Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(12):51-63

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Recent applications of polylactic acid in pharmaceutical and medical industries

Ramzi A. Abd Alsaheb[1], Azzam Aladdin[1], Nor Zalina Othman[1], Roslinda Abd Malek[1], Ong Mei Leng[2], Ramlan Aziz[1] and Hesham A. El Enshasy[1,3*]

[1]Institute of Bioproduct Development (IBD), Universiti Teknologi Malaysia (UTM), Skudai, Johor, Malaysia
[2]Harita Go Green Snd. Bhd., 75450 Ayer Keroh, Melaka, Malaysia
[3]City for Scientific Research and Technology Applications, New Burg Al Arab, Alexandria, Egypt

---

ABSTRACT

Polylactic acid (PLA) is a biodegradable polymer with special properties that has been studied intensively during the last decades. PLA is one of the most promising biopolymers used in nowadays and have large number of applications in food, packaging, medical and pharmaceutical industries. In addition, with the extensive use of exogenous implementation of different materials in human body for repair of different types of soft and hard tissues in many surgeries, there was enormous need to apply natural, biodegradable, non-inflammatory and biocompatible materials. PLA and its co-polymer composites showed superior characters over other materials in tissue engineering applications. This review is focused on providing comprehensive information about the most recent and promising applications of PLA in the pharmaceutical and medical fields, such as in tissue engineering, pharmaceutical, injury management and drugs delivery system.

Keywords: Polylactic acid, PLA, biopolymer, drug delivery, tissue engineering, Nanotechnology.

INTRODUCTION

For many years, lactic acid have been produced by different kinds of microorganisms and widely applied in food and chemical industries [1,2] More recently, many new applications have been reported for this acid in both medical and pharmaceutical field and become one of the main ingredient in wellness industries in general [3,4].However, lastly the lactic acid polymer (polylactic acid or PLA) received high attention as potential candidate for many pharmaceutical and medical applications. This due to its mechanical and biological unique properties such as: biocompatibility, biodegradability, and thermoplastic process ability. Convenience of biopolymers is dictated by its capability to tune the material properties to fulfill engineering limitations [5]. PLA is aliphatic polyester, having extraordinary preferences over several polymers, and may be a piece of the arrangement. Since 1970's, PLA have been approved by the US food and drug administration (FDA) for food and pharmaceutical applications. The prime benefits of PLA are renewability, biocompatibility, process capability and energy saving [6].In addition, the non-toxic and non-carcinogenic effects on the human body make Polylactic acid and its degradation products like H_2O and CO_2aacceptable candidate for biomedical application such as in sutures, clips and drug delivery systems (DDS). Due to the larger thermal processing ability compared to other biomaterials like polyethylene glycol, polyhydroxylalkanoates (PHA), and poly α-caprolactone; the processing of PLA can be achieved by film casting, extrusion, blow molding and fiber spinning [7]. The extension, of utilizing gadgets as a part of human body with

contamination least and aggravation to allow common medicament has constrained specialists to hunt down biodegradable and biocompatible choices. Among the biopolymers used in medical and pharmaceuticals industries these days, PLA is considered as one of the best materials. PLA has gained the attention in many applications due to its organics source[8,9].The properties and prospects in various recent synthesis techniques as well as the applications of PLA in biomedical, clinical, injury management and drug delivery system will be highlighted in this review. Figure 1 show the cycle of PLA in nature.

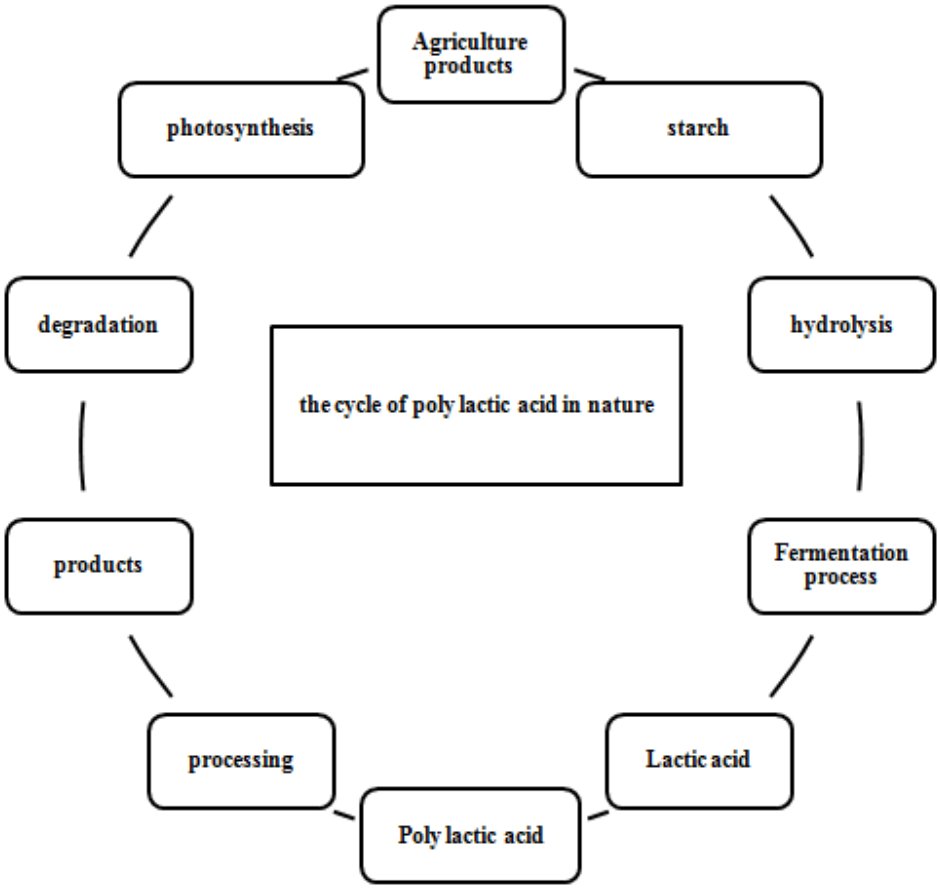

Fig. 1. The cycle of Polylactic acid in nature[10]

In spite of having colossal properties and being eco-accommodating PLA likewise has a few negative marks in meeting with the prerequisite of specific applications: (1) it has very low degradation rate which sometimes takes many years because of hydrolysis of backbone ester group, which obstructs biomedical and food packaging applications(2) challenging mechanical performance applications based on the PLA's brittleness (<10% extension at break) (3)polylactic acid can cause inflammatory response from the tissues of living hosts due to its strong hydrophobicity, having low affinity with cells when it is used as a tissue engineering material. (4) the limited gas barrier properties of PLA which avert its complete access to industrial sectors such as packaging [11].

However, PLA has not got the merited consideration considering its aforementioned demerits and cost. In many case, diverse strategies for mass or surface adjustment of PLA has been analyzed by scientist through presenting different segments or controlling its surface energy, surface charge and surface roughness, which are subject to the requirement of specific applications. Past reviews have analyzed distinct parts of the chemistry and engineering of PLA. For example: one review was focused on the melt-solid polycondensation of lactic acid (LA) and presented an overview of the production of PLA fibers by various methods, along with correlations between the structure and the properties of the fibers [12]. Rasal *et al.*[13] has analyzed PLA's chemical modification, whereas the previous 5-15 years technologies and modern ideas focusing on fly-high work will be discussed in this study introducing the new applications with highly promised future in both pharmaceutical and medical fields. Moreover, traditional studies

involving the synthesis, modification, and applications of PLA in biomedical sector will be introduced fundamentally to provide a more comprehensive description of PLA.

