

Si-modified BHA bioceramics as a drug delivery system: Effect of modification method on structure and *Rifampicin* release

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Abstract

The work is devoted to the investigation of two different methods for introduction of silicon into ceramics, based on biogenic hydroxyapatite (BHA), on the structure and properties. Thus, porous samples of Si-modified BHA-based ceramics containing 2 or 5 wt.% Si were prepared by using two different precursors, i.e. poly-methylsiloxane polyhydrate and fine silica (Aerosil[®] 200) powder. After the modification with silicon a marked change in the structure of material was observed. The use of Aerosil[®] 200 permits preparation of a more uniform structure as compared to that obtained by using polymethylsiloxane polyhydrate. However, the latter promotes an increase in both the porosity of samples (from 43 to 62.3%) and their solubility in saline (from 0.18 to 1.20 wt.%/day) as compared to the results obtained after the modification with Aerosil[®] 200, where maximal porosity and solubility were 48.5% and 0.23 wt.%/day, respectively. At the same time, the modification of hydroxyapatite ceramics with silicon using silica makes it possible to prolong release of a drug (e.g. Rifampicin) out of sample pores for the first 24 h as compared to the ceramics modified with polymethylsiloxane polyhydrate.

Keywords: hydroxyapatite, silica, porous materials, Rifampicin, biomedical application

I. Introduction

Calcium phosphate materials are widely used for replacement of defective areas of bone tissue and represent a major group of implant materials for bone plastics. Among them, hydroxyapatite (HA) of different origin is now the most popular thanks to the fact that its chemical composition is the closest to that of the mineral component of human bone tissue [1,2]. Over recent decades researchers have actively been developing materials on the HA-basis, paying a particular attention to modifying its composition with various chemical elements, including silicon. The important role of silicon in processes of bone tissue mineralization is well-known [3–5]. On one hand, a positive effect of silicon on the bone tissue metabolism is of great interest. In addition, the strength and biocompatibility of porous silica itself also promote its broad application in orthopedics and tissue engineering. Furthermore, fine silica powder has

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recently found a lot of applications as a carrier of various drugs thanks to small particle size, available developed surface, high chemical purity and physiological biocompatibility [6–9].

Accordingly, simultaneous actions of updated boneplastic materials and antimicrobial drugs attract great interest, especially in cases of the absence of clinic manifestation of infectious processes accompanied with a high risk of their arising. Antimicrobial therapy is particularly urgent for bone-purulent infections such as osteomyelitis and bone tuberculosis. Methods for rational antimicrobial therapy are chosen for each individual case taking into account the peculiarities of the patient, especially his sensibility towards antibiotics. Antibiotics are introduced by various techniques, for example through veins, muscles, bones or mouth, depending on the particular case. For more severe disease, it is frequently necessary to use combination of different methods for antibiotic therapy [10].

The problem of local delivery of antibiotics so far remains urgent. Generally, implant materials are mixed

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with antibiotics just before a surgeon operation, but in this case the antibiotic is removed out of the operation area very rapidly. Furthermore, unlike traditional administration of drugs and their distribution all over the organism, aimed delivery permits decrease in the drug dosage and minimizes its action on other cells, that is, side effects [11].

Hence the development of materials that can provide local delivery of drugs is one of the most important problems to be solved by material science researchers. The scientists of Frantsevich Institute for Problems of Materials Science of NAS of Ukraine have shown the possibility to saturate powders of synthetic HA with *Rifampicin*, which is an antibiotic with a broad spectrum of action and high activity towards tuberculosis mycobacterium [12]. Moreover, they confirmed the possibility of using 200–400 μ m granules of synthetic HA and HA/tricalcium phosphate mixtures as drug (*Rifampicin*) carriers [13].

Our previous paper [14] has shown that modification of the biogenic HA (BHA) with 5 wt.% of silicon via introduction of polymethylsiloxane polyhydrate followed by sintering at 600 °C positively affects the properties of ceramics *in vitro*. In particular, it decreases pH of saline and increases the solubility in it by 7 times as compared to the silicon-free BHA ceramics. The possibility to saturate the Si-modified powders and compacted porous ceramics with antibiotics has also been demonstrated. Herein introduction of silicon into ceramics increases the level of impregnation with *Rifampicin* and allows control of *Rifampicin* release into saline.

