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Characteristics, interactions and coating adherence of heterogeneous polymer/drug coatings for biomedical devices

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ABSTRACT

With this rise in surgical procedures it is important to focus on the mobility and safety of the patient and reduce the infections that are associated with hip replacements. We examine the mechanical properties of gentamicin sulphate as a model antimicrobial layer for titanium-alloy based prosthetic hips to help prevent methicillin-resistant *Staphylococcus aureus* infection after surgery. A top layer of poly(lactic-co-glycolic acid) is added to maintain the properties of the gentamicin sulphate as well as providing a drug delivery system. Through the use of nanoindentation and micro-scratch techniques it is possible to determine the mechanical and adhesive properties of this system. Nanoindentation determined the modulus values for the poly(lactic-co-glycolic acid) and gentamicin sulphate materials to be 8.9 and 5.2 GPa, respectively. Micro-scratch established that the gentamicin sulphate layer is strongly adhered to the Ti alloy and forces of 30 N show no cohesive or adhesive failure. It was determined that the poly(lactic-co-glycolic acid) is ductile in nature and delaminates from the gentamicin sulphate layer of at 0.5 N.

1. Introduction

There is much discussion and divided opinion about whether implanted biomaterials should be inert or active. One opinion is that a biomaterial should exist in contact within the human body without causing harm to the body [1]. Another opinion says that the function of a biomaterial should be for directing a course of treatment through controlled interactions with the human body [2]. Currently, the primary objective of total hip arthroplasty (THA) is for the successful formation of an interface between the implant and the bone, the potential for the material to reduce infection and possible rejection of the implant still exists. Surgical site infection (SSI) is one of the most devastating complications of THA affecting between 1 and 2% of patients. In Ireland the number of patients undergoing THA per annum is 4500 meaning that 45–90 people are affected [3]. This number jumps to between 750 and 1500 in the UK, 1000–2500 in Germany and between 3200 and 6400 in the US [4–6]. This can lead to the removal of the implant and can also put the life of the patient in serious risk [2].

Staphylococcus aureus is the most common organism affecting in the region of 40–50% of infected patients with methicillin-resistant *S. aureus* (MRSA) accounting for 20–30% of these (or 10–15% of total infections) [7,8]. Early and delayed onset of infection is directly related to THA while late onset of infection is usually a result of hematogenous seeding. Delayed and late onset of infection is rare and the majority of cases require prosthetic removal [9]. Walls et al. [10], studied 15 patients who contracted MRSA after THA and discovered that 50% of the infections was as a direct result of the implant. The treatment for a *S. aureus* infection is long and arduous consisting of 4–6 weeks of pathogen-specific intravenous therapy with rifampin. This is followed by 3–6 months of oral therapy of doxycycline, minocycline, or trimethoprim-sulfamethoxazole with some patients requiring replacement surgery [11].

Over the last few years antibiotic impregnated cement spacers have been used to avoid infection and promote early ambulation [12]. Liu et al., [13] loaded strontium-containing hydroxyapatite (Sr-HA) bone cement with gentamicin sulphate to generate an efficient bioactive antibiotic drug delivery system for treatment of bone defects. This method allows for GS release of 38% *w*/*w* (by weight) which is a big improvement on previous studies which show ~2–10% *w*/*w* [14,15]. Gentamicin sulphate (GS) is a bactericidal antibiotic which is widely used in humans and animals and is active against *S. aureus* and MRSA [16]. Previous studies and products have incorporated GS into poly(methyl methacrylate) (PMMA) bone cement to hold the implant in place; however, this method is outdated as companies are moving away from bone cement as a result of bone cement implantation syndrome which increases the risk of morbidity and mortality [17,18]. This technique is only effective if the dissolution fluids can penetrate the polymer matrix to release

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the antibiotics and more often than not the drug remains embedded in the cement. The control of the drug release is extremely dependent on the porosity of the polymer and release rates are generally low and ineffective [19]. Belt et al., [20] studied the gentamicin released from six different commercial PMMA bone cements. The total amount of GS released ranged between 4 and 17%, surface roughness and porosity being the two most influential parameters in terms of release. It was concluded that the bone cements which released the most GS within 6 h of implantation were of most benefit to the patient. Stallman et al., [21] studied the in vitro release of GS from PMMA beads of six different injectable carriers. The release rates observed (36–84%) were considerably higher than the PMMA bone cement previously reported. However, PMMA has a major drawback it is not biodegradable and requires surgery to be removed. As a result, a different drug delivery method would be better suited.

Poly(lactic-co-glycolic acid) (PLGA) is the most widely used biodegradable polymer in vivo where dissolving in the body is required and provides a way to control GS delivery similar to PMMA but without removal surgery. It has FDA approval, is biocompatible and has been extensively studied as a delivery carrier for drugs, proteins, DNA, RNA and peptides [22,23]. The mechanical strength, and the ability of the copolymer to undergo hydrolysis leading to biodegradation, is directly influenced by the degree of crystallinity of the PLGA. This is dependent on the ratio of the crystalline PGA to the amorphous PLA, larger quantities of PGA lead to faster degradation with the exception of a ratio of 50:50 which has the fastest degradation rates [24]. Lecároz et al., [25] successfully reduced *Brucella melitensis* infection by encapsulating 30 μg of gentamicin in PLGA microparticles. The PGA to PLA ratio was 75:25 as larger amounts of the hydrophilic PGA allowed for the largest quantities of gentamicin encapsulation. Abdelghany et al., [26] were able to achieve higher gentamicin levels by changing the pH of the gentamicin solution. This allows for the deprotonation of the amino moieties from NH_3^- to NH_2 making the GS less hydrophilic and more acquiescent to bonding to the PLGA copolymer.

