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NEW ADVANCEMENTS OF BIOPLASTICS IN MEDICAL APPLICATIONS

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ABSTRACT: The bio-plastics that are produced either from fossil material or can be synthesized from biomass or renewable resources, such as Poly-lactic acid **(**PLA), Polyethylene glycol (PEG) and Poly - ε - caprolactone (PCL) are been reported as a material of choice for biomedical applications due to their good physical properties such as crystallinity, storage modulus, glass transition temperature and bioresorbable property. These biodegradable polymers have wide applications in tissue engineering, wound management, drug delivery, orthopedic devices, manufacturing of fibrous and porous scaffolds. Co-polymerizing these biodegradable monomers in varying proportions with other polymer has extended stiffens and physico-chemical properties. Depending on the origin of their materials, bio-plastics are different in their monomer composition and physical property, which make them interesting from medical point of view. This review thus highlights the synthesis and blending of bio-plastics along with their degradation process when used as in biomedical devices. These biodegradable plastics have hydrolysable linkages in the backbones such as esters, orthoester, anhydride, carbonate, amide, urea and urethane that make them biocompatible to human body. The biocompatibility of such biomedical devices is depends on several factors like site of implantation, material-tissue interactions, temperature and humidity.

INTRODUCTION: As the technology advances and population increases, plastic materials are widely used in daily life and in industries. These synthetic plastic materials pose very harmful effects on environment, as they are non-bio-degradable such as polyethylene, poly-butyrene, polystyrene, poly-vinyl chloride and polyethylene terephthalate. To overcome the problem of non-biodegradability, biodegradable plastics have been emerged as an alternative to traditional plastics (which have high degradability) [1].

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Biodegradable plastics are that kind of plastics that will decompose naturally, when environmental microorganisms metabolize and break down the chemical bonds present in the structure of biopolymer.

Bio-plastics offer an advantage to earth by reducing carbon footprint and use of fossil fuel. Bio-plastics are completely biodegradable and can be recycled. Some plants also help in producing biodegradable plastics (like genetically engineered plant *Arabidopsis thaliana*). The plant utilizes their enzymes for producing plastic with the help of microorganisms. Microorganisms produce plastic by consuming carbon sources and sunlight and convert it into energy [2, 3]. Many researchers performed the transformation by transferring respective genes into plants that encodes for

enzymes, which is responsible for the production of plastic using its cellular process. Plastics derived from plants extracted using a solvent. The plastics separated from the solvent by the process of distillation. Hence, the plastic derived from renewable feedstock reduces the greenhouse gas emission.

A biodegradable plastic has many advantages such as reduction in the accumulated hazardous non-degradable synthetic plastic, which will not, consumed by the wild animals as their feedstock and minimizes the injuries to them. Moreover, bioplastics is degrades enzymatically into monomers and oligomers by soil microorganisms, thus productivity of soil will increase randomly [4].

Bioplastics: Bioplastics are the material, which further degraded into their constituent monomer without the generation of nontoxic fumes in the environment and are biocompatible when used in the biomedical application. Bioplastics may be biodegradable or biologically degradable based on their synthesis resources. Biologically degradable plastics are produce from the renewable feedstocks deteriorated physically and chemically and degraded completely when treated with microorganisms (fungi and bacteria) with the production of CO_2 (aerobic), CH_4 (anaerobic) and water. Bio-derived plastics may be biodegradable (PCL) and non-biodegradable (bio-polyethylene) [5].

Nowadays, biodegradable aliphatic polyesters like PLA, PCL, Poly lactic-co-glycolic acid (PLGA) and poly-hydroxyalkanoate (PHA) as well as their copolymers are use in the human- body for biomedical applications. Li (2006) in his review summarized that people use the word “degradable” in general term and use “biodegradable” for polymers which are biologically degraded by the action of enzymes, introduced *in vitro* or produced by surrounding living cells [6]. Many biodegradable polymers have hydrolysable linkages in the backbones such as esters, orthoester, anhydride, carbonate, amide, urea and urethane. The ester bonds - containing aliphatic polyesters have outstanding biocompatibility and contain variable physical, chemical and biological properties. Among the aliphatic polyesters, PHA is the most widely used in biomedical applications due to the biocompatibility [7].

Biodegradable polyesters may degrade in the environment because of their main - chain structure characteristic and their hydrophilicity and crystallinity. Latest researches have shown that the balance between the hydrophilicity and hydrophobicity of polyester molecules will become crucial for the binding of enzyme to the substrate and the subsequent hydrolytic enzyme actions [8].

Biocompatibility of Bioplastics: Biocompatibility is the ability of a material to perform an appropriate host response in a particular application[1]. However, the recent definition of biocompatibility gives the detailed description of the biological mechanism [9]. Cell culture systems used for evaluating *in vitro* biocompatibility, or cytotoxicity. Studies are been done on *in vivo* experimental, histological and pathological examination of the peri-implant and various host responses mainly immunogenic, carcinogenic and thrombogenic responses. The complicacy of these host responses results in a series of temporal and spatial processes, which involves numerous mechanisms of material–tissue interactions that were closely interdependent. If one considers the field of biologically stable materials and permanently implants the devices, the primary goal is to minimize and adjust the material - tissue interactions.