Additionally, it has been established that modification of HA ceramics with silicon (2 and 5 wt.%) via introduction of polymethylsiloxane polyhydrate leads to a marked increase in the specific surface area (from 6.1 to 59.8 m²/g), changes the shape of grains (from plate-like to round) and decreases the average grain size (from 0.65 down to 0.1 μ m) [15]. The obtained materials exhibit a porosity of 56.0–62.3% and strength of 27–33 MPa, which is consistent with the strength of spongy human bone tissue [15]. Moreover, it was determined that introduction of silicon dioxide in the form of fine silica powder Aerosil[®] 200 (Germany) in amounts 2–5% significantly changes the structure of the ceramics, making it more porous and finer [16].

The authors have shown that fixation and release of antibiotic are easier for porous samples than for powders [14]. This is the reason why porous Si-modified BHAbased ceramics were investigated in the present work. The aim of this work was to carry out comparative investigation between BHA-based ceramics obtained by two different Si-modification methods and the influence of the used methods on the structure and properties of the produced biomaterial, in particular on its sorption activity towards antibiotic.

II. Experimental

The starting material was biogenic hydroxyapatite (BHA) Osteoapatyt Keramichnyi[®](Ukraine) powder with the average particle size of $\leq 160 \,\mu\text{m}$. Two different methods were used to prepare porous samples of Simodified BHA-based ceramics with the silicon content equal to 2 and 5 wt.%. In the first one Si-modified BHA-based ceramics were produced with the use of polymethylsiloxane polyhydrate ((CH₃SiO_{1.5}) · *x*H₂O)_n (*x* = 30–45, n $\rightarrow \infty$) (Kreoma-Pharm Company, Ukraine). The precursor BHA powder was subjected to mixing

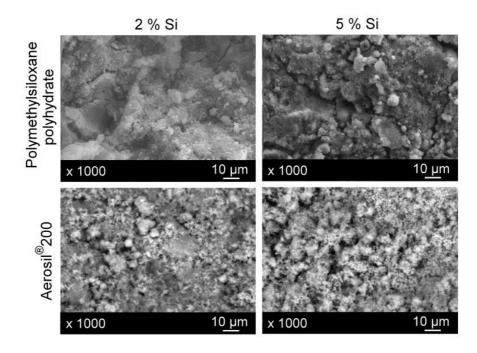


Figure 1. SEM micrographs of Si-modified BHA ceramics samples (fractured surface) prepared using polymethylsiloxane polyhydrate and Aerosil[®] 200

with polymethylsiloxane polyhydrate dissolved in water and drying at 100 °C, followed by uniaxial pressing at 50 MPa and sintering in a muffle furnace up to 600 °C in air [15]. In the other method for preparation of Si-modified BHA-based ceramics fine silica powder (Aerosil[®] 200, Germany) was used as a source of silicon. The starting powders (BHA and silica) were homogenized, than uniaxially pressed at 50 MPa to prepare samples with a diameter of 15 mm and finally sintered at 600 °C in a muffle furnace [16].

The structure of prepared samples was examined using a scanning electron microscope REM-106I (Selmi, Ukraine). Total porosity was calculated on the basis of the apparent density and the density measured at room temperature using the Archimedes method with toluene as an immersion liquid. Open porosity was determined by hydrostatic weighing in toluene.

Investigation of solubility in vitro of porous samples was carried out in an isotonic saline solution (0.9% NaCl) at a solid/liquid ratio of 1:30 after two-day exposition in a thermostat at 36.5 ± 0.5 °C followed by determination of mass loss on an analytic balance "OHAUS Pioneer PA214C" ("OHAUS Corporation", China) with an accuracy of 0.0001 g.

In order to study the absorptivity of bioceramic samples, in particular the kinetics of drug release from their surfaces, a widely-acted antibiotic Rifampicin produced at the ZAO "NPTs Borshchahovskyi KhFZ" was used. Saturation of samples with the antibiotic was performed using an alcohol solution of Rifampicin with a concentration of 15 g/l. Bioceramic samples were immersed into the solution for 36h (10ml of the solution per 1g of the sample) and after that the alcohol was evaporated. The drug concentration on the samples was determined by photometric analysis (FEK-56M, Russia). Release of Rifampicin from bioceramic samples was studied in saline (0.9% NaCl solution), which is an isotonic solution for human blood serum. The Rifampicin-loaded bioceramic samples were immersed in the saline (50 ml of the solution per 0.1 g of the material) and incubated at 37 °C. After predetermined time intervals (30 min, 3 h and 24 h), 10 ml of the solution was taken from the flask for measuring the *Rifampicin* concentration by photometric analysis (FEK-56M, Russia). The 0.9% NaCl solution served as a control solution [14].