2-Physical and chemical properties of Polylactic acid

Several distinct forms of polylactide exist due to the chiral nature of lactic acid: poly-L-lactide, for example,(PLLA) is the product resulting from polymerization of L, L-lactide (also known as L-lactide). PLLA hascrystalline structure of about 37%, glass transition temperature 60–65 °C, melting temperature 173–178 °C and tensile modulus 2.7–16 GPa. Heat-resistant PLA can withstand temperatures of 110 °C.PLA is soluble in chlorinated solvents; hot benzene, tetrahydrofuran, and dioxane[14].Polylactic acid has extensively brought down most extreme constant use temperature regardless of having comparative mechanical properties to PETE polymer. Therefore, polylactic acid can be converted into fibers and film like thermoplastics.

On the other hand, the melting temperature and heat deflection temperature of PLLA can be raised by 40–50 °C and 60-190 °C, respectively, by physical mixing of polymer with PDLA (poly-D-lactide)[15].Extremely periodic stereo complex having enhanced crystallinity can be formed by PDLA and PLLA. With the blending ratio of 1:1, maximum temperature stability is achieved, but also there is a significant improvement even at lower concentrations of 3–10% of PDLA. In the latter case, there is an increase in the crystallization rate due to PDLA action as a nucleating agent. However, due to the higher crystallinity of the PLDA it has biodegradation rate slower than for PLA [16].

Table 1. Chemical and physical properties of polylactic acid derivatives[17]

Properties	PLLA	PDLA	PDLLA
Melting temperature (*T*m)/ °C	180	180	Variable
Crystalline structure	Hem crystalline	Crystalline	Amorphous
Decomposition temperature/°C	200	200	180-200
Glass transition temperature(*T*g)/ °C	55-60	50-60	Variable
Elongation at break/ (%)	20-30	20-30	Variable
Half-life in 37°C normal saline	4-6 months	4-6 months	2-3 months
Breaking strength/ (g/d)	5.0-6.0	4.0-5.0	Variable

3. Structure of polylactic acid

PLA is usually synthesized using a range of polymerization processes. These include: polycondensation, ring opening polymerization and azeotopic dehydration condensation reaction. However, the common route for lactic acid and polylactic acid is summarized in Figure: 1. The different processes applied for the production lactic acid polymer (PLA) are summarized in table 2. This table discussed in details the advantages and disadvantages of the five main ways to produce Polylactic acid in industry.

Table 2: The advantages and disadvantages of polylactic acid[19].

Synthesis methods	Advantages	Disadvantages
Ring-opening polymerization	High molecular weight Polylactic acid	Requires strict purity of the lactide monomer, related high cost
Biosynthesis	Efficient, nontoxic, no pollution, low cost, One-step	Under development (not fully industrially mature process)
New solutions (polymerization Conditions, new catalysts)	Efficient, non-toxic, no pollution , high molecular weight Polylactic acid	Under development (not fully industrially mature process)
Solution polycondensation	Economical, easy to control, One-step	side reactions, pollution, Impurities low molecular weight Polylactic acid
Melt polycondensation	One-step, easy to control, economical	sensitivity to reaction conditions, high reaction temperature, low molecular weight Polylactic acid

Despite being very inexpensive methods, in the polycondensation methods, it was very difficult to get solvent-free high molecular weight Polylactic acid form polycondensation method involving solution polycondensation and melt polycondensation. The aqueous solution of commercial lactic acid was distilled under decreased pressures and high temperatures. Then mixing of the distillation process product was done with the catalyst and solvent before charging

to the reactor under heating. The resulted polymer was mixed in solvent and precipitated two times with excess methanol while the byproduct (water) was constantly removed azeotropically.

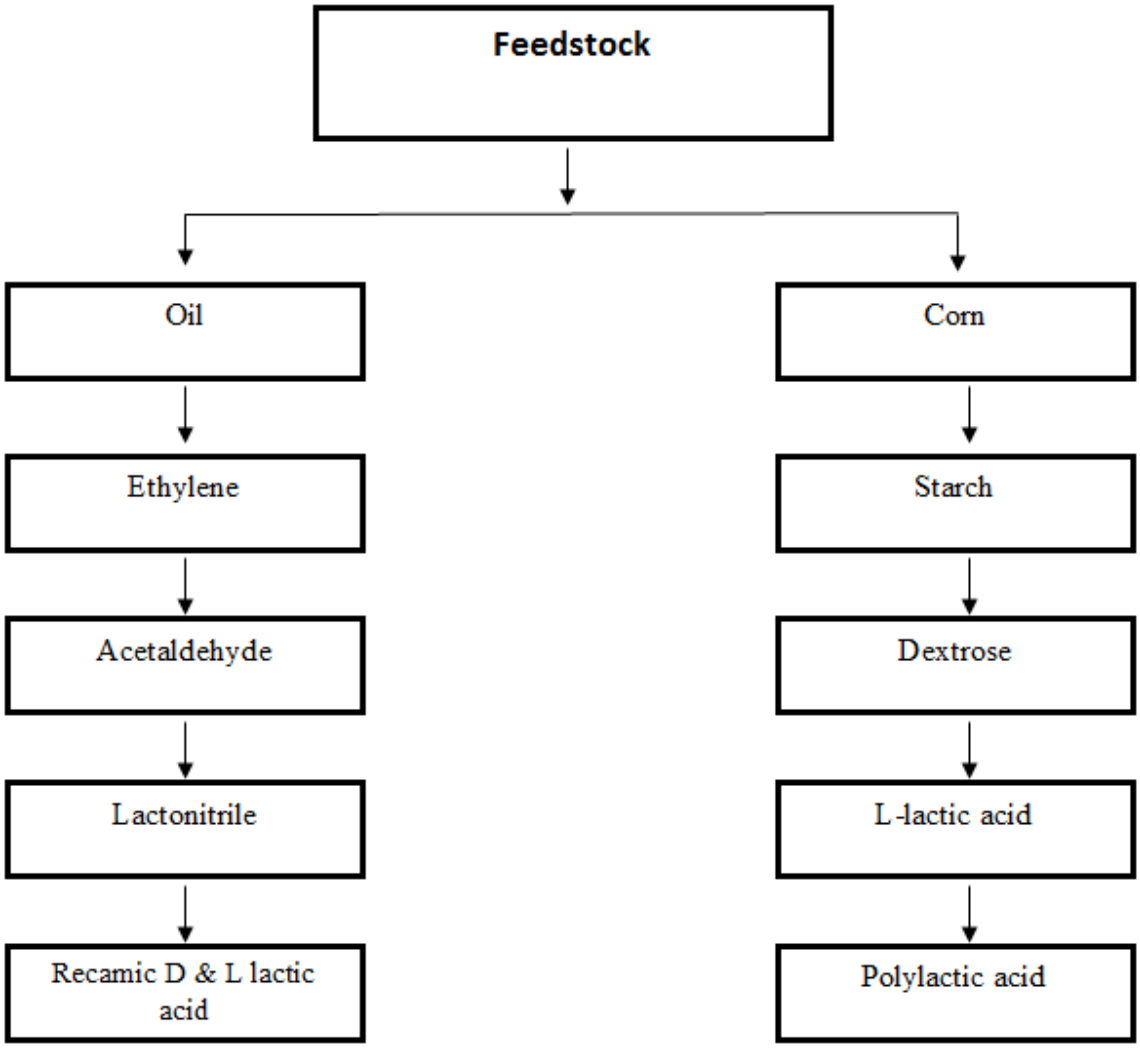

Figure: 2. Lactic acid and polylactic acid preparation processes[18]

Tin (II) chloride was the most regularly utilized catalyst and could be recouped toward the end of the reaction. The coupling agents like isocyantes, epoxides or peroxides, could be used for producing a range of molecular weights due to low to intermediate molecular weight polymer used in the reaction.

