DENTAL MATERIALS XXX (2018) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.intl.elsevierhealth.com/journals/dema

Antimicrobial photodynamic active biomaterials for periodontal regeneration

B.W. Sigusch[a], S. Dietsch[a], A. Berg[b], A. Voelpel[a], A. Guellmar[a], U. Rabe[a], M. Schnabelrauch[b], D. Steen[c], B. Gitter[c], V. Albrecht[c], D.C. Watts[d], S. Kranz[a,*]

[a] Department of Conservative Dentistry and Periodontology, University Hospitals Jena, An der alten Post 4, 07743 Jena, Germany
[b] Biomaterials Department, INNOVENT e.V. Pruessingstrasse 27 B, 07745 Jena, Germany
[c] biolitec research GmbH, Otto-Schott-Str. 15, 07745 Jena, Germany
[d] University of Manchester, School of Medical Sciences,Oxford Road, M13 9PL Manchester, UK

ARTICLE INFO

Article history:
Received 13 April 2018
Received in revised form
18 June 2018
Accepted 18 June 2018
Available online xxx

Keywords:
Biomaterial
Laser
Photodynamic therapy
Periodontitis
Periodontal bone regeneration
aPDT
Photosensitizer
Enterococcus faecalis
Porphyromonas gingivalis

ABSTRACT

Objective. Biomaterials for periodontal regeneration may have insufficient mechanical and antimicrobial properties or are difficult to apply under clinical conditions. The aim of the present study was to develop a polymeric bone grafting material of suitable physical appearance and antimicrobial photodynamic activity.

Methods. Two light curable biomaterials based on urethane dimethacrylate (BioM1) and a tri-armed oligoester-urethane methacrylate (BioM2) that additionally contained a mixture of β-tricalcium phosphate microparticles and 20 wt% photosensitizer mTHPC (PS) were fabricated and analyzed by their compressive strength, flexural strength and modulus of elasticity. Cytotoxicity was observed by incubating eluates and in direct-contact to MC3T3-E1 cells. Antimicrobial activity was ascertained on *Porphyromonas gingivalis* and *Enterococcus faecalis* upon illumination with laser light (652 nm, $1 \times 100\,J/cm^2$, $2 \times 100\,J/cm^2$).

Results. The compressive strength, flexural strength and elastic modulus were, respectively, 311.73 MPa, 22.81 MPa and 318.85 MPa for BioM1 + PS and 742.37 MPa, 7.58 MPa and 406.23 MPa for BioM2 + PS. Both materials did not show any cytotoxic behavior. Single laser-illumination (652 nm) caused total suppression of *P. gingivalis* (BioM2 + PS), while repeated irradiation reduced *E. faecalis* by 3.7 (BioM1 + PS) and 3.1 (BioM2 + PS) log-counts.

Significance. Both materials show excellent mechanical and cytocompatible properties. In addition, irradiation with 652 nm induced significant bacterial suppression. The manufactured biomaterials might enable a more efficient cure of periodontal bone lesions. Due to the mechanical properties functional stability might be increased. Further, the materials are antimicrobial upon illumination with light that enables a trans-mucosal eradication of residual pathogens.

* *Corresponding author.*
E-mail address: Stefan.Kranz@med.uni-jena.de (S. Kranz).
https://doi.org/10.1016/j.dental.2018.06.026

1. Introduction

Periodontitis is a chronic and highly prevalent inflammatory disease of bacterial origin that is characterized by a progressive destruction of the alveolar bone, periodontal ligament and root cementum.

To prevent inflammation and further destruction of the periodontal hard and soft tissues, the initial treatment is mainly aimed at the destruction and removal of supra- and subgingival microbial biofilms. In general, this is accomplished by a professional dental cleaning followed by mechanical debridement and smoothening of the root surface. The procedure is often accompanied by a systemic administration of antibiotics or local application of antiinfective agents [1–3].

Especially in times of growing antibiotics resistance, the search for alternative antiinfective approaches is of major concern. In periodontitis treatment, measures such as the antimicrobial Photodynamic Therapy (aPDT) are therefore increasingly applied as an adjunct to the common scaling and root planning procedures. In case of aPDT, microbes are lethally damaged by highly reactive oxygen radicals that are formed upon illumination of a so-called photosensitizer (often a deep colored dye) with light of its absorption wavelength [4]. As already shown in numerous studies, aPDT is capable in suppressing oral bacteria and fungi sufficiently [5–12].