III. Results and discussion

Figure 1 demonstrates the structure of fractured surface of the Si-modified BHA ceramics prepared with polymethylsiloxane polyhydrate and Aerosil[®] 200. Comparison of the structures formed upon using different methods permits one to conclude that the use of Aerosil[®] 200 yields a more uniform structure. The samples prepared using polymethylsiloxane polyhydrate exhibit a gel-like structure whereas the ceramics prepared from the fine silica are characterized by crystalline a grained structure containing fine particles.

The introduction of silicon into the BHA ceramics composition using polymethylsiloxane polyhydrate and Aerosil[®] 200 does not affect the material phase composition, as shown in our previous papers [15,16]. The X-ray diffraction analysis showed the presence of the HA phase (Ca₅(PO₄)₃(OH), Card # 9-432) for all compositions, but because of high specific surface area and amorphous nature silica cannot be seen in the pattern. The presence of silicon was confirmed by chemical analysis and IR spectroscopy. Moreover, the preservation of the maximum of the main vibration bands of the BHA ceramics upon the introduction of silicon by two different methods into its composition indicates that the structural elements and the type of their vibrations do not change.

The results for the apparent density of the unmodified and silicon-modified BHA ceramics are shown in Fig. 2. One can see that the apparent density decreases after modification of the BHA ceramics with silicon: the higher the silicon content, the lower the apparent density. Herein for the samples prepared with polymethylsiloxane polyhydrate the apparent density is lower than

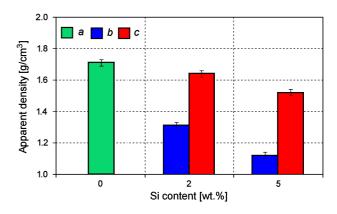


Figure 2. Apparent density of unmodified (a) and Simodified BHA ceramics prepared using polymethylsiloxane polyhydrate (b) and Aerosil[®] 200 (c)

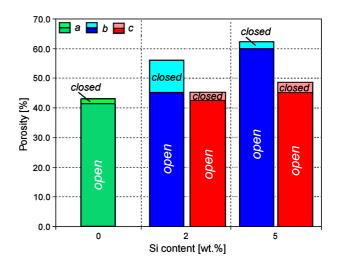


Figure 3. Porosity character of unmodified (a) and Simodified BHA ceramics prepared using polymethylsiloxane polyhydrate (b) and Aerosil[®] 200 (c)

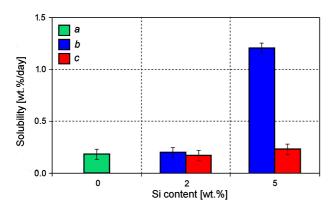


Figure 4. Solubility in saline of unmodified (a) and Simodified BHA ceramics prepared using polymethylsiloxane polyhydrate (b) and Aerosil[®] 200 (c) (2 days)

that of the samples prepared with fine silica powder, which may be related to the elimination of the organic compound under sintering. These findings are consistent with the data on porosity presented in Fig. 3. The study of porosity revealed that modification of BHA with silicon makes it possible to increase the porosity of samples alongside with preservation of its predominantly open structure, which is a required characteristic for bioactive materials. Herein modification of the BHA ceramics using fine Aerosil[®] 200 slightly increases the total porosity of the sample, from 43.0 to 48.5%, whereas in the case of the sample prepared with polymethylsiloxane polyhydrate the total porosity rises up to 62.3%.

Investigation of solubility of the Si-modified BHAbased ceramics revealed that the rate of sample dissolution for 2 days significantly depends on the method for silicon introduction into the ceramics (Fig. 4). Introduction of silicon in the form of Aerosil[®] 200 powder practically does not affect the dissolution rate, which slightly increases the latter for samples with 5 wt.% Si, whereas polymethylsiloxane polyhydrate markedly affects the solubility, namely increases it, as it has been established by the authors before [14].

