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Exploring the utilization of polylactic acid-based materials in medicine: Contemporary innovations and trends

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Abstract. A biocompatible, non-toxic substance is polylactic acid (PLA), which is also biodegradable. This material has been studied for decades and has been commercially used in some fields. The potential of defined PLA for different medical applications, including drug delivery systems, wound healing, bone implants, and vascular grafts, was described in this paper. Various methods of characterization and modification of PLA have been investigated to optimize its properties for specific applications. Typically, additional polymers are introduced into PLA to enhance its functional properties. The key feature of PLA is its capacity for degradation in the human body without introducing harmful byproducts. Adjustments to PLA composition can control degradation rates, influencing drug delivery or the persistence of implants. By applying a cold plasma treatment in order to alter the PLA-based polymer's surface, the capacity of the material to transport drugs may be changed. The change of parameters in coaxial electrospinning can produce different PLA-based products for different use. However, certain challenges remain, such as improving the adhesion of PLA and production of low-price PLA.

Keywords: polylactic acid, drug delivery, wound healing, implant, vascular graft.

1. Introduction

Polylactic acid (PLA), a new kind of degradable and nontoxic material shows great potential to be used in medical [1]. It presents little toxicity to humans and the environment, which makes it a suitable material to be used in case that needs to contact with the human body [2]. Compared to traditional materials used in the medical field, PLA poses little risk to both humans and the environment. It is an ideal choice in a situation that needs to contact the human body for a long period. It can even guide the cells to fully fix the damage and be decomposed. Nothing would leave after the damage has been fixed, since it is a biodegradable material [3]. Only lactic acid, water and carbon dioxide will be produced when it is decomposed by the human body which is the normal metabolic waste of humans [4, 5]. This means, that the degradation process of PLA does not introduce any alien and potentially harmful elements to humans and the environment. In addition, the biocompatibility of PLA is excellently great. When PLA is used in vivo, neither locally nor systemically untoward reactions will happen [6]. So it is a perfect material to be used in vivo. Almost all medical treatment tried their best to make sure the immune system will not respond to the things that need to access to inner environment of humans. PLA has been commercially used for years [7]. The most notable application is for treating cardiovascular diseases as a graft material. It can replace damaged blood vessels or bypass them. And it can degrade naturally within the body and leave no permanent foreign material inside the body, so fewer

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complications post-surgery will be presented. By reducing costs and improving preparation methods, mass production can be achieved. Another feature in synthesizing PLA is that it is a crystal structure and can be modified simply by controlling the rate of freezing, which makes it have different properties to adapt to multiple applications. One of the most important things is the crystallization structure might have effects on the properties of the final product when PLA has combined with other polymers. Since the properties of PLA is good for medicine, there are lots of limitations of pure PLA. It needs to compose with other materials to achieve ideal properties. Additional benefits of PLA are that it can be used for 3D printing [8]. The temperature required to print with PLA is about 200°C which is a relatively low temperature for material used in 3D printing. Benefiting from these safety and convenience properties, it has become a popular material to be studied.

2. Drug delivery

PLA is able to be decomposed in the human body and released non-toxic compounds such as lactic acid and carbon dioxide. These properties made it a suitable material for drug delivery. By adjusting the additive polymers on the chain release rate and target organ for drugs, PLA can be modified. However, because of its poor wettability, hydrophobicity, and absence of certain functional groups, PLA has poor adhesion. Polymers based on PLA with the addition of other polymers can solve many problems. Ammara Rafique et al. synthesized and tested pure PLA films and polyethylene glycol (PEG) based films with basic polymer in different concentrations [9]. And their surface properties were modified by cold plasma treatment. Pure PLA films of all concentrations did not form porous structures at their surface and appeared to be denser. However, the films containing both PEG and PLA showed a more porosity and permeability structure. But these properties decreased as the increase of concentration of PLA, because PLA was harder and a higher concentration of it decreased the number of pores on the surface. These samples appeared to have higher porosity and swelling ratio after being exposed to argon plasma for 1 minute. This surface structure was very suitable to deliver drugs. The size and numbers of these pores were critical for porous PLA films, because they are related to the uptake and release of drug molecules. Usually, this kind of smaller size pore and higher porosity material is suitable for wound healing.

