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POLYMER MATERIALS AND THEIR USAGE IN VETERINARY PRACTICE

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Abstract: In the field of regenerative medicine and tissue engineering, the use of such materials has been included for a short time, serving not only as a replacement for damaged or missing tissue, but also as a support for the surrounding tissues and cells. Such materials should not only be passively tolerated by the cell, but should also actively promote the growth, differentiation and other processes involved in tissue regeneration. The latest approach is the use and development of bioresorbable and biodegradable polymeric materials. Such materials, with their biocompatibility, degradability and suitable mechanical properties, support the overgrowth of new tissue. The application of such materials is used not only in the human but also in the veterinary field. This study approaches the use of polymeric materials processed by additive technology in veterinary practice in several case studies. It presents not only the use of new methods of materials processing, but also an individualized approach and progress in therapeutic approaches.

1 Introduction

Polymers are considered to be the widest group of materials and therefore they are increasingly used especially in the field of regenerative medicine and implantology. Since polymers can be divided into natural and synthetic, their usage is not limited only to be a part of medical devices, equipment, invasive or non-invasive devices, but they also become the therapeutic basis itself.

Several different classes of polymers are currently used in veterinary practice, which differ in their chemical structure, synthetic methods, reaction to living organism and biodegradability. The most useful non-degradable polymers used in veterinary practice include silicone, polyurethane and EVA copolymers. Polymers such as poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA) are considered to be biodegradable and therefore belong to the class of degradable polymers.

The process of degradation of polymeric materials is accompanied by a process of cleavage of the polymer chain, which leads to a loss of molecular weight, resulting in erosion of the material, which can be defined as weight loss of the material due to the cleavage process.

The use of degradable and non - degradable polymeric materials ranges from orthotic - prosthetic solutions, through implants to controlled drug distribution systems.

1.1 Non-degradable polymers

Silicones

The rise of silicone materials began in the 1960s, when it was concluded that they were characterized by chemical and thermal stability, low surface tension, hydrophobicity and gas permeability, resulting in their dominant position in the biocompatibility and biodiversity of materials. Nowadays, they are considered to be one of the most thoroughly tested biomaterials and are used for the production of medical devices, personalized implants, drug carriers, or as parts of invasive and non-invasive medical devices [1].

Polyurethane (PU)

Polyurethanes or polyurethane elastomers are known for their molecular structure to be similar to that of human proteins. A closer examination of the material revealed that the absorption of proteins, which is a side effect of the blood clotting process, is considerably slower or lower than for other materials. This ability makes PU an ideal material for the needs of various medical applications in which adhesive forces, biomimetic or antithrombotic properties are required.

Polyurethanes are widely used in the cardiovascular field as an insulating electrode material in the implantation of an artificial heart or pacemaker, due to their elastomeric properties, which are accompanied by toughness, tear resistance, abrasion resistance and a high degree of biocompatibility with a living organism [2-4].

Polyethylene glycol (PEG)

Polyethylene glycol is widely used in the medical, chemical and pharmaceutical industries because it is non-toxic and highly soluble. It is also considered a biocompatible synthetic, hydrophilic polyether compound that can be used in biomedical applications.

PEG is most often used as part of laxatives, where it serves as a drug carrier in the form of an inactive substance. The form and process of drug administration depends on the usage of PEG because the compound binds antibody-drug conjugates. If it is necessary to improve the systematic administration of the medicament, it can be used in the form of a coating [5].

Poly(methyl methacrylate) (PMMA)

Poly(methyl methacrylate) is commercially known as plexiglass or acrylic glass. In the field of orthopedics and surgery, it is referred to as the so-called "bone cement". It is also used for the production of aids in dental and ophthalmic practice and for the distribution of medicines. Its wide scope is due to the fact that by changing the ratios of dimethylaminoethyl methacrylates, methacrylic acid and methacrylic acid esters, it can be categorized as synthetic cationic, anionic or neutral polymer. An example is a study by Gupta et al., Which provided an overview of materials used as carriers for gastrointestinal drugs, stating that up to twenty materials are made on the basis of PMMA [6,7].