The noticeable effect of the method for silicon introduction on the bioceramic sample dissolution rate can be related to the difference in the porous structure of samples. Despite the predominant fraction of open porosity in all samples, the total porosity of the BHAbased ceramics prepared with Aerosil[®] 200 is by 20% lower than that of ones modified with polymethylsiloxane polyhydrate.

The investigation into a possibility of saturation of compact porous samples from the unmodified and S-modified ceramics with *Rifampicin* in an alcohol solution (15 g/l) shows up the efficiency of this process. The best saturation with *Rifampicin*, namely 42.1–48.5 mg/g, was achieved for the Si-modified BHA ceramics obtained using polymethylsiloxane polyhydrate whereas in the case of the ceramics prepared with Aerosil[®] 200 saturation was 22.8–27.3 mg/g.

Figure 5 represents the kinetic curves of Rifampicin

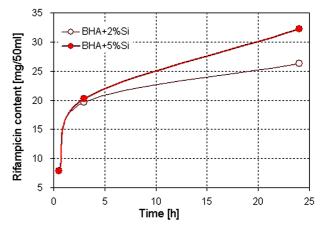


Figure 5. Kinetic curves of *Rifampicin* release from the sample surface into saline for Si-modified BHA ceramics prepared using Aerosil[®] 200

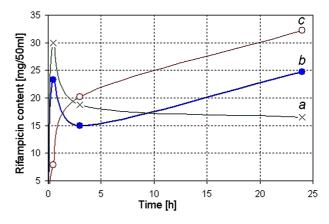


Figure 6. Kinetic curves of *Rifampicin* release from the surface of unmodified (a) and Si-modified BHA ceramics prepared using polymethylsiloxane polyhydrate (b) and Aerosil[®] 200 (c)

release from samples modified using fine silica into saline as a function of the silicon content in the material. As seen, the higher the silicon content, the greater amount of the released Rifampicin for 24 h. For comparison, Fig. 6 shows the kinetic curves of *Rifampicin* release from the Si-modified BHA-based bioceramics into the saline solution depending on the method for silicon introduction. As seen, the use of fine silica powder changes the behavior of the kinetic curve. For the unmodified BHA samples, most of the absorbed Rifampicin is released during the first 30 min of contact with the saline solution. On the other hand, the Si-modified ceramics (5 wt.% Si) during 1 h releases smaller amount of antibiotic, which thus confirms the possibility of the antibiotic action prolongation. After 24 h the opposite picture is observed: the lowest amount of Rifampicin leaves the unmodified BHA ceramics and the highest one releases the ceramics modified with Aerosil[®] 200. Therefore, it may be suggested that in the case of Si-modified ceramics, strong chemical bonds are formed during saturation, that is, it is chemisorption that retards the antibiotic release.

IV. Conclusions

The effect of method for introduction of silicon into BHA ceramics on the structure and properties of the material has been studied. It was established that introduction of silicon using the organic silicon compound polymethylsiloxane polyhydrate promotes more noticeable increase in both the sample porosity (from 43 to 62.3%) and solubility in the physiological solution (from 0.18 to 1.20 mass%/day) as compared to modification of samples with Aerosil[®] 200: in the latter case the maximal porosity and solubility were 48.5% and 0.23 wt.%/day, respectively.

Also, a possibility of saturation of the Si-modified ceramics with antibiotic (*Rifampicin*) has been demonstrated. Better saturation parameters (to 48.5 mg/g) were achieved for the ceramics obtained using polymethyl-siloxane polyhydrate, whereas the saturation parameter for the samples prepared with fine silica powder did not exceed 27.3 mg/g.

Additionally, it was established that the method for modification of HA ceramics with silicon using Aerosil[®] 200 allows one to prolong the drug release from porous compact samples for the first 24 h as compared to the ceramics prepared via introduction of polymethylsiloxane polyhydrate. In our opinion, in the latter case the drug is released from the surface of sample firstly, not from its volume. Then its release steadily decreases followed by significant increase due to release out of ceramic sample pores, i.e. out of the sample volume.

The materials obtained are promising for implants as carriers of drugs in medicine application to treat bone purulent infections, especially in cases of replacement of defective areas of bone tissue simultaneously with antimicrobial therapy.

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