Current Topics

Bioceramic Research on Intelligent Implants and Drug Delivery System

Organic–Inorganic Composites Designed for Biomedical Applications

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Received May 30, 2013

Several varieties of ceramics, such as Bioglass-type glasses, sintered hydroxyapatite and glass-ceramic A–W, exhibit specific biological affinity, *i.e.*, direct bonding to surrounding bone, when implanted in bony defects. These bone-bonding ceramics are called bioactive ceramics and are utilized as important bone substitutes in the medical field. However, there is a limitation to their clinical applications because of their inappropriate mechanical properties. Natural bone takes a kind of organic–inorganic composite, where apatite nanocrystals are precipitated on collagen fibers. Therefore, problems with the bioactive ceramics can be solved by material design based on the composites. In this paper, current research topics on the development of bioactive organic–inorganic composites inspired by actual bone microstructure have been reviewed in correlation with preparation methods and various properties. Several kinds of inorganic components have been found to exhibit bioactivity in the body environment. Combination of the inorganic components with various organic polymers enables the development of bioactive organic–inorganic composites. In addition, novel biomedical applications of the composites to drug delivery systems, scaffolds for tissue regeneration and injectable biomaterials are available by combining drugs or biological molecules with appropriate control of its microstructure.

Key words organic–inorganic composite; bioactivity; bone substitute; drug delivery; tissue regeneration

1. BIOACTIVE CERAMICS FOR BONE TISSUE REPAIR

Ceramic biomaterials are useful for hard tissue reconstruction due to their high mechanical strength and hardness. However, they pose a problem when implanted in bony defects because they are encapsulated by fibrous tissues and consequently isolated from the surrounding bone.[1] This is a normal reaction for protecting our living body from foreign substances. This type of biological response is called bioinert.

Several varieties of ceramics have been found to exhibit bone-bonding performance. They are called bioactive ceramics, meaning that they can elicit biological activity. Bioglass-type glasses in the system Na_2O–CaO–SiO_2–P_2O_5,[2,3] sintered hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$)[4] and glass ceramics A–W[5] are known to be bioactive ceramics. In the glass-ceramic A–W, oxyfluorapatite ($Ca_{10}(PO_4)_6(O,F_2)$) and β-wollastonite ($CaO \cdot SiO_2$) crystals are dispersed in a MgO–CaO–SiO_2 glassy matrix.

Most bioactive ceramics bond to bone through a low crystalline apatite layer formed on their surfaces in the body environment, created by a chemical reaction with body fluid. The apatite formation *in vivo* can be also observed in simulated body fluid (SBF; Na^+ 142.0, K^+ 5.0, Mg^{2+} 1.5, Ca^{2+} 2.5, Cl^- 147.8, HCO_3^- 4.2, HPO_4^{2-} 1.0 and SO_4^{2-} 0.5 mol/m^3) with a similar concentration to inorganic ions as human blood plasma.[6] In order to construct fundamental knowledge on novel bioactive materials design, apatite formation behavior on materials with different surface structures has been investigated in SBF by using metal oxide hydrogels and self-assembled monolayers (SAMs). Based on these results, several surface functional groups, such as Si–OH,[6,7] Ti–OH,[7,8] Zr–OH,[9] Ta–OH,[10] Nb–OH,[11] $COOH$,[12] PO_3H_2[12] and SO_3H[13,14] are found to be effective for triggering the heterogeneous nucleation of the apatite. In addition to surface functional groups, apatite formation is governed not only by the functional groups but also several other factors, such as ion release enhancing the apatite nucleation from the materials,[15] and by a spatial gap constructed on the material surfaces.[16]

Tricalcium phosphate (TCP, $Ca_3(PO_4)_2$) is well known as a bioabsorbable ceramic. It is completely replaced by regenerated bone tissue after a long implantation period. TCP ceramics also show direct bone-bonding after being implanted in the body, although the apatite formation is not observed at the ceramic–bone interface, as is typical with bioactive ceramics.[17]

2. CERAMIC–POLYMER COMPOSITES

Even bioactive ceramics cannot substitute in load-bearing portions of bone, because their fracture toughness is lower and their Young's modulus is higher than those of human cortical bone. In addition, these ceramics are difficult to form

