CHLORAMPHENICOL LOADED PCL/CALCIUM PHOSPHATE COMPOSITE COATINGS FOR BONE REPLACEMENT APPLICATIONS

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КОМПОЗИТНЫЕ ПКЛ/КАЛЬЦИЙ-ФОСФАТНЫЕ ПОКРЫТИЯ С ВВЕДЕННЫМ ХЛОРАМФЕНИКОЛОМ ДЛЯ НУЖД ЗАМЕЩЕНИЯ ДЕФЕКТОВ КОСТЕЙ

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Аннотация. *В работе рассмотрены вопросы высвобождения антибактериального лекарственного средства из композитных полимер/кальций-фосфатных покрытий, полученных методом микродугового оксидирования на поверхности образцов титановых имплантатов. Получены образцы кальций-фосфатных покрытий, пропитанных раствором поли (ε-капролактона) с сорастворенным хлорамфениколом в концентрациях 5, 15 и 25 масс.% соответственно. Исследована смачиваемость поверхности покрытий и произведено моделирование процесса высвобождения хлорамфеникола в биологическую среду. Показано, что пропитка раствором полимера снижает смачиваемость поверхности покрытий, как в присутствии сорастворенной лекарственной субстанции, так и без нее. Увеличение содержания хлорамфеникола приводит к повышению смачиваемости и, как следствие, к увеличению скорости высвобождения лекарственного средства.*

Introduction. Finding solutions to further improve bone tissue regeneration and eliminate infections that can possibly occur during the procces of implantation are key tasks in modern traumatology and orthopedics. One of the most promising ways is to modify the implant surface with the bioactive coatings containing an antibacterial agent. To obtain those coatings plasma electrolytic oxidation (PEO) is commonly used. Similarity of the physico-mechanical properties of obtained calcium phosphate coatings with the main component of bones - hydroxyapatite leads to high biological compatibility stimulating tissue repair, while the antibiotic suppresses the causative agents of infection. Meanwhile, the problem of poor mechanical characteristics of the coating remains actual. In our previous work [1], we have already demonstrated the effectiveness of coating impregnation with a polymeric solution based on poly (ε-caprolactone) in order to improve coating elasticity. The aim of this work was to investigate the effectiveness of chloramphenicol incorporation into the resulting coatings, as well as the process of antibiotic release into the buffer medium simulating biological fluids.

Research methods. Samples fabrication is described in our previous publication [1]. The samples obtained were titanium disks with a calcium phosphate coating deposited by the PEO method, which was impregnated with a solution of polycaprolactone (PCL) in hexafluoroisopropanol with concentrations of chloramphenicol of 5, 15, and 25 wt.%, respectively.

The wettability of samples was characterized by deposing of 3 μl drops of polar (water and glycerin) liquids using Krüss Easy Drop contact angle measurement system. Droplets were placed at different position on samples and images were captured after the 1 min and 2 min disposition of each drop. All the data were obtained from an average made from the measurements taken at five different spots on the surface of the respective sample, with the standard deviations all shown.

Drug release study. Samples were immersed in Phosphate Buffer Saline (PBS, pH 7.4) at 25 ºC with three replicates for each group of samples. At predetermined time points, a 1 mL aliquot was withdrawn for further analysis and replaced with an identical volume of the fresh medium. The amount of released chloramphenicol was determined using high performance liquid chromatography (HPLC). Chloramphenicol concentration was determined by HPLC (Milichrom A-02, Russia), using a C18 column (2×75 mm, 3.5 μm, Milichrom, Russia) with Water/Acetonitrile 7:3 v/v as the mobile phase. The retention time of chloramphenicol was found to be 3.0 min, at a flow rate of 0.2 μL/min at 35 °C. The drug was detected at λ=278 nm using an injection volume of 20 μL. The amount of the released chloramphenicol was converted to the weight using a calibration curve and then plotted as a cumulative amount of the drug released against time.

Results. Wettability is one of the key parameters of medical devices intended for implantation into the human body. Measurement results are presented in Table 1. The most hydrophilic coating was the one obtained using the PEO method, whereas after impregnation with polycaprolactone, the surface wettability of the samples significantly (more than 2 times) worsens due to the hydrophobicity of polycaprolactone. However, with an increase in the chloramphenicol content in the coatings, a tendency to the contact angle decrease is observed.

Table 1

Water contact angles after 1 minute of exposure

	Ti PEO	Ti PEO PCL	Ti PEO PCL Chl 5%	Ti PEO PCL Chl 15%	Ti PEO PCL Chl 25%
Q, deg	22,6±10,3	67,5±1,1	68,5±1,6	63,8±2,6	50,05±1,75

To check the preservation of bacteriostatic properties of titanium samples with antibacterial coating for 7 days, the drug release profiles were studied. The obtained profiles are presented in Figure 1. The highest total value of released drug corresponded to the sample with the highest initial concentration of chloramphenicol (25 wt.%), and the lowest, similarly, to the sample with the lowest concentration (5 wt.%).

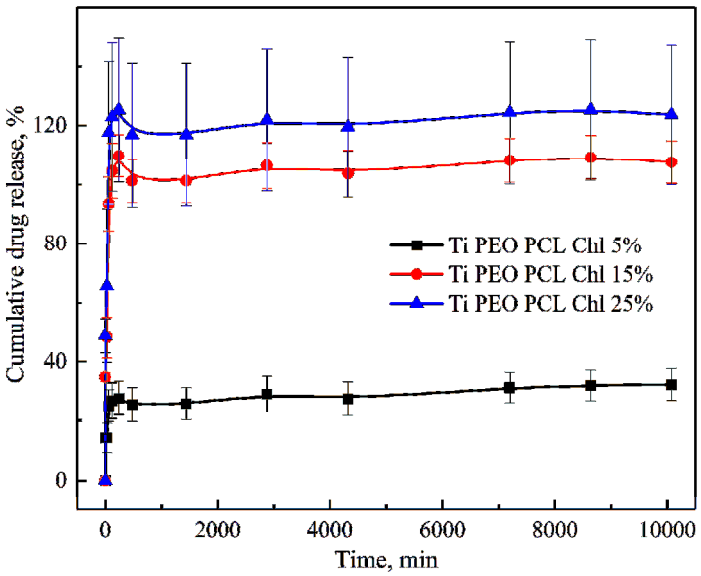

Fig. 1. Chloramphenicol release profiles. Seven days of exposure in PBS at 25 ºC

The bulk of released chloramphenicol took only 2 hours to be burst released from all samples. The hydrophobicity of the PCL surface impedes the release medium permeation into the coatings. Therefore, a relatively slow drug release during next 7 days of the experiment is hypothesized to be due to the gradual wetting of the surface, the ensuing permeation of the medium into the fibers and the consequent release of the drug from them. In contrast, a three times higher amount of released drug from 15wt.% and 25 wt.% samples is directly related to an increased surface wettability of the coatings surface, which is demonstrated above in Table 1.

With the measurement error given, it can be assumed that the amount of drug released from the samples with 15wt.% and 25 wt.% is approximately equal. This may be due to the poor solubility of chloramphenicol in aqueous solutions, as a result of which more than a certain limiting concentration of the drug cannot be released into the buffer solution.

Conclusion. Thus, it was shown that the drug release of the from the coatings continues during the entire considered period of time (7 days). The drug release profiles and results of the surface wettability study of the obtained materials allow us to conclude that the concentration of chloramphenicol equal to 15 wt.% is the most suitable for further research and development of osteo-substituting materials.

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