Poly (lactide -co- glycolide) Fiber: An Overview

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ABSTRACT

Co-polymers of lactide and glycolide, referred to as PLGA, have generated tremendous interest because of their excellent biocompatibility, biodegradability and mechanical strength. Various polymeric devices like microspheres, microcapsules, nanoparticles, pellets, implants, and films have been fabricated using these polymers. They can be transformed by spinning into filaments for subsequent fabrication of desirable textile structures. Spinning may be accomplished by various routes. The fibers may be fabricated into various forms and may be used for implants and other surgical applications such as sutures. They are also easy to formulate into various delivery systems for carrying a variety of drug classes. The present article presents a review on the production of PLGA fiber by various methods, along with correlations between structure and properties of the fibers. The applications of these fibers in biomedical domains are also discussed.

Keywords: PLGA; Fiber; Spinning; Medical applications

INTRODUCTION

During the past two decades significant advances have been made in the development of degradable polymeric materials for biomedical applications [1, 2]. Degradation is important in biomedicine for many reasons. For example degradation of the polymeric implant means surgical intervention may not be required in order to remove the implant at the end of its functional life, eliminating the need for a second surgery. Consequently, a wide range of natural or synthetic polymers capable of undergoing degradation by hydrolytic or enzymatic routes are being investigated for biomedical applications [3]. Even though the biomedical applications of enzymatically degradable natural polymers such as collagen dates back thousands of years, the application of synthetic biodegradable polymers started only in the latter half of 1960s [4].

However, the past two decades have seen the development of a range of new generation synthetic biodegradable polymers and analogous natural polymers specifically developed for biomedical applications. *Table I* illustrates various natural and synthetic biodegradable polymers [5].

TABLE I. Natural and synthetic biodegradable polymers [5].

Polymer	Base
Polysaccharides	Natural
Proteins	Natural
Polyesters	Synthetic
Polyanhydrides	Synthetic
Poly(ureas)	Synthetic

Degradable polyesters derived from three monomers, lactide, glycolide and caprolactone (CL), are commonly used clinically. They are characterized by degradation times ranging from days to years, depending on formulation and initial molecular weight [7]. Poly (glycolic acid) (PGA), poly (lactic acid) (PLA), and their copolymers are the most widely used synthetic degradable polymers in medicine. Of this family of linear aliphatic polyesters, PGA has the simplest structure and consequently enjoys the largest associated literature base. Since PGA is highly crystalline, it has a high melting point and low solubility in organic solvents. In order to adapt the materials properties of PGA to a wider range of possible applications, researchers undertook an intensive investigation of copolymers of PGA with the more hydrophobic polymers [6]. Among the co-polyesters investigated, extensive research has been performed in developing a full range of poly (lactide-co-glycolide) (PLGA). Different ratios of PLGAs have been commercially developed and are being investigated for a wide range of biomedical applications [3]. The major

popularity of these biocompatible copolymers can be attributed in part to their approval by the Food and Drug Administration (FDA) for use in humans, their good process ability which enables fabrication of a variety of structures and forms and controllable degradation rates [7]. They also can be transformed by spinning into filaments for subsequent fabrication of desirable textile structures. Featured with excellent characteristics, such as biodegradability, biocompatibility, mild undesirable host reactions, and three-dimensional and directional porous structures, PLGA fibers, whose diameters range from nanometers to millimeters, are broadly studied and used as different biomaterials. For example, the commercialization of the copolymer for the bioabsorbable high strength suture, VICRYL was taken up by Ethicon in 1972 [8, 9]. As such, there has been extensive investigation into their use as an ideal biomaterial for temporary medical applications, such as controlled drug delivery systems and as scaffolds for tissue engineering. Various studies have investigated different properties and applications of PLGA [1,3,10] but few studies investigated different fabrication methods of PLGA fibers. The present article presents a review of the chemistry and different properties of PLGA and production of PLGA fiber by various methods, along with correlations between structure and properties of the fibers. The applications of these fibers in biological and medical domains are also discussed.

CHEMISTRY OF PLGA

The chemistry of PLGA involves the copolymerization of lactic and glycolic acid monomers. Glycolic acid (HOCH2COOH) is the smallest α-hydroxy acid (*Figure 1*). Lactic acid (HOCH3CHCOOH) is a simple chiral molecule which exists as two enantiomers, L- and D-lactic acid (*Figure 2*), differing in their effect on polarized light [11,12].

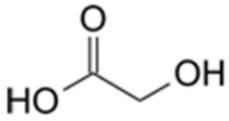

FIGURE 1. Chemical structure of glycolic acid.

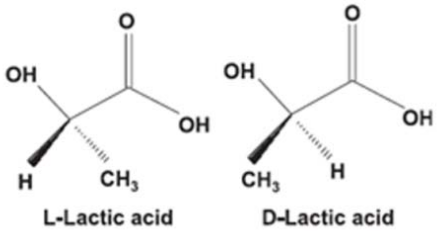

FIGURE 2. Optical isomers of lactic acid [11, 12].

High-molecular-weight polymers and copolymers of glycolic and lactic acid are not possible to obtain by direct condensation of the related carboxylic acids because of the reversibility of the condensation reaction, backbiting reactions, and the high extent of reaction required. Therefore, high-molecular-weight polymers and copolymers of glycolide and L- and D-lactides are prepared by ring-opening addition polymerization of their respective cyclic dimers. (*Figure 3 and Figure 4*).

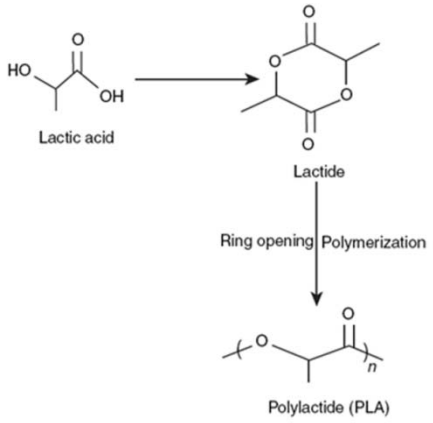

FIGURE 3. The ring opening polymerization of the cyclic diester of lactic acid, lactide [7].

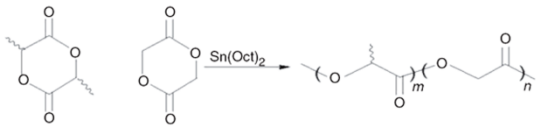

FIGURE 4. Synthesis of PLGA [7].

The synthesis of this copolymer is carried out generally with the use of tin compounds as initiators. Common catalysts used in the preparation of this polymer include tin (II) 2-ethylhexanoate, tin (II) alkoxides, or aluminum isopropoxide [13]. However, the complete elimination of highly toxic tin

compounds from the polymers is practically impossible [14] which results in their slow penetration into patient, blood circulation systems. Several attempts were made to use less toxic initiator, zinc lactate [15] and calcium [16] and zirconium acetylacetonates [17, 18]. Only zinc chloride and zirconium acetylacetonate have allowed one to obtain copolymers of glycolide with lactide with high enough molecular masses to be used in production of surgical materials.

PROPERTIES OF PLGA

Depending on the ratio of lactide to glycolide used for the polymerization, different forms of PLGA can be obtained. These are usually identified in regard to the monomer ratio used (for example. PLGA 75:25 identifies a copolymer whose composition is 75% lactic acid and 25% glycolic acid). It is noteworthy that there is no linear relationship between the ratio of glycolic acid to lactic acid and the physicomechanical properties of their copolymers. Whereas PGA is highly crystalline, crystallinity is rapidly lost in PLGA copolymers. These morphological changes lead to an increase in the rates of hydration and hydrolysis. Thus, copolymers tend to degrade more rapidly than either PGA or PLA. All PLGAs are amorphous rather than crystalline. The mechanical strength, swelling behavior, capacity to undergo hydrolysis and, subsequently, the biodegradation rate are directly influenced by the crystallinity of the PLGA. The degree of crystallinity and the melting point are directly related to the molecular weight of the polymer. Physical properties such as the molecular weight affect the mechanical strength of the polymer and its ability to be formulated as a drug delivery device; also these properties may control the polymer biodegradation rate and hydrolysis. It has a glass transition temperature (Tg) of 45°C and an inherent viscosity of 0.5-0.8 mPa. The Tgs of the PLGA copolymers are above the physiological temperature of 37°C and hence they are normally glassy in nature. Thus, they have a fairly rigid chain structure, which gives them significant mechanical strength to be formulated as a degradable device. It has been reported that the Tgs of PLGA decrease with the decrease of lactide content in the co-polymer composition with decreasing molecular weight. Unlike the homopolymers of lactide acid (LA) and glycolide acid (GA) which show poor solubility, PLGA can be dissolved by a wide range of common solvents, including chlorinated solvents, tetrahydrofuran, acetone, or ethyl acetate [7]. PLGA physical properties have been shown to depend upon multiple factors, including the initial molecular weight, [19] the ratio of lactide to glycolide, [20] the size of the device, [21] exposure to water [22] and storage temperature [23]. In both *in vitro* and *in vivo*, the PLGA co-polymer undergoes degradation in an aqueous environment (hydrolytic degradation or biodegradation) through cleavage of its backbone ester linkages. The polymer chains undergo bulk degradation and the degradation generally occurs at a uniform rate throughout the PLGA matrix. A three-phase mechanism for PLGA degradation has been proposed:

1. Random chain scission process that the molecular weight of the polymer decreases significantly, but no appreciable weight loss and no soluble monomer products are formed.

2. In the middle phase, a decrease in molecular weight accompanied by a rapid loss of mass and soluble oligomeric and monomer products are formed.
3. Soluble monomer products formed from soluble oligomeric fragments. This phase is that of complete polymer solubilization [24].

The degradation rates of the PLGAs are dependent on many factors including the molar ratio of lactide and glycolide acids in the polymer chain, molecular weight of the polymer, the degree of crystallinity, the Tg of the polymer and nature of the incubating media [24, 25]. The higher the content of glycolide units, the lower the time required for degradation. An exception to this rule is the copolymer with 50:50 monomers' ratio which exhibits the faster degradation (about two months). In addition, polymers that are end-capped with esters (as opposed to the free carboxylic acid) demonstrate longer degradation half-lives [13]. Miller et al. have shown that the (PLGA, 50:50) is very hydrolytically unstable and the resistance to hydrolytic degradation was found to be more pronounced at either end of the co-polymer composition range [26]. However it is necessary to explain that a major limitation of the PLGAs applications is acidic degradation products during degradation.