In contrast, to get high molecular weight PLA without using chain extenders or adjuvant the azeotropic dehydration, condensation reaction of lactic acid was used generally. In this process lower molecular weight polymers were obtained (less than 30 kDa.)[20].

The most frequently used catalyst that can also be attained when reaction completes was tin (II) chloride. The coupling agents like isocyantes, epoxides or peroxides, can be used for the production of range of molecular weights because of the low molecular weight polymer used in the reaction. The azeotropic dehydration condensation reaction of lactic acid can be used to produce high molecular weight PLA utilizing chain extenders. Normally lower molecular weight polymers (less than 30 kDa) have been produced using this technique. Whereas, many studies have reported an increase in the molecular weight of PLA polymers using polycondensation method involving

aqueous solution of lactic acid to producepolylactic acid in the presence of two catalysts (tin (II) chloride and succinic anhydride) [21].

Lactic acid can be polymerized to produce polylactic acid polymers by direct poly-condensation under controlled temperatures and pressures without catalyst, solvent or initiators. The effects of the reaction temperature and pressure on the resulting molecular weights have been studied. The results showed that at 200 °C after about 90 h under vacuum, high molecular weights of 90 kDa could be attained. In addition, other technique using the organic solvents was developed by Mitsui Toatsu chemical company to prepare poly-DL-lactic acid (PDLLA) by directs solution polycondensation[22].In this process the lactic acid, catalysts, and solvents were mixed in a reactor so as to produce high molecular weights polymer of300 kDa. On the other hand, the most commonly used technique to produce higher molecular weight PLA was ring-opening polymerization (ROP), occurred by ring opening of the lactide (cyclic dimmer of lactic acid) in the presence of a catalyst. This method consists of three steps: (1) polycondensation of LA monomers to low-molecular weight polylactic acid, (2) depolymerization of the PLA into the lactide and (3) catalytic ring-opening polymerization of the lactide intermediate. This result in PLA with a controlled molecular weight the whole process is shown is figure 3**.**

Conversely, the requirement of comparatively complex additional purification for this operation, raise the cost of PLA production as compared to the one prepared by polycondensation method.

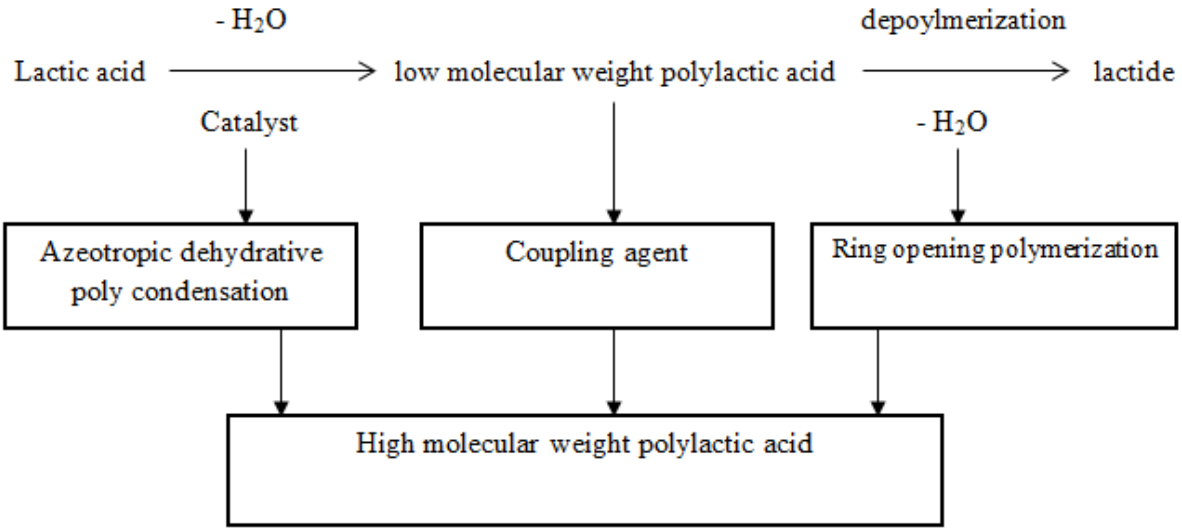

Figure: 3 Polylactic acid production by ring opening depolymerization processes[23]

Residence time, temperature, consternation and catalyst type can be manipulated to control the molecular weight of PLA produced by ROP. The control over the ratio and sequence of D- and L-lactic acid units in the final polymer can also be achieved. A novel method to produce high weight PLA polymer from lactide by using a solvent free and new distillation process and a range of biodegradable polylactic acid copolymers consisting of mesolactide or D-lactide has recently described in details[24].

4- Polylactic acid biomedical and pharmaceutical Applications

The biodegradable polymers have been studied extensively for medical and pharmaceutical applications. Thisbased on their advantages over nondegradable biomaterials include eliminating the need to remove implants and providing long term biocompatibility. The most common synthetic biodegradable polymers in medical and pharmaceutical applications are the poly (α-hydroxyacid)s, including polylactic acid (PLA), poly glycolic acid (PGA) and polydioxanone (PDS)[25]. Polylactic acid offers unique features of biodegradability, biocompatibility, thermoplastic process ability and eco-friendliness that offer potential applications as commodity plastics, as in packaging, agricultural products, disposable materials and medical textile industry. Because of its favorable characteristics, PLA has been utilized as ecological material as well as surgical implant material and drug delivery systems, and also as porous scaffolds for the growth of neo-tissue [26,27]. The use of polylactic acid in these applications is not only based on its biodegradability but also it made from renewable resources. PLA is being used because of its compatibility and provides excellent properties in addition to its low price [28]. Various devices have been prepared

from different PLA types including degradable sutures, drug releasing microparticles, nanoparticles, and porous scaffolds for cellular applications. The diversification of PLA applications is such that a single polymer may prove useful in many applications by simple modifications of its physical chemical structure. In many cases the polymer can be blended or copolymerized with other polymeric or nonpolymeric components to achieve the desired behavior. The surface properties of materials play a critical role in determining their applications, especially for biomaterials in biocompatibility. Different surface modification strategies, such as physical, chemical, plasma, and radiation induced methods, have been employed to create desirable surface properties of PLA biomaterials. Because biodegradable polymer implants temporarily remain in the body and disappear upon degradation, thus it is not necessary to perform a secondary operation to remove them after the defect site is repaired. Thus, they have an important application in the medical field. As a fiber the PLLA is not suitable for sutures, due to its low degradation rate. On the other hand, in applications that require long retention of the strength, such as ligament and tendon reconstruction, and stents for vascular and urological surgery, PLLA fiberis usually the preferred material[29].