The interaction between the living environment and the material should be suitable and stable for long - term treatments and performances. In contrast, in the fields of bioresorbable and biodegradable polymers, the situation is completely different with an extent of complexity offered due to the by-products of degradation and resorption of the implants, which are capable to interacting strongly with living systems. Therefore, biocompatibility is one of the factors that must be examined before selecting the biodegradable polymers, which are used in medical devices, for making scaffolds and in drug-delivery systems. Generally, devices made of bioresorbable polymers are effectively tolerate by living tissue [10], because their biocompatibilities depend mainly on the factors concisely discussed below. The large contributor for the secondary inflammatory reactions is the release of acidic products *via* degradation of bio-resorbable polymers and implants. The site of implantation is another important factor, which affects inflammation responses.

The chemical composition of the by-products may lead to local temporary disturbances if the ability of the surrounding tissues to remove the by-products is low, because of their low vascularization or metabolic activity. For example, the increase in osmotic pressure or change in pH exhibited, by the accumulation of local fluid or formation of transient sinus [11]. Therefore, problems of biocompatibility of bio-resorbable polymers (aliphatic polyesters) are associated to biodegradability and bio-resorbability.

The determination of both the rate of degradation of the polymer and the removal of specific tissues are critical for the determination of the concentration of by-product present in the tissue and resulting host response. Pitt *et al*., has done the detailed study of the inflammatory response of PCL and PLA copolymers post implantation in male Wistar rats [12]. The activation of neutrophils and mild localized inflammation occurs by injecting microspheres into the body. The neutrophils rapidly activated by using PCL microspheres and it can be confirmed by measuring the generation of superoxide anion measured by making use of chemi - luminescence. The release of chemotactic factors occurs by the activation of neutrophils that leads to inflow of a huge number of neutrophils entering into the affected site and causes inflammation.

The main clearance mechanism is the phagocytosis of the drug loaded with PCL microspheres via white blood cells through which foreign materials removed from the body [13]. The inflammatory reactions in bones were less noticeable as than that in muscles. The researchers has not discussed this observation in detail, but some have hypothesized the above discussed primary inflammatory reaction in muscle this must be because of a good vascularization of muscle tissues and a large amount of material that implanted. The tissue reaction of implantable microspheres containing PCL manufactured through solvent evaporation process observed by implantation in the brain of Wistar rats [14].

Aliphatic Biodegradable Polyesters and Copolymers:

1. Poly-Lactic Acid (PLA): Poly-lactic acid is the smallest organic molecules from natural origin, that are optically active with either L (+) or D (-) stereoisomer, produced by animals, plants and microorganisms in nature [15]. In 1780, lactic acid was first isolated and published [16]. Carothers in his review mentioned the dimerization of lactic acid into lactide by ring-opening polymerization. He also mentioned that lactic acid would undergo reversible polymerization *i.e.* characteristic of six atoms cyclic ester [17]. The polymers formed by six-membered cyclic esters called linear polyesters and, at some instance, the chains opened and replaced by hydroxyl (OH) and carboxylic (COOH) groups.

The polymerization and the depolymerization both takes place by interchanging the esters [18]. In 1960's, the biodegradability and non-toxicity of these polymers for use in biomedical applications became perceivable [19]. PLA have become one of most promising polymer due to their biocompatibility and biodegradability and have wide range of applications in biomedical science and biotechnology.

Synthesis of PLA: PLA is thermoplastic aliphatic polyester produced by condensation polymerization of lactic acid (2-hydroxy-propionic acid). Lactic acid obtained from tapioca, corn and starch from plant roots, sugarcanes, and many other resources produced by fermentation of starch and sugar by the action of bacteria. As the synthesis of PLA accomplished by condensation of two monomeric units with the release of one water molecule, it cannot directly polymerize into a desired material. The fermentation of carbohydrates (such as rice, corn *etc*.) is most widely used, to produce more than 90% of lactic acid. Dutta and Henry (2006) mentioned the methods of synthesizing and purifying the PLA found in two enantiomers L-Lactic acid and D-Lactic acid [20].

PLA obtained from the fermentation of renewable feedstocks is a pseudolplastic, non- Newton fluid.

Biodegradation Properties of PLA: Biodegradation has wide range of definitions; some definitions depend on the similar concept: the material is converting into carbon dioxide (CO_2), methane (CH_4) and water (H_2O) by the action of microorganisms. Furthermore, as stated by the Japanese Biodegradable Polymer Society (JBPS),

the biodegradation is a phenomenon in which the polymer breaks down into H_2O and CO_2 by the action of microorganisms present naturally in the environment, and the JBPS termed these biodegradable polymers as Green Plastic. There are two types of biodegradation known, *i.e.* aerobic biodegradation or anaerobic biodegradation. If no residue left that mean the complete biodegradation and complete mineralization was expected and the original polymer is converting into the gaseous products completely. The rate of biodegradation depends on several factors, such as temperature and humidity, and some chemical parameters such as molecular weights and composition of PLA.

The biodegradation of PLA has studied in bodies of animal and human for medical applications such as implants, making surgical sutures, and for drug delivery system. In these conditions, biodegradation of PLA occurs initially by hydrolysis and meta-bolization of the soluble oligomers by cells [21, 22].

