Overview of Polylactic acid and its derivatives in medicinal applications

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Abstract. Biopolymers are most commonly used in many medical applications nowadays. Polylactic acid is widely used for many biological applications due to its biocompatible, biodegradable, and non-toxic properties. In this review, Polylactic acid usage in medical applications like tissue engineering, fracture repairs, orthopedic, drug delivery carriers, antimicrobial agents, stents is considered. The current medical field scenario briefly reviewed to assess Polylactic acid's potential usage and its derivatives in biomedical applications.

1. Introduction

Lactic acid-based polymer degrades by hydrolysis in the human body quickly and does not produce a harmful compound. Poly Lactic acid (PLA) is preferred in medicinal applications. PLA is a thermoplastic having properties like bio-compatible and biodegradation, and PLA is obtained from lactic acid. This PLA was found by Carothers in 1932, by heating lactic acid under vacuum. Later, DuPont [1] made PLA in higher molecular weight, and it was patented in 1954. The primary method for producing lactic production is from natural materials containing Carbohydrates such as rice and corn. This PLA is used in many medical applications, mainly in tissue engineering, such as scaffolds for autografted new skin, wound covers.[2] This tissue engineering field might be a new method. However, a replacement of the nose by Gaspro Tagliacozzian and anatomy at Bologna's university back in the 16th century. (1546-99) [3].

In 1976, ESB (European society for biomaterials) defined a biomaterial as the "nonviable material which is to interact with biological systems" but now ESB is defining it as "material intended to interface with the biological system to evaluate, treat, augment or replace any tissue, organ or function in the body." This shows the increase in the usage and application of PLA. The significant advantages of PLA are they do not damage bones when placed in the body; they reduce the medical cost because the second stage of surgery is not required for removing the implant. Bioabsorbable polymer makes cells to regenerate tissue and release Drugs like antibiotics, painkillers, and anti-inflammatories. This polymer will not block the passage to computed tomography (CT) scans. The major disadvantages are low toughness and slow degradation rate. This can cause an inflammatory reaction, and it can be overcome by blending with D-lactic acid, D, L - lactic acid monomers, or monomers like Glycolide[2]. PLA is a
3D-printable bio-polymer which, in addition, strengthens its role during (COVID-19) pandemic. In 2016 11% of the annual increase was experienced by the bioplastic field, which results in a revenue of more than 2.6 billion USD. FDA (food AND DRUG administration) has approved PLA to make contact with biological fluids. PLA, joined with HA (Hydroxyapatite), had secured great success in this field. PLA capability can be explained more in the formation of new bone, especially scaffolds of pla can achieve this output with the assistance of glass-like calcium phosphate.[5] PLA is a bioabsorbable polymer, and it is used as plates or screws, and orthopedic surgeons use that in recent days [4]. There are mainly three lactic acid polymers they are PLA, PDLA, PDLLA. Each of them has a different glass transition (Tg) and melting temperature (Tm). Among them, PLLA has the highest Tg and Tm. PLA is used in various fields, but it plays a vital role in a biomedical application, specifically sue to the advanced discoveries in the micro and nano level PLA based materials. Further, PLA polymer can be utilized in all kinds of manufacturing processes in order to produce the desired the medical implants or instruments.

In this paper, PLA usage in medical applications has been reviewed under four main categories, as shown in Figure 1.

![Polylactic Acid (PLA) in Medicinal Applications](image)

Figure 1. Applications of PLA in different categories of medical treatments

2. Tissue Engineering
Tissue engineering is a promising methodology in treating malfunction or lost organs where patients are treated by utilizing their cells. Polymer support for recovery usually happens. Additionally, they help in cell attachment, advancing cell development. They are exceptionally permeable with a colossal surface volume proportion, precisely rigid, and pliant. These polymers are prepared by basic hydrolysis, which can be processed by the human body and hence are utilized for bio clinical application [5].