Ethylene-vinyl acetate copolymer (EVA)

EVA is a random copolymer of ethylene and vinyl acetate. It is used for the delivery of drugs in laminated transdermal systems in the form of a membrane or subsoil. Ethylene vinyl acetate copolymer has also been shown to be an effective matrix and membrane for the controlled delivery of atenolol, triprolidine and furosemide [8].

Poly(vinyl alcohol) (PVA)

PVA is considered to be a synthetic hydrophilic linear polymer whose structural properties depend on the degree of polymerization and the degree of hydrolysis (i.e. the superstructure of the two monomers) because it generally occurs as a copolymer of vinyl alcohol and vinyl acetate. It is used in the pharmaceutical and biomedical engineering industries to replace soft tissues in the field of lenses, artificial cartilage or parts of the artificial heart, due to its simple structure and properties such as non-carcinogenicity, biocompatibility, strength and adhesion. Chemically and physically modified PVA structures are used in the food and textile industries [9].

Polyether ether ketone (PEEK)

PEEK material is one of the thermoplastic polymers with mechanical properties that are significantly close to the properties of human bone. For this reason, it has been presented to the professional public since the 1990s as a replacement for conventional metallic materials in the field of biomedical applications. It is currently used in additive technologies to make hard tissue replacement implants.

The surface of the PEEK polymer is biologically inert and hydrophobic, which does not allow protein absorption and cell adhesion. For this reason, it is increasingly enriched with ceramic and other bioactive materials to improve surface properties [10, 11].

1.2 Degradable polymers

Poly(lactic acid) (PLA)

PLA is one of the thermoplastics with good mechanical properties, biocompatibility and high biodegradability. PLA is obtained from lactic acid, degraded by a hydrolysis process, the rate of degradation being determined by the reactivity of the polymer with the catalysts and water.

PLA scaffolds are used to support various cell types in applications in the cardiovascular, orthopedic, bladder, muscle, bone, cartilage and tendon applications.

To innovate the required properties, various ceramic and polymeric materials are added to the PLA material, which makes it possible to increase or decrease the rate of degradation or to improve the osteoinductive properties [12-19].

Poly(glycolic acid) (PGA)

PGA material was discovered in 1954 as the first degradable synthetic polymer. It was initially rejected by the professional public due to its poor thermal and hydrolytic stability. However, the hydrolytic sensitivity of PGA was later used in the manufacture of polymeric devices, which were indicated for decomposition in humid environments and thus in the human body. With a controlled drug delivery system, PGA can be defined as a solid erodible matrix with a controlled release rate [20].

Polycaprolactone (PCL)

PCL is also a biodegradable material, but is more stable than polylactides due to less frequent ester linkages to the monomer, which ultimately prolongs the degradation time due to enzymatic hydrolysis in the body of PCL chain fragments. The rate of degradation further depends on shape, molecular weight, residual monomer content,

autocatalysis and other factors. In general, complete degradation of the PCL polymer takes 2 to 3 years in the biological environment.

Polycaprolactone itself is characterized by a low degree of biocompatibility but excels in elastic properties together with the ability to form various mixtures, composites and copolymers make it a desired material in the creation of support structures for hard tissues and scaffolds in the field of tissue engineering [21-25].

Poly(lactic-co-glycolic acid) (PLGA)

PLGA is one of the biodegradable polymers based on aliphatic polyester, containing synthetic copolymers of lactic acid and glycolic acid. Due to its biocompatible properties and biodegradable nature, it is used for the distribution of drugs in the living organism or as a carrier for the delivery of bioactive molecules [26,27].

Chitosan

Chitosan is one of the naturally occurring polymers in hard shellfish shells. It excels in its physico-chemical and biological properties, making it an application in many fields, including the medical, food, chemical, cosmetic, water, mining and biochemical industries.

Its main disadvantage is its insolubility in aqueous solutions, which greatly limits its widespread use in living organisms. By modifying some functional groups of chitosan, it is possible to improve its solubility and thus expand the possibilities of application. Such chemical modifications produce many types of chitosan derivatives that are non-toxic, biocompatible and biodegradable. Chitosan nanoparticles improve the body's immune function and, thanks to simple modifications, are also used as drug carriers [28-32].

