Preparation of CaO@TiO₂−SiO₂ Biomaterial with a Sol–Gel Method for Bone Implantation

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ABSTRACT: The calcium phosphate spherical material with a hierarchical structure has been used as a bone implantation material. To improve the properties of the implant material, the compositions of calcium phosphate, silicon, and titanium are crucial. The presence of silicon on the surface of the phosphate–calcium material accelerates the bonding of the implant with the bone (osseointegration). The aim of this work was to develop a sol–gel method to prepare spherical calcium-phosphate@TiO₂−SiO₂ biomaterials for bone implantation. The CaO@TiO₂−SiO₂ biomaterial with a core–shell structure was synthesized by the sol–gel method. The biological properties of the materials were studied with a simulated body fluid (SBF). The sample had a spherical shape. The sample exhibited bioactive properties because an increase in the content of calcium and phosphorus ions in the shell and the presence of precipitated ions from the solution were detected on the surface. The TiO₂−SiO₂ framework was uniformly fixed on the CaO core. Heat treatment of the hybrid mesostructure led to the formation of mesoporous materials with a specific regular structure in the nanometer size in the shell, which is necessary for the fixation of biological cells when the sample is introduced into the biological medium. The formation of a calcium–phosphate layer on the materials and the release of soluble silicon and calcium ions into the SBF are the key factors for the rapid connection of these materials with tissue. The results demonstrate that the CaO@TiO₂−SiO₂ biomaterial with a core–shell structure is a good candidate for bone implantation.

INTRODUCTION

The process of restoration and replacement of bone defects, metal prostheses, metal alloys, polymers, calcium phosphate ceramics, glass ceramics, and bone grafts are widely used in bone implantation.1−8 The bone implant materials should have high strength and stability when implanted in the human body. These materials remain in the body for a long time and play the role of a reinforcement or a passive matrix in the formation of bone tissue.7−10 Glass ceramic, aluminum ceramic, and titanium implants show osteoinductive properties.11 The osteoinductive properties of calcium phosphate materials varied significantly depending on the size of macropores with the same chemical compositions.12,13 The recommended size of macropores is at least 300 μm, which contributes to nutrition and cellular spreading over the surface of macropores and to form capillaries in the implant.12−17

Calcium phosphate materials are widely applied in various forms.17 The layered spherical materials with a hierarchical structure, which are designed to fill the volumes of the complex shapes during the restoration of bone tissue, have been used as biomedical materials.18,19 To improve the functional properties of the implant material, the compositions of calcium phosphate, silicon, and titanium are crucial.20−24 It has been reported that the presence of silicon on the surface of the phosphate–calcium material accelerates the bonding of the implant with the bone (osseointegration).16,17,24,25 Carlisle et al.16,27 reported that silicon is vital for normal growth and development of skeletal tissues. With insufficient silicon nutrition, various bones would undergo deformation; in cartilage tissues, there is a decrease in the level of collagen and noncollagen proteins.5,7 It is established that in the initial stages of osteoid mineralization with an increase of calcium content, an increase in silicon content was observed.16,23 In the later stage of the formation of hydroxyapatite crystals, the silicon content decreased markedly and it was less than 0.01% in the mature bone tissue.12,23 Partial replacement of phosphate groups by silicate reduces the size of the crystallites, changes the structure of grains of phosphate–calcium materials, and increases their dissolution rate in body fluids.
thereby accelerating the remodeling process by the mechanism of precipitation from extracellular fluids.

To develop a phosphate–calcium-based biomaterial with specific physicochemical and functional properties, a layered composite with biologically active ions was prepared by the sol–gel method in this study. The aim of this work was to develop a method to prepare spherical calcium–phosphate@TiO2–SiO2 biomaterials and to investigate the physicochemical properties and its application on bone implantation. The sol–gel method28–31 was used to synthesize the TiO2–SiO2 sol in this study. It was coated on CaO to form a core–shell structure. The calcium-containing sample of the TOKEM-200 cation exchanger based on acryl-divinylbenzene was chosen because of its high selectivity to Ca2+.