The PLA nanofibrous scaffolds have desirable, including high surface area, biomimicry of local extracellular architecture, and mechanical property, which make it reasonable for designing scaffolds for a specific organ transplant, for example, musculoskeletal, apprehensive, cardiovascular, and cutaneous tissue building [6]. The tissue-Engineered skin (ES) provides more benefits than skin autografts for the treatment of consuming wounds. Scaffolds were created with bioactive gelatin shells and biodegradable cores of polylactic acid (PLA) and polycaprolactone (PCL) and checked with gelatin monofilament frameworks. It is observed that mechanical properties were fundamentally upgraded utilizing CoA scaffolds. Instead, its capacity to cure these injuries, designed skin shows diminished biomechanical properties, which lead to increased inflammatory response, in an extreme case, it leads to graft rejection, making it difficult to make and precisely apply [7].

A contextual analysis examining human fat tissue’s capacity, multipotent immature stem cell to be conveyed to and get by inside the bladder, and urethral smooth muscle has been finished. Lipoaspirate was obtained from female patients and was handled to yield a pluripotent populace of prepared lipoaspirate (PLA) cells. For tissue delivery, PLA cells were fluorescently marked and suspended in Hanks’ solution. To consider PLA reasonability in different creature models of 8 Rnu athymic hamsters and 6 SCID mice were infused with PLA cells into the bladder and urethra. Test and control creatures
were consumed 2, 4, 8, and 12 weeks after infusion, and the bladders and urethras were examined. Assessment 2, 4, 8, and 12 weeks after infusion showed PLA cell suitability and capable of fusing into the beneficiary smooth muscle [8].

The traditional electrospinning process manufactured fibrous scaffolds with various proportions of polylactic acid and Chitosan. After crosslinking by the glutaraldehyde fume, it is discovered that the diameter of PLA fiber diminished, and mechanical properties were improved. PLA to Chitosan in proportions of 7:1 was found to help cardiomyocyte suitability, inspire cell elongation, and improve sarcomere α-actinin and troponin I. PLA/chitosan filaments have incredible potential for building heart tissue and for fastening the regeneration of myocardia [9].

3. Bone Repair

PLA was widely used for bone therapy, like the implementation of medicinal implants after injury. However, the infection caused due to the presence of bacteria damages the healing and repairing ability of the bone tissue. Silver nanoparticles aligned on the inner of polylactic acid and gelatin composite fibers by electrospinning for improving the backlog faced while using other bone implant materials. However, these silver nanoparticles promoted the nucleation, and the development of calcium salt on the fiber takes place. Excellent adherence and proliferation on composite fiber's surface were possessed by the vascular endothelial cells and resulted in fine angiogenic properties. Polylactic acid/gel mass ratio of 91:9 and the average silver content of 7% given the encouraging results in the experimental laboratory conditions [10].

In critical defect sites present in bone, the grafts of granular types can be filled and which also results in the formation of interlinked voids by piling up of granules, led to the formation of bone tissues and blood vessels. The freeze dripping method was used to fabricate Poly (lactic-co-glycolic acid)/calcium phosphate cement composite (PLA/CPC) pellets, which had the structure of sea island [11]. Calcium phosphate (Cap) based materials showed outstanding bioactivity and biocompatibility, which made it vulnerable to be used for biomedical applications. Amorphous salt of calcium (calcium phosphate) nanospheres and Hydroxyapatite (HA) nanorods were intermixed with Poly (d,l-lactic acid) (PLA) to manufacture the composite nanofibers exhibit the good mineralization behaviors in simulated body fluid. ACP-PLA and the HA-PLA composite nanofibers exhibited strong biocompatibility. The bone defect repair properties of the ACP-PLA and the HA-PLA composite nanofibers within our body were primarily studied, And results were favorable for the application of nano PLA fibers [12].

The critical role possessed by bone repair is to align the dislocated bone quickly and to heal it. The use of metals in fixation devices causes various problems like reduction in bone density, palpation, and temperature sensitivity. In order to avoid this complexity, PLA is preferred. From the biowaste of fish scales, Hydroxyapatite is obtained and filed in the PLA matrix to form the bio-composite of PLA/HAp. At various compositions of HAp, different properties such as thermal and mechanical properties were analyzed. The observation resulted that the PLA/HAp bio-composite had a potential significance towards an open reduction in palpation and sensitiveness in internal fixation devices of fractured bone [13].