Three dimensional porous scaffolds of PLA have been created for culturing different cell types used in cell based gene therapy for cardiovascular diseases, muscle tissues, bone and cartilage regeneration [30-32]. One application of PLLA in the form of injectable microspheres is temporary fillings in facial reconstructive surgery. PLLA microspheres have also been used as an embolic material in trans-catheter arterial embolization, which is an effective method to manage arteriovenous fistula and malformations, massive hemorrhage, and tumors [34]. Microspheres and microcapsules have been widely applied in drug delivery systems (DDS) for the prolonged administration of a wide variety of medical agents such as contraceptives, narcotic antagonists, local anesthetics, and vaccines. DDS with peptides and proteins have also gathered much attention, since they are specifically effective with comparatively low doses [35]. Release of drugs from these systems is based on several mechanisms that include diffusion and polymer degradation (hydrolysis or enzymatic degradation) [36].

4.1 Tissue engineering:

Tissue engineering is a technique whose concept was introduced in 1988 by the reconstruction of the biological tissues using biomaterials giving a three dimensional scaffold under specific physiological conditions. This technique has emerged as promising substitute tissue or organ transplantation while attracting enormous attention in science, engineering and medicine. Scaffolds made from different materials have been tested to fulfill various needs in tissue engineering[37].Certain metals despite having good mechanical properties are not suitable for scaffold application due to their non-degradability in the biological environment.

World has seen astonishing accomplishments in human organ reconstruction based on tissue engineering in the last two decades. During the early days, tissues were harvested from the culturing of cells using biostable materials. With the passage of time, the disappearance of the support from the plantation site leaving behind a perfect tissue is a key factor in the recent enormous attraction of biodegradable materials. In this process, surface properties play a vital role in determining the application of a certain material, especially for biomaterials in biocompatibility[38,39].

Chemical, physical, plasma and radiation induced methods have been employed for modifying the surface of PLA biomaterials to attain the desired surface properties. The main constraint in the study of mineralized tissue engineering with good osteoconductive properties involving inorganic materials such as HAP or calcium phosphates is poor processability into porous material. In contrast, for specific needs an excellent flexibility of design can be attained by their composition and structure manipulation[40].Being a type of important aliphatic polyester PLA has many applications in the field of biomedical such as suture, bone fixation material, and tissue engineering due to is degradability. The utilization of PLA involves as ecological material as well as surgical implant material and drug delivery systems, and also as porous scaffolds for the growth of neo-tissue [41].Biodegradability and production from renewable resources are not the sole features making PLA useful for its applications. To obtain all the desired properties in a single material for an application is difficult. However, due to the diversity in the applications of PLA a single polymer by simple variations in its Physical-chemical structure may be useful for various applications. For the applications involving longer retention time such as reconstruction of tendon and ligament and stents for urological surgery, the preferred material is PLLA. PLA has been produced for culturing different cell types involving cell based gene therapy for neurological, cardiovascular and orthopedic conditions[42].

Following properties an ideal scaffold must have for its utilize in tissue engineering (1) biocompatibility, for scaffolds well integrated into host tissues without resulting in any immune response (2) porosity, with appropriate pore size, size allocation and mechanical function, to permit cell or tissue growth and the abstraction of metabolic waste (3) mechanical strength, to withstand local stress and protect the pore structure for tissue regeneration (4)

biodegradability, most significant property of scaffold. Vital components of an efficient tissue engineering approach are synthetic scaffolds[43].

Temporary filling in facial reconstructive surgery is one of the uses of PLLA in the form of inject able microspheres. Managing arteriovenous fistula and malformations, massive hemorrhage, and tumors fistula and malformations, massive hemorrhage, and tumors has been done by the utilization of PLLA microspheres as an embolic material. Sander et al. did the estimate PLA microfibers for tissue response utilizing rat-subcutaneous implantation. The capsule width very low for the thin fiber and fiber diameter field from 5- 15 mm was observed [44].

Osteogenic stem cells seeded on scaffolds of this material and implanted in bone defects or subcutaneously can recapitulate both developmental processes of bone formation: endochondral ossification and intramembranous ossification [45,46]. Due to the high strength of (PLLA) mesh, it is possible to create 3D structures such as trays and cages an exciting application, for which the (PLA) offer tremendous potential, is bone fixation devices, since the metallic fixations have several disadvantages. Recently, biodegradable materials have been replaced the traditionally used metallic materials for the fixation of fractured bones in the forms of plates, pins, screws, and wires. Since materials for bone fixation require high strength, similar to that of bone, (PLA) has a large application in this field. Three dimensional (3D) electro weave fibrous scaffolds is a possibility tissue engineering device for bone renewal. Using electro spinning process with mechanical amplification process a 3D micro fibrous PLLA has been generated. 1.8-fold more amount osteoblasts amplification than for electro spun 2D nanofibrous membrane has been attained also the utilization of 3D frameworks for osteoblast expansion has been analyses. *In vivo* results further demonstrated that 3D micro fibrous matrices afford a perfect substrate to cell invasion and bone development following 2 to 4 weeks when utilizing a rabbit calvarias defect model [47].Table 3 provides a comprehensive overview about the commercially available PLA bone fixation devises commonly used worldwide.

Table 3 the commercially available PLA bone fixation[48].

Manufacturer	Material	product	country
Gunze	Drawn PLLA	Pin, Screw, Miniplate, Rod, Interference screw	Japan
Centerpulse orthopedics	PDLLA	Interference screw	USA
Takiron	Drawn PLLA	Pin, Screw, Miniplate, Rod,	Japan
Arthrex	Drawn PLLA	Interference screw	USA
Phusis	P(LLA/DLLA)	Interference screw	France
Linvatec	Drawn PLLA	Suture anchor	USA
Biomet orthopedics	Drawn PLLA	Mini screw	USA
Geistlich biomaterial	P(LLA/DLLA	Fixation pins for GTR and GBR membranes	Switzerland
Linvatec	Drawn PLLA	Suture anchor	USA
Conmed (bionx implants)	SR-PLLA Drawn PLLA	Pin, Screw, Meniscus arrow	USA
J&J (codman, Depuy and Mitec)	PLLA Drawn PLLA	Rivet for skull Suture anchor	USA

4.2Wound handling

Polylactic acid and its copolymers were utilized in a field of wound management, such as surgical sutures, healing dental extraction wounds. Appreciated the effectiveness and eventuality of PLA stents for the treatment of war injuries. The stents made of PLA were effective in the treatment of war injuries where PLA stents were degraded so that they were easily taken off by the human body. Therefore, PLA stents represented a promising aftertime for the treatment of scratches and injuries [49].

4.3Drug delivery system

For therapeutic potential maximization and side effects minimization there has been a need for the targeted delivery of the bioactive materials to specific body parts. Various types of particles like liposomes, solid lipid nanoparticles, and biodegradable polyesters such as PLA and PLGA have been used as delivery tools for biomedical uses[50].Due to the biocompatibility, biodegradability, better encapsulation, and lower toxicity biodegradable polymers (PLA, Gelatin, and PCL) have been utilized as drug delivery systems. Erosion, diffusion and swelling are one of the ways by which polymeric drug release occurs. The degradation initiates after the infiltration of water into the device for biodegradable polyesters containing monomers connected to each other by ester bonds the erosion of the device occurs as ester bonds break by hydrolytic ester cleavage. Two methods of erosion for degradable polymers are homogeneous or bulk and heterogeneous or surface erosion[51].In the encapsulation process of many drugs like

psychotic, restenosis, hormones, oridonin, dermatotherapy and protein, PLA and their copolymers have been utilized in nanoparticle form. Solvent evaporation, solvent displacement, salting out and emulsion solvent diffusion are the various methods utilized for obtaining these nanoparticles [52]. In this process, PLA is first dissolved in acetone, the solution is then added in an aqueous solution with mild stirring and the solvent is then evaporated under reduced pressure at room temperature to produce PLA nanoparticles. The fluorescent particles were acquired by the same process by dissolving fluorescent dye and PLA acetone Polylactic acid nano particles have been tested in human skin revealing that they can purpose the active sites into hair follicles which makes them a stellar candidate as a drug delivery layout [53].