RESULTS AND DISCUSSION

The choice of cation exchanger for the production of spherical materials was based on the results of the physicochemical properties and selectivity of sorbents to the Ca2+ ion.32 In order to form the bioactive material with a spherical shape, the TiO2–SiO2 sol was prepared. Because the stability of sol is important in practice, the viscosity of the TiO2–SiO2 sol was used as a criterion for the coating ability of sol and the results are listed in Table 1.

Table 1. Viscosity and pH Value of Sol vs Storage Time

| storage time, days | viscosity, mm2/s | pH      |
|-------------------|-----------------|---------|
| 0                 | 2.36            | 7.61    |
| 2                 | 3.15            | 7.43    |
| 3                 | 2.94            | 7.50    |
| 4                 | 3.12            | 6.25    |
| 7                 | 3.20            | 6.02    |
| 14                | 3.21            | 4.58    |

Table 1 shows that the viscosity of the sol after preparation increased dramatically with time in the first 2 days. This was due to the hydrolysis and polycondensation, coarsening of the particles, and the transition of the solution to a colloid.33–35 The sol was coated on the surface of the substrate, and the film was formed at a viscosity of 2.81 mm2/s. The film-forming ability of the sol was achieved by hydrolysis and polycondensation (eqs 1–4), as well as by the electrostatic interaction between dissolved ions and solvent molecules. All of these processes lead to an increase in viscosity with storage time.

\[
\text{Si(OC}_2\text{H}_5\text{)}_4 + \text{H}_2\text{O} \rightarrow \text{Si(OC}_2\text{H}_5\text{)}_3\text{OH} + \text{C}_2\text{H}_5\text{OH}
\]  

(1)

\[
\text{2Si(OC}_2\text{H}_5\text{)}_3\text{OH} \rightarrow (\text{H}_2\text{C}_2\text{O})_3\text{Si} - \text{O} - \text{Si(OC}_2\text{H}_5\text{)}_3 + \text{H}_2\text{O}
\]

(2)

\[
\text{Ti(OC}_4\text{H}_9\text{)}_4 + \text{H}_2\text{O} \rightarrow \text{Ti(OC}_3\text{H}_7\text{)}_4\text{OH} + \text{C}_2\text{H}_5\text{OH}
\]

(3)

\[
\text{Ti(OC}_4\text{H}_9\text{)}_4\text{OH} \rightarrow (\text{H}_2\text{C}_2\text{O})_4\text{Ti} - \text{O} - \text{Ti(OC}_3\text{H}_7\text{)}_4 + \text{H}_2\text{O}
\]

(4)

In the process of sol preparation, polycondensation reaction of tetraethoxysilane and tetrabutoxytitanium plays an important role. It leads to the formation of a molecular network in the solution. In the solution, orientational interactions dominated in the first 3 days. Therefore, on the second day, the viscosity of the solution increased sharply, and on the third day, it decreased to a value of 3.12 mm2/s. After that, a new structure was formed in the sol because of the orientational polarization processes, which occurred due to the electrostatic interaction of dissolved substances among themselves and alcohol molecules. Phosphoric acid increased the acidity of the solution and accelerated the reactions of hydrolysis and condensation. At the same time, the growth of the particles slowed down, and the chain formation and the gel networks started.36 The sol was stable on the fourth day with a viscosity of 3.12 mm2/s.

According to the thermal analysis data, only exothermic peaks of the sample were observed in the temperature range between 400 and 600 °C because of the combustion of alcohol, thermal oxidative degradation of ethoxy groups, and the organic component of the cation exchanger. The kinetic parameters of the processes were calculated by the Metzer–Horowitz method. The low values of the activation energy between 57 and 84 kJ/mol indicated that the processes were physical, instead of chemical interaction.

The presence of characteristic bands in the IR spectra (Figure 1) confirms the presence of water and organic compounds in both samples at 60 and 600 °C, corresponding to water vibrations in the range of 1794.3–1540.0 cm−1. The IR bands of the samples are listed in Table 2.