SPINNING OF PLGA FIBERS

The transformation of PLGA into textile structures such as fibers is complicated and depends on different variables such as structural changes in the copolymer during processing. Extrusion of the copolymer into monofilament and multifilament may be achieved by fiber formation mechanisms such as melt spinning, solution spinning, and electrospinning. There are distinct features of each of these processes that are subsequently reflected in fiber properties.

Melt Spinning

Owing to the thermoplastic nature of PLGA, it is possible to melt the polymer under reasonable conditions. In the melt spinning process polymer is melted, filtered, and extruded through the spinneret. The melt is drawn from the spinneret hole at a melt temperature. In the draw zone the extruded filaments are cooled to the solidification temperature and further to below the glass transition temperature.

Finally, the filaments come to the take-up bobbins, and the temperature of the filaments is less than the Tg. Melt spinning of PLGA was one of the first methods used to produce fibers. Various research groups have studied the melt spinning of PLA and PLGA fibers under various processing conditions [27-35]. Wang et al. [34] have used centrifugal melt spinning technique to fabricate fiber matrix of PLGA (85:15, Mw = 50,000–75,000). This technique is well suited for thermoplastic polymers of low Tg. The fabricated fibers were used as scaffolds for cell culture. Intra et al. [35] have developed the suture by melt extruding a mixture of PLGA (75:25) pellets and drug that induce potent anti-tumor immune responses. To prepare the immunostimulatory suture, they loaded ground up PLGA pellets and drug that was endotoxin free into a Dynisco extruder hopper and sutures were extruded from a melted (≤70 ◦C) mixture of PLGA pellets and drug. The suture preparation uses an extrusion process is simple, reproducible and adaptable for loading of a wide variety of anti-tumor molecules, cytokines, antigens and immunostimulants in combination or alone. Many studies have been carried out to investigate the structure and property relationship in PGA and PLA fibers [36-40]. It is well known that the degree of crystallinity and mechanical properties of polymeric fibers can be greatly influenced by processing conditions [36-38]. In typical fiber processing, two process techniques are routinely used to manipulate the fiber properties. One technique involves the orientation process and the other technique involves the annealing process. Fu et al. [41] have investigated the structure and property changes of PLGA fiber during many different fiber process stages. These stages include an orientation stage, a hot-stretching stage and an annealing stage. Samples used were random copolymers based on (PLGA 10:90). This resin had Mw of 60,000, Mn of 22,000 and a polydispersity of 2.8. Results show that the first encountered orientation roll temperature can have a significant impact on the structure formation by the process of nucleation-controlled kinetics, while the second encountered pre-annealing roll temperature is critical to the growth of the crystallites and overall crystallinity. Higher hot-stretching temperature increases the tensile strength, crystallinity and crystal size because it can reduce the internal stress in the restrained amorphous chains. In the annealing stage, samples can gain a significant increase in crystallinity and crystal size while heat shrinkage in the vicinity of Tg significantly decreases. The annealing process has proven to be the key step to stabilize the fiber properties near Tg [41].

Wet Spinning

Sometimes, melt spinning is not possible, either because the copolymer degrades while melting or the melt is thermally unstable [42]. The solution spinning methods, dry spinning and wet spinning, are usually utilized for polymers that do not melt. In both methods polymer is dissolved into solution and the polymer solution is filtrated, dearated, and pumped through the spinneret [43]. In dry spinning, solvents are removed by thermal evaporation while in wet spinning the coagulation of the polymer is carried out in another fluid that is compatible with the spinning solvent but is not itself a solvent for the polymer [44,45] In practice, as the viscose polymer solution enters into the coagulation bath, phase separation begins due to solvent out-flow and nonsolvent in-flow and the polymer precipitates as fibrils [46,47].

There is several studies used solution spinning to produce PLGA fibers [48-56]. Nelson et al. [48] have described a simple and repeatable method for wet-spinning of PLGA monofilament fibers. The effects of solvents type, polymer concentrations and draw ratios on the wide range of fiber properties were investigated. PLGA (50:50, intrinsic viscosity: 0.66–0.80) was dissolved in methylene chloride or chloroform at a concentration of 20 w/v%. The polymer flow rate was typically between 0.02 and 0.1 mL/min. Results show that the chosen solvent system and polymer composition greatly affected the external morphology of the filaments. The difference in properties observed between a 7.5 w/v% fiber and an 8 w/v% fiber was due to macro structural changes in the polymer fiber. As the solvent diffused outward into the coagulation bath, and the coagulating bath fluid diffused into the polymer stream, the outer edge of the polymer stream became either polymer poor with dispersed aggregates of polymer rich phases, or the outer edge became polymer rich with entrapped polymer-poor dispersed phases. Dramatic changes in tensile strength occur over relatively small changes in the draw ratio from 23:1 to 26:1, but after that it remains relatively constant out to a draw ratio of 40:1. Percent crystallinity does not appear to be a function of draw ratio. This will be an unexpected finding for those familiar with melt-extrusion, where strain-induced crystallization generally results in increased crystallinity as the draw ratio increases,

resulting in an increase in mechanical strength. In wet-extrusion, however, it does not appear to be the case; crystallinity is relatively constant for all draw ratios. Crow et al. [49] have created biodegradable fibers of PLLA and PLGA that encapsulated a water-soluble drug by wet-spinning a water-in-oil emulsion.

Drug release kinetics and changes in molecular weight were investigated over time. Methylene chloride was used as solvent and bovine serum albumin (BSA) was used as a model drug for the release studies and as a surfactant to stabilize the emulsion. Hexane was used as a coagulation medium. As the emulsion flowed into the coagulation bath, a fiber began to form. The mean linear velocity of the emulsion in the spinneret was 0.385 m/min, whereas at the bobbin it was 16 m/min; giving a draw ratio of 41. This draw ratio induces significant mechanical strain on the forming fiber. The polymer type and the amount of aqueous phase incorporated into the polymer solution through emulsification were both important to how the fibers respond in an *in vitro* environment. Polymer type significantly affected drug release and molecular weight degradation. Aqueous phase incorporation significantly affected molecular weight degradation for PLLA, but less so for PLGA, and results in a significant difference in drug release rates for both fiber types. Wen et al. [50] have fabricated biodegradable permeable PLGA hollow fiber membranes (HFMs) using a wet phase inversion technique. By varying several parameters, such as the spinneret size, solvent and non-solvent pair, polymer concentration, flow rate, precipitation method, drop height, and small molecular pore-forming agents, PLGA HFMs with variable sizes, surface morphologies, porosities, and diffusive permeability were obtained. PLGA (50:50, Mw = 51.9 kDa, Mn = 34 kDa and intrinsic viscosity = 0.2 dL/g) was used as a model degradable polymer. Results indicate that by using a wet phase inversion technique, degradable HFMs with variable size, inner and outer surface morphologies, porosity, and permeability with potential applications for nerve tract guidance conduits can be fabricated. The *in vitro* degradation behavior of PLGA HFMs was assessed in phosphate buffered saline (PBS) (0.1M, pH 7.4, 37 1C) under static culture conditions. As shown in *Figure 5* there was no observable weight loss in the first two weeks, after which weight loss due to the dissolution of water-soluble chains in the polymer occurred and accelerated as a result of the degradation. The loss of structural integrity by breaking down into fragments did not occur with the HFMs until four weeks and the HFMs completely disappeared by eight weeks. In addition, as judged by the changes in material morphology and the weight loss over time, the PLGA HFMs degraded homogeneously, with the surface and the bulk degrading at approximately the same rate.

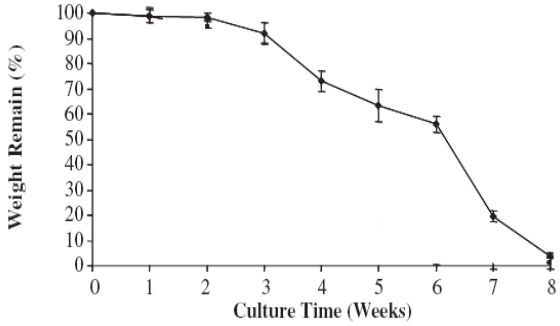

FIGURE 5. Degradation behavior of PLGA HFMs in 0.1M PBS culture: Weight changes of PLGA HFMs over time in culture.

Ellis and Chaudhuri [51] have produced PLGA hollow fiber membranes using 1, 4-dioxane and 1-methyl-2-pyrrolidinone (NMP) as solvents and water as the nonsolvent by dry/wet and wet-spinning. The effect of key fiber spinning variables to assess the controllability of the fiber properties was examined. The development of a hollow fiber spinning process critically depends on the rheology of the polymer solution thus both the polymer concentration and the nature of the solvent are important. The characteristics of a membrane cast using immersion precipitation are dependent on the polymer-solvent nonsolvent interactions since this affects the precipitation process. Dioxane-water and NMP-water both have high mutual affinities so porous structures are expected to form and were selected for this reason. *Figure 6* shows the viscosity of (P_{DL}LGA 50:50) dissolved in dioxane and NMP.

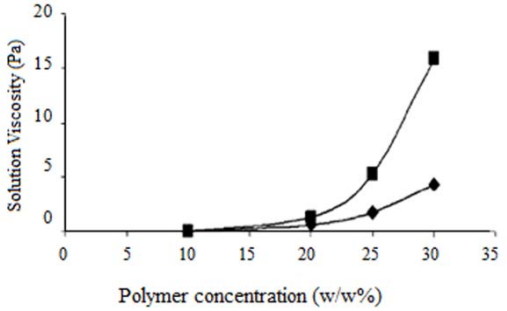

FIGURE 6. Viscosity profile for 50:50 in NMP and dioxane. Readings were taken at 258C [51].
■ Dioxane as the solvent
◆ NMP as the solvent