Various studies showed that the nanotopography of materials plays a key role in directing stem cell differentiation. Biodegradable nanopillar arrays of polylactic acid (PLA) of various diameters were produced using anodic aluminum oxide nanowall arrays as a template. Fabricated nanopillar PLA is subjected into Human adipose-derived stem cells (hADSCs). The study resulted in a valuable information about the interface between stem cells and nanoarray structures, from this conclusion PLA usage in bone regeneration is affirmative. This nano array PLA are viable as patches and strips for spine fusion, repair of bone crack and tooth enamel restoration [14].
4. Drug Delivery

PLA's primary usage is in drug delivery as it can dissolve easily in extracellular environment and biodegradability property. The fundamental improvement of electrospun membranes contains the capability to acquire fine fibers of many nanometres with a vast surface area and the chance for these membranes to be controlled and handled for several distinct functions. This filed investigator measures the carry technique that manipulates the discharge of drugs from polymer-based sandwich membranes manufactured using electrospinning processes [15]. These electrospun membranes contain Poly (lactic acid) (PLA) as it is one of the particular favorable biodegradable polymers. The carry technique that governs the drug delivery was reviewed through the discharge kinetics of a bioactive means in physiological serum, which was utilized as a physical fluid simulation. Immich et al. [16] mathematically modeled the drug delivery operation by a power law, the standard Higuchi equation, and Frick's Second law was utilized and concluded that the manipulation over the discharge of the drug is conditional on the thickness of the membrane a bit than the concentration of the drug.

Conti et al. [17] evolved a procedure to yield PLA nanoparticles. The procedure includes emulsion solvent evaporation, emulsion solvent extraction, interfacial phase deposition, spray coating, and the melting method. The first aim of particle-based carries for trans epidermal drug delivery has to turn into the scope of greater attentiveness in dermatology. Rancan et al. [18] analyzed the applicability of biodegradable polylactic acid (PLA) particles filled by the fluorescent dyes as carriers for transepidermal drug delivery. The invasion figure of PLA particles (238 and 365 nm) and dye discharge from the particles was analyzed in human skin explants utilizing fluorescence microscopy, confocal laser scanning microscopy, and flow cytometry. PLA particles invaded into 50% of the vellus hair follicles, approaching a most significant distance downwards correlating to the sebaceous gland entrance in 12-15% of all detected follicles. The particles' aggregation in the follicular ducts travel with a dye discharge to the viable epidermis and its preservation in the sebaceous glands for up to 24 hours. Kinetic studies in vitro, in addition to skin explants, exposed that, although steady in aqueous solution, the disintegration of the particles and the unusual discharge of integrated dye happened upon connection with organic solvents and the skin surface. These discoveries advice that particles of PLA polymers are ideal carriers for the hair follicle.

Genotoxicological estimation [19] is a determining part of the battery experiment in a toxicological study. For the comprehensive functions of PLA, the actual work assessed the potential cytotoxic and genotoxic outcome of PLA in CHO-K1 cells and its physicochemical properties. No cytotoxic and genotoxic effects of PLA were detected by colorimetric tetrazolium assay (XTT) analysis. The clonogenic constancy assay that PLA did not interrupt the replicative cell homeostasis, neither exhibited genotoxic outcome as proved by comet and micronucleus assays. Thermogravimetric properties of PLA were not changed after contion with cells, and this film exhibited the capability to suck up and discharge Europium (111) complex. All these facts recommend the Genotoxicological well-being of PLA for more implementation in drug delivery systems.

5. Scaffolds

Maria Giovanna et al. [20] studied the highly porous scaffold prepared by the Thermally Induced Phase Separation technique (TIPS) with the help of Polylactic acid; Dicalcium phosphate dehydrates (DPCD). The pores of new scaffolds range from 10-20µm, whereas in 10Casi, it ranges from 10-100µm. The scaffolds are also used in materials for bone regeneration.