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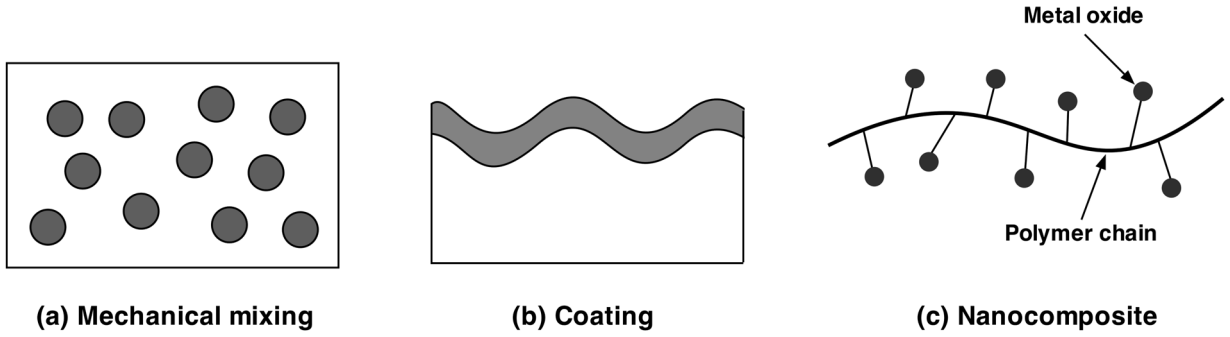

Fig. 1. Representative Techniques for Preparation of Organic–Inorganic Composites

Table 1. Apatite–Polymer Composites Prepared from Organic Polymers Modified with Functional Groups by Soaking in SBF or Related Solutions

Functional group	Polymer
Carboxyl group	Alginate[26]
	Carboxymethylcellulose[27]
	Synthetic aromatic polyamide[28]
	Poly-γ-glutamic acid[29]
Phosphate group	Chitin[30]
Sulfo group	Synthetic aromatic polyamide[13]
	Polyethylene[14]

into the desired shapes during implantation. Novel bioactive bone substitutes with high flexibility and high machinability are desired in the medical field. Natural bone takes a kind of organic–inorganic composite, where apatite nanocrystals are precipitated on collagen fibers.[18] Therefore the organic–inorganic composites inspired by the bone structure are expected to solve these problems. Moreover, novel material design as a drug delivery carrier is available by appropriate control of the pore structure and hydrophilicity of the organic or inorganic phase.

Representative techniques for the preparation of such composites are summarized in Fig. 1. The most popular preparation method of organic–inorganic composites is mechanical mixing of ceramic powder and a polymer. Mechanical and biological properties of these composites are governed by the mixing ratio. Addition of larger amounts of the bioactive ceramic powder is advantageous for high bioactivity, because its bioactivity is based on surface reactivity with body fluid. However, the addition of an excess amount of the ceramics can cause brittleness in the material. Therefore, optimization of the composition is quite important. Various composites such as apatite–poly-L-lactic acid,[19] apatite–polyethylene,[20] Bioglass-type glass–polyethylene,[21] apatite–collagen,[22] β-TCP–carboxymethyl chitin,[23] and apatite–cellulose[24] have recently been investigated. Composites with mechanical strength and Young's modulus analogous to natural bone have also been developed.

Coating is also a popular process for fabrication of the composites. SBF can also be used for the apatite coating on organic polymers. Polymers containing functional groups with the potential for apatite nucleation are available for use as substrates of the apatite–polymer composites. Such composites can be fabricated by simple soaking in SBF. If the apatite-forming ability of the polymer cannot be achieved easily, then 1.5×SBF solution can be used instead.[25] Apatite–polymer composites fabricated in SBF or more concentrated solutions

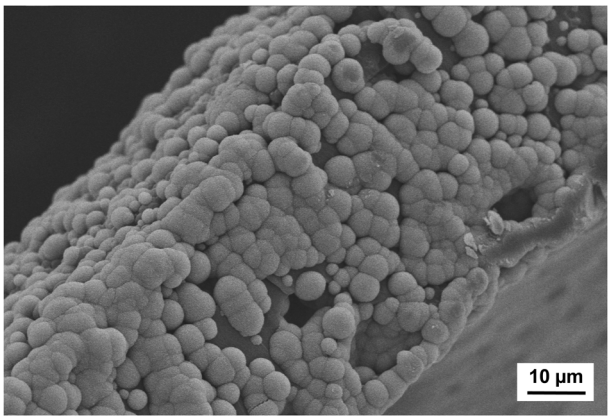

Fig. 2. Apatite Particles Formed on a Plant-Derived Polypeptide Film in 1.5SBF

are summarized in Table 1. An apatite layer formed on a kind of plant-derived polypeptide film is shown in Fig. 2.

