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Porosity and pore size effect on the properties of sintered Ti35Nb4Sn alloy scaffolds and their suitability for tissue engineering applications

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ABSTRACT

Porous scaffolds manufactured via powder metallurgy and sintering were designed for their structure (i.e. pore size and porosity) and mechanical properties (stiffness, strength) to be controlled and tailored to mimic those of human bone. The scaffolds were realised to fulfil three main objectives: (i) to obtain values of stiffness and strength similar to those of trabecular (or spongy) bone, with a view of exploiting these as bone grafts that permit cell regeneration, (ii) to establish a relationship between stiffness, strength and density that allows tailoring for mass customisation to suit patient's needs; and (iii) to assess alloy cytotoxicity and biocompatibility via *in vitro* studies. The results obtained using a very low stiffness alloy (Ti35Nb4Sn) further lowered with the introduction of nominal porosity (30–70%) with pores in the ranges 180–300 μm and 300–500 μm showed compatibility for anatomical locations typically subjected to implantation and bone grafting (femoral head and proximal tibia). The regression fitting parameters for the linear and power law regressions were similar to those found for bone specimens, confirming a structure favourable to capillary network formation. Biological tests confirmed non-cytotoxicity of the alloy. Scaffolds of porosity nominal 50%vol and pore range 300–500 μm performed best in the adhesion and propagation assays due to a good balance between surface area and pore cavity volume.

1. Introduction

In 2013 the orthopaedic trauma devices market was valued at $5.7 billion and it is expected to grow further to $9.4 billion by 2020 at an annual growth rate of 7.2% [1]. An increasing aging population, not only in developed countries but also through the urbanisation of emerging markets, together with obesity epidemics and advances in clinical research are fuelling the demand for these devices. At present patients who carry implants from bone grafting in load-bearing locations such as knee, hip, ankle, etc. are outliving them, and seniors >70 years expect a durable implant replacement that will continue maintaining their quality of life. Drawbacks to the current existing implants are 'loosening' effects due to (i) "stress shielding" (i.e. when the implant is stiffer than the bone itself, it bears the load, so bone remodelling is hindered and healing retarded as cell count decays [2]) and (ii) lack of appropriate osteoconductive paths that allow the bone-forming cells to migrate into the porous implant and reside there, with the desired side effect of locking the device in place. In order to overcome these limitations to create better performing and longer-lasting implants, there is a need for a design and manufacturing strategy that allows engineering of the macrostructure of the implant and permits the tailoring of its mechanical properties to match that of the patient's host tissue.

Solid titanium alloys have been proven to provoke implant loosening due to their high stiffness (compared to that of bone) and non-porous interfaces [3], and alloys containing vanadium, cobalt, chrome, and nickel have been discarded because the ions eroded from the implants enter the blood stream and produce toxic deposits in soft organs such as liver and kidneys [4]. Beta-alloys Ti-Nb-Sn have received much attention recently due to their bone tissue compatibility [5], good corrosion resistance when tested at body-like pH and temperature conditions [6], and their lower stiffness when compared to other ternary Ti alloys, with Ti35Nb4Sn having one of the lowest Young's modulus of the group [7,8]. Low stiffness values are achieved by the stabilisation of β-phase Ti at the working temperature (i.e. body temperature). Elemental Ti at room

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temperature presents a α-type crystal (hexagonal) configuration and at high temperatures it exhibits an allotropic β-phase (cubic crystal configuration) that can become stable at room temperature with the addition of β-phase forming and stabilising elements (e.g. Nb, Sn [8–11]), which achieves a reduction in the Young's modulus (i.e. from E ~116 GPa in α-phase Ti alloys [12] to ~40 GPa in β-phase Ti alloys [8] – both fabricated by casting or melting and the latter cold rolled). The stiffness can be further lowered by introducing a porous structure. Techniques such as foaming or sintering with space-holders have been reported in literature [13,14]. Shape holder materials such as ammonium hydrogen carbonate, urea, sodium fluoride and chloride, saccharose and PMMA have been used in the manufacture of porous materials to control porosity and pore size [14–18]. Examples of stabilised beta-alloys of Ti fabricated using powder metallurgy coupled with the space-holder/sintering method in order to lower their stiffness and control their strength are Ti7.5Mo [19], Ti40Nb [20], Ti24Nb4Zr8Sn [21], Ti10Nb10Zr [22], and the namely-toxic Ti6Al4V [23] and TiNi [24]. The stiffness- and strength-to-weight ratios can thus be optimised to match the mechanical properties of bone and these cavities engineered to promote cell proliferation, which results in anchoring the bone graft in place to minimise loosening in the mid- to long-term.