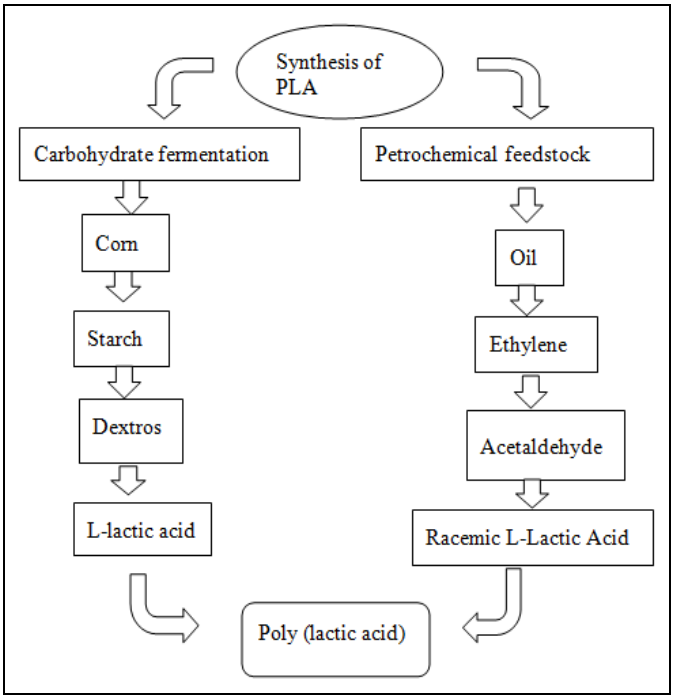

FIG. 1: SYNTHESIS OF PLA

Medical Applications of PLA:

(a) PLA in Tissue Engineering: The PLA is most widely used biopolymers in medical applications because of its biocompatibility as well as its bio-dissolvability in the human body by the hydrolysis of the ester backbone to obtain non-harmful and non-toxic compounds after degradation. Hydrolysis is the most important degradation mode for PLA polymers used for medical applications.

Zhang *et al*., (2011) composed composites of PLA / octa-decyl amine functionalized Nano-diamond (ND-ODA) and use in tissue engineering [23]. The composites were prepared by dissolving PLA in chloroform while dispersing ND - ODA in chloroform and both solutions further sonicated. The chloroform dissolved PLA and ND - ODA dispersion solution mixed to obtain thin films of the PLA / octa-decyl amine composites by chloroform evaporation. Furthermore, ND - ODA and composites are nontoxic to murine osteoblasts. Besides that, PLA and their copolymers, like PLA polyethylene glycol (PLA - PEG) block copolymer and PLA-p-dioxanone - polyethylene glycol (PLA-p-DPEG) block copolymer, are using as carriers for bone morphogenetic proteins (BMPs) [23].

BMPs are biologically active molecules that have the ability of initiating new bone formation, and they used for clinical applications in combination with biomaterials, such as bone-graft replacements to stimulate bone repair. On the contrary, the bone that is forming by degradation of PLA was in very small quantity. Hence, PLA copolymers used to overcome the problem of low molecular weight PLA. Chang *et al*., (2007) produced PLA scaffold and analyzed the ability of the scaffold, which acts as a carrier for the recombinant bone morphogenetic protein 2 (rhBMP2) [24].

(b) PLA in Wound Management: PLA and their copolymers used in various applications of wound management, like for making surgical sutures, healing dental wounds, and preventing postoperative adhesions. Li *et al*., (2011) analyzed the capability and contingency of PLA ureteral stents used for treating the ureteral injuries. PLA stents are degradable type that later can be removed from human body [25]. Consequently, PLA stents displayed a promising future in the treatment of ureteral injuries. Qin *et al*., (2006) in his work used PLA polymer blends to prevent postoperative adhesions. The PLA blends are more flexible as compared to pure PLA because the mechanical properties of pure PLA such as tensile strength, Young's modulus and glass transition temperature were higher as compared to the PLA blends [26].

Brekke mentioned the use of PLA for improving the ability of dental wound healing, and they mentioned that a surgical dressing made from PLA

could reduce the incidence of mandibular third molar extraction wound failure [27].

(c) PLA in Drug Delivery System: In drug delivery systems, the drug could release persistently for different period up to one year. PLA are using in drug delivery system because it is completely biodegradable, it has better encapsulation capacity, biocompatible and less toxic. Polymeric drug release occurs in three ways: erosion, diffusion and swelling. The degradation occurs when water enters the biodegradable polymer containing monomers connected by ester bonds with each other. The ester bonds breaks randomly by hydrolytic ester cleavage, leading to subsequent erosion of the device. For degradable polymers, erosion occurs by two methods, which are homogeneous / bulk erosion and heterogeneous / surface erosion [28]. PLA and their copolymers in the form of nano-particles were in the encapsulation process of many drugs, such as psychotic, restenosis, hormones, oridonin, dermatotherapy, and protein (BSA) [29]. Methods to obtain these nano-particles are solvent evaporation, solvent displacement, salting out, and emulsion solvent diffusion. Ling and Huang [30] used the poly (lactic-co-glycolic) acid nano-particles for loading the drug, paclitaxel.

Rancan *et al*., (2009) investigated the use of PLA nanoparticles (PLA - NPs) loaded with fluorescent dyes as carriers for trans-epidermal drug delivery [31]. PLA - NPs produced by solvent evaporation method. In this method, PLA first dissolved in acetone, the solution was then mixes with an aqueous solution with continuous stirring, and the solvent was then allowing evaporating under lowered pressure at room temperature to obtain the PLA - NPs. To obtain fluorescent particles, where fluorescent dye along with PLA dissolved in acetone and then same method followed. PLA-NPs examined on human skin were ideal contenders for designing of drug delivery systems, which could target active compounds into hair follicles.