Here, we examine the mechanical properties and adherence of GS and PLGA on prosthetic hip implants comprised of Ti–6Al–4V. The GS will prevent surgical site infections during hip replacement and over the following weeks while the PLGA acts to protect the drug layer and provide some controlled release. A salient aspect of implementing this system is gaining an understanding of the mechanical and adhesive properties of the materials. Due to thermal and mechanical loads the mechanical compatibility, chemical bonding, and microstructural change at interfaces play an important role in determining ultimate properties and service life of these materials. Weakly bonded GS could result in easy delamination reducing the impact it has on SSI.

As PLGA/GS composites, in various forms, have been reported it would be prudent to examine the methods in which the mechanical properties are determined. PLGA is FDA approved there are extensive reports on its mechanical properties which are controllable by adjusting the ratio of the PLA/PGA polymers. PLGA can be formed in spheres, films and 3D scaffolds to incorporate or encapsulate a vast amount of materials [27–29]. The mechanical properties of these subsequent systems can be measured via nanoindentation, scratch testing, tensile testing and peel-off testing [30–33]. There are no previous studies that examine the mechanical strength properties of GS as it is usually incorporated into a system as a dopant or a composite. There are many reports that examine the properties of bone cement/GS matrices but none report data on the bulk material [33,34,35].

By depositing a thick layer of GS and determining its mechanical strength and adhesion it will be possible to have a positive impact on post-implant infection. The top layer of PLGA protects the GS layer mainly from any moisture damage as the polymer is hydrophobic in contrast to the hydrophilic drug. Through the use of nanoindentation and micro-scratch techniques we show that it is possible to measure the mechanical properties of the materials and determine the forces needed to separate and delaminate the two layers. We can also access the adhesive strength of the drug to the Ti implant and deem if it's suitable for implantation.

2. Materials and methods

2.1. Materials

Ti–6Al–4V coupons with a diameter of 26 mm and a thickness of 3.5 mm were grit blasted with Al_2O_3 particles. These are representative of the complex prosthetic implants but their modified geometry allows for the use of typical characterisation techniques. The coupons were cleaned with ethanol and DI water before being vacuum dried for 6 h. GS (50:50) was dissolved in H_2O and the coupons were then coated using an ultrasonic spray method. The coupons were allowed to dry under vacuum for 24 h. The PLGA was coated on top of the GS in the same manner except acetone was used as the solvent. For analysis purposes GS only and PLGA only coupons were prepared alongside the bilayer system.

2.2. Characterisation

The surface morphology of the coated coupons was determined with a high-resolution (<1 nm) field emission Zeiss Ultra Plus SEM equipped with a Gemini column. The PLGA samples and Ti substrates were coated in Au prior to imaging. Confocal laser microscopy analysis was performed using an Olympus Fluoview FV1000 confocal microscope with a Kr/Ar laser (488 nm laser excitation). For analysis the GS was doped with fluorescein and the PLGA was doped with Texas red prior to deposition on the metal substrate. The topographical data was obtained using a Park XE-100 microscope in non-contact mode with SSS-NCHR tips. FT-IR data were recorded on an IR660, Varian infrared spectrometer and measurements were performed in the spectral range of 4000–500 cm^{-1}, with a resolution of 4 cm^{-1} with data averaged over 32 scans. Thermogravimetric analysis (TGA) was performed using a TA Instruments Q-500 analyser. The balance purge consisted of pure nitrogen (25 ml min^{-1}) and temperatures were recorded from 0 °C to 800 °C at a heating rate of 4 °C min^{-1}. Profilometry measurements were carried out using a Dektak 6M profilometer fitted with a 12.5 μm radius tip.

2.3. Mechanical testing

The mechanical properties of the materials were obtained using an MTS Nano-Indenter XP fitted with a pyramidal Berkovich diamond tip. Modulus and hardness values as a function of indentation depth were extracted using a continuous stiffness measurement (CSM), using a 1.5 nm sinusoidal displacement at 45 Hz superposed on quasi-static indentation motion. The thermal drift correction was set at 0.03 nm s^{-1}. An array of 25 indents was done on GS on the Ti substrate to maximum load (650 mN). This was done to ascertain the range of depth of the material. A second array of 25 indents was done on PLGA Ti substrate to maximum load and a third array of 25 indents was done on PLGA on GS. Modulus and hardness values were obtained from a depth of 500–1500 nm for each material.

Microscratch experiments were performed on a CSEM Micro Scratch Tester (MST) equipped with a Vickers tip with a diameter of 300 μm. The tip was moved, laterally, across the surface of the PLGA on top of GS to understand the adhesion of the two layers. Another test was done on only GS to study its adherence to the substrate. Measurements were done at different progressive loads between 0.3–30 N at a rate of 0.5 mm min^{-1}.