There is a comprehensive set of data available on the mechanical properties of bone. Caution is advised when cross-comparing from studies undertaken using different measuring techniques as these influence the order of magnitude of the results [25,26]. Comparable values of elastic modulus and compressive strength have been reported in the ranges of 3–20 GPa, and 10–180 MPa, respectively [2,27]. The elastic modulus of human bone tissue has been shown to depend strongly on anatomical location, bone tissue type (e.g. cortical or trabecular) [28], on the health of the individual [29], and to a lesser extent on gender or age [30,31]. These ranges are narrower for properties of trabecular bone in areas typically subjected to implantation of devices. Elastic moduli have been reported for femoral heads as 2.6–11.2 GPa [32], femoral neck 1.5–4.5 GPa [28], and proximal tibia bone 3.27–10.58 GPa [33]. Patients affected by osteoporosis or osteoarthritis have been seen to show a decrease of 22% or 14%, respectively [29,34], in values for elastic moduli in compression. Femoral head subchondral bone plate elastic moduli as low as 3–10 GPa have been observed in patients more severely affected by these conditions [29]. Compressive strengths on femur head are in the range of 4–16 MPa, the lower values corresponding to an aged population [27], for femoral neck 11.5–23.6 MPa [35], and for tibial trabecular bone the range has been reported as 3–33 MPa [27].

Bone ingrowth requires that the bone graft is osteoconductive (i.e. it guides the bone ingrowth by providing cells with a structure/scaffold that promotes cell proliferation) so this shall lead to successful osseointegration of the implant, that is, sequential cell differentiation and maturation to create cells within the scaffold [36]. A definitive pore size value for optimal bone growth has not been agreed among researchers because it is not the sole factor for an enhanced bone healing effect. Other variables such as mechanical stiffness to provide a good mechanical matching between bone and bone graft (i.e. artificial implant), and surface chemistry and roughness to anchor and long-term attachment of cells, need also to be considered. However, the current consensus is that osteoblast migration into porous spaces occurs if the cavities are larger than 50 μm [37]; for non-load bearing condition sizes should be 50–125 μm [38], and for load-bearing applications the pore size range should be 50–500 μm [39].

The purpose of the presented work was to systematically study the effect of porosity and pore size on the mechanical properties of a reportedly low-stiffness Ti alloy (Ti35Nb4Sn) so that an optimum structure could be defined with a view of pursuing bioengineering applications by avoiding mechanical properties mismatching between the scaffold and the host bone tissue. Porous scaffolds spanning a broad range of porosity (30–70 %vol) were manufactured in two pore size ranges (a lower range 180–500 μm and a higher range 300–500 μm) which were created in the sintered scaffolds by a space-holder. Biological functionality was pursued so the scaffolds had to be non-cytotoxic as well as promoters of a good degree of cell adhesion and growth that could indicate promising qualities as osteoconductive and osteoinductive substrates.

2. Materials and methods

2.1. Porous scaffolds preparation

Elemental powders of Ti (Alfa Aesar, USA, 99.5% purity, ≤45 μm, −325 mesh), Nb (Aldrich, Germany, 99.8% purity, <45 μm, −325 mesh) and Sn (Alfa Aesar, USA, 99.8% purity, ≤45 μm, −325 mesh) were blended together according to the desired composition of Ti 61 %wt, Nb 35 %wt and Sn 4 %wt. This alloy is referred as Ti35Nb4Sn thereafter. Mechanical alloying was performed in a planetary ball mill (Fritsch, Germany, Pulverisette 6 Monomill) under argon atmosphere and using stainless steel grinding bowl and balls (10 mm diam). The ball-to-powder weight ratio was 10:1. The milling was carried out at room temperature with a rotation speed of 200 rpm for 12 h. This preparation time was chosen in accordance with previous experimental work that focused on the influence of ball milling time and the quality of the resulting mechanically alloyed powder material [40]. An additive, 2 %wt stearic acid (CH_3 $(CH_2)_{16}$ COOH), was included as a process control agent (PCA) to be absorbed on the surface of the metal particles and assist the development of a desired fine microstructure during ball milling as well as to prevent cold welding to the surface of the vessel and balls during milling. Previous studies have shown this %wt to be a good compromised amount to promote cold welding without fracturing becoming the dominant effect [13].

The ball-milled powders were mixed with the space-holder material, urea ($CO(NH_2)_2$) (Fisher, UK, 99% purity, in two particle size ranges: 180–300 μm and 300–500 μm). Given the particle size of the urea, the powder-to-space-holder volume ratio used was adjusted in order to yield a certain porosity ratio value (nominally from 30% to 70%). Therefore, both the pore size and the porosity ratio could be controlled independently. The powder/urea mixture was then uniaxially cold compacted at a pressure of 250 MPa into cylindrical green compacts with a diameter of 16 mm and a height of 8 mm. These were placed in a calcination oven, heated at 2 °C/min from room temperature up to 250 °C and kept at that temperature for 2 h to sublimate the space-holder and leave voids behind. It was important to ensure this process did not happen too quickly as it could affect the integrity of the compacted cylinders and produce striations. The subsequent sintering took place in an atmosphere-controlled (argon) furnace (Lenton Thermal Designs, UK) previously vacuum-flashed thoroughly. The green compacts, with only the metal powders in the porous structure, were heated up to 1100 °C at a heating rate of 5 °C/min, and held at this temperature for 3 h. The furnace was then allowed to cool to room temperature. Samples with no space-holder were also manufactured following the same pressing/sintering process. These will be referred to as non-porous sintered scaffolds. All samples were wet ground and polished using a 240-grit silicon carbide cloth. Finally they were cleaned using acetone and soapy water in an ultrasonic bath for 5 min, and left to air dry. The specimen's surface was examined with a scanning electron microscope (FEI, USA, Quanta 3D FEG dual beam, 3.5 nm, 30 kV) and measurements performed.