2 Usage of polymer implants in veterinary practice

2.1 Preclinical testing of polymer materials – Case study 1

As part of preclinical testing, the different variations of PEEK polymeric material were tested on a rabbit animal model in collaboration with University of Veterinary Medicine and Pharmacy (UVMaP) in Košice. The material was produced at the Slovak Technical University (STU) in Bratislava using the technological process of extrusion on a twin screw device (Labtech Engineering, Thailand). A total of 4 variations of materials were produced:

1. PEEK polymer without additives,
2. PEEK polymer with the addition of tricalcium phosphate (TCP); proportion 85 : 15,
3. PEEK polymer with the addition of hydroxyapatite (HA); proportion 85 : 15,
4. PEEK polymer with the addition of TCP and HA; proportion 80 : 5 : 15.

A healthy, adult rabbit weighing 4.5kg was selected for implantation. The prepared implant structures were treated with a hot air sterilizer Titanox (TITANOX S.r.l, Italy) before the implantation. During the procedure, the rabbit femurs were penetrated by using a drill. The individual defects were subsequently filled with prepared implant structures and the wound site was closed with a suture. The health status of the rabbit was observed during 12 weeks, with ongoing follow-ups at 2nd and 10th week and no changes in health status were noted. At the 12th week the rabbit was euthanized with goal to examine the results.

Based on the explanted femurs (Figure 1), it was confirmed that the PEEK polymer is a bioinert material, as there was no interaction between inserted implant and the bone, in addition the implanted structure separated from the femur. In the case of composites with the addition of ceramic materials, it can be argued that the osteointegration process took place based on observations (Figure 2) using a Stemi DV4 stereomicroscope and an AxioCam ERc5s camera (Carl-Zeiss, Germany) [33].

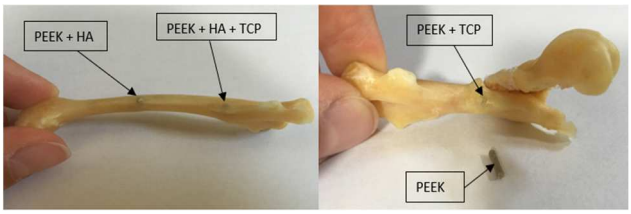

Figure 1 Explanted rabbit femurs with embedded implant structures

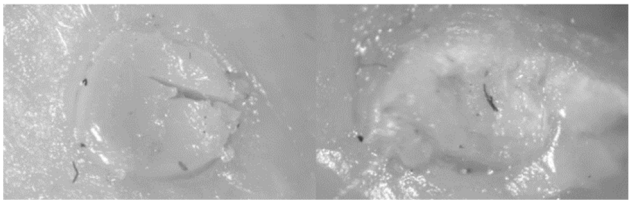

Figure 2 Stereomicroscopy at 50x zoom, the left side: PEEK polymer enriched with HA; the right side: PEEK polymer enriched with HA and TCP

2.2 Soft tissue replacement – Case study 2

Another case study that was performed in collaboration with UVMaP was a case of extensive damage to the skin layer on the front limbs of a dog. These defects also contained portions of necrotic tissue that had to be surgically removed (Figure 3).

Figure 3 Skin defects after removal of the necrotic tissue and fur

Due to the extensive damage, it was necessary to provide the bridging effect to the defect for sufficient support for the growth of emerging tissue. The implant structure was manufactured on a Deltiq2 device from Trilab company (Czech Republic). Using FFF (Fused Filament Fabrication) technology, a mesh structure was prepared from PCL and polypropylene (PP) materials in order to ensure a suitable overgrowth of the newly formed tissue, to accelerate its growth and to heal the wound.

The time set for the application of the implant structure was not predetermined and depended on the wound healing rate. Overall, new tissue was formed in 3 weeks after the application of the porous structure to the site of the skin defect, and the treated wound showed no signs of inflammatory or other reaction. After removal of the implant structure, the wound completely healed (Figure 4).

Figure 4 The left side: applied porous structure; the right side: rate of the healing process 3 weeks after implantation

2.3 Hard tissue replacement – Case study 3

Another study that was performed in collaboration with UVMaP was an adult rabbit weighing 4.5kg, diagnosed with a femur fracture. For the needs of the study, the polymeric material PEEK was chosen, which is characterized by excellent mechanical properties and chemical stability. The design of the implant structure consisted in the surgical explanting of the damaged part of the femur. For the purpose of creating a 3D model of the implant, a segment was scanned by an Identica scanner (MEDIT corp., South Korea) and the final version modeled in Meshmixier software (Autodesk Inc., USA). Implant was manufactured on a device Vshaper 270 MED (Vshaper, Poland) based on FFF technology.