Morphological control of the calcium phosphate crystals has been attempted *via* precipitation in hydrogels as a reaction field. Yokoi *et al.* synthesized the calcium phosphate crystals in polyacrylamide hydrogels using aqueous process, and investigated effects of concentrations of calcium and phosphate ions as a precursor.[31] Granular apatite was formed at high phosphate concentration, while spherulitic octacalcium phosphate (OCP, $Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$) was formed at low phosphate concentration. OCP has potential to intercalate various substances including drugs and biological molecules due to its layer structure. Therefore these findings would provide fundamental knowledge for precise control in drug release behavior of the calcium phosphate nanoparticles.

In addition, polymer coating is effective for control of the bioabsorbability of porous ceramics, which can serve as attractive scaffolds supporting bone tissue regeneration. Especially, interconnected pores with size in 100–400 μm are believed to be effective for the bone ingrowth. Porous α-TCP ceramics are expected to have high mechanical strength, since they can be sintered at high temperature. However, the solubility of α-TCP is higher than β-TCP. Therefore, implanted α-TCP is likely to be completely resorbed before sufficient bone repair. Kitamura *et al.* applied hydroxypropylcellulose coating to porous α-TCP.[32] The coated sample showed controlled bioabsorption corresponding to new bone formation.

The polymer coating on porous ceramic biomaterials is also effective for improvement of their handling properties. Ishikawa and colleagues have developed a carbonate apatite porous body by using polyurethane foam as a template, and

Table 2. Bioactive Organic–Inorganic Composites Prepared by Sol–Gel Method

Inorganic component	Polymer component	
	Natural polymer	Synthetic polymer
Silicon oxide	Starch[34]	Poly(dimethylsiloxane) (PDMS)[40,41]
	Carboxymethylcellulose[35]	Poly(2-hydroxyethyl methacrylate) (pHEMA)[42]
	Chitin[36]	Poly(vinyl alcohol) (PVA)[43]
	Chitosan[37]	Polycaprolactone[44]
	Polyglutamic acid[38]	Poly(methyl methacrylate) (PMMA)[45,46]
	Alginate[39]	Aromatic polyamide[47]
		Poly(lactic-*co*-glycolic acid) (PLGA)[48]
Titanium oxide	Not reported	Poly(tetramethylene oxide) (PTMO)[49]
		pHEMA[50]
Zirconium oxide	Not reported	Polycaprolactone[51]
Tantalum oxide	Not reported	PTMO[52]

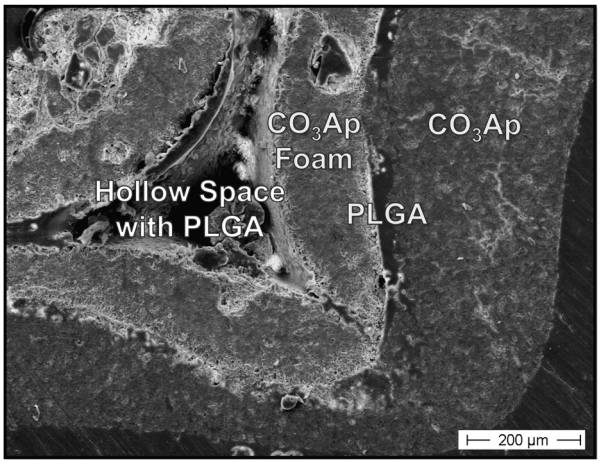

Fig. 3. Cross-Sectional View of Porous Carbonate Apatite Coated with PLGA

"CO_3Ap Foam" means the porous apatite.

attempted a coating of poly(lactic-*co*-glycolic acid) (PLGA) on the porous body under a vacuum condition.[33] Figure 3 shows a cross-sectional view of the coated ceramics. The coated PLGA makes direct contact with the porous carbonate apatite. The obtained porous carbonate apatite coated with PLGA can be easily machined to the desired shapes by a dental router, while that without PLGA broke into small pieces, as shown in Fig. 4.

3. DESIGN OF BIOACTIVE NANOCOMPOSITES

It is difficult to obtain composites with high homogeneity at a nanometer level by the mere mechanical mixing of ceramics and polymers. However, on the basis of the mechanism of apatite formation on bioactive ceramics, organic–inorganic composite materials with bone-bonding ability can be developed by organic modification of inorganic components with an ability for apatite nucleation at the nanometer level (Fig. 1).

High-temperature treatment is difficult to be applied to the preparation of these nanocomposites, since the organic polymers can be easily decomposed by the treatment. Sol–gel processing is one of the more promising methods for preparing these composites, because the reaction progresses at relatively low temperature. This process utilizes hydrolysis and polycondensation of metal alkoxides. Various bioactive nanocomposites can be designed from metal oxides and natural or synthetic polymers, as summarized in Table 2.