Detailed explanation for different types of polymers used in the drug delivery system applications is shown in figure 4.

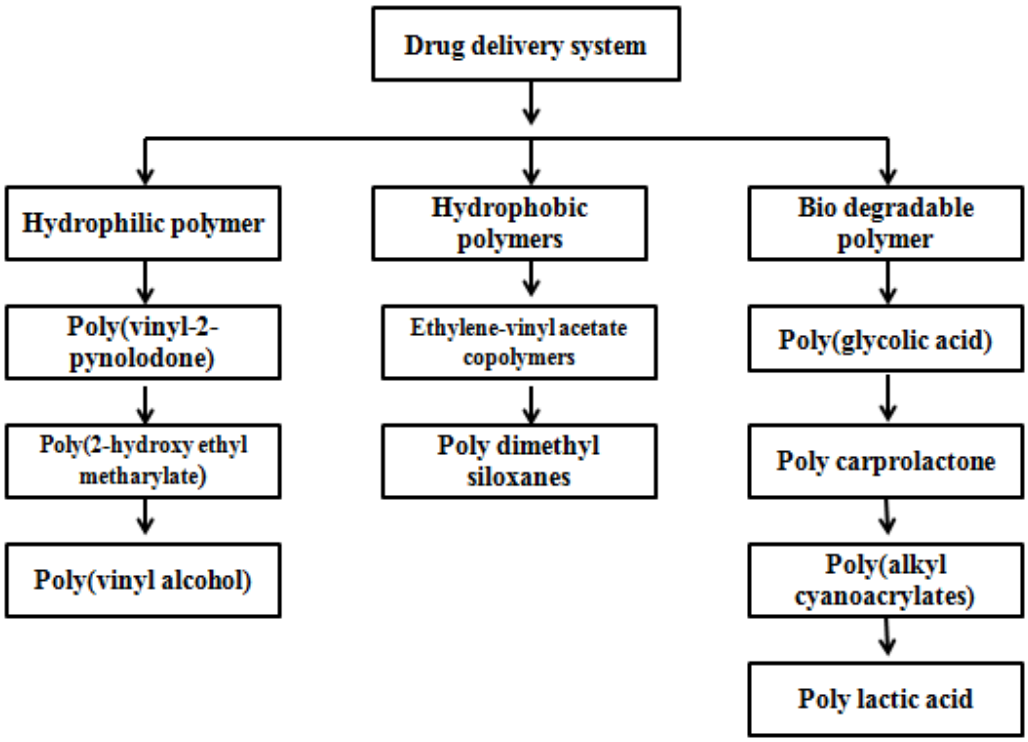

Figure: 4 Different types of polymer commonly applied in the drug delivery system

4.4 Composites

To improve the quality and reduce the cost of production, lactic acid polymerizes with other monomers or PLA is usually blended with other polymers. Polylacticglycolic acid, a copolymer, has been approved by (FDA) for the clinical uses. Other product such as VIRYL (Ethicon, Inc.) is composed of lactic acid and glycolic acid in ration of 2:23. The primary application of this copolymer is in controlled drug release. The ester linkages in PLA are sensitive to both chemical hydrolysis and enzymatic chain cleavage. Therefore, PLA is often mixed with starch to increase biodegradability and to reduce its price. Starch concentration in PLA/starch mixture is a key parameter determines the mechanical properties of the blend. Tensile strength and elongation decreases as starch concentration increases. Starch is a hydrophilic polymer and sensitive to water and PLA is hydrophobic and water repellent. Water absorption increases as the starch concentration increases. Nevertheless, the crispness of the starch/PLA blend is a major drawback in many applications. To overcome this limitation, a number of low molecular weight plasticizers such as glycerol, sorbitol and triethyl citrate are applied. Blends of (PLA) and starch (10–20) % have been commercialized as Novon (Ecostar, Germany). One type (PLA) can be formed miscible blend with other isomer (PLA) and with other various polymers, such as a Poly ethylene oxide[54], polyvinyl acetate [55],and polyethylene glycol [56].As (PLA) remains relatively costly, it is applied as a matrix in biocomposites combined with natural fibers. With Jute (PLA) composite tensile strength and tensile modulus increased with a little decrease in the elongation at maximum stress compared with (PLA).

The high crystallinity of PLA interferes with controlled degradation, reducing compatibility with soft tissues and presenting an obstacle to the application as biodegradable soft plastics. Many approaches to overcome these problems have been applied. For example, stereocopolymer according to enantiomeric composition, block copolymerization with other polymers, branched (PLLA) or blend with other polymers were carried out to inhibit the degradation rate by varying the crystallinity [57,58].

Ohya *et al.*, [59]reported a method to achieve graft polymerization of (LA) on polysaccharides using trimethylsilyl (TMS) protected polysaccharides. By introducing (TMS) protecting groups with trimethylsilanechloride/pyridine, low molecular weight polysaccharides become soluble in organic solvents and the figure of the initiating groups (i.e.,The number of grafts chains) can be controlled. PLA grafted polysaccharides with various distances and numbers of graft chains were synthesized using a trimethylsilyl protection method. The graft-copolymer films exhibited a lower glass transition temperature (Tg); melting temperature, crystallinity, and higher viscosity properties compared to PLA films. Moreover, the usefulness of graft copolymer as a plasticizer was investigated with (1:4) blend films prepared from the graft copolymers and PLA. The blend films showed lower (Tg) and crystallinity, and higher viscosity properties compared to PLA films [60].

Different types of chemicals such as citrate esters, have been used to plasticize PLA. Recently, plasticizers such as polyethylene glycol (PEG), glucose monitors and partial fatty acid esters were applied in this process [61].This was used mainly to improve the flexibility and impact resistance of PLA. Calcium phosphate ceramics such as hydroxyapatite or β-tricalcium phosphate shows high biological compatibility and safety in living tissues, such that, currently, they are applied clinically as biomaterials for bone repair. These ceramics, all the same, have disadvantages in that their stamina is not sufficiently high and that their modulus of elasticity (80–100 GPA) is much more eminent than that of natural bone. Materials with a high modulus induce a problem of stress shielding which leads to bone resorption. Since the stress shielding is apt to occur due to use of rigid materials such as conventional metals or ceramics, bioresorbable materials with modulus of elasticity that is alike to that of natural bone (5–15 GPA) are requisite for some applications such as bone plates or temporary internal fixation of bones broken or damaged. PLA bioresorbability make it a great potential candidates for many clinical applications. The resorption rate is controllable by the degree of polymerization or copolymerizing. The modulus of elasticity of PLA, however, is much lower (2–3 GPA) than natural bone. Wang *et al.*, [62]prepared the composite of PLA and β-Ca $(PO_3)_2$ fibers for medical applications. Poly L-lactic acid, poly L-lactic acid-co-citric acid, polyethylene glycol multiblock copolymers (PLLA), (PLCA) and (PEG) were synthesized through a poly condensation reaction and the properties of scaffolds such as puffing up and degradation behaviors, sound structure and mechanical module were fully investigated. The mechanical flexibility improves as the content of (PLLA), (PLCA) and (PEG) copolymers in the scaffolds increases. The survey indicates that the modification of (PLLA) scaffold with (PLLA), (PLCA) and (PEG) broaden its applications in tissue technology. To use as setting out materials in the medical industry, it demands a high purity of all compounds and advanced quality systems. Regulatory aspects such as current Good Manufacturing Practices (cGMP) and drug or device master files have to be brought into account when producing PLA for medical applications [63].

