Medical application of polylactide (PLA)

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In this paper, the possibilities of using polylactide (PLA) in various fields of medicine are briefly mentioned. Also, the most important characteristics of this biomaterial are described and examples of the two most common polymers that have significant medical applications are given.

Key Words: *polylactic acid, biomaterial, biodegradable polymers*

1. INTRODUCTION

Polylactide (PLA) or polylactic acid is a biodegradable and biocompatible biomaterial obtained from lactic acid, extracted from sugar cane or corn starch. It is aliphatic polyester [1]. In living organisms, it can be easily decomposed, by the action of hydrolytic enzymes, into carbon dioxide and water, and then expelled through the kidneys or respiration in the form of CO_2 [2]. Due to its biocompatibility, after application, it will cause a minimal reaction of the organism, and by virtue of its biodegradability, it will facilitate postoperative recovery because there is no need for its removal. It is often in combination with other compounds to fulfill the requirement about properties which implant need to have [3]. There are different forms of this biomaterial, among them poly-l-lactide (PLLA) and polylactide-co-glycolide are most commonly used for medical purposes. The projected growth of the global polylactide market to approximately $3 billion by 2028 is anticipated due to its cost-effectiveness and widespread availability. The low production costs associated with polylactide (PLA) make it a compelling choice for various industries seeking economically viable solutions. With raw materials readily accessible, particularly lactic acid derived from renewable sources like corn starch, the market for PLA is expected to expand further [4].

The aim of this review is to present some areas of medicine in which it is possible to apply implants made of PLA biomaterial.

2. THEORETICAL CONSIDERATION

2.1. Polylactide (PLA)

This widely applied biomaterial has a special role in medicine. Its inherent natural composition facilitates seamless integration into the human body and ensures effortless decomposition within it. PLA is obtained by polymerization of lactide. Lactides, a cyclic dimer of lactic acid, exists in two forms: D and L. Thus, polylactide can also have L or D form. The end products of decomposition are included in the normal tissue metabolism giving non-toxic products. Besides, different processing and combination with other materials can significantly change its properties and thus the area of application [5].

2.1.1. PLLA (poly-l-lactide)

PLLA is one of the most frequently investigated bioresorbable polymers based on lactide. It represents the L form of polylactide. Poly-l-lactide (PLLA) is a semi-porous, biocompatible and biodegradable polymer whose degree of crystallinity depends on the molar mass and processing parameters [6].

It is most frequently utilized for:

1. Synthesis of microcapsules for the gradual release of drugs

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2. Synthesis of foam, which, due to its porosity, is used in tissue engineering

3. As a polymer carrier that ensures adhesion and differentiation of osteoblasts in in vivo conditions [7].

Several factors impact the properties and structure of PLLA, including the choice of solvents used for the synthesis procedure, the level of vacuum applied during polymer drying, the concentration of initiators, and the recrystallization of monomers. Control and management of PLLA polymer crystallization kinetics was achieved by different methods, of which isothermal crystallization showed satisfactory results.

The PLLA degradation process is complex [8-9]. It is considered that the amorphous areas of PLLA represent centers where hydrolytic processes begin and that the size of PLLA spherulites does not play a significant role in the biodegradation process.

During biodegradation, there is a decrease in the pH of the environment, molar mass, modulus and tensile strength, and an increase in crystallinity. Due to the fact that they reduce the pH value, they can induce inflammatory reactions. In order to prevent this from happening, it was proposed to combine the polymer with basic components, such as bioactive glasses and calcium phosphates [9-10].

2.1.2. Polylactide-co-glycolide (PLGA)

Polylactide-co-glycolide, also known as PLGA, is a biodegradable lactide polymer, commonly used in drug development and tissue engineering. It is a copolymer composed of lactic acid (lactide) and glycolic acid monomers, which are natural compounds in the body.

PLGA is widely used due to its biocompatibility and biodegradability. In the body, it can be decomposed into constituent monomers, which are then metabolized and eliminated by natural means. PLGA can be synthesized with different ratios of lactic to glycolic acid, which allows the physical and chemical properties of the material to be tailored.

For example, PLGA with a higher proportion of glycolic acid is more hydrophilic and degrades faster, while PLGA with a higher proportion of lactic acid is more hydrophobic and degrades more slowly.

PLGA has many potential applications in medicine, including drug delivery systems, tissue engineering and surgical sutures. Its biocompatibility and biodegradability make it a safe and effective choice for these applications.

In vivo tests have proven that this copolymer can be inductive for the creation and adsorption of collagen, the connective tissue component.

