in PLGA structure dramatically influences the degradation rate of the polymer. Li et al., proposed a new method to access repeating-sequence of PLGA copolymers with different tacticities [32]. The results of this project revealed that sequenced PLGA can be used in biomedical application such as drug delivery. In this application release kinetic of the biomolecule/drug was obviously affected by polymer degradation rate.

PLGA Properties

Wide range of usual solvents consists of chlorinated solvents, tetrahydrofuran, acetone, ethyl acetate and so on can be utilized for PLGA synthesis [33]. Physical properties of PLGA can be affected by miscellaneous factors such as molecular weight of monomers, ratio of LA: GA, storage temperature and the exposure time to water [34]. We can find two enantiomer isomers of LA (e.g., D and L, according to methyl group on the end carbon of PLA). In contrast, GA with crystalline structure doesn't have methyl side groups. Therefore, D-, L- and D, L- isomers can be existed for PLGA. In aqueous environments degradation of PLGA can be occurred with four stages : (1) hydration: van der Waals and hydrogen bonds in PLGA structure deteriorate with water diffusion into the amorphous regions of the polymer and this phenomenon is a factor in glass transition temperature (T_g) reduction; (2) molecular weight decreases and the covalent bonds destroy; (3) integrity is diminished by loosening and degradation processes and as a consequence mass loss reduction is occurred by auotocatalyzing carboxylic end group and cleavage of the backbone covalent bonds; (4) solubilization : the resulting products of cleaved bonds are soluble in the aqueous environment[35]. Different parameters can influence on the rate of PLGA degradation: (I) molecular weight: degradation time of PLGA increased with molecular weight ranging from weeks to months; (II) ratio of LA to GA: PLA degradation rate is less than PGA because of the methyl side group presence in PLA chain. Hence, this side group makes PLA more hydrophobic than PGA. Degradation rate of PLGA with 50:50 ratio of constituting monomers exhibits the fastest rate among the other PLGA copolymers; (III) stereochemistry: two isomers (D and L lactic acid) usually used for PLGA fabrication. The degradation rate of PLGA increases in amorphous D, L regions; and (IV) end group of polymer: end-capping of the end-group of polymers with esters lead to the vast degradation time[36,37]. A less noticeable factor that can affect the degradation rate of PLGA is the device shape. It influences on approachability of water milieu. In addition, acidic media is a very important factor that can increase the PLGA degradation rate due to autocatalysis[38]. Since, T_g of PLGA is above 37 °C, it behaves as a rigid structure at ambient temperature. This characteristic decreases with raising amount of lactic acid and molecular weight [39].

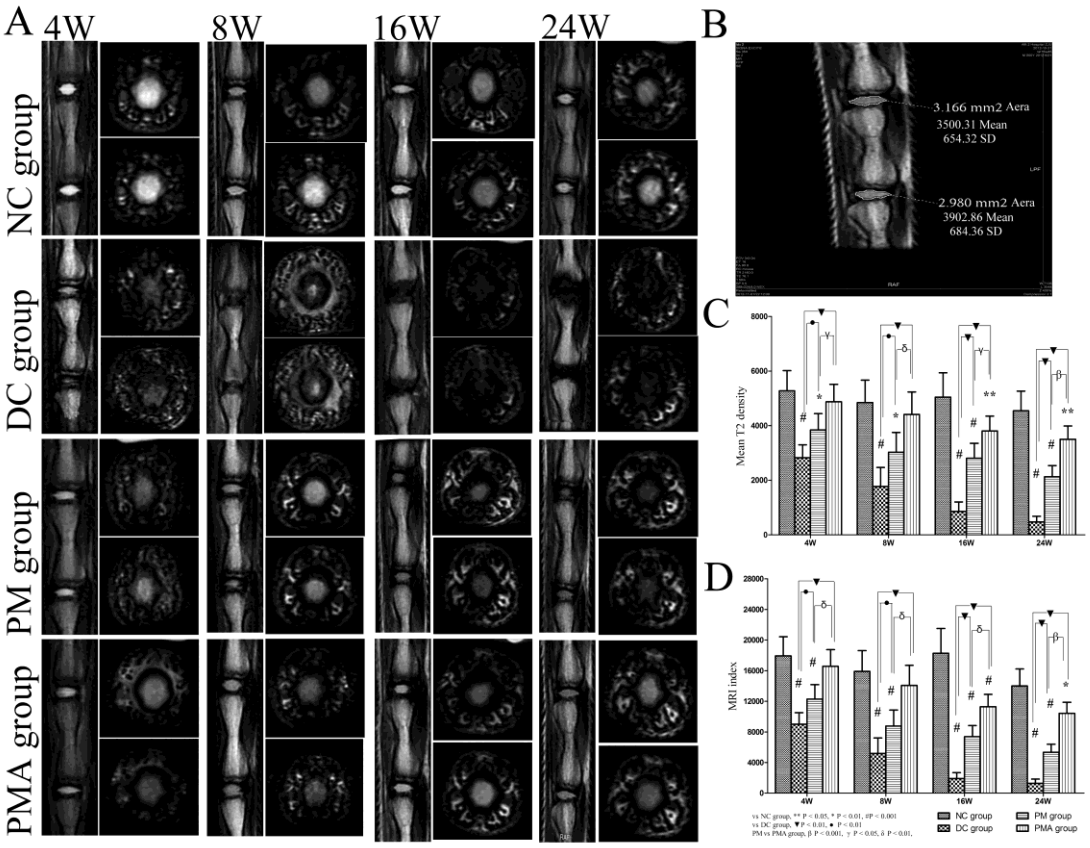
PLGA scaffolds applications in rehabilitating AC tissue

Replacement and reconstruction of avascular tissues such as cartilage has been an importance issue for many years [40]. PLGA is a prominent biodegradable polymer that can be used for cartilage tissue engineering applications. PLGA has been utilized in a wide variety of shapes for cartilage tissue regeneration, such as films, porous scaffolds and hydrogels. Therefore, in this article an attempt was made to consider PLGA scaffolds and microspheres for such application. Numerous techniques have been used to fabricate scaffolds, such as solvent casting, particulate leaching, gas foaming, phase separation, electrospinning and etc. These techniques have merits and demerits [41]. Ultra-thin non-woven fibers with nanometer to micron diameter can be fabricated with electro-spinning process [42]. Previous studies showed that different process parameters such as solvent (e.g., acetone and dichloromethane), distance between collector/nozzle (ranging from 10 to 25 cm), applied voltage (from 10 to 30 kv), and eventually concentration of polymer (from 15 to 25 w/w) could be affected distinctly all properties of the electrospun fibers [42-44]. The advantages of this process consist of: extremely high surface-to-volume ratio, tunable porosity with acceptable pore size, and achieving the sufficient physicochemical properties [45]. Furthermore, electrospun nano/micro fibers composite scaffolds showed enhanced mechanical properties, suitable attachment, spreading, and differentiation of cells seeded on them [46]. In 2012, Gang et al. proposed a three-dimensional (3D) PLGA microfibrous scaffold with 90% porosity produced by electrospinning technique for biomedical applications. Biological assessment confirmed that highly porous scaffolds fabricated by this method have fibrous structure with high specific surface area, and sufficient interconnected pores number could be the best candidate for cartilage repair. Recently, stem cells role in cartilage reconstruction have been confirmed. Stem cells are undifferentiated cells with high replication ability. Mesenchymal stem cells (MSCs) can be differentiated into variety of cells such as: osteoblast, chondroblast, and adipocyte [40]. Hence, in the past decades many prominent researches have been doneby scientists on tissue reconstruction. Uematsu et al., fabricated 3D PLGA scaffold seeded with MSCs to repair defects in rabbit knees [47]. It was shown that the defects in the rabbit knees were regenerated with new hyaline cartilage at 12 weeks after transplantation. They also observed that this scaffold provides facilitated infiltration of MSCs without using growth factor. As reported by Xin et al, blending electrospun nanofiber PLGA scaffold with human mesenchymal stem cells (hMSCs) can accommodate continuous differentiation of hMSCs into osteoblasts and chondroblasts [48]. In 2015, our group fabricated a 3D nanocomposite PLGA scaffold via SC/PL for AC applications. Physical, mechanical, and in vitro evaluation showed that this structure has a prerogative in order to use for AC due to high porosity percentage, suitable interconnected pore structure, sufficient compression modulus of elasticity, considerable compressive strength, and predominant water absorption, weight loss, biodegradation rate, and good response from adipose-derived mesenchymal stem cells (ADMSCs) cultivated on it [11,12]. From the other point of view, recently it has been shown that blend PLGA with bioactive bioceramics could be useful for osteochondral abnormalities. For instant, in 2011, researcher showed that osteochondral composite scaffolds prepared of PLGA and tricalcium phosphate could be considered in order to repair cartilage defects in pigs [22]. Alsoour work revealed that optimized amount of 45Sbioactive glass nanoparticles (≤ 25%wt.) could have a vital role in cartilage repair [11, 12]. Chen et al. prepared PLGA/collagen cobweb-like scaffolds and showed that the mechanical properties and MSCs metabolism such as differentiation, geneexpression and high cell density could be affected with this structure and indicated that this scaffolds is a promising way to AC reconstruction [49]. In another research, shin et al., fabricated a blend nanofiber scaffolds consist of $PLGA_{75/25}$ and $PLGA_{50/50}$ with equal ratio and showed that physical, mechanical and cellular activity could be enhanced and they stated that this scaffold could be considered as a good way to cartilage regeneration [50]

Drug delivery systems (DDSs) with assisted PLGA for AC regeneration

As mentioned in the literatures, AC has no ability to undergo successful repair. Numerous strategies have been employed to regenerate AC but all of them inflict further rigorous damages and fibrocartilage tissue formation. Since, the novel therapy entitled drug delivery has been explored by administration bioactive agents (e.g., drugs, growth factors, and other bioactive molecules) in order to safely delivering with highly efficient of above factors to damaged tissues. For AC treatment, several attempts such as intra-cartilage injection of signaling molecules such as TGF-β1, BMP-2, and IGF-1 have been investigated, but none of them show appropriate results due to induce osteophytes. The cause of this phenomenon is uncontrollable release of these factors. To obtain sustain release of these factors in order to achieve local delivery with low dosage, osteochondral implants composed of PLGA as drug carrier by compression molding have been examined for full thickness defects of rabbits. Only 50 % of these implants have been reported to be successful for neo-cartilage formation and the others displayed inferior mechanical properties as compared with native cartilage [51].Nowadays, entrapment and delivery of drugs, growth factors, and other regulatory molecules with biodegradable polymeric biomaterials (e.g., natural or synthetic) have gained a lot of attention as a non-invasive mean to restore normal cartilage performance. PLGA microspheres are the best candidate that recently has been achieved great amount of notification in this field [52]. For instance, researchers have been demonstrated PLGA micro and nanospheres loaded with paclitaxel, betamethasone, and a water-soluble cortico-steroid has merits and demerits for AC regeneration such as anti-inflammatory potential, anti-swelling, and a number of side effects, respectively[51]. In another study, researchers have been shown that TP508 synthetic peptide with ability to binding domain of thrombin that incorporated into PLGA microspheres, appears that has restoration potential for AC [51]. Ko et al demonstrated intra-cartilage injectable solfuraphane (SFN)-PLGA microsphere could be manipulate as a useful DDSs for osteoarthritis (OA). They exhibited that with using SFN-PLGA microspheres, the expression of inflammatory markers such as COX-2, ADAMTS-5 and MMP-2 is not pending away. Furthermore, the progression of surgically treatment-induced OA in rats with SFN-PLGA microspherehas been shown a time-consuming method [53]. In 2012, zhang and huang designed an intra-cartilage sustain release DDSs of lornoxicam (Lnxc) loaded PLGA microspheres for treatment OA disease. Swelling and pharmacodynamics analysis have been displayed suitable plasma drug concentration, high retention time, and good targeting efficiency for Lnxc-loaded PLGA microspheres in rats' joints. In addition, they have been expressed predominantly biocompatibility and considerable healing AC damage by papain with using Lnxc-loaded PLGA microspheres after 30 days [54]. In another study, Eswaramoorthy et al. prepared a sustain release and long-term efficiency DDSs of Parathyroid hormone (PTH)-loaded PLGA microspheres in order to suppress early OA. However, they have been exhibited that the effect of fabricated microspheres on the healing rat knee cartilage was similar to that of a once-every-three-day injection of PTH[55]. There are many factors that can affect the rate of drug release from biodegradable PLGA microspheres, for instance: i) molecular weight; ii) moisture content and iii) glass transition temperature (T_g). As well as, the release and degradation rates of entrapped bioactive molecules in polymeric materials (e.g., PLGA microspheres) is related to LA: GA ratio. In 2011, Andreas et al. prepared biodegradable insulin-loaded PLGA microspheres by encapsulation and solvent evaporation technique [56]. They used three emulsification methods, solid-in-oil-in-water (s/o/w), water-in-oil-in-water (w/o/w) and oil-in-oil-in-water (o/o/w) for fabrication PLGA-insulin microspheres. They showed w/o/w technique was the appropriate procedure since optimum insulin release could be achieved. Another promising process to reconstruct a degenerative tissue is gene therapy. Nowadays, it was confirmed that gene incorporation can influence on the scaffolds properties. SOX9 gene plays as a suitable gene for

chondrogenesis and differentiation of stem cells to chondroblasts. Moreover, high expression levels of Col2a1and aggrecan genes are the other role of this gene [41,45]. PLGA microspheres loaded with dexamethasone, polyplexed SOX9, and heparinized TGF-β were synthesized by Sun Park et al., Cultured human mesenchymal stem cells with these microspheres showed expression of the chondrogenesis-related genes of collagen II and ECM of glycosaminoglycan (GAG) secretion [57]. Recently, a new application of PLGA microspheres loaded with dexamethasone and TGF-β3 showed nucleus pulposus (NP) regeneration that lead to back pain relief. They fabricated an appropriate cell carrier for NP abnormalities by designing a nano-structured PLGA microspheres which was loaded with dexamethasone and then coated with growth factor embedded heparin/poly($_L$-lysine) via layer by layer technique for rat disc regeneration. Results showed that degenerative intervertebral disc can reconstruct by seeding adipose-derived stem cells (ADSCs) on the microspheres. Moreover, after transplantation, disc height values increased from 63% to 73%. In addition, MRI signal intensities showed rising from 47% to 76% before and after transplantation, respectively (Fig. 1). According to the results it can be concluded that ADSCs-seeded PLGA microspheres could regenerate defects in intervertebral disc in vivo [58]. In 2015, Kee Woong Jang used a novel method to cartilage repair entitled low intensity ultrasound therapy. In this project he prepared microbubbles of PLGA containing doxorubicin and affected these microspheres with low intensity ultrasound. The result of this work have been indicated that sustain release kinetic of doxorubicin and whatever PLGA microbubbles degradation rate increased with ultrasound wave, the more amount of drug could be released and accelerating the AC defects with affecting the progenitor and MSCs [59].



Figu. 1. Representative T2 MRI scans (A), measured area of interest in NP, mean signal intensity and standard deviation (B), quantitative analysis of mean T2 intensity (C) and MRI index (D) of different experimental groups (Reproduced from [ref. 58], with permission from [Elsevier]).

Conclusion and future trends

Chondral and osteochondral injuries due to trauma or other pathology commonly result in the evolution of osteoarthritis, finally leading to continuing total joint impairment. The restricted ability of articular cartilage to regenerate makes joint arthroplasty an inevitable surgical intervention. This Review describes the potential use of PLGA scaffolds and microspheres in cartilage repair. PLGA has suitable physic-chemical properties, biocompatibility, and biodegradability rate. Animalstudies showed the enhance cartilage regeneration with application of PLGA scaffolds and microspheres with and without loaded drugs. This synthetic biodegradable polyester deserves more attention to improve its biological interaction with cartilage tissue. In this regard, effect of different scaffolds structures, the size of the particles, and use of various drugs can be evaluated.

Conflict of interest statement

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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