LI Ruiduan et al. modified PLA by introducing several polymers and made the material both lipophilic and hydrophilic [10]. So It can be specialized at loading docetaxel which is an anticancer drug, and become a potential treatment for cancer. PLA was copolymerized with 2-amino-1, 3-propanediol carbonic ester (CAB) and formed [P(LA-co-CA)]. [P(LA-co-CA)] was further copolymerized with mPEG-ALD and formed [P(LA-co-CA)- mPEG]. SEM images showed that this copolymer was in the form of a regular sphere with an average particle diameter of 90 nm. The test with Na_2SO_4 showed that this copolymer was extremely stable in the physiological environment. When the load was at 9.7% which was the best condition for this material, 70% of loaded drugs can be released within 72 h. The experiment showed that introducing amphiphilic polymers to PLA is a good way to establish a drug delivery system for docetaxel.

Rancan Fiorenza et al. synthesized PLA nanoparticles and investigated the effects of it on drug delivery to the skin [11]. The penetration proles were investigated through staining analysis. Particles of 228 nm were used to load nile red and particles of 365 nm were used to load coumarin-6. Both of NP penetrated 50% of vellus hair follicles. And this result indicated that its maximum penetration depth was correlated with the deepest part of the infundibulum. The disseminated lipophilic dye penetrated the viable epidermis, diffusing towards the sebaceous gland, and eventually accumulating in the areas filled with sebum. The hypothesis that PLA nanoparticles could release the drugs that they carried within hours when topically applied on skin explants was confirmed by these results. PLA accumulated and released the loaded dye. The aggregates also formed within the hair follicle duct. These PLA particles are easy to be mass produced. Researchers are attempting to enhance the penetration prole and kinetics of medication release after successfully encapsulating a variety of medicines in PLA NPs.

Yue Na et al. synthesized nanoparticles based on Polylactic-co-glycolic acid (PLGA) to enable them to traverse the blood-brain barrier (BBB) [12]. This modification showed significant potential to

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supplant large-dose treatments that typically led to multiple undesirable side effects. The zeta potential, hydrophilicity, and particle size of the nanomaterials all had an impact on their capacity to cross the BBB. They concluded that several ligands could be employed to modify these nanoparticles further. Notably, the introduction of shuttle peptides as ligands can ensure the particles' successful passage through the BBB, leading to targeted drug delivery. PLGA-based nanoparticles, due to their mutable properties, can be adapted for a multitude of uses, demonstrating vast potential. The successful adaptation and modification of these nanoparticles open a promising path in the field of targeted drug delivery, which can result in more efficient treatment options with fewer side effects.

Zhifang Ma et al. synthesized a SiO_2-based nanocarrier coated with polylactic acid and folate in order to carry target drugs to treat cancer [13]. Since various tumor cells overexpress the receptor for Folic Acid (FA), its conjugation enhances the nanocarrier with the ability to target cancer. So cellular internalization can be improved, thereby increasing the efficiency of drug delivery to cancerous cells. Doxorubicin (Dox) was the drug used to test the target delivery ability of this material in their study. TEM image showed that SiO_2-Dox NP was spherical and monodispersed. The average diameter was around 77 nm. Results showed that PLA coating successfully prevented the decomposition of SiO_2-Dox NPs at normal physiological conditions. When NPs were adsorbed by protein in cancer cells, PLA could no longer protect SiO_2-Dox and most of the structures would be decomposed within 3 days causing medications to be released. This property minimized the risk of medicines being released too early and the long-term toxicity of nanoparticles' accumulation. As a result, this nanocarrier presents itself as a potential carrier for the delivery of chemotherapy drugs.