However, it is interesting to notice that large quantities of stable β-anhydrite II (AII), a specific type of dehydrated gypsum and a by-product of lactic acid production process, can be melt blended with bio-sourced and biodegradable PLA to produce economically interesting novel composites with high tensile force and thermal stability [64].

4.5 Nanotechnology

Poly (lactic-co-glycolic acid) is a copolymer synthesized by random ring opening copolymerization of two different monomers, the cyclic dimers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid (Figure 5). Nowadays, it is the best defined biomaterial available for nanotechnology based on the pharmaceutical and biomedical applications with respect to design and performance. The common catalysts used in the preparation of this copolymer include tin (II) 2-ethylhexanoate, tin (II) alkoxides or aluminum isopropoxide. During polymerization, successive monomeric units (of glycolic or lactic acid) are linked together in (PLGA) by ester linkages, thus yielding a linear, amorphous aliphatic polyester product[65]. The forms of (PLGA) are usually identified by the monomers ratio used. The most frequently used copolymer in the nanotechnology is usually composed of 50% lactic acid and 50% glycolic acid.

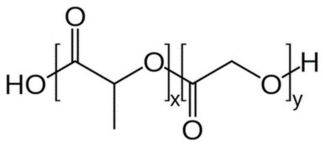

Figure 5: Structure of polylactic-co-glycolic acid (x is the number of lactic acid units and y is number of glycolic acid units)[66]

Polylactic-co-glycolic acid have different physical characteristics such as size, morphology, and size distribution. Therefore, it can be synthesized by controlling the parameters specific to the synthesis method employed. Zambaux et al., [65] reported that the most commonly used method for (PLGA) formation is the single or double emulsion solvent evaporation. Single emulsion process involves oil in water emulsification, while the double emulsion process is water in oil in water method. The water in oil in water method is best suited to encapsulate water soluble drugs, such as peptides, proteins and vaccines, while the oil in water method is ideal for water insoluble drugs, such as steroids [66,67].

In some conditions, solid/oil/water techniques have been exploited with (PLGA) based microspheres, especially for a higher drug loading of high water soluble peptides, such as insulin. In summary, for the oil in water method, (PLGA) is first solute in a water immiscible, volatile organic solvent (e.g., dichloromethane); then the drug is added to the polymer solution to produce a solution of the drug particles. After that the drug solution is emulsified by appropriate temperature and stirring conditions in a larger volume of water in the presence of an emulsifier such as poly vinyl alcohol to yield oil in water emulsion. Poly vinyl alcohol (PVA) is used to stabilize the emulsion, since it forms particles of relatively small sizes and uniform size distribution [66]. Followed by solvent removal by either evaporation or extraction to harden the oil droplets, the solid nanospheres obtained are then washed and collected by filtration, sieving or centrifugation. These are then dried under appropriate conditions or are lyophilized to give the final free flowing injectable nanosphere product. Many researchers have used this method to produce (PLGA)mostly in size 100 nm. (PLGA) was colloidal in the range of diameter from 10 to 1000 nm, with the therapeutic agent either entrapped into or adsorbed or chemically coupled onto the polymer matrix. A typical manner for preparation of (PLGA) containing plasmid DNA or other drugs[68,69].

The polylactic-co-glycolic acid (PLGA) is biodegradable in the body due to they undergo hydrolysis of their ester linkages in the presence of water to produce the original monomers, lactic acid and glycolic acid Figure 6, which are byproducts of various metabolic pathways in the body under normal physiological conditions [70]. The degradation rate of (PLGA) polymers is related to the monomer ratio used in production; the polymer containing a (50:50) ratio of lactic and glycolic acids is hydrolyzed much faster than those containing higher proportions of either of the two monomers [67]. The degradation products are easily metabolized in the body via the Krebs cycle and are eliminated [71]. Thus, there is very minimal systemic toxicity associated with using (PLGA) for drug delivery or biomaterial applications. Athanasiou et al (1996) documented, during *in vivo* and *in vitro* studies testing the toxicity biocompatibility, the results demonstrated that (PLGA) nanomaterials have satisfactory bio-compatibility and absence of significant toxicity. The in vivo studies involved applications in bone, articular cartilage and the meniscus, and a significant number of other studies performed in situ in muscle or other soft tissues. All the previous studied support the potential *in vivo* application of(PLGA) biomaterials, although some cases reported inflammatory responses [70].

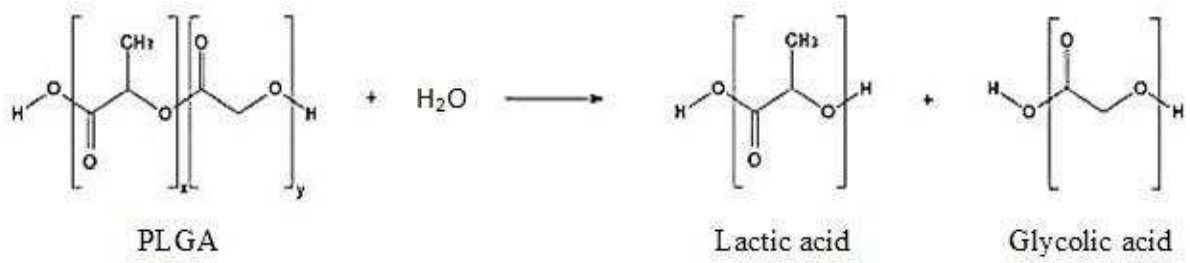

Figure 6: hydrolysis of polylactic-co-glycolic acid (PLGA)[66]

The biodistribution studies demonstrate that (PLGA) delivery enhances accumulation of diagnostic or therapeutic agents by the enhanced permeability and retention effect. For example, when indocyanine green was delivered

through (PLGA) in healthy mice using a fluorometric assay method, the led to higher indocyanine green deposit in organs (two to eight times) as well as in blood (five to ten times) compared with free solution, indicating the enormous potential of (PLGA) as a delivery system for indocyanine green for its use in tumor diagnosis and photodynamic therapy[72]. This effect is enhanced when the NP is shielding with a poly(ethylene glycol/oxide) surface modification [61]. Coating the nanoparticle surface with a hydrophilic polymer, such as poly ethylene glycol (PEG), has been shown to confer long circulation properties to polylacticacid,(PLGA), polycaprolactone and polyphosphazene nanoparticles. The presence of the hydrophilic polymeric chains on the surface of the nanoparticles is considered to sterically stabilize them against opsonization and subsequent phagocytocis[74] .