(d) PLA in Orthopedic Devices: Biodegradable polymers used in orthopedic applications to avoid a second surgical procedure to remove unnecessary hardware. PLA polymers are required to prepare biodegradable suture anchors, screws and fixation pins [32]. These absorbable screws and pins have been widely used in clinical applications, more commonly where high mechanical strength was not required. In some cases, high mechanical strength of the PLA was required, so that techniques used to improve the mechanical properties of PLA, specifically impact tensile strength and modulus of fracture in bone fixation, where both metal and biodegradable plate, pins and rods has limited their applications in fracture fixation [33]. Bostman *et al*., [34] mentioned that PLA copolymers were bio-compatible in the human body. They also stated their risk that 6 out of 120 patients treated with pins manufactured from copolymers of PLA / PGA might develop an aseptic cavity at the emplacement site, which is very low and resolved by further modifications [35].

2. Poly lactic-co-glycolic Acid (PLGA): PLGA is one of the most beneficial synthetic biodegradable polymers used in the biomedical field and has been approved by FDA (US Food and Drugs Administration) and European Medicine Agency) [36]. PLGA has attracted significant interest as a principle material for medical applications because of its biocompatibility and biodegradation rate depending upon the molecular weight of polymer and ratio of its copolymer. According to FDA, PLGA is safe to use in human body, provided better interaction with biological materials by modifying its surface properties.

PLGA is a hydrophilic, crystalline polymer with comparatively fast deterioration rate as compared to other biodegradable polymers. Typically, the PLGA co-polymers are preferable compared to its constituent homo-polymers for the mixture of bone replacement constructs, as PLGA recommend high-grade control as compared to its degradation properties by differing the ratio of its monomers. The PLGA offers broad range of degradation rates, controlled by amalgam of the chains, both hydrophobic / hydrophilic and crystalline nature of the polymer [37]. PLGA is usually used in conjunction with other materials including ceramics, biologically active glass, in order to provide PLGA more bionics and able to intensify bone reformation [38]. Hence, PLGA - based bone replacements have classified according to their types and application: such as scaffolds, fibers, hydrogels or microspheres [39].

Synthesis of PLGA: Different kinds of PLGA can obtain by using different ratios of lactide and glycolide. These are classified on ratio basis of monomers used. The ratio of the general PLGA is 75: 25 (where 75% lactic acid and 25% glycolic acid). Different processing techniques are use for synthesizing PLGA and the physico-chemical properties of the final product strongly affected by the process parameters. Among all the processes, the solution poly-condensation process of Lactic acid and Glycolic acid at 120 °C with continuous removal of water permits the production of low molecular weight PLGA (< 10 kDa) [40, 41]. The enzymatic ring-opening polymerization takes place in presence of enzyme lipases, under favourable reaction conditions including temperature, pH and pressure, but this reaction is time consuming, as a result low molecular weight PLGA gets produced [42].

Properties of PLGA: Physical properties of PLGA depends on various parameters, such as molecular weight of the monomers, the ratio of lactic acid and glycolic acid, the response time to water and the temperature at which it can be stored [43]. PLGA found in two forms such as D and L-isomers, due to presence of two enantiomeric isomers of lactide (*e.g.* D and L isomers, based on the position of pendant methyl group present on the alpha carbon of PLA). While Glycolic acid does not have the methyl side group (as compared to Lactic acid), that makes it highly crystalline, copolymers of PLGA are amorphous in nature. PLGA degrades by breakdown of its ester linkages, *via* bulk or heterogeneous erosion, in aqueous environments.

Thoroughly its degradation is carried out in three steps: (i) Hydration: where water gets perforated through the amorphous region and obstruct hydrogen bonds and the Vander Waals forces, as a result glass transition temperature (Tg) decreases. In initial degradation, covalent bonds cleaved by decreasing molecular weight. (ii) Constant degradation: auto-catalyzation of the degradation process by the carboxylic end groups, and mass loss occurs when covalent bonds in the backbone gets cleaved in bulk, as a result they lose their integrity. (iii) Solubilization: the fragments are then broken down into molecules that are soluble in the aqueous environment [44]. PLGA dissolved by using different solvents such as chlorinated solvents, tetrahydrofuran, acetone or ethyl acetate [45] and it can be drawn into different shape and size, which can encapsulate bio-molecules of different size range.

Besides degradation, Lactic acid and Glycolic acid obtained as by-products. The degradation rate of PLGA is long lasting and affected by wide range of parameters. Increased molecular weight of conventional PLGAs (*i.e.,* from 10-20 to 100 kDa), absorbs less amount of water and degrade at very slow rate, therefore, due to presence of methyl side groups in PLA, PLGA is more hydrophobic as compared to PGA. In contrast to this rule there is a copolymer (having PLA and PGA in ratio 50:50) which degrades rapidly. Stereochemistry, the most frequently used mixture of monomers for fabrication of PLGA are D and L-lactic acid monomers, because the penetration of water is high in amorphous region of D, L monomer, that accelerates the rate of degradation of PLGA.

Functionalization of end-groups: the end-capped polymers having ester end (opposed by free carboxylic group) indicates longer degradation half-lives [46, 47]. However, the degradation behaviour of PLGA is highly influenced by the shape of the device based on the penetrability of water. Moreover, the surrounding media that is acidic in nature escalates the degradation rate of the PLGA owing to autocatalysis. Shaui has given a detailed description of the preparation of porous scaffolds of PLGA / nano-HA composite through selective laser sintering, with well-governed pore architectures, in addition, high manifestation of the biologically active ceramics on the surface of the scaffold [48].

