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Controlled release of metronidazole from composite poly-ε-caprolactone/alginate (PCL/alginate) rings for dental implants

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ABSTRACT

Objective. Dental implants provide support for dental crowns and bridges by serving as abutments for the replacement of missing teeth. To prevent bacterial accumulation and growth at the site of implantation, solutions such as systemic antibiotics and localized delivery of bactericidal agents are often employed. The objective of this study was to demonstrate a novel method of controlled localized delivery of antibacterial agents to an implant site using a biodegradable custom fabricated ring.

Methods. The study involved incorporating a model antibacterial agent (metronidazole) into custom designed poly-ε-caprolactone/alginate (PCL/alginate) composite rings to produce the intended controlled release profile. The rings can be designed to fit around the body of any root form dental implants of various diameters, shapes and sizes.

Results. In vitro release studies indicate that pure (100%) alginate rings exhibited an expected burst release of metronidazole in the first few hours, whereas Alginate/PCL composite rings produced a medium burst release followed by a sustained release for a period greater than 4 weeks. By varying the PCL/alginate weight ratios, we have shown that we can control the amount of antibacterial agents released to provide the minimal inhibitory concentration (MIC) needed for adequate protection. The fabricated composite rings have achieved a 50% antibacterial agent release profile over the first 48 h and the remaining amount slowly released over the remainder of the study period. The PCL/alginate agent release characteristic fits the Ritger–Peppas model indicating a diffusion-based mechanism during the 30-day study period.

Significance. The developed system demonstrates a controllable drug release profile and the potential for the ring to inhibit bacterial biofilm growth for the prevention of diseases such as peri-implantitis resulting from bacterial infection at the implant site.

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1. Introduction

The use of osseointegrated dental implants for the replacement of lost teeth has become common and well accepted in dentistry. Advances in biomaterials research and titanium implant manufacturing techniques have resulted in a wide selection of implants being used in restorative dentistry. Despite reports of high success rates in dental implants, 5–11% of dental implants fail [1] and require complete removal due to either bacterial infection or improper loading conditions during mastication. Bacteria accumulate on the surface almost immediately after implantation *via* a series of events that is initiated by the adsorption of the molecules from the saliva to produce a conditioning film called pellicle [2]. This film provides a surface for attachment of the initial colonizers, which are mainly comprised of Gram-positive streptococci (such as *Streptococcus oralis*, *Streptococcus mitis*) and actinomyces species [3]. Within thirty minutes, the first colonies are formed [4,5] by surface attachment and simultaneous proliferation and co-aggregation [6]. The attached bacteria and their progeny continuously secrete proteins, enzymes [7], and insoluble extracellular polysaccharides [8] that form a biofilm, which promotes co-existence with secondary colonizers and facilitates survival by resisting antibacterial agents [9]. The continuous development of biofilms can progress into peri-implantitis and often requires the complete removal of the implant [1,10].

Several strategies have been developed to prevent implant failure caused by bacterial accumulation on the implant surface. The most common ones include oral ingestion of antibiotics prescribed for a period of time and local injection of antibiotics at the site of implantation during the initial weeks following placement [1]. Advanced strategies include coating the implant surface with anti-adhesive polymers [11] to prevent bacterial accumulation at the implant site. Several antibiotics have been used for clinically such as Chlorhexidine, Tetracyclines and Sanguinarine which are prescribed based on the types of bacterial infection diagnosed [12]. Metronidazole is a first-line of antibiotics for treating anaerobic infections in oral disease, and also has a low minimum inhibitory concentration of 90% (MIC_{90}) against *B. fragilis* species that are the most frequently encountered anaerobic pathogens clinically [13]. A commercial lipid-like gel based on glyceryl monooleate (GMO) and triglyceride (sesame oil) containing 25% metronidazole (Elyzol; Dumex-Alpharma, Denmark) has been used for over 30 years for periodontal diseases [12,13]. Some studies report that Elyzol is not effective for periodontal treatment due to poor microbiological inhibition [14]. This is probably due to the fact that the Elyzol gel is susceptible to elimination from the periodontal pocket due to its gel form factor [15].

Besides systemic administration of antibiotics and/or local delivery of antibacterial agents, matrix-based solutions have also been studied to perform local controlled release of the agents for the treatment of periodontal diseases. Aliphatic polyesters such as poly-ε-caprolactone (PCL) have been widely used for different biomedical application purposes. Due to its biocompatibility and non-toxic degradation within the human body [16], PCL is one of the most suitable biomaterials used in controlled drug release applications. PCL is a hydrophobic and biodegradable polymer under physiological conditions [17], and has been researched extensively for the controlled delivery of drugs contained within a matrix. Kyun and co-workers [18] showed that by embedding minocycline in PCL, it is possible to obtain sustained release of the drug within the periodontal pocket for up to seven days and can eliminate bacteria from the periodontal pocket. Manufacturing processes such as electrospinning have produced PCL nanofibers for dental applications such as scaffolds for periodontal regeneration [19,20], and electrospun PCL nanofibers with metronidazole for long term sustained drug release [21]. Due to its relatively dense structure, PCL based matrices do not provide the necessary burst release of antibacterial agents needed for the initial 48 h post-implantation.

Another example of a biodegradable hydrophilic matrix material is alginate, a naturally occurring polysaccharide produced from the structural component of brown algae and bacteria [22]. In addition to its non-toxicity and biodegradability, alginate forms hydrogels under mild conditions when immersed in a divalent ion solution [23]. Consequently, alginate has been used extensively in pharmaceutical industries as a dental impression material [24], wound dressing material between bone and periosteum in the jaws [25], and in oral drug delivery [26]. Creating a composite of two polymeric biomaterials is one approach to developing new biomaterials exhibiting combinations of properties that cannot be obtained by the individual polymers themselves. Sodium alginate has significant burst release property in the first couple of hours [27] while polymers such as PCL and/or PLGA can delay drug diffusion to slow the release rate at which drug molecules are exposed in an aqueous environment [28]. While several laboratory solutions have been proposed, clinically relevant solutions demand ease of use by the dentist and any proposed solution should not add to the complexity of the placement procedure, particularly paying attention to prevent scratching the surface of the metal implant. Ideally, the solution must be integrated into the implant with minimal post-implantation visits made by the patient while protecting them from further infection during the healing process.

In this study, we have developed a ring like implantable device encapsulated with a candidate antibacterial agent whose release can be customized for the lifetime of the implant. This device is made from a composite of biocompatible and biodegradable polymers (calcium-alginate hydrogels and poly-ε-caprolactone) encapsulated with metronidazole for the localized delivery of the agent at the implant site. This application ensures high concentration of drug around the implant, and reduces side effects associated with a systemic drug application. A possible placement of the annular ring would be around the body of a root form dental implant adjacent to the bone crest as shown in Fig. 1. We have devised a fabrication process to produce customized blends of the two polymers (Alginate and PCL) to form custom shaped rings of virtually any dimension, size and shape to fit various dental implants. Molds of the desired shape were prepared into which discrete regions of poly-ε-caprolactone/alginate was solvent casted and encapsulated with known quantities of metronidazole (MZ). Our studies show that by tuning the relative weight percentages of PCL to alginate, we can customize the release profiles of MZ from the composite annular ring. Finally, the