It is necessary to sterilize all medical implants after fabrication and prior to their surgica l placement to reduce the risk of infection and other complications. Athanasiou *et al.* [73]well documented the advantages and disadvantages of the common terminal sterilization methods of dry heat, steam, ethylene oxide gas and ionizing radiations. Among them, steam and dry heat sterilizations are carried out at high temperatures and can cause severe degradation and hydrolysis of polymeric microparticles; ethylene oxide is not applicable due to its toxic residues. The γ-irradiation causes instability, deterioration and cross linking breakage of polymer chains but it is currently the more frequently used method for terminal sterilization of (PLGA)nanodevices. Many studies are still focused on the development of a suitable method for sterilizing (PLGA) devices [75, 76]. For instance, Shearer et al.(2006) the effects of sterilization with ethanol, ultraviolet irradiation, peracetic acid, and antibiotic solution on the structure of (PLGA) hollow fiber scaffolds and found that none of the sterilization methods are ideal in terms of sterilizing the sample without causing structural changes [76]. However, they suggested that the antibiotic treatment would provide a convenient, effective method with which to sterilize (PLGA) hollow fibers for use as Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals [76]. Medications, such as peptide, protein, antibody, vaccine and gene-based drugs, may not be delivered using routine delivery methods because they might be susceptible to enzymatic degradation or cannot be absorbed into the systemic circulation efficiently enough, owing to molecular size and charge issues, to be therapeutically effective. Therefore, many efforts have been focused on the targeted delivery where the drug is only active in the target area of the body, such as tumor tissues, and sustained release formulations in which the drug is released over a period of time in a controlled manner. A wide variety of natural and synthetic biodegradable polymers have been investigated for drug targeting or prolonged drug release [67, 78].

Polylactic-co-glycolic acid is a polymer approved by the FDA for drug delivery owing to its biodegradability, drug biocompatibility, suitable biodegradation kinetics and mechanical properties and ease of processing. It has been widely used to formulate into different biodegradable devices, such as microparticles, (PLGA), implants and miscellaneous devices, as well as in situ formed devices. Biodegradable (PLGA) have been investigated for sustained and targeted localized delivery of different agents, including drugs, proteins and peptides, and recently plasmid DNA, owing to their ability to protect DNA from degradation in endolysosomes[79].Owing to their subcellular and submicron size, PLA delivery systems have distinct advantages for drug delivery. PLGA can penetrate deep into tissues through fine capillaries, across the fenestration present in the epithelial lining (e.g., liver) and, generally, are taken up efficiently by the cells. This allows efficient delivery of therapeutic agents to target sites (tissue or organ) in the body.PLGA also have the advantage of sustaining the release of the encapsulated therapeutic agent over a period of days to several weeks compared with natural polymers that have a relatively short duration of drug release [61]. PLGA has been a common choice in the production of a variety of biomedical devices, such as grafts, sutures, implants and prosthetic devices [65].

CONCLUSION

According to the previously published work on PLA, it is possible to notice that the bio absorbable and biodegradable poly acid from the renewable resources for pharmaceutical and biomedical applications have attracted more attention of many researchers and industries. During last five years, the studies on the PLA drug delivery manor such as anticancer agents and vaccine immunotherapy have resulted in a significant development in PLA production and treatment strategies. The polylactic acid composites need to be further improved and to accepted by the market. However, we think in the next five years mere researches will be focused on the thorough evaluation for biodistrubutin, toxicity and pharmacokinetics before using polylactic acid materials in the clinical trials such as cancer. For example, the studies of polylactic-co-glycolic acid as vaccine candidates will more focus on developing the features to providing the delivery with suitable surface molecules for recognizing the immune system and much

effective targeting. We believe that PLA will help in improving the treatment of many diseases and play more important manors in stem cell and tissue engineering research.

REFERENCES

[1] NZOthman; HA. El Enshasy; R Abdel Malek; MR Sarmidi; R Aziz.*Deutsche LebensmittelRundschau*. **2009**, 105, 444-450.
[2] S-T Yang; HA El Enshasy;N Thongchul. Bioprocessing Technologies in Integrated Biorefinery for Production of Biofuels, Biochemicals, and Biopolymers from Biomass, 1st. Edition, John Wiley&Sons, USA. **2013**
[3] MR Sarmidi; HA El Enshasy. *Int. J. Biotechnol. Well. Ind*. **2012**, 1, 3-28.
[4]R AbdAlsaheb; A Aladdin; NZ Othman;R AbdMalek; OM Leng;R Aziz, HA El Enshasy;*J. Chem. Pharm. Res.***2015**, 7, 729-735.
[5]VS GiitaSilverajah; NA Ibrahim;.NZainuddin; WMZ Wan Yunus; H Abu Hassan. *Molecules*.**2012,** 11729-11747.
[6] M Jamshidian; EA Tehrany; M Imran; Jacquot M; S Desobry. *Compehensive Rev in Food Sci and Food Safety*. **2010,** 9, 552-571.
[7] K Yuniarto; BA Welt; APurwanto; HK Purwadaria; A Abdellatief. *J Appl. Pack. Res.* **2014,** 6, 51-57.
[8] K Fukushima; Y Kimura, *J. Polymer Sci.*Part A. *Polymer Chem.*,**2008**, 46, 3714-3722.
[9] M Hirata; K. Kobayashi ;Y. Kimura; J. Polymer Sci. *PolymerChem*., **2010**, 48, 794.
[10]VVink; *Polymer Degradation and Stability*,**2003**, 80, 3, 403-419.
[11] R MRasal;DHirt. *J Biomed Mat Res. Part A*, **2009**, 88, 4, 1079-1086.
[12] T Maharana; BMohanty;Y S Negi. *Prog.Polym Sci.***2009,**34, 1, 99-124.
[13]RM .Rasal; AVJanorkar;DE Hirt.*Prog.Polym. Sci.***2010**,35, 338-356.
[14]SInkinen;M Hakkarainen;ACAlbertsson;ASödergård.*Biomacromolecules*. **2011,** 12, 523-532.
[15]FCarrasco; J Gámez-Pérez;OSantana;MLMaspoch. *Polym. Degrad. Stab*. **2010,**95, 116-125.
[16]SSaeidlou;MAHuneault;H Li;CBPark.*Prog. Polym. Sci.*, **2012**,37, 1657-1677.
[17]DGarlotta. *J. Polym. Environm.***2001**,9, 63-84.
[18]RDatta;M Henry. *J. Chem. Technol. Biotechnol.* **2006,** 81, 1119-1129.
[19]F Achmad. *Chem. Eng. J.* **2009**, 151,342-350.
[20]JR Dorgan; B Braun; JR Wegner; DM Knauss. *ACS, Symp. Ser.* **2006**,939,102–125.
[21]ZLei;YBai; SWang.*Chin. Sci. Bull*.**2005,** 50,2390–2392.
[22]JR Lasprilla;ARMartinez;BHLunelliJardini; ALFilho.*Biotechnol. Adv.* **2012,**30, 321–382.
[23]E Kim;W Shin; KYoo; JSChung.*J. Mol. Cat. A. Chem.* **2009**,298, 36-39.
[24]SSaeidlou; MA Huneault; H Li;CBPark.*Prog. Polym. Sci.* **2012**,37, 1657-1677.
[25]JCMiddleton; AJ Tipton. *Biomaterials*.**2000,**21, 2335-2346.
[26] BN Gupta;N Revagade; J.Hilborn. *ProgPolym. Sci*. **2007**, 32, 455-482.
[27] H Yamane;K Sasai, *Polymer*. **2003**, 44, 2569-2575.
[28] RE Drumright;PR Gruber; DE Henton.*Adv. Materials.* **2000,**12, 1841-1846.
[29] L Dürselen;M Dauner;HHierlemann; H Planck; LEClaes; AIgnatius.*J Biomed. Mat. Res.***2001**, 58, 666-672.
[30]DLCoutu; AMYousefi;J Galipeau. *J Cell Biochem*.**2009**, 108, 537-546.
[31]M Kellomäki; H Niiranen;K Puumanen; NAshammakhi; T Waris; P Törmälä. *Biomaterials*. **2000**, 21, 2495-2505.
[32]BJ Papenburg;J Liu; GAHiguera; AMBarradas;J de Boervan Blitterswijk. *Biomaterials*. **2009,**30, 6228-6239.
[33]BL Eppley;L Morales; RWood; JPensler; J Goldstein; RJ Havlik; M Habal; A Losken; JK William; F Burstein; AA Rozelle; Sadove AM.*Plast.Reconstr. Surg*. **2004**, 15, 850-856.
[34]MJImola; VL Schramm.*Laryngoscope*.**2002**, 112, 1897-1901.
[35]ML Tan;PF Choong; CR Dass.*Peptides*.**2010**, 31,184-193.
[36]MA Valantin; C Aubron-Olivier; J Ghosn; ELaglenne;MPauchard; HSchoen; R Bousquet; P Katz; D Costagliola; C Katlama.*AIDS*. **2003**, 17, 2471-2477.
[37]CLiu; C Naiyi; NMD Brown; Meenan BJ.*Surface Coatings Technol*.**2004**.185, 311-320.
[38]JW Huang, *J. Appl. Polym. Sci*. **2009,**112,1688-1694.
[39]CJ Bringham;AJ Sinskey. *Int.J. Biotechnol. Well. Ind*.**2012**, 1, 53-60.
[40]R Langer;PVacanti.*Tissue Eng. Sci.***1993**,260, 920-926.
[41] JR Bain. *Transplant. Proc.* **1998,** 30, 2762- 2767
[42]BJ Papenburg;J Liu; GA Higuera;AMCBarradas;J de Boer;CA van Blitterswijk; M Wessling; D Stamatialis. *Biomaterials.***2009**, 30, 6228-6239.