However, in periodontitis therapy, patients that have experienced the initial anti-inflammatory treatment often suffer from persistent alveolar bone defects and decreased tissue levels [13–15]. In order to support regeneration of the injured periodontium grafting materials might be inserted [16]. These include a whole range of materials such as barrier membranes, autografts, demineralized and freeze-dried bone allografts, bovine-derived xenografts and the combination of membranes and filler substances as well as the local application of growth factors such as Emdogain® or GEM 21S® [15,17–19].

All of these measures are likely to support periodontal regeneration. But, if the applied materials do not meet the clinical requirements exactly, problems might arise. In those cases, the implanted grafts might be rejected, delocalized or encapsulated by fibrous tissue causing a restriction of the materials' biological function [20].

Sometimes, surgeons are also confronted with insufficient mechanical and antibacterial properties or the application of the material is time consuming and too complicated.

However, up to now, there is no grafting material available that unites osteoinductive and -conductive characteristics with local antimicrobial activity and satisfactory physical stability. In this regard, our group already published data showing that polymers of poly(vinyl butyral-*co*-vinyl alcohol-*co*-vinyl acetate), urethane methacrylate or functionalized oligolactones are of promising characteristics [21].

Based on these results, the aim of the present study was to design an innovative synthetic grafting material that can easily be applied during periodontal surgery, shows mechanical properties similar to alveolar bone and is of sufficient antimicrobial activity. In order to turn the material antiinfective, the potent photosensitizer meta-tetra(hydroxyphenyl)chlorin (mTHPC) was incorporated that can be activated by illumination with red light of 652 nm and already demonstrated efficient antimicrobial activity [5,7].

2. Materials and methods

2.1. Chemicals

D,L-Lactide was purchased from Purac Biochem (Gorinchem, The Netherlands). Urethan dimethacrylate (UDMA), a mixture of two isomeric monomers (Fig. 1) and polyethylene glycol 400 (PEG 400) extended UDMA (P-UDMA) were received from Esstech (Essington, USA).

2-Isocyanatoethyl methacrylate (IEM), stannous octoate, dibutyltin dilaurate (DBTL), camphorquinone, ethyl 4-dimethylaminobenzoate and several solvents were obtained from Sigma–Aldrich Chemie (Taufkirchen, Germany).

β-Tricalcium phosphate (β-TCP Cerasorb®) was supplied by Curasan (Frankfurt am Main, Germany).

2.2. Photosensitizer mTHPC

The photosensitizer mTHPC (also known as Temoporfin), which was kindly provided by biolitec research (Jena, Germany), is a very potent second-generation photosensitizer (for its chemical structure: see Fig. 3) and is the active ingredient in the drug Foscan® which is already approved for photodynamic treatment of non-melanoma skin cancer (biolitec, Jena, Germany). The photodynamic reaction of mTHPC is activated by irradiation with light of 652 nm.

In the present study, the hydrophobic photosensitizer mTHPC was mixed with β-tricalcium phosphate microparticles (β-TCP) at a concentration of 20 wt% and added to the polymeric base materials (also see below). Specimens without photosensitizer and β-TCP served as controls. The mixture of mTHPC and β-TCP is abbreviated as 'PS' throughout the entire study.

The added mTHPC is expected to generate sufficient antibacterial activity upon irradiation with red laser light at 652 nm, while β-TCP mainly functioned as porogen and was used as carrier for the photosensitizer.

2.3. Biomaterial 1 (BioM1)

Biomaterial 1 (BioM1) is based on UDMA (Fig. 1) mixed with a photoinitiator system consisting of camphorquinone and ethyl 4-dimethylaminobenzoate in a ratio of 1:1. Both com-

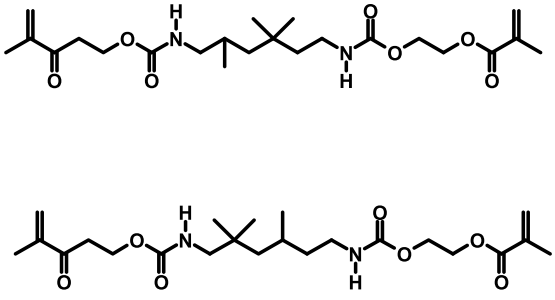

Fig. 1 – Chemical structure of the urethane dimethacrylate isomers of UDMA (used in BioM1).

Please cite this article in press as: Sigusch BW, et al. Antimicrobial photodynamic active biomaterials for periodontal regeneration. Dent Mater (2018), https://doi.org/10.1016/j.dental.2018.06.026