The fabricated implant was surgically inserted into the defect area and anchored using a personalized fixation (Figure 5), which was made of titanium material, to ensure stability. The procedure was completed by closing the wound with a suture and administering anti-inflammatory drug treatment. The health status of the rabbit was observed during 12 weeks, with ongoing follow-ups at 2nd week and 10th week, and no changes in health status were noted. At the end of 12th week, the rabbit was euthanized, the personalized fixation was removed and explanted femur was subjected to additional evaluation (Figure 6).

Figure 5 The left side: surgical implantation of the manufactured implant; the right side: a rabbit after a successful implantation with personalized fixation

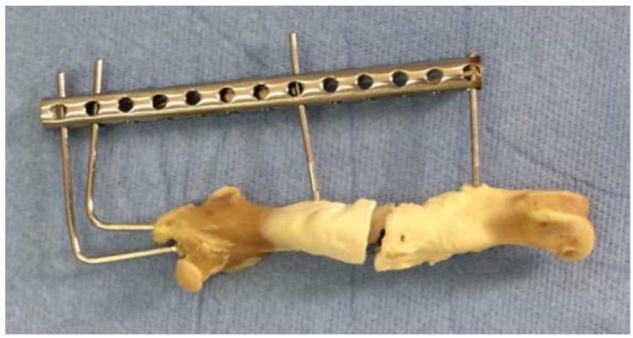

Figure 6 Explanted personalized fixation with overgrown implant strucure

The hypothesis of implant overgrowth could not be confirmed, as it can be seen in Figure 6, the osteointegration process did occur, but the implant itself did not interact with the bone tissue. Instead, the implant was overgrown by bone callus which confirmed bioinert properties of the PEEK polymer material [33].

2.4 Soft tissue replacement – Case study 4

Another use of polymeric materials processed by 3D printing technology was the production of an implant for a dog diagnosed with a traumatic tracheal defect. The dog was admitted to the UVLaF clinic, where he underwent basic clinical examinations. Given the location and extent of damage to the tracheal rings and surrounding structures, the nursing staff concluded that the use of traditional treatment options might not be successful. For this reason, the idea of using 3D printing to remove such extensive damage has been adopted. The aim of this case study was to create a personalized tracheal implant based on data obtained from a CT scan so that the original respiratory function could be restored. The therapeutic procedure was divided into two stages:

First stage (habituation) - creation of a temporary anatomical implant made of PMMA material using PolyJet technology (Figure 7), for temporary closure of the defect, but not the entire wound.

The second stage - involved the removal of the temporary implant and its replacement with an implant from biodegradable PCL material (Figure 7), manufactured on a Bioplotter (Envisiontec, USA). Surgical closure of the wound and surrounding soft tissues also occurred at this stage.

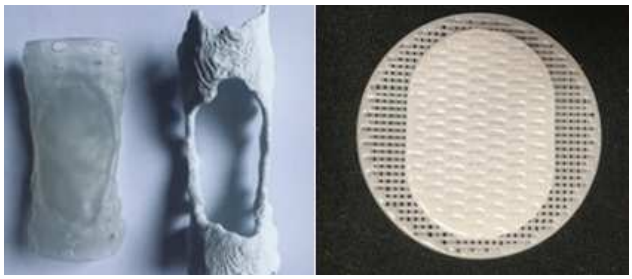

Figure 7 The left side: a temporary implant of anatomical shape that was implanted in the first stage; the right side: a biodegradable implant applied in the second stage

Several days after the insertion of the temporary implantation structure, signs of implant detachment were observed in the dog, accompanied by massive seceration of the subcutaneous structures and significant mucus deposition on the inside of the defect (Figure 8). After the six days, the polymer implant had to be surgically removed and the defect was subsequently covered with a biodegradable implant, slightly extending beyond the surrounding tracheal rings.

Figure 8 The left side: a temporary implant covered with mucus; the right side: an inserted biodegradable implant

Eight months after the primary implantation, the dog underwent a native CT and endoscopic examination, which showed that the tracheal defect healed to the full extent, with no clinical signs of upper airway damage observed throughout the dog. Despite the severity and extent of the defect, biphasic implantation has been shown to be successful.