Conclusively, the glass transition temperature (Tg) of the PLGA studied to be above 37 °C and, thus, PLGA exhibit glass-like behaviour, displaying the rigid chain structure. Moreover, the glass transition temperature (Tg) of PLGA will decrease, if the lactic acid contents in the copolymer decreases, as well with decrease in molecular weight of the copolymer [49].

Medical Applications of PLGA:

PLGA used in Bone Tissue Engineering:

A) Porous PLGA-HA Scaffolds: Kim and his co-workers (2006) reported a novel method for

producing a polymeric / nano - HA composite scaffold through gas forming and particulate leaching (GF/PL) method without making use of organic solvents [50]. The scaffolds produced by gas forming and particulate leaching (GF/PL) exhibit highly porous structure, shows intensified mechanical properties and an outstanding growth of cell, the activity of alkaline phosphatases and *in vitro* mineralized scaffolds in comparison to scaffolds fabricated by the solvent casting / particulate leaching (SC/PL) method.

Ebrahimian - Hosseinabadi [51] in 2011, by using thermally induced phase separation (TIPS) method, prepared a bionic scaffold at temperature 60 °C, depending on PLGA and a Nano - biphasic component (nBCP), containing powdered forms of HA and β-tri-calcium phosphate as stiffening materials. The maximum and optimum values of yield strength and Young's modulus, amongst the scaffolds obtained by composites of nBCP were 20% - 30% (w/w) [52].

B) Fibrous Scaffolds: These scaffolds are supposed to have exceptional potential for bone tissue reformation. Several processes to obtain micro and Nano-fibrous composite scaffolds have used [53]. Morgan (2007) used the wet-spinning method for obtaining hollow fibers, as scaffolds applied in combination with human bone marrow stromal cell that helps in initiating natural bone fixation and reconstruction [47]. In comparison, the nano-fibrous composites possess similar structure to natural bone extracellular matrix (ECM) and they can take secondary stimuli to the cultured cells.

The electro-spinning is the process, that represent simple and versatile technique used for fabricating extremely thin non-interweaved fibers whose diameter is in nanometers to microns range [54]. Furthermore, in bone regeneration electro spun fibers are assumed to play a role in sustaining mechanical properties, still as allowing bio-degradability, and acting as a real osteoconductive scaffold after addition or being coated by ceramic particles [54, 55].

C) Hydrogels: Hydrogels are another class of scaffolds that commonly used for tissue engineering applications. Hydrogels, such as fibrin, hyaluronic acid and Pluronic F127, have shown promising result for effective growth factor delivery [56]. As reported by Dhillon *et al*., [57] blending PLGA with a plasticizer, such as poly - ethylene glycol (PEG), allows the production of temperature-sensitive material with a reduced Tg of 37 °C. This scaffold system has recently demonstrated to assist bone repair *in vivo* in a murine calvarial defect model [59]. However, there are drawbacks to use hydrogels for bone regeneration as they have low mechanical strength, which can hinder their individual use as bone replacements [58].

D) Injectable Microspheres: Amorphous PLGA copolymers are suitable for biomedical applications, as provides a more homogeneous dispersion of the active species in the polymer matrix [59]. The PLGA microspheres were fabricating by conventional oil / water emulsification method to obtain biomimetic Injectable microspheres by addition of HA. Recently, negatively charged inorganic HA nanoparticles were assembling together with positively charged PLGA microspheres dispersed in deionized water to create a cohesive colloidal gel [60]. This material was held together by electrostatic forces that may be disrupted by facilitate extrusion, moulding, or injection.

PLGA in Dentistry: PLGA materials prove to be effective in a wide variety of dental applications. These used in a multitude of ways, from developing screws for bone fixation [61 - 63] treating periodontal pathogens [64] and producing buccal mucosa [65] or indirect pulp-capping procedures [66, 67]. PLGA can be used in periodontal treatment, for better local administration of antibiotics and to decrease the systemic side effects of general antibiotic delivery [68] in the form of PLGA implants, disks [69], and dental films [70].

In addition, gel composite fabrics of PLGA used in bone regeneration [71], as high degradable PLGA and SiO_2 - CaO gel nonwoven fabrics that exposed to simulated body fluid for 1 week led to a deposition of a layer of apatite crystals on their surface [72]. Granular composite of gatifloxacin-loaded PLGA and b-tricalcium phosphate is local delivery means in the treatment of osteomyelitis, as the composite managed to deliver gatifloxacin slowly and showed sufficient bacterial activity *in vitro* against

Streptococcus milleri and *Bacteroides*n *fragilis*, microorganisms responsible for osteomyelitis. Also, after only 4-week implantation GFLX-loaded PLGA and TCP managed to significantly reduce the inflammation and support the osteoconduction and vascularization of the treated sites in rabbit mandible [73]. Moreover, sterilized PLGA scaffold is a promising material for producing tissue engineered buccal mucosa [67]. Additionally, PLGA composites with bio-ceramics can be used in direct pulp capping [74,] either by incorporating growth factors into PLGA micro particles or by direct pulp capping with PLGA composites of mechanically exposed teeth.

However, no hard tissue in direct pulp capping with PLGA and pulp necrosis was evident due to the low adhesion of PLGA to the pulp despite the biocompatibility shown in cellular test. Therefore, PLGA composites with bio-ceramics remain a better option than PLGA alone in pulp capping, with better tissue response as compared to calcium hydroxide [68]. The promising results of the PLGA materials suggest the need for further studies mainly in the domain of delivery of substances to the dental tissues or concerning the pulp capping abilities exhibited by the PLGA composites.