2.2. Application of polylactide and its copolymers in various fields of medicine

Table 1. Forms of PLA implants applicable in various fields of medicine

Fields of medicine	Forms of implants PLA
1. Orthopedics [11-13]	screws, plates, pins, bone fragments, surgical thread, menisci
2. Plastic surgery [14]	injectable fillers, bone fragments
3. Maxillofacial surgery [15]	bone fragments
4. Neurosurgery [16-19]	carrier of antimicrobial agents, construction of antimicrobial surfaces
5. Reconstructive surgery [20-22]	bone fragments, matrix for stem cells, skin coverings
6. Urology [23-25]	urinary stents, matrix for stem cells, tissue replacement
7. Oncology [26-28]	capsule of the antitumor drug carrier, compensation of the postoperative cavity, tumor marker carrier
8. Dentistry [29-30] ,	bone fragments of the jaw, parts of dental implants, surgical threads
9. Pharmacology [31]	construction of the capsule of the medical substance carrier
10. Microbiology [32-33]	carrier of antimicrobial agents, construction of antimicrobial surfaces

Following presentation in Table, a description of each application will be provided.

1. Application of PLA in orthopedics

In orthopedic surgery, the primary use of PLA implants is to stabilize broken bones or support bone fusion during the healing process. The forms of screws, plates, and needles are most often used [11]. In addition to fracture repair, they are also used for ligament reconstruction, making threads for suturing soft structures, meniscus replacement, and muscle stabilization. The method of fixation depends on various factors, the nature of the fracture, the general health of the patient and the surgeon's assessment [12]. Due to the biodegradability of PLA implants, intervention to remove the synthetic material after surgery is unnecessary. The biocompatible nature of PLA reduces the risk of long-term complications caused by permanent metal implants. PLA can be combined with materials, where an implant with the required properties is formed. For example, combining PLA with biological materials, collagen or hyaluronic acid, increases biocompatibility leading to faster healing. The combination with ceramic materials, hydroxyapatite, or with biomaterials, based on calcium or metal materials, titanium, creates implants, pins and screws for fixation, with increased mechanical durability. Combination with biologically active materials, solutions with bone cells or bone growth factors, is used for stimulation and better healing of broken bones. It should be emphasized that advanced 3D printing techniques adapt the PLA implant to the individual and his specific anatomical needs [13].

2. Application of PLA in plastic surgery

PLA finds application in plastic surgery, especially in dermal fillers. These injectable substances serve to restore facial volume, reduce the visibility of wrinkles and improve general facial features. Traditional dermal fillers consist of hyaluronic acid, while PLA-based fillers offer an alternative that provides added volume, stimulation of collagen production, giving a more natural and long-lasting skin effect. The advantage of PLA-based dermal fillers is that they decomposition absorb over time. The use of PLA in plastic surgery is developing over time [14].

3. Application of PLA in maxillofacial surgery

Maxillofacial surgery involves the treatment of all those conditions affecting the jaw, facial bones and skull bones. Fractures, deformities and other structural problems are corrected in surgical interventions with plates and screws, as is the case in orthopedics. The use of PLA implants in maxillofacial surgery is a promising area of research and development [15].

4.Application of PLA in neurosurgery

In the field of neurosurgery, PLA biomaterial is applied for skull bone reconstruction and as an auxiliary material for tissue engineering. As in orthopedics and maxillofacial surgery, as well as in neurosurgical interventions, the use of PLA biodegradable plates and screws is in skull reconstruction after trauma, or in providing support for bone healing [16]. More specific and complex use of PLA is in nerve regeneration, as a biodegradable support. In cases of nerve damage or injury, PLA scaffolds provide a structure for nerve growth and aid in the repair process [17]. With the insertion of the Schwann cell and the necessary nutrients into the structure of the implant, PLA films or patches are formed, the process is more advanced for the formation of the dura mater protective membrane. The function of the PLA patch is to close dura defects after neurosurgical interventions of the brain and spinal cord [18]. An additional application of PLA lies in the construction of sustained-release drug capsules. This is especially important when considering drugs with a prolonged therapeutic effect in nearby and inoperable tumors [19].

5. Application of PLA in reconstructive surgery

In tissue reconstructive surgery, bone tissue is most often reconstructed where PLA together with other materials, e.g. ceramics, enables the replacement of damaged or missing bone parts. Also, in oncological surgery, structures are reconstructed after the procedure [20]. In dermal reconstruction, PLA is used to repair skin defects or wounds, such as repair after removal of tumors or scars or in mass burns [21]. In the field of tissue engineering, PLA serves as a matrix for stem cells, which show capacity for tissue regeneration after application [22]. Interestingly, PLA has shown use in the reconstruction of anatomical structures such as the auricles and the nose.

6. Application of PLA in urology

In urology, PLA materials are used to make urological stents (expansion of narrowed or obstructive parts of the ureter) [23]. In addition, there is direct application of urethral reconstructive materials to restore the ureter and provide structural support [24]. And in tissue engineering in urology, where the growth of damaged cells of urethral tissue, mainly epithelium, is promoted. There is also an application of PLA in the release of drugs in specific segments of the urethral system, which is explained in more detail in section 9 [25].