Sangamesh et al. [21] analyzed scaffolds produced by Electrospun fibers of varying fiber diameters that were performed to examine their effectiveness in the application of skin regeneration. In the electrospinning method, PLAGA is fabricated and produced matrices of varying diameters. The matrices
have an average pore diameter between 10-14µm. With the help of Human skin fibroblasts, progressive growth in fiber matrices ranging from 350-1100mm is achieved. Macro Santoro et al. [22] used the polycondensation method to produce a synthetic polyester Polylactic. These scaffolds are used in regenerative and drug delivery applications and shown progressive results. Vincenzo Guarino [23] concluded that composite scaffolds represent a valuable approach for achieving spongy tissues, which is one of the complex issues. Spongy Scaffolds are composed of ε-caprolactone matrix. Of the total porosity, High porosity degree of 79.7% was achieved. The peaks were achieved at ca10 and 200µm. By Invitro degradation, Marrow stromal cells and human osteoblasts have reached a plateau at three weeks, when then proliferate on the scaffold and promote migration of bone cells within the fiber arrangement.

Sudip Mondal et al. [24] studied the 3D printed scaffolds with different orientations to achieve optimum functionality and mechanical properties of manufacturing-based scaffolds for biomedical applications. 3D polylactic acid and Hydroxy-apatite modified PLA scaffolds made up of 3D printing mechanical properties have been examined. For load-bearing bone tissue scaffolds, Compression strength is the primary criterion. These findings help to found out that at the orientation of 90° has maximum compressive strength. For 90° 3D printed PLA-Hap scaffolds, stability up to 47.16% is produced.

Abdalla Abdal Hayet al [25] have shown reasonable interest in regenerative medicine and studied about the nanofiber scaffold. Practical application on the nanofiber scaffold is restricted due to low hydrophilicity and reduced ductility. The average fiber diameter of the coated nanofiber matrix is about 1265 ± 222 nm was found out by the research on the in situ deposition of polyvinyl alcohol (PVA) onto the post electrospun PLA nanofibers. The fiber diameter is more significant than pristine, which is about 650±180nm, by the in-vitro experiment based on EA's cell attachment and MIT assay. Hy926 human endothelial cells, cytocompatibility performance of natural, and PLA fibers with PVA is observed. Thus, more favorable attachment and proliferation behavior on hydrophilic PLA composite scaffold showed that the results of cytocompatibility on human cells were induced than that of pristine PLA.

John M. Moran told that the determination of effects of scaffold composition on physical properties, adhesion, and growth of bovine articular chondrocytes on polylactic acid (PLA) and polyglycolic acid (PGA) composites was the objective of polyglycolic acid for cartilage tissue engineering. The composites with fractional PLA contents ranging from 0 to 68% was obtained when nonwoven meshes of PGA were coated with PLA by the solvent evaporation technique. Thus, in addition to PLA, ranging from less than 1KPa for PGA to approximately 20KPa for scaffolds with 68% PLA content, the scaffold's compressive modulus linearly increases. The addition of polylactic acid content decreased the cell seeding from 48% for PGA scaffolds and 27% for 68% PLA scaffolds. Thus, the above studies provide vital information for the design of cartilage tissue engineering.

The review concluded that Polylactic acid could be engineered and suitable for many applications in medicines. Food and drug administration approved the usage of PLA in tissues, scaffolds, bone implants, etc. Many studies proved that the engineered version of PLA has low immunogenicity.

6. Conclusions
In summary, PLA and its different versions proved that they are suitable for possible biomedical applications. Various aspects like biocompatibility, immunogenicity, degradability, sensitivity are tested by many researchers and provided valuable insights on how various methodologies to produce PLA based micro and nano tissues and scaffolds. Moreover, with the aid of nanotechnology, more research work can be initiated in the future to explore the possible extended usage of biopolymers.
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