3. Poly (ε- caprolactone) (PCL): In early 1930's one of the earliest polymers synthesized by the Carothers group was Poly caprolactone (PCL) [17]. PCL became commercially available and various efforts required in order identifying synthetic polymers that can degrade with the help of microorganisms [75]. PCL can be produced either by ring-opening polymerization of ε-caprolactone by making use of various catalysts (including anionic, cationic and co-ordination) or by free radical ring-opening polymerization of 2-methylene-1- 3-dioxepane [76]. PCL is hydrophobic (water fearing) and semi-crystalline in nature; its crystallinity decreases with increase in molecular weight. The properties of PCL such as good solubility, low melting point (59 - 64 °C) and extraordinary blending compatibility has encouraged thorough research into its potential application in the biomedical field [77,].

Therefore, during the resorbable-polymer-boom, in 1970s and 1980s, the PCL and their copolymers were extensively used in variety of drug-delivery devices. Several advantages of PCL such as: its degradation kinetics and mechanical properties can be tailored, ease of shaping and manufacturing allows suitable pore sizes that are favourable to growing tissue and permits the controlled delivery of drug encapsulated within their matrix. For enabling favourable cell response functional groups added, that provides the polymer more hydrophilicity, adhesiveness, or biocompatibility. Owing to the fact that PCL degrades at very slow rate as compared to poly glycolide (PGA), poly D, L-lactide (PDLA) and their copolymers and hence they were initially used in drug-delivery devices that remain functional for over 1 year and also in suture materials (Maxon TM) that degrades slowly.

The medical device industries were eager to replace metal devices (such as plates, screws, nails, *etc.*) by using biodegradable material for fabricating implants; although PCL have poor mechanical properties to be used for high load bearing applications. Additionally, both the medical device and drug-delivery community accounted that faster resorbable polymer also had fewer percieved disadvantages corresponding to the long-term degradation (the degradation time for PCL is around 3 - 4 years) and intracellular resorption pathways.

A comeback of PCL has propelled back into the domain of biomaterials with the rise of a new field, specifically tissue engineering. The huge comeback of PCL during the 1990's and 2000's has originated from the understanding that PCL possesses better rheological and viscoelastic properties over many of its resorbable-polymer counterparts, which render it easy to fabricate and manipulate into a large range of scaffolds [78, 79,] . In fact, PCL can be used in wide variety of scaffold manufacturing technologies and its comparatively economical manufacturing routes, as compared to other aliphatic polyesters, is highly advantageous.

Synthesis of PCL: PCL is synthesized by the ring-opening polymerization of the cyclic monomer ε-caprolactone and was studied by Carothers and his colleagues in early 1930's [17]. PCL is a semi-crystalline in nature, the glass transition temperature (*Tg*) of PCL is -60 °C and melting point may vary from 59 and 64 °C, determined by the crystalline nature of PCL which permits the

ease of formulation at comparatively low temperatures. The average molecular weight of PCL may differ from 3000 to 80,000 g/mol and can classify based on their molecular weight [80]. PCL is completely dissolvable in variety of solvents at room temperature including chloroform ($CHCl_3$ or trichloromethane), dichloromethane (DCM or methylene chloride), carbon tetrachloride (CCl_4), benzene, toluene, cyclohexanone ($(CH_2)_5CO$) and 2-nitropropane (2-NP). PCL has less solubility in solvents such as acetone, 2-butanone (also known as methyl ethyl ketone (MEK)), ethyl acetate (EA), dimethyl formamide (DMF) and acetonitrile (CH 3CN) and is indissoluble in alcohol, petroleum ether and diethyl ether [81]. It has been use in conjunction with other polymers such as cellulose propionate (CP), cellulose acetate butyrate (CAB), polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA) for influencing the release rate of drug from microcapsules [82].

The compatibility of PCL with different polymers relies on the ratios involved and is mostly use to have better command over the penetrability of the delivery systems. PCL copolymers can be made using several monomers, *e.g.*, ethylene oxide (C_2H_4O), polyvinylchloride (PVC), chloroprene (commonly known as Neoprene), polyethylene glycol (PEG), polystyrene (PS), diisocyanates (urethanes), tetrahydrofuran, diglycolide, dilactide, valero lactone, substitutes of caprolactones, 4-vinyl anisole (methoxy styrene), styrene (ethenyl benzene, vinyl benzene, and phenylethene), methyl methacrylate (MMA) and ethylene vinyl acetate (EVA) [83].

Biodegradation: PCLs can be biodegraded with the help of bacteria and fungi that are outdoor living organisms, but they cannot biodegrade in the bodies of animal and human because they have the lack of suitable enzymes [84]. However, that has not to say that they are not bioresorbable, but preferably, that the procedure takes much longer, propagate through hydrolytic degradation. It is broadly accepted that hydrolytic degradation of poly (-hydroxy) esters begin through either surface or bulk degradation pathways.

Surface degradation or erosion implies the hydrolytic scission only at the surface of the polymer backbone [85]. This situation appears when the rates of hydrolytic cleavage of chain and the making of oligomers and monomers, which disperse into the surroundings, is rapid than the rate of water intrusion into the polymer bulk. This generally results in thinning of the polymer with respect to time without influencing the molecular weight of the inner bulk of the polymer, which would usually remain unchanged over the period of degradation [86]. When the water enters the entire polymer bulk degradation occurs, that because the hydrolysis all over the entire polymer matrix due to random hydrolytic chain scission, an overall reduction in molecular weight takes place. When the water molecule diffuses into the polymer bulk, hydrolysis of the chains enables the monomers or oligomers to diffuse out of the polymer bulk, slowly erosion will occur and equilibrium for the diffusion - reaction would attained.

