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BIOACTIVE CORE MATERIAL FOR POROUS LOAD-BEARING IMPLANTS

ABSTRACT

So far state of knowledge on biodegradable materials is reviewed. Among a variety of investigated materials, those composed of polymers and ceramics may be considered as only candidates for a core material in porous titanium alloy. The collagen and chitosan among natural polymers, polyhydroxy acids among synthetic polymers, and hydroxyapatite and tricalcium phosphate among ceramics are proposed for further research. Three essential conditions for a core material are defined as: biodegradation rate “in vitro” and “in vivo” close to bone tissue in-growth rate, high compression strength and ability to form nanoporous open structure inside the material for vascularisation. Possible deposition techniques of a core material within the macropores of metallic scaffold include infiltration of titanium porous structure with polymer scaffold followed by precipitation of phosphate nanoparticles, and mixing of phosphate and polymers before deposition followed by controlled precipitation inside the pores.

Key words: *biodegradation, polymers, ceramics*

BACKGROUND

The load-bearing implants are almost exclusively produced in a solid form, obtained by casting and/or mechanical cutting. On the other hand, a variety of materials for tissue engineering is developed as scaffolds, which make it possible to fill in with growing tissue. The last solution for load-bearing implants has been for many years rejected as not allowing carry on substantial mechanical stresses. A single medically applied exception was Trabecullar metal made of Ta [1], even if for titanium alloys the fabrication techniques of porous matrixes have been already developed [2]. On the other hand, fabrication of honey-comb metallic structures and filling them in with some polymers has been applied for many years in shipbuilding industry for decks and light weight boats with a great success.

Since many years the Bio-Nano-Med Research Group at Gdańsk University of Technology has developed an idea to create the bioactive implants based on porous metallic matrixes filled in with biodegradable core material slowly degrading in biological environment and being substituted with bone tissue [3]. Such implant has a principal advantage as compared to others: it would be highly biocompatible and better anchored to a body decreasing the risk of its loosening. and supporting long term mechanical stability.

At first, the metallic matrix must be made of non-toxic highly biocompatible material, in this case Ti13Zr13Nb alloy, demonstrating open porous structure with pores, wide enough, to allow osteoblasts to migrate, adhere and proliferate, i.e. to allow nutrients penetrate through whole metallic structure. Such structure should possess pores up to 500 μm in size and porosity at least 60% (in Trabecular, to compare, it is 80%). The porous structure may appear in total volume or be limited only to a surface layer for two reasons: (i) the cells may not be able to migrate for long distances and (ii) metallic structure may not reach the necessary compression strength. The so far attempts have resulted in fabrication of porous structures made of Ti13Zr13Nb highly biocompatible and non-toxic alloy by two techniques: (i) powder metallurgy with a space holder and (ii) rapid prototyping by selective laser melting, which will be described in detail elsewhere. The porous structures have demonstrated very good connection of adjacent grains and high strength.

The core material must have biodegradation rate corresponding to the bone tissue in-growth rate, and it must adhere to implant surface and form, together with it, a structural composite material. The development of such material is extremely difficult.

This paper reviews current state on degradable materials of potential importance for implants: biodegradable metals, ceramics, polymers and composite materials. This following, the idea of a core material for developed titanium implant, its fabrication and infiltration techniques are proposed.

BIODEGRADABLE METALS

Recently, there have been a number of researches made on Mg as a potential biodegradable metal [5, 6]. Biodegradation is relatively slow and for that reason Mg implants are proposed. Even if they may be totally substituted by grown bone tissue, they have serious disadvantage: corrosion of Mg is associated with evolution of hydrogen and increasing local value of pH, which may results in an irritation or even degradation of surrounding bone tissue.

BIODEGRADABLE POLYMERS

The polymers are biodegradable by either hydrolysis or by enzymatic degradation into shorter chains. in a progressive manner. The biodegradation is influenced by many factors, such as chemical structure of the polymer, length of polymer chain, its molecular weight, hydrophilicity and crystalline state [7].

Both natural and synthetic polymers may be prone to degradation in biological environment [8]. Among natural materials the collagen, chitosan and chitin, glucosamine and demineralized bone were proposed [9, 10]. Among synthetic biodegradable polymers, PGA (polyglycolide, poly (glycolic acid)), PLA (polylactide, poly (lactic acid)), PLGA (polylactic acid polymer and glycolic acid), PLLA (poly-L -lactic acid), polyanhydrides, polifumarates, polyorthoesters, polycarbonates, polycaprolactones and some others have been investigated and applied [9, 10, 11]. Natural polymers promote better adhesion and cell functions, but may show genotoxicity and contain patogens. It is also difficult to control their mechanical properties, biodegradability and manufacturability [9, 10].

