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Inkjet printed antibiotic- and calcium-eluting bioresorbable nanocomposite micropatterns for orthopedic implants

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ABSTRACT

Inkjet printing of antibiotic- and calcium-eluting micropatterns was explored as a novel means of preventing the formation of biofilm colonies and facilitating osteogenic cell development on orthopedic implant surfaces. The micropatterns consisted of a periodic array of ~50 μm circular dots separated by ~150 μm. The composition of the micropatterns was controlled by formulating inks with rifampicin (RFP) and poly(D,L-lactic–co-glycolic) acid (PLGA) dissolved in an organic solvent with ~100 nm biphasic calcium phosphate (BCP) nanoparticles suspended in the solution. During printing RFP and PLGA co-precipitated to form a nanocomposite structure with ~10–100 nm RFP and the BCP particles dispersed in the PLGA matrix. The rate of RFP release was strongly influenced by the RFP loading in the micropattern, particularly on the first day. The RFP-containing micropatterns effectively prevented the formation of *Staphylococcus epidermidis* biofilm colonies due to their ability to kill bacteria prior to forming colonies on the patterned surfaces. The BCP-containing micropatterns printed on the surface of the alloy TiAl6V4 significantly accelerated osteoblast cell differentiation, as measured by alkaline phosphatase expression and calcium deposition, without compromising cell proliferation.

1. Introduction

The use of orthopedic implants continues to grow due to our aging, as well as increasingly more active and obese, populations, with about one million hip and knee replacement procedures performed in the USA every year [1]. While our capability to design and produce orthopedic implants has significantly improved over the past several decades, hospital acquired bacterial infection during implantation has emerged as one of the leading causes of implant failures. Infections occur at a rate of a few percent for hips and knees and 15% for open wound trauma rods [2]. Infection occurs because opportunistic bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermidis* adhere to the implant surface, proliferate and form biofilm colonies [3,4]. In biofilm microenvironments bacterial cells are encapsulated by extracellular matrices and exhibit extraordinary resistance to host defenses and antibiotics [1–4]. Because of antibiotic-resistant biofilm formation standard care is limited to the surgical removal of infected devices, resulting in significant patient trauma and clinical costs. Antibiotic-loaded bioresorbable polymeric coatings have been found to be effective in reducing biofilm formation on orthopedic implant surfaces in in vitro and in vivo studies [5–7]. However, these coatings cover the entire surface of implants, significantly delaying and interfering with osseointegration until the coatings are degraded over several months. At the other extreme conventional hydroxyapatite (HAp) and calcium phosphate coatings, which are mainly designed and utilized for their osteoconductive properties, have very limited capability for controlled antibiotic release. For example, porous biomimetic apatite coatings can be loaded with antibiotics, but these delivery methods typically exhibit initial bursts followed by very low release rates with depletion of the antibiotics within several hours [8,9].

In this paper we report the possibility of using antibiotic- and calcium-eluting bioresorbable micropatterns as a new pathway to modify orthopedic implant surfaces for both wound healing and infection preventing functions. An inkjet printing process was developed to produce micropatterns containing biphasic calcium phosphate (BCP) nanoparticles and rifampicin (RFP) nanoparticles dispersed in a biodegradable matrix of poly(D,L-lactic–co-glycolic) acid (PLGA). The role of the RFP nanoparticles is to provide steady antibiotic release for a few weeks to kill bacteria near the Ti6Al4V alloy implant surface. At the same time new bone tissue is expected to directly and rapidly grow onto the micropatterned titanium alloy surface due to: (1) the osteoconductive properties of the Ti alloy surface; (2) the availability of calcium phosphate necessary for osteoblast cell recruitment and mineralization; (3) the microscale dimensions of the patterned

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