3. Wound healing

It is a complex process for wounds to be healed, and covering the wounds with wound dressings would increase the rate of healing significantly. One of the most important factors affecting the healing rate is keeping moisture at a suitable range. Newly grown skin cells can transfer faster to the position of the wound from the edge, which means the wound will close faster with suitable moisture. Furthermore, wound dressings can carry antibiotics to prevent bacteria reproduction and collagen to accelerate the formation rate of fibroblasts. Mehdi Hajikhani et al. packed cefazolin and collagen inside scaffolds and released them at a controllable rate to achieve a faster healing rate [14]. The core was made of PLA, and the shell was made of polyvinylpyrrolidone (PVP). SEM results showed that the surface is smooth and even. No crack was observed. The diameter of the fiber was significantly increased when PEO and cefazolin were added to PLA. Scaffolds must be strong enough to act as a wound dressing. A lower concentration of collagen will result in higher tensile strength of the scaffold. FTIR results showed that collagen and PVP formed hydrogen bonds. In general, a higher concentration of collagen samples had longer bacteria resistivity time. It can keep releasing cefazolin for days and the test was carried out on the mice. Sample with less than 20% concentration of collagen showed a good ability to heal the wound.

Polylactic acid and pectin can be used to compose a biodegradable hybrid aerogel which could stimulate wound healing. And this aerogel is able to load drugs which means non-steroidal anti-inflammatory drug (NSAID) medications are feasible to be carried [15]. NSAIDs are able to lessen pain and promote hormone release, which speeds up the healing process. Pectin-PLA aerogels were infused with two NSAIDs, Diclofenac (DCF) and Indomethacin (IND), along with oxygen-generating compounds, sodium percarbonate (SPO) and calcium peroxide (CPO). A notable thing is that ethyl lactate (EL) must reach 120 ℃ to dissolve the PLA effectively. The formation of the gel was controlled by both the cooling step and antisolvent addition. Results revealed that the PLA skeleton had pectin aerogel trapped inside of it and the structure has large voids. However, these hydrophilic aerogels might degrade in a moist environment. In addition, oxygen will be released to help heal the wound due to the decomposition of SPO and CPO. The significant capacity for water absorption and the swelling ability of this material makes them particularly compelling in the context of wound-dressing applications, providing both comfort and therapeutic benefits.

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4. Implant

If bones suffered too much damage, they will not be able to regenerate. Bone is made of 65-70% inorganic mineral and 25-30% organic material which can be considered to be a composite material. Implants might have some risk no matter it is autografts or allografts. Compared to synthetic hydroxyapatite, bioglass has a higher level of bioactivity, greater bone regeneration, and better gene activation. Furthermore, it can bond to both hard and soft tissue. It can release a certain amount of precipitation of Ca and P. These precipitations will be dehydrated and transferred to hydroxycarbonate apatite and accelerate the recovery rate at the damaged position. However, intrinsic brittleness and flaw sensitivity limited the use of pure bioglass (BG). Therefore, it's crucial to use a novel substance to address these issues. PLA is a suitable material to combine with BG [16]. PLA can provide elastic modulus and low elongation at break to compensate for BG which lack of these properties. In addition, a combination of BG and PLA will decompose and release a relatively neutral product to minimize the risk of inflammatory reaction. Using thermally induced phase separation (TIPS) can disperse the BG phase in PLA to produce positive effects on their mechanical properties. Filaments produced by TIPS can be used in 3D printing and made suitable scaffolds for bones to recover. Composite material after introducing TIPS, BG particles distributed in PLA matrix homogeneously. After these spheres were mixed and ground, BG dispersion was improved in the composite filament. PLA-BG scaffold was confirmed to be cell compatible by a 21 days lasting test, and the result showed that there were no immune responses observed. The addition of BG particles made the surface of 3D-printed scaffolds rougher, as demonstrated by SEM. It is important because cell behaviour can be enhanced by this nanoscale roughness. In addition, dispersed BG can access the biological environment no matter if it was in vitro or in vivo. The mechanical properties of scaffolds matter a lot. When BG particles were introduced to 3D-printed scaffolds, the compressive strength rose by 80%. When a small amount of BG (5%) was added to the PLA matrix, it can distribute evenly in PLA and enhance the structure.