Collagen is a natural component of an extracellular matrix (ECM) and the most often proposed biodegradable natural polymer. Its advantage is due to its positive impact on the formation of vascularised tissue [11]. Moreover, it can appear in a form of hydrogel, makes it possible to introduce growth factors promoting angiogenesis, such as VEGF - vascular endothelial growth factor. Collagen hydrogel consistency facilitates infiltration into the pores of metal scaffolding.

Chitosan (CTS) is a polymer with chitin representing a group of biopolymers based on glucosamine. The degree of acetylation (DA) of chitosan is a structural parameter influencing the solubility, degree of crystallinity, density, electrical charge, susceptibility to enzymatic degradation, and thus the rate of degradation; the higher the DA, the faster biodegradation [10]. It is not osteoconductive so that it needs an addition of bioceramics.

Synthetic biodegradable polymers are designed mainly for soft tissue and as carriers of drugs [12]. Among their main features are: three-dimensional crosslinking resulting in a structure similar to natural elastin, high flexibility and elasticity similar to that exhibited by the tissue-like mechanical properties, and variable biodegradability. The mostly applied polymers include: PLA, PGA, PLGA and PLLA.

PLA is a thermoplastic, biocompatible and completely biodegradable aliphatic polyester, which is derived from lactic acid. PLA degrades by hydrolysis and is broken down into natural metabolites. Also PGA, one of the simplest aliphatic polyesters, is biodegradable by hydrolysis. PLGA is a copolymer obtained by a combination of units of PGA and PLA. PLLA, a biodegradable polymer, derived from semicrystalline lactic acid degrades into water and carbon dioxide. Thus, all these three synthetic polymers decompose to simple and totally removed compounds. The rate of degradation of copolymers can be adjusted by changing the chemical composition, such as ratio of LA/GA in the copolymer PLGA, by changes in degree of crystallinity, and molecular weight [9]. The hydrophilic PGA degrades intensively than the hydrophobic PLA [13].

Among another polymers or copolymers there are biodegradable compounds composed of: succinimide (SI) and lactic acid, (LA)-PSI-co-LA [14], copolymer of methyl methacrylate and N-vinylpyrrolidone [15], Polyactive ® based on polyethylene oxide (PEO) and polybutylene terephthalate (PBT) [16] able to bind to the bone and highly osteoconductive, porous PLLA composite scaffold containing rhBMP2, which promotes formation of a new bone within 2 weeks [17].

Important form of biodegradable species is hydrophilic cross-linked polymers [18]. The cross-linking may be initiated by physical mechanisms, such as changes in temperature, pH or ionic environment, and chemical mechanisms, including the special chemical compounds or light. The polymers can be directly injected to repair connective tissue. For this purpose, some natural polymer as a fibrin and an alginate, a polysaccharide containing mannuronic and guluronic acids are applied. Among the synthetic polymers used as hydrogels, the copolymers based on polyethylene and polypropylene oxide (PEO-PPO-PEO), and easy to photopolymerisation, the polyethylene oxide diacrylate (PEODA) are used. These hydrogels as isolated chemical species demonstrate weak mechanical properties.

Another synthetic biodegradable hydrogels are proposed as a tool for injectable delivery of cells and porous materials for bone regeneration. In [9] the porous polymer based on PEG is proposed after its modification with some peptides, able to facilitate the adhesion and spreading of cells. In [19] the biodegradable hydrogel was based on polyethylene glycol and ethylene polyester. Biodegradable, cross-linked multifunctional macromer has been developed as aminohexylo-propylene polyphosphate acrylate [20]. The sebacic acid polyglycerol PGS is a biodegradable polymer used in many medical applications, such as replacement of a soft tissue, especially heart muscle, blood, nerves and connective tissue [21]. An interesting proposal is the use of injectable polymer based on biodegradable polyurethane [22].

BIODEGRADABLE CERAMICS

There are no many ceramics that may be biodegradable. The bone substituting materials are mainly hydroxyapatite HA and β-tricalcium phosphate TCP ceramics, bioactive glass, or allografts such as demineralized human bone tissue without collagen or collagen-containing obtained from the bone morphogenetic proteins, growth factors like VEGF, TGF-1, TGF- 2 and BMP-3 [10]. The β - TCP $Ca_3(PO_4)_2$ has a high propensity for bone resorption and biodegradation in the environment of a living organism [23], whereas the HA is non-biodegradable ceramics.