The internal autocatalysis was provoked by the degradation mechanism through the carboxyl and hydroxyl end group by-products when the equilibrium of diffusion reaction was disturbed. Because the surface oligomers and carboxyl groups may freely diffuse into the surroundings (during the surface erosion condition), while in the case of bulk degradation an acidic gradient can be produced in the form of the newly generated carboxyl end group formed during the cleavage of ester bonds by the internal concentration of autocatalysis products. This, in turn, increases the internal degradation as compared to the surface, resulting in as an outer layer of higher molecular weight skin along with a lower molecular weight, degraded, interior.

When the internal oligomers become small enough that quickly diffuses *via* the outer layer, followed by the beginning of weight loss, and decreased rate of chain scission producing a hollow structure having the higher molecular weight. The quick release of acid by - products and these oligomers can result in inflammatory reactions *in vivo*, as described in the literature of bioresorbable device [87]. In addition to poor vascularization or low metabolic activity, local and temporary disturbances may arise to the surrounding tissue unable to buffer the pH change this has been observed from an example of fiber-reinforced PGA pins used in the orthopedic surgery due to which osmotic pressure is increased by the local fluid accumulation at the time of rapid degradation [99].

The homopolymer PCL takes total degradation time of 2 – 4 years (depending upon the initial molecular weight of the device) [88]. The rate of hydrolysis can be changed by copolymerization by making use of other lactones or glycolide / lactide. Various other studies on degradation using PCL in different *in vitro* (saline) and *in vivo* (rabbit) conditions describes that both the rates of hydrolytic degradation were similar, and thus concluded that involvement of enzymes was not a significant factor in the first degradation phase (that is 0 – 12 months) in the process of degradation [89].

The PCL go through a two - stage degradation process: firstly, the hydrolytic cleavage of ester groups that is non-enzymatic, secondly, when polymer is crystalline in nature and having low molecular weight (< 3000). Ali and coworkers (1993) [90] studied the mechanism of *in vitro* degradation of PCL with the help of gel permeation chromatography, differential scanning calorimetry and scanning electron microscopy. Persenaire and coworkers (2001) [91] suggested mechanism of two-stage thermal degradation of PCL and it was observed in the first stage that there was a statistical breakage of the polyester chains through pyrolysis reaction of ester. While the second stage leads to the formation of ε-caprolactone (which is a cyclic monomer) as result of an unfastening process of depolymerization.

Sivalingam and coworkers studied the thermal degradation in two ways in bulk and solution [92] and observed that the polymer degraded by random cleaving of the chain and specific cleavage of chain at the end in solution and bulk, respectively. Pitt and coworkers displayed that, the *in vivo* degradation mechanism of PCL, PLA and other copolymers was qualitatively. The rate of degradation of random copolymers was higher as compared to those of the homo polymers under same conditions [93]. Furthermore, the rate of degradation of PCL / PLA block copolymers was observed to be an intermediate of PCL or PLA homo polymers and it will increase with increase in PLA content ranging from 0 – 40% [94].

Although, when the content of PLA was greater than 40%, the rate of degradation was observe to increase as compared to that of the homopolymer [95]. The degradation kinetics of PCL extremely depends upon the molecular weight of the polymer. The structures having high molecular weight take more time to degrade, as moderated through the length of the polymer chain. The polymers with higher molecular weight increases the length of the chain requiring the cleavage of large number of ester bonds as a result it generate water-soluble monomers / oligomers which helps in proceeding erosion; degradation accordingly takes longer time. Recently Sun and co-workers outlined a long-term study in which degradation of PCL *in vivo* observed in rats for 3 years [96]. In rats, for the detection of the rates of distribution, absorption and excretion of PCL, radioactive labelling was use.

The results displayed that the shape of the capsules made of PCL with an initial molecular weight of (66,000 g/mol) remain intact after 2-year implantation, and can be broken down into low molecular weight (8000 g/mol) particles at the end of 30 months. The molecular weight of PCL reduced linearly with respect to time. Into the subcutaneous layers in rats, PCL linked with Tritium with molecular weight 3000 g/mol was implants for investigating the absorption and excretion. The first radioactive tracers detected after 15 days of implantation in plasma. Simultaneously, radioactive excreta recovered from feces and urine. Since, 92% of the accumulative radioactive tracer that were implanted gets excreted through excreta and urine after 135 days of implantation [97].

Pulkkinen [98] and his coworkers manifested that PCL linked with 2,2-bis (2-oxazoline) (also known as PCL-O) was degraded enzymatically *in vitro* through surface erosion, which allows the novel use of PCL-O for drug delivery system and various other medical applications. The *in vivo* evaluation of the rate of degradation, erosion (causes weight loss) and toxicity of PCL-O poly (ester-amides) was done. PCL along with the three PCL-O polymers having different block lengths of PCL (such as 1500, 3900, 7500 g/mol) were melt-pressed to form the discs and implanted in (Wistar rats) in subcutaneous layer (dosage was ~340 mg/kg) at the time ranging from 1week, 4 weeks and 12 weeks. After 12 weeks of an implantation, weight loss of polymer discs was observed up to 16.5% for the most considerably linked PCL-O polymer (whose block length 1500 g/mol),

although no weight loss was noticed with other polymers. NMR, differential scanning calorimetry (DSC) and gel permeation chromatography (GPC) techniques also scanning electron microscopy (SEM) micrographs pre and post implantation were carried out and *in vitro* hydrolysis studies inclusively indicates the *in vivo* surface erosion of PCL-O polymers based on the enzyme.