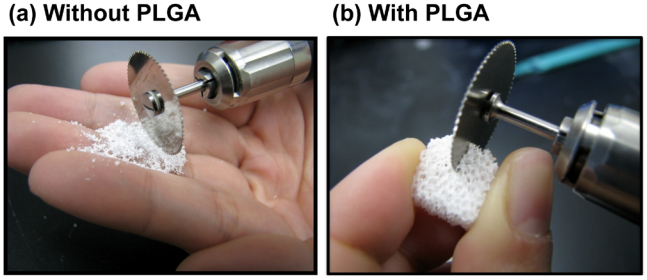

Fig. 4. Cutting of Porous Carbonate Apatite without (a) and with (b) PLGA Coating by a Dental Router

4. BIOMEDICAL APPLICATIONS OF THE COMPOSITES

Various biomedical applications, such as drug delivery systems, scaffolds for tissue regeneration, and injectable biomaterials, can be provided with the use of composites, with appropriate selection of their components and microstructure. Drug release from composites is significantly affected by various factors such as micropore structure, hydrophilicity of the components, and size of the composite particles. The ability to control the release of drugs is important in avoiding side effects caused by excessive dosage.

Son *et al.* attempted the coating of PLA loaded with dexamethasone on porous apatite scaffolds.[53] They showed that these prepared scaffolds have the ability to release dexamethasone for over 1 month. The drug release caused the proliferation and differentiation of human embryonic palatal mesenchymal cells and subsequent production of an extracellular matrix *in vitro*. Composite nanoparticles sensitive to stimuli such as pH and salt concentration have been developed from mesoporous silica by coating with stimuli-sensitive polymers.[54] These composites are useful in developing novel drug delivery carriers with high performance, *i.e.*, with an ability to accurately control drug release corresponding to the surrounding environment.

Oyane *et al.* attempted coating of the apatite layer with immobilized biological molecules, such as laminin, a kind of cell adhesion protein, on polymer substrates.[55] They demonstrated that epithelial-like cells attached to the substrates showed en-

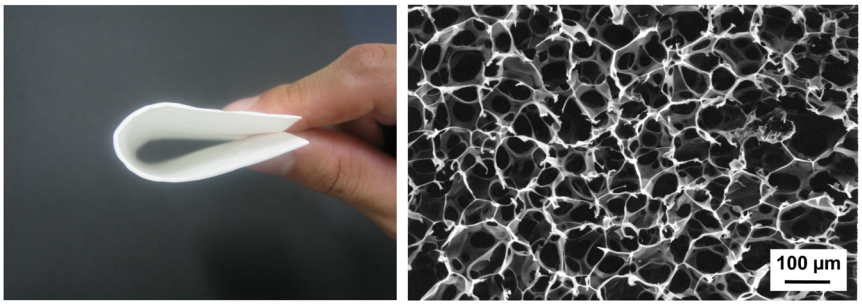

Fig. 5. Chitosan–Silicate Porous Membranes Prepared by Sol–Gel Route

hanced cell spreading.

Scaffolds can be designed for the regeneration of various tissues. For angiogenesis, Furuzono and colleagues developed composite scaffolds from poly(L-lactide-*co*-ε-caprolactone) microspheres coated with apatite nanoparticles by a surfactant-free emulsion route.[56] Intramuscular co-implantation of the microspheres with bone marrow mononuclear cells induced enhanced angiogenesis.[57] These are useful as injectable scaffolds for the treatment of severe ischemic disorders. The composites are also applicable to nerve fiber regeneration. Shirosaki developed chitosan–silicate composites by the sol-gel process, as shown in Fig. 5. They demonstrated that the prepared porous membranes significantly improved nerve fiber regeneration *in vivo*.[58]

Injectable bone substitutes with self-setting ability in the body can be designed from organic–inorganic nanocomposites. Kim *et al.* prepared apatite–carrageenan composites exhibiting thermoreversibility.[59] Gelation temperature of the carrageenan was adjusted by K^+ ion concentrations added to the gels. It is assumed that the added K^+ contributes to the steric structure of the carrageenan.

5. CONCLUSION

Material design based on organic–inorganic composites not only improves weak points in ceramic biomaterials, but also provides various biological functions such as drug delivery and tissue regeneration. It is desirable that the developed composites can be applied to the repair of various tissues, and thus contribute to providing a high quality of life (QOL) for patients.

Acknowledgments This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas for "Fusion Materials: Creative Development of Materials and Exploration of Their Function through Molecular Control" (No. 2206) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

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