7. Application of PLA in oncology

The pivotal role of PLA in oncology is in the production of capsules of drugs from the list. These capsules serve as carriers for antitumor agents, which enable their inclusion in the immediate vicinity of neoplastic lesions. It is known that the inherent attributes of PLA are biodegradability and biocompatibility, with medicinal value. Encapsulation of drugs in a PLA matrix facilitates controlled and gradual release, providing nuances in the modulation of drug kinetics. Controlled drug release enables optimization of therapeutic efficiency by maintaining a localized drug concentration at the tumor site, thus facilitating systemic exposure. Furthermore, the localized deployment of PLA-encapsulated drugs contributes to a targeted therapeutic approach, minimizing collateral damage to healthy tissues. In essence, tailored formulations enabled by PLA not only improve pharmacokinetic profiles, but also offer a pragmatic avenue to increase therapeutic outcomes in oncological interventions. [26]. Also, the cavity after removal can be reconstructed with this material, which is powerfully important in the brain, due to the need for gradual reduction where a large change in intracranial pressure is avoided. Recent research shows the importance of this material in the production of carriers for the detection of specific tumor markers, such as pancreatic tumors. These carriers can be used to more precisely determine tumor distribution and improve the possibility of its detection and monitoring [27-28].

8. Application of PLA in dentistry

In dentistry, materials containing PLA play a crucial role in the production of screws for bone fixation and the restoration of bone structures. PLA imparts desirable properties such as biodegradability and biocompatibility to these materials, making them suitable for long-term implant stability and minimizing the need for removal procedures. PLA's unique attributes position it as a promising material in dental applications, contributing to both structural support and regenerative processes within the field of dental interventions [29]. During surgical tooth extractions or major operations of the oral cavity, dentists will frequently choose resorbable PLA threads. Also, in dental implantology, polylactide materials can be used to make implant parts that are temporarily needed, and then bioresorbed, which facilitates the procedure and reduces the need for additional interventions [30].

9. Application of PLA in pharmacology

The distinctive characteristics inherent to PLA position it as a particularly compelling biomaterial for the formulation of drug capsules within the realm of pharmacology. The controlled and gradual degradation of PLA facilitates a meticulous release of pharmaceutical agents, orchestrating their targeted delivery to specific anatomical sites within the human organism. This strategic approach involves a nuanced understanding of human anatomy and physiology, exemplified by considerations such as the optimal conditions for capsule decomposition, including temperature and pH values, during transit to predetermined locations, such as the large intestine. The judicious design of PLA-based capsules thus ensures a temporally extended and precisely orchestrated drug presence, contributing to enhanced therapeutic efficacy while aligning with the intricacies of the physiological milieu [31]. One of such syntheses and tests is carried out in the Laboratory for Radiation Physics and Chemistry 030, in the Vinca Nuclear Institute in Belgrade, where work is being done to improve the properties of such capsules that have the potential for clinical application.

10. Application of PLA in microbiology

When it is said in microbiology, first of all, it means the antimicrobial effect of the material, which includes PLA. The long-term effect would be that these materials can be modified and enriched with substances that have an antimicrobial effect. Such materials can provide long-term specific antimicrobial properties, which is important in the control and prevention of infections. There is also known controlled release of antimicrobial agents which may be useful in preventing the growth of microorganisms on implants or other medical devices, Apart from the carrier of chemical substances, physical and mechanical properties can have an antimicrobial role [32]. With special treatment, smooth and hydrophobic surfaces can be obtained, which retain bacteria more easily and make cleaning easier. This surface modification can prevent the adhesion of bacteria and other microorganisms [33].

3. CONCLUSION

This paper briefly describes the applications of polylactide (PLA) in various fields of medicine, it is important to emphasize that each of these applications requires appropriate processing of the material itself using different physical, chemical and mechanical procedures and/or combining it with other materials, both polymeric and ceramic. metal etc. Although the application of this material is still widespread today due to its biocompatibility and bioresorbability, it is believed that the application of this material in medicine will only develop and increase, with the discovery of new combinations of PLA and other, as yet, unexplored materials. In recent decades, the growing use of PLA has triggered intensive research and development aimed at improving its characteristics. Focus is increasingly being placed on optimizing the basic physical and chemical properties of PLA to meet the demands of various applications.

In parallel, researchers are committed to designing new copolymers that will improve the performance of PLA, either during the synthesis process or through post-processing and modification. These efforts include work on increasing the strength of the material, improving resistance to high temperatures, improving breathability and achieving optimal biodegradation properties. Designing copolymers opens the door to new application possibilities, enabling PLA to meet the specific requirements of different industries, especially for medical applications [34].

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REZIME

MEDICINSKA PRIMENA POLILAKTIDA (PLA)

U ovom radu su ukratko navedene mogućnosti primene polilaktida (PLA) u različitim oblastima medicine. Takođe, opisane su najznačajnije karakteristike ovog biomaterijala i dati primeri dva najzastupljenija polimera koja imaju značajnu medicinsku primenu

Ključne reči: *polilaktidna kiselina, biomaterijali, biodegradabilni polimeri*