Solubility characteristics of the material based on porous hydroxyapatite ceramics coated with PLGA

D Lytkina¹, A Gutsalova¹, M Pozdniakov¹, L Heinrich¹² and V Kozik¹
¹National Research Tomsk State University, Russia
²University of Muenster, Germany

E-mail: darya-lytkina@yandex.ru

Abstract. Composites based on a porous hydroxyapatite carcass with a coating of PLGA were obtained. According to the SEM images, it was found that, the composites had a different coating character depending on the porosity of the HA framework. After 1 week, the dissolution rate of composites increases relative to pure PLGA, and the growth is proportional to the increasing of the amount of pore-forming agent in the material by 20-50%. The dissolution rate of HA in the composition of materials also increases since the second week, because the diffusion of the solvent in the HA increases as the result of PLGA hydrolysis.

1. Introduction
Currently, hydroxyapatite (HA) and a copolymer of lactide and glycolide (PLGA) are among the most popular components for obtaining bioresorbable materials for bone tissue repair [1]. Typically, HA promotes osteointegration [2], as is a component of native bone tissue, PLGA serves as a degraded carrier of HA, as well as a modifier of some of its properties. Conventionally, such materials can be divided into PLGA fibers with included HA particles [3,4], polymer films and molded blocks filled with HA [5,6], foams [7] and ceramic materials with polymer coating [8]. Solubility of such materials depends on the method of their preparation, their surface characteristics, crystallinity of the components and molecular weight of used PLGA. Previously, the approaches of preparation of a porous ceramic frame material covered with PLGA were made, and it was shown than such material is able to maintain mechanical strength during the process of dissolution for a long time. So, studying of the solubility characteristics of the materials based on HA-ceramics coated with PLGA and estimation of the time of their degradation in a model solution is the aim of this work.

2. Experimental

2.1. Preparation of initial components and composite materials
The original HA was obtained by a liquid-phase microwave method [2]. PLGA (Mw = 80 000) was obtained by coordination polymerization via ring opening polymerization of lactide and glycolide (lactide/glycolide ratio is 80/20) [9,10].

Materials were obtained in 2 stages. First one - obtaining a porous HA frame with usage of soluble NaCl as pore-forming agent. Varying of NaCl amounts, 3 types of HA frames with different porosity were obtained. Second stage – impregnation of the obtained scaffolds in the PLGA solution under ultrasound action. In details, materials preparation is described in [8]. The compositions of the materials are presented in Table 1.
Table 1. Composition of the materials

| Samples | K1 | K2 | K3 |
|---------|----|----|----|
| Amount of pore-forming agent (NaCl), mass. % | 10 | 25 | 50 |
| PLGA content, mass. % | 5 | 7 | 17 |

2.2. Study of the materials surfaces morphology
The morphology of materials surfaces were analyzed on a Gemini Zeiss 1540 EsB microscope at accelerating voltages of 5-10 kV using secondary and backscattered electron detectors. The survey was carried out with preliminary deposition of silver onto the surface of samples on Polaron SC 7640 sputter coater.

2.3. Determination of the materials solubility
To evaluate the solubility of materials experiment was conducted complex comprising HA solubility in the composition of materials (control of Ca$^{2+}$ ion concentration), and the mass loss of the material over time. Solubility of pure HA and HA in the materials was determined by the total concentration of calcium ions Ca$^{2+}$ by trilonometric titration in the presence of eriochrome black T with ammonia buffer (pH 9-10). For this purpose, samples were incubated in saline solution (ω (NaCl) = 0.9%) at 37 °C for 7 days to reach saturation with respect to solid phase. The mean values of the concentrations of Ca$^{2+}$ ions (mol / l) and the confidence interval (with correlation index = 0.95) for them were calculated from three parallel measurements.

The materials degradation time were determined by measuring of the material mass loss after it was kept in sodium phosphate buffer for 28 days at 37 °C (weighing after drying).

3. Results and discussion
SEM images were obtained for composites (figure 1). All 3 composites are characterized by different coverage of HA surface with PLGA.

![Figure 1. SEM images of composite materials a) K1, b) K2, c) K3.](image)

PLGA coating of K1 samples were localized on the surface of HA particles in form of non-uniform single aggregates. For K2 samples uniform “island-like” coating with large number of phase boundaries between ceramics and polymer over its entire surface were formed. At the same time, K3 is completely covered with polymer, but the coating is non-uniform, as evidenced by large aggregates on the surface of ceramics.

According to the results obtained (figure 2), in the series from K1-K3, the solubility of HA decreases, probably due to the fact that the amount of PLGA increases, and the diffusion of calcium ions through the polymer layer becomes difficult.
However, with further incubation of samples in saline solution, polymer degradation occurs, which leads to a shift in the pH of the medium to a more acidic region and an increase in the solubility of HA. After 15 days of exposure, the opposite is true - in the K1-K3 series, the solubility of HA increases in accordance with an increase in the amount of PLGA by 2-6 times, which will positively affect the material resorption (figure 3).
4. Conclusions
The components of the composites have a mutual influence on the solubility of each other, since HA is
the main phosphate capable of influencing the hydrolysis of PLGA, and PLGA in turn, as a result of
hydrolysis, and helps lower the pH of the medium, which also enhances the dissolution of HA. The
dissolution rate of composites increases relative to pure PLGA from the second week, in proportion to
the increase in the amount of blowing agent in the material by 20-50%. The solubility of HA in the
composition of materials increases from the second week, since in the process of PLGA hydrolysis, the
diffusion of the solvent to HA increases.

Acknowledgements
This work was supported by Russian Foundation for Basic Research (project number 17-03-00698\19).

References
[1] Zhou H, Lawrence J G and Bhaduri S B 2012 Acta Biomaterialia 8 1999-2016
[2] Rasskazova L A, Korotchenko N M and Zeer G M 2013 Russian Journal of Applied Chemistry 86 691-695
[3] Syusyukina V A, Shapovalova Ye, Korotchenko N M and Kurzina I A 2017 Russian Journal of
Applied Chemistry 90 112
[4] Kurzina I A, Churina E G, Shapovalova E G, Syusyukina V A and Kzhyshkowska J G 2018
Bioceramics Development and Applications 8 109-1-109-7
[5] Rasskazova L A, Lytkina D N, Shapovalova E G, Botvin V V, Pozdniakov M A, Filimoshkin A G, Korotchenko N M and Kozik V V 2015 Russian Journal of Applied Chemistry 88 669-675
[6] Shapovalova Ye, Ly'tkina D N, Rasskazova L A, Zhuk I V, Gudima A, Filimoshkin A G, Korotchenko N M, Kurzina I A and Kzhy'shkovska Y G 2016 Key Engineering Materials 683 475-480
[7] Montjovent M O, Mathieu L, Schmoeke H, Mark S, Bourban P E, Zambelli P Y, Laurent-
Applegate L A and Pioletti D P 2007 Journal of Biomedical Materials Research Part A 83 41-51
[8] Lytkina D, Berezovskaya A, Korotchenko N, Kurzina I and Kozik V 2017 AIP Conf. Proc. 1899 020015-1-020015-6
[9] Botvin V, Pozdniakov M and Filimoshkin A 2017 Polymer degradation and stability 146 126-131
[10] Kurzina I A, Pukhova I V, Botvin V V et al 2015 AIP Conf. Proc 1688 030033-1–030033-7