BIODEGRADABLE COMPOSITE MATERIALS

Development of composites refers to the fact that human bone is composed of collagen and hydroxyapatite, i.e. biopolymer and bioceramics. Therefore all composite materials are based on combination of these two groups. Biodegradable polymer matrices are usually natural polymers, and synthetic polymers such as polyhydroxy acids (PLA, PGA, PCL), saturated aliphatic polyesters like a polypropylene fumarate (PPF) and polihydroksyalkanates (PHB, PHBV, P4HB, PHBHHx, PHO), and others. Bioactive ceramic phases include bioglasses and bioceramics, mainly calcium phosphates [24].

The most common solution is a material composed of collagen and phosphate, often used as nanogranules or nanofibers [25-27]. The effect of three-dimensional pore structure of HA and collagen on biological and mechanical properties is important [28]. A presence and content of HA has a significant impact on mechanical properties as well as cell proliferation [29].

In many cases, a typical composition is enriched with another polymer. In [86] the mixture of collagen and chitosan was applied resulting in bone mineralization with relatively high strength. In [30] the self-organizing nanocomposites were prepared by adding glutaraldehyde as a cross-linking agent. In [31] the composite biomaterial was obtained from HA, collagen and hyaluronic acid HIA, revealing high cohesion and a very good biocompatibility. The mineralization of type I collagen was enhanced by using a polymer-induced liquid precursor, acid polypeptide poliaspartamide [32], resulting in a composite HA and nanostructured bone collagen.

Another research direction was a use of HA with chitosan or chitin, often containing other compounds. In [33] the mixture of 25-75% of HA and chitin was proposed as noncitotoxic and degradable “in vivo”. For biodegradable cross-linked chitosan with HA and gelatin, the scaffolds with porosity up to 90% biomineralised in 3 weeks [34].

Popular polymers for biodegradable composite materials are polyhydroxy acids. In [35] the synthesis of nanocomposite HA and chitosan, in the presence of polylactic acid, was proposed. The HA particles had an elongated shape with a diameter of 50 nm and length of 300 nm, distributed in the matrix chitosan – PLA. The addition of PLA caused higher compressive strength and greater modulus of elasticity.

The composite nanohydroxyapatite with chitosan enriched with pectin produced a scaffold yielding a compressive strength of 14 MPa, as well as supporting the adhesion and cell proliferation [36]. In [36] the bioresorbable scaffolds made of nanoHA on surface composed of chitosan and gelatin were obtained in a solution of $Ca(NO_3)_2 * Na_3PO_4$.

An important research direction is the use of phosphates, like HA, TCP or carbonated hydroxyapatite (CHA) in combination with various degradable biopolymers. The composite materials investigated so far include: HA and PLLA [38-49], HA + PLGA and PLGA + CF [49], PLGA + β-TCP [50]. The latest study confirmed biocompatibility "in vitro" and "in vivo" of PLGA and its composites. The degradation time corresponded to the process of bone regeneration. In [51] the PLGA microspheres coated with apatite similar to bone mineral were proposed. Moreover, biodegradable or biostable ceramics were used. In [52] the mechanical and biological properties in vitro were analysed for a material, in which the polymer matrix based on both components with different biological behavior: biostable polysulfone (PSU) and bioabsorbable PGLA. The specimens of polymer modified bioactive hydroxyapatite particles were derived from animal bones. The addition of HA particles into PSU and PGLA caused a reduction in durability of composites in creep conditions in relation to the starting materials. The tested composites showed the favorable biological behavior in simulated biological environment. The bioactive particles on the surface can act as an anchor for bone tissue in contact with the material, which ensures a good adhesion. .

Influence of the production technique on properties of tested composites was observed. In [53] the chemically synthesized HA of high degree of crystallinity and PLLA obtained from L-lactide and nontoxic initiator were investigated. The composite material was prepared by mixing completely dissolved PLLA and HA granules. The composite was compacted by cold pressing and hot sintering at pressures of 49-490 MPa and temperature varied form 20-184°C. The material revelaed relatively high value of a compressive strength - 93 MPa,. In [54] the synthesis of microspheres of CHA, osteoconductive and biodegradable bioceramics, was followed by incorporation of electrospinned fibers of hydroxybiturene-hydroxyvalerianate copolymer (PHBV). Another approach to produce scaffolds PLGA / HA by a gas foaming and particulate leaching, GF/PL, was made without the use of organic solvents. This method allowed obtaining the scaffold composed of biodegradable polymer - ceramics with a better ability to regenerate bone from conventionally produced.

