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Adding functionality with additive manufacturing: Fabrication of titanium-based antibiotic eluting implants

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ABSTRACT

Additive manufacturing technologies have been utilised in healthcare to create patient-specific implants. This study demonstrates the potential to add new implant functionality by further exploiting the design flexibility of these technologies. Selective laser melting was used to manufacture titanium-based (Ti-6Al-4V) implants containing a reservoir. Pore channels, connecting the implant surface to the reservoir, were incorporated to facilitate antibiotic delivery.

An injectable brushite, calcium phosphate cement, was formulated as a carrier vehicle for gentamicin. Incorporation of the antibiotic significantly ($p = 0.01$) improved the compressive strength (5.8 ± 0.7 MPa) of the cement compared to non-antibiotic samples. The controlled release of gentamicin sulphate from the calcium phosphate cement injected into the implant reservoir was demonstrated in short term elution studies using ultraviolet-visible spectroscopy. Orientation of the implant pore channels were shown, using micro-computed tomography, to impact design reproducibility and the back-pressure generated during cement injection which ultimately altered porosity. The amount of antibiotic released from all implant designs over a 6 hour period (<28% of the total amount) were found to exceed the minimum inhibitory concentrations of *Staphylococcus aureus* (16 μg/mL) and *Staphylococcus epidermidis* (1 μg/mL); two bacterial species commonly associated with periprosthetic infections. Antibacterial efficacy was confirmed against both bacterial cultures using an agar diffusion assay. Interestingly, pore channel orientation was shown to influence the directionality of inhibition zones. Promisingly, this work demonstrates the potential to additively manufacture a titanium-based antibiotic eluting implant, which is an attractive alternative to current treatment strategies of periprosthetic infections.

1. Introduction

Generally, total joint arthroplasty is a successful procedure that restores function and improves patient quality of life. Despite the introduction of standardised strategies, such as laminar flow clean air operating rooms and pre-operative antibiotics, periprosthetic infection still occurs in approximately 1–2% of patients following a total joint arthroplasty procedure [1,2]. When periprosthetic infections do occur they can lead to a need for rescue or revision surgery, and ultimately device failure. As such, implant infection represents one of the most costly complications in orthopaedic surgery.

Clinical procedures for the treatment of periprosthetic infection, include irrigation and debridement with component retention [3], as well as one- and two-stage exchange arthroplasty [4,5]. Two-stage exchange arthroplasty involves the implantation of an interim antibiotic-loaded component after removal of the original components. Commonly, antibiotic-loaded polymethylmethacrylate (PMMA) is used in the form of beads or cast into a mould and implanted [6–8]. PMMA cements set via an exothermic reaction, reaching temperatures between 70 and 120 °C [9]. This thermal behaviour limits the antibiotics PMMA may be combined with and it has been shown to result in tissue necrosis [10,11]. Other disadvantages include chemical necrosis due to leakage of unreacted monomer, shrinkage during polymerisation, and its inability to be resorbed [12]. The interim period in a two-stage exchange arthroplasty may range from 6 to 12 weeks depending on individual

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surgeon decision, and evidence of infection clearance and healing [13]. During this time, patients may be encouraged to walk with partial weight-bearing [14]. Complications associated with the interim period include sacral pressure sores and fractures on re-implantation [14]. Furthermore, increased morbidity from two-stage compared to one-stage exchange has been reported [15]. Some of these complications may be associated with the inactivity of the patient between procedures in a two-stage exchange arthroplasty.

Current orthopaedic implants are manufactured from stainless steels, cobalt chromium molybdenum alloys, and titanium alloys using traditional manufacturing methods (e.g. machining, forging, and investment casting) [16]. These processes have been optimised over a number of decades resulting in implants that can withstand long-term cyclic loading. In recent years, the use of additive manufacturing (AM) techniques in medicine has gained much attention [17–21]. Generally, AM techniques use a layer-by-layer approach to build parts from computer aided design (CAD) models. In comparison to conventional methods, this approach enables material wastage to be reduced and greater geometrical design freedom.

Selective laser melting (SLM) is an AM technology that may be used to manufacture metal components [22–25]. During this process, a focused laser beam is used to selectively heat a bed of metallic powder above the materials melting point causing the particles to melt and fuse together. After completion of each two-dimensional (2D) layer, the build platform is lowered by a pre-set thickness and the coating blade spreads a fresh layer of powder on top. This process is repeated until the full 3-dimensional (3D) geometry has been built. All processing is conducted in a chamber flooded with inert gas, usually nitrogen or argon to minimise oxygen-content.

To date, bone prostheses manufactured via AM technologies have primarily been employed clinically in relatively low load-bearing areas, such as the Food and Drug Administration approved OsteoFab® (Oxford Performance Materials); a patient specific polymer based cranial device. The introduction of metallic AM implants in high fatigue applications, such as permanent components of hip or knee implants, has been hindered by their rough surface features acting as fatigue crack initiation sites. Shorter fatigue life has been previously demonstrated through a comparative fatigue study of additively manufactured and equivalent rolled Ti-6Al-4V dental implants [26].

