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Evaluation of sorption capacity of antibiotics and antibacterial properties of a cyclodextrin-polymer functionalized hydroxyapatite-coated titanium hip prosthesis

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ABSTRACT

Infection still present as one of common complications after total hip replacement (~2.5%), which may cause serious outcomes. For preventing such risk, loading antibiotics onto implants for increasing local drug concentration at targeted sites could be a solution. This study aims at modifying the surface of hydroxyapatite (HA) coated titanium hip implant material (Ti–HA) with polymer of cyclodextrin (polyCD) for loading antibiotics, to achieve a sustained local drug delivery. Two widely applied antibiotics (tobramycin and rifampicin) in orthopedic surgery were loaded alone or in combination. The drug adsorption isotherm, drug release kinetics and drug's efficacy were thoroughly investigated. The results proved that polyCD coating significantly improved the affinity of both drugs to Ti–HA surface, while the mechanism of drug–polyCD interaction varies from the nature of drug, courtesy of the structural complex of polyCD. The advantage of dual-drug loading was highlighted by its strong efficacy against both *Staphylococcus aureus* and *Enterobacter cloacae*, which overcomes the limitation of mono-drug loading for an effective treatment against both bacterial strains. The prolonged antibacterial activity of antibiotic loaded Ti–HA-polyCD samples confirmed that polyCD could be a promising drug-delivery system, for sustained antibiotics release or other potential applications *e.g.*, antimitotic agent release.

1. Introduction

The hip prostheses are widely used for elderly patients suffering from primary coxarthrosis (73%), dysplasia, osteonecrosis or following femoral neck fractures (Delaunay et al., 2009). Total hip replacement (THR) is one of the most common surgeries performed in France (120 000 prostheses per year) and in the world (800 000 prostheses per year) (Market research, 2011). Historically the metal prostheses were fixed with poly(methyl methacrylate) (PMMA) cement loaded with or without gentamicin in order to limit the risk of infection. Due to recurrent problem (exothermic chemical reaction, degradation, *etc.*) with the cement, the cemented implants were replaced progressively by cementless designs with porous coating (TiO_2, hydroxyapatite (HA)) to achieve biologic fixation (*i.e.*, osseointegration). In theory, the cementless hip prostheses are expected to reduce the chance of infection and loosening of the prosthesis, which are two major complications of THR surgery. Many research, however, (Dale et al., 2009) indicates that they are associated with higher rates of infection than cemented prostheses (0.3–1.7%) (Pozo and Patel, 2009; Barsoum et al., 2010). In France, 11% of failed primary hip arthroplasties were tied to infection (Delaunay et al., 2013).

Implant-associated infection generally results from bacterial adhesion to the implant surface and subsequent bio-film formation (Zilberman and Elsner, 2008), which shields the microorganisms from host defense mechanisms and antimicrobial agents (Dunne, 2002; Donlan and Costerton, 2002). To prevent infection, high dose of antibiotic administered *per os* is routinely executed, however, has a limited effect due to very low diffusion into the mineral bone matrix (Thomes et al., 2002; Ruszczak and Friess, 2003). In

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addition, certain drawbacks including systemic toxicity and creation of antibiotic resistant bacterial strains are observed frequently. Therefore, development of local drug delivery system and anti-biofilm approaches are highly recommended.

Gentamicin-loaded bone cements, introduced by Buchholz and Engelbrecht (1970) have shown their benefit in reducing infection rate after primary hip and knee replacement (Engesaeter et al., 2003; Bourne, 2002) and remain as the gold standard for cemented prosthesis. Local antibiotic delivery has been proved to reduce surface biotic colonization *in vitro* and prevent biofilm formation *in vivo* (Schmidmaier et al., 2006; Kalicke et al., 2006), owing to the improved drug bioavailability, reduced drug overdose effect, and declined susceptibility to antibiotic resistance (Wu and Grainger, 2006; Baroli, 2009). While regarding to cementless hip prostheses, in absence of bone cement, there is a need for appropriate new drug carriers with the necessary amount of drug to offer an antibacterial effect for a defined period of time at the targeted implant/tissue interface.