Increasingly, the application of nanohydroxyapatite is postulated [55, 56]. In [57] HA and CHA nanoparticles were incorporated on polycaprolaktone in the form of a hydrogel. HA molecules had the shape of needles with an average length of 50 nm. The addition of HA and CHA increased the bioactivity and biocompatibility of polymer matrix. Another composite material for bone tissue engineering [58] consisted of nanoparticles of fluorohydroksyapatite (nFHA) and polyurethane with porous structure. The first material was synthesized by sol-gel technique. Scaffolds were 50-250 μm in pore size and open structure. Porosity and average pore size decreased, and the compression module increased with HA content. It is also possible [59] to produce nanocomposite consisting of HA and poly-L-aspartamic acid (HA-PASP). HA particles may be succcesfully [60] dispersed in polihydroksybutyrate (PHB) resulting in bioactive and biodegradable composite for bone replacement and regeneration. The stiffness and strength of the composite is determined by the content of ceramics, as demonstrated e.g. for HA and TCP in the incorporated copolymer (PHB-PHV) [61]. Another attempt [62, 63] was taken using as a base polymer - semicrystalline caprolactone, which is resorbable aliphatic polyester, with, however, weak mechanical properties. To improve properties and promote osteoconductivity, HA particles were added to the PCL matrix. The content of 20 or 32% of HA resulted in a significant increase of mechanical strength, especially the elasticity modulus. The improvement also underwent osteoconductivity. Biodegradable composite hydrogels are materials still used in soft tissue engineering. Some biodegradable composites [64] can be obtained by photochemical crosslinking based on polyphotoesters and PEG. Macromers were biocompatible with the osteoblasts and they did not disclose toxicity up to 0.5 mg/dm^3 of content. Another biodegradable multifunctional macromer initiated photochemically, is poly-6-phosphate aminohexylopropylene synthesized together with acrylic groups (PPE-HA)-ACRL [65]. This group is composed of flexible hydrogels, which, at increasing acrylate content exhibit, high mechanical strength. No cytotoxicity at concentrations up to 10 mg/dm^3 were observed. In [66] a hybrid material based on PLLA sponge coated by collagen fibers and infiltrated with PLLA hydrogel was investigated. The use of a hydrogel, however, resulted in complete disappearance of the porous structure. The improved technique of producing the material by placing microsponge collagen particles into the pores of a synthetic polymer was proposed.

There are some diacrylates (DA) as components [67] of scaffolds: polypropylene-fumarate and fumarate diakrylate (PPF/PF-DA), macrocomposite PPF/PF-DA with mechanically reinforced microparticles or nanoparticles of aluminum gels, low molecular weight PPF/PF-DA. In all cases, no adverse effects were observed after implantation into the body. Polifumarates form the basis for many osteoconductive scaffolds [68]. Poliydroxyalkanates are biodegradable polyesters produced by microorganisms in the unsustainable growth conditions. In composite they are used as: a poly-3-hydroxybutyrate PHB, a copolymer of PHB and PHBV hydroxywalerianate 3, poly-4-hydroxybutyrate (p4HB), a copolymer of PHB and 3-hydroksyheksylate (PHBBHHx). polihydroksybutyrate (PHB) and its copolymers with hydroxyheksanate and hydroxywalerianate [69-72]. The biodegradable composites HA – polyphosphasene were developed and described in [73, 74].

Carbon nanotubes as filler were the subject to several studies. Technique for producing nanocomposites [75] included dispersing multi-wall carbon nanotubes in water, functionalizing them by the addition of a surfactant (sodium dodecyl sulfate), followed by their biomimetic mineralization in a solution containing Ca/P. A key problem seems to improve the interfacial adhesion between polymer and nanoparticles [76].

For an increase in mechanical properties even such reinforcements as regenerated cellulose (viscose) and banana fibers (abaca) were used for biocomposites based on polylactide (PLA) [77]. Both fibers increased stiffness and strength.