The *in vivo* evaluation shows that the PCL-O polymer is highly compatible, safe and sensitive towards enzymes. The *in vivo* evaluation was base on the conclusion of the studies such as hematology, clinical chemistry and histology of the area and organs of the implantation (such as heart, liver, kidney, brain *etc*.) [99]. In the last a few decades more than 1000 papers being published the literature of the biomaterials and tissue-tissue-engineering, which used scaffolds, based on PCL, only a few researchers have mentioned the methods of the degradation and the kinetics of resorption of the scaffolds made of PCL [100].

PCL in Drug-Delivery Systems: PCL is suitable for controlled delivery of drug due to various advantages: high permeability for several drugs, excellent biocompatibility and it can completely excrete from the body once get bio-resorbed. PCL is suitable for long-term drug delivery system expanding up to more than 1 year because the rate of its biodegradation is slower than that of other polymers. PCL also has the capability of making compatible blends by using other polymers, which can influence the degradation kinetics; it can also ease the altering to fulfill desirable drug release profiles [101].

The rate of drug release from PCL based on factors such as the type of formation, techniques of preparation, the content of PCL, percentage, and size of the drug loaded within the microcapsules. Because PCL has higher permeability so it has mixed with other polymers for improving stress, resistance against cracks and for controlling the release rate of the drug. In last few years, PCL have become a major area of research in order to develop controlled drug delivery systems mainly used for proteins and peptides [102]. Lemmouchi and his co-workers have studied the *in-vivo* and *in-vitro* release of the drugs that have selected such as isometamidium chloride and ethidium bromide from the rods made up of poly caprolactone-poly L-lactic acid (PCL–PLLA), poly caprolactone-poly D-lactic acid (PCL–DLLA) and PCL–TMC [103].

PCL Applied in Tissue Engineering: An interdisciplinary field of science that use the principles of life sciences and engineering in order to obtain biological replacements that helps in replacing, retaining, or improving the functions of whole organs or tissues (including bone, cartilage, and blood vessels) is known as tissue engineering [104]. Certain structural and mechanical properties required by the tissues involved in the repairing process of tissues for appropriate functioning. The term tissue engineering is also being involved in performing specific biochemical functions employing cells inside a support system that artificially created (including an artificial liver, or pancreas).

In tissue engineering, some powerful developments made that helps in yielding a unique set of implementation strategies and tissue replacement. A unique opportunity has been create for fabricating tissues in the lab from the blends of engineered extracellular matrices (also known as "scaffolds"), biologically active molecules and cells by making scientific advancements in stem cells, growth and differentiation factors, biomaterials, and biomimetic environments.

Due to the low melting point, superior rheological and mechanical property, PCL has gain a lot of attention as biomaterial in cardiovascular and bone tissue engineering. PCL is a biomaterial, which offers itself extremely well for the fabrication of scaffold. PCL is an extremely adaptable bioresorbable polymer and because of its accomplished rheological properties it can be utilized approximately by any of the polymer processing technology for producing wide range of scaffolds [6].

The scaffolds are of supporting the attachment of cells, cell proliferation and *in vitro* differentiation and it can transplant *in vivo*. There is a broad range of techniques used for manufacturing scaffolds for tissue engineering, but one should pay attention to the specifications of the scaffolds and for understanding the exchange of factors influencing the composition and design criteria of the material. The most advantageous characteristic of any

polymeric scaffold implantable material will be co-ordination of degraded polymer by the substitution of the natural tissue produced by the cells.

The kinetics of resorption and degradation of the scaffold are created to permit the implanted cells to increase rapidly and secrete their individual extracellular matrix in the dynamic and static cell-implantation stage (that is from 1 - 12 weeks) as associated with the scaffold slowly resorbs leaving enough places for cell multiplication and the growth of new tissues. The 3D scaffolds were used to maintain the physical support till the time engineered tissues have adequate mechanical integrity to support it. Chen *et al*., (2015) have been fabricated 3D nanofibrous scaffolds composed of poly-(ε-caprolactone) (PCL) using the electro spinning method [105]. The following features are advantageous for scaffold candidates[106].

The growth of cells and transport of metabolic waste and nutrients requires 3-D and extremely permeable structures with having an interconnected pore network. Bioresorbable and biocompatible material with controlled rate of resorption for matching the *in-vivo* and / or *in-vitro* growth of cells / tissues. The appropriate surface chemistry of biomaterials is required for the attachment, proliferation and differentiation of the cells. The mechanical property of biomaterial should match the properties of tissues at the implantation site.

CONCLUSION: As according to this reported brief review, the biodegradable biopolymers such as PCL. PLA and PLGA could have various biomedical applications such as in tissue engineering, drug delivery and biomedical devices due the good biocompatibility and bioresorbable property. In addition, however the biopolymers have several biomedical applications a few chemical and physical modifications is required to improve the mechanical property to completely get absorbed into the implanted site. The development of modified and blended biomaterials to make it biocompatible and less crystallized is cost effective. A few academic attentions are required for the development method to prepare bio-compatible bioplastics and application in other biomedical field for the next generation implantation.

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