[43] K Yagihara;S Okabe; J Ishii; T Amagasa; M Yamashiro; S Yamaguchi; S Yokoya; T Yamazaki; Y Kinoshita.*Int. J. Oral Maxillofac. Surg***. 2003,**42,962-969.
[44] JB Lee;HN Park;WK Ko;MS Bae;DN Heo; DH Yang; IK Kwon.*J. Biomed. Natotech.* **2013,** 9, 424-429.
[45]DJBehonick; Z Xing; S Lieu;JM Buckley;JC Lotz; RS Marcucio. Z Werb; T Miclau; C Colnot.*PLoS One*.**2007,** 2, e1150.
[46] AI Caplan. *Tissue Eng.Part B.***2009**, 15, 195-200.
[47]JH Park; BGChung; WG Lee; J Kim; MD Brigham; JShim;S Lee; CM Hwang; NG Durmus; U Demirci; A Khademhosseini. *Biotechnol. Bioeng.* **2010**,106, 138-148.
[48]Auras, L. T. Lim, S. E. M. Selke and H. Tsuji, Poly (lactic acid). Synthesis, structures, properties, processing, and applications, John Wiley & Sons, Hoboken, NJ, USA, **2010**
[49] XOZhang;J Intra;AKSalem.*J Microencapsulation.* **2008**,25, 1-12.
[50] C Roney.*J. Cont. Release.* **2005**108,193-214.
[51]A Kumari; SK Yadav;SC Yadav.*Colloids and Surfaces B: Biointerf.* **2010,**75, 1-18.
[52]FRancan;DPapakostas;SHadam;S Hackbarth;T Delair; C Primard;B Verrier;WSterry;U Blume- Peytavi. *Vogt A Pharmaceut. Res*.**2009**, 26, 2027- 2036.
[53]V Lassalle; ML Ferreira.*Macromol. Biosci.***2007**, 7, 767-783.
[54]AJ Nijenhuis;E Colstee;WA Grijpma;AJ Pennings.*Polymer*. **1996**,37, 5849-5857.
[55] AM Gajria;V Davé;RA Gross;SP McCarthy. *Polymer*. **1996,**37, 437-444.
[56] M Sheth; RA Kumar; V Davé;RA Gross;SPMcCarthy.*J Appl. Polym Sci.* **1997**,66, 1495-1505.
[57]O Martin;L Averous.*Polymer* **2001**, 42, 6209-6219.
[58]Tsuji; *Polymer*. **2002**, 43,1789-1796.
[59] Y Ohya;S Maruhashi; TOuchi.*Macromolec. Chem. and Phys*. **1998,** 199,2017-2022.
[60] T Ouchi;TKontani;Y Ohya.*Polymer* **2003**, 44, 3927-3933.
[61] AS Hoffman. *Adv. Drug Deliv. Rev.* **2009**,64. 18-23.
[62]Y Wang;YLi;X Pei; L Yu; Y Feng. *J. Biotechnol*.**2012**,129, 510-515.
[63] D Bendix.*Polym. Degrad. Stab*. **1998 ,**59, 129-135.
[64]M Murariu;A Da Silva Ferreira; MPluta;L Bonnaud;M Alexandre;P Dubois. *Eur. Polym. J*.**2008**,44, 3842–3852.
[65]M Zambaux; FBonneaux; R Gref; P Maincent;E Dellacherie;MJAlonso; P Labrude; C Vigneron.*J.Control. Release*. **1998,** 50, 31-40.
[66] HK Makadia;SJSiegel.*Polymers* **2011**,3, 1377-1397.
[67]RA Jain;*Biomaterials* **2000,** 21, 2475-2490.
[68]F-YCheng; SPWang; T-LTsai; P-C Wu; D-B Shieh.*Biomaterials*. **2008** ,29, 2104-2112.
[69] J Panyam;WZ Zhou;SPrabha;SK Sahoo; VLabhasetwar,*FASEB.* **2002,** 16, 1217-1226.
[70] KA Athanasiou; GGNiederauer;CM Agrawal.*Biomaterials.* 1996**,**17, 93-102.
[71]JM Anderson; MS Shive.*Adv. Drug Deliv. Rev.* **2012**, 64, 72-82.
[72]V Saxena;M Sadoqi; J Shao. *Int. J. Pharmaceut.* **2006**,308, 200-204.
[73] K Avgoustakis. *Curr. Drug Deliv.* **2004,** 1, 321-333.
[74] LE Van vlerken; ZDuan; SRLittle; MVSeiden; MM Amiji.*Mol. Pharmaceut.* **2008,**5, 516-526.
[75] M Igartua;RM Hernández;JE Rosas; ME Patarroyo; JL Pedraz.*Eur. J Pharmaceut. Biopharmaceut.* **2008,** 69, 519-526.
[76] H Shearer;MJ Ellis; SPPerera;JB Chaudhuri. *Tissue Eng.* **2006**, 12, 2717-2727.
[77] SK Sahoo; V Labhasetwar. *Drug Discov. Today*. **2003,** 8, 1112-1120.
[78] J Panyam;V Labhasetwar.*Adv. Drug Deliv. Rev.* **2003**,55,329-347.
[79]SV Vinogradov; TKBronich; AVKabanov. *Adv. Drug Deliv. Rev.***2002,** 54, 135-147.