Hybrid organic-inorganic compounds are an interesting alternative in tissue engineering. One example is a derivative of chitosan (N, N-dikarboxymetyl chitosan DCMC) [78]. This compound forms stable gels when mixed with calcium acetate as a result of calcium chelation, while the addition of hydrogenated calcium phosphate produces a clear solution which, after dialysis and cold treatment, brought out an amorphous inorganic component suitable for bone reconstruction. Another example was an incorporation of calcium ions and Si-OH groups on the organic substances (hydroxymetacrylate HEMA) to yield bioactive hybrids [79]. The hybrid material containing calcium salts derived from siloxanes initiated the formation of apatite in Kokubo solution. Finally in [80] a relatively simple nanocomposite composed of HA and chitosan phosphate (CSP) containing 10-60% wt. HA was proposed, with proven interaction between HA and CSP, which allows the material to be qualified as a hybrid composite. The mechanical properties of the material increases with increasing HA content. The material was citocompatible and osteogenic in vivo.

The bioglassy scaffold are not very developed. In [81] the macroporous bioactive scaffold was produced with a use of crosslinked gelatin nanocomposite and bioactive glass nanoparticles. The resulting nanocomposite had pores ranged between 0 and 250 nm and a porosity of 72-86%, with chemical bonds between the nanoparticles of bioglass and gelatin.

In [82] were obtained semisynthetic hydrogels based on diacrylates deposited on a collagen porous membrane. The pore size was larger than that in typical hydrogels, allowing consider a hybrid hydrogel based on poly (NIPAM-co-DEGDA) as a superporous scaffold.

INFILTRATION TECHNIQUES

It is useless to design a biodegradable core material as a single compound: magnesium among metals can have negative effect on tissues, ceramics are unable to carry high mechanical loads without cracking, and polymers have poor mechanical properties. From that viewpoint, the core material should compose of biodegradable polymer and fully or partially biodegradable ceramic.

As the possible polymers, both natural and synthetic polymers can be taken into account. Among natural polymers, both collagen and chitosan may be used, and among synthetic polymers, copolymers PPLA, PGLA, and simple polyhydroxy acids PLA and PGA are to be investigated. Among ceramics, HA or its mixture with non-biodegradable β-TCP are the best candidates. There are several conditions discussed below which should be taken into account when looking for an optimal composition of the core material.

The degradation rate should be similar to the rate of bone tissue in-growth. This condition should be reached by a use of varying fractions of different compounds. Both, enzymatic (for polymers) and hydrolytic (for ceramics) degradation can be considered in future research.

The ability to carry mechanical loads depends on many factors: atomic bonds, intrinsic structure (particularly, porosity degree and morphology of pores), adhesion of core material to the titanium interface, rigidity and compression strength. For that reason the contribution from insoluble HA should be investigated as well as a physical form of a core material, i.e. an use of hydrogel instead of crystalline or amorphous material. To reach good adhesion, the ceramic nanoparticles can be applied. The limitation of porous structure to only surface layer as a means for better mechanical properties should be checked.

The essential issue is to produce porous three dimensional material nanonetwork. There are many techniques developed especially for polymers, like [9]: foaming gas dissolution and crystallization, electrospinning. To obtain a composition of HA and collagen the chemical co-precipitation was used [83]. In [84] the denaturation at 120°C was applied to prevent degradation of collagen. Another approach to fabricate a mixture of polymer and nanohydroxyapatite was to prepare dispersion of HA in polymer matrix [85]. In order to obtain nanohydroxyapatite, HA was deposited on bioorganic substances such as collagen or chondroitin sulfate [86]. This issue seems to be one of the most difficult problems as an appearance of nanoporous structure inside the core material could spoil its mechanical strength.

There are possible infiltration techniques that should be studied at the beginning. The first one the infiltration of titanium porous structure with polymer (by e.g. sol-gel technique) which can result in scaffold structure followed by precipitation of phosphate nanoparticles inside. The second could involve mixing of phosphate and polymers and co-precipitation inside the pores of metallic porous implant.

CONCLUSIONS

Basing on the literature reviewing the promising core material, only composites may be considered, with collagen and chitosan as natural polymers, polyhydroxy acids and their co-polymers as synthetic polymers as well as HA and β-TCP.

From the point of view of material properties for the core material in porous titanium alloy, three has to be considered: proper biodegradation rate in vitro and in vivo; high compression strength; ability to form nanoporous open structure inside.

As the most plausible, two fabrication techniques for a composite material inside the macropores are postulated: (i) infiltration of titanium porous structure with polymer followed by precipitation of phosphate nanoparticles or (ii) mixing of phosphate and polymers and co-precipitation inside the pores of metallic porous implant.

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