2.5 Soft tissue replacement – Case study 5

The last study that was performed with cooperation with UVLaF, where a domestic pig was diagnosed with a tracheal defect. Based on previous experience, only a porous implant structure was used for the case, without the application of a temporary anatomical implant.

The implant was manufactured from PCL material, which was processed in the form of pellets in a Filamentmaker (3DEVO, the Netherlands). The produced filament with a diameter of 1.75 ± 0.05 mm was subsequently used for the production of an implant on a 3D printer Deltiq 2 (Trilab, Czech Republic), which works on the principle of FFF technology. The implant was designed in Magics software (Materialize, Belgium) and consisted of 4 porous layers to support the growth and adhesion of the newly formed tissue.

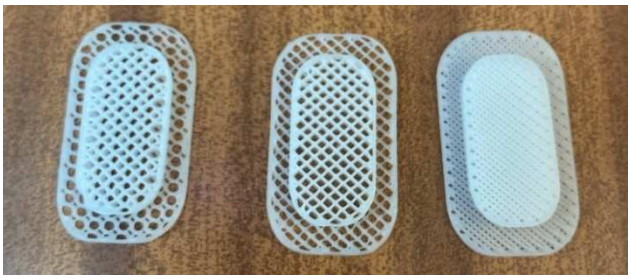

Figure 9 D

Prior to surgery, the implant was sterilized with high percent alcohol because damage to and fine deformation could occur when placed in a sterilization device due to the high temperature. After insertion of the implant at the defect site (Figure 9), the wound was completely closed and the pig was given anti-inflammatory drug treatment.

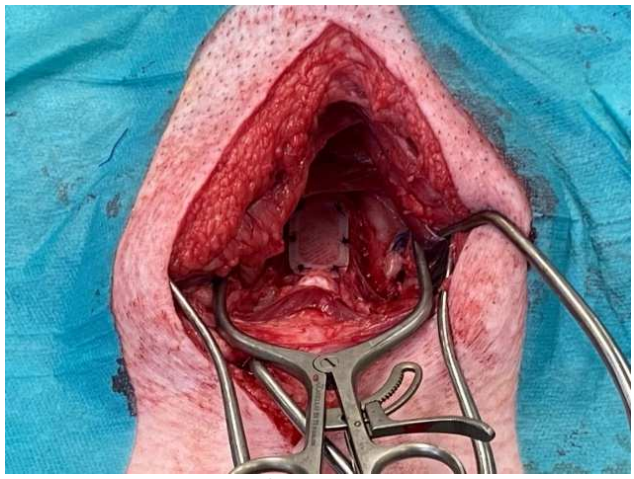

Figure 10 Application of a porous tracheal implant in a pig

More comprehensive results from the case study cannot be provided due to the fact that the study is still ongoing.

3 Results

The implementation of case studies on rabbit models confirmed the bioinert properties of the polymeric material PEEK, which is characterized by excellent mechanical properties and resistance to degradation, but biologically due to its hydrophobic surface does not support protein absorption or cell adhesion. In the case study of composite materials made of PEEK polymer enriched with bioactive ceramic materials HA and TCP, a course of osteointegration between the inserted implant and the rabbit femur was observed. Based on this observation, it is possible to confirm the influence of ceramic materials in the process of bone defect regeneration. In case studies performed on dog models, the application of porous structures made of polymeric PCL material managed to create an overlap of defects (in the case of the tracheal implant, there was a restoration of respiratory function as well) and was provided sufficient support to the emerging tissue which speeded up the regeneration process of damaged tissue. In the case of a study performed on a pig model, a tracheal defect was also covered with a porous

implant structure made of polymeric PCL material, to restore anatomical respiratory function.

4 Conclusions

In medical applications, the use of polymeric materials is quite common. The combination of standard procedures and new technologies creates new therapeutic possibilities in regenerative medicine and tissue engineering. Polymer processing technology is currently focused on 3D printing. And it is the connection of this technology with new materials that creates an individualized approach in human and veterinary medicine. Testing this synergy on animal models significantly pushes the imaginary boundaries of standard procedures in human medicine.

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