The bending vibrations of –CH2 and –CH3 groups were detected in the range of 1319.3–1405.1 cm−1.37–41 It can be explained by the fact that adsorbed water was released from the material and initiated the hydrolysis reaction of polysiloxanes on the surface. As a result, alcohol was also released by the following reaction.40

![Figure 1. IR spectra of materials (a) dried at 60 °C and (b) annealed at 600 °C.](https://dx.doi.org/10.1021/acsomega.0c03335)
The structure of the material was formed by silicon–oxygen and phosphorus–oxygen groups. It is confirmed by the presence of bands at 859–871 cm$^{-1}$ in the IR spectra, which correspond to the stretching asymmetric vibrations of Si$\equiv$O–Si, stretching symmetric vibrations of Si$\equiv$O–P, and stretching symmetric vibrations of PO$_4$ respectively. The stretching symmetric vibrations of Si$\equiv$O–Si and P–O–P bonds were detected only in the sample pretreated at 600 °C, corresponding to the band at 712.2 cm$^{-1}$.

The vibration of the Ti–O bond was identified only for the sample pretreated at 600 °C. The stretching symmetric vibrations of Si$\equiv$O–Ti are attributed to the bands at 380, 590–620, 930–965 920–950, and 1040–1078 cm$^{-1}$. In addition, tetrahedral SiO$_4$ and PO$_4$ groups were present in the material. The group of bands in the range of 680–780 cm$^{-1}$ is attributed to the symmetric vibrations of bridge Si–O–Si bonds in [SiO$_4$]-tetrahedra. The absorption bands in the low-frequency region of 400–550 cm$^{-1}$ are associated with bending vibrations of the O–Si–O end bonds and with vibrations of the calcium–oxygen bonds in [CaO$_6$]-octahedral.

The scanning electron microscopy (SEM) results (Figure 2) show that the sample had a spherical shape. The TiO$_2$–SiO$_2$ framework was uniformly coated on the CaO cation exchanger. Heat treatment of hybrid mesostructure led to the formation of a regular structure in the nanometer size range, which is necessary for the fixation of biological cells when the sample is introduced into the biological medium. Elemental analysis (Figure 2) shows a uniform distribution of all elements throughout the sample.

The bioactivity of the material was studied in vitro by keeping the sample in cell-free simulated body fluid (SBF) blood plasma for 14 days. The sample was placed in the model medium at a constant temperature of 37 ± 0.5 °C and pH 7.4. The solution was changed every day for 14 days to maintain its pH constant. The composition of the SBF solution was the same as that reported in the literature. Investigation of the morphology of the coatings after immersion in the SBF solution identified large, loose particles on the surface, as shown in Figure 3. It is favorable for bone growth and formation of a durable implant–bone connection.

After keeping the sample in the SBF solution, the mineralization and precipitation of calcium phosphate compounds on the active centers of the coating surface were observed. This was confirmed by an increase in the content of Ca and P according to the results of X-ray microanalysis (Figure 4).

As soon as the sample was immersed in the SBF, a rapid increase in the pH of the medium was observed on the first day. After that, the increase in pH was not significant (Figure 5).

An increase in pH created a favorable environment for the crystallization of the calcium phosphate layer on the surface of the material. There are three stages in the process of complete bonding of bioactive:

1. Rapid exchange of Na$^+$ and Ca$^{2+}$ with H$^+$ or H$_2$O$^+$ from solution:
In this study, the CaO@TiO$_2$–SiO$_2$ biomaterial with a core–shell structure was synthesized by the sol–gel method. The framework of the material was TiO$_2$–SiO$_2$, and the inner part was filled with CaO. The mixture of tetrabutoxytitanium and tetraethoxysilane was added to the phosphoric acid/butanol solution. It was aged at room temperature for 3 days. The calcium-containing samples of the cation exchanger were immersed in the sol for 12 h, followed by drying at 60 °C for 60 min. After drying, the sample was subjected to the stepwise heat treatment at 150, 250, and 350 °C, each for 30 min, and at 600 °C for 6 h. The sample was characterized by viscosity, thermogravimetry, dynamic scanning calorimetry, infrared spectroscopy, SEM, and energy-dispersive microanalysis. The biological properties of the materials were studied with the SBF.