In the context of the challenges discussed above, the use of a device that would enable patients to fully weight-bear whilst eluting antibiotics during the interim period of a two-stage exchange arthroplasty is an attractive concept. This could be achieved by manufacturing an implant that is mechanically robust enough to withstand the patient's weight but also contains a reservoir that could be filled with an injectable antibiotic eluting biomaterial. To maintain and tailor structural properties a honeycomb type lattice could be introduced within the reservoir region. The geometrical freedom possible from AM technologies would facilitate the manufacture of such an intricate internal architecture, which would not be possible via traditional methods. Furthermore, if the device was used only in the interim period this would circumvent any long-term fatigue issues. Design of a metallic device that satisfies mechanical criteria would remove this demand from the antibiotic eluting material allowing for selection to be solely focused on desired therapeutic properties. This strategy in comparison to the use of antibiotic-loaded PMMA, which must fulfil both mechanical and therapeutic demands, may present advantages.

This paper presents a preliminary study to assess the feasibility of utilising SLM to manufacture an antibiotic eluting implant. Simplified cylindrical implants were designed to incorporate a reservoir connected to the surface extremities via a series of channels. A calcium phosphate cement, brushite, was selected as an antibiotic carrier and injected into the AM metallic implant. This material was chosen since, in comparison to PMMA, it sets at lower temperatures and is highly resorbable at physiological conditions [27]. The influence of pore orientation (horizontal, vertical, 45° incline) on the release profile of gentamicin sulphate from the implant was assessed. Antibacterial efficacy was demonstrated against two bacterial species commonly associated with periprosthetic infections. Overall, this work highlights the potential to add further value and functionality to orthopaedic implants by exploiting the advantages that AM technologies bring to manufacturing.

2. Materials and methods

2.1. Brushite cement formulation

Dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$) (DCPD), otherwise known as brushite, is a calcium phosphate phase that is several orders of magnitude more soluble than hydroxyapatite in physiological conditions [27]. Clinically, cements with a high injectability and a setting time between 5 and 15 min are desirable as this allows time for prosthesis implantation and adjustment but does not prolong the operation excessively.

A brushite cement formulation with an injectability of >80% through a 15G (1.829 mm) needle and a setting time of approximately 12 min was preselected for this study (data not shown). The cement was formulated using β-tricalcium phosphate (β-$Ca_3(PO_4)_2$) (β-TCP) synthesised using a previously reported method [28]. β-TCP and monocalcium phosphate monohydrate ($Ca(H_2PO_4)_2 \cdot H_2O$, Innophos, USA) (MCPM) powders were dry mixed in stoichiometric ratios (Eq. (1)) for 30 s using a spatula. The powder components were then mixed with deionised water at a 2:1 powder-to-liquid ratio (PLR) for 30 s to form a workable paste.

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2 \cdot H_2O + 7H_2O \rightarrow 4CaHPO_4 \cdot 2H_2O \quad (1)$$

Antibiotic loaded brushite cements were prepared by dissolving gentamicin sulphate (Sigma Aldrich, UK) at a concentration of 100 mg/mL into deionised water prior to mixing with the powder components giving a final concentration of 50 mg per 1 g of cement.

2.2. Manufacture of cement cylinders

Prepared cement pastes (Section 2.1) were formed into cylinders (diameter = 6 mm; height = 12 mm) by either casting or injecting into a PTFE split mould. Cast cylinders were made by pouring cement paste into the mould positioned on a Denstar-500 powered vibrating platform (Denstar, Korea). Injected cylinders were formed by loading cement pastes into a 5 mL syringe with 15G (1.829 mm internal diameter) needle after mixing and injecting into the split mould. Both cast and injected cement cylinders were left to set in the mould for 1 h in an incubator at 37 °C, demoulded, and stored in an incubator at 37 °C until use. Injected cement cylinders were manufactured so as to simulate the intended clinical delivery method and this was compared with cast versions (n = 10) as this is the typical process used in the literature [29,30].

2.3. Additive manufacture of implant models

Implant models (Fig. 1a) were fabricated from Ti-6Al-4V gas atomised powder (TLS Technik, Germany) sized 20–50 μm using a M2 Cusing® SLM system (Concept Laser, Germany), which employs an Nd:YAG laser with a wavelength of 1075 nm, spot size of 60 μm and a maximum laser output power of 400 W. The process parameters were optimised to reduce residual porosity and achieve the designed hole geometry for elution of gentamicin. The parameters used were 150 W laser power, 1750 mm/s scanning speed, 20 μm slice thickness, and hatch spacing of 75 μm. Support structures were built between the substrate base and each individual implant to provide stability during the build. Manufacture was conducted in a chamber flooded with argon gas to minimise oxygen pick-up to <0.1%.