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Drug Delivery Systems for Bone Tissue Regeneration: Functionalized Porous Zirconia Scaffolds

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Extended Abstract

According to statistical data, more than 6 million bone fractures occur and even 500,000 bone graft surgeries are performed yearly in the United States alone, making bone fractures a relatively common problem [1]. Although bone tissue exhibits self-healing properties, this ability may be lost in the case of large-area fractures, as a result such bone tissue lesions need to be filled with a substitute material [2]. Since bone scaffolds are sensitive to bacterial contamination when implanted, up to 10% of surgical interventions end up with revision surgery due to implant-related infections [3]. Zirconium oxide (ZrO_2) is considered a biomaterial with great potential in biomedical applications. It is characterised by high biocompatibility with bone tissue and good mechanical properties [4], such as resistance to wear and corrosion [5]. However, due to its low bioactivity, its fixation with bone is poor. To improve its bioactivity, various methods are used, such as sandblasting, base or acid treatments, polishing, or coating [5]. Furthermore, porous scaffolds are known to better promote osteoblast migration and growth than solid scaffolds [2]. The open pore structure allows the supply of nutrients and the elimination of metabolic waste that support the formation of new bone tissue [4]. Implants that can reveal the ability to deliver drugs in a controlled manner are considered an improved solution to prevent implant-related infections compared to conventional treatment methods [5].

The aim of this work was to manufacture porous zirconia scaffolds and functionalise them with bioactive coatings containing antibiotic-loaded polymer nanoparticles (NPs) to improve their bioactivity and achieve the antibacterial effect. For this purpose, gentamicin was encapsulated in poly(lactic-co-glycolic acid) (PLGA) by the double emulsion method. Porous zirconia scaffolds were fabricated using the polymer foam replication method. To do so, polyurethane foams (in size of 1 cm x 1 cm x 1 cm) were immersed in a ZrO_2 slurry and left at 37°C for 30 min to dry. After that time, this process was repeated and then the foams coated with ceramic slurry were dried and sintered at 1450°C for 2 h. As a bioactive layer, we used a calcium phosphate (CaP) coating that was deposited on the scaffolds using a two-step biomimetic co-precipitation method in ten times concentrated simulated body fluid (10xSBF). In the first step, the scaffolds were immersed in 10xSBF for 24 h at 37°C. In the second step, the scaffolds were incubated in 10xSBF supplemented with NPs suspension under dynamic conditions (shaking at a speed of 150 rpm for another 24 h).

The scaffolds obtained in this way were observed with an optical microscope and scanning electron microscopy (SEM). Porosity was measured by the hydrostatic method and mechanical properties in compressive test were assessed. X-ray diffractometry analysis was performed to identify the phase composition and check the difference between coated and uncoated scaffolds. In addition, a biological evaluation was performed with osteoblast-like MG-63 cells and the antimicrobial properties with *Staphylococcus aureus* were verified by the Kirby-Bauer method with the use of material extracts (after 4 h of incubation in phosphate-buffered saline).

Observations with SEM confirmed that scaffolds have open porous microstructure and biomimetic co-precipitation is an effective method for the deposition of the CaP layer on a ZrO_2 substrate and the immobilization of NPs between the crystals of the CaP coating. Moreover, the presence of NPs in the solution had no negative impact on the CaP crystallisation process. The developed materials were non-toxic for MG-63 cells and showed antibacterial properties due to released gentamycin. In

summary, the process presented in our work is an efficient technique that allows to produce zirconia scaffolds that are characterised by an open porous microstructure, improved bioactivity, and antibacterial properties.

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