It can be seen that while the 20% solutions have similar viscosities, at 25% polymer concentration the 50:50 P_{DL}LGA-dioxane solution has over twice the viscosity of the 50:50 P_{DL}LGA-NMP solution and 2.5 times the viscosity at 30%. The dense sponge-like pores and absence of macrovoids seen with P_{DL}LGA membranes cast using dioxane suggests that the polymer-solvent interaction had a significant effect on demixing likely to be due to P_{DL}LGA having a relatively high affinity for dioxane. The finger-like structure of P_{DL}LGA membranes cast from a P_{DL}LGA-NMP solution suggest that the NMP-cast membranes underwent instantaneous demixing whereas the sponge-like structure of the dioxanecast membranes suggest that they were formed by delayed demixing. The pores with dense skins of the dioxane-cast membranes would only allow molecular diffusion and would prevent the flow of the larger proteins found in media. NMP was selected over dioxane as the solvent for use in the phase inversion spin casting processes to fabricate the membrane scaffolds. This was based primarily on the macrostructure of the resulting membrane, on the wide range of polymer concentrations with viscosities suitable for spinning, and the relatively low toxicity and volatility compared to dioxane. The pore structure of the hollow fibers can be controlled by altering the air gap and temperature during the spinning process, no air gap resulting in the more porous surface and a higher temperature resulting in a more porous wall [51]. Hwang et.al [52] have developed a method to produce PLGA microfibers within a microfluidic chip based wet spinning for the generation of 3D tissue engineering scaffolds. The synthesis of PLGA fibers was achieved by using a polydimethylsiloxane (PDMS)-based microfluidic spinning device in which linear streams of PLGA dissolved in dimethyl sulfoxide (DMSO) were precipitated in a glycerol-containing water solution. By changing the flow rate of PLGA solution from 1 to 50 μL/min with a sheath flow rate of 250 or 1000 μL/min, fibers were formed with diameters that ranged from 20 to 230 μm. *Figure 7* shows the schematic of a microfluidic chip and a cover glass winding device for the aligned PLGA fibers. The core solution (10% PLGA in DMSO) and sheath solution (mixture of glycerin and distilled water with 50% (v/v)) were introduced into each inlet, respectively. The schematic of PLGA fiber generation is illustrated in *Figure 7b*. At the position where the two fluids merged (around the dotted rectangle of *Figure 7a*), the sheath fluid surrounded the tip of the core glass while the core fluid extruded through the core glass to form a stable coaxial flow because of microfluidic phenomena. At the interface between the core PLGA solution and sheath fluid, the exchange of DMSO and water occurs and the polymer in the liquid phase solution is solidified. The size of the fibers was easily controllable by changing the core and sheath fluid flow rates. This chip-based fabrication method has several advantages over conventional techniques. For example, the fabrication apparatus is simple, the chip is small, and the resulting fiber size can be easily controlled by varying flow conditions [52].

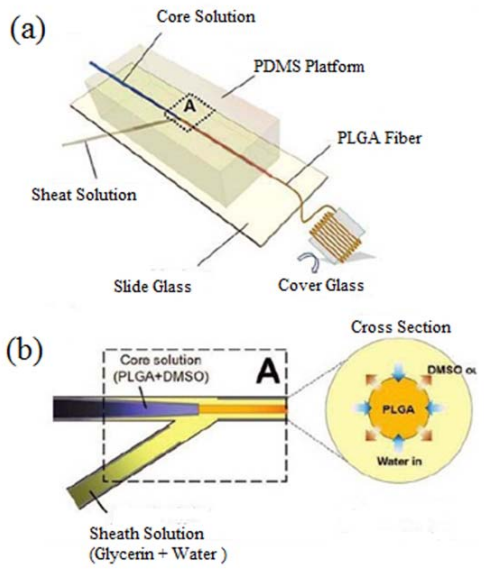

FIGURE 7. (a) Schematic of a microfluidic chip and a cover glass winding device for the aligned PLGA fibers. (b) Principle of the phase inversion process during polymer precipitation [52].

Electrospinning

Electrospinning is another interesting technique for spinning PLGA (and other polymers). In the electrospinning process, a polymer solution or melt is subjected to strong electric fields, and then the liquid-phase polymer is ejected from a nozzle. The diameter of the ejected fibers is significantly reduced as they travel toward a collector. *Figure 8* shows schematically an electrospinning system.

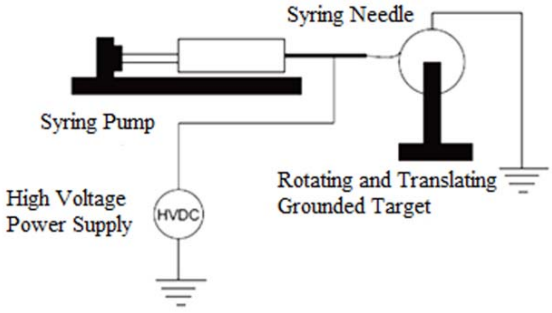

FIGURE 8. Schematic of electrospinning system [5].

The electrospinning process of the PLGA has been widely studied [57-60]. Bini et.al has fabricated PLGA nanofibers by the electrospinning process. Hexafluoroisopropanol (HFIP) was used as a solvent to dissolve PLGA microfibers under gentle stirring to obtain different concentrations ranging from 2 to 7 wt% solution. A high voltage of 12 kV was applied to the needle using a high voltage power supply. The morphology of the nanofibers spun with different concentrations of the polymer solution was studied. A 7 wt% concentration of (PLGA 10:90) produced a stable nanofiber without any beads and it was found to be the optimum concentration for electrospinning [57]. In another attempt nonwoven nanofibrous structures of PLGA were produced via electrospinning to develop biodegradable scaffolds. To obtain nanofibrous structure having various average diameters and porosities, electrospinning of PLGA was also carried out with quaternary ammonium salt (benzyl triethylammonium chloride, (BTEAC)), which was soluble in the electrospinning solvent of PLGA and easily removable from the resulting ultrafine fibers. The changes in the fiber diameter and morphology by adding salt or changing solvent were investigated in terms of solution viscosity, surface tension, dielectric constant, and conductivity. It was found that the conductivity of the PLGA solution was a major parameter affecting the morphology and diameter of the electrospun PLGA fibers. In addition, the diameter of the electrospun PLGA nanofibers was strongly dependent on a dielectric constant of solvent [58]. Zhao et.al has fabricated the electrospun PLGA fibrous scaffolds under the different process parameters. The influence of polymer solution concentration, electric field strength, and feeding rate on fiber morphology and diameter was investigated. The diameter of nanofibers increased with the PLGA concentration and feeding rate, but the electric field strength exerted only minor effects on the average diameter of the nanofibers. Some studies have investigated the degradation behavior of nanofibers and nanofiber matrices prepared by electrospinning [61-63]. Zong et al has studied the structural and morphological changes of electrospun PLGA (LA/GA ratio 10/90) membranes during *in vitro* degradation as a function of time. On the basis of their results, the structure and morphology changes of electrospun PLGA nanofiber membranes during *in vitro* degradation could be divided into four stages: A schematic diagram of these changes during *in vitro* degradation is shown in *Figure 9.* In stage I (within the first day of incubation), as the incubation temperature is near the glass transition temperature (Tg), a rapid thermally induced crystallization process takes place, forming the typical two-phase lamellar morphology. In stage II, the polymer chains in the amorphous regions between the lamellar stacks begin to degrade due to hydrolysis. This chain scission process enhances the mobility of the noncrystalline chains, which leads to further crystallization. This process is often termed as cleavage-induced crystallization, which usually forms defective crystal lamellae with smaller sizes. Very little mass of the sample is lost during these first two stages. In stage III (6-12 days of incubation), the degradation rate of the electrospun membrane increases after some degraded oligomers are formed and trapped inside of the sample, which autocatalyze the degradation reaction with acidic end groups. The amorphous regions disappear faster than the crystalline regions, resulting in fragmented samples with very high crystallinity. As the molecular weight of the polymer falls below a critical value, the degraded oligomers would become soluble in water. Large mass loss and water uptake are thus observed. At this point, the degraded sample is much more hydrophilic than the initial sample. Stage IV can be marked as the onset point of the significant mass loss from the crystalline region of PLA10GA90, as has been observed 12 days after incubation.

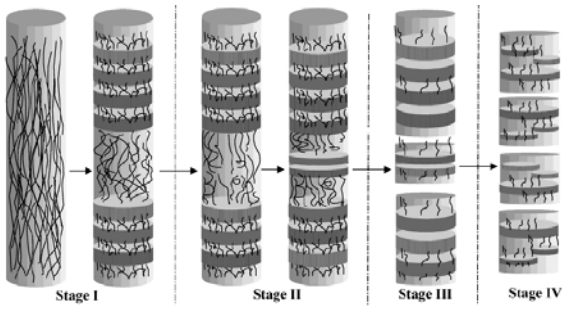

FIGURE 9. Schematic diagram of a four-stage model of structure and morphology changes of electrospun PLA10GA90 membranes during *in vitro* degradation.

Electrospinning is also a good technique to produce drug loaded nanofibers. However incorporation and sustained release of water-soluble bioactive agents, especially proteins, growth factors, and Deoxyribonucleic acid (DNA), by conventional electrospinning techniques remains challenging, due to low solubility and easy inactivation in common organic solvents [64, 65]. Compared with conventional electrospinning, coaxial electrospinning is essentially modified or extended of the former with a major difference in the configuration of spinneret. One of the advantages in using such technique is to protect easily denatured biological agents and potentially to wrap all substances in the core regardless of drug-polymer interactions. On the other hand, core-shell structure fibers electrospun from

coaxial electrospinning can potentially provide a better therapeutic effect, reduced toxicity, and sustained drug release [66]. There are several study used this technique to produced bioactive agents loaded core-shell ultrafine fibers [67-69]. For example, You et al [68] fabricated core–shell structured fibers with PLGA as shell and poly(ethylene oxide) (PEO) -containing BSA as core by coaxial electrospinning. Micrographs of Transmission electron microscopy (TEM) demonstrated that nanofibers had smooth surface and the structure of core-shell was obtained successfully (*Figure 10*).

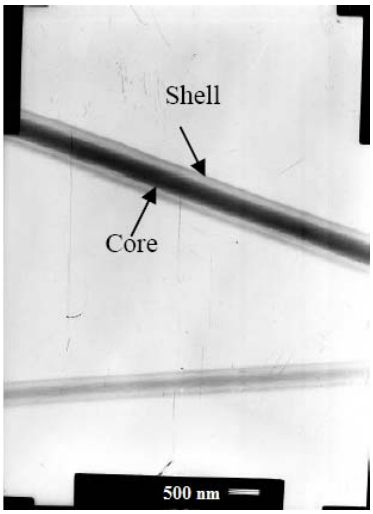

FIGURE 10. TEM micrographs of core-shell nanofibers.

Results suggested that PEO/PLGA core-shell ultrafine fibers could be produced and used as bioactive molecules carrier for tissue regeneration. Comprehensive data on PLGA fiber spinning are presented in *Table II*.

MEDICAL APPLICATIONS OF PLGA FIBERS

Copolymers of lactide and glycolide acid combine certain desired properties such as biodegradability, biocompatibility, pliability, miscibility with a wide variety of active compounds [63,70-72]. Other advantages of this copolymer utilization in biomedical applications are: possibility of controlling its physico-mechanical properties, chemical or physical modification of its surface properties, ability to immobilize cells or biomolecules within it or on the surface. For this reason it found interesting medical and pharmaceutical application in the last decades. Following are the major applications of the PLGA fibers in biomedical domain.