Ahmed Fouly et al. used extraction from corn cob (CC) as a natural filler and mixed it with PLA to produce composite filament [17]. This composite filament can be used for 3D printing. It can be used to replace deteriorated joints after being 3D-printed. Because the design of these parts is extremely complex, 3D-print is the best choice to produce parts. However, the mechanical properties of 3D-printed parts were poor. This problem can be solved by introducing PLA to CC. When the proportion of corn cob was 10 wt.%, the composite material reached its highest hardness which was 10% higher than pure PLA. And at this point, there was an increase of 6% in Young's modulus and 12% in the ultimate compressive strength. In addition, the wear resistance of PLA-CC composite was better than pure PLA. If the bonding strength between PLA and CC can be enhanced, the mechanical properties can be further improved.

5. Vascular grafts

The most common reason causing death is because of cardiovascular diseases. Some cardiovascular diseases such as myocardial infarction was caused by blocked blood vessels. Vascular autograft was a solution to these diseases, but some patients can’t use this method due to some obstacles such as age. Although polyethylene terephthalate grafts have been proven to be a great success to act as substitutions to large diameter vessels (>6 mm), it is not suitable to substitute smaller diameter vessels (<5 mm). An electrospinning procedure was used to make PLA vascular scaffolds [18]. The scaffolds were a three-layered nanofibrous structure. The core of this structure was polyvinyl alcohol (PVA) multifilament. The middle layer was PVA nanofibers and the outer layer was PLA fibres produced by electrospun. Water can be used to remove the core and middle layers. So PLA hollow nanofibrous structure can be obtained. The diameter of the vascular graft, which was inside the structure, was 3 mm, and it was dependent on the diameter of the structure's central portion. The middle layer was thin and can be easily dissolved in water. The diameter of the PLA fibres was maintained at 100-350 nm. So, these PLA fibres can reveal a cellular infiltration. FTIR results showed that PLA did not undergo hydrolysis during the process of removing PVA. Controlling the electrospinning time allows one to alter the mechanical characteristics. Increasing the outer layer electrospinning time can enhance the tensile strength. Cells on PLA nanofibers

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kept growing for 14 days, which indicates that the vascular graft had no cytotoxicity. After 7 days of the experiment, the whole surface of the vascular graft was coated in human fibroblast cells. But there was still a problem. A hemolytic material typically has to have a hemolysis percentage of at least 5%. The sample only presented a hemolysis percentage of 2.45%. Therefore, it still needs further modification to become available for vascular graft.

Chaojing Li et al. synthesized a vascular graft (cVG) with PLA fabric and polycaprolactone (PCL) [19]. The mechanical characteristics are the most important consideration of small-diameter blood conduits. These textile-based vascular prostheses could potentially provide an alternative approach to the evolution of in-situ tissue-engineered vascular grafts. The test's findings demonstrated that the prostheses were produced with superior tensile qualities using PLA fabric. The PLA tubular construction did not collapse under radial stress owing to the pores on PCL. Although cVG became softer than its initial state, it still maintained its shape. PLA would degrade faster than PCL because there were more carbonyl groups in PLA, so the composite vascular prosthesis' mechanical degradation rates may differ. In general, investigations have been made into the degrading characteristics of vascular prostheses having a bi-component composite structure. This improved knowledge serves as a solid basis for the development of in-situ tissue-engineered vascular prostheses.

6. Conclusion

PLA has demonstrated potential use in medical fields owing to its biocompatibility, low toxicity, and degradability. It has been successful in vascular grafts and is showing potential in drug delivery systems, wound dressings, and bone implants. By controlling the rate of PLA's degradation, it is possible to regulate the medication delivery or the duration of an implant until it has been degraded within the body. Moreover, the material's versatility allows it to be combined with other polymers or materials to improve its properties or introduce new functionality, such as enhanced strength or porosity. However, there are some limitations such as weak adhesion and inadequate hemolysis percentage in vascular grafts So it is necessary to carry out further research on the modification of PLA and more potential applications of this material can be developed. And the price of it will be eventually reduced by investigating innovative approaches to PLA's preparation. In general, PLA-based materials show great potential in the medical field.

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