In order to accomplish a controlled local drug release for cementless hip prostheses, much research has focused on loading antibacterial agents *via* polymer as PEG, PLA, PGA, and PMMA (Kim et al., 2008; Maddikeri et al., 2008; O'neill and O'sullivan, 2010; Neut et al., 2011) or inorganic coating (HA) on the porous surface of the implant. Among the studied antibiotic carriers, HA coating on titanium (Ti–HA) implants has surplus value by providing excellent mechanical fixation and a reliable osseointegration (Oosterbos et al., 2004; Cho et al., 2010). Hence, many studies investigated the potential of HA as vectors of bioactive molecules, and different methods like ink jet or surface induced mineralization (Alt et al., 2011; Campbell et al., 2000) were applied to incorporate the antibiotic into HA or carbonated HA coatings (Stigter et al., 2002, 2004). However, limited amount of adsorbed antibiotics in the coating layer and weak drug/carrier interaction are incapable of sustaining drug release. The antibacterial activity of above-mentioned coating can last no longer than three days, which is far from necessary for fighting the infection. The ideal antibiotic release system for treating implant-related infection should provide an appropriate and effective release profile of antibiotics at the implant site. Such controlled local drug release firstly is characterized by a high initial release rate (burst release) in order to respond to the elevated risk of bacterial infection linked to the initial shock. Since 6 h post implantation is "decisive period" to prevent initial bacterial adhesion, it will be critical for the long-term success of an implant (Hetrick and Schoenfisch, 2006). Next to burst release phase, a sustained release phase at an effective level for inhibiting the occurrence of latent infection should present (Zilberman and Elsner, 2008). Unfortunately, it is very difficult to define the time necessary for an extended-release dependent on amount/nature of the bacteria and the selected antibiotic or association of antibiotic. Nevertheless, we believe that it is not necessary to have a local antibiotic therapy for several months at the risk of creating resistant strains and we believe that the burst effect is very important to eradicate most or all of the bacteria. The extended release for a few days seems reasonable to prevent any recurrence of surgical site infection.

Our previous studies (Taha et al., 2013; Hoang Thi et al., 2010) have shown remarkable success of cyclodextrin (CD) polymer (polyCD, a cross-linking product between CD and polycarboxylic acid) coating in improving drug release profile of various implant materials. The interest of CD lies on their ability to form inclusion complexes (drug/CD) in its hydrophobic cavity with various types of guest molecules, which brought about their widespread applications in biomedical and pharmaceutical industries. Moreover, as a drug delivery platform, polyCD can better adhere to the implant surface and accommodate more types of drug owing to the negatively charged reticulated structures. Encouragingly, our precedent work (Taha et al., 2013) of polyCD functionalized Ti–HA implant *via* a specific coating process has already presented very promising results with a model drug molecule-toluidine blue O (TBO) for sustained delivery, and the potential for antibiotic (gentamicin) release.

The objective of present study was to further explore the versatility of polyCD drug delivery system by loading different antibiotic molecules alone or combined on polyCD functionalized Ti–HA implant. Tobramycin and rifampicin were opted for their high efficiency in clinical use and difference in chemical composition and antibacterial spectrum. Particularly, the assay on tobramycin/rifampicin association was to examine the dual-drug loading potential of polyCD system, which can enlarge the

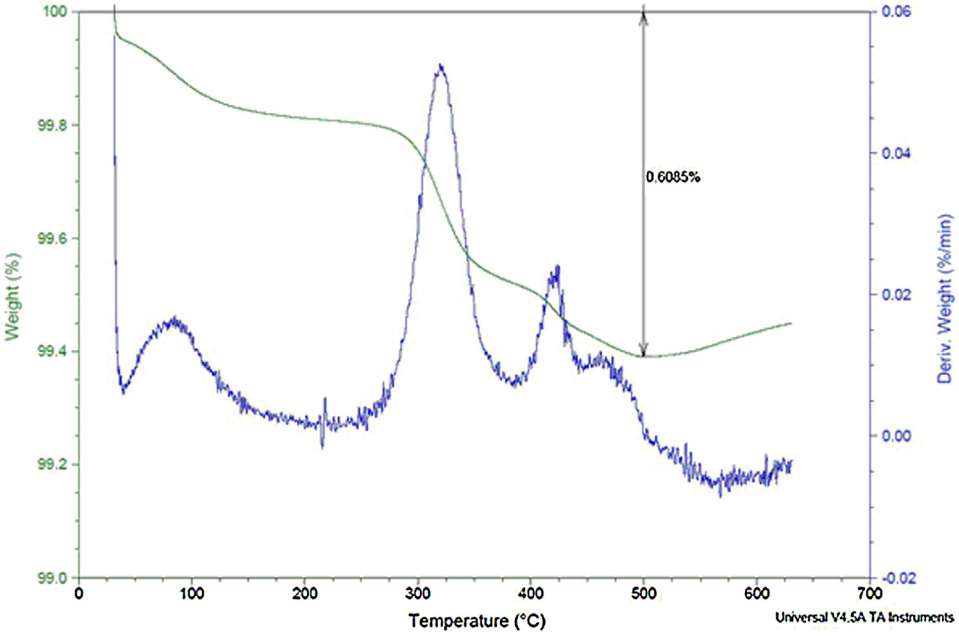

Fig. 1. Thermogravimetric analysis of the polyBTCA/MeβCD treated Ti–HA samples.