After immersing CaO@TiO$_2$–SiO$_2$ biomaterials in the SBF, the sample exhibited bioactive properties because an increase in the content of calcium and phosphorus ions and the presence of precipitated ions from the solution were detected on the surface. The IR bands corresponding to Si–O–Si, Si–O–P, Si–O–Ti, SiO$_2$, and PO$_4$ were detected. The SEM results showed that the sample had a spherical shape. The TiO$_2$–SiO$_2$ framework was uniformly distributed on the CaO cation exchanger. Heat treatment of the hybrid mesostructures led to the formation of mesoporous materials with a regular structure in the nanometer size range and a highly developed surface, which is necessary for the fixation of biological cells when the sample is introduced into the biological medium. Elemental analysis shows a uniform distribution of all elements throughout the sample. The formation of a calcium–phosphate layer on bioactive materials and the release of soluble silicon and calcium ions into the surrounding tissues are the key factors for the rapid connection of these materials with tissue. Acceleration of the formation of the calcium–phosphate layer on the surface of the material occurs with an increase of pH.

**EXPERIMENTAL SECTION**

**Chemicals.** Tetraethoxysilane (Puriss. Spec., Germany), orthophosphoric acid (Puriss. spec. Himmed Russia), calcium nitrate (Puriss. Spec. Himmed Russia), tetrabutoxytitanium (Puriss. Spec. Germany), and butyl alcohol were used as received from vendors.

**Synthesis of Materials.** It is known that the stability of the sol is dependent on the preparation method. In this study, the preparation of sol was carried out according to the method reported in the literature. To obtain spherical biomaterials, the shell was TiO$_2$–SiO$_2$, and the inner part was filled with Ca$^{2+}$ oxide. The sample was denoted as CaO@TiO$_2$–SiO$_2$. The calcium-containing sample of the cation exchanger (TOKEM-200) based on acryl-divinylbenzene was used because of its high selectivity to Ca$^{2+}$.

In order to form a frame of a bioactive material with a spherical shape, a stable sol was prepared. A mixture of tetrabutoxytitanium (65 mol %) and tetraethoxysilane (30 mol %) was added to the solution of phosphorus acid/butanol. It was aged at room temperature for 3 days. The calcium-containing sample of the cation exchanger was immersed in the phosphate-containing sol for 12 h, followed by drying at 60 °C for 60 min. After drying, the sample was subjected to the stepwise heat treatment at 150, 250, and 350 °C, each for 30 min, and at 600 °C for 6 h.

**Characterization.** To study the coating ability of the TiO$_2$–SiO$_2$ sol, the viscosity of the sol was measured with a glass viscometer with a capillary diameter of 0.99 mm at 25 °C. The thermal stability of the sample was studied by a synchronous thermal analyzer (STA 449 C Jupiter) in the oxygen atmosphere by the shape of the thermogravimetric (TG) and differential scanning calorimetry curves in the temperature range between 60 and 900 °C. The activation energy of each stage of thermal destruction of the sol was determined by the method for thermographic and TG measurements with the Metzger–Horowitz equation.

The IR spectra of the samples were recorded on a Nicolet 6700 FTIR spectrometer in the frequency range 400–4000 cm$^{-1}$.
The structure and chemical compositions of the samples were analyzed on a Hitachi TM-3000 scanning electron microscope with the Quantax-70 attachment for energy-dispersive microanalysis (EDX).

The biological properties of the materials were studied with a SBF. The sample was immersed in the SBF solution at 37 °C for 14 days, after which the surface morphology of the material was examined with a Hitachi TM-3000 scanning electron microscope with the Quantax-70 attachment for EDX.

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**Notes**

The authors declare no competing financial interest.

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