Suture

Sutures are the most widely used materials in wound closure and have been in use for many centuries. They are, in general made up of fibers from natural or synthetic polymers. Polymeric fibers could be absorbable or nonabsorbable. The most important advantage of synthetic absorbable sutures is their reproducible degradability inside a biological environment. Due to the development of these synthetic fibers, they have replaced some natural fibers [7]. PLGA has been approved by the FDA for use as a suture material because of features that offer crucial advantages [73]. In the 1960s and 1970s, research on absorbable suture materials such as Dexon (100% PGA) and Vicryl (10:90 PLGA) indicated good tissue compatibility and opened the door to the use of biodegradable polymer implants for other clinical applications [74-78]. Ethicon, Inc. has developed and sold a multifilament suture of PLGA, Vicryl, [79, 80] which is now the typical type of biodegradable suture, as a best seller. The surface is coated with surfactants to improve the gliding of the string. There is another type of the product called Vicryl Rapid, which is irradiated to increase the rate of bioabsorbance [81, 82]. Ethicon, Inc. has developed a new product, PANACRYL which has a low rate of bioabsorbance by increasing the LA/GA ratio. It loses a half of its tenacity by six months, and is completely absorbed in a few years. Their main products have relatively large diameters and are applied to defects which require a high tension in orthopedic surgery. For suture applications, PLGA must have a high concentration of GA for achieving proper mechanical and degradation properties [7]. Absorbable sutures such as PLGA has tremendous development value and has bright application prospects because of excellent biocompatibility, absence of tissue reaction, high strength and toughness, moderate stretchability, lack of toxicity and irritation, and controllable degradability. Owing to these excellent properties and extensive application sectors, they earned widespread attention as medical-care materials in the textile sector globally. One of the most interesting developments in recent times is combination of surgical sutures with bioactive materials. Novel bioactive materials have been prepared by coating violet resorbable Vicryl sutures with a bioactive glass powder derived from a co-precipitation method [83]. The other clinical bioactive sutures are Vicryl Plus [84]. Vicryl Plus is polyglactin 910 coated with triclosan. Several studies comparing the handling of Vicryl Plus with Vicryl showed no significant differences in handling and a

possible advantage in terms of postoperative pain [85,86]. Animal model studies have shown that polyglactin 910 suture coated with triclosan (Vicryl Plus) inhibits bacterial colonization of suture after direct *in vivo* challenge with S. aureus.[85] Vicryl Plus is more expensive, of course, than Vicryl, but it is approved by FDA and widely available. With the first wave of bioactive sutures already in the market place, research is directed to the development of future products such as sutures that could potentially demonstrate not only antimicrobial activity but also anesthetic and antineoplastic functions [87]. Application of suture as carrier of different drugs, proteins, cytokines and antibodies has been widely investigated [88-90]. Intra et.al [35] have developed an immunostimulatory suture that could have the dual function of closing the site of tumor excision and providing sustained localized delivery of immunostimulatory ligands that prevents local tumor recurrence, so that surgeons can effectively close the wound following removal of the tumor and simultaneously provide local therapy for control and elimination of minimal residual disease [90].

Pharmaceutical

The drug delivery system was developed for the purpose of bringing, up taking, retaining, releasing, activating, localizing and targeting the drugs at the right timing, period, dose and place. The biodegradable polymer can contribute largely to this technology by adding its own characters to the drugs. In this approach, the copolymers of PLGA, PLA-CL and PGA-CL are commonly used, because the copolymer can be prepared in the moderate condition, has the similar stiffness to the body, has the appropriate degradability, and has the low crystallinity enough to be mixed well with many kinds of drugs. The history of biodegradable polymers in drug delivery systems dates back to 1970 when PLGA was used to control the release of narcotics. Controlled drug release from these systems has been explained by different mechanisms: Fickian diffusion through the polymer matrix, diffusion through water filled pores created upon swelling of the matrix and delivery by erosion of the polymer matrix [91, 93] but most systems have been based on the erosion of the drug-containing polymer, whereby

TABLE II. Comprehensive data on PLGA fiber spinning.

Workers	Type of Spinning	Process Highlight	Advantages	Limitations
Li et al (2001)	Electrospinning	A novel PLGA structure for tissue-engineering applications was developed.	The nanofibrous structure has a high surface area-to-volume ratio.	……
Kim et al (2003)	Electrospinning	Medicated biodegradable PLGA-based nanofibrous scaffolds containing hydrophilic antibiotic drug were fabricated.	The successful incorporation and sustained release of drug from nanofibrous scaffolds was demonstrated.	……
Nelson et al (2003)	Wet spinning	The effect of solvent systems, polymer blends, and winding rates on properties of fibers reported.	Applied technique avoids the large capital, space, and raw material requirements of conventional melt-extrusion of polymers.	……
Bini et al (2004)	Electrospinning	Nanofibrous nerve guide conduit was fabricated.	Fibrous biomaterials can mimic the nano-sized dimension of natural extracellular matrix (ECM).	……
You et al (2005)	Electrospinning	The effect of conductivity of the PLGA solution on diameter of fiber was reported.	……	The morphology of ultrafine fibers strongly depends on the solution properties.
You et al (2005)	Electrospinning	Structural and morphological changes during *in vitro* degradation of PLA, PGA and PLGA were reported.	In comparison with microfiber nonwovens, a nanofiber matrix has an extremely high specific surface area and high interfiber pores.	……
Crow et al (2005)	Wet spinning	PLLA and PLGA fibers were prepared by wet spinning a water-in-oil emulsion and were used for drug delivery system.	This method leads to create a fiber scaffold at room temperature.	……

Wen et al (2006)	wet phase inversion technique	Hollow fiber membranes (HFMs) of PLGA were fabricated for use as nerve tract guidance channels.	This technique allows for fine-tuning of the permeability, inner and outer surface morphologies, tube size, and even highly aligned textures during fabrication.	……
Morgan et al (2007)	Wet spinning	Use of porous P_{DL}LGA hollow fibers as scaffold.	This technique allows controllable fabrication of porous fibers with a uniform hollow core and rough surface area.	……
Zhao et al (2008)	Electrospinning	The effect of polymer solution concentration, electric field strength, and feeding rate on scaffold properties was reported.	The electrospun scaffold can not only mimic the nano-sized dimension of (ECM) but also its spatial organization on the mesoscopic scale.	……
Hwang et al (2008)	Microfluidic spinning	A method developed to produce PLGA microfibers within a microfluidic chip	This process is simple, cost-effective, and compatible with many biological materials and can be used to generate microlevel diameter and uniform fibers in a reproducible and scalable manner.	……
Mack et al (2009)	Wet spinning	Biodegradable filaments for the controlled delivery of dexamethasone or levofloxacin described.	Benefits of a wet-processed filament include a porous microstructure, room temperature processing conditions, and diameters of suture-like scale.	……
Xie et al (2010)	Melt spinning	A methodology developed to quickly neutralize the acidic degradation products of PLGA fibrous scaffolds.	……	Because of the size and cost of melt-extrusion equipment, and the large amount of raw material required, it has not been well suited to bench-top, laboratory quantities.
Intra et al (2011)	Melt spinning	Melt extruding a mixture of PLGA pellets and CpG ODN to produce immunostimulatory suture.	……	High temperatures in melt spinning limit protein loading for the controlled delivery of bioactive molecules.

the drug is released gradually by hydrolytic degradation and/ or morphological changes in the polymer [94]. Several drug delivery vehicles composed of PLGA, such as microspheres, microcapsules, nanospheres and nanofibers have been developed for the controlled release of drugs or protein. The biodegradability of PLGA fibers has inspired several studies on controlled drug delivery systems 93-95]. On the basis of a similar concept, Crow et al. [49] produced PLGA biodegradable fiber that encapsulated a water-soluble drug by wet-spinning a water-in-oil emulsion. This technique of fiber extrusion involves using an aqueous emulsion in a modified wet extrusion process. The key point of using an emulsion is that the sensitive biological molecules, such as proteins, growth factors, cytokines, enzymes, and so on, are exposed to an aqueous, biologically friendly environment. In this case, the coagulation fluid used was hexane, and the syringe pump was adjusted to flow at a constant rate of 0.05 mL/min. As the emulsion flowed into the coagulation bath, a fiber began to form. The fiber was removed from the bath and wrapped around a rotating bobbin that wound the fiber at a constant linear rate of 16 m/min. Results show that these fibers are 2.4% by mass drug, which is slowly released, making these fibers potential candidates for implantation as drug delivery devices and/or tissue-engineering substrates. This study demonstrated that drug release rates and molecular weight degradation are a function of the amount of aqueous phase added as an emulsion during fabrication. Mack et al. [56] focused on monofilaments made from three types of amorphous PLGA, with 50:50 (Resomer RG 506), 75:25 (Resomer RG 756), and 100:0 ratios of lactide to glycolide (P_{DL}LA). Using dimethyl sulfoxide (DMSO) as a solvent and water as an anti-solvent, levofloxacin or dexamethasone containing filaments were prepared. *Table III* shows the processing conditions for all of the filaments used for these experiments. *Table IV* lists the diameters of each filament after extrusion and one day of incubation in PBS at 37 °C. Water swells the filaments, with the degree of swelling ranging from 25% to 49% by mass depending on composition. Influx of water with incubation in PBS is accompanied by an increase in filament diameter, particularly for filaments made with Resomer RG 506. Representative SEMs of filaments 506-L1 and -L2 are shown in *Figure 11*.

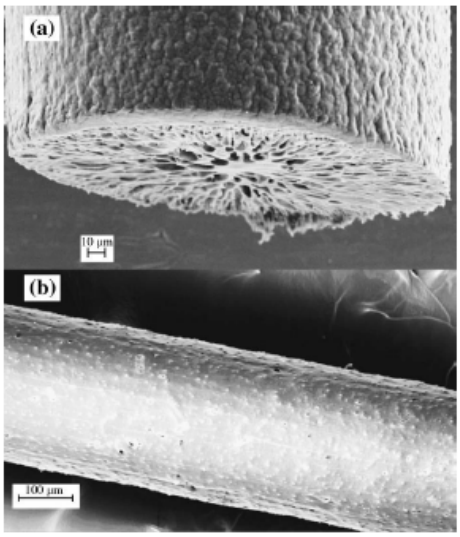

FIGURE 11. SEM images for filaments a) 506-L1 and b) 506-L2. Filament 506-L2 (made from a suspension of levofloxacin) shows large, discrete surface protuberances while 506-L1 has a rough surface.

A cross-section of 506-L1 shows the internal porosity of the polymeric filaments. Other filaments reveal similar cross sectional morphology. The exterior surfaces of the filaments are different. Filament 506-L1 has a rough surface but larger surface protuberances are apparent for 506-L2. To compare the effects of PLGA type to final fiber properties, 506-L1, 756-L1 and P_{DL}LA-L1 filaments were made with formulations that were the same except for polymer type. Filaments prepared from each polymer displayed a triphasic release curve profile, with an initial fast release followed by a plateau of slow release that accelerates as the polymer structure degrades (*Figure 12*). Higher lactide content should lead to slower polymer degradation and drug release.

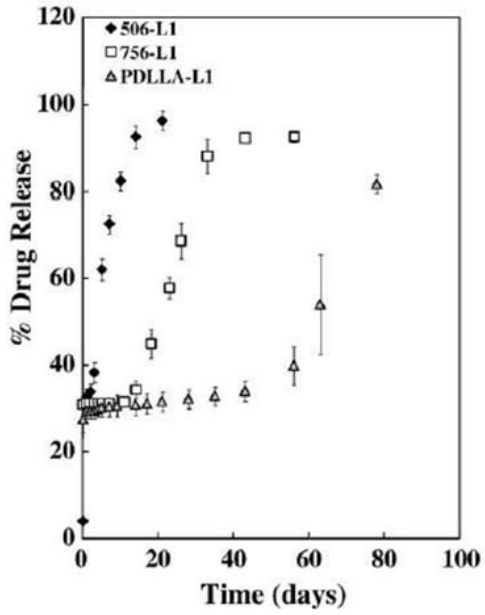

FIGURE 12. The release profile of filaments made from different polymers.

Halliday et al. [96] produced poly-lactide-co-glycolide wet-spun fibers loaded with the novel antiepileptic drug Levetiracetam (LEV), and investigated their morphology, *in vitro* drug release characteristics, and brain biocompatibility in adult rats. LEV-loaded PLGA fibers were made by wet spinning the PLGA-LEV solution through a 1:4 isopropanol: hexane (v/v) coagulation bath. PLGA with two different mole ratios of lactide: glycolide were investigated: PLGA 85:15 and PLGA 75:25. Solvents were acetone and dichloromethane (DCM). The best performing structures released LEV constantly for at least five months *in vitro*, and were found to be highly brain biocompatible following month-long implantations in the motor cortex of adult rats.

TABLE III. Processing conditions for filaments.

Sample	Polymer	Drug type	Solution Composition(%Wt)			Solution temperature(°C)	Coagulation time(s)
			Polymer	DMSO	Drug		
506-L1	RG 506	Levofloxacin	23.3	69.8	7.0	25	45
506-L2	RG 506	Levofloxacin	22.2	66.7	11.1	23	45
506-L3	RG 506	Levofloxacin	23.3	69.8	7.0	60	45
506-L4	RG 506	Levofloxacin	23.8	71.4	4.8	25	45
506-L5	RG 506	Levofloxacin	23.3	69.8	7.0	25	55
506-L6	RG 506	Levofloxacin	23.3	69.8	7.0	25	35
506-D1	RG 506	Dexamethasone	23.3	69.8	7.0	25	45
506-D2	RG 506	Dexamethasone	20.4	61.2	18.4	25	45
756-L1	RG756	Levofloxacin	23.3	69.8	7.0	25	45
756-L2	RG756	Levofloxacin	22.2	66.7	11.1	25	45
PDLLA-L1	PDLLA	Levofloxacin	23.3	69.8	7.0	25	45

TABLE IV. Filament Diameter after extrusion and one day of incubation in PBS at 37ºC.

Sample	Diameter (μm)	
	Initial	1 day
506-L1	255	287
506-L2	259	314
506-L3	266	283
506-L4	250	284
506-L5	261	322
506-L6	252	271
506-D1	270	269
506-D2	285	304
756-L1	288	297
756-L2	294	300
PDLLA-L1	299	311

LEV release profiles from PLGA 85:15 and 75:25 fibers are shown in *Figure 13*. Both formulations of PLGA 85:15 fibers exhibited a burst of LEV release within 24 h. The burst from fibers with a 28.6% LEV loading was 89%, whereas from fibers with 10.4% w/w LEV loading it was 34%. These fibers with 10.4% LEV gradually and continuously released the remaining LEV until 98 days of incubation. PLGA 75:25 fibers with a 16.7% LEV loading also exhibited a substantial initial burst, releasing 69% of their LEV content in the first 24 h of incubation. LEV continued to be released rapidly for 1 week with 80% of their initial LEV load detected in solution.

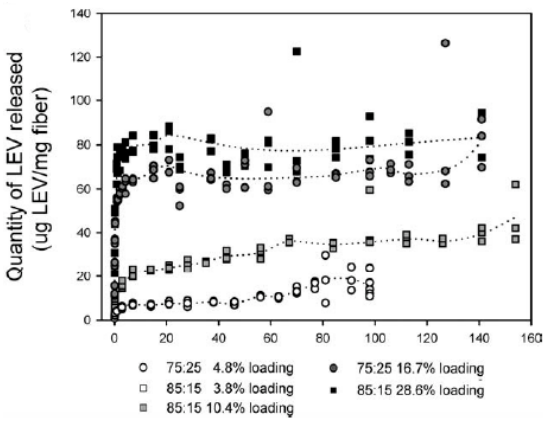

FIGURE 13. Release of Levetiracetam from PLGA fibers in vitro.

PLGA 75:25 fibers with 4.8% w/w LEV released only 28% of their LEV content in the first 24 h of incubation, and then gradually released LEV until a delayed burst occurred at 90 days. This delayed burst correlated with observations that the fiber structure was no longer intact.

Implants

PLGA fibers have proved effective as implants and supports in the human body. Athanasiou et al. [97,98] have used implants fabricated from a (PLGA, 50:50) to deliver growth factors to sites of osteochondral defects in rabbit knees in an attempt to regenerate cartilage and the underlying bone. They have reported satisfactory results. These devices function not only as controlled release systems for the delivery of proteins over a period of time but also as scaffolds for the growth of neo-tissue. An *in vitro* study of this implant has shown that the protein is released in a sigmoid fashion over a period of 10 weeks and the implant is fully degraded by this time.

Tissue Engineering

Tissue engineering is an interdisciplinary and multidisciplinary field that aims at developing biological substitutes to restore, maintain, or improve tissue function. Scaffolding materials for tissue engineering can be any biomimetic biomaterials that mimic one or multiple characteristics of natural extracellular matrix (ECM) [99], supporting cell attachment, proliferation, differentiation, and neo-tissue generation [100]. To fulfill the diverse needs in tissue engineering, various materials have been exploited as scaffolds for tissue regeneration. The initial requirement of the scaffold is to hold cells and tissues together in spite of partial degradation. This reflects the importance of mechanical strength in the initial stages; therefore, biological performance comes into the picture. Polymeric biodegradable scaffolds combine advantages of synthetic and natural materials. The physical properties of synthetic polymers, such as mechanical strength and degradation rate, can be manipulated according to requirements, with fewer batch-to-batch variations than are typical with natural materials [101]. Amongst the different classes of biodegradable polymers, the thermoplastic aliphatic polyesters like PLA, PGA, especially their copolymer, PLGA, have attracted immense interest due to their favorable properties such as good biocompatibility, suitable biodegradability, and mechanical strength [102]. They have been extensively investigated for applications in drug release, gene delivery [103-105] and engineering different types of tissue including cartilage, blood vessel and tendon [106-108]. PLGA may be fabricated into various shapes (e.g. filament, braided, knitted, nonwoven or film) as required of the organ construction. Li et.al [109] has been developed PLGA structure with a unique architecture produced by an electrospinning process for tissue-engineering applications. The electrospun structure, composed of PLGA fibers ranging from 500 to 800 nm in diameter, features a morphologic similarity to the extracellular matrix of natural tissue, which is characterized by a wide range of pore diameter distribution, high porosity, high surface area-to-volume ratio and effective mechanical properties

which are favorable parameters for cell attachment, growth, and proliferation. Such a structure meets the essential design criteria of an ideal engineered scaffold. Another attempt [110] was made to explore the potential of using PLGA (10: 90) biodegradable polymer as scaffolds for nerve tissue engineering, acting as carriers for cells. Scaffolds were made using PLGA microfiber and PLGA nanofiber prepared by the electrospining process. Attempt was also made to develop microbraided and aligned microfiber scaffolds. *In vitro* studies were carried out using C-17.2 nerve stem. The cells attached and differentiated on the four types of scaffolds studied. All the scaffolds maintained their structural integrity. The cells were attached more on the surface in the case of PLGA nanofiber scaffold. The cells were distributed randomly on the surface. The differentiated neurite took a random orientation on the scaffold. In the microbraided and aligned microfiber scaffolds, the cells were found to be aligned along the direction of the fiber. The neurites attached and grew along the direction of the fiber. Thus, on the aligned microfiber scaffolds aligned orientation of the cells was achieved. Comprehensive data on PLGA fiber applications are presented in *Table V*.

CONCLUSION

Featured with excellent characteristics, such as biodegradability, biocompatibility, mild undesirable host reactions, three-dimensional and directional porous structures, PLGA fibers, whose diameters range from nanometers to millimeters, is broadly studied and used as different biomaterials. Therefore investigation of production of PLGA fiber by various methods is very important. However, because of its innate hydrophobicity and its high price, applications of this copolymer in biomedical domain have some limitations [111]. This article presents a review on the production of PLGA fiber by various methods including melt spinning, solution spinning, and electrospinning along with correlations between structure and properties of the fibers. The applications of these fibers in biomedical domains are also discussed.

TABLE V. Comprehensive data on PLGA fiber applications.

Year	Workers	Type of application	Process highlight
2004	Blaker et al	Suture	A novel silver-doped bioactive glass powder was used to coat resorbable Vicryls (polyglactin 910) and non-resorbable Mersilks surgical sutures, thereby imparting bioactive, antimicrobial and bactericidal properties to the sutures.
2004	Bretcanu et al	Suture	Composites based on violet resolbabale Vicryl suture coated with bioactive glass were prepared.
2006	Zurita et al	Suture	The preparation of mono- and multifilament sutures incorporating ibuprofen as an anti-inflammatory agent was considered.
2006	Edmiston et al	Suture	A standardized *in vitro* microbiologic model was used to assess bacterial adherence and the antibacterial activity of a triclosan-coated polyglactin 910 (braided) suture against selected Gram-positive and Gram-negative bacteria.
2007	Togo et al	Suture	The usefulness of synthetic absorbable sutures (Vicryl) in preventing surgical site infection (SSI) after hepatectomy was evaluated.
2009	Mingmalairak et al	Suture	The efficacy and safety of new antibacterial suture (Vicryl Plus) compared with a traditional braided suture (Vicryl).
2010	Weinstein et al	Suture	Ketoprofen was implanted into PLGA suture using liquid and supercritical carbon dioxide. The effect of temperature, pressure (and hence density), and exposure time were explored on the ability of the sutures to absorb ketoprofen.
2011	Intra et al	Suture	Melt extruding a mixture of PLGA pellets and CpG ODN to produce immunostimulatory suture.
2002	Li et al	Tissue-engineering	A novel PLGA structure for tissue-engineering applications developed.
2003	Nelson et al	Tissue-engineering	The effect of solvent systems, polymer blends, and winding rates on properties of fibers reported.
2004	Bini et al	Tissue-engineering	Nanofibrous nerve guide conduit fabricated. The feasibility of *in vivo* nerve regeneration was investigated.
2005	You et al	Tissue-engineering	The effect of conductivity of the PLGA solution on morphology and diameter of fiber reported.
2005	You et al	Tissue-engineering	Structural and morphological changes during *in vitro* degradation of PLA, PGA and PLGA reported.
2006	Wen et al	Tissue-engineering	Degradable hollow fiber membranes were described that have been fabricated from PLGA copolymers for nerve guidance channel applications using phase-inversion techniques.
2007	Ellis et al	Tissue-engineering	The effect of wet spinning variables on hollow fiber properties and PLA: PGA ratio on cell attachment and proliferation reported.

2007	Morgan et al	Tissue-engineering	This study provides evidence that porous P_{DL}LGA hollow fiber–HBMSC graft is an innovative biomaterial that offers new approaches to mesenchymal cell expansion, which could be utilized as a scaffold for skeletal tissue generation.
2008	Zhao et al	Tissue-engineering	This study demonstrated that the fiber morphology and diameter of the electrospun PLGA scaffolds could be tailored by controlling fabrication parameters.
2008	Hwang et al	Tissue-engineering	Emerging application of a microfluidic chip in the fabrication of fiber-based scaffolds for directional cell growth was demonstrated.
2009	Meneghello et al	Tissue-engineering	Improvement of fiber properties by introduction of PVA to PLGA.
2010	Xie et al	Tissue-engineering	A methodology developed to quickly neutralize the acidic degradation products of PLGA fibrous scaffolds.
2010	Dong et al	Tissue engineering	This is the first study to evaluate long-term PGA, PLGA, and P(LLA-CL) nanofiber degradation *in vitro* with cell culture.
2005	Crow et al	Drug delivery	PLLA and PLGA fibers prepared by wet spinning process and used for drug delivery system.
2009	Mack et al	Drug delivery	Biodegradable filaments for the controlled delivery of examethasone or levofloxacin were described.
2012	Halliday et al	Drug delivery	Wet-spun fibers loaded with the novel antiepileptic drug Levetiracetam were produced, and their morphology, *in vitro* drug release characteristics, and brain biocompatibility in adult rats were investigated.
2005	Crow et al	Drug delivery	Biodegradable fibers of PLA and PLGA that encapsulated a water-soluble drug were created by wet-spinning a water-in-oil emulsion.
2010	Puppi et al	Drug delivery	PLGA meshes loaded with retinoic acid (RA) were prepared by electrospinning to combine the biological effects of RA and the advantages of electrospun meshes to enhancing the mass transfer features of controlled release systems and cell interaction with polymeric scaffolds.
2011	Meng et al	Drug delivery	Drug (Fenbufen, FBF)-loaded (PLGA) and PLGA/gelatin nanofibrous scaffolds were fabricated via electrospinning technique.
2003	Zong et al	Surgical implants	The structural and morphological changes of electrospun (PLGA, 10/90) membranes during *in vitro* degradation were studied as a function of time.

REFERENCES

[1] Chandra R, Rustgi R "Biodegradable polymers". *Prog Polym Sci*, Vol 23, 1998, pp. 1273–1335.

[2] Schmack G, Tandler B, Vogel R, Beyreuther R, Jacobsen S and Fritz H.G "Biodegradable fibers of poly(L-lactide) produced by high-speed melt spinning and spin drawing". *Journal of Applied Polymer Science*, Vol 73, 1999, pp. 2785-2797.

[3] Nair L S and Laurencin C T "Biodegradable polymers as biomaterials". *Prog Polym Sci*, Vol 32, 2007, pp. 762-798.

[4] Barbucci R "Integrated biomaterial science" 2002, Kluwer Academic/Plenum, new york .

[5] Gupta B Revagade N and Hilborn J "Poly(lactic acid) fiber: An overview". *Prog Polym Sci*, Vol 32, 2007, pp. 455-482.

[6] Lanza R, langer R and Vacanti J "Principles of Tissue Engineering",1997, elsevier, P 1291.

[7] Pillai CKS and Sharma C P "Review Paper: Absorbable Polymeric Surgical Sutures: Chemistry, Production, Properties, Biodegradability, and Performance". *Journal of Biomaterials Applications*, Vol 25, 2010, pp . 291-366.

[8] Pitt G G, Gratzl M M, Kimmel G L, Surles J and Sohindler A "Aliphatic polyesters II. The degradation of poly(DL-lactide),poly(e-caprolactone) and their copolymers *in vivo*". *Biomaterials*, Vol 2, 1981, pp. 215-220.

[9] Tsuji H and Ikada Y " Properties and morphology of poly (L-lactide) 4. Effect of structural parameters on long term hydrolysis of poly(L-lactide)in phosphate-buffered solution". *Polym Deg Stab*, Vol 67, 2000, pp. 179–189.

[10] Merkli A, Tabatay C, Gurny R, Heller J "biodegradable polymers for the controlled release of ocular drugs". *Prog Polym Sci*, Vol 23, 1998, pp. 563-580.

[11] Lunt J "Large scale production, properties and commercial applications of polylactic acid polymers". *Polym Deg Stab,* Vol 59, 1998, pp. 145–52.

[12] Lunt J, Shafer A L "Polylactic acid polymers from corn: applications in the textiles industry". *J Ind Text*, Vol 29, 2000, pp. 191–205.

[13] Astete C E and Sabliov C M "Synthesis and characterization of PLGA nanoparticles". *Journal of Biomaterials Science – Polymer*, Vol 3, 2006, pp. 247–289.

[14] Schwach G, Coudane J, Engel R, Vert M "More about the polymerization of lactides in the presence of stannous octoate". *J Polym Sci Part A*, Vol 35, 1997, pp. 3431-3440.

[15] Kreiser-Saunders I and Kricheldorf H R "Polylactones, 39: Zn lactate-catalyzed copolymerization of L-lactide with glycolide or ε-caprolactone ". *Macromolecular Chemistry and Physics* Vol 199, 1998, pp. 1081-1087.

[16] Dobrzynski P, Kasperczyk J, Bero M, "Application of calcium acetylacetonate to the polymerization of glycolide and copolymerization of glycolide with ε-caprolactone and L-lactide". *Macromolecules*, Vol 32, pp. 4735-4737.

[17] Bero M, Dobrzynski P, Kasperezyk J "Application of zirconium (IV) acetylacetonate to the copolymerization of glycolide with ε-caprolactone and lactide". *J Polym Bull*, Vol 42, 1999, pp. 131-139.

[18] Dobrzynski P, Kasperczy J, Janeczek H, Bero M "Synthesis of Biodegradable Copolymers with the Use of Low ToxicZirconium Compounds. 1. Copolymerization of Glycolide with L-Lactide Initiated by Zr(Acac)4". *Macromolecules,* Vol 34, 2001 pp. 5090-8.

[19] Mehta R C, Thanoo B C, Deluca P P "Peptide containing microspheres from low molecular weight and hydrophilic poly(d,l-lactide-co-glycolide)". *Journal of Controlled Release*, Vol 41, 1996, pp. 249-257.

[20] De Jong S J, Arias E R, Rijkersb D T S, van Nostruma C F, Kettenes-van den Boschc J J, Henninka W E, "New insights into the hydrolytic degradation of poly(lactic acid): Participation of the alcohol terminus". *Polymer*, Vol 42, 2001, pp.2795-2802.

[21] Siepmann J, Elkharraz K, Siepmann F, Klose D "How Autocatalysis Accelerates Drug Release from PLGA-Based Microparticles: A Quantitative Treatment". *Biomacromolecules* Vol. 6, 2005, pp. 2312-2319.

[22] Badri Viswanathan N, Patil S S, Pandil J K, Lele A K, Kulkarni M G, Mashelkar R A "Morphological changes in degrading PLGA and P(DL)LA microspheres: implications for the design of controlled release systems". *Journal of Microencapsulation*, Vol 18, 2001, pp. 783-800.

[23] Shameem M, Lee H and DeLuca P P "A short-term (accelerated release) approach to evaluate peptide release from plga depot formulations". *AAPS Journal*, Vo1, 1999, pp. 6-8.

[24] Achim G "Mechanisms of polymer degradation and erosion". *Biomaterials*, Vol. 17, 1996 pp. 103-114.

[25] Ravivarapu H B, Burton K, DeLuca P P "Polymer and microsphere blending to alter the release of a peptide from PLGA microspheres". *European Journal of Pharmaceutics and Biopharmaceutics*, Vol. 50, 2000, pp. 263-270.

[26] Miller R A, Brady J M and Cutright D E "Degradation rates of oral resorbable implants (polylactates and polyglycolates): Rate modification with changes in PLA/PGA copolymer ratios". *Journal of Biomedical Materials Research* Vol 11, 1977, pp. 711-719.

[27] Fambri L, Pegoretti A, Fenner R, Incardona S D, Migliaresi C "Biodegradable fibres of poly(L-lactic acid) produced by melt spinning". *Polymer*, Vol 38, 1977, pp. 79-85.

[28] Cicero J A and Dorgan J R "Physical Properties and Fiber Morphology of Poly(lactic acid) Obtained from Continuous Two-Step Melt Spinning". *Journal of Polymers and the Environment*, Vol. 9, 2001, pp. 1-10.

[29] Yuan X, Mak A, Kwok K W, Yung B, Yao K "Characterization of poly(L-lactic acid) fibers produced by melt spinning". *Journal of Applied Polymer Science*, Vol 81, 2001, pp. 251-260.

[30] Cicero J, Dorgan J, Garrett J, Runt J, Lin S "Effects of molecular architecture on two-step, melt-spun poly(lactic acid) fibers". *Journal of Applied Polymer Science*, Vol 86, 2002, pp. 2839-2846.

[31] Cicero J, Dorgan J, Janez J, Garrett J, Runt J, Lin S "Supramolecular morphology of two-step, melt-spun poly(lactic acid) fibers". *Journal of Applied Polymer Science,* Vol 86, 2002, pp. 2828-2838.

[32] Schmack G, Tändler B, Optiz1 G, Vogel R, Komber H, Häußler L, Voigt D S, Weinmann S, Heinemann M, Fritz H G "High-Speed Melt Spinning of Various Grades of Polylactides". *Journal of Applied Polymer Science*. Vol. 91, 2004, pp. 800-806.

[33] Xie S, Zhu Q, Wang B, Gu H, Liu W, Cui L, Cen L, Cao Y "Incorporation of tripolyphosphate nanoparticles into fibrous poly-(lactide-co-glycolide) scaffolds for tissue engineering". *Biomaterials,* Vol 31, 2010, pp. 5100-5109.

[34] Wang L, Shi J, Liu L, Secret E, Chen Y "Fabrication of polymer fiber scaffolds by centrifugal spinning for cell culture studies". *Microelectronic Engineering,* Vol 88, 2011, pp. 1718-1721.

[35] Intra J, Zhang X Q, Williams R L, Zhu X, Sandler A D, Salem A K "Immunostimulatory sutures that treat local disease recurrence following primary tumor resection". *Biomedical Materials*, Vol 6, 2011, pp. 1-5.

[36] Postema A R, Luiten A H, Oostra H, Pennings A J "High-strength poly(L-lactide) fibers by a dry-spinning/hot-drawing process. II. Influence of the extrusion speed and winding speed on the dry-spinning process". *Journal of Applied Polymer Science*, Vol 39, 1990, pp. 1275-1288.

[37] Penning J P, Dijkstra H, Pennings A J "Preparation and properties of absorbable fibres from l-lactide copolymers". *Polymer,* Vol 3, 1993, pp. 942-951.

[38] Leenslag J W and Pennings, A J "High-strength poly(l-lactide) fibres by a dry-spinning/hot-drawing process". *Polymer,* Vol.28, 1987, pp. 1695-1702.

[39] Okuzaki H, Kubota I, Kunugi T "Mechanical properties and structure of the zone-drawn poly(L-lactic acid) fibers". *Journal of Polymer Science Part B: Polymer Physics*, Vol. 37, 1999, pp.991-996.

[40] Postema A R and Pennings A J "Study on the drawing behavior of poly(L-lactide) to obtain high-strength fibers". *Journal of Applied Polymer Science*, Vol 37, 1989, pp. 2351-2369.

[41] Fu B X, Hsiao B S, Chen G, Zhou J, Koyfman I, Jamiolkowski D D, Dormier E "Structure and property studies of bioabsorbable poly(glycolide-co-lactide) fiber during processing and *in vitro* degradation". *Polymer,* Vol 43, 2002, pp. 5527-5534.

[42] Wang Y, Steinhoff B, Brinkmann C, Alig I "In-line monitoring of the thermal degradation of poly(l-lactic acid) during melt extrusion by UV-vis spectroscopy". *Polymer,* Vol 49, 2008, pp. 1257-1265.

[43] Fourne F "Synthetic Fibers – Machines and Equipment, Manufacture, Properties".1999 hanser/gardner, Ohio P. 930.

[44] GuptaV B, Kothari V "Manufactured fiber technology" 1997, Chapman and Hall london.

[45] Arbab S, Noorpanah P, Mohammadi N, Soleimani M "Designing index of void structure and tensile properties in wet-spun polyacrylonitrile (PAN) fiber. I. Effect of dope polymer or nonsolvent concentration". *Journal of Applied Polymer Science*, Vol.109, 2008, pp. 3461-3469.

[46] Arbab S, Mohammadi N, Noorpanah P "The synergistic effect of dope concentration and jet-drawing on structure development of wet-spun poly(acrylonitrile)" *epolymer*, Vol 80, 2008.

[47] Arbab S, Noorpanah P, Mohammadi N, Zeinolebadi A "Simultaneous effects of polymer concentration, jet-stretching, and hot-drawing on microstructural development of wet-spun poly(acrylonitrile) fibers". *Polymer Bulletin*, Vol 66, 2011 pp.1267-1280.

[48] Nelson K D, Romero A, Waggoner P, Crow B, Borneman A, Smith G M "Technique Paper for Wet-Spinning Poly(L-lactic acid) and Poly(DL-lactide-co-glycolide) Monofilament Fibers". *Tissue Engineering*, Vol 9, 2003, pp. 1323-1330.

[49] Crow B B, Borneman A F, Hawkins D L, Smith G M, Nelson K D "Evaluation of *in vitro* drug release, pH change, and molecular weight degradation of poly(L-lactic acid) and poly(D,L-lactide-co-glycolide) fibers". *Tissue Engineering*, Vol 11, 2005, pp. 1077-1084.

[50] Wen X, Tresco P A "Fabrication and characterization of permeable degradable poly(dl-lactide-co-glycolide) (PLGA) hollow fiber phase inversion membranes for use as nerve tract guidance channels". *Biomaterials*, Vol 27, 2006, pp. 3800-3809.

[51] Ellis M J, Chaudhuri J B "Poly(lactic-co-glycolic acid) hollow fibre membranes for use as a tissue engineering scaffold". *Biotechnology and Bioengineering*, Vol 96, 2007, pp.177-187.

[52] Hwang C M, Khademhosseini A, Park Y, Sun K, Lee S H "Microfluidic chip-based fabrication of PLGA microfiber scaffolds for tissue engineering". *Langmuir,* Vol 24, 2008, pp.6845-6851.

[53] Shim I K., Lee, S Y, Park Y J, Lee M C, Lee S H, Lee J Y and Lee S J "Homogeneous Chitosan-Plga Composite Fibrous Scaffolds for Tissue Regeneration." *Journal of Biomedical Materials Research Part A*, Vol 84A(1), 2008, pp. 247-255.

[54] Meneghello G, Parkerb D J, Ainsworthb B J, Pererab S P, Chaudhurib J B, Ellisb M J, De Bank P A "Fabrication and characterization of poly(lactic-co-glycolic acid)/polyvinyl alcohol blended hollow fibre membranes for tissue engineering applications". *Journal of Membrane Science*, Vol 344, 2009, pp. 55-61.

[55] Morgan S M, Tilley S, Perera S, Ellis M J, Kanczler J, Chaudhuri J B, Oreffo R O C "Expansion of human bone marrow stromal cells on poly-(dl-lactide-co-glycolide) (P_{DL}LGA) hollow fibres designed for use in skeletal tissue engineering". *Biomaterials*, Vol 28, 2007, pp. 5332-5343.

[56] Mack, B.C., K.W. Wright, and M.E. Davis, "A biodegradable filament for controlled drug delivery". *Journal of Controlled Release*, Vol 139, 2009, pp. 205-211.

[57] Bini T B, Gao S, Tan T C, Wang S, Lim A, Hai L B, krishna S R "Electrospun poly(L-lactide-co-glycolide) biodegradable polymer nanofibre tubes for peripheral nerve regeneration". *Nanotechnology*, Vol. 15, 2004, pp. 1459-1464.

[58] You Y, Lee S J, Min B M, Park W H "Effect of solution properties on nanofibrous structure of electrospun poly(lactic-co-glycolic acid)". *Journal of Applied Polymer Science,* Vol 99, 2006, pp. 1214-1221.

[59] Zhao L, He C, Gao Y, Cen L, Cui L, Cao Y "Preparation and cytocompatibility of PLGA scaffolds with controllable fiber morphology and diameter using electrospinning method". *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, Vol. 87B, 2008, pp. 26-34.

[60] Kim K, Yu M, Zong X, Chiu J, Fang D, Seo Y S, Hsiao B, Chu B "Control of degradation rate and hydrophilicity in electrospun non-woven poly(d,l-lactide) nanofiber scaffolds for biomedical applications". *Biomaterials*, Vol 24, 2003, pp. 4977-4985.

[61] You Y, Min B M, Lee S J, Lee T S, Park W H "*In vitro* degradation behavior of electrospun polyglycolide, polylactide, and poly(lactide-co-glycolide)". *Journal of Applied Polymer Science*, Vol 95, 2005, pp. 193-200.

[62] Zong X, Ran S, Kim K S, Fang D, Hsiao B S, Chu B "Structure and morphology changes during *in vitro* degradation of electrospun poly (glycolide-co-lactide) nanofiber membrane" *Biomacromolecules*, Vol 4, 2003, pp. 416-23.

[63] Dong Y, Yong T, Liao S, Chan C K, Stevens M M, Ramakrishna, S "Distinctive degradation behaviors of electrospun polyglycolide, poly(DL-lactide-co-glycolide), and poly(L-lactide-co-epsilon-caprolactone) nanofibers cultured with/without porcine smooth muscle cells". *Tissue Eng Part A* Vol. 16, 2010, pp. 283-298.

[64] Kim K, Luu Y K, Chang C, Fang D, Hsiao B S, Chu B,Hadjiargyrou M "Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co-glycolide)-based electrospun nanofibrous scaffolds". *Journal of Controlled Release,* Vol.98, 2004, pp. 47-56.

[65] Luu Y K, Kim K, Hsiao B S, Chu B, Hadjiargyrou. M. "Development of a nanostructured DNA delivery scaffold via electrospinning of PLGA and PLA–PEG block copolymers' *Journal of Controlled Release*. 2003, Vol. 89, pp. 341–353.

[66] Huang H H, He C L, Wang H S, Mo X. M. "Preparation of coreshell biodegradable microfibers for long-term drug delivery" *Journal of biomedical materials research Part A*. Vol. 90 (4), 2009, pp. 1243-1251.

[67] Hong Y, Fujimoto K, Hashizume R Guan J, Stankus J J,Tobita K, and Wagner W R. "Generating Elastic, Biodegradable Polyurethane/Poly(lactide-co-glycolide) Fibrous Sheets with Controlled Antibiotic Release via Two-Stream Electrospinning", *Biomacromolecules,* Vol. 9, 2008, pp. 1200–1207.

[68] You R Q, Zhang H B," Preparation of Protein Loaded Core-Shell PEO/PLGA Ultrafine Fibers by Coaxial Electrospinning", Bioinformatics and Biomedical Engineering, (iCBBE) 2011 5th International Conference, 2011.

[69] Tiwari S K, Tzezana R, Zussman E, Venkatraman S S." Optimizing partition-controlled drug release from electrospun core–shell fibers", *International Journal of Pharmaceutics*, Vol. 392, 2010, pp.209-217.

[70] Schakenraad J M, Hardonk M J, Feijen J, Molenaar I, Nieuwenhuis P J "Enzymatic activity toward poly(L-lactic acid) implants". *J. Biomed. Mater. Res*, Vol. 24, 1990, pp. 529-545.

[71] Moran J M, Pazzano D, Bonassar L J " Characterization of Polylactic Acid–Polyglycolic Acid Composites for Cartilage Tissue Engineering " *Tissue Engineering*, Vol 9, 2003, pp. 63-70.

[72] Mikos A G, Temenoff J S "Formation of highly porous biodegradable scaffolds for tissue engineering". *EJB Electronic Journal of Biotechnology*, Vol 3, 2000, pp.1-6.

[73] Benicewicz B C, Hooper P "Review : Polymers for Absorbable Surgical Sutures—Part I". *Journal of Bioactive and Compatible Polymers*, Vol 5, 1990, pp. 453-472.

[74] Horton C E, Adamson J E, Mladick R A, Carraway J H "Vicryl synthetic absorbable sutures". *Am Surg*, Vol 40, 1974, pp. 729-731.

[75] Postlethwait RW "Polyglycolic acid surgical suture". *Arch Surg*, Vol. 101, 1970, pp. 489-494.

[76] Frazza E J and Schmitt E E "A new absorbable suture". *J Biomed Mater Res Symp*, Vol 5, 1971, pp. 43-58.

[77] Racey G L, Wallace W R, Cavalaris C J, Marguard J V" Comparison of a polyglycolic-polylactic acid suture to black silk and plain catgut in human oral tissues". *J Oral Surg*, Vol 36, 1978, pp.766-770.

[78] Cutright D E, Beasley J D, Perez B "Histologic comparison of polylactic and polyglycolic acid sutures". *J Oral Surg*, Vol 32, 1971, pp. 165-173.

[79] Craig P H, Williams J A, Davis K W, Magoun A D, Levy A J, Bogdansky S, Jones J P "A biologic comparison of polyglactin 910 and polyglycolic acid synthetic absorbable sutures". *Surgery Gynecology and Obstetrics,* Vol 141, 1975, pp. 1-10.

[80] Blomstedt B, Jacobsson S I ″Acta Chirurgica Scandinavica" 1977 pp. 259.

[81] Zhang L, Chu C C, Loh I H "Effect of a combined gamma irradiation and Parylene plasma treatment on the hydrolytic degradation of synthetic biodegradable sutures". *J Biomed Mater Res,* Vol 27, 1993, pp. 1425-1441.

[82] Tandon S C, Kelly J, Turtle M, Irwin S T "Irradiated polyglactin 910: a new synthetic absorbable suture". J R Coll Surg Edinb, Vol 40 1995, pp. 185-187.

[83] Bretcanu O, Verné E, Borello L, Boccaccini A R " bioactivity of degradable polymer suture coated with bioactive glass". journal of materials science: materials in medicine Vol 15, 2004, pp. 893-899.

[84] Neligan P C " Bioactive Sutures", *Plast Reconstr Surg*, Vol 118, 2006, pp. 1645-47.

[85] Storch M L, Rothenburger S J and Jacinto G." Experimental efficacy study of Coated Vicryl Plus Antibacterial Suture in guinea pigs challenged with Staphylococcus aureus".*Surg. Infect. (Larchmt.),* Vol. 5, 2004, pp. 281-288.

[86] Go´mez-Alonso A, Garcı´a-Criado F J, Parren˜o-anchado F C, Garcı´a-Sa´nchez J E, Garcı´a-Sa´nchez E, Parren˜o-Manchado A, Zambrano-Cuadrado Y." Study of the efficacy of Coated VICRYL Plus_Antibacterial suture (coated Polyglactin 910 suture with Triclosan) in two animal models of general surgery", *Journal of Infection*,Vol. 54, 2007, pp. 82-88.

[87] Neligan P C and P S E F T A Committee "Bioactive Sutures". *Plastic and Reconstructive Surgery*, Vol 118, 2006, pp. 1645-1647

[88] Shibuya T Y, Kim S, Nguyen K, Parikh P, Wadhwa A, Brockardt C, Do J "Covalent linking of proteins and cytokines to suture: Enhancing the immune response of head and neck cancer patients". *The Laryngoscope*, Vol 113, 2003, pp. 1870-1884.

[89] Shibuya T Y, Wei W Z, Zormeier M, Ensley J, Sakr W, Mathog R H, Meleca R J, Yoo G, June C H, Levine B, Lum L G "Anti-CD3/Anti-CD28 Monoclonal Antibody–Coated Suture Enhances the Immune Response of Patients With Head and Neck Squamous Cell Carcinoma" . *ARCH OTOLARYNGOL HEAD NECK SURG,* Vol 125, 1999, pp. 1229-1234.

[90] Shibuya T Y, Kim S, Nguyen K, Do J, McLaren C E, Li K T, Chen W P, Parikh P, Wadhwa A, Zi X, Chen V Y, Wong H S, Armstrong W B, Clinical G H "Bioactive Suture: A Novel Immunotherapy for Head and Neck Cancer". *Clinical Cancer Research*, Vol 10, 2004, pp. 7088–7099.

[91] Miyajima M, Koshika A, Okada J, Kusai A, Ikeda M "The effects of drug physico-chemical properties on release from copoly (lactic/glycolic acid matrix". *International Journal of Pharmaceutics*, Vol 169, 1998, pp. 255-263.

[92] Siepmann J, Göpferich A "Mathematical modeling of bioerodible, polymeric drug delivery systems". *Advanced Drug Delivery Reviews,* Vol 48, 2001, pp. 229-247.

[93] Langer R, Peppas N "Chemical and physical structure of polymers as carriers for controlled release of bioactive agents: a review". *Journal of Macromolecular Science, Part C: Polymer Reviews,* Vol 23, 1983, pp. 61-126.

[94] Meng Z X, Xu X X, Zheng W, Zhou H M, Li L, Zheng Y F, Lou X "Preparation and characterization of electrospun PLGA/gelatin nanofibers as a potential drug delivery system" . *Colloids and Surfaces B: Biointerfaces*, Vol 84, 2011, pp. 97-102.

[95] Puppi D, Piras A M, Detta N, Dinucci D, Chiellini F "Poly (lactic-co-glycolic acid) electrospun fibrous meshes for the controlled release of retinoic acid". *Acta Biomaterialia*, Vol 6, 2010, 1258–1268.

[96] Halliday A J, et al. "*In vivo* biocompatibility and *in vitro* characterization of poly-lactide-co-glycolide structures containing levetiracetam, for the treatment of epilepsy". *Journal of Biomedical Materials Research Part A,* Vol 100A(2), 2012, pp. 424-431.

[97] Athanasiou K A, Schmitz J P, Schenck R C, Clem M, Aufdemorte T, Bovan B D "Biodegradable carriers of TGF-/I in rabbit osteochondral defects". *Trans Orthop Res Sot*. Vol 18, 1992, pp. 288.

[98] Athanasiou K A, Schenck R C, Constantinides G, Sylvia V, Aufdemorte T, Boyan B D "The use of biodegradable implants for repairing large articular cartilage defects in the rabbit". *Tram Orthop Res Sac*, Vol 17, 1992, pp. 72.

[99] Ma P X "Biomimetic materials for tissue engineering". *Adv Drug Deliv Rev*, Vol 60, 2008, pp. 184-198.

[100] Liu X, Ma P X "Polymeric scaffolds for bone tissue engineering". *Ann Biomed Eng*, Vol. 32, 2004, pp. 477-86.

[101] Davis M W, Vacanti J P "Toward development of an implantable tissue engineered liver". *Biomaterials.*Vol 17, 1996, pp. 365-372.

[102] Jain R A "The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices" . *Biomaterials,* Vol 21, 2000, pp. 2475-2490.

[103] Jeon O, Kang S W, Lim H W, Hyung Chung J, Kim B S "Long-term and zero-order release of basic fibroblast growth factor from heparin-conjugated poly(L-lactide- co-glycolide) nanospheres and fibrin gel". *Biomaterials*, Vol 27, 2006, pp. 1598-607.

[104] Kang S W, Lim H, Seo S W, Jeon O, Lee M, Kim B S "Nanosphere-mediated delivery of vascular endothelial growth factor gene for therapeutic angiogenesis in mouse ischemic limbs. *Biomaterials*, Vol 29, 2008, pp. 1109-1117.

[105] Gwak S J, Kim B S "Poly (lactic-co-glycolic acid) nanosphere as a vehicle for gene delivery to human cord blood-derived mesenchymal stem cells: comparison with polyethylenimine". *Biotechnol Lett*, Vol 30, 2008 pp. 1177-1182.

[106] Xu Z C, Zhang W J, Li H, Cui L, Cen L, Zhou G D, Liu W, Cao Y "Engineering of an elastic large muscular vessel wall with pulsatile stimulation in bioreactor". *Biomaterials*, Vol 29, 2008, pp.1464-1472.

[107] Liu W, Chen B, Deng D, Xu F, Cui L, Cao Y "Repair of tendon defect with dermal fibroblast engineered tendon in a porcine model". *Tissue Eng Part A*, Vol 12, 2006, pp. 775-88.

[108] Cao D, Liu W, Wei X, Xu F, Cui L, Cao Y "*In vitro* tendon engineering with avian tenocytes and polyglycolic acids: a preliminary report". *Tissue Eng Part A*, Vol 12, 2006, pp. 1369-1377.

[109] Li W J, Laurencin C T, Caterson E J, Tuan R S, Ko F K "Electrospun nanofibrous structure: A novel scaffold for tissue engineering". *J Biomed Mater Res*, Vol 15, 2001, pp. 613-621.

[110] Bini T B, Gao S, Wang S, Ramakrishna S "Poly(l-lactide-co-glycolide) biodegradable microfibers and electrospun nanofibers for nerve tissue engineering: an *in vitro* study". *J Mater Sci,* Vol. 41, 2006, pp 6453–6459.

[111] Athanasiou K A, Neiderauer G, Agrawal C M "Sterilization, toxicity, biocompatibility and clinical applications of polylacticacid/polyglycolic acid copolymers". *Biomaterials* Vol